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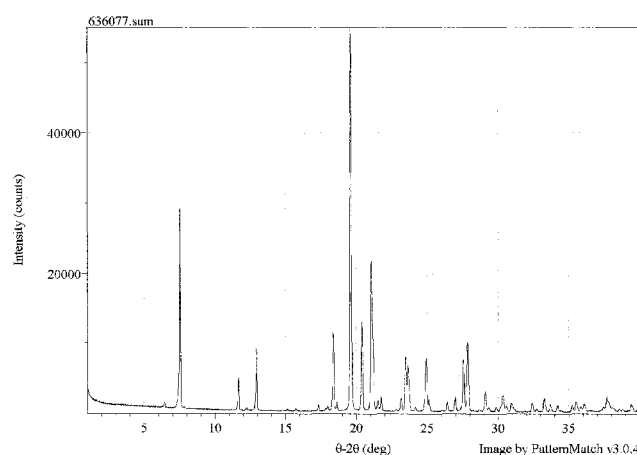
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(54) Title: DI-PIDOTIMOD BENZATHINE AND SOLID FORMS THEREOF

Figure 1 – X-ray powder diffraction pattern of Form M di-pidotimod benzathine



(57) Abstract: The present invention relates to di-pidotimod benzathine. In particular, it relates to di-pidotimod benzathine in solid form such as in crystalline or amorphous; specific polymorphs are also disclosed such as Form M. Form H and hydrate Form H of di-pidotimod benzathine, in an additional aspect of the invention, solvates and cocrystals of hydrate Form H di-pidotimod benzathine are provided. In a further aspect of the invention, variable isopropanol solvates; variable ethanol solvates; variable hydrates; and a particular anhydrate are provided. Particular solid forms include variable isopropanol solvates Form J and Form O of di-pidotimod benzathine; variable ethanol solvates Form S and Form W of di-pidotimod benzathine; variable hydrate Form X of di-pidotimod benzathine; and anhydrate Form T of di-pidotimod benzathine. In further aspects of the invention, processes for making such solid forms are provided. In additional aspects of the invention, methods of treating infections or inflammatory diseases using one or more of such solid forms are provided.



DI-PIDOTIMOD BENZATHINE AND SOLID FORMS THEREOF

[0001] Pidotimod, whose chemical name is (4R)-3-(5-oxo-L-prolyl)-1,3-thiazolidine-4-carboxylic acid, was first disclosed in IT1231723. It is a synthetic peptide-like molecule provided with an *in vitro* and *in vivo* immunomodulating action (Giagulli et al., *International Immunopharmacology*, 9, 2009, 1366-1373). The immune system assists in maintaining a homeostatic balance between the human body and all foreign substances. An abnormality in this balance may cause a defective or aberrant response towards non-self substances, as well as loss of tolerance toward self-antigens. In such cases, the immune system imbalance exhibits clinically as signs of disease.

[0002] Pidotimod has been shown to induce dendritic cell maturation and up-regulate the expression of HLA-DR and co-stimulatory molecules CD83 and CD86, which are integral to communication with adaptive immunity cells. Pidotimod has also been shown to stimulate dendritic cells to release pro-inflammatory molecules such as MCP-1 and TNF- α cytokines, and to inhibit thymocyte apoptosis caused by a variety of apoptosis-inducing molecules. Pidotimod exerts a protective action against infectious processes, although not through direct antimicrobial or antiviral action. Rather, pidotimod stimulates both innate and acquired immunity by enhancing humoral and cell-mediated immunity mechanisms.

[0003] Pidotimod, which may be administered as solid or liquid forms, for example, via an oral route, has been shown to increase natural resistance to viral or bacterial infections in animal models. Efficacy demonstrated in patients includes respiratory, urinary and genital infections, in particular recurrent respiratory infections in pediatric patients, respiratory infections in asthmatic patients and chronic obstructive pulmonary disease in adults and elderly patients.

[0004] Besides exhibiting activity to illnesses characterized by immune defects, pidotimod has been reported to be of benefit in to patients with other kinds of diseases, not directly related to immune defects, including gastroenterology diseases such as ulcerative colitis and irritable bowel syndrome,

and dermatological diseases such as psoriasis and atopic dermatitis where symptoms relating to these diseases have been attenuated. In gastroenterology diseases pidotimod may be administered either by oral or by rectal route. Oral route or topical application, for example in creams or gels containing pidotimod, may be used to treat dermal conditions.

[0005] Further use of pidotimod includes treatment of inflammatory diseases, in particular those characterized by an aberrant activation of the non-canonical NF-kB pathway. Diseases implicated by such activation include allergic diseases, autoimmune diseases, and numerous other inflammatory diseases. Allergic diseases include allergic rhinitis, allergic conjunctivitis, contact dermatitis, eczema and allergic vasculitis. Autoimmune diseases include alopecia areata, ankylosing spondylitis, autoimmune cardiomyopathy, autoimmune connective tissue diseases, autoimmune enteropathy, autoimmune hepatitis, autoimmune peripheral neuropathy, autoimmune pancreatitis, autoimmune polyendocrine syndrome, autoimmune thrombocytopenic purpura, autoimmune urticaria, autoimmune uveitis, celiac disease, chronic fatigue syndrome, cystic fibrosis, Hashimoto's thyroiditis, idiopathic pulmonary fibrosis, idiopathic thrombocytopenic purpura, IGA nephropathy, juvenile idiopathic arthritis (or juvenile rheumatoid arthritis, or Still's disease) Kawasaki's disease, lichen planus, lupus erythematosus, rheumatoid arthritis, rheumatic fever, Sjögren's syndrome, spondyloarthropathy, temporal arteritis (or giant cell arteritis), urticarial vasculitis, and vitiligo. Other inflammatory diseases include Alzheimer's disease, atherosclerosis, chronic liver diseases, chronic nephropathy, gastritis, glomerulonephritis, hydradenitis suppurativa, hypogammaglobulinemia, interstitial cystitis, lichen sclerosus, liver steatosis, metabolic syndrome, obesity, Parkinson's disease, pemphigus vulgaris, post-ischemic inflammation, Raynaud's phenomenon, restless leg syndrome, retroperitoneal fibrosis, and thrombocytopenia.

[0006] Many compounds when delivered as formulations, including orally available compounds, are delivered as salts. In the art, there has been some work reported on creating salts of pidotimod. Salts are often preferable over free acids and bases for a number of reasons including increased solubility and ease of

handling. Previous salts of pidotimod have been found to be unstable or poorly soluble. Thus, there is a need for a salt of pidotimod with sufficient stability and solubility.

SUMMARY OF INVENTION

[0007] In one aspect of the invention, di-pidotimod benzathine is provided.

[0008] In an additional aspect of the invention, a solid form of di-pidotimod benzathine is provided.

[0009] In another aspect of the invention, crystalline di-pidotimod benzathine is provided.

[0010] In a further aspect of the invention, amorphous di-pidotimod benzathine is provided.

[0011] In yet another aspect of the invention, Form M di-pidotimod benzathine is provided.

[0012] In an additional aspect of the invention, hydrate Form H di-pidotimod benzathine is provided.

[0013] In another aspect of the invention, Form H di-pidotimod benzathine is provided.

[0014] In yet another aspect of the invention, Form T of di-pidotimod benzathine is provided.

[0015] In an additional aspect of the invention, Form X of di-pidotimod benzathine is provided.

[0016] In further aspects of the invention, solvates, cocrystals and hydrates of di-pidotimod benzathine, a solid form of di-pidotimod benzathine, crystalline di-pidotimod benzathine, amorphous di-pidotimod benzathine, Form M di-pidotimod benzathine and Form H di-pidotimod benzathine are provided.

[0017] In an additional aspect of the invention, solvates and cocrystals of hydrate Form H di-pidotimod benzathine or Form X of di-pidotimod benzathine are provided.

[0018] In another aspect of the invention, isopropanol solvates of di-pidotimod benzathine are provided.

[0019] In a further aspect of the invention, ethanol solvates of di-pidotimod benzathine are provided.

[0020] In further aspects of the invention, processes for making solid di-pidotimod benzathine, crystalline di-pidotimod benzathine, amorphous di-pidotimod benzathine, Form M di-pidotimod benzathine, hydrate Form H di-pidotimod benzathine, Form H di-pidotimod benzathine isopropanol solvates, ethanol solvates, Form X and Form T of di-pidotimod benzathine are provided.

[0021] In additional aspects of the invention, methods of treating infections or inflammatory diseases using one or more of di-pidotimod benzathine, solid di-pidotimod benzathine, crystalline di-pidotimod benzathine; amorphous di-pidotimod benzathine, Form M di-pidotimod benzathine, Form H di-pidotimod benzathine or solvates, cocrystals or hydrates thereof, isopropanol solvates, ethanol solvates, Form X and Form T of di-pidotimod benzathine are provided.

[0022] In further aspects of the invention, methods of treating infections such as respiratory infections in children using one or more of hydrate Form H di-pidotimod benzathine, isopropanol solvates, ethanol solvates, Form X, or Form T of di-pidotimod benzathine are provided.

[0023] In yet a further aspect of the invention, compositions of one or more of di-pidotimod benzathine, solid di-pidotimod benzathine, crystalline di-pidotimod benzathine; amorphous di-pidotimod benzathine, Form M di-pidotimod benzathine, Form H di-pidotimod benzathine, hydrate Form H di-pidotimod or solvates, cocrystals or hydrates thereof, isopropanol solvates, ethanol solvates, Form X and Form T of di-pidotimod benzathine are provided.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] Figure 1 is an x-ray powder diffraction pattern of Form M di-pidotimod benzathine.

[0025] Figure 2 is a peak-picked x-ray powder diffraction pattern of Form M di-pidotimod benzathine.

[0026] Figure 3 is a differential scanning calorimetry thermogram of Form M di-pidotimod benzathine.

[0027] Figure 4 is a Raman spectrum of Form M di-pidotimod benzathine.

[0028] Figure 5 is a truncated ^{13}C solid-state NMR spectrum of Form M di-pidotimod benzathine.

[0029] Figure 6 is an infrared spectrum of Form M di-pidotimod benzathine.

[0030] Figure 7 is a ^1H solution-state NMR spectrum of Form M di-pidotimod benzathine.

[0031] Figure 8 is an indexing solution of Form M di-pidotimod benzathine.

[0032] Figure 9 is an x-ray powder diffraction pattern of hydrated Form H di-pidotimod benzathine.

[0033] Figure 10 is an infrared spectrum of hydrated Form H di-pidotimod benzathine.

[0034] Figure 11 is an x-ray powder diffraction pattern of Form H di-pidotimod benzathine.

[0035] Figure 12 is an x-ray powder diffraction pattern of amorphous di-pidotimod benzathine.

[0036] Figure 13 is a modulated differential scanning calorimetry thermogram of amorphous di-pidotimod benzathine.

[0037] Figure 14 is an infrared spectrum of amorphous di-pidotimod benzathine.

[0038] Figure 15 is an indexing solution for hydrated Form H di-pidotimod benzathine.

[0039] Figure 16 is an indexing solution for Form H di-pidotimod benzathine.

[0040] Figure 17 is a ^1H solution-state NMR spectrum of Form H di-pidotimod benzathine.

[0041] Figure 18 is a peak-picked x-ray powder diffraction pattern of Form J di-pidotimod benzathine.

[0042] Figure 19 is a differential scanning calorimetry thermogram of Form J di-pidotimod benzathine.

[0043] Figure 20 is an infrared spectrum of Form J di-pidotimod benzathine.

[0044] Figure 21 is a ^1H solution-state NMR spectrum of Form J di-pidotimod benzathine.

[0045] Figure 22 is an indexing solution for Form J pidotimod benzathine.

[0046] Figure 23 is peak-picked x-ray powder diffraction pattern of Form O di-pidotimod benzathine.

[0047] Figure 24 is a differential scanning calorimetry thermogram of Form O di-pidotimod benzathine.

- [0048] Figure 25 is an infrared spectrum of Form O di-pidotimod benzathine.
- [0049] Figures 26a and 26b are a ^1H solution-state NMR spectrum of Form O di-pidotimod benzathine.
- [0050] Figure 27 is a peak-picked x-ray powder diffraction pattern of Form S di-pidotimod benzathine.
- [0051] Figure 28 is a differential scanning calorimetry thermogram of Form S di-pidotimod benzathine.
- [0052] Figure 29 is an infrared spectrum of Form S di-pidotimod benzathine.
- [0053] Figure 30 is a ^1H solution-state NMR spectrum of Form S di-pidotimod benzathine.
- [0054] Figure 31 is a peak-picked x-ray powder diffraction pattern of Form W di-pidotimod benzathine.
- [0055] Figure 32 is differential scanning calorimetry thermogram of Form W di-pidotimod benzathine.
- [0056] Figure 33 is an infrared spectrum of Form W di-pidotimod benzathine.
- [0057] Figure 34 is a ^1H solution-state NMR spectrum of Form W di-pidotimod benzathine.
- [0058] Figure 35 is a peak-picked x-ray powder diffraction pattern of Form X di-pidotimod benzathine.
- [0059] Figure 36 is a differential scanning calorimetry thermogram of Form X di-pidotimod benzathine.
- [0060] Figure 37 is an infrared spectrum of Form X di-pidotimod benzathine.
- [0061] Figure 38 is a ^1H solution-state NMR spectrum of Form X di-pidotimod benzathine.
- [0062] Figure 39 is a peak-picked x-ray powder diffraction pattern of Form T di-pidotimod benzathine.
- [0063] Figure 40 is differential scanning calorimetry thermogram of Form T di-pidotimod benzathine.
- [0064] Figure 41 is an infrared spectrum of Form T of di-pidotimod benzathine.
- [0065] Figure 42 is a ^1H solution-state NMR spectrum of Form T di-pidotimod benzathine.

[0066] Figure 43 is a thermogravimetric analysis thermogram of Form J di-pidotimod benzathine.

[0067] Figures 44a and 44b are a thermogravimetric analysis thermogram of Form O di-pidotimod benzathine.

[0068] Figure 45 is a thermogravimetric analysis thermogram of Form S di-pidotimod benzathine.

[0069] Figure 46 is a thermogravimetric analysis thermogram of Form W di-pidotimod benzathine.

[0070] Figure 47 is a thermogravimetric analysis thermogram of Form X di-pidotimod benzathine.

[0071] Figure 48 is a thermogravimetric analysis thermogram of Form T di-pidotimod benzathine.

[0072] Figure 49 is an indexing solution for Form S di-pidotimod benzathine.

[0073] Figure 50 is an indexing solution for Form X di-pidotimod benzathine.

DEFINITIONS

[0074] Unless otherwise defined, all terms of art, notations and other scientific terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this disclosure pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference; thus, the inclusion of such definitions herein should not be construed to represent a substantial difference over what is generally understood in the art.

[0075] The terms “approximately” and “about” herein refers to the range of the experimental error, which may occur in a measurement.

[0076] The terms “comprising”, “having”, “including” and “containing” are to be construed as open-ended terms (i.e. meaning “including, but not limited to”) and are to be considered as providing support also for terms as “consist essentially of”, “consisting essentially of”, “consist of” or “consisting of”.

[0077] The terms “consist essentially of”, “consisting essentially of” are to be construed as a semi-closed terms, meaning that no other ingredients which materially affects the basic and novel characteristics of the invention are included (optional excipients may thus included).

[0078] The terms “consists of”, “consisting of” are to be construed as a closed term.

[0079] The term “antisolvent” herein refers to a liquid used to solidify materials such as in a crystallization. Suitable antisolvents for the crystallization process include, ethers, esters, hydrocarbons and any mixtures thereof.

[0080] The term “pharmaceutically acceptable excipient” or “pharmaceutically acceptable adjuvant” herein refers to a substance devoid of any pharmacological effect of its own and which does not produce adverse reactions when administered to a mammal, preferably a human. Pharmaceutically acceptable excipients and adjuvants are well known in the art and are disclosed, for instance in the *Handbook of Pharmaceutical Excipients, sixth edition 2009*, herein incorporated by reference.

DETAILED DESCRIPTION

[0081] The term "solid form" is often used to refer to a class or type of solid-state material. One kind of solid form is a "polymorph" which refers to two or more crystalline materials having the same chemical formula but differing in solid-state structure. Salts may be polymorphic. Different polymorphs of elements are termed allotropes. Carbon possesses the well-known allotropes of graphite, diamond, and buckminsterfullerene. Polymorphs of molecular compounds, such as active pharmaceutical ingredients (“APIs”), are often prepared and studied in order to identify compounds meeting scientific or commercial needs including, but not limited to improved solubility, dissolution rate, hygroscopicity, and stability.

[0082] Other solid forms include solvates and hydrates of compounds including salts. A solvate, as used herein, is a compound wherein a solvent molecule is present either bound in the crystal structure together with another compound, such as an API, or unbound such that the molecule is not part of the crystal structure. When the solvent is water, the solvent is termed a hydrate. Solvates and hydrates may be of a fixed stoichiometry (e.g., a monohydrate) of variable as in a variable hydrate or variable solvate. In variable hydrates and solvates, non-stoichiometric amounts of water or solvents are present, often within channels in the crystal lattice. The solvent or water in the variable hydrate or

solvate may, however, come from either bound or unbound water or solvent as the case may be.

[0083] In order to identify the presence of a particular solid form, one of ordinary skill typically uses a suitable analytical technique to collect data on the form for analysis. For example, chemical identity of solid forms can often be determined with solution-state techniques such as ^{13}C -NMR or ^1H -NMR spectroscopy and such techniques may also be valuable in determining the stoichiometry or the presence of “guests” such as water or solvent in a hydrate or solvate respectively. These spectroscopic techniques may also be used to distinguish, for example, solid forms without water or solvent in the unit cell or otherwise (often referred to as “anhydrates”), from hydrates or solvates.

[0084] Solution-state analytical techniques do not provide information about the solid state as a substance and thus, for example, solid-state techniques may be used to distinguish among solid forms such as anhydrates or polymorphs of solvates or polymorphs of hydrates. Examples of solid-state techniques which may be used to analyze and characterize solid forms, including anhydrates and hydrates, include single crystal x-ray diffraction, x-ray powder diffraction (“XRPD”), solid-state ^{13}C -NMR spectroscopy, Infrared (“IR”) spectroscopy, Raman spectroscopy, and thermal techniques such as Differential Scanning Calorimetry (DSC), Thermal Gravimetric Analysis (TGA), melting point, and hot stage microscopy.

[0085] When attempting to distinguish solid forms such as crystalline forms based on analytical data, one looks for data with which to characterize the form. For example, when there are two polymorphs of a compound (e.g., Form I and Form II), one can use x-ray powder diffraction peaks to characterize the forms when one finds a peak in a Form I pattern at an angle where no such peak is present in the Form II pattern. In such a case, that single peak distinguishes Form I from Form II and may act to characterize Form I. When more forms are present, then a similar analysis is also done for the other polymorphs. Thus, to characterize Form I against the other polymorphs, one would look for peaks in Form I at angles where such peaks are not present in the x-ray powder diffraction patterns of

the other polymorphs. The collection of peaks, or indeed a single peak, which distinguishes Form I from the other known polymorphs is a collection of peaks, which may be used to characterize Form I. If, for example, two peaks characterize a polymorph then those two peaks can be used to identify the presence of that polymorph and hence characterize the polymorph. Those of ordinary skill in the art will recognize that there are often multiple ways, including multiple ways using the same analytical technique, to characterize polymorphic forms of a compound. For example, one may find that three x-ray powder diffraction peaks characterize a polymorph. Additional peaks could also be used, but are not necessary, to characterize the polymorph in other embodiments using up to and including an entire diffraction pattern. Although all the peaks within an entire diffractogram may be used to characterize a crystalline form, one may instead, and typically does as disclosed herein, use a subset of that data to characterize such a crystalline form. Other techniques besides x-ray powder diffraction, such as Raman spectroscopy, infrared spectroscopy, differential scanning calorimetry, and solid-state ^{13}C NMR spectroscopy may also be used to distinguish and characterize solid forms.

[0086] When analyzing data to distinguish an anhydrate from a solvate or hydrate, one can often rely on the fact that the two solid forms have different chemical composition – one having solvent or water in the unit cell or otherwise associated with the chemical structure and the other not. Thus, this feature alone may be used to distinguish the forms of the compound and it may not be necessary to identify peaks in the anhydrate, for example, which are not present in the hydrate or vice versa. For example, an anhydrate of a crystalline form I of a compound may be distinguished from a monohydrate of that compound based solely on water content. Distinguishing data from other analytical techniques may also be used to characterize these forms.

[0087] In some instances, there is only one known crystalline form for a particular compound. In such instances, one may use any number of analytical techniques, and data within such techniques, to characterize a form. For example, in x-ray powder diffraction, peaks at low angle are often well separated and have sufficient signal to provide characteristic data. For a particular chemical

compound, a single peak or multiple peaks may be used to characterize the particular crystalline form of that compound.

[0088] When analyzing different crystalline forms of a chemical compound, it is useful to recognize that the term “Form” references a particular chemical formula. For example, the use of the term “Form M” herein is in reference to the chemical formula di-pidotimod benzathine. Likewise, “hydrate Form H” or “hydrated Form H” is also in reference to di-pidotimod benzathine, but with a different crystalline structure including water associated with that crystalline structure. When using data to characterize a particular crystalline structure, such characterization may be done with different analytical techniques. For example, in some embodiments, Form M may be characterized with a single x-ray powder diffraction peak whereas in other embodiments, multiple x-ray powder diffraction peaks may be used or even additional techniques. Thus, the use of the term “Form M” by itself does not incorporate any particular data from analytical techniques to describe or characterize that Form.

[0089] Solid forms may also be amorphous. Amorphous forms lack long-range order and are typically more unstable than crystalline forms of the same chemical formula. Amorphous forms are often identified in an x-ray pattern by an “amorphous halo” that appears as opposed to sharp diffraction peaks. Such a material that exhibits such a halo is referred to as “x-ray amorphous”. As used herein, the term “amorphous” refers to di-pidotimod benzathine which exhibits, in a powder x-ray diffraction pattern, an amorphous halo such as, for example, the one found in Figure 12. In addition to a halo, amorphous forms often exhibit a glass transition temperature which may be used to characterize the amorphous form. The glass transition temperature may be measured with modulated differential scanning calorimetry as seen in Figure 13. Other analytical techniques, such as infrared spectroscopy, may be used to characterize amorphous solid forms.

[0090] X-ray powder diffraction is one of the most commonly used solid-state analytical techniques used to characterize solid forms. An x-ray powder diffraction pattern is an x-y graph with $^{\circ}2\theta$ (diffraction angle) on the x-axis and intensity on the y-axis. The peaks within this plot may be used to characterize a

crystalline solid form. The data is often represented by the position of the peaks on the x-axis rather than the intensity of peaks on the y-axis because peak intensity can be particularly sensitive to sample orientation (see Pharmaceutical Analysis, Lee & Web, pp. 255-257 (2003)). Thus, intensity is not typically used by those skilled in the art to characterize solid forms.

[0091] As with any data measurement, there is variability in x-ray powder diffraction data. In addition to the variability in peak intensity, there is also variability in the position of peaks on the x-axis. This positional variability can, however, typically be accounted for when reporting the positions of peaks for purposes of characterization. Such variability in the position of peaks along the x-axis derives from several sources. One comes from sample preparation. Samples of the same crystalline material, prepared under different conditions may yield slightly different diffractograms. Factors such as particle size, moisture content, solvent content, and orientation may all affect how a sample diffracts x-rays. Another source of variability comes from instrument parameters. Different x-ray instruments operate using different parameters and these may lead to slightly different diffraction patterns from the same crystalline solid form. Likewise, different software packages process x-ray data differently and this also leads to variability. These and other sources of variability are known to those of ordinary skill in pharmaceutical arts.

[0092] Due to such sources of variability, it is common to recite x-ray diffraction peaks using the word "about" prior to the peak value in $^{\circ}2\theta$ which typically presents the data to within 0.1 or 0.2 $^{\circ}2\theta$ of the stated peak value depending on the circumstances. The x-ray powder diffraction data corresponding to the solid forms of di-pidotimod benzathine of the invention were collected on instruments, which were routinely calibrated and operated by skilled scientists. Accordingly, the variability associated with these data would be expected to be closer to $\pm 0.1^{\circ}2\theta$ than to $\pm 0.2^{\circ}2\theta$ and indeed likely less than 0.1 with the instruments used herein. However, to take into account that instruments used elsewhere by those of ordinary skill in the art may not be so maintained, for example, most crystalline x-ray powder diffraction peaks cited herein have been reported with a variability on the order of $\pm 0.2^{\circ}2\theta$ and are intended to be reported

with such a variability whenever disclosed herein and are reported in the specification to one significant figure after the decimal even though analytical output may suggest higher precision on its face.

[0093] X-ray powder diffraction data may also be used, in some circumstances, to determine the crystallographic unit cell of the crystalline structure. The method by which this is done is called “indexing.” Indexing is the process of determining the size, shape, and symmetry of the crystallographic unit cell consistent with the peak positions in a suitable x-ray powder diffraction pattern. Indexing provides solutions for the three unit cell lengths (a,b,c), three unit cell angles (α , β , γ), and three Miller index labels (h,k,l) for each peak. The lengths are typically reported in Angstrom units and the angles in degree units. The Miller index labels are unit less integers. Successful indexing indicates that the sample is composed of one crystalline phase and is therefore not a mixture of crystalline phases.

[0094] Raman spectroscopy and infrared spectroscopy are techniques that may also be used to characterize solid forms. These spectroscopic techniques may be used independently or one or both of them may be used together with x-ray powder diffraction. In Raman spectra, Raman scattered light is plotted on the x-axis of a graph in the units of "wavenumber"(cm⁻¹) with intensity on the y-axis. In infrared spectra, absorbed light is plotted on the x-axis of a graph also in "wavenumber" (cm⁻¹) with intensity on the y-axis. Variation in the position of Raman and infrared peaks also exists and may be due to sample conditions as well as data collection and processing. The typical variability in Raman and infrared spectra reported herein is on the order plus or minus 2.0 cm⁻¹. Thus, the use of the word "about" when referencing Raman or infrared peaks is meant to include this variability and all Raman and infrared peaks disclosed herein are intended to be reported with such variability.

[0095] ¹³C solid-state NMR spectroscopy is another technique used to characterize solid forms. In this technique, perturbations in magnetization are plotted as “ppm” along the x-axis with intensity in the y-axis and, like x-ray, the resulting peaks may be used to distinguish and characterize solid forms. The typical variability in the sorts of NMR spectra reported herein is on the order of

plus or minus 2 ppm. Thus, the use of the word "about" when referencing ^{13}C solid-state NMR spectral peaks is meant to include this variability and all NMR peaks disclosed herein are intended to be reported with such variability

[0096] Thermal methods are another typical technique to characterize solid forms. Different polymorphs of the same compound often melt at different temperatures. Thus, the melting point of a polymorph, as measured by methods such as capillary melting point, DSC, and hot stage microscopy, alone or in combination with techniques such as x-ray powder diffraction, IR spectroscopy, or both, may be used to characterize polymorphs or other solid forms.

[0097] As with any analytical technique, melting points determinations are also subject to variability. Common sources of variability include instrumental variability, experimental technique such as sample handling and preparation, and colligative properties such as the presence of other solid forms or other impurities within a sample whose melting point is being measured.

[0098] Variability is also present when determining the amount of solvent in a solvate or water in a hydrate. There are multiple techniques for making such a determination. Although single-crystal x-ray powder diffraction is typically definitive with respect to solvents of crystallization or water of crystallization in stoichiometric solvates or stoichiometric hydrates, it is not always possible or practical to obtain single crystals suitable for analysis. When using other techniques, such as solution-state ^1H NMR and thermal methods such as TGA, the variability in those techniques introduce added variability in calculating the molar content of a solvent or water.

[0099] The variability with respect to analytical techniques such as x-ray powder diffraction, NMR, and infrared spectroscopy and others does not take into account variable solvates (or hydrates). For example, for a stoichiometric solvate having 1 mole of ethanol, the variability associated with an analytical response such as x-ray powder diffraction would not materially differ when compared with that of an anhydrate. The situation changes however, when considering a non-stoichiometric (i.e. variable) solvate or hydrate. For example, the variability associated when comparing a monomolar ethanol solvate with a trimolar ethanol solvate or other amounts of solvate within the same variable ethanol solvate

would likely increase with x-ray powder diffraction, and other techniques, because different solvent amounts may perturb the structure differently. In other words, the variability associated with changing solvent content could contribute to an increased variability in various analytical responses that would not otherwise occur when looking at stoichiometric solvates or stoichiometric hydrates.

[00100] In many embodiments, after the term “one or more peaks” a list is provided. This language is not meant to state or imply that the presence of peaks other than those in the list means that the embodied form is not present. On the contrary, other peaks may be present which may be due, as the case may be, to other compounds such as impurities or other forms or may be due to peaks which have not been specifically expressed as characteristic for that particular embodiment. Other peaks may also be present if the analytical data is collected on a composition such as a pharmaceutical composition containing excipients.

[00101] As used herein, the term di-pidotimod benzathine refers to the salt containing two pidotimod ions for every benzathine.

[00102] The invention is further directed to different solid forms of di-pidotimod benzathine including several crystalline forms and the amorphous form including solvates, cocrystals, and hydrates of those forms.

[00103] One such crystalline form is crystalline Form M di-pidotimod benzathine, also referred to herein as “Form M” or “Form M di-pidotimod benzathine”. The present invention is also directed to Form M and solvates, cocrystals and hydrates of Form M. Form M is an anhydrate crystalline form of the chemical compound di-pidotimod benzathine meaning that there is no evidence of any solvated solvents or water of hydration in the structure. The ¹H NMR spectrum of Form M is consistent with a di-Pidotimod benzathine salt and shows no evidence of water or process solvents (Figure 7). Form M was further found to be non-hygroscopic below 75% relative humidity, but hygroscopic above such a relative humidity. Form M was indexed revealing a pure phase and the solution and unit cell parameters are provided in Figure 8.

[00104] As a crystalline solid form, Form M was characterized using solid-state analytical techniques. Such techniques include x-ray powder diffraction, differential scanning calorimetry, Raman spectroscopy, infrared spectroscopy, and

^{13}C solid-state NMR spectroscopy. Each technique alone or in combination with each other may be used to characterize Form M as, for example, set forth below in the various embodiments.

[00105] In one embodiment of the invention, Form M di-pidotimod benzathine is characterized by an x-ray powder diffraction pattern substantially the same as that in Figure 1. In Figure 2, a peak-picked version of Figure 1 is provided. Smaller subset of peaks may be used to characterize Form M di-pidotimod benzathine alone or in combination with other analytical techniques. For example, the peak at about $7.6^\circ 2\theta$ or at about $19.6^\circ 2\theta$ may be used to characterize Form M di-pidotimod benzathine. In other embodiments, and further illustrating that a subset of peaks may be used, one or both of these two peaks in addition to the peaks at about 11.7, 12.9, 18.4, 20.4, or $21.1^\circ 2\theta$ may be used to characterize Form M di-pidotimod benzathine. In further embodiments, any one of the peaks at about 11.7, 12.9, 18.4, 20.4, or $21.1^\circ 2\theta$ may be used to characterize Form M di-pidotimod benzathine.

[00106] In additional embodiments, DSC may be used to characterize Form M di-pidotimod benzathine. The DSC thermogram of Form M exhibits a characteristic endotherm onset temperature at about 172°C as seen in Figure 3. DSC may be used alone or in combination with other analytical techniques to characterize Form M di-pidotimod benzathine. For example, any one or more of the x-ray powder diffraction peaks at about 7.6, 19.6, 11.7, 12.9, 18.4, 20.4, or $21.1^\circ 2\theta$ together with endotherm onset temperature at about 172°C may be used to characterize Form M. Specific embodiments include, but are not limited to, the peak at $7.6^\circ 2\theta$ and an endotherm onset temperature at about 172°C ; the peak at $19.6^\circ 2\theta$ and an endotherm onset temperature at about 172°C ; one or more of the peaks at 11.7, 12.9, 18.4, 20.4, or $21.1^\circ 2\theta$ and an endotherm onset temperature at about 172°C ; and a peak at about $7.6^\circ 2\theta$ or at about $19.6^\circ 2\theta$ together with one or more peaks at about 11.7, 12.9, 18.4, 20.4, or $21.1^\circ 2\theta$ and an endotherm onset temperature at about 172°C .

[00107] In further embodiments, Raman spectroscopy may be used to characterize Form M di-pidotimod benzathine. For example, the Raman spectrum in Figure 4 may be used to characterize Form M di-pidotimod benzathine. Smaller

subsets of peaks within the Raman spectrum may also be used to characterize Form M di-pidotimod benzathine alone or in combination with other techniques. For example, one or more peaks at about 778, 1004, 1217, 1611, 2948, or 3075 cm^{-1} may be used to characterize Form M di-pidotimod benzathine. Raman spectroscopy may be used alone or together with other analytical techniques to characterize Form M di-pidotimod benzathine. For example, Raman spectroscopy, together with DSC may be used to characterize Form M di-pidotimod benzathine. In such embodiments, one or more peaks at about 778, 1004, 1217, 1611, 2948, or 3075 cm^{-1} and an endotherm onset temperature at about 172°C may be used to characterize Form M di-pidotimod benzathine. In other embodiments, Raman spectroscopy and x-ray powder diffraction may be used together to characterize Form M di-pidotimod benzathine. For example, any one or more of the x-ray powder diffraction peaks at about 7.6, 19.6, 11.7, 12.9, 18.4, 20.4, or 21.1°2 θ , and in particular one or both of the peaks at about 7.6 or 19.6°2 θ , in combination with any one or more of the Raman spectral peaks at about 778, 1004, 1217, 1611, 2948, or 3075 cm^{-1} may be used to characterize Form M di-pidotimod benzathine. In such embodiments, the Form M di-pidotimod benzathine may further be characterized by an endotherm onset temperature at about 172°C.

[00108] In additional embodiments, ^{13}C solid-state nuclear magnetic resonance spectroscopy may be used to characterize Form M di-pidotimod benzathine. For example, the NMR spectrum in Figure 5 (about 20 ppm to 190 ppm) may be used to characterize Form M di-pidotimod benzathine. Smaller subsets of peaks within the ^{13}C solid-state nuclear magnetic resonance spectrum may also be used to characterize Form M di-pidotimod benzathine alone or in combination with other techniques. For example, one or more of the peaks at about 24.5, 29.7, 34.8, 46.1, 64.4, 168.6, 179.5, or 181.2 ppm may be used to characterize Form M di-pidotimod benzathine. In some embodiments, ^{13}C solid-state nuclear magnetic resonance spectroscopy may be used with differential scanning calorimetry to characterize Form M di-pidotimod benzathine. For example, one or more of the peaks at about 24.5, 29.7, 34.8, 46.1, 64.4, 168.6, 179.5, or 181.2 ppm in the ^{13}C solid-state nuclear magnetic resonance spectrum in combination with an

endotherm onset temperature at about 172°C may be used to characterize Form M di-pidotimod benzathine. In other embodiments, ^{13}C solid-state nuclear magnetic resonance spectroscopy may be used with x-ray powder diffraction to characterize Form M di-pidotimod benzathine. For example, one or more of the peaks at about 24.5, 29.7, 34.8, 46.1, 64.4, 168.6, 179.5, or 181.2 ppm in the ^{13}C solid-state nuclear magnetic resonance spectrum in combination with one or more of the peaks at about 7.6, 19.6, 11.7, 12.9, 18.4, 20.4, or 21.1°2 θ in the x-ray powder diffraction pattern, and in particular one or both of the peaks at about 7.6 and 19.6°2 θ , may be used to characterize Form M di-pidotimod benzathine. In such embodiments, Form M di-pidotimod benzathine may further be characterized by an endotherm onset temperature at about 172°C. In other embodiments, ^{13}C solid-state nuclear magnetic resonance spectroscopy may be used with Raman spectroscopy to characterize Form M di-pidotimod benzathine. For example, one or more of the peaks at about 24.5, 29.7, 34.8, 46.1, 64.4, 168.6, 179.5, or 181.2 ppm in the ^{13}C solid-state nuclear magnetic resonance spectrum in combination with one or more of the peaks at about 778, 1004, 1217, 1611, 2948, or 3075 cm^{-1} in the Raman spectrum may be used to characterize Form M di-pidotimod benzathine. In such embodiments, an endotherm onset temperature at about 172°C may further be used to characterize Form M di-pidotimod benzathine.

[00109] In additional embodiments, infrared spectroscopy may be used to characterize Form M di-pidotimod benzathine. For example, the spectrum in Figure 6 may be used to characterize Form M di-pidotimod benzathine. Smaller subsets of peaks within the infrared spectrum may also be used to characterize Form M di-pidotimod benzathine alone or in combination with other techniques. For example, one or more of the peaks at about 696, 742, 1257, 1277, 1557, 1633, 1666, or 1697 cm^{-1} may be used to characterize Form M di-pidotimod benzathine. In other embodiments, one or more of the peaks at about 696, 742, 1257, 1277, 1557, 1633, 1666, or 1697 cm^{-1} in the infrared spectrum in combination with an endotherm onset temperature at about 172°C may be used to characterize Form M di-pidotimod benzathine. For other embodiments, infrared spectroscopy may be used in combination with x-ray powder diffraction to characterize Form M di-pidotimod benzathine. For example, one or more of the peaks at about 696, 742,

1257, 1277, 1557, 1633, 1666, or 1697 cm^{-1} in the infrared spectrum in combination with one or more of the peaks at about 7.6, 19.6, 11.7, 12.9, 18.4, 20.4, or 21.1°2 θ in the x-ray powder diffraction pattern, and in particular one or both of the peaks at about 7.6 and 19.6°2 θ may be used to characterize Form M di-pidotimod benzathine. In other embodiments, infrared spectroscopy may be used with ^{13}C solid-state nuclear magnetic resonance spectroscopy to characterize Form M di-pidotimod benzathine. For example, one or more of the peaks at about 696, 742, 1257, 1277, 1557, 1633, 1666, or 1697 cm^{-1} in the infrared spectrum in combination with one or more of the peaks at about 24.5, 29.7, 34.8, 46.1, 64.4, 168.6, 179.5, or 181.2 ppm in the ^{13}C solid-state nuclear magnetic resonance spectrum may be used to characterize Form M di-pidotimod benzathine.

[00110] Another crystalline form described herein is crystalline hydrate Form H di-pidotimod benzathine, also referred to herein as “hydrate Form H” or “hydrate Form H di-pidotimod benzathine”. The present invention is also directed to solvates of hydrate Form H and cocrystals of hydrate Form H. Hydrate Form H is a hydrated crystalline form of the chemical compound di-pidotimod benzathine meaning that the crystalline material contains water of hydration. Hydrate Form H may have variable amounts of water, which may be detectable by ^1H NMR as set forth in the solution-state proton NMR parameters of Example 2. Under such circumstances where water is detected by Karl Fischer titration, hydrate Form H may contain less than 10% by weight water including less than 9% water and less than 8.5% water. Hydrate Form H may also contain between about 8.5% and 9.0% water, including between about 8.6% and about 8.9% by weight water. Karl Fischer measurements on a sample of hydrate Form H prepared hereunder prior to drying reveal a water content of about 8.8% by weight, which is consistent with a structure containing 4 equivalents of water. The indexing solution for hydrate Form H in Figure 15 reveals a unit cell consistent with that of a solvate or hydrate.

[00111] Upon drying, the indexing solution reveals a smaller volume consistent with the loss of water and the ^1H NMR spectrum of the dried material, which is consistent with a di-Pidotimod benzathine salt, lacks solvent or water signals (Figure 17). Crystalline Form H di-pidotimod benzathine, also referred to herein as “Form H” or “Form H di-pidotimod benzathine”, is a crystalline material where

solvent and water signals are absent and therefore not detected as shown in the ^1H NMR spectrum of Figure 17 collected using the corresponding parameters of Example 2. The lack of such signals indicates the sample is substantially free of water or solvent. It may be prepared by drying hydrated Form H. The present invention is also directed to Form H and solvates, cocrystals, and hydrates thereof.

[00112] As a crystalline solid form, hydrate Form H was characterized using solid-state analytical techniques including x-ray powder diffraction and infrared spectroscopy. Each technique alone or in combination with each other may be used to characterize hydrate Form H as, for example, set forth below in the various embodiments.

[00113] In one embodiment of the invention, hydrate Form H di-pidotimod benzathine may be characterized by an x-ray powder diffraction pattern substantially the same as that in Figure 9. Smaller subset of peaks may be used to characterize hydrate Form H di-pidotimod benzathine alone or in combination with other analytical techniques. For example, the peak at about $7.2^\circ 2\theta$ may be used to characterize hydrate Form H di-pidotimod benzathine. Although the diffraction pattern of Form M also possesses an x-ray powder diffraction peak at about $7.2^\circ 2\theta$, Form M is an anhydrate and can be distinguished from hydrate Form H by water content using techniques such as Karl Fisher. In a further embodiment, the peak at about $4.4^\circ 2\theta$ may be used to characterize hydrate Form H di-pidotimod benzathine. Thus, any one or both of the peaks at about 4.4 or $7.2^\circ 2\theta$ may be used to characterize hydrate Form H. Other peaks may also be used in other embodiments. For example, one or both of the peaks at about 4.5 or $7.2^\circ 2\theta$ in combination with one or more peaks at about 5.5 , 9.0 , or $18.7^\circ 2\theta$ may be used to characterize hydrate Form H.

