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(54) Title: BIOSYNTHESIS OF CYCLOLAVANDULYL DERIVATIVES OF AROMATIC COMPOUNDS

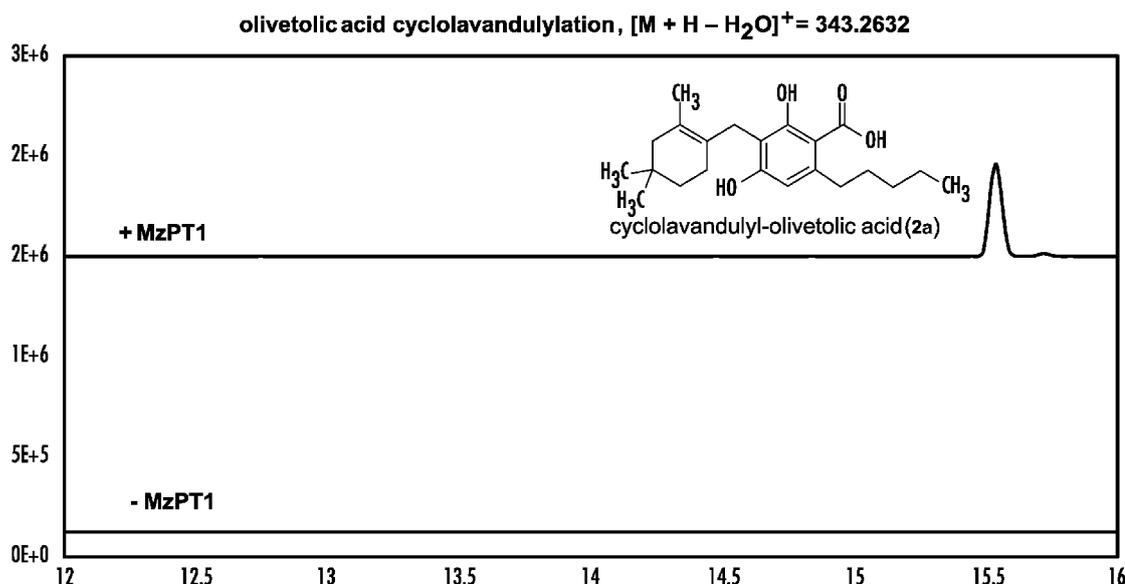


FIG. 5E

(57) Abstract: The present disclosure relates to compositions comprising cyclolavandulyl derivatives of aromatic compounds, such as cannabinoids, flavonoids, and alkaloids, and methods for preparing and using the compositions.

Declarations under Rule 4.17:

- *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))*

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:

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INTERNATIONAL SEARCH REPORT

International application No.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - INV. - C07C 13/20; C07C 13/18 (2023.01)

ADD. - A61K 31/015; C07C 5/00 (2023.01)

CPC - INV. - C07C 13/20; C07C 13/18 (2023.08)

ADD. - C07C 5/00; A61K 31/015 (2023.08)

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 database consulted during the international search (name of database 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. |
|-----------|---|-----------------------|
| A | US 2016/0221923 A1 (SHIN-ETSU CHEMICAL CO. LTD.) 04 August 2016 (04.08.2016) entire document | 1 |
| A | PUBCHEM, SID 37510570, Modify Date: 05 December 2007 [retrieved on 14 September 2023], Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/substance/37510570 > entire document | 1 |
| A | TOMITA et al., Structure and Mechanism of the Monoterpene Cyclolavandulyl Diphosphate Synthase that Catalyzes Consecutive Condensation and Cyclization, Angewandte Chemie International Edition, Vol. 56, 18 September 2017 [retrieved on 17 July 2023]. Retrieved from the Internet: <URL: https://onlinelibrary.wiley.com/toc/15213773/2017/56/47 >. Pgs. 14913-14917 | 1 |
| A | WO 2021/046640 A1 (KARE CHEMICAL TECHNOLOGIES INC.) 18 March 2021 (18.03.2021) entire document | 1 |
| A | US 7,361,483 B2 (KUZUYAMA et al.) 22 April 2008 (22.04.2008) entire document | 1 |

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

"D" document cited by the applicant in the international application

"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

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/019381

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. forming part of the international application as filed.
 - b. furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
 accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/019381

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 extra sheet(s).

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.:
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.

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Continued from Box No. 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 1-7 are drawn to compounds of structural formula (Ia) or (Ib).

Group II: claims 8-17 and 23-33 are drawn to methods for preparing a cyclolavandulyl-substituted aromatic compounds.

Group III+: claims 18-22 are drawn to compositions comprising a prenyltransferase, a cyclolavandulyl pyrophosphate of compound (1) and an aromatic compound selected from a compound of structural formula (III), (IV), (V), and (VI).

Group IV+: claims 34-40 are drawn to compositions comprising a cyclolavandulyl diphosphate synthase (CLDS), dimethylallyl pyrophosphate, a prenyltransferase, and an aromatic compound selected from a compound of structural formulas (III), (IV), (V), and (VI).

The first invention of Group I+ is restricted to a compound of structural formula (Ia) wherein R1 is the first shown moiety wherein each R2 -H; R3 is -H; and R4 is -H. It is believed that claim 1 reads on this first named invention and thus this claim will be searched without fee to the extent that it reads on the above embodiment.

The first invention of Group III+ is restricted to a composition comprising a prenyltransferase selected to be NphB (SEQ ID NO: 8), a cyclolavandulyl pyrophosphate of compound (1) and an aromatic compound selected to be a compound of structural formula (III) wherein each R2 -H; R3 is -H; and R4 is -H.

