

REVISED VERSION

(19) World Intellectual Property
Organization
International Bureau



(10) International Publication Number
WO 2012/156537 A9

(43) International Publication Date
22 November 2012 (22.11.2012)

(51) International Patent Classification:

A61K 31/135 (2006.01) *A61K 31/44* (2006.01)
A61K 31/165 (2006.01) *A61K 31/495* (2006.01)
A61K 31/18 (2006.01) *A61P 7/02* (2006.01)
A61K 31/40 (2006.01)

(21) International Application Number:

PCT/EP2012/059414

(22) International Filing Date:

21 May 2012 (21.05.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/519,345 19 May 2011 (19.05.2011) US
61/519,346 19 May 2011 (19.05.2011) US

(71) Applicant (for all designated States except US):
ORYZON GENOMICS, S.A. [ES/ES]; Calle Sant Ferran
74, E-08940 Cornellà de Llobregat (ES).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MAES, Tamara**
[BE/ES]; Calle Sant Ferran 74, E-08940 Cornellà de
Llobregat (ES). **MARTINELL PEDEMONTE, Marc**
[ES/ES]; Calle Sant Ferran 74, E-08940 Cornellà de
Llobregat (ES).

(74) Agent: **MEIER, Jürgen**; VOSSIUS & PARTNER,
Siebertstraße 4, 81675 München (DE).

(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, RW, SD, SL, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, 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).

Declarations under Rule 4.17:

— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii))

Published:

— with international search report (Art. 21(3))

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

10 January 2013

Date of publication of the revised international search
report:

7 March 2013

(15) Information about Correction:

see Notice of 7 March 2013

(54) Title: LYSINE DEMETHYLASE INHIBITORS SUCH AS CYCLYL CYCLOPROPAMINE DERIVATIVES FOR USE IN THE TREATMENT OF THROMBOSIS AND CARDIOVASCULAR DISEASES

(57) Abstract: The invention relates to methods and compositions for the treatment or prevention of thrombosis, thrombus formation, a thrombotic event or complication, or a cardiovascular disease or event. In particular, the invention relates to an LSD inhibitor such as a 2-cyclylcyclopropan-1-amine derivative, a phenelzine derivative and a propargylamine derivative, for use in treating or preventing thrombosis, thrombus formation, a thrombotic event or complication, or a cardiovascular disease or event.



WO 2012/156537 A9

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/135 A61K31/165 A61K31/18 A61K31/40 A61K31/44
A61K31/495 A61P7/02

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)

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 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 2004/176469 A1 (THOMAS THOMAS NADACKAL [US]) 9 September 2004 (2004-09-09)	1-24, 27-32, 34-64,72
Y	claims 1,4,6,32-33 paragraph [0047] claim 4; table 2; compounds tranylcyproamine, phenelzine, propargylamine	67-71
X	----- WO 2004/020415 A1 (ASTRAZENECA AB [SE]; HENRIKSSON KRISTER [SE]; MUNCK AF ROSENSCHOELD MA) 11 March 2004 (2004-03-11)	1-24, 27-32, 34-64,72
Y	claim 11; examples 43-46 page 28, lines 4-7 ----- -/--	67-71

 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

11 September 2012

Date of mailing of the international search report

26/11/2012

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

Renard, Delphine

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/059414

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 94/27947 A1 (RHONE POULENC RORER LTD [GB]; FENTON GARRY [GB]; MASON JONATHAN STEPHE) 8 December 1994 (1994-12-08)	1-24, 27-32, 34-64,72
Y	compounds p-t (examples 16-20) claims 1-11, 17	67-71

X	WO 00/34283 A1 (ASTRAZENECA UK LTD [GB]; ASTRAZENECA AB [SE]; GUILLE SIMON [GB]; HARDER) 15 June 2000 (2000-06-15)	1-24, 27-32, 34-64, 67,72
Y	claims 1-15 page 13, line 16 - page 14, line 15	68-71

X	KHALEEL AHMED ET AL: "Ticagrelor: a new reversible oral antiplatelet agent", INTERNATIONAL RESEARCH JOURNAL OF PHARMACY,, vol. 1, no. 1, 1 January 2010 (2010-01-01), pages 62-69, XP009162670,	1-24, 27-32, 34-64,72
Y	Tricagrelor and its mechanism of action; page 63	67-71

