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(54) Title: TETRANDRINE FAMILY PHARMACEUTICAL FORMULATIONS AND METHOD

(57) Abstract: Drug formulations, methods and their use in treatment of diseases using formulations of pure di-acids salts of tetrandrine family members, especially d-tetrandrine di-hydrochloride combined with a pharmaceutical diluent or carrier. The present invention relates to pharmaceutical formulations of a family of bisbenzylisoquinoline alkaloids. The specific family is referred to herein as the "tetrandrine family."

TETRANDRINE FAMILY PHARMACEUTICAL FORMULATIONS AND METHOD

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Patent Application No. 61/792,849, entitled TETRANDRINE FAMILY PHARMACEUTICAL FORMULATIONS AND METHOD, filed on March 15, 2013, the entire contents of which are incorporated by reference.

FIELD AND BACKGROUND OF THE INVENTION

[0002] The present invention relates to pharmaceutical formulations of a family of bisbenzylisoquinoline alkaloids. The specific family is referred to herein as the "tetrandrine family."

[0003] The tetrandrine family bisbenzylisoquinolines have two nitrogen locations and hence can exist in the free base form or as a mono or di-acid salt. Because of the enhanced solubility of the salt form of pharmaceutical ingredients, the salt forms are used in formulating pharmaceutical compositions. The active ingredient thus solubilizes more quickly and enters the bloodstream faster.

[0004] However, the di-acid chlorides of the tetrandrine family members, most importantly the dihydrochloride (DHC), are a difficult molecule to produce using standard pharmaceutical processing. As a result, all known formulators in the world use an *in situ* procedure as part of the compounding methodology. This leads to variations in content uniformity and tablet-to-tablet potency variances.

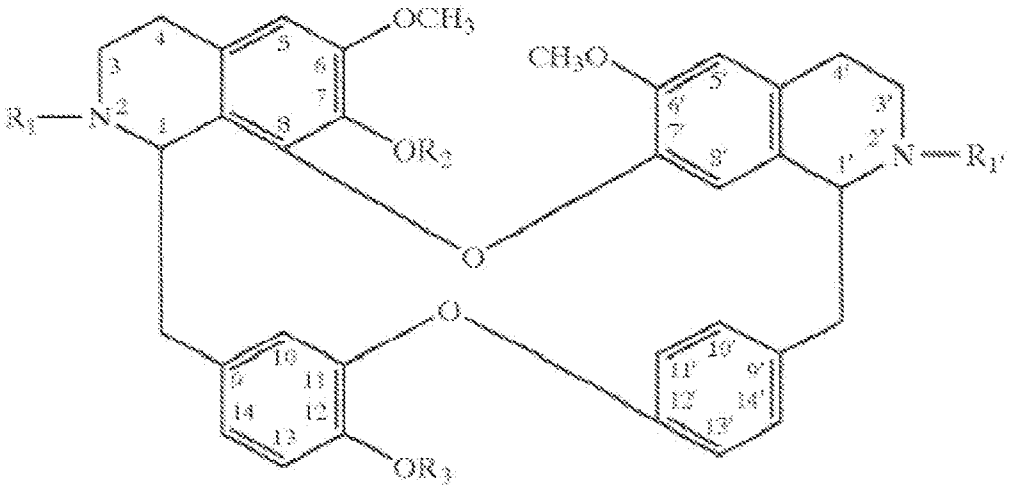
SUMMARY OF THE INVENTION

[0005] The present invention uses pure di-acid salts of tetrandrine family members, preferably d-tetrandrine, and most preferably d-tetrandrine di-hydrochloride, in pharmaceutical formulations. In a preferred embodiment, the di-acid salts are formed by spray drying. As used herein, the term "pure di-acid salt of a tetrandrine family member" means greater than 99% pure on an anhydrous basis.

