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Published:
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(88) Date of publication of the international search report: 17 July 2003

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:** AMMONIUM SALTS OF HEMOGLOBIN ALLOSTERIC EFFECTORS, AND USES THEREOF

(57) **Abstract:** The present invention comprises compounds including inositol hexaphosphate and 2, 3-diphosphoglycerate alone or with red blood cells, compositions thereof, and methods capable of delivering a broad range of anionic molecules to the cytoplasm of mammalian cells. In certain embodiments, the present invention relates to compounds, compositions thereof, and methods that enhance the ability of mammalian red blood cells to deliver oxygen, by delivering a ligand for the allosteric site of hemoglobin to the cytoplasm of the red blood cells for treating a mammal afflicted with anemia, coronary infarction, pulmonary disease, congestive heart failure, diabetes, myocardial infarction, stroke, peripheral vascular disease, intermittent claudication, circulatory shock, hemorrhagic shock, chronic hypoxia, altitude sickness, arteriosclerosis, respiratory alkalemia, metabolic alkalosis, sickle cell anemia, reduced lung capacity, gangrene, anaerobic infections, carbon monoxide poisoning, nitric oxide poisoning, or cyanide poisoning.

WO 02/009723 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/24514

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/661 A61K31/6615 A61K31/132 A61P7/00 A61P9/00
A61P39/02 A61K31/66

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, MEDLINE, PAJ, CHEM ABS Data, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 397 846 A (WEINER MURRAY ET AL) 9 August 1983 (1983-08-09) column 3, line 10 -column 6, line 68; claims 1-12 ---	1-7,10, 11, 14-25, 30-33
X	EP 0 342 955 A (SANWA KAGAKU KENKYUSHO CO) 23 November 1989 (1989-11-23) abstract page 2, line 1 -page 4, line 5 page 9, line 1 -page 10, line 47; claims 1-7 --- -/--	1-11, 14-23, 30-33

[X] Further documents are listed in the continuation of box C.

[X] 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	Date of mailing of the international search report
27 September 2002	- 5. 03. 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	A. Jakobs

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 344 997 A (SANWA KAGAKU KENKYUSHO CO) 6 December 1989 (1989-12-06) the whole document	1-11, 14-23, 30-33
X	EP 0 342 956 A (SANWA KAGAKU KENKYUSHO CO) 23 November 1989 (1989-11-23) abstract page 2, line 1 -page 3, line 46; claims 1-8	1-11, 14-23, 30-33
X	EP 0 349 143 A (SANWA KAGAKU KENKYUSHO CO) 3 January 1990 (1990-01-03) abstract page 2, line 1 -page 3, line 30; claims 1-6	1-11, 14-23, 30-33
E	WO 02 10177 A (GMP COMPANIES INC) 7 February 2002 (2002-02-07) the whole document	1-33
X	BARNIKOL, W. K. R. ET AL: "Fine structure of oxygen-hemoglobin binding as a tool to study pharmacological effects: hemoglobin as a buffer of oxygen partial pressure" FUNKT. BIOL. MED., vol. 2, no. 4, 1983, pages 245-249, XP008008021 abstract page 245, column 1, paragraph 1 -column 2, paragraph 1 page 246, column 1, paragraph 4 -column 2, paragraph 2 page 248, column 1, paragraph 5 -column 2, paragraph 2	1-30,33
X	DATABASE MEDLINE [Online] 15 November 1985 (1985-11-15) POILLON W N ET AL: "Deoxygenated sickle hemoglobin. Modulation of its solubility by 2,3-diphosphoglycerate and other allosteric polyanions." Database accession no. NLM4055763 XP002215068 abstract & THE JOURNAL OF BIOLOGICAL CHEMISTRY. UNITED STATES 15 NOV 1985, vol. 260, no. 26, 15 November 1985 (1985-11-15), pages 13897-13900, ISSN: 0021-9258	1-30,33

