(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 March 2019 (21.03.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/055294 A1

(51) International Patent Classification:
A61K 31/55 (2006.01) *A61P 11/14* (2006.01)

(21) International Application Number:
PCT/US2018/049851

(22) International Filing Date:
07 September 2018 (07.09.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/606,161 12 September 2017 (12.09.2017) US

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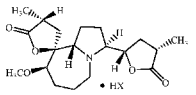
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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.

WO 2019/055294 A1

(54) Title: SOLID FORMS OF STEMOSPIRONINE AND ITS SALTS



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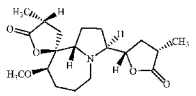

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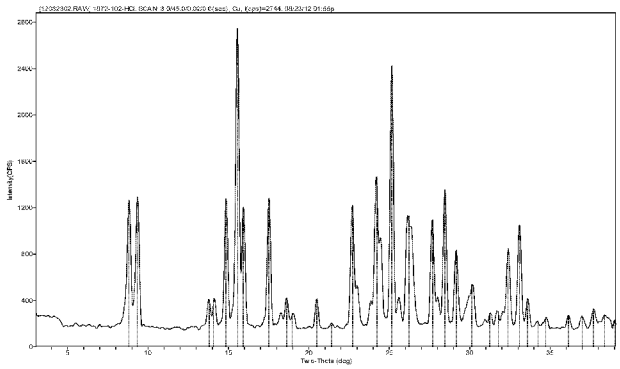


FIG. 1

(57) Abstract: Disclosed are stemospironine salts of Formula 1: wherein HX represents HCl, HBr, L-tartaric acid, D-tartaric acid, sulfuric acid, (+)-(1S)-10-camphorsulfonic acid, ethanesulfonic acid and ethane-1,2-disulfonic acid. This invention also provides crystalline polymorph forms of the compound of Formula 1 wherein HX is HCl, stemospironine hydrochloride. This invention also provides a new crystalline form of the compound of Formula 2, stemospironine free base: Also disclosed are compositions containing one or more compounds of Formula 1, methods for controlling cough comprising administering a therapeutically effective amount of a compound of Formula 1, and methods for preparing compounds of Formula 1. Also disclosed is a method for preparing crystalline stemospironine hydrochloride polymorph Form II from stemospironine hydrochloride polymorph Form I.

[Continued on next page]

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, 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, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

TITLE

SOLID FORMS OF STEMOSPIRONINE AND ITS SALTS

FIELD OF THE INVENTION

This invention relates to certain solid forms of stemospironine and its salts, certain polymorph forms thereof and compositions, methods of their use as therapeutic agents, and methods for their preparation.

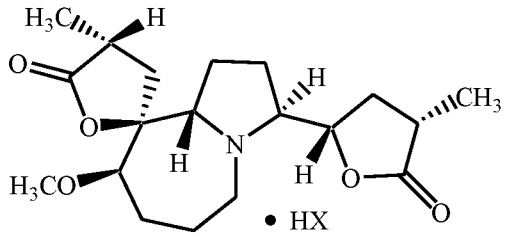
BACKGROUND OF THE INVENTION

The roots and rhizomes of the plant family Stemonacae have provided a rich source of structurally novel polycyclic alkaloids referred to as *Stemona* alkaloids. Initial interest in these substances stemmed from the use of plant materials in herbal teas used in Chinese folk medicine. The use of one such *Stemona* alkaloid, stemospironine, as an antitussive is disclosed in PCT Patent Publication WO 2009/046635.

There is a continuing need for new salts and polymorphs of stemospironine having properties that can contribute to their usefulness as pharmaceuticals, such as improved solubility properties to optimize bioavailability on therapeutic administration, improved taste characteristics, etc.

SUMMARY OF THE INVENTION

This invention is directed to stemospironine salts of Formula **1**:



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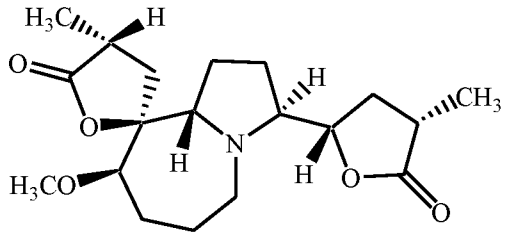
wherein HX represents hydrogen chloride, hydrogen bromide, L-tartaric acid, D-tartaric acid, sulfuric acid, (+)-(1S)-10-camphorsulfonic acid, ethanesulfonic acid and ethane-1,2-disulfonic acid. Each crystalline salt is characterized by peaks appearing in its X-ray powder diffraction (XRPD) pattern.

This invention also provides crystalline polymorph forms of the compound of Formula **1** wherein HX is hydrogen chloride, i.e. stemospironine hydrochloride. Each polymorph form is characterized by the peaks appearing in its X-ray powder diffraction (XRPD) pattern.

This invention also provides a new crystalline form of the compound of Formula **2**, i.e. stemospironine free base:



2

The crystalline form is characterized by the peaks appearing in its X-ray powder diffraction (XRPD) pattern.

This invention also relates to a pharmaceutical composition comprising one or more compounds of Formula **1** (i.e. in a therapeutically effective amount) and a pharmaceutically acceptable carrier.

This invention further relates to a method of controlling cough, i.e. as an antitussive agent, comprising administering to human a therapeutically effective amount of a compound of Formula **1** (e.g. as a composition described herein).

This invention also provides methods for the preparation of salts of Formula **1**.

This invention also provides a method for the preparation of crystalline polymorph forms of Compound **1** wherein X is hydrogen chloride, i.e. stemospironine hydrochloride.

This invention also provides a method for the preparation of a crystalline form of a compound of Formula **2**, stemospironine free base.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** shows a characteristic X-ray powder diffraction pattern of crystalline polymorph Form I of the 1:1 hydrochloric acid salt of stemospironine.

FIG. **2** shows a characteristic X-ray powder diffraction pattern of crystalline polymorph Form II of the 1:1 hydrochloric acid salt of stemospironine.

FIG. **3** shows a characteristic pattern of crystalline 1:1 hydrobromic acid salt of stemospironine.

FIG. **4** shows a characteristic X-ray powder diffraction pattern of crystalline 1:1 L-tartaric acid salt of stemospironine.

FIG. **5** shows a characteristic X-ray powder diffraction pattern of crystalline 1:1 D-tartaric acid salt of stemospironine.

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FIG. **6** shows a characteristic X-ray powder diffraction pattern of crystalline 1:1 sulfuric acid salt of stemospironine.

FIG. **7** shows a characteristic X-ray powder diffraction pattern of crystalline 1:1 (+)-(1S)-10-camphorsulfonic acid salt of stemospironine.

FIG. **8** shows a characteristic X-ray powder diffraction pattern of crystalline 1:1 ethanesulfonic acid salt of stemospironine.

FIG. **9** shows a characteristic X-ray powder diffraction pattern of crystalline 1:1 1,2-ethanedisulfonic acid salt of stemospironine.

FIG. **10** shows a characteristic X-ray powder diffraction pattern of crystalline stemospironine.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, carriers and/or dosage forms which are suitable for use in contact with the tissues of human beings and excessive toxicity, irritation, allergic response, or other problems or complications, commensurate with a reasonable benefit/risk ratio.

As used herein, the term "effective amount of" refers to an amount of a compound, or a combination of compounds, of the present invention effective when administered alone or in combination as an antitussive agent.

The term crystalline "polymorph" refers to a particular crystalline form of a chemical compound that can crystallize in different crystalline forms, these forms having different arrangements and/or conformations of the molecules in the crystal lattice. Although polymorphs can have the same chemical composition, they can also differ in composition due the presence or absence of co-crystallized water or other molecules, which can be weakly or strongly bound in the lattice. Polymorphs can differ in such chemical, physical and biological properties as crystal shape, density, hardness, color, chemical stability, melting point, hygroscopicity, suspensibility, dissolution rate and biological availability. One skilled in the art will appreciate that a polymorph can exhibit beneficial effects (e.g., suitability for preparation of useful formulations, improved solubility, etc.), relative to another polymorph or a mixture of polymorphs of the same compound. Preparation and isolation of a particular polymorph of a compound can be achieved by methods known to those skilled in the art including, for example, crystallization using selected solvents and temperatures.

Embodiments of the present invention as described in the Summary of the Invention include:

Embodiment 1. The salt of Formula **I** described in the Summary of the Invention in crystalline form.

Embodiment 2. The salt of Embodiment 1 wherein HX is hydrogen chloride, in the form of a polymorph Form I that exhibits an X-ray powder diffraction pattern as exemplified in FIG. **1**.

Embodiment 3. The salt of Embodiment 1 wherein HX is hydrogen chloride, in the form of a polymorph Form I that exhibits an X-ray powder diffraction pattern having characteristic peaks, expressed in degrees 2θ, as shown in Table **1**.

Embodiment 4. The salt of Embodiment 1 wherein HX is hydrogen chloride, in the form of a polymorph Form II that exhibits an X-ray powder diffraction pattern as exemplified in FIG. **2**.

Embodiment 5. The salt of Embodiment 1 wherein HX is hydrogen chloride, in the form of a polymorph Form II that exhibits an X-ray powder diffraction pattern having characteristic peaks, expressed in degrees 2θ, as shown in Table **2**.

Embodiment 6. The salt of Embodiment 1 wherein HX is hydrogen bromide, that exhibits an X-ray powder diffraction pattern as exemplified in FIG. **3**.

