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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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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.

(54) Title: MORPHINE AND MORPHINE PRECURSORS

(57) Abstract: Methods and materials related to the use of morphine, morphine precursors (e.g., reticuline), and inhibitors of morphine synthesis or activity to treat diseases, to reduce inflammation, or to restore normal function are provided.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/35628

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 31/44(2006.01)

USPC: 514/282

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)

U.S. : 514/282

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)

STN ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	Database HCAPLUS on STN Online, NO. 1996:34749, LIU et al. 'Morphine Stimulates Nitric Oxide Release from Invertebrate Microglia,' abstract, Brain Research, 1996, Vol. 722(1,2), pp. 125-131.	1 ----- 2-5 and 9-18
X --- Y	Database HCAPLUS on STN Online, NO. 1999:276859, FIMIANI et al. 'Morphine and Anadamide Stimulate Intracellular Calcium Transients in Human Arterial Endothelial Cells: Coupling to Nitric Oxide Release,' abstract, Cellular Signalling, 1999, Vol. 11(3), pp.189-193.	1 ----- 2-5 and 9-18
X --- Y	Database HCAPLUS on STN Online, NO. 1997:710843, XU et al. 'Intravenous Morphine Increases Release of Nitric Oxide from Spinal Cord by an alpha-adrenergic and Cholinergic Mechanism,' abstract, Journal of Neurophysiology, 1997, Vol. 78(4), pp. 2072-2078.	1 ----- 2-5 and 9-18



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 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

09 June 2006 (09.06.2006)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/35628

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	Database HCAPLUS on STN Online, NO. 2004:255001, ZHU et al. 'Opiate Alkaloids and Nitric Oxide Production in the Nematode Ascaris Suum,' abstract, Journal of Parasitology, 2004, Vol. 90(1), pp. 15-22.	1 ----- 2-5 and 9-18
X --- Y	Database HCAPLUS on STN Online, NO. 2004:367898, STEFANO et al. 'Morphine Enhances Nitric Oxide Release in the Mammalian Gastrointestinal Tract Via the mu3 opiate receptor subtype: A hormonal Role for Endogenous Morphine,' abstract, Journal of Physiology and Pharmacology, 2004, Vol. 55(1,Pt.2), pp. 279-288.	1 ----- 2-5, 9-18
A	US 6,403,602 B1 (CROOKS et al.) 11 June 2002 (11.06.2002), see entire documents.	1-5 and 9-18
A	US 5,879,705 A (HEAFIELD et al.) 09 March 1999 (09.03.1999), see entire documents.	1-5 and 9-18
A	US 6,124,282 A (SELLERS et al.) 26 September 2000 (26.09.2000), see entire documents.	1-5 and 9-18

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/35628

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:
Please See Continuation 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 additional fees, this Authority did not invite payment of any 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.: 1-5 and 9-18

- 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.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

- I. Claims 1-5, 9-18, drawn to a method for inducing nitric oxide release from cells in a mammal, comprising administering to said animal a morphine or morphine-6beta-glucuronide.
- II. Claims 19-23, 27-36, drawn to a method for inducing nitric oxide release from cells in a mammal, comprising administering to said animal a thebaine or codeine.
- III. Claims 37-41, 45-52, drawn to a method for inducing nitric oxide release from cells in a mammal, comprising administering to said animal a reticuline, norlaudanoline and salutaridine.
- IV. Claims 53-57, 62-69, drawn to a method for inducing nitric oxide release from cells in a mammal, comprising administering to said animal a dopamine or L-DOPA.
- V. Claims 1, 6-8, 70-77 drawn to a method for inducing nitric oxide release from cells in a mammal, comprising administering to said animal a morphine or morphine-6beta-glucuronide in combination with selenium, L-arginine and/or calcium.
- VI. Claims 19, 24-26, drawn to a method for inducing nitric oxide release from cells in a mammal, comprising administering to said animal a thebaine or codeine in combination with selenium, L-arginine and/or calcium.
- VII. Claims 37, 42-44, drawn to a method for inducing nitric oxide release from cells in a mammal, comprising administering to said animal a reticuline, norlaudanoline and salutaridine in combination with selenium, L-arginine and/or calcium.
- VIII. Claims 53, 59-61 drawn to a method for inducing nitric oxide release from cells in a mammal, comprising administering to said animal a dopamine or L-DOPA in combination with selenium, L-arginine and/or calcium.
- IX. Claims 91-105 drawn to a method for increasing production of morphine in a mammal, comprising administering composition comprises one or more agents selected from the group consisting of reticuline, norlaudanoline, salutaridine, thebaine and codeine.
- X. Claims 106-113, drawn to a method for treating disease conditions (i.e., schizophrenia, mania, depression, psychosis, chronic pain, paranoia, autism, stress, Alzheimer's disease, Parkinson's disease, proinflammatory disease, autoimmune disease, histolytic medullary reticulosis, lupus, arthritis, atherosclerosis, neural vasculopathy, gastrointestinal condition and addiction), comprising administering one or more agents selected from the group consisting of reticuline, norlaudanoline, salutaridine, thebaine and codeine.
- XI. Claims 114-124, drawn to a method for treating disease conditions (i.e., schizophrenia, mania, depression, psychosis, chronic pain, paranoia, autism, stress, Alzheimer's disease, Parkinson's disease, proinflammatory disease, autoimmune disease, histolytic medullary reticulosis, lupus, arthritis, atherosclerosis, neural vasculopathy, gastrointestinal condition and addiction), comprising administering morphine or morphine-6b-glucuronide.
- XII. Claims 70-79 and 125 drawn to a composition comprising morphine and selenium
- XIII. Claims 80-87, drawn to a composition comprising morphine and arginine.
- XIV. Claims 88-90, drawn to a composition comprising L-DOPA and dopamine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/35628

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted. The inventions listed as Groups I-XIV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature linking groups I-XIV appears to that they all relate to a the activity of morphine in increasing nitroxide release or synthesis. However, such activity of morphine or morphine analogs are known in the art (Brain Research, abstract, 1996, Vol. 722, No. 1-2, pp. 125-131; Cellular Signalling, abstract, 1999, Vol. 11, No.3, pp. 189-193; Journal of Neurophysiology, abstract, 1997, Vol. 78(4), 2072-2078). Therefore, the technical feature linking the inventions of groups I-XIV does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art. Accordingly, Groups I-XIV are not linked by the same or a corresponding special technical feature as to form a single general inventive concept.