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(54) Title: METHODS AND COMPOSITIONS FOR BLOCKING THE CALCIUM CASCADE

(57) Abstract: Methods and compositions are provided for blocking the calcium cascade. More particularly, compositions and methods are provided that inhibit histamine reactions triggered by the calcium cascade, and those other reactions causally connected to the cascade using the naturally occurring pH gradients in the body to deliver therapeutic doses of metal ions which block the calcium cascade, or by conventional means.



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/07489

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(7) : A61K 31/28,31/295,31/30,31/315,31/32; 33/00,33/24,33/26, 33/30,33/3233A61P 17/00,31/04,31/22
 US CL : 424/617,630,638-643,646-650,682-686,688-692,697,698; 514/492-495,499-500,502.
 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. : 424/617,630,638-643,646-650,682-686,688-692,697,698; 514/492-495,499-500,502.

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)
 Please See Continuation Sheet

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 Embase on STN, Elsevier (Philadelphia, PA, USA), No. 81136844, CASSELS-BROWN, G. 'A comparative study of fucidin ointment and cicatrin cream in the treatment of impetigo,' abstract, British Journal of Clinical Practice, 1981, 35/4, 1530155). | 1-3, 16-17 ----- 1-3, 16-17 |
| X --- Y | Database Embase on STN, Elsevier (Philadelphia, PA, USA), No. 83193540, BRONSON, D.M. et al. 'Acrodermatitis enteropathica. Recognition at long last during a recurrence in a pregnancy,' abstract, Journal of the American Academy of dermatology, 1983, 9/1 (140-144). | 1-3, 16-18 ----- 1-3, 16-18 |
| X --- Y | US 6,231,889 A (RICHARDSON et al.) 15 May 2001 (15.05.2001), column 7, lines 38-43, paragraph bridging columns 6-7, claims 5, 23, 24, 27-29 and 32, column 14, Example 5, column 15, Table VI. | 1-2,6-7,14-15,17-18 ----- 1-2,6-7,14-15,17-18 |
| X --- Y | US 5,622,724 A (BRYCE-SMITH) 22 April 1997 (22.04.1997), column 3, lines 26-40 and 58-62, column 4, lines 29-67, column 4, lines 49-51 and 66, claims 1-8. | 1-2,4-5,7-9,17-18 ----- 1-2,4-5,7-13,17-18 |
| Y | US 4,956,385 A (EBY, III) 11 September 1990 (11.09.1990), column 3, lines 5-28 and 53-56. | 1-2,4-5,7-13,17-18 |

Further documents are listed in the continuation of Box C. See patent family annex.

| * Special categories of cited documents: | "T" |
|---|--|
| "A" document defining the general state of the art which is not considered to be of particular relevance | 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 |
| "E" earlier application or patent published on or after the international filing date | "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 |
| "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) | "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 |
| "O" document referring to an oral disclosure, use, exhibition or other means | "&" document member of the same patent family |
| "P" document published prior to the international filing date but later than the priority date claimed | |

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| Date of the actual completion of the international search 18 March 2005 (18.03.2005) | Date of mailing of the international search report 09 JUN 2005 |
| Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230 | Authorized officer <i>John Park</i> JOHN PARK Telephone No. 571-272-1600 |

INTERNATIONAL SEARCH REPORT

International application No.

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BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

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 order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-18, drawn to method of inhibiting calcium ion excitation secretion cascade comprising administering at least one metal ion, wherein the metal ion is a heavy metal ion such as zinc, copper, manganese, iron or tin.

Group II, claims 1-18, drawn to method of inhibiting calcium ion excitation secretion cascade comprising administering at least one metal ion, wherein the metal ion is not a heavy metal ion, e.g., magnesium, aluminum, classified in Class .

The inventions listed as Groups I and II do not relate to a single general 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: Group I is directed to the therapeutic use of heavy metal ions, whereas Group II is directed to the therapeutic use of metal ions that are not heavy metals. Clearly, none of the metals can be considered to be sharing any common structure; and further, the metals do not all belong to one recognized class of chemicals since heavy metals are categorized separately from non-heavy metals in both the U.S. classification system and IPC. Heavy metal active agents are classified in U.S. Class 424, subclasses 617-656 and IPC(7) A61K 33/24-33/38. Metal ions that are not heavy metal ions are classified elsewhere. Therefore, the heavy metals and ions thereof clearly belong to a separately recognized class of chemical substances. Moreover, the metals are so distinct that use of one of the metals is not actually indicative or suggestive of use of the other metals in the absence of nexus type art. Therefore, the contribution over the prior art, *a priori*, is in the use of these distinct types of metal ions.

Therefore, there is no technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The contribution over the prior art that each of the inventions makes over the prior art, considered as a whole, is in the use of the metal ions for therapy of various diseases associated with calcium ion excitation secretion cascade, such as rhinitis. Hence, use of different metal ions (heavy metal ions or non-heavy metal ions) define a separate and distinct contribution over the prior art. The claims therefore lack a unity of invention.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/07489

Continuation of B. FIELDS SEARCHED Item 3:

WEST, Search Terms: zinc, copper, cupric, manganese, iron, tin, rhinitis, herpes, herpetic, hsv, impetigo. STN Online, FILES
MEDLINE, HCAPLUS and EMBASE, Search Terms: copper, cupric, zinc, zn, impetigo.