

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT NO. : 8,536,122 B2

APPLICATION NO. : 13/412283

DATED : September 17, 2013

INVENTOR(S) : Jesper Lau et al.

Page 1 of 2

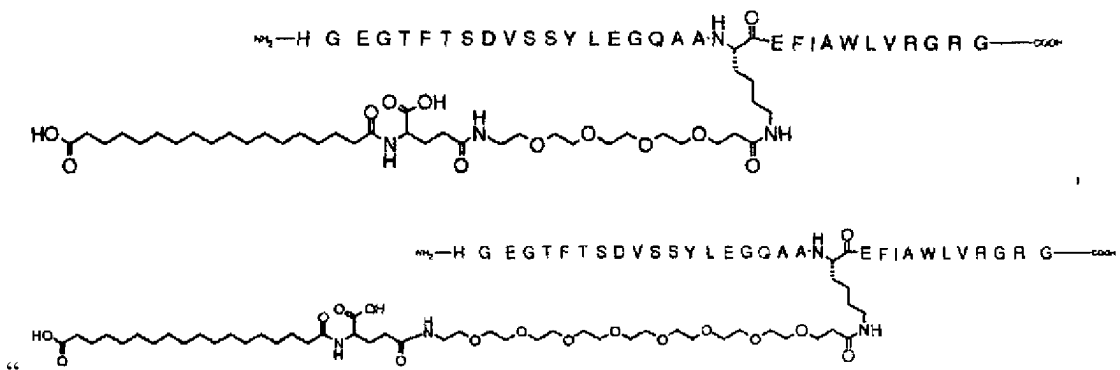
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Please replace claim 1, column 123, line 41 with the following:

“Xaa₃₀ is Ala, Glu, or Arg;”

Please replace claim 12, column 125, line 42 to column 132, line 15 with the following:

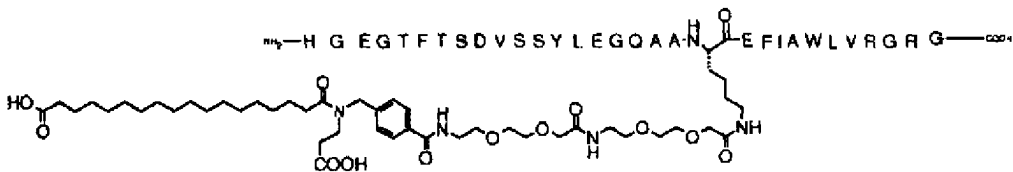
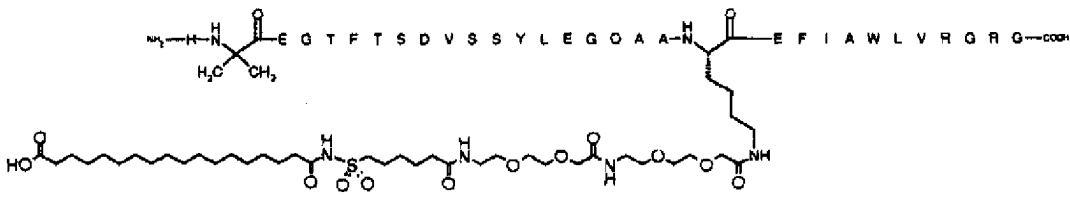
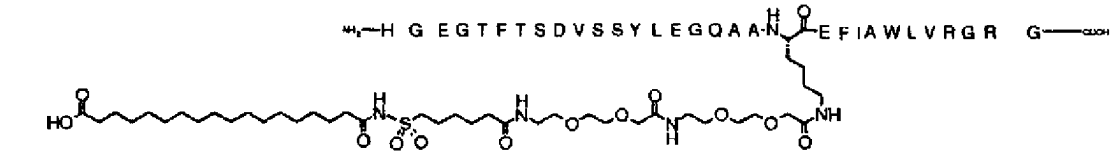
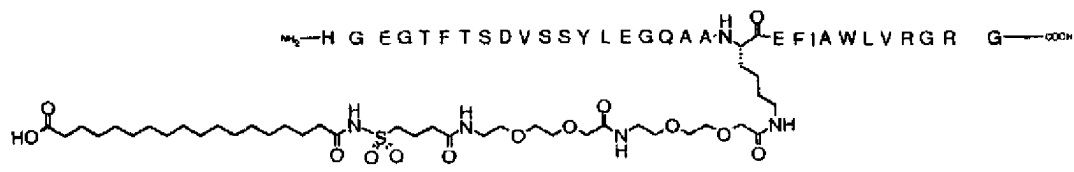
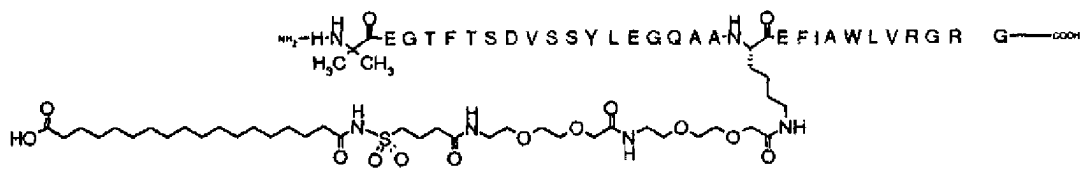
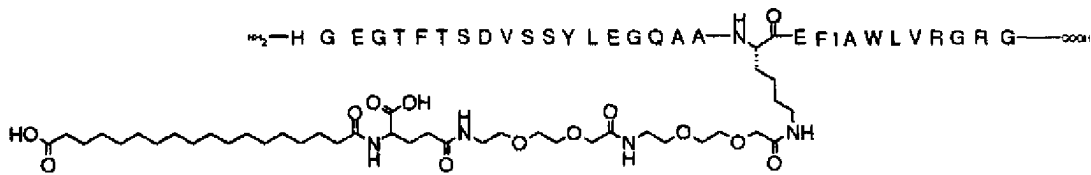


Signed and Sealed this
Fourteenth Day of April, 2015

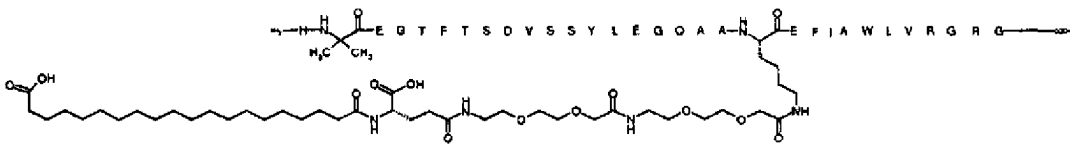
Michelle H. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office

(continued)



and



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Jesper Lau et al.

Patent No.: 8,536,122

Issued: September 17, 2013

For: Acylated GLP-1 Compounds

**REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 C.F.R. § 1.322**

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

Upon reviewing the above-identified patent, Patentee noted typographical errors which should be corrected.

In the Claims:

At column 123, claim number 1, line number 41, please replace “Xaa₃₃ is Ala, Glu or Arg;” with “Xaa₃₀ is Ala, Glu or Arg;”

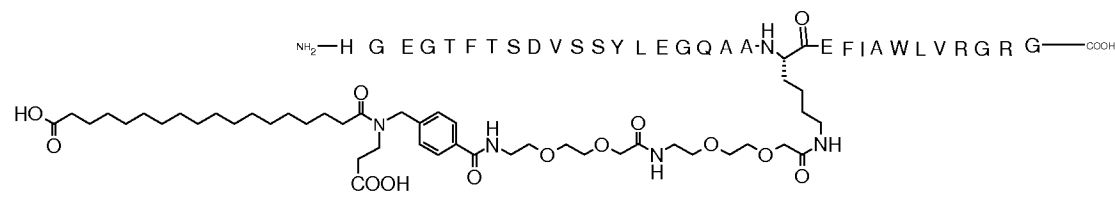
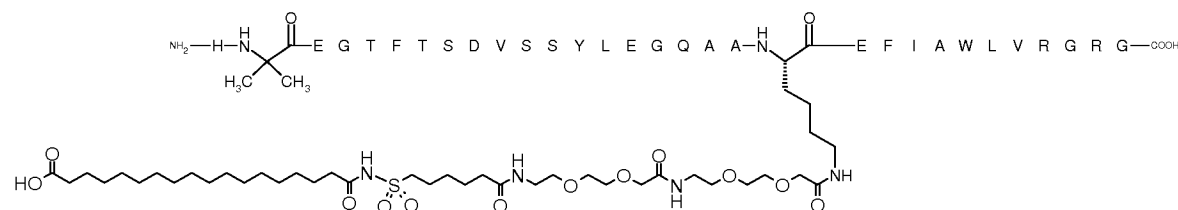
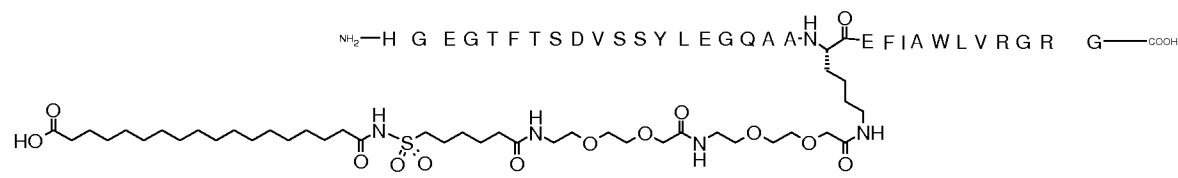
Chemical structures of the four peptides are shown below:

