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(54) Title: PROTEIN HYDROLYSATE ENRICHED IN PEPTIDES INHIBITING DPP-IV AND THEIR USE

(57) Abstract: Disclosed is a protein hydrolysate having DPP-IV inhibiting activity, the hydrolysate being enriched in peptides having a length of 2-8 amino acids comprising at least one proline residue, an isolated peptide derivable from such a protein hydrolysate, or a mixture thereof, and the use of such protein hydrolysate or isolated peptide for the manufacture of a medicament, food supplement, beverage or food product for prophylaxis and/or treatment of a DPP-IV mediated condition, in particular chosen from the group of obesity, type 2 diabetes mellitus and an immunological disorder.



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A. CLASSIFICATION OF SUBJECT MATTER				
INV. C12N9/48	C07K14/47	C12P21/06		
A61K38/06	A61K38/07	A61K38/08		
A61P3/10	A61P37/00	A61K38/01		
		C07K1/12		
		A61K38/05		
		A61P9/02		
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) C12N C12P C07K A61K A61P				
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, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data, Sequence Search				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	WO 2004/022083 A (DSM IP ASSETS B.V; VAN DER HEYDEN, LUCAS, CYRIL, GERARD; VAN LOON, LUC) 18 March 2004 (2004-03-18) claims page 8, line 5 - page 10, line 2; examples 2,3 <div style="text-align: center;">----- -/--</div>	1-4,9, 10,12		
<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 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 </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 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
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	Date of mailing of the international search report			
11 October 2006	26/10/2006			
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Böhmerova, Eva			

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2005/050056

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>HERNANDEZ-LEDESMA BLANCA ET AL: "Angiotensin converting enzyme inhibitory activity in commercial fermented products. Formation of peptides under simulated gastrointestinal digestion." JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, vol. 52, no. 6, 24 March 2004 (2004-03-24), pages 1504-1510, XP008057959 ISSN: 0021-8561 abstract 'Stimulation of gastrointestinal digestion' tables 1,2</p>	1-5,7
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X	<p>DATABASE WPI Section Ch, Week 200316 Derwent Publications Ltd., London, GB; Class B04, AN 2003-160072 XP002402536 & JP 2002 284668 A (COSMO PROD KK) 3 October 2002 (2002-10-03) abstract</p>	1,2
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INTERNATIONAL SEARCH REPORT

International application No
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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>LEMIEUX L ET AL: "APPLICATION OF REVERSED-PHASE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY TO THE SEPARATION OF PEPTIDES FROM PHOSPHORYLATED ANDDEPHOSPHORYLATED CASEIN HYDROLYSATES" JOURNAL OF CHROMATOGRAPHY, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 473, no. 1, 1989, pages 189-206, XP009070046 ISSN: 0021-9673 tables 1,2 abstract</p>	1-5,7
X	<p>LEMIEUX L ET AL: "SEPARATION OF A CASEIN HYDROLYZATE BY HPSEC WITH A NEW MOBILE PHASE AND CHARACTERIZATION OF PEPTIDES BY FABMS" ANALYTICA CHIMICA ACTA, ELSEVIER, AMSTERDAM, NL, vol. 352, no. 1 - 3, 10 October 1997 (1997-10-10), pages 399-409, XP009070061 ISSN: 0003-2670 abstract page 400, left-hand column, last paragraph - right-hand column, paragraph 4; table 1</p>	1-5,7
X	<p>VAN DER VEN CORNELLY ET AL: "Reversed phase and size exclusion chromatography of milk-protein-hydrolysates: Relation between elution from reversed phase column and apparent molecular weight distribution" INTERNATIONAL DAIRY JOURNAL, vol. 11, no. 1-2, 2001, pages 83-92, XP002401826 ISSN: 0958-6946 page 84, left-hand column, paragraph 4 - page 85, right-hand column, paragraph 1; table 4</p>	1-5,7
X	<p>LEMIEUX L ET AL: "HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY OF CASEIN HYDROLYSATES PHOSPHORYLATED AND DEPHOSPHORYLATED" JOURNAL OF CHROMATOGRAPHY, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 519, no. 2, 2 November 1990 (1990-11-02), pages 299-321, XP009070060 ISSN: 0021-9673 abstract page 300, paragraph 3 - page 302, paragraph 1; table II</p>	1-5,7

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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>PERPETUO E A ET AL: "Biochemical and pharmacological aspects of two bradykinin-potentiating peptides obtained from tryptic hydrolysis of casein" JOURNAL OF PROTEIN CHEMISTRY, vol. 22, no. 7-8, November 2003 (2003-11), pages 601-606, XP002980616 ISSN: 0277-8033 abstract page 602, right-hand column, paragraph 5 - page 603, left-hand column, paragraph 1</p>	1-5,7
X	<p>LANGE C ET AL: "Global expression profiling and physiological characterization of Corynebacterium glutamicum grown in the presence of L-valine." APPLIED AND ENVIRONMENTAL MICROBIOLOGY, vol. 69, no. 5, May 2003 (2003-05), pages 2521-2532, XP002401827 ISSN: 0099-2240 abstract page 2528, left-hand column, last paragraph - page 2529, left-hand column, paragraph 1</p>	7
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International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	----- WO 03/002593 A (PROBIODRUG AG; DEMUTH, HANS, ULRICH; HOFFMANN, TORSTEN; MANHART, SUSAN) 9 January 2003 (2003-01-09) claims page 3, line 11 - line 25; tables 1-3,8,9	7-14
A	----- US 2004/152745 A1 (JACKSON PAUL ET AL) 5 August 2004 (2004-08-05) claims paragraphs [0010] - [0014]	7-14
A	----- US 2001/020006 A1 (DEMUTH HANS-ULRICH ET AL) 6 September 2001 (2001-09-06) paragraphs [0014] - [0022]	7-14
P,X	----- WO 2005/081628 A (CHAY 13 MEDICAL RES GROUP N V [NL]; SIDELMAN ZVI [IL]) 9 September 2005 (2005-09-09) page 10, line 21 - page 21, line 16 page 61, line 3 - page 62, line 19	1-3,5-13
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

The present claims 1-6,9-14 encompass products uses of an agent defined only by its desired function - a protein hydrolysate having DPP-IV inhibiting activity, contrary to the requirements of clarity of Article 6 PCT, because the result-to-be-achieved type of definition does not allow the scope of the claim to be ascertained. The fact that any protein hydrolysate could be screened does not overcome this objection, as the skilled person would not have knowledge beforehand as to whether it would fall within the scope claimed. Undue experimentation would be required to screen hydrolysates randomly. The claims cover all products having this characteristic whereas the application provides support within the meaning of Art. 6 PCT and/or disclosure within the meaning of Art. 5 PCT for only a very limited number of such products. I

Furthermore, the product itself is defined by the preparation thereof - a protein hydrolysate (so-called product-by-process claim) which renders the scope of the protection sought further unclear. Due to the combination of a product-by-process definition and a result-to be achieved definition the claims so lack clarity and support and the application so lacks disclosure that a meaningful search over the whole scope of the claims is impossible. Thus, the search has been limited to the embodiments which appear to be clear and disclosed - protein hydrolysates, preferably casein hydrolysates, containing peptides having a length of 2-8 amino acids comprising at least one proline residue, preferably the peptides of claims 5-8, and the hydrolysates prepared in the examples.

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.

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Box 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:
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 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:

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/NL2005/050056

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