The first invention of Group IV+ is restricted to a composition comprising a cyclolavandulyl diphosphate synthase (CLDS) selected to be amino acid sequence of SEQ ID NO: 2, dimethylallyl pyrophosphate, a prenyltransferase selected to be NphB (SEQ ID NO: 8), and an aromatic compound selected to be a compound of structural formula (III) wherein each R2 -H; R3 is -H; and R4 is -H.

Applicant is invited to elect additional formula(e), prenyltransferase(s), and/or cyclolavandulyl diphosphate synthase(s) for each additional compound/composition to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e), prenyltransferase(s), and/or cyclolavandulyl diphosphate synthase(s) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of structural formula (Ia) wherein R1 is the first shown moiety wherein each R2 -H; R3 is -COOH; and R4 is -H. 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+, II, III+, and IV+ 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+, compounds of structural formula (Ia) or (Ib), are not present in Groups II, III+, and IV+; the special technical features of Group II, methods for preparing a cyclolavandulyl-substituted aromatic compounds, are not present in Groups I+, III+, and IV+; the special technical features of Group III+, compositions comprising a prenyltransferase, a cyclolavandulyl pyrophosphate of compound (1) and an aromatic compound selected from a compound of structural formula (III), (IV), (V), and (VI), are not present in Groups I+, II, and IV+; and the special technical features of Group IV+, compositions comprising a cyclolavandulyl diphosphate synthase (CLDS), dimethylallyl pyrophosphate, a prenyltransferase, and an aromatic compound selected from a compound of structural formulas (III), (IV), (V), and (VI), are not present in Groups I+, II, and III+.

The Groups I+, III+, and IV+ formulae do not share a significant structural element requiring the selection of alternatives for R1, prenyltransferase where "the prenyltransferase is selected from: (i) NphB (SEQ ID NO: 8) or a variant of NphB comprising an amino acid sequence having at least 90%, at least 95%, at least 97%, at least 98%, or at least 99% identity to any one of SEQ ID NO: 8; (ii) NphBM31s (SEQ ID NO: 6) or a variant of NphBM31s comprising an amino acid sequence having at least 90%, at least 95%, at least 97%, at least 98%, or at least 99% identity to any one of SEQ ID NO: 6; (iii) a prenyltransferase comprising an amino acid sequence or any one of SEQ ID NO: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19; and (iv) a variant prenyltransferase comprising an amino acid sequence having at least 90%, at least 95%, at least 97%, at least 98%, or at least 99% identity to any one of SEQ ID NO: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19," and cyclolavandulyl diphosphate synthase where "wherein the cyclolavandulyl diphosphate synthase (CLDS) is a polypeptide comprises an amino acid sequence of SEQ ID NO: 2 or 4, or a variant of SEQ ID NO: 2 or 4; optionally, wherein the variant of SEQ ID NO: 2 or 4 comprises an amino acid sequence having at least 90%, at least 95%, at least 97%, at least 98%, or at least 99% identity to SEQ ID NO: 2 or 4," and accordingly these groups lack unity a priori.

Additionally, even if Groups I+, II, III+, and IV+ were considered to share the technical features of a compound having the core structure of formula (Ia) or (Ib); a composition comprising a prenyltransferase, a cyclolavandulyl pyrophosphate of compound (1) and an aromatic compound having the core structure of structural formula (III), (IV), (V), or (VI); and a composition comprising a cyclolavandulyl diphosphate synthase (CLDS), dimethylallyl pyrophosphate, a prenyltransferase, and an aromatic compound having the core structure of structural formulas (III), (IV), (V), or (VI), these shared technical features do not represent a contribution over the prior art as disclosed by US 2016/02219323 A1 to Shin-Etsu Chemical Co., Ltd. (hereinafter, "Shin"), US 7,361,483 B2 to Kuzuyama et al. (hereinafter, "Kuzuyama"), the publication entitled "Structure and Mechanism of the Monoterpene Cyclolavandulyl Diphosphate Synthase that Catalyzes Consecutive Condensation and Cyclization" by Tomita et al. (hereinafter "Tomita"), and WO 2021/046640 A1 to Kare Chemical Technologies Inc. (hereinafter, "Kare").

Shin teaches a compound having the core structure of formula (Ia) or (Ib) (Abstract, the (2,4,4-trimethyl-2-cyclohexenyl)methyl ester compound (4)).

Kuzuyama teaches a composition comprising a prenyltransferase (Claim 2, composition comprising an aromatic prenyltransferase consisting of the amino acid sequence of SEQ ID NO:2).

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Tomita teaches a composition comprising a cyclolavandulyl pyrophosphate of compound (1) (Pg. 14917, Fig. 3, end product of CLDS-catalyzed reaction); and a composition comprising a cyclolavandulyl diphosphate synthase (CLDS) (Pg. 14915, Fig. 1a CLDS structure; Pg. 14917, Fig. 3, CLDS-catalyzed reaction), and dimethylallyl pyrophosphate (Pg. 14913, Scheme 1, DMAPP as shown).

Kare teaches a composition comprising an aromatic compound having the core structure of structural formula (III), (IV), (V), or (VI) (Pg. 23, Lns. 26-29; see also Pg. 24, Lns. 1-3, preparing compounds of the Formula (I) comprising: (a) contacting an α,β -unsaturated ketone of Formula (XXI), wherein Formula (XXI) is an aromatic compound).

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