Embodiment 7. The salt of Embodiment 1 wherein HX is hydrogen bromide, that exhibits an X-ray powder diffraction pattern having characteristic peaks, expressed in degrees 2θ, as shown in Table **3**.

Embodiment 8. The salt of Embodiment 1 wherein HX is L-tartaric acid, that exhibits an X-ray powder diffraction pattern as exemplified in FIG. **4**.

Embodiment 9. The salt of Embodiment 1 wherein HX is L-tartaric acid, that exhibits an X-ray powder diffraction pattern having characteristic peaks, expressed in degrees 2θ, as shown in Table **4**.

Embodiment 10. The salt of Embodiment 1 wherein HX is D-tartaric acid that exhibits an X-ray powder diffraction pattern as exemplified in FIG. **5**.

Embodiment 11. The salt of Embodiment 1 wherein HX is D-tartaric acid that exhibits an X-ray powder diffraction pattern having characteristic peaks, expressed in degrees 2θ, as shown in Table **5**.

Embodiment 12. The salt of Embodiment 1 wherein HX is sulfuric acid, that exhibits an X-ray powder diffraction pattern as exemplified in FIG. **6**.

Embodiment 13. The salt of Embodiment 1 wherein HX is sulfuric acid, that exhibits an X-ray powder diffraction pattern having characteristic peaks, expressed in degrees 2θ, as shown in Table **6.**

Embodiment 14. The salt of Embodiment 1 wherein HX is (+)-(1S)-10-camphorsulfonic acid, that exhibits an X-ray powder diffraction pattern as exemplified in FIG. 7.

Embodiment 15. The salt of Embodiment 1 wherein HX is (+)-(1S)-10-camphorsulfonic acid, that exhibits an X-ray powder diffraction pattern having characteristic peaks, expressed in degrees 2θ, as shown in Table 7.

Embodiment 16. The salt of Embodiment 1 wherein HX is ethanesulfonic acid, that exhibits an X-ray powder diffraction pattern as exemplified in FIG. **8**.

Embodiment 17. The salt of Embodiment 1 wherein HX is ethanesulfonic acid, that exhibits an X-ray powder diffraction pattern having characteristic peaks, expressed in degrees 2θ, as shown in Table **8**.

Embodiment 18. The salt of Embodiment 1 wherein HX is 1,2-ethanedisulfonic acid, that exhibits an X-ray powder diffraction pattern as exemplified in FIG. **9.**

Embodiment 17. The salt of Embodiment 1 wherein HX is 1,2-ethanedisulfonic acid, that exhibits an X-ray powder diffraction pattern having characteristic peaks, expressed in degrees 2θ, as shown in Table **9**.

Embodiment 18. A crystalline form of the compound of Formula **2**, i.e. stemospironine free base, that exhibits an X-ray powder diffraction pattern as exemplified in FIG. **10**.

Embodiment 19. A crystalline form of the compound of Formula **2**, i.e. stemospironine free base, that exhibits an X-ray powder diffraction pattern having characteristic peaks, expressed in degrees 2θ, as shown in Table **10**.

This invention provides a pharmaceutical composition comprising one or more compounds of Formula **1** and a pharmaceutically acceptable carrier. Of note as embodiments of such compositions are compositions comprising a compound corresponding to any of the embodiments described above.

This invention provides a method of controlling cough comprising administering to a human a therapeutically effective amount of a compound of Formula **1**. Of note as embodiments of such methods are methods comprising applying a therapeutically effective amount of a compound corresponding to any of the embodiments described above. Of particular note are embodiments where compounds are applied as compositions of this invention. Also of particular note are embodiments where compounds are administered orally.

The present invention further discloses a method for preparing crystalline stemosporinine salts of Formula **1** from stemosporinine, a compound of Formula **2**,

and an acid HX, comprising:

A) dissolving the compound of Formula **2**, stemospironne, in a suitable first solvent to form a solution A;

B) adding an acid HX, optionally dissolved in a sutiable second solvent, to solution A to form a reaction mixture;

C) optionally adding a third solvent; and

D) separating the resulting solid, i.e. a compound of Formula **1**, from the reaction mixture.

The first and second solvents are independently selected from the group consisting of water, methanol, ethanol, isopropanol and acetonitrile.

The third solvent is independently selected from the group consisting of methyl *tert*-butyl ether, heptane and hexane.

The acid HX is selected from the group consisting of hydrogen chloride, hydrogen bromide, L-tartaric acid, D-tartaric acid, sulfuric acid, (+)-(1S)-10-camphorsulfonic acid, ethanesulfonic acid and ethane-1,2-disulfonic acid.

The present invention further discloses a method for preparing crystalline stemospironne hydrochloride polymorph Form II comprising:

A) dissolving crystalline stemospironne hydrochloride polymorph Form I in acetonitrile at 50 °C;

B) evaporating said acetonitrile solution at at 50 °C;

C) recovering crystalline stemospironne hydrochloride polymorph Form II ; and

D) drying said stemospironne hydrochloride polymorph Form II.

The polymorph salts of the present invention (i.e. a compound of Formula **1** wherein HX is hydrogen chloride) may be in a non-solvated form or a solvated form, in particular in a hydrated form or an alcoholated form.

The polymorph salts of the present invention (i.e. a compound of Formula **1** wherein HX is hydrogen chloride) may be in an amorphous form or in various crystalline forms thereof, or in a form of a mixture of these forms.

Polymorph forms of the present invention are characterized by the peaks appearing in the X-ray powder diffraction (XRPD) pattern. The XRPD patterns of the polymorphs of this invention were measured by a Rigaku Miniflex X-ray Powder Diffractometer (XRPD) instrument.

X-ray radiation is from Copper Cu at 1.054056Å with K_β filter. X-ray power is 30 KV, 15 mA. Sample powder is dispersed on a zero-background sample holder. General measurement conditions are: start angle – 3; stop angle – 45; scan speed – 2 deg/min.

EXAMPLE 1a

Preparation of polymorph Form I of the 1:1 hydrochloric acid salt of stemospironine

A stirred suspension of stemospironine (2.24 g, 6.37 mmol) in methanol (15 mL) was heated to 55 °C over 15 min. To the resulting solution was added 1.0 M hydrogen chloride in isopropanol (7.33 mL, 7.33 mmol, 1.15 equiv) followed by methyl *tert*-butyl ether, and the resulting slurry was stirred at room temperature for 8 h. The resulting solid was filtered, washed with methyl *tert*-butyl ether (10 mL) and dried under reduced pressure at 20-21 °C to afford the title compound (1.32 g, 92.6%) as a crystalline solid which was characterized by XRPD. FIG. **1** shows a characteristic X-ray powder diffraction (XRPD) pattern of polymorph Form 1 of the 1:1 hydrochloric acid salt of stemospironine. Characteristic peaks, expressed in degrees 2θ, are listed in Table **1**.

Table **1**

Angle 2θ [°]	Relative Intensity (%)
8.818	42.1
9.333	43.2
13.806	9.3
14.065	9
14.853	40.6
15.568	100
15.931	38.9
17.514	42.7
18.621	9.6
18.966	4.8
20.494	10
22.731	41.2
24.228	48.7
25.159	85.2
26.217	35.3
27.697	33.9
28.455	44.2

29.167	23.9
30.124	13.4
32.384	25.4
33.101	33.8
33.584	9.3

EXAMPLE 1b

Preparation of polymorph Form II of the 1:1 hydrochloric acid salt of stemospironine

Evaporation of an acetonitrile solution of the polymorph Form I of the 1:1 hydrochloric acid salt of stemospironine (prepared as described in Example 1a) at 50 °C afforded the title compound which was characterized by XRPD. FIG. **2** shows a characteristic X-ray powder diffraction (XRPD) pattern of polymorph Form II of the 1:1 hydrochloric acid salt of stemosporinine. Characteristic peaks, expressed in degrees 2θ, are listed in Table **2**.

Table **2**

Angle 2θ [°]	Relative Intensity (%)
8.772	8.4
9.294	100
13.795	26.7
14.137	8.3
14.825	6.6
15.47	25.6
15.889	14.7
17.456	13.3
18.579	23.2
22.702	20.8
23.047	9.5
24.39	39.2
25.128	18.1
25.593	8.5
26.174	24.6
27.929	22.4
28.389	6.9
29.153	11.3
29.993	28

32.39	11.9
33.083	7.4
33.55	8.1
36.186	4.2
37.594	11
39.215	5.3
39.851	7.8
42.139	4.7

EXAMPLE 2

Preparation of the 1:1 hydrobromic acid salt of stemospironine

Using the method of Example 1a, the title compound (96.3%) was obtained as a crystalline solid which was characterized by XRPD. FIG. **3** shows a characteristic X-ray powder diffraction (XRPD) pattern of stemospironine monohydrobromide. Characteristic peaks, expressed in degrees 2θ, are listed in Table **3**.

Table **3**

Angle 2θ [°]	Relative Intensity (%)
8.664	10.9
9.434	67.3
13.648	4.7
14.179	13.8
15.188	7.1
15.84	45
17.588	19.4
20.174	12.4
21.559	5.6
22.755	54.7
23.644	17.8
24.567	100
25.924	42.1
26.445	8.8
27.666	22.4
27.949	33.5
28.827	9.2
29.306	20.1

30.268	14.1
31.1	5.1
32.198	29.4
33.95	13
36.298	14.6
42.236	7.3

EXAMPLE 3

Preparation of the 1:1 L-tartaric acid salt of stemospironine

To a stirred solution of stemosporinnne (395 mg, 1.14 mmol) and L-tartaric acid (195 mg, 1.29 mmol, 1.15 equiv) in acetonitrile (3 mL) and methanol (1 mL) was added methyl *tert*-butyl ether (5 mL), and the resulting slurry was stirred at room temperature for 5 h. The resulting solid was filtered, washed with methyl *tert*-butyl ether (1.5 mL) and dried under reduced pressure at 20-21 °C to afford the title compound (553 mg, 98.0 %) as a crystalline solid which was characterized by XRPD. FIG. **4** shows a characteristic X-ray powder diffraction (XRPD) pattern of the 1:1 L-tartaric acid salt of stemospironine. Characteristic peaks, expressed in degrees 2θ, are listed in Table **4**.

