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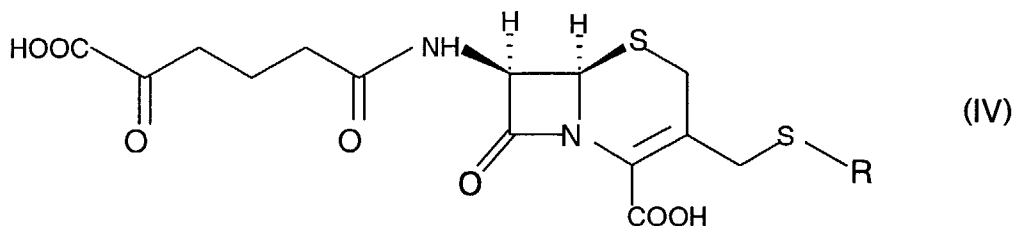
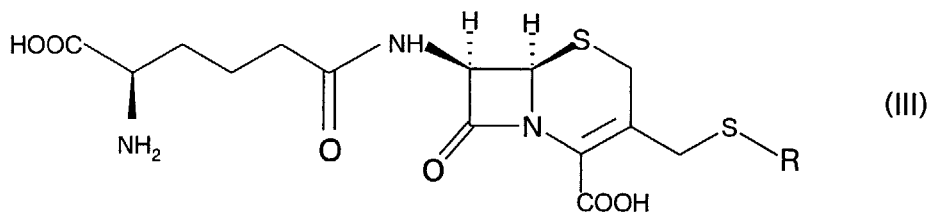
01201426.2	19 April 2001 (19.04.2001)	EP
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(54) Title: ENZYMATIC PROCESS FOR PREPARING CEPHALOSPORANIC ACID DERIVATIVES USING α -KETOACID DERIVATIVES(57) Abstract: A process for preparing cephalosporanic acid derivatives comprises the steps of enzymatically converting a 3-thiolated cephalosporin C compound of formula (III) into a 3-thiolated- α -ketoadipyl-7-aminocephalosporanic acid derivative of formula (IV), wherein R is a heterocyclic group comprising at least a nitrogen atom. Compounds of formula (IV) are used in the preparation of cephalosporin C antibiotics and derivatives thereof.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D501/04 C07D501/36 C12P35/06

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 C07D

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)

CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 19 39 341 A (GLAXO LABORATORIES LTD.) 5 February 1970 (1970-02-05) claims 1-40; example 13 ---	1-65
Y	CH 520 709 A (GLAXO LABORATORIES LTD.) 31 March 1972 (1972-03-31) claims 1-39 ---	29, 40-58
Y	BIOTECHNOLOGY AND BIOENGINEERING, vol. 46, no. 6, 1995, pages 510-513, XP001093638 tables I-IV ----- -/--	1-65



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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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

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G document member of the same patent family

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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	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 1198450 XP002211689 abstract & DE 21 37 386 A (TAKEDA CHEM. IND.) 31 May 1972 (1972-05-31)	55
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 600138 XP002211691 abstract & DE 22 39 947 A (TAKEDA CHEM. IND.) 15 March 1973 (1973-03-15)	55
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 599207 XP002211690 abstract & CH 601 312 A (FUJISAWA PHARM.) 14 July 1978 (1978-07-14)	55,56
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 1097400,1062954,1061615 XP002213731 abstract & ZA 6 802 695 A (FUJISAWA PHARM. CO.) 1967	55,56
X	DE 23 32 045 A (FUJISAWA PHARMACEUTICAL CO. LTD.) 10 January 1974 (1974-01-10) claims 16,19	40-58, 61,62
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 1063938 XP002213732 abstract & JP 04 638007 A (SUGIMOTO KEIITI ET AL.) 1976	55
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INTERNATIONAL SEARCH REPORT

