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(71) Applicant *(for all designated States except US)*: **LEXICON PHARMACEUTICALS, INC.** [US/US]; 8800 Technology Forest Place, The Woodlands, TX 77381 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **WU, Wenxue** [US/US]; 53 Zaitz Farm Road, Princeton Junction, New Jersey 08550 (US). **ZHANG, Haiming** [CN/US]; 3 Coburn Road, Pennington, New Jersey 08534 (US).

(74) Agent: **BACHRACH, Max**; Lexicon Pharmaceuticals, Inc., 8800 Technology Forest Place, The Woodlands, TX 77381 (US).

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(54) **Title:** SOLID FORMS OF *(E)* -1- (4- ( (IR, 2S, 3R) -1, 2, 3, 4-TETRAHYDROXYBUTYL) -1H-IMIDAZOL-2-YL) ETHANONE OXIME

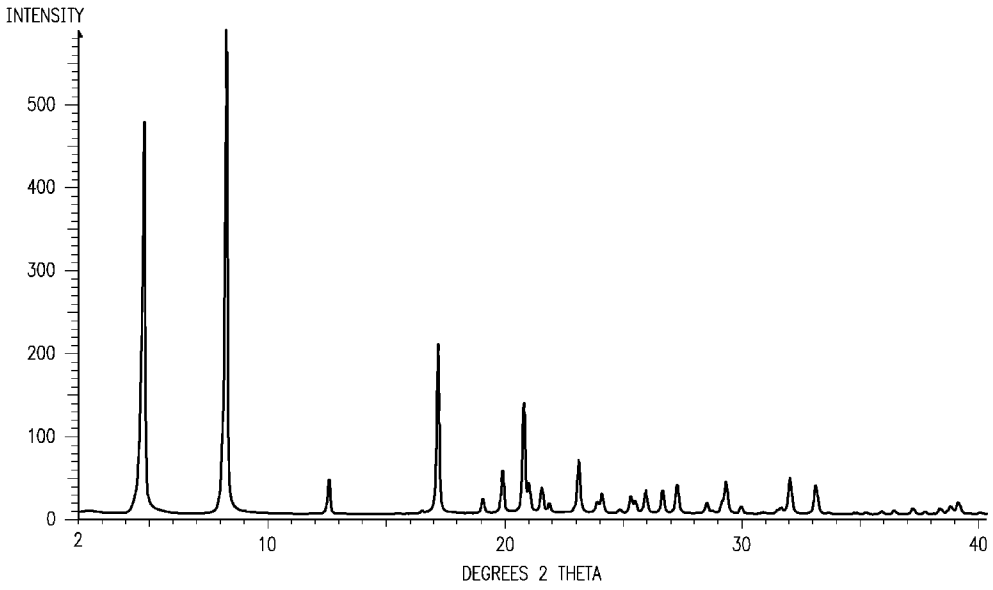


FIG. 1

(57) **Abstract:** Amorphous and crystalline solid forms of *(E)*-M (4-((1 R,2S,3R)-1,2,3,4-tertahydroxybutyl)- 1 H-imidazol-2-yl)ethanone oxime are disclosed. These specific solid forms may be used as sphingosite-1 phosphate modulators for treating autoimmune and inflammatory diseases.

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# SOLID FORMS OF (E)-1-(4-((1R,2S,3R)-1,2,3,4-TETRAHYDROXYBUTYL)-1H-IMIDAZOL-2-YL) ETHANONE OXIME

This application claims priority to U.S. provisional application no. 60/923,037, filed April 12, 2007, the entirety of which is incorporated herein by reference.

## 1. FIELD OF THE INVENTION

This invention relates to solid forms of *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime and methods of their use for the treatment, prevention and management of various diseases and disorders.

## 2. BACKGROUND

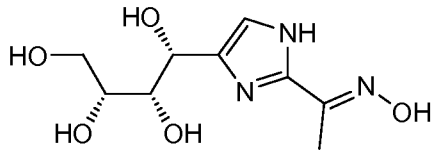
Different solid forms of the same compound can have substantially different properties. For example, the amorphous form of a drug may exhibit different dissolution characteristics and different bioavailability patterns than its crystalline form(s), properties which can affect how the drug must be administered to achieve optimal effect. Amorphous and crystalline forms of a drug may also have different handling properties (*e.g.*, flowability, compressibility), dissolution rates, solubilities and stabilities, all of which can affect the manufacture of dosage forms. Consequently, access to multiple forms of a drug is desirable for a variety of reasons. Moreover, regulatory authorities (*e.g.*, the U.S. Food and Drug Administration) may require the identification of all solid (*e.g.*, polymorphic) forms of a new drug substance before approving products containing it. A. Goho, Science News 166(8):122-123 (2004).

Compounds may exist in one or more crystalline forms, but the existence and characteristics of those forms cannot be predicted with any certainty. In addition, no standard procedure exists for the preparation of all possible polymorphic forms of a compound. And even after one polymorph has been identified, the existence and characteristics of other forms can only be determined by additional experimentation. *Id.*

The compound *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime affects the sphingosine-1-phosphate pathway, and is believed to be useful in the treatment of diseases such as rheumatoid arthritis and type I diabetes. *See* U.S. patent application 11/698,253 to Augeri *et al.*, filed January 25, 2007.

## 3. SUMMARY OF THE INVENTION

This invention is directed, in part, to novel solid forms of *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime:




and hydrates thereof. Solid forms include amorphous and crystalline forms.

The invention also encompasses dosage forms comprising the solid forms, and methods of their use to manage, treat and prevent a variety of diseases and disorders.

## 4. BRIEF DESCRIPTION OF THE FIGURES

Certain aspects of this invention can be understood with reference to the following figures:

Figure 1 provides a X-ray power diffraction spectrum of a crystalline form of anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime. The spectrum was obtained on a Bruker D8 Advance system using copper Kα radiation, a range of 2-50 degrees 2θ, a step size of 0.017 degrees 2θ, and a step time of 103 s with a VANTEC-1 detector.

Figure 2 provides a Raman spectrum of a crystalline form of anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime. The spectrum was obtained on a Bruker RFS100 spectrometer using a 1064 nm Nd:YAG laser (10 mW) for excitation and a germanium detector. The spectrum was measured over the range of 3500 – 25 $cm^{-1}$ with a resolution of 2 $cm^{-1}$.