DESCRIPTION OF THE PREFERRED EMBODIMENT

[0006] The tetrandrine family members have been found effective in treating multi-drug resistance in a variety of diseases and conditions, including cancer and malaria. See U.S. Patents 5,025,020; 5,332,747; 6,528,519; 6,911,454; 6,124,315 and 6,962,927. The formulation of these active ingredients into suitable pharmaceutical delivery systems is thus very important.

[0007] The tetrandrine family members have the following structural formula:



Where R_1 and R_1' are the same or different shortchained carbon based ligand including without limitation, CH_3, CO_2CH_3 or H; and R_2 is CH_3 or C_2H_5; and R_3 is CH_3 or hydrogen;

and where the chemical structure preferably has the "S" isomeric configuration at the C-1' chiral carbon location.

[0008] The preferred members of the tetrandrine family include the following representative examples, which are not intended to be exhaustive: d-tetrandrine, isotetrandrine, hernandezine, berbamine, pycnamine, phaeanthine, obamegine, ethyl fangchinoline and fangchinoline. In all of these examples, R_1 and R_1' constitute the methyl group. Variation within the group occurs in that R_2 and R_3 may constitute either a methyl group or hydrogen, and the isometric configuration of the compounds at the C-1 and C-1' chiral carbon positions is either R (rectus) or S (sinister). The rules for R and S configuration can be found in Morrison and Boyd, "Organic Chemistry," 4th Edition, copyright 1983 by Allyn and Bacon, at pp. 138-141. In addition, hernandezine includes a methoxy group at the C-5 position.

[0009] The most preferred member of the claimed tetrandrine family is d-tetrandrine. Methods for extracting and/or purifying d-tetrandrine are disclosed in U.S. Patents 6,218,541 and in Published Patent Application No. 2011/0105755.

[0010] The di-acid salt of the tetrandrine family member is made by dissolving a purified member of the tetrandrine family, preferably d-tetrandrine, in exactly 2 molar equivalents of dilute acid, preferably hydrochloric acid (5-20% molar) in a vessel. The resulting clear solution is filtered to remove any residual solids into a glass feeding vessel. The solution is tested to assure that the potency of di-acid is within the specified limits. A spray drier is set with a wall temperature of 240-400 C. The atomizer is set to feed the di-acid salt solution at a rate of 1-2 liters/minute. The spray dried di-acid salt is captured in a poly bag lined container to yield 90-95% of the assayed di-acid salt in the feed solution. The solid di-acid salt is tested and released for formulation into capsules, though other dosage forms can be used. The di-

acid salt used is preferably prepared from 99.9% pure tetrandrine family member, using exactly 2 equivalents of hydrochloric acid. The resulting solid di-acid salt contains only residual water and substantially no other impurities. As used herein, the term "pure di-acid salt of a tetrandrine family member" means greater than 99% pure on an anhydrous basis.

[0011] The dosage level used in humans will vary from case to case. However, it is anticipated that one would typically administer the tetrandrine family member drug at from about 50 to about 1000 mg per square meter per day, more preferably 250-700, and most preferably about 500, for from about 4 to about 14 days, during the course of treatment with a principle drug for treating the disease being treated.

[0012] The tetrandrine family members have known applications as primary or solo use drugs, as for example in the treatment of malaria, and in reducing hypertension. However, they are also known for use in conjunction with other drugs. The ratio of the tetrandrine family member to a principle or secondary drug will also vary from patient to patient, and from drug to drug, within a range of from about 0.04:1 to about 170:1. A more typical range would be from about 1:1 to 100:1, more preferably from 25:75 to 75:25.

[0013] The preferred formulations comprise a di-acid salt member of the d-tetrandrine family combined with a suitable pharmaceutical carrier. The pharmaceutical carrier can be a liquid or a solid composition. A liquid carrier will preferably comprise water, possibly with additional ingredients such as .25% carboxymethylcellulose. The solid carrier or diluent used is preferably pregelatinized starch. It may also be formulated with other ingredients, such as colloidal silicone dioxide, sodium lauryl sulfate and magnesium stearate.