ational Application No
PCT/EP 02/04353

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 26 26 026 A (MERCK PATENT GMBH) 22 December 1977 (1977-12-22) claim 1 ----	40-56
X	O. H. JUSTIZ ET AL.: "One-Pot Chemoenzymatic Synthesis of 3'-Functionalized Cephalosporins (Cefazolin) by Three Consecutive Biotransformations in Fully Aqueous Medium" J. ORG. CHEM., vol. 62, no. 26, 1997, pages 9099-9106, XP002177920 cited in the application * Schemes 4 & 5 * ----	1-65
Y	EP 0 496 993 A (ANTIBIOTICOS S.P.A.) 5 August 1992 (1992-08-05) claims 1-12 ----	1-65
Y	WO 00 78989 A (ANTIBIOTICS, S.A.U.) 28 December 2000 (2000-12-28) claims 1-37 ----	1-65
Y	EP 0 517 200 A (MINISTERO DELL' UNIVERSITA' E DELLA RICERCA SCIENTIFICA E TECNOLOGICA) 9 December 1992 (1992-12-09) claims 1-10 ----	1-65
Y	EP 0 583 817 A (ASAHI KASEI KOGYO KABUSHIKI KAISHA) 23 February 1994 (1994-02-23) claims 1-12 ----	1-15, 21-28, 30-39, 55-60, 63-65
Y	EP 0 492 495 A (HOECHST AG) 1 July 1992 (1992-07-01) claims 1-6 ----	1-15, 21-65
Y	GB 1 385 685 A (GLAXO LABORATORIES, LTD.) 26 February 1975 (1975-02-26) cited in the application claims 1-40 ----	1-15, 21-65
Y	J. E. BALDWIN ET AL.: "Cleavage of the 5-amino-5-carboxy-2-oxapentanoyl side chain from enzymatically synthesised penicillins and cephalosporins" BIOORG. MED. CHEM. LETT., vol. 5, no. 21, 1995, pages 2507-2512, XP002207185 * Schemes 2 & 4 * ----- -/--	1-65

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ational 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.
Y	PATENT ABSTRACTS OF JAPAN vol. 011, no. 322, 20 October 1987 (1987-10-20) & JP 62 107798 A (ASAHI CHEM. IND. CO., LTD.), 19 May 1987 (1987-05-19) abstract ---	1-28, 30-39, 55-60, 63-65
Y	PATENT ABSTRACTS OF JAPAN vol. 005, no. 152, 25 September 1981 (1981-09-25) & JP 56 085298 A (ASAHI CHEM. IND. CO., LTD.), 11 July 1981 (1981-07-11) abstract ---	1-15, 21-39, 55-65
X	CHEMICAL ABSTRACTS, vol. 86, no. 15, 11 April 1977 (1977-04-11) Columbus, Ohio, US; abstract no. 106611r, page 514; XP002207186 abstract -& JP 51 088694 A (TOYO JOZO CO., LTD.) 3 August 1976 (1976-08-03) ---	55-58
X	CHEMICAL ABSTRACTS, vol. 80, no. 13, 1 April 1974 (1974-04-01) Columbus, Ohio, US; abstract no. 70820t, page 348; XP002207187 abstract -& JP 48 075587 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 11 October 1973 (1973-10-11) ---	55-58
X	"The Merck Index on CD-ROM, Version 12:2" 1997, MERCK & CO. INC., WHITEHOUSE STATION, NJ, USA XP002177921 * Entries #1967, 2001, 1985, 1965, 1964, 1981 & 1966 * ---	55-57
Y	WO 90 12110 A (BIOPURE CORP.) 18 October 1990 (1990-10-18) page 3, line 13 - line 16; claims 1,10 ---	1-65
X	DE 20 56 983 A (CIBA-GEIGY AG) 9 June 1971 (1971-06-09) example 2 ---	29, 40-56, 61,62
Y	DE 19 53 861 A (FUJISAWA PHARMACEUTICAL CO. LTD.) 6 May 1971 (1971-05-06) claims 1-21 ---	1-65
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INTERNATIONAL SEARCH REPORT

tional 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.
Y	EP 0 436 355 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 10 July 1991 (1991-07-10) claims 1,3 -----	1-65
X	NL 6 411 521 A (GLAXO LABORATORIES LTD.) 5 April 1965 (1965-04-05) examples 3-5 -----	40-55