

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 July 2008 (10.07.2008)

PCT

(10) International Publication Number
WO 2008/081463 A3

- (51) International Patent Classification:
A61K 47/48 (2006.01) A61P 43/00 (2006.01)
- (21) International Application Number:
PCT/IL2008/000033
- (22) International Filing Date: 6 January 2008 (06.01.2008)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/878,391 4 January 2007 (04.01.2007) US
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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
- the filing date of the international application is within two months from the date of expiration of the priority period

- (88) Date of publication of the international search report:
31 December 2008

(54) Title: WATER SOLUBLE REACTIVE DERIVATIVES OF CARBOXY POLYSACCHARIDES AND FIBRINOGEN CONJUGATES THEREOF

(57) Abstract: The present invention provides water-soluble reactive esters of carboxy polysaccharides and derivatives thereof. The reactive carboxy polysaccharide derivatives are useful per se in aqueous solutions or specifically for the formation of water-soluble covalent fibrinogen conjugates. A preferred conjugate is a hyaluronic acid-fibrinogen conjugate and fibrin adhesive, clot or matrix derived from it. Methods of preparation and methods of use in tissue repair and regeneration are disclosed.



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INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2008/000033

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K47/48 A61P43/00

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)
 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, BIOSIS, EMBASE, COMPENDEX

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 325 270 A (GREEN CROSS CORP [JP]) 26 July 1989 (1989-07-26) the whole document claims 1-7	1,2,9, 10,12, 13,15-18
Y	ALMANY L ET AL: "Biosynthetic hydrogel scaffolds made from fibrinogen and polyethylene glycol for 3D cell cultures" BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB, vol. 26, no. 15, 1 May 2005 (2005-05-01), pages 2467-2477, XP004673411 ISSN: 0142-9612 abstract	1-18

Further documents are listed in the continuation of Box C.

See patent family annex.

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| <p>* Special categories of cited documents :</p> <ul style="list-style-type: none"> *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 | <ul style="list-style-type: none"> *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. *Z* document member of the same patent family |
|--|---|

Date of the actual completion of the international search 31 October 2008	Date of mailing of the international search report 06/11/2008
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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 Orlando, Michele
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2008/000033

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BULPITT P ET AL: "NEW STRATEGY FOR CHEMICAL MODIFICATION OF HYALURONIC ACID: PREPARATION OF FUNCTIONALIZED DERIVATIVES AND THEIR USE IN THE FORMATION OF NOVEL BIOCOMPATIBLE HYDROGELS" JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, WILEY, NEW YORK, NY, US, vol. 47, no. 2, 1 January 1999 (1999-01-01), pages 152-169, XP000913609 ISSN: 0021-9304 the whole document	19-25, 29,74, 77-79
Y	page 156, column 1, paragraph 2; figure 2 page 166, column 2, paragraph 3 - page 168, column 1, paragraph 1	31-37
X	LUO Y ET AL: "HYALURONIC ACID-N-HYDROXYSUCCINIMIDE: A USEFUL INTERMEDIATE FOR BIOCONJUGATION" BIOCONJUGATE CHEMISTRY, ACS, WASHINGTON, DC, US, vol. 12, 1 January 2001 (2001-01-01), pages 1085-1088, XP001222037 ISSN: 1043-1802	19-24, 29,74, 77,78
Y	the whole document page 1085, column 2, paragraphs 2,4; figure 1	22-28
Y	WO 92/20349 A (GENZYME CORP [US]) 26 November 1992 (1992-11-26) the whole document page 5, lines 6-12; example 1	22-28
Y	WO 00/16818 A (AESCHLIMANN DANIEL [GB]; BULPITT PAUL [GB]) 30 March 2000 (2000-03-30) the whole document page 8, line 3 - page 9, line 14; example 9	31-37
Y	WO 95/24429 A (FIDIA ADVANCED BIOPOLYMERS SRL [IT]; RIGHETTO ZEFFERINO [IT]; BELLINI) 14 September 1995 (1995-09-14) the whole document page 6, line 20 - page 7, line 31 examples 1-11 page 11, lines 8-13	22-25, 27,28
Y	US 5 209 776 A (BASS LAWRENCE S [US] ET AL) 11 May 1993 (1993-05-11) the whole document column 4, lines 33-57; claims 1-22	1-18
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2008/000033

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/100440 A (BARTHOLDY CONSULTADORA E SERV [PT]; VOLPATO IVO [IT]; BIZZINI BERNARD) 19 December 2002 (2002-12-19) the whole document page 31, line 25 - page 32, line 9 -----	1-18
P,A	WO 2007/102149 A (PROCHON BIOTECH LTD [IL]; AMIT BOAZ [IL]; WORTZEL AVRAHAM [IL]; YAYON) 13 September 2007 (2007-09-13) page 12, lines 13-23 -----	
A	US 2006/159733 A1 (PENDHARKAR SANYOG M [US] ET AL) 20 July 2006 (2006-07-20) claims 1,3,10 -----	
A	EP 0 111 311 A (NIHON MEDIPHYSICS CO LTD [JP]) 20 June 1984 (1984-06-20) -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2008/000033

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.:

1-37, 74-79
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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-18

A water-soluble carboxy polysaccharide-fibrinogen conjugate comprising an amide bond between a carboxylic functional group of the polysaccharide and an amino functional group of the fibrinogen. Excluding the subject-matter of inventions 2-4.

2. claims: 19-37,74-79

An aqueous solution comprising a carboxy polysaccharide active ester, wherein the solution is substantially free of an activator, and a method for the preparation of the same. Excluding the subject-matter of inventions 1, 3 and 4.

3. claims: 38-55

A carboxy polysaccharide-fibrin clot comprising a water-soluble carboxy polysaccharide-fibrinogen conjugate and thrombin, wherein said conjugate comprises an amide bond between a carboxylic functional group of the polysaccharide and an amino functional group of the fibrinogen. Excluding the subject-matter of inventions 1, 2 and 4.

4. claims: 56-73

A porous fibrin matrix comprising a carboxy polysaccharide-fibrin clot comprising a water-soluble carboxy polysaccharide-fibrinogen conjugate, wherein the conjugate comprises an amide bond between a carboxy functional group of the polysaccharide and an amino functional group of the fibrinogen. Excluding the subject-matter of inventions 1-3.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IL2008/000033

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