[00114] In additional embodiments, hydrate Form H may be characterized by infrared spectroscopy. In one embodiment of the invention, hydrate Form H di-pidotimod benzathine may be characterized by an infrared spectrum pattern substantially the same as that in Figure 10. Smaller subset of peaks may be used to characterize hydrate Form H di-pidotimod benzathine alone or in combination with other analytical techniques. In further embodiments, infrared spectroscopy may be used alone or in combination with x-ray powder diffraction to characterize

hydrate Form H di-pidotimod benzathine. For example, one or more of the peaks at about 1389, 1609, 1649, or 1717 cm^{-1} in the infrared spectrum may be used to characterize hydrate Form H. Additionally, in other embodiments, one or more of the peaks at about 1389, 1609, 1649, or 1717 cm^{-1} in the infrared spectrum in addition to one or more peaks at about 4.5, 5.5, 7.2, 9.0, or 18.7°2 θ in the x-ray powder diffraction pattern may be used to characterize hydrate Form H di-pidotimod benzathine.

[00115] Form H may further be distinguished from hydrate Form H by the unit cell volume based on comparing the unit cell dimensions of the indexing solutions in Figure 15 with Figure 16, which differ by about 50 cubic Angstroms.

[00116] In another embodiment, Form H di-pidotimod benzathine may be characterized by an x-ray powder diffraction pattern substantially the same as that in Figure 11. Smaller subset of peaks may be used to characterize hydrate Form H di-pidotimod benzathine alone or in combination with other analytical techniques. Form H may be distinguished from Form M by one or more peaks at about 4.4, 5.5, 8.9, 14.4, or 16.6 °2 θ using x-ray powder diffraction. Thus, Form H may be characterized by an x-ray powder diffraction pattern comprising one or more peaks at about 4.4, 5.5, 8.9, 14.4, or 16.6 °2 θ and substantially no water or solvent content as detected by solution state ^1H NMR. In particular, Form H may be characterized by an x-ray powder diffraction pattern comprising one or more peaks at about 4.4, 5.5, or 8.9 °2 θ and substantially no water or solvent content as detected, for example, by solution state ^1H NMR.

[00117] The present invention is also directed to amorphous di-pidotimod benzathine and solvates, cocrystals or hydrates thereof. Amorphous di-pidotimod benzathine may be characterized by a halo in its x-ray powder diffraction pattern such as that which seen in Figure 12.

[00118] In another embodiment, amorphous di-pidotimod benzathine may be characterized by an infrared spectrum substantially the same as that in Figure 14. Smaller subset of peaks may be used to characterize amorphous di-pidotimod benzathine alone or in combination with other analytical techniques. In further embodiments, amorphous di-pidotimod benzathine may be characterized by an infrared spectrum comprising one or more peaks at about 699, 752, 833, 1321,

1377, 1497, 1645, or 1680 cm^{-1} alone or together with an amorphous halo in an x-ray powder diffraction pattern.

[00119] In further embodiments, amorphous di-pidotimod benzathine may be characterized by a glass transition temperature of about 53°C. Amorphous di-pidotimod benzathine may be further characterized by glass transition temperature of about 53°C together with either or both of an amorphous halo in an x-ray powder diffraction pattern and/or one or more peaks at about 699, 752, 833, 1321, 1377, 1497, 1645, or 1680 cm^{-1} in an infrared spectrum.

[00120] A further crystalline form is crystalline Form J di-pidotimod benzathine, also referred to herein as "Form J". Form J is a variable isopropanol solvate crystalline form of di-pidotimod benzathine.

[00121] For example, under circumstances where Form J has been prepared and analyzed, up to about 3.2 moles of isopropanol alcohol are associated with Form J. When dried as noted above, unbound isopropanol can be removed such that the amount of isopropanol remaining is about 2.3 moles per mole of di-pidotimod benzathine. This result is consistent with the indexing solution suggesting that about 2 moles of isopropanol may be bound with the di-pidotimod benzathine.

[00122] The molecular weight of di-pidotimod benzathine is about 728.9. The molecular weight of isopropanol is about 60. Thus, from a weight perspective, 2 moles of isopropanol corresponds to about 14.1% isopropanol. By comparison, 3.2 moles of isopropanol correspond to about 20.9% isopropanol by weight.

[00123] Form J was capable of indexing as shown in Figure 22. The volume of the unit cell was found to be about 2411 cubic Angstroms. Based on considerations of unit cell volume and molecular volumes predicted for di-pidotimod benzathine and isopropanol from Hofmann's estimate of crystal densities using an atomic approach (Acta Cryst. (2002) B57, 489-493), the unit cell has sufficient space for about 2 moles of isopropanol. Additional isopropanol in Form J would be unbound. Thus, Form J is an isopropanol solvate capable of containing up to about 3.2 moles of isopropanol.

[00124] The ^1H NMR spectrum of Form J shows there to be about 3.2 moles of isopropanol for each mole of di-pidotimod benzathine (Figure 21). A thermal

study was also performed using both DSC and TGA. By TGA, for example, a 7.3% weight loss was observed between about 24.7°C and 40°C (Figure 43) which corresponds to about 0.9 moles of isopropanol. Such loss may be due to unbound isopropanol. Figure 43 shows a further weight loss of 12.0% between about 40.0°C and 98.1°C which corresponds to an endotherm seen in the DSC of Figure 19 having an onset of about 67.9°C, corresponding to about 1.7 moles of isopropanol.

[00125] As a crystalline solid form, Form J may be characterized using solid-state analytical techniques. Such techniques include x-ray powder diffraction and infrared spectroscopy. Each technique alone or in combination with each other may be used to characterize Form J as, for example, set forth below in the various embodiments.

[00126] In one embodiment of the invention, Form J is an isopropanol solvate of di-pidotimod benzathine containing up to about 3.2 moles of isopropanol per mole of di-pidotimod benzathine. In other embodiments, the amount of isopropanol in Form J is up to about 2 moles of isopropanol. In still other embodiments, it is about 2 moles of isopropanol.

[00127] In still other embodiments, Form J may be characterized by a peak-picked x-ray powder diffraction pattern substantially the same as that in Figure 18. Smaller subset of peaks may be used to characterize Form J di-pidotimod benzathine alone or in combination with other analytical techniques. For example, one or more of the peaks at about 16.2°2 θ or 17.3°2 θ may be used to characterize Form J di-pidotimod benzathine. In other embodiments, and further illustrating that a subset of peaks may be used, one or more of the peaks at about 16.2°2 θ or 17.3°2 θ may be used to characterize together with one or more of the peaks at about 6.1°2 θ , 8.8°2 θ , and 21.6°2 θ . In these embodiments, the amount of isopropanol in Form J may be up to about 3.2 moles, including up to about 2 moles and further including about 2 moles of isopropanol per mole of di-pidotimod benzathine.

[00128] In additional embodiments, infrared spectroscopy may be used to characterize Form J di-pidotimod benzathine. For example, the spectrum in Figure 20 may be used to characterize Form J di-pidotimod benzathine. Smaller

subsets of peaks within the infrared spectrum may also be used to characterize Form J di-pidotimod benzathine alone or in combination with other techniques. For example, one or more of the peaks at about 1574 cm^{-1} or 1328 cm^{-1} may be used to characterize Form J di-pidotimod benzathine. In other embodiments, one or more of the peaks at about 1574 cm^{-1} or 1328 cm^{-1} and one or more of the peaks at about 1687 cm^{-1} , 1656 cm^{-1} , or 1387 cm^{-1} in the infrared spectrum may be used to characterize Form J. In other embodiments, one or more of the infrared spectral peaks at about 1574 cm^{-1} or 1328 cm^{-1} and, optionally, one or more of the peaks at about 1687 cm^{-1} , 1656 cm^{-1} , or 1387 cm^{-1} in combination with one or more of the peaks at about $16.2^{\circ}2\theta$ or $17.3^{\circ}2\theta$, and, optionally one or more peaks at $6.1^{\circ}2\theta$, $8.8^{\circ}2\theta$, and $21.6^{\circ}2\theta$ in the x-ray powder diffraction pattern may be used to characterize Form J di-pidotimod benzathine. In these embodiments, the amount of isopropanol in Form J may be up to about 3.2 moles, including up to about 2 moles and further including about 2 moles of isopropanol per mole of di-pidotimod benzathine.

[00129] The isopropanol solvates of the invention further include isopropanol solvates other than Form J. For example, when Form J is dried, such as in accordance with Example 30, a new diffraction pattern appears which reflects a new isopropanol solvate termed Form O, also known as Form O di-pidotimod benzathine. Thus, the isopropanol solvates of the invention include both Form J and Form O. Form O is a variable isopropanol solvate of di-pidotimod benzathine with a different crystalline structure than Form J.

[00130] The ^1H NMR spectrum of Form O shows there to be about 0.6 moles of isopropanol for each mole of di-pidotimod benzathine (Figure 26a). When prepared from Form M (Example 31A – method 3), a sample of Form O showed about 1.2 moles of isopropyl alcohol (Figure 26b). A thermal study was also performed using both DSC and TGA. By TGA, for example, a 10% weight loss was observed between about 25.3°C and 62.6°C and between about 62.6°C and 93.7°C (Figure 44a) which corresponds to about 1.3 moles of isopropanol in total. Such loss may be due to both bound and unbound isopropanol. An endotherm occurs at 63.2°C (peak maximum) in the DSC, and is directly followed by an exotherm at 75.6°C . The endothermic event may be due to the loss of additional

bound isopropanol. A second thermal study was conducted on a different sample of Form O prepared from Form M, in that study, a weight loss in two steps – about 2.2% loss from approximately 24 °C to 61 °C and about 10.9% from approximately 61 °C to 120 °C were observed (See Figure 44b). Combined, these steps account for about 1.8 moles of IPA and may be due to both bound and unbound isopropanol.

[00131] As a crystalline solid form, Form O may be characterized using solid-state analytical techniques. Such techniques include x-ray powder diffraction. Each technique alone or in combination with each other may be used to characterize Form O as, for example, set forth below in the various embodiments.

[00132] In some embodiments of the invention, Form O di-pidotimod benzathine contains between about 0.6 and about 1.8 moles of isopropanol for each mole of di-pidotimod benzathine.

[00133] In other embodiments, Form O may be characterized by a peak-picked x-ray powder diffraction pattern substantially the same as that in Figure 23. Smaller subset of peaks may be used to characterize Form O di-pidotimod benzathine alone or in combination with other analytical techniques. For example, the peaks at about $17.7^{\circ}2\theta$ or $22.0^{\circ}2\theta$ may be used to characterize Form O di-pidotimod benzathine. In other embodiments, and further illustrating that a subset of peaks may be used, the peaks at about $17.7^{\circ}2\theta$ or $22.0^{\circ}2\theta$ may be used to characterize together with one or more of the peaks at about $6.2^{\circ}2\theta$, $8.8^{\circ}2\theta$ and $11.2^{\circ}2\theta$. In these embodiments, the amount of isopropanol in Form O may be between about 0.6 moles and about 1.3 moles such as about 0.6 moles or about 1.3 moles per mole of di-pidotimod benzathine.

[00134] Another crystalline form of the invention is termed Form S di-pidotimod benzathine, also referred to herein as “Form S”. Form S is a variable ethanol solvate of the di-pidotimod benzathine where the ethanol may be bound or unbound. A ^1H NMR spectrum of Form S shows there to be about 4 moles of ethanol for each mole of di-pidotimod benzathine (Figure 30). In another preparation of Form S, about 2 moles of ethanol were detected by ^1H NMR spectroscopy. A thermal study was also performed using both DSC and TGA. By TGA, for example, a 5.8% weight loss was observed between about 25.4°C and

133.7°C (Figure 45) which corresponds to about 1.0 mole of ethanol. In the DSC, an endotherm onset of about 100.2°C was observed followed by an exotherm with a peak onset of about 120.7°C which suggests loss of ethanol followed by recrystallization. In another preparation of Form S, a thermal study showed that about 3.1 moles of ethanol are present.

[00135] Form S was indexed as shown in Figure 49. The volume of the unit cell was found to be about 6165 cubic Angstroms. Based on considerations of unit cell volume and molecular volumes predicted for di-pidotimod benzathine and isopropanol from Hofmann's estimate of crystal densities using an atomic approach (Acta Cryst. (2002) B57, 489-493), the unit cell has sufficient space for about 9 moles of ethanol. Additional ethanol in Form S would be unbound. Thus, Form S is an ethanol solvate capable of containing up to about 9 moles of ethanol of crystallization.

[00136] As a crystalline solid form, Form S may be characterized using solid-state analytical techniques. Such techniques include x-ray powder diffraction and infrared spectroscopy. Each technique alone or in combination with each other may be used to characterize Form S as, for example, set forth below in the various embodiments.

[00137] In some embodiments of the invention, Form S di-pidotimod benzathine contains about 9 moles of ethanol for each mole of di-pidotimod benzathine. In other embodiments, Form S is about 1.0 mole of ethanol per mole of di-pidotimod benzathine.

[00138] In other embodiments, Form S may be characterized by a peak-picked x-ray powder diffraction pattern substantially the same as that in Figure 27. Smaller subset of peaks may be used to characterize Form S di-pidotimod benzathine alone or in combination with other analytical techniques. For example, one or more peaks at about $2.5^{\circ}2\theta$, $5.8^{\circ}2\theta$, $8.5^{\circ}2\theta$, or $11.6^{\circ}2\theta$ may be used to characterize Form S. In other embodiments, and further illustrating that a subset of peaks may be used, one or more of the peaks at about $7.6^{\circ}2\theta$ may be used to characterize Form S. In these embodiments, the amount of ethanol in Form S may be up to about 9 moles of ethanol per mole of di-pidotimod

benzathine including about 1.0 mole of ethanol per mole of di-pidotimod benzathine.

[00139] In additional embodiments, infrared spectroscopy may be used to characterize Form S. For example, the spectrum in Figure 29 may be used to characterize Form S di-pidotimod benzathine. Smaller subsets of peaks within the infrared spectrum may also be used to characterize Form S di-pidotimod benzathine alone or in combination with other techniques. For example, one or more of the peaks at about 1702 cm^{-1} or 1666 cm^{-1} may be used to characterize Form S di-pidotimod benzathine. In other embodiments, one or more of the peaks at about 1702 cm^{-1} or 1666 cm^{-1} and one or more of the peaks at about 1571 cm^{-1} , 1502 cm^{-1} , or 697 cm^{-1} in the infrared spectrum may be used to characterize Form S. In other embodiments, one or more of the infrared spectral peaks at about 1702 cm^{-1} or 1666 cm^{-1} and, optionally, one or more of the peaks at about 1571 cm^{-1} , 1502 cm^{-1} , or 697 cm^{-1} in combination with one or more of the peaks at about $2.5^{\circ}2\Theta$, $5.8^{\circ}2\Theta$, $8.5^{\circ}2\Theta$, or $11.6^{\circ}2\Theta$, and, optionally, the peak at $7.6^{\circ}2\Theta$ in the x-ray powder diffraction pattern may be used to characterize Form S. In these embodiments, the amount of ethanol in Form S may be up to about 9 moles of ethanol per mole of di-pidotimod benzathine including about 1.0 mole of ethanol per mole of di-pidotimod benzathine.

[00140] The ethanol solvates of di-pidotimod benzathine of the invention include Form S as well as other ethanol solvates. For example, when x-ray amorphous di-pidotimod benzathine is exposed to ethanol in accordance with Examples 36, 37 and 38, a diffraction pattern different than that of Form S appears. This pattern reflects an ethanol solvate which is not Form S and is termed Form W, which is also referred to as Form W di-pidotimod benzathine. Thus, the ethanol solvates of the invention include both Form S and Form W.

[00141] The ^1H NMR spectrum of Form W shows there to be about 0.4 moles of ethanol for each mole of di-pidotimod benzathine (Figure 34). A thermal study was also performed using both DSC and TGA. By TGA, for example, a 9.7% weight loss was observed between about 24.4°C and 134.7°C (Figure 46) which corresponds to about 1.7 moles of ethanol. Thus, the data show that Form W may contain between about 0.4 and about 1.7 moles of ethanol.

[00142] As a crystalline solid form, Form W may be characterized using solid-state analytical techniques. Such techniques include x-ray powder diffraction and infrared spectroscopy. Each technique alone or in combination with each other may be used to characterize Form S as, for example, set forth below in the various embodiments.

[00143] In embodiments of the invention, Form W di-pidotimod benzathine contains between about 0.4 and about 1.7 moles of ethanol for each mole of di-pidotimod benzathine including about 0.4 moles and 1.7 moles of ethanol per mole of di-pidotimod benzathine.

[00144] In other embodiments, Form W is characterized by a peak-picked x-ray powder diffraction pattern substantially the same as that in Figure 31. Smaller subset of peaks may be used to characterize Form W di-pidotimod benzathine alone or in combination with other analytical techniques. For example, the presence of one or more of the peaks at about $13.3^{\circ}2\theta$ or $18.8^{\circ}2\theta$ may be used to characterize Form W di-pidotimod benzathine. In other embodiments, and further illustrating that a subset of peaks may be used, the presence of one or more of the peaks at about $13.3^{\circ}2\theta$ or $18.8^{\circ}2\theta$ may be used to characterize together with one or more of the peaks at about $6.6^{\circ}2\theta$, $7.6^{\circ}2\theta$, or $12.7^{\circ}2\theta$. In these embodiments, the amount of ethanol in Form W may be between about 0.4 moles and 1.7 moles of ethanol per mole of di-pidotimod benzathine including about 0.4 moles and about 1.7 moles of ethanol.

[00145] In additional embodiments, infrared spectroscopy may be used to characterize Form W di-pidotimod benzathine. For example, the spectrum in Figure 33 may be used to characterize Form W di-pidotimod benzathine. Smaller subsets of peaks within the infrared spectrum may also be used to characterize Form W di-pidotimod benzathine alone or in combination with other techniques. For example, one or more of the peaks at about 1689 cm^{-1} or 1576 cm^{-1} may be used to characterize Form W di-pidotimod benzathine. In other embodiments, one or more of the peaks at about 1689 cm^{-1} or 1576 cm^{-1} in the infrared spectrum in combination with one or more of the peaks at 1653 cm^{-1} , 1391 cm^{-1} or 698 cm^{-1} may be used to characterize Form S. In other embodiments, the presence of one or more of the infrared spectral peaks at about 1689 cm^{-1} or 1576 cm^{-1} and,

optionally, one or more of the peaks at 1653 cm^{-1} , 1391 cm^{-1} or 698 cm^{-1} together with one or more peaks at about $13.3^{\circ}2\theta$ or $18.8^{\circ}2\theta$ in the x-ray powder diffraction pattern may be used to characterize Form W di-pidotimod benzathine. In further embodiments, one or more of the peaks at about 1689 cm^{-1} , 1653 cm^{-1} , 1576 cm^{-1} , and 1391 cm^{-1} in the infrared spectrum in combination with one or more peaks at about $13.3^{\circ}2\theta$ or $18.8^{\circ}2\theta$ in the x-ray powder diffraction pattern may be used to characterize Form W di-pidotimod benzathine. In other embodiments, the peaks at about 1689 cm^{-1} , 1653 cm^{-1} , 1576 cm^{-1} , and 1391 cm^{-1} in the infrared spectrum in combination with one or more of the peaks at about $13.3^{\circ}2\theta$ or $18.8^{\circ}2\theta$ and, optionally, one or more of the peaks at about $6.6^{\circ}2\theta$, $7.6^{\circ}2\theta$, or $12.7^{\circ}2\theta$ may be used to characterize Form W. In these embodiments, the amount of ethanol in Form W may be between about 0.4 moles and 1.7 moles of ethanol per mole of di-pidotimod benzathine including about 0.4 moles and about 1.7 moles of ethanol.

[00146] In other embodiments of the invention, Form X di-pidotimod benzathine, also referred to herein as “Form X” is provided. Form X is a variable hydrate of di-pidotimod benzathine, other than hydrated Form H, where the water may be bound or unbound. A Karl Fischer water content test was performed on a mixture of Form X and Form H. The mixture was estimated to be between 20% and 40% Form H and one or more unidentified materials with the remaining Form X. The estimation was based upon an evaluation of x-ray powder diffraction patterns. Karl Fischer analysis indicated the mixture contained approximately 9.1% water or 4 moles of water per mole of di-pidotimod benzathine. It has previously been determined that Form H, a variable hydrate, contains up to about 4 moles of water per mole of di-pidotimod benzathine. Since the sample analyzed contains approximately 60% Form X, then 2.4 moles of the 4 moles of water in the sample may belong to Form X.

[00147] A thermal study was also performed using both DSC and TGA. By TGA, for example, a 3.1% weight loss was observed between about 23.2°C and 122.7°C (Figure 47) which corresponds to about 1.3 moles of water. Thus, these data show that Form X is a variable hydrate capable of containing between about 1.3 and 2.4 moles of water per mole of di-pidotimod benzathine. Upon vacuum

drying between about 47°C and 52°C for 1 day, Form X dehydrated into a disordered crystalline material.

[00148] Form X was indexed as shown in Figure 50. The indexing solution revealed that the minor peak at about $10.8^{\circ}2\theta$ in Figure 35 is not part of the indexing solution. Form X indicated a volume of 962 cubic Angstroms. Based on considerations of unit cell volume and molecular volumes predicted for di-pidotimod benzathine and isopropanol from Hofmann's estimate of crystal densities using an atomic approach (Acta Cryst. (2002) B57, 489-493), the unit cell has sufficient space for about 3 moles of water. Thus, the material identified contained both Form X and an unidentified material.

[00149] As a crystalline solid form, Form X may be characterized using solid-state analytical techniques. Such techniques include x-ray powder diffraction and infrared spectroscopy. Each technique alone or in combination with each other may be used to characterize Form X as, for example, set forth below in the various embodiments.

[00150] In some embodiments of the invention, Form X contains between about 1.3 and 2.4 moles of water per mole of di-pidotimod benzathine.

[00151] In many embodiments, Form X is characterized by a peak-picked x-ray powder diffraction pattern substantially the same as that in Figure 35 other than the peak at about $10.8^{\circ}2\theta$. Smaller subset of peaks may be used to characterize Form X di-pidotimod benzathine alone or in combination with other analytical techniques. For example, one or more of the peaks $12.6^{\circ}2\theta$, $13.3^{\circ}2\theta$, or $19.6^{\circ}2\theta$ may be used to characterize Form X. In other embodiments, one or more of the peaks at about $12.6^{\circ}2\theta$, $13.3^{\circ}2\theta$, or $19.6^{\circ}2\theta$ and one or more of the peaks at about $7.1^{\circ}2\theta$ and $7.5^{\circ}2\theta$ may be used to characterize Form X. In other embodiments, and further illustrating that a subset of peaks may be used, one or more of the peaks at about $12.6^{\circ}2\theta$, $13.3^{\circ}2\theta$, and $19.6^{\circ}2\theta$ may be used to characterize Form X. In many of these embodiments, Form X may contain between about 1.3 and about 2.4 moles of water per mole of di-pidotimod benzathine.

[00152] In additional embodiments, infrared spectroscopy may be used to characterize Form X di-pidotimod benzathine. For example, the spectrum in

Figure 37 may be used to characterize Form X di-pidotimod benzathine. Smaller subsets of peaks within the infrared spectrum may also be used to characterize Form X di-pidotimod benzathine alone or in combination with other techniques. For example, the peak at about 1691 cm^{-1} may be used to characterize Form X. In other embodiments, the peak at about 1691 cm^{-1} and one or more of the peaks at about 1652 cm^{-1} , 1574 cm^{-1} , 1390 cm^{-1} or 700 cm^{-1} in the infrared spectrum may be used to characterize Form X. In other embodiments, the peak at about 1691 cm^{-1} , and optionally, one or more of the peaks 1652 cm^{-1} , 1574 cm^{-1} , 1390 cm^{-1} , or 700 cm^{-1} , in combination with the one or more peaks at about $12.6^{\circ}2\theta$, $13.3^{\circ}2\theta$, or $19.6^{\circ}2\theta$ and, optionally, one or more of the peaks at about $7.1^{\circ}2\theta$ and $7.5^{\circ}2\theta$ in an x-ray powder diffraction pattern, may be used to characterize Form X. In these embodiments, the amount of water in Form X may be between about 3.1% and about 5.6%. Another crystalline form of the invention is crystalline Form T di-pidotimod benzathine, also referred to herein as "Form T". Form T is an anhydrate of di-pidotimod benzathine meaning that there is no evidence of any solvated solvents or water of hydration in the structure. The ^1H NMR spectrum of Form T is consistent with a di-pidotimod benzathine salt and shows no evidence of acetonitrile.

[00153] As a crystalline solid form, Form T was characterized using solid-state analytical techniques. Such techniques include x-ray powder diffraction and infrared spectroscopy. Each technique alone or in combination with each other may be used to characterize Form T as, for example, set forth below in the various embodiments.

[00154] In one embodiment of the invention, Form T di-pidotimod benzathine is characterized by a peak-picked x-ray powder diffraction pattern substantially the same as that in Figure 39. Smaller subset of peaks may be used to characterize Form T di-pidotimod benzathine alone or in combination with other analytical techniques. For example, one or more of the peaks at about $5.1^{\circ}2\theta$, $8.1^{\circ}2\theta$ or $16.1^{\circ}2\theta$ may be used to characterize Form T di-pidotimod benzathine. In other embodiments, and further illustrating that a subset of peaks may be used, one or more of these three peaks in addition to the peaks at about $6.9^{\circ}2\theta$ or $9.1^{\circ}2\theta$ may be used to characterize Form T di-pidotimod benzathine.

[00155] In additional embodiments, infrared spectroscopy may be used to characterize Form T di-pidotimod benzathine. For example, the spectrum in Figure 41 may be used to characterize Form T di-pidotimod benzathine. Smaller subsets of peaks within the infrared spectrum may also be used to characterize Form T di-pidotimod benzathine alone or in combination with other techniques. For example, one or more of the peaks at about 1722 cm^{-1} , 1576 cm^{-1} , 1515 cm^{-1} , or 752 cm^{-1} may be used to characterize Form T di-pidotimod benzathine. In other embodiments, one or more of the peaks at about 1722 cm^{-1} , 1576 cm^{-1} , or 1515 cm^{-1} in the infrared spectrum in combination with the peak at about 700 cm^{-1} may be used to characterize Form T. For other embodiments, infrared spectroscopy may be used in combination with x-ray powder diffraction to characterize Form T di-pidotimod benzathine. For example, one or more of the peaks at about 1722 cm^{-1} , 1576 cm^{-1} , 1515 cm^{-1} or 752 cm^{-1} , and optionally, the peak at about 700 cm^{-1} , in the infrared spectrum in combination with one or more of the peaks at about $5.1^{\circ}2\theta$, $8.1^{\circ}2\theta$ or $16.1^{\circ}2\theta$ in the x-ray powder diffraction pattern, and, optionally, one or more of the peaks at about $6.9^{\circ}2\theta$ or $9.1^{\circ}2\theta$ may be used to characterize Form T di-pidotimod benzathine.

[00156] Other embodiments of the present disclosure include compositions containing di-pidotimod benzathine or a solid form thereof such as amorphous di-pidotimod, Form H, Form M, or solvates, cocrystals and hydrates thereof as well hydrate Form H, solvates and cocrystals of hydrate Form H, an ethanol solvate, such as Form S or Form W, an isopropanol solvate, such as Form J or Form O, a hydrate such as Form X, or an anhydrous form such as Form T, as well as combination of such solid forms. Such compositions may be pharmaceutical compositions including one or more pharmaceutically acceptable excipients and/or adjuvants including, without limitation: antifoaming agents, antimicrobial preservatives, antioxidant agents, bulking agents, capsule shells, carriers, chelating and/or complexing agents, coating agents, colloid stabilizing agents, coloring agents, desiccants, diluents, disintegrants, emollients, emulsifying agents, film-forming agents, filtering aids, flavors and fragrances, free radical scavengers, glidants and/or anticaking agents, lubricants, ointment bases, water, pH modifiers (acidifying agents, alkalizing agents, buffering agents), plasticizers, polymer

membranes, propellants, reducing agents, release-modifying agents, sequestering agents, solvents, sorbents, stiffening agents, suppository bases, suspending and/or viscosity-increasing agents, sweetening agents, tonicity agents, transfer ligands, vehicles, water-repelling agents, wet binders, wetting and/or solubilizing agents. The compositions of the present disclosure can thus include any one or a combination of the following: a pharmaceutically acceptable excipient(s), adjuvant(s) or agent(s); other medicinal agent(s); pharmaceutical agent(s); known to those skilled in the art. These excipients will often be biologically inactive and can be administered to humans without causing deleterious side effects or interactions.

[00157] Suitable excipients may include, but are not limited to: mannitol, polyvinylpyrrolidone, sodium saccharin, methacrylic acid co-polymer, ethylcellulose, orange flavor, sodium carbonate, silicon dioxide, saccharose, sodium carboxymethyl cellulose cross-linked, magnesium stearate, lactic acid, glycerin, xanthan gum, hydroxypropyl chitosan, petrolatum, octyldodecanol, cetearyl alcohol, glyceryl stearate, DL-alfa tocopheryl acetate, polyoxyl-20 cetostearyl ether, cyclomethicone, sodium benzoate, potassium sorbate, allantoin, hydroxyethyl cellulose, sodium hyaluronate, sodium methylparaben, sodium propylparaben or mixtures thereof.

[00158] In one embodiment of the invention, the solid-form di-pidotimod benzathine dosage form is an oral dosage form. Exemplary oral dosage forms include tablets, capsules, powders, solutions, syrups, suspensions and lozenges, which may be prepared by any conventional method of preparing pharmaceutical oral dosage forms. Oral dosage forms, such as tablets, may contain one or more of the conventional, pharmaceutically acceptable additional formulation ingredients, including but not limited to, release modifying agents, glidants, compression aides, disintegrants, effervescent agents, lubricants, binders, diluents, flavors, flavor enhancers, sweeteners and preservatives. These ingredients are selected from a wide variety of excipients known in the pharmaceutical formulation art. Depending on the desired properties of the oral dosage form, any number of ingredients may be selected alone or in combination for their known use in preparing such dosage forms as tablets.

[00159] In one embodiment of the invention, the solid-form di-pidotimod benzathine dosage form is a topical form. Exemplary topical dosage forms include emulsions, ointments, gels, jellified emulsions, and lotions, which may be prepared by any conventional method of preparing pharmaceutical topical dosage forms. Topical dosage forms, such as emulsions, may contain one or more pharmaceutically acceptable formulation ingredients, including but not limited to, emollients, film former polymers, emulsifiers, thickeners, humectants, silicones, antioxidants, moisturizers, preservatives, surfactants, solubilizers, chelating agents, buffering agents, lenitive, anti-itching agents, and plasticizers. These ingredients are selected from a wide variety of excipients known in the pharmaceutical formulation art. Depending on the desired properties of the topical dosage form, any number of ingredients may be selected alone or in combination for their known use in preparing such dosage forms.

[00160] In other embodiments, amorphous di-pidotimod, hydrate Form H, Form M, Form H, solvates, cocrystals or hydrates thereof, solvates or cocrystals of hydrate Form H, an ethanol solvate, such as Form S or Form W, an isopropanol solvate, such as Form J or Form O, a hydrate such as Form X, or an anhydrous form such as Form T or a combination thereof may be used to (a) induce dendritic cell maturation and up-regulate the expression of HLA-DR and co-stimulatory molecules CD83 and CD86; (b) stimulate dendritic cells to release pro-inflammatory molecules such as MCP-1 and TNF- α cytokines; and/or (c) to inhibit thymocyte apoptosis caused by a variety of apoptosis-inducing molecules.

[00161] Such forms of di-pidotimod benzathine may further be used to increase natural resistance to viral or bacterial infections in patients including respiratory, urinary and genital infections, in particular recurrent respiratory infections in pediatric patients, respiratory infections in asthmatic patients, and chronic obstructive pulmonary disease in adults and elderly patients. Inflammatory diseases may also be treated with such solid forms of di-pidotimod benzathine.

[00162] Such solid forms of di-pidotimod benzathine may also be used to treat gastroenterology diseases such as ulcerative colitis and irritable bowel syndrome, and dermatological diseases such as psoriasis and atopic dermatitis where symptoms relating to these diseases have been attenuated. In gastroenterology

diseases the solid forms of pidotimod may be administered either by oral or by rectal route. Oral route or topical application, for example in creams or gels containing such solid forms, may be used to treat dermal conditions.

[00163] Further use of such solid forms includes treatment of inflammatory diseases, in particular those characterized by activation of the non-canonical NF- κ B pathway. Diseases implicated by such activation include allergic diseases, autoimmune diseases, and numerous other inflammatory diseases. Allergic diseases include allergic rhinitis, allergic conjunctivitis, contact dermatitis, eczema and allergic vasculitis. Autoimmune diseases include alopecia areata, ankylosing spondylitis, autoimmune cardiomyopathy, autoimmune connective tissue diseases, autoimmune enteropathy, autoimmune hepatitis, autoimmune peripheral neuropathy, autoimmune pancreatitis, autoimmune polyendocrine syndrome, autoimmune thrombocytopenic purpura, autoimmune urticaria, autoimmune uveitis, celiac disease, chronic fatigue syndrome, cystic fibrosis, Hashimoto's thyroiditis, idiopathic pulmonary fibrosis, idiopathic thrombocytopenic purpura, IGA nephropathy, juvenile idiopathic arthritis (or juvenile rheumatoid arthritis, or Still's disease) Kawasaki's disease, lichen planus, lupus erythematosus, rheumatoid arthritis, rheumatic fever, Sjögren's syndrome, spondyloarthropathy, temporal arteritis (or giant cell arteritis), urticarial vasculitis, and vitiligo. Other inflammatory diseases include Alzheimer's disease, atherosclerosis, chronic liver diseases, chronic nephropathy, gastritis, glomerulonephritis, hydradenitis suppurativa, hypogammaglobulinemia, interstitial cystitis, lichen sclerosus, liver steatosis, metabolic syndrome, obesity, Parkinson's disease, pemphigus vulgaris, post-ischemic inflammation, Raynaud's phenomenon, restless leg syndrome, retroperitoneal fibrosis, and thrombocytopenia.

[00164] In other embodiments the salification processes for preparing di-pidotimod benzathine are provided. Di-pidotimod benzathine can be prepared as a solution by treating pidotimod with N,N-dibenzylethylamine (benzathine) in one or more suitable solvents; 0.5 to 0.6 equivalents of benzathine are preferably used; the temperature range preferably used is from 70°C to 80°C. Examples of suitable solvents are dipolar aprotic organic solvents, such as dimethylformamide,

dimethyl sulfoxide, N-methylpyrrolidone, N,N-dimethylacetamide. Other examples of suitable solvents include variable mixtures of at least a dipolar aprotic organic solvent and at least an alcohol; preferred mixtures include 20 to 40 parts by volume of dipolar aprotic organic solvent and 60 to 80 parts by volume of alcohol. Preferred alcohols are C₁-C₄ alkanols, such as methanol and ethanol. Other examples of suitable solvents include water and mixture of water and alcohols.

[00165] In other embodiments, crystallization processes for preparing Form M di-pidotimod benzathine are provided. Form M di-pidotimod benzathine can be obtained by adding seeds of di-pidotimod benzathine salt Form M as such or as a slurry in ethylacetate isopropylacetate, n-butylacetate, isobutylacetate, sec-butylacetate, toluene or anisole, preferably ethylacetate, to a solution of di-pidotimod benzathine in a dipolar aprotic organic solvent such as dimethylformamide, dimethyl sulfoxide, N-methylpyrrolidone, N,N-dimethylacetamide. This is then followed by the addition of an antisolvent causing the formation of solids in the solution. The antisolvent is normally selected from ethylacetate, isopropylacetate, n-butylacetate, isobutylacetate, sec-butylacetate, anisole and toluene. Cooling followed by removal of the solvents by filtration and isolating the solid by drying thereby results in the formation of Form M.

[00166] Form M di-pidotimod benzathine can also be obtained by slurrying Form H into a suitable liquid followed by isolating the solid therein by techniques such as cooling and drying. Examples of suitable liquids include ethyl acetate and anisole or mixtures thereof. Further embodiments include Form M obtainable by such processes.

[00167] Hydrated Form H may be prepared in other embodiments. For example, hydrated Form H di-pidotimod benzathine can be obtained by precipitating it from a solution of di-pidotimod benzathine in a variable mixture of at least a dipolar aprotic organic solvent and at least an alcohol causing the formation of solids in the solution. Typical temperature range is from 55°C to 20°C. Preferred mixtures include 20 to 40 parts by volume of dipolar aprotic organic solvent and 60 to 80 parts by volume of alcohol. Preferred dipolar aprotic organic solvents are dimethylformamide, dimethyl sulfoxide, N-

methylpyrrolidone, N,N-dimethylacetamide; preferred alcohols are C₁-C₄ alkanols, such as methanol and ethanol. The solids may then be isolated, such as after stirring under ambient conditions, by, for example filtration or drying or both, to yield hydrate Form H di-pidotimod benzathine. Further embodiments include hydrate Form H obtainable by such processes.

[00168] In other embodiments, hydrate Form H may be prepared from amorphous di-pidotimod benzathine. For example, hydrate Form H may be prepared by heating amorphous di-pidotimod benzathine for sufficient time. The preferable temperature range used is from 35°C to 45°C; 7-8 days is the typical time range. In addition, amorphous benzathine di-pidotimod can convert into hydrate Form H when exposed to a humid environment. Typical humidity range is between 60% RH and 75% RH. Further embodiments include hydrate Form H obtainable by such processes.

[00169] Form H di-pidotimod benzathine may be prepared in other embodiments such as by vacuum drying hydrate Form H under sufficient conditions so as to remove substantially all of the water associated with hydrate Form H; typical temperature and time ranges being from 20°C to 25°C and from 15 to 24 hours, respectively. Further embodiments include Form H obtainable by such processes.

[00170] Amorphous di-pidotimod benzathine may be prepared in other embodiments. For example, an aqueous solution of di-pidotimod benzathine is frozen. The resulting frozen sample is then lyophilized to form amorphous di-pidotimod benzathine. Typical temperature and time ranges being from -50°C to -60°C and from 15 to 20 hours, respectively. Further embodiments include amorphous di-pidotimod benzathine obtainable by such processes.

[00171] A limited number of pidotimod salts have been prepared in the literature. Comparative examples 11-14 repeat the preparation of those salts and compare them to di-pidotimod benzathine prepared herein. One such salt, the amantadine salt, as prepared in Example 11, was found to be substantially more unstable than, for example, Form M di-pidotimod benzathine. As Example 13 illustrates, when stressed, the prior art amantadine salt was found to be substantially less stable than Form M. When measured by x-ray powder

diffraction, the amantadine salt underwent a polymorphic change, which was evident at the 2-week data point and was essentially complete at the 4-week time point. By comparison, Form M was stable throughout the entire study under the same conditions. In Example 14, the solubilities of pidotimod, Form M pidotimod benzathine and pidotimod amantadine of the prior art were compared head-to-head. As the data show, in both water and standard simulated biological fluids, Form M was found to be substantially more soluble. Indeed, in SGF, Form M was over 6 times more soluble than the amantadine salt of the prior art. Solubility often plays an important role in preparing an oral dosage form and often more soluble compounds are preferred over less soluble ones.

[00172] In Example 12, four other prior art di-pidotimod salts were prepared based on the literature references. Several different embodiments of these salts were prepared and, without exception, the solids that were isolated all deliquesced either completely or partially under conditions where Form M di-pidotimod benzathine is stable. In one instance, the reproduction did not yield in isolated solid whatsoever calling into question the veracity of the reference.

[00173] In various embodiments, processes for preparing isopropanol solvates are provided. Such processes generally provide for the treating of a solid form of di-pidotimod benzathine with a solvent mixture comprising isopropanol and, often, water. Isolation of the resulting solids then leads to an isopropanol solvate. Partial desolvation of one isopropanol solvate may also lead to the formation of another isopropanol solvate. Examples of such isopropanol solvates include Form J and Form O. Further embodiments include isopropanol solvates obtainable by such processes.

[00174] For example, with respect to processes for making Form J, Form M may be dissolved in a suitable solvent mixture containing isopropanol and recrystallized. Often, such a suitable solvent mixture also comprises water. Crystallization may be by conventional methods such as cooling, for example to about 2°C to yield Form J. Form J may also be prepared by treating Form M with a suitable solvent containing isopropanol until a slurry forms and then isolating the solids by conventional methods such as vacuum filtration to afford Form J. In other embodiments, Form J may be prepared by treating Form H in a solvent

containing isopropanol until a solution forms. Such a solvent mixture usually also contains water. Crystallization by conventional methods such as by hot filtering and cooling and repeating the dissolution crystallization process yields Form J. Further embodiments include Form J obtainable by such processes.

[00175] In other embodiments, processes for making Form O are provided. Such processes include desolvating Form J. In one such embodiment, Form J may be desolvated to afford Form O by placing Form J in an open container under ambient conditions for about 22.5 hours. In other embodiments, Form O may be prepared by treating Form H with a suitable solvent mixture containing isopropanol to form and mixing to form solids in the mixture. Isolation of the solids and drying affords Form O. Form O may be further prepared by treating Form M in an aqueous solvent mixture, such as isopropanol and water, and removing the solvent to yield Form O. The solvent mixture so used often contains water. Further embodiments include Form O obtainable by such processes.

