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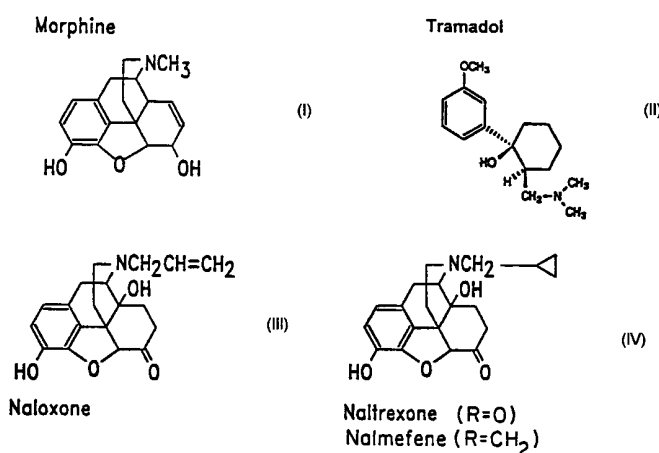
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[Continued on next page]

(54) Title: OPIOID ANTAGONISTS CONTAINING COMPOSITIONS FOR ENHANCING ANALGESIC POTENCY OF TRAMADOL AND ATTENUATING ITS ADVERSE SIDE EFFECTS



(57) Abstract: The invention generally relates to compositions and methods with tramadol and an opioid antagonist to enhance analgesic potency and/or attenuate one or more adverse effects of tramadol, including adverse side effect(s) in humans such as nausea, vomiting, dizziness, headache, sedation (somnolence) or pruritis. This invention relates to compositions and methods for selectively enhancing the analgesic potency of tramadol and simultaneously attenuating anti-analgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects associated with the administration of tramadol. The methods of the present invention comprise administering to a subject an analgesic or subanalgesic amount of tramadol and an amount of excitatory opioid receptor antagonist such as naltrexone or nalmefene effective to enhance the analgesic potency of tramadol and attenuate the anti-analgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects of tramadol.



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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/12493

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/485 //(A61K31/485,31:135)

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 A61K

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, CHEM ABS Data, EPO-Internal, CANCERLIT, EMBASE, MEDLINE, PAJ, 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	<p>MARCUS, K. T. ET AL: "Naloxone does not reverse tramadol -induced suppression of formalin-evoked pain behavior or spinal cord fos expression in the rat"</p> <p>SOCIETY FOR NEUROSCIENCE ABSTRACTS, (1995) VOL. 21, NO. 1-3, PP. 1409. MEETING INFO.: 25TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE SAN DIEGO, CALIFORNIA, USA NOVEMBER 11-16, 1995 ,</p> <p>XP000956426</p> <p>the whole document</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>1,2,4, 8-10,12, 16-18, 20,24, 25,28, 30-32, 35, 37-39, 42,44, 45,48, 50-52, 55,57, 58,61</p>

☒ 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
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- \*O\* document referring to an oral disclosure, use, exhibition or other means
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\*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.

\*Z\* document member of the same patent family

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/12493

## 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>COLLART, L. ET AL: "Partial inhibition of tramadol antinociceptive effect by naloxone in man."  BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, (1993) VOL. 35, NO. 1, PP. 73P. MEETING INFO.: MEETING OF THE BRITISH PHARMACOLOGICAL SOCIETY CLINICAL PHARMACOLOGY SECTION OXFORD, ENGLAND, UK SEPTEMBER 9-11, 1992 ,  XP000957482</p> <p>the whole document</p>	<p>1,2,4,  8-10,12,  16-18,  20,24,  25,28,  30-32,  35,  37-39,  42,44,  45,48,  50-52,  55,57,  58,61</p>
X	<p>SPILLER, HENRY A. (1) ET AL: "Prospective multicenter evaluation of tramadol exposure."  JOURNAL OF TOXICOLOGY CLINICAL TOXICOLOGY, (1997) VOL. 35, NO. 4, PP. 361-364. ,  XP000951488</p> <p>page 363, column 2, paragraph 3 - paragraph 4</p>	<p>1,2,4,  8-10,12,  16-18,  20,24,  25,28,  30-32,  35,  37-39,  42,44,  45,48,  50-52,  55,57,  58,61</p>
X	<p>DESMEULES, J. A. ET AL: "Contribution of monoaminergic modulation to the analgesic effect of tramadol"  BR. J. CLIN. PHARMACOL. (1996), 41(1), 7-12 ,  XP000950042</p> <p>abstract</p>	<p>1,2,4,  8-10,12,  16-18,  20,24,  25,28,  30-32,  35,  37-39,  42,44,  45,48,  50-52,  55,57,  58,61</p>

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 2, 6-10, 14-18, 22-24, 28-31, 35-38, 42-44, 48-51, 55-57, 61-64, 68-72, 75, 76.

Present claims 1, 2, 6-10, 14-18, 22-24, 28-31, 35-38, 42-44, 48-51, 55-57, 61-64, 68-72, 75 and 76 relate to a compound defined by reference to a desirable characteristic or property, namely "an excitatory opioid receptor antagonist" or "similarly acting opioid alkaloid and opioid peptide".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the opioid receptor antagonists specifically defined in the claims, with due regard to the general idea underlying the application.

The applicant's attention is drawn to the fact that claims, or parts of 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.