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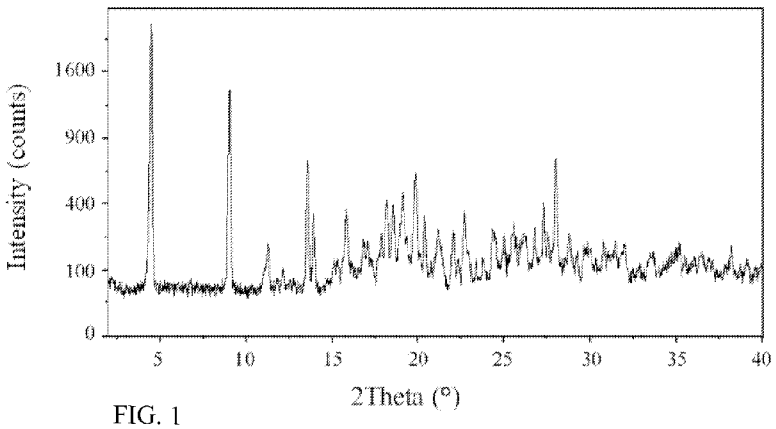


FIG. 1

(57) Abstract: Disclosed are novel polymorphic trihydrated forms of the sodium salt of 4-tert-butyl-N-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl] benzenesulfonamide. One embodiment of the present invention is directed to a crystalline form ofthe sodium salt of 4-tert-butyl-N-[4-chloro-2-(l-oxy-pyridine-4-carbonyl)- 25 phenyl]-benzenesulfonamide (hereinafter "Compound A _ crystalline trihydrate form I"), wherein the crystalline form is characterized by an X-ray powder diffraction pattern comprising diffraction angles (°28), when measured using Cu Ka radiation, at about 4.5, 9.0, 13.6, 13.9, 15.8, 17.8, 18.2, 18.5, 19.1, 19.9, 20A, 21.2, 22.1, 22.7, 24.3, 25.0, 25.6, 26.2,26.8,27.3,27.6,28.0,28.8, and 30.8.

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POLYMORPHIC FORMS OF THE SODIUM SALT OF 4-TERT-BUTYL-N-[4-CHLORO-2-(1-OXY-PYRIDINE-4-CARBONYL)-PHENYL]-BENZENESULFONAMIDE

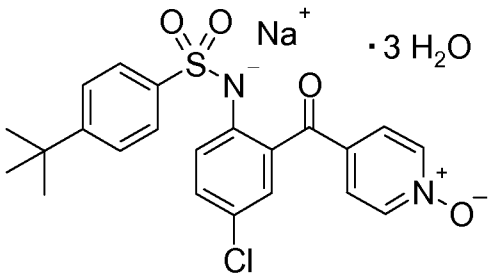
BACKGROUND OF THE INVENTION

In the pursuit of a developable form of a solid, orally-administered pharmaceutical compound, a number of specific features are sought. Although an amorphous form of a pharmaceutical compound may be developed, compounds having high crystallinity are generally preferred. Often such highly crystalline compounds are salts.

International Publication Number WO 2004/046092 describes a series of compounds which are indicated as antagonists of the CCR9 receptor, and which are indicated as being useful in the treatment of CCR9-mediated disorders. Specifically disclosed in that application is the compound 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide. Identification of a stable, crystalline form of such compound with suitable properties for oral administration would be highly desirable for the treatment of CCR9-mediated diseases.

SUMMARY OF THE INVENTION

The present invention relates to novel polymorphic trihydrated forms of the sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide (hereinafter "Compound A"). The compounds of the invention are represented by Structure (I):



(I)

The compounds of this invention are useful for antagonizing the CCR9 receptor, and for treating diseases such as inflammatory bowel disease, including Crohn's disease and ulcerative colitis.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows an X-ray powder diffraction pattern of Compound A - crystalline trihydrate form I.

Fig. 2 shows an X-ray powder diffraction pattern of Compound A - crystalline trihydrate form II.

Fig. 3 shows a Raman spectrum of Compound A - crystalline trihydrate form I.

Fig. 4 shows a Raman spectrum of Compound A - crystalline trihydrate form II.

Fig. 5 shows a differential scanning calorimetry trace of Compound A - crystalline trihydrate form I.

Fig. 6 shows a differential scanning calorimetry trace of Compound A - crystalline trihydrate form II.

Fig. 7 shows a thermogravimetric analysis trace of Compound A - crystalline trihydrate form I.

Fig. 8 shows a thermogravimetric analysis trace of Compound A - crystalline trihydrate form II.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to novel polymorphic trihydrated forms of the sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide. One embodiment of the present invention is directed to a crystalline form of the sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide (hereinafter "Compound A - crystalline trihydrate form I"), wherein the crystalline form is characterized by an X-ray powder diffraction pattern comprising diffraction angles (°2θ), when measured using Cu K_α radiation, at about 4.5, 9.0, 13.6, 13.9, 15.8, 17.8, 18.2, 18.5, 19.1, 19.9, 20.4, 21.2, 22.1, 22.7, 24.3, 25.0, 25.6, 26.2, 26.8, 27.3, 27.6, 28.0, 28.8, and 30.8. Another embodiment of the present invention is directed to Compound A - crystalline trihydrate form I, wherein the crystalline form is

characterized by an X-ray powder diffraction pattern comprising diffraction angles (°2θ), when measured using Cu K_α radiation, at about 4.5, 9.0, 13.6, 13.9, 15.8, 19.9, 20.4, and 28.0. A further embodiment of the present invention is directed to Compound A - crystalline trihydrate form I, wherein the crystalline form is characterized by an X-ray powder diffraction pattern comprising diffraction angles (°2θ), when measured using Cu K_α radiation, at about 4.5, 9.0, 13.6, 19.9, and 28.0.

Another embodiment of the present invention is directed to Compound A - crystalline trihydrate form I, wherein the crystalline form is characterized by an X-ray powder diffraction pattern substantially in accordance with Fig. 1.

Another embodiment of the present invention is directed to Compound A - crystalline trihydrate form I, wherein the crystalline form provides a Raman spectrum containing peaks at about 656, 688, 743, 803, 1125, 1154, 1162, 1286, 1469, 1544, 1587, 1596, 1656, 1672, 2904, 2964, and 3071 cm^{-1}. A further embodiment of the present invention is directed to Compound A - crystalline trihydrate form I, wherein the crystalline form provides a Raman spectrum containing peaks at about 688, 743, 803, 1125, 1154, 1162, 1286, 1587, 1596, 1656, and 1672 cm^{-1}. A still further embodiment of the present invention is directed to Compound A - crystalline trihydrate form I, wherein the crystalline form provides a Raman spectrum containing peaks at about 688, 743, 1154, 1596, 1656, and 1672 cm^{-1}.

Another embodiment of the present invention is directed to Compound A - crystalline trihydrate form I, wherein the crystalline form provides a Raman spectrum substantially in accordance with Fig. 3.

Another embodiment of the present invention is directed to Compound A - crystalline trihydrate form I, wherein the crystalline form provides a differential scanning calorimetry trace substantially in accordance with Fig. 5 and/or a thermogravimetric analysis trace substantially in accordance with Fig. 7.

