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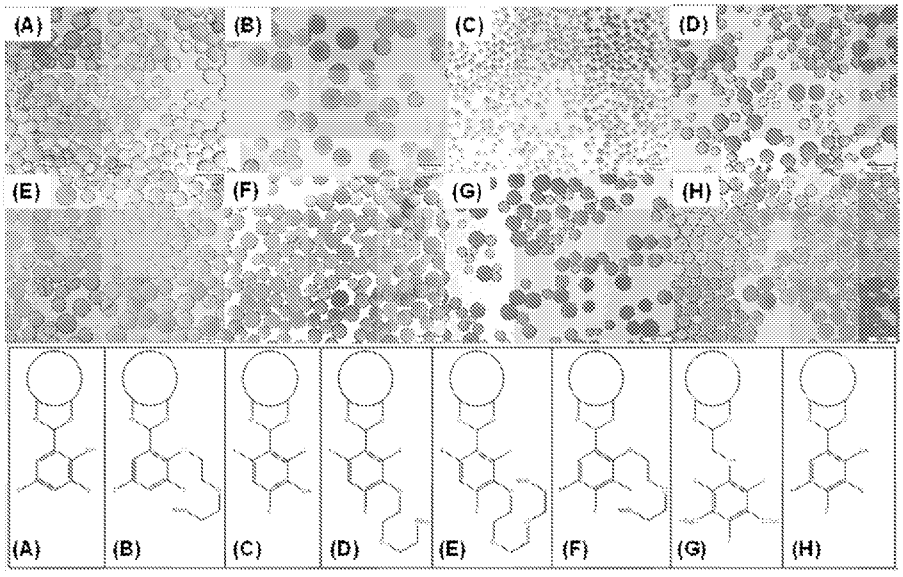
(54) Title: RADIOPAQUE POLYMERS

FIGURE 1



(57) Abstract: A hydrophilic polymer comprising pendent groups of the formula I: Wherein: W is independently selected from –OH, -COOH, $-SO_3H$, $-OPO_3H$, -O-(C_{1-4}alkyl), -O-(C_{1-4}alkyl)OH, -O-(C_{1-4}alkyl)R^2, -O-$(C_2H_5O)_qR^1$ –(C=O)-O-C_{1-4}alkyl and –O-(C=O)C_{1-4}alkyl; or a group –BZ; wherein –OH, COOH, O-PO_3H and SO_3H maybe in the form of a pharmaceutically acceptable salt; wherein: B is a bond, or a straight branched alkanediyl, oxyalkylene, alkylene oxaalkylene, or alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents; and Z is an ammonium, phosphonium, or sulphonium phosphate or phosphonate ester zwitterionic group; X is either a bond or a linking group having 1 to 8 carbons and optionally 1 to 4 heteroatoms selected from O, N and S; G is a coupling group through which the group of the formula I is coupled to the polymer and is selected from ether, ester, amide, carbonate, carbamate, 1,3 dioxolone, and 1,3 dioxane; R^1 is H or C_{1-4} alkyl; R^2 is –COOH, $-SO_3H$, or $–OPO_3H_2$ q is an integer from 1 to 4; n is an integer from 1 to 4; p is an integer from 1 to 3; and n + p is

WO 2020/003147 A3

[Continued on next page]

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(74) **Agent: RODGERS, Matthew, William**; BTG International Limited, 5 Fleet Place, London Greater London EC4M 7RD (GB).

(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, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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26 November 2020 (26.11.2020)

from 2 to 5; and wherein -COOH, $-OPO_3H_2$ and $-SO_3H$ as well as phenolic -OH maybe in the form of a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C08F8/48 C08F8/28 C08F8/30 C08F16/06 C08F20/06
C08L101/14 A61K49/04 C08L29/04 A61K9/16 A61K31/704
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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)
C08F C08L A61K A61L

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 practicable, 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 4 406 878 A (DEBOER CHARLES D [US]) 27 September 1983 (1983-09-27) claims 1-3; example column 2, lines 33-49 column 3, line 5 - column 6, line 49 -----	1-12,14, 15, 17-19, 21-23
X	CN 105 968 244 A (UNIV HENAN TECHNOLOGY) 28 September 2016 (2016-09-28) paragraphs [0032] - [0033]; claims 1-4; examples 10-11 ----- -/--	1,2, 4-11,14, 17-19

[X] Further documents are listed in the continuation of Box C.

