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— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR)

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— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

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(88) Date of publication of the international search report:
6 November 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS FOR THE PRODUCTION OF TYROSINE, CINNAMIC ACID AND PARA-HYDROXYCINNAMIC ACID

(57) Abstract: Genes encoding phenylalanine ammonia-lyase (PAL), tyrosine ammonia lyase (TAL) and phenylalanine hydroxylase (PAH) have been introduced into a host organism for the production of *Para*-hydroxycinnamic acid (PHCA). The introduction of these genes results in the redirection of carbon flow in the host, optimizing the flow of carbon from glucose to PHCA. The intermediates, tyrosine and cinnamic acid are also produced.



WO 02/090523 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/18551

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12P 1/00, 7/00, 7/40; C12 N 9/00, 9/02, 9/04, 9/88
 US CL : 435/41, 132, 136, 183, 189, 190, 232; 536/23.2

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)
 U.S. : 435/41, 132, 136, 183, 189, 190, 232; 536/23.2

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)
 WEST, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X, P | US 6,368,837 (Gatenby et al.) 9 April 2002 (09.04.2002), column 1, line 1 to column 40, line 39. | 1-4, 6-10, and 12 |
| Y | Howles et al. Overexpression of L-phenylalanine ammonia-lyase in transgenic tobacco plants reveals control points for flux into phenylpropanoid biosynthesis. Plant Physiology. 1996, Vol. 112(4), pp. 1617-1624 | 1-4, 6-10, and 12 |
| A | Erlandsen et al. Structural comparison of bacterial and human iron-dependent phenylalanine hydroxylases: similar fold, different stability and reaction rates. J Mol Biol. 12 July 2002, Vol. 320(3), pp. 645-61 | 1-4, 6-10, and 12 |
| A | Kyndt et al. Characterization of a bacterial tyrosine ammonia lyase, a biosynthetic enzyme for the photoactive yellow protein. FEBS Lett. 13 Feb 2002, Vol. 512(1-3), pp. 240-4. | 1-4, 6-10, and 12 |

Further documents are listed in the continuation of Box C.

See patent family annex.

| * | Special categories of cited documents: | "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 |
|-----|---|-----|--|
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "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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| "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) | "&" | document member of the same patent family |
| "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 | | |

Date of the actual completion of the international search

23 March 2003 (23.03.2003)

Date of mailing of the international search report

07 APR 2003

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/18551

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

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

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

2. Claim Nos.: 5 and 11
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:
claims are directed to nucleotide/amino acid sequence which are not in sequence compliance.

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

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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

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 fee, this Authority did not invite payment of any additional fee.
 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.
- No protest accompanied the payment of additional search fees.