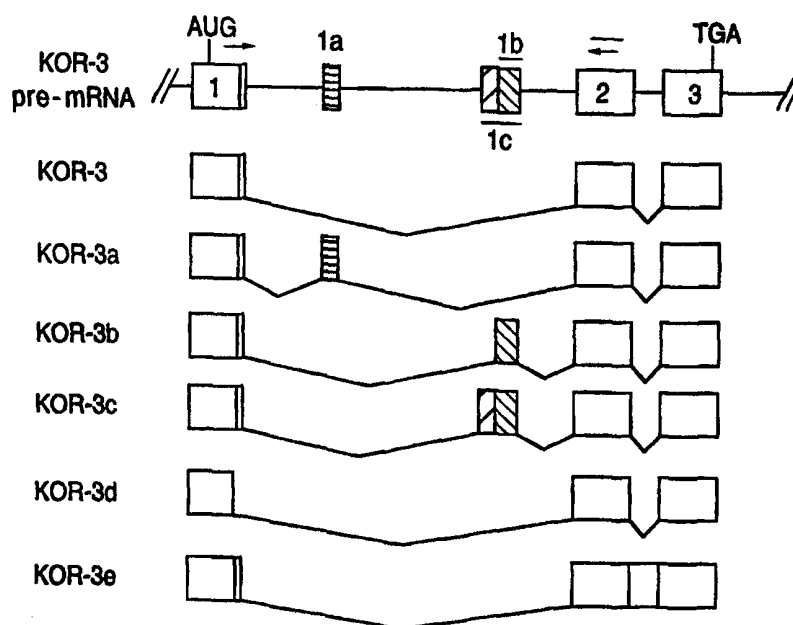




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: IDENTIFICATION AND CHARACTERIZATION OF SPLICE VARIANTS OF KAPPA3-RELATED OPIOID RECEPTOR (KOR3) GENE



(57) Abstract

The present invention encompasses novel splice variant forms of the muopioid receptor-1 (KOR-3) and the polynucleotide sequences encoding the KOR-3 splice variants. The invention further encompasses methods of screening for compositions regulating the KOR-3 splice variant activities and the development of therapeutic modalities directed to regulating activity. Regulation of the KOR-3 splice variant activities may impact the physiological processes of analgesia and weight management.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/15977

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/705 G01N33/50 A01K67/027 C07K16/28

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)

IPC 7 C12N C07K G01N A01K

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 12616 A (SLOAN KETTERING INST CANCER) 11 May 1995 (1995-05-11) the whole document	1-4, 21-29, 36-44, 51-66, 70,71, 76-80
X	WO 94 28132 A (ARCH DEV CORP ;BELL GRAEME I (US); REISINE TERRY (US); YASUDA KAZU) 8 December 1994 (1994-12-08) see whole document, particularly figure 14, examples X,XV,4-6,9 -/--	1-4, 21-29, 36-44, 51-66, 76-80

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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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.

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Date of the actual completion of the international search

2 February 2000

Date of mailing of the international search report

11. 05. 2000

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/15977

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE EMBL - EMROD [Online] Entry MMUOR3S04, Acc.no. U32928, 28 July 1996 (1996-07-28) PAN, Y.X. ET AL.: "Mus musculus opioid receptor (KOR-3) gene, exon-2." XP002129521 the whole document ---	5,6
A	DATABASE EMBL - EMROD [Online] Entry MMUOR3S06, Acc.no. U32930, 28 July 1996 (1996-07-28) PAN, Y.X. ET AL.: "Mus musculus opioid receptor (KOR-3) gene, exon 3." XP002129522 the whole document ---	5,6
A	NISHI, M. ET AL.: "Structure and chromosomal mapping of genes for the mouse kappa-opioid receptor and an opioid receptor homologue (MOR-C)." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 205, no. 2, 15 December 1994 (1994-12-15), pages 1353-7, XP002129517 the whole document ---	
A	WANG, J.B. ET AL.: "cDNA cloning of an orphan opiate receptor gene family member and its splice variant." FEBS LETTERS, vol. 348, 1994, pages 75-9, XP002129518 the whole document ---	
P,X	PAN, Y.-X. ET AL.: "Identification and differential regional expression of KOR-3/ORL-1 gene splice variants in mouse brain." FEBS LETTERS, vol. 435, 11 September 1998 (1998-09-11), pages 65-8, XP002129519 the whole document -----	1-12, 21-29, 36-44