1. **Peptide 1:** $\text{NH}_2\text{-H G EGTFTSDVSSYLEGQAA-NH-CH(CH}_2\text{CH}_2\text{CH}_2\text{NH-CO-EFIAWLVRRGR G-COOH)}$

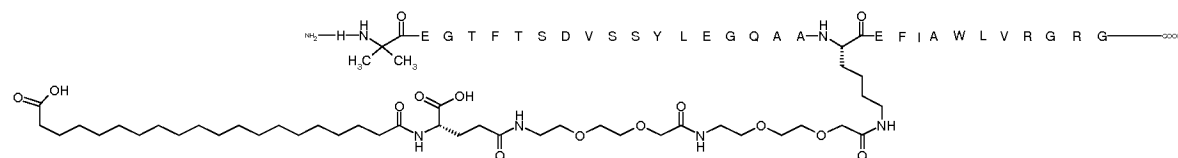
2. **Peptide 2:** $\text{NH}_2\text{-H G EGTFTSDVSSYLEGQAA-NH-CH(CH}_2\text{CH}_2\text{CH}_2\text{NH-CO-EFIAWLVRRGR G-COOH)}$

3. **Peptide 3:** $\text{NH}_2\text{-H G EGTFTSDVSSYLEGQAA-NH-CH(CH}_2\text{CH}_2\text{CH}_2\text{NH-CO-EFIAWLVRRGR G-COOH)}$

4. **Peptide 4:** $\text{NH}_2\text{-H-N(CH}_3\text{)(CH}_3\text{)-EGTFTSDVSSYLEGQAA-NH-CH(CH}_2\text{CH}_2\text{CH}_2\text{NH-CO-EFIAWLVRRGR G-COOH)}$



and



The errors were not in the application as filed by applicant; accordingly no fee is required.

Transmitted herewith is a proposed Certificate of Correction effecting such amendment. Patentee respectfully solicits the granting of the requested Certificate of Correction.

Applicant believes no fee is due with this request. However, if a fee is due, please charge our Deposit Account No. 14-1447, under Order No. 7140.214-US from which the undersigned is authorized to draw.

Patent No.: 8,536,122

Docket No.: 7140.214-US

Dated: January 19, 2015

Respectfully submitted,

Electronic signature:

/Richard W. Bork, Reg. No. 36,459/

Richard W. Bork

Registration No.: 36,459

NOVO NORDISK INC

800 Scudders Mill Road

Plainsboro, New Jersey 08536

(609) 987-5800

Attorney For Applicant

**UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION**

Page 1 of 5

PATENT NO. : 8,536,122
APPLICATION NO. : 13/412,283
ISSUE DATE : September 17, 2013
INVENTOR(S) : Jesper Lau et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Please replace claim 1, column 123, line 41 with the following:

"Xaa₃₀ is Ala, Glu, or Arg;"

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Richard W. Bork
NOVO NORDISK INC
800 Scudders Mill Road
Plainsboro, New Jersey 08536

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

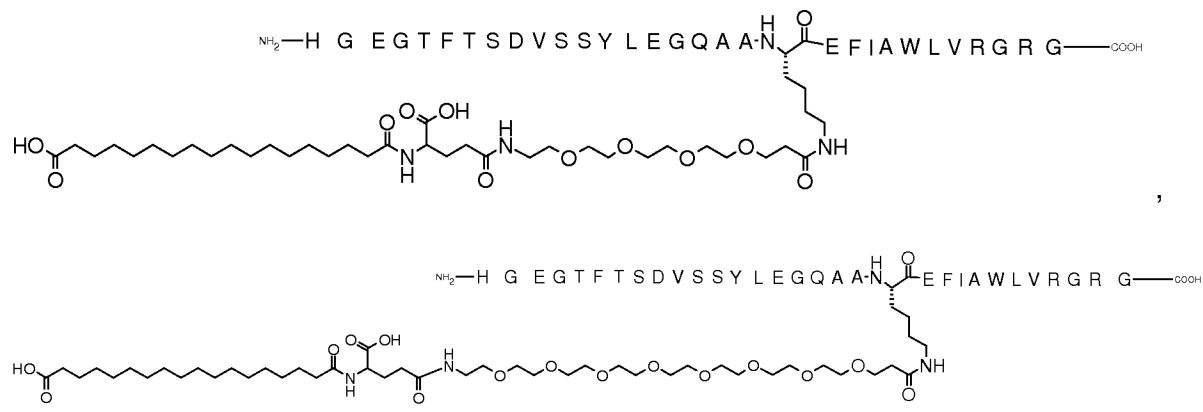
Page 2 of 5

PATENT NO. : 8,536,122
APPLICATION NO. : 13/412,283
ISSUE DATE : September 17, 2013
INVENTOR(S) : Jesper Lau et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Please replace claim 12, column 125, line 42 to column 132, line 15 with the following:

“ ...



MAILING ADDRESS OF SENDER (Please do not use customer number below):

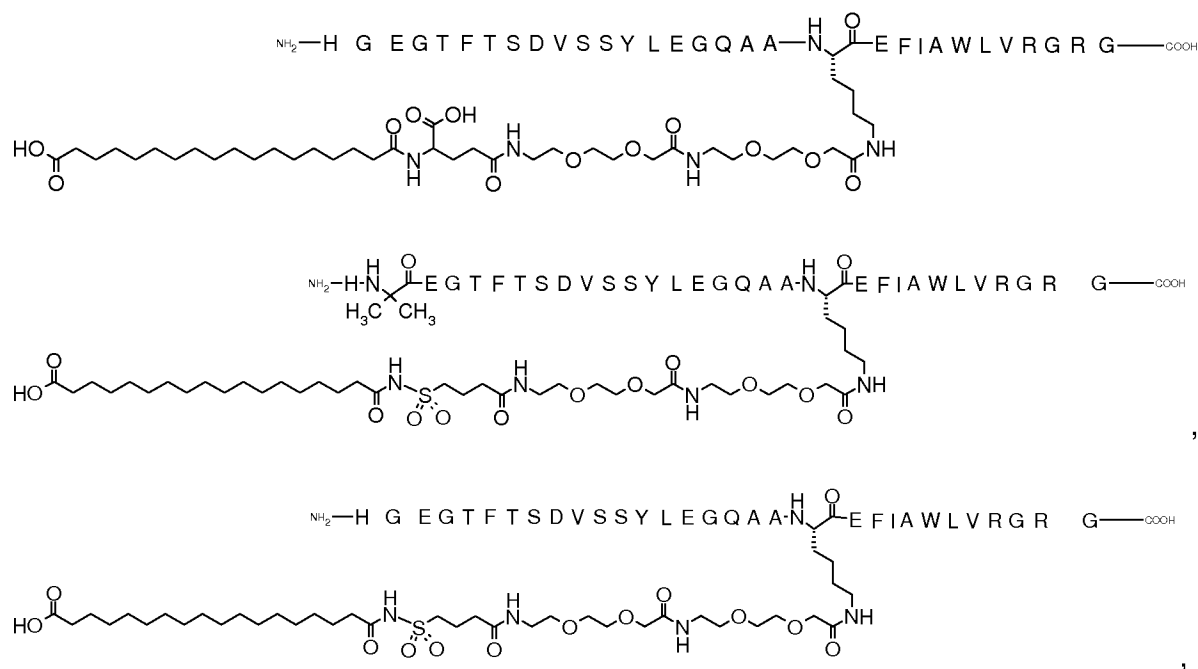
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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 3 of 5

PATENT NO. : 8,536,122
 APPLICATION NO. : 13/412,283
 ISSUE DATE : September 17, 2013
 INVENTOR(S) : Jesper Lau et al.