Table **4**

Angle 2θ [°]	Relative Intensity (%)
10.873	59.5
12.296	42.4
14.346	5
15.269	100
16.703	28.5
17.363	53.7
18.277	62.5
18.979	40.6
19.871	10.6
20.409	42.3
22.259	29.8
23.388	47.9
24.589	18.2
25.362	42.2
26.002	21.6
26.96	15.9

27.551	5.5
28.973	21.3
29.758	8.1
30.31	6.3
31.063	11.2
31.914	15.4
35.009	22.4
35.603	12
36.677	8
37.476	8.3
38.172	9.2
38.918	6.8
39.497	5.1
40.682	4.5
41.781	6

EXAMPLE 4

Preparation of the 1:1 D-tartaric acid salt of stemospironine

Using the method of Example 3 stemosporinnne and D-tartaric acid yielded the title compound as a crystalline solid which was characterized by XRPD. FIG. **5** shows a characteristic X-ray powder diffraction (XRPD) pattern of the 1:1 D-tartaric acid salt of stemospironine. Characteristic peaks, expressed in degrees 2θ, are listed in Table **5**.

Table **5**

Angle 2θ [°]	Relative Intensity (%)
9.834	100
11.641	12.9
12.342	3.5
13.487	3.1
14.967	3.3
15.957	48.1
17.457	6.3
18.57	14.4
19.583	20.2
20.583	46.4
21.63	5

22.655	19.4
24.738	8.8
25.312	6.8
27.084	7.2
27.63	4
29.432	8.9
30.163	7
31.035	6.6
34.582	3.8
35.16	4.3
36.489	5.6
38.156	3.5
40.849	1.5
41.401	1.9

EXAMPLE 5

Preparation of the 1:1 sulfuric acid salt of stemospironine

Using the method of Example 3 stemosporinnne and sulfuric acid yielded the title compound as a crystalline solid which was characterized by XRPD. FIG. **6** shows a characteristic X-ray powder diffraction (XRPD) pattern of the 1:1 sulfuric acid salt of stemospironine. Characteristic peaks, expressed in degrees 2θ, are listed in Table **6**.

Table **6**

Angle 2θ [°]	Relative Intensity (%)
7.13	100
9.257	13.4
9.801	5.8
14.061	19.5
15.365	10
16.515	11
18.379	7.7
19.319	7.5
20.778	34
22.888	11.1
23.794	10.3
25.016	11.2

25.931 6.5

EXAMPLE 6

Preparation of the 1:1 (+)-(1S)-10-camphorsulfonic acid salt of stemospironine

Using the method of Example 3 stemosporinnne and (+)-(1S)-10-camphorsulfonic acid, yielded the title compound as a crystalline solid which was characterized by XRPD. FIG. 7 shows a characteristic X-ray powder diffraction (XRPD) pattern of the 1:1 (+)-(1S)-10-camphorsulfonic acid salt of stemospironine. Characteristic peaks, expressed in degrees 2θ, are listed in Table 7.

Table 7

Angle 2θ [°]	Relative Intensity (%)
6.519	100
9.225	7.5
12.798	11.9
13.237	23.4
13.696	3.3
14.586	36.9
15.136	17.7
17.005	37.1
17.474	5.8
18.221	35
19.393	20.9
20.411	50.1
21.673	9.8
22.6	30.9
23.431	12.3
24.022	22.7
26.059	13.1
27.062	12.5
29.172	12.2
32.865	7.9
38.199	7

EXAMPLE 7

Preparation of the 1:1 ethanesulfonic acid salt of stemospironine

Using the method of Example 3 stemosporinnne and ethanesulfonic acid yielded the title compound as a crystalline solid which was characterized by XRPD. FIG. **8** shows a characteristic X-ray powder diffraction (XRPD) pattern of the 1:1 ethanesulfonic acid salt of stemospironine. Characteristic peaks, expressed in degrees 2θ, are listed in Table **8**.

Table **8**

Angle 2θ [°]	Relative Intensity (%)
7.32	100
7.847	1.1
9.597	11.1
12.406	3.3
13.611	5.3
15.135	10.4
15.816	8.7
17.558	2.8
17.928	6.5
18.596	15.5
19.139	5.9
19.99	3.2
21.484	4.6
22.063	3.7
22.721	68.3
23.671	10.7
25.139	18.4
26.022	4.9
27.916	3.7
28.39	3.9
29.297	16
29.894	8.1
31.844	4.9
34.902	3.9
35.639	7.3
36.154	5.1
36.701	7.2
37.276	2.4

EXAMPLE 8

Preparation of the 1:1 1,2-ethanedisulfonic acid salt of stemospironine

Using the method of Example 3 stemosporinnne and 1,2-ethanedisulfonic acid yielded the title compound as a crystalline solid which was characterized by XRPD. FIG. **9** shows a characteristic X-ray powder diffraction (XRPD) pattern of the 1:1 1,2-ethanedisulfonic acid salt of stemospironine. Characteristic peaks, expressed in degrees 2θ, are listed in Table **9**.

Table **9**

Angle 2θ [°]	Relative Intensity (%)
9.067	9.7
10.94	84.3
11.385	24.9
12.92	55
13.546	15.2
14.129	56.4
15.391	52.4
17.292	93.8
17.842	16.3
19.703	72.1
20.246	34.7
20.8	21.1
21.158	100
21.827	29.5
22.768	44.3
23.55	22.3
24.438	58.7
25.361	89.5
26.736	44.4
27.319	15.5
27.642	18.6
28.393	44.2
29.485	11.4
30.552	12.7
30.959	11.3

33.172	11.5
35.006	10.9
35.509	17.4
36.309	7
37.155	13.6
37.722	6.9
38.359	5.7
41.195	19

EXAMPLE 9

Preparation of crystalline stemospironine free base

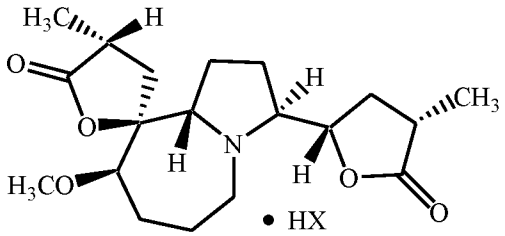
Evaporation of an acetonitrile solution of the stemospironine free base at 25 °C afforded the title compound which was characterized by XRPD. FIG. **10** shows a characteristic X-ray powder diffraction (XRPD) pattern of crystalline stemosporinine. Characteristic peaks, expressed in degrees 2θ, are listed in Table **10**.

Table **10**

Angle 2θ [°]	Relative Intensity (%)
9.959	10.9
10.304	2.3
12.927	18.2
13.318	6
14.535	6.6
15.216	5.3
17.515	4.5
17.952	4.6
19.701	100
21.435	10.5
22.634	3.7
23.978	2
24.575	1.9
25.53	4.3
26.285	8.3
28.543	4.9
31.009	5.7

What is claimed is:

1. A stemospironine salt of Formula **1**,



1

wherein HX is selected from the group consisting of hydrogen chloride, hydrogen bromide, L-tartaric acid, D-tartaric acid, sulfuric acid, (+)-(1S)-10-camphorsulfonic acid, ethanesulfonic acid and ethane-1,2-disulfonic acid.

2. The salt of Claim 1 in crystalline form.

3. The salt of Claim 2 wherein HX is hydrogen chloride, in the form of a polymorph Form I that exhibits an X-ray powder diffraction pattern having at least the 2θ reflection positions

2θ
8.818
9.333
13.806
14.065
14.853
15.568
15.931
17.514
18.621
18.966
20.494
22.731
24.228
25.159

26.217
27.697
28.455
29.167
30.124
32.384
33.101
33.584

4. The salt of Claim 2 wherein HX is hydrogen chloride, in the form of a polymorph Form II that exhibits an X-ray powder diffraction pattern having at least the 2θ reflection positions

2θ
8.772
9.294
13.795
14.137
14.825
15.47
15.889
17.456
18.579
22.702
23.047
24.39
25.128
25.593
26.174
27.929
28.389
29.153
29.993

32.39
33.083
33.55
36.186
37.594
39.215
39.851
42.139

5. The salt of Claim 2 wherein HX is hydrogen bromide that exhibits an X-ray powder diffraction pattern having at least the 2θ reflection positions

2θ
8.664
9.434
13.648
14.179
15.188
15.84
17.588
20.174
21.559
22.755
23.644
24.567
25.924
26.445
27.666
27.949
28.827
29.306
30.268
31.1

32.198
33.95
36.298
42.236

6. The salt of Claim 2 wherein HX is L-tartaric acid that exhibits an X-ray powder diffraction pattern having at least the 2θ reflection positions

2θ
10.873
12.296
14.346
15.269
16.703
17.363
18.277
18.979
19.871
20.409
22.259
23.388
24.589
25.362
26.002
26.96
27.551
28.973
29.758
30.31
31.063
31.914
35.009
35.603