Another embodiment of the present invention is directed to a crystalline form of the sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide (hereinafter "Compound A - crystalline trihydrate form II"), wherein the crystalline form is characterized by an X-ray powder diffraction pattern comprising diffraction angles (°2θ), when measured using Cu K_α radiation, at about 4.5, 9.1, 13.6, 13.9, 15.8, 16.8, 17.8, 18.2, 18.5, 18.9, 19.3, 19.7, 19.9, 21.3, 22.1, 22.7, 22.9, 24.3, 25.6, 25.9, 26.8, 28.0, 28.8, and 31.3. A further embodiment of the present invention is directed

to Compound A - crystalline trihydrate form II, wherein the crystalline form is characterized by an X-ray powder diffraction pattern comprising diffraction angles (°2θ), when measured using Cu K_α radiation, at about 4.5, 9.1, 13.6, 13.9, 18.2, 19.9, 22.7, 24.3, 26.8, and 28.0. A further embodiment of the present invention is directed to Compound A - crystalline trihydrate form II, wherein the crystalline form is characterized by an X-ray powder diffraction pattern comprising diffraction angles (°2θ), when measured using Cu K_α radiation, at about 4.5, 9.1, 18.2, 19.9, 24.3, and 28.0.

Another embodiment of the present invention is directed to Compound A - crystalline trihydrate form II, wherein the crystalline form is characterized by an X-ray powder diffraction pattern substantially in accordance with Fig. 2.

Another embodiment of the present invention is directed to Compound A - crystalline trihydrate form II, wherein the crystalline form provides a Raman spectrum containing peaks at about 656, 668, 719, 743, 751, 803, 1125, 1154, 1162, 1173, 1286, 1469, 1544, 1587, 1596, 1612, 1656, and 1673 cm^{-1}. A further embodiment of the present invention is directed to Compound A - crystalline trihydrate form II, wherein the crystalline form provides a Raman spectrum containing peaks at about 668, 743, 1125, 1154, 1286, 1587, 1596, 1612, 1656, and 1673 cm^{-1}. A still further embodiment of the present invention is directed to Compound A - crystalline trihydrate form II, wherein the crystalline form provides a Raman spectrum containing peaks at about 668, 743, 1154, 1612, 1656, and 1673 cm^{-1}.

Another embodiment of the present invention is directed to Compound A - crystalline trihydrate form II, wherein the crystalline form provides a Raman spectrum substantially in accordance with Fig. 4.

Another embodiment of the present invention is directed to Compound A - crystalline trihydrate form II, wherein the crystalline form provides a differential scanning calorimetry trace substantially in accordance with Fig. 6 and/or a thermogravimetric analysis trace substantially in accordance with Fig. 8.

It is well known and understood to those skilled in the art that the apparatus employed, humidity, temperature, orientation of the powder crystals, and other parameters involved in obtaining an X-ray powder diffraction (XRPD) pattern may cause some variability in the appearance, intensities, and positions of the lines in the diffraction pattern. An X-ray powder diffraction pattern that is "substantially in accordance" with that of Figures 1 or 2 provided herein is an XRPD pattern that would be considered by one

skilled in the art to represent a compound possessing the same crystal form as the compound that provided the XRPD pattern of Figures 1 or 2. That is, the XRPD pattern may be identical to that of Figures 1 or 2, or more likely it may be somewhat different. Such an XRPD pattern may not necessarily show each of the lines of the diffraction patterns presented herein, and/or may show a slight change in appearance, intensity, or a shift in position of said lines resulting from differences in the conditions involved in obtaining the data. A person skilled in the art is capable of determining if a sample of a crystalline compound has the same form as, or a different form from, a form disclosed herein by comparison of their XRPD patterns. For example, one skilled in the art can overlay an XRPD pattern of a sample of a sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide, with Fig. 1 and, using expertise and knowledge in the art, readily determine whether the XRPD pattern of the sample is substantially in accordance with the XRPD pattern of Compound A - crystalline trihydrate form I. If the XRPD pattern is substantially in accordance with Fig. 1, the sample form can be readily and accurately identified as having the same form as Compound A - crystalline trihydrate form I. Similarly, a person skilled in the art is capable of determining if a given diffraction angle (expressed in °2θ) obtained from an XRPD pattern is at about the same position as a value presented herein.

"A compound of the invention" means a sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide, specifically the crystalline forms defined herein as Compound A - crystalline trihydrate form I and Compound A - crystalline trihydrate form II.

The invention includes a therapeutic method for treating or ameliorating a CCR9-mediated disorder in a subject in need thereof comprising administering to a subject in need thereof an effective amount of a compound of the invention or a composition comprising an effective amount of a compound of the invention and an optional pharmaceutically acceptable carrier.

As used herein, the phrase "CCR9-mediated disorder" and related phrases and terms refer to a condition or disease characterized by inappropriate, i.e., less than or greater than normal, CCR9 functional activity. Inappropriate CCR9 functional activity might arise as the result of CCR9 expression in cells which normally do not express CCR9, increased CCR9 expression (leading to, e.g., inflammatory and immunoregulatory disorders and diseases) or decreased CCR9 expression. Inappropriate CCR9 functional

activity might also arise as the result of TECK secretion by cells which normally do not secrete TECK, increased TECK expression (leading to, e.g., inflammatory and immunoregulatory disorders and diseases) or decreased TECK expression. A CCR9-mediated disorder may be completely or partially mediated by inappropriate CCR9 functional activity. However, a CCR9-mediated disorder is one in which modulation of CCR9 results in some effect on the underlying condition or disease (e.g., a CCR9 antagonist results in some improvement in patient well being in at least some patients).

"Effective amount" means that amount of drug substance (i.e. a compound of the present invention) that elicits the desired biological response in a subject. Such response includes alleviation of the symptoms of the disease or disorder being treated. The effective amount of a compound of the invention in such a therapeutic method is about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range the dosage may be 0.005 to 0.05, 0.05 to 0.5, 0.5 to 5.0, or 5.0 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It is to be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including age, body weight, hereditary characteristics, general health, gender, diet, mode and time of administration, rate of excretion, drug combination, and the nature and severity of the particular condition being treated.

Administration methods include administering an effective amount of the compound or composition of the invention at different times during the course of therapy or concurrently in a combination form. The methods of the invention include all known therapeutic treatment regimens.

Diseases and conditions associated with inflammation, immune disorders, infection and cancer may be treated or prevented with the present compounds, compositions, and

methods. In one group of embodiments, diseases or conditions, including chronic diseases, of humans or other species can be treated with an inhibitor of CCR9 function. These diseases or conditions include: (1) allergic diseases such as systemic anaphylaxis or hypersensitivity responses, drug allergies, insect sting allergies and food allergies, (2) inflammatory bowel diseases, such as Crohn's disease, ulcerative colitis, ileitis and enteritis, (3) vaginitis, (4) psoriasis and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria and pruritus, (5) vasculitis, (6) spondyloarthropathies, (7) scleroderma, (8) asthma and respiratory allergic diseases such as allergic asthma, allergic rhinitis, hypersensitivity lung diseases and the like, (9) autoimmune diseases, such as fibromyalagia, scleroderma, ankylosing spondylitis, juvenile RA, Still's disease, polyarticular juvenile RA, pauciarticular juvenile RA, polymyalgia rheumatica, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, polyarticular arthritis, multiple sclerosis, systemic lupus erythematosus, type I diabetes, type II diabetes, glomerulonephritis, and the like, (10) graft rejection (including allograft rejection), (11) graft-v-host disease (including both acute and chronic), (12) other diseases in which undesired inflammatory responses are to be inhibited, such as atherosclerosis, myositis, neurodegenerative diseases (e.g., Alzheimer's disease), encephalitis, meningitis, hepatitis, nephritis, sepsis, sarcoidosis, allergic conjunctivitis, otitis, chronic obstructive pulmonary disease, sinusitis, Behcet's syndrome and gout, (13) pulmonary fibrosis and other fibrotic diseases, and (14) irritable bowel syndrome.

Preferably, the present methods are directed to the treatment of diseases or conditions selected from inflammatory bowel disease, including Crohn's disease and ulcerative colitis; allergic diseases such as psoriasis, atopic dermatitis, and asthma; and autoimmune diseases such as rheumatoid arthritis.

