



(51) International Patent Classification:
C07D 471/04 (2006.01) *C07D 213/18* (2006.01)

(21) International Application Number:
PCT/IB2010/054186

(22) International Filing Date:
16 September 2010 (16.09.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/247,218 30 September 2009 (30.09.2009) US

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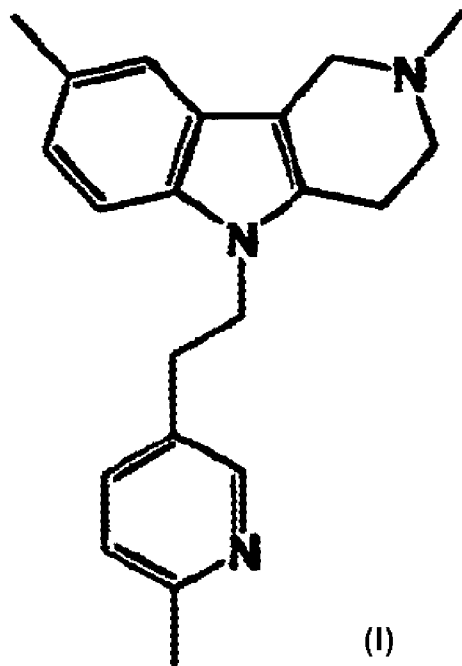
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG,

[Continued on next page]

(54) Title: NOVEL FORMS OF (2,8-DIMETHYL-5-[2-(6-METHYLPYRIDIN-3-YL)ETHYL]-3,4-DIHYDRO-1H-PYRIDO[4,3-B] INDOLE)



(I)

(57) Abstract: The present invention relates to novel solid forms of latrepirdine, also known as Dimebon) designated Form A, Form B, and a noncrystalline form, and relates to methods for the preparation of each form. The present invention also relates to a novel MVP oxalate salt and hydrate thereof, and its preparation and use in the preparation of latrepirdine.



ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

**NOVEL FORMS OF (2,8-DIMETHYL-5-[2-(6-METHYLPYRIDIN-3-YL)
ETHYL]-3,4-DIHYDRO-1H-PYRIDO[4,3-B]INDOLE)**

FIELD OF THE INVENTION

The present invention relates to novel solid forms of (2,8-dimethyl-5-[2-(6-methylpyridin-3-yl) ethyl]-3,4-dihydro-1h-pyrido[4,3-b]indole) designated Form A, Form B, and a noncrystalline form, characterized by one or more features of their X-ray powder diffraction patterns, ¹³C solid state nuclear magnetic resonance spectra, Infrared spectra, Raman spectra, and melting points. The present invention also relates to methods for the preparation of each form.

BACKGROUND OF THE INVENTION

(2,8-dimethyl-5-[2-(6-methylpyridin-3-yl)ethyl]-3,4-dihydro-1h-pyrido[4,3-b]indole), hereinafter referred to as "latrepirdine", is also known in the literature as dimebon. Latrepirdine is useful for the treatment of various disorders such as Alzheimer's disease, neurodegenerative disorders, Huntington's Disease, and schizophrenia (see, for example, U.S. Pat. No. 6,187,785; and U.S. Pat. Appl. Pub. Nos. 2007/0117835, US20070117834 and 2007/0225316). Latrepirdine and methods for synthesizing it are disclosed in PCT publication no. WO 2009/111540, filed March 4, 2008. Certain existing methods of making pyridylethyl-substituted carbolines involve the use of methylvinylpyridine ("MVP"). The existing synthetic routes using MVP have several drawbacks. First, MVP is increasingly unavailable from commercial suppliers, making its acquisition and use inconvenient and expensive. In addition, if not stored and handled properly, MVP is subject to polymerization. For this reason, it is often stored in the presence of stabilizers and purification by distillation is required prior to its use in certain reactions. The methods described herein address one or more of the existing drawbacks to using MVP in the synthesis of pyridylethyl-substituted carbolines such as latrepirdine.

The present invention also relates to novel solid forms of latrepirdine free base that demonstrate adequate in-vitro flux for use in transdermal dosage forms.

Based on a chemical structure, one cannot predict with any degree of certainty whether a compound will crystallize, under what conditions it will crystallize, how many crystalline solid forms of the compound might exist, or the solid-state structure of any of those forms. A key characteristic of any crystalline drug is the polymorphic behavior of such a material. In general, crystalline forms of drugs are preferred over noncrystalline forms of drugs, in part, because of their superior stability. For example, in many situations, a noncrystalline drug converts to a crystalline drug form upon storage. Because noncrystalline and crystalline forms of a drug typically have differing physical properties and chemical properties, such interconversion is undesirable for safety reasons in pharmaceutical usage. The different physical properties exhibited by different solid forms of a pharmaceutical compound can affect important pharmaceutical parameters such as storage, stability, compressibility, density (important in formulation and product manufacturing), and dissolution rates (important in determining bioavailability). Stability differences may result from changes in chemical reactivity (e.g., differential hydrolysis or oxidation, such that a dosage form comprising a certain polymorph can discolor more rapidly than a dosage form comprising a different polymorph), mechanical changes (e.g., tablets can crumble on storage as a kinetically favored crystalline form converts to thermodynamically more stable crystalline form), or both (e.g., tablets of one polymorph can be more susceptible to breakdown at high humidity). Solubility differences between polymorphs may, in extreme situations, result in transitions to crystalline forms that lack potency and/or that are toxic. In addition, the physical properties of a crystalline form may also be important in pharmaceutical processing. For example, a particular crystalline form may form solvates more readily or may be more difficult to filter and wash free of impurities than other crystalline forms (i.e., particle shape and size distribution might be different between one crystalline form relative to other forms).

There is no one ideal physical form of a drug because different physical forms provide different advantages. The search for the most stable form and for such other forms can be difficult and the outcome unpredictable. Thus it is

important to seek a variety of unique drug forms, e.g. salts, polymorphs, non-crystalline forms, which may be used in various formulations. The selection of a drug form for a specific formulation or therapeutic application requires consideration of a variety of properties, and the best form for a particular application may be one which has one specific important good property while other properties may be acceptable or marginally acceptable.

The successful development of a drug requires that it meet certain requirements to be a therapeutically effective treatment for patients. These requirements fall into two categories: (1) requirements for successful manufacture of dosage forms, and (2) requirements for successful drug delivery and disposition after the drug formulation has been administered to the patient.

Different crystalline solid forms of the same compound often possess different solid-state properties such as melting point, solubility, dissolution rate, hygroscopicity, powder flow, mechanical properties, chemical stability and physical stability. These solid-state properties may offer advantages in filtration, drying, and dosage form manufacturing unit operations. Thus, once different crystalline solid forms of the same compound have been identified, the optimum crystalline solid form under any given set of processing and manufacturing conditions may be determined as well as the different solid-state properties of each crystalline solid form.

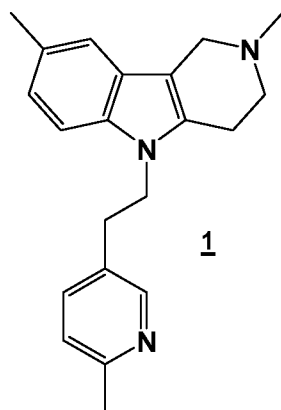
Polymorphs of a molecule can be obtained by a number of methods known in the art. Such methods include, but are not limited to, melt recrystallization, melt cooling, solvent recrystallization, desolvation, rapid evaporation, rapid cooling, slow cooling, vapor diffusion and sublimation. Polymorphs can be detected, identified, classified and characterized using techniques such as, but not limited to, differential scanning calorimetry (DSC), thermogravimetry (TGA), X-ray powder diffractometry (XRPD), single crystal X-ray diffractometry, solid state nuclear magnetic resonance (NMR), infrared (IR) spectroscopy, Raman spectroscopy, and hot-stage optical microscopy.

The present invention is directed to noncrystalline and crystalline (Form A and Form B) forms of latrepirdine free base. The present invention is also

directed to noncrystalline polymer dispersions containing latrepirdine. The invention is also directed to compositions, including pharmaceutical compositions, containing noncrystalline, or one or more crystalline solid forms of latrepirdine free base. The invention is further directed to processes for preparing noncrystalline and crystalline solid forms of latrepirdine free base.

SUMMARY OF THE INVENTION

Latrepirdine is (2,8-dimethyl-5-[2-(6-methylpyridin-3-yl)ethyl]-3,4-dihydro-1H-pyrido[4,3-b]indole), a known compound, having the structure 1:



It is an object of the present invention to provide crystalline and noncrystalline forms of latrepirdine free base.

It is a further object of the present invention to provide crystalline forms latrepirdine which have not been previously isolated or characterized.

It is a further object of the present invention to provide such crystalline forms in substantially pure form and/or in admixture with crystalline forms inherently made by prior art processes but not characterized as isolated crystalline forms. "Substantially pure" means that the form contains no more than 10% impurities.

It is a further object of the present invention to provide methods for the production of such crystalline forms with specific characterization identification.

In one embodiment, the present invention comprises a Form A of latrepirdine. Said Form A can have one or more characteristics selected from the group consisting of:

- I) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): 12.4, 16.1, and $17.4^\circ 2\theta \pm 0.2^\circ 2\theta$;
- II) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): 8.9, 12.4, 16.1, and $17.4^\circ 2\theta \pm 0.2^\circ 2\theta$;
- III) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): 8.9, 12.4, 16.1, 16.8, and $17.4^\circ 2\theta \pm 0.2^\circ 2\theta$;
- IV) a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 714, 1207, and $1356 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- V) a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 714, 856, 1207, and $1356 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- VI) a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 357, 714, 856, 1207, and $1356 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- VII) a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 667, 897, and $1354 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- VIII) a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 667, 778, 897, and $1354 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- IX) an infrared spectrum comprising the following wavenumber (cm^{-1}) values: 667, 778, 897, 1124, and $1354 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- X) a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 126.2, 132.8, and $157.4 \text{ ppm} \pm 0.2 \text{ ppm}$;
- XI) a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 33.4, 126.2, 132.8, and $157.4 \text{ ppm} \pm 0.2 \text{ ppm}$;
- XII) a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 33.4, 46.7, 126.2, 132.8, and $157.4 \text{ ppm} \pm 0.2 \text{ ppm}$;
- XIII) a melting point of $105 \pm 5^\circ \text{C}$;

- XIV) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $12.4^\circ 2\theta \pm 0.2^\circ 2\theta$, and a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 1207 and $1356 \pm 4 \text{ cm}^{-1}$;
- XV) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $16.1^\circ 2\theta \pm 0.2^\circ 2\theta$ and a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 1207 and $1356 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- XVI) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $17.4^\circ 2\theta \pm 0.2^\circ 2\theta$ and a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 1207 and $1356 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- XVII) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $12.4^\circ 2\theta \pm 0.2^\circ 2\theta$, and a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 644 and $714 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- XVIII) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $16.1^\circ 2\theta \pm 0.2^\circ 2\theta$ and a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 644 and $714 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- XIX) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $12.4^\circ 2\theta \pm 0.2^\circ 2\theta$ and a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 132.8 and $157.4 \text{ ppm} \pm 0.2 \text{ ppm}$;
- XX) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $16.1^\circ 2\theta \pm 0.2^\circ 2\theta$ and a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 132.8 and $157.4 \text{ ppm} \pm 0.2 \text{ ppm}$; and
- XXI) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $17.4^\circ 2\theta \pm 0.2^\circ 2\theta$ and a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 132.8 and $157.4 \text{ ppm} \pm 0.2 \text{ ppm}$.

In a second embodiment, the present invention comprises a Form B of latrepirdine. Said Form B can have one or more characteristics selected from the group consisting of:

- I) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): 8.1 , 17.5 , and 19.5° $2\theta \pm 0.2^\circ$ 2θ ;
- II) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): 8.1 , 17.5 , 17.8 , and 19.5° $2\theta \pm 0.2^\circ$ 2θ ;
- III) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): 8.1 , 17.5 , 17.8 , 19.5 , and 24.2° $2\theta \pm 0.2^\circ$ 2θ ;
- IV) a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 831 , 851 , and $1215 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- V) a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 702 , 831 , 851 , and $1215 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- VI) a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 702 , 831 , 851 , 1201 and $1215 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- VII) an infrared spectrum comprising the following wavenumber (cm^{-1}) values: 566 , 795 , and $1177 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- VIII) an infrared spectrum comprising the following wavenumber (cm^{-1}) values: 566 , 583 , 795 , and $1177 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- IX) an infrared spectrum comprising the following wavenumber (cm^{-1}) values: 566 , 583 , 795 , 1123 , and $1177 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- X) a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 139.3 , 149.6 , and $154.2 \text{ ppm} \pm 0.2 \text{ ppm}$;
- XI) a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 25.6 , 139.3 , 149.6 , and $154.2 \text{ ppm} \pm 0.2 \text{ ppm}$;
- XII) a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 25.6 , 119.3 , 139.3 , 149.6 , and $154.2 \text{ ppm} \pm 0.2 \text{ ppm}$;
- XIII) a melting point of $117 \pm 5^\circ \text{ C}$;

- XIV) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $8.1^\circ 2\theta \pm 0.2^\circ 2\theta$ and a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 831 and $1215 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- XV) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $17.5^\circ 2\theta \pm 0.2^\circ 2\theta$ and a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 831 and $1215 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- XVI) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $19.5^\circ 2\theta \pm 0.2^\circ 2\theta$ and a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 831 and $1215 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- XVII) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $8.1^\circ 2\theta \pm 0.2^\circ 2\theta$ and a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 646 and $715 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- XVIII) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $19.5^\circ 2\theta \pm 0.2^\circ 2\theta$ and a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 646 and $715 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- XIX) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $8.1^\circ 2\theta \pm 0.2^\circ 2\theta$ and ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 139.3 and $154.2 \text{ ppm} \pm 0.2 \text{ ppm}$;
- XX) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $17.5^\circ 2\theta \pm 0.2^\circ 2\theta$ and ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 139.3 and $154.2 \text{ ppm} \pm 0.2 \text{ ppm}$; and
- XXI) an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): $19.5^\circ 2\theta \pm 0.2^\circ 2\theta$ and ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 139.3 and $154.2 \text{ ppm} \pm 0.2 \text{ ppm}$.

In a third embodiment, the present invention comprises a noncrystalline form of latrepirdine. Said noncrystalline form can have one or more characteristics selected from the group consisting of:

- I) a Raman spectrum comprising the following wavenumber (cm^{-1}) values: $1573 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- II) a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 646 and $715 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- III) a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 346, 704, and $715 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- IV) a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 346, 704, 715, and $1206 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- V) a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 346, 704, 715, 1206, and $1573 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$;
- VI) a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 134.8 and $156.7 \text{ ppm} \pm 0.2 \text{ ppm}$;
- VII) a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 134.8, 149.5, and $156.7 \text{ ppm} \pm 0.2 \text{ ppm}$;
- VIII) a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 118.2, 134.8, 149.5, and $156.7 \text{ ppm} \pm 0.2 \text{ ppm}$; and
- IX) a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 118.2, 127.0, 134.8, 149.5, and $156.7 \text{ ppm} \pm 0.2 \text{ ppm}$.

In a fourth embodiment, the present invention comprises a method of stabilizing a noncrystalline form of latrepirdine free base through the preparation of a solid dispersion with a polymeric system. The polymeric system preferably consists of one or more of the following polymers: polyvinylpyrrolidone (PVP), cellulose acetate phthalate (CAP), and hydroxypropylmethyl cellulose acetate succinate (HPMC-AS). Stabilized non-crystalline forms of latrepirdine free base are also embraced.

In a fifth embodiment, the present invention provides a method of preparing crystalline latrepirdine Form A by one or more of the methods selected from the group consisting of:

- I) Crystallization from a latrepirdine free base solution;

- II) Crystallization from a latrepirdine free base solution by evaporation;
- III) Crystallization from a latrepirdine free base solution at elevated temperatures;
- IV) Crystallization from a latrepirdine free base solution by evaporation at elevated temperatures;
- V) Crystallization from a latrepirdine free base solution by evaporation of toluene;
- VI) Crystallization from a latrepirdine free base solution by evaporation of ethyl acetate;
- VII) Crystallization from a latrepirdine free base solution by evaporation of heptane; and
- VIII) Crystallization from a latrepirdine free base solution by evaporation of isopropyl alcohol.

In a sixth embodiment, the present invention provides a method of preparing crystalline latrepirdine Form B by one or more of the methods selected from the group consisting of:

- I) Crystallization from a latrepirdine free base solution;
- II) Crystallization from a latrepirdine free base solution by evaporation;
- III) Crystallization from a latrepirdine free base solution at room temperature;
- IV) Crystallization from a latrepirdine free base solution by evaporation at room temperature;
- V) Crystallization from a latrepirdine free base solution by evaporation of toluene;
- VI) Crystallization from a latrepirdine free base solution by evaporation of ethyl acetate;
- VII) Crystallization from a latrepirdine free base solution by evaporation of heptane; and
- VIII) Crystallization from a latrepirdine free base solution by evaporation of isopropyl alcohol.

In a seventh embodiment, the present invention provides a method of preparing noncrystalline latrepirdine by one or more of the methods selected from the group consisting of:

- I) Cooling a latrepirdine free base melt or liquid;
- II) Evaporating a solvent from a latrepirdine free base solution;
- III) Spray-drying a latrepirdine free base solution;
- IV) Spray-drying a polymer and latrepirdine free base solution;
- V) Spray-drying a latrepirdine free base solution with CAP, PVP, or HPMCAS polymers;
- VI) Evaporating a solvent from a latrepirdine free base and polymer solution; and
- VII) Evaporating a solvent from a latrepirdine free base solution with CAP, PVP, or HPMCAS polymers.

In an eighth embodiment, the present invention comprises an anhydrous form of MVP oxalate having an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): 7.6 , 15.4 , and $22.8^\circ 2\theta \pm 0.2^\circ 2\theta$.

In a ninth embodiment, the present invention comprises a monohydrate form of MVP oxalate having an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): 9.8 , 16.8 , and $18.8^\circ 2\theta \pm 0.2^\circ 2\theta$.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is further described by the following nonlimiting examples, which refer to the accompanying Figures 1 to 28, short particulars of which are given below.

Figure 1. Diffractogram of Form A of latrepirdine free base carried out on a Siemens D5000 diffractometer.

Figure 2. Diffractogram of Form B of latrepirdine free base carried out on a Siemens D5000 diffractometer.

Figure 3. Diffractogram of latrepirdine free base HPMCAS solid dispersion carried out on a Siemens D5000 diffractometer.

Figure 4. Diffractogram of latrepirdine free base CAP solid dispersion carried out on a Siemens D5000 diffractometer.

Figure 5. Diffractogram of latrepirdine free base PVP dispersion carried out on a Siemens D5000 diffractometer.

Figure 6. FT-Raman spectrum of Form A of latrepirdine free base carried out on a Nicolet NXR FT-Raman accessory attached to a Nicolet 6700 FTIR spectrometer.

Figure 7. FT-Raman spectrum of Form B of latrepirdine free base carried out on a Nicolet NXR FT-Raman accessory attached to a Nicolet 6700 FTIR spectrometer.

Figure 8. FT-Raman spectrum of noncrystalline latrepirdine free base carried out on a Nicolet NXR FT-Raman accessory attached to a Nicolet 6700 FTIR spectrometer.

Figure 9. FT-Raman spectrum of latrepirdine free base HPMCAS solid dispersion carried out on a Nicolet NXR FT-Raman accessory attached to a Nicolet 6700 FTIR spectrometer.