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KEMPF, I. ET AL: "The allosteric effector molecule 2,3-bisphosphoglycerate as a function of protonation in aqueous solutions - an FTIR study" J. MOL. STRUCT., vol. 269, no. 1-2, 1992, pages 65-74, XP008008022 abstract page 65, paragraph 1 -page 66, paragraph 2 ---	1-30,33
X	ADACHI, KAZUHIKO ET AL: "Nucleation-controlled aggregation of deoxyhemoglobin S. Effect of organic phosphates on the kinetics of aggregation of deoxyhemoglobin S in concentrated phosphate buffer" BIOCHIM. BIOPHYS. ACTA (1980), 624(2), 372-7, XP008008020 the whole document ---	1-30,33
Y	JP 55 147295 A (NIPPON SHINYAKU CO LTD) 17 November 1980 (1980-11-17) abstract ---	1-33
Y	EP 0 472 772 A (KRUESS GMBH) 4 March 1992 (1992-03-04) the whole document ---	1-33
X	SUGDEN, M. C. ET AL: "Effects of phosphoenolpyruvate, other glycolytic intermediates and methylxanthines on calcium uptake by a mitochondrial fraction from rat pancreatic islets" DIABETOLOGIA (1978), 15(3), 173-80, XP008008019 abstract page 173, column 1-2 ---	1,10,31
T	DATABASE MEDLINE [Online] September 2002 (2002-09) VINCENT STÉPHANE P ET AL: "Transport of the highly charged myo-inositol hexakisphosphate molecule across the red blood cell membrane: a phase transfer and biological study." Database accession no. NLM12110302 XP002215069 abstract & BIOORGANIC & MEDICINAL CHEMISTRY. ENGLAND SEP 2002, vol. 10, no. 9, September 2002 (2002-09), pages 2825-2834, ISSN: 0968-0896 --- -/--	1-33

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BENESCH R.E. ET AL: "Bispyridoxal polyphosphates: a new class of specific intramolecular crosslinking agents for hemoglobin" BIOCHEM. BIOPHYS. RES. COMMUN., vol. 1988, no. 156, 2001, pages 9-14, XP001074348 abstract the whole document -----	1-33

International application No.
PCT/US 01/24514

INTERNATIONAL SEARCH REPORT

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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 30-33 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. [X] 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:

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.:

4. [X] 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.:

1-33 (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: 1-33 (partially)

   Use of a salt complex of an aliphatic ammonium cation and inositol hexaphosphate for the treatment of anemia, pulmonary disease, congestive heart failure, diabetes, myocardial infarction, stroke, peripheral vascular disease, intermittent claudication, circulatory shock, hemorrhagic shock, chronic hypoxia, altitude sickness, arteriosclerosis, respiratory alkalemia, metabolic alkalosis, sickle cell anemia, reduced lung capacity, gangrene, anaerobic infections, carbon monoxide poisoning, nitric oxide poisoning, or cyanide poisoning, said compounds per se and compositions comprising these compounds.

2. Claims: 1-33 (partially)

   Use of a salt complex of an aliphatic ammonium cation and phosphorylated glyceric acid for the treatment of anemia, pulmonary disease, congestive heart failure, diabetes, myocardial infarction, stroke, peripheral vascular disease, intermittent claudication, circulatory shock, hemorrhagic shock, chronic hypoxia, altitude sickness, arteriosclerosis, respiratory alkalemia, metabolic alkalosis, sickle cell anemia, reduced lung capacity, gangrene, anaerobic infections, carbon monoxide poisoning, nitric oxide poisoning, or cyanide poisoning, said compounds per se and compositions comprising these compounds.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-33 relate to a compound/composition/use/method defined by reference to the following expressions/wordings:
a salt complex of an aliphatic ammonium cation and an anionic ligand for a mammalian receptor, a ligand for the allosteric site of hemoglobin, a lipophilic, water soluble ammonium cation, amonoalkyl, dialkyl, trialkyl, tetraalkyl ammonium moiety, a primary ammonium cation, an anionic ligand for a mammalian receptor,c1-c6 alkyl ammonium ions, c3-c6 cycloalkyl ammonium ions, pulmonary disease, a therapeutically useful substance.
The use of these expressions/wordings in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the compounds specifically disclosed in the description as far as relating to the first invention, namely to cyclohexylamine added to inositol hexaphosphate per se and in relation to the treatment of disorders/diseases/uses as specified in claims 30-33.

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/24514

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