36.677
37.476
38.172
38.918
39.497
40.682
41.781

7. The salt of Claim 2 wherein HX is D-tartaric acid that exhibits an X-ray powder diffraction pattern having at least the 2θ reflection positions

2θ
9.834
11.641
12.342
13.487
14.967
15.957
17.457
18.57
19.583
20.583
21.63
22.655
24.738
25.312
27.084
27.63
29.432
30.163
31.035
34.582
35.16

36.489
38.156
40.849
41.401

8. The salt of Claim 2 wherein HX is sulfuric acid that exhibits an X-ray powder diffraction pattern having at least the 2θ reflection positions

2θ
7.13
9.257
9.801
14.061
15.365
16.515
18.379
19.319
20.778
22.888
23.794
25.016
25.931

9. The salt of Claim 2 wherein HX is (+)-(1S)-10-camphorsulfonic acid that exhibits an X-ray powder diffraction pattern having at least the 2θ reflection positions

2θ
6.519
9.225
12.798
13.237
13.696
14.586
15.136

17.005
17.474
18.221
19.393
20.411
21.673
22.6
23.431
24.022
26.059
27.062
29.172
32.865
38.199

10. The salt of Claim 2 wherein HX is ethanesulfonic acid that exhibits an X-ray powder diffraction pattern having at least the 2θ reflection positions

2θ
7.32
7.847
9.597
12.406
13.611
15.135
15.816
17.558
17.928
18.596
19.139
19.99
21.484
22.063

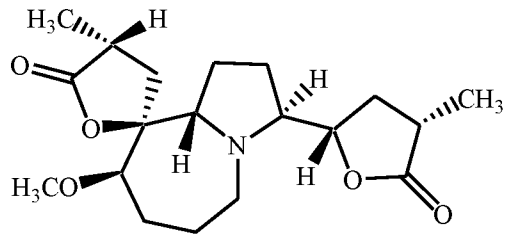
22.721
23.671
25.139
26.022
27.916
28.39
29.297
29.894
31.844
34.902
35.639
36.154
36.701
37.276

11. The salt of Claim 2 wherein HX is 1,2ethanedisulfonic acid that exhibits an X-ray powder diffraction pattern having at least the 2θ reflection positions

2θ
9.067
10.94
11.385
12.92
13.546
14.129
15.391
17.292
17.842
19.703
20.246
20.8
21.158
21.827

22.768
23.55
24.438
25.361
26.736
27.319
27.642
28.393
29.485
30.552
30.959
33.172
35.006
35.509
36.309
37.155
37.722
38.359
41.195

12. A crystalline form of the compound of Formula **2,** stemospironine free base,



2

that exhibits an X-ray powder diffraction pattern having at least the 2θ reflection positions

2θ
9.959

10.304
12.927
13.318
14.535
15.216
17.515
17.952
19.701
21.435
22.634
23.978
24.575
25.53
26.285
28.543
31.009

13. A pharmaceutical composition comprising one or more compounds of Claim 1 and a pharmaceutically acceptable carrier.

14. A method of controlling cough comprising administering to a human a therapeutically effective amount of a compound of Claim 1.

15. A method for preparing crystalline stemosporinine salts of Formula **1** from stemosporinine, a compound of Formula **2** and an acid HX, comprising:

A) dissolving the compound of Formula **2,** stemospironne, in a suitable first solvent to form a solution A;

B) adding an acid HX, optionally dissolved in a sutiable second solvent, to solution A to form a reaction mixture;

C) optionally adding a third solvent to precipitate the salt of Formula **1**; and

D) separating the resulting solid, i.e., a compound of Formula **1**, from the reaction mixture.

16. The method of Claim 15 wherein the first and second solvents are independently selected from the group consisting of water, methanol, ethanol, isopropanol, dichloromethane, ethyl acetate and acetonitrile.

17. The method of Claim 15 wherein the third solvent is selected from the group consisting of methyl *tert*-butyl ether, heptane and hexane.

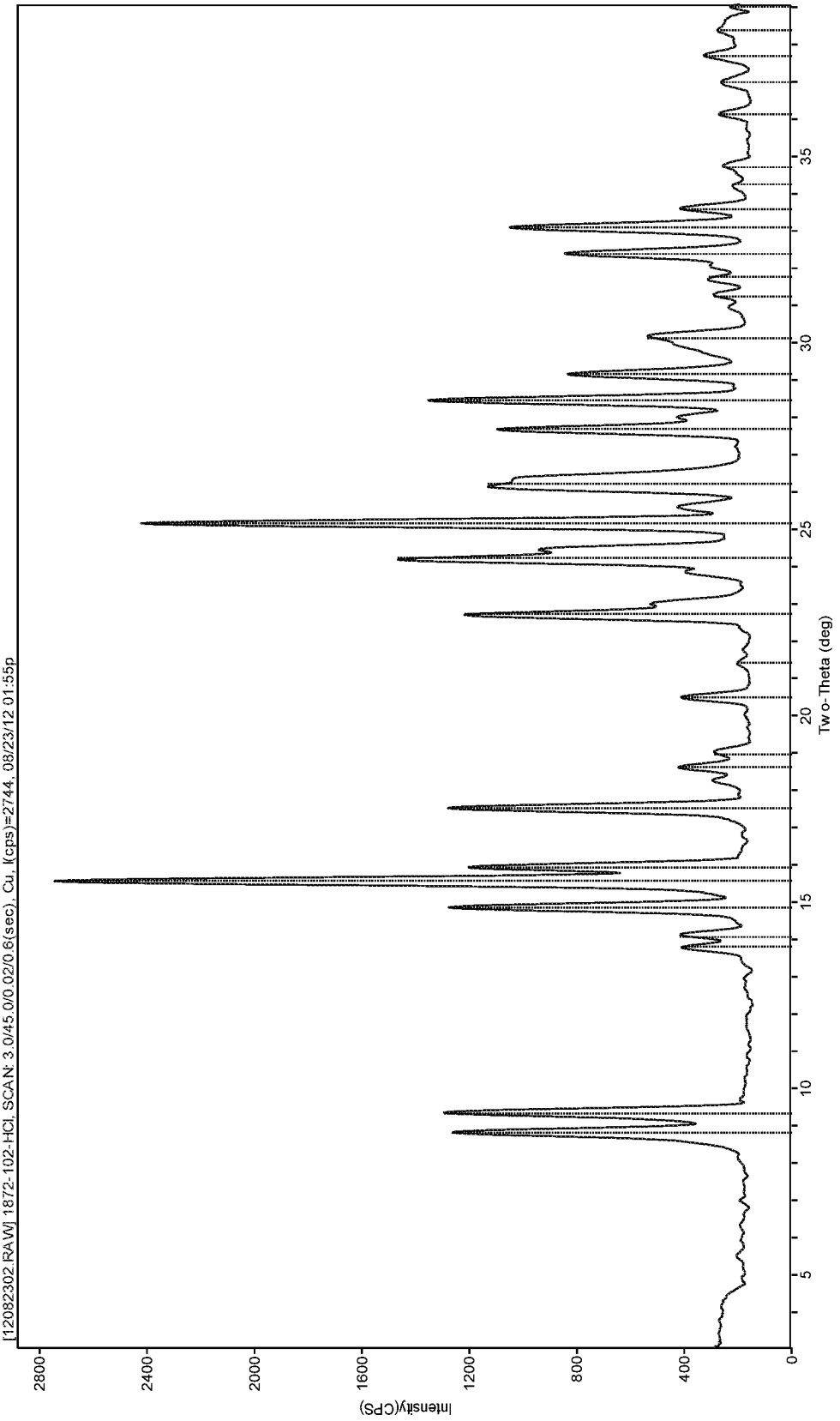
18. A method for preparing crystalline stemospironne hydrochloride polymorph Form II comprising:

A) dissolving crystalline stemospironne hydrochloride polymorph Form I in acetonitrile at 50 °C;

B) evaporating said acetonitrile solution at 50 °C;

C) recovering crystalline stemospironne hydrochloride polymorph Form II; and

D) drying said stemospironne hydrochloride polymorph Form II.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Intensity(CPS)
2800
2400
2000
1600
1200
800
400
0
5
10
15
20
25
30
35
Two-Theta (deg)