More preferably, the present methods are directed to the treatment of inflammatory bowel disease, including Crohn's disease and ulcerative colitis.

The compounds and compositions of the present invention can be combined with other compounds and compositions having related utilities to prevent and treat the condition or disease of interest, such as inflammatory conditions and diseases, including inflammatory bowel disease, allergic diseases, psoriasis, atopic dermatitis and asthma, and those pathologies noted above. Selection of the appropriate agents for use in combination therapies can be made one of ordinary skill in the art. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various

disorders. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

Combination therapy includes co-administration of a compound of the invention and said other agent, sequential administration of a compound of the invention and the other agent, administration of a composition containing a compound of the invention and the other agent, or simultaneous administration of separate compositions containing a compound of the invention and the other agent.

The invention further includes the use of a compound of the invention as an active therapeutic substance, in particular in the treatment of CCR9-mediated disorders. In particular, the invention includes the use of a compound of the invention in the treatment of inflammatory bowel disease, including Crohn's disease and ulcerative colitis.

In another aspect, the invention includes the use of compounds of the invention in the manufacture of a medicament for use in the treatment of the above disorders.

"Pharmaceutically acceptable carrier" means any one or more compounds and/or compositions that are of sufficient purity and quality for use in the formulation of a compound of the invention that, when appropriately administered to a human, do not produce an adverse reaction, and that are used as a vehicle for a drug substance (i.e. a compound of the present invention).

The invention further includes the process for making the composition comprising mixing a compound of the invention and an optional pharmaceutically acceptable carrier; and includes those compositions resulting from such a process, which process includes conventional pharmaceutical techniques. For example, a compound of the invention may be nanomilled prior to formulation. A compound of the invention may also be prepared by grinding, micronizing or other particle size reduction methods known in the art. Such methods include, but are not limited to, those described in U.S. Pat. Nos. 4,826,689,

5,145,684, 5,298,262, 5,302,401, 5,336,507, 5,340,564, 5,346,702, 5,352,459, 5,354,560, 5,384,124, 5,429,824, 5,503,723, 5,510,118, 5,518,187, 5,518,738, 5,534,270, 5,536,508, 5,552,160, 5,560,931, 5,560,932, 5,565,188, 5,569,448, 5,571,536, 5,573,783, 5,580,579, 5,585,108, 5,587,143, 5,591,456, 5,622,938, 5,662,883, 5,665,331, 5,718,919, 5,747,001, PCT applications WO 93/25190, WO 96/24336, and WO 98/35666, each of which is incorporated herein by reference. The pharmaceutical compositions of the invention may be prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company), the entire teachings of which are incorporated herein by reference.

The compositions of the invention include ocular, oral, nasal, transdermal, topical with or without occlusion, intravenous (both bolus and infusion), and injection (intraperitoneally, subcutaneously, intramuscularly, intratumorally, or parenterally). The composition may be in a dosage unit such as a tablet, pill, capsule, powder, granule, liposome, ion exchange resin, sterile ocular solution, or ocular delivery device (such as a contact lens and the like facilitating immediate release, timed release, or sustained release), parenteral solution or suspension, metered aerosol or liquid spray, drop, ampoule, auto-injector device, or suppository; for administration ocularly, orally, intranasally, sublingually, parenterally, or rectally, or by inhalation or insufflation.

Compositions of the invention suitable for oral administration include solid forms such as pills, tablets, caplets, capsules (each including immediate release, timed release, and sustained release formulations), granules and powders.

The oral composition is preferably formulated as a homogeneous composition, wherein the drug substance (i.e. a compound of the present invention) is dispersed evenly throughout the mixture, which may be readily subdivided into dosage units containing equal amounts of a compound of the invention. Preferably, the compositions are prepared by mixing a compound of the invention with one or more optionally present pharmaceutical carriers (such as a starch, sugar, diluent, granulating agent, lubricant, glidant, binding agent, and disintegrating agent), one or more optionally present inert pharmaceutical excipients (such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and syrup), one or more optionally present conventional tableting ingredients (such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid,

magnesium stearate, dicalcium phosphate, and any of a variety of gums), and an optional diluent (such as water).

Binding agents include starch, gelatin, natural sugars (e.g. glucose and beta-lactose), corn sweeteners and natural and synthetic gums (e.g. acacia and tragacanth). Disintegrating agents include starch, methyl cellulose, agar, and bentonite.

A compound of the invention may also be administered *via* a delayed release composition, wherein the composition includes a compound of the invention and a biodegradable slow release carrier (e.g. a polymeric carrier) or a pharmaceutically acceptable non-biodegradable slow release carrier (e.g. an ion exchange carrier).

Biodegradable and non-biodegradable delayed release carriers are well known in the art. Biodegradable carriers are used to form particles or matrices which retain a drug substance(s) (i.e. a compound of the present invention) and which slowly degrade/dissolve in a suitable environment (e.g. aqueous, acidic, basic and the like) to release the drug substance(s). Such particles degrade/dissolve in body fluids to release the drug substance(s) (i.e. compounds of the present invention) therein. The particles are preferably nanoparticles (e.g. in the range of about 1 to 500 nm in diameter, preferably about 50-200 nm in diameter, and most preferably about 100 nm in diameter). In a process for preparing a slow release composition, a slow release carrier and a compound of the invention are first dissolved or dispersed in an organic solvent. The resulting mixture is added into an aqueous solution containing an optional surface-active agent(s) to produce an emulsion. The organic solvent is then evaporated from the emulsion to provide a colloidal suspension of particles containing the slow release carrier and the compound of the invention.

Tablets and capsules represent an advantageous oral dosage unit form. Tablets may be sugarcoated or filmcoated using standard techniques. Tablets may also be coated or otherwise compounded to provide a prolonged, control-release therapeutic effect. The dosage form may comprise an inner dosage and an outer dosage component, wherein the outer component is in the form of an envelope over the inner component. The two components may further be separated by a layer which resists disintegration in the stomach (such as an enteric layer) and permits the inner component to pass intact into the duodenum or a layer which delays or sustains release. A variety of enteric and non-enteric layer or coating materials (such as polymeric acids, shellacs, acetyl alcohol, and cellulose acetate or combinations thereof) may be used.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

EXAMPLE 1

Preparation of:

An anhydrous crystalline sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide

A reaction vessel was charged with 300 g 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide, 4,737 mL Industrial Methylated Spirits (IMS), and 302.4 mL water. 27.245 g sodium hydroxide pellets were added to the slurry at 25 °C. The reaction mixture was agitated at ambient temperature for 50 minutes, followed by heating to ~78 °C to dissolve all solids. The clear solution was then filtered while maintaining the temperature above 55 °C throughout the filtration process. After filtration, the filtered solution was reheated to 75 °C and then cooled to 55 °C and seeded with 3.0 g Compound B - anhydrous crystalline form (prepared by an analogous procedure) as a slurry in 15 mL IMS at ambient temperature. The slurry was held at 55 °C overnight and then cooled to 45 °C. Vacuum distillation was employed while heating the reactor jacket to 65 °C and not allowing the slurry temperature to exceed 55 °C, leaving ~1,500 mL of slurry in the reactor. The slurry was cooled to -10 °C, held at that temperature overnight, and then transferred to a filter dryer and settled for 10 minutes. The jacket temperature of the filter was pre-chilled to -10 °C. The mother liquors were removed to break-through using 0.5 to 1 bar nitrogen pressure. The crystallizer was charged with a first pre-chilled wash of 1,200 mL IMS, chilled to -10 °C. The wash was transferred to the cake in the filter, agitated for 10 minutes, settled for 10 minutes, and removed under 0.5 to 1 bar nitrogen pressure. The washing of the filter cake was repeated two additional times under the same conditions. The jacket temperature of the filter was increased to 20 °C and the cake was blown-down under 0.5 to 1 bar nitrogen pressure until the solvent being removed was reduced to a trickle. The wet cake was dried at 70 °C with agitation under vacuum to provide 258.3 g of the title compound as a yellow crystalline solid.