[0014] Exemplary capsule formulations include the following:

50 mg d-Tetrandrine di-hydrochloride

384 mg Pregelatinized Starch NF (Starch 1500)

4.4 mg Colloidal Silicon Dioxide (Cab-O-Sil M5)

0.4 mg Sodium Lauryl Sulfate NF

1.0 mg Magnesium Stearate NF;

100 mg d-Tetrandrine di-hydrochloride

70 mg microcrystalline cellulose

0.2 mg sodium lauryl sulfate

0.6 mg magnesium stearate; and

200 mg d-Tetrandrine di-hydrochloride

25.2 mg Pregelatinized Starch 1500 NF

1.5 mg Silicon Dioxide USP

0.25 mg Sodium Lauryl Sulfate NF

1.25 mg Magnesium Stearate USP.

Although the d-tetrandrine used in these formulations is the di-hydrochloride, the 50, 100 and 200 mg weights used the free base weights. Thus the actual amount of active used was slightly greater than the 50, 100 and 200 mgs indicated.

[0015] The 200 mg capsule formulation is most preferred. The most preferred dose of about 500 mg/square meter/day is roughly 1000 mg per day for a 190 pound patient six feet tall. Such a patient can fulfill the dosage requirements by taking five capsules during the course of

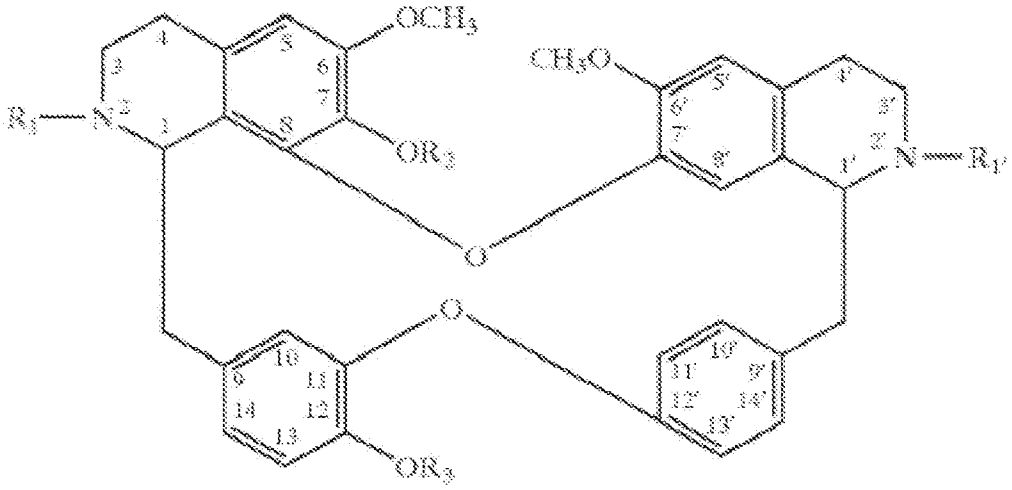
the day, for example three in the morning and two in the evening, or one at a time spaced out over the day. A woman weighing 125 pounds at a height of five feet six inches would require four 200 mg capsules during the course of the day.

[0016] The various diseases which have been treated using tetrandrine family members in conjunction with principle drugs for treating the diseases, and the principle drugs used, are disclosed in U.S. Patents 5,025,020; 5,332,747; 6,528,519; 6,911,454; 6,124,315 and 6,962,927.

[0017] Of course, it is understood that the forgoing are preferred embodiments of the invention, and that variations can be employed without departing from the spirit of the invention as set forth in the appended claims, interpreted in accordance with the principles of patent law.

CLAIMS

1. A pharmaceutical formulation comprising: the pure di-acid salt of a tetrandrine family member having the following formula:



where R_1 and R_1' are the same or different short chained carbon based ligand including without limitation, CH_3, CO_2CH_3 or H; and R_2 is CH_3 or C_2H_5; and R_3 is CH_3 or hydrogen; and a pharmaceutical carrier.