Figure 10. FT-Raman spectrum of latrepirdine free base CAP solid dispersion carried out on a Nicolet NXR FT-Raman accessory attached to a Nicolet 6700 FTIR spectrometer.

Figure 11. FT-Raman spectrum of latrepirdine Free base PVP dispersion carried out on a Nicolet NXR FT-Raman accessory attached to a Nicolet 6700 FTIR spectrometer.

Figure 12. FT-IR spectrum of Form A of latrepirdine free base carried out on a Nicolet 6700 FTIR spectrometer equipped with a Specac Golden Gate Mk II single reflection diamond ATR accessory.

Figure 13. FT-IR spectrum of Form B of latrepirdine free base carried out on a Nicolet 6700 FTIR spectrometer equipped with a Specac Golden Gate Mk II single reflection diamond ATR accessory.

Figure 14. FT-IR spectrum of latrepirdine free base HPMCAS solid dispersion carried out on a Nicolet 6700 FTIR spectrometer equipped with a Specac Golden Gate Mk II single reflection diamond ATR accessory.

Figure 15. FT-IR spectrum of latrepirdine free base CAP solid dispersion carried out on a Nicolet 6700 FTIR spectrometer equipped with a Specac Golden Gate Mk II single reflection diamond ATR accessory.

Figure 16. FT-IR spectrum of latrepirdine free base PVP dispersion carried out on a Nicolet 6700 FTIR spectrometer equipped with a Specac Golden Gate Mk II single reflection diamond ATR accessory.

Figure 17. ^{13}C CPMAS SSNMR spectrum of Form A of latrepirdine free base carried out on a on a Bruker-Biospin 4 mm BL HFX CPMAS probe positioned into a wide-bore Bruker-Biospin DSX 500 MHz NMR spectrometer.

Figure 18. ^{13}C CPMAS SSNMR spectrum of Form B of latrepirdine free base carried out on a on a Bruker-Biospin 4 mm BL HFX CPMAS probe positioned into a wide-bore Bruker-Biospin DSX 500 MHz NMR spectrometer.

Figure 19. ^{13}C arbon CPMAS SSNMR spectrum of latrepirdine free base HPMCAS solid dispersion carried out on a on a Bruker-Biospin 4 mm BL HFX CPMAS probe positioned into a wide-bore Bruker-Biospin DSX 500 MHz NMR spectrometer at 10°C.

Figure 20. ^{13}C CPMAS SSNMR spectrum of latrepirdine free base CAP solid dispersion carried out on a on a Bruker-Biospin 4 mm BL HFX CPMAS probe positioned into a wide-bore Bruker-Biospin DSX 500 MHz NMR spectrometer at 10°C.

Figure 21. ^{13}C CPMAS SSNMR spectrum of latrepirdine free base PVP dispersion carried out on a on a Bruker-Biospin 4 mm BL HFX CPMAS probe positioned into a wide-bore Bruker-Biospin DSX 500 MHz NMR spectrometer at 10°C.

Figure 22. Thermogram of Form A of latrepirdine free base carried out on a Mettler-Toledo 821^e DSC.

Figure 23. Thermogram of Form B of latrepirdine free base carried out on a Mettler-Toledo 822^e DSC.

Figure 24. Thermogram of latrepirdine free base HPMCAS solid dispersion carried out on a TA Q1000 DSC.

Figure 25. Thermogram of latrepirdine free base CAP solid dispersion carried out on a TA Q1000 DSC.

Figure 26. Thermogram of latrepirdine free base PVP dispersion carried out on a TA Q1000 DSC.

Figure 27. Diffractogram of the anhydrous form of MVP oxalate carried out on a Bruker D8 diffractometer.

Figure 28. Diffractogram of the monohydrate form of MVP oxalate carried out on a Bruker D8 diffractometer.

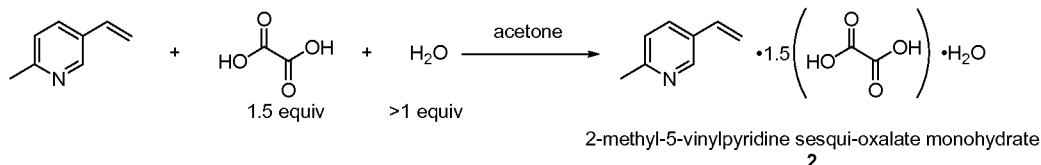
DETAILED DESCRIPTION OF THE INVENTION

Typical preparations of 2-methyl-5-vinylpyridine (MVP) contain a number of isomeric impurities that originate from impurities in the starting material, 2-methyl-5-vinylpyridine. Being a liquid, the best way to purify MVP is via distillation. Since the impurities are the same molecular weight and have similar vapor pressures distillation is ineffective at removing them. Even with repeated distillation the level of remaining impurities requires that extra purification steps are necessary in the synthesis of latrepirdine in order to produce material of acceptable quality for a pharmaceutical agent. It has been found that even though it's weakly basic MVP will form salts with several acids and the crystallization of these salts purges impurities to the level at which further purifications during the synthesis of latrepirdine are unnecessary. For example, MVP forms a salt with oxalic acid that contains oxalic acid and MVP in a 1.5 to 1 molar ratio. The salt may be isolated in its anhydrous form if it is prepared in anhydrous solvents. The anhydrous form readily picks up one mole of water to form a stable monohydrate. The monohydrate can be isolated directly by performing the crystallization in solvents with a small amount of water present. Accordingly, salts of MVP formed by reacting MVP with an acid, and hydrates thereof, are embraced by the invention. For example, provided herein is an oxalate salt of MVP and a hydrate thereof, such as a monohydrate.

The salt can be converted in situ to the free base of MVP suitable for the preparation of latrepirdine by several methods. The salt can be treated with aqueous solutions of bases such as sodium hydroxide (NaOH), potassium hydroxide (KOH), sodium carbonate (Na₂CO₃), potassium

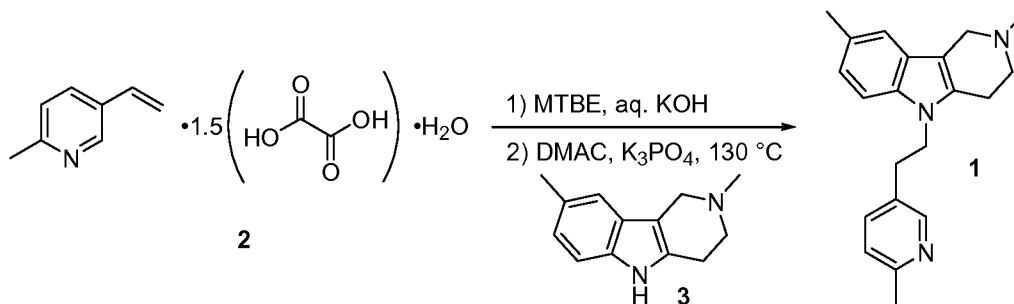
carbonate (K_3CO_3), and extracted into an appropriate organic solvent such as methyl *tert*-butyl ether (MTBE), ethyl acetate (EtOAc), or diethyl ether (Et₂O), or a slurry of the salt in an organic solvent can be treated with an amine that's a stronger base than MVP (for example, triethylamine, diisopropylethylamine, ethylenediamine, etc.) converting the MVP salt to the amine salt and leaving MVP in solution.

Scheme 1



Preparation of 2-methyl-5-vinylpyridine sesqui-oxalate monohydrate (MVPO, **2**): 2-methyl-5-vinylpyridine (4.0 g, 86.5% pure, 29.04 mmol) was dissolved in 8 ml acetone. Water (2.00 equiv, 58.07 mmol, 1.05 mL) was added and the mixture was stirred at room temperature. In a separate flask oxalic acid (4.00 g, 1.5 equiv) was dissolved in 16 ml of acetone. The oxalic acid solution was added dropwise to the flask containing the 2-methyl-5-vinylpyridine solution. The resulting white slurry was stirred at RT overnight. The solids were filtered and rinsed with 12 ml acetone. Nitrogen was pulled through the filter cake with vacuum for 30 minutes. 5.94g (89% yield) of a white solid was obtained. Karl Fisher analysis showed 6.25% water (6.6% theory for monohydrate). HPLC assay showed the material to be 93.45% pure.

Scheme 2



Scheme 2 shows the use of 2-methyl-5-vinylpyridine sesqui-oxalate monohydrate (**2**) to prepare 2,8-dimethyl-5-[2-(6-methylpyridin-3-yl)ethyl]-3,4-dihydro-1H-pyrido[4,3-b]indole (**1**): **1** (5 g) was slurried in 25 ml of methyl t-butyl ether. 4M Potassium hydroxide was added until the pH of the aqueous layer was ~14. The layers were separated and the MTBE layer was washed twice with 25ml 1N KOH then once with brine. The MTBE solution was dried over MgSO₄ and filtered. The solvent was removed at reduced pressure.

Twice more, 25ml of MTBE was added and the solvent again removed under reduced pressure. The resulting liquid (~1.69 g) was added to a mixture of 5.7 ml of dimethylacetamide and **3** (1.9 g, 9.35 mmoles). To this mixture was charged K₂PO₄ (9.35 mmoles; 2.05 g). The mixture was heated to 130 °C and held at that temperature until HPLC shows >85% conversion to **1**. Accordingly, provided herein is latrepirdine obtained by combining 2-methyl-5-vinylpyridine sesqui-oxalate monohydrate with 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. Latrepirdine is produced under conditions by which the starting materials 2-methyl-5-vinylpyridine sesqui-oxalate monohydrate and 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole react together to form latrepirdine, such as the conditions detailed herein. A process for producing latrepirdine is also provided, where the process comprises combining 2-methyl-5-vinylpyridine sesqui-oxalate monohydrate with 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole under conditions by which latrepirdine is produced.

The HCl salt of MVP crystallizes from dioxane in low yield and the resulting salt is not any more pure than the starting MVP. Unlike the HCl salt, when the oxalate salt crystallizes it purges the MVP isomers to low levels making the MVP useful as an intermediate for pharmaceuticals as well as removing large amounts of the inert methylethylpyridine (MEP).

Form A, Form B and the noncrystalline form of latrepirdine can be characterized by their X-ray powder diffraction patterns, ¹³C solid state nuclear magnetic resonance spectra, Infrared spectra, Raman spectra, and melting points. Additionally, these forms can be characterized by specific values and sets of values associated with features in their respective X-ray powder diffraction patterns, ¹³C solid state nuclear magnetic resonance spectra, Infrared spectra, Raman spectra, and melting points. A characteristic set of values may be composed of values derived from a single analytical technique or from more than one analytical technique.

The terms polyvinylpyrrolidone, cellulose acetate phthalate, and hydroxypropylmethyl cellulose acetate succinate are abbreviated with PVP, HPMC-AS, and CAP, respectively. The term "room temperature" as used

herein refers to the temperature range of 20 °C to 23 °C. The term "characterize" as used herein means to select an appropriate set of data capable of distinguishing one solid form from another. That set of data in X-ray powder diffraction is the value of the positions of one or more reflections, reported in degrees 2θ . The selection of specific latrepirdine free base X-ray powder diffraction peaks that enable determination of a particular form is said to characterize that form. The term "identify" as used herein means taking a selection of characteristic data for a solid form and using those data to determine whether that form is present in a sample. In X-ray powder diffraction, these data are the values that characterize the form in question as discussed above. For example, once one determines that a select number of X-ray diffraction peaks characterize a particular solid form of latrepirdine free base, one can use those peaks to determine whether that form is present in a sample containing latrepirdine free base. This sample could be composed either entirely of latrepirdine free base or of latrepirdine free base in a mixture of components (i.e., a pharmaceutical tablet or transdermal formulation). A typical variability for a peak value associated with an FT-Raman, Dispersive Raman, and FT-Infrared measurement is on the order of plus or minus 4 cm^{-1} . A typical variability for a peak value associated with a ^{13}C chemical shift is on the order of plus or minus 0.2 ppm for crystalline material. A typical variability for a peak value associated with a differential scanning calorimetry endotherm onset temperature is on the order of plus or minus 5° C.

X-ray Powder Diffraction

Crystalline Forms A and B, and noncrystalline latrepirdine were characterized by their X-ray powder diffraction (XRPD) patterns. The X-ray powder diffraction patterns were carried out on a Siemens D5000 diffractometer using copper radiation (wavelength: 1.54056Å). The instrument was equipped with a line focus X-ray tube. The tube voltage and amperage were set to 38 kV and 38 mA, respectively. The divergence and scattering slits were set at 1 mm, and the receiving slit was set at 0.6 mm. Diffracted $\text{Cu K}\alpha_1$ radiation ($\lambda = 1.54056\text{Å}$) was detected by a Sol-X energy dispersive X-ray detector. Samples were prepared for analysis by placing them in a quartz

holder and each sample was rotated at 33 revolutions/minute during data acquisition. A theta two theta continuous scan at $0.2^\circ 2\theta$ /minute (12 sec./ $0.04^\circ 2\theta$ step) from 3.0 to $40.0^\circ 2\theta$ was used. Data were collected and analyzed using BRUKER AXS DIFFRAC PLUS software Version 2.0. An alumina standard was analyzed to check the instrument alignment. It should be noted that Bruker Instruments purchased Siemens; thus, Bruker D5000 instrument is essentially the same as a Siemens D5000. Eva Application 9.0.0.2 software was used to visualize and evaluate PXRD spectra. PXRD data files (.raw) were not processed prior to peak searching. Generally, a Threshold value of 1 and a Width value of 0.3 were used to make preliminary peak assignments. The output of automated assignments was visually checked to ensure validity and adjustments manually made if necessary. Additionally, peaks were manually assigned within spectra if appropriate.

To perform an X-ray diffraction measurement on a Bragg-Brentano instrument like the Bruker system used for measurements reported herein, the sample is typically placed into a holder which has a cavity. The sample powder is pressed by a glass slide or equivalent to ensure a random surface and proper sample height. The sample holder is then placed into the instrument. The incident X-ray beam is directed at the sample, initially at a small angle relative to the plane of the holder, and then moved through an arc that continuously increases the angle between the incident beam and the plane of the holder. Calibration errors and sample height errors often result in a shift of all the peaks in the same direction. Small differences in sample height when using a flat holder will lead to large displacements in XRPD peak positions. A systematic study showed that, using a Shimadzu XRD-6000 in the typical Bragg-Brentano configuration, sample height difference of 1 mm lead to peak shifts as high as $1^\circ 2\theta$ (Chen et al.; *J Pharmaceutical and Biomedical Analysis*, 2001; 26,63). These shifts can be identified from the X-ray diffractogram and can be eliminated by compensating for the shift (applying a systematic correction factor to all peak position values) or recalibrating the instrument. As mentioned above, it is possible to rectify

measurements from the various machines by applying a systematic correction factor to bring the peak positions into agreement.

Due to differences in instruments, samples, and sample preparation, the peak values are reported herein with an estimate of variability for the peak values. This is common practice in the solid-state chemical arts because of the variation inherent in peak values. A typical variability of the 2θ x-axis value for powder x-ray diffraction is on the order of plus or minus $0.2^\circ 2\theta$. Variability in peak intensity is a result of how individual crystals are oriented in the sample container with respect to the external X-ray source (known as "preferred orientation"). This orientation effect does not provide structural information about the crystal. Tables 1-2 list peak positions in degree 2θ and relative peak intensities $\geq 1\%$ for X-ray powder diffraction patterns of each crystalline form of latrepirdine disclosed in the present application. Note that the relative peak intensity values may change depending on the crystal size, morphology, and preferred orientation. The X-ray powder diffraction patterns for noncrystalline latrepirdine exhibit broad features in the range from $5^\circ 2\theta$ to about $30^\circ 2\theta$, which is consistent with noncrystalline material.

Table 1. XRPD Peak List for Form A of Latrepirdine Free base

Angle (Degree 2 θ)	Relative Intensity (≥ 1 %)
5.4	9
7.9	17
8.9	50
10.2	21
10.7	26
12.4	17
14.2	6
16.1	100
16.8	28
17.4	45
17.8	25
19.0	22
20.0	3
20.5	4
20.9	12
21.4	22
22.0	42
23.0	4
23.8	11
24.5	27
25.3	6
25.6	5
26.3	7
26.6	5
27.1	4
27.6	3
28.3	19
29.3	3

Angle (Degree 2 θ)	Relative Intensity (≥ 1 %)
29.8	3
30.2	4
30.4	4
30.8	3
31.0	3
31.6	2
32.6	9
32.8	8
33.6	9
34.6	3
34.8	3
35.2	5
36.4	3
37.4	3
37.6	3
37.7	3
38.2	3
38.5	3
39.0	2
39.5	3

Table 2. XRPD Peak List for Form B of Latrepirdine Free base

Angle (Degree 2 θ)	Relative Intensity (≥ 1 %)
8.1	100
9.2	7
10.6	11
11.7	10

Angle (Degree 2 θ)	Relative Intensity ($\geq 1\%$)
13.6	7
14.2	6
15.1	4
16.3	35
17.5	83
17.8	42
18.4	2
19.5	24
20.7	4
21.1	8
21.4	8
21.6	17
22.2	43
23.3	40
23.6	10
24.2	67
24.5	28
24.9	4
25.8	25
26.3	4
26.7	5
26.9	6
27.1	3
27.8	2
28.3	9
28.6	4
30.5	2
31.1	3
31.9	2

Angle (Degree 2 θ)	Relative Intensity ($\geq 1\%$)
32.1	2
32.6	3
32.8	20
33.3	2
33.8	6
34.1	7
34.7	3
35.2	3
35.8	4
36.6	3
37.4	2
37.4	2
37.8	7
38.4	2
38.9	2
39.2	2
39.4	2

Raman Spectroscopy

Raman spectra were collected for latrepirdine Forms A and B using a Nicolet NXR FT-Raman accessory attached to an FT-IR bench. The spectrometer was equipped with a 1064 nm Nd:YAG laser and a liquid nitrogen cooled Germanium detector. Prior to data acquisition, instrument performance and calibration verifications were conducted using polystyrene. Samples were analyzed in glass NMR tubes that were spun during spectral collection. The spectra were collected using 0.5 W of laser power and 100 co-added scans. The collection range was 4000-300 cm^{-1} . All spectra were recorded using 4 cm^{-1} resolution and Happ-Genzel apodization. Three

separate spectra were recorded for each sample, which were subsequently averaged and intensity normalized prior to peak picking.

Raman spectra of noncrystalline latrepirdine were collected using a dispersive Renishaw Raman microscope. Sample excitation was performed using a high-powered NIR diode laser (785 nm) providing approximately 50 mW of laser power at the sample. A 50x microscope objective was utilized for collection of all spectral data. The range of spectral detection was 1800-100 cm^{-1} , and an acquisition time of 10 seconds was utilized.

Raman spectra were collected for the latrepirdine solid dispersions using a Nicolet NXR FT-Raman accessory attached to an FT-IR bench. The spectrometer was equipped with a 1064 nm Nd:YAG laser and a liquid nitrogen cooled Germanium detector. Prior to data acquisition, instrument performance and calibration verifications were conducted using polystyrene. Samples were analyzed in glass NMR tubes that were rotated during spectral collection. The spectra were collected using 0.5 W of laser power and 400 co-added scans. The collection range was 3700-300 cm^{-1} . All spectra were recorded using 2 cm^{-1} resolution and Happ-Genzel apodization. Two separate spectra were recorded for each sample, which were subsequently averaged and intensity normalized prior to peak picking. The position of the latrepirdine related bands in the solid dispersions are reported in the following tables. These bands were chosen as such if there was no overlap between the excipient peaks and the latrepirdine related peaks.