EXAMPLE 2

Preparation of:

A crystalline sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide (Compound A - crystalline trihydrate form I)

200 mg of an anyhydrous crystalline sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide was weighed into a 20-mL vial containing a stir bar. Water (1.0 mL) and 1 M sodium hydroxide (21.0 μL) were added, the vial was tightly capped, and the solution was stirred for 3 hours at 25 °C. The resulting solid was isolated using a Büchner funnel, and the filter cake was air-dried for 2 hours to provide the title compound as a yellow solid.

The X-ray powder diffraction (XRPD) pattern of this material is shown in Fig. 1 and a summary of the diffraction angles and d-spacings is given in Table I. The XRPD analysis was conducted on a PANanalytical X'Pert Pro Diffractometer, model PW3040/60, serial number DY2407 using an X'Celerator detector. The acquisition conditions included: Cu K_α radiation (λ = 1.54059 Å), generator tension: 45kV, generator current: 40mA, start angle: 2.0°2θ, end angle: 50.0°2θ, step size: 0.0167°2θ, time per step: 40.005 seconds. The sample was prepared using zero background (front fill) technique.

TABLE I

Diff. Angle [°2θ]	d-spacing [Å]
4.5118	19.56946
9.0391	9.77548
13.5572	6.52611
13.9365	6.34934
15.8342	5.59241
17.838	4.96845
18.1805	4.87561
18.5409	4.78165
19.1043	4.64189
19.8797	4.46255
20.3967	4.35058
21.2175	4.1841
22.0896	4.02085
22.722	3.91034

24.3406	3.65386
25.0422	3.55305
25.5611	3.48209
26.2406	3.39344
26.7996	3.32391
27.3238	3.26132
27.5795	3.23166
28.0276	3.18101
28.774	3.10017
30.7952	2.90115

The Raman spectrum of the title compound was recorded on a Nicolet NXR 9650 FT-Raman Spectrometer, at 4 cm^{-1} resolution with excitation from a Nd:YVO4 laser (λ = 1064 nm). The Raman spectrum of this material is shown in Fig. 3 with major peaks observed at 656, 688, 743, 803, 1125, 1154, 1162, 1286, 1469, 1544, 1587, 1596, 1656, 1672, 2904, 2964, and 3071cm^{-1}.

The differential scanning calorimetry (DSC) thermogram of the title compound was recorded on a TA Instruments Q1000 Differential Scanning Calorimeter and is shown in Fig. 5. The sample was weighed into an aluminium pan, a pan lid placed on top and lightly crimped without sealing the pan. The experiments were conducted using a heating rate of 15 °C/min.

The thermogravimetric analysis (TGA) thermogram of the title compound was recorded on a TA Instruments Q5000 Themrogravimetric Analyzer and is shown in Fig. 7. The experiments were conducted using a heating rate of 15 °C/min.

EXAMPLE 3

Preparation of:

A crystalline sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide (Compound A - crystalline trihydrate form II)

400 mg of an anyhydrous crystalline sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide was weighed into a 20-mL vial containing a stir bar. Acetonitrile (1.1 mL), water (107 µL) and 1 M sodium hydroxide (43.0 µL) were added, the vial was tightly capped, and the solution was stirred for 24 hours

at 25 °C. The resulting solid was isolated using a Büchner funnel, and the filter cake was air-dried for 2 hours to provide the title compound as a yellow solid.

The X-ray powder diffraction (XRPD) pattern of this material is shown in Fig. 2 and a summary of the diffraction angles and d-spacings is given in Table II. The XRPD analysis was conducted on a PANanalytical X'Pert Pro Diffractometer, model PW3040/60, serial number DY2407 using an X'Celerator detector. The acquisition conditions included: Cu K_α radiation (λ = 1.54059 Å), generator tension: 45kV, generator current: 40mA, start angle: 2.0°2θ, end angle: 50.0°2θ, step size: 0.0167°2θ, time per step: 40.005 seconds. The sample was prepared using zero background (front fill) technique.

TABLE II

Diff. Angle [°2θ]	d-spacing [Å]
4.5389	19.45267
9.0653	9.74725
13.608	6.50188
13.8925	6.36936
15.8095	5.60111
16.8103	5.26982
17.8351	4.96926
18.1773	4.87646
18.5148	4.78833
18.8917	4.69365
19.3112	4.59262
19.7213	4.49803
19.918	4.45405
21.2562	4.17657
22.0611	4.02598
22.6801	3.91747
22.8751	3.88452
24.3391	3.65408
25.5589	3.48239
25.9388	3.43223
26.7697	3.32756
27.9776	3.18658
28.7822	3.0993
31.2504	2.85991

The Raman spectrum of the title compound was recorded on a Nicolet NXR 9650 FT-Raman Spectrometer, at 4 cm^{-1} resolution with excitation from a Nd:YVO4 laser (λ = 1064 nm). The Raman spectrum of this material is shown in Fig. 4 with major peaks observed at 656, 668, 719, 743, 751, 803, 1125, 1154, 1162, 1173, 1286, 1469, 1544, 1587, 1596, 1612, 1656, and 1673 cm^{-1}.

The differential scanning calorimetry (DSC) thermogram of the title compound was recorded on a TA Instruments Q1000 Differential Scanning Calorimeter and is shown in Fig. 6. The sample was weighed into an aluminium pan, a pan lid placed on top and lightly crimped without sealing the pan. The experiments were conducted using a heating rate of 15 °C/min.

The thermogravimetric analysis (TGA) thermogram of the title compound was recorded on a TA Instruments Q5000 Themrogravimetric Analyzer and is shown in Fig. 8. The experiments were conducted using a heating rate of 15 °C/min.

What is claimed is:

1. A crystalline form of a sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide, wherein the crystalline form is characterized by an X-ray powder diffraction pattern comprising diffraction angles, when measured using Cu K_α radiation, at about 4.5, 9.0, 13.6, 13.9, 15.8, 19.9, 20.4, and 28.0 °2θ.

2. A crystalline form of a sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide, wherein the crystalline form is characterized by an X-ray powder diffraction pattern substantially in accordance with Figure 1.

3. A crystalline form of a sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide, wherein the crystalline form provides a Raman spectrum containing peaks at about 688, 743, 803, 1125, 1154, 1162, 1286, 1587, 1596, 1656, and 1672 cm^{-1}.

4. A crystalline form of a sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide, wherein the crystalline form provides a Raman spectrum substantially in accordance with Figure 3.

5. A pharmaceutical composition comprising the crystalline form according to any one of claims 1-4 and a pharmaceutically acceptable carrier.

6. A method of preparing a pharmaceutical composition comprising admixing the crystalline form according to any one of claims 1-4 and a pharmaceutically acceptable carrier.

7. A crystalline form of a sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide, wherein the crystalline form is characterized by an X-ray powder diffraction pattern comprising diffraction angles, when measured using Cu K_α radiation, at about 4.5, 9.1, 13.6, 13.9, 18.2, 19.9, 22.7, 24.3, 26.8, and 28.0 °2θ.

8. A crystalline form of a sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide, wherein the crystalline form is characterized by an X-ray powder diffraction pattern substantially in accordance with Figure 2.

9. A crystalline form of a sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide, wherein the crystalline form provides a Raman spectrum containing peaks at about 668, 743, 1125, 1154, 1286, 1587, 1596, 1612, 1656, and 1673 cm^{-1}.