[X] See patent family 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 application or patent 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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hollender, C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2019/055382

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.:

1-19, 26-34(completely); 21-25(partially)

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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/055382

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/115023 A1 (BIOSPHERE MEDICAL INC [US]) 21 July 2016 (2016-07-21) claims 1,4-9,12-16,18,19,20,21 paragraphs [0054], [0055], [0057], [0059], [0060] paragraphs [0078] - [0079]; examples 1-12,14-16; tables 1-4	1,3,7,8, 10,11, 14-19, 21-23, 25,26
X	EP 0 436 316 A1 (SOVAK MILOS [US]) 10 July 1991 (1991-07-10) claims 7-10; examples 15-21; table 1 page 3, lines 14-17	1,3,7,8, 10,11, 14,15, 17-19, 23,24
X	ERIC BROWN ET AL: "Syntheses and copolymerization of new water-soluble polyiodinated acrylic monomers", MAKROMOLEKULARE CHEMIE, RAPID COMMUNICATIONS,, vol. 6, no. 7, July 1985 (1985-07), pages 503-507, XP002761672, ISSN: 0173-2803, DOI: 10.1002/MARC.1985.030060709 the whole document	1,3, 7-11, 14-19, 23,24
A	ASHRAFI KOOROSH ET AL: "Characterization of a novel intrinsically radiopaque Drug-eluting Bead for image-guided therapy: DC Bead LUMI(TM)", JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 250, 8 February 2017 (2017-02-08), pages 36-47, XP029953355, ISSN: 0168-3659, DOI: 10.1016/J.JCONREL.2017.02.001 the whole document	1,2,4-8, 13-19, 21-25
X	TALEKAR, RAHUL SUBHASH ET AL: "Nonreductive Deiodination of ortho-Iodo-Hydroxylated Arenes Using Tertiary Amines", JOURNAL OF ORGANIC CHEMISTRY , 70(21), 8590-8593 CODEN: JOCEAH; ISSN: 0022-3263, 2005, XP055732156, DOI: 10.1021/JO051191X abstract table 2, reagent 10f	29,30

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/055382

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PAUL R. JONES ET AL: "The role of substituents and solvents in promoting "medium-size" ring-chain tautomerism", JOURNAL OF ORGANIC CHEMISTRY, vol. 55, no. 12, 1 June 1990 (1990-06-01), pages 3891-3896, XP055733291, US ISSN: 0022-3263, DOI: 10.1021/jo00299a036 page 3891, compounds C-11 and C-17	31,32
X	STEPHEN HORNE ET AL: "The Regiospecific p-Deiodination of 2,4-Di-iodo Phenols; a New Synthesis of Aflatoxin B2", JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, vol. 1, 1990, pages 39-41, XP055733258, GB ISSN: 0022-4936, DOI: 10.1039/c39900000039 scheme 1, table 1, entry 2	31
X	J H WILKINSON ET AL: "The Biological Action of Substances Related to Thyroxine. 3. SUBSTANCES DERIVED FROM 3,5-DIIODO-4-HYDROXYBENZALDEHYDE AND RELATED COMPOUNDS", BIOCHEMICAL JOURNAL, vol. 49, 1951, pages 714-718, XP055733263, ISSN: 0264-6021, DOI: 10.1042/bj0490714 tables 1-2	31
X	PI-TAI CHOU ET AL: "Studies of the triplet state of the proton-transfer tautomer in salicylaldehydes", CHEMICAL PHYSICS LETTERS, vol. 370, no. 5-6, 21 March 2003 (2003-03-21), pages 747-755, XP055733286, NL ISSN: 0009-2614, DOI: 10.1016/S0009-2614(03)00165-9 figure 1; table 1	31
X	PISCOPO, EUGENIO ET AL: "Experimental observations on the iodination of phenolic compounds for the synthesis of intermediates of pharmaceutical chemical interest", BOLLETTINO - SOCIETA ITALIANA DI BIOLOGIA SPERIMENTALE , 59(1), 44-50 CODEN: BSIBAC; ISSN: 0037-8771, 1983, XP009523103,	31
A	tables I,II	27,28