FIG. 1

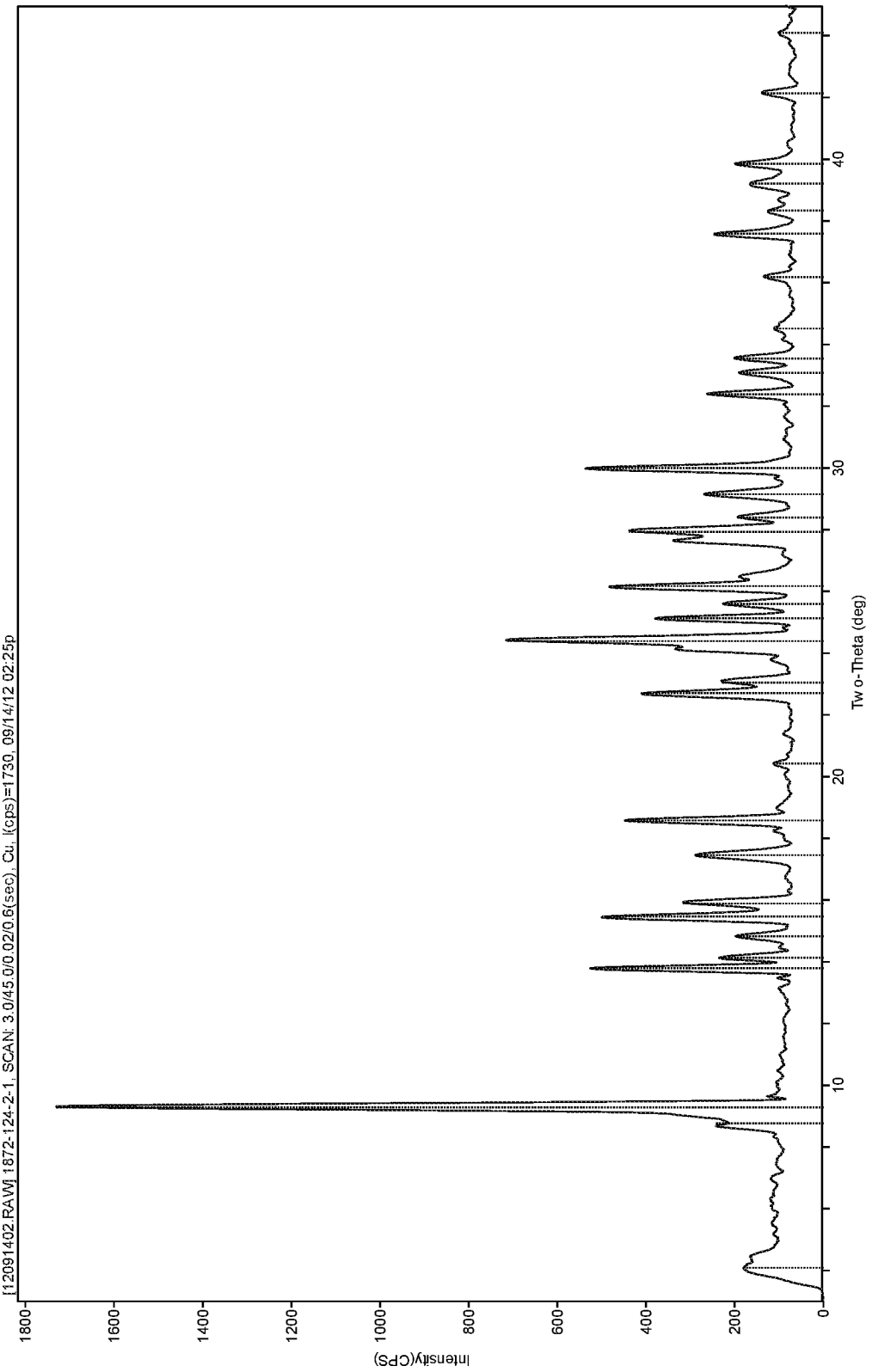
[12091402.RAW] 1872-124-2-1, SCAN: 3.0/45.0/0.02/0.6(sec), Cu, I(cps)=1730, 09/14/12 02:25p
Intensity(CPS)
Tw o-Theta (deg)
0
200
400
600
800
1000
1200
1400
1600
1800
10
20
30
40

FIG. 2

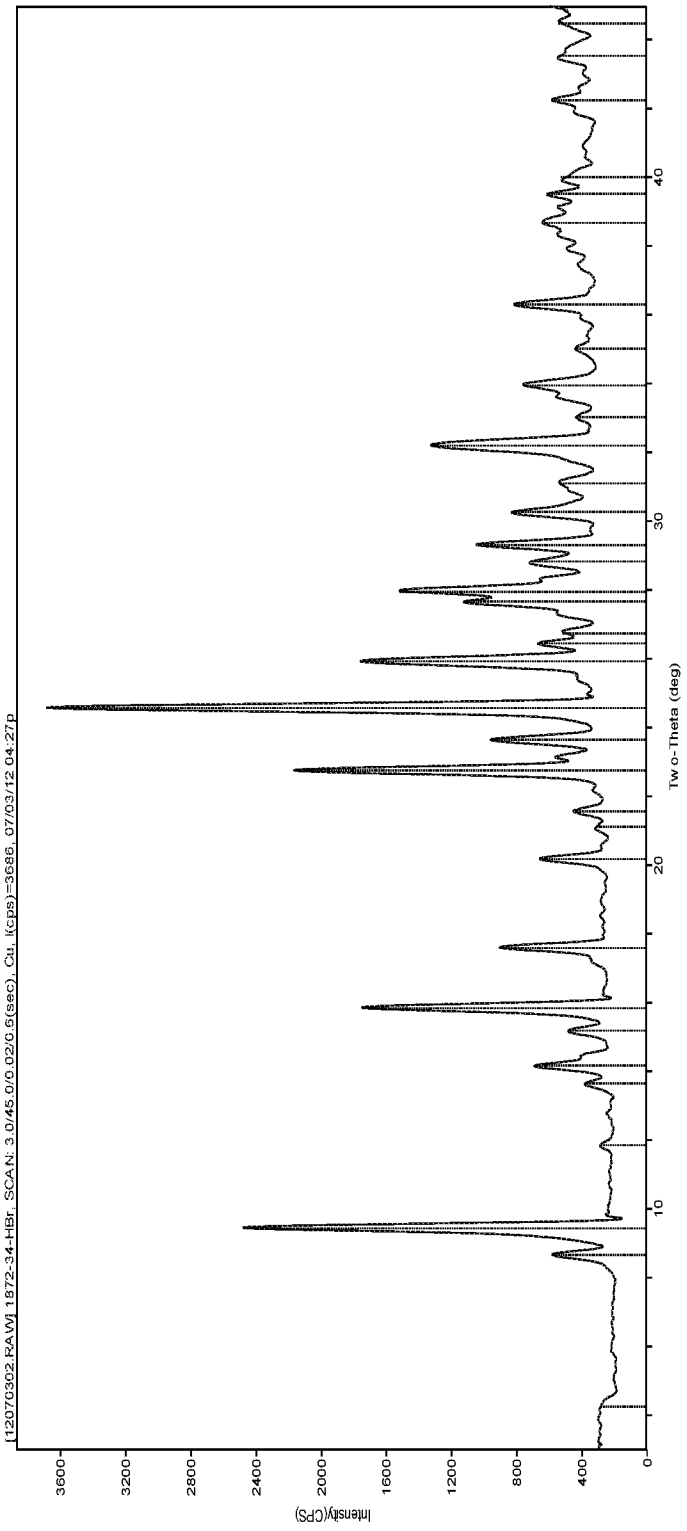
[120703O2.RAW] 1872-34-HBr, SCAN: 3.0/45.0/0.02/0.6(sec), Cu, (kcps)=3686, 07/03/12 04:27p
Intensity(CPS)
Two-Theta (deg)
0
400
800
1200
1600
2000
2400
2800
3200
3600
10
20
30
40

FIG. 3

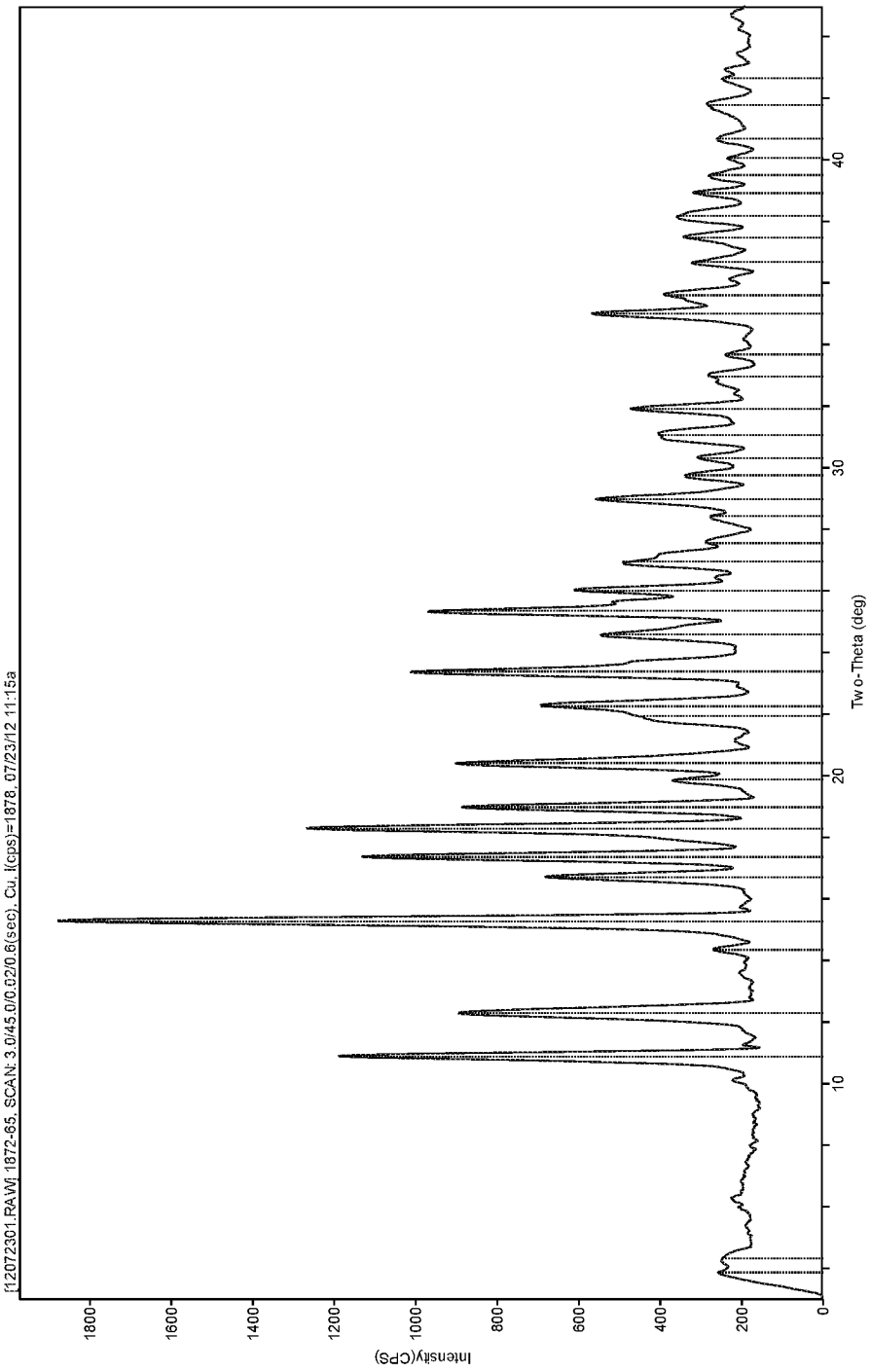
[120723O1.RAW] 1872-65, SCAN: 3.0/45.0/0.02/0.6(sec), Cu, I(cps)=1878, 07/23/12 11:15a
Intensity(CPS)
Two-Theta (deg)
0
200
400
600
800
1000
1200
1400
1600
1800
10
20
30
40