10. A crystalline form of a sodium salt of 4-*tert*-butyl-*N*-[4-chloro-2-(1-oxy-pyridine-4-carbonyl)-phenyl]-benzenesulfonamide, wherein the crystalline form provides a Raman spectrum substantially in accordance with Figure 4.

11. A pharmaceutical composition comprising the crystalline form according to any one of claims 7-10 and a pharmaceutically acceptable carrier.

12. A method of preparing a pharmaceutical composition comprising admixing the crystalline form according to any one of claims 7-10 and a pharmaceutically acceptable carrier.

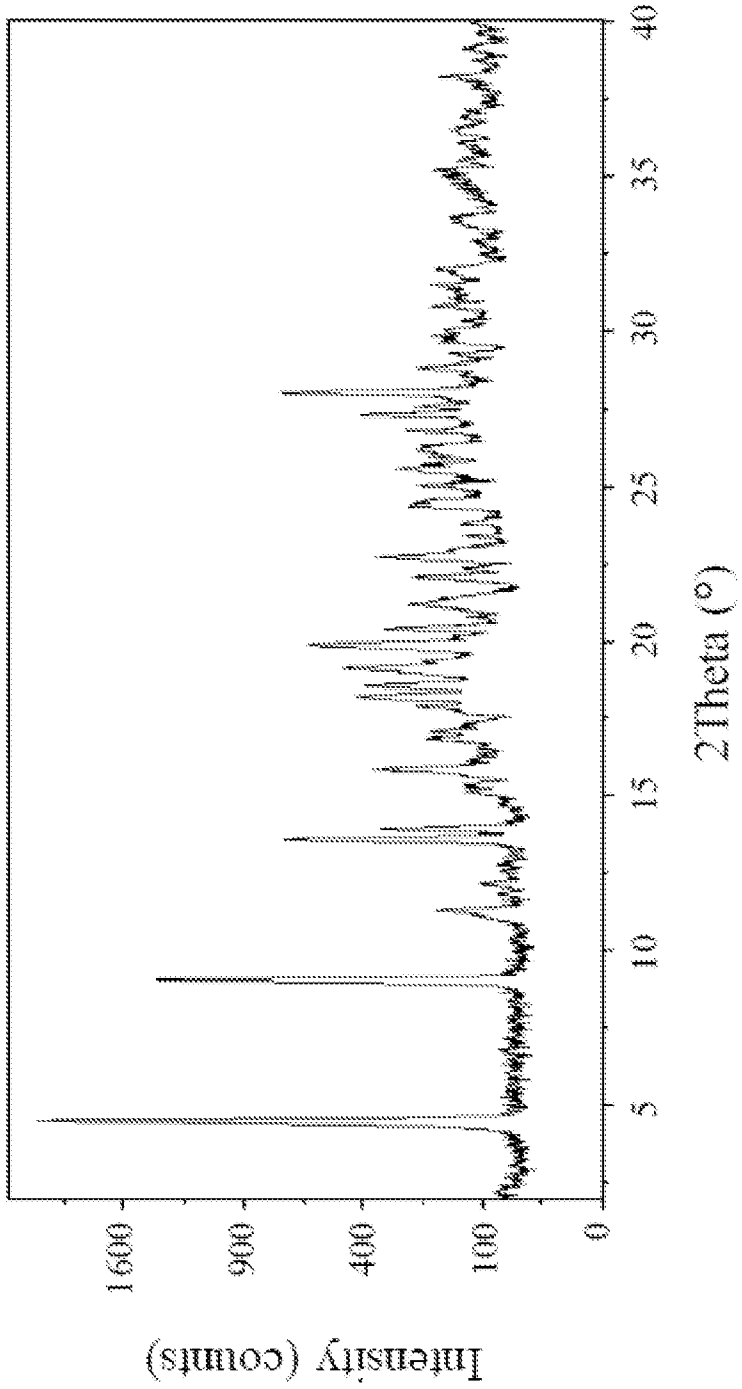

Intensity (counts)
1600
900
400
100
0
5
10
15
20
25
30
35
40
2Theta (°)

FIG. 1

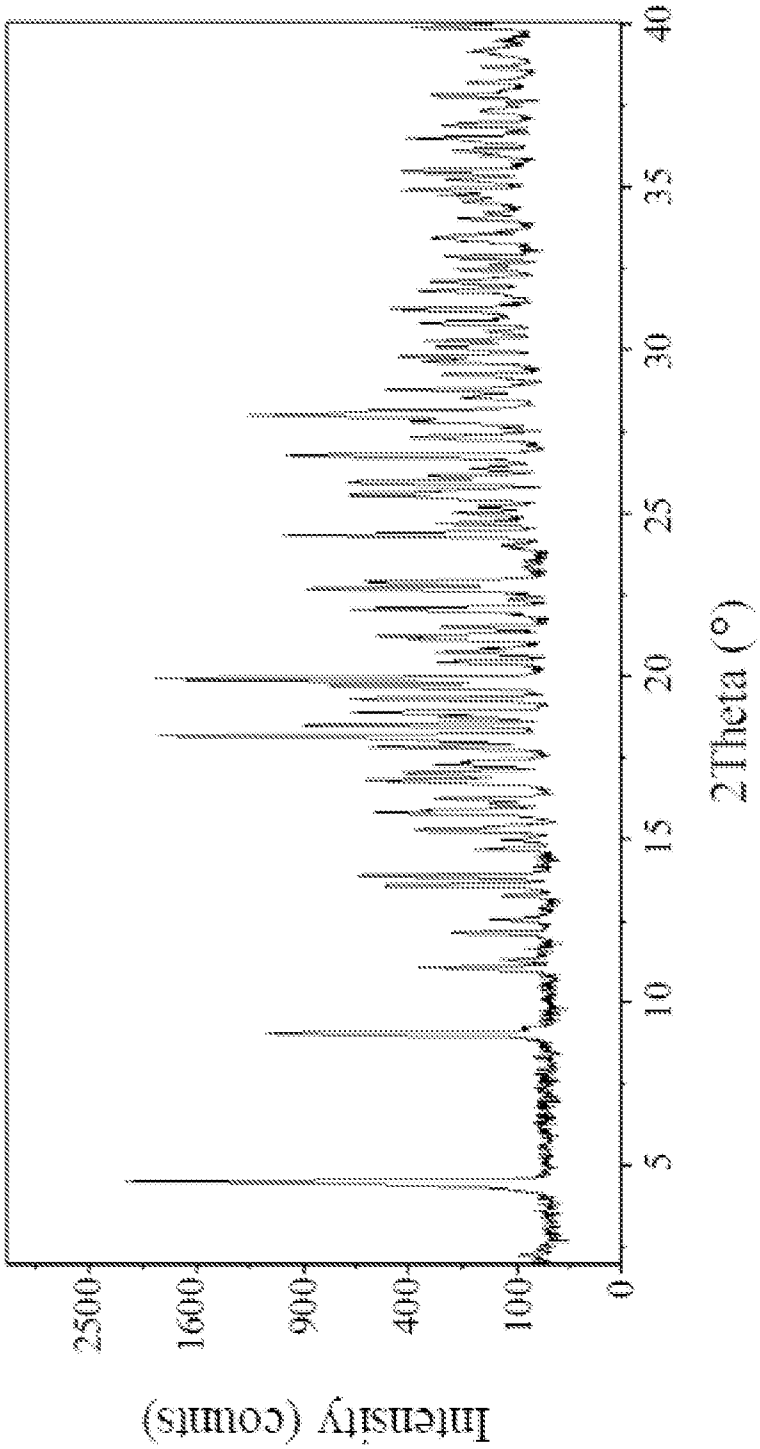

Intensity (counts)
2500
1600
900
400
100
0
5
10
15
20
25
30
35
40
2Theta (°)