Peaks were manually identified using the Thermo Nicolet Omnic 7.3a software. Peak position was picked at the peak maximum, and peaks were only identified as such, if a slope was observed on each side of a maximum; shoulders on peaks were not included. The peak position has been rounded to the nearest whole number using standard practice (0.5 rounds up, 0.4 rounds down). The relative intensity values were grouped into strong (S), medium (M) and weak (W) using the following divisions: strong (1-0.75); medium (0.74-0.3) and weak (0.29 and below).

Tables 3-8 list peak positions in wavenumbers and relative peak intensities for Raman spectra of the solid forms of latrepirdine disclosed in the

present application. Although specific Raman peak values are reported herein there does exist a range for these peak values due to differences in instruments, samples, and sample preparation. This is common practice in the solid-state chemical arts because of the variation inherent in peak values. A typical variability of the wavenumber (cm^{-1}) x-axis value for Raman spectroscopy is on the order of plus or minus 4 cm^{-1} . Note that the peak values determined with a dispersive Raman instrument are generally expected to be consistent with those determined with a FT-Raman instrument, i.e., within the variability described above. Thus, it is acceptable to identify a solid form of Latrepirdine using either a FT-Raman or dispersive Raman instrument using the peak values reported in Tables 3-8.

Table 3. Raman Peak List for Form A of Latrepirdine Free Base

Wavenumber (cm^{-1})	Relative Intensity
323	W
357	W
378	W
392	W
411	W
427	W
465	W
497	W
523	W
534	W
575	W
582	W
601	W
644	W
669	W
714	M
730	W

Wavenumber (cm ⁻¹)	Relative Intensity
745	W
773	W
781	W
801	W
822	W
856	M
898	W
914	W
921	W
949	W
972	W
994	W
1018	W
1030	W
1041	W
1062	W
1128	W
1141	W
1159	W
1174	W
1189	W
1207	M
1249	W
1286	W
1305	W
1313	W
1341	W
1356	M
1375	M

Wavenumber (cm ⁻¹)	Relative Intensity
1445	M
1472	M
1570	M
1593	M
1601	M
1623	W
2674	W
2728	W
2742	W
2785	M
2841	W
2860	M
2926	S
2969	M
3004	W
3036	M
3130	W
3199	W

Table 4. Raman Peak List for Form B of Latrepirdine Free Base

Wavenumber (cm ⁻¹)	Relative Intensity
320	M
332	M
351	M
368	M
392	W
430	W
440	W

Wavenumber (cm ⁻¹)	Relative Intensity
463	M
472	M
525	M
551	W
567	W
584	W
604	W
646	M
702	M
715	W
734	W
762	W
796	W
816	W
831	M
851	M
864	W
883	W
910	W
926	W
954	W
970	W
998	W
1012	W
1038	W
1051	W
1063	W
1124	W
1140	W

Wavenumber (cm ⁻¹)	Relative Intensity
1161	W
1178	W
1201	M
1215	M
1228	W
1252	W
1261	W
1282	W
1301	W
1311	W
1340	M
1357	W
1363	W
1375	M
1433	M
1446	M
1470	M
1473	M
1568	M
1591	M
1600	M
1622	W
2667	W
2686	W
2718	W
2743	W
2767	W
2782	W
2807	W

Wavenumber (cm ⁻¹)	Relative Intensity
2834	W
2860	M
2893	S
2924	S
2932	S
2942	M
2954	M
2976	M
3006	W
3033	M
3131	W
3199	W

Table 5. Raman Peak List for Noncrystalline Latrepirdine Free Base

Wavenumber (cm ⁻¹)	Relative intensity
323	W
346	W
372	W
389	W
442	W
465	W
498	W
524	W
551	W
573	W
585	W
602	W
646	W

Wavenumber (cm ⁻¹)	Relative intensity
670	W
704	M
715	M
761	W
833	W
852	M
899	W
974	W
1016	W
1032	W
1132	W
1143	W
1163	W
1179	W
1206	S
1250	W
1303	W
1315	W
1342	W
1364	W
1378	W
1446	W
1473	M
1573	S
1596	S

Table 6. Raman Peak List for Latrepirdine HPMCAS Solid Dispersion

Wavenumber (cm ⁻¹)	Relative intensity
323	W
349	W
373	W
390	W
414	W
442	W
465	M
499	W
524	W
552	W
571	W
584	W
602	W
646	M
667	W
703	M
715	M
761	W
798	W
851	M
897	W
910	W
930	W
949	W
973	W
1015	W
1030	W
1043	W
1062	W

Wavenumber (cm ⁻¹)	Relative intensity
1131	W
1142	W
1161	W
1177	W
1204	M
1248	W
1263	W
1301	W
1313	W
1340	W
1362	M
1377	M
1448	M
1470	M
1570	M
1594	M
1621	W
1744	W
2733	W
2783	W
2837	M
2925	S
3037	M

Table 7. Raman Peak List for Latrepirdine CAP Solid Dispersion

Wavenumber (cm ⁻¹)	Relative Intensity
322	W
348	W

Wavenumber (cm ⁻¹)	Relative Intensity
372	W
412	W
441	W
464	W
476	W
499	W
523	W
552	W
572	W
601	W
646	M
703	M
713	M
761	W
799	W
832	M
851	M
910	W
962	W
973	W
1017	M
1037	M
1142	W
1161	M
1178	W
1206	M
1248	W
1263	W
1300	M

Wavenumber (cm ⁻¹)	Relative Intensity
1329	M
1341	M
1362	M
1378	M
1446	M
1469	M
1531	W
1571	M
1597	S
1739	W
2733	W
2786	W
2934	S
3036	M
3063	M

Table 8. Raman Peak List for Latrepirdine PVP Solid Dispersion

Wavenumber (cm ⁻¹)	Relative Intensity
322	W
349	W
374	W
391	W
442	W
465	M
498	W
525	W
552	W
572	W

Wavenumber (cm ⁻¹)	Relative Intensity
584	W
603	W
646	W
668	W
704	M
714	M
759	W
798	W
832	W
852	M
897	W
932	W
973	W
1016	W
1031	W
1130	W
1143	W
1161	W
1176	W
1204	M
1227	W
1248	W
1313	W
1340	W
1363	W
1377	M
1425	M
1446	M
1470	M

Wavenumber (cm ⁻¹)	Relative Intensity
1570	M
1593	M
1623	W
1675	W
2673	W
2732	W
2782	W
2922	S
3035	M

Infrared Spectroscopy

The infrared spectra for crystalline Forms A and B of Latrepirdine free base were acquired using a Nicolet 6700 FTIR spectrometer equipped with a KBr beamsplitter and a d-TGS KBr detector. A Specac Golden Gate Mk II single reflection diamond ATR accessory was used for sampling. A nitrogen purge was connected to the IR bench as well as the ATR accessory. The Golden Gate ATR anvil was in the up position when the air background is collected. Powder samples were compressed against the diamond window by the Golden Gate anvil. A torque wrench was used to apply 20 cN·m of torque to the anvil compression control knob.

Spectra were collected at 2 cm⁻¹ resolution with 256 co-added scans. The collection range was 4000-525 cm⁻¹. Happ-Genzel apodization was used. No additional sample preparation is needed with the ATR technique. Two separate spectra were collected, with decompression and mixing of the powder performed between spectral collections. Any powder that adhered to the anvil was removed, as well as any powder adhered to the diamond window. These scans were averaged and the resulting average spectrum was reported.

Spectral peaks were identified manually using the Thermo Nicolet Omnic 7.3a software. The spectra were intensity normalized prior to peak picking. Peak position was picked at the peak maximum, and peaks were only identified as such, if there was a slope observed on each side of a maximum; shoulders on peaks were not included. Both peak position and relative intensity values are reported in the peak tables. The peak position has been rounded to the nearest whole number using standard practice (0.5 rounds up, 0.4 rounds down). The relative intensity values were grouped into strong (S), medium (M) and weak (W) using the following divisions: strong (1-0.75); medium (0.74-0.3) and weak (0.29 and below).

Spectral features in the region between 2400-1900 cm^{-1} are present in all spectra run by the Golden Gate d-ATR and should be ignored (Ferrer, N.; Nogués-Carulla, J.M. *Diamond and Related Materials* **1996**, 5, 598-602. Thongnopkun, P.; Ekgasit, S. *Diamond and Related Materials* **2005**, 14, 1592-1599. Pike Technologies Technical Note: *Pike Reflections*, **Winter 2002**, Vol. 7/1; www.piketech.com).

Tables 9-13 list peak positions in wavenumbers and relative peak intensities for the infrared spectra of the solid forms of latrepirdine disclosed in the present application. Although specific infrared peak values are reported herein there does exist a range for these peak values due to differences in instruments, samples, and sample preparation. This is common practice in the solid-state chemical arts because of the variation inherent in peak values. A typical variability of the wavenumber (cm^{-1}) x-axis value for infrared spectroscopy is on the order of plus or minus 4 cm^{-1} .

Table 9. Infrared Peak List for Form A of Latrepirdine Free Base

Wavenumber (cm^{-1})	Relative Intensity
587	W
602	W
637	W
647	M

Wavenumber (cm ⁻¹)	Relative Intensity
667	M
714	M
731	M
741	M
778	S
800	W
818	M
825	W
853	W
860	M
897	M
919	W
954	W
971	M
992	W
1017	M
1030	M
1039	M
1047	M
1060	M
1124	S
1140	M
1158	M
1171	M
1188	M
1204	M
1234	M
1249	M
1253	M

Wavenumber (cm ⁻¹)	Relative Intensity
1280	M
1302	M
1340	M
1354	S
1361	M
1374	M
1382	M
1393	M
1428	M
1449	M
1456	M
1470	M
1482	M
1492	M
1566	M
1592	W
1600	M
1622	W
2633	W
2674	W
2693	W
2741	M
2763	M
2782	M
2839	M
2869	M
2925	M
2953	M
2968	M

Wavenumber (cm ⁻¹)	Relative Intensity
3003	W
3022	M
3033	W
3058	W
3096	W

Table 10. Infrared Peak List for Form B of Latrepirdine Free Base

Wavenumber (cm ⁻¹)	Relative Intensity
552	W
566	M
583	M
605	W
635	W
643	W
647	W
702	W
715	W
734	M
748	W
760	M
795	S
829	M
850	W
866	M
881	W
910	W
925	W
954	W

Wavenumber (cm ⁻¹)	Relative Intensity
970	M
997	W
1028	M
1035	M
1042	W
1049	W
1062	W
1123	M
1133	W
1142	M
1159	W
1177	M
1185	W
1192	W
1201	W
1215	W
1227	M
1249	W
1261	W
1281	W
1300	M
1309	W
1335	M
1342	M
1359	M
1368	W
1384	W
1391	M
1425	M

Wavenumber (cm ⁻¹)	Relative Intensity
1433	M
1445	M
1456	M
1467	M
1481	W
1494	W
1567	W
1590	W
1596	W
1600	W
1621	W
2670	W
2686	W
2711	W
2741	W
2763	W
2778	W
2806	W
2833	W
2840	W
2863	W
2894	W
2922	W
2941	W
2953	W
3005	W
3018	W
3032	W
3053	W

Table 11. Infrared Peak List for Latrepirdine HPMCAS Solid Dispersion

Wavenumber (cm ⁻¹)	Relative Intensity
638	M
646	M
666	M
702	W
714	W
733	M
748	W
760	W
789	M
825	M
862	W
897	M
909	M
952	M
973	M
1048	S
1123	M
1140	M
1232	M
1299	W
1339	W
1361	W
1425	W
1449	W
1471	M
1566	W
1601	W

Wavenumber (cm ⁻¹)	Relative Intensity
1621	W
1739	M
2781	W
2836	W
2876	W
2921	W
3463	W

Table 12. Infrared Peak List for Latrepirdine CAP Solid Dispersion

Wavenumber (cm ⁻¹)	Relative Intensity
594	M
601	M
646	M
650	M
694	M
711	M
735	M
746	M
790	M
826	M
858	W
903	M
972	M
1035	S
1124	M
1159	M
1175	M
1232	S

Wavenumber (cm ⁻¹)	Relative Intensity
1279	W
1362	M
1432	M
1469	M
1486	M
1568	W
1592	W
1602	W
1739	M
2738	W
2782	W
2867	W
2924	W
3020	W

Table 13. Infrared Peak List for Latrepirdine PVP Solid Dispersion

Wavenumber (cm ⁻¹)	Relative Intensity
645	M
664	M
732	M
759	M
787	M
825	M
908	M
932	M
954	M
971	M
1001	M

Wavenumber (cm ⁻¹)	Relative Intensity
1015	M
1029	M
1061	W
1124	M
1142	M
1159	M
1173	M
1203	M
1226	M
1249	M
1269	S
1283	S
1339	M
1359	m
1392	M
1420	S
1458	M
1486	M
1566	M
1601	M
1667	S
2780	M
2869	M
2917	M

¹³C solid state NMR

¹³C solid state NMR spectra were collected for latrepirdine Forms A and B at ambient pressure on a Bruker-Biospin 4 mm BL HFX CPMAS probe positioned into a wide-bore Bruker-Biospin DSX 500 MHz (¹H frequency)

NMR spectrometer. Approximately 80 mg of sample were tightly packed into a 4 mm ZrO₂ rotor. The packed rotor was oriented at the magic angle and spun at 15.0 kHz. The ¹³C solid state spectrum was collected using a proton decoupled cross-polarization magic angle spinning experiment (CPMAS). The cross-polarization contact time was set to 2.0 ms. A proton decoupling field of approximately 85 kHz was applied. 3,584 scans were collected for Form A using a recycle delay of 3.4 seconds. 22,528 scans were collected for Form B using a recycle delay of 3.7 seconds. The carbon spectrum was referenced using an external standard of crystalline adamantane, setting its upfield resonance to 29.5 ppm.

¹³C solid state NMR spectra were collected for the latrepirdine noncrystalline solid dispersions at ambient pressure on a Bruker-Biospin 4 mm BL HFX CPMAS probe positioned into a wide-bore Bruker-Biospin Avance DSX 500 MHz (¹H frequency) NMR spectrometer. Approximately 80 mg of sample were tightly packed into a 4 mm ZrO₂ rotor for each sample analyzed. Rotor caps fitted with O-rings were used to seal the rotors. Samples were cooled with a direct stream of nitrogen onto the rotor having an output temperature of 10°C at a flow rate of 935 liters/hour. Packed rotors were oriented at the magic angle and spun at 15.0 kHz. The ¹³C solid state spectrum was collected using a proton decoupled cross-polarization magic angle spinning experiment (CPMAS). The cross-polarization contact time was set to 2.0 ms. A proton decoupling field of approximately 85 kHz was applied. 8,192 scans were collected with recycle delay of 2.8 seconds. The carbon spectrum was referenced using an external standard of crystalline adamantane, setting its upfield resonance to 29.5 ppm.

Tables 14-18 list peak positions in parts per million and relative peak intensities for the ¹³C solid state NMR spectra of the solid forms of latrepirdine disclosed in the present application. Intensities can vary depending on the actual setup of the CPMAS experimental parameters and the thermal history of the sample. CPMAS intensities are not necessarily quantitative. Although specific ¹³C solid state NMR peak values are reported herein there does exist a range for these peak values due to differences in instruments, samples, and

sample preparation. This is common practice in the solid-state chemical arts because of the variation inherent in peak values. A typical variability for a ^{13}C chemical shift (ppm) x-axis value is on the order of plus or minus 0.2 ppm for a crystalline solid.

Table 14. ^{13}C ssNMR Peak List for Form A of Latrepirdine Free Base

^{13}C Chemical Shifts [ppm]	Intensity
157.4	8
152.3	4
135.5	6
134.2	9
132.8	11
128.0	3
126.2	11
123.9	5
122.1	7
118.3	5
109.7*	2
108.2	9
53.4	2
51.5	2
50.2	2
46.7	6
44.2	8
33.4	7
23.9	12

* Peak shoulder

Table 15. ^{13}C ssNMR Peak List for Form B of Latrepirdine Free base

^{13}C Chemical Shifts [ppm]	Intensity
154.2	7
149.6	5
139.3	5
134.9*	9
134.2	12
127.1	9
126.7	9
124.6	8
124.3*	7
119.3	6
108.3	6
107.2	8
52.5	6
51.6	6
45.5	12
30.9	5
25.6	8
24.0	5
21.8	9

* Peak shoulder

Table 16. ^{13}C ssNMR Peak List for Latrepirdine HPMCAS Solid Dispersion

^{13}C Chemical Shifts [ppm]	Intensity
170.3	3
156.8	4
149.8	2
134.8	10

¹³ C Chemical Shifts [ppm]	Intensity
132.0	6
127.0	9
122.9	6
118.0	4
108.5	6
103.8	5
84.3	6
74.8	10
70.4*	Peak shoulder
61.2	10
52.6	4
46.1	6
32.9	3
23.9	9
21.9	12
17.1	1

* Peak shoulder

Table 17. ^{13}C ssNMR Peak List for Latrepirdine CAP Solid Dispersion

^{13}C Chemical Shifts [ppm]	Intensity
170.4	6
156.7	3
149.5	2
134.8	8
130.4	9
127.0	8
123.7*	Peak shoulder
118.2	2
109.0	3
101.8	3
73.2	7
63.5	2
51.2	4
45.1	4
33.8	2
21.4	12

* Peak shoulder

Table 18. ^{13}C ssNMR Peak List for Latrepirdine PVP Solid Dispersion

^{13}C Chemical Shifts [ppm]	Intensity
174.7	8
156.6	2
149.9	2
134.9	7

131.8	4
127.0	7
122.5	4
117.9	3
108.5	4
52.6	4
43.0	12
32.1	12
24.0	7
19.1	8

* Peak shoulder

Thermal Analysis

Differential scanning calorimetry (DSC) was performed with a Mettler-Toledo 821[°] DSC instrument for Form A and a Mettler-Toledo 822[°] DSC instrument for Form B. Samples of approximately 5 mg were weighed into standard aluminum pans (40µl). Each pan was crimped and vented with a pinhole with a perforated cover. Measurements were conducted at 5 °C/minute with a 60 mL/minute nitrogen purge unless otherwise noted. The temperature and heat flow were calibrated using indium and tin standards, respectively. Melting onset temperatures were determined using Mettler-Toledo STAR^e software Version 8.10. Melting point onset values can be reported with the modifier "about," which is standard terminology in the solid-state chemical arts and is meant to account for changes in melting point due to differences in particle size and/or chemical impurities, as well as variability introduced into melting point measurements by the analytical instrument and methodology employed. These sources introduce a variability for melting onset temperatures that is typically less than about $\pm 5^{\circ}$ C. The melting onset temperatures of latrepirdine free base Forms A and B are provided in Table 19.

Table 19. Melting Onset Temperatures for Forms A and B of
Latrepirdine Free Base

Latrepirdine Form	Temperature (° C)
A	105
B	117

The melting onset temperatures for Forms A and B were also measured using a hot-stage microscopy method to confirm the DSC results. Hot-stage microscopy evaluation was conducted using an Olympus BX60 optical microscope equipped with a Linkam LTS 350 hot stage and controlled with Linksys32 1.2.1 software. Solids were viewed under cross-polarized light with a 530 nm wave plate and heated at 5 °C/minute from room temperature. Onset temperatures were determined visually, i.e., upon observation of sample melting. Melting point onset values can be reported with the modifier "about," which is standard terminology in the solid-state chemical arts and is meant to account for changes in melting point due to differences in particle size and/or chemical impurities, as well as variability introduced into melting point measurements by the analytical instrument and methodology employed. The melting onset temperatures for Forms A and B were determined in this manner were consistent with the values reported using the DSC method described for Forms A and B, i.e., about 105° C and 117° C.

