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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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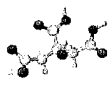
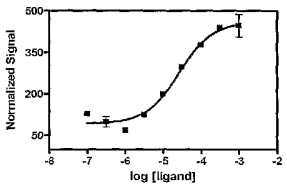
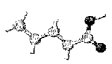
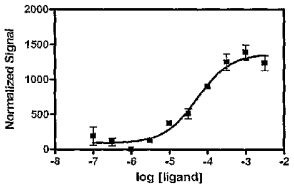
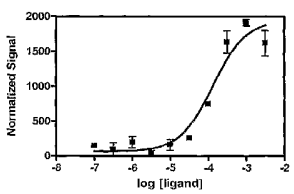
[Continued on next page]

(54) Title: NATURAL LIGAND OF G PROTEIN COUPLED RECEPTOR RCC356 AND USES THEREOF

R	COOH	STRUCTURE	CONCENTRATION-RESPONSE CURVE	Log Ec50
CITRIC ACID				
(COOH)2-(CH2)2-C-OH	COOH			
BUTYRIC ACID - BUTANOIC ACID				
CH3 - (CH2)2	COOH			-4.479 M
VALERIC ACID - PENTANOIC ACID				
CH3 - (CH2)3	COOH			-4,013M
ISOVALERIC ACID - ISOPENTANOIC ACID				
(CH3)2 - (CH2)2	COOH			-4,602 M

(57) Abstract: The invention relates to the identification of isovaleric acid as a natural ligand of the RCC356 G-protein coupled receptor (GPCR). The invention encompasses the use of the interaction of RCC356 polypeptides and isovaleric acid as the basis of screening assays for agents that modulate the activity of the RCC356 receptor. The invention also encompasses diagnostic and other assays performed based upon the RCC356/isovaleric acid interaction, as well as kits for performing diagnostic and screening assays.

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ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

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9 November 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/001904

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/566 A61P35/00 A61P25/00 A61K31/19 C07K16/00
A61K38/00 A61K39/395 C12Q1/68

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)
G01N

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, 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	MALNIC B ET AL: "Combinatorial receptor codes for odors." CELL. 5 MAR 1999, vol. 96, no. 5, 5 March 1999 (1999-03-05), pages 713-723, XP002188611 ISSN: 0092-8674	19, 30-33, 56-61, 76-80
Y	page 721, column 2, paragraph 4 - page 722, column 1, paragraph 2; figure 6	1-18,20, 21
L	"Blast sequences Q8TCB6 and Q9WU90"[Online] XP002356012 Retrieved from the Internet: URL:http://genopole.toulouse.inra.fr/blast /wblast2.html> [retrieved on 2005-11-25] the whole document	1-21, 30-33, 37, 42-47, 55-61, 64-66, 69,70, 73,76-80

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[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 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	Date of mailing of the international search report
19 July 2006	02/08/2006

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schlegel, B

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/001904

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/213004 A1 (JAKOBOVITS AYA ET AL) 13 November 2003 (2003-11-13) paragraphs [0040], [0183] - [0194], [0246] - [0263]; claims 15,43-46	37,43, 44,55
X	S. BUDAVARI ET AL.: "The Merck Index; an Encyclopedia of Chemicals, Drugs, and Biologicals" 1989, MERCK & CO., INC , RAHWAY, N.J., USA , XP002390458 ISBN: 911910-28-X page 823, column 2; compound 5120 page 266, column 1; compound 1760	22-25,34
Y	US 2003/096299 A1 (WITTAMER VALERIE ET AL) 22 May 2003 (2003-05-22) paragraph [0175]	1-18,20, 21
A	BROWN ANDREW J ET AL: "The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids." THE JOURNAL OF BIOLOGICAL CHEMISTRY. 28 MAR 2003, vol. 278, no. 13, 28 March 2003 (2003-03-28), pages 11312-11319, XP002240154 ISSN: 0021-9258 page 11317, column 2, paragraph 2 abstract	1-21, 30-33, 37, 42-47, 55-61, 64-66, 69,70, 73,76-80

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/001904

Box 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 26-29,35,36,38-41,48-54,62,63,67,68,71,72,74,75
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:

see FURTHER INFORMATION sheet PCT/ISA/210

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 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:

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 fee, this Authority did not invite payment of any additional fee.

