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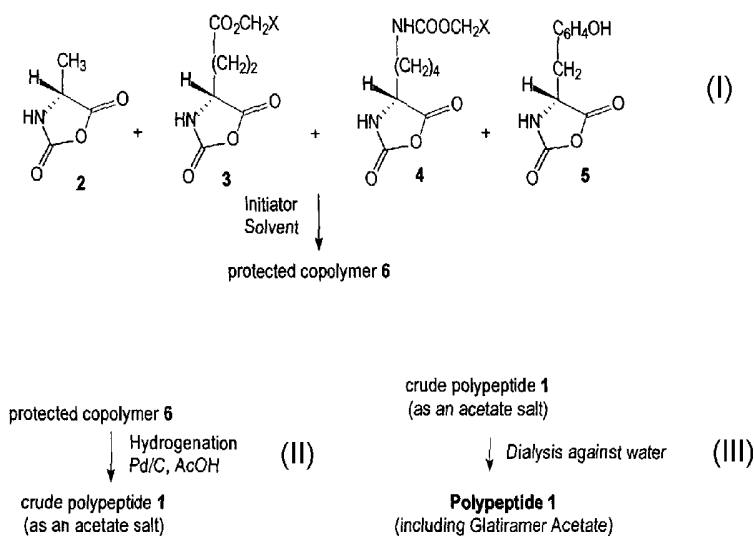
- (51) International Patent Classification⁷: C07K 14/00, 1/06
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13 November 2003 (13.11.2003)
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10/326,994 24 December 2002 (24.12.2002) US
- (71) Applicant (for all designated States except US): APOTEX PHARMACHEM INC. [CA/CA]; 34 Spalding Drive, Brantford, Ontario N3T 6B8 (CA).
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ,

[Continued on next page]

(54) Title: PROCESS FOR THE PREPARATION OF GLATIRAMER ACETATE BY POLYMERISATION OF N-CARBOXY ANHYDRIDES OF L-ALANINE, L-TYROSINE, BENZYL L-GLUTAMATE AND BENZYLOXYCARBONYL L-LYSINE



(57) Abstract: A process for the preparation of a polypeptide designated in the present invention as 1, composed of the following amino acid units in the structure, namely: L-alanine, L-glutamic acid, L-lysine and L-tyrosine randomly arranged in the polypeptide 1, or pharmaceutically acceptable salts thereof, comprising the steps of: (a) polymerization of a mixture of the N-carboxyanhydrides of L-alanine, L-tyrosine, a protected L-glutamate and a protected L-lysine to obtain protected copolymer 6 or salt thereof; formula (I), (b) deprotection of the protected copolymer 6 (or salt thereof) to produce polypeptide 1 or a pharmaceutically acceptable salt thereof in one single step; formula (II), (c) separation and purification of the polypeptide 1 (or a pharmaceutically acceptable salt) to obtain a purified polypeptide 1. Formula (III).

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- CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- of inventorship (Rule 4.17(iv)) for US only
- Published:**
- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report:**
7 October 2004
- 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.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 03/01744

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/00 C07K1/06

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 7 C07K

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)

EPO-Internal, BIOSIS, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A Y	US 3 849 550 A (ARNON R ET AL) 19 November 1974 (1974-11-19) the whole document	1-39, 42, 43 1-39, 42, 43
Y	<p style="text-align: center;">-----</p> FELIX A M ET AL: "RAPID REMOVAL OF PROTECTING GROUPS FROM PEPTIDES BY CATALYTIC TRANSFER HYDROGENATION WITH 1 4 CYCLO HEXADIENE" JOURNAL OF ORGANIC CHEMISTRY, vol. 43, no. 21, 1978, pages 4194-4196, XP002273767 ISSN: 0022-3263 whole document, in particular table I <p style="text-align: center;">----- -/--</p>	1-39, 42, 43

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
- *E* earlier document 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

17 March 2004

Date of mailing of the international search report

18. 08. 04

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 03/01744

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GOWDA D CHANNE ET AL: "Heterogeneous catalytic transfer hydrogenation in peptide synthesis." LETTERS IN PEPTIDE SCIENCE, vol. 9, no. 4-5, 2002, pages 153-165, XP009027879 ISSN: 0929-5666 the whole document, in particular scheme 8 -----	1-39,42, 43
Y	EPTON R ET AL: "CATALYTIC TRANSFER HYDROGENATION OF POLY(ACRYLOYLMORPHOLINE)-BASED PEPTIDE-RESIN ASSEMBLIES AND OF DERIVED PEPTIDE SEGMENTS" POLYMER OCT 1982, vol. 23, no. 11, October 1982 (1982-10), pages 1685-1687, XP001180305 the whole document -----	1-39,42, 43

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 03/01744

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: 1-6
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:
see FURTHER INFORMATION sheet PCT/ISA/210

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 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:

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 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.:
1-37, 38-39(part), 42-43(part)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-6

Present claims 1-6 lack clarity within the meaning of Article 6 PCT, since the terms "afford", "substantially" (in claim 1) and "initiator" (in claim 5) are not clear.

Furthermore, said claims lack support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such processes. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to claim 7, i.e. in which the deprotection step has been defined according to claim 7.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 03/01744

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 3849550	A	19-11-1974	IL 36670 A	10-09-1974
			CA 1006508 A1	08-03-1977
			CH 570167 A5	15-12-1975
			DE 2217817 A1	16-11-1972
			FR 2133926 A5	01-12-1972
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