FIG. 2

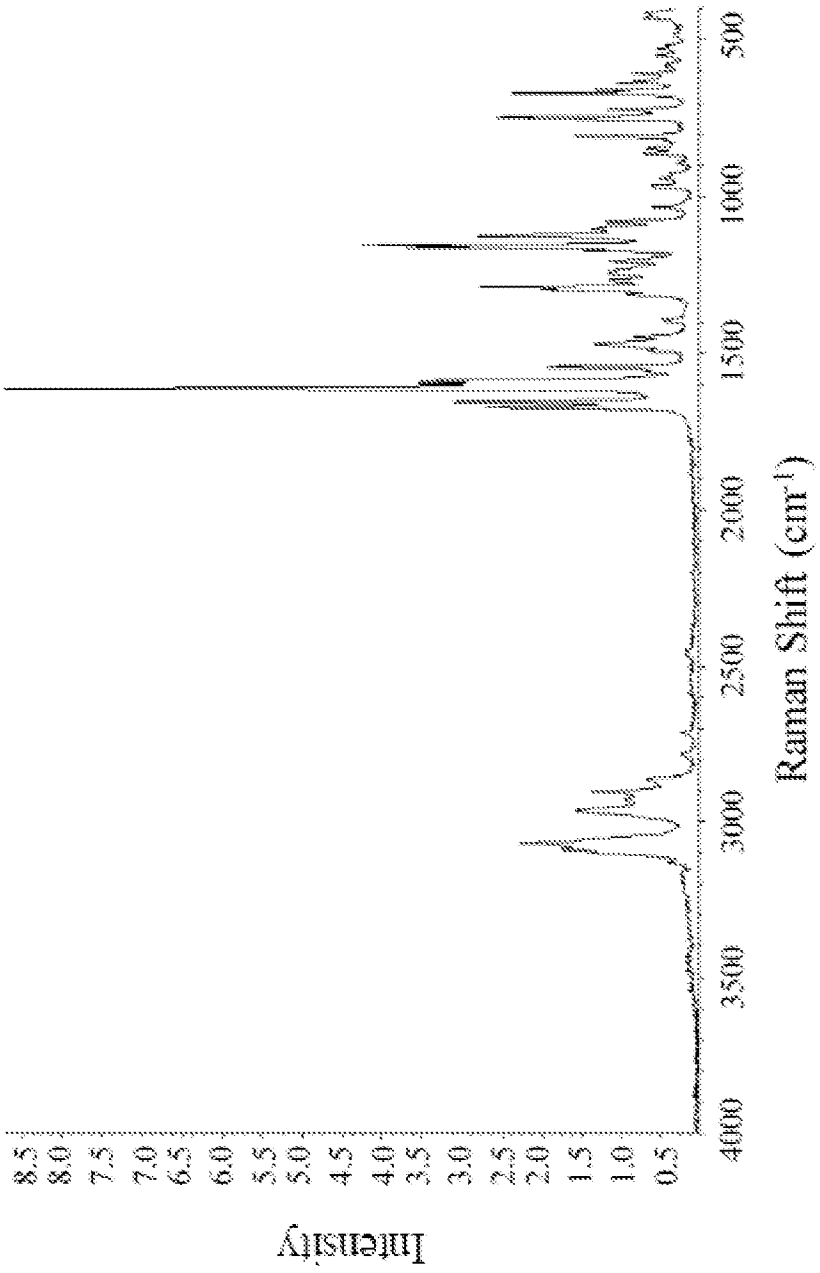

Intensity
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
4000
3500
3000
2500
2000
1500
1000
500
Raman Shift (cm-1)

FIG. 3

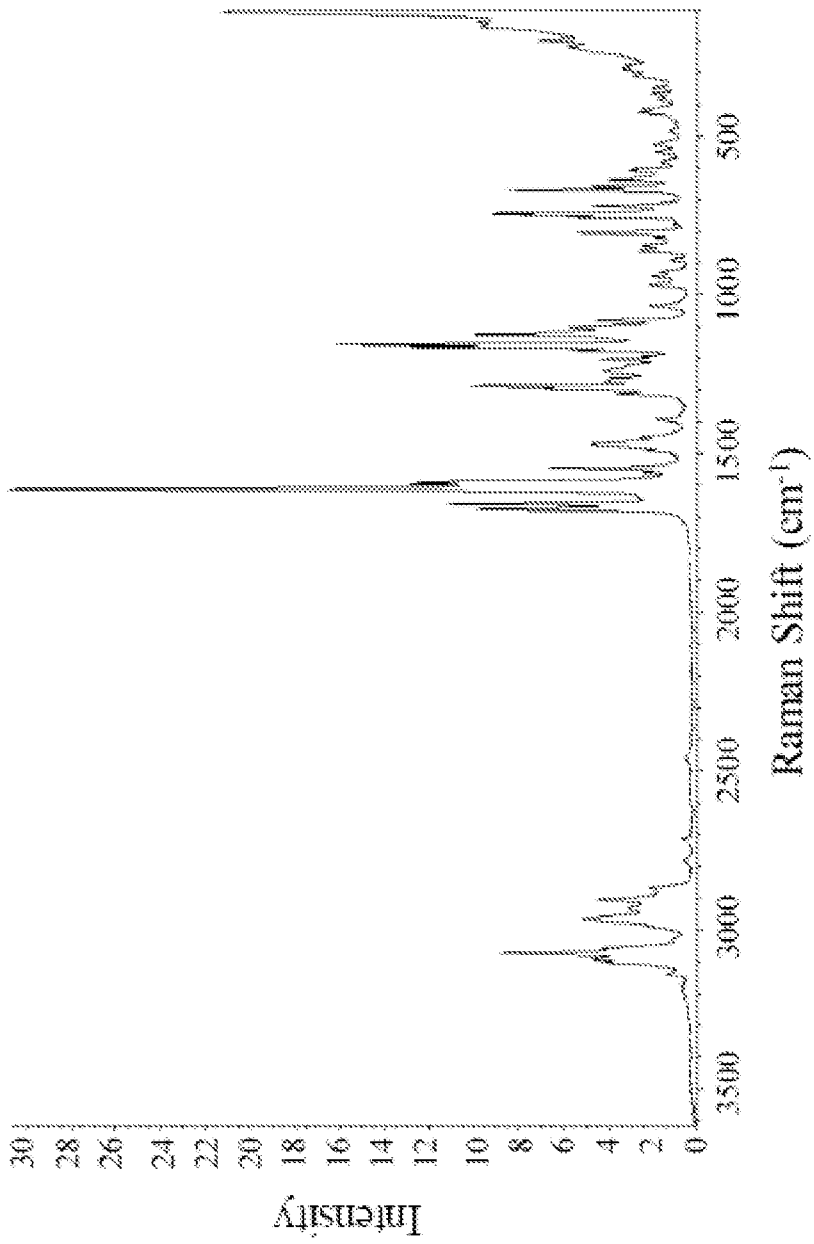

Intensity
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
3500
3000
2500
2000
1500
1000
500
Raman Shift (cm-1)

