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(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, 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.

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28 March 2013

(54) Title: MONOAMINE OXIDASE INHIBITORS AND METHODS FOR TREATMENT AND DIAGNOSIS OF PROSTATE CANCER

(57) Abstract: A mechanism of monoamine oxidases (MAOs) driven epithelium-to-mesenchymal transition (EMT) is disclosed. Also disclosed are methods for treating cancer by inhibiting or suppressing MAOs in cancer cells. Novel MAOs inhibitors, such as small molecules, siRNA, shRNA, antisense oligonucleotides, aptamers, decoys, and pharmaceutical compositions useful for treating cancer by disrupting the workings of MAOs are provided. In particular, a class of conjugates formed by covalently conjugating near infrared dye 783, IR-780, and MHI-148 to a MAO inhibitor, such as clorgyline, with and without encapsulation it in a nanoparticle is provided. Other aspects of the invention include methods for forming the nano-conjugates, method for monitoring treatment progress in a cancer patient by monitoring the changes in MAO activity, methods for screening patients who are at risk of cancer or differentiating different forms of cancer by assaying the level and location of MAO activity.



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/048407

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/352 A61K31/357 A61K31/381 A61K31/404 A61B5/00 C12N15/113 ADD. A61P35/00 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) A61K A61P A61B C12N 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, BIOSIS, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/042933 A2 (UNIV NORTHWESTERN [US]; BERGAN RAYMOND C [US]; SCHEIDT KARL A [US]) 15 April 2010 (2010-04-15) page 2, line 24 - page 4, line 17 page 70 - page 71; compounds 7, 10 -----	1,3,6,16
X	DE 10 2007 002386 A1 (ANALYTICON DISCOVERY GMBH [DE]) 17 July 2008 (2008-07-17) claims 3, 7, 13, 14 -----	6
X	WO 00/66576 A1 (G J CONSULTANTS PTY LTD [AU]; JOANNOU GEORGE EUSTACE [AU]) 9 November 2000 (2000-11-09) page 4, line 27 - page 5, line 10 page 7, lines 5-11 ----- -/--	1
☒ 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 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 20 November 2012		Date of mailing of the international search report 13/02/2013
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 Collins, Sally

INTERNATIONAL SEARCH REPORT

International application No.
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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.:

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.:
1, 3, 6, 16

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/US2012/048407

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PEEHL, D. M.; CORAM, M.; KHINE, H.; REESE, S.; NOLLEY, R.; ZHAO, H. J.: "The significance of Monoamine oxidase A expression in high grade prostate cancer", JOURNAL OF UROLOGY, vol. 180, 2008, pages 2206-2211, XP025507306, cited in the application page 2210, column 2, paragraph 1-2 -----	1,3,6,16
A,P	WO 2012/018761 A2 (CENERX BIOPHARMA INC [US]; BRAND BARRY SCOTT [US]; BURCH DANIEL JOESPH) 9 February 2012 (2012-02-09) page 2, line 6 - page 3, line 18 -----	1,3,6,16
A	FLAMAND V ET AL: "864 MONOAMINE OXIDASE A: A NEW CANDIDATE THERAPEUTIC TARGET FOR ADVANCED PROSTATE CANCER", EUROPEAN UROLOGY SUPPLEMENTS, XX, XX, vol. 9, no. 2, 1 April 2010 (2010-04-01), page 274, XP027029380, ISSN: 1569-9056 [retrieved on 2010-04-01] the whole document -----	1,3,6,16
A	FLAMAND, V.; ZHAO, H. J.; PEEHL, D. M.: "Targeting monoamine oxidase A in advanced prostate cancer", JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, vol. 136, 2010, pages 1761-1771, XP019849130, cited in the application page 1764; figure 1 page 1770, column 2, paragraph 3 -----	1,3,6,16
A	ZHAO, H. J.; FLAMAND, V.; PEEHL, D. M.: "Anti-oncogenic and pro-differentiation effects of clorgyline, a monoamine oxidase A inhibitor, on high grade prostate cancer cells", BMC MEDICAL GENOMICS, vol. 2, 2009, page 2, XP021060681, cited in the application the whole document -----	1,3,6,16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/048407

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010042933 A2	15-04-2010	US 2010137425 A1 WO 2010042933 A2	03-06-2010 15-04-2010
DE 102007002386 A1	17-07-2008	AU 2008204631 A1 CA 2675029 A1 DE 102007002386 A1 EP 2137207 A2 JP 2010515695 A US 2010048921 A1 WO 2008083678 A2	17-07-2008 17-07-2008 17-07-2008 30-12-2009 13-05-2010 25-02-2010 17-07-2008
WO 0066576 A1	09-11-2000	AT 342895 T AT 492525 T AU 777324 B2 AU 2008243189 A1 AU 2009217436 A1 CA 2371765 A1 CA 2727692 A1 DE 60031400 T2 EP 1189897 A1 EP 1743881 A1 US 7056952 B1 US 2005222248 A1 US 2008125481 A1 US 2009209655 A1 US 2010273891 A1 WO 0066576 A1	15-11-2006 15-01-2011 14-10-2004 04-12-2008 15-10-2009 09-11-2000 09-11-2000 20-09-2007 27-03-2002 17-01-2007 06-06-2006 06-10-2005 29-05-2008 20-08-2009 28-10-2010 09-11-2000
WO 2012018761 A2	09-02-2012	NONE	

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

1. claims: 1, 3, 6, 16

Compounds 11-14, their use as Monoamine oxidase A inhibitors and their use in medicine

1.1. claims: 1, 3, 16(all partially)

Compound 11, its use as Monoamine oxidase A inhibitor and its use in medicine

1.2. claims: 1, 3, 16(all partially)

Compound 12, its use as Monoamine oxidase A inhibitor and its use in medicine

1.3. claims: 1, 3, 16(all partially)

Compounds 13-14, their use as Monoamine oxidase A inhibitors and their use in medicine

1.4. claim: 6

Nano-dye conjugates comprising compounds 11-14 and their use in medicine

2. claims: 2, 17

Use of Monoamine oxidase inhibitors which are not further defined in inventions subjects 1 or 3-4 to treat prostate cancer

3. claims: 4, 5, 7-9, 18(completely); 14, 15(partially)

Near infrared dye-nano conjugates and their use as monoamine oxidase inhibitors and in treating cancer

4. claims: 10, 11

Nucleic acid based gene silencing agents, their use as monoamine oxidase inhibitors and their use in treating cancer

5. claims: 12, 13(completely); 14, 15(partially)

Method of delivering cytotoxic agents to a cancer cell by conjugating them to a nanoparticle dye.

6. claims: 19-25

Methods for screening for risk of cancer, diagnosing cancer
and monitoring treatment of cancer by determining monoamine
oxidase activity in a patient.
