



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁵ : C07H 9/06, 13/04, 15/04 C07H 15/12, A61K 47/48	A3	(11) International Publication Number: WO 91/18911 (43) International Publication Date: 12 December 1991 (12.12.91)
(21) International Application Number: PCT/US91/03687 (22) International Filing Date: 24 May 1991 (24.05.91) (30) Priority data: 529,343 25 May 1990 (25.05.90) US (71) Applicant: GENZYME CORPORATION [US/US]; One Kendall Square, Cambridge, MA 02139 (US). (72) Inventors: COLON, Marcelo ; BO. Jaquas BZ 280, Gurabo, Puerto Rico 00658 (US). DAVIS, Jeffrey, T. ; 14 Hovey Street, Watertown, MA 02172 (US). RASMUSSEN, James, R. ; 75-83 Cambridge Parkway E411, Cambridge, MA 02142 (US). BOROWSKI, Marianne ; 437 Marlborough Street, Boston, MA 02115 (US). WAN, Barbara, Y. ; 83 Willow Street, Tewksbury, MA 01876 (US). HIRANI, Shirish ; 130 Dartmouth Street, #703, Boston, MA 02116 (US).	(74) Agents: SUNSTEIN, Bruce, D. et al.; Bromberg & Sunstein, 10 West Street, Boston, MA 02111 (US). (81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 14 May 1992 (14.05.92)	
(54) Title: OLIGOSACCHARIDE OXAZOLINES, OLIGOSACCHARIDE CONJUGATES AND METHODS OF PREPARATION THEREOF		
(57) Abstract <p>This invention relates to a method of producing peracetyloxazolines from peracetyl saccharides. The method involves reacting the starting material, a peracetyl saccharide, with a reagent combination, to directly produce the peracetyl oxazoline. This method may be used for the activation of oligosaccharides, wherein an oligosaccharide containing a reducing GlcNAc terminus is activated by the formation of an oxazoline at the terminal GlcNAc, and then coupled with a bifunctional spacer to provide an oligosaccharide-spacer conjugate. The activated oligosaccharide-spacer conjugate is then coupled to a protein, such as granulocyte colony stimulating factor or γ-interferon, providing a neoglycoprotein conjugate. The invention provides a method for forming neoglycoprotein conjugates which may improve biological and physicochemical properties of the protein. For example, serum lifetime or efficiency of drug delivery of the peptide to a target organ or cell may be improved.</p>		

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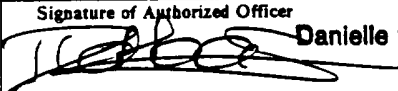
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+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

INTERNATIONAL SEARCH REPORT

International Application No **PCT/US 91/03687**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.C1.5 C 07 H 15/12	C 07 H 9/06 A 61 K 47/48	C 07 H 13/04 C 07 H 15/04
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.C1.5	C 07 H 9/00 A 61 K 47/00	C 07 H 13/00 C 07 H 15/00
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	WO,A,8804323 (GENZIME CORP.) 16 June 1988, see figures 2-5; page 16, line 22 - page 20, line 14; examples 1-4 ---	16-25, 27
X	EP,A,0098252 (SVENSKA SOCKERFABRIKS AB) 11 January 1984, see page 57, figure 2; page 23, line 1 - page 24, line 12; page 28, line 25 - page 29, line 4; examples 48-50; claims 1,10 ---	1-6,16, 17,24, 28,34, 39,42,7 ,10
X	Carbohydrate Research, vol. 124, 1983, (Amsterdam, NL), B. MARIO PINTO et al.: "Preparation of glycoconjugates for use as artificial antigens: A simplified procedure", pages 313-318, see scheme 1; table 1 --- -/-	16-18, 23-25,7 ,8,10
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"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</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"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.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
02-10-1991	07.04.92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	 Danielle van der Haas	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	Carbohydrate Research, vol. 174, 1988, (Amsterdam, NL), S. NAKABAYASHI et al.: "The preparation of a partially protected heptasaccharide-asparagine intermediate for glycopeptide synthesis", pages 279-289, see the whole document ---	1,16,48 -50,58-62
P,X	Journal of Organic Chemistry, vol. 55, no. 12, 8 June 1990, (Easton, US), G. MAGNUSSON et al.: "Prespacer glycosides in glycoconjugate chemistry. Dibromoisobutyl glycosides for the synthesis of neoglycolipids, neoglycoproteins, neoglycoparticles, and soluble glycosides", pages 3932-3946, see scheme I; chart I; scheme II ---	1,2,16, 34,48-50,7,10
P,X	Angewandte Chemie, International Edition in English, vol. 29, no. 9, September 1990, (Weinheim, DE), W. GÜNTHER et al.: "Synthesis of a beta-mannosyl-chitobiosyl-asparagine conjugate - A central core region unit of the N-glycoproteins", pages 1050-1051, see the whole document ---	1,16,48 -50
X	Journal of the American Chemical Society, vol. 97, no. 14, 9 July 1975, (Washington, DC, US), R. LEMIEUX et al.: "The properties of a "synthetic" antigen related to the human blood group lewis A", pages 4076-4083, see page 4077 -----	16,17, 18,23, 24,25, 28,7,8, 10

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

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

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

2. Claim numbers _____ 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. Claim numbers _____ because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 8.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

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

1. Claims 1-6, 16-62 For further information please see form PCT/ISA/206 dated by 24.10.1991
2. Claims 7-15

1. As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application
2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims: _____
3. 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 claim numbers: _____
1-6, 16-62
4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

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

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

US 9103687
SA 48387

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 25/03/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8804323	16-06-88	EP-A- 0299007	18-01-89
EP-A- 0098252	11-01-84	JP-A- 59025399	09-02-84
		US-A- 4675392	23-06-87