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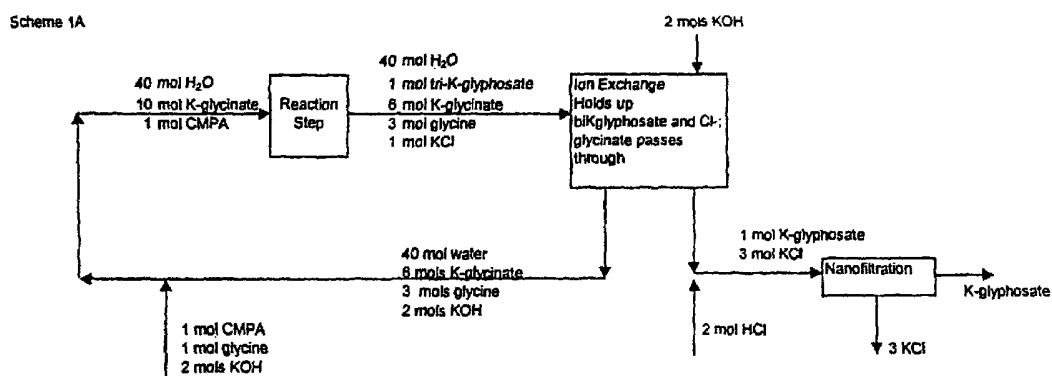
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, 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, NA, 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.

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[Continued on next page]

(54) Title: PROCESS FOR THE PREPARATION OF N-PHOSPHONO-METHYLGLYCINE AND DERIVATIVES THEREOF



(57) Abstract: N-phosphonomethylamines are produced by reaction of an amine substrate with a halomethylphosphonic acid or salt thereof, a hydroxymethylphosphonic acid or salt thereof, or a dehydrated self-ester dimer, trimer or oligomer of hydroxymethylphosphonic acid. Among the products that may be prepared according to the process are N-phosphonomethylaminocarboxylic acids such as (e.g.) glyphosate, N-phosphonomethylaminoalkanoles such as (e.g.) hydroxyethylaminomethylphosphonic acid, and N-acylaminoethylphosphonic acids such as (e.g.) N-carbamylaminomethylphosphonic acid. Certain reactions are conducted with a substantial excess of amine reactant in order to drive the conversion while avoiding excessive formation of bis(N-phosphonomethyl)amine by-products. Other reactions use a secondary amine substrate (such as iminodiacetic acid) and can be conducted at substantial equimolar ratios of halomethylaminomethylphosphonic acid or hydroxyaminomethylphosphonic acid to secondary amine reactant without significant formation of bis(phosphonomethyl)amine by-products. Further disclosed is a process for the preparation of hydroxymethylphosphonic acid self-ester dimers, trimers and oligomers by azeotropic dehydration.

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FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
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4 August 2005

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.

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- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

INTERNATIONAL SEARCH REPORT

Intern: Application No
PCT/US2004/027413

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07F9/38		
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 C07F		
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, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 661 298 A (MIRVISS ET AL) 28 April 1987 (1987-04-28) cited in the application Examples	1-75, 143-158
X	FR 2 276 312 A (BUDAPESTI VEGYIMUEK) 23 January 1976 (1976-01-23) cited in the application Ex. 1-2	1-75, 143-158
X	US 3 977 860 A (FRANZ ET AL) 31 August 1976 (1976-08-31) cited in the application Example 1	1-75, 143-158
X	FR 2 568 882 A (UNION EXPLOSIVOS RIO TINTO SA) 14 February 1986 (1986-02-14) Ex. 1-2	1-75, 143-158
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		
<input checked="" type="checkbox"/> 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	"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	
"E" earlier document but published on or after the international filing date	"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	
"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)	"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.	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search <div style="text-align: center; font-size: 1.2em;">12 May 2005</div>	Date of mailing of the international search report <div style="text-align: center; font-size: 1.2em;">03. 06. 2005</div>	
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 <div style="text-align: center; font-size: 1.2em;">Fritz, M</div>	