Figure 3 provides a X-ray power diffraction spectrum of a crystalline form of *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime dihydrate. The spectrum was obtained on a Bruker D8 Advance system using copper Kα radiation, a range of 2-50 degrees 2θ, a step size of 0.017 degrees 2θ, and a step time of 103 s with a VANTEC-1 detector.

Figure 4 provides a Raman spectrum of a crystalline form of *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime dihydrate. The spectrum was obtained on a Bruker RFS100 spectrometer using a 1064 nm Nd:YAG laser (10 mW) for

excitation and a germanium detector. The spectrum was measured over the range of 3500 – 25 $cm^{-1}$ with a resolution of 2 $cm^{-1}$.

Figure 5 provides a view of a molecule from a crystal structure obtained from a single crystal of *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime dihydrate. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms are displayed with an arbitrarily small radius.

## 5. DETAILED DESCRIPTION

This invention is directed, in part, to novel solid forms of *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime, which is a potent suppressor of circulating lymphocytes.

### 5.1. Definitions

Unless otherwise indicated, the terms "manage," "managing" and "management" encompass preventing the recurrence of the specified disease or disorder in a patient who has already suffered from the disease or disorder, and/or lengthening the time that a patient who has suffered from the disease or disorder remains in remission. The terms encompass modulating the threshold, development and/or duration of the disease or disorder, or changing the way that a patient responds to the disease or disorder.

Unless otherwise indicated, the terms "prevent," "preventing" and "prevention" contemplate an action that occurs before a patient begins to suffer from the specified disease or disorder, which inhibits or reduces the severity of the disease or disorder. In other words, the terms encompass prophylaxis.

Unless otherwise indicated, a "prophylactically effective amount" of a compound is an amount sufficient to prevent a disease or condition, or one or more symptoms associated with the disease or condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the disease. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

Unless otherwise indicated, a solid that is "substantially amorphous" is substantially free of crystalline compound. Examples of a substantially amorphous solid compound contain less than about 20, 15, 10, 5, 3 or 1 weight percent crystalline compound.

Unless otherwise indicated, a solid that is "substantially crystalline" is substantially free of amorphous compound. Examples of a substantially crystalline solid compound contain less than about 20, 15, 10, 5, 3 or 1 weight percent amorphous compound.

Unless otherwise indicated, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment or management of a disease or condition, or to delay or minimize one or more symptoms associated with the disease or condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment or management of the disease or condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of a disease or condition, or enhances the therapeutic efficacy of another therapeutic agent.

Unless otherwise indicated, the term "include" has the same meaning as "include, but are not limited to," and the term "includes" has the same meaning as "includes, but is not limited to." Similarly, the term "such as" has the same meaning as the term "such as, but not limited to."

Unless otherwise indicated, one or more adjectives immediately preceding a series of nouns is to be construed as applying to each of the nouns. For example, the phrase "optionally substituted alky, aryl, or heteroaryl" has the same meaning as "optionally substituted alky, optionally substituted aryl, or optionally substituted heteroaryl."

It should be noted that a chemical moiety that forms part of a larger compound may be described herein using a name commonly accorded it when it exists as a single molecule or a name commonly accorded its radical. For example, the terms "pyridine" and "pyridyl" are accorded the same meaning when used to describe a moiety attached to other chemical moieties. Thus, the two phrases "XOH, wherein X is pyridyl" and "XOH, wherein X is pyridine" are accorded the same meaning, and encompass the compounds pyridin-2-ol, pyridin-3-ol and pyridin-4-ol.

It should also be noted that if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or the portion of the structure is to be interpreted as encompassing all stereoisomers of it. Moreover, any atom shown in a drawing with unsatisfied valences is assumed to be attached to enough hydrogen atoms to satisfy the valences. In addition, chemical bonds depicted with one solid

line parallel to one dashed line encompass both single and double (*e.g.*, aromatic) bonds, if valences permit.

### 5.2. Solid Forms

This invention encompasses solid forms of *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime.

One embodiment of the invention encompasses anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime. In a particular embodiment, the compound is amorphous. In another, the compound is crystalline. A particular crystalline form provides a X-ray powder diffraction (XRPD) pattern with peaks at about 4.7, 8.2, 12.5, 17.1, 19.9, 20.8, 29.3, 32.0 and/or 33.1 degrees 2θ. As those skilled in the art are well aware, the relative intensities of peaks in a XRPD pattern can vary depending on how the sample is prepared and how the data is collected. With this in mind, an example of a XRPD pattern of this crystalline form is provided in Figure 1. An example of a Raman spectrum of this crystalline form is provided in Figure 2.

Another embodiment of the invention encompasses *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime monohydrate. In a particular embodiment, the compound is amorphous. In another, the compound is crystalline. As measured by differential scanning calorimetry (DSC), a particular crystalline form has a melting point of roughly 153°C (broad peak).

Another embodiment of the invention encompasses *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime dihydrate. In a particular embodiment, the compound is amorphous. In another, the compound is crystalline. A particular form provides a XRPD pattern with peaks at about 12.5, 14.1, 16.9, 20.4, 25.2 and/or 27.0 degrees 2θ. An example of a XRPD pattern of this crystalline form is provided in Figure 3. An example of a Raman spectrum of this crystalline form is provided in Figure 4.

This invention encompasses mixtures of crystalline and amorphous forms of the compounds disclosed herein (*e.g.*, mixtures containing less than about 50, 40, 30, 20, 10, 5 or 1 weight percent amorphous material). Also encompassed are mixtures of anhydrous, monohydrate and dihydrate *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime (*e.g.*, mixtures containing less than about 50, 40, 30, 20, 10, 5 or 1 weight percent anhydrous, monohydrate or dihydrate).

### 5.3. Methods of Use

This invention encompasses a method of modulating (*e.g.*, increasing) the amount of S1P in a patient (*e.g.*, a mouse, rat, dog, cat or human) in need thereof, which comprises administering to the patient an effective amount of a compound of the invention (*i.e.*, a compound disclosed herein).