Hot-stage microscopy evaluation can also be conducted to determine the solid-state form of latrepirdine free base present within a formulation as it is being developed as well as in the finished drug product. Experimental practices are similar to those described above, whereby the formulation is placed onto a microscope slide for evaluation. The melting onset temperatures determined in this manner for a patch formulation containing either Form A or Form B were also consistent with the values reported using the DSC method described for Forms A and B, i.e., about 105° C and 117° C.

Differential Scanning Calorimetry (DSC) was performed with a TA DSC (Q1000) for noncrystalline latrepirdine free base. Samples of approximately 5

mg were weighed into Perkin Elmer hermetic aluminum pans (40 μ l) upon equilibration at less than 5% RH at 22° C. Glass transition measurements were conducted at 2°C/minute heating rate with 1°C amplitude and 100 seconds frequency. The nitrogen purge was 50mL/minute unless otherwise noted. The temperature was calibrated using indium. Glass transition temperatures (T_g) were determined at the mid point of the transition using TA Instruments Universal Analysis 2000. The glass transition temperatures for noncrystalline latrepirdine are provided in Table 20.

Table 20. Glass Transition Temperatures for Noncrystalline Latrepirdine Free Base

Latrepirdine Solid	T _g (° C)
Noncrystalline Latrepirdine	- 1
HPMCAS Solid Dispersion	62
CAP Solid Dispersion	85
PVP Solid Dispersion	33

EXAMPLES

The following non limiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

Example 1. Preparation of MVP: MVPO (1, 2.5 g) was slurried in 12.5 ml of MTBE. Triethylamine was added (2.49 g 24.59 mmoles) and stirred at room temperature for 2.5 hr. The salts were collected by filtration and NMR analysis of the salt indicated that no MVP was present only triethylamine. The filtrate was likewise examined by NMR and showed the presence of MVP and a small amount of triethylamine. The filtrate can be concentrated in the same manner as above and used to prepare **3** as described above in scheme 2.

Example 2: Preparation of latrepirdine free base from the hydrochloride salt

2-methyltetrahydrofuran (17.2 moles; 1.73 L; 1.48 Kg) was added to a 4 L, multineck jacketed reactor with overhead stirring, pitched blade impeller and thermocouple, containing latrepirdine dihydrochloride salt (1.00 equiv

[limiting reagent]; 806 mmoles; 345 grams). To a thick slurry that formed, a 1 Molar, aqueous solution of sodium hydroxide (1.25 equiv, 2.01 moles; 2.01 L; 2.09 Kg) was slowly added over approximately 45 minutes. During the addition of the sodium hydroxide solution, the slurry became oily. The sample was stirred for approximately 30 minutes after the addition of the sodium hydroxide solution ended. The stirring was stopped to allow the 2 phases to separate. The organic layer was collected, water was added (55.5 moles; 1.00 L, 1.00 Kg), and stirred vigorously. The stirring was stopped to allow the 2 phases to separate and the bottom aqueous layer (pH ~12-14) was removed. If a layer at the interface was present, it was collected with the organic layer. The organic phase was washed two additional times using the same procedure. As white solids were observed during the washing steps, 1L of 2-methyltetrahydrofuran (9.97 moles; 859 grams) was added to ensure that latrepirdine free base was solubilized. Water was then added (55.5 moles; 1.00 L, 1.00 Kg) to the organic phase and stirred vigorously. The stirring was stopped to allow the 2 phases to separate and the bottom aqueous layer (pH ~8) was removed. If a layer at the interface was present, it was removed with the aqueous layer. The organic phase was washed an additional time using the same procedure. The aqueous layer (pH ~7) and grey interface layer were removed. The organic phase was dried using magnesium sulfate (332 moles; 40.0 grams). After 15 minutes of stirring, the sample was filtered using a Whatman #2 filter and washed with 2-methyltetrahydrofuran (0.3 L).

Example 3. Preparation of latrepirdine free base Form A (Method 1):

The organic layer from Example 1 was rapidly evaporated (rotary evaporation, full vacuum, approximately 40°C water bath) in 2 portions. 2-methyltetrahydrofuran was quickly removed to produce an off white solid. The solids were added together and completely dried in a high-vacuum oven to produce 247 grams of latrepirdine Form A.

Example 4. Preparation of latrepirdine free base Form A (Method 2):

A solution of latrepirdine free base was prepared in isopropyl alcohol at a concentration of 8 mg/mL. The solvent was fully evaporated at 50°C to produce Form A.

Example 5. Preparation of latrepirdine free base Form A (Method 3):

A solution of latrepirdine free base was prepared in toluene at a concentration of 21 mg/mL. The solvent was fully evaporated at 50°C to produce Form A.

Example 6. Preparation of latrepirdine free base Form A (Method 4):

A solution of latrepirdine free base was prepared in ethyl acetate at a concentration of 13 mg/mL. The solvent was fully evaporated at 50°C to produce Form A.

Example 7. Preparation of latrepirdine free base Form A (Method 5):

Form B (22 mg) was slurried in 4 mLs of heptane at room temperature for approximately one day. The slurry was filtered to produce a solution. The solution was evaporated at 50°C to produce Form A.

Example 8. Preparation of latrepirdine free base Form B (Method 1):

A solution of latrepirdine free base was prepared in toluene at a concentration of 23 mg/mL. The solvent was fully evaporated at room temperature to produce Form B.

Example 9. Preparation of latrepirdine free base Form B (Method 2):

A solution of latrepirdine free base was prepared in ethyl acetate at a concentration of 13 mg/mL. The solvent was fully evaporated at room temperature to produce Form B.

Example 10. Preparation of latrepirdine free base Form B (Method 3):

A solution of latrepirdine free base was prepared in isopropyl alcohol at a concentration of 8 mg/mL. The solvent was fully evaporated at room temperature to produce Form B.

Example 11. Preparation of latrepirdine free base Form B (Method 4):

Form B (21 mg) was slurried in 4 mLs of heptane at room temperature for approximately one day. The slurry was filtered to produce a solution. The solution was evaporated at room temperature to produce Form B.

Example 12. Preparation of noncrystalline latrepirdine (Method 1):

Noncrystalline latrepirdine was prepared by transferring approximately 10 mg of crystalline Form B latrepirdine into a Mettler Toledo pan and heating to 140 °C at 20 °C/minute in a differential scanning calorimeter. The sample

was then cooled at 100 °C/minute to -40 °C to produce noncrystalline latrepirdine.

Example 13. Preparation of noncrystalline latrepirdine (Method 2):

Noncrystalline latrepirdine was prepared by adding 500 mg of crystalline Form B to a platinum crucible and heating the sample to 140-170°C in an oven for 5-10 minutes. The sample was removed from the oven and immediately placed in liquid nitrogen bath for 5 minutes to produce noncrystalline latrepirdine.

Example 14. Preparation of latrepirdine HPMCAS and CAP noncrystalline solid dispersions:

Noncrystalline latrepirdine solid dispersions were prepared by spray drying, which included dissolving crystalline free base in organic solvents to form a solution. Useful solvents include those which are volatile, have a normal boiling point of about 150°C or less, exhibit relatively low toxicity, and can be removed from final product such that the level of solvent in the drug product meets the International Committee on Harmonization (ICH) guidelines for residual solvent.

In addition to solvent and drug substance, the solution contained various matrix-forming polymeric excipients. Latrepirdine solid dispersions were prepared using HPMCAS-MG (hydroxypropyl methyl cellulose acetate succinate – medium granular) and cellulose acetate phthalate CAP (1:1 w/w). Matrix-forming agents help stabilize noncrystalline latrepirdine, preventing or retarding formation of crystalline latrepirdine.

1. Preparation of latrepirdine HPMC-AS noncrystalline dispersion

Dispersion composition is reported in terms of the weight percent (wt %) drug in the dispersion. For example, a 50-wt % dispersion consists of 1 part (by weight) latrepirdine and 1 parts (by weight) HPMC-AS. Dispersion was prepared by pumping a 2% w/w feed solution (latrepirdine and HPMC-AS dissolved in acetone) to an atomizer inside a drying chamber. The atomizer breaks the solution up into a plume of small droplets (typically less than 100 µm in diameter). Atomization and solvent removal occur in a chamber where process conditions are controlled. The driving force for solvent removal was

provided by maintaining the partial pressure of the solvent in the chamber below the vapor pressure of the solvent at the temperature of the drying droplets. Solution flow rates of 0.060 to 0.960 L/hr through the atomizer were used, and were varied depending on the type of nozzle, the size of the chamber, and the drying conditions, which include the inlet temperature and the flow rate of the drying gas through the chamber. The drying gas was introduced into the chamber at a temperature of about 75°C. The large surface-to-volume ratio of the droplets and the large driving force for evaporation of solvent leads to rapid solidification times for the droplets. Solidification time of latrepirdine HPMCAS dispersion was approximately 500ms. Rapid solidification helps maintain uniformity and homogeneity of noncrystalline drug substance within and among particles. The solid powder was collected from the gas stream using a filter system.

The particles of noncrystalline latrepirdine solid dispersions remained in the chamber for about 1200 seconds to about 3600 seconds following solidification, during which time additional solvent evaporated from the particles. Generally, the solvent level of noncrystalline latrepirdine solid dispersion as it exits the chamber is less than about 10% w/w and is often less than 2% w/w. Following formation, noncrystalline latrepirdine solid dispersions were dried in vacuum oven under 30mm Hg pressure for 1 hour. After drying, residual solvent level is typically less than about 0.5% w/w.

2. Preparation of latrepirdine CAP noncrystalline dispersion:

Dispersion composition is reported in terms of the weight percent (wt %) drug in the dispersion. For example, a 50-wt % dispersion consists of 1 part (by weight) latrepirdine and 1 parts (by weight) CAP. Dispersions were prepared by pumping a 1% w/w feed solution (latrepirdine and CAP dissolved in 1:1 methanol: acetone) to an atomizer inside a drying chamber. The atomizer breaks the solution up into a plume of small droplets (typically less than 100 µm in diameter). Atomization and solvent removal occur in a chamber where process conditions are controlled. The driving force for solvent removal was provided by maintaining the partial pressure of the solvent in the chamber below the vapor pressure of the solvent at the

temperature of the drying droplets. Solution flow rates of 0.060 to 0.960 L/hr through the atomizer were used, and were varied depending on the type of nozzle, the size of the chamber, and the drying conditions, which include the inlet temperature and the flow rate of the drying gas through the chamber. The drying gas was introduced into the chamber at a temperature of about 85°C. The large surface-to-volume ratio of the droplets and the large driving force for evaporation of solvent leads to rapid solidification times for the droplets. Solidification time of latrepirdine CAP dispersion was approximately 500ms. Rapid solidification helps maintain uniformity and homogeneity of noncrystalline drug substance within and among particles. The solid powder was collected from the gas stream using a filter system.

The particles of noncrystalline latrepirdine dispersion remained in the chamber for about 1200 seconds to about 3600 seconds following solidification, during which time additional solvent evaporated from the particles. Generally, the solvent level of noncrystalline latrepirdine dispersion as it exits the chamber is less than about 10% w/w and is often less than 2% w/w. Following formation, noncrystalline latrepirdine dispersions were dried in vacuum oven under 30mm Hg pressure for 1 hour. After drying, residual solvent level is typically less than about 0.5% w/w.

Example 15. Preparation of latrepirdine PVP-XL noncrystalline dispersion:

Latrepirdine PVP solid dispersion was prepared by an evaporative drying process using a Buchi Rotavapor. Equal amounts of Form B latrepirdine and PVP were added to a methanol in a round bottom flask to form a solution. The solution was evaporated at 60°C, using 45 rpm rotation, and a 30 mbar vacuum. The resulting sample was then transferred to a vacuum oven for secondary drying at 50mBar pressure for one hour to produce a Latrepirdine PVP-XL noncrystalline dispersion.

Example 16. Detection of Crystalline Form in a Patch Using Hot-Stage Microscopy

Formulation 1: Particles consisting entirely of latrepirdine free base Form B were added and mixed into a silicone adhesive consisting of a 50:50

mixture of DOW CORNING® BIO-PSA 7-4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive, in heptane as the only solvent, forming a suspension of latrepirdine free base Form B particles. The suspension was then spread onto a suitable release liner or backing film to produce a film with a coating weight of about 12 mg/cm². The film was then exposed to ambient conditions for 15 minutes and then placed in a heated oven with temperatures of 92 – 102 °C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The resulting formulation was determined to contain latrepirdine free base Form B by evaluation of its powder X-ray diffraction pattern.

Hot-Stage Microscopy: Hot-stage microscopy evaluation was conducted using an Olympus BX60 optical microscope equipped with a Linkam LTS 350 hot stage and controlled with Linksys32 1.2.1 software. Solids were viewed under cross-polarized light with a 530 nm wave plate and heated at 5 °C/minute from room temperature. Onset temperatures were determined visually, i.e., upon observation of sample melting. Melting of crystalline material was observed within formulation 1 at approximately 120 °C.

Example 16. Preparation of anhydrous MVP oxalate:

MVP oxalate (459 mg) was placed in a 50 °C vacuum desiccator for approximately 1 hour. Approximately 6 mL of anhydrous ethyl acetate were added. After 2 days of stirring, the solids were isolated by vacuum filtration. The solids were then dried in an 80 °C vacuum oven for approximately 10 minutes. The sample was removed from the oven and immediately stored in a desiccated chamber.

Example 17. Preparation of hydrated MVP oxalate:

MVP oxalate (315 mg) was suspended in approximately 5 mL of ethyl acetate saturated with water. After 5 days, the solids were isolated by vacuum filtration. The solids were then dried briefly in a 40 °C vacuum oven. The sample was removed from the oven and stored for 30 minutes in a 75% relative humidity chamber.

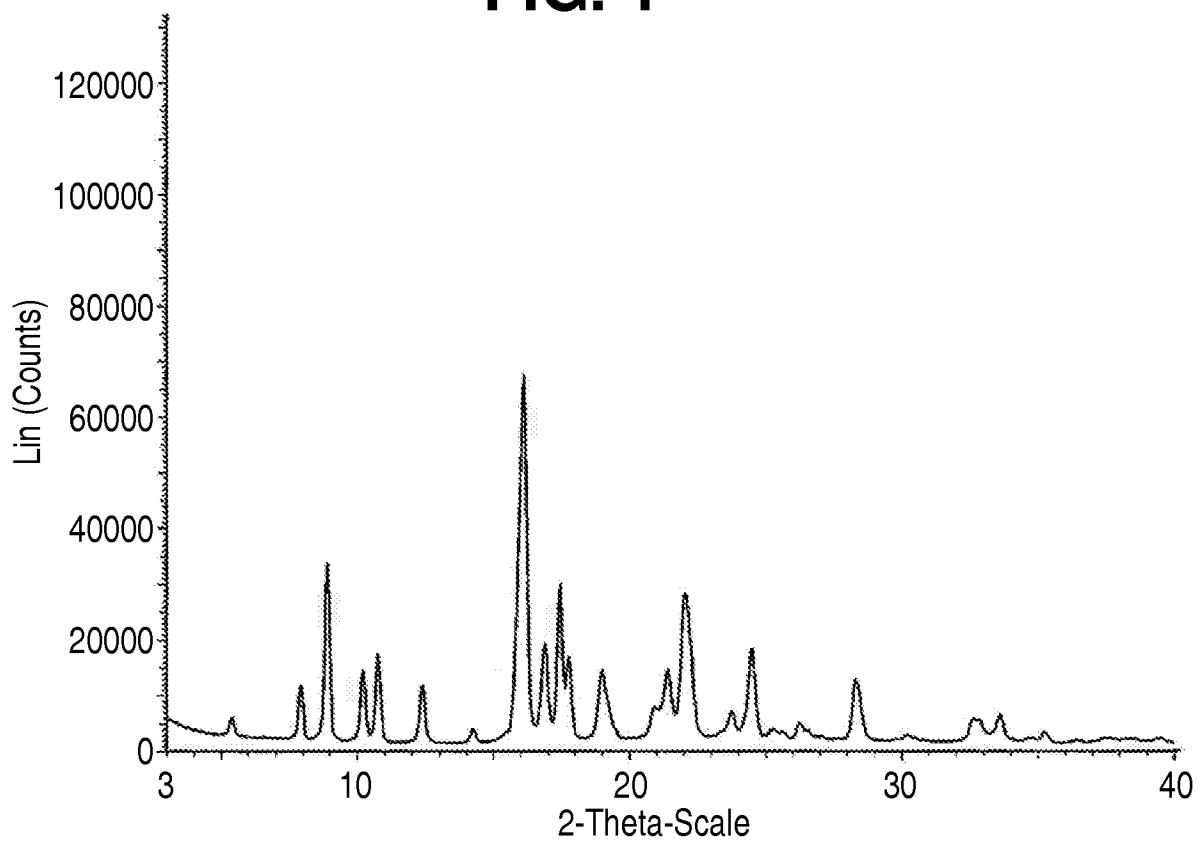
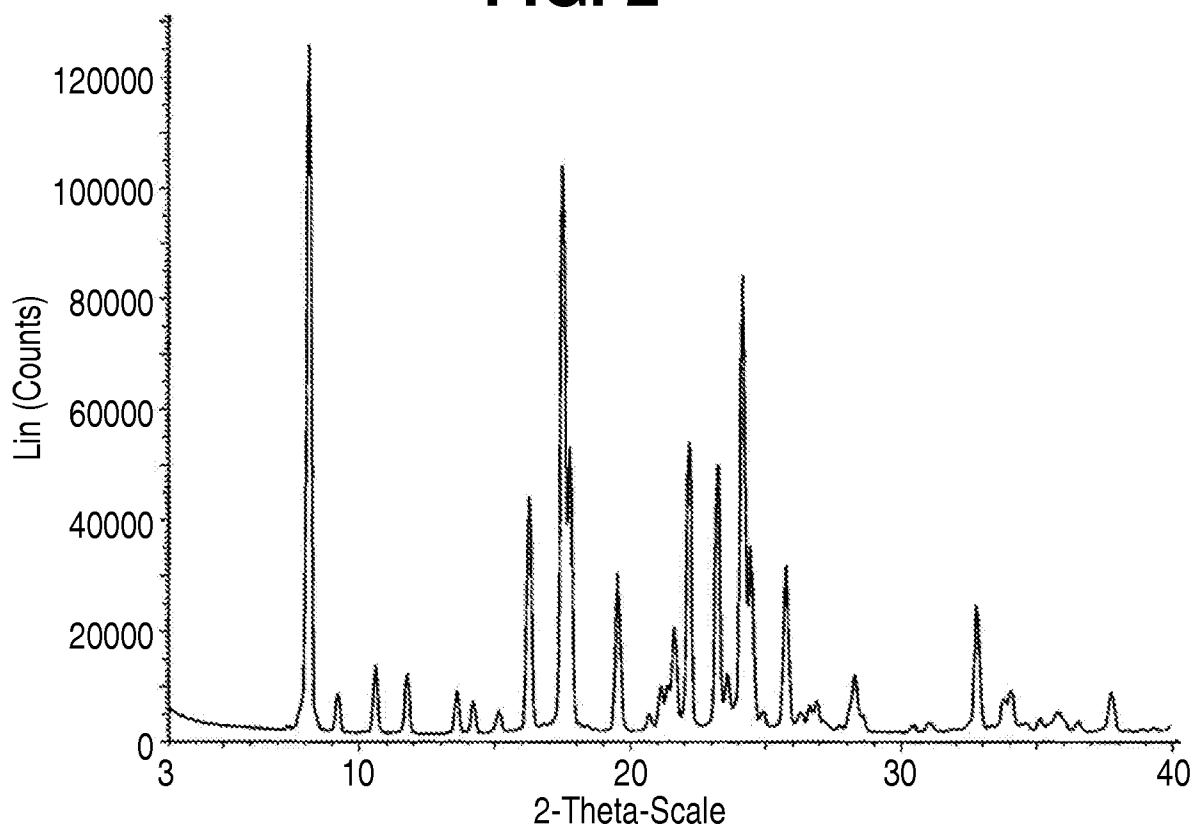
CLAIMS

