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(54) Title: RAPID ACTING INSULIN ANALOGUES

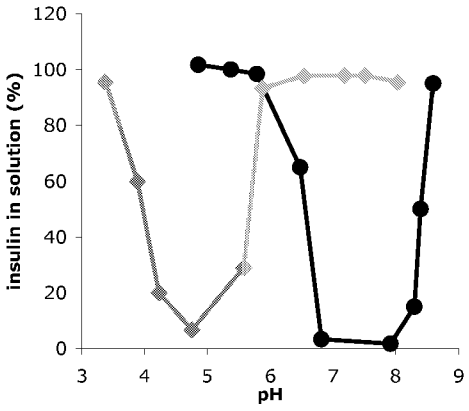

Fig. 1

(57) Abstract: The invention is related to fast acting insulin analogues which can form soluble mixtures (pre-mixed or self-mixed) with long acting insulin analogues. The fast action is achieved through monomerizing substitutions/deletions in the C-terminus of the B-chain of human insulin and the mixability with long acting insulin analogues is achieved through a substitution of the Zn-binding H is in position B10 of human insulin with lie, VaI, Ala or Phe. In one embodiment the invention is related to fast acting insulin analogues in which at least one of the natural amino acid residues in position B22-B30 in the human B-chain has been substituted with another amino acid residue having the effect of promoting formation of the monomeric form of insulin, the H is amino acid residue in position 10 in the B-chain is substituted with lie, VaI, Ala or Phe and wherein further one or more of the amino acid residues in position B22-B30 optionally have been deleted.

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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/62

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, MEDLINE, BIOSIS, EMBASE, 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	WO 2006/053906 A (NOVO NORDISK AS [DK]; OLSEN HELLE BIRK [DK]; KAARSHOLM NIELS CHRISTIAN) 26 May 2006 (2006-05-26) page 9, line 11 - page 13, line 16	1-3,7-15
X	SCHWARTZ G P ET AL: "A HIGHLY POTENT INSULIN: DES-(B26-B30)-(ASPB10,TYRB25-NH2)INSULIN(HUMAN)" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC.; US, vol. 86, no. 2, 1 January 1989 (1989-01-01), pages 458-461, XP000008386 ISSN: 0027-8424 abstract	1-3,7-15

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[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
4 November 2008	19/03/2009

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/060597

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HELLER S R: "Insulin Analogues" CURRENT MEDICAL RESEARCH AND OPINION, HANTS, GB, vol. 18, no. 1, 1 January 2002 (2002-01-01), pages S40-S47, XP002249365 the whole document	1-3,7-15
X	EP 0 214 826 A (NOVO INDUSTRI AS [DK] NOVONORDISK AS [DK]) 18 March 1987 (1987-03-18) abstract	1-3,7-15
A	WO 2007/041481 A (BIODEL INC [US]; STEINER SOLOMON S [US]; POHL RODERIKE [US]) 12 April 2007 (2007-04-12) abstract	14,15
P,X	WO 2007/096332 A (NOVO NORDISK AS [DK]; NAVER HELLE [DK]; KJELDSEN THOMAS BOERGLUM [DK]) 30 August 2007 (2007-08-30) abstract; claim 1	1-3,7-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2008/060597

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.:

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.:

1-3, 7-15 (each claim partially)

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:

Invention 1: claims 1-3, 7-15 (each claim partially)

Fast acting insulin analogue, wherein the amino acid at position B22 in the human B-chain is substituted with another amino acids residue promoting formation of the monomeric form of insulin and further the natural His at position 10 of the B-chain is substituted with Ile; the corresponding pharmaceutical compositions.

Invention 2: claims 1-3,7-15 (each claim partially)

Fast acting insulin analogue, wherein the amino acid at position B23 in the human B-chain is substituted with another amino acids residue promoting formation of the monomeric form of insulin and further the natural His at position 10 of the B-chain is substituted with Ile; the corresponding pharmaceutical compositions.

Inventions 3-9: claims 1-3, 7-15 (each claim partially)

Respectively, a fast acting insulin analogue, wherein the amino acid at one of the positions B24-B30 in the human B-chain is substituted with another amino acids residue promoting formation of the monomeric form of insulin and further the natural His at position 10 of the B-chain is substituted with Ile; the corresponding pharmaceutical compositions.

Inventions 10-18: claims 1-4, 7-15 (each claim partially)

Respectively, a fast acting insulin analogue, wherein the amino acid at positions B22-B30 in the human B-chain is substituted with another amino acids residue promoting formation of the monomeric form of insulin and further the natural His at position 10 of the B-chain is substituted with Val; the corresponding pharmaceutical compositions.

Inventions 19-27: claims 1, 2, 5, 7-15 (each claim partially)

Respectively, a fast acting insulin analogue, wherein the amino acid at positions B22-B30 in the human B-chain is substituted with another amino acids residue promoting formation of the monomeric form of insulin and further the natural His at position 10 of the B-chain is substituted with Ala; the corresponding pharmaceutical compositions.

Inventions 28-36: claims 1, 2, 4-15 (each claim partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Respectively, a fast acting insulin analogue, wherein the amino acid at positions B22-B30 in the human B-chain is substituted with another amino acids residue promoting formation of the monomeric form of insulin and further the natural His at position 10 of the B-chain is substituted with Phe; the corresponding pharmaceutical compositions.

Inventions 37-45: claims 1, 6-15 (each claim partially)

Respectively, a fast acting insulin analogue, wherein the amino acid at positions B22-B30 in the human B-chain is substituted with another amino acids residue promoting formation of the monomeric form of insulin and further the natural His at position 10 of the B-chain is substituted with Ser; the corresponding pharmaceutical compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/060597

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006053906 A	26-05-2006	JP 2008520628 T	19-06-2008
EP 0214826 A	18-03-1987	AR 241801 A1	30-12-1992
		AT 113061 T	15-11-1994
		AU 593274 B2	08-02-1990
		AU 6206686 A	05-03-1987
		CA 1306212 C	11-08-1992
		CN 86106574 A	03-08-1988
		CS 8606310 A2	12-09-1990
		DE 3650101 D1	24-11-1994
		DE 3650101 T2	23-02-1995
		DE 10075008 I1	18-05-2000
		ES 2001624 A6	01-06-1988
		FI 863512 A	01-03-1987
		GR 862233 A1	31-12-1986
		HU 42526 A2	28-07-1987
		IE 66138 B1	13-12-1995
		IL 79887 A	21-11-1991
		JP 2662390 B2	08-10-1997
		JP 62053999 A	09-03-1987
		LU 90484 A9	21-02-2000
		NL 990042 I1	01-02-2000
		NO 863474 A	02-03-1987
		NZ 217406 A	29-05-1989
		PH 25772 A	18-10-1991
		US 5618913 A	08-04-1997
		YU 4188 A1	30-06-1990
		YU 148486 A1	30-04-1991
WO 2007041481 A	12-04-2007	NONE	
WO 2007096332 A	30-08-2007	EP 1991575 A1	19-11-2008