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/055382

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BOUGAULT, J. ET AL: "Some halogenated derivatives of salicylic aldehyde. II. Preparation of 3,5-diiodoacetylsalicylaldehyde and of the diacetyl acetals of 5-bromo and 3,5-diiodoacetylsalicylaldehyde. Pharmacodynamic data on these compounds", BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE 630-2 CODEN: BSCFAS; ISSN: 0037-8968, 1949, XP009523104, page 630, compounds IIb and IVb ----	31
X	COVELLO, M. ET AL: "New synthetic iodo-organic compounds: o-alkoxybenzaldehydes, o-alkyloxyacetophenones, and iodine-containing analogs", FARMACO, EDIZIONE SCIENTIFICA , 19(8), 675-87 CODEN: FRPSAX; ISSN: 0430-0920, 1964, XP009523105, abstract table II, compounds XVII-XVIII ----	31
A	PISCOPO, EUGENIO ET AL: "New synthetic iodine-containing organic compounds. 3,4,5-Triiodosalicylic acid and derivatives", RENDICONTO DELL'ACCADEMIA DELLE SCIENZE FISICHE E MATEMATICHE, NAPLES , VOLUME DATE 1980, 47, 253-62 CODEN: RASFAM; ISSN: 0370-3568, 1981, XP009523109, abstract page 254, scheme A, compound (I) page 256, scheme B ----	27,28
A	JP H06 345705 A (TERUMO CORP) 20 December 1994 (1994-12-20) paragraph [0018] ----	33,34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2019/055382

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4406878 A	27-09-1983	NONE	
CN 105968244 A	28-09-2016	NONE	
WO 2016115023 A1	21-07-2016	AU 2016206983 A1	13-07-2017
		EP 3245236 A1	22-11-2017
		EP 3660061 A1	03-06-2020
		US 2016200670 A1	14-07-2016
		US 2019231908 A1	01-08-2019
		WO 2016115023 A1	21-07-2016
EP 0436316 A1	10-07-1991	AU 637435 B2	27-05-1993
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		JP H04208232 A	29-07-1992
JP H06345705 A	20-12-1994	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 3, 26(completely); 1, 2, 4-12, 14-19, 21-25(partially)

A hydrophilic polymer comprising pendant groups of the formula I (see independent claim 1) wherein G is a coupling group through which the group of the formula I is coupled to the polymer and is selected from an ether, an ester, an amide, a carbonate and a carbamate.
A polymer according to the dependent claims 4-12, 14-19 wherein G is selected from an ether, an ester, an amide, a carbonate and a carbamate coupling group in formula I or G is selected from an ether, an ester, a carbonate and a carbamate coupling group in Formula Ia (see claim 6).
A polymer according to dependent claim 2 wherein G is selected from an ether, an ester, a carbonate and a carbamate coupling group in Formula I.
A polymer according to dependent claim 3 wherein G is selected from an ester and an amide coupling group in Formula I.
A polymer as defined above which additionally comprises a pharmaceutical active ingredient.
A microsphere comprising a polymer as defined above.
A flowable composition comprising a polymer as defined above.
A composition comprising a polymer as defined above as a solution in either an aqueous or organic solvent which is miscible with water.
A method of treatment comprising delivering a polymer as defined above to a blood vessel of a subject in need thereof, such as to form an embolus.

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2. claims: 13, 27-34(completely); 1, 2, 4-12, 14-19, 21-25(partially)

A hydrophilic polymer comprising pendant groups of the formula I (see independent claim 1) wherein G is a coupling group through which the group of the formula I is coupled to the polymer and is selected from a 1,3 dioxolane and 1,3 dioxane group.
A polymer according to the dependent claims 2 and 4-19 wherein G is selected from a 1,3 dioxolane coupling group and a 1,3 dioxane coupling group in formula I, formula Ib (see claim 6) or formula 1c (see claim 13).
A polymer as defined above which additionally comprises a pharmaceutical active ingredient.
A microsphere comprising a polymer as defined above.
A flowable composition comprising a polymer as defined above.
A composition comprising a polymer as defined above as a solution in either an aqueous or organic solvent which is miscible with water.
A method of treatment comprising delivering a polymer as

defined above to a blood vessel of a subject in need thereof, such as to form an embolus.
Compounds as defined in independent claims 27, 29, 31 and 33 and their respective dependent claims 28, 30, 32 and 34 (which comprise a precursor group M allowing the formation of 1,3 dioxolane and 1,3 dioxane coupling groups when reacted with a hydrophilic polyhydroxylated polymer).

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3. claims: 20(completely); 21-25(partially)

A polymer according to any of claims 1-19 which is substituted by groups other than those in W (see formula I in claim 1 for the meaning of W), which are charged at pH 7.4.
A polymer according to claim 20 which additionally comprises a pharmaceutical active ingredient.
A microsphere comprising a polymer as defined above.
A flowable composition comprising a polymer as defined above.
A composition comprising a polymer as defined above as a solution in either an aqueous or organic solvent which is miscible with water.
A method of treatment comprising delivering a polymer as defined above to a blood vessel of a subject in need thereof, such as to form an embolus.
