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(54) Title: STABILIZATION OF AQUEOUS COMPOSITIONS OF PROTEINS WITH DISPLACEMENT BUFFERS

(57) Abstract: An aqueous composition having increased protein stability is obtained by : a. determining a pH at which the protein has stability at the desired temperature; b. adding to the composition at least one displacement buffer wherein the displacement buffer has a pKa that is at least 1 unit greater or less than the pH of step (a); and c. adjusting the pH of the composition to the pH of step (a); wherein the aqueous composition does not comprise a conventional buffer at a concentration greater than about 2 mM and wherein the conventional buffer has a pKa that is within 1 unit of the pH of step (a).



WO 2008/084237 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/000082

A. CLASSIFICATION OF SUBJECT MATTER		
INV. A61K47/18 A61K39/29	A61K47/14 A61K9/08	A61K47/22 A61K38/44 A61K38/27
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) 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, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A X A X A	<p>EP 0 884 053 A (LILLY CO ELI [US]) 16 December 1998 (1998-12-16)</p> <p>page 6, line 44 - line 47; examples 1,2 -----</p> <p>US 4 476 118 A (BRANGE JENS J V [DK] ET AL) 9 October 1984 (1984-10-09)</p> <p>examples 6,7 -----</p> <p>US 2005/272657 A1 (O'CONNOR BARBARA H [US] ET AL) 8 December 2005 (2005-12-08)</p> <p>paragraphs [0027], [0029]; claim 10; example IV ----- -/--</p>	<p>1-34, 36-108, 114-184 35,113</p> <p>1-34, 36-108, 114-184 35,113</p> <p>1-34, 36-108, 113-184 35</p>
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the International filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"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</p> <p>"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</p> <p>"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.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the International search	Date of mailing of the International search report	
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Name and mailing address of the ISA/ 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	Authorized officer: Giménez Miralles, J	

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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	EP 1 506 786 A (DAIICHI SUNTORY PHARMA CO LTD [JP]; KANGAWA KENJI [JP]) 16 February 2005 (2005-02-16)	1-108, 114-184
A	paragraph [0031]; example 5	113
X	EP 0 938 902 A (JAPAN CHEM RES [JP]) 1 September 1999 (1999-09-01)	1-34, 36-108, 114-184
A	paragraphs [0044], [0047], [0048], [0050]; examples	35,113
E	WO 2008/066322 A (DAEWOONG CO LTD [KR]; KIM SUN-HEE [KR]; LEE SANG-KIL [KR]; AHN HYEA-KY) 5 June 2008 (2008-06-05) the whole document	1-108, 113-184

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2008/000082

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 report covers only those claims for which fees were paid, specifically claims Nos.:

1-108, 113-184 (in part)
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: 33 (in part); 1-32,34,36-108,114-184 (in part)

Method of increasing protein stability in aqueous composition by adding a displacement buffer as defined in claim 1 and adjusting pH to a pH value at which protein is stable, wherein the composition does not comprise a conventional buffer at a concentration greater than 2 mM, WHEREIN the displacement buffer is TRIS. Aqueous composition obtainable.

2. claims: 33 (in part); 1-32,34,36-47,49-90,92-108,114-184 (in part)

Method of increasing protein stability in aqueous composition by adding a displacement buffer as defined in claim 1 and adjusting pH to a pH value at which protein is stable, wherein the composition does not comprise a conventional buffer at a concentration greater than 2 mM, WHEREIN the displacement buffer is purine. Aqueous composition obtainable.

3. claims: 33 (in part); 1-32,34,36-47,49-90,92-108,114-184 (in part)

Method of increasing protein stability in aqueous composition by adding a displacement buffer as defined in claim 1 and adjusting pH to a pH value at which protein is stable, wherein the composition does not comprise a conventional buffer at a concentration greater than 2 mM, WHEREIN the displacement buffer is cytosine. Aqueous composition obtainable.

4. claims: 35; 1-32,34,36-47,49-108,114-184 (in part)

Method of increasing protein stability in aqueous composition by adding a displacement buffer as defined in claim 1 and adjusting pH to a pH value at which protein is stable, wherein the composition does not comprise a conventional buffer at a concentration greater than 2 mM, WHEREIN the displacement buffer is lactate. Aqueous composition obtainable.

5. claims: 48 (in part); 1-32,34,36-47,49-90,92-108,114-184 (in part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Method of increasing protein stability in aqueous composition by adding a displacement buffer as defined in claim 1 and adjusting pH to a pH value at which protein is stable, wherein the composition does not comprise a conventional buffer at a concentration greater than 2 mM, WHEREIN the displacement buffer is histidine. Aqueous composition obtainable.

6. claims: 91 (in part); 1-32,34,36-47,49-90,92-108,114-184 (in part)

Method of increasing protein stability in aqueous composition by adding a displacement buffer as defined in claim 1 and adjusting pH to a pH value at which protein is stable, wherein the composition does not comprise a conventional buffer at a concentration greater than 2 mM, WHEREIN the displacement buffer is lysine. Aqueous composition obtainable.

7. claims: 109; 1-108,114-184 (in part)

Aqueous composition as defined above wherein the protein is glucose oxidase.

8. claims: 110; 1-108,114-184 (in part)

Aqueous composition as defined above wherein the protein is catalase.

9. claims: 111; 1-108,114-184 (in part)

Aqueous composition as defined above wherein the protein is uricase.

10. claims: 112; 1-108,114-184 (in part)

Aqueous composition as defined above wherein the protein is hepatitis B antigen.

11. claims: 113; 1-108,114-184 (in part)

Aqueous composition as defined above wherein the protein is human growth hormone.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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