Another embodiment encompasses a method of reducing the number of T-cells in the blood of a patient, which comprises administering to the patient an effective amount of a compound of the invention.

Another embodiment encompasses a method of treating, managing or preventing a disease affected by (or having symptoms affected by) S1P levels, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of a compound of the invention.

Another embodiment encompasses a method of suppressing immune response in a patient, which comprises administering to the patient an effective amount of a compound of the invention.

Another embodiment encompasses a method of treating, managing or preventing an autoimmune or inflammatory disease or disorder, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of a compound of the invention. Examples of diseases and disorders include ankylosing spondylitis, asthma (*e.g.*, bronchial asthma), atopic dermatitis, Behcet's disease, graft-vs-host disease, Kawasaki syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, pollinosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleroderma, transplant rejection (*e.g.*, of organ, cell or bone marrow), type 1 diabetes, and uveitis.

Additional diseases and disorders include Addison's Disease, anti-phospholipid syndrome, autoimmune atrophic gastritis, achlorhydra autoimmune, Celiac Disease, Crohn's Disease, Cushing's Syndrome, dermatomyositis, Goodpasture's Syndrome, Grave's Disease, Hashimoto's thyroiditis, idiopathic adrenal atrophy, idiopathic thrombocytopenia, Lambert-Eaton Syndrome, pemphigoid, pemphigus vulgaris, pernicious anemia, polyarteritis nodosa, primary biliary cirrhosis, primary sclerosing cholangitis, Raynauds, Reiter's Syndrome, relapsing polychondritis, Schmidt's Syndrome, Sjogren's Syndrome, sympathetic ophthalmia, Takayasu's Arteritis, temporal arteritis, thyrotoxicosis, ulcerative colitis, and Wegener's granulomatosis.

The amount, route of administration and dosing schedule of a compound will depend upon factors such as the specific indication to be treated, prevented, or managed, and the age, sex and condition of the patient. The roles played by such factors are well known in the art, and may be accommodated by routine experimentation. In a particular embodiment, a compound is administered to a human patient in an amount of about 0.5, 1, 2.5 or 5 mpk.

### 5.4. Pharmaceutical Formulations

This invention encompasses pharmaceutical compositions comprising one or more compounds of the invention. Certain pharmaceutical compositions are single unit dosage forms suitable for oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), or transdermal administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The formulation should suit the mode of administration. For example, oral administration requires enteric coatings to protect the compounds of this invention from degradation within the gastrointestinal tract. Similarly, a formulation may contain ingredients that facilitate delivery of the active ingredient(s) to the site of action. For example, compounds may be administered in liposomal formulations, in order to protect them from degradative enzymes, facilitate transport in circulatory system, and effect delivery across cell membranes to intracellular sites.

The composition, shape, and type of a dosage form will vary depending on its use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage

form used to treat the same disease. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. *See, e.g.*, *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

#### 5.4.1. Oral Dosage Forms

Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

Typical oral dosage forms are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by conventional methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary. Disintegrants may be incorporated in solid dosage forms to facility rapid dissolution. Lubricants may also be incorporated to facilitate the manufacture of dosage forms (*e.g.*, tablets).

#### 5.4.2. Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are specifically sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or

suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

### 5.4.3. Transdermal, Topical and Mucosal Dosage Forms

Transdermal, topical, and mucosal dosage forms include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990); and *Introduction to Pharmaceutical Dosage Forms*, 4th ed., Lea & Febiger, Philadelphia (1985). Transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied.

Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers may be used to assist in delivering active ingredients to the tissue.

The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates may also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery.

In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

## 6. EXAMPLES

Aspects of this invention can be understood from the following examples, which do not limit its scope.

### 6.1. Example 1: Preparation of Crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-Tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone Oxime Dihydrate

To a 3-neck, 3-L round bottom flask equipped with a mechanical stirrer, a temperature controller and a condenser were charged with 1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone (100.0 g, 434.4 mmol), hydroxylamine hydrochloric acid salt (45.2 g, 1.5 equiv), sodium acetate (53.4 g, 1.5 equiv) and methanol (HPLC grade, 1.0L, 10X). The above solution was heated at 65°C with stirring for 2 h.

To the mixture was then added a solution of HCl in isopropanol (freshly prepared by slow addition of 92.7 ml AcCl to 200 ml isopropanol at 0°C, 3.0 equiv) over 15 min and resulting mixture stirred at 65°C for 3 h. The mixture was diluted with MeOH (1.0L, 10X) and cooled to room temperature and the precipitated sodium chloride was removed by filtration. The solids were washed with MeOH (100 ml, 1X) and the solution was concentrated at 40°C under vacuum until solids started to form (~200 ml). Water (1.0 L, 10X) was then added and the residual organic solvents were removed at 40°C under vacuum. A polish filtration was performed to afford a clear yellow solution. To this solution was slowly added 50% NaOH aqueous solution at room temperature so that the temperature of the mixture did not exceed 40°C, until the pH reached 7.2 (7.0 – 7.5). The resulting solution was then heated to 65°C to form a homogeneous solution, and concentrated under vacuum at 65°C (60-70°C) until the solution reached ~500 ml (5X) overall volume. The mixture was then cooled to room temperature slowly, further cooled to 0°C, and stirred at 0°C for 1 h. The solids were collected by filtration and washed with water (0°C, 100 ml, 1X x2) to afford a white crystalline solid.

To the above wet solid was added water (400 ml) and the resulting mixture was heated to 70-80°C until all dissolved. The solution was cooled to room temperature and then stirred at 0°C for 1 h. The solids were collected by filtration and washed with water (0°C,

100 ml, 1X x2) and then dried under vacuum at 30°C overnight to afford 99.4 g of the title compound.

### 6.2. Example 2: Preparation of Anhydrous Crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-Tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone Oxime

The solid from Example 1 was slurried with EtOH (800 ml, 8X) and heated at 75°C for 1h. The resulting mixture was cooled to 0°C and stirred at 0°C for 1h. The white solid was collected by filtration and washed with EtOH (0°C, 100 ml, 1X, x2) and dried at 50°C under vacuum to constant weight to give the title compound.

### 6.3. Example 3: Preparation of Crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-Tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone Oxime Monohydrate

The title compound was obtained by drying the crystalline dihydrate from Example 1 under vacuum at 50°C for about two days.