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/15977

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOLLEREAU, C. ET AL.: "ORL1, a novel member of the opioid receptor family. Cloning, functional expression and localization." FEBS LETTERS, vol. 341, 1994, pages 33-8, XP002129516 cited in the application the whole document	1-4, 21-29, 36-44, 51,52
X	--- PAN, Y.-X- ET AL.: "Cloning and functional characterization through antisense mapping of a kappa3-related opioid receptor" MOLECULAR PHARMACOLOGY, vol. 47, June 1995 (1995-06), pages 1180-8, XP000867529 abstract page 1187, right-hand column, paragraph 2; figures 5,6	1-4, 21-29, 36-44, 51,52
Y	--- HALFORD, W.P. ET AL.: "Functional role and sequence analysis of a lymphocyte orphan opioid receptor." JOURNAL OF NEUROIMMUNOLOGY, vol. 59, 1995, pages 91-101, XP000867789 abstract page 99, left-hand column, paragraph 2 - paragraph 4; figures 1,6	1-12,19, 21-29
Y	--- PASTERNAK G W ET AL: "Pasternak and Standifer reply - The KOR3 receptor and the kappa3-opioid receptor may be splice variants of the same gene" TRENDS IN PHARMACOLOGICAL SCIENCES,GB,ELSEVIER TRENDS JOURNAL, CAMBRIDGE, vol. 17, no. 6, 1 June 1996 (1996-06-01), pages 217-218, XP004034560 ISSN: 0165-6147 the whole document	1-12,19, 21-29
A	--- DATABASE EMBL - EMROD [Online] Entry MMUOR3S02, Acc.no. U32926, 28 July 1996 (1996-07-28) PAN, Y.X. ET AL.: "Mus musculus opioid receptor (KOR-3) gene, exon 1." XP002129520 the whole document --- -/--	5,6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 15977

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:
Remark: Although claims 70-75, and claim 80 in as far as an in vivo method is concerned, 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.
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 II Observations where unity of invention is lacking (Continuation of item 2 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.:

see additional sheet, subject 1.

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

1. Claims: 5-12,24-29,37-44 completely, and 1-4,19,21-23,36, 51-80 partially

Mouse KOR-3 variants A,B,C and E as represented in figures 2-5, or those with comparable immunogenic or pharmacologic activity, nucleic acids encoding them, as represented in figures 9-12, complements thereof, fragments of the nucleic acids or their complements comprising at least 15 nucleotides, vectors comprising said nucleic acids, methods for screening compositions for opioid activity using said peptides, transgenic non-human animal expressing said proteins, pharmaceutical compositions comprising said peptides, and the use of said variant peptides in diagnostic methods.

2. Claims: 13-14,30-31,45-46 completely and 1-4,19,21-23,36, 51-80 partially

Rat KOR-3 variant A as represented in figure 6, or those with comparable immunogenic or pharmacologic activity, nucleic acid encoding said variant, as represented in figure 13, complements thereof, fragments of the nucleic acids or their complements comprising at least 15 nucleotides, vector comprising said nucleic acid, methods for screening compositions for opioid activity using said peptide, transgenic non-human animal expressing said protein, pharmaceutical composition comprising said peptide, and the use of said variant peptide in diagnostic methods.

3. Claims: 15-18,20,32-35,47-50 completely and 1-4,19,21-23, 36,51-80 partially

Human KOR-3 variants A and D as represented in figures 7 and 8, or those with comparable immunogenic or pharmacologic activity, nucleic acids encoding them, as represented in figures 14 and 15, complements thereof, fragments of the nucleic acids or their complements comprising at least 15 nucleotides, vectors comprising said nucleic acids, methods for screening compositions for opioid activity using said peptides, transgenic non-human animal expressing said proteins, pharmaceutical compositions comprising said peptides, and the use of said variant peptides in diagnostic methods.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern: 1al Application No

PCT/US 99/15977

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9512616 A	11-05-1995	US 5747279 A	05-05-1998
		AU 1089095 A	23-05-1995
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WO 9428132 A	08-12-1994	AU 678266 B	22-05-1997
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