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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

[Continued on next page]

(54) Title: GLUCAGON ANTAGONISTS

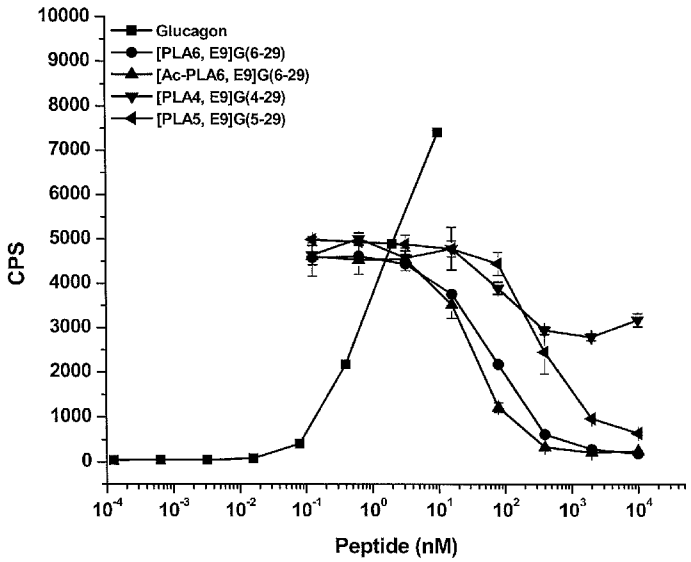


Fig. 8: Inhibition 0.8mM glucagon-induced cAMP release

(57) Abstract: Glucagon antagonists are provided which comprise amino acid substitutions and/or chemical modifications to glucagon sequence. In one embodiment, the glucagon antagonists comprise a native glucagon peptide that has been modified by the deletion of the first two to five amino acid residues from the N-terminus and (i) an amino acid substitution at position 9 (according to the numbering of native glucagon) or (ii) substitution of the Phe at position 6 (according to the numbering of native glucagon) with phenyl lactic acid (PLA). In another embodiment, the glucagon antagonists comprise the structure A-B-C as described herein, wherein A is PLA, an oxy derivative thereof, or a peptide of 2-6 amino acids in which two consecutive amino acids of the peptide are linked via an ester or ether bond.

WO 2009/058662 A3

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
7 January 2010

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80973

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 15/09, A61K 38/00 (2009.01)
USPC - 435/69.2, 514/2
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 – 435/69.2, 514/2

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 practicable, search terms used)
WEST – PGPB,USPT,USOC,EPAB,JPAB; Dialog Classic Files ? 654, 652, 351, 349, 315, 6, 35, 65, 155; USPTO Web Page; Google Scholar; Google Patents; NCBI Protein BLAST; Search terms -- glucagon antagonist, sequence, C-terminal extension, dimer, linker, Fc, *polyethylene glycol, hyperglycemia, carrier*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X – Y	US 6,667,136 B1 (MARSHALL et al.) 13 January 2004 (13.01.2004) col 2, ln 61-63; col 3, ln 43-48; ln 54-59; ln 65-67; col 4, ln 27-31; col 6, ln 28-35, ln 57-65; col 18, ln 62-67; col 20, ln 41-47; col 22, ln 41-45; col 27, ln 18-20; SEQ ID NOS: 12, 71	1-4, 6-10, 13, 24, 33, 35 ——— 14, 15, 37
Y	US 5,783,674 A (GEYSEN) 21 July 1998 (21.07.1998) col 3, ln 42-46; col 4, ln 35-47, ln 53-59; col 7, ln 14-17	14
Y	PAN et al. "Design of a Long Acting Peptide Functioning as Both a Glucagon-like Peptide-1 Receptor Agonist and a Glucagon Receptor Agonist" J. Biol. Chem.; 5 May 2006; Vol. 281, No 18; pp 12506-12515. Table 1.	15
Y	US 2007/0042956 A1 (JOHANSEN et al.) 22 February 2007 (22.02.2007) para [0767], [0770]	37

☐ 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
06 June 2009 (06.06.2009)	26 JUN 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80973

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.: 25 and 46-91
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 1-4, 6-10, 13-15, 24, 33, 35, and 37, directed to a glucagon antagonist comprising SEQ ID NO: 42, or a derivative thereof.
Group II: claims 1, 2, 11, 33 and 34, directed to a glucagon antagonist, limited to SEQ ID NO: 9. (The applicant may elect to pay an additional fee for the search of each of SEQ ID NO's: 10, 11, 12, 16, 17, 18, 43, 44, or 45).
Group III+: claims 1, 2, 5, 12, and 38-41, directed to a glucagon antagonist, limited to SEQ ID NO: 46. (The applicant may elect to pay an additional fee for the search of SEQ ID NO: 47).

- 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.:
1-4, 6-10, 13-15, 24, 33, 35, and 37, limited to SEQ ID NO: 42.

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80973

Continuation of Box III: Lack of Unity of Invention

Group IV+: claim 1, 2, 16-20, 36, directed to a glucagon antagonist, limited to SEQ ID NO: 7. Group IV also contains subgroup A: claims 21-23, directed to a glucagon antagonist, limited to SEQ ID NO: 8. (The applicant may elect to pay an additional search fee for each of SEQ ID NO's: 8, 36, 37, 38, 39, 40 and 41 in Group III, or SEQ ID NO: 37 or 38 in subgroup A).
Group V+: claims 26-32, and 42-48, directed to a glucagon antagonist comprising the native sequence of glucagon, modified by deletion of two to five amino acid residues from the N-terminus of SEQ ID NO:1, and substitution of the aspartic acid at position nine of SEQ ID NO: 1.

The inventions listed as Groups I - V 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-V are glucagon antagonists, wherein each Group is directed to an antagonist having a particular sequence, or set of sequences.

The only common technical element shared by the above groups is that they are related to Glucagon antagonists having particular sequences. This common technical element does not represent an improvement over the prior art of US 2007/0128193 A1 to O'Neil et al. (see abstract, and SEQ ID NO: 1, in particular, in comparison to SEQ ID NO: 11 of the present application). Therefore, the inventions of Groups I-V lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.