### 6.4. Example 4: Single Crystal Structure of *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-Tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone Oxime Dihydrate

A single crystal structure of *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-Tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime dihydrate was obtained using a SMART 1K CCD area detector with a fine-focus sealed tube, MoKα, as the radiation source. The structure solution was obtained using SHELXS-97 (Sheldrick, 1990) software, and SHELXL-97 (Sheldrick, 1997) was used as the refinement program. The refinement technique was full-matrix least-squares on $F^2$. The goodness of fit on $F^2$ was 1.037.

The single crystal form exhibited the properties listed in Table 1, below.

**Table 1. Sample and Crystal Data**

| | | |
|---|---|---|
| Crystal habit | Colorless needle | |
| Crystal system | Triclinic | |
| Space group | *P*1 | |
| Unit cell dimensions | $a$ = 4.7937(6) Å | α= 100.133(4)° |
| | $b$ = 7.1414(9) Å | β= 96.745(4)° |
| | $c$ = 9.6975(11) Å | γ = 94.557(4)° |
| Volume | 322.84(7) $Å^3$ | |
| Z | 1 | |
| Density (calculated) | 1.447 $Mg/m^3$ | |

Figure 5 provides a view of a molecule of the compound from the crystal structure. Referring to Figure 5, select bond lengths are provided in Table 2, and select bond angles are provided in Table 3.

**Table 2. Select bond lengths (Å)**

| | | | |
|---|---|---|---|
| O1-C1 | 1.425(3) | O1-H1C | 0.83(7) |
| O2-C2 | 1.431(3) | O2-H2B | 0.85(6) |
| O3-C3 | 1.430(3) | O3-H3B | 0.84(4) |
| O4-C4 | 1.433(3) | O4-H4B | 0.87(7) |
| O5-N3 | 1.407(3) | O5-H5A | 0.80(5) |
| O6-H6B | 0.86(5) | O6-H6C | 0.90(6) |
| O7-H7A | 0.87(5) | O7-H7B | 0.87(5) |
| N1-C7 | 1.349(4) | N1-C6 | 1.373(3) |
| N1-H1D | 0.94(4) | N2-C7 | 1.335(4) |
| N2-C5 | 1.386(3) | N3-C8 | 1.290(4) |
| C1-C2 | 1.518(4) | C2-C3 | 1.535(3) |
| C3-C4 | 1.537(3) | C4-C5 | 1.501(3) |
| C5-C6 | 1.363(4) | C7-C8 | 1.468(3) |
| C8-C9 | 1.485(4) | | |

**Table 3. Select bond angles (°)**

| | | | |
|---|---|---|---|
| C1-O1-H1C | 109(4) | C2-O2-H2B | 116(4) |
| C3-O3-H3B | 114(3) | C4-O4-H4B | 102(4) |
| N3-O5-H5A | 96(4) | H6B-O6-H6C | 117(5) |
| H7A-O7-H7B | 110(4) | C7-N1-C6 | 107.5(2) |
| C7-N1-H1D | 130(2) | C6-N1-H1D | 122(2) |
| C7-N2-C5 | 104.8(2) | C8-N3-O5 | 110.6(2) |
| O1-C1-C2 | 112.2(2) | O2-C2-C1 | 111.1(2) |
| O2-C2-C3 | 109.52(19) | C1-C2-C3 | 112.8(2) |
| O3-C3-C2 | 109.7(2) | O3-C3-C4 | 111.3(2) |
| C2-C3-C4 | 111.67(19) | O4-C4-C5 | 106.7(2) |
| O4-C4-C3 | 110.7(2) | C5-C4-C3 | 111.2(2) |
| C6-C5-N2 | 110.2(2) | C6-C5-C4 | 127.1(2) |
| N2-C5-C4 | 122.7(2) | C5-C6-N1 | 106.0(2) |
| N2-C7-N1 | 111.5(2) | N2-C7-C8 | 125.9(2) |
| N1-C7-C8 | 122.6(2) | N3-C8-C7 | 115.0(2) |
| N3-C8-C9 | 124.8(3) | C7-C8-C9 | 120.2(2) |

All references (*e.g.*, patents and patent applications) cited above are incorporated herein by reference in their entireties.

## CLAIMS

What is claimed is:

1. A substantially amorphous solid form of *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime or a hydrate thereof.

2. The solid form of claim 1, wherein the *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime is anhydrous.

3. The solid form of claim 1, wherein the hydrate is a monohydrate.

4. The solid form of claim 1, wherein the hydrate is a dihydrate.

5. A substantially crystalline solid form of *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime or a hydrate thereof.

6. The solid form of claim 5, wherein the *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime is anhydrous.

7. The solid form of claim 5, wherein the hydrate is a monohydrate.

8. The solid form of claim 5, wherein the hydrate is a dihydrate.

9. Crystalline anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime.

10. The crystalline anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime of claim 9, which has a X-ray powder diffraction spectrum that comprises peaks at about 4.7, 8.2 and 12.5 degrees 2θ.

11. The crystalline anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime of claim 9, which has a X-ray powder diffraction spectrum that comprises peaks at about 17.1, 19.9 and 20.8 degrees 2θ.

12. The crystalline anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime of claim 9, which has a X-ray powder diffraction spectrum that comprises peaks at about 29.3, 32.0 and 33.1 degrees 2θ.

13. The crystalline anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime of claim 9, which has a X-ray powder diffraction spectrum that is substantially the same as that shown in Figure 1.

14. The crystalline anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime of claim 9, which has a Raman spectrum that is substantially the same as that shown in Figure 2.

15. Crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime monohydrate.

16. Crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime dihydrate.

17. The crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime dihydrate of claim 16, which has a X-ray powder diffraction spectrum that comprises peaks at about 12.5, 14.1 or 16.9 degrees 2θ.

18. The crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime dihydrate of claim 16, which has a X-ray powder diffraction spectrum that comprises peaks at about 20.4, 25.2 and 27.0 degrees 2θ.

19. The crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime dihydrate of claim 16, which has a X-ray powder diffraction spectrum that is substantially the same as that shown in Figure 3.

