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(71) Applicant: **UNIVERSITY COLLEGE DUBLIN, NATIONAL UNIVERSITY OF IRELAND, DUBLIN** [IE/IE]; Belfield 4, Dublin (IE).

(72) Inventors: **KINSELLA, Therese, B.**; 75 Avoca Park, Avoca Avenue, Blackrock, Dublin (IE). **GUIRY, Patrick**; 51 Deerpark Road, Mount Merrion, Dublin (IE). **REID, Helen**; 73, Orchard Way, Greenwood Walk, Ayrfield 13, Dublin (IE). **O'CONNOR, Barry**; 32 Newcastle Manor Square, Newcastle, Dublin (IE).

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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:
26 June 2014

(54) Title: THROMBOXANE RECEPTOR ANTAGONISTS

(57) Abstract: The invention generally relates to compounds that function as TP antagonists for treating thrombosis and other cardiovascular, renal, or pulmonary diseases. In some embodiments, the invention provides a compound including a substituted nitro phenoxy phenyl, a sulfonylurea, and an alkyl group. In some embodiments, the invention provides a method of treating thrombosis by administering an antithrombotic compound that preferentially binds to a thromboxane receptor, has preferential binding for either TPalpha (TPα) or TPbeta (TPβ) receptor subtype.

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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 A61K31/18 A61K31/216 A61K31/44 A61P7/02
C07D213/71 C07D213/89 C07C311/54
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 C07D 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 practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, 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	JULIEN HANSON ET AL: "Design, Synthesis, and SAR Study of a Series of N -Alkyl- N ' -[2-(aryloxy)-5-nitrobenzenesulfonyl]ureas and -cyanoguanidine as Selective Antagonists of the TP[alpha] and TP[beta] Isoforms of the Human Thromboxane A 2 Receptor", JOURNAL OF MEDICINAL CHEMISTRY, vol. 50, no. 16, 1 August 2007 (2007-08-01), pages 3928-3936, XP055072676, ISSN: 0022-2623, DOI: 10.1021/jm070427h Compounds falling under the definition of claims 1, 2, 3: see e.g. compounds in table 2:9w, 9x, 9y, 9z, and in particular compounds 9w, 9z, corresponding to the preferred compounds XXXVI and XXXVIII of pages 23-24 of the present application (945716-18-7 and 945716-19-8), as TP -/--	1-5, 10-19, 22-30

[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
30 January 2014	09/05/2014

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	Veronese, Andrea

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	alpha and beta thromboxane A2 antagonists effective to inhibit platelet blood clotting -----	
X	JULIEN HANSON ET AL: "Synthesis and Pharmacological Evaluation of Novel Nitrobenzenic Thromboxane Modulators as Antiplatelet Agents Acting on Both the Alpha and Beta Isoforms of the Human Thromboxane Receptor", JOURNAL OF MEDICINAL CHEMISTRY, vol. 49, no. 12, 1 June 2006 (2006-06-01), pages 3701-3709, XP055072715, ISSN: 0022-2623, DOI: 10.1021/jm060108a Compounds as defined in claims 1 as thromboane receptor antagonists, and as inhibitors of platelet aggreagation useful for treating e.g. cardiocirculatory disorders: see the compounds disclosed in the examples, and in particular compounds 7a-7g in tables 1-3. See abstract and discussion -----	1-5, 10-19, 22-30
X	HANSON JULIEN ET AL: "In vitro and in vivo pharmacological characterization of BM-613 [N-n-pentyl-N'-[2-(4'-methylphenylamino)-5 -nitrobenzenesulfonyl]urea], a novel dual thromboxane synthase inhibitor and thromboxane receptor antagonist.", THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS APR 2005, vol. 313, no. 1, April 2005 (2005-04), pages 293-301, XP002719494, ISSN: 0022-3565 BM-613, a nitrobenzenesulfonylurea as a Thrombone receptor antabonist acting on TP-alpha and TP-beta and its activity as antiplatelet and antithrombotic agent (see abstract, figures, results and conclusion) -----	1-5, 10-19, 22-30
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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROLIN S ET AL: "BM-573, a dual thromboxane synthase inhibitor and thromboxane receptor antagonist, prevents pig myocardial infarction induced by coronary thrombosis.", THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS JUL 2003, vol. 306, no. 1, July 2003 (2003-07), pages 59-65, XP002719495, ISSN: 0022-3565 BM-573, a nitrobenzenesulfonylurea as a thromboxane receptor antagonist acting on TP-alpha and TP-beta and its activity as antiplatelet aggregation and antithrombotic agent (see abstract, figures, results and conclusion)	1-5, 10-19, 22-30
X	S. ROLIN ET AL: "Activity of a novel dual thromboxane A2receptor antagonist and thromboxane synthase inhibitor (BM-573) on platelet function and isolated smooth muscles", PROSTAGLANDINS, LEUKOTRIENES AND ESSENTIAL FATTY ACIDS, vol. 65, no. 2, 1 August 2001 (2001-08-01) , pages 67-72, XP055065961, ISSN: 0952-3278, DOI: 10.1054/plef.2001.0290 Torasemide and related nitrobenzene sulfonylurea derivatives (e.g. BM-519, BM-500, BM-573), as thromboxane receptor antagonists and their activity as antiplatelet aggregation and antithrombotic agent (see abstract, figures, results and conclusion)	1-5, 10-19, 22-30
X	WO 00/42004 A1 (UNIV LIEGE [BE]; DELARGE JACQUES [BE]; DOGNE JEAN MICHEL [BE]; MASEREE) 20 July 2000 (2000-07-20) See the thromboxane inhibitors defined in the Markush formula of claim 1 (page 41) and in the examples, and their use to inhibit platelet agggregation (see table 3 in page 31) and for treating cardiovascular disorders (claim 10)	1-5, 10-19, 22-30