FIG. 4

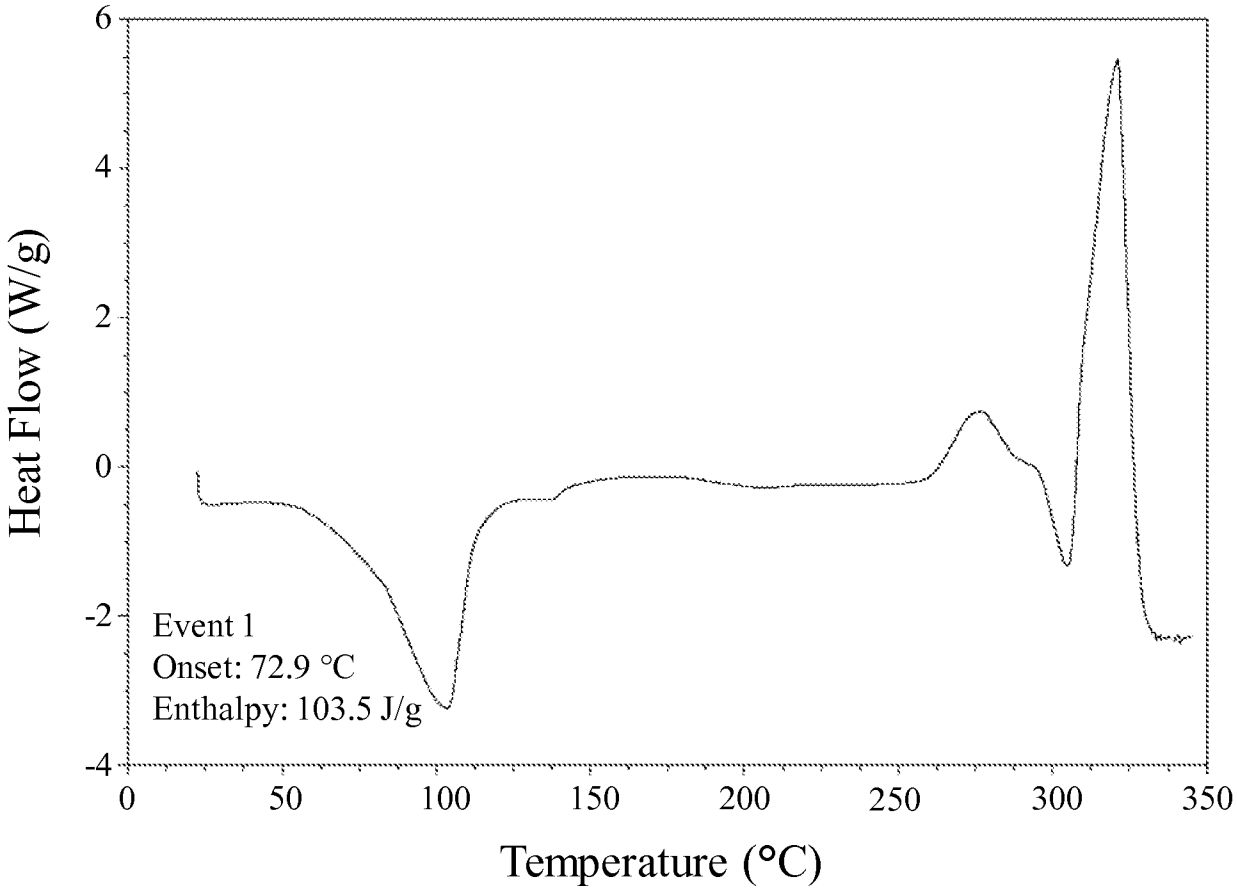

Heat Flow (W/g)
6
4
2
0
-2
-4
0
50
100
150
200
250
300
350
Temperature (°C)
Event 1
Onset: 72.9 °C
Enthalpy: 103.5 J/g

FIG. 5

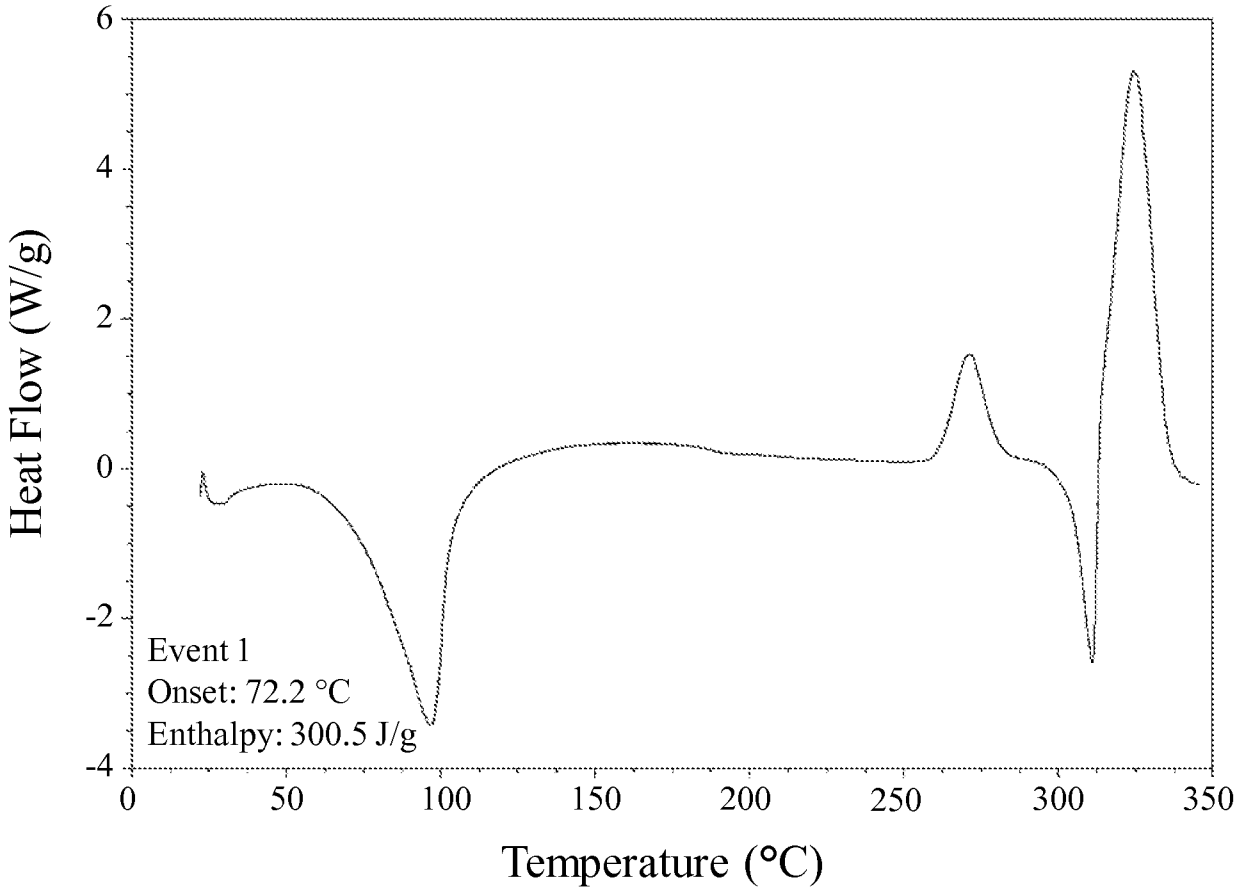

Heat Flow (W/g)
6
4
2
0
-2
-4
0
50
100
150
200
250
300
350
Temperature (°C)
Event 1
Onset: 72.2 °C
Enthalpy: 300.5 J/g