20. The crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime dihydrate of claim 16, which has a Raman spectrum that is substantially the same as that shown in Figure 4.

21. The crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime dihydrate of claim 16, which is triclinic and occupies a *P*1 space group.

22. A composition comprising the solid form of claim 1 or 5 and a pharmaceutically acceptable excipient.

23. A composition comprising the crystalline anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime of claim 9 and a pharmaceutically acceptable excipient.

24. A composition comprising the crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime monohydrate of claim 15 and a pharmaceutically acceptable excipient.

25. A composition comprising the crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime dihydrate of claim 16 and a pharmaceutically acceptable excipient.

26. A single unit dosage form comprising the solid form of claim 1 or 5.

27. A single unit dosage form comprising the crystalline anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime of claim 9.

28. A single unit dosage form comprising the crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime monohydrate of claim 15.

29. A single unit dosage form comprising the crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime dihydrate of claim 16.

30. A method of reducing the number of circulating lymphocytes in a patient, which comprises administering to the patient an effective amount of the solid form of claim 1 or 5.

31. A method of reducing the number of circulating lymphocytes in a patient, which comprises administering to the patient an effective amount of the crystalline anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime of claim 9.

32. A method of reducing the number of circulating lymphocytes in a patient, which comprises administering to the patient an effective amount of the crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime monohydrate of claim 15.

33. A method of reducing the number of circulating lymphocytes in a patient, which comprises administering to the patient an effective amount of the crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime dihydrate of claim 16.

34. A method of modulating the amount of S1P in a patient, which comprises administering to the patient an effective amount of the solid form of claim 1 or 5.

35. A method of modulating the amount of S1P in a patient, which comprises administering to the patient an effective amount of the crystalline anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime of claim 9.

36. A method of modulating the amount of S1P in a patient, which comprises administering to the patient an effective amount of the crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime monohydrate of claim 15.

37. A method of modulating the amount of S1P in a patient, which comprises administering to the patient an effective amount of the crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime dihydrate of claim 16.

38. A method of suppressing immune response in a patient, which comprises administering to the patient an effective amount of the solid form of claim 1 or 5.

39. A method of suppressing immune response in a patient, which comprises administering to the patient an effective amount of the crystalline anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime of claim 9.

40. A method of suppressing immune response in a patient, which comprises administering to the patient an effective amount of the crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime monohydrate of claim 15.

41. A method of suppressing immune response in a patient, which comprises administering to the patient an effective amount of the crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime dihydrate of claim 16.

42. A method of treating, managing or preventing an autoimmune or inflammatory disease or disorder, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of the solid form of claim 1 or 5.

43. A method of treating, managing or preventing an autoimmune or inflammatory disease or disorder, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of the crystalline anhydrous *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime of claim 9.

44. A method of treating, managing or preventing an autoimmune or inflammatory disease or disorder, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of the crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime monohydrate of claim 15.

45. A method of treating, managing or preventing an autoimmune or inflammatory disease or disorder, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of the crystalline *(E)*-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime dihydrate of claim 16.

46. The method of one of claims 42-45, wherein the autoimmune or inflammatory disease or disorder is rheumatoid arthritis, graft-vs-host disease, type I diabetes, or uveitis.

