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26 March 2009

(54) Title: HIGH PURITY PEPTIDES

(57) Abstract: The invention relates to methods for the preparation of highly purified peptides. The peptides are prepared in high optical purity of at least about 98.5%, and preferably at least about 99%. Specifically, Nesiritide (SEQ. ID NO. 1) having a purity of at least 99% as measured by HPLC and containing about 0.05% to about 0.5% [D-His] -Nesiritide (SEQ. ID NO. 1) as measured by chiral GC/MS.

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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K1/06 C07K14/00

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)
C07K

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	CAMARERO J A ET AL: "Solution versus solid-phase cyclization strategies for large sidechain lactam-bridged peptides: a comparative study." JOURNAL OF PEPTIDE SCIENCE : AN OFFICIAL PUBLICATION OF THE EUROPEAN PEPTIDE SOCIETY 1995 JUL-AUG, vol. 1, no. 4, July 1995 (1995-07), pages 241-250, XP002491403 ISSN: 1075-2617 Strategy A. ----- -/--	1-12

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

[X] 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 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
20 January 2009	23/02/2009

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, Fax: (+31-70) 340-3016	Vogt, Titus

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/002869

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AKAJI K ET AL: "DISULFIDE BOND FORMATION USING THE SILYL CHLORIDE SULFOXIDE SYSTEM FOR THE SYNTHESIS OF A CYSTINE PEPTIDE" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 114, no. 11, 1992, pages 4137-4143, XP009104376 ISSN: 0002-7863 cited in the application the whole document	1-17,19, 25,26
X	"Scientific Discussion for the approval of angiox" INTERNET CITATION, [Online] XP002419048 Retrieved from the Internet: URL:http://www.emea.eu.int/humandocs/PDFs/EPAR/angiox/103304en6.pdf> [retrieved on 2007-01-01] the whole document	28
X	LIGHT P: "NESIRITIDE CITRATE" IDRUGS, CURRENT DRUGS LTD, GB, vol. 2, no. 3, 1 January 1999 (1999-01-01), pages 259-264, XP008065093 ISSN: 1369-7056 the whole document	19,25,26
X,P	WO 2007/033383 A (NOVETIDE LTD [IL]; TEVA PHARMA [US]; TOVI AVI [IL]; EIDELMAN CHAIM [IL]) 22 March 2007 (2007-03-22) claims	28
A	WO 2004/092202 A (NOVETIDE LTD [IL]; TEVA PHARMA [US]; TOVI AVI [IL]; EIDELMAN CHAIM [IL]) 28 October 2004 (2004-10-28)	
A	WO 2006/041945 A (NOVETIDE LTD [IL]; TEVA PHARMA [US]; TOVI AVI [IL]; EIDELMAN CHAIM [IL]) 20 April 2006 (2006-04-20)	
X	SUN ET AL: "Use of Ssp dnaB derived mini-intein as a fusion partner for production of recombinant human brain natriuretic peptide in Escherichia coli" PROTEIN EXPRESSION AND PURIFICATION, ACADEMIC PRESS, SAN DIEGO, CA, vol. 43, no. 1, 1 September 2005 (2005-09-01), pages 26-32, XP005004617 ISSN: 1046-5928 figures 5,6	19,25,26
X	WO 2006/045503 A (LONZA AG [CH]; DROZ ANNE-SOPHIE [CH]; SCHNIDRIG JASMINE [CH]; STUDER N) 4 May 2006 (2006-05-04) claims	28

INTERNATIONAL SEARCH REPORT

International application No.
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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:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an 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 reportcovers only those claims for which fees were paid, specifically claims Nos.:

1-17 and partially claims 18, 20-24 (invention 1) and claims 19, 25, 26 28 (inventions 5 and 7).

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 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-17, 19, 25, 26, 28 and partially claims 18,20-24

Subject matter of inventions 1, 5 and 7.

Invention 1: claims 1-17 and partially claims 18,20-24

Method for the synthesis of peptide comprising acid-labile (U,Y) and orthogonal protecting groups (X), wherein if the peptide contains two or more thiol residues then all thiol residues are protected by the acid labile protecting groups (U).

Invention 2: Partially claims 18, 20-24.

Method of claim 18 wherein X=U= an acid labile protecting group.

Invention 3: partially claims 18, 20-24.

Method of claim 18, wherein X=U= orthogonal cleavable.

Invention 4: partially claims 18, 20-24.

Method of claim 18, wherein X= acid labile, and U= orthogonal cleavable.

Invention 5: claims 19, 25, 26.

Nesiritide.

Invention 6: claim 27.

Teriparatide.

Invention 7: claim 28.

Bivalirudin.

Invention 8: claim 29.

Exenatide.

Invention 9: claim 30.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Sermorelin.

Invention 10: claim 31.

Corticorelin.

Invention 11: claim 32.

Enfuvirtide.

Invention 12: claim 33.

Thymosin alpha 1.

Invention 13: claim 34.

Pramlintide.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/002869

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 1805204 A2	11-07-2007
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