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(54) Title: ANTISENSE OLIGONUCLEOTIDES FOR METABOTROPIC GLUTAMATE RECEPTOR TYPE 1 (mGluR₁)

(57) Abstract: The present invention relates to antisense oligonucleotides for metabotropic glutamate receptor type 1 (mGluR₁). There is provided oligonucleotides that hybridize to a mRNA encoding mGluR₁ or a splice variant thereof. There is also provided a method for treating a patient having a disorder related to an elevated glutamate level, such as chronic pain, or to enhance an opioid effect or to reduce opioid dependence and/or tolerance, which comprises the administration of such an oligonucleotide. Specific pain treatment is thereby obtained.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/00824

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/00 C07K14/705

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

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)

BIOSIS, MEDLINE, EPO-Internal, WPI Data, EMBASE, CHEM ABS Data, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MUKHIN A ET AL: "Activation of metabotropic glutamate receptor subtype mGluR1 contributes to post-traumatic neuronal injury." JOURNAL OF NEUROSCIENCE, (1996 OCT 1) 16 (19) 6012-20., XP000943935 the whole document	1-19
X	YOUNG M R ET AL: "Antisense ablation of type I metabotropic glutamate receptor mGluR1 inhibits spinal nociceptive transmission." JOURNAL OF NEUROSCIENCE, (1998 DEC 1) 18 (23) 10180-8., XP000943934 the whole document	1-19



Further documents are listed in the continuation of box C.



Patent family members are listed in 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

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INTERNATIONAL SEARCH REPORT

International Application No

PC1/CA 00/00824

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
0,X	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; FUNDYTUS, M. E. (1) ET AL: "An antisense oligonucleotide targeting mGluR1 attenuates allodynia/hyperalgesia in a model of chronic inflammation in rats." retrieved from STN XP002153939 abstract & SOCIETY FOR NEUROSCIENCE ABSTRACTS, (1998) VOL. 24, NO. 1-2, PP. 1870. MEETING INFO.: 28TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE, PART 2 LOS ANGELES, CALIFORNIA, USA NOVEMBER 7-12, 1998 SOCIETY FOR NEUROSCIENCE.,	1-19
0,X	--- DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; FUNDYTUS, M. E. (1) ET AL: "Antisense oligonucleotides targeting group I mGluRs attenuate nerve constriction-induced hyperalgesia and allodynia." retrieved from STN XP002153940 abstract & SOCIETY FOR NEUROSCIENCE ABSTRACTS, (1997) VOL. 23, NO. 1-2, PP. 1013. MEETING INFO.: 27TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE, PART 1 NEW ORLEANS, LOUISIANA, USA OCTOBER 25-30, 1997,	1-19
0,X	--- FAN, Z. (1) ET AL: "Inhibition of kindling by mGLUR1 antisense." SOCIETY FOR NEUROSCIENCE ABSTRACTS, (1998) VOL. 24, NO. 1-2, PP. 1936. MEETING INFO.: 28TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE, PART 2 LOS ANGELES, CALIFORNIA, USA NOVEMBER 7-12, 1998 SOCIETY FOR NEUROSCIENCE., XP000943868 abstract --- -/--	1-19

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/00824

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GANNON R L ET AL: "In situ hybridization of antisense mRNA oligonucleotides for AMPA, NMDA and metabotropic glutamate receptor subtypes in the rat suprachiasmatic nucleus at different phases of the circadian cycle." BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1994 JUN) 23 (4) 338-44., XP000943864 the whole document	1-8, 13-15
T	--- FUNDYTUS M.E.: "Common mechanisms underlying opioid tolerance and dependence, and neuropathic pain: Role of metabotropic glutamate receptors." PAIN RESEARCH AND MANAGEMENT, (2000) 5/1 (40-48)., XP000995096 see refs. 146 and 147	1-19
A	--- FUNDYTUS M E ET AL: "In vivo antinociceptive activity of anti-rat mGluR1 and mGluR5 antibodies in rats." NEUROREPORT, (1998 MAR 9) 9 (4) 731-5., XP002128754 the whole document -----	1-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 00/00824

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.: 9-12, 16-19
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
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:

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 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.:
1, 3-6, 9-19; and 2, 7-8 partially

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

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

1. Claims: 1, 3-6, 9-19; and 2,7,8 partially

antisense oligo derived from the sequence of a mGluR1 gene, in particular those characterised by the sequence of SEQ IDs NO:1-11, and related matter

2. Claims: 1-19, partially

invention 2: antisense oligo derived from the sequence of a mGluR1 gene characterised by the sequence of SEQ IDs NO:12-14 and related matter.

invention 3: antisense oligo derived from the sequence of a mGluR1 gene characterised by the sequence of SEQ IDs NO:15-19 and related matter.

invention 4: antisense oligo derived from the sequence of a mGluR1 gene characterised by the sequence of SEQ ID NO:20 and related matter.

invention 5: antisense oligo derived from the sequence of a mGluR1 gene characterised by the sequence of SEQ IDs NO:21-27 and related matter.

invention 6: antisense oligo derived from the sequence of a mGluR1 gene characterised by the sequence of SEQ IDs NO:28-30 and related matter.

invention 7: antisense oligo derived from the sequence of a mGluR1 gene characterised by the sequence of SEQ IDs NO:31-36 and related matter.

invention 8: antisense oligo derived from the sequence of a mGluR1 gene characterised by the sequence of SEQ IDs NO:37-39 and related matter.