X	WO 2010/014921 A2 (US HEALTH [US]; JACOBSON KENNETH A [US]; MELMAN ARTEM [US]; WANG BEN B) 4 February 2010 (2010-02-04)	1-24, 27-32, 34-64,72
Y	claims 1-17 compound 13b	67-71

X	WO 2005/037843 A1 (VERTEX PHARMA [US]; JIMENEZ JUAN-MIGUEL [GB]; GREEN JEREMY [US]; GAO H) 28 April 2005 (2005-04-28)	1-24, 27-32, 34-64, 67,72
Y	claims 78-79, 88, 98 compound v127	68-71

X	WO 2009/145856 A1 (PORTOLA PHARM INC [US]; BAUER SHAWN M [US]; JIA ZHAOZHONG J [US]; SONG) 3 December 2009 (2009-12-03)	1-24, 27-32, 34-64,72
Y	paragraph [0449] claims 69-71	67-71

X	US 2005/009832 A1 (SUN CONNIE LI [US] ET AL) 13 January 2005 (2005-01-13)	1-24, 27-32, 34-64,72
Y	claims 109, 113 paragraph [1549]; compound 192	67-71

X	WO 2007/025144 A1 (UNIV ILLINOIS CHICAGO [US]; KOZIKOWSKI ALAN [US]; KUROME TORU [US]; SE) 1 March 2007 (2007-03-01)	1-24, 27-32, 34-64,72
Y	page 53; figure scheme15; table 1 paragraph [0147]	67-71

-/--		

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/059414

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 193 268 A1 (APPLIED RESEARCH SYSTEMS [AN]) 3 April 2002 (2002-04-03)	1-24, 27-32, 34-64,72
Y	claim 18 compound 59	67-71
A	----- WO 2010/084160 A1 (ORYZON GENOMICS SA [ES]; GUIBOURT NATHALIE [ES]; ORTEGA MUNOZ ALBERTO) 29 July 2010 (2010-07-29) cited in the application claims 1-29	1-72
A	----- EP 1 741 708 A1 (SANOFI AVENTIS DEUTSCHLAND [DE]) 10 January 2007 (2007-01-10) table 1; compound 1k paragraph [0095]	1-72
A	----- US 2010/292225 A1 (CHAMOIN SYLVIE [FR] ET AL) 18 November 2010 (2010-11-18) claims 1-12, 17, 25 paragraph [0586]; compound 87	1-72
E	----- WO 2012/107498 A1 (ORYZON GENOMICS SA [ES]; BAKER JONATHAN ALLEMAN [ES]; CASTRO PALOMINO) 16 August 2012 (2012-08-16) the whole document	1-72

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/059414

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.:

24(completely); 1-23, 27-32, 34-64, 67-72(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 24(completely); 1-23, 27-32, 34-64, 67-72(partially)

lsl1 inhibitors and in particular
2-carbocyclylcyclopropan-1-amine for use in the treatment of
thrombosis or cardiovascular diseases

2. claims: 25, 26, 33(completely); 1-23, 27-32, 34-64,
67-72(partially)

2-heterocyclylcyclopropan-1-amine for use in the treatment
of thrombosis or cardiovascular diseases

3. claims: 65(completely); 1-19, 63, 67-72(partially)

phenelzine compound for use in the treatment of thrombosis
or cardiovascular diseases

4. claims: 66(completely); 1-19, 63, 67-72(partially)

propargylamine compound for use in the treatment of
thrombosis or cardiovascular diseases

