



(51) International Patent Classification:

A61K 8/41 (2006.01) *A61Q 11/00* (2006.01)
A61K 8/49 (2006.01) *A61Q 17/02* (2006.01)
A61K 31/00 (2006.01) *A61Q 19/00* (2006.01)

(21) International Application Number:

PCT/EP2012/054046

(22) International Filing Date:

8 March 2012 (08.03.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

11157329.1 8 March 2011 (08.03.2011) EP

(71) Applicants (for all designated States except US):

B.R.A.I.N. BIOTECHNOLOGY RESEARCH AND INFORMATION NETWORK AG [DE/DE]; Darmstädter Strasse 34-36, 64673 Zwingenberg (DE). **ZINKE, Holger** [DE/DE]; Kirchbergstrasse 44, 64646 Heppenheim (DE).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **KROHN, Michael** [DE/DE]; Alexanderstrasse 8, 64653 Lorsch (DE).

(74) Agent: **HUENGES, Martin**; Maiwald Patentanwalts GmbH, Elisenhof Elisenstrasse 3, 80335 Munich (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, 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:

1 August 2013

(54) Title: SMALL MOLECULE MODULATORS OF THE COLD AND MENTHOL RECEPTOR TRPM8

(57) Abstract: The present invention relates to the use of compounds which are capable of producing a cooling sensation when they are brought into contact with the human body. In particular, the present invention relates to the use of compounds modulating TRPM8, and optionally to the use of compounds selectively exhibiting agonist activity at the TRPM8 channel. Such compounds have applications in many fields, particularly in oral and personal hygiene products and foodstuffs, but also in pharmaceutical composition products, cosmetics, textile products and packaging products. The present invention further relates to products containing such compounds and to the medical use of such compounds.



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/054046

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K8/41 A61K8/49 A61K31/00 A61Q11/00 A61Q17/02
 A61Q19/00
 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 A61Q

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	MA SHERKHELI ET AL: "Menthol derivative WS-12 selectively activates transient receptor potential melastatin-8 (TRPM8) ion channels.", PAKISTAN JOURNAL OF PHARMACEUTICAL SCIENCES OCT 2008 LNKD- PUBMED:18930858, vol. 21, no. 4, October 2008 (2008-10), pages 370-378, XP002664432, ISSN: 1011-601X the whole document ----- -/--	1-4,7, 11-13,15

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 7 March 2013	Date of mailing of the international search report 18/06/2013
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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 Donovan-Beermann, T
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/054046

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHERKHELI MUHAMMAD AZHAR ET AL: "Characterization of selective TRPM8 ligands and their structure activity response (S.A.R) relationship.", JOURNAL OF PHARMACY & PHARMACEUTICAL SCIENCES : A PUBLICATION OF THE CANADIAN SOCIETY FOR PHARMACEUTICAL SCIENCES, SOCIÉTÉ CANADIENNE DES SCIENCES PHARMACEUTIQUES 2010 LNKD-PUBMED:20816009, vol. 13, no. 2, 2010, pages 242-253, XP002664433, ISSN: 1482-1826 the whole document	1-4,7, 11-13,15
X	----- ORTAR GIORGIO ET AL: "(-)-Menthylamine derivatives as potent and selective antagonists of transient receptor potential melastatin type-8 (TRPM8) channels.", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1 MAY 2010 LNKD- PUBMED:20378345, vol. 20, no. 9, 1 May 2010 (2010-05-01), pages 2729-2732, XP002664434, ISSN: 1464-3405 the whole document	1,3,4,7, 11,12,15
X	----- WO 2008/015403 A1 (UNIV EDINBURGH [GB]; FLEETWOOD-WALKER SUSAN [GB]; MITCHELL RORY [GB];) 7 February 2008 (2008-02-07) pages 3,4,6,10; claims 1,2,7	1-4,7, 10-13,15
X	----- EP 2 186 506 A1 (SYMRISE GMBH & CO KG [DE]) 19 May 2010 (2010-05-19) pages 2-4,6; claims; examples	1-4,7,8, 14
X	----- WO 2008/138162 A1 (GIVAUDAN SA [CH]; YANG XIAOGEN [US]; JIA ZHONGHUA [US]; LI RONGRONG [U]) 20 November 2008 (2008-11-20) pages 2-3 pages 15-17; claims	1-4,7-9, 14
X	----- EP 2 168 957 A2 (SYMRISE GMBH & CO KG [DE]) 31 March 2010 (2010-03-31) pages 7-9; claims	1-4,7-9, 14
X	----- WO 2010/026094 A1 (BASF SE [DE]; SUBKOWSKI THOMAS [DE]; BOLLSCHWEILER CLAUS [DE]; WITTENB) 11 March 2010 (2010-03-11) cited in the application pages 1-2 pages 9-10; claims; examples	1-4,7-15
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/054046

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 2005/121116 A1 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; RITCHIE TIMOTHY JOHN [GB]) 22 December 2005 (2005-12-22) pages 1,19-25; examples 1,5,10,18,22,23,25,27,31,32 -----	1-5,7, 11-13,15
X	US 4 166 862 A (ANTUS SANDOR [HU] ET AL) 4 September 1979 (1979-09-04) column 1 - column 2; example 14 -----	1-5,7
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X	ANKER, DANIEL ET AL: "Spectres de RMN des dérivés benzopyroniques en milieu acide", TETRAHEDRON, vol. 25, no. 20, 1969, pages 5027-5045, XP002664436, ISSN: 0040-4020 page 5033; table 3; compounds 20,21 -----	1-6
X	A. LEVAI ET AL: "ChemInform Abstract: New Procedures for the Preparation of Isoflavones with Unsubstituted Ring A.", CHEMINFORM, vol. 23, no. 43, 27 October 1992 (1992-10-27), pages NO-NO, XP055013024, ISSN: 0931-7597, DOI: 10.1002/chin.199243183 the whole document -----	1-6
X	TUROV, A. V. ET AL: "Use of lanthanide shift reagents for studying pyridine analogs of isoflavones", CHEMISTRY OF HETEROCYCLIC COMPOUNDS (NEW YORK) (TRANSLATION OF KHIMIYA GETEROTSIKLICHESKIKH SOEDINENII), vol. 34, no. 3, 1998, pages 308-311, XP002664437, DOI: 0009-3122 compound IV -----	1-6
X	US 3 178 442 A (LASZLO BENCZE WILLIAM) 13 April 1965 (1965-04-13) example 6 -----	1-6
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/054046

