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- (71) Applicant (for all designated States except US): **WARWICK EFFECT POLYMERS LIMITED** [GB/GB]; Department of Chemistry, University of Warwick, Coventry, West Midlands CV4 7AL (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **HADDLETON, David** [GB/GB]; 3 Whitehead Drive, Kenilworth, Warwickshire CV8 2TP (GB). **LECOLLEY, Francois** [FR/GB]; Department of Chemistry, University of Warwick, Coventry CV4 7AL (GB). **TAO, Lei** [CN/GB]; Department of Chemistry, University of Warwick, Coventry CV4 7AL (GB). **MANTOVANI, Giuseppe** [IT/GB]; Department of Chemistry, University of Warwick, Coventry CV4 7AL (GB). **CARMICHAEL, Adrian** [GB/GB]; Department of Chemistry, University of Warwick, Coventry CV4 7AL (GB).
- (74) Agents: **ELSY, David** et al.; Withers & Rogers, Goldings House, 2 Hays Lane, London SE1 2HW (GB).
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(54) Title: LIVING RADICAL POLYMERIZATION INITIATOR COMPRISING A FUNCTIONAL GROUP CAPABLE OF REACTING WITH POLYPEPTIDES OR THE LIKE, COMB POLYMER OBTAINED THEREWITH, POLYPEPTIDE CONJUGATES AND DRUGS OBTAINED THEREFROM

(57) Abstract: The application provides a method of producing a comb polymer comprising the steps of: (a) Providing: (i) a plurality of monomers which are linear, branched or star-shaped, substituted or non-substituted, and have an olefinically unsaturated moiety, the olefinically unsaturated moiety being capable of undergoing addition polymerisation; (ii) an initiator compound; the initiator compound comprising a homolytically cleavable bond. (iii) a catalyst capable of catalysing the polymerisation of the monomer; and (b) Causing the catalyst to catalyse, in combination with the initiator, the polymerisation of a plurality of the monomers to produce the comb polymer Catalysts and polymers obtainable by the process are also provided. Preferably, the comb polymer is capable of binding proteins and may be produced from monomers which are alkoxy polyethers, such as poly(alkyleneglycol) or polytetrahydrofuran.



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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/GB2004/002608

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C08F2/38 C08F293/00 C08F299/02 C08F290/06 A61K47/48

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 C08F A61K

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, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/47661 A (UNIV WARWICK ; HADDLETON DAVID MARK (GB)) 18 December 1997 (1997-12-18) cited in the application claims 10-12; figure 7 -----	35, 36, 41
P, X	WO 03/062290 A (BIOCOMPATIBLES UK LTD ; LEWIS ANDREW LENNARD (GB)) 31 July 2003 (2003-07-31) examples 2-4, 10	35, 36
P, X	example 10 -----	37
E	WO 2004/063237 A (BIOCOMPATIBLES UK LTD ; LEPPARD SIMON WILLIAM (GB); LEWIS ANDREW LENNA) 29 July 2004 (2004-07-29) claim 43; examples 1a, 1b, 2-4 ----- -/--	35-41



Further documents are listed in the continuation of box C.



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
- *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.
- *G* document member of the same patent family

Date of the actual completion of the international search

4 February 2005

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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, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Wirth, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB2004/002608