[00176] In other embodiments, processes for preparing ethanol solvates are provided. Such processes generally provide for the treating of a solid form of di-pidotimod benzathine with a solvent mixture comprising ethanol. Isolation of the resulting solids then leads to an ethanol solvate. Pre-treatment of the di-pidotimod benzathine solid with an anhydrous solvent, such as methanol, may also occur. Further embodiments include ethanol solvates obtainable by such processes. Examples of such ethanol solvates include Form S and Form W.

[00177] In further embodiments, processes for making Form S are provided. In one such embodiment, Form M is treated with an anhydrous solvent such as anhydrous methanol followed by the isolation of solids. Such solids are then dried and treated with ethanol to yield, upon isolation Form S. Further embodiments include Form S obtainable by such processes.

[00178] In other embodiments, processes for preparing Form W are provided. For example, x-ray amorphous di-pidotimod benzathine may be exposed to vapor-phase ethanol so as to provide Form W. In other embodiments, Form M is dissolved in a solvent and lyophilized. The lyophilized solid is then exposed to vapor-phase ethanol to afford Form W. The solvent used is often water. The

treatment with vapor-phase ethanol may occur in a closed container. Further embodiments include Form W obtainable by such processes.

[00179] In additional embodiments, processes for preparing Form X are provided. Form X may be prepared by exposing Form W to ambient conditions for sufficient time to convert Form W into Form X. For example, in a closed environment, such conversion may take longer than in an open environment. Further embodiments include Form X obtainable by such processes.

[00180] In still further embodiments, processes for preparing Form T are provided. Form T may be prepared by exposing x-ray amorphous material to vapor-phase acetonitrile and drying the sample. Further embodiments include Form T obtainable by such processes.

[00181] EXAMPLES

[00182] **Example 1** – Solid Form Screen

[00183] An extensive solid form screen was done with di-pidotimod and thirty-one (31) coformers in a total of seventy-three (73) experiments. Only three salt/cocrystal formers were successful in forming salts or co-crystals with di-pidotimod. One such salt/cocrystal former was benzathine which was found to form a 2:1 salt with pidotimod. Crystalline pidotimod free acid was used as an input material for all experiments with salt/cocrystal formers. Crystallizations were attempted with the free acid and the salt/cocrystal formers under numerous crystallization conditions. Resulting solids were all analyzed with x-ray powder diffraction and in some instances other techniques as well.

[00184] **Example 2** – Analytical Techniques used in analyzing di-pidotimod benzathine

[00185] X-ray powder diffraction analysis (XRPD): the data were collected in transmission mode with a PAN analytical X'Pert PRO MPD diffractometer using an incident beam of Cu radiation (1.54059 Å) produced using an Optix long, fine-focus source. An elliptically graded multilayer mirror was used to focus Cu K α X-rays through the specimen and onto the detector. Prior to the analysis, a silicon specimen (NIST SRM 640d) was analyzed to verify the observed position of the Si 111 peak is consistent with the NIST-certified position. A specimen of the sample was sandwiched between 3- μ m-thick films and analyzed in transmission

geometry. A beam-stop, short anti-scatter extension, anti-scatter knife edge, were used to minimize the background generated by air. Soller slits for the incident and diffracted beams were used to minimize broadening from axial divergence. Diffraction patterns were collected using a scanning position-sensitive detector (X'Celerator) located 240 mm from the specimen and Data Collector software v. 2.2b. A scan range of 1.00 to 40.00° 2 θ with a step size of 0.017° 2 θ was used to collect data over a range of 716 to 1947 seconds with a scan speed of 1.2 to 3.3°/minute and a revolution time of 1.0 second. A divergence slit was set at 1/2° before the mirror.

[00186] Light microscopy analysis: images on several samples were collected using a Leica DM LP microscope equipped with a SPOT Insight™ color digital camera. Each sample was placed on a glass slide, a cover glass was placed over the sample, and a drop of mineral oil was added to cover the sample by capillarity. Each sample was observed using a 10x, 20x and 40x objectives with 0.25, 0.40 and 0.75 numerical apertures and with crossed polarizers and a first order red compensator. Images were captured using SPOT software (v. 4.5.9). A micron bar was inserted onto each image as a reference for particle size.

[00187] Differential scanning calorimetric analysis: data were collected using a TA Instruments Q2000 differential scanning calorimeter. Temperature calibration was performed using NIST-traceable indium metal. The sample was placed into a T zero platinum DSC pan, covered with a lid and crimped. The weight was then accurately recorded. A weighed platinum pan configured as the sample pan was placed on the reference side of the cell. The sample was heated from -30 °C to 250 °C at 10 °C/minute.

[00188] Solution proton nuclear magnetic resonance analysis: for figure 7, the spectrum was acquired at ambient temperature with an Agilent DD2-400 spectrometer at a ¹H Larmor frequency of 399.822 MHz. The sample was dissolved in deuterated dimethylsulfoxide containing tetramethylsilane. The spectrum was acquired with a ¹H pulse width of 6.5 μ s, a 5 second acquisition time, a 2.5 second delay between scans, a spectral width of 6410 Hz with 64102 data points, and 40 co-added scans. The free induction decay was processed using Varian VNMR 6.1C software with 131072 points and an exponential line

broadening factor of 0.2 Hz to improve the signal-to-noise ratio. The residual peak from incompletely deuterated solvent is at approximately 2.50 ppm. The spectrum was referenced to internal tetramethylsilane at 0.0 ppm. For Figure 17, the proton solution NMR spectrum was acquired on a Varian ^{UNITY}INOVA-400 spectrometer at a ¹H Larmor frequency of 399,798 MHz. The sample was dissolved in NMR-grade DMSO-d₆. The ¹H NMR spectrum represents 40 co-added transients collected with a 6 msec pulse and a relaxation delay time of 5 seconds. The free induction decay (FID) was exponentially multiplied with a 0.2 Hz Lorentzian line broadening factor to improve the signal-to-noise ratio.

[00189] Solid state ¹³C cross polarization magic angle spinning (CP/MAS) NMR analysis: spectrum was acquired at ambient temperature on an Agilent DD2-400 spectrometer (Larmor frequencies: ¹³C = 100.550 MHz, ¹H = 399.820 MHz). The sample was packed into a 4 mm PENCIL type zirconia rotor and rotated at 12 kHz at the magic angle. The spectrum was acquired with phase modulated (SPINAL-64) high power ¹H decoupling during the acquisition time using a ¹H pulse width of 2.6 μs (90°), a ramped amplitude cross polarization contact time of 5 ms, a 30 ms acquisition time, a 120 second delay between scans, a spectral width of 45 kHz with 2678 data points, and 400 co-added scans. The free induction decay was processed using Varian VNMR 6.1C software with 65536 points and an exponential line broadening factor of 10 Hz to improve the signal-to-noise ratio. The first three data points of the free induction decay were back predicted using the VNMR linear prediction algorithm to produce a flat baseline. The chemical shifts of the spectral peaks were externally referenced to the carbonyl carbon resonance of glycine at 176.5 ppm.

[00190] Infrared spectra analysis: data were acquired on Nicolet FTIR 6700 Fourier transform infrared spectrophotometer (Thermo Nicolet) equipped with an Ever-Glo mid/far IR source, a potassium bromide beamsplitter, and a deuterated triglycine sulfate detector. Wavelength verification was performed using NIST SRM 1921b (polystyrene). An attenuated total reflectance accessory (Thunderdome™, Thermo Spectra-Tech), with a germanium (Ge) crystal was used for data acquisition. Each spectrum represents 256 co-added scans collected at a spectral resolution of 4 cm⁻¹. A background data set was acquired with a clean

Ge crystal. A Log 1/R (R = reflectance) spectrum was obtained by taking a ratio of these two data sets against each other.

[00191] Fourier Transform Raman analysis: The FT Raman spectrum was acquired on a FT-Raman 960 spectrometer (Thermo Nicolet) equipped with an indium gallium arsenide (InGaAs) detector. Wavelength verification was performed using sulfur and cyclohexane. Each sample was prepared for analysis by preparing a pellet using a pellet press and placing in a pellet holder. Approximately 1.002 W of Nd:YVO₄ laser power (1064 nm excitation wavelength) was used to irradiate the sample. Each spectrum represents 256 co-added scans collected at a spectral resolution of 4 cm⁻¹.

[00192] Indexing of XRPD patterns of Form M di-pidotimod benzathine and hydrate Form H di-pidotimod benzathine was done using X'Pert High Score Plus 2.2a (2.2.1). The XRPD pattern of Form H di-pidotimod benzathine was indexed by refining previously obtained unit cell parameters with Checkcell. Space groups consistent with the assigned extinction symbol, unit cell parameters, and derived quantities are tabulated in the respective figures providing the indexing solution for each form.

[00193] Modulated differential scanning calorimetric analysis: data were collected using a TA Instruments Q2000 differential scanning calorimeter equipped with a refrigerated cooling system (RCS). Temperature calibration was performed using NIST-traceable indium metal. The sample was placed into an aluminum DSC pan, and the weight was accurately recorded. The pan was covered with a lid perforated with a laser pinhole, and the lid was hermetically sealed. A weighed, crimped aluminum pan was placed on the reference side of the cell. Data were obtained using a modulation amplitude of ± 1 °C and a 60 second period with an underlying heating rate of 2 °C/minute from 50 to 220 °C. The reported glass transition temperature is obtained from the inflection point of the step change in the reversing heat flow versus temperature curve.

[00194] **Example 3-** Di-pidotimod benzathine salification process-method 1.

[00195] A solution of N,N-dibenzylethylenediamine (0.5 molar equivalent) in dimethylformamide was added to a solution of pidotimod in dimethylformamide at 80°C and stirred for 30 minutes.

[00196] **Example 4-** Di-pidotimod benzathine salification process-method 2.

[00197] N,N'-dibenzylethylamine (0.5 molar equivalent) was added to a solution of pidotimod in dimethylformamide and methanol (30/70 vol/vol) at 55°C.

[00198] **Example 5-**Di-pidotimod benzathine salification process method 3

[00199] N,N-dibenzylethylenediamine (0.5 molar equivalent) and pidotimod were added to water followed by sonication at room temperature.

[00200] **Example 6-**Preparation of di-pidotimod benzathine salt Form M seeds.

[00201] Di-pidotimod benzathine hydrate Form H (795.1 mg) of Example 26 and ethyl acetate (8 ml) was stirred in an oil bath at approximately 45 °C for 3 days. Solids were isolated by vacuum filtration and then vacuum dried at approximately 40 °C for 1 day. Solids were analyzed by XRPD and resulted in Form M.

[00202] **Example 7 -** Preparation of di-pidotimod benzathine Form M – method 1

[00203] A slurry of di-pidotimod benzathine salt Form M seeds in ethyl acetate was added to a solution of di-pidotimod benzathine previously prepared as described in Example 3. The slurry was stirred for 1 hour then cooled to 70 °C and ethyl acetate was added over approximately 6 hours. The slurry was stirred for 1 hour then cooled to 0 °C and then held stirring for 12 hours before discharging for filtration. The filter cake was washed with ethyl acetate then dried under vacuum at 40 °C for 3 days. (Yield: 80% mol/mol). X-ray powder diffractograms of materials prepared by this method 1 are represented in Figures 1 and 2. A differential scanning calorimetry thermogram of Form M di-pidotimod benzathine is represented in Figure 3. A raman spectrum of Form M di-pidotimod benzathine is represented in Figure 4. A ¹³C solid-state NMR spectrum of Form M di-pidotimod benzathine is represented in Figure 5. An infrared spectrum of Form M di-pidotimod benzathine is represented in Figure 6. A ¹H solution-state NMR spectrum of Form M di-pidotimod benzathine is represented in Figure 7. An indexing solution of Form M di-pidotimod benzathine is represented in Figure 8.

[00204] **Example 8 -** Preparation of di-pidotimod benzathine Form M – method 2

[00205] A solution of di-pidotimod benzathine previously prepared as described in Example 4, was slowly cooled to ambient temperature and the resulting solid was vacuum dried in the oven at ambient temperature to give Form H. Form H was then slurred in anisole for 3 days at room temperature and then for further 4 days at 50°C. The slurry was cooled down to room temperature and the solid filtered and dried under vacuum at 40°C to constant weight. (Yield: 87% mol/mol). Refer to the figures associated with Example 7 for the analytical characterization of di-pidotimod benzathine Form M obtained by this method 2.

[00206] **Example 9** - Preparation of di-Pidotimod Benzathine Form M – method 3

[00207] A solution of di-pidotimod benzathine, previously prepared as described in Example 4, was slowly cooled to ambient temperature and the resulting solid was vacuum dried in the oven at ambient temperature to give Form H. Form H was then slurred in ethyl acetate for 4 days at room temperature and then for further 3 days at 40°C. The slurry was cooled down to room temperature and the solid filtered and dried under vacuum at room temperature for 2 hours. (Yield: 85% mol/mol). Refer to the figures associated with Example 7 for the analytical characterization of di-pidotimod benzathine Form M obtained by this method 3.

[00208] **Example 10** – Preparation of hydrated Form H

[00209] A solution of di-pidotimod benzathine, previously prepared as described in Example 4, was slowly cooled to ambient temperature and white solids precipitated. The slurry was held stirring at ambient temperature for approximately 4 hours. The solids were then isolated by vacuum filtration and air-dried. An X-ray powder diffractogram of hydrated Form H di-pidotimod benzathine is represented in Figure 9. An infrared spectrum of hydrated Form H di-pidotimod benzathine is represented in Figure 10. An indexing solution for hydrated Form H di-pidotimod benzathine is represented in Figure 15.

[00210] **Example 11** – Preparation of Form H and conversion to hydrated Form H

[00211] Hydrated Form H (from Example 6) (~4 g) was placed in a crystallization dish. The dish was covered with porous paper secured with an

elastic band. The covered dish was placed inside a vacuum oven at ambient temperature overnight. XRPD analysis resulted in Form H. The sample was left under ambient conditions for 11 months and then re-analyzed and found to be hydrated Form H by x-ray powder diffraction. X-ray powder diffractograms of Form H di-pidotimod benzathine is represented in Figures 11. Indexing solution for Form H di-pidotimod benzathine is represented in Figure 16. ¹H solution-state NMR spectrum of Form H di-pidotimod Benzathine is represented in Figure 17.

[00212] Example 12 – Preparations of hydrated Form H from amorphous di-pidotimod benzathine

[00213] Preparation 1

[00214] Di-pidotimod benzathine X-ray amorphous material (49.7 mg) was placed in a glass vial. The vial was covered with porous paper secured with an elastic band. The covered dish was placed inside an oven at approximately 60 °C for 8 days. XRPD analysis resulted in hydrated Form H.

[00215] Preparation 2

[00216] Di-pidotimod benzathine X-ray amorphous material (48.7 mg) was placed in a glass vial. The vial was placed uncapped inside a relative humidity chamber (~75% RH). The chamber was placed inside an oven at approximately 40 °C. After 8 days, the solids were analyzed by XRPD and resulted in hydrated Form H.

[00217] Preparation 3

[00218] Di-pidotimod benzathine X-ray amorphous material (49.7 mg) was placed in a glass vial. The vial was placed uncapped inside a larger vial containing heptane (~10 ml). The larger vial was capped to allow vapor stressing to occur. After 8 days, the solids were isolated and resulted in hydrated Form H by XRPD.

[00219] Example 13 – Preparation of X-ray amorphous di-pidotimod benzathine

[00220] Pidotimod (499.7 mg) and 0.5 molar equivalents of benzathine (254.1 mg) were dissolved in water with sonication. The solution was frozen in a thin layer on the walls of a round bottom flask by manual swirling in a bath of dry ice and isopropanol. The sample was then placed on a lyophilizer with a cold finger

at approximately -50 °C for approximately 17 hours. Solids were isolated and XRPD analysis resulted in X-ray amorphous material as represented in Figure 12. A modulated differential scanning calorimetry thermogram of amorphous di-pidotimod benzathine is represented in Figure 13. An infrared spectrum of amorphous di-pidotimod benzathine is represented in Figure 14.

[00221] **Example 14** – Preparation of Pidotimod

[00222] Pidotimod was prepared following Example 1 of EP0422566 A1.

[00223] **Comparative Example 15** – Preparation of Pidotimod Amantadine

[00224] Pidotimod Amantadine salt was prepared following CN101768157A.

[00225] **Comparative Example 16** – Preparation of other Pidotimod salts

[00226] Several additional pidotimod salts were prepared. The patent references listed below provided the bases for performing the experiment. In many cases it was not possible to follow the examples. For example, in six of the preparations (CN101768156A Embodiment 2, CN1680427 Embodiment 3, CN102100664A Embodiment 2, CN101411684A Embodiment 5, CN1014235816A Embodiment 2, and CN101766603 Embodiment 3) the slurries formed using the listed counterion did not dissolve into ethanol despite the teachings of the respective patent reference. After preparation, each material was isolated, submitted to an accelerated stability program as indicated with the results below. Note “RH” means relative humidity and “RT” is room temperature.

[00227]

Counterion	Patent Reference	Physical Stability
L-Arginine	CN1680427A Embodiment 1	Deliquesced: 40% RH, RT
	CN101768156A Embodiment 1	Deliquesced: 57% RH, 41 °C
	CN101768156A Embodiment 2	No salt formation occurred
L-Lysine	CN1680427A Embodiment 2	Deliquesced: 40% RH, RT
Meglumine	CN1680427A	Deliquesced: 57% RH, 41

	Embodiment 3	°C
Potassium	CN102100664A Embodiment 2	Deliquesced: 40% RH, RT
	CN102101881A Embodiment 1	Deliquesced: 30% RH, RT
	CN102101881A Embodiment 2	Partial deliquescence: 52% RH, RT
Sodium	CN101411684A Embodiment 5	Partial deliquescence: 57% RH, 41 °C
	CN101766603A Embodiment 3	Partial deliquescence: 57% RH, 41 °C
	CN1014235816A Embodiment 2	Partial deliquescence: 57% RH, 41 °C

[00228] Comparative Example 17 –

[00229] The physical stability of di-pidotimod benzathine Form M prepared in accordance with Example 3 was compared with Pidotimod amantadine prepared in accordance with Example 11 by exposing a sample of each to 60 °C for 4 weeks. The samples were analyzed at 0, 2 and 4 week time points by x-ray powder diffraction. Form M showed no degradation by x-ray during the course of the entire experiment. By comparison, pidotimod amantadine showed significant degradation towards a different crystalline form after only 2 weeks and after 4 weeks had converted completely to a different crystalline form.

[00230] Comparative Example 18 –

[00231] The solubilities of Pidotimod, Form M di-pidotimod benzathine (Example 5), and pidotimod amantadine (Example 11) were compared in three different solvent systems at ambient temperature: water and two bio-relevant media, Simulated Gastric Fluid (SGF) and Fed State Simulated Intestinal Fluid (FeSSIF). The obtained results are reported in the following table.

Input Material	Solvent	Solubility (mg/mL)
Pidotimod	FeSSIF	73

	SGF	35
	Water	41
di-Pidotimod Benzathine	FeSSIF	1707
	SGF	2769
	Water	755
Pidotimod Amantadine Material A	FeSSIF	410
	SGF	450
	Water	355

[00232] In all cases, Form M di-pidotimod benzathine was found to be significantly more soluble.

[00233] Comparative Example 19

[00234] The preparation process of a topical solution of pidotimod and Form M di-pidotimod benzathine (Example 5), were compared in terms of time and steps number required to obtain a clear solution.

[00235] The compositions of the liquid formulations obtained with Pidotimod and Pidotimod form M are reported in the following table, in weigh %:

	Batch #	P-14-213	P-14-212
	Ingredient	g/100ml (%w/v)	
1	Purified Water	70	70
2	Disodium Edta Ph.Eur.Bp,Us	0.05	0.05
3	Pidotimod	--	5.00
3A	Pidotimod Form M	7.5	
4	Tromethamine 20% Water Solution	--	12.70
5	Purified Water	q.s. to 100 ml	q.s. to 100 ml

[00236] In a first step, the formulations were prepared by mixing the ingredients 1 to 3 (in the case of batch P-14-212) or 1 to 3A (in the case of batch P-14-213) using a suitable closed vessel provided with a stirrer. The resulting mixture was stirred for 60 minutes at room temperature. After that period, the formulations containing Pidotimod (batch P-14-212) resulted to be opalescent and to have undissolved particulate matters whilst the formulations containing

Form M di-pidotimod benzathine (prepared as per Example 5 and included in the formulation batch P-14-213) resulted to be clear and free from particulate matters.

[00237] To dissolve the particulate matters present in the formulation containing Pidotimod, a second step was used involving the addition of a basic neutralizing agent, (tromethamine 20% water solution, ingredient 4) such said second step taking about 30 minutes.

[00238] Thus, the liquid topical formulations prepared using Form M di-pidotimod benzathine (prepared as per Example 5 and included in the formulation batch P-14-213) permits to realize a more economical, less time consuming, environment friendly production process.

[00239] Example 20

[00240] A granulate for oral administration having the following w/w % composition was prepared:

1. Form M di-pidotimod benzathine (Example 5)	
26.67%	
2. Mannitol	3.33%
3. Polyvinylpyrrolidone	0.10%
4. Sodium saccharin	0.60%
5. Methacrylic acid copolymer	0.15%
6. Ethylcellulose	0.80%
7. Orange flavor	
16.67%	
8. Sodium carbonate anhydrous	5.67%
9. Silicon dioxide	0.33%
10. Coloring agents	0.04%
11. Saccharose	q.s. to
100%	

[00241] In a vessel, polyvinylpyrrolidone, methacrylic acid copolymer and ethylcellulose were dissolved in a suitable quantity of water and mixed until a clear solution resulted (solution A). In another vessel, Form M di-pidotimod benzathine and mannitol were combined. Solution A was sprayed onto the Form M di-pidotimod benzathine/mannitol mixture to form homogeneous granulates

and dried. The remaining components were added to the obtained granulate and then mixed to homogeneity.

[00242] Example 21

[00243] A tablet for oral administration having the following w/w % composition was prepared:

1. Form M di-pidotimod benzathine (Example 5)

72.70%

2. Mannitol

17.65%

3. Sodium Carboxymethyl cellulose crosslinked 4.55%

4. Ethylcellulose 4.00%

5. Magnesium stearate 1.10%

[00244] An aqueous solution of ethylcellulose was sprayed onto a mixture of Form M di-pidotimod benzathine and diluents to form a homogeneous granulate. After drying, sodium carboxymethyl cellulose (cross-linked) and magnesium stearate were added and mixed to homogeneity. The mixture was then compressed with a tableting machine to make tablets.

[00245] Example 22

[00246] An oil in water cream having the following w/w % composition was prepared:

1. Form M di-pidotimod benzathine (Example 5)

10.00%

2. Lactic Acid 0.20%

3. Disodium EDTA 0.10%

4. Glycerin 7.00%

5. Xanthan Gum 0.25%

6. Hydroxypropyl Chitosan 0.30%

7. Paraffinum Liquidum 2.00%

8. Petrolatum 8.00%

9. Octyldodecanol 3.50%

10. Cetearyl alcohol 2.00%

11. Glyceryl Stearate 3.00%

12.	Polyoxyl-20 Cetostearyl Ether	1.50%
13.	Dl-alfa Tocopheryl Acetate	0.002%
14.	Cyclomethicone	3.00%
15.	Sodium Benzoate	0.20%
16.	Potassium Sorbate	0.15%
17.	Purified Water	q.s. to 100.00%

[00247] Components 1, 2, 3, 4, and 5 were combined with water to form a suspension. Additional xanthan gum was added and dispersed to achieve a homogeneous mixture. Component 6 was solubilized in water and then stirred into the mixture. The mixture was heated to about 70°C - 75°C. A separate mixture (Mixture 2) was prepared by combining components 7, 8, 9, 10, 11, 12, 13 and 14 at about 70°C - 75°C. The two mixtures were combined and heated to about 60°C and homogenized for about 10 minutes. The resulting mixture was cooled to about 40°C, preservatives (component 15 and 16) were added, the mixture homogenized, water was added which was followed by another homogenization. The resulting mixture was cooled to room temperature while stirring to form an oil-in-water cream.

[00248] Example 23

[00249] A topical gel formulation having the following w/w % composition was prepared:

1.	Water	50.00%
2.	Form M di-pidotimod benzathine (Example 5)	10.00%
3.	Disodium EDTA	0.10%
4.	Glycerin	5.00%
5.	Allantoin	0.150%
6.	Hydroxyethylcellulose	1.50%
7.	Hydroxypropyl Chitosan	0.50%

8.	Sodium Hyaluronate	0.15%
9.	Sodium Methylparaben	0.30%
10.	Sodium Propylparaben	0.05%
11.	Purified water	q.s to 100.00%

[00250] Components 1, 2, 3, 4, 5, 8, 9 and 10 were combined and mixed until homogeneity was obtained. Component 6 was added while homogenizing. Separately, component 7 was solubilized in part of water and added it in the main vessel while stirring. Component 11 was added to the obtained mixture and the mixing process continued until homogeneity and gel formation.

[00251] Analytical Techniques used in analyzing di-pidotimod benzathine

[00252] X-ray powder diffraction analysis (XRPD) data were collected in transmission mode with a PAN analytical X'Pert PRO MPD diffractometer using an incident beam of Cu radiation (1.54059 Å) produced using an Optix long, fine-focus source. An elliptically graded multilayer mirror was used to focus Cu K α X-rays through the specimen and onto the detector. Prior to the analysis, a silicon specimen (NIST SRM 640d) was analyzed to verify the observed position of the Si 111 peak is consistent with the NIST-certified position. A specimen of the sample was sandwiched between 3- μ m-thick films and analyzed in transmission geometry. A beam-stop, short anti-scatter extension, anti-scatter knife edge, were used to minimize the background generated by air. Soller slits for the incident and diffracted beams were used to minimize broadening from axial divergence. Diffraction patterns were collected using a scanning position-sensitive detector (X'Celerator) located 240 mm from the specimen and Data Collector software v. 2.2b. A scan range of 1.00°2 θ to 39.98 or 39.99°2 θ with a step size of 0.017°2 θ was used to collect data over a range of 716 to 720 seconds with a scan speed of 3.2 to 3.3°/minute and a revolution time of 1.0 second. A divergence slit was set at 1/2° before the mirror.

[00253] Differential scanning calorimetric analysis data were collected using a TA Instruments Q2000 differential scanning calorimeter. Temperature calibration was performed using NIST-traceable indium metal. The sample was placed into a T zero aluminum DSC pan, covered with a lid and crimped. The weight was then

accurately recorded. A weighed aluminum pan configured as the sample pan was placed on the reference side of the cell. The sample was heated from -30°C to 250°C at $10^{\circ}\text{C}/\text{minute}$.

[00254] Other than for Form W (Example 36), solution proton nuclear magnetic resonance analysis: the spectra were acquired at ambient temperature with an Agilent DD2-400 spectrometer at a ^1H Larmor frequency of 399.822 MHz. The sample was dissolved in deuterated dimethylsulfoxide containing tetramethylsilane. The spectrum was acquired with ^1H pulse widths of 5.7 or 6.7 μs , a 2.5 second delay between scans, spectral widths of 6377.6 or 6410.3 with 63776 or 64102 data points, and 40 co-added scans. The free induction decay was processed using Varian VNMR 6.1C software with 131072 points and an exponential line broadening factor of 0.2 Hz to improve the signal-to-noise ratio. The residual peak from incompletely deuterated solvent is at approximately 2.50 ppm. The spectrum was referenced to internal tetramethylsilane at 0.0 ppm.

[00255] For Form W (Example 36), the spectrum was acquired on a Varian UNITYINOVA-400 spectrometer at a ^1H Larmor frequency of 399,798 MHz. The sample was dissolved in NMR-grade DMSO- d_6 . The ^1H NMR spectrum represents 40 co-added transients collected with a 7 msec pulse and a relaxation delay time of 6 seconds. The free induction decay (FID) was exponentially multiplied with a 0.2 Hz Lorentzian line broadening factor to improve the signal-to-noise ratio.

[00256] Infrared spectra analysis data were acquired on Nicolet FTIR 6700 Fourier transform infrared spectrophotometer (Thermo Nicolet) equipped with an Ever-Glo mid/far IR source, a potassium bromide beamsplitter, and a deuterated triglycine sulfate detector. Wavelength verification was performed using NIST SRM 1921b (polystyrene). An attenuated total reflectance accessory (ThunderdomeTM, Thermo Spectra-Tech), with a germanium (Ge) crystal was used for data acquisition. Each spectrum represents 256 co-added scans collected at a spectral resolution of 4 cm^{-1} . A background data set was acquired with a clean Ge crystal. A $\text{Log } 1/R$ (R = reflectance) spectrum was obtained by taking a ratio of these two data sets against each other.

[00257] Indexing of XRPD patterns of di-pidotimod benzathine was done using X'Pert High Score Plus 2.2a (2.2.1) or propriety SSCI software TRIADS™ (covered by United States Patent No. 8,576,985). Space groups consistent with the assigned extinction symbol, unit cell parameters, and derived quantities are tabulated in the respective figures providing the indexing solution for each form.

[00258] Coulometric Karl Fischer analysis data were collected using a Mettler Toledo DL39 Karl Fischer titrator with a Stromboli oven attachment. Two replicates of the sample were placed into the drying oven set at a temperature of approximately 170 °C. The drying oven was purged into the titrator vessel with dry nitrogen. The samples were then titrated by means of a generator electrode, which produces iodine by electrochemical oxidation: $2\text{I}^- \rightarrow \text{I}_2 + 2\text{e}^-$. A NIST-traceable water standard (Hydranal Water Standard 10.0) was analyzed to check the operation of the coulometer.

[00259] Thermogravimetric analysis (TGA) data were collected using a TA Instruments 2050 thermogravimetric analyzer. Temperature calibration was performed using nickel and Alumel™. Each sample was placed in a platinum pan and inserted into the TG furnace. The furnace was heated under a nitrogen purge. The sample was heated from ambient to 350 °C at 10°C/minute.

[00260] **Example 24** – Preparation of Form M

[00261] A solution of N,N'-dibenzylethylenediamine (0.5 molar equivalent) in dimethylformamide was added to a solution of Pidotimod in dimethylformamide at 80 °C then stirred for 30 minutes before a slurry of Form M seeds from Example 6 in ethyl acetate was added. The slurry was stirred for 1 hour then cooled to 70 °C and ethyl acetate was added over approximately 8 hours. The slurry was stirred for 1 hour then cooled to 0 °C at a rate of 0.2 °C/minute and then held stirring for 12 hours before discharging for filtration. The filter cake was washed with ethyl acetate then dried under vacuum at 40 °C for 2 days. The structure was verified by x-ray powder diffraction.

[00262] **Example 25** – Preparation of Form H

[00263] Form H (~4 g) from Example 26 was placed in a crystallization dish. The dish was covered with porous paper secured with an elastic band. The

covered dish was placed inside a vacuum oven at ambient temperature overnight. XRPD analysis resulted in Form H with peak shifting.

[00264] Example 26 – Preparation of hydrated Form H

[00265] Pidotimod (4.0169 g) was dissolved in dimethylformamide/methanol (30/70 vol/vol) (50 ml) at approximately 55 °C. 0.5 molar equivalents of benzathine were added (1.93 ml). The solution was slowly cooled to ambient temperature, and white solids precipitated. The slurry was held stirring at ambient temperature for approximately 4 hours. The solids were then isolated by vacuum filtration and air dried. XRPD analysis resulted in hydrated Form H.

[00266] Example 27 - Preparation of di-pidotimod benzathine Form J – method 1

[00267] Di-pidotimod benzathine Form M (299.0 mg) from Example 24 was dissolved in isopropanol/water (90/10 v/v) (2 ml) at 50°C while stirring. The solution was filtered hot through a 0.2 µm nylon filter into a pre-warmed vial. The clear solution was cooled quickly to 2°C. A thick slurry resulted and solids were collected by vacuum filtration. X-ray powder diffraction indicated the material was composed of di-Pidotimod Benzathine Form J. X-ray powder diffractograms of materials prepared by this method 1 are represented in Figure 18. A differential scanning calorimetry thermogram of Form J di-pidotimod benzathine is represented in Figure 19. ¹H solution-state NMR spectrum of Form J di-pidotimod benzathine is represented in Figure 21. The indexing solution of Form J di-pidotimod benzathine is represented in Figure 22. A thermogravimetric analysis thermogram of Form J is represented in Figure 43.

[00268] Example 28 - Preparation of di-pidotimod benzathine Form J – method 2

[00269] Di-pidotimod benzathine Form M (375.2 mg) from Example 24 was stirred at ambient temperature in isopropanol/water (90/10 v/v) (2 ml). After two days of stirring, a thick slurry resulted. Additional isopropanol/water (90/10 v/v) (1 ml) was added and stirring continued at ambient temperature. After four additional days of stirring, solids were isolated by vacuum filtration. X-ray powder diffraction indicated the material was composed of di-pidotimod

benzathine Form J. An infrared spectrum of the Form J so made is in Figure 20. The structure was further verified by x-ray powder diffraction.

[00270] Example 29 - Preparation of di-pidotimod benzathine Form J – method 3

[00271] Di-pidotimod benzathine Form H with peak shifting (dried material) (113.1 mg) from Example 25 was dissolved with stirring in isopropanol/water (90/10 v/v) (3 ml) at approximately 55°C. The solution was filtered hot through a 0.2 µm filter into a pre-warmed vial. The vial was immediately placed in an isopropanol/ice bath. Solids were observed after approximately 2 minutes, but re-dissolved upon reaching ambient temperature. The sample was further stirred at 2 - 8°C for approximately 1 day. Solids were isolated and analyzed by x-ray powder diffraction. Di-pidotimod benzathine Form J resulted as determined by x-ray powder diffraction.

[00272] Example 30 - Preparation of di-pidotimod benzathine Form O – method 1

[00273] Di-pidotimod benzathine Form J of Example 27 was placed in an open vial under ambient conditions for approximately 22.5 hours. X-ray powder diffraction analysis indicated the material was composed of di-pidotimod benzathine Form O. X-ray powder diffractograms of materials prepared by this method 1 are represented in Figure 23. A differential scanning calorimetry thermogram of Form O di-pidotimod benzathine is represented in Figure 24. An infrared spectrum of Form O di-pidotimod benzathine is represented in Figure 25. A ¹H solution-state NMR spectrum of Form O di-pidotimod benzathine is represented in Figure 26. A thermogravimetric analysis thermogram of Form O is represented in Figures 44a and 44b.

[00274] Example 31 - Preparation of di-pidotimod benzathine Form O – method 2

[00275] Di-pidotimod benzathine Form H with peak shifting (dried material) (80.1 mg) of Example 25 was added to isopropanol/water (90/10 v/v) (0.5 ml). The mixture was stirred at ambient temperature for 14 days. The solids were isolated by decanting the solvent and allowing the solids to air dry under nitrogen gas for approximately 1 hour. X-ray powder diffraction indicated the material

was composed of di-pidotimod benzathine Form O. X-ray powder diffraction was used to confirm structure.

[00276] Example 31A – Preparation of di-pidotimod benzathine Form O – method 3

[00277] Di-pidotimod benzathine Form M (499.8 mg) made according to Example 24 was stirred at ambient temperature in isopropanol/water (90/10 v/v) (4 ml). After six days of stirring, the mother liquor was decanted and a portion of the solids (87.2 mg) was placed in a vial and loosely capped. The vial was placed inside a box with a continuous nitrogen flow. After one day, the solids were analyzed by X-ray powder diffraction. The solids were composed of di-pidotimod benzathine Form O.

[00278] **Example 32** – Preparation of di-pidotimod benzathine Form S – method 1

[00279] Di-pidotimod benzathine Form M (552.9 mg) from Example 24 and anhydrous methanol (~5 ml) was stirred at ambient temperature for 12 days. Solids were isolated by vacuum filtration and dried under vacuum at 65°C for 2 days. A portion of the dried solids (202.8 mg) were added to ethanol (6.4 ml), and the mixture was stirred at ambient temperature for 4 days. Solids were isolated by vacuum filtration. Structure was confirmed by x-ray powder diffraction.

[00280] **Example 33** – Preparation of di-pidotimod benzathine Form S – method 2

[00281] Di-pidotimod benzathine Form M (552.9 mg) from Example 24 and anhydrous methanol (~5 ml) was stirred at ambient temperature for 12 days. Solids were isolated by vacuum filtration and dried under vacuum at 65°C for 2 days. A portion of the dried solids (127.4 mg) were added to ethanol (2.1 ml), and the mixture was stirred at ambient temperature for 1 day. Solids were isolated by vacuum filtration. X-ray powder diffraction indicated the material was composed of di-pidotimod benzathine Form S.

[00282] **Example 34** – Preparation of di-pidotimod benzathine Form S – method 3

[00283] Di-pidotimod benzathine Form S of Example 32 was placed in a vial. The vial was left uncapped and placed inside a box with a nitrogen gas flow.

After approximately 1 hour, solids were removed and analyzed by x-ray powder diffraction. X-ray powder diffraction indicated the material was composed of di-pidotimod benzathine Form S. X-ray powder diffractograms of materials prepared by this method 1 are represented in Figure 27. A differential scanning calorimetry thermogram of Form S di-pidotimod benzathine is represented in Figure 28. An infrared spectrum of Form S di-pidotimod benzathine is represented in Figure 29. A ^1H solution-state NMR spectrum of Form S di-pidotimod benzathine is represented in Figure 30. A thermogravimetric analysis thermogram of Form S is represented in Figure 45. An indexing solution of Form S is represented in Figure 49.

[00284] Example 35 - Preparation of di-pidotimod benzathine Form W – method 1

[00285] Di-pidotimod benzathine x-ray amorphous material (111.26 mg) of Example 13 was placed inside a 1-dram vial. The 1-dram vial was placed uncapped inside a larger, 20 ml, vial containing ethanol (4 ml). The larger vial was capped and left under ambient conditions. After 12 days, the 1-dram vial containing the sample was removed from the larger vial. X-ray powder diffraction indicated the material was composed of di-pidotimod benzathine Form W.

[00286] Example 36 - Preparation of di-pidotimod benzathine Form W – method 2

[00287] Form M (185.67 mg) from Example 24 was dissolved in water (10 ml), and the solution was filtered through a 0.2 μm nylon filter. The solution was frozen in a thin layer on the walls of a round bottom flask by manual swirling in a bath of dry ice and acetone. The sample was then placed on a lyophilizer with a cold finger at approximately -50°C and lyophilized for approximately 1 day. The material (108.3 mg) was placed inside a 1-dram vial. The 1-dram vial was placed uncapped inside a larger, 20 ml, vial containing ethanol (~5 ml). The larger vial was capped and left under ambient conditions. After 13 days, the 1-dram vial containing the sample was removed from the larger vial. X-ray powder diffraction indicated the material was composed of di-Pidotimod Benzathine Form W. X-ray powder diffractograms of materials prepared by this method 1 are

represented in Figure 31. A differential scanning calorimetry thermogram of Form W di-pidotimod benzathine is represented in Figure 32. An infrared spectrum of Form W di-pidotimod benzathine is represented in Figure 33. A ^1H solution-state NMR spectrum of Form W di-pidotimod benzathine is represented in Figure 34. A thermogravimetric analysis thermogram of Form W is represented in Figure 46.

[00288] Example 37 - Preparation of di-pidotimod benzathine Form W – method 3

[00289] Form M (598.4 mg) from Example 24 was dissolved in water (20 ml), and the solution was filtered through a 0.2 μm nylon filter. The solution was frozen in a thin layer on the walls of a round bottom flask by manual swirling in a bath of dry ice and acetone. The sample was then placed on a lyophilizer with a cold finger at approximately -50°C and lyophilized for approximately 2 days. The material (~600 mg) was placed inside a 20 ml vial. The 20 ml vial was placed uncapped inside a larger vial containing ethanol (~30 ml). The larger vial was capped and left under ambient conditions. After 4 days, the 20 ml vial containing the sample was removed from the larger vial. X-ray powder diffraction indicated the material was composed of di-Pidotimod Benzathine Form W.

[00290] Example 38 - Preparation of di-pidotimod benzathine Form X – method 1

[00291] Di-pidotimod benzathine Form W (111.26 mg) of Example 13 was placed inside a vial. The vial was capped and left under ambient conditions for 15 days. X-ray powder diffraction indicated the material was composed of di-pidotimod benzathine Form X. X-ray powder diffractograms of materials prepared by this method 1 are represented in Figure 35. A differential scanning calorimetry thermogram of Form X di-pidotimod benzathine is represented in Figure 36. An infrared spectrum of Form X di-pidotimod benzathine is represented in Figure 37. A ^1H solution-state NMR spectrum of Form X di-pidotimod benzathine is represented in Figure 38. A thermogravimetric analysis thermogram of Form X is represented in Figure 47. An indexing solution is represented in Figure 50.

[00292] Example 39 - Preparation of di-pidotimod benzathine Form X – method 2

[00293] Di-pidotimod benzathine Form W of Example 37 was placed inside a vial. The vial was uncapped and left under ambient temperature and ambient humidity (approximately 40 to 44%) for 3 days. X-ray powder diffraction indicated the material was composed of di-pidotimod benzathine Form X and also contained approximately 20% Form H.