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/059414

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004176469	A1	09-09-2004	NONE
WO 2004020415	A1	11-03-2004	AR 041066 A1 27-04-2005 AT 348816 T 15-01-2007 AU 2003253557 A1 19-03-2004 BR 0313635 A 21-06-2005 CA 2495853 A1 11-03-2004 CN 1688550 A 26-10-2005 DE 60310582 T2 22-11-2007 DK 1542977 T3 19-03-2007 EP 1542977 A1 22-06-2005 ES 2277143 T3 01-07-2007 HK 1077061 A1 25-05-2007 IL 166826 A 15-06-2009 IS 7767 A 22-03-2005 JP 2006503019 A 26-01-2006 KR 20050059093 A 17-06-2005 MX PA05002066 A 08-06-2005 MY 137562 A 27-02-2009 NZ 538443 A 29-09-2006 PT 1542977 E 28-02-2007 RU 2326117 C2 10-06-2008 UA 81635 C2 25-01-2008 US 2005245586 A1 03-11-2005 US 2006276524 A1 07-12-2006 WO 2004020415 A1 11-03-2004 ZA 200501139 A 27-12-2006
WO 9427947	A1	08-12-1994	AU 6803594 A 20-12-1994 WO 9427947 A1 08-12-1994
WO 0034283	A1	15-06-2000	AR 023920 A1 04-09-2002 AR 058967 A2 05-03-2008 AR 072756 A2 22-09-2010 AT 261970 T 15-04-2004 AT 418547 T 15-01-2009 AT 513816 T 15-07-2011 AU 766618 B2 23-10-2003 BR 9915883 A 21-08-2001 CA 2351709 A1 15-06-2000 CN 1334816 A 06-02-2002 CZ 300280 B6 08-04-2009 CZ 300373 B6 06-05-2009 CZ 20011962 A3 14-11-2001 DE 69915675 D1 22-04-2004 DE 69915675 T2 17-02-2005 DE 122011100004 I1 08-09-2011 DK 1135391 T3 28-06-2004 DK 1386917 T3 29-08-2011 DK 1386921 T3 23-03-2009 EG 24814 A 21-09-2010 EP 1135391 A1 26-09-2001 EP 1386909 A1 04-02-2004 EP 1386917 A1 04-02-2004 EP 1386921 A1 04-02-2004 EP 2322513 A2 18-05-2011 ES 2216623 T3 16-10-2004 ES 2318081 T3 01-05-2009

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/059414

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		HK 1039933 A1	08-10-2004
		HK 1061246 A1	05-06-2009
		HK 1061684 A1	10-02-2012
		HU 0105081 A2	29-05-2002
		ID 29927 A	25-10-2001
		IL 143232 A	29-12-2008
		IL 183969 A	31-03-2011
		JP 4202607 B2	24-12-2008
		JP 5043749 B2	10-10-2012
		JP 2002531567 A	24-09-2002
		JP 2007084551 A	05-04-2007
		JP 2008266345 A	06-11-2008
		JP 2011016831 A	27-01-2011
		KR 20060091056 A	17-08-2006
		KR 20070007971 A	16-01-2007
		KR 20070086540 A	27-08-2007
		LU 91819 I2	01-08-2011
		NO 2011007 I1	06-06-2011
		NO 20012725 A	31-07-2001
		NZ 511778 A	31-10-2003
		PL 348724 A1	03-06-2002
		PT 1135391 E	30-07-2004
		PT 1386921 E	23-02-2009
		RU 2317990 C2	27-02-2008
		SI 1135391 T1	31-08-2004
		SI 1386917 T1	30-09-2011
		SI 1386921 T1	30-04-2009
		SK 7492001 A3	07-01-2002
		TR 200101567 T2	21-12-2001
		TW 1229674 B	21-03-2005
		US 6525060 B1	25-02-2003
		US 2003144305 A1	31-07-2003
		US 2006025590 A1	02-02-2006
		US 2007265282 A1	15-11-2007
		US 2008214812 A1	04-09-2008
		US 2010069408 A1	18-03-2010
		US 2012165348 A1	28-06-2012
		WO 0034283 A1	15-06-2000

WO 2010014921	A2	04-02-2010	
		AU 2009276411 A1	04-02-2010
		CA 2732320 A1	04-02-2010
		EP 2331542 A2	15-06-2011
		JP 2011529917 A	15-12-2011
		US 2011171130 A1	14-07-2011
		WO 2010014921 A2	04-02-2010