(continued)



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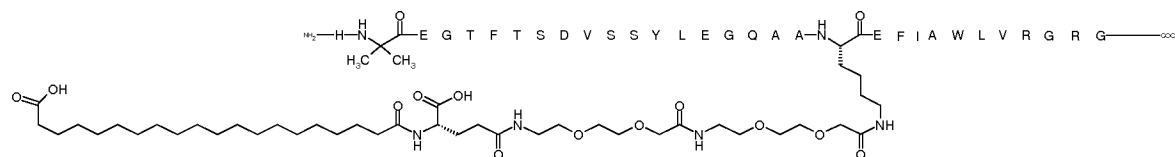
**UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION**

Page 5 of 5

PATENT NO. : 8,536,122
APPLICATION NO. : 13/412,283
ISSUE DATE : September 17, 2013
INVENTOR(S) : Jesper Lau et al.

(continued)

and



MAILING ADDRESS OF SENDER (Please do not use customer number below):

Richard W. Bork
NOVO NORDISK INC
800 Scudders Mill Road
Plainsboro, New Jersey 08536



UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/412,283	09/17/2013	8536122	7140.214-US	9438

23650 7590 08/28/2013
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Jesper Lau, Farum, DENMARK;
Florencio Zaragoza Dörwald, Smorum, DENMARK;
Paw Bloch, Taastrup, DENMARK;
Thomas Kruse Hansen, Herlev, DENMARK;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

Attorney Docket No.: 7140.214-US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Jesper Lau et al.

Application No.: 13/412,283

Confirmation No.: 9438

Filed: March 5, 2012

Art Unit: 1658

For: Acylated GLP-1 Compounds

Examiner: M. M. Cordero Garcia

AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. 1.312

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam:

Prior to issuance of the patent, applicant respectfully requests entry on this amendment under 37 C.F.R. 1.312 for the above-captioned patent application.

AMENDMENTS TO THE CLAIMS are reflected in the Listing of Claims which begins on page 2 of this paper.

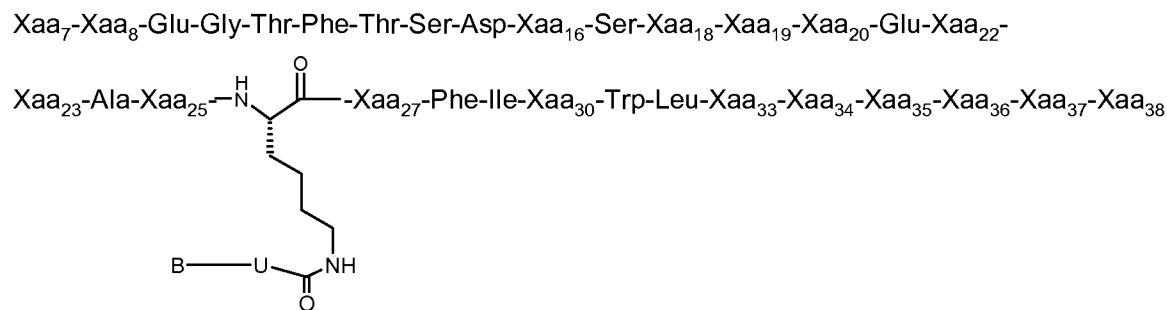
REMARKS begin on page 10 of this paper.

AMENDMENTS TO THE CLAIMS:

The following Listing of Claims replaces all prior versions, and listings, of claims.

LISTING OF CLAIMS

32. (Currently Amended) A compound of formula II (SEQ ID No. 3):



wherein

Xaa₇ is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^α-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine, or 4-pyridylalanine;

Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa₁₆ is Val or Leu;

Xaa₁₈ is Ser, Lys, or Arg;

Xaa₁₉ is Tyr or Gln;

Xaa₂₀ is Leu or Met;

Xaa₂₂ is Gly, Glu, or Aib;

Xaa₂₃ is Gln, Glu, Lys, or Arg;

Xaa₂₅ is Ala or Val;

Xaa₂₇ is Glu or Leu;

Xaa₃₀ is Ala, Glu, or Arg;

Xaa₃₃ is Val or Lys;

Xaa₃₄ is Lys, Glu, Asn, or Arg;

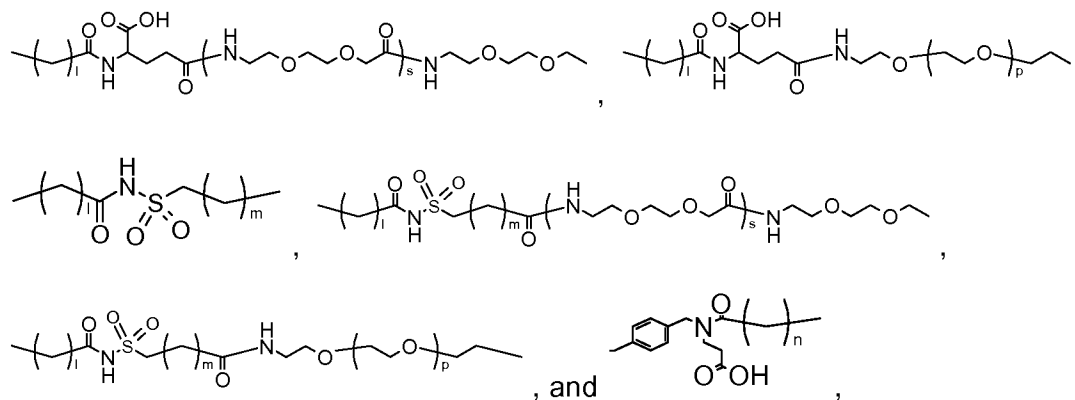
Xaa₃₅ is Gly or Aib;

Xaa₃₆ is Arg, Gly, Lys, or is absent;

Xaa₃₇ is Gly, Ala, Glu, Pro, Lys, or is absent;

Xaa₃₈ is Lys, Ser, amide, or is absent; and

where U is a spacer selected from



where n is 12, 13, 14, 15, 16, 17, or 18,

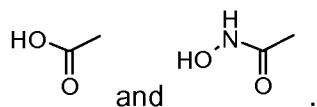
l is 12, 13, 14, 15, 16, 17, or 18,

m is 0, 1, 2, 3, 4, 5, or 6,

s is 0, 1, 2, or 3,

p is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23; and

where B is an acidic group selected from



33. (Currently Amended) A GLP-1 analog according to claim 32, wherein

Xaa₇ is His or desamino-histidine;

Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys or Aib;

Xaa₁₆ is Val;

Xaa₁₈ is Ser;

Xaa₁₉ is Tyr;

Xaa₂₀ is Leu;

Xaa₂₂ is Gly, Glu or Aib;

Xaa₂₃ is Gln or Glu;

Xaa₂₅ is Ala;

Xaa₂₇ is Glu;

Xaa₃₀ is Ala or Glu;

Xaa₃₃ is Val;

Xaa₃₄ is Lys or Arg;

Xaa₃₅ is Gly or Aib;

Xaa₃₆ is Arg or Lys

Xaa₃₇ is Gly, amide or is absent; and

Xaa₃₈ is absent.

34. (Previously Presented) A GLP-1 analog according to claim 33, wherein

Xaa₇ is His

Xaa₈ is Gly, or Aib;

Xaa₁₆ is Val;

Xaa₁₈ is Ser;

Xaa₁₉ is Tyr;

Xaa₂₀ is Leu;

Xaa₂₂ is Glu or Aib;

Xaa₂₃ is Gln;

Xaa₂₅ is Ala;

Xaa₂₇ is Glu;

Xaa₃₀ is Ala;

Xaa₃₃ is Val;

Xaa₃₄ is Lys or Arg;

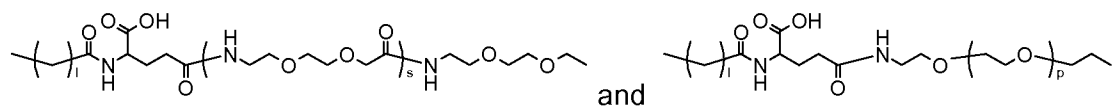
Xaa₃₅ is Gly or Aib;

Xaa₃₆ is Arg

Xaa₃₇ is Gly and

Xaa₃₈ is absent.