[00294] **Example 40** - Preparation of di-pidotimod benzathine Form T

[00295] Di-pidotimod benzathine x-ray amorphous material (154.94 mg) of Example 13 was placed inside a 20 ml vial. The 20 ml vial was placed uncapped inside a larger glass vial containing acetonitrile (~30 ml). The larger vial was capped and left under ambient conditions. After 9 days, the 20 ml vial containing the sample was removed from the larger vial. The vial was capped with perforated aluminum foil and placed in a vacuum oven at 64 - 65°C for 10 days. Solids were stored in a closed vial and the vial was placed in a bag containing desiccant for 15 days. The sample was additionally dried under vacuum at 64°C for 3 days. The x-ray powder diffraction was consistent with di-pidotimod benzathine Form T. X-ray powder diffractograms of material prepared by this method are represented in Figure 39. A differential scanning calorimetry thermogram of Form T di-pidotimod benzathine is represented in Figure 40. An infrared spectrum of Form T di-pidotimod benzathine is represented in Figure 41. A ¹H solution-state NMR spectrum of Form T di-pidotimod benzathine is represented in Figure 42. A thermogravimetric analysis thermogram of Form T is represented in Figure 48.

[00296] All examples presented are representative and non-limiting. The above-described embodiments may be modified or varied, without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described.

CLAIMS

1. Di-pidotimod benzathine.
2. A solid form of di-pidotimod benzathine.
3. Crystalline di-pidotimod benzathine.
4. Form M of di-pidotimod benzathine characterized by an x-ray powder diffraction pattern comprising a peak at about $7.6^{\circ}2\Theta$ and/or at about $19.6^{\circ}2\Theta$, optionally further comprising one or more peaks at about 11.7, 12.9, 18.4, 20.4, or $21.1^{\circ}2\Theta$.
5. Form M of di-pidotimod benzathine characterized by an endotherm having an onset temperature at about 172°C and/or by a Raman spectrum comprising one or more peaks at about 778, 1004, 1217, 1611, 2948, or 3075 cm^{-1} and/or by a ^{13}C solid-state nuclear magnetic resonance spectrum comprising one or peaks at about 24.5, 29.7, 34.8, 46.1, 64.4, 168.6, 179.5, or 181.2 ppm and/or by an infrared spectrum comprising one or more peaks at about 696, 742, 1257, 1277, 1557, 1633, 1666, or 1697 cm^{-1} .
6. Form M of di-pidotimod benzathine characterized by an x-ray powder diffraction pattern substantially the same as that in Figure 1 and/or Figure 2 and/or by a Raman spectrum substantially the same as that in Figure 4 and/or by a ^{13}C solid-state nuclear magnetic resonance spectrum from about 20 ppm to 190 ppm substantially the same as that in Figure 5 and/or by an infrared spectrum substantially the same as that in Figure 6.
7. Hydrated Form H of di-pidotimod benzathine characterized by an x-ray powder diffraction pattern having peaks at about 7.2 and/or $4.5^{\circ}2\Theta$, optionally further comprising one or more peaks at about 5.5, 9.0, or $18.7^{\circ}2\Theta$.
8. Hydrated Form H of di-pidotimod benzathine characterized by an infrared spectrum having one or more peaks at about 1389, 1609, 1649, or 1717 cm^{-1} and/or by an x-ray powder diffraction pattern having substantially the same x-ray powder diffraction pattern as that of Figure 9 and/or by an infrared spectrum having substantially the same infrared spectrum as that of Figure 10.

9. Hydrated Form H of di-pidotimod benzathine of claim 7 or 8 wherein the water content is less than 10% by weight or less than 9% by weight or less than about 8.5% by weight or between about 8% and 9% by weight or between about 8.5% and 9.0% by weight or between about 8.6% and 8.9% by weight.
10. Amorphous di-pidotimod benzathine.
11. Amorphous di-pidotimod benzathine of claim 10 characterized by an x-ray powder diffraction pattern having substantially the same diffraction pattern as Figure 12 and/or by a glass transition temperature of about 53 °C and/or by an infrared spectrum comprising one or more peaks at about 699, 752, 833, 1321, 1377, 1497, 1645, or 1680 cm^{-1} .
12. Form H of di-pidotimod benzathine characterized by an x-ray powder diffraction pattern comprising one or more peaks at about 4.4, 5.5, 8.9, 14.4, or 16.6 $^{\circ}2\Theta$ and/or by an x-ray powder diffraction pattern comprising one or more peaks at about 4.4, 5.5, or 8.9 $^{\circ}2\Theta$.
13. Solvates, cocrystals and/or hydrates of di-pidotimod benzathine according to anyone of claims 1 to 12.
14. An isopropanol solvate of di-pidotimod benzathine.
15. Form J of di-pidotimod benzathine isopropanol solvate characterized by an x-ray powder diffraction pattern comprising a peak at about 16.2 $^{\circ}2\Theta$ or 17.3 $^{\circ}2\Theta$, optionally further comprising one or more peaks at about 6.1 $^{\circ}2\Theta$, 8.8 $^{\circ}2\Theta$, and 21.6 $^{\circ}2\Theta$.
16. Form J of di-pidotimod benzathine isopropanol solvate characterized by an infrared spectrum comprising one or more peaks at about 1574 cm^{-1} or 1328 cm^{-1} and/or by an infrared spectrum comprising one or more peaks at about 1687 cm^{-1} , 1656 cm^{-1} , or 1387 cm^{-1} and/or by an infrared spectrum comprising one or more peaks at about 1574 cm^{-1} or 1328 cm^{-1} and/or by an infrared spectrum comprising one or more peaks at about 1687 cm^{-1} , 1656 cm^{-1} , or 1387 cm^{-1} and/or by an infrared spectrum comprising one or more peaks at about 1574 cm^{-1} or 1328 cm^{-1} and/or by an infrared spectrum comprising one or more peaks at about 1687 cm^{-1} , 1656 cm^{-1} , or 1387 cm^{-1} .

17. Form J of di-pidotimod benzathine isopropanol solvate of claim 15 or 16 wherein the amount of isopropanol is up to about 3.2 moles of isopropanol for each mole of di-pidotimod benzathine, preferably about 2 moles for each mole of di-pidotimod benzathine.
18. Form O of di-pidotimod benzathine isopropanol solvate characterized by an x-ray powder diffraction pattern comprising a peak at about $17.7^{\circ}2\theta$ or $22.0^{\circ}2\theta$, optionally further comprising one or more peaks at about $6.2^{\circ}2\theta$, $8.8^{\circ}2\theta$, and $11.2^{\circ}2\theta$.
19. Form O of di-pidotimod benzathine isopropanol solvate of claim 18 wherein the amount of isopropanol is between about 0.6 moles of isopropanol and about 1.8 moles of isopropanol for each mole of di-pidotimod benzathine.
20. An ethanol solvate of di-pidotimod benzathine.
21. Form S of di-pidotimod benzathine ethanol solvate characterized by an x-ray powder diffraction pattern comprising one or more peaks at about $2.5^{\circ}2\theta$, $5.8^{\circ}2\theta$, $8.5^{\circ}2\theta$, or $11.6^{\circ}2\theta$ and/or further comprising a peaks at about $7.6^{\circ}2\theta$ and/or by an infrared spectrum comprising one or more peaks at about 1702 cm^{-1} or 1666 cm^{-1} and/or by an infrared spectrum comprising one or more peaks at about 1571 cm^{-1} , 1502 cm^{-1} , or 697 cm^{-1} and/or by an infrared spectrum comprising one or more peaks at about 1702 cm^{-1} or 1666 cm^{-1} and/or by an infrared spectrum comprising one or more peaks at about 1571 cm^{-1} , 1502 cm^{-1} , or 697 cm^{-1} .
22. Form S of di-pidotimod benzathine ethanol solvate of claim 21 wherein the amount of ethanol is up to about 9 moles of ethanol for each mole of di-pidotimod benzathine, preferably about 2 moles for each mole of di-pidotimod benzathine.
23. Form W of di-pidotimod benzathine ethanol solvate characterized by an x-ray powder diffraction pattern comprising one or more peaks at about $13.3^{\circ}2\theta$ or $18.8^{\circ}2\theta$ and/or further comprising peaks at about $6.6^{\circ}2\theta$, $7.6^{\circ}2\theta$, or $12.7^{\circ}2\theta$ and/or by an infrared spectrum comprising one or more peaks at about 1689 cm^{-1} or 1576 cm^{-1} and/or by an infrared spectrum comprising one or more peaks at about 1653 cm^{-1} , 1391 cm^{-1} or

- 698 cm^{-1} and/or by an infrared spectrum comprising one or more peaks at about 1689 cm^{-1} or 1576 cm^{-1} and/or by an infrared spectrum comprising one or more peaks at about 1653 cm^{-1} , 1391 cm^{-1} or 698 cm^{-1} .
24. Form W of di-pidotimod benzathine ethanol solvate of claim 23 wherein the amount of ethanol is between about 0.4 moles of ethanol and about 1.7 moles of ethanol for each mole of di-pidotimod benzathine.
25. Form X of di-pidotimod benzathine characterized by an x-ray powder diffraction pattern comprising one or more peaks at about $12.6^{\circ}2\theta$, $13.3^{\circ}2\theta$, or $19.6^{\circ}2\theta$ and/or further comprising peaks at about $7.1^{\circ}2\theta$ or $7.5^{\circ}2\theta$ and/or by an infrared spectrum comprising a peak at about 1691 cm^{-1} and/or by an infrared spectrum comprising one or more peaks at about 1652 cm^{-1} , 1574 cm^{-1} , 1390 cm^{-1} or 700 cm^{-1} .
26. Form X of di-pidotimod benzathine of claim 25 wherein the amount of water is up to about 3 moles of water for each mole of di-pidotimod benzathine.
27. Form T of di-pidotimod benzathine characterized by an x-ray powder diffraction pattern comprising one or more peaks at about $5.1^{\circ}2\theta$, $8.1^{\circ}2\theta$ or $16.1^{\circ}2\theta$ and/or further comprising peaks at about $6.9^{\circ}2\theta$ or $9.1^{\circ}2\theta$ and/or by an infrared spectrum comprising a peak at about 1722 cm^{-1} , 1576 cm^{-1} , 1515 cm^{-1} , or 752 cm^{-1} and/or by an infrared spectrum comprising a peak at about 700 cm^{-1} .
28. A composition comprising di-pidotimod benzathine of any one of claims 1-27 and one or more pharmaceutically acceptable excipients and/or one or more pharmaceutically acceptable adjuvant..
29. Di-pidotimod benzathine of any of claims 1-27 for use as a medicament.
30. Di-pidotimod benzathine of claim 29 for use in the treatment of viral or bacterial infections; respiratory, urinary or genital infections; ulcerative colitis or irritable bowel syndrome; treat psoriasis or atopic dermatitis; diseases characterized by non-canonical NF-kB pathway activation.
31. A processes for preparing di-pidotimid benzathine, which comprises treating pidotimod with benzathine in one or more suitable solvents, preferably dipolar aprotic organic solvents or mixtures thereof with

alcohols or mixtures of water with alcohols, more preferably said one or more dipolar aprotic organic solvents are selected from dimethylformamide, dimethyl sulfoxide, N-methylpyrrolidone, N,N-dimethylacetamide and said alcohols are C₁-C₄ alkanols.

32. A processes for preparing Form M di-pidotimod benzathine, which comprises slurring Form H di-pidotimid benzathine into a suitable liquid, preferably ethyl acetate, anisole or a mixture thereof.
33. A processes for preparing hydrate Form H di-pidotimid benzathine, which comprises precipitating it from a solution of di-pidotimod benzathine in a mixture of at least a dipolar aprotic organic solvent and at least an alcohol, preferably said at least a dipolar aprotic organic solvent is selected from dimethylformamide, dimethyl sulfoxide, N-methylpyrrolidone, N,N-dimethylacetamide and said at least an alcohol is a C₁-C₄ alkanol..
34. A processes for preparing hydrate Form H di-pidotimid benzathine, which comprises heating amorphous di-pidotimod benzathine, preferably to a temperature from 35°C to 45°C and/or for 7 to 8 days, and/or exposing amorphous benzathine di-pidotimod to a humid environment and/or vacuum drying hydrate Form H di-pidotimid benzathine, preferably at the vacuum drying temperature from 20°C to 25°C and/or for 15 to 24 hours.
35. A processes for preparing amorphous di-pidotimod benzathine, which comprises subjecting a frozen aqueous solution of di-pidotimod benzathine to lyophilization.
36. A process for preparing an isopropanol solvate of di-pidotimod benzathine comprising dissolving di-pidotimod benzathine on or more suitable solvents wherein one of the solvents is isopropanol and recrystallizing to form an isopropanol solvate of di-pidotimod benzathine.
37. A process for preparing Form J comprising treating Form M with a suitable solvent mixture comprising isopropanol to make a solution and crystallizing Form J from the solution, preferably wherein the solvent mixture further comprises water, and/or slurring Form M with a solvent mixture comprising isopropanol, preferably further comprising isolating Form J.

38. A process for preparing Form O comprising desolvating Form J, preferably wherein desolvation occurs by exposure to ambient conditions, and/or treating Form H with a suitable solvent mixture comprising isopropanol to form solids and isolating the solids, preferably wherein the solvent mixture further comprises water.
39. A process for preparing ethanol solvates of di-pidotimod benzathine comprising treating a solid form of di-pidotimod benzathine with a solvent mixture comprising ethanol.
40. A process for preparing Form S comprising treating Form M with an anhydrous solvent; isolating the resulting solids, and treating the resulting solids with ethanol to provide Form S, preferably wherein the anhydrous solvent is methanol.
41. A process for preparing Form W comprising treating x-ray amorphous di-pidotimod benzathine to vapor-phase ethanol and/or lyophilizing Form M and treating the lyophilized solid with vapor-phase ethanol.
42. A process for preparing Form X comprising exposing Form W to ambient conditions for sufficient time to provide Form X.
43. A process for preparing Form T comprising treating x-ray amorphous di-pidotimod benzathine to vapor-phase acetonitrile.

Figure 1 – X-ray powder diffraction pattern of Form M di-pidotimod benzathine

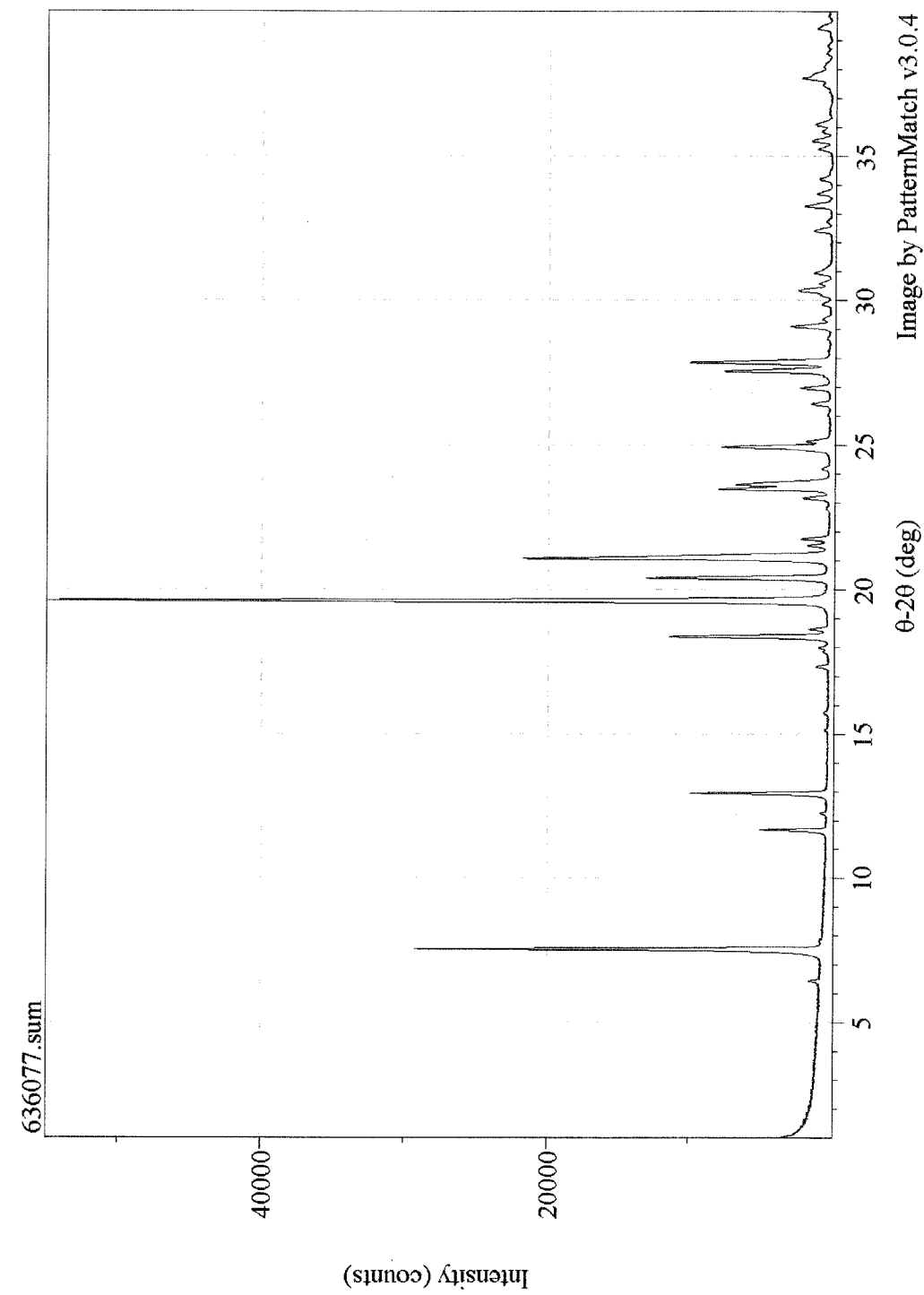


Figure 2 - Peak-picked x-ray powder diffraction pattern of Form M di-pidotimod benzathine
Observed peaks for XRPD file 636077 collected with Cu-K α radiation.

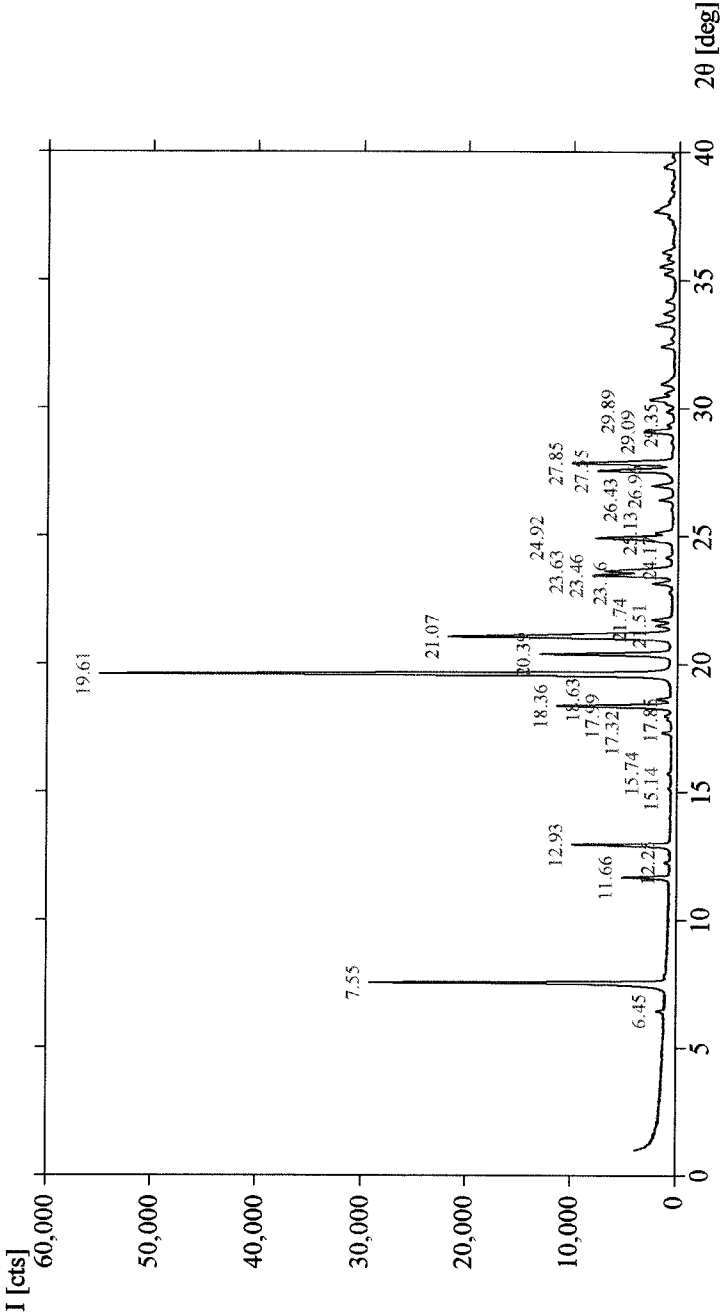


Figure 3 - Differential scanning calorimetry thermogram of Form M di-pidotimod benzathine

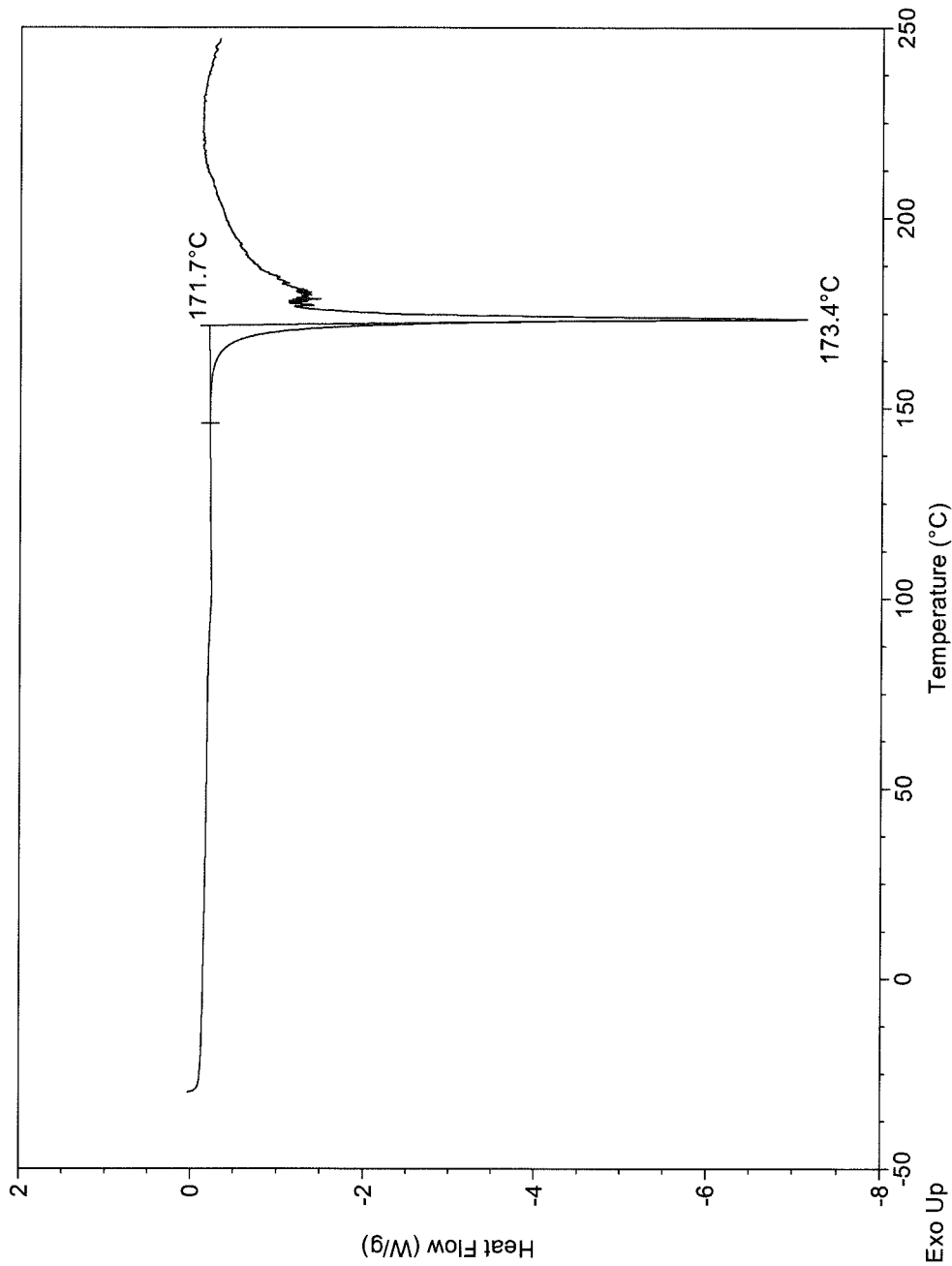
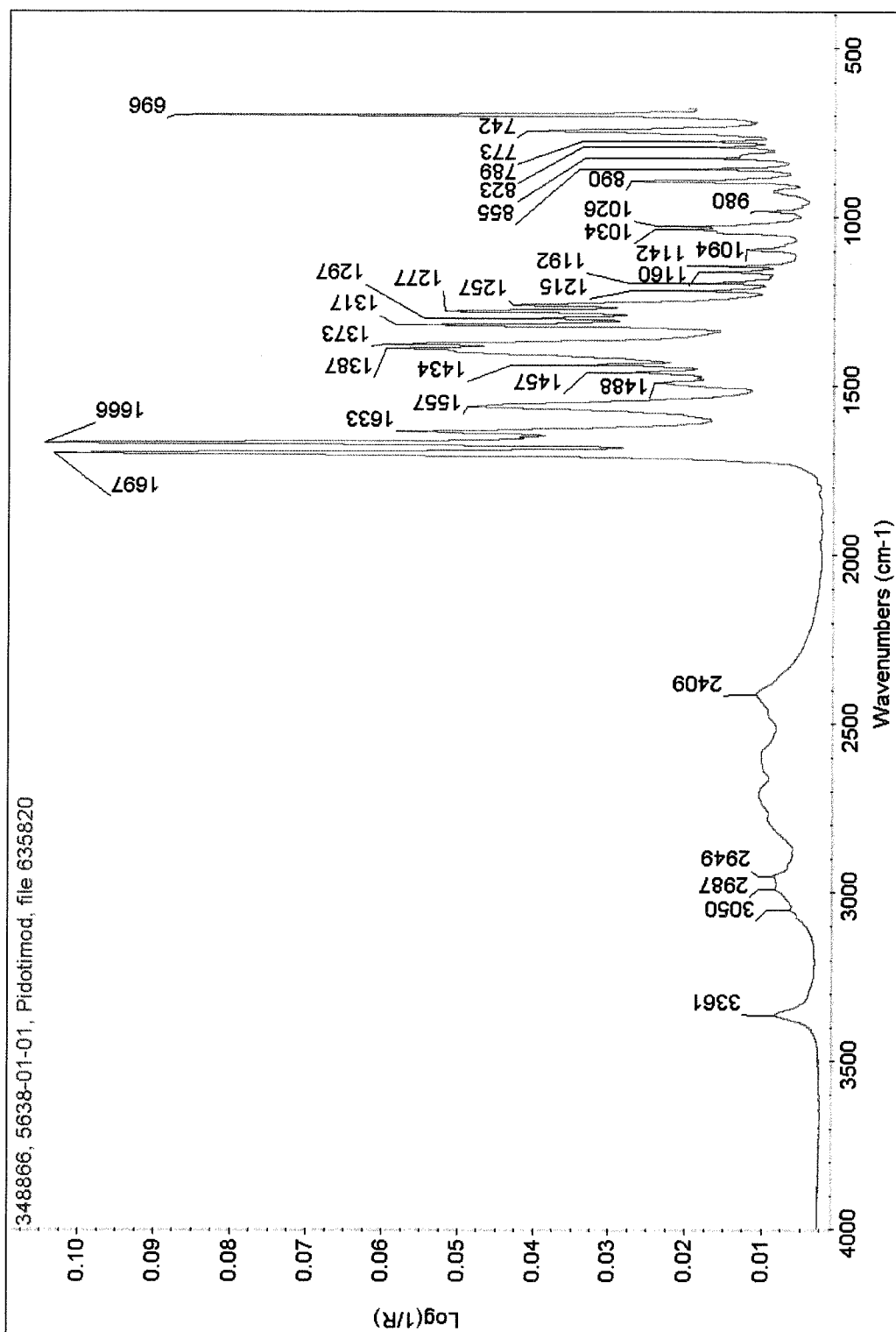
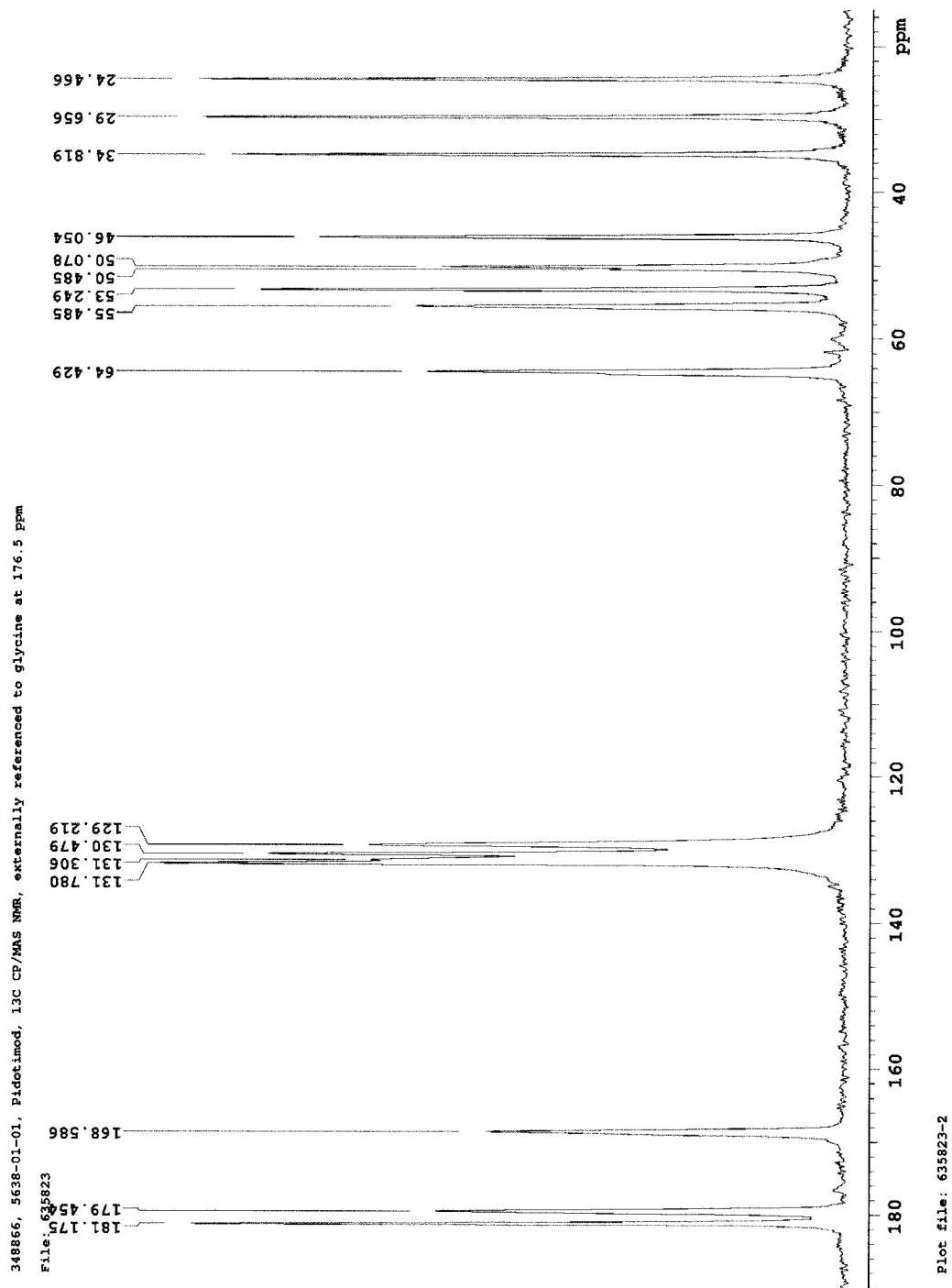


Figure 4 - Raman spectrum of Form M di-pidotimod benzathine

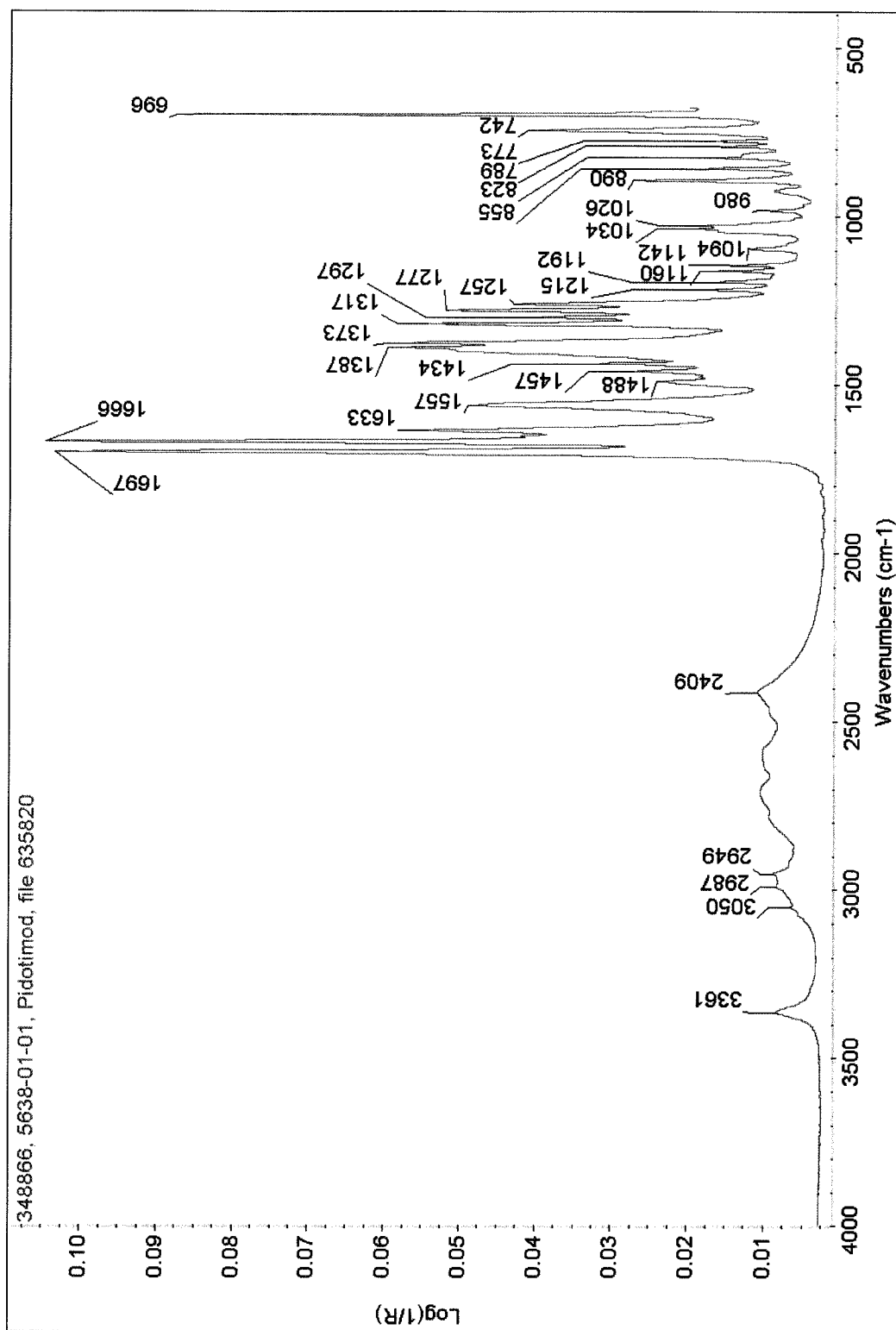


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Figure 5 - Truncated ^{13}C solid state NMR spectrum of Form M di-pidotimod benzathine

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Figure 6 - Infrared spectrum of Form M di-pidotimod benzathine



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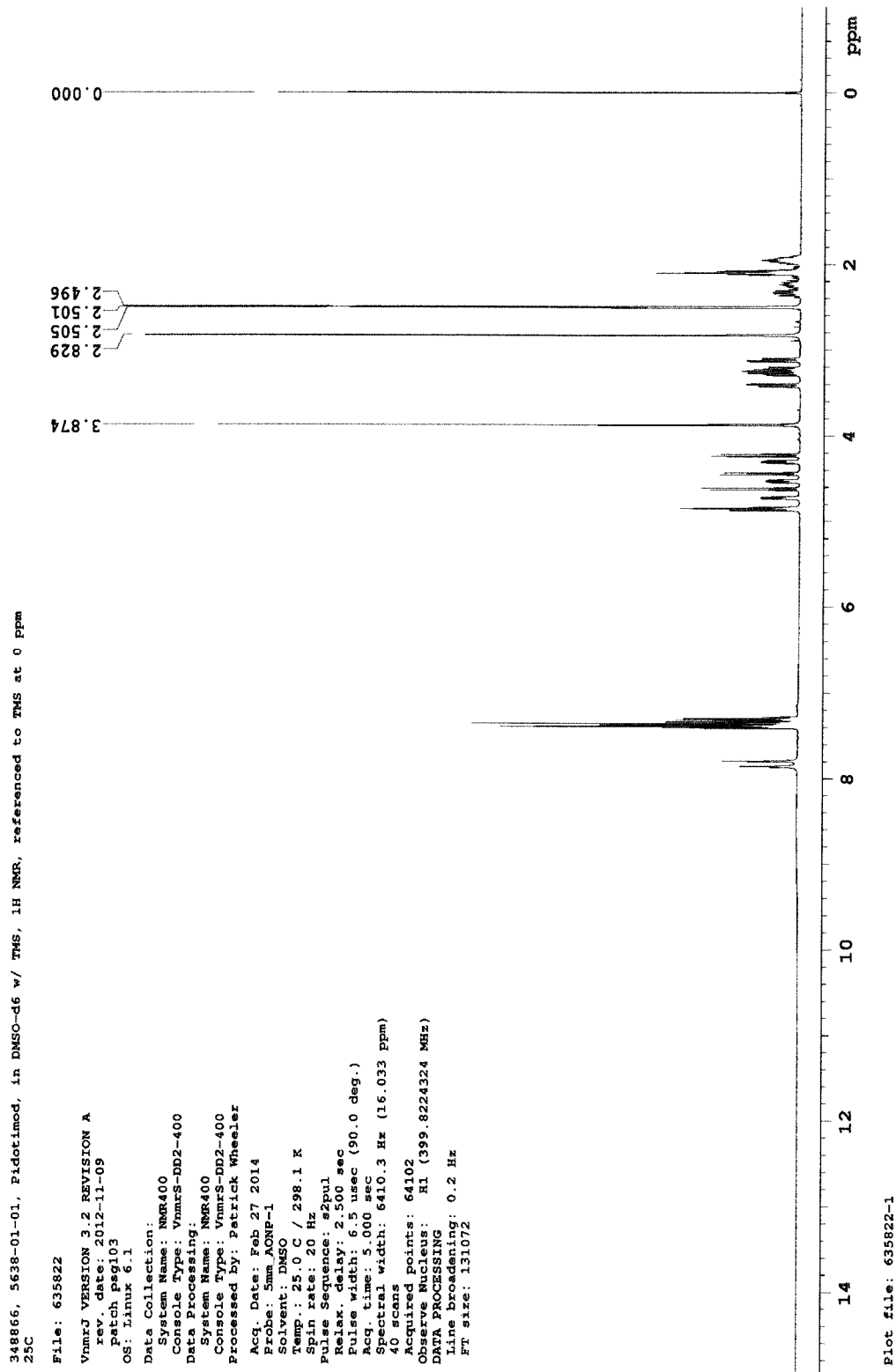
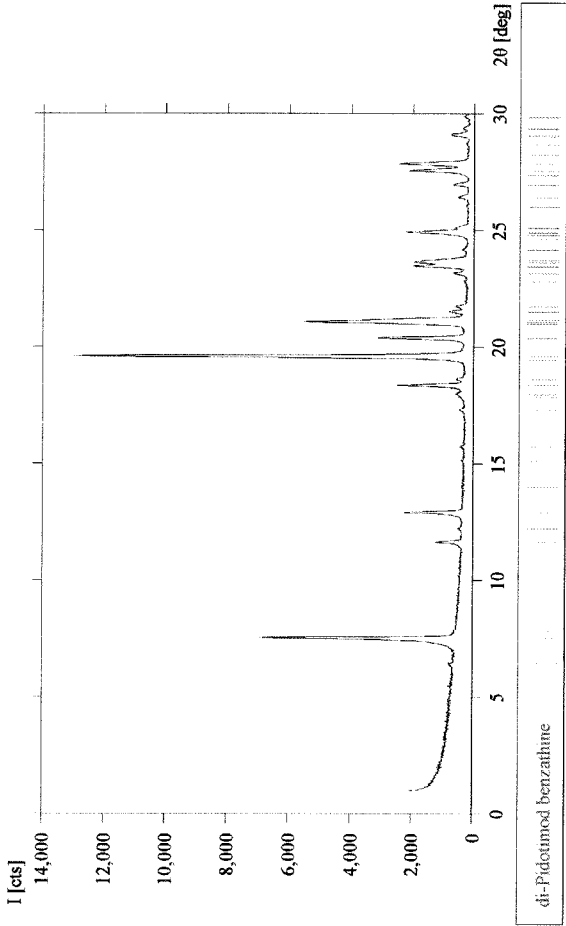
Figure 7- ^1H solution-state NMR spectrum of Form M di-pidotimod benzathine

