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(54) Title: USE OF APOPTOSIS INDUCING AGENTS IN THE PREPARATION OF A MEDICAMENT FOR THE TREATMENT OF LIVER DISEASES

(57) Abstract: The present invention is based on the finding that the artificial induction of hepatic stellate cell (HSC) apoptosis *in vivo* can promote the resolution of liver fibrosis. Thus, the present invention provides methods for treating liver disease in a subject involving administration of an inducer of apoptosis which is capable of selectively inducing hepatic stellate cell apoptosis in the liver of the subject or of an agent which is capable of giving rise to such an inducer in the subject. In addition, the invention provides methods for treating liver fibrosis in a subject comprising the selective delivery of an inducer of apoptosis specifically to the hepatic stellate cells of the subject or of an agent which is capable of giving rise to an inducer of hepatic stellate cell apoptosis.

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| A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/548 A61K31/496 A61K31/454 A61P1/16 | | | | |
| 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) EPO-Internal, BIOSIS | | | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | | | |
| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. | | |
| X | HADENGUE A ET AL: "Beneficial hemodynamic effects of ketanserin in patients with cirrhosis: possible role of serotonergic mechanisms in portal hypertension." HEPATOLOGY (BALTIMORE, MD.) UNITED STATES 1987 JUL-AUG, vol. 7, no. 4, July 1987 (1987-07), pages 644-647, XP009023170 ISSN: 0270-9139 * See results and discussion * abstract; figures 1-3 ----- -/-- | 1-11, 15, 16, 21, 22, 24-29 | | |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. | | | | |
| <input checked="" type="checkbox"/> Patent family members are listed in annex. | | | | |
| ° Special categories of cited documents : | | | | |
| <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> *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 </td> <td style="width: 50%; border: none; vertical-align: top;"> *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 </td> </tr> </table> | | | *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 |
| *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 <p style="text-align: center; font-size: 1.2em;">14 May 2004</p> | | Date of mailing of the international search report <p style="text-align: center; font-size: 1.2em;">20.07.2004</p> | | |
| Name and mailing address of the ISA European Patent Office, P.B. 5618 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | | Authorized officer <p style="text-align: center; font-size: 1.2em;">Veronese, A</p> | | |

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| A | WRIGHT M C ET AL: "GLIOTOXIN STIMULATES THE APOPTOSIS OF HUMAN AND RAT HEPATIC STELLATE CELLS AND ENHANCES THE RESOLUTION OF LIVER FIBROSIS IN RATS" GASTROENTEROLOGY, W.B.SAUNDERS COMPANY, PHILADELPHIA, US, vol. 121, no. 3, September 2001 (2001-09), pages 685-698, XP009017602 ISSN: 0016-5085 abstract figures * See discussion, page 696-697 * | 1-4,17, 18 |

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| A | <p>WRIGHT M C ET AL: "Gliotoxin stimulates apoptosis in cultured rat hepatic stellate cells" JOURNAL OF HEPATOLOGY, vol. 30, no. SUPPL. 1, 1999, page 98, XP009022977 ISSN: 0168-8278 abstract</p> | 1-4,17, 18 |
| A | <p>US 6 197 749 B1 (HAMURO JUNJI ET AL) 6 March 2001 (2001-03-06) column 40, lines 29,30 * See column 6, line 21: "gliotoxin and derivatives" * * See column 10, lines 49, 60, 61: hepatitis and hepatic cyrrhosis * column 14, line 21 column 24, lines 53,54 column 26, line 2 table 1</p> | 1-4,17, 18 |
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| X | <p>US 2002/037934 A1 (ABRAMSON STEVEN ET AL) 28 March 2002 (2002-03-28) column 1, paragraphs 5,6 claim 3 column 2, paragraph 12</p> | 1-8,19, 21,22, 24,25, 28,29 |

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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| X | <p>WO 91/13622 A (BETH ISRAEL HOSPITAL) 19 September 1991 (1991-09-19)</p> <p>page 11, lines 27,30 page 16, lines 4,12,15</p> | 1-8,19, 21,22, 24,25, 28,29 |
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| A | <p>WO 97/32585 A (LAI CHING SAN ; MEDINOX INC (US)) 12 September 1997 (1997-09-12) page 16, line 33 page 21, line 11; claim 29</p> | 1-8,11, 21-28 |

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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| A | WO 02/18330 A (EKWURIBE NNOCHIRI N ; RIGGS SAUTHIER JENNIFER (US); NOBEX CORP (US); M) 7 March 2002 (2002-03-07) page 2, lines 14-23 page 19, lines 5,6 page 8, lines 11-13 ----- | 1-8,11, 21-28 |

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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.: 1-8, 21, 22, 24-29 (partially)
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-8, 11, 21-27 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.: 1-8, 21, 22, 24-29
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 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.:
1-11, 21-29
- 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 I.1

Although claims 1-8,11,21-27 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 I.2

Claims Nos.: 1-8,21,22,24-29

The term "inducer of hepatic stellate cell apoptosis" relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, claims 1-8,21,22, 24-29 so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely for the specific classes of compounds claimed in claims 9, 19, 20, 23, in particular in relation to the treatment of liver diseases.

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-8,11, 21, 22, 24-28 (partial), 9-10 (complete)

Use of antagonists of the 5HT2B receptor for the manufacture of a medicament for the treatment of liver diseases.

2. claims: 1-8, 11, 21, 22, 24-28 (partial), 12-16 (complete)

Use of a nuclei acid construct inducing hepatic stellate cell apoptosis for the manufacture of a medicament for the treatment of liver diseases.

3. claims: 1-8,11, 21, 22, 24-28 (partial), 17, 18 (complete)

Use of gliotoxin or of a derivative thereof for the manufacture of a medicament for the treatment of liver diseases.

4. claims: 1-8,11, 19, 21, 22, 24-28 (partial)

Use of a nerve growth factor or of a derivative thereof for the manufacture of a medicament for the treatment of liver diseases.

5. claims: 1-8,11, 19, 21, 22, 24-28 (partial), 20 (complete)

Use of an antagonist of the p75 receptor (in particular spiperidone), for the manufacture of a medicament for the treatment of liver diseases.

6. claims: 1-8,11, 21, 22, 24-28 (partial), 23 (complete)

Use of sulfasalazine or of a derivative thereof for the manufacture of a medicament for the treatment of liver diseases.

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