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>John C. Leffingwell: "Cool without Menthol & Cooler than Menthol and Cooling Compounds as Insect Repellents", Leffingwell & Associates</p> <p>10 April 2010 (2010-04-10), 3 December 2010 (2010-12-03), pages 1-19, XP002664438, Internet Archive Retrieved from the Internet: URL:http://web.archive.org/web/20101203145738/http://leffingwell.com/cooler_than_menthol.htm [retrieved on 2011-11-23] the whole document</p> <p style="text-align: center;">-----</p>	1-15
A	<p>WO 2006/092074 A1 (GIVAUDAN SA [CH]; COLE LUCIENNE [US]; FURRER STEFAN MICHAEL [US]; GALO) 8 September 2006 (2006-09-08) the whole document</p> <p style="text-align: center;">-----</p>	1-15

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.:

1-15(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: 1-15(partially)

A product comprising a compound that selectively modulates TRMP8, wherein the product is chosen from cosmetic composition, food composition, textile product, pharmaceutical product or packaging product, wherein the compound has further selective agonist activity, preferably at least three times greater than the activity of the compound on TRPA1, and wherein the compound has the general formula V.2. Further said product comprising a compound of formula V.3, use of said compounds in one of the above products, further specifications of said products, use of said compounds in therapy and further pain treatment, use of said compounds as cooling agents and a in vitro method for modulating the cold and menthol receptor TRPM8 with said compounds.

2. claims: 1-15(partially)

A product comprising a compound that selectively modulates TRMP8, wherein the product is chosen from cosmetic composition, food composition, textile product, pharmaceutical product or packaging product, wherein the compound has further selective agonist activity, preferably at least three times greater than the activity of the compound on TRPA1, and wherein the compound has the general formula I.2. Further said product comprising a compound of formula I.3, use of said compounds in one of the above products, further specifications of said products, use of said compounds in therapy and further pain treatment, use of said compounds as cooling agents and a in vitro method for modulating the cold and menthol receptor TRPM8 with said compounds.

3. claims: 1-15(partially)

A product comprising a compound that selectively modulates TRMP8, wherein the product is chosen from cosmetic composition, food composition, textile product, pharmaceutical product or packaging product, wherein the compound has further selective agonist activity, preferably at least three times greater than the activity of the compound on TRPA1, and wherein the compound has the general formula II.2. Further said product comprising a compound of formula II.3, use of said compounds in one of the above products, further specifications of said products, use of said compounds in therapy and further pain treatment, use of said compounds as cooling agents and a in vitro method for modulating the cold and menthol receptor TRPM8 with said compounds.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

4. claims: 1-15(partially)

A product comprising a compound that selectively modulates TRMP8, wherein the product is chosen from cosmetic composition, food composition, textile product, pharmaceutical product or packaging product, wherein the compound has further selective agonist activity, preferably at least three times greater than the activity of the compound on TRPA1, and wherein the compound has the general formula III.2. Further said product comprising a compound of formula III.3, use of said compounds in one of the above products, further specifications of said products, use of said compounds in therapy and further pain treatment, use of said compounds as cooling agents and a in vitro method for modulating the cold and menthol receptor TRPM8 with said compounds.

5. claims: 1-15(partially)

A product comprising a compound that selectively modulates TRMP8, wherein the product is chosen from cosmetic composition, food composition, textile product, pharmaceutical product or packaging product, wherein the compound has further selective agonist activity, preferably at least three times greater than the activity of the compound on TRPA1, and wherein the compound has the general formula IV.2. Further said product comprising a compound of formula IV.3, use of said compounds in one of the above products, further specifications of said products, use of said compounds in therapy and further pain treatment, use of said compounds as cooling agents and a in vitro method for modulating the cold and menthol receptor TRPM8 with said compounds.

6. claims: 1-15(partially)

A product comprising a compound that selectively modulates TRMP8, wherein the product is chosen from cosmetic composition, food composition, textile product, pharmaceutical product or packaging product, wherein the compound has further selective agonist activity, preferably at least three times greater than the activity of the compound on TRPA1, and wherein the compound has the general formula VI.2. Further said product comprising a compound of formula VI.3, use of said compounds in one of the above products, further specifications of said products, use of said compounds in therapy and further pain treatment, use of said compounds as cooling agents and a in vitro method for modulating the cold and menthol receptor TRPM8 with said compounds.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. claims: 1-15(partially)

A product comprising a compound that selectively modulates TRMP8, wherein the product is chosen from cosmetic composition, food composition, textile product, pharmaceutical product or packaging product, wherein the compound has further selective agonist activity, preferably at least three times greater than the activity of the compound on TRPA1, and wherein the compound has the general formula VII.2. Further said product comprising a compound of formula VII.3, use of said compounds in one of the above products, further specifications of said products, use of said compounds in therapy and further pain treatment, use of said compounds as cooling agents and a in vitro method for modulating the cold and menthol receptor TRPM8 with said compounds.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/054046

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