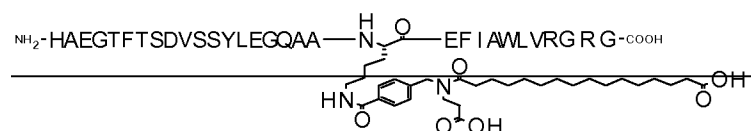
35. (Previously Presented) A GLP-1 analog according to claim 32, wherein said GLP-1 analog comprises Aib⁸ or Gly⁸ in position 8 of the GLP-1(7-37) sequence.
36. (Previously Presented) A GLP-1 analog according to claim 35, wherein said GLP-1 analog comprises Aib⁸.
37. (Previously Presented) A GLP-1 analog according to claim 32, wherein said GLP-1 analog comprises no more than six amino acid residues which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1).
38. (Previously Presented) A GLP-1 analog according to claim 32, wherein said GLP-1 analog comprises no more than 3 amino acid residues which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1).
39. (Previously Presented) A GLP-1 analog according to claim 32, wherein said GLP-1 analog comprises only one lysine residue.
40. (Previously Presented) A GLP-1 analog according to claim 32, which is
Aib⁸,Arg³⁴-GLP-1(7-37) or
Aib^{8,22},Arg³⁴-GLP-1(7-37).
41. (Previously Presented) A compound according to claim 32, wherein U is a spacer selected from



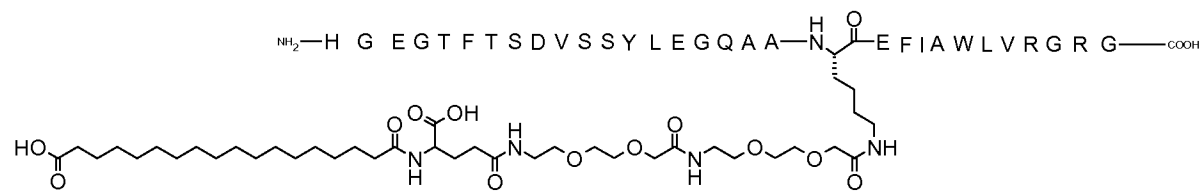
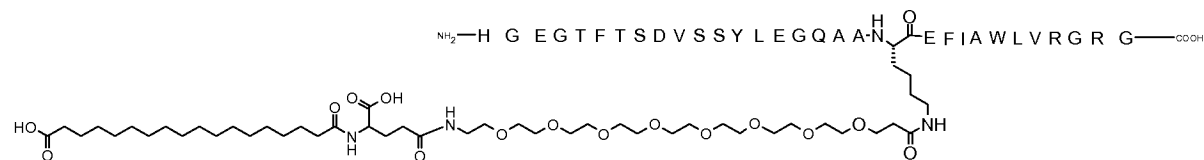
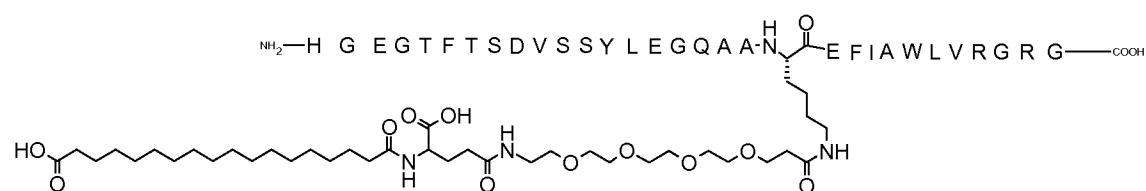
42. (Previously Presented) A compound according to claim 41, wherein B is

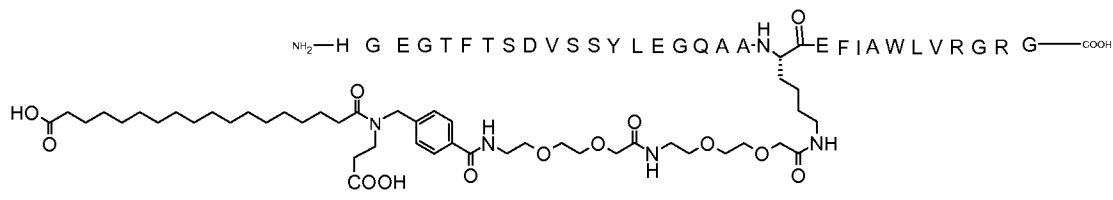
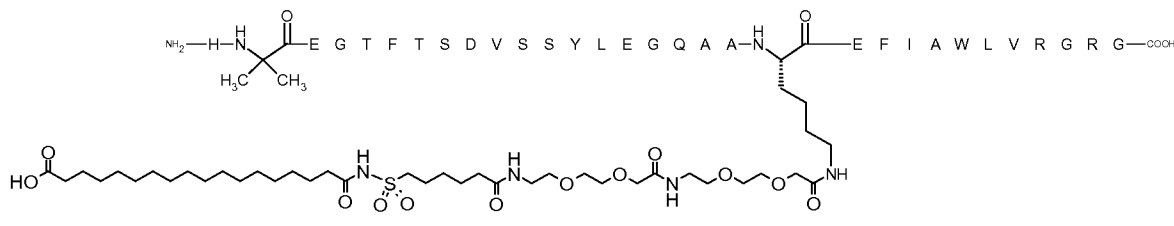
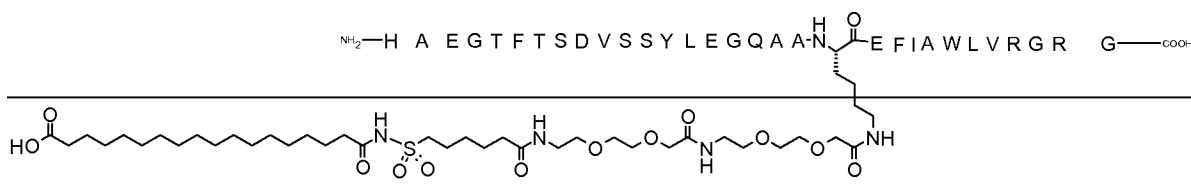
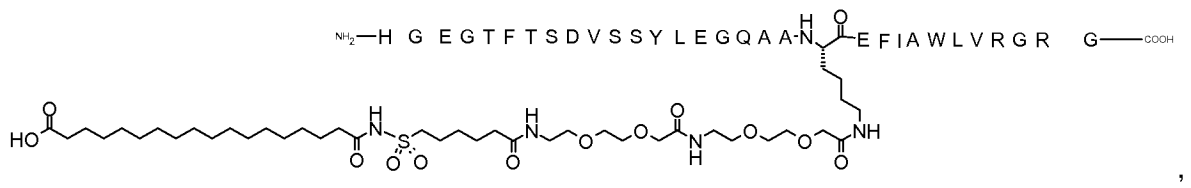
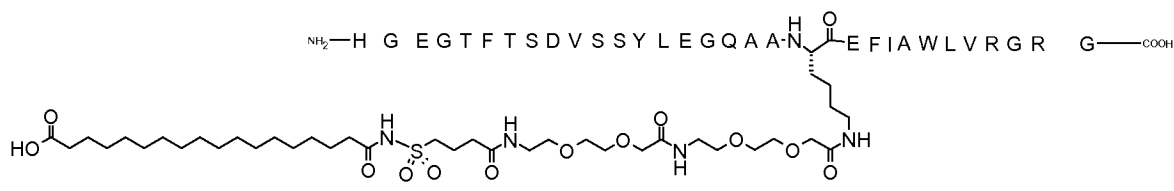
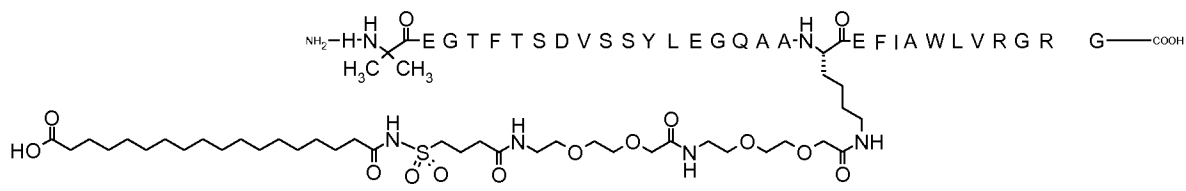