FIG. 4

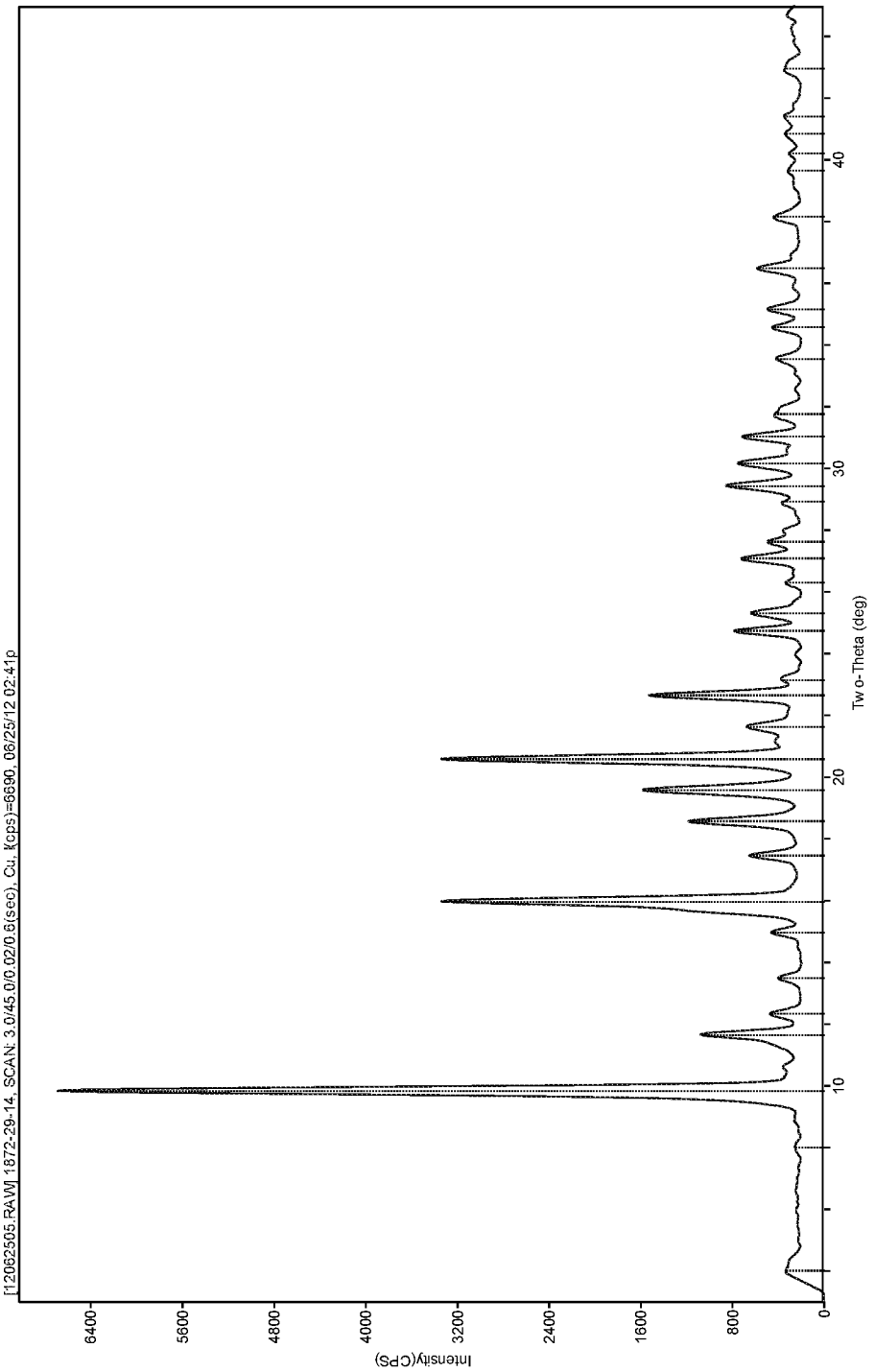
[12062505.RAW] 1872-29-14, SCAN: 3.0/45.0/0.02/0.6(sec), Cu, k(cps)=6690, 06/25/12 02:41p
Intensity(CPS)
6400
5600
4800
4000
3200
2400
1600
800
0
10
20
30
40
Two-Theta (deg)

FIG. 5

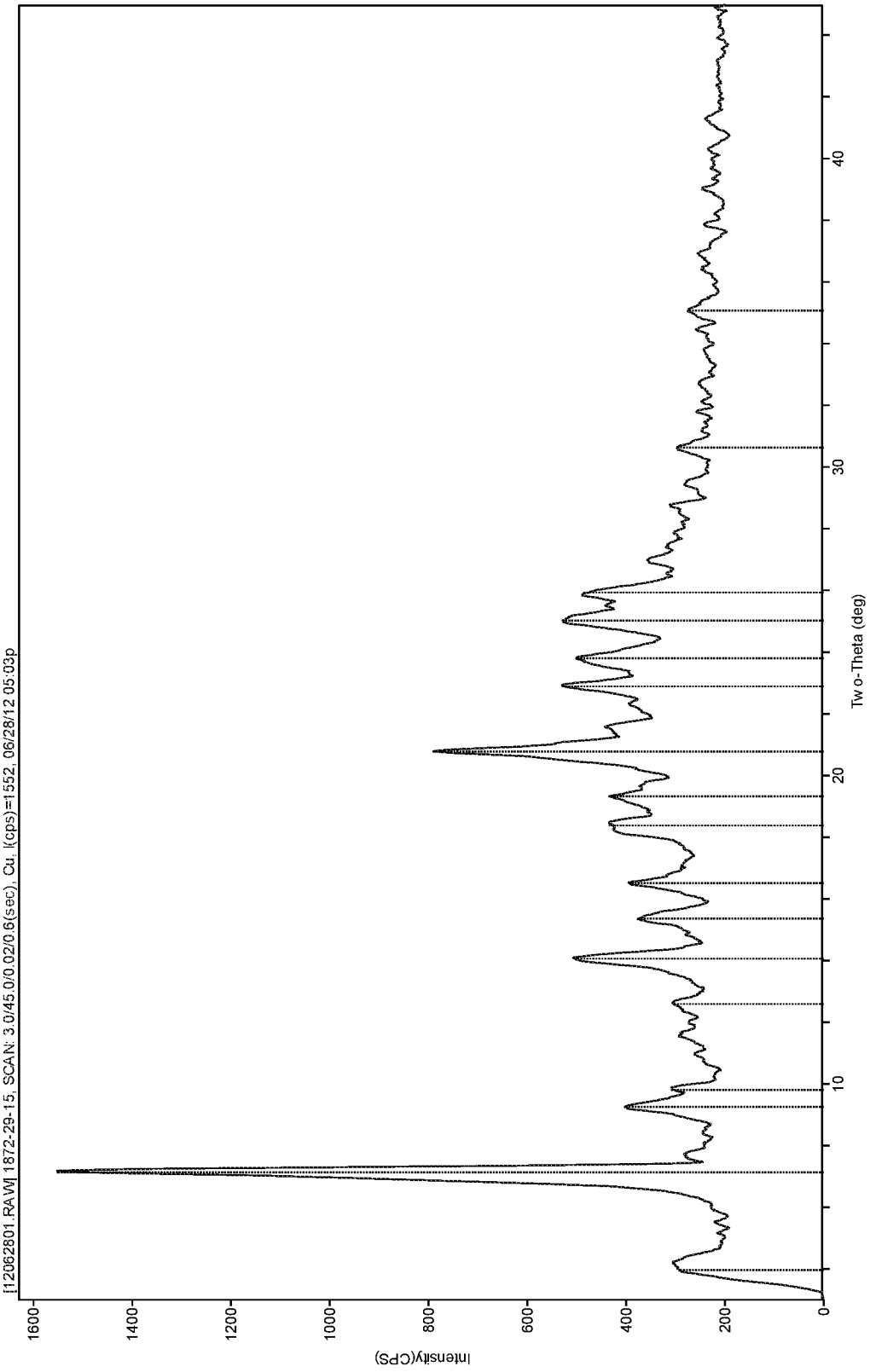
I12062801.RAW] 1872-29-15, SCAN: 3.0/45.0/0.02/0.6(sec), Cu, I(cps)=1552, 06/28/12 05:03p
Intensity(CPS)
Tw o-Theta (deg)
0
200
400
600
800
1000
1200
1400
1600
10
20
30
40

