

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 March 2012 (29.03.2012)

PCT

(10) International Publication Number
WO 2012/040138 A3

(51) International Patent Classification:

C07C 213/00 (2006.01) C07C 215/08 (2006.01)
C07C 213/02 (2006.01) C07C 217/10 (2006.01)
C07C 213/06 (2006.01)

(21) International Application Number:

PCT/US2011/052253

(22) International Filing Date:

20 September 2011 (20.09.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/384,882 21 September 2010 (21.09.2010) US

(71) Applicants (for all designated States except US): **GE HEALTHCARE LIMITED** [GB/GB]; Amersham Place, Little Chalfont Buckinghamshire HP7 9NA (GB). **IMPERIAL COLLEGE** [GB/GB]; 52 Princes Gate, South Kensington SW7 2PG (GB).

(71) Applicant (for MG only): **MEDI-PHYSICS, INC.** [US/US]; 101 Carnegie Center, Princeton, NJ 08540 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ABOAGYE, Eric, Ofori** [GB/GB]; Imperial College of Science Technology & Medicine, Hammersmith Hospital Campus, Du Cane Road, London W12 0NN (GB). **ROBINS, Edward, George** [GB/SG]; Singapore Bioimaging Consortium, Agency, for Science Technology and Research, 11 Biopolis Way #02-02 Helios Building, Singapore 138667 (SG). **SMITH, Graham** [GB/GB]; Imperial College, Hammersmith Hospital Campus, Du Cane Road, London W12 0NN (GB). **ZHAO, Yongjun** [CN/CN]; 4-1201, Jin-Chen Star, Su Zhou Industrial Park, Qi Hong Road, Jiang Su Province, 215121 (CN). **LEYTON, Julius** [GB/GB]; Imperial College, Hammersmith Hospital Campus, Du Cane Road, London W12 0NN (GB). **TURTON, David** [GB/GB]; Hammersmith Imanet Limited, Cyclotron Building, Hammersmith Hospital, Du Cane Road,

London W12 0NN (GB). **WILSON, Anthony** [GB/GB]; 1 Wood Street, Waddesdon Buckinghamshire HP18 0LL (GB). **BHALLA, Rajiv** [GB/GB]; GE Healthcare Limited, The Grove Centre, White Lion Road, Amersham Buckinghamshire HP7 9LL (GB). **BRICKUTE, Diana** [GB/GB]; 138 Brookscroft Road, London E17 4JR (GB).

(74) Agents: **LEE, Christine** et al.; GE Healthcare, Inc., 101 Carnegie Center, Princeton, NJ 08540 (US).

(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, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(88) Date of publication of the international search report:

18 May 2012

(54) Title: CHOLINE ANALOGS AS RADIOTRACER

(57) Abstract: Novel radiotracer(s) for Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) imaging of disease states related to altered choline metabolism (e.g., tumor imaging of prostate, breast, brain, esophageal, ovarian, endometrial, lung and prostate cancer - primary tumor, nodal disease or metastases). The present invention also describes intermediate(s), pre-cursor(s), pharmaceutical composition(s), methods of making, and methods of use of the novel radiotracer(s).



WO 2012/040138 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/052253

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C213/00 C07C213/02 C07C213/06 C07C215/08 C07C217/10
ADD.

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)
C07C

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	J. LEYTON ET AL: "[18F]Fluoromethyl-[1,2-2H4]-Choline: A Novel Radiotracer for Imaging Choline Metabolism in Tumors by Positron Emission Tomography", CANCER RESEARCH, vol. 69, no. 19, 1 October 2009 (2009-10-01), pages 7721-7728, XP055017080, ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-09-1419 page 7721, right-hand column, last paragraph - page 7722, left-hand column, paragraph 1 page 7723; figure 1A abstract ----- -/--	1,4-21



Further documents are listed in the continuation of Box C.



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 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.
"&" document member of the same patent family

