



- (51) **International Patent Classification:**
A61K 31/235 (2006.01)
- (21) **International Application Number:**
PCT/US2014/019327
- (22) **International Filing Date:**
28 February 2014 (28.02.2014)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
61/771,368 1 March 2013 (01.03.2013) US
61/885,058 1 October 2013 (01.10.2013) US
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- (74) **Agents:** MANDRA, Raymond, R. et al.; Fitzpatrick, Cella, Harper & Scinto, 1290 Avenue of the Americas, New York, NY 10104 (US).
- (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, DK, DM,

DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, 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, 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.

- (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, 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).

Declarations under Rule 4.17:

— *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))*

- (88) **Date of publication of the international search report:**
23 October 2014



WO 2014/134413 A3

(54) **Title:** CYRRHETINIC ALKYL ESTERS AND PROTECTED DERIVATIVES THEREOF

(57) **Abstract:** The present invention is directed to cyrrhetic alkyl ester compounds, a method of making the compounds, cosmetic compositions containing the compound(s) and methods of using the same for the treatment of inflammation in human skin. The compounds and cosmetic compositions containing thereof provide various advantageous properties to the human skin.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/019327

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 31/235 (2014.01) USPC - 514/510 According to International Patent Classification (IPC) or to both national classification and IPC</p>																	
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) IPC(8) - A61K 31/235 (2014.01) USPC - 514/510</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched CPC - A61K 31/235 (2014.06)</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatBase, Orbit, STN, PubChem, Google Scholar</p>																	
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>US 2004/0147494 A1 (POTTER et al) 29 July 2004 (29.07.2004) entire document</td> <td>1, 2, 6-8, 20-22</td> </tr> <tr> <td>A</td> <td>US 2010/0099760 A1 (SAFE et al) 22 April 2010 (22.04.2010) entire document</td> <td>1-3, 6-10, 20-22</td> </tr> <tr> <td>A</td> <td>US 2007/0292537 A1 (JONES et al) 20 December 2007 (20.12.2007) entire document</td> <td>1-3, 6-10, 20-22</td> </tr> <tr> <td>A</td> <td>US 2004/0013618 A1 (PASSI et al) 22 January 2004 (22.01.2004) entire document</td> <td>1-3, 6-10, 20-22</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	US 2004/0147494 A1 (POTTER et al) 29 July 2004 (29.07.2004) entire document	1, 2, 6-8, 20-22	A	US 2010/0099760 A1 (SAFE et al) 22 April 2010 (22.04.2010) entire document	1-3, 6-10, 20-22	A	US 2007/0292537 A1 (JONES et al) 20 December 2007 (20.12.2007) entire document	1-3, 6-10, 20-22	A	US 2004/0013618 A1 (PASSI et al) 22 January 2004 (22.01.2004) entire document	1-3, 6-10, 20-22
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<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/></p>																	
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>“A” document defining the general state of the art which is not considered to be of particular relevance</td> <td>“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</td> </tr> <tr> <td>“E” earlier application or patent but published on or after the international filing date</td> <td>“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</td> </tr> <tr> <td>“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)</td> <td>“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</td> </tr> <tr> <td>“O” document referring to an oral disclosure, use, exhibition or other means</td> <td>“&” document member of the same patent family</td> </tr> <tr> <td>“P” document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			“A” document defining the general state of the art which is not considered to be of particular relevance	“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	“E” earlier application or patent but published on or after the international filing date	“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	“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)	“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	“O” document referring to an oral disclosure, use, exhibition or other means	“&” document member of the same patent family	“P” document published prior to the international filing date but later than the priority date claimed						
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<p>Date of the actual completion of the international search</p> <p>08 August 2014</p>		<p>Date of mailing of the international search report</p> <p>28 AUG 2014</p>															
<p>Name and mailing address of the ISA/US</p> <p>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201</p>		<p>Authorized officer:</p> <p>Blaine R. Copenheaver</p> <p>PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</p>															

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/019327

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:

Claims 1, 2, 6-8, and 20-22 have been analyzed subject to the restriction that the claims read on the formula (I) as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a compound of formula (I); or a cosmetically acceptable salt thereof, wherein R1 is H; R2 is a substituted or unsubstituted C1 to C6 alkyl; a cosmetic composition thereof; and a method of treating inflammation thereof.

<See Extra 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 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.:

1-3, 6-10, and 20-22 as they read on the elected species (See Extra Sheet).
- 4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/019327

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

Claims 1, 3, 6, 9, 10, and 20-22 have been analyzed subject to the restriction that the claims read on the formula (I) as described in the Response to the Invitation to Pay Additional Fees in the International Application dated 23 June 2014. The claims are restricted to a compound of formula (I); or a cosmetically acceptable salt thereof, wherein R1 is H; R2 is the shown o-C(=O)R3-phenyl ring group shown; R3 is a C1-C6 alkyl; a cosmetic composition thereof; and a method of treating inflammation thereof.

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 1-10 and 20-22 are drawn to compounds of formula (I), cosmetic compositions thereof, and methods of treatment thereof.

Group II: claims 11-19 are drawn to methods of making the compound of formula (I).

The first invention of Group I+ is restricted to a compound of formula (I); or a cosmetically acceptable salt thereof, wherein R1 is H; R2 is a substituted or unsubstituted C1 to C6 alkyl; a cosmetic composition thereof; and a method of treating inflammation thereof. It is believed that claims 1, 2, 6-8, and 20-22 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 compound of formula (I); or a cosmetically acceptable salt thereof, wherein R1 is a protecting group; R2 is a substituted or unsubstituted C1 to C6 alkyl; a cosmetic composition thereof; and a method of treating inflammation 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+, cosmetic compositions and methods of treatment thereof, are not present in Group II; and the special technical features of Group II, methods of making the compound of formula (I), 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 and R2.

The Groups I+ and II share the technical features of a compound of formula (I) or a cosmetically acceptable salt thereof; a cosmetic composition comprising up to 75% by weight of the compound; and a method of treating inflammation comprising administering to a host in need of such treatment a therapeutically effective amount of the compound thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2004/0147494 to Potter et al. teach a compound of formula (I) or a cosmetically acceptable salt thereof, wherein R1 is H; and R2 is an unsubstituted C1 to C6 alkyl (see Para. [0243], 3 β -Hydroxy-11-oxo-18 β -glycyrrhetic acid methyl ester (DGS01056 A) (STX 195) (22)); a cosmetic composition comprising up to 75% by weight of the compound thereof (see Abstract, use of a compound in the manufacture of a medicament to inhibit 11 β -HSD activity, wherein the compound is selected from glycyrrhetic acid derivatives; Para. [0129], pharmaceutical compositions can be administered...topically in the form of a lotion, solution, cream, ointment or dusting powder, by use of a skin patch...; Para. [0144], the compound or composition of the present invention may be useful in the treatment of...inflammatory disease, dermatological disorders...); and a method of treating inflammation comprising administering to a host in need of such treatment a therapeutically effective amount of the compound thereof (see Para. [0135], ...composition may be formulated for...transdermal administration. Depending upon the need, the agent may be administered at a dose of from 0.01 to 30 mg/kg body weight, such as from 0.1 to 10 mg/kg, more preferably from 0.1 to 1 mg/kg body weight).

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>