FIG. 6

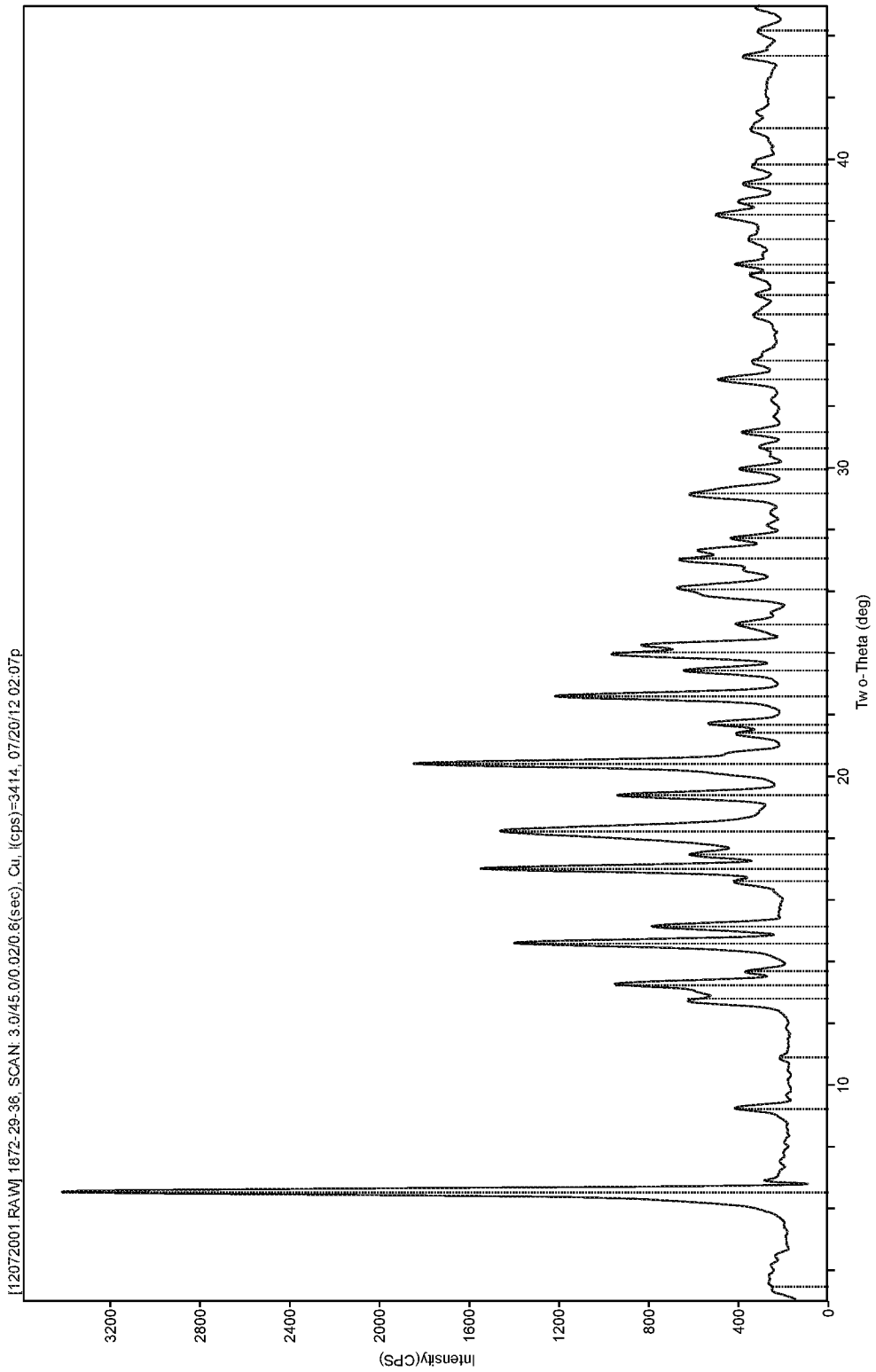
[12072001.RAW] 1872-29-36, SCAN: 3.0/45.0/0.02/0.6(sec), Cu, I(cps)=3414, 07/20/12 02:07p
Intensity(CPS)
3200
2800
2400
2000
1600
1200
800
400
0
10
20
30
40
Two-Theta (deg)

FIG. 7

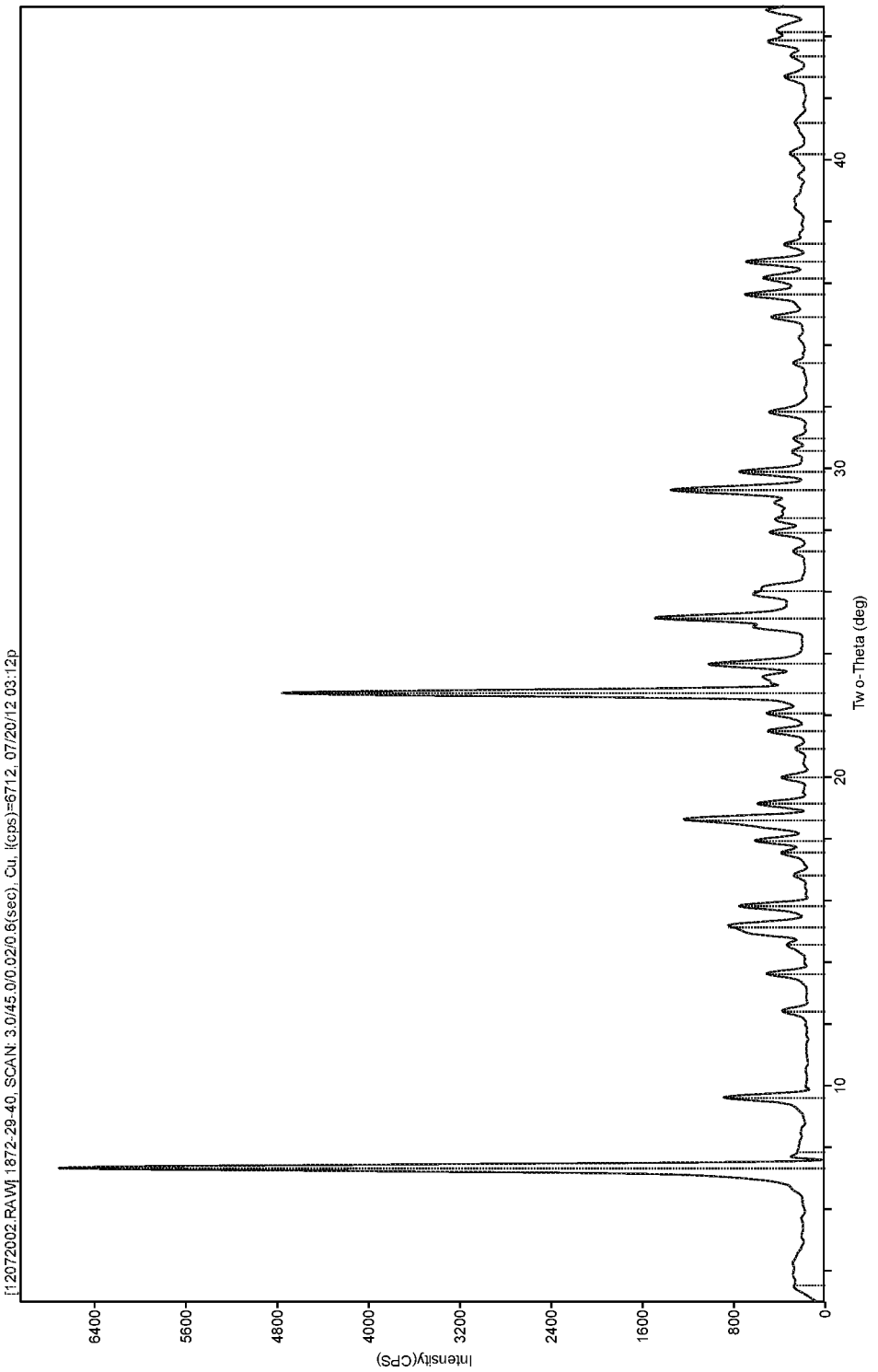
[12072002.RAW] 1872-29-40, SCAN: 3.0/45.0/0.02/0.6(sec), Cu, I(cps)=6712, 07/20/12 03:12p
Intensity(CPS)
6400
5600
4800
4000
3200
2400
1600
800
0
10
20
30
40
Tw o-Theta (deg)