2. The pharmaceutical formulation of claim 1, wherein the tetrandrine family member has the "S" isomeric configuration at the C-1′ chiral carbon location.

3. The pharmaceutical formulation of claim 2 comprising: the pure di-acid salt of d-tetrandrine.

4. The pharmaceutical formulation of claim 3 wherein the pharmaceutical carrier comprises: a solution containing .20-.30% carboxymethylcellulose.

5. The pharmaceutical formulation of claim 3 wherein the pharmaceutical carrier comprises: a pregelatinized starch carrier.

6. The pharmaceutical formulation of claim 5 also comprising: colloidal silicone dioxide, sodium lauryl sulfate and magnesium stearate.

7. The pharmaceutical formulation of claim 6 comprising:

50 mg d-tetrandrine di-acid salt,

384 mg Pregelatinized Starch NF (Starch 1500),

4.4 mg Colloidal Silicon Dioxide (Cab-O-Sil M5),

0.4 mg Sodium Lauryl Sulfate NF, and

1 mg Magnesium Stearate NF.

8. The pharmaceutical formulation of claim 6 comprising:

200 mg d-tetrandrine di-acid salt,

25.2 mg Pregelatinized Starch 1500 NF,

1.5 mg Silicon Dioxide USP,

0.25 mg Sodium Lauryl Sulfate NF, and

1.25 mg Magnesium Stearate USP.

9. The pharmaceutical formulation of claim 6 comprising:

100 mg d-tetrandrine di-acid salt,

70 mg microcrystalline cellulose,

0.2 mg sodium lauryl sulfate, and

0.6 mg magnesium stearate.

10. The pharmaceutical composition of claim 1 wherein the di-acid salt of the tetrandrine family member is made by dissolving a purified member of the tetrandrine family in 2 molar equivalent solution of dilute acid, and fed through a spray drier set with a wall temperature of 240-400 C, and an atomizer set to feed the di-acid salt solution at a rate of 1-2 liters/minute.

11. The pharmaceutical composition of claim 10 wherein the dilute acid used is 5-20% molar hydrochloric acid.

12. The pharmaceutical formulation of claim 10 wherein the tetrandrine family member has the "S" isomeric configuration at the C-1' chiral carbon location.

13. The pharmaceutical formulation of claim 12 wherein the tetrandrine family member comprises d-tetrandrine.

14. A method of treating ailments comprising administering to the patient the pharmaceutical composition of claim 1.

15. The method of claim 14, wherein the tetrandrine family member has the "S" isomeric configuration at the C-1′ chiral carbon location.

16. The method of claim 15 wherein the tetrandrine family member is the pure di-acid salt of d-tetrandrine.

17. The method of claim 16, wherein the wherein the pharmaceutical carrier of the pharmaceutical composition comprises: a solution containing .20-.30% carboxymethylcellulose.

18. The method of claim 16, wherein the pharmaceutical carrier comprises: a pregelatinized starch carrier.

19. The method of claim 18 wherein the pharmaceutical formulation used also comprises: colloidal silicone dioxide, sodium lauryl sulfate and magnesium stearate.

20. A method of treating ailments of claim 14, in which said pharmaceutical composition of claim 1 is administered in conjunction with a principle drug used to treat such ailment.

21. A method of treating ailments of claim 20, wherein the tetrandrine family member has the "S" isomeric configuration at the C-1′ chiral carbon location.