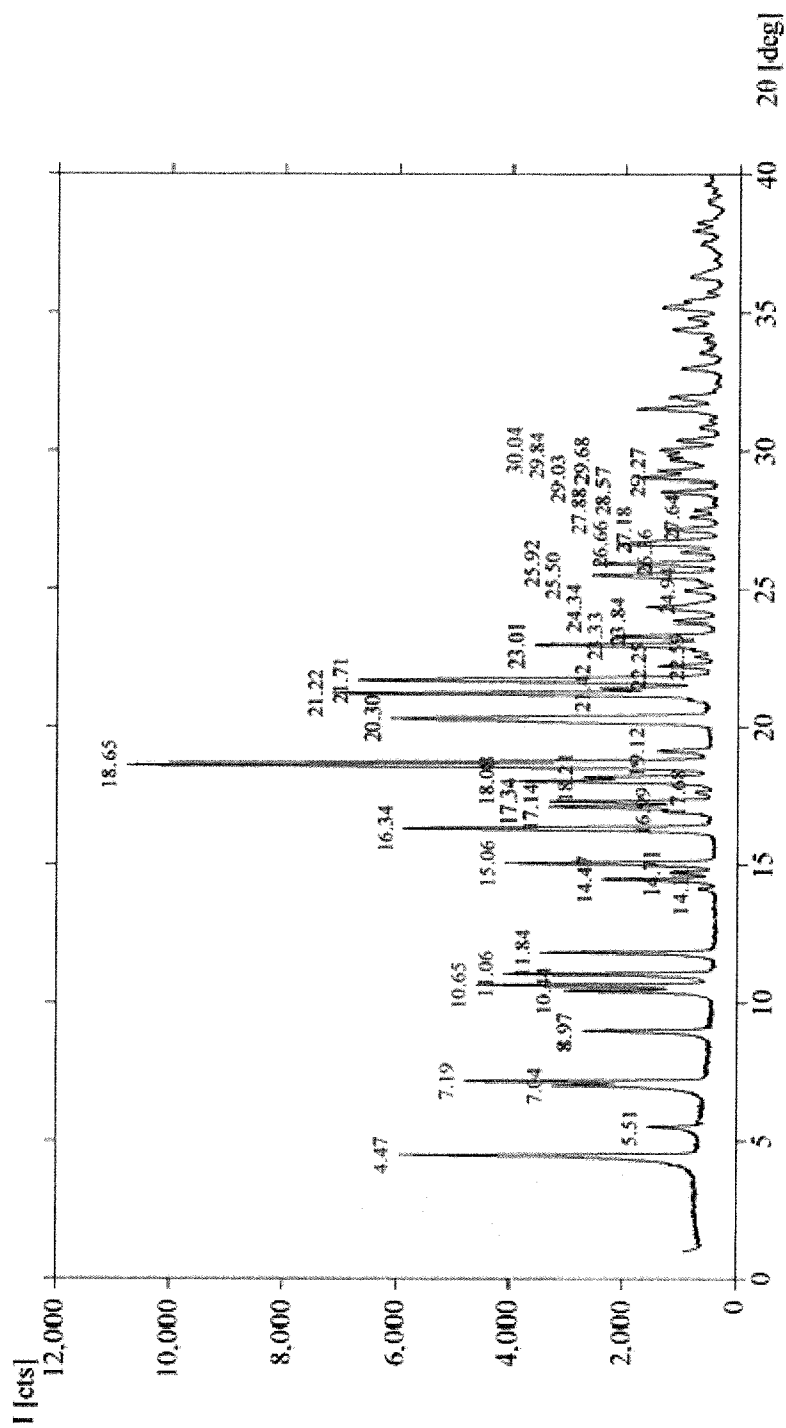
Figure 8 - Indexing solution of Form M di-pidotimod benzathine
Indexing results for XRPD file 609528 collected with Cu-K α radiation.



di-Pidotimod benzathine	
Bravais Type	C-Centered Monoclinic
a [Å]	25.287
b [Å]	5.091
c [Å]	15.381
α [deg]	90
β [deg]	117.19
γ [deg]	90
Volume [Å ³ /cell]	1,761.3
Chiral Contents?	Chiral
Extinction Symbol	C 1 - 1
Space Group(s)	C2 (5)
Source	Manual Input

Figure 9 - X-ray powder diffraction pattern of hydrated Form H di-pidotimod benzathine

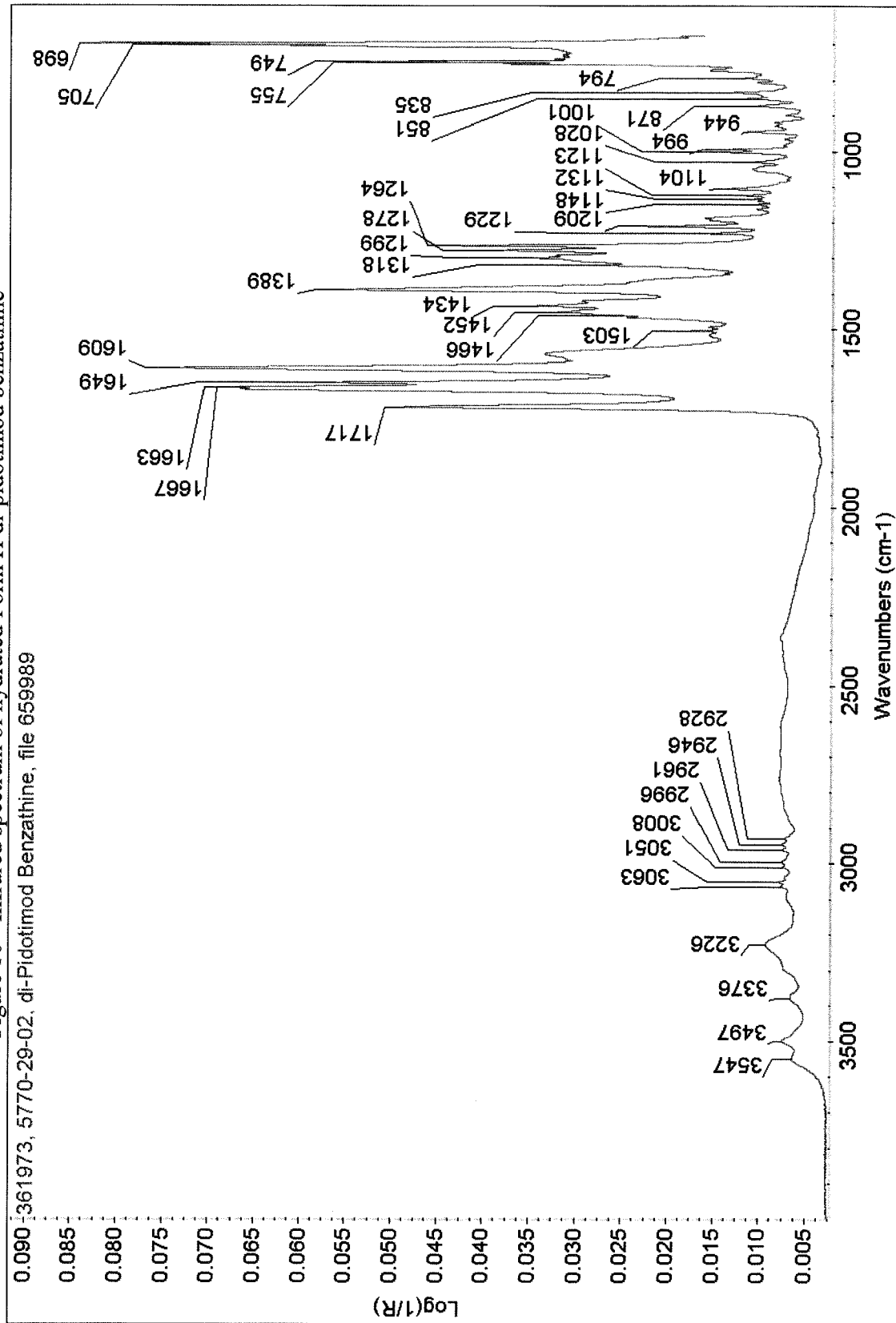
Observed peaks for XRPD file 601844 collected with Cu-K α radiation.



Output rendered using Triads™ v2.0

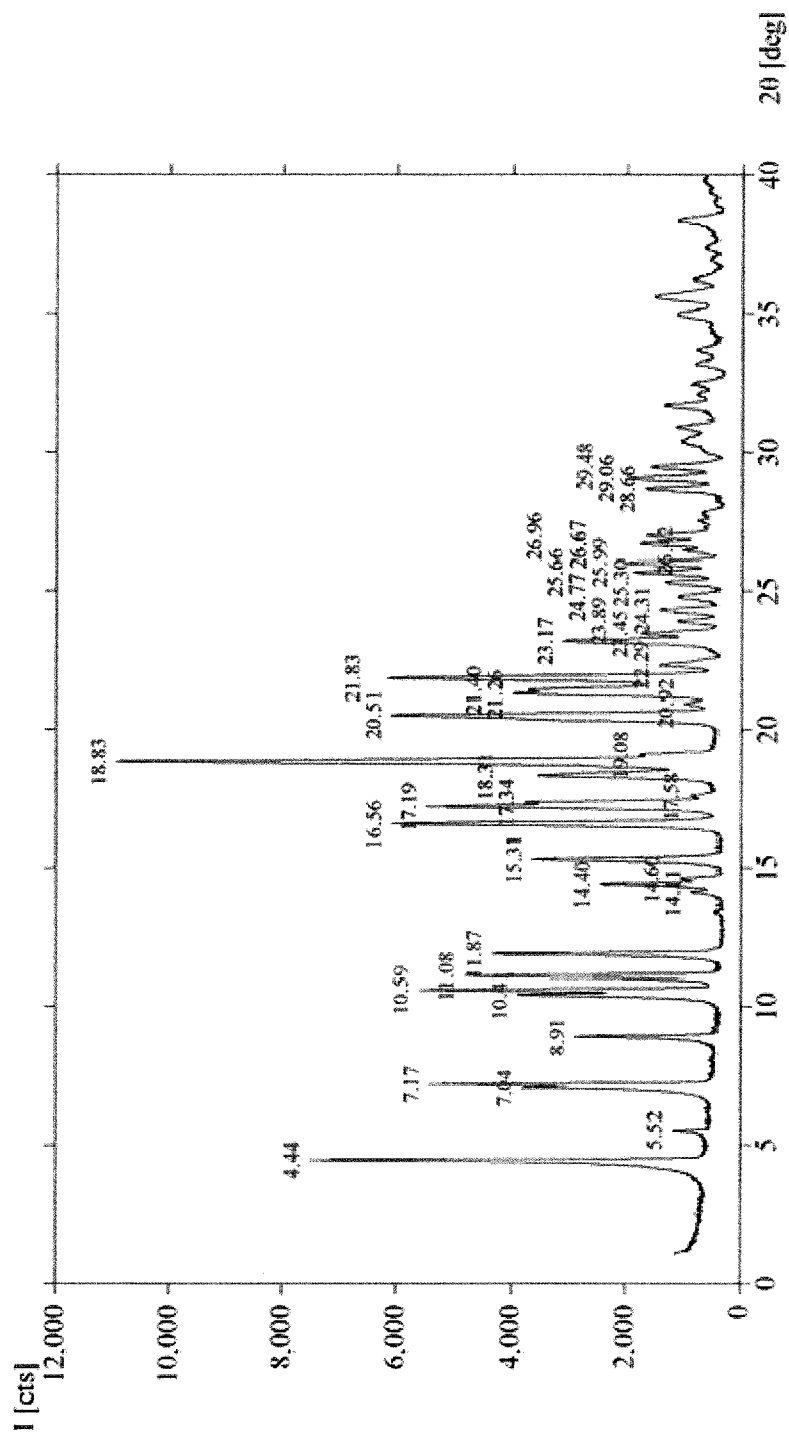
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Figure 10 - Infrared spectrum of hydrated Form H di-pidotimod benzathine
0.090-361973, 5770-29-02, di-Pidotimod Benzathine, file 659989



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Figure 11 - X-ray powder diffractograms of Form H di-pidotimod benzathine
Observed peaks for XRPD file 603280 collected with Cu-K α radiation.



Output rendered using Triads™ v2.0

Figure 12 - X-ray powder diffraction pattern of amorphous di-pidotimod benzathine

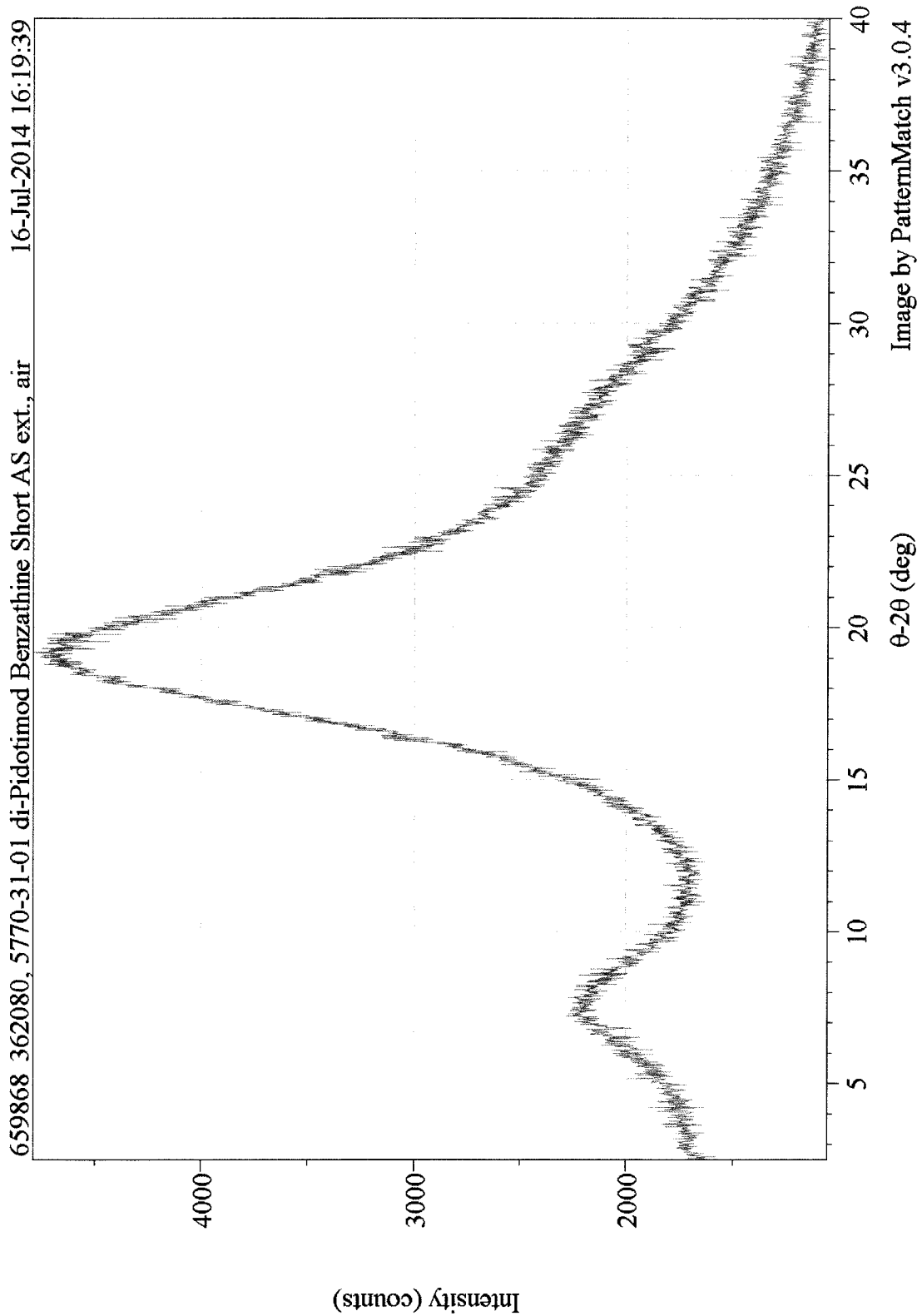
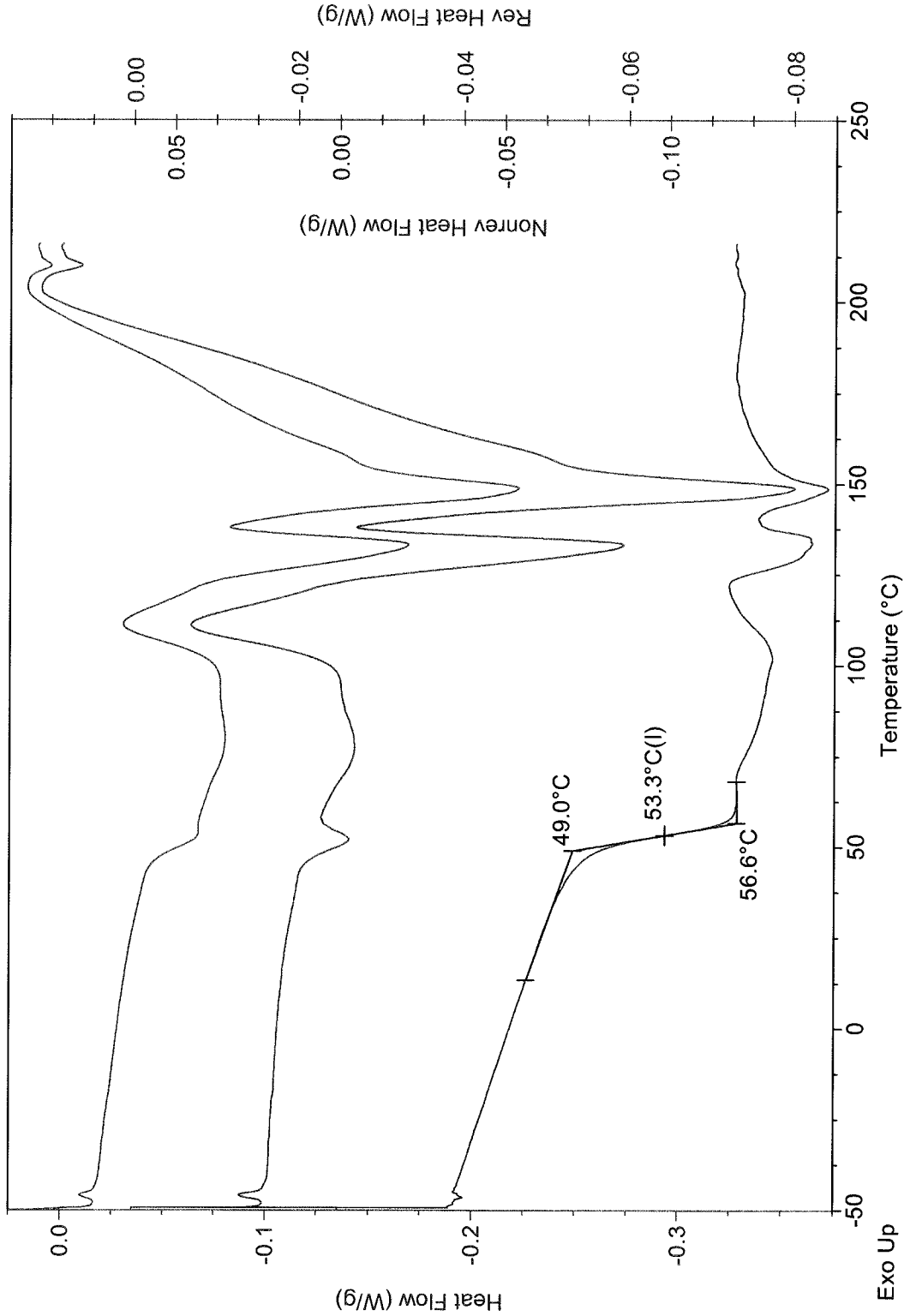


Figure 13 - Modulated differential scanning calorimetry thermogram of amorphous di-pidotimod benzathine



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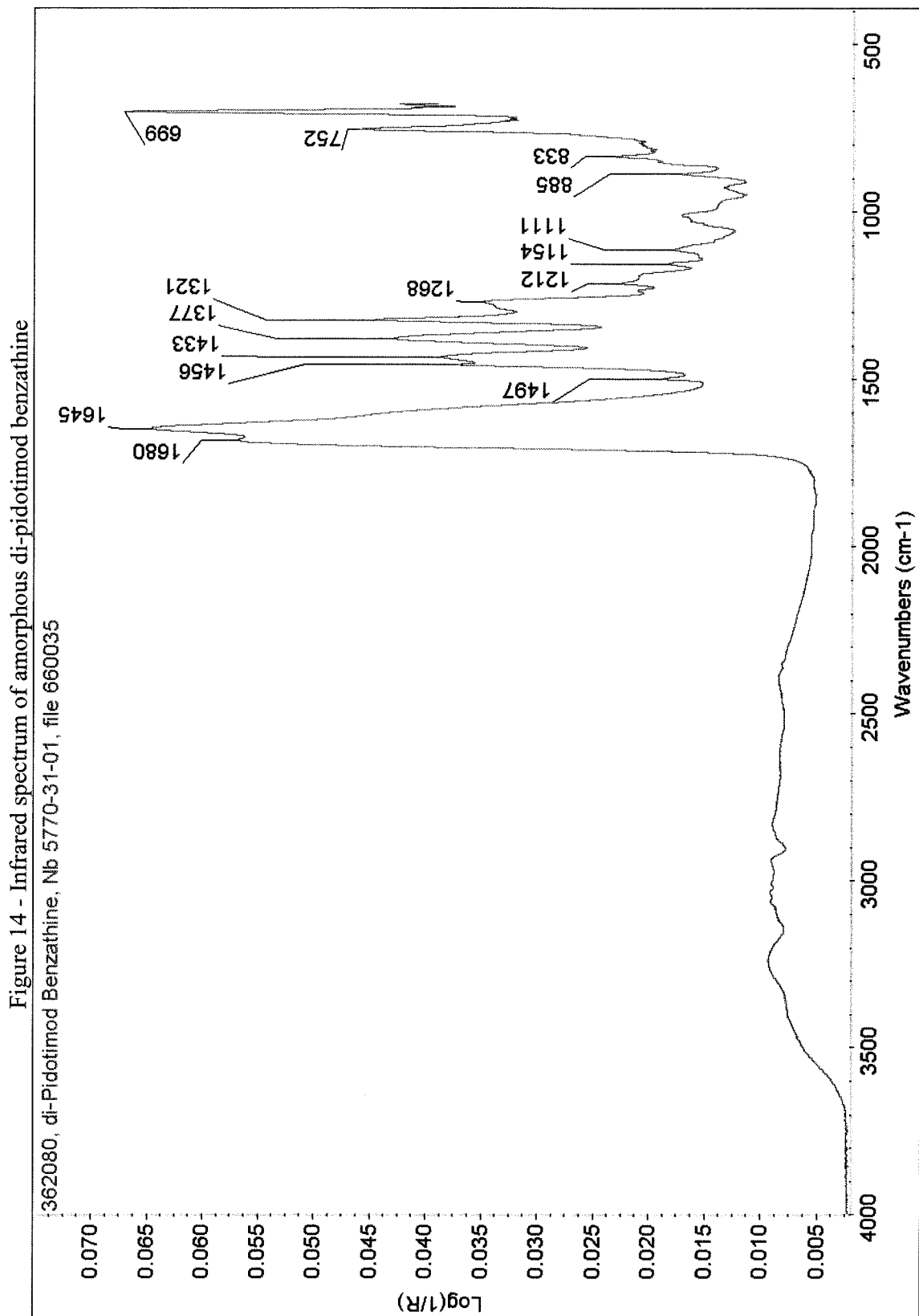
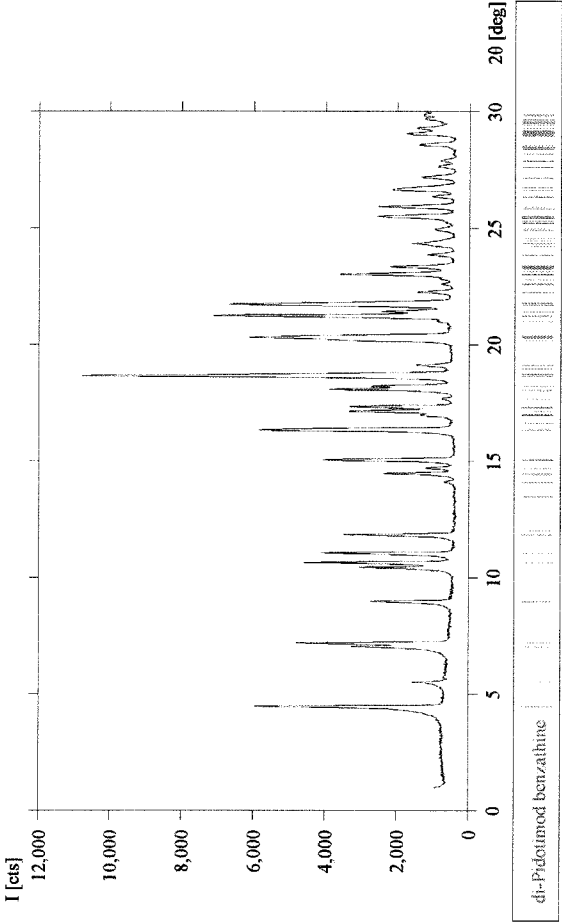


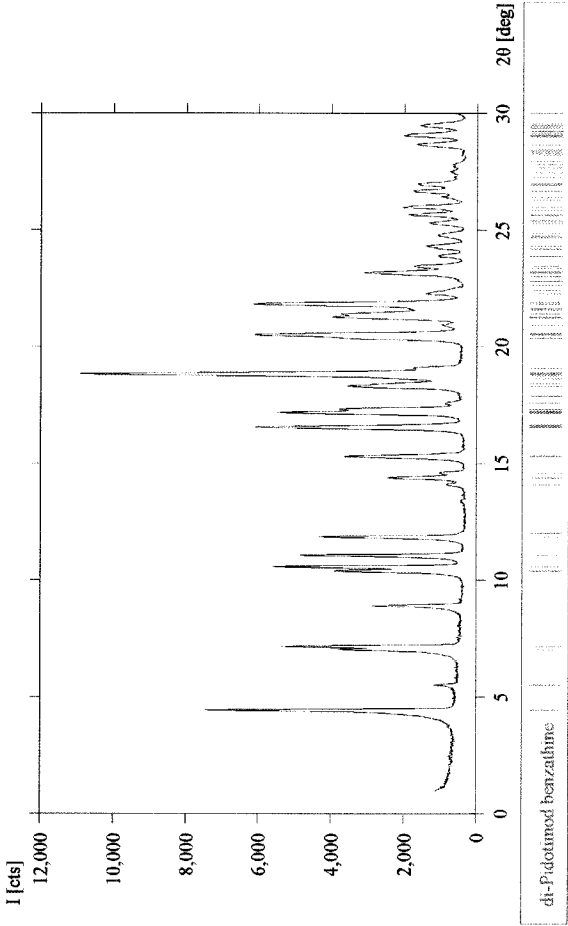
Figure 15 - Indexing solution for hydrated Form H di-pidotimod benzathine

Indexing results for XRPD file 601844 collected with Cu-K α radiation.



di-Pidotimod benzathine	
Bravais Type	C-Centered
a [Å]	Monoclinic
b [Å]	31.952
c [Å]	6.049
α [deg]	25.071
β [deg]	90
γ [deg]	128.29
Volume [Å ³ /cell]	90
Chiral Contents?	3,803.3
Extinction Symbol	Chiral
Space Group(s)	C 1 - 1
	C2 (5)
Source	Manual Input

Figure 16 - Indexing solution for Form H di-pidotimod benzathine
Indexing results for XRPD file 603280 collected with Cu-K α radiation.



di-Pidotimod benzathine	
Bravais Type	C-Centered Monoclinic
a [Å]	31.911
b [Å]	5.937
c [Å]	25.200
α [deg]	90
β [deg]	128.19
γ [deg]	90
Volume [Å ³ /cell]	3,752.4
Chiral Contents?	Chiral
Extinction Symbol	C1 - 1
Space Group(s)	C2 (5)
Source	Manual Input

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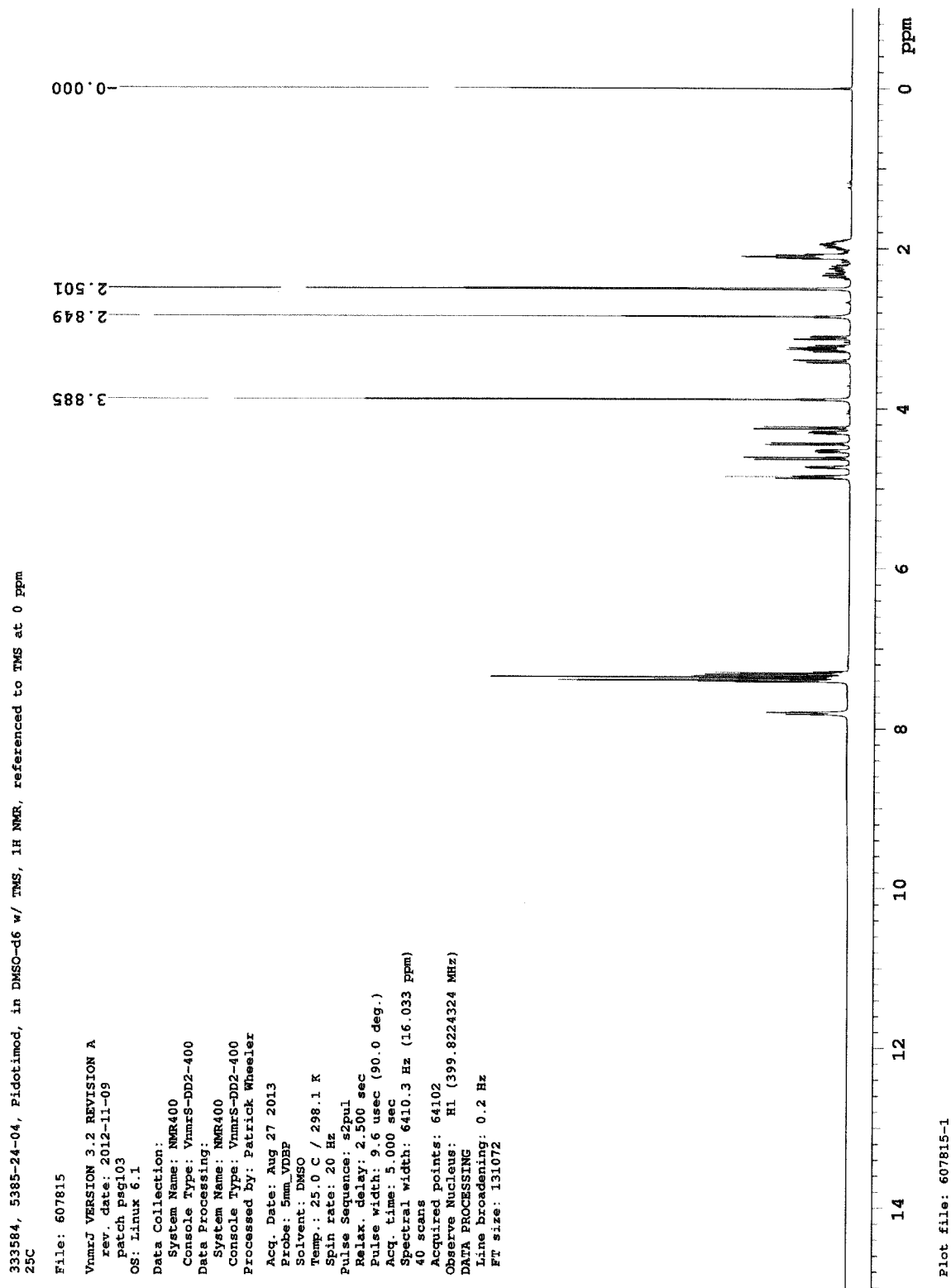
Figure 17 - ¹H solution-state NMR spectrum of Form H di-pidotimod benzathine

Figure 18 - Peak-picked x-ray powder diffraction pattern of Form J di-Pidotimid Benzathine

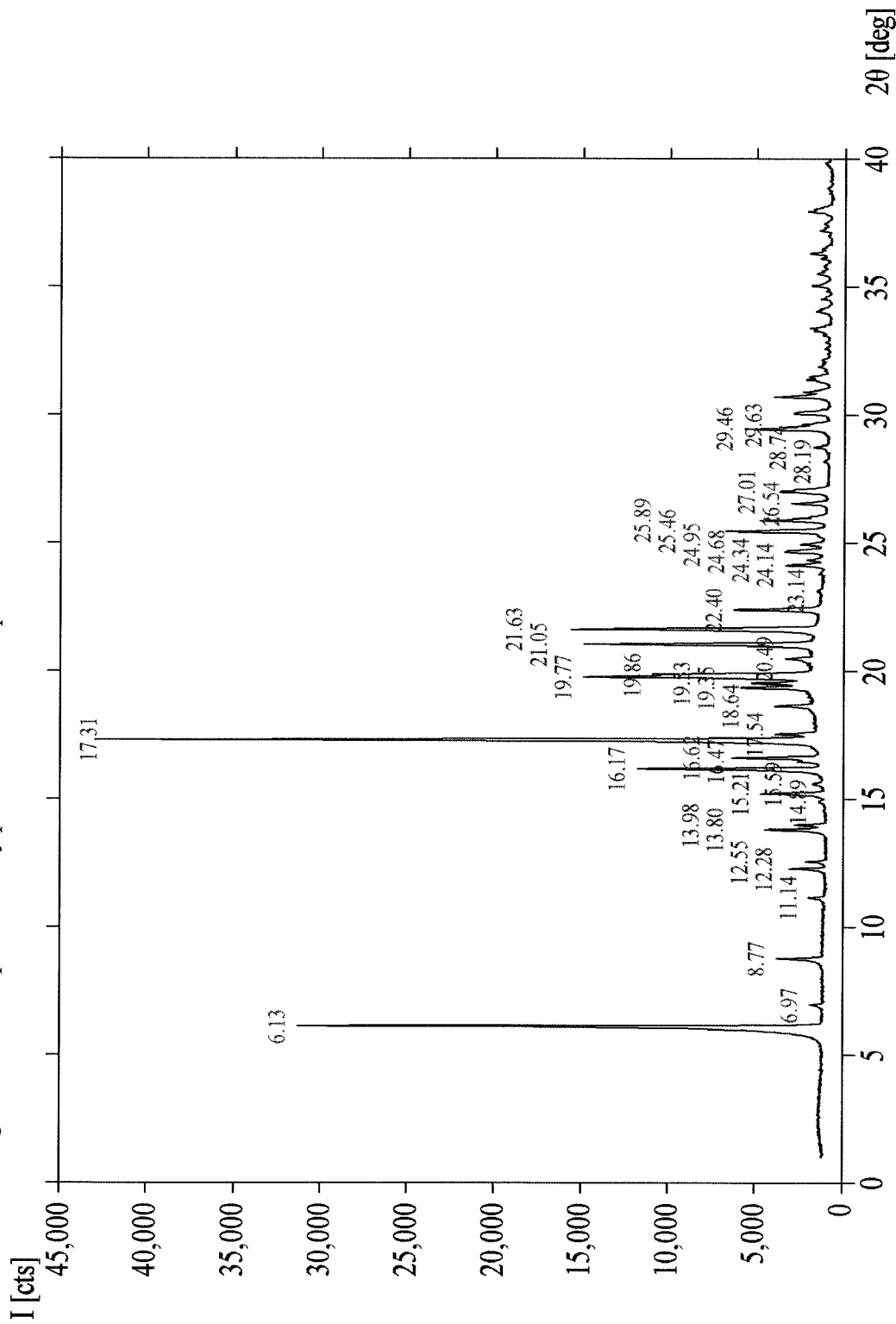
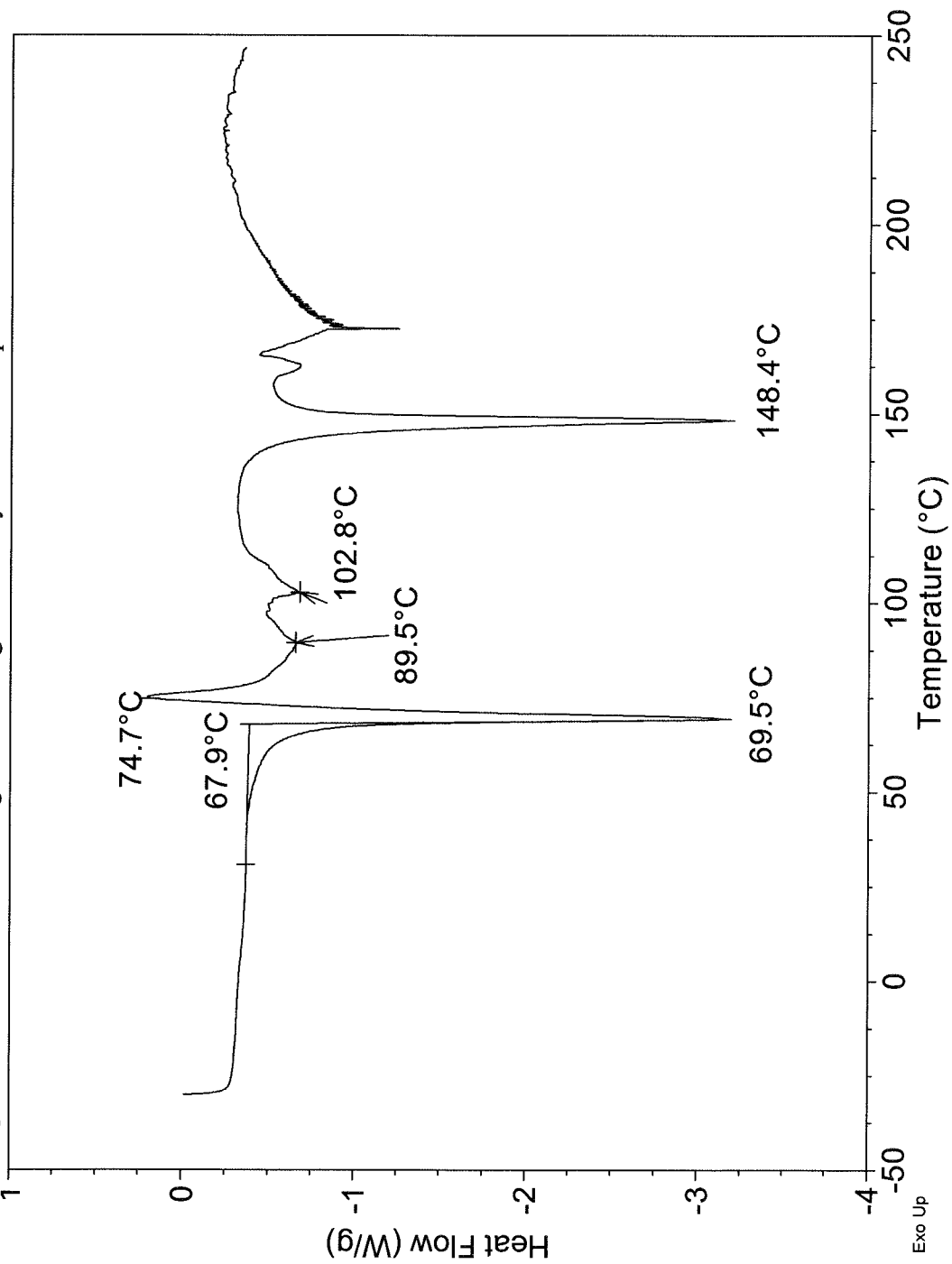
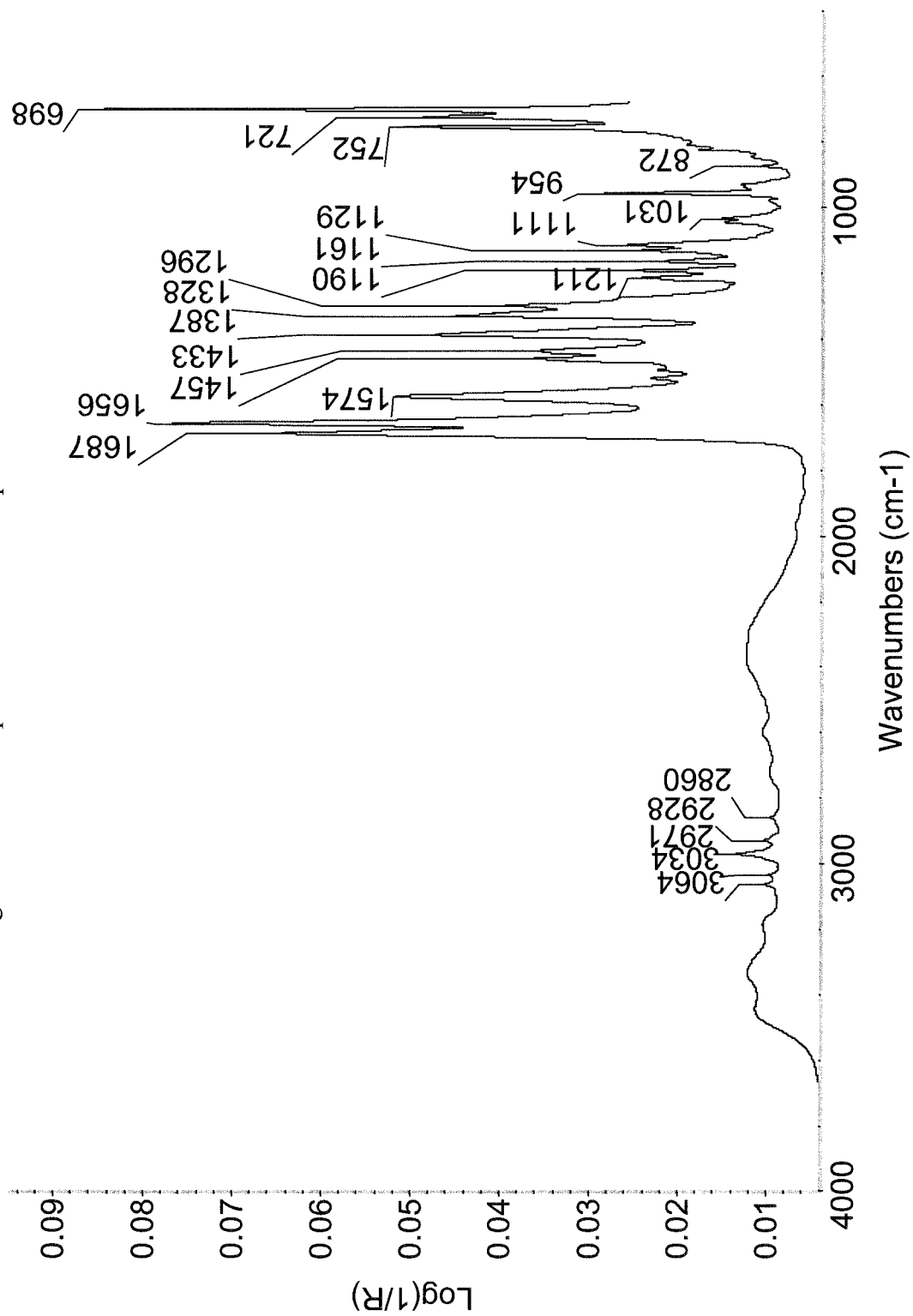