43. (Currently Amended) A compound according to claim 32 selected from the following:

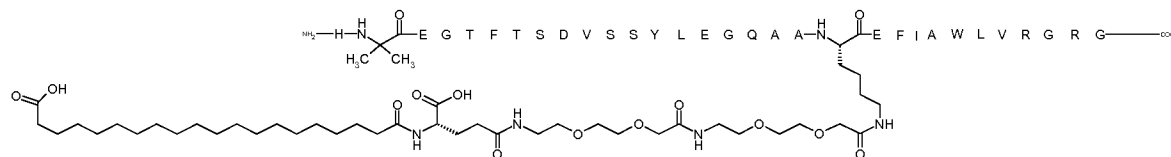


~~N-ε²⁶-(4-[[N-(2-carboxyethyl)-N-(15-carboxypentadecanoyl)amino]methyl]benzoyl)[Arg34]GLP-1-(7-37),~~





and



44. (Previously Presented) A pharmaceutical composition comprising a compound according to claim 32, and a pharmaceutically acceptable excipient.
45. (Previously Presented) A pharmaceutical composition comprising a compound according to claim 43, and a pharmaceutically acceptable excipient.
46. (Previously Presented) A method for treating hyperglycemia and/or type 2 diabetes in a subject, said method comprising administering to a subject in need of such treatment an effective amount of a GLP-1 analog according to claim 32.
47. (Previously Presented) A method for treating hyperglycemia and/or type 2 diabetes in a subject, said method comprising administering to a subject in need of such treatment an effective amount of a GLP-1 analog according to claim 43.

REMARKS:

Summary of Claim Amendments and Pending Claims

By entry of the present amendment, claims 32, 33 and 43 have been amended to remove Ala as an amino acid option at position 8 of the claimed compounds. Accordingly, claims 32-47 are pending and at issue, and claim 32 is an independent claim. No new matter has been added by these amendments.

Conclusion

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 14-1447, under Order No. 7140.214-US from which the undersigned is authorized to draw.

The undersigned invites the Examiner to contact him by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Dated: August 6, 2013

/Richard W. Bork, Reg. No. 36,459/
Richard W. Bork, Reg. No. 36,459
Novo Nordisk Inc
Customer Number: 23650
(609) 987-5800

Please use the following customer number for all correspondence regarding this application.

23650

PATENT TRADEMARK OFFICE



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/412,283	03/05/2012	Jesper Lau	7140.214-US	9438
23650	7590	08/12/2013		
NOVO NORDISK INC. INTELLECTUAL PROPERTY DEPARTMENT 800 Scudders Mill Road Plainsboro, NJ 08536			EXAMINER CORDERO GARCIA, MARCELA M	
			ART UNIT 1658	PAPER NUMBER
			NOTIFICATION DATE 08/12/2013	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nnipatent@novonordisk.com
KSHL@novonordisk.com
KISW@novonordisk.com

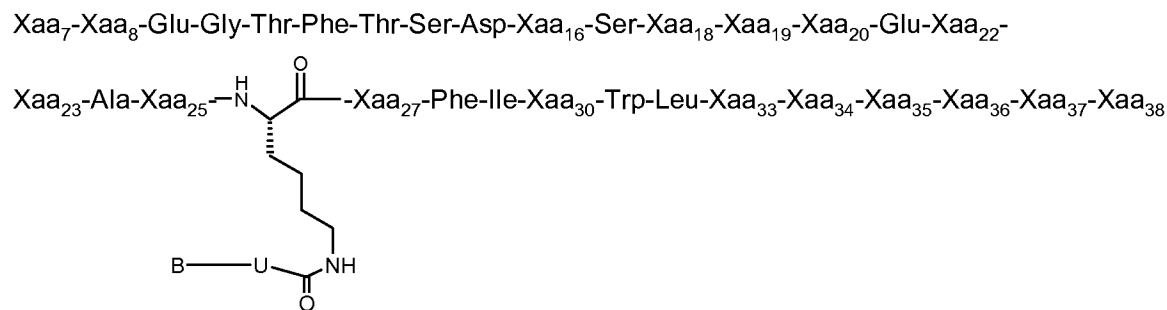
Response to Rule 312 Communication	Application No. 13/412,283	Applicant(s) LAU ET AL.
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1658
-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address -- 1. ☒ The amendment filed on <u>06 August 2013</u> under 37 CFR 1.312 has been considered, and has been: a) ☒ entered. b) ☐ entered as directed to matters of form not affecting the scope of the invention. c) ☐ disapproved because the amendment was filed after the payment of the issue fee. Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue. d) ☐ disapproved. See explanation below. e) ☐ entered in part. See explanation below.		
/KARLHEINZ R SKOWRONEK/ Supervisory Patent Examiner, Art Unit 1658		/MARCELA M CORDERO GARCIA/ Primary Examiner, Art Unit 1658

AMENDMENTS TO THE CLAIMS:

The following Listing of Claims replaces all prior versions, and listings, of claims.

LISTING OF CLAIMS

32. (Currently Amended) A compound of formula II (SEQ ID No. 3):



wherein

Xaa₇ is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^α-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine, or 4-pyridylalanine;

Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa₁₆ is Val or Leu;

Xaa₁₈ is Ser, Lys, or Arg;

Xaa₁₉ is Tyr or Gln;

Xaa₂₀ is Leu or Met;

Xaa₂₂ is Gly, Glu, or Aib;

Xaa₂₃ is Gln, Glu, Lys, or Arg;

Xaa₂₅ is Ala or Val;

Xaa₂₇ is Glu or Leu;

Xaa₃₀ is Ala, Glu, or Arg;

Xaa₃₃ is Val or Lys;

Xaa₃₄ is Lys, Glu, Asn, or Arg;

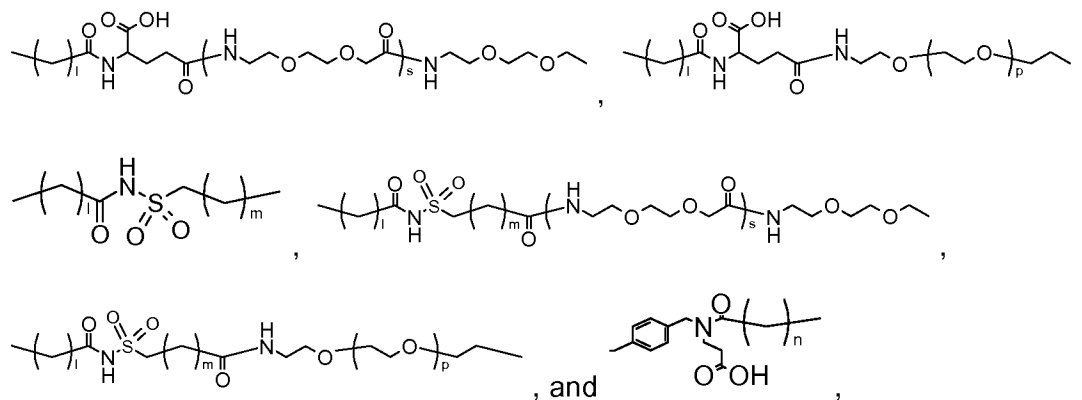
Xaa₃₅ is Gly or Aib;

Xaa₃₆ is Arg, Gly, Lys, or is absent;

Xaa₃₇ is Gly, Ala, Glu, Pro, Lys, or is absent;

Xaa₃₈ is Lys, Ser, amide, or is absent; and

where U is a spacer selected from



where n is 12, 13, 14, 15, 16, 17, or 18,

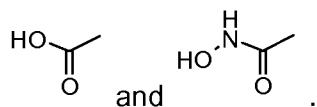
l is 12, 13, 14, 15, 16, 17, or 18,

m is 0, 1, 2, 3, 4, 5, or 6,

s is 0, 1, 2, or 3,

p is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23; and

where B is an acidic group selected from



33. (Currently Amended) A GLP-1 analog according to claim 32, wherein

Xaa₇ is His or desamino-histidine;

Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys or Aib;

Xaa₁₆ is Val;

Xaa₁₈ is Ser;

Xaa₁₉ is Tyr;

Xaa₂₀ is Leu;

Xaa₂₂ is Gly, Glu or Aib;

Xaa₂₃ is Gln or Glu;

Xaa₂₅ is Ala;

Xaa₂₇ is Glu;

Xaa₃₀ is Ala or Glu;

Xaa₃₃ is Val;

Xaa₃₄ is Lys or Arg;

Xaa₃₅ is Gly or Aib;

Xaa₃₆ is Arg or Lys

Xaa₃₇ is Gly, amide or is absent; and

Xaa₃₈ is absent.