FIG. 8

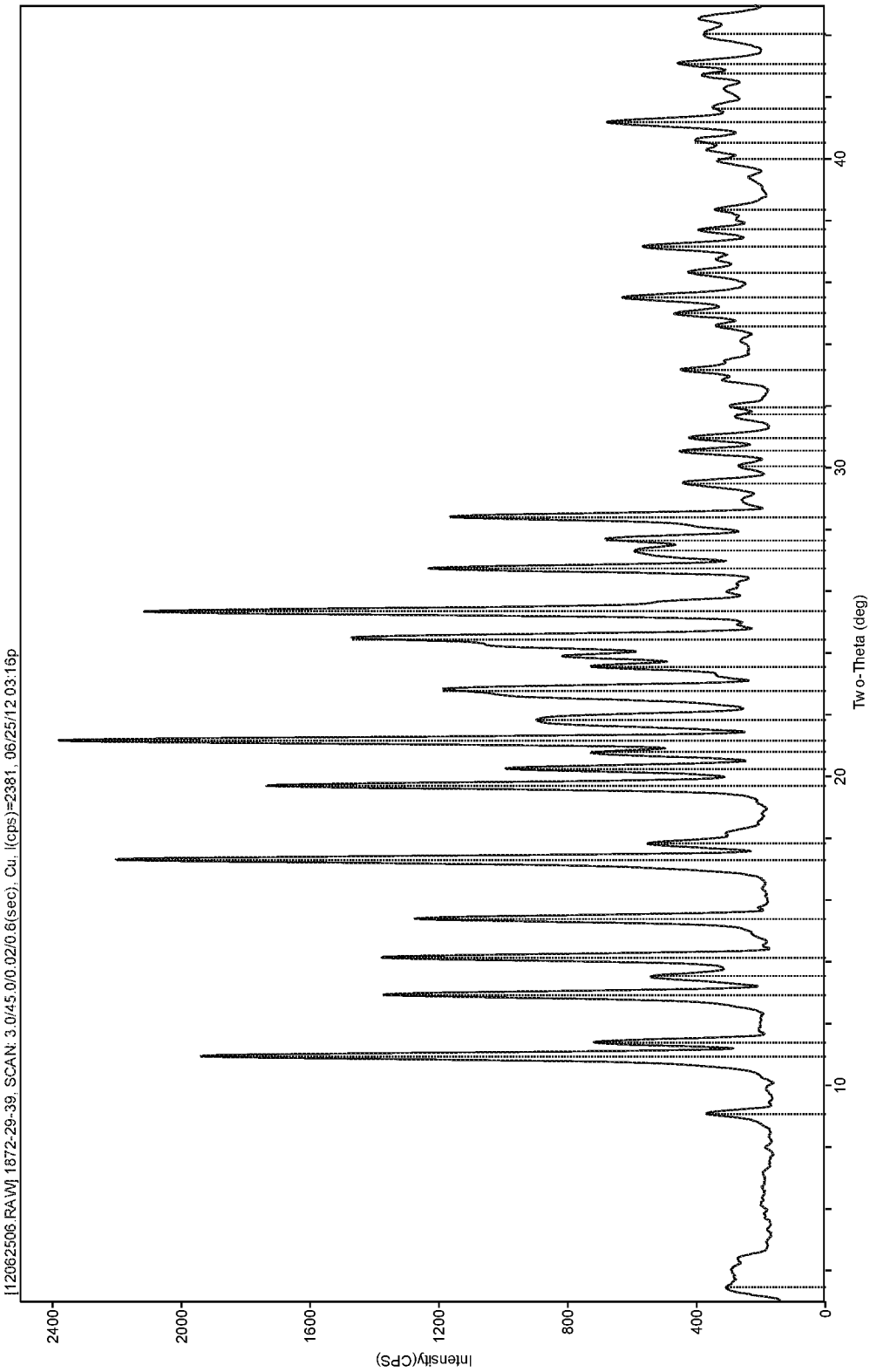
[12062506.RAW] 1872-29-39, SCAN: 3.0/45.0/0.02/0.6(sec), Cu, I(cps)=2381, 06/25/12 03:16p
Intensity(CPS)
2400
2000
1600
1200
800
400
0
10
20
30
40
Two-Theta (deg)

FIG. 9

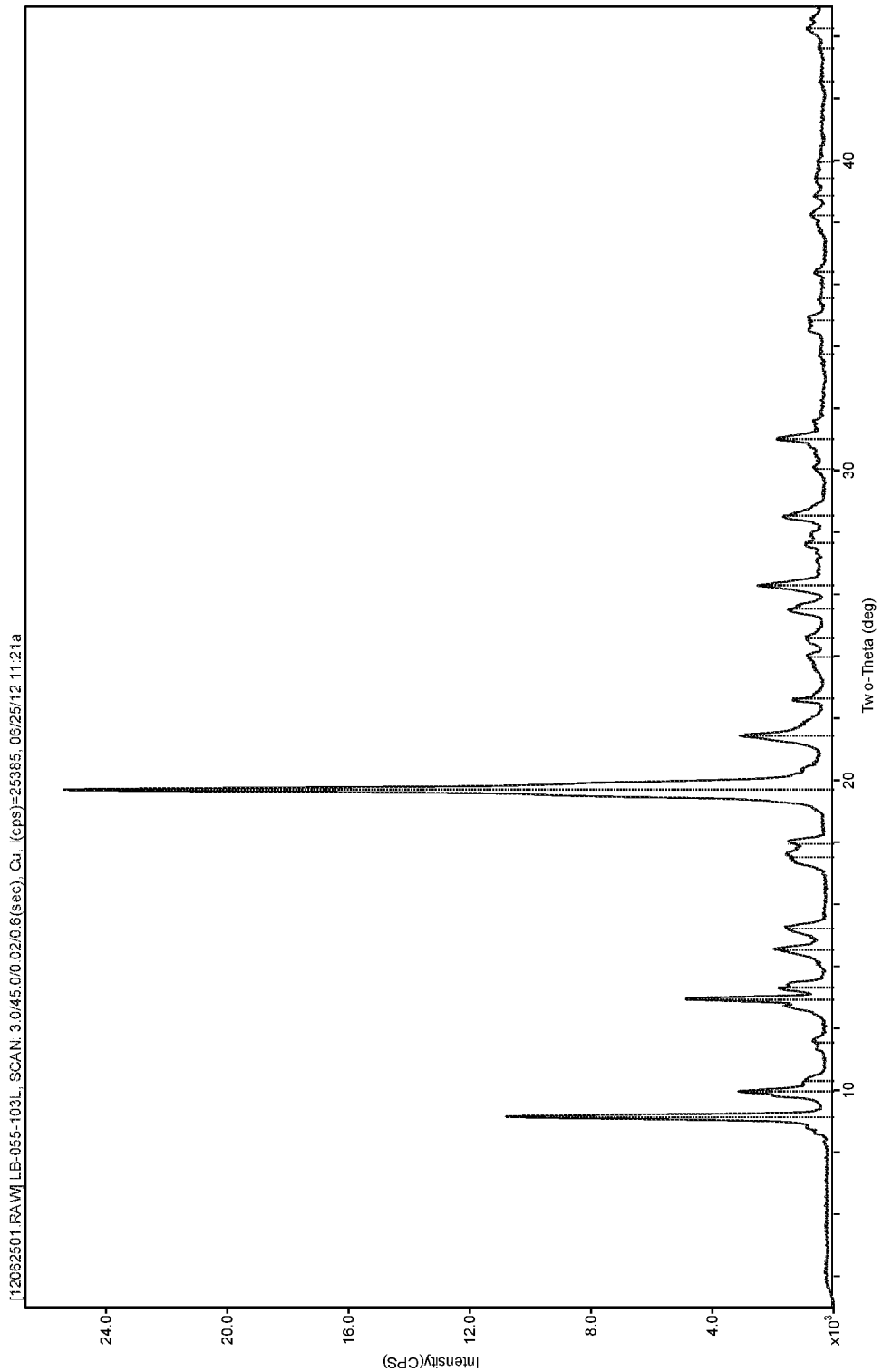
[12062501.RAW] LB-055-103L, SCAN: 3.0/45.0/0.02/0.6(sec), Cu, I(cps)=25385, 06/25/12 11:21a
Intensity(CPS)
x10³
24.0
20.0
16.0
12.0
8.0
4.0
10
20
30
40
Two-Theta (deg)

FIG. 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/49851

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/55; A61P 11/14 (2018.01)
CPC - A61K 31/55; C07B 2200/13

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)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/0060564 A1 (BUT, P-HP et al.) 15 March 2007; paragraphs [0009], [0012], [0015], [0030], [0046], [0052], [0058]; claims 1-3, 7	1, 13-14
A	US 2003/0229071 A1 (LIN, G et al.) 11 December 2003; figures 1A-1C, paragraphs [0091], [0094]-[0098]	2-12
A	FUKAYA, H et al., Absolute Structures of Stemona-Lactam S and Tuberostemospiroline, Alkaloids from Stemona tuberosa, Chemical and Pharmaceutical Bulletin 61(10), pages 1085-1089, 2013; page 1085, figure 1; page 1086, column 2, paragraph 2; page 1087, column 1, paragraph 1	2-12
A	WO 2009/046635 A1 (SHANGHAI INSTITUTE MATERIA MEDICA, et al.) 16 April 2009; paragraphs [0022]-[0025]	12
A	US 2009/0176818 A1 (IZUMIMOTO, N et al.) 09 July 2009; paragraphs [0001], [0044], [0052]	15-17
A	YE, Y et al., Alkaloids of Stemona Japonica, Phytochenustry 37(4), pages 1205-1208, 1994; page 1205, column 2, paragraph 3	15-18
A	LINDSAY, KB, The asymmetric synthesis of polyfunctional pyrrolidine alkaloids and their analogues, Doctoral thesis, Department of Chemistry, University of Wollongong, pages 1-75, 2003; page 74, Scheme 4.10; page 75, paragraph 2	15-17
A	PILLI, RA et al., The chemistry of Stemona alkaloids: An update, Natural Product Reports 27, pages 1908-1937, 2010; abstract; page 1931, Scheme 17; page 1932, column 2, paragraph 1	18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 2018 (14.10.2018)	24 OCT 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)