We claim:

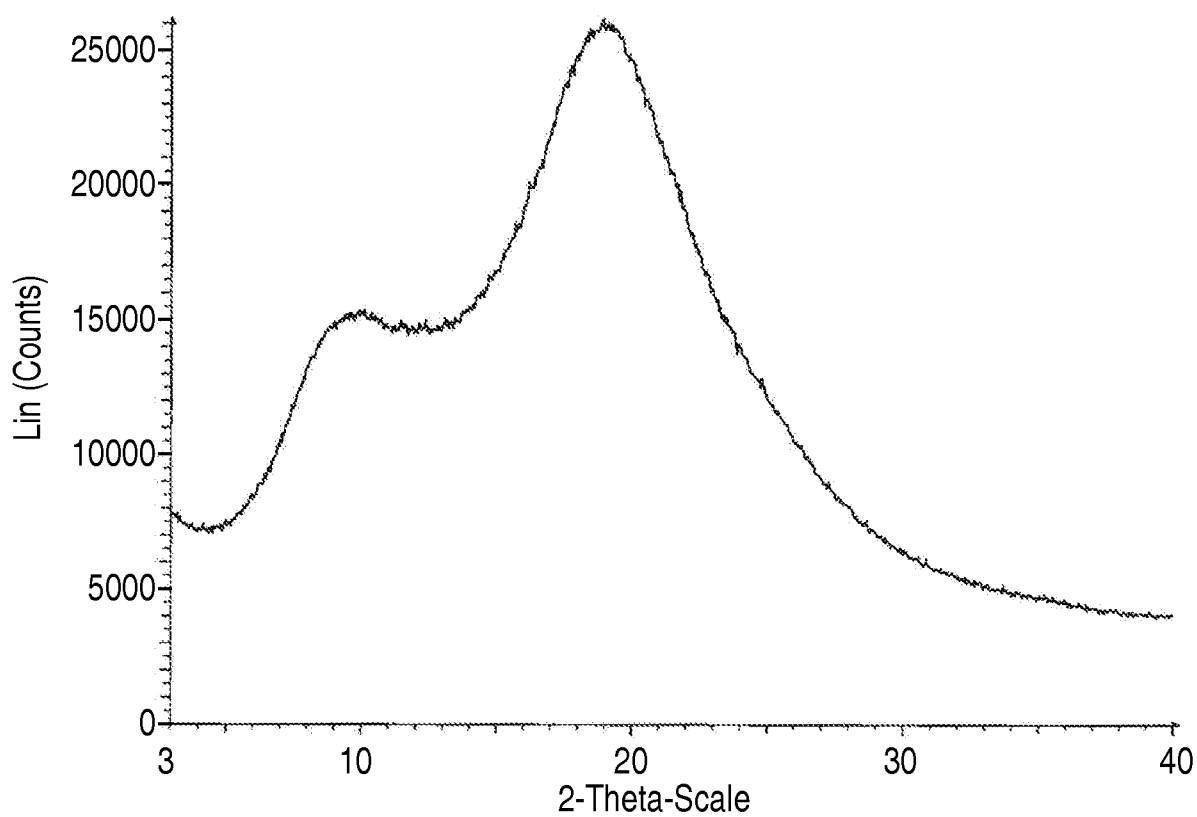
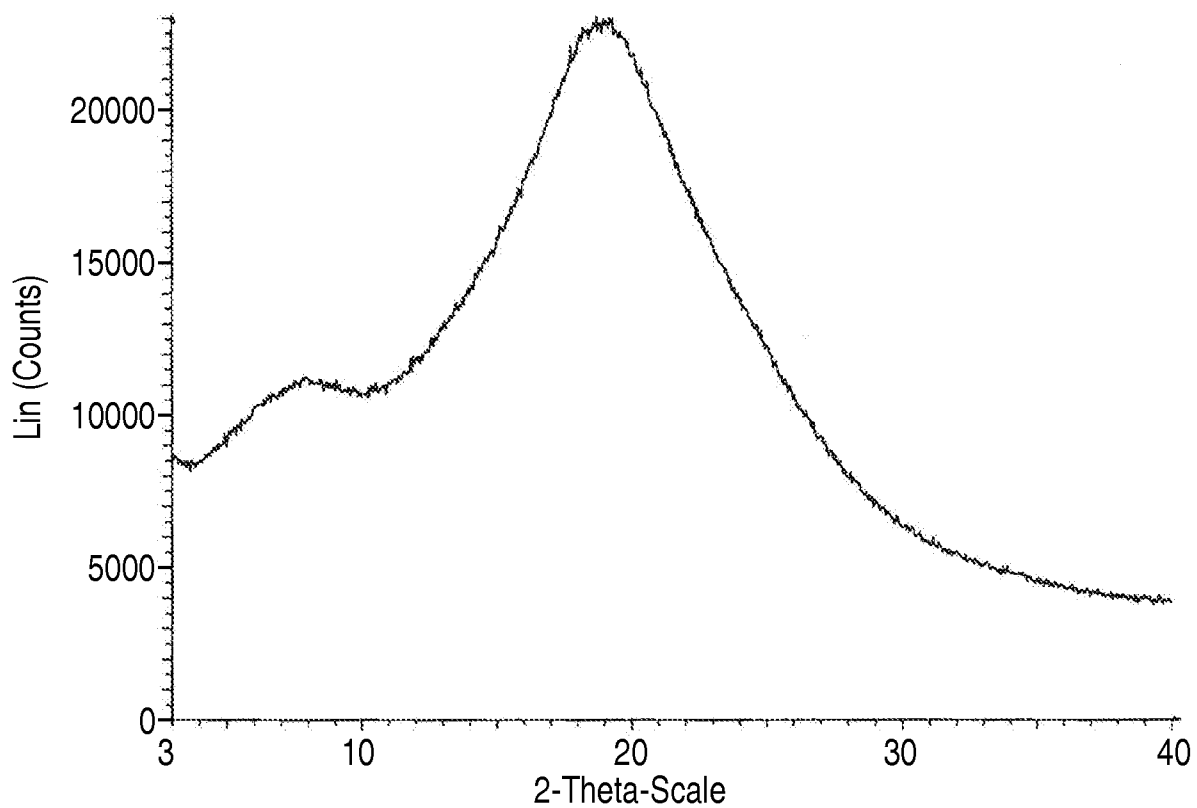
1. Latrepirdine Form A.
2. A crystalline form of latrepirdine having an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): 12.4 , 16.1 , and $17.4^\circ 2\theta \pm 0.2^\circ 2\theta$;
3. A crystalline form of latrepirdine having a Raman spectrum comprising the following wavenumber (cm^{-1}) values: 714 , 1207 , and $1356 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$.
4. A crystalline form of latrepirdine having a melting point of $105 \pm 5^\circ \text{C}$.
5. A crystalline form of latrepirdine having an X-ray powder diffraction reflection at $16.1^\circ 2\theta \pm 0.2^\circ 2\theta$ and Raman bands at 1207 and $1356 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$.
6. A noncrystalline form of latrepirdine free base.
7. A noncrystalline form of latrepirdine free base having Raman bands at 346 and $1573 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$.
8. A noncrystalline form of latrepirdine free base having Raman bands at 646 and $715 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$.
9. A noncrystalline form of latrepirdine free base having Raman bands at 346 , 704 , and $715 \text{ cm}^{-1} \pm 4 \text{ cm}^{-1}$.
10. A noncrystalline form of latrepirdine prepared as a solid dispersion composed of at least one polymer system.
11. A crystalline form of 2-methyl-5-vinylpyridine oxalate.
12. A crystalline form of 2-methyl-5-vinylpyridine oxalate having an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): 7.6 , 15.4 , and $22.8^\circ 2\theta \pm 0.2^\circ 2\theta$.
13. A crystalline form of 2-methyl-5-vinylpyridine oxalate having an X-ray powder diffraction pattern comprising the following 2θ values measured using Cu $K_{\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$): 9.8 , 16.8 , and $18.8^\circ 2\theta \pm 0.2^\circ 2\theta$.

14. A process for making a crystalline 2-methyl-5-vinylpyridine oxalate complex.
15. A crystalline 2-methyl-5-vinylpyridine oxalate complex wherein the molar ratio of oxalic acid to 2-methyl-5-vinylpyridine is 1.5 to 1.
16. A process for the preparation of latrepirdine that utilizes a crystalline 2-methyl-5-vinylpyridine oxalate, an organic solvent, and a base.
17. The process of claim 16 wherein the base is selected from sodium hydroxide, potassium hydroxide, sodium carbonate, or potassium carbonate.
18. The process of claim 16 wherein the organic solvent is selected from methyl *tert*-butyl ether, ethyl acetate, or diethyl ether, triethylamine, diisopropylethylamine, or ethylenediamine.

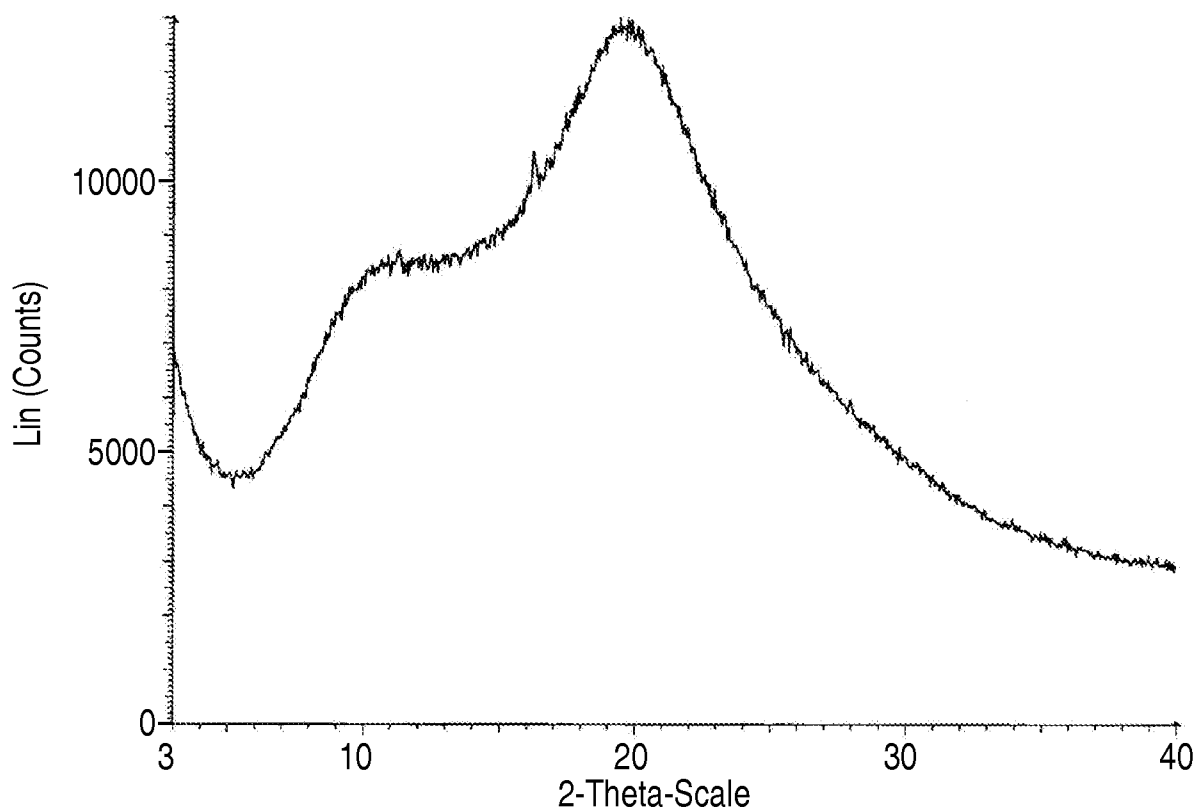
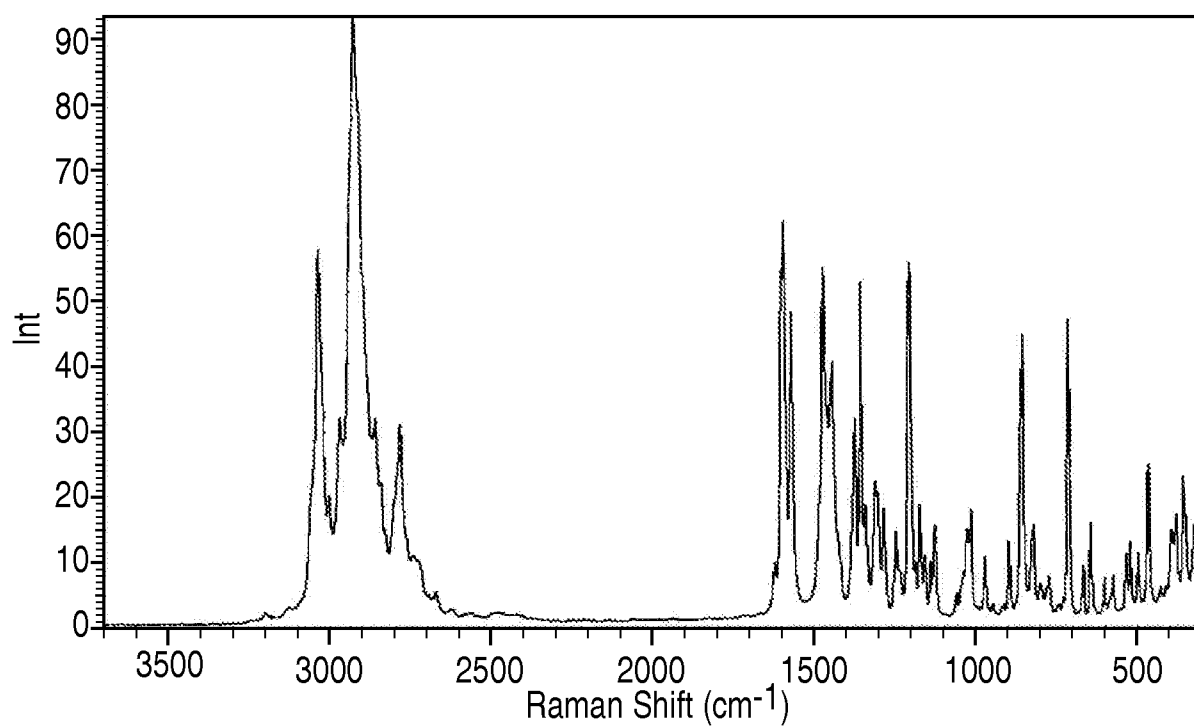
1/15

FIG. 1**FIG. 2**

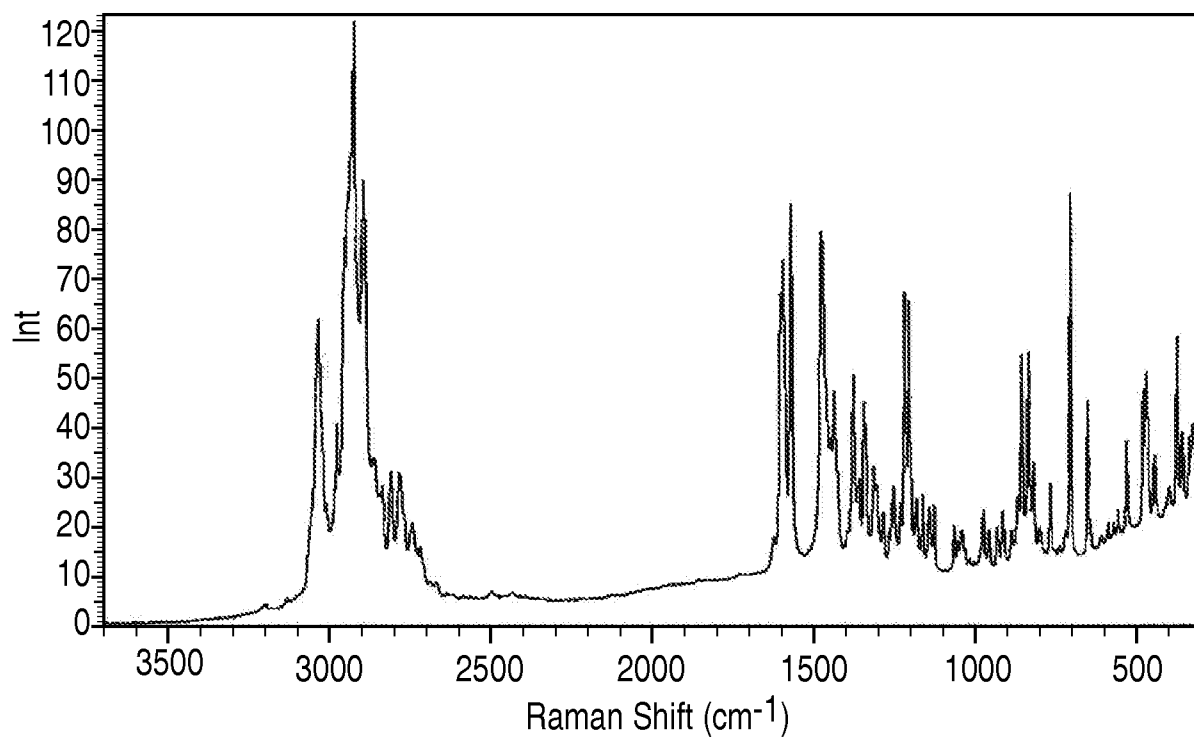
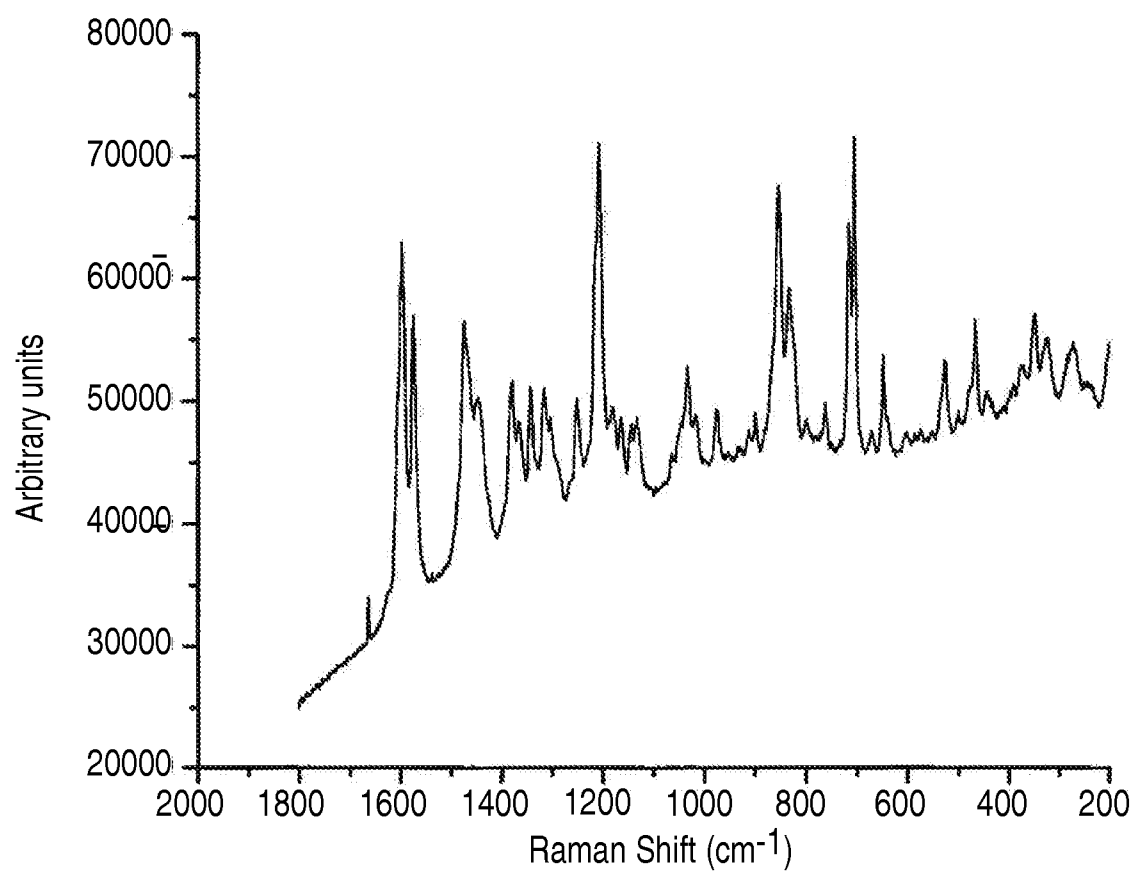
2/15