34. (Previously Presented) A GLP-1 analog according to claim 33, wherein

Xaa₇ is His

Xaa₈ is Gly, or Aib;

Xaa₁₆ is Val;

Xaa₁₈ is Ser;

Xaa₁₉ is Tyr;

Xaa₂₀ is Leu;

Xaa₂₂ is Glu or Aib;

Xaa₂₃ is Gln;

Xaa₂₅ is Ala;

Xaa₂₇ is Glu;

Xaa₃₀ is Ala;

Xaa₃₃ is Val;

Xaa₃₄ is Lys or Arg;

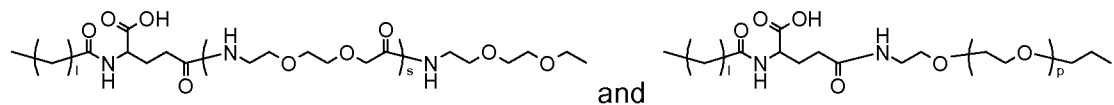
Xaa₃₅ is Gly or Aib;

Xaa₃₆ is Arg

Xaa₃₇ is Gly and

Xaa₃₈ is absent.

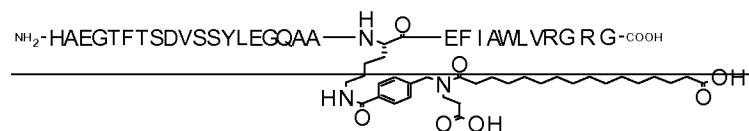
35. (Previously Presented) A GLP-1 analog according to claim 32, wherein said GLP-1 analog comprises Aib⁸ or Gly⁸ in position 8 of the GLP-1(7-37) sequence.
36. (Previously Presented) A GLP-1 analog according to claim 35, wherein said GLP-1 analog comprises Aib⁸.
37. (Previously Presented) A GLP-1 analog according to claim 32, wherein said GLP-1 analog comprises no more than six amino acid residues which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1).
38. (Previously Presented) A GLP-1 analog according to claim 32, wherein said GLP-1 analog comprises no more than 3 amino acid residues which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1).
39. (Previously Presented) A GLP-1 analog according to claim 32, wherein said GLP-1 analog comprises only one lysine residue.
40. (Previously Presented) A GLP-1 analog according to claim 32, which is
Aib⁸,Arg³⁴-GLP-1(7-37) or
Aib^{8,22},Arg³⁴-GLP-1(7-37).
41. (Previously Presented) A compound according to claim 32, wherein U is a spacer selected from



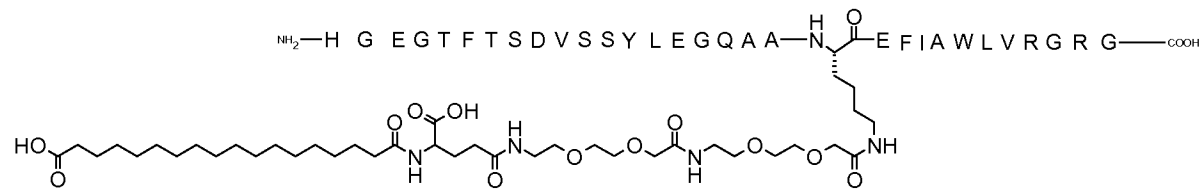
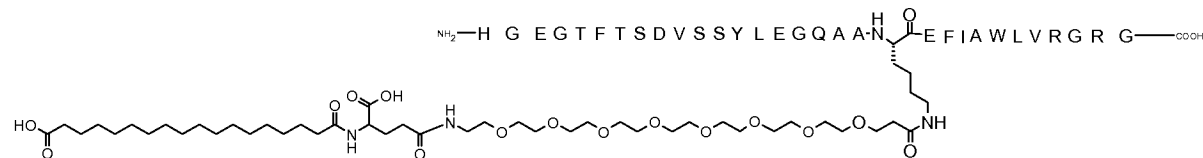
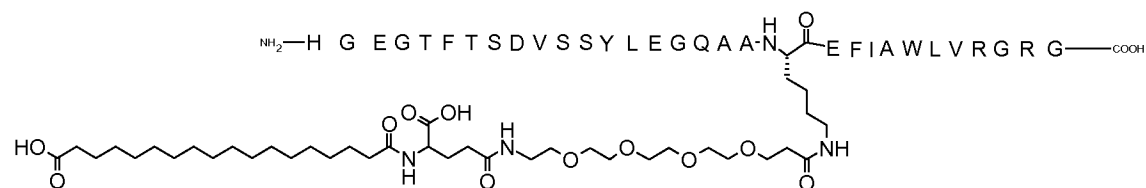
42. (Previously Presented) A compound according to claim 41, wherein B is

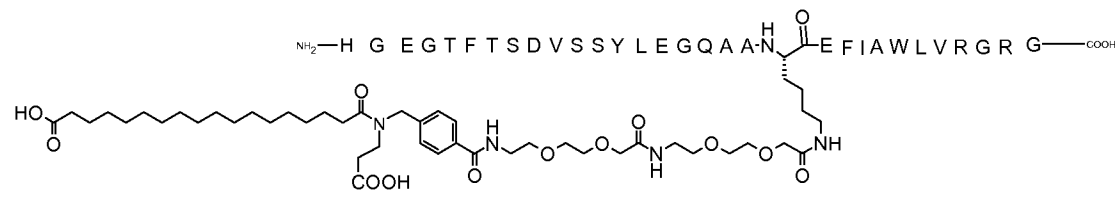


43. (Currently Amended) A compound according to claim 32 selected from the following:

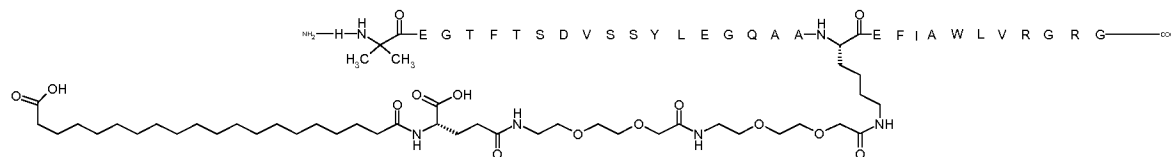


~~N-ε²⁶-(4-[[N-(2-carboxyethyl)-N-(15-carboxypentadecanoyl)amino]methyl]benzoyl][Arg34]GLP-1-(7-37),~~





MPI EXHIBIT 1003 PAGE 31



44. (Previously Presented) A pharmaceutical composition comprising a compound according to claim 32, and a pharmaceutically acceptable excipient.
45. (Previously Presented) A pharmaceutical composition comprising a compound according to claim 43, and a pharmaceutically acceptable excipient.
46. (Previously Presented) A method for treating hyperglycemia and/or type 2 diabetes in a subject, said method comprising administering to a subject in need of such treatment an effective amount of a GLP-1 analog according to claim 32.
47. (Previously Presented) A method for treating hyperglycemia and/or type 2 diabetes in a subject, said method comprising administering to a subject in need of such treatment an effective amount of a GLP-1 analog according to claim 43.

REMARKS:

Summary of Claim Amendments and Pending Claims

By entry of the present amendment, claims 32, 33 and 43 have been amended to remove Ala as an amino acid option at position 8 of the claimed compounds. Accordingly, claims 32-47 are pending and at issue, and claim 32 is an independent claim. No new matter has been added by these amendments.

Conclusion

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 14-1447, under Order No. 7140.214-US from which the undersigned is authorized to draw.