FIG. 6

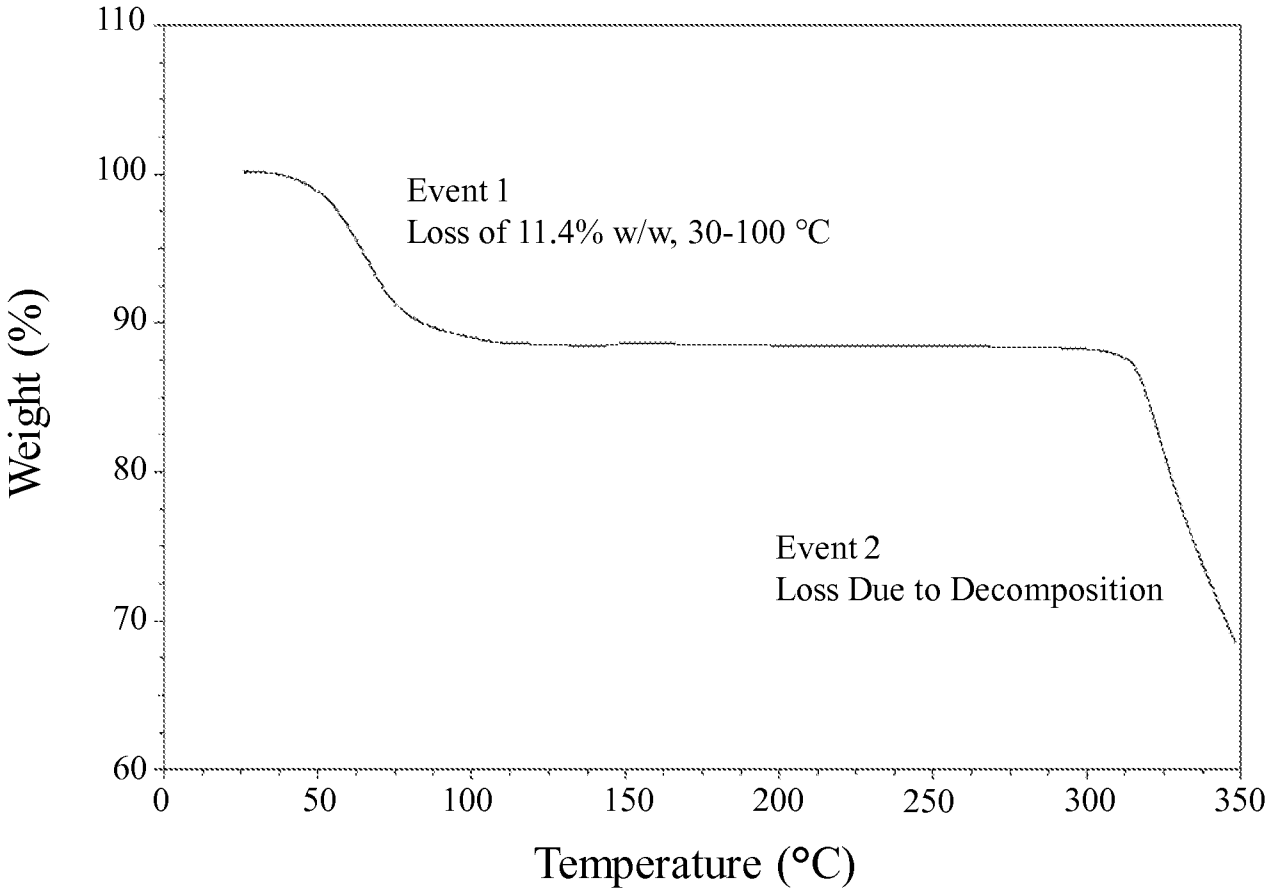

110
100
90
80
70
60
Weight (%)
Event 1
Loss of 11.4% w/w, 30-100 °C
Event 2
Loss Due to Decomposition
0
50
100
150
200
250
300
350
Temperature (°C)

FIG. 7

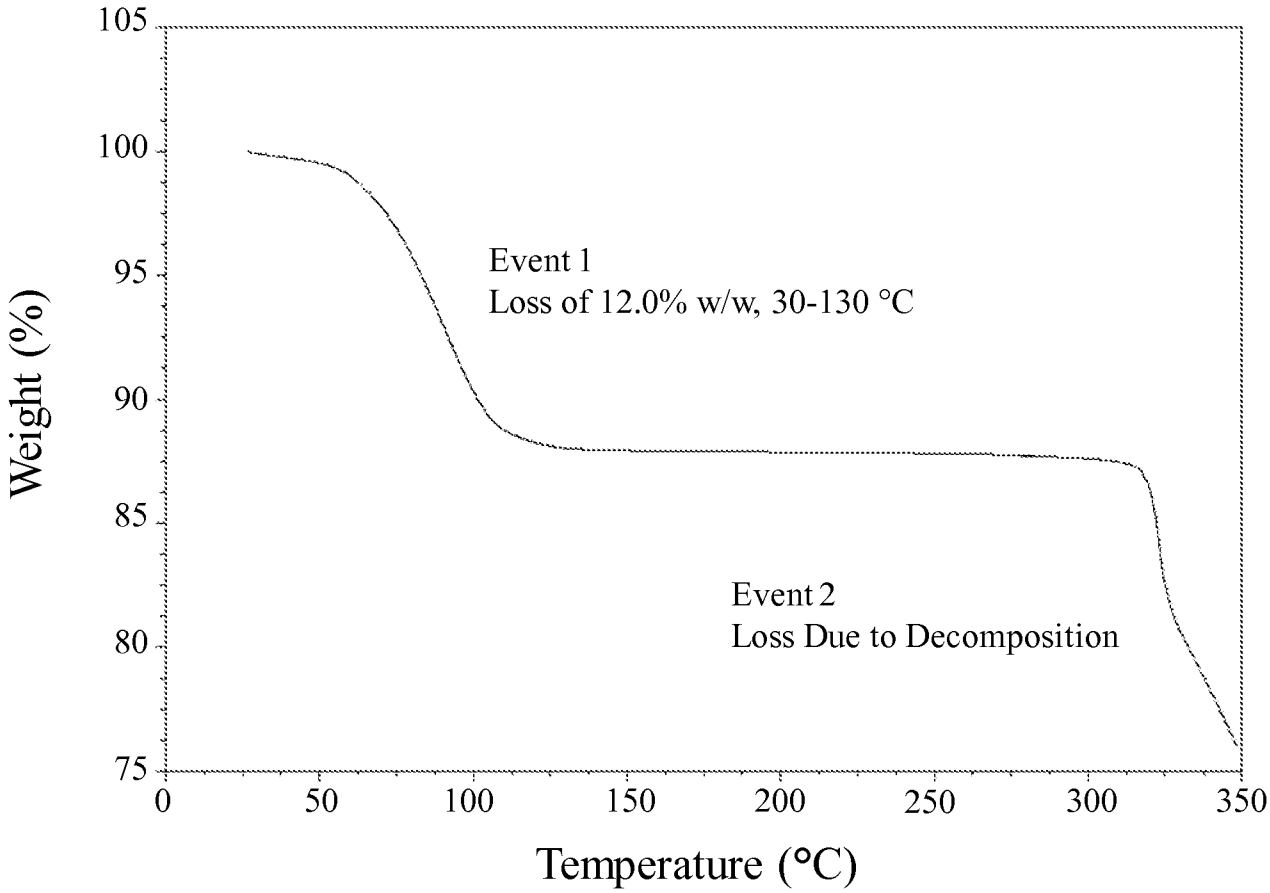

105
100
95
90
85
80
75
Weight (%)
0
50
100
150
200
250
300
350
Temperature (°C)
Event 1
Loss of 12.0% w/w, 30-130 °C
Event 2
Loss Due to Decomposition

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/047512

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/4409 (2012.01)
USPC - 514/354
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)
IPC(8) - A61K 31/4409, 4425; C07D 213/50, 89 (2012.01)
USPC - 514/354, 357, 358; 546/314, 328, 347, 348

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)
PatBase, Orbit, STN, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2008/0161345 A1 (UNGASHE et al) 03 July 2008 (03.07.2008) entire document	1-12
A	US 2004/0038976 A1 (FLEMING et al) 26 February 2004 (26.02.2004) entire document	1-12
A	US 2005/0250820 A1 (CHEN) 10 November 2005 (10.11.2005) entire document	1-12
A	US 2010/0234364 A1 (BASAK et al) 16 September 2010 (16.09.2010) entire document	1-12
A	US 2011/0118248 A1 (UNGASHE et al) 19 May 2011 (19.05.2011) entire document	1-12

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 September 2012	28 SEP 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774