FIG. 3**FIG. 4**

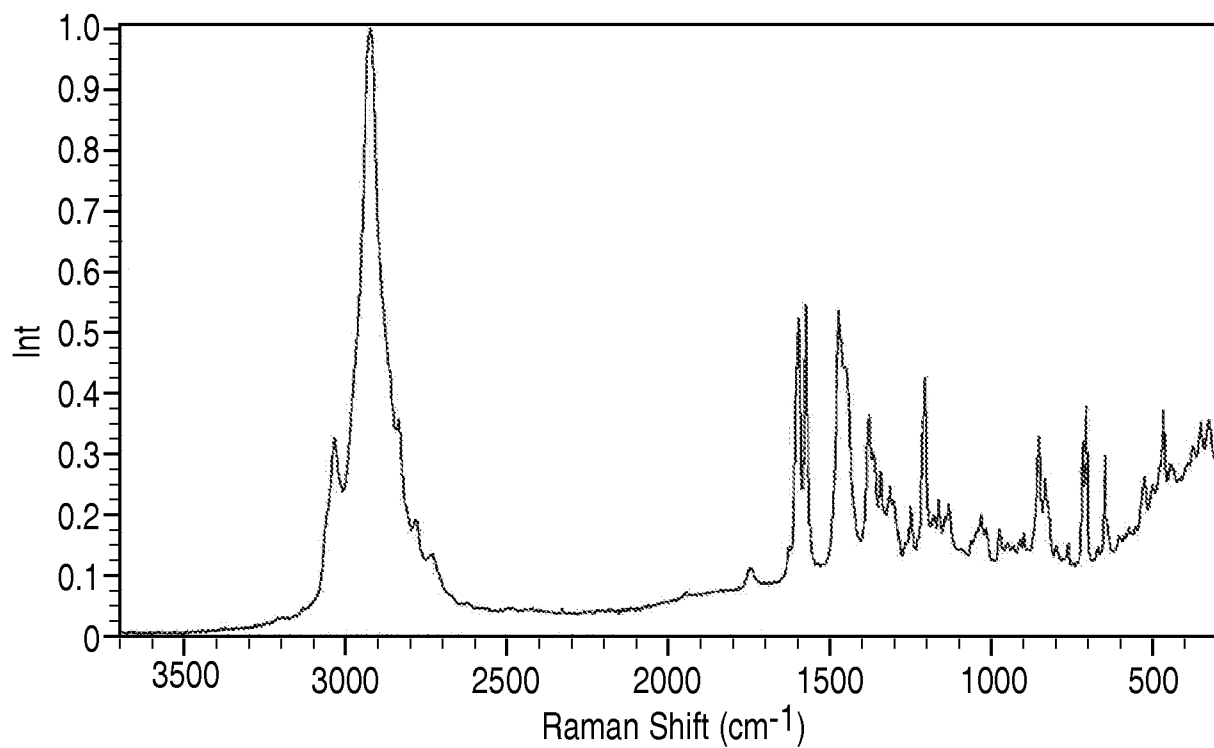
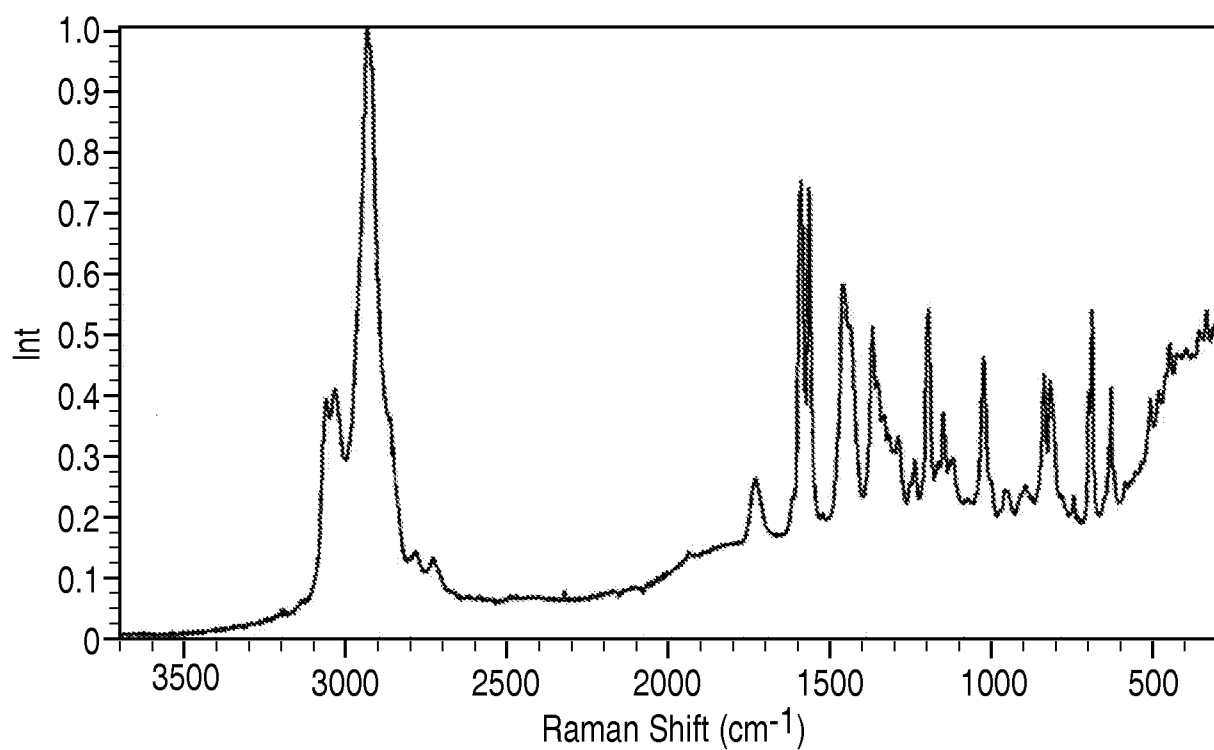
3/15

FIG. 5**FIG. 6**

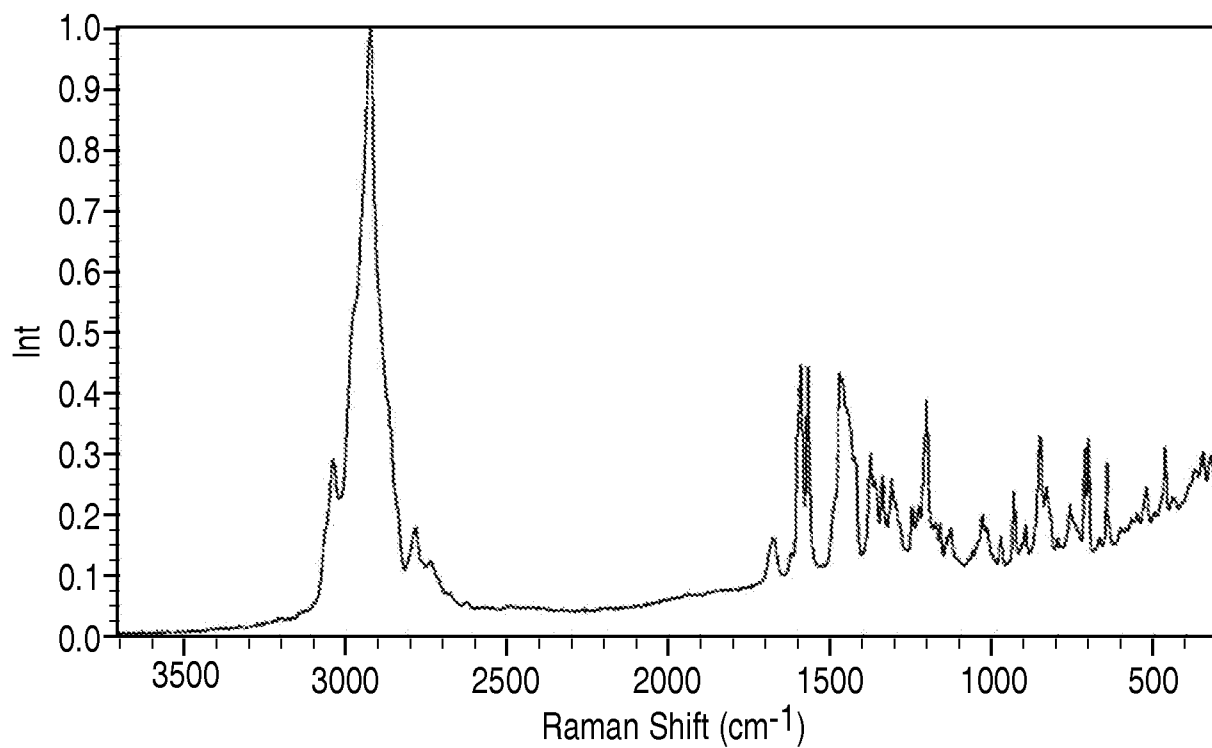
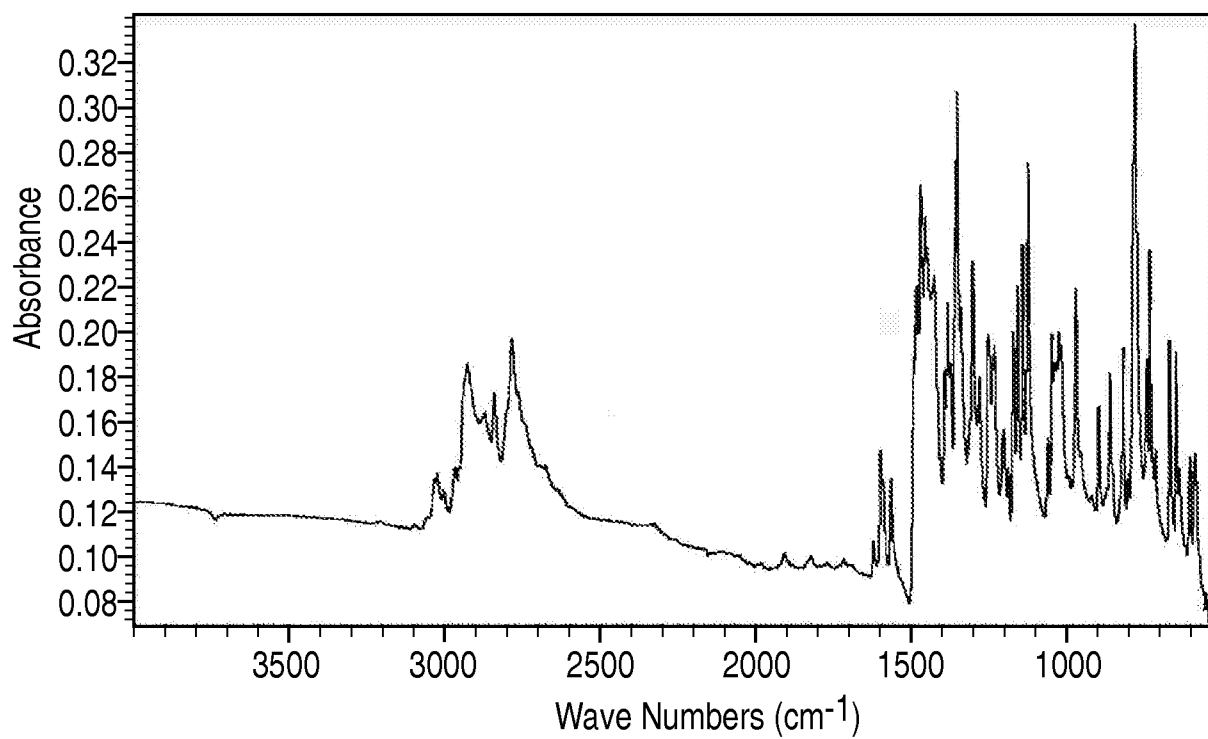
4/15

FIG. 7**FIG. 8**

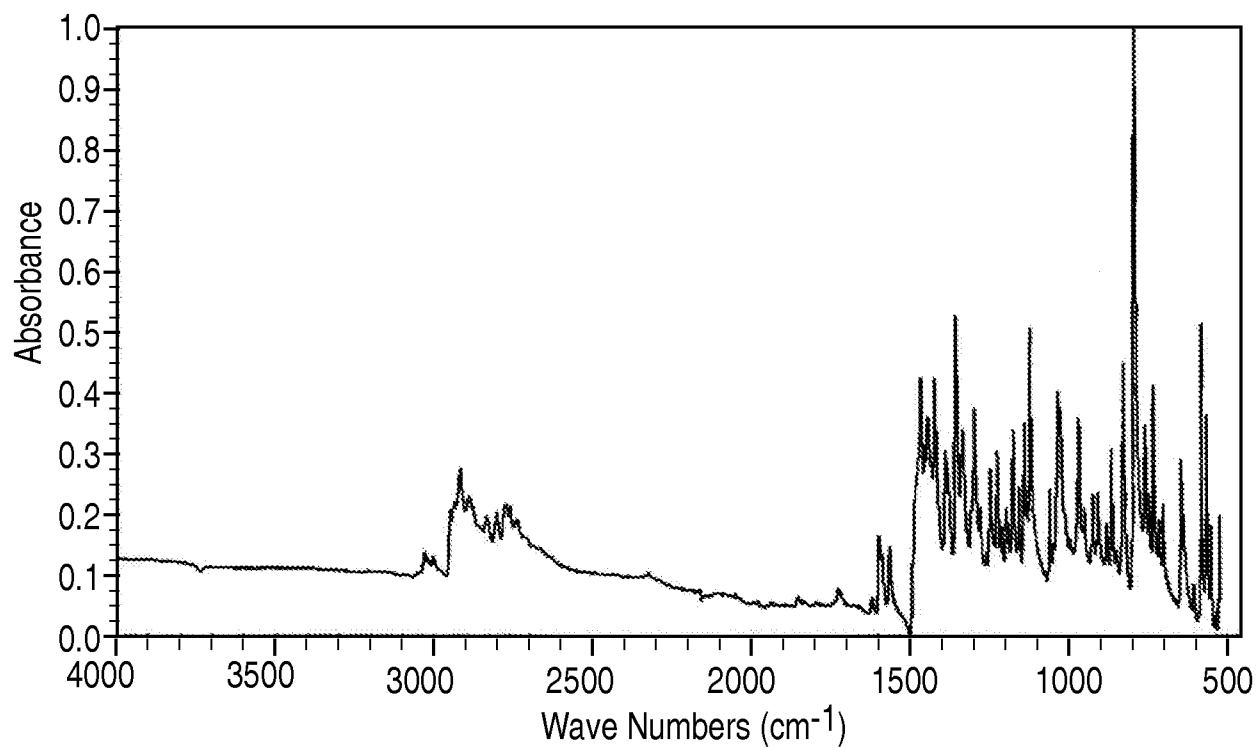
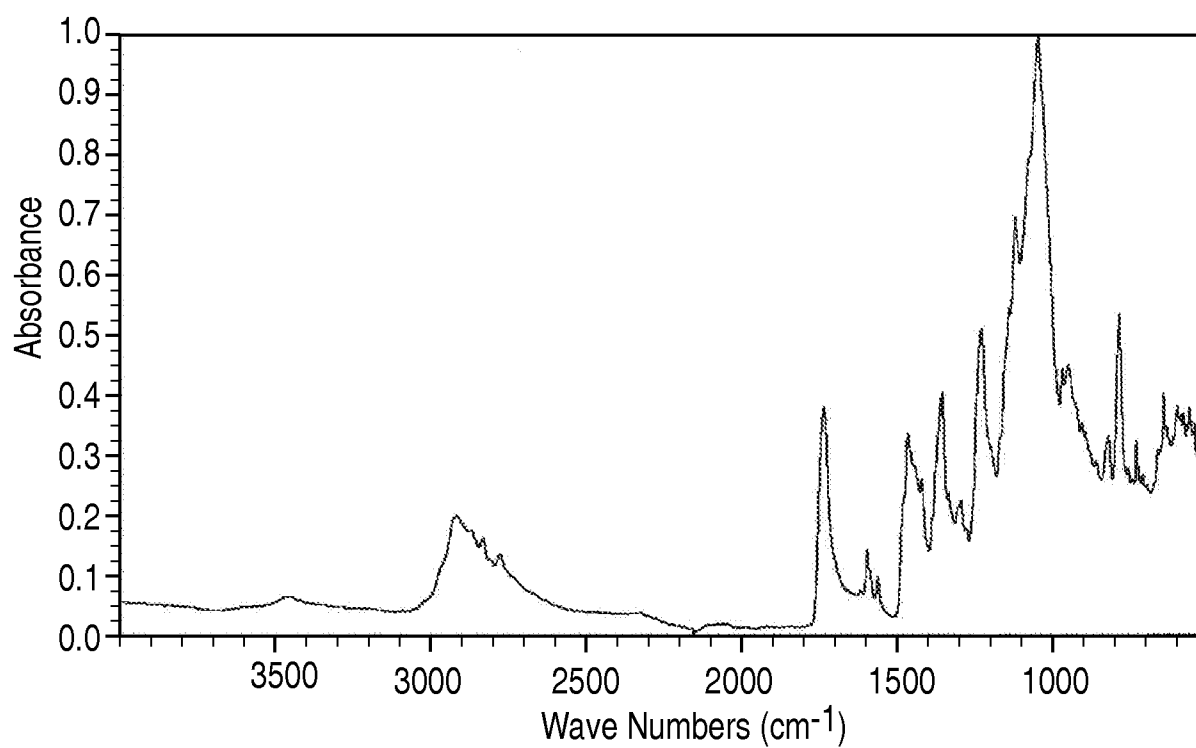
5/15