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HADDLETON, DAVID M. ET AL: "Phenolic ester-based initiators for transition metal mediated living polymerization" MACROMOLECULES , 32(26), 8732-8739 CODEN: MAMOBX; ISSN: 0024-9297, 1999, XP002314659 page 8733, column 2; figure 7 -----	35-39, 41
X	NARAIN, RAVIN ET AL: "Direct Synthesis and Aqueous Solution Properties of Well-Defined Cyclic Sugar Methacrylate Polymers" MACROMOLECULES , 36(13), 4675-4678 CODEN: MAMOBX; ISSN: 0024-9297, 31 May 2003 (2003-05-31), XP002314660 figure 2 -----	1, 4-6, 8, 9, 13-16, 19, 22, 29, 31, 35-37, 41-43, 45
X	WANG, ARMES: "Facile atom transfer radical polymerization of methoxy capped oligo(ethylene glycol) methacrylate in aqueous media at ambient temperature" MACROMOLECULES, vol. 33, 2000, pages 6640-6647, XP002315896 figures 1, 11 -----	1-6, 8-11, 13, 14, 22, 29-31, 35, 36, 42-45
A	HADDLETON, PERRIER, BON: "Copper (I).mediated living radical polymerization in the presence pf oxyethylene groups: online 1H NMR spectroscopy to investigate solvents effects" MACROMOLECULES, vol. 33, 10 November 2000 (2000-11-10), pages 8246-8251, XP002295368 scheme1 -----	1-56
A	WANG X-S ET AL: "FACILE SYNTHESIS OF ACIDIC COPOLYMERS VIA ATOM TRANSFER RADICAL POLYMERIZATION IN AQUEOUS MEDIA AT AMBIENT TEMPERATURE" MACROMOLECULES, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 33, no. 2, 25 January 2000 (2000-01-25), pages 255-257, XP000898356 ISSN: 0024-9297 the whole document -----	1-56

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/002608

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:
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.:
subjects 1 and 2
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

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

1. claims: 1-56 (when the moiety capable of reacting with a peptide comprises a succinimidyl group)

In claim 37, the following groups are concerned:
 succinimidyl succinate, propionate, butanoate, N-hydroxy
 succinimidyl, succinimidyl carbonate;
 In claim 39, the 3rd, 8th, 9th, 10th formulas;
 In claim 41, the third, and fourth compounds

2. claims: 1-56 (when the moiety capable of reacting with a peptide is an aldehyde or a protected aldehyde)

In claim 37: propionaldehyde, acetaldehyde
 In claim 40: second formula;
 In claim 41: 7th and 8th formulas.

3. claims: 1-56 (when the moiety comprises a SO₂ group))

Claim 37: tresylate and vinyl sulfone
 Claim 39: second compound

4. claims: 1-56 (when the moiety comprises an aromatic group)

Claim 37: benzotriazole, triazine, pyridyl sulfide;
 Claim 39: first, 4th, 5th, 6th, 7th, 12th, 14th, 15th
 formulas;
 Claim 41: first, second formulas

5. claims: 1-56 (when the moiety comprises maleimide)

claim 37: maleimide
 claim 39: 13th formula
 claim 40: first and third formulas
 claim 41: 9th formula

6. claims: 1-56 (when the moiety is iodoacetamide)

Claim 37: iodoacetamide
 claim 39: 11th formula

7. claims: claims 1-56 (when the initiator is represented by the 5th formula of claim 41)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claim 41: 5th formula

8. claims: 1-56 (when the initiator is represented by the 6th
formula of claim 41)

claim 41: 6th formula

9. claims: 1-56 (when the initiator is represented by the 10th
formula of claim 41)

claim 41: 10th formula

10. claims: 1-56 (the initiator being represented by the 11th
formula of claim 41)

claim 41: 11th formula

11. claims: 1-12, 14 (part), 24-34, 35-36 (part), 42-56 (when the
initiator is a thioester containing
compound or a xanthate)

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB2004/002608

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9747661	A	18-12-1997	AT 207082 T	15-11-2001
			AU 735085 B2	28-06-2001
			AU 3099297 A	07-01-1998
			CA 2258006 A1	18-12-1997
			DE 69707452 D1	22-11-2001
			DE 69707452 T2	27-06-2002
			EP 0906342 A1	07-04-1999
			WO 9747661 A1	18-12-1997
			US 6310149 B1	30-10-2001
WO 03062290	A	31-07-2003	EP 1465933 A1	13-10-2004
			WO 03062290 A1	31-07-2003
WO 2004063237	A	29-07-2004	WO 2004063237 A1	29-07-2004