

**PCT**WELTORGANISATION FÜR GEISTIGES EIGENTUM  
Internationales BüroINTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE  
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

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| <b>(51) Internationale Patentklassifikation<sup>6</sup> :</b><br><br><b>C12P 13/00, 1/00</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <b>A1</b> | <b>(11) Internationale Veröffentlichungsnummer: WO 99/24597</b><br><br><b>(43) Internationales Veröffentlichungsdatum:</b> 20. Mai 1999 (20.05.99)                                                                                                                                                                                                                                                                 |
| <b>(21) Internationales Aktenzeichen:</b> PCT/EP98/07124<br><b>(22) Internationales Anmeldedatum:</b> 9. November 1998 (09.11.98)<br><br><b>(30) Prioritätsdaten:</b><br>197 49 480.3      8. November 1997 (08.11.97)      DE<br><br><b>(71) Anmelder (für alle Bestimmungsstaaten ausser US):</b><br>SIGMA-TAU INDUSTRIE FARMACEUTICHE RI-<br>UNITE S.P.A. [IT/IT]; Viale Shakespeare, 47, I-00144<br>Roma (IT).<br><br><b>(72) Erfinder; und</b><br><b>(75) Erfinder/Anmelder (nur für US):</b> KLEBER, Hans-Peter<br>[DE/DE]; Platanenweg 42, D-04416 Großdeuben (DE).<br>CANOVAS-DIAZ, Manuel [ES/ES]; Cuesta de la Luz,<br>31, Urb. Azahar D 3, E-30001 Santo Angel-Murcia (ES).<br>OBON, José Maria [ES/ES]; Libertad, 1.7 A, E-30009<br>Murcia (ES). IBORRA, José Luis [ES/ES]; Nuestra Sedora<br>de los Buena Libros, 5.4 F, E-30008 Murcia (ES).<br><br><b>(74) Anwalt:</b> MARSH, Roy, D.; Hoffmann . Eitle, Arabellastrasse<br>4, D-81925 München (DE).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |           | <b>(81) Bestimmungsstaaten:</b> AU, BR, CA, CN, JP, KR, MX, US,<br>europäisches Patent (AT, BE, CH, CY, DE, DK, FI, FR,<br>GB, GR, IE, IT, LU, MC, NL, PT, SE).<br><br><b>Veröffentlicht</b><br><i>Mit internationalem Recherchenbericht.<br/>         Vor Ablauf der für Änderungen der Ansprüche zugelassenen<br/>         Frist; Veröffentlichung wird wiederholt falls Änderungen<br/>         eintreffen.</i> |
| <b>(54) Title:</b> METHOD FOR PRODUCING L-CARNITINE FROM CROTONOBETAINE<br><br><b>(54) Bezeichnung:</b> VERFAHREN ZUR HERSTELLUNG VON L-CARNITIN AUS CROTONOBETAIN<br><br><b>(57) Abstract</b><br><br>The invention relates to a method for producing L(-)-carnitine. The aim of the invention is to depict a method which permits the synthesis of L(-)-carnitine from crotonobetaine, crotonobetaine salts or derivatives in an ecologically advantageous manner by immobilizing cells of <i>Escherichia coli</i> 044 K74 in a continuously operating cell recycle reactor. Growing or resting cells of <i>E. coli</i> are retained in a continuously operating cell recycle reactor by micro or ultrafiltration membranes which are arranged as a flat membrane module or hollow chamfer module.<br><br><b>(57) Zusammenfassung</b><br><br>Die Erfindung betrifft ein Verfahren zur Herstellung von L(-)-Carnitin. Das Wesen der Erfindung besteht darin, ein Verfahren dazustellen, daß in ökonomisch vorteilhafter Weise die Synthese von L(-)-Carnitin aus Crotonobetain, Crotonobetainsalzen oder Derivaten durch immobilisierte Zellen von <i>Escherichia coli</i> 044 K74 in einem kontinuierlich arbeitenden Zell-Recycle-Reaktor erlaubt. Wachsende oder ruhende Zellen von <i>E. coli</i> werden in einem kontinuierlich arbeitenden Zell-Recycle-Reaktor durch Mikro- bzw. Ultrafiltrationsmembranen, die als Flachmembran- oder Hohlfasermodul angeordnet sind, zurückgehalten. |           |                                                                                                                                                                                                                                                                                                                                                                                                                    |

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/07124

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 C12P13/00 C12P1/00

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 6 C12P

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 practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                       | Relevant to claim No. |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | CHEMICAL ABSTRACTS, vol. 115, no. 1,<br>8 July 1991<br>Columbus, Ohio, US;<br>abstract no. 6956,<br>JUNG, H. ET AL: "Production of L(-)-<br>carnitine by biotransformation"<br>XP002096268<br>see abstract<br>& DECHEMA BIOTECHNOL. CONF. (1990), 4(P.T.<br>B, LECT. DECHEMA ANNU. MEET. BIOTECHNOL.<br>8TH, 1990), 1041-4 CODEN: DBCOEU,<br>---<br>-/-- | 1                     |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search

11 March 1999

Date of mailing of the international search report

25/03/1999

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International Application No

PCT/EP 98/07124

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                            | Relevant to claim No. |
|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X        | CHEMICAL ABSTRACTS, vol. 117, no. 19,<br>9 November 1992<br>Columbus, Ohio, US;<br>abstract no. 187989,<br>JUNG, HEINRICH ET AL: "L-(-)- Carnitine<br>synthesis by stereoselective hydration of<br>crotonobetaine"<br>XP002096269<br>see abstract<br>& PROC. - EUR. CONGR. BIOTECHNOL., 5TH<br>(1990), VOLUME 1, 251-4. EDITOR(S):<br>CHRISTIANSEN, CLAUS; MUNCK, LARS;<br>VILLADSEN, JOHN. PUBLISHER: MUNKSGAARD,<br>COPENHAGEN, DEN. CODEN: 57RVAO,<br>---- | 1                     |
| A        | EP 0 320 460 A (SIGMA TAU IND FARMACEUTI)<br>14 June 1989<br>see claims<br>----                                                                                                                                                                                                                                                                                                                                                                               | 1                     |
| P,X      | CHEMICAL ABSTRACTS, vol. 128, no. 2,<br>12 January 1998<br>Columbus, Ohio, US;<br>abstract no. 12603,<br>OBON, JOSE MARIA ET AL: "L-(-)- Carnitine<br>production with immobilized Escherichi<br>coli cells in continuous reactors"<br>XP002096270<br>see abstract<br>& ENZYME MICROB. TECHNOL. (1997), 21(7),<br>531-536 CODEN: EMTED2; ISSN: 0141-0229,<br>-----                                                                                             | 1                     |