The undersigned invites the Examiner to contact him by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Dated: August 6, 2013

/Richard W. Bork, Reg. No. 36,459/
Richard W. Bork, Reg. No. 36,459
Novo Nordisk Inc
Customer Number: 23650
(609) 987-5800

Please use the following customer number for all correspondence regarding this application.

23650

PATENT TRADEMARK OFFICE

Electronic Acknowledgement Receipt

EFS ID:	16509306
Application Number:	13412283
International Application Number:	
Confirmation Number:	9438
Title of Invention:	ACYLATED GLP-1 COMPOUNDS
First Named Inventor/Applicant Name:	Jesper Lau
Customer Number:	23650
Filer:	Richard W. Bork/Csaba Attila Szakolczai
Filer Authorized By:	Richard W. Bork
Attorney Docket Number:	7140.214-US
Receipt Date:	06-AUG-2013
Filing Date:	05-MAR-2012
Time Stamp:	11:56:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 140
RAM confirmation Number	10028
Deposit Account	141447
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	7140214US_PetitionCorrectInventor.pdf	76999 26d71699845e3cd741eb55b76d610da266534520	no	1

Warnings:

Information:

2	Application Data Sheet	7140214US_SADS.pdf	87583 db3c1c0c2bee7968908eac3172148e51482a17c8	no	7
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Warnings:

Information:

This is not an USPTO supplied ADS fillable form

3	Amendment after Notice of Allowance (Rule 312)	7140214US_312_AMEND.pdf	155480 a257377aa7e937152e47047f7b65ff79c7089ce1	no	10
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Warnings:

Information:

4	Fee Worksheet (SB06)	fee-info.pdf	30333 e8ecc141d507e4938643b0d223c427d37080eacb	no	2
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Warnings:

Information:

Total Files Size (in bytes):	350395
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/412,283	03/05/2012	Jesper Lau	7140.214-US	9438
23650	7590	06/13/2013		
NOVO NORDISK INC. INTELLECTUAL PROPERTY DEPARTMENT 800 Scudders Mill Road Plainsboro, NJ 08536			EXAMINER CORDERO GARCIA, MARCELA M	
			ART UNIT 1658	PAPER NUMBER
			NOTIFICATION DATE 06/13/2013	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nnipatent@novonordisk.com
KSHL@novonordisk.com
KISW@novonordisk.com



UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office

Address : COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
13/412,283	05 March, 2012	LAU ET AL.	7140.214-US

NOVO NORDISK INC. INTELLECTUAL PROPERTY DEPARTMENT 800 Scudders Mill Road Plainsboro, NJ 08536	EXAMINER	
	MARCELA M. CORDERO GARCIA	
	ART UNIT	PAPER
	1658	20130604

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Richard W. Bork on 6/4/2013.

The application has been amended as follows:

IN THE CLAIMS:

In claim 36 at line 1, the final semi-colon has been replaced by a period.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karlheinz R. Skowronek can be reached on (571)-272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCELA M CORDERO GARCIA/
Primary Examiner, Art Unit 1658

Notice of Allowability	Application No. 13/412,283	Applicant(s) LAU ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1658	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 2/28/2013 and TD filed on 5/1/2013 and approved on 5/2/2013.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 32-47. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☒ All b) ☐ Some *c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☒ Certified copies of the priority documents have been received in Application No. 11/908,834.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Interim copies:

- a) ☐ All b) ☐ Some c) ☐ None of the: Interim copies of the priority documents have been received.

Applicant has **THREE MONTHS FROM THE "MAILING DATE"** of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date ____.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|--|
| 1. ☐ Notice of References Cited (PTO-892) | 5. ☒ Examiner's Amendment/Comment |
| 2. ☒ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date <u>See Continuation Sheet</u> | 6. ☒ Examiner's Statement of Reasons for Allowance |
| 3. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 7. ☐ Other _____. |
| 4. ☒ Interview Summary (PTO-413),
Paper No./Mail Date <u>20130426-A</u> . | |

/MARCELA M CORDERO GARCIA/
Primary Examiner, Art Unit 1658

Continuation of Attachment(s) 2. Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date: 8/28/2012, 9/7/2012, 5/1/2013.



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NOTICE OF ALLOWANCE AND FEE(S) DUE

23650 7590 05/08/2013
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

EXAMINER

CORDERO GARCIA, MARCELA M

ART UNIT

PAPER NUMBER

1658

DATE MAILED: 05/08/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

13/412,283

03/05/2012

Jesper Lau

7140.214-US

9438

TITLE OF INVENTION: ACYLATED GLP-1 COMPOUNDS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1780	\$300	\$0	\$2080	08/08/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

23650 7590 05/08/2013
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/412,283	03/05/2012	Jesper Lau	7140.214-US	9438

TITLE OF INVENTION: ACYLATED GLP-1 COMPOUNDS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1780	\$300	\$0	\$2080	08/08/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
CORDERO GARCIA, MARCELA M	1658	514-007200

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached. ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.	2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____ (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____ 3 _____
---	---

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/412,283	03/05/2012	Jesper Lau	7140.214-US	9438

23650 7590 05/08/2013
NOVO NORDISK INC.
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800 Scudders Mill Road
Plainsboro, NJ 08536

EXAMINER

CORDERO GARCIA, MARCELA M

ART UNIT PAPER NUMBER

1658

DATE MAILED: 05/08/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Examiner-Initiated Interview Summary	Application No. 13/412,283	Applicant(s) LAU ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1658	

All participants (applicant, applicant's representative, PTO personnel):

(1) MARCELA M. CORDERO GARCIA. (3) ____.

(2) RICHARD W. BORK. (4) ____.

Date of Interview: 30 April 2013.

Type: ☒ Telephonic ☐ Video Conference
 ☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
 If Yes, brief description: ____.

Issues Discussed ☐ 101 ☒ 112 ☐ 102 ☐ 103 ☒ Others
 (For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 46 and 47.

Identification of prior art discussed: N/A.

Substance of Interview
 (For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Examiner contacted Applicant's representative to request a TD for US 8,129,343 and to request authorization for an examiner's amendment to clarify claims 46-47, that would place the application in condition for allowance. Applicant's representative agreed to file the TD, which was received on 5/1/2013 and approved on 5/2/2013 and provided authorization for the proposed amendment (see attached Examiner's amendment).

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

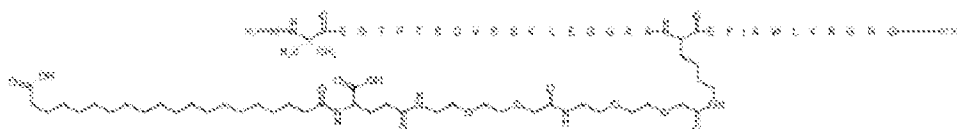
☐ Attachment

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-26, 29-30, in the reply filed on 2/28/2013 is acknowledged. With respect to Applicant's arguments, Examiner agrees that claim 29-30 should have been included in Group I.

Applicant's election of the species:



N-ε²⁵-{2-[2-[2-[2-[2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy]ethoxy]acetylamino]ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.

in the reply filed on 2/28/2013 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Upon reconsideration, **the restriction requirement as set forth in the Office action mailed on 12/31/2012 is hereby withdrawn.** In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Status of the claims

Claims 1-31 were originally filed. Claims 1-31 have been cancelled. Claims 32-47 are new claims. Claims 32-47 are presented for examination on the merits.

Terminal Disclaimer

The terminal disclaimer filed on 5/1/2013 for US 8,129,343 has been reviewed and accepted.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Richard W. Bork on 4/30/2012.

The application has been amended as follows:

IN THE CLAIMS:

In claim 46, at line 1, the phrase "treating hyperglycemia, type 2 diabetes" has been deleted and replaced by the phrase ---treating hyperglycemia and/or type 2 diabetes---.

In claim 47, at line 1, the phrase "treating hyperglycemia, type 2 diabetes" has been deleted and replaced by the phrase ---treating hyperglycemia and/or type 2 diabetes---.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

The closest prior art is that of Knudsen et al. (US 6,268,343, cited in the IDS dated 8/28/2012) which describes GLP-1 analogs encompassing the instantly claimed generic sequence (e.g., cols. 9-10, 12-16), and include lipophilic substituents (B), e.g., $\text{HOOC}(\text{CH}_2)_m\text{CO-}$ wherein m is an integer from 4 to 24, more preferably m is 12, 14, 18, 20 (e.g., col. 19). However Knudsen et al. do not teach the instantly claimed U spacers required by the instant claimed products and methods, nor are they obvious over the prior art..