FIG. 9**FIG. 10**

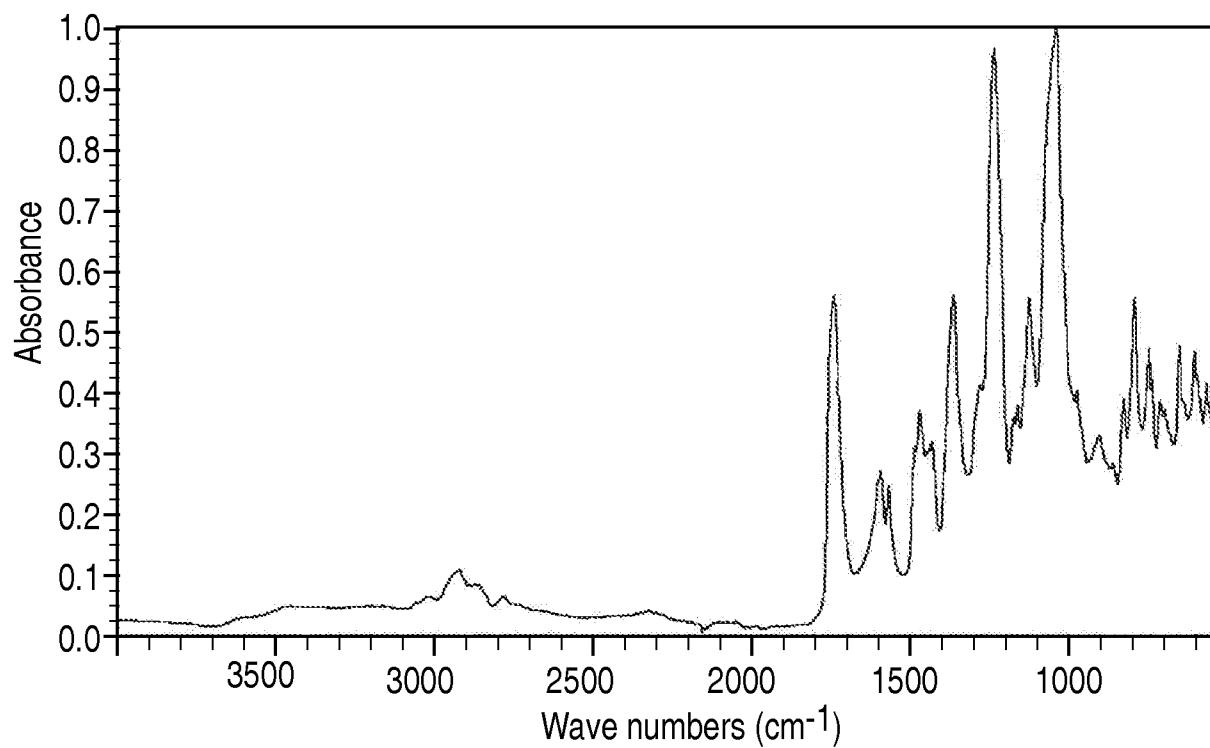
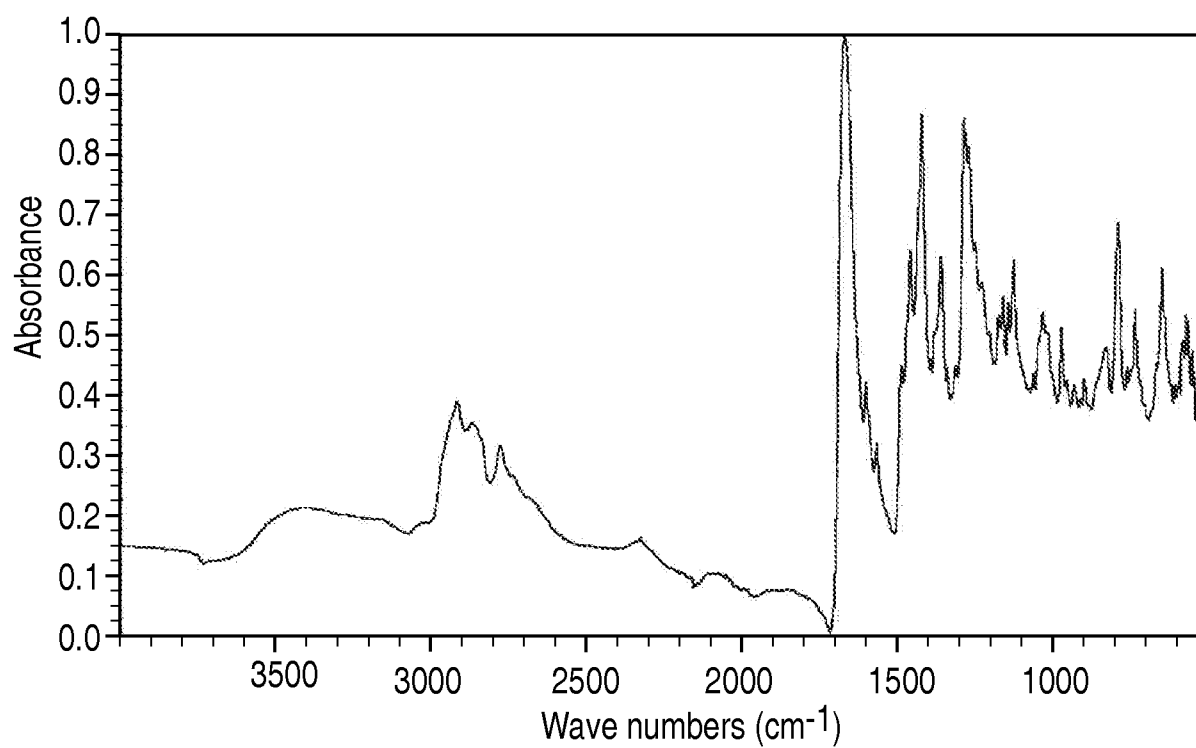
6/15

FIG. 11**FIG. 12**

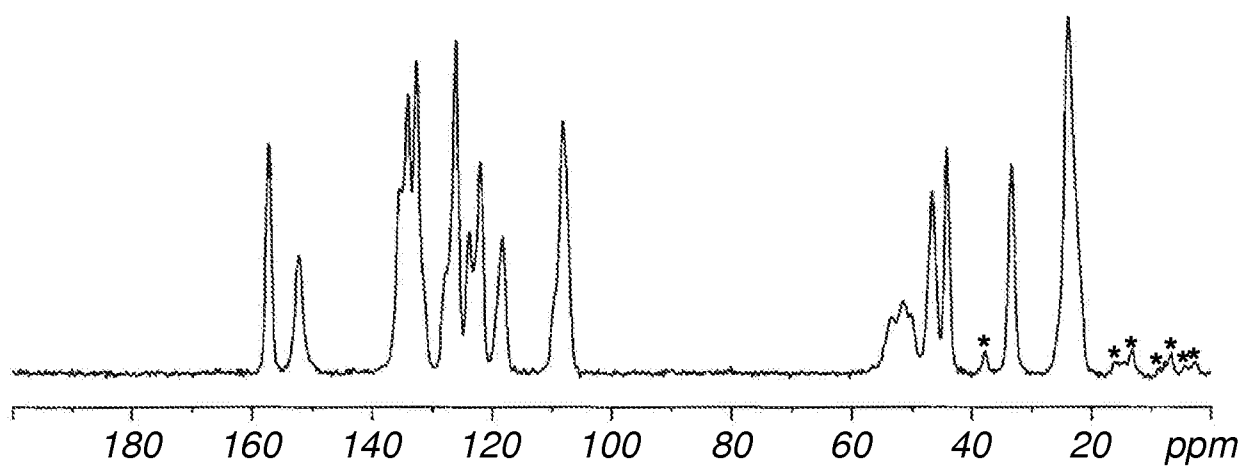
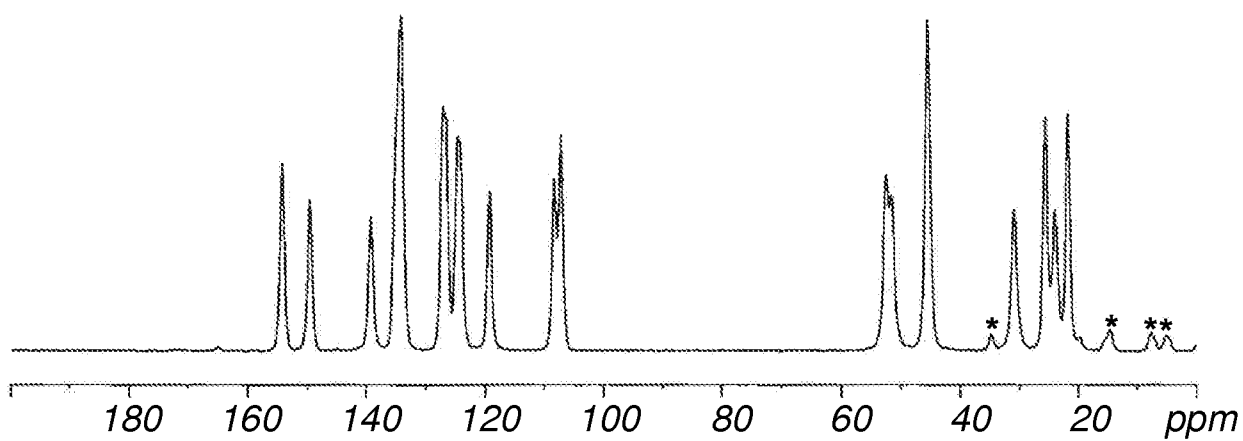
7/15

FIG. 13**FIG. 14**

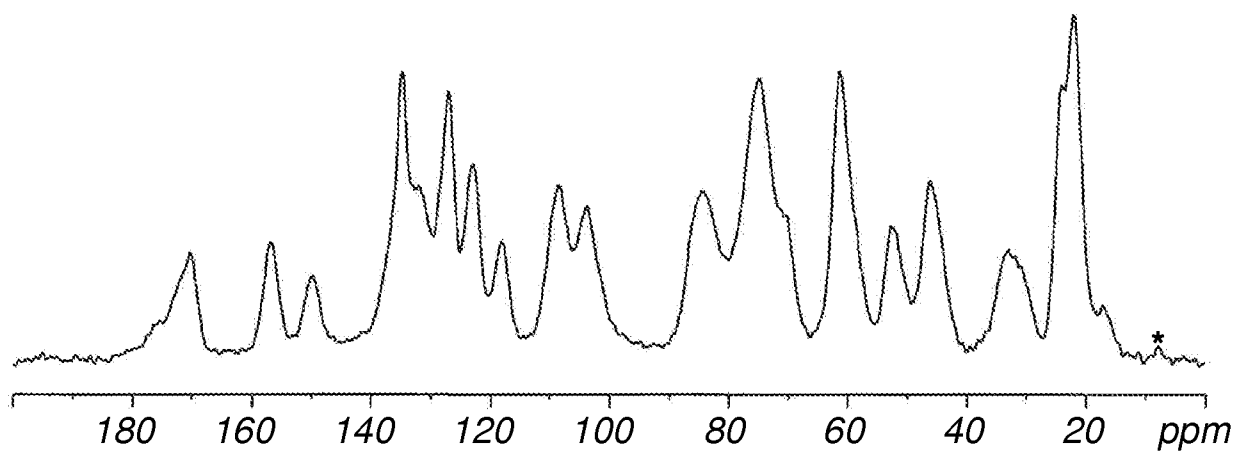
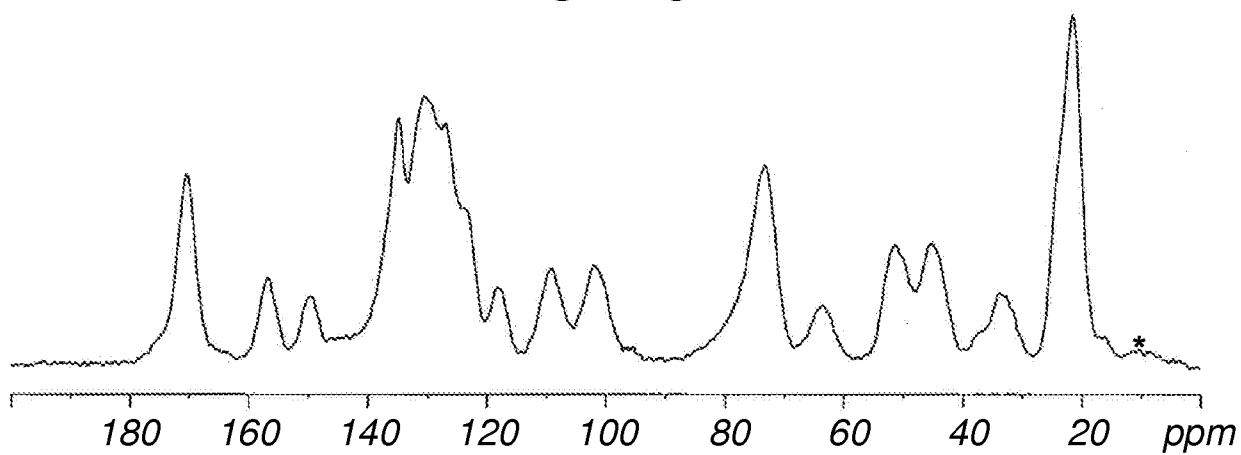
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FIG. 15**FIG. 16**

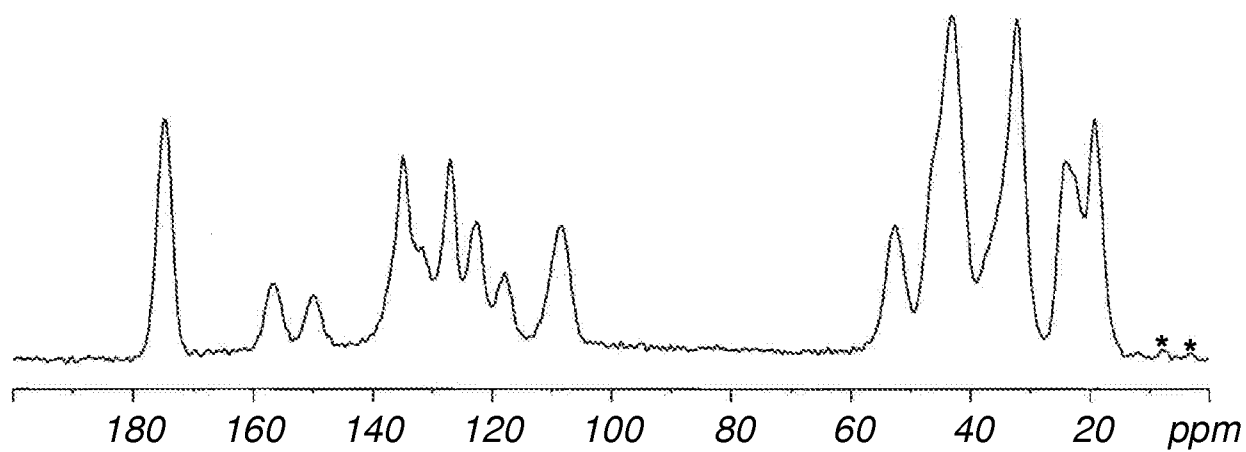
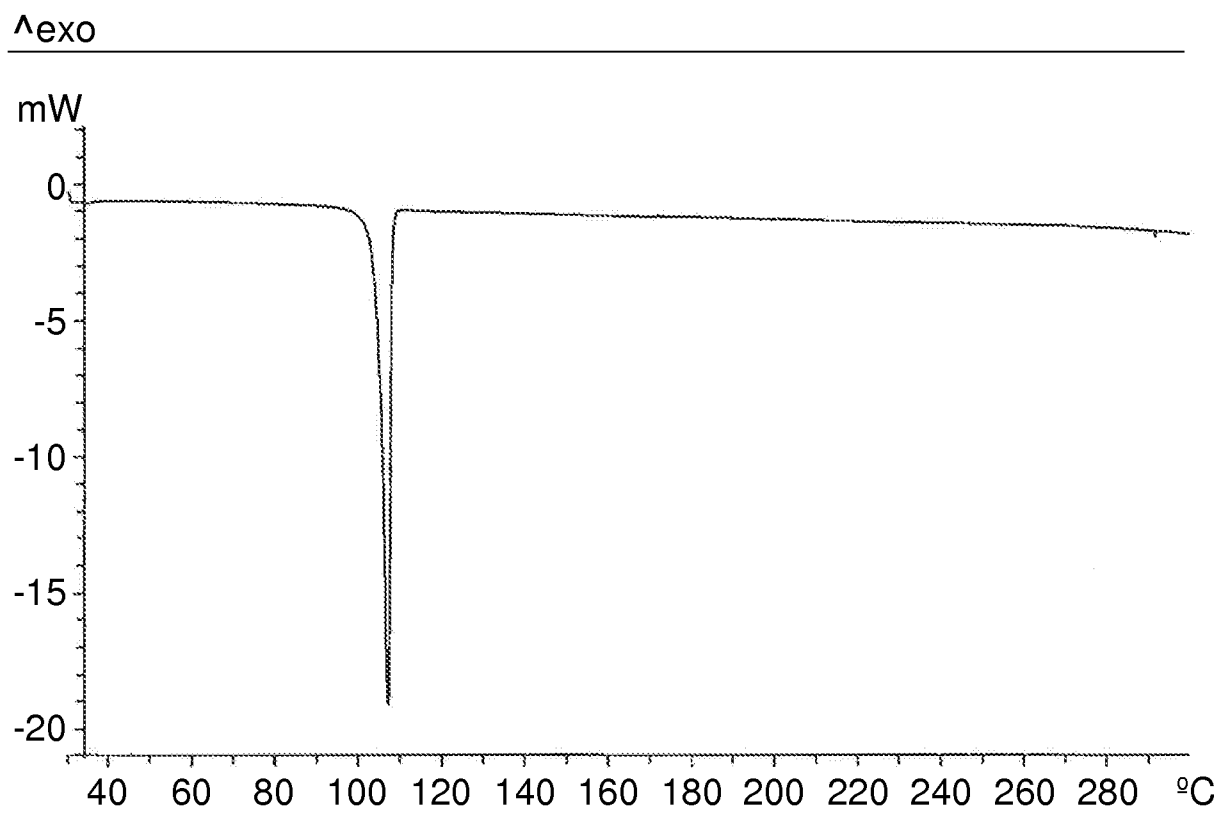
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FIG. 17**FIG. 18**