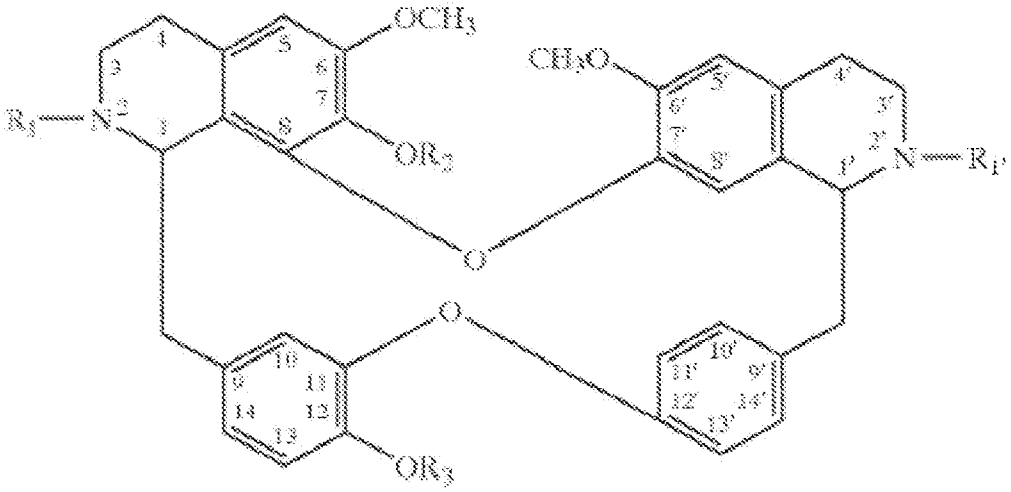
22. A method of treating ailments of claim 21, wherein the tetrandrine family member is the pure di-acid salt of d-tetrandrine.

23. A method of treating ailments of claim 22, wherein the pharmaceutical carrier of the pharmaceutical composition comprises a solution containing .20-.30% carboxymethylcellulose.

24. A method of treating ailments of claim 22, wherein the pharmaceutical carrier comprises: a pregelatinized starch carrier.

25. A method of treating ailments of claim 24 wherein the pharmaceutical formulation used also comprises: colloidal silicone dioxide, sodium lauryl sulfate and magnesium stearate.

26. A method of forming the di-acid salt of a tetrandrine family member having the following formula:



where R_1 and R_1' are the same or different short chained carbon based ligand including without limitation, CH_3, CO_2CH_3 or H; and R_2 is CH_3 or C_2H_5; and R_3 is CH_3 or hydrogen, said method comprising: dissolving a purified member of the tetrandrine family in a 2 molar equivalent

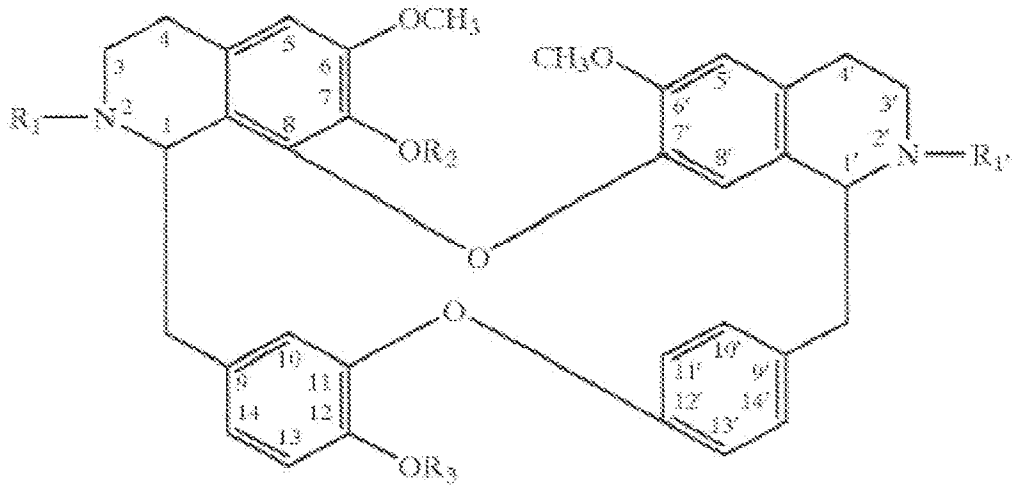
dilute acid solution, feeding said solution through a spray drier set with a wall temperature of 240-400 C, and an atomizer set to feed the di-acid salt solution at a rate of 1-2 liters/minute.