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.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claim 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 26-29,35,36,38-41,48-54,62,63,67,68,71,72,74,75

Claims 26-29, 35-36, 38-41 are directed to a second medical use of any of the above listed compounds, i.e. propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, hexanoic acid, isohexanoic acids, heptanoic acid, isoheptanoic acids, octanoic acid, isooctanoic acids, nonanoic acid, isononanoic acids, valproic acid, isovaleramide, caproic acid, oenanthylic acid, caprylic acid, hexahydrobenzoic acid, pelargonic acid and 5-hexenoic acid.
Claims 48-54 are directed to methods of diagnosing isovaleric-acid related olfactory malfunction or a CNS-disorder (specifically epilepsy).
Claims 62 and 63 relates to the use of a kit according to claims 56-59 for screening anticancer compounds or compounds to treat a CNS disorder or disease.
Claims 67 and 68 are directed to the use of a kit comprising RCC356 for the diagnosis or prognosis of CNS-related diseases or isovaleric acid-related olfactory malfunction, respectively.
Claims 71 and 72 envisage to the use of a transgenic animal for RCC356 or an ortholog thereof to study the progression of CNS disorders (specifically epilepsy) or diseases and/or treatment of (isovaleric-related) olfactory malfunction.
Claims 74 and 75 are directed to the use of a RCC356 knock out to study the effect of RCC356 on the progression of isovaleric acid-related olfactory malfunction or CNS disorders or diseases, respectively.

Claims 26-29, 35, 36, 38-41, 48-54, 62, 63, 67, 68, 71, 72, 74 and 75 lack however so severely support under Article 6 PCT and the application as a whole lacks so severly disclosure under Article 5 PCT, that the subject-matter of these claims has not be searched according to Article 17(2)(a)(ii) and (b)) PCT.

The following reasons are given for the objection under lack of support and disclosure:
No experimental data has been provided for supporting the teaching that ligands of RCC356 can influence any of the diseases mentioned above (i.e. cancer of prostate, cervix, uterus, rectum, stomach or kidney or epilepsy) nor does the prior art support this teaching. As regards the dysfunction "isovaleric acid-related olfactory malfunction" no disease with this name is known to the skilled person, and there is no data suppporting the mere existence of the disease/dysfunction named.
On p.44: par.2 of the description it is described that RCC356 has been observed in the prior art document US6790631 to be overexpressed in certain cancer types. The mere fact that a protein is overexpressed in a

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

disease does however not prove any causal relationship between this protein and the disease. Even less it can be deduced that any ligand binding to this protein will have an influence in the course of the disease.
As regards a potential treatment of epilepsy, it would appear from the description (p.44: par.3) that it is not ensured that RCC356 is expressed in brain and that isovaleric acid is involved in epilepsy, let alone that RCC356 is involved in the mechanism of epilepsy and a potential effect of isovaleric acid in epilepsy is due to binding to RCC356.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/001904

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003213004 A1	13-11-2003	CA 2447564 A1	21-11-2002
		EP 1539805 A2	15-06-2005
		JP 2005512509 T	12-05-2005
		WO 02092842 A2	21-11-2002
US 2003096299 A1	22-05-2003	AT 309543 T	15-11-2005
		CA 2450587 A1	23-01-2003
		DE 60207254 D1	15-12-2005
		DE 60207254 T2	13-07-2006
		DK 1405083 T3	20-03-2006
		WO 03006996 A2	23-01-2003
		EP 1405083 A2	07-04-2004
		ES 2252494 T3	16-05-2006
		JP 2005500047 T	06-01-2005
		US 2003104478 A1	05-06-2003