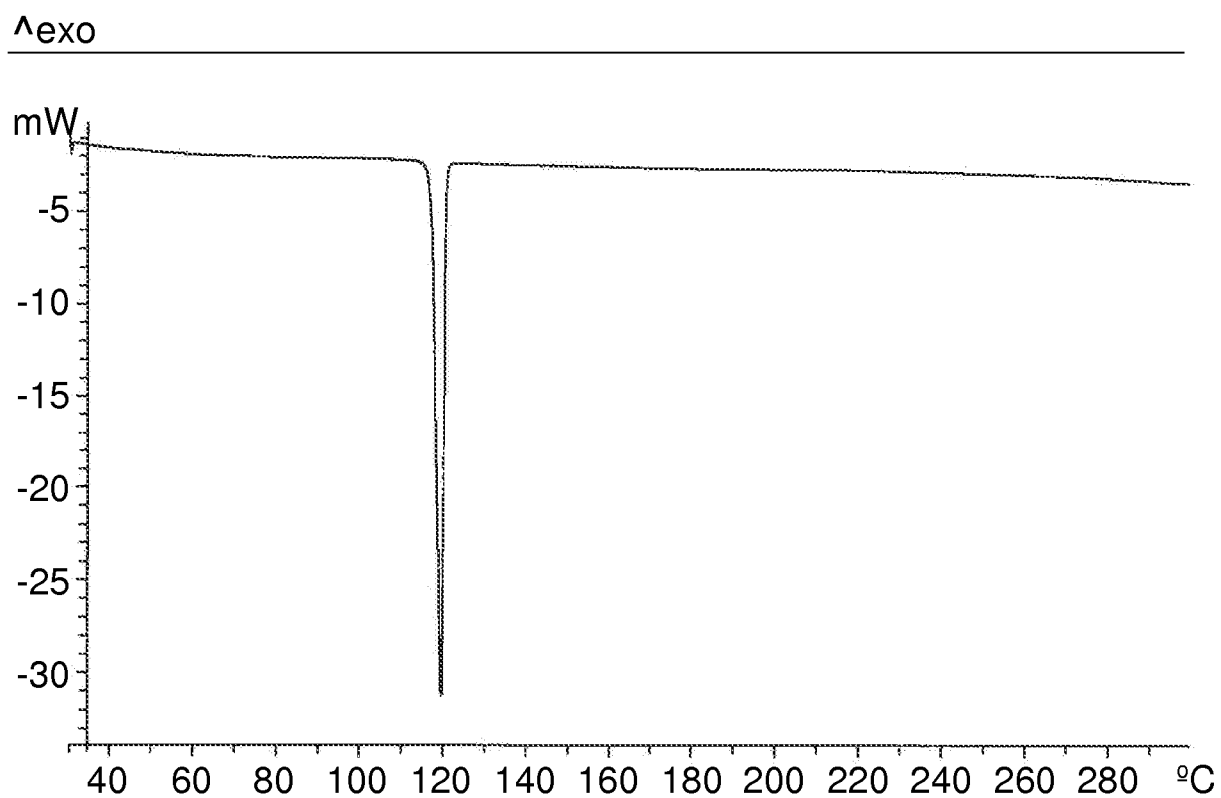
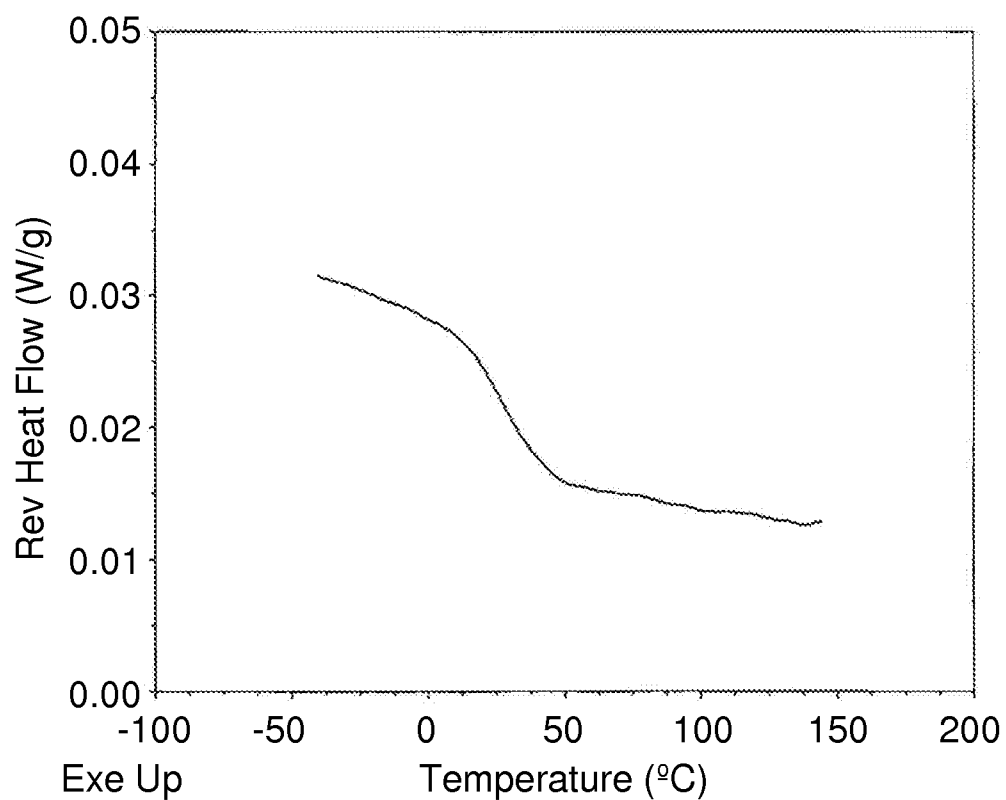
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FIG. 19**FIG. 20**

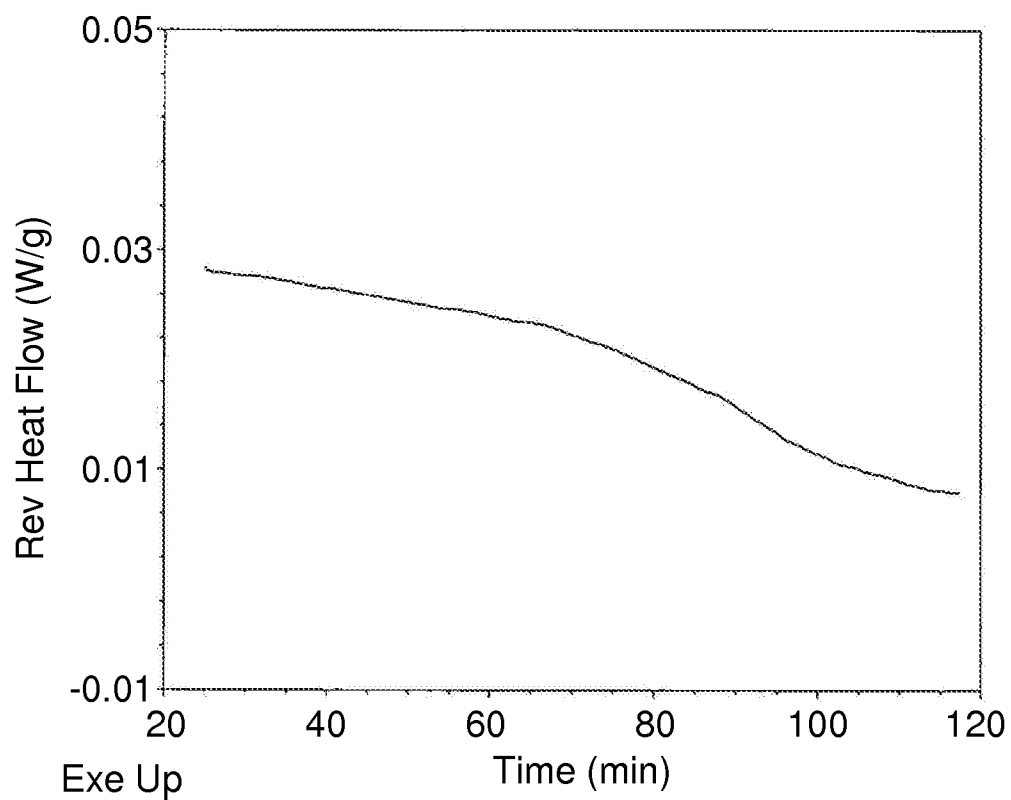
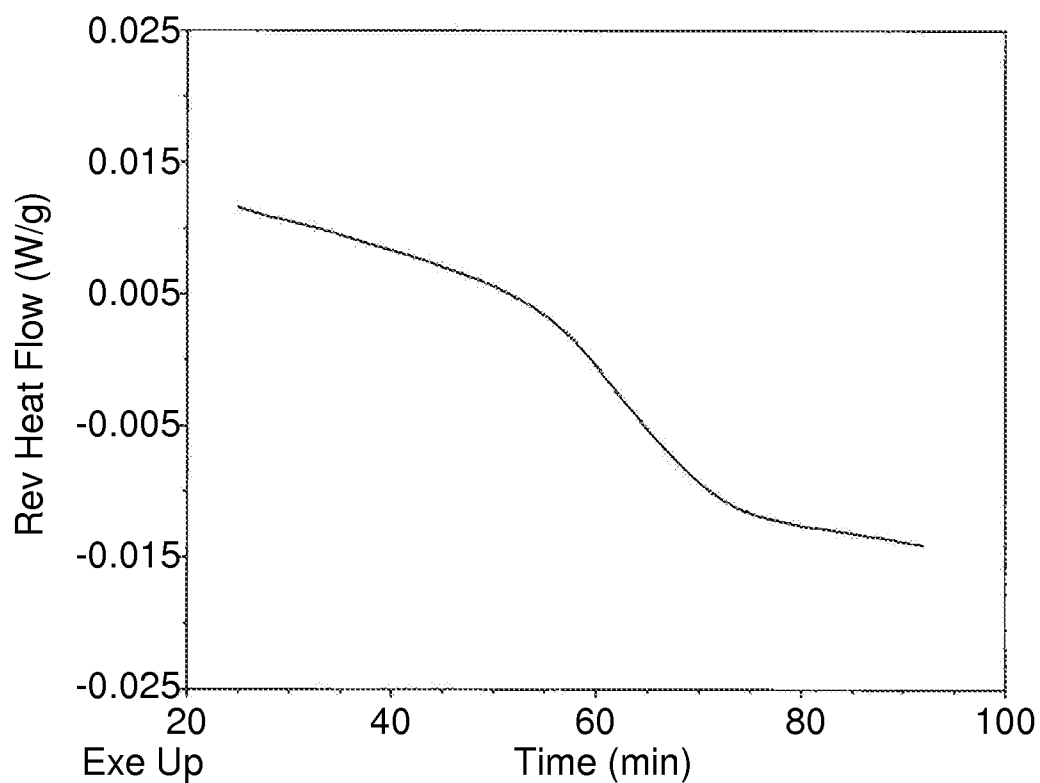
11/15

FIG. 21**FIG. 22**

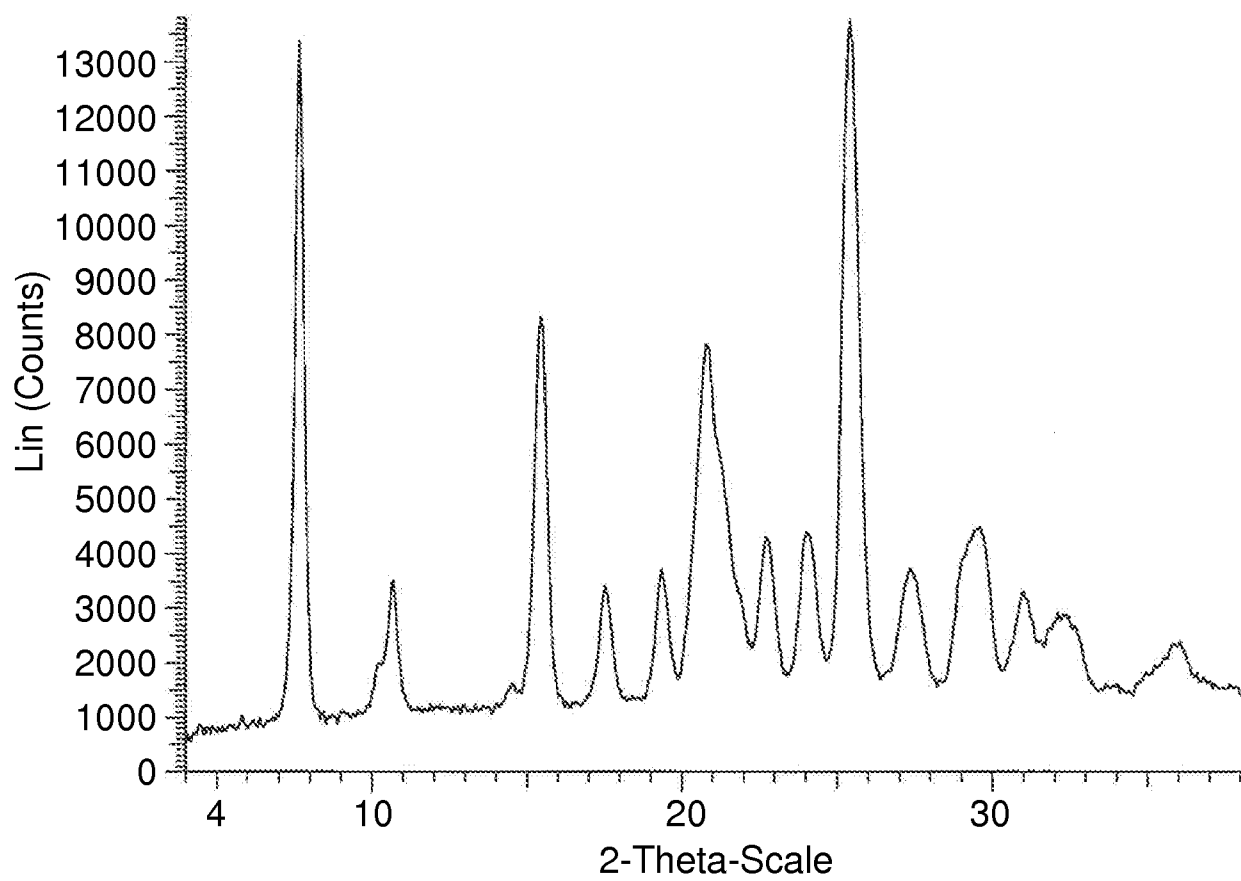
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FIG. 23**FIG. 24**

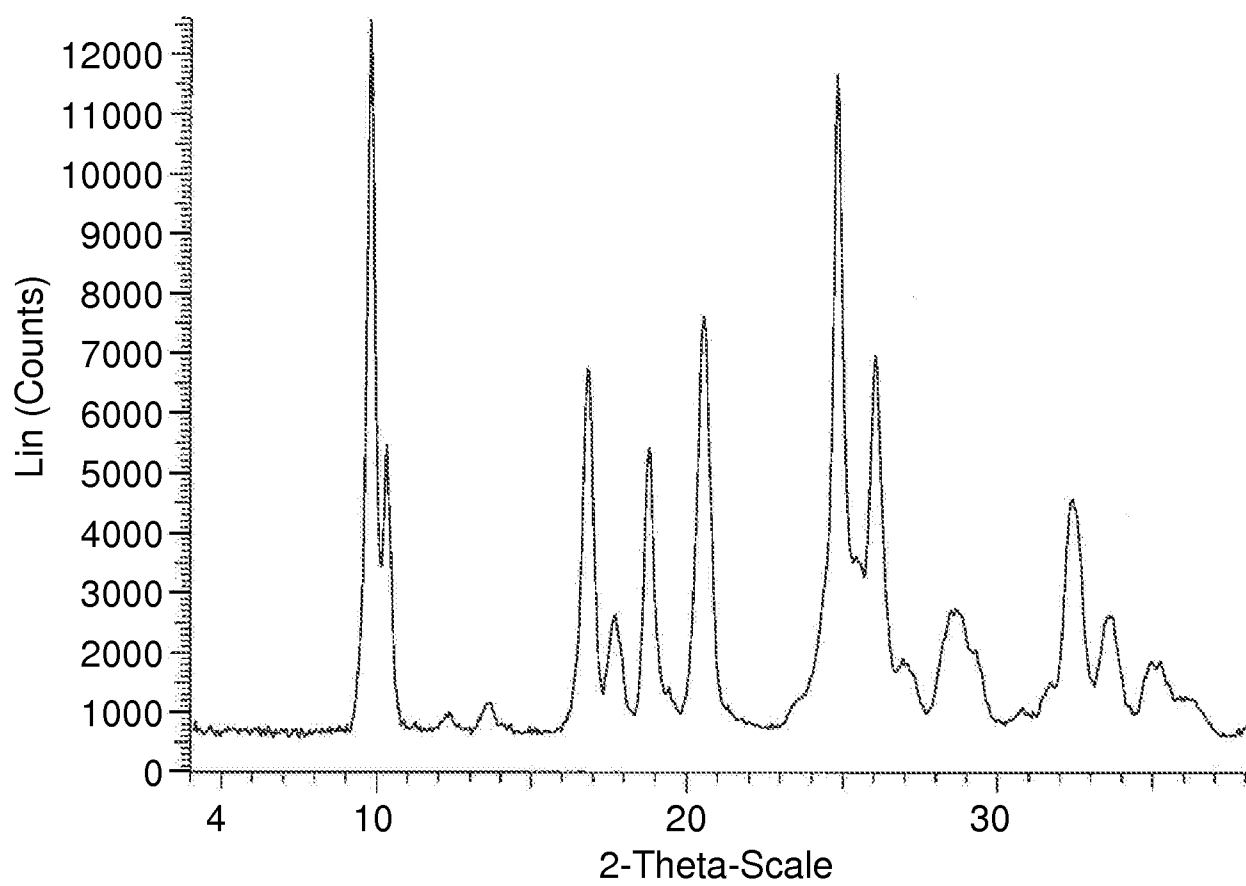
13/15

FIG. 25**FIG. 26**

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FIG. 27

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FIG. 28

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2010/054186

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D213/18

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

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, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/111540 A1 (MEDIVATION NEUROLOGY INC [US]; WOLLOWITZ SUSAN [US]; KATAISTO ERIK W []) 11 September 2009 (2009-09-11) cited in the application page 25 - page 30; examples 4,6,8,9	1-5
X	KOST, A. N. ET AL: "Indole chemistry. XXXIII. Pyridylethylation of the imino group in indole compounds" CHEMISTRY OF HETEROCYCLIC COMPOUNDS (A TRANSLATION OF KHIMIYAGETEROTSIKLICHESKIKH SOEDINENII), vol. 9, no. 2, February 1973 (1973-02), pages 191-195, XP002610670 PLENUM PRESS CO., NEW YORK, NY. ISSN: 0009-3122 page 192; table 1; compound 7 page 194, line 4 - line 13 ----- -/-	1-5



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

"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

22 November 2010

Date of mailing of the international search report

21/02/2011

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Fink, Dieter

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/054186

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	GAO, MINGZHANG ET AL: "[11C]Dimebon, radiosynthesis and lipophilicity of a new potential PET agent for imaging of Alzheimer's disease and Huntington's disease" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , 20(8), 2529-2532 CODEN: BMCLE8; ISSN: 0960-894X, vol. 20, no. 8, 15 April 2010 (2010-04-15), pages 2529-2532, XP002610671 page 2531, column 2, line 10 - line 18 -----	1-5
X,P	WO 2010/057104 A2 (AUSPEX PHARMACEUTICALS INC [US]; GANT THOMAS G [US]; SHAHBAZ MANOUCHEH) 20 May 2010 (2010-05-20) page 41 - page 42; example 4 (Step 5) -----	1-5
X,P	WO 2010/067085 A2 (WISTA LAB LTD [SG]; WILLIAMSON CRAIG [GB]; STOREY JOHN MERVYN DAVID [G] 17 June 2010 (2010-06-17) page 67 - page 68, "Synthesis 11" -----	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2010/054186

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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
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:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable 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 report covers 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.:

1-5

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/IB2010/054186

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009111540	A1	11-09-2009	NONE
WO 2010057104	A2	20-05-2010	US 2010125085 A1 20-05-2010
WO 2010067085	A2	17-06-2010	NONE

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5

the crystalline form of latrepirdine according to the present compound claims 1-5;

2. claims: 6-10

the noncrystalline form of latrepirdine according to the present compound claims 6-9 and the solid dispersion comprising a noncrystalline form of latrepirdine according to the present composition claim 10;

3. claims: 11-18

the 2-methyl-5-vinylpyridine oxalate salt/complex according to the present compound claims 11-13 and 15, and the processes according to the present claims 14 and 16-18.
