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(54) Title: PREPARATION OF TERPENOID COMPOUNDS

(57) Abstract: The present invention provides a process for the preparation of a compound of formula (I). Included in this invention is an *in vivo* process for the preparation of compound of formula (I) in recombinant cells. The present invention also provides recombinant cells which may be used in said process. The present invention also provides polypeptides which can be used in the present invention. The present invention also provides further processes for the preparation of further compounds.



WO 2024/256472 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2024/066253

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 13*ter*.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/EP2024/066253

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1 - 18, 23 - 26, 31
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/EP2024/066253

A. CLASSIFICATION OF SUBJECT MATTER				
INV. C12P17/04	C07D307/92	C12N9/04		
C12N9/88	C12N9/90	C12P7/04		
C12N9/02	C12P7/24	C12N9/18		
C12P7/62				
ADD.				
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) C12P C12N C07D				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, COMPENDEX, EMBASE, FSTA, WPI Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
A	WO 2010/139719 A2 (BASF SE [DE]; BREUER MICHAEL [DE] ET AL.) 9 December 2010 (2010-12-09) cited in the application abstract; claims page 7 - page 8 -----	1 - 14, 23 - 26		
A	WO 2022/003017 A1 (GIVAUDAN SA [CH]) 6 January 2022 (2022-01-06) abstract; claims page 7 - page 9; compound III page 13; example 8 ----- - / - -	1 - 14, 23 - 26		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.				
* Special categories of cited documents : <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> </tr> </table>			"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
"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			
18 February 2025	03/03/2025			
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Schröder, Gunnar			

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/066253

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/005097 A1 (FIRMENICH & CIE [CH]) 14 January 2021 (2021-01-14) cited in the application	31
A	abstract; claims page 4 embodiment 17; page 56 embodiment 87; page 84	1-14, 23-26
X	----- US 2020/385700 A1 (MOODY THOMAS SHAW [IE] ET AL) 10 December 2020 (2020-12-10) claims 5-8; example 4 -----	15-18
X	ANDREAS SCHNEIDER ET AL: "Harnessing the Structure and Dynamics of the Squalene-Hopene Cyclase for (-)-Ambroxide Production", ANGEWANDTE CHEMIE INTERNATIONAL EDITION, VERLAG CHEMIE, HOBOKEN, USA, vol. 62, no. 22, E2023016, 18 April 2023 (2023-04-18), pages 1-10, XP072536251, ISSN: 1433-7851, DOI: 10.1002/ANIE.202301607 cited in the application article no. e202301607 abstract; figures 1, 2 - & Schneider A ET AL: "Supporting information for: Harnessing the Structure and Dynamics of the Squalene-Hopene Cyclase for (-)-Ambroxide Production", Angewandte Chemie International Edition (online), 20 March 2023 (2023-03-20), pages i, 1-34, XP093249720, Retrieved from the Internet: URL:https://onlinelibrary.wiley.com/action /downloadSupplement?doi=10.1002%2Fanie.202 301607&file=anie202301607-sup-0001-misc_in formation.pdf pages 17, 21, ----- -/--	15-18

INTERNATIONAL SEARCH REPORT

International application No PCT/EP2024/066253

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BENÍTEZ-MATEOS ANA I. ET AL: "Spheroplasts preparation boosts the catalytic potential of a squalene-hopene cyclase", NATURE COMMUNICATIONS, vol. 13, no. 1, 6269, 21 October 2022 (2022-10-21), pages 1-9, XP093116646, UK ISSN: 2041-1723, DOI: 10.1038/s41467-022-34030-0 Retrieved from the Internet: URL:https://www.nature.com/articles/s41467-022-34030-0> abstract; figures 3, 4 -----</p>	15-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/EP2024/066253

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010139719 A2	09-12-2010	CN 102449158 A	09-05-2012
		EP 2438182 A2	11-04-2012
		EP 3404108 A1	21-11-2018
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US 2020385700 A1	10-12-2020	BR 112019015747 A2	17-03-2020
		CN 110312796 A	08-10-2019
		EP 3585887 A1	01-01-2020
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		US 2020385700 A1	10-12-2020
		WO 2018157021 A1	30-08-2018

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-14, 23-26, 31

Process for the preparation of a compound of formula (I), i.e. ambroxide, or of compounds of formula (IV) or (V) by enzymatic conversion, wherein each of the processes comprises a step of converting a compound of formula (III), i.e. geranylgeranial, into a compound of formula (IV), i.e. farnesylacetone, using an enal-cleaving enzyme; Use of a polypeptide having enal-cleaving enzyme activity to produce a compound of formula (IV), (V), (VI), (I) and/or a derivative thereof.

2. claims: 15-18

Recombinant cell comprising a compound of formula (I) and one or more compound(s) selected from the group of formula (II), formula (III), formula (IV), formula (V) and formula (VI); cell culture fermentation medium comprising said cell

3. claim: 19

A reaction mixture comprising a compound of formula (I) and one or more compound(s) selected from the group of formula (II), formula (III), formula (IV), formula (V) and formula (VI)

4. claims: 20, 30(all partially)

A compound of formula (I) obtainable by the process according to claims 1-14; use thereof as a perfuming ingredient

5. claims: 20, 30(all partially)

A compound of formula (I) obtainable from the recombinant cell according to claims 15-18; use thereof as a perfuming ingredient

6. claims: 20, 30(all partially)

A compound of formula (I) obtainable from the reaction mixture of claim 19; use thereof as a perfuming ingredient

7. claims: 21, 22

Process for the preparation of a compound of formula (VI),

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

i.e. homofarnesol, from a compound of formula (IV), i.e. farnesylacetone, in 2 enzymatic conversion steps

8. claims: 27, 28

Process for the preparation of a compound of formula (I), i.e. ambroxide, from a compound of formula (V), i.e. homofarnesylacetate, in 2 enzymatic conversion steps

9. claims: 29 (completely); 30 (partially)

A compound obtained or obtainable by the process of any of claims 21 to 28; use thereof as a perfuming ingredient