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	SYLVIE-MIREILLE BAMBI-NYANGUILE ET AL: "Synthesis and pharmacological evaluation of 2-aryloxy/arylamino-5-cyanobenzenesulfonyl ureas as novel thromboxane A2 receptor antagonists", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 65, 13 April 2013 (2013-04-13), pages 32-40, XP055099435, ISSN: 0223-5234, DOI: 10.1016/j.ejmech.2013.04.033 See the compounds 7a-7i defined in table 1, as thromboxane receptor antagonists, and their use to prevent platelet aggregation (see abstract, tables, figures and discussion)	1-5, 10-19, 22-30
X,P	CHIARA CUSTODI ET AL: "Fitting the complexity of GPCRs modulation into simple hypotheses of ligand design", JOURNAL OF MOLECULAR GRAPHICS AND MODELLING, vol. 38, 20 July 2012 (2012-07-20), - 2012, pages 70-81, XP055099454, ISSN: 1093-3263, DOI: 10.1016/j.jmgm.2012.07.002 See compound 18 of table 5	1,10,11
Y	US 6 231 600 B1 (ZHONG SHENG-PING [US]) 15 May 2001 (2001-05-15) the whole document	1-5, 10-19, 22-30
Y	US 2005/152943 A1 (HEZI-YAMIT AYALA [US] ET AL) 14 July 2005 (2005-07-14) the whole document	1-5, 10-19, 22-30

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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.:

1-5, 15-19(completely); 10-14, 22-30(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: 1-5, 15-19(completely); 10-14, 22-30(partially)

   Compounds as defined in formula (I), as thromboxane receptor antagonists and their uses in treatment of the conditions indicated in the claims, and products such as medical devices, containing them, as defined in the claims.

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2. claims: 6, 10-14, 20, 22-30(all partially)

   Sulfonamide compounds not substituted on the nitrogen of the sulfonamide group, as defined in structures XV, XVI, XVII, XVIII, XIX (see clam 6), as thromboxane receptor antagonists and their uses in treatment of the conditions indicated in the claims, and products such as medical devices containing them, as defined in the claims.

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3. claims: 7, 8, 21, 31(completely); 9-14, 22-30, 32(partially)

   Compounds as defined in formula (XXII in claims 7-8, and in formula LVIII as defined in claim 9), where R10 is not nitro and is one of the residues as indicated in claims 7-8, as thromboxane receptor antagonists and their uses in treatment of the conditions indicated in the claims, and products such as medical devices, containing them, as defined in the claims.

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4. claims: 6, 9-14, 20, 22-30, 32(all partially)

   Compounds as defined in formula (XX, LVII, LX, comprising an heterocyclic group), as thromboxane receptor antagonists and their uses in treatment of the conditions indicated in the claims, and products such as medical devices, containing them, as defined in the claims.

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5. claims: 6, 10-14, 20, 22-30(all partially)

   Compounds as defined in formula (XIV, XXI, not comprising a sulfonamide group), as thromboxane receptor antagonists and their uses in treatment of the conditions indicated in the claims, and products such as medical devices, containing them, as defined in the claims.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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