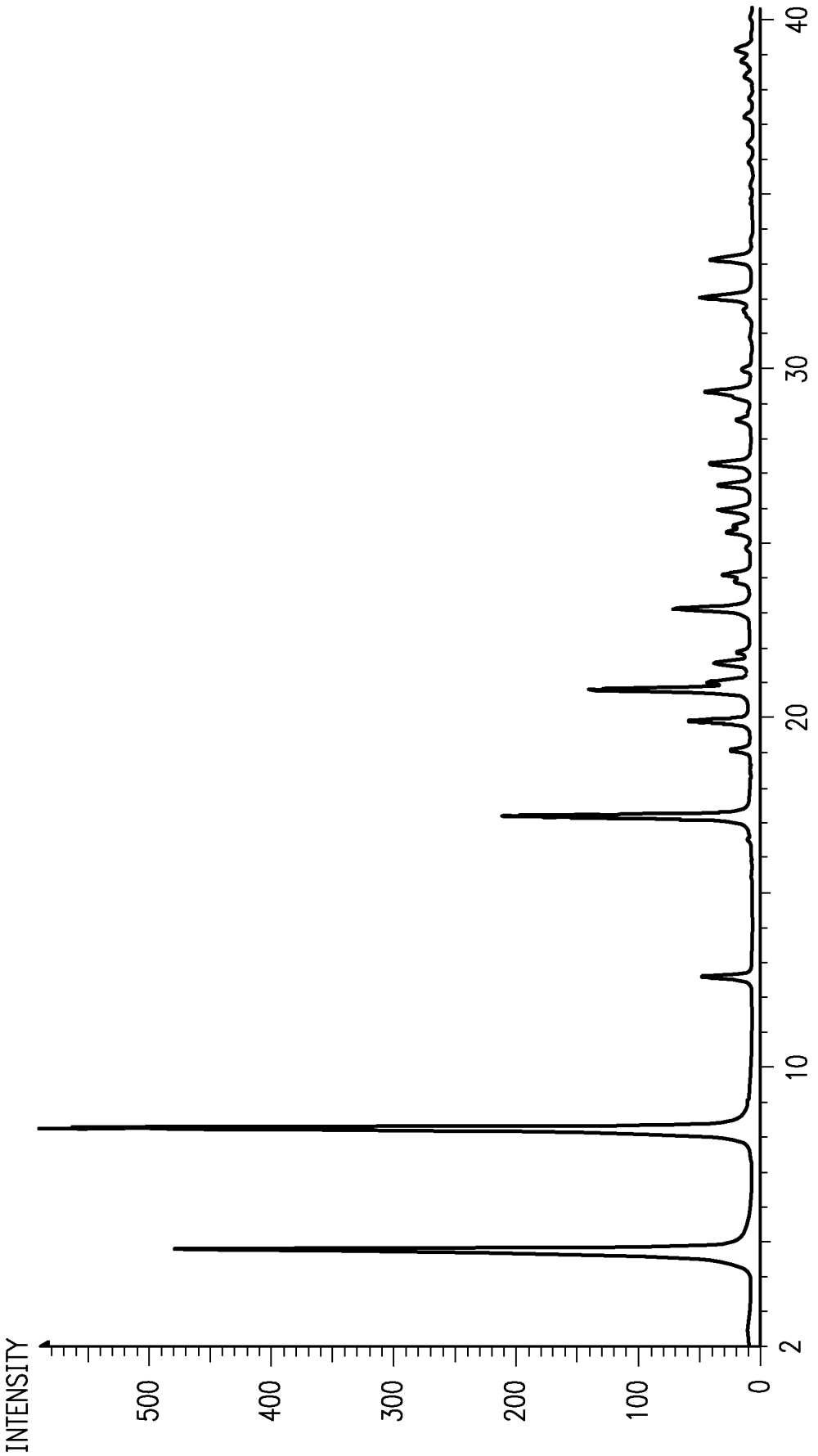
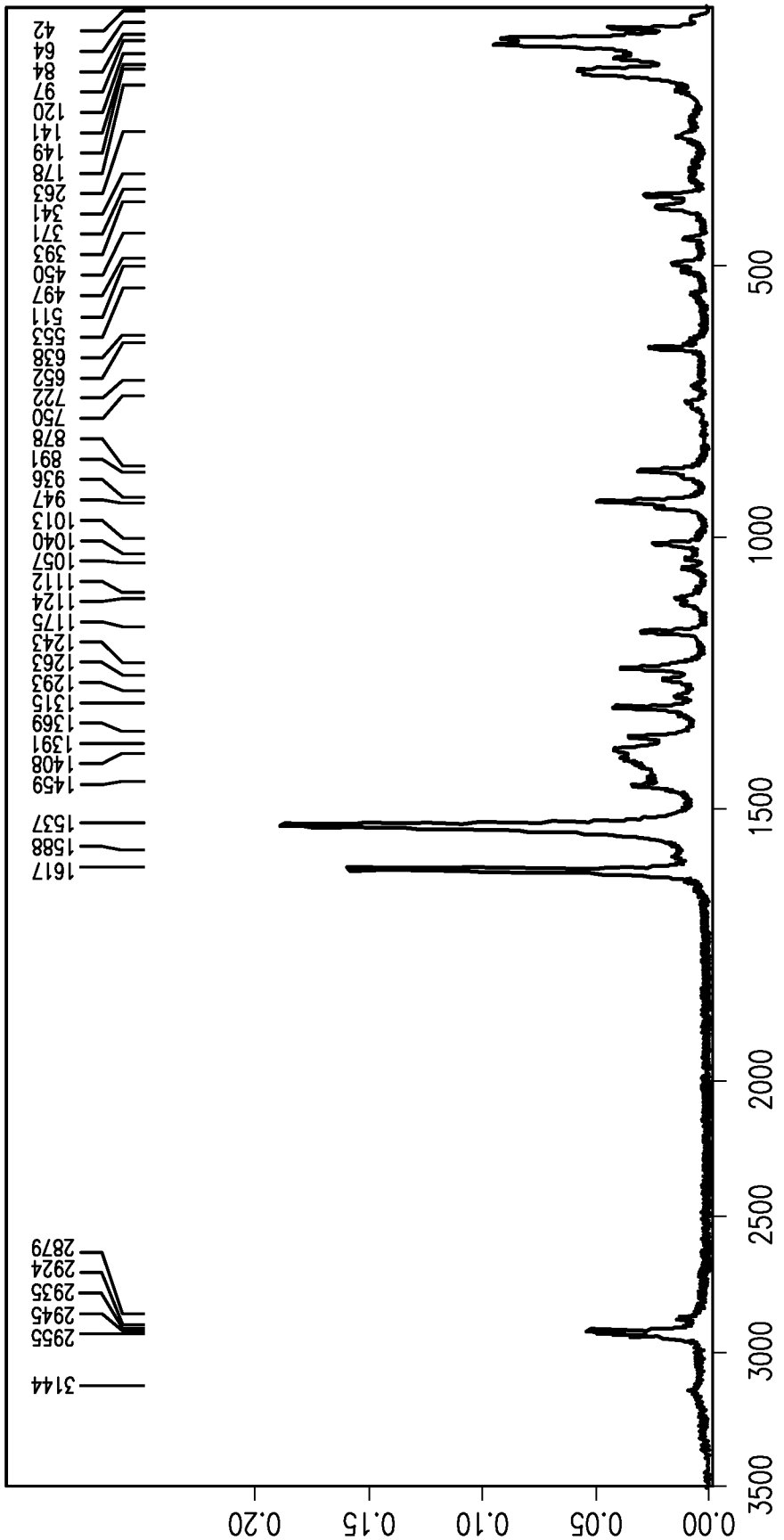