Figure 19 - Differential thermogram scanning calorimetry of Form J di-pidotimod benzathine



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Figure 20- Infrared spectrum of Form J di-pidotimod benzathine



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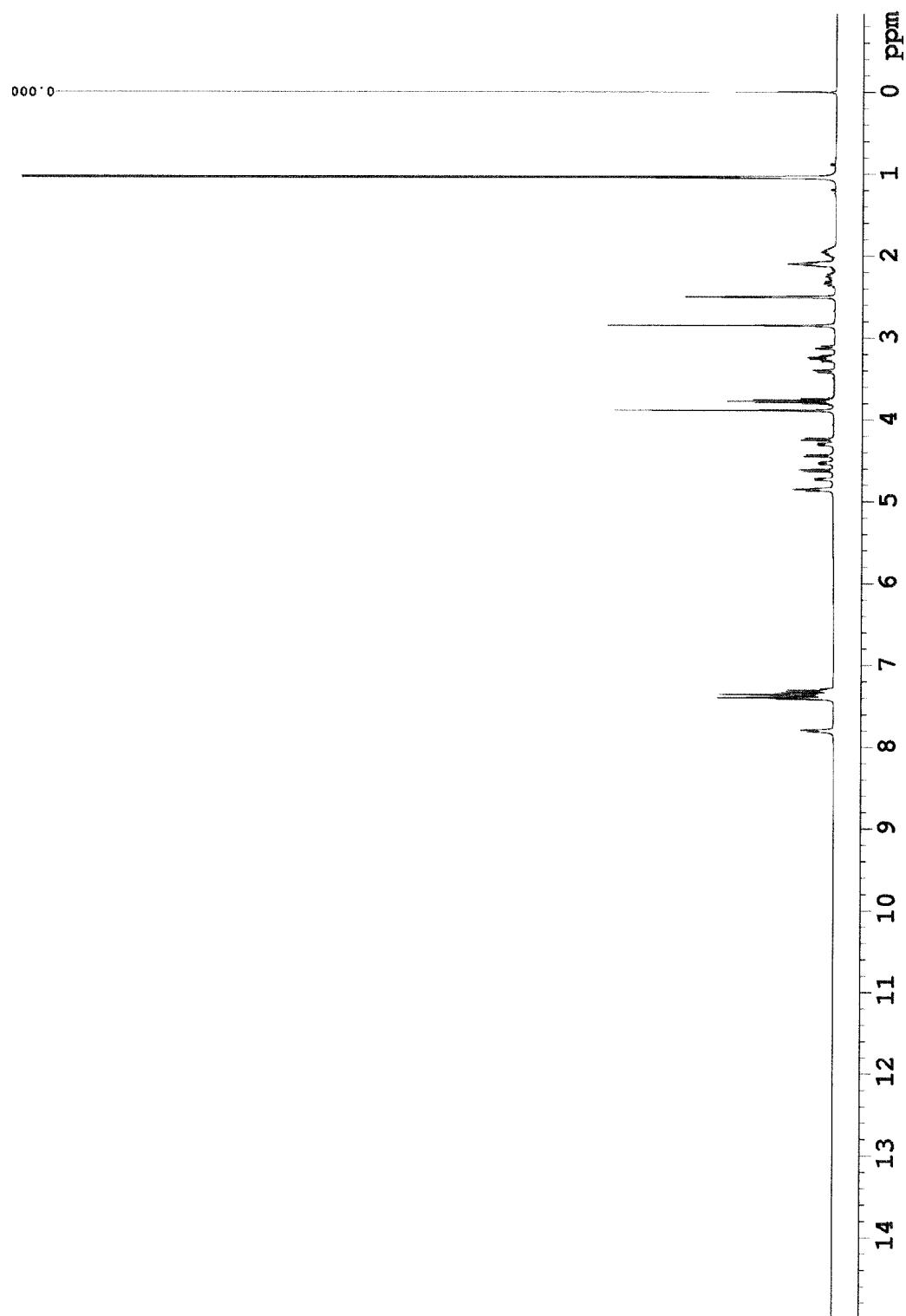
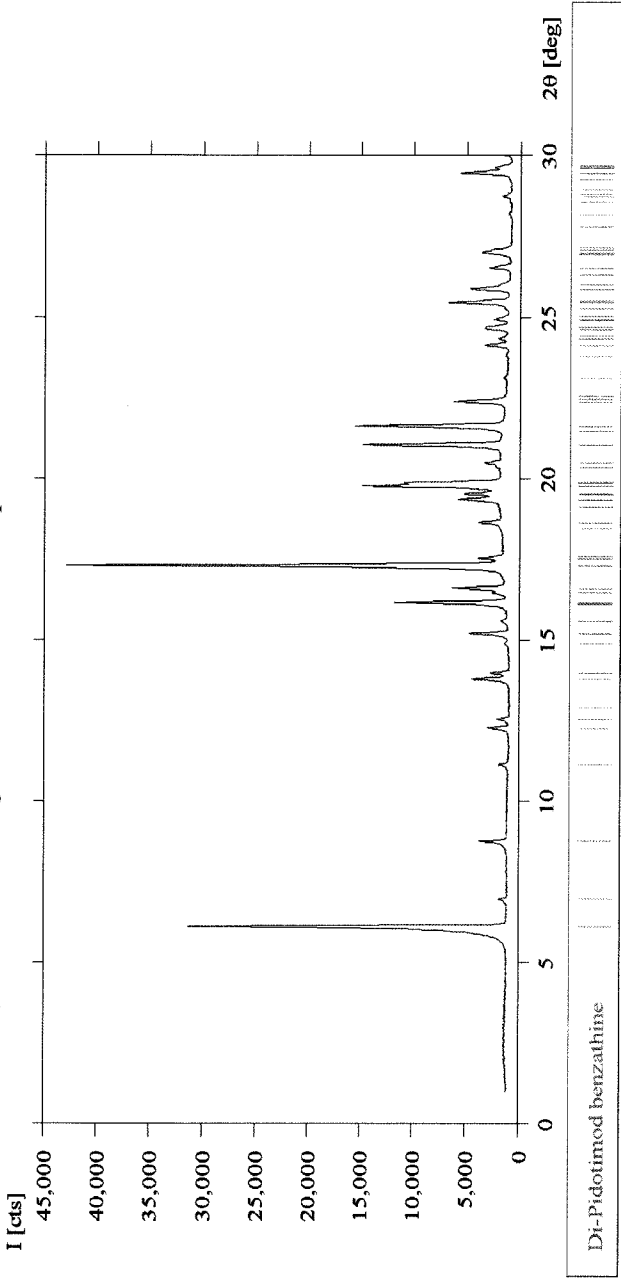
Figure 21- ^1H solution-state NMR spectrum of Form J di-pidotimod benzathine

Figure 22- Indexing solution of Form J di-pidotimod benzathine



Di-Pidotimod benzathine	
Bravais Type	Primitive
a [Å]	Orthorhombic
b [Å]	14.088
c [Å]	28.811
α [deg]	5.941
β [deg]	90
γ [deg]	90
Volume [Å ³ /cell]	2,411.4
Chiral Contents?	Chiral
Extinction Symbol	P 2 ₁ 2 ₁ -
Space Group(s)	P2 ₁ 2 ₁ 2 (18)

Figure 23 - Peak-picked x-ray powder diffraction pattern of Form O di-Pidotimod Benzathine

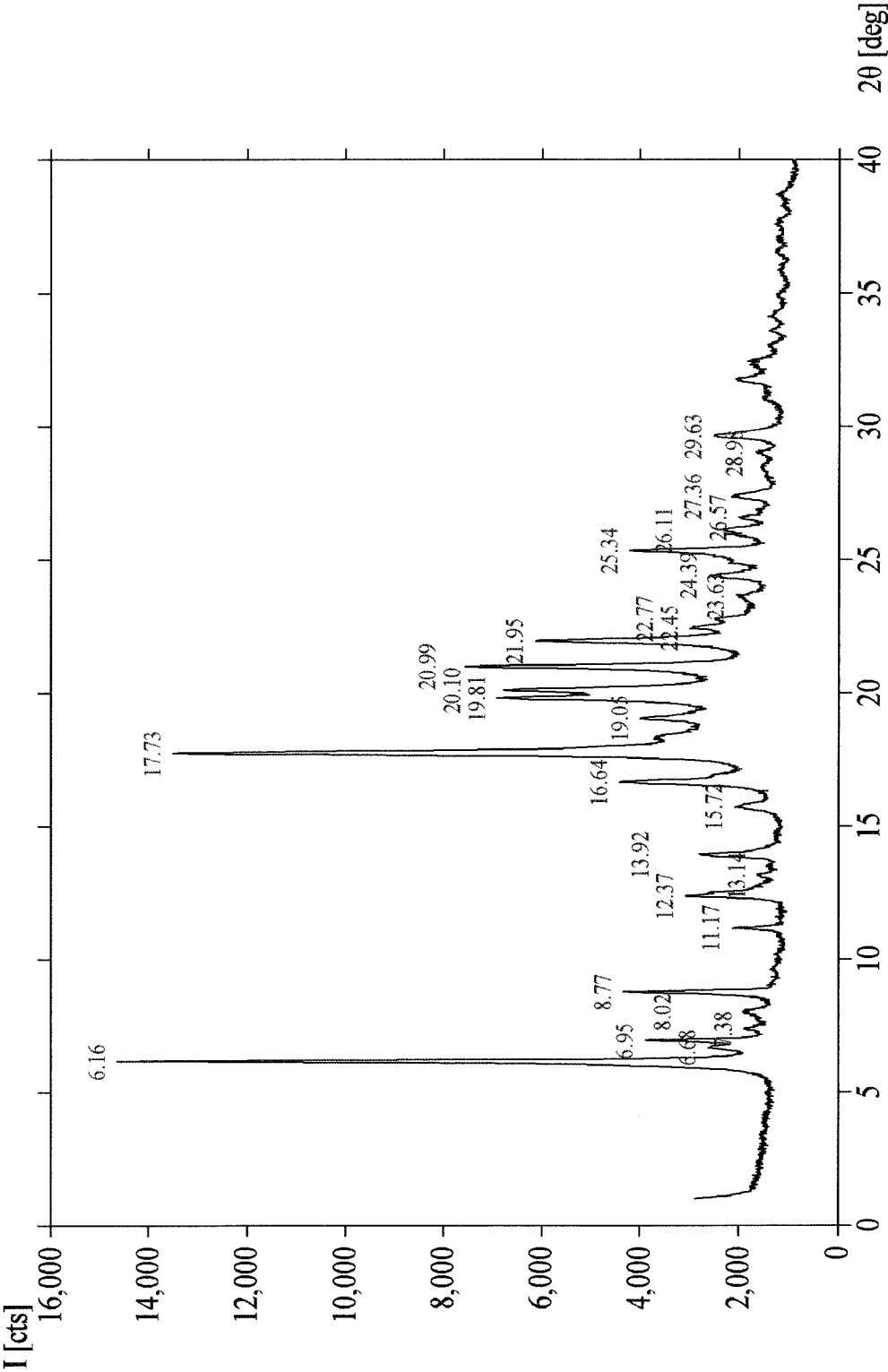
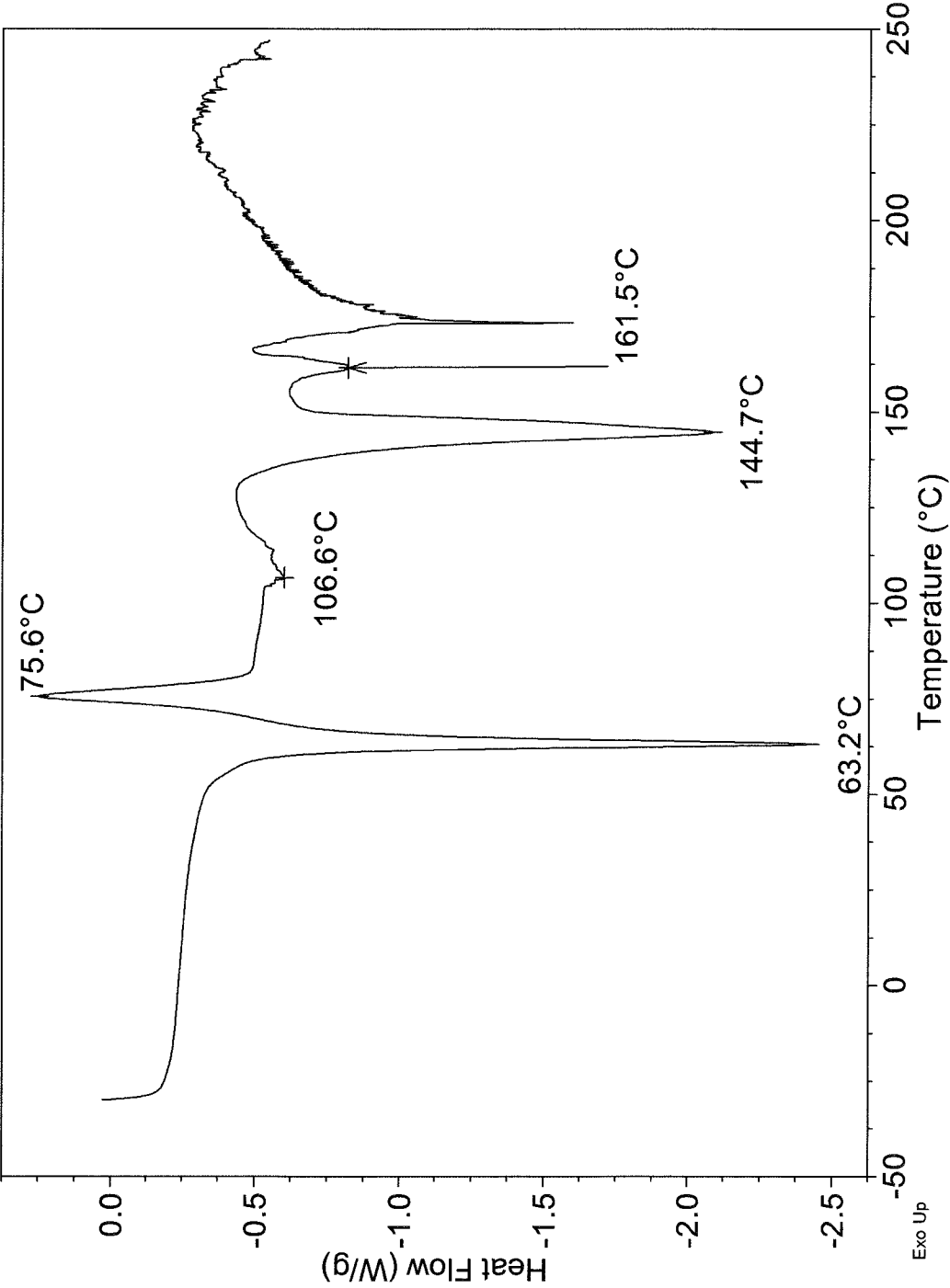


Figure 24 - Differential thermogram scanning calorimetry of Form O di-pidotimod benzathine



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Figure 25-Infrared spectrum of Form O di-pidotimod benzathine

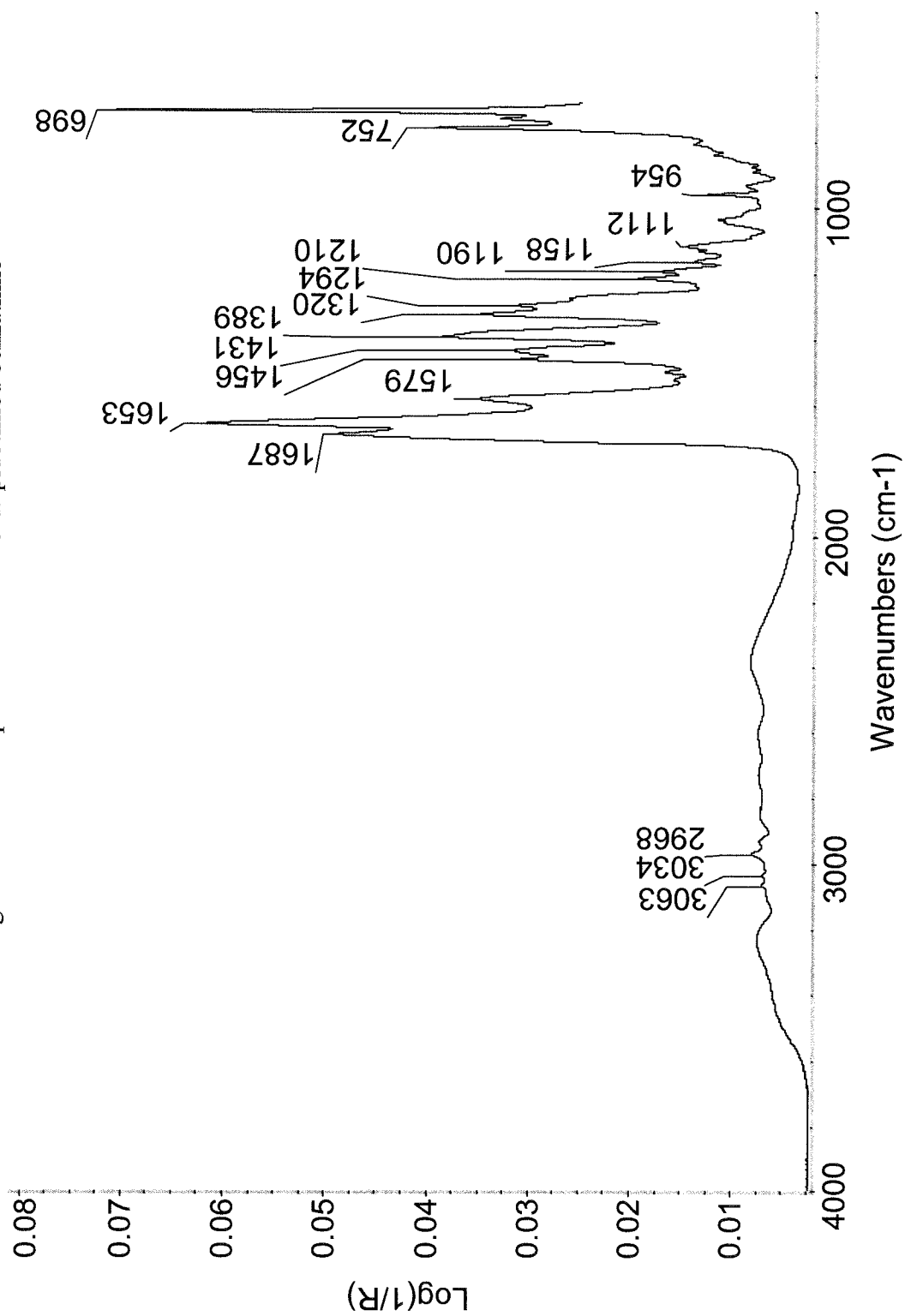


Figure 26a - ¹H solution-state NMR spectrum of Form O di-pidotimod benzathine

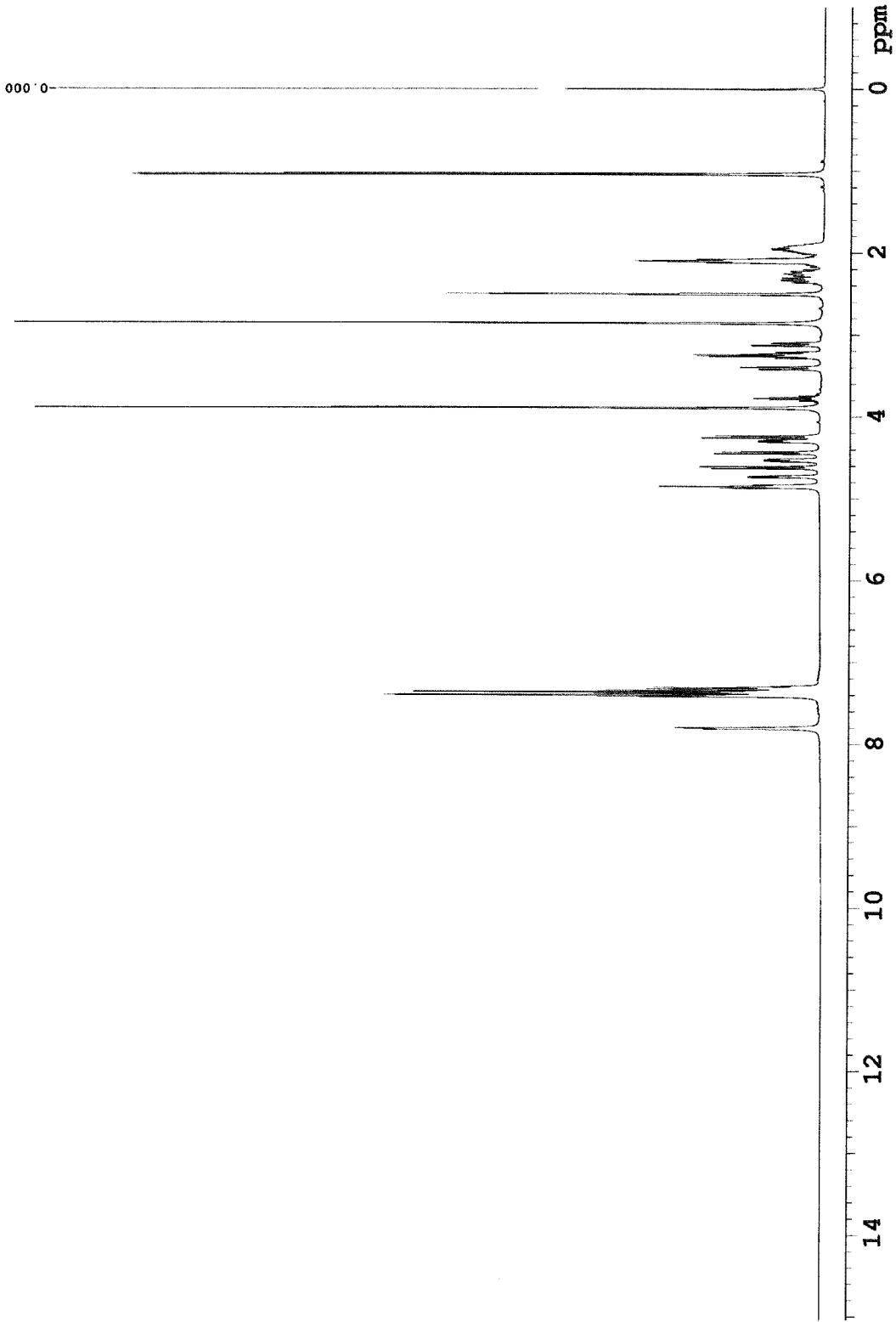
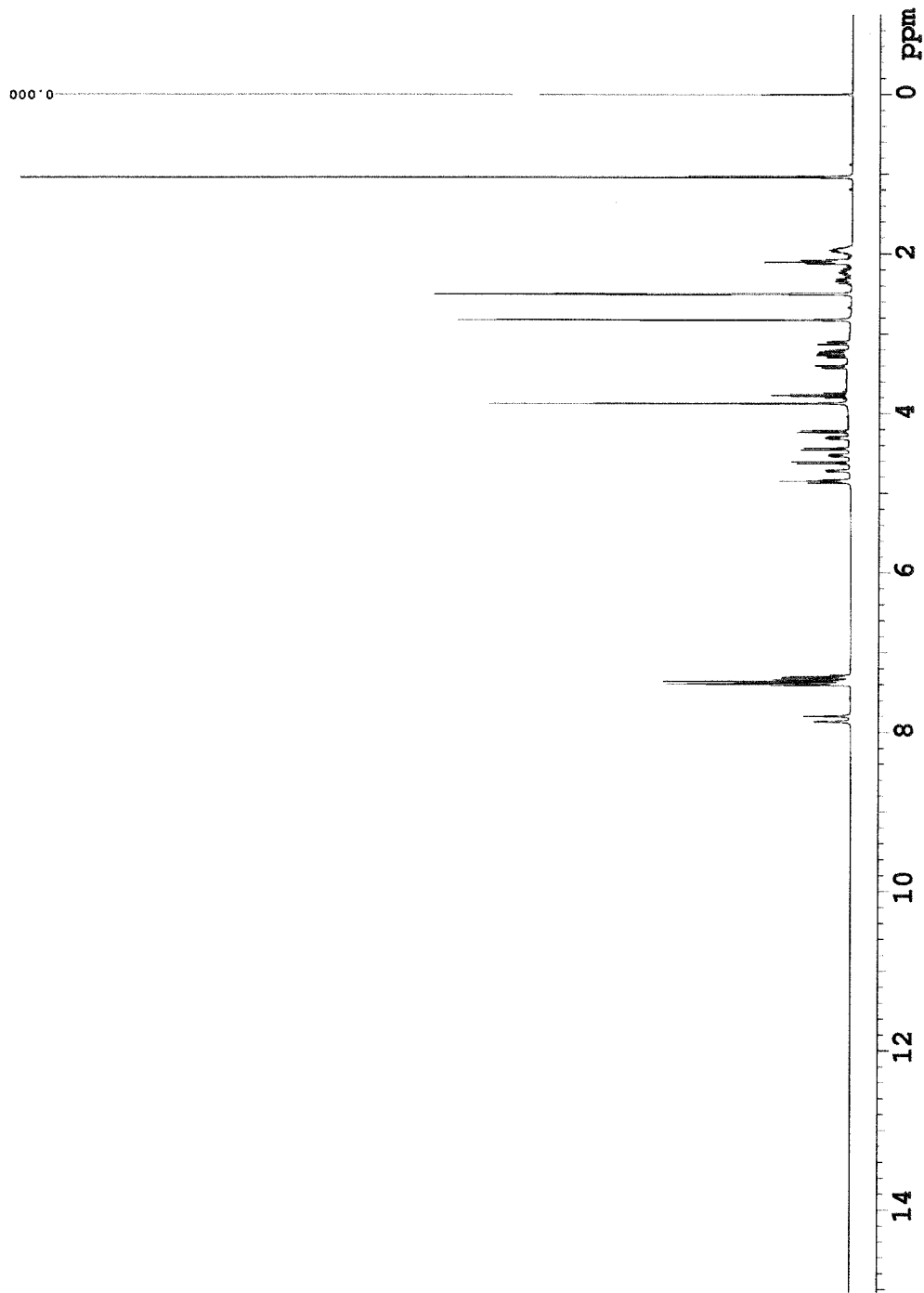


Figure 26b - ¹H solution-state NMR spectrum of Form O di-pidotimod benzathine



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Figure 27 - Peak-picked x-ray powder diffraction pattern of Form S di-Pidotimod Benzathine

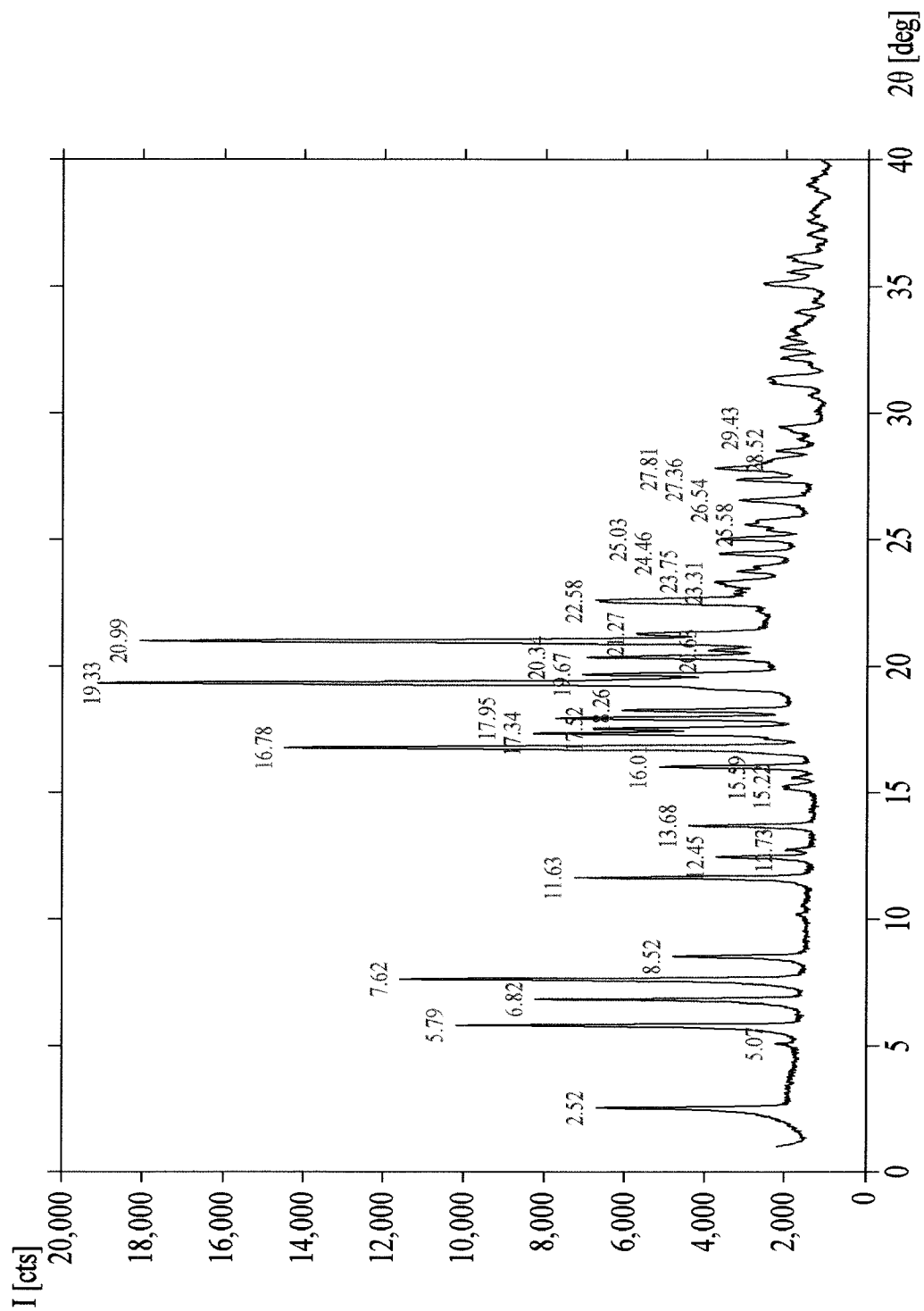
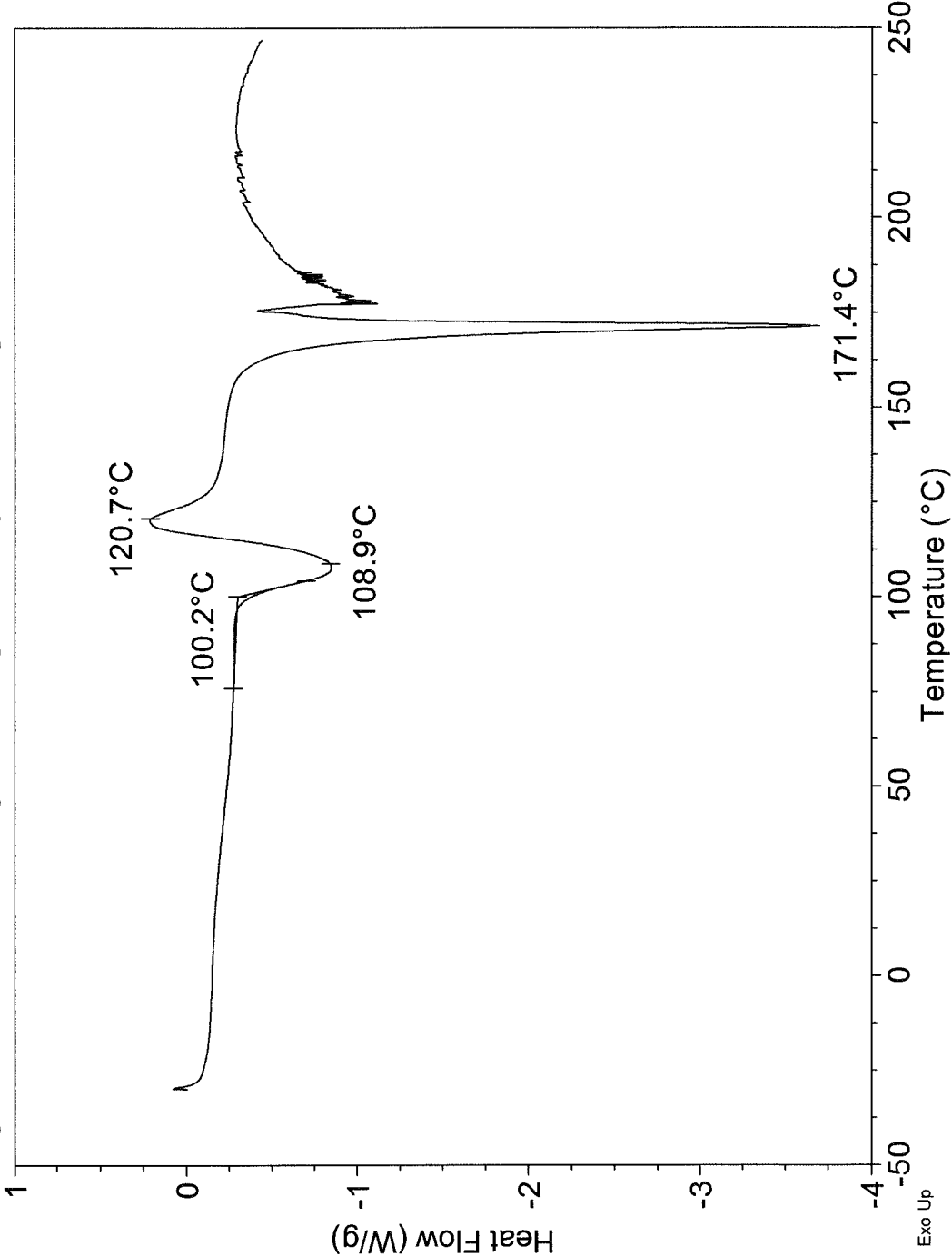


Figure 28 - Differential thermogram scanning calorimetry of Form S di-pidotimod benzathine



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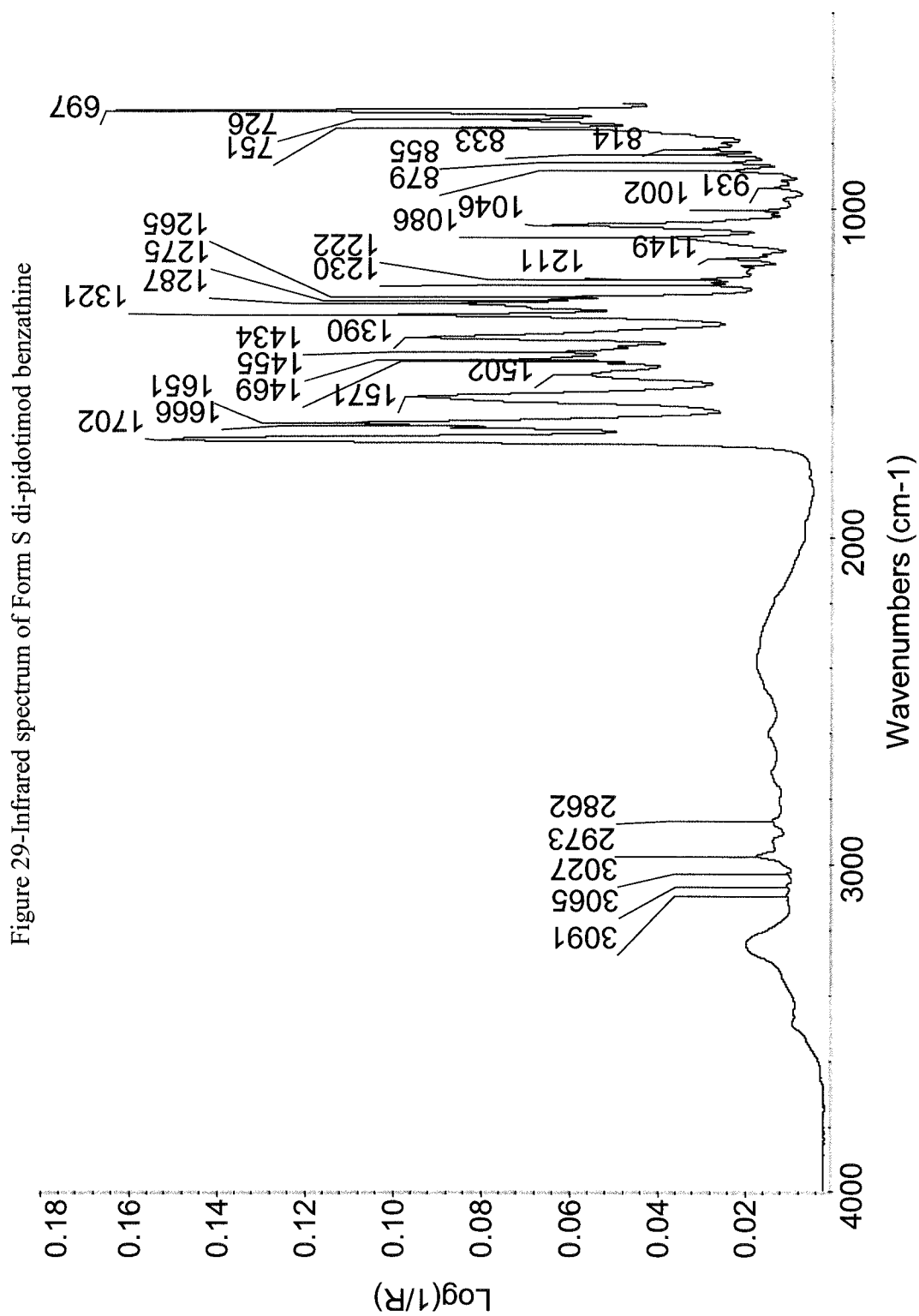
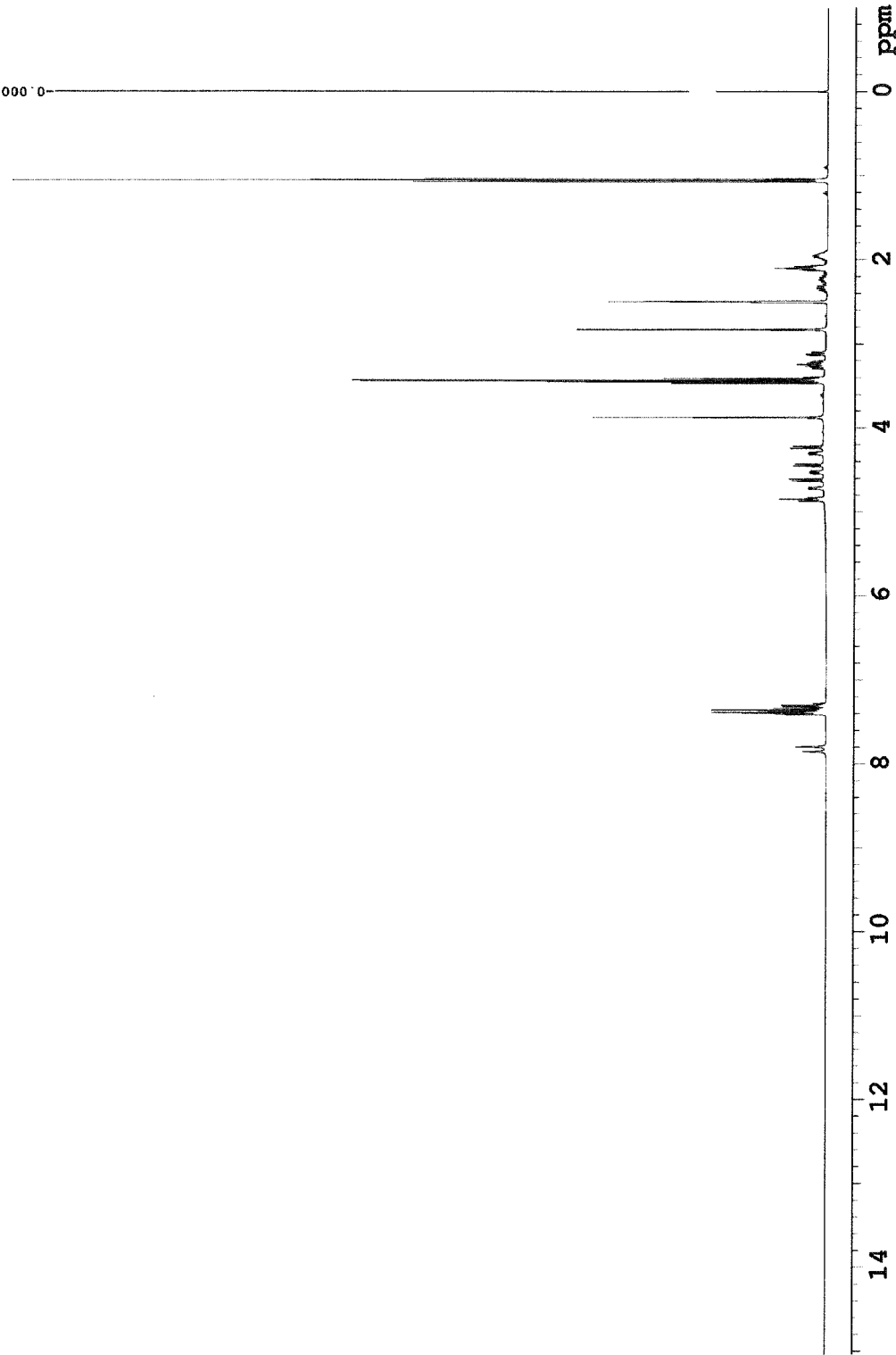