27. The method of claim 26 wherein the dilute acid used is 5-20% molar hydrochloric acid.

28. The method off claim 27 wherein the tetrandrine family member has the "S" isomeric configuration at the C-1' chiral carbon location.

29. The method of claim 28 wherein the tetrandrine family member comprises d-tetrandrine.

30. The pure di-acid salt of a tetrandrine family member having the following formula:

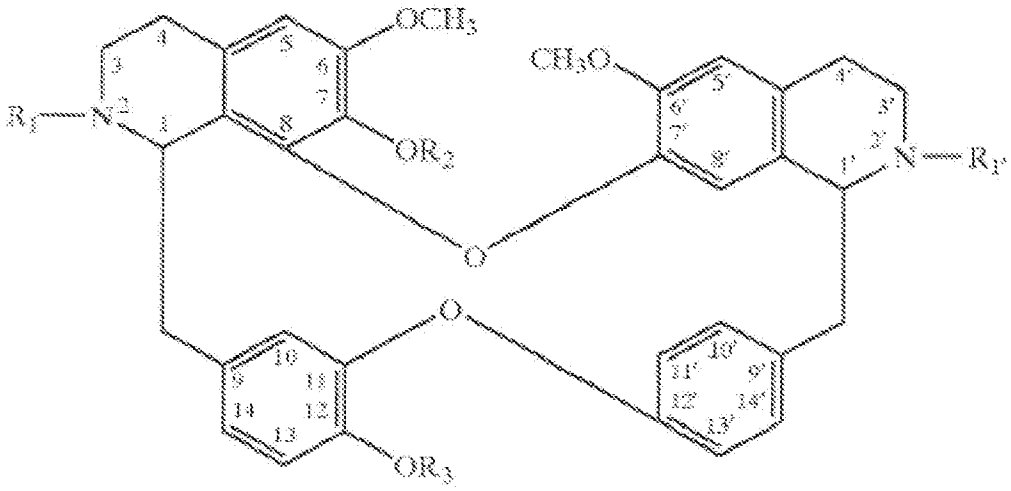


where R_1 and R_1' are the same or different short chained carbon based ligand including without limitation, CH_3, CO_2CH_3 or H; and R_2 is CH_3 or C_2H_5; and R_3 is CH_3 or hydrogen.

31. The pure di-acid salt of claim 30, wherein the tetrandrine family member has the "S" isomeric configuration at the C-1′ chiral carbon location.

32. The pure di-acid salt of claim 31 wherein the tetrandrine family member is d-tetrandrine.

33. The di-acid salt of a tetrandrine family member having the following formula:



where R_1 and R_1' are the same or different short chained carbon based ligand including without limitation, CH_3, CO_2CH_3 or H; and R_2 is CH_3 or C_2H_5; and R_3 is CH_3 or hydrogen, which is made by the process of claim 26.

34. The di-acid salt of claim 33, wherein the tetrandrine family member has the "S" isomeric configuration at the C-1′ chiral carbon location.

35. The di-acid salt of claim 34 wherein the tetrandrine family member is d-tetrandrine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/021195

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/4725 (2014.01)
USPC - 514/308
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/4725 (2014.01)
USPC - 514/308