FIG. 1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393
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497
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947
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1057
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1293
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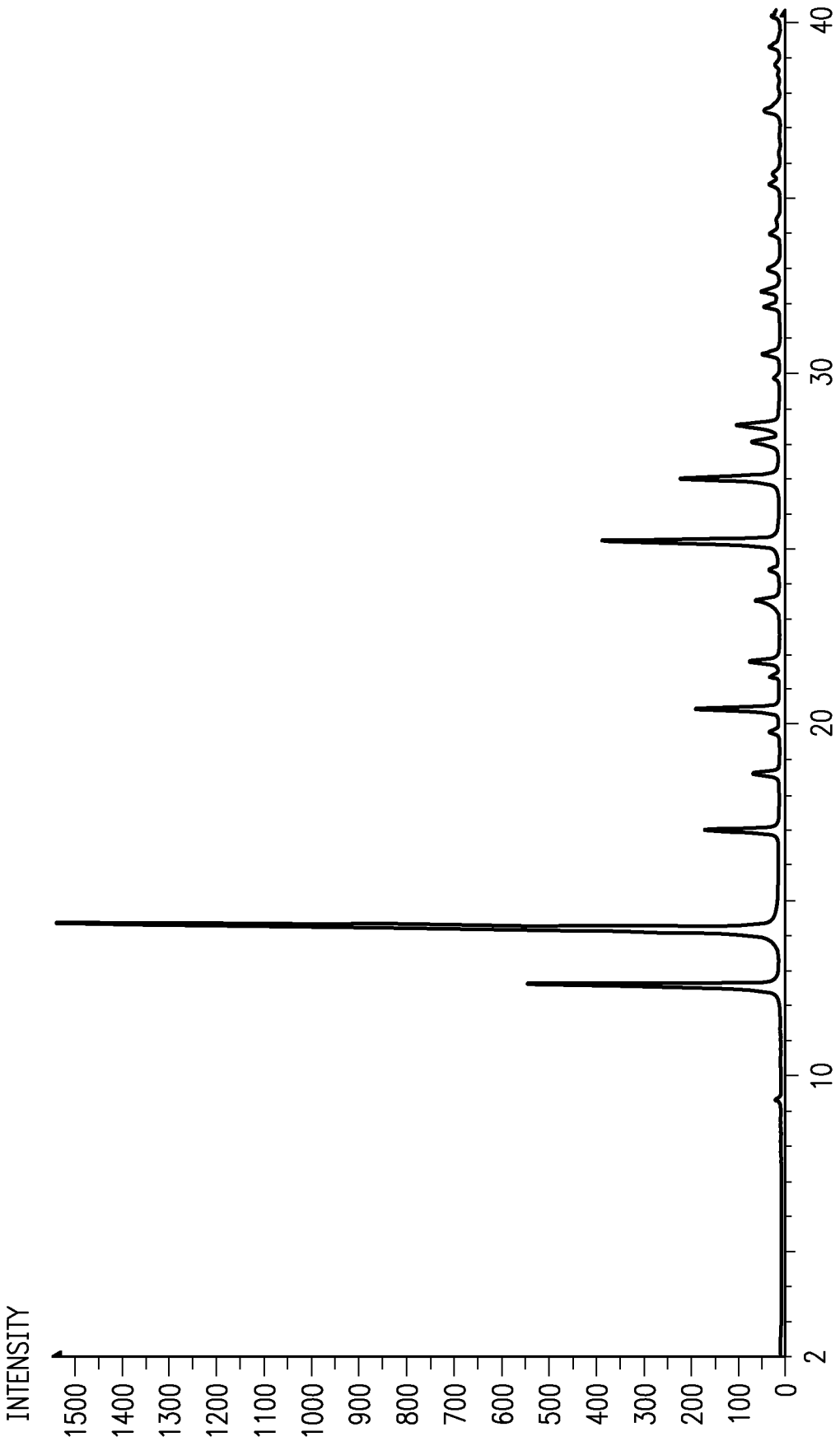
3144

FIG. 2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30
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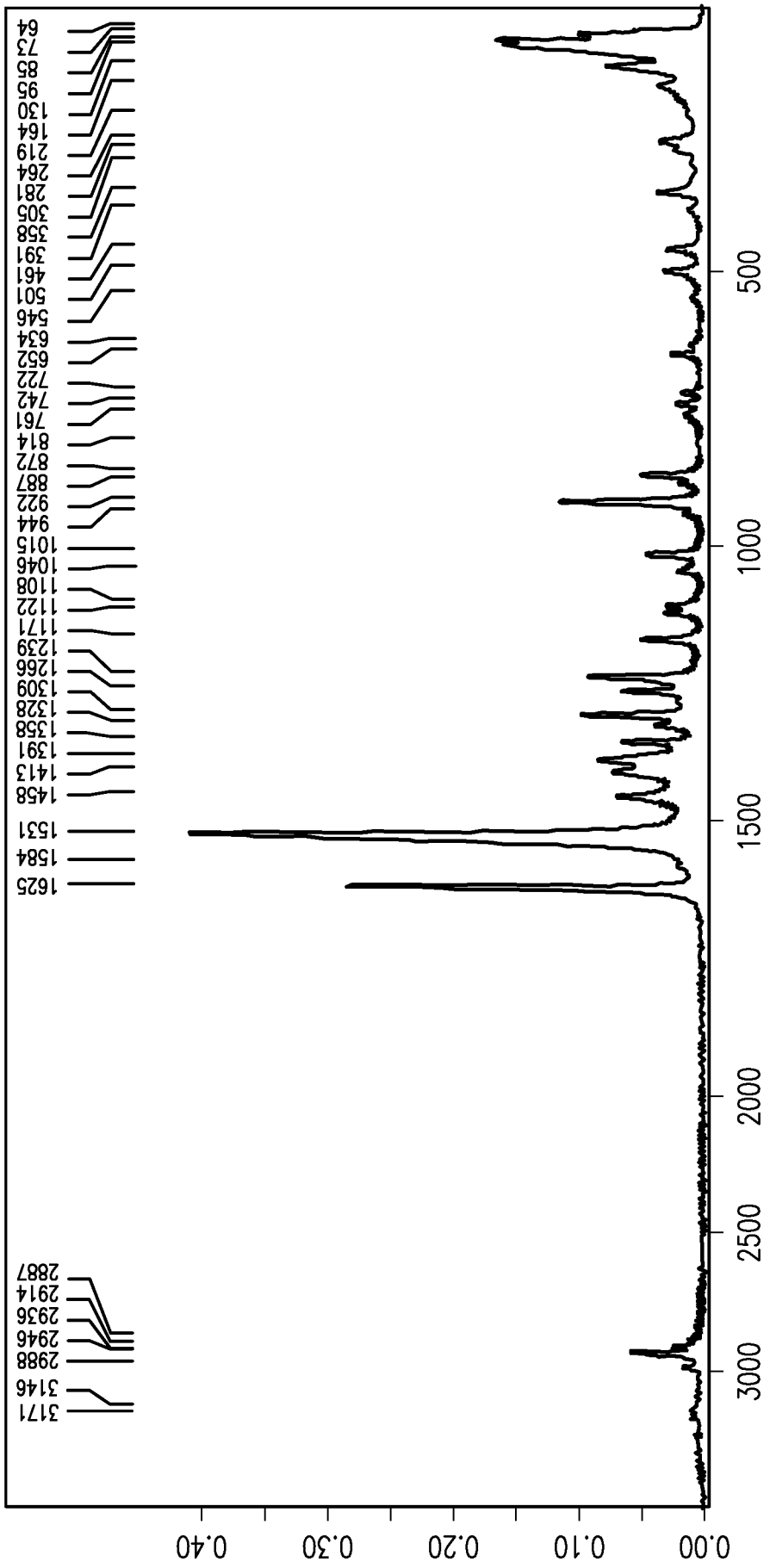
DEGREES 2 THETA

