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(88) Date of publication of the international search report:
28 March 2013

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(54) Title: AROMATIC-CATIONIC PEPTIDES AND USES OF SAME

(57) Abstract: A finished pharmaceutical product adapted for oral delivery of an aromatic-cationic peptide, wherein the product comprises a therapeutically effective amount of the peptide; at least one pharmaceutically acceptable pH-lowering agent; and at least one absorption enhancer effective to promote bioavailability of the active agent. The product is adapted for use in a method for enhancing the bioavailability of a therapeutic aromatic-cationic peptide delivered orally.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/42261

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/00 (2012.01)
USPC - 514/1.1
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)
USPC: 514/1.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/1.1
(keyword limited; terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google; PubMed
Search terms: aromatic-cationic peptide, ph-lowering agent, absorption enhancer, bioavailability, substantially free, acid-resistant protective vehicle, Phe-D-Arg-Phe-Lys

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0134279 A1 (STERN) 14 June 2007 (14.06.2007) abstract; para [0020], [0024], [0041]-[0042], [0044], [0053]-[0054], [0057], [0060]-[0061], [0067]	1-15
Y	US 2006/0084606 A1 (SZETO et al.) 20 April 2006 (20.04.2006) para [0009], [0072], [0074], [0082], [0149]	1-15
A	SZETO "Cell-permeable, mitochondrial-targeted, peptide antioxidants AAPS J."; 21 April 2006 (21.04.2006); Vol. 8, No. 2; pages E277-E283	1-15

☐ Further documents are listed in the continuation of Box C. ☐

* 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 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
20 November 2012 (20.11.2012)	07 DEC 2012

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/42261

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:
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 1-15, directed to a finished pharmaceutical product adapted for oral delivery of an aromatic-cationic peptide, the product comprising:
(a) a therapeutically effective amount of the aromatic-cationic peptide;
(b) at least one pharmaceutically acceptable pH-lowering agent; and
(c) at least one absorption enhancer effective to promote bioavailability of the active agent, wherein the pH-lowering agent is present in the finished pharmaceutical product in a quantity which, if the product were added to 10 milliliters of 0.1 M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of the solution to no higher than 5.5, and wherein an outer surface of the product is substantially free of an acid-resistant protective vehicle.

- Please see extra sheet for continuation -

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 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.:
1-15

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.

Continuation of Box III: Lack of Unity of Invention

Group II: claims 16-25, directed to a method for enhancing the bioavailability of a therapeutic aromatic-cationic peptide delivered orally in a subject in need of such enhancement, the method comprising selectively releasing the aromatic-cationic peptide, together with at least one pH-lowering agent and at least one absorption enhancer, into the subject's alimentary canal from a finished pharmaceutical product adapted for delivery of the aromatic-cationic peptide, wherein an outer surface of the product is substantially free of an acid resistant protective vehicle, wherein the pharmaceutical product is released into the alimentary canal in a quantity which, if added to 10 milliliters of 0.1 M aqueous sodium bicarbonate solution, would be sufficient to lower pH of the solution to no higher than 5.5.

Group III: claims 26, and 27, directed to a pharmaceutical composition for oral delivery of aromatic-cationic peptide comprising:
(A) a therapeutically effective amount of the aromatic-cationic peptide linked to a membrane translocator, the membrane translocator possesses the capability of being at least partially cleaved from the active peptide in vivo by an enzyme;
(B) at least one pharmaceutically acceptable pH-lowering agent and/or protease inhibitor; and (C) an acid-resistant protective vehicle effective to transport the pharmaceutical composition through the stomach of a patient while preventing contact between the aromatic-cationic peptide and stomach proteases.

Group IV: claims 28-36, 38, directed to a pharmaceutical composition for nasal delivery of aromatic-cationic peptide comprising:
(1) the aromatic-cationic peptide; and
(2) a bioavailability enhancing agent selected from the group consisting of a fatty acid, a sugar ester of a fatty acid and a mixture thereof.

Group V: claim 37, directed to a method of improving the stability of a liquid pharmaceutical composition of aromatic cationic peptide, comprising adding citric acid or a salt thereof in a concentration from 10 to about 50 mM to the composition.

Group VI: claim 39, directed to a method of treating or preventing an overweight condition or obesity comprising administering to a subject in need an effective amount of aromatic-cationic peptide in conjunction with a peptide having the amino acid sequence Cys-Ser-Asn-Leu-Ser-Thr Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Xaa-Xaa-Gly-Xaa-Xaa-Thr-Xaa, wherein amino acids 26, 27, 28, 29, and 31 can be any naturally occurring amino acid, and wherein amino acid 31 is optionally amidated.

The inventions listed as Groups I - VI 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:

The special technical feature of the claims of Groups I-VI claims are indicated in the Group descriptions, above.

The only common technical element shared by the above groups is that they are related to aromatic-cationic peptides. Groups I-IV share the common technical element of an absorption enhancer, wherein, for Groups I-III the enhancer is for oral delivery. Groups I and II share the common technical element "wherein an outer surface of the product is substantially free of an acid-resistant protective vehicle". Groups IV and V share the common technical element of the formulation including citric acid. These common technical elements do not represent an improvement over the combined prior art of US 2007/0134279 A1 to Stern, which teaches "pharmaceutical product adapted for oral delivery of a physiologically active peptide agent, wherein the product comprises a therapeutically effective amount of the active peptide agent; at least one pharmaceutically acceptable pH-lowering agent; and at least one absorption enhancer effective to promote bioavailability of the active agent, wherein the pH-lowering agent is present in the finished pharmaceutical product in a quantity which, if the product were added to 10 milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of the solution to no higher than 5.5, and wherein an outer surface of the product is substantially free of an acid-resistant protective vehicle. The product is adapted for use in a method for enhancing the bioavailability of a therapeutic peptide active agent delivered orally" (abstract).

Although Stern does not explicitly recite that active peptide is an aromatic-cationic peptide, it was clear from the teaching of Stern that the disclosed product was adaptable for delivery of any known pharmaceutical peptide (para [0020], [0024]). Further, in a related disclosure, Szeto teaches an aromatic-cationic peptide for pharmaceutical administration (para [0009]) for treatment of pain (para [0074]). It would have been obvious to one of skill in the art that it would be desirable for a therapeutic agent intended for the treatment of pain to be absorbed into the body as quickly as possible, as treatments for pain relief are usually not undertaken until pain has already occurred (i.e., the treatments are not undertaken prophylactically), and therefore, relief is needed immediately. It further would have been obvious that the inclusion of an enteric coating, even at a volume "as low as possible", would interfere with rapid absorption. Given that the active peptide in the composition taught by Stern was combined with an absorption enhancer, it would have been obvious that the increased protection afforded by the enteric coating would not be necessary, or at least could be substantially omitted while still allowing a substantial amount of the peptide to be absorbed, in order to allow absorption of the peptide as quickly as possible. Accordingly, it would have been obvious to one of skill in the art to include the aromatic-cationic peptide of Szeto in the pharmaceutical product taught by Stern in order to enable oral delivery of said peptide, while protecting the peptide from digestive acids and enabling rapid absorption thereof.

Therefore, the inventions of Groups I-VI lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.