Title: POLYPEPTIDES DERIVED FROM AMYLOID PRECURSOR PEPTIDE (APP) AND THEIR USES

Abstract: The invention provides a compound having formula X₁₁₋₁⁻Arg-Xaa-Arg-Xaa² in which X₁₁ and Xaa² are up to 30 amino acid residues and Xaa is an amino acid residue. A preferred compound is the tripeptide Arg-Glu-Arg which corresponds to amino acid residues 328 to 330 of human amyloid precursor protein. The invention further provides a derivative of a polypeptide having the formula: X₁₁₋₁⁻Arg-Xaa-Arg-Xaa² wherein X₁₁ and Xaa², which may be the same or different, each represents from zero to 30 natural or synthetic amino acid residues or derivatives thereof and Xaa represents a natural or synthetic amino acid residue or derivative thereof, at least one functional group of at least one said amino acid residue or derivative thereof being protected by a protective group. The compounds of the invention are believed to be useful in the treatment of Alzheimer’s disease and as cognitive enhancers.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7  C07K14/47  C07K5/09  C07K5/11  C07K5/103  A61K38/17
    C07K4/00  C07K14/00  C07K7/06  A61K38/03  A61K38/06
    A61K38/07  A61K38/08  A61K38/16  A61P25/28  C07K5/00

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)

IPC 7  C07K  A61K  A61P

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>WO 94 098008 A (SAITOHSUNAO;UNIV CALIFORNIA (US)) 11 May 1994 (1994-05-11) cited in the application claims 3-50; figure 1</td>
<td>1-80</td>
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<td>RIST BEATE ET AL: &quot;The bioactive conformation of neuropeptide Y analogues at the human Y-2-receptor.&quot; EUROPEAN JOURNAL OF BIOCHEMISTRY, Vol. 247, No. 3, 1997, Pages 1019-1028, XP001135256 abstract; figure 1; table 1 page 1020, column 1, line 1 - line 9 page 1020, column 2, line 47 - line 51</td>
<td>1-12, 44-55, 64,67</td>
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Further documents are listed in the continuation of box C. 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 data 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

*"S" document member of the same patent family

Date of the actual completion of the international search

16 April 2003

Date of mailing of the international search report

05.05.03

Name and mailing address of the ISA

European Patent Office, P.O. 5818 Patentfles 2
NL-2280 HV Rijswijk
Tel. (+31-70) 540-2040, Tx. 31 651 spo nl
Fax. (+31-70) 340-3016

Authorized officer

Jenn, T

Form: PCT/ISA/210 (second sheet) (July 1992)
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<tr>
<td>X</td>
<td>US 5 958 883 A (SNOW ALAN D) 28 September 1999 (1999-09-28) claims 1,3-5</td>
<td>44-55, 64,66-72</td>
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<td>X</td>
<td>NINOMIYA, HARUAKI ET AL: &quot;Amino acid sequence RERMS represents the active domain of amyloid beta/A4 protein precursor that promotes fibroblast growth&quot; JOURNAL OF CELL BIOLOGY (1993), 121(4), 879-86, 1993, XP009005688 cited in the application abstract; table 1 page 885, column 1, line 60 - column 2, line 2; table 1</td>
<td>32-35, 50-64, 66-80</td>
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<td>X</td>
<td>WO 98 09985 A (YEDA RESEARCH AND DEVELOPMENT CO. LTD., ISRAEL; EISENBACK-SCHWARTZ, MIC) 12 March 1998 (1998-03-12) claims 1,3,15,18,19,22</td>
<td>1-43, 50-80</td>
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<td>JAMES, J. A. ET AL: &quot;Basic amino acids predominate in the sequential autoantigenic determinant of the small nuclear 70K ribonucleoprotein&quot; SCANDINAVIAN JOURNAL OF IMMUNOLOGY (1994), 39(6), 557-66, 1994, XP009005691 abstract; figures 4-9; table 1</td>
<td>1-36, 44-67,74</td>
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<td>WO 97 00063 A (DONALDSON CYNTHIA J ; LEWIS KATHY A (US); RIVIER JEAN E F (US); SAW) 3 January 1997 (1997-01-03) page 61; example XXI page 64, line 22 - line 24 page 61, line 24 - line 27; claim 36</td>
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<td>WO 98 21327 A (FOURNIER ALAIN ; MERKEN LUC (FR); RHONE POULENC ROPER SA (FR)) 22 May 1998 (1998-05-22) page 7, line 30 - line 32; claims 4,13,18</td>
<td>44-47, 50-53, 64-72</td>
</tr>
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</table>
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. 
   - Claims Nos.: [ ]
   - because they relate to subject matter not required to be searched by this Authority, namely:
     - Although claims 36, 41-43, 71-74 and 78-80 are directed to a method of treatment of the human/animal body, the search can only be carried out and based on the alleged effects of the compound/composition.