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 31/4725 (2014.06)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Orbit, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,627,195 A (HU) 06 May 1997 (06.05.1997) entire document	1-6, 10-17, 20-23
Y	CHEN et al. "The Alkaloids of Han-Fang-Chi" J. Biol. Chem. 1935, 109: Pgs. 681-685. [retrieved on 16 July 2014]. Retrieved from the Internet. <http://www.jbc.org/content/109/2/681.short>. entire document	1-6, 10-17, 20-23
Y	US 5,192,802 A (RENCHER) 09 March 1993 (09.03.1993) entire document	1-6, 10-17, 20-23
Y	EP 2 491 930 A1 (HAAS et al) 29 August 2012 (29.08.2012) entire document	5, 6
Y	US 6,962,927 B1 (VAN DYKE) 08 November 2005 (08.11.2005) entire document	20-23

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

* 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 application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 July 2014	11 AUG 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/021195

<Continued from Box III: Observations where unity of invention is lacking>

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-25 are drawn to a pharmaceutical formulation comprising: the pure di-acid salt of a tetrandrine family member having the formula shown in claim 1, and a method of treatment thereof.

Group II: claims 26-35 are drawn to method of forming the di-acid salt of a tetrandrine family member having the formula shown in claim 26; and the di-acid salt product thereof.

The first invention of Group I+ is restricted to a pharmaceutical formulation comprising: the pure di-acid salt of a tetrandrine family member having the formula shown in claim 1, where R1 and R1' are the same short chained carbon based ligand of CH3; R2 is CH3; and R3 is CH3; and a pharmaceutical carrier, wherein the pharmaceutical carrier comprises: a solution containing 0.20-0.30% carboxymethyl- cellulose; and a method of treatment thereof. It is believed that claims 1-4, 10-17, and 20-23 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a pharmaceutical formulation comprising: the pure di-acid salt of a tetrandrine family member having the formula shown in claim 1, where R1 is CO2CH3 and R1' is CH3; R2 is CH3; and R3 is CH3; and a pharmaceutical carrier, wherein the pharmaceutical carrier comprises: a solution containing 0.20-0.30% carboxymethyl- cellulose; and a method of treatment thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ and II do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I+, pharmaceutical formulations comprising the pure di-acid salt of a tetrandrine family member, are not present in Group II; and the special technical features of Group II, methods of forming the di-acid salt of a tetrandrine family member, are not present in Group I+.

The Groups I+ formulae do not share a significant structural element, requiring the selection of alternatives for the compound variables R1, R1', R2, and R3.

The Groups I+ and II share the technical features of a pharmaceutical formulation comprising: the pure di-acid salt of a tetrandrine family member having the formula shown in claim 1, and a method of treating ailments comprising administering to the patient the pharmaceutical composition thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 5,627,195 A to Hu teaches a pharmaceutical formulation comprising: a di-acid salt of a tetrandrine family member having the formula shown in claim 1, where R1 and R1' are CH3; R2 is CH3; and R3 is CH3; and a pharmaceutical carrier; and a method of treating ailments comprising administering to the patient the pharmaceutical composition thereof (Col. 1 Lns. 20-27, method of treating a subject with ocular inflammation associated with keratitis or conjunctivitis. The method includes administering (e.g., topically, orally. subconjunctivally, or intramuscularly) to the subject a composition which contains an amount of tetrandrine or a tetrandrine agonist and a pharmaceutically acceptable carrier...; Col. 5 Lns. 50-64, Example 1, ...After conversion to the hydrochloride form. tetrandrine was
soluble in water...).

Additionally, "The Alkaloids of Hang-Fang-Chi" to Chen et al. teach the pure di-acid salt of a tetrandrine family member having the formula shown in claim 1, where R1 and R1' are CH3; R2 is CH3; and R3 is CH3 (Pgs. 683-684, ...Tetrandrine hydrochloride, C38H42O6N2- 2HCl, can be best prepared by suspending the pure base in a small amount of water and adding, drop by drop, 5 per cent hydrochloric acid until the solution is just acid to litmus. The whole is evaporated to dryness and redissolved in absolute alcohol or a mixture of butyl and ethyl alcohol. The hydrochloride crystallizes in colorless prisms...).

The inventions listed in Groups I+ and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

<End Box III: Observations where unity of invention is lacking>