Figure 30 - ¹H solution-state NMR spectrum of Form S di-pidotimod benzathine



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Figure 31 - Peak-picked x-ray powder diffraction pattern of Form W di-Pidotimod Benzathine

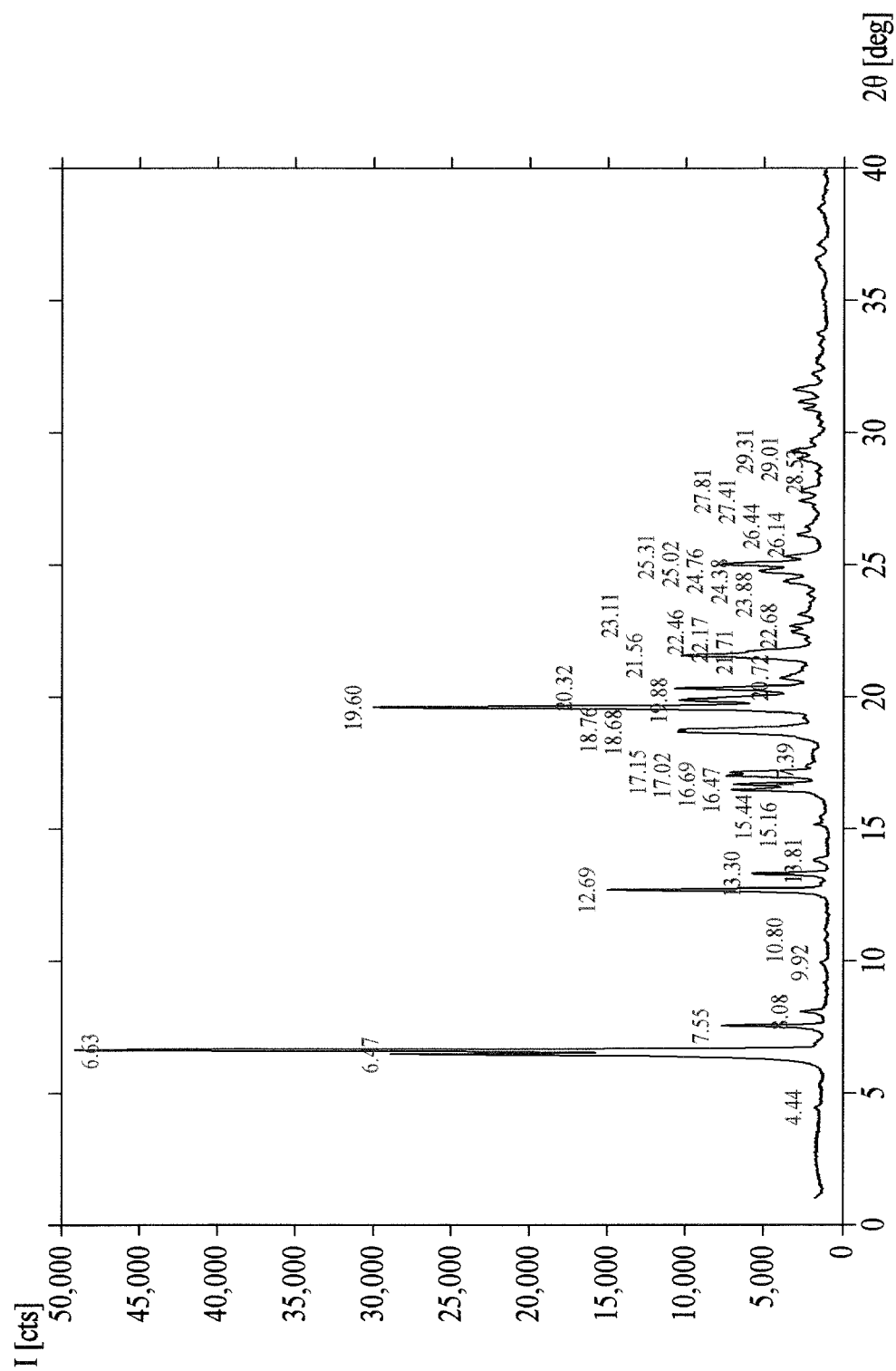
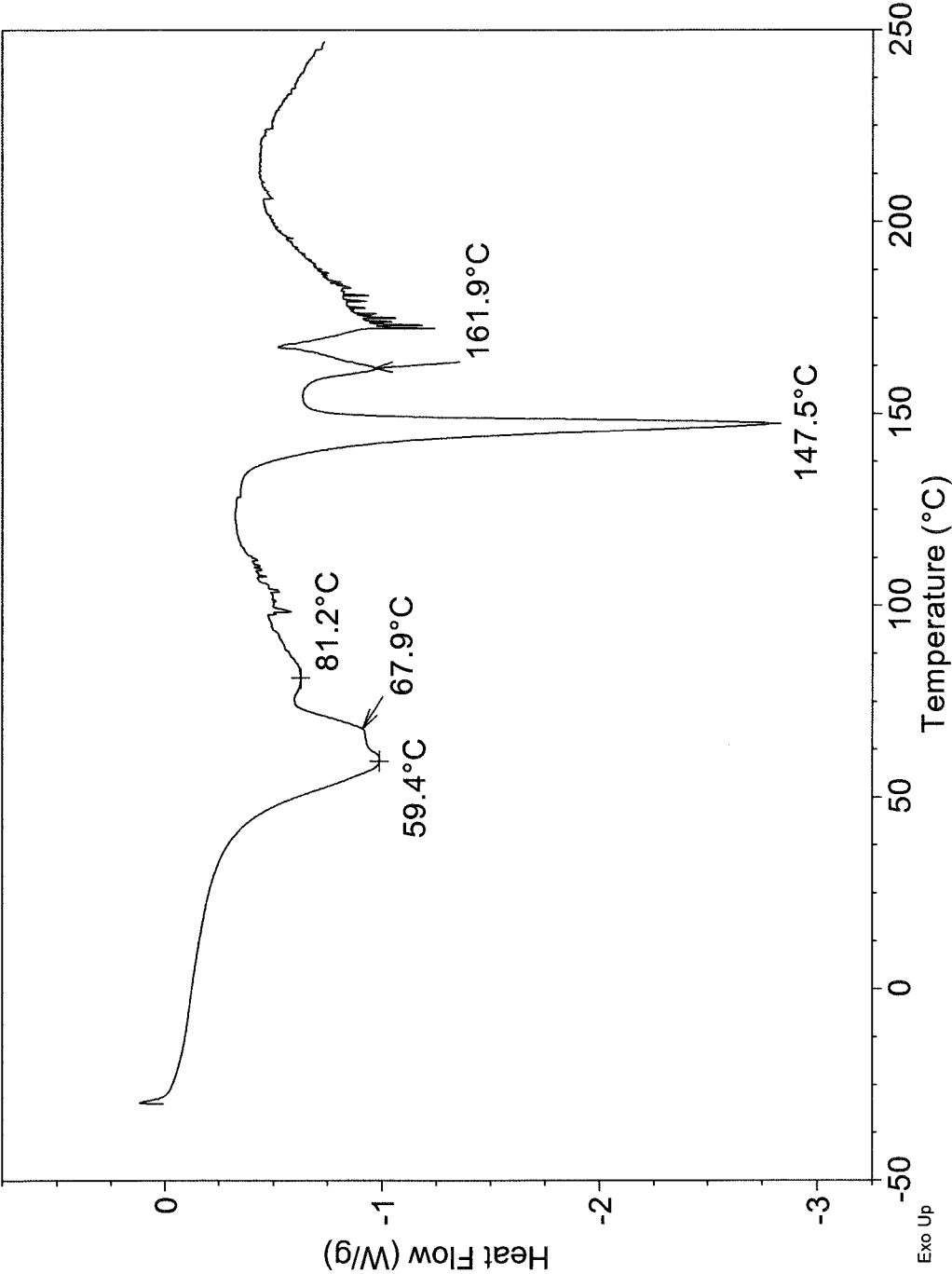
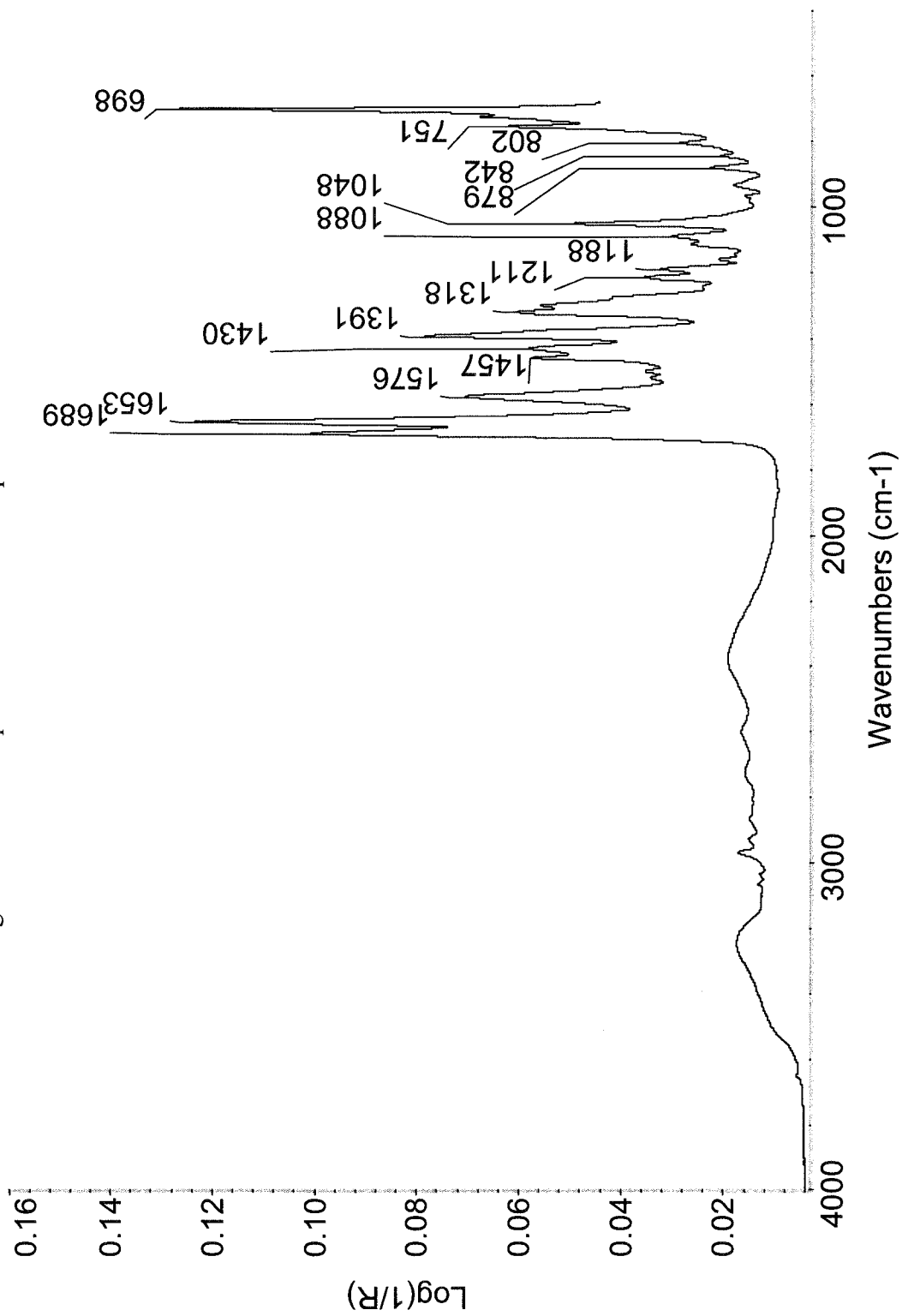


Figure 32 - Differential thermogram scanning calorimetry of Form W di-pidotimod benzathine



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Figure 33-Infrared spectrum of Form W di-pidotimod benzathine



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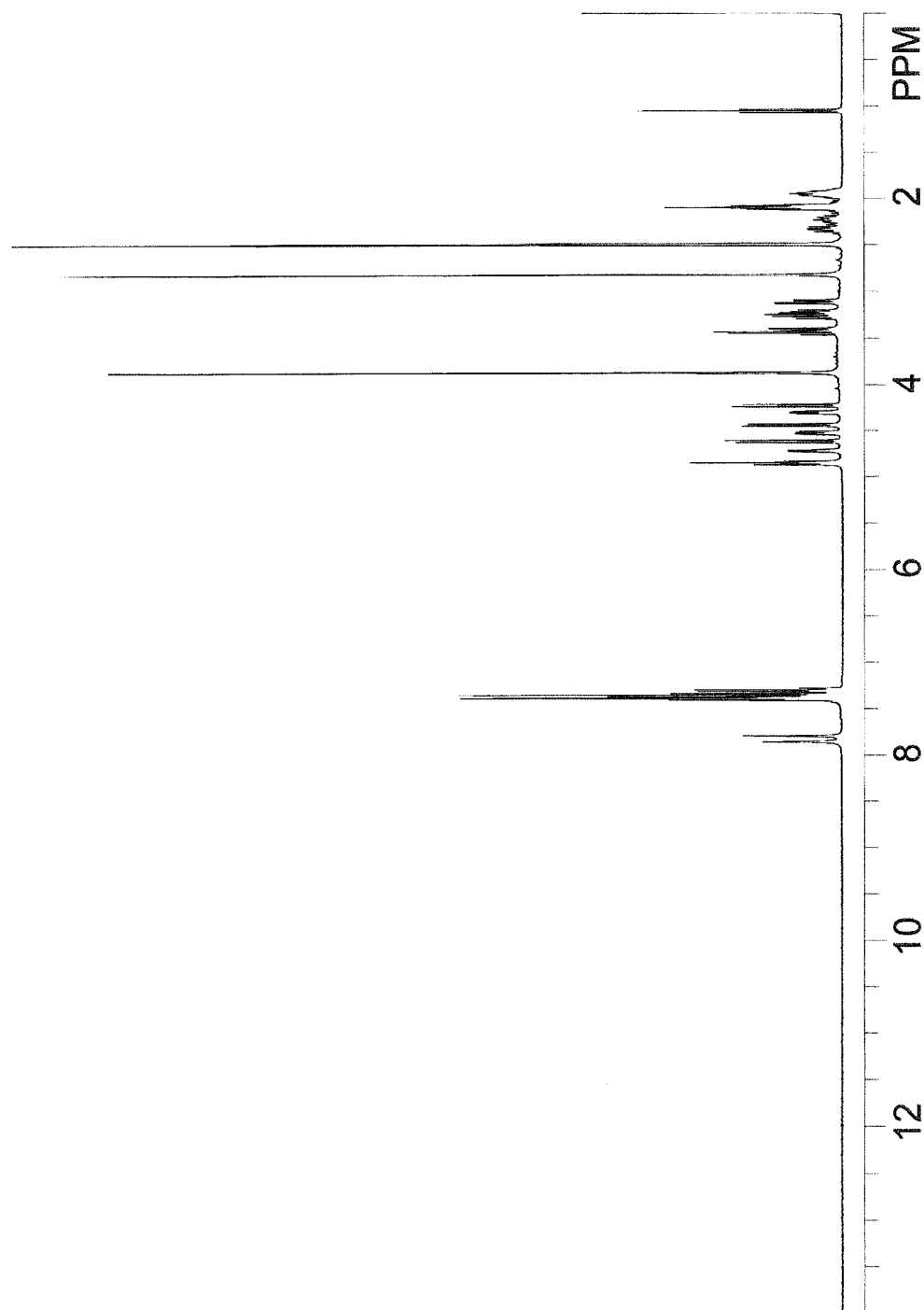
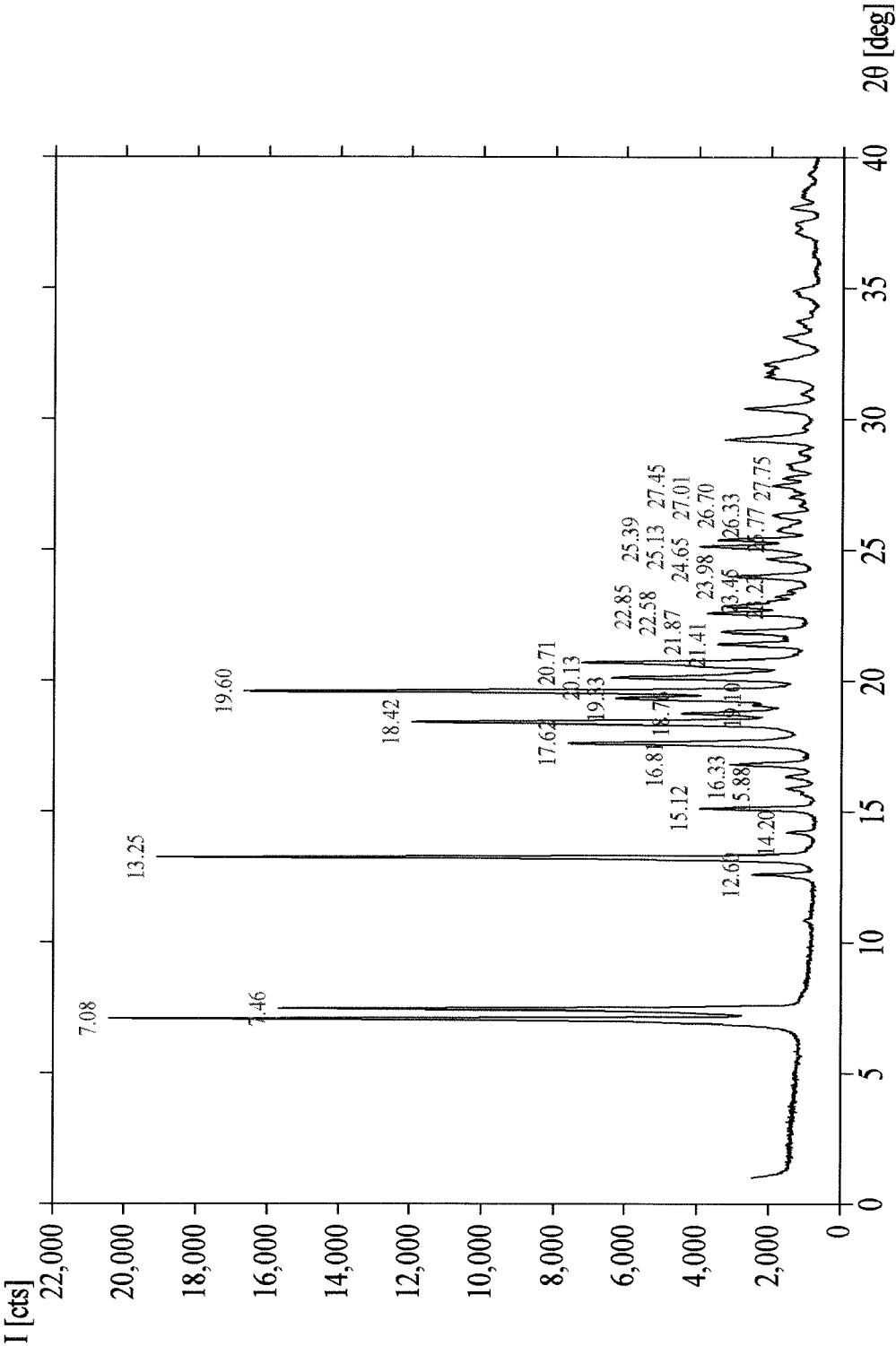
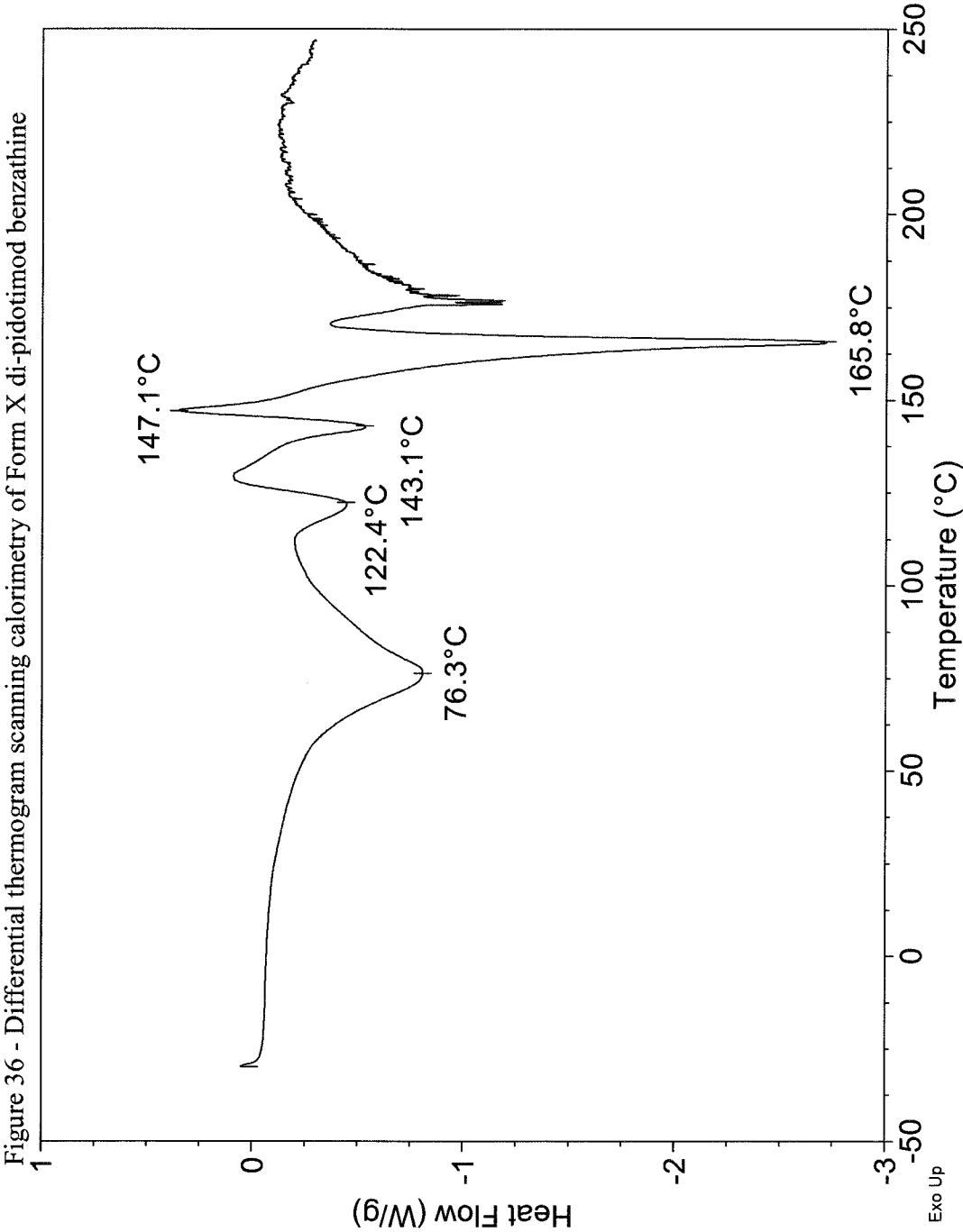
Figure 34 - ^1H solution-state NMR spectrum of Form W di-pidotimod benzathine

Figure 35 - Peak-picked x-ray powder diffraction pattern of Form X di-Pidotimod Benzathine





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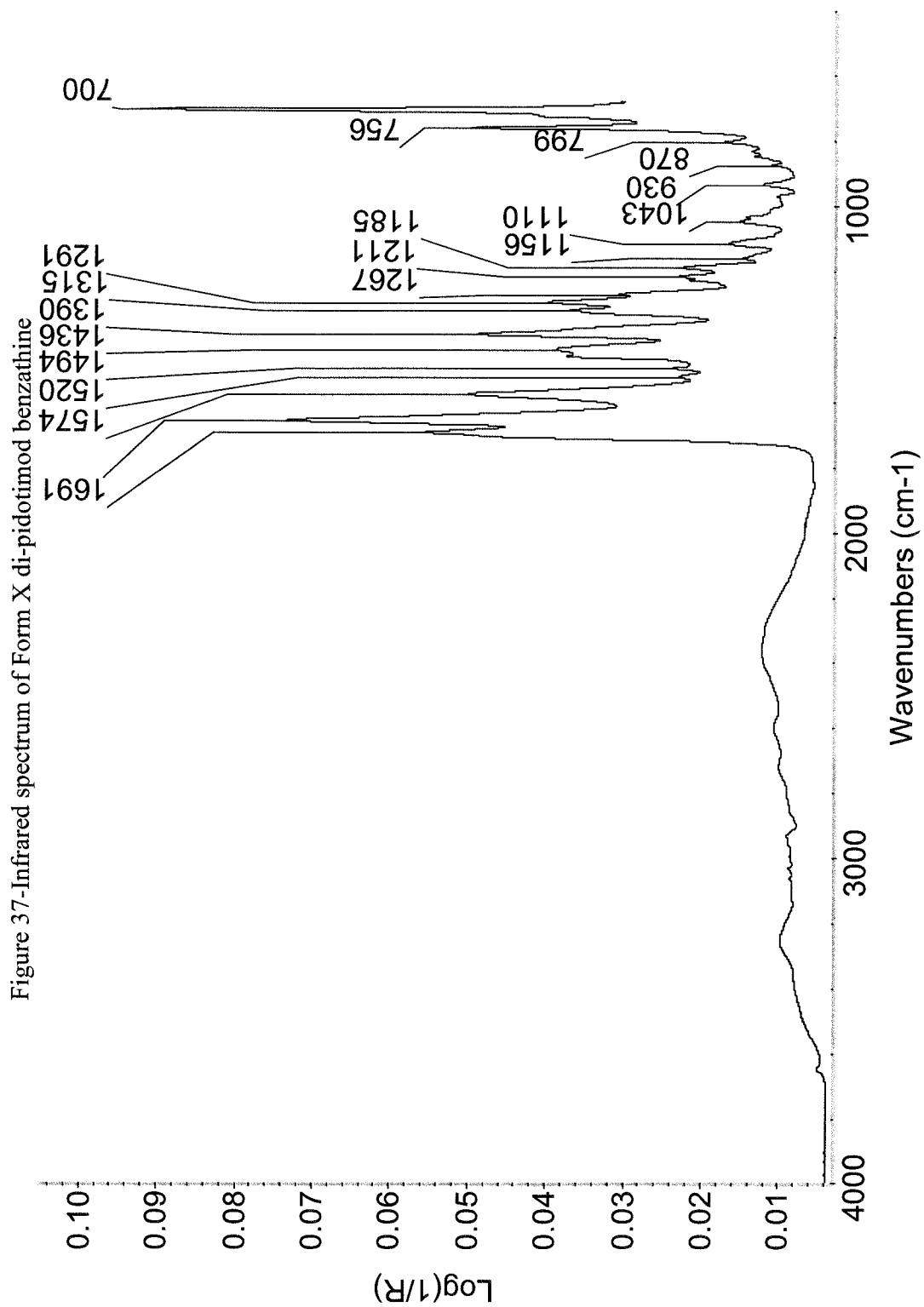


Figure 38 - ¹H solution-state NMR spectrum of Form X di-pidotimod benzathine

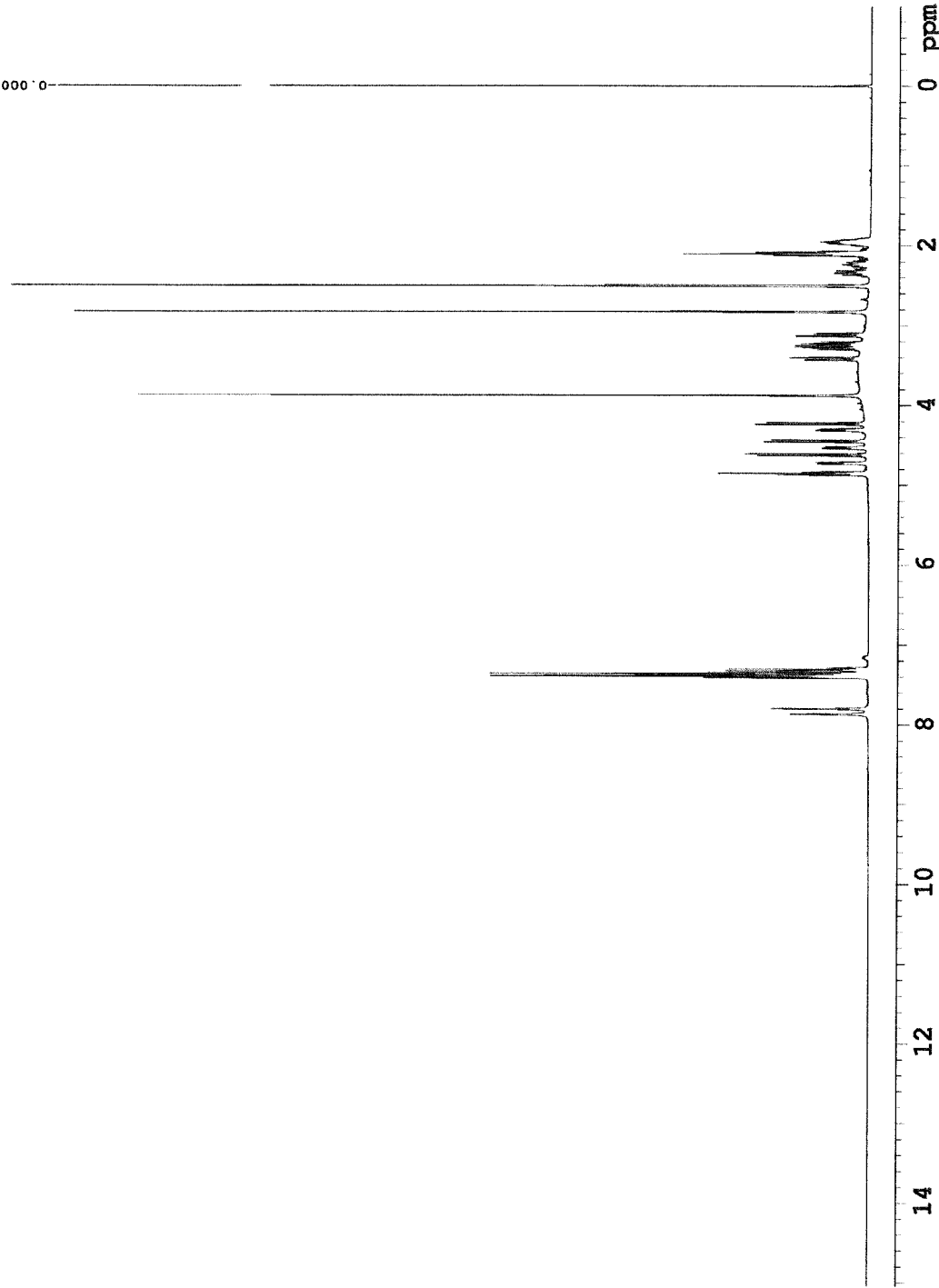
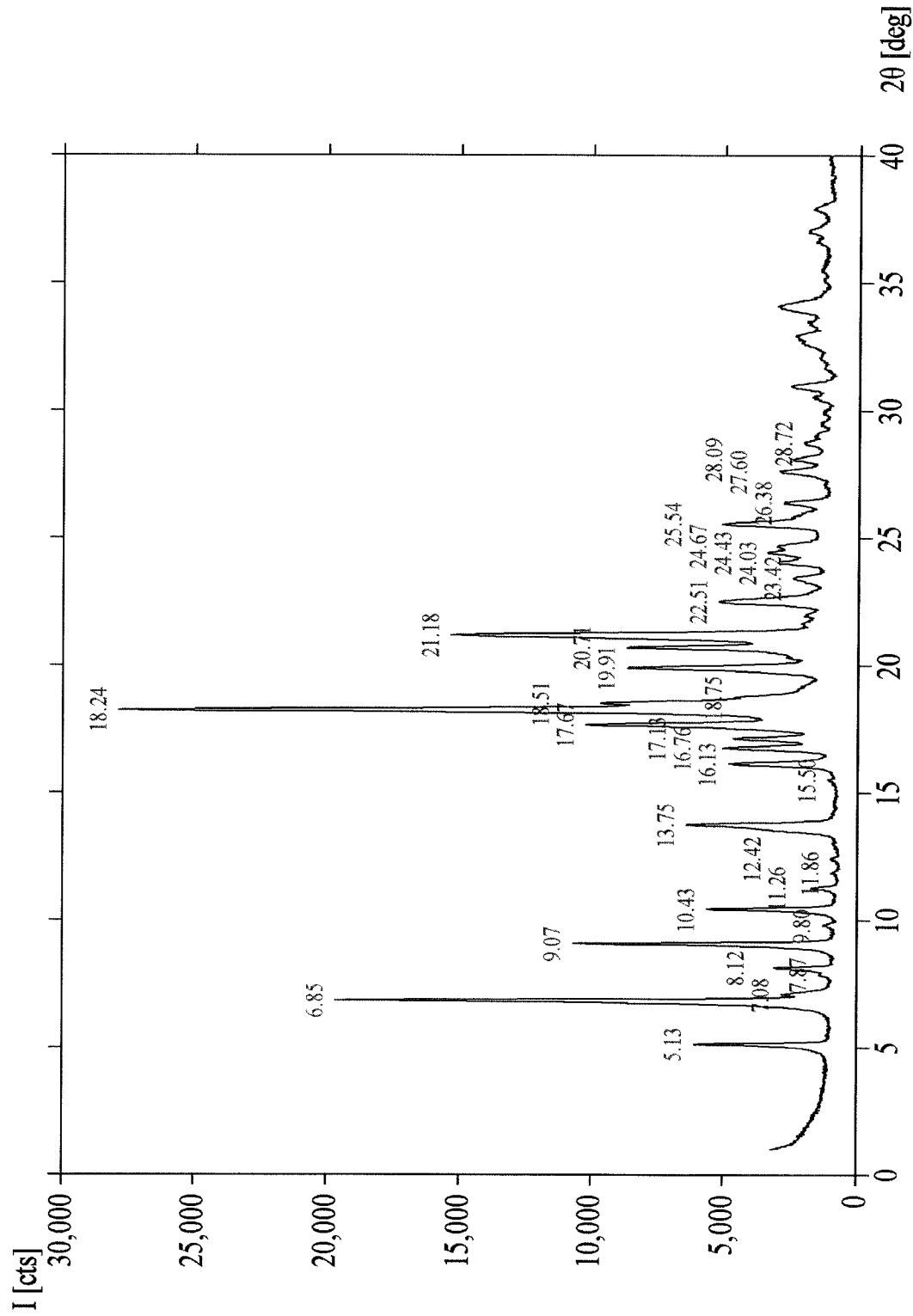
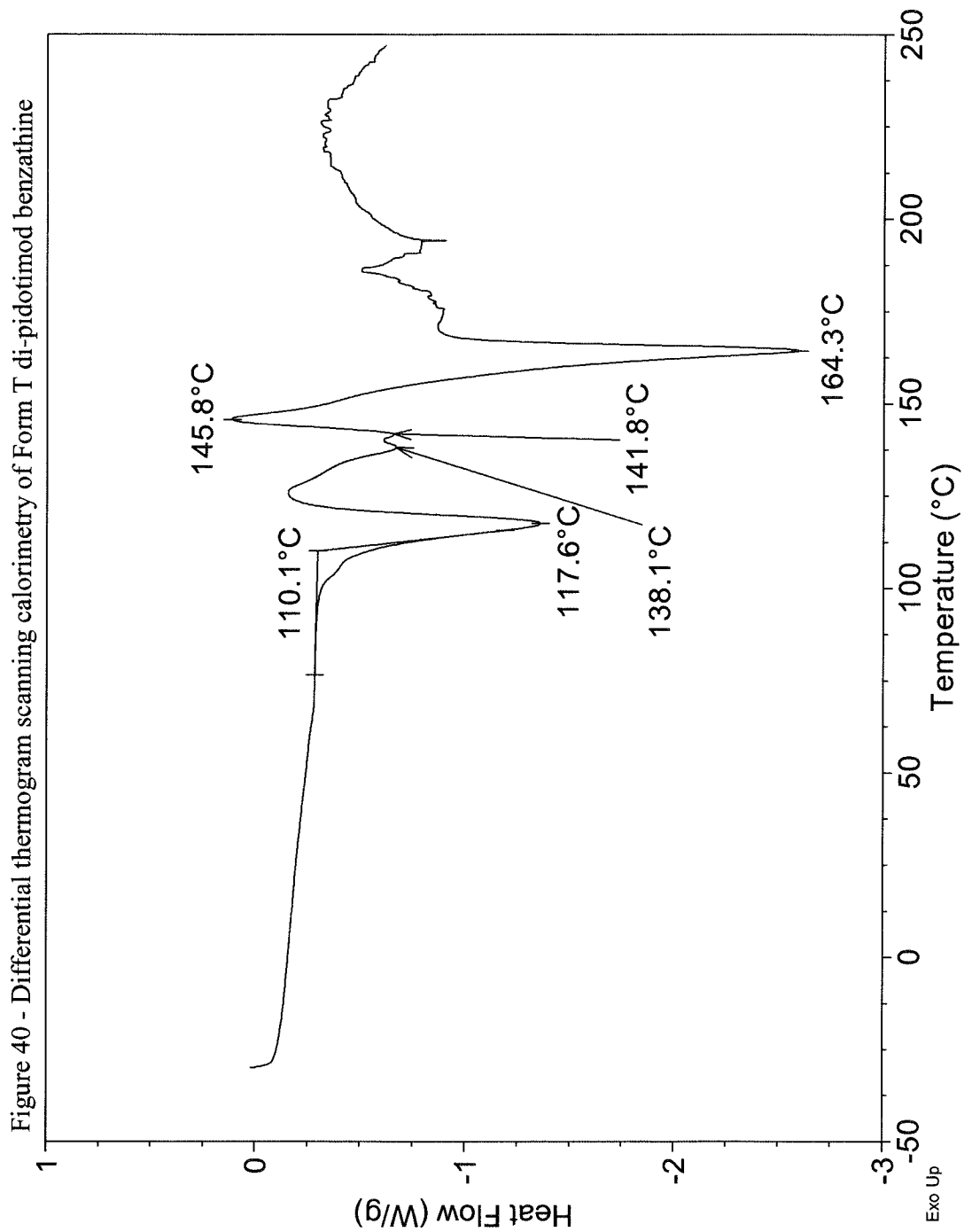


Figure 39 - Peak-picked x-ray powder diffraction pattern of Form T di-Pidotimod Benzathine





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Figure 41 - Infrared spectrum of Form T di-pidotimod benzathine