2. 
   - Claims Nos.: 1-80
   - 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. [x] 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.:
   - 1-14, 29, 36-55, 64, 67-80 (all in part); 32-35(full)

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.
- [x] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)
FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

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

1. Claims: 1-31, 36-73 (all in part)
   
   A derivative of a polypeptide comprising the sequence RXaaR wherein said sequence RXaaR is not comprised in a sequence such as AKERLEAKRXaaR or RXaaRMSQVM or MVQSMRXaaR or RXaaRHKAELREKA and wherein said derivative of said polypeptide does not have the sequence PG-RER (wherein PG is at least one protecting group for the first Arginine), and wherein said derivative of said polypeptide is not the peptide RER, RERM, MRER, RERMS or SMRER (i.e. a derivative of a polypeptide comprising the sequence RXaaR which is not part of inventions 2-11 as defined hereinafter). The use of said derivative of a polypeptide in medicine, its use in the preparation of a medicament for use in the treatment of a neurodegenerative disease or as a cognitive enhancer, and a pharmaceutical composition comprising said polypeptide.

2. Claims: 1-14, 29, 36-55, 64, 67-73 (all in part), 32-35 (full)
   
   A tripeptide having the sequence PG-RER wherein PG is at least one protecting group for the first Arginine, and its use in medicine, its use in the preparation of a medicament for use in the treatment of a neurodegenerative disease or as a cognitive enhancer, and a pharmaceutical composition comprising said tripeptide.

3. Claims: 1-31, 36-59, 64, 66-73 (all in part)
   
   A derivative of a polypeptide comprising the sequence AKERLEAKRXaaR, and its use in medicine, its use in the preparation of a medicament for use in the treatment of a neurodegenerative disease or as a cognitive enhancer, and a pharmaceutical composition comprising said polypeptide.

4. Claims: 1-31, 36-59, 64-73 (all in part)
   
   A derivative of a polypeptide comprising the sequence RXaaRMSQVM, and its use in medicine, its use in the preparation of a medicament for use in the treatment of a neurodegenerative disease or as a cognitive enhancer, and a pharmaceutical composition comprising said polypeptide.

5. Claims: 1-31, 36-55, 60-73 (all in part)
   
   A derivative of a polypeptide comprising the sequence MVQSMRXaaR, and its use in medicine, its use in the preparation of a medicament for use in the treatment of a neurodegenerative disease or as a cognitive enhancer, and a
pharmaceutical composition comprising said polypeptide.

   A derivative of a polypeptide comprising the sequence RXaaRHKAELREKA, and its use in medicine, its use in the preparation of a medicament for use in the treatment of a neurodegenerative disease or as a cognitive enhancer, and a pharmaceutical composition comprising said polypeptide.

7. Claims: 50-55,64,67-80 (all in part)
   The peptide RER and its use in medicine, its use in the preparation of a medicament for use in the treatment of a neurodegenerative disease or as a cognitive enhancer, and a pharmaceutical composition comprising said peptide.

8. Claims: 50-55,64,66-80 (all in part)
   The peptide RERM and its use in medicine, its use in the preparation of a medicament for use in the treatment of a neurodegenerative disease or as a cognitive enhancer, and a pharmaceutical composition comprising said peptide.

9. Claims: 44-55,64,65,67-80 (all in part)
   The peptide MRER and its use in medicine, its use in the preparation of a medicament for use in the treatment of a neurodegenerative disease or as a cognitive enhancer, and a pharmaceutical composition comprising said peptide.

10. Claims: 50-55,64,66-80 (all in part)
    The peptide RERM and its use in medicine, its use in the preparation of a medicament for use in the treatment of a neurodegenerative disease or as a cognitive enhancer, and a pharmaceutical composition comprising said peptide.

11. Claims: 44-55,64,65,67-80 (all in part)
    The peptide SMRER and its use in medicine, its use in the preparation of a medicament for use in the treatment of a neurodegenerative disease or as a cognitive enhancer, and a pharmaceutical composition comprising said peptide.
Continuation of Box I.2

Claims Nos.: 1-80

Present claims 1-31 and 36-73 (all in part and all referring to invention 1 as defined in this Partial International Search Report) relate to an extremely large number of possible compounds/products/methods. In the present case, the claims according to invention 1 so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Moreover, all the concrete examples disclosed in the application concern compounds/products/methods which are not part of said invention 1, therefore no meaningful search can be carried out for the compounds/products/methods according to invention 1.

Consequently, the search has been carried out for invention 2 which appears to be supported and disclosed, namely those parts relating to the compounds/products/methods involving a tripeptide having the sequence PG-RER wherein PG is at least one protecting group for the first Arginine.

The search has also been carried out for invention 7, for which additional fees have been paid for.

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.
<table>
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<td>AU 2895192 A</td>
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