WO 2005037843	A1	28-04-2005	
		AT 451376 T	15-12-2009
		AU 2004282172 A1	28-04-2005
		CA 2542113 A1	28-04-2005
		CN 1894258 A	10-01-2007
		CN 1897950 A	17-01-2007
		CN 101824043 A	08-09-2010
		EP 1692140 A1	23-08-2006
		ES 2338234 T3	05-05-2010
		HK 1096673 A1	03-09-2010
		JP 2007509848 A	19-04-2007
		JP 2011241231 A	01-12-2011
		US 2005148603 A1	07-07-2005

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/059414

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2010280026 A1	04-11-2010
		US 2012183577 A1	19-07-2012
		WO 2005037843 A1	28-04-2005

WO 2009145856	A1	03-12-2009	AU 2009251863 A1
			03-12-2009
			CA 2723205 A1
			03-12-2009
			CN 102066340 A
			18-05-2011
			DO P2010000310 A
			15-03-2011
			EA 201001619 A1
			30-06-2011
			JP 2011518158 A
			23-06-2011
			KR 20100126863 A
			02-12-2010
			SV 2010003706 A
			23-03-2011
			WO 2009145856 A1
			03-12-2009

US 2005009832	A1	13-01-2005	NONE

WO 2007025144	A1	01-03-2007	US 2009203750 A1
			13-08-2009
			WO 2007025144 A1
			01-03-2007

EP 1193268	A1	03-04-2002	AR 033999 A1
			21-01-2004
			AU 8799101 A
			08-04-2002
			AU 2001287991 B2
			07-12-2006
			BG 107633 A
			28-11-2003
			BR 0114223 A
			01-07-2003
			CA 2421209 A1
			04-04-2002
			CN 1568322 A
			19-01-2005
			CZ 20030884 A3
			13-08-2003
			EE 200300119 A
			15-04-2005
			EP 1193268 A1
			03-04-2002
			EP 1322642 A2
			02-07-2003
			HK 1072768 A1
			23-03-2007
			HR P20030214 A2
			28-02-2005
			HU 0302980 A2
			29-12-2003
			JP 4927304 B2
			09-05-2012
			JP 2004509957 A
			02-04-2004
			MX PA03002568 A
			06-10-2003
			NO 20031375 A
			26-03-2003
			NZ 524542 A
			24-09-2004
			PL 361687 A1
			04-10-2004
			SK 3662003 A3
			07-10-2003
			UA 75891 C2
			16-06-2003
			US 2004077854 A1
			22-04-2004
			WO 0226733 A2
			04-04-2002
			YU P21803 A
			25-05-2006
			ZA 200301746 A
			03-03-2004

WO 2010084160	A1	29-07-2010	EP 2389362 A1
			30-11-2011
			US 2012004262 A1
			05-01-2012
			WO 2010084160 A1
			29-07-2010

EP 1741708	A1	10-01-2007	AR 054801 A1
			18-07-2007
			AT 423777 T
			15-03-2009
			AU 2006264051 A1
			04-01-2007
			BR PI0612817 A2
			30-11-2010
			CA 2612601 A1
			04-01-2007
			CN 101213184 A
			02-07-2008
			DK 1904476 T3
			15-06-2009
			EP 1741708 A1
			10-01-2007

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/059414

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		EP 1904476 A1	02-04-2008
		ES 2322964 T3	02-07-2009
		HK 1122552 A1	24-02-2012
		IL 188383 A	29-02-2012
		JP 4991711 B2	01-08-2012
		JP 2008543959 A	04-12-2008
		KR 20080039348 A	07-05-2008
		PT 1904476 E	04-05-2009
		TW 200800941 A	01-01-2008
		US 2008167342 A1	10-07-2008
		UY 29639 A1	31-01-2007
		WO 2007000248 A1	04-01-2007

US 2010292225	A1	18-11-2010	AR 076908 A1
			AU 2010247414 A1
			CA 2761859 A1
			CO 6470898 A2
			CU 20110207 A7
			EA 201101618 A1
			EP 2429995 A1
			MA 33358 B1
			PE 04032012 A1
			SG 175925 A1
			SV 2011004061 A
			TW 201100382 A
			US 2010292225 A1
			UY 32640 A
			WO 2010130796 A1

WO 2012107498	A1	16-08-2012	NONE