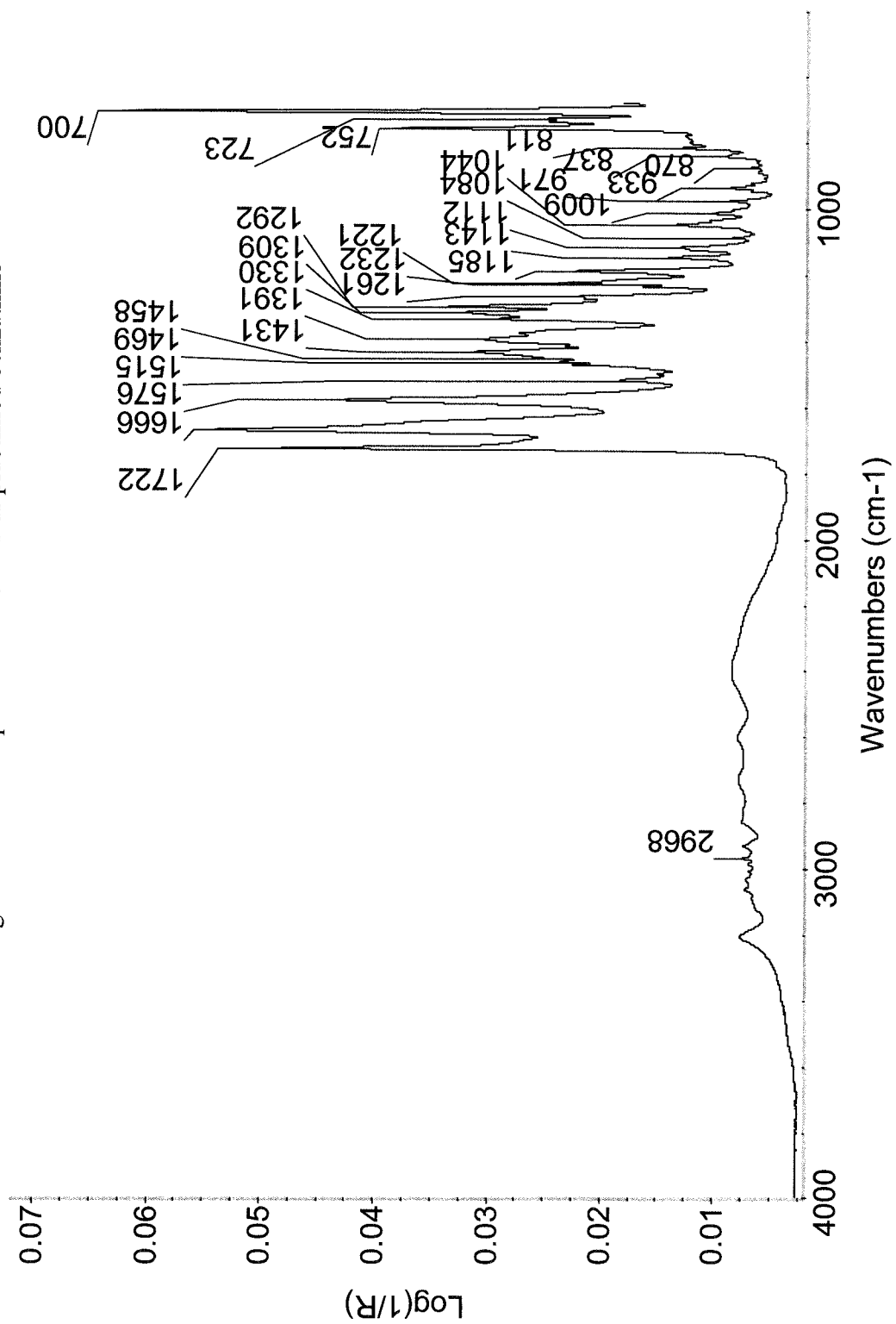


Figure 42 - ¹H solution-state NMR spectrum of Form T di-pidotimod benzathine

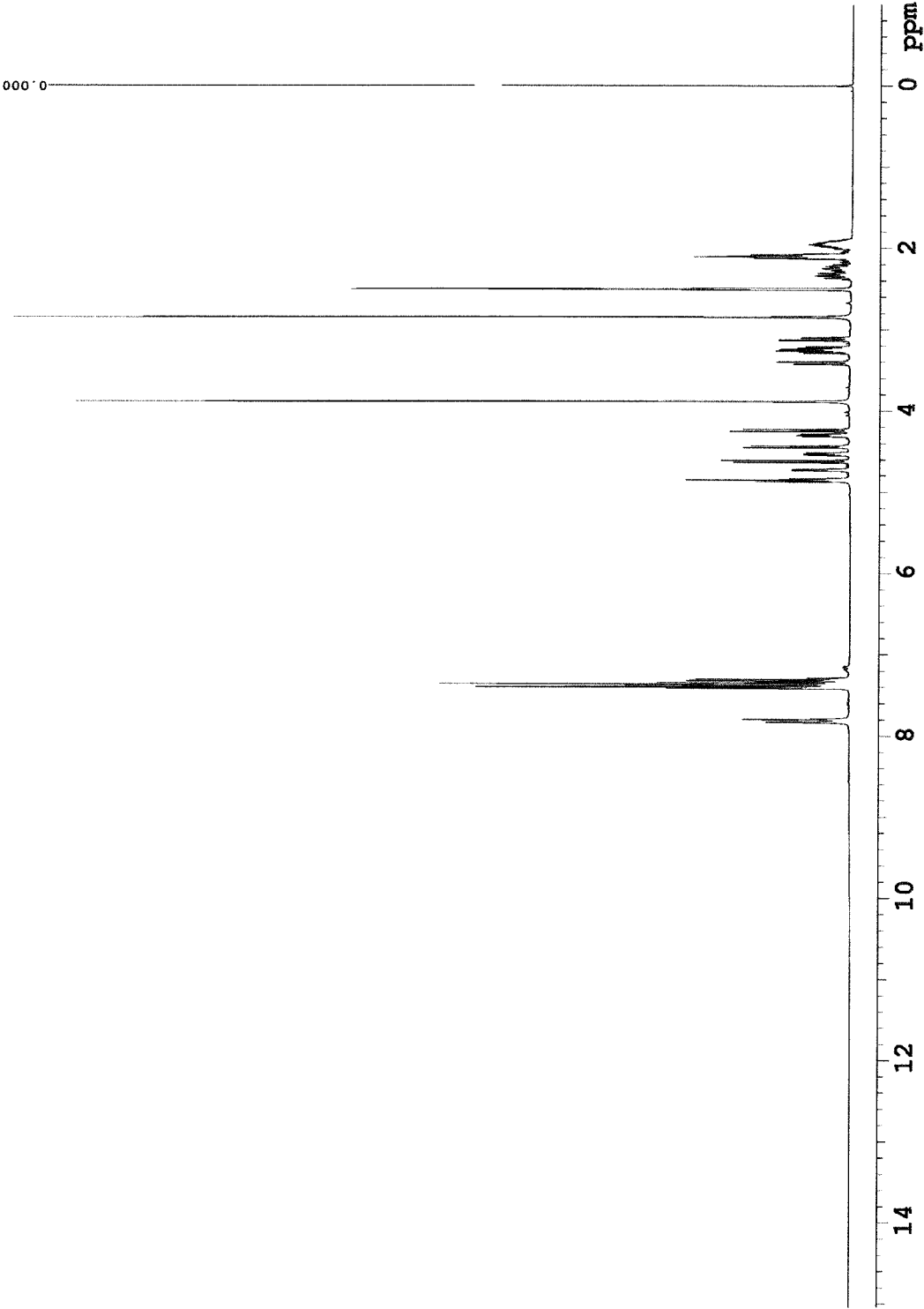


Figure 43 – Thermogravimetric analysis thermogram of Form J di-pidotimod benzathine

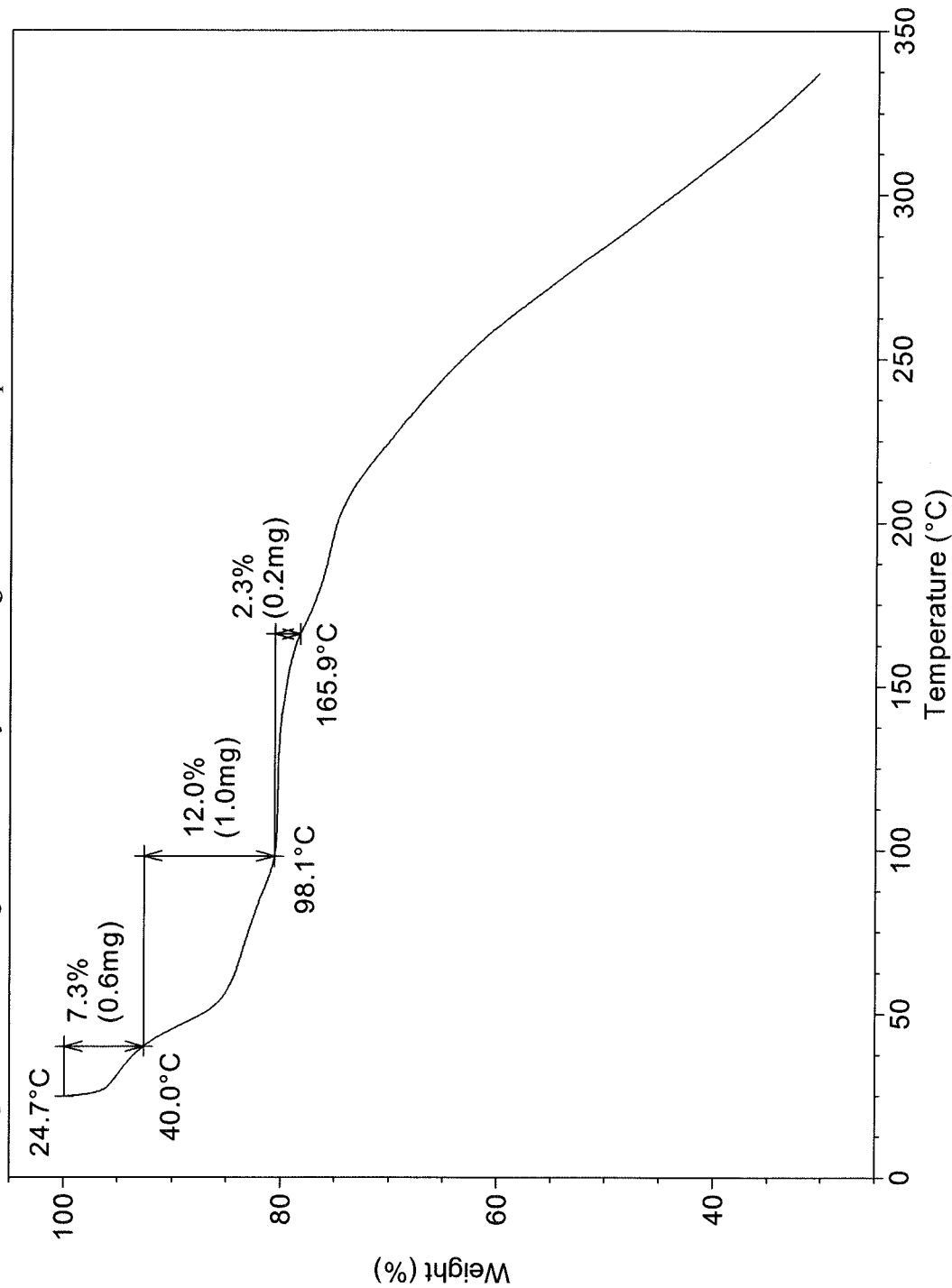


Figure 44a – Thermogravimetric analysis thermogram of Form O di-pidotimod benzathine

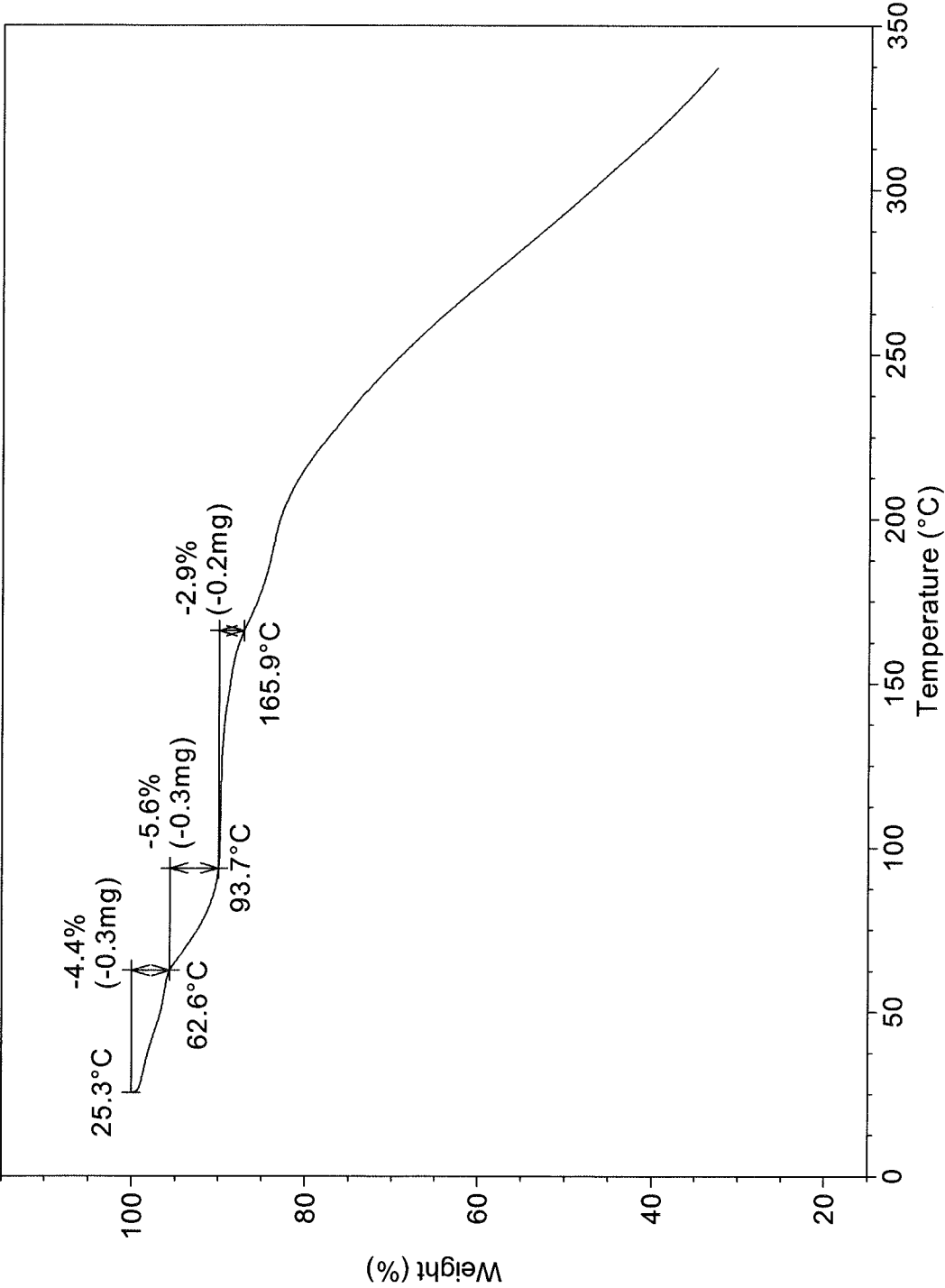


Figure 44b – Thermogravimetric analysis thermogram of Form O di-pidotimod benzathine

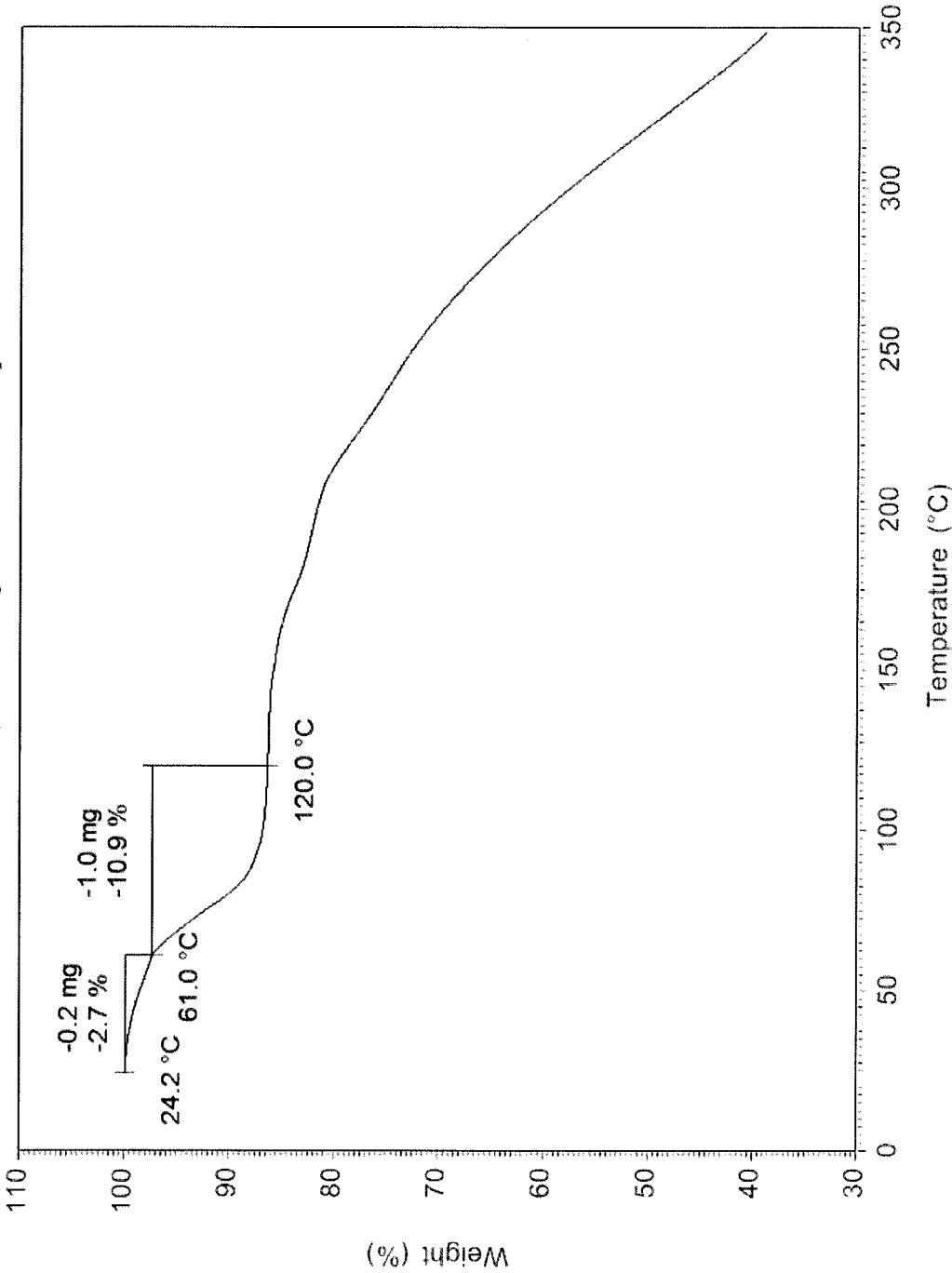


Figure 45 – Thermogravimetric analysis thermogram of Form S di-pidotimod benzathine

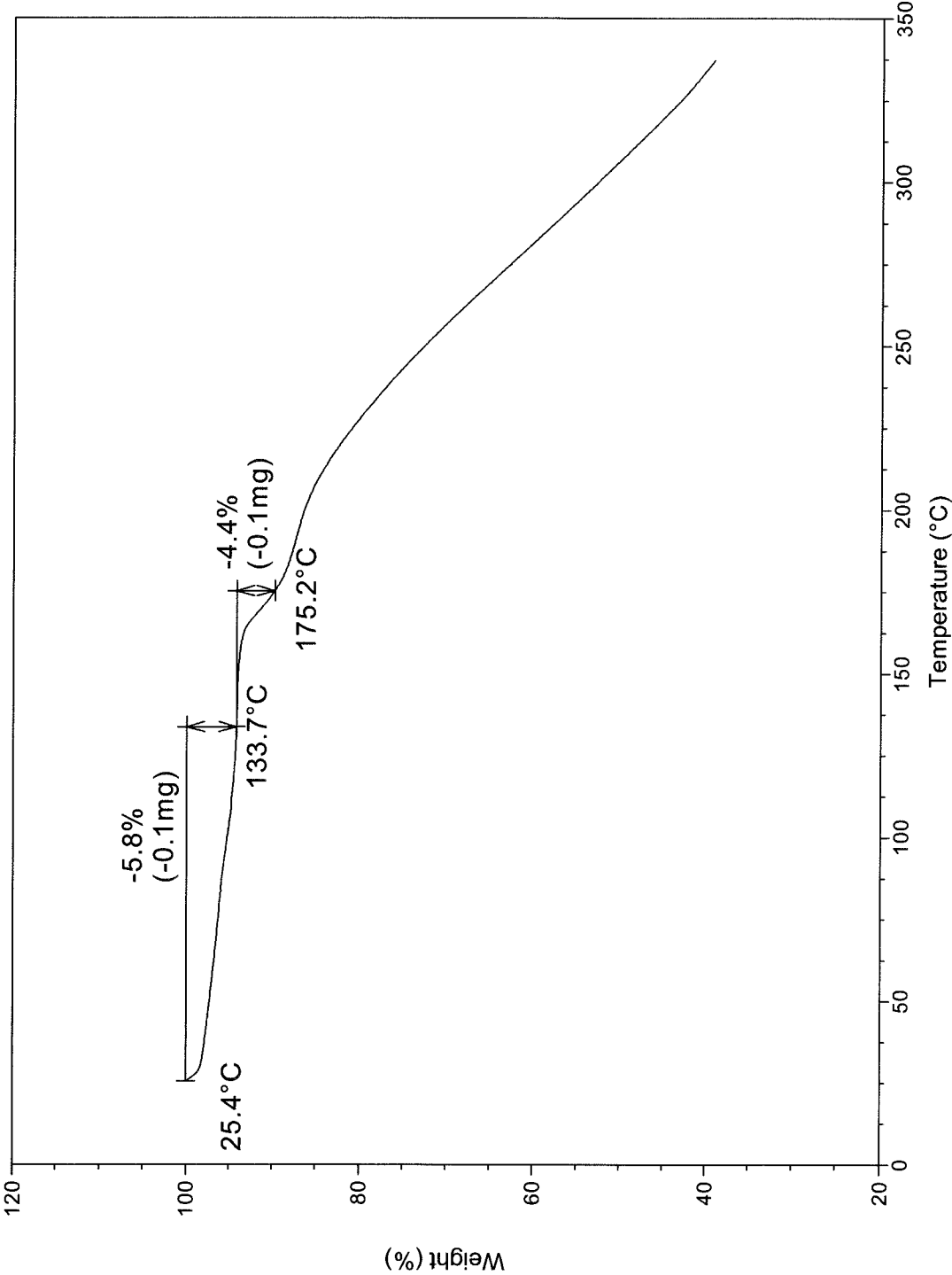


Figure 46 – Thermogravimetric analysis thermogram of Form W di-pidotimod benzathine

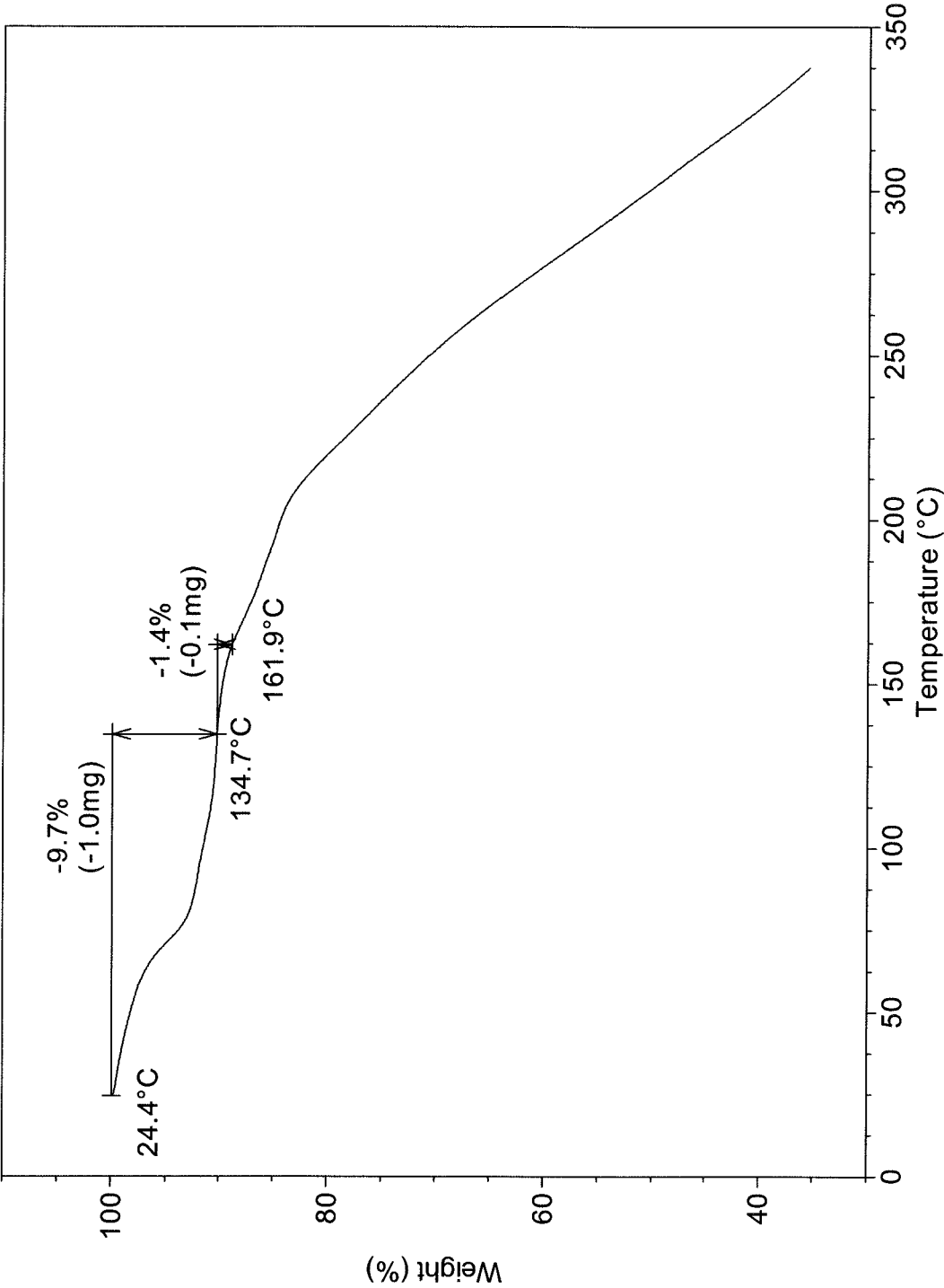


Figure 47 – Thermogravimetric analysis thermogram of Form X di-pidotimod benzathine

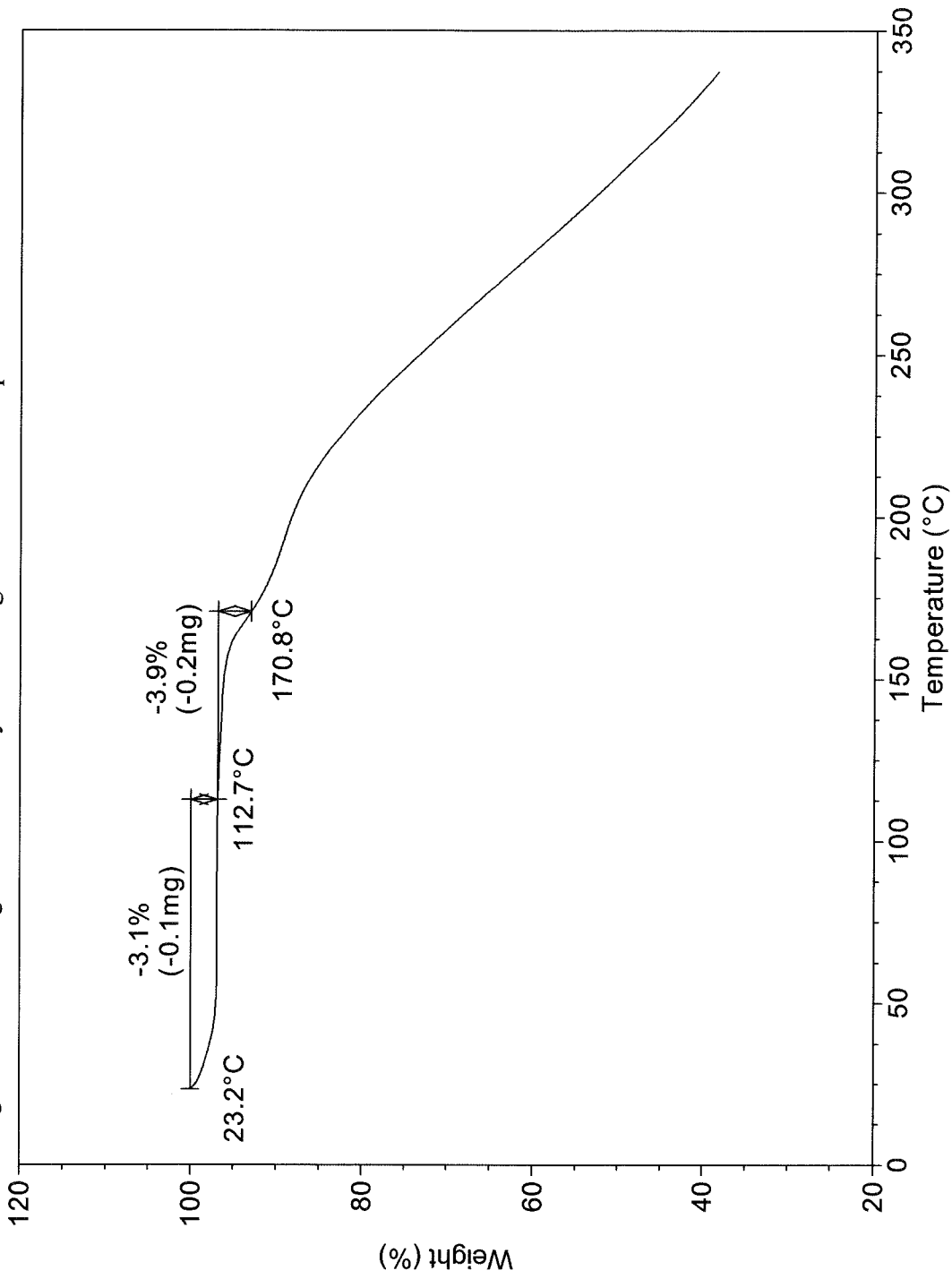


Figure 48 – Thermogravimetric analysis thermogram of Form T di-pidotimod benzathine

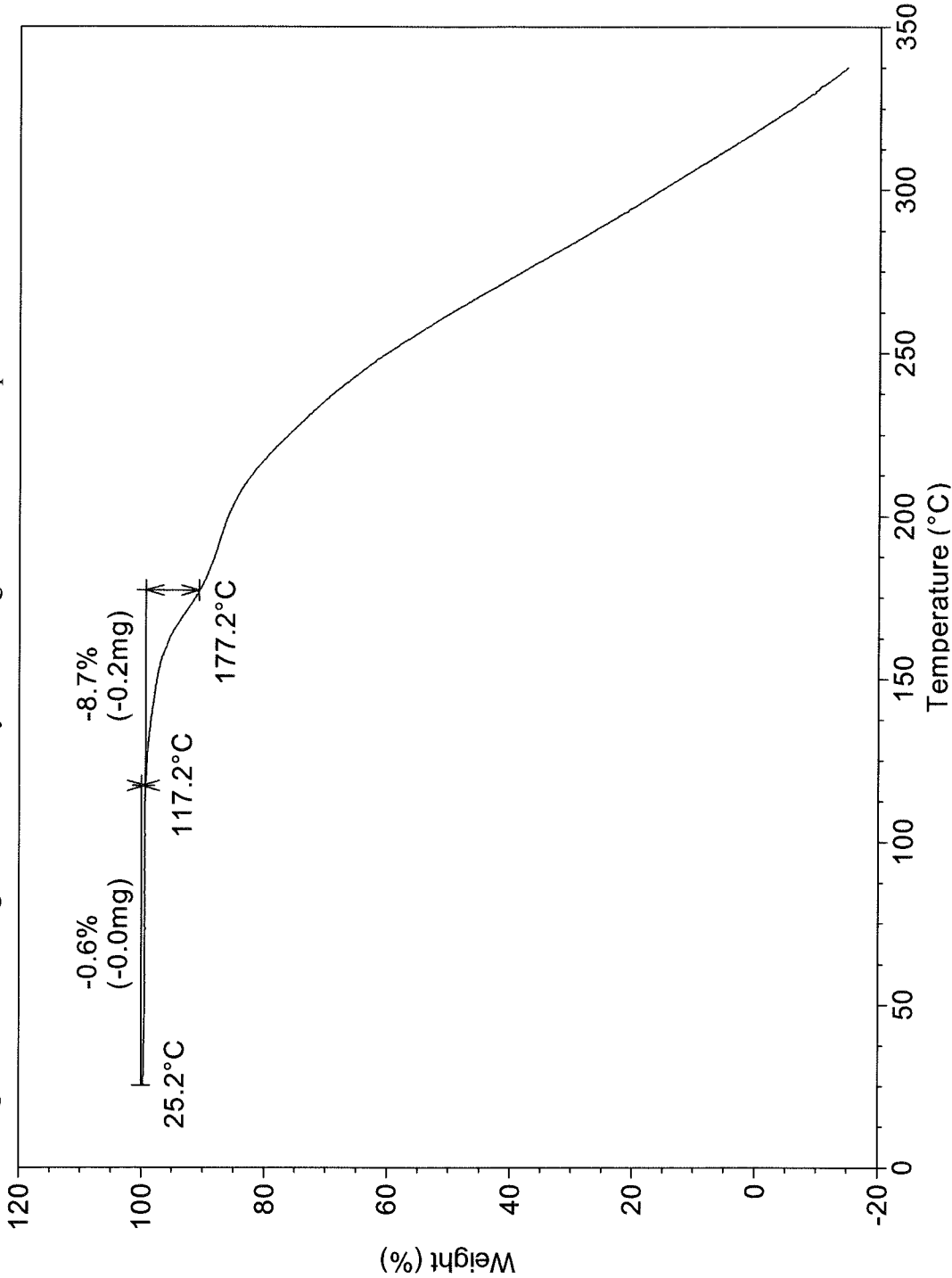
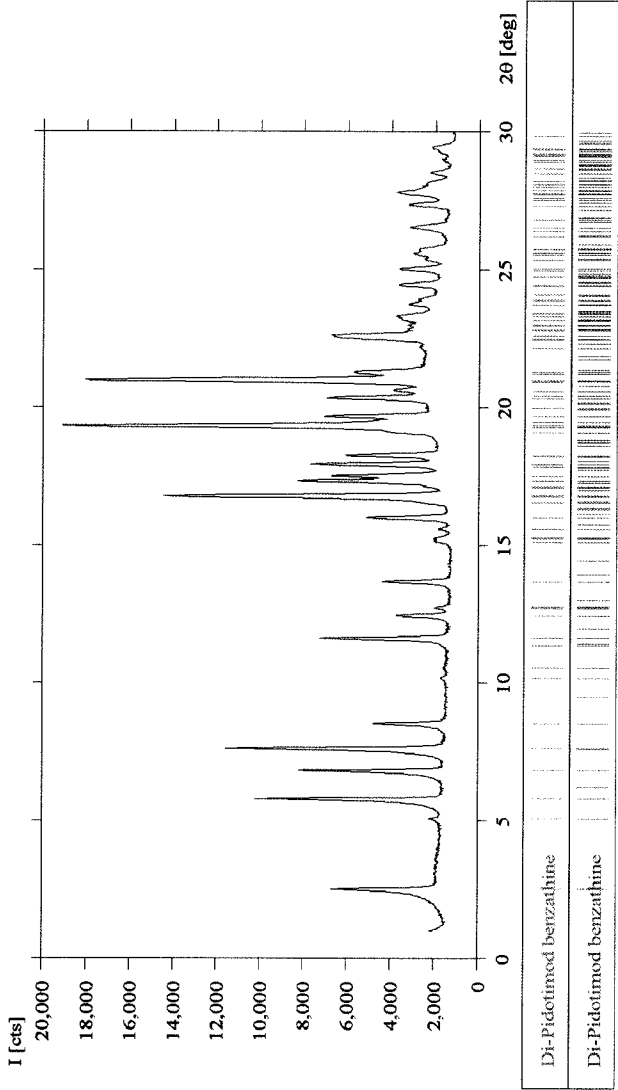
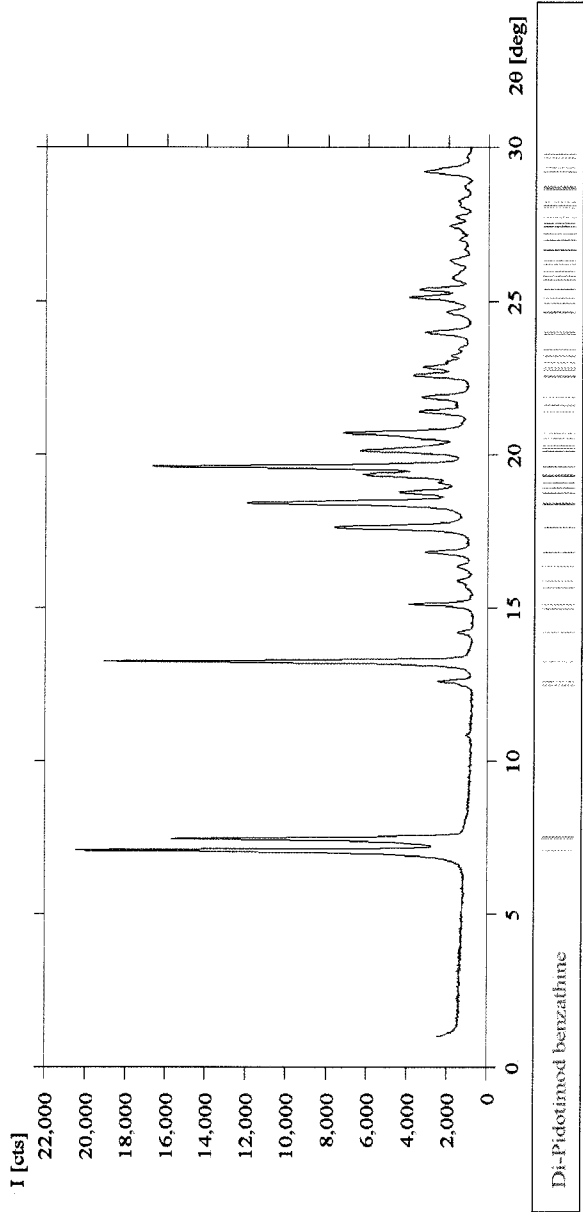


Figure 49 – Indexing solution for Form S di-pidotimod benzathine



Di-Pidotimod benzathineDi-Pidotimod benzathine		
Bravais Type	Body-Centered	Primitive
a [Å]	Orthorhombic	Orthorhombic
b [Å]	5.695	5.695
c [Å]	15.569	15.569
α [deg]	69.526	69.526
β [deg]	90	90
γ [deg]	90	90
Volume [Å ³ /cell]	6,164.7	6,164.6
Chiral Contents?	Chiral	Chiral
Extinction Symbol	I - - -	P 2 ₁ 2 ₁ 2 ₁
Space Group(s)	I222 (23)	P2 ₁ 2 ₁ 2 ₁ (19)

Figure 50 – Indexing solution for Form X di-pidotimod benzathine



Di-Pidotimod benzathine	
Bravais Type	Triclinic
a [Å]	5.784
b [Å]	13.645
c [Å]	14.068
α [deg]	62.46
β [deg]	87.65
γ [deg]	78.16
Volume [Å ³ /cell]	961.7
Chiral Contents?	Chiral
Extinction Symbol	P -
Space Group(s)	P1 (1)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/050439

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D417/06 A61K31/4025 A61P11/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; WANG, HANBIN: "Immunostimulant intramuscular injection of pidotimod", XP002738864, retrieved from STN Database accession no. 2010:863370 cited in the application abstract & CN 101 766 603 A (BEIJING HOPE HUGE PHARMACEUTICAL SCIENCE AND TECHNOLOGY CO., LTD., PEO) 7 July 2010 (2010-07-07) ----- -/--	1-43



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"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

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Date of the actual completion of the international search

10 March 2016

Date of mailing of the international search report

21/03/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Fax: (+31-70) 340-3016

Authorized officer

Gregoire, Ariane

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/050439

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YANG, XIHONG: "Water soluble pidotimod complex salt, and its preparation method", XP002738865, retrieved from STN Database accession no. 2006:518550 cited in the application abstract & CN 1 680 427 A (PEOP. REP. CHINA) 12 October 2005 (2005-10-12) -----	1-43
A	GIAN VINCENZO ZUCCOTTI ET AL: "Pidotimod: the past and the present", ITALIAN JOURNAL OF PEDIATRICS, BIOMED CENTRAL LTD, LONDON, UK, vol. 39, no. 1, 6 December 2013 (2013-12-06), page 75, XP021170482, ISSN: 1824-7288, DOI: 10.1186/1824-7288-39-75 abstract -----	1-43
A	GOULD ET AL: "Salt selection for basic drugs", INTERNATIONAL JOURNAL OF PHARMACEUTICS, ELSEVIER BV, NL, vol. 33, no. 1-3, 1 November 1986 (1986-11-01), pages 201-217, XP025813036, ISSN: 0378-5173, DOI: 10.1016/0378-5173(86)90055-4 [retrieved on 1986-11-01] table 1 -----	1-43