Date of the actual completion of the international search

15 February 2012

Date of mailing of the international search report

12/03/2012

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Dunet, Guillaume

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/052253

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GRAHAM SMITH ET AL: "Radiosynthesis and pre-clinical evaluation of [18F]fluoro-[1,2-2H4]choline", Nuclear Medicine and Biology, vol. 38, no. 1 1 September 2010 (2010-09-01), pages 39-51, XP002667666, DOI: 10.1016/j.nucmedbio.2010.06.012 Retrieved from the Internet: URL: http://www.sciencedirect.com/science/article/pii/S0969805110003252 [retrieved on 2012-02-15]	1,4-21
Y	abstract * scheme 1 *; page 43, left-hand column * scheme 2 *; page 44, left-hand column * scheme 4 *; page 45 page 41, left-hand column, paragraph 2 - right-hand column, paragraph 1 page 50, left-hand column, paragraph 2 page 50, right-hand column, paragraph 2 -----	3
X	JEHANGIR S. MISTRY ET AL: "Neurochemistry of aging. 2. Design, synthesis and biological evaluation of halomethyl analogs of choline with high affinity choline transport inhibitory activity", JOURNAL OF MEDICINAL CHEMISTRY, vol. 34, no. 7, 1 July 1991 (1991-07-01), pages 2031-2036, XP055017160, ISSN: 0022-2623, DOI: 10.1021/jm00111a016 * scheme 1 *; page 2032, left-hand column; compounds 2, 3, 4 * preparation of compounds 2, 3 and 4 *; page 2035, left-hand column, paragraph 4-6 -----	1,2,8-10
X	R.G. BRIDGES ET AL: "The incorporation of analogues of choline into the phospholipids of the larva of the housefly, Musca domestica", JOURNAL OF INSECT PHYSIOLOGY, vol. 16, no. 4, 1 April 1970 (1970-04-01), pages 579-593, XP055017201, ISSN: 0022-1910, DOI: 10.1016/0022-1910(70)90092-2 * part C of the table *; page 581; table 1 page 580, last paragraph - page 581, paragraph 1 ----- -/--	1,2,9,10

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/052253

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 92/20646 A1 (GASTAUD JEAN MARIE [FR]) 26 November 1992 (1992-11-26) abstract * formula III *; page 7 pages 19-20; example VII -----	1,2,6,8, 9
X	ZHANG M-R ET AL: "Development of an automated system for synthesizing <18>F-labeled compounds using [<18>F]fluoroethyl bromide as a synthetic precursor", APPLIED RADIATION AND ISOTOPES, vol. 57, no. 3, 1 September 2002 (2002-09-01), pages 335-342, XP004370242, ELSEVIER, OXFORD, GB ISSN: 0969-8043, DOI: 10.1016/S0969-8043(02)00075-1 abstract * scheme 1 *; page 336 -----	13
X	LIM ET AL: "AUTOMATED PRODUCTION OF [18F]FECH AND [18f]FCH: PREPARATION AND USE OF [18F]FLUOROALKANE SULFONATES AS FLUOROALKYLATION AGENTS", JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS, vol. 46, 1 August 2003 (2003-08-01), page S46, XP002313484, JOHN WILEY, CHICHESTER, GB ISSN: 0362-4803, DOI: 10.1002/JLCR.757 abstract page S46 -----	13
X	WO 2005/009928 A2 (QUEEN S HEALTH SYSTEMS [US]; LIM JOHN L [US] QUEEN S MEDICAL CT [US];) 3 February 2005 (2005-02-03)	1,2,9, 10,13
Y	paragraph [0072] - paragraph [0073] page 19 claims 1-35 paragraph [0028] -----	3
Y	WO 2006/082108 A2 (SCHERING AG [DE]; KAUFMANN PHILIP [CH]; WEBER BRUNO [DE]; BUCK ALFRED) 10 August 2006 (2006-08-10)	3
A	abstract * formula (I) *; page 15 page 18, lines 12-17 claims 1-39 ----- -/--	1,2,4-21

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/052253

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KRYZA ET AL: "Fully automated [^{18}F]fluorocholine synthesis in the TracerLab MXFDG Coincidence synthesizer", NUCLEAR MEDICINE AND BIOLOGY, vol. 35, no. 2, 8 February 2008 (2008-02-08), pages 255-260, XP022460575, ELSEVIER, NY, US ISSN: 0969-8051 abstract page 256; figure 1 pages 256-257, paragraph 2.2. page 258; figure 2 -----	13,19,20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/052253

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9220646	A1	26-11-1992	EP 0538436 A1 28-04-1993
			FR 2676224 A1 13-11-1992
			JP H06500340 A 13-01-1994
			US 5399590 A 21-03-1995
			WO 9220646 A1 26-11-1992
WO 2005009928	A2	03-02-2005	AU 2004259769 A1 03-02-2005
			CA 2538520 A1 03-02-2005
			CN 1886362 A 27-12-2006
			CN 101913973 A 15-12-2010
			EP 1660433 A2 31-05-2006
			JP 2006528648 A 21-12-2006
			KR 20060101754 A 26-09-2006
			WO 2005009928 A2 03-02-2005
WO 2006082108	A2	10-08-2006	NONE