FIG. 3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1584
1531
1458
1413
1391
1358
1328
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1122
1108
1046
1015
944
922
887
872
814
761
742
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281
264
219
164
130
95
85
73
64

FIG. 4

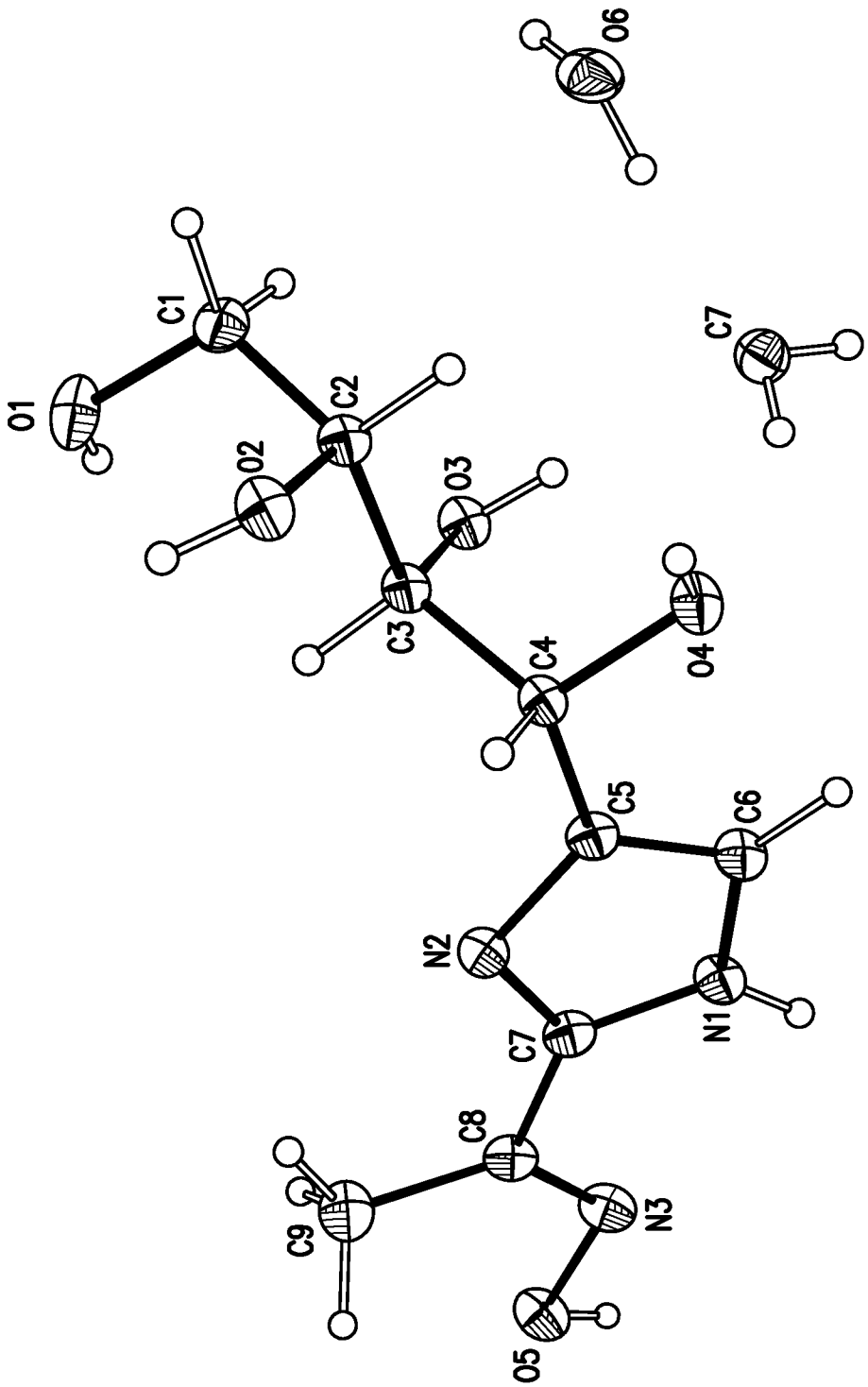


FIG. 5

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/060036

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D233/64 A61K31/4164 A61P29/00 A61P37/00

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 practical, search terms used)
EPO-Internal, BEILSTEIN Data, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | WO 2007/100617 A (LEXICON GENETICS INC [US]; AUGERI DAVID J [US]; BAGDANOFF JEFFREY [US]) 7 September 2007 (2007-09-07) cited in the application Claims 1-119; example 6.4 | 1-46 |
| A | WO 97/46543 A (UNIV WOLLONGONG [AU]; PYNE STEPHEN GEOFFREY [AU]; UNG ALISON THAVARY [) 11 December 1997 (1997-12-11) Claims 1-43; Formulae (I), (II), (V); examples | 1-46 |

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 31 July 2008 | 14/08/2008 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Kirsch, Cécile |

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/060036

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | HALWEG K M ET AL: "A CONVENIENT SYNTHESIS OF 2-ACETYL-4(5)-(1(R),2(S),4-TETRAHYDROXYBUTY L)-IMIDAZOLE" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, vol. 50, no. 7, 1 January 1985 (1985-01-01), pages 1134-1136, XP002446300 ISSN: 0022-3263 Formula (I); 1st paragraph | 1-46 |
| A | BRITAIN ET AL: "Polymorphism in Pharmaceutical Solids passage" POLYMORPHISM IN PHARMACEUTICAL SOLIDS, XX, XX, 1 January 1999 (1999-01-01), pages 235-238, XP002278123 the whole document | 1-46 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/060036

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 30-46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/060036

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2007100617 A | 07-09-2007 | US 2007208063 A1 | 06-09-2007 |
| WO 9746543 A | 11-12-1997 | AU 2881797 A | 05-01-1998 |
| | | ZA 9704811 A | 30-12-1997 |