INTERNATIONAL SEARCH REPORT

Inter Application No

PCT/US2004/027413

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>HUANG ET AL.: JOURNAL OF NANJING INSTITUTE OF FORESTRY, 1984, pages 43-59, XP009043652 NANJING, PRC cited in the application p. 44, reaction equations the whole document</p> <p>-----</p>	1-75, 143-158
X	<p>CAMERON ET AL.: "Organophosphorous compounds as potential fungicides. Part I." PHOSPHOROUS AND SULFUR, vol. 40, 1988, pages 183-198, XP009047520 Scheme 1</p> <p>-----</p>	76-139
X	<p>MAIER: "Organic phosphorous compounds 98. Synthesis and Properties of N-methylaminoethylphosphonic acid an derivatives" PHOSPHOROUS, SULFUR, AND SILICON, vol. 62, 1991, pages 29-34, XP009047521 p. 31, third reaction</p> <p>-----</p>	76-139
X	<p>HUDSON ET AL.: "An approach to the development of organophosphorous fungicides" PHOSPHOROUS, SULFUR, AND SILICON, vol. 109, 1996, pages 345-348, XP009047522 Scheme 1, first reaction equation</p> <p>-----</p>	76-139
X	<p>LOMBAERT ET AL.: "N-Phosphonomethyl Dipeptides and their Phosphonate Prodrugs, a New Generation of Neutral Endopeptidase (NEP, EC 3.4.24.11) Inhibitors" J. MED. CHEM., vol. 37, 1994, pages 498-511, XP002327949 Scheme 1, reaction 6 --> 7, variant a</p> <p>-----</p>	159
A	<p>AVILA ET AL.: "Chemical and Mutagenic Analysis of Aminomethylphosphonate Biodegradation" J. AM. CHEM. SOC., vol. 109, no. 22, 1987, pages 6758-6764, XP002327950 p. 6764, left col., 5th par. (synthesis of 2)</p> <p>-----</p>	160-187
X	<p>AVILA ET AL.: "Chemical and Mutagenic Analysis of Aminomethylphosphonate Biodegradation" J. AM. CHEM. SOC., vol. 109, no. 22, 1987, pages 6758-6764, XP002327950 p. 6764, left col., 5th par. (synthesis of 2)</p> <p>-----</p>	159
A	<p>AVILA ET AL.: "Chemical and Mutagenic Analysis of Aminomethylphosphonate Biodegradation" J. AM. CHEM. SOC., vol. 109, no. 22, 1987, pages 6758-6764, XP002327950 p. 6764, left col., 5th par. (synthesis of 2)</p> <p>-----</p>	160-187

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INTERNATIONAL SEARCH REPORT

Intern:	Application No
	PCT/US2004/027413

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DU S ET AL: "Synthesis and evaluation of putative oxocarbenium intermediate mimic in the KD08P synthase-catalyzed reaction as a tool for the design of potent inhibitors for lipopolysaccharide biosynthesis" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 7, no. 19, 7 October 1997 (1997-10-07), pages 2469-2472, XP004136466 ISSN: 0960-894X	159
A	Scheme 2; reaction step b (6 --> 7) -----	160-187
X	WALLACE E M ET AL: "DESIGN AND SYNTHESIS OF POTENT, SELECTIVE INHIBITORS OF ENDOTHELIN-CONVERTING ENZYME" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 41, 1998, pages 1513-1523, XP001094342 ISSN: 0022-2623	159
A	Scheme 4; reaction 20 --> 22 -----	160-187
Y	STORZ ET AL.: "N-Monoalkylation of Tetra-O-benzyl-D-arabinonamide: Synthesis of Some Open-Chain Analogues of N-Acetylneuraminic Acid and Their Evaluation as Sialidase Inhibitors" HELV. CHIM. ACTA, vol. 81, no. 10, 1998, pages 1896-1907, XP002327951 p. 1898, reaction of 9 to 13 -----	214-224
Y	US 2 328 358 A (PIKL JOSEF) 31 August 1943 (1943-08-31) p. 1, right col., lines 3-28 the whole document -----	214-224

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/027413

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.: 188-210
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:

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.:
1-139, 143-187, 211-224

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 188-210

Claims 188-210 could not be searched, as their subject-matter is not clear:

Independent claim 188 refers to a process for the preparation of a compound IV (this compound having groups R2, R3 and R4 which are not defined) by reacting an amino alcohol with a compound V which is, however, identical to compound IV,

i.e. these claims relate to a reaction wherein one of the starting materials is identical with the product, both molecules having substituents which are not defined.

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-75,143-158

Process for the preparation of N-phosphonomethyl glycine and derivatives thereof using halomethylphosphonic acid as starting material

2. claims: 76-139

Process for the preparation of hydroxy- and alkoxyalkylaminomethylphosphonic acid and derivatives thereof using halomethylphosphonic acid as starting material

3. claims: 140-142

Process for the preparation of tris(phosphonomethyl)amine using halomethylphosphonic acid as starting material

4. claims: 159-224

Process for the preparation of N-phosphonomethyl glycine and derivatives thereof using hydroxymethylphosphonic acid as starting material

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern.....pplication No

PCT/US2004/027413

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4661298	A	28-04-1987	NONE	
FR 2276312	A	23-01-1976	DE 2528633 A1 FR 2276312 A1 RO 65811 A1 YU 150475 A1	05-02-1976 23-01-1976 15-07-1979 30-06-1982
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern.....pplication No PCT/US2004/027413
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FR 2568882	A	FR 2568882 A1 GR 851956 A1 MX 160682 A	14-02-1986 09-12-1985 06-04-1990
US 2328358	A	31-08-1943	NONE