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karlheinz R. Skowronek can be reached on (571)-272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1658

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCELA M CORDERO GARCIA/
Primary Examiner, Art Unit 1658

MMCG 04/2013

Receipt date: 05/01/2013

Doc code: IDS

Doc description: Information Disclosure Statement (IDS) Filed

13412283 - GALL: 1658

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		13412283	
	Filing Date		2012-03-05	
	First Named Inventor	Jesper Lau		
	Art Unit	1658		
	Examiner Name	M. M. Cordero Garcia		
	Attorney Docket Number	7140.214-US		

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	1	2004/093823	WO	A2	2004-11-04	Lilly Co Eli		☐
	2	03/058203	WO	A2	2003-07-17	Lilly Co Eli		☐

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	Attorney Docket Number	7140.214-US		

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	Declaration of Per Franklin Nielsen, 2012	☐
	2	Annual Report 2003 Novo Nordisk A/S	☐
	3	Curry, Stephen, PLASMA ALBUMIN AS A FATTY ACID CARRIER, Advances in Molecular and Cell Biology, 2004, vol. 33, pp. 29-46	☐
	4	Annual Report 2004, Novo Nordisk A/S	☐
	5	Nauck et al., THE ONCE-WEEKLY HUMAN GLP-1 ANALOGUE..., EASD, 2012, 49TH ANNUAL MEETING	☐
	6	INTERNATIONAL NON-PROPRIETARY NAMES..., 2003, VOL. 17(2), PP. 115, 125	☐
	7	TABLE OF S.C. HALF-LIFE(MINING) AND POTENCY DATA 2011	☐

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Examiner Signature	/Marcela Cordero Garcia/	Date Considered	05/02/2013
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

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CERTIFICATION STATEMENT

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OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Richard W. Bork, Reg. No. 36,459/	Date (YYYY-MM-DD)	2013-05-01
Name/Print	Richard W. Bork	Registration Number	36459

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Receipt date: 09/07/2012

Doc code: IDS

Doc description: Information Disclosure Statement (IDS) Filed

13412283 - GALL: 1658

Approved for use through 07/31/2012. OMB 0651-0031

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	1	2005/028516	WO	A2	2005-03-31	Novo Nordisk As et al.		☐
	2	2003/013573	WO	A1	2003-02-20	Epix Medical Inc et al.		☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
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Examiner Signature	/Marcela Cordero Garcia/	Date Considered	04/26/2013
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Name/Print	Richard W. Bork	Registration Number	36459

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	Examiner Name	M. M. Cordero Garcia	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		13412283
	Filing Date		2012-03-05
	First Named Inventor	Jesper Lau	
	Art Unit	1658	
	Examiner Name	M. M. Cordero Garcia	
	Attorney Docket Number	7140.214-US	

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	Declaration of Per Franklin Nielsen, 2012	☐
	2	Annual Report 2003 Novo Nordisk A/S	☐
	3	Curry, Stephen, PLASMA ALBUMIN AS A FATTY ACID CARRIER, Advances in Molecular and Cell Biology, 2004, vol. 33, pp. 29-46	☐
	4	Annual Report 2004, Novo Nordisk A/S	☐
	5	Nauck et al., THE ONCE-WEEKLY HUMAN GLP-1 ANALOGUE..., EASD, 2012, 49TH ANNUAL MEETING	☐
	6	INTERNATIONAL NON-PROPRIETARY NAMES..., 2003, VOL. 17(2), PP. 115, 125	☐
	7	TABLE OF S.C. HALF-LIFE(MINING) AND POTENCY DATA 2011	☐

If you wish to add additional non-patent literature document citation information please click the Add button **Add**

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	13412283
Filing Date	2012-03-05
First Named Inventor	Jesper Lau
Art Unit	1658
Examiner Name	M. M. Cordero Garcia
Attorney Docket Number	7140.214-US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Richard W. Bork, Reg. No. 36,459/	Date (YYYY-MM-DD)	2013-05-01
Name/Print	Richard W. Bork	Registration Number	36459

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Jesper Lau et al.

Application No.: 13/412,283

Confirmation No.: 9438

Filed: March 5, 2012

Art Unit: 1654

For: Acylated GLP-1 Compounds

Examiner: M. M. Cordero Garcia

AMENDMENT AND RESPONSE TO RESTRICTION REQUIREMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

In response to the Office Action dated December 31, 2012, please amend the above-identified U.S. patent application as follows:

AMENDMENTS TO THE CLAIMS are reflected in the Listing of Claims which begins on page 2 of this paper.

REMARKS begin on page 8 of this paper.

AMENDMENTS TO THE CLAIMS:

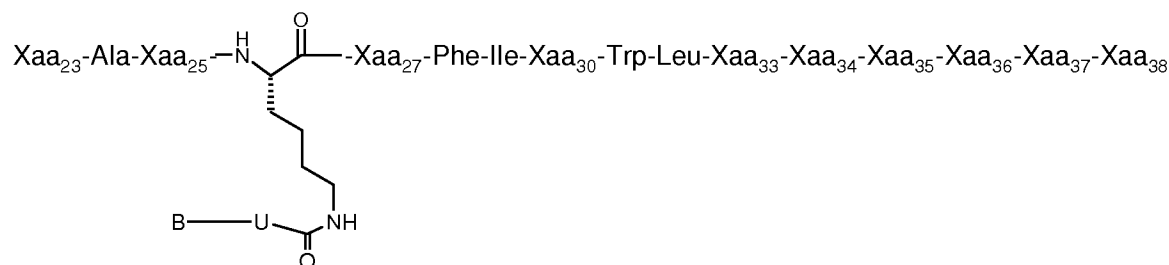
The following Listing of Claims replaces all prior versions, and listings, of claims.

LISTING OF CLAIMS

1-31 (Cancelled).

32. (New) A compound of formula II (SEQ ID No. 3):

Xaa₇-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa₁₆-Ser-Xaa₁₈-Xaa₁₉-Xaa₂₀-Glu-Xaa₂₂-



wherein

Xaa₇ is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^α-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine, or 4-pyridylalanine;

Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa₁₆ is Val or Leu;

Xaa₁₈ is Ser, Lys, or Arg;

Xaa₁₉ is Tyr or Gln;

Xaa₂₀ is Leu or Met;

Xaa₂₂ is Gly, Glu, or Aib;

Xaa₂₃ is Gln, Glu, Lys, or Arg;

Xaa₂₅ is Ala or Val;

Xaa₂₇ is Glu or Leu;

Xaa₃₀ is Ala, Glu, or Arg;

Xaa₃₃ is Val or Lys;

Xaa₃₄ is Lys, Glu, Asn, or Arg;

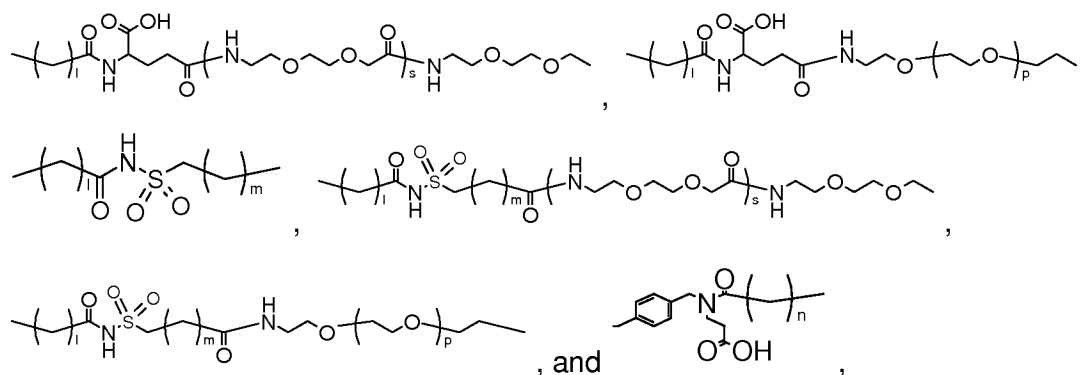
Xaa₃₅ is Gly or Aib;

Xaa₃₆ is Arg, Gly, Lys, or is absent;

Xaa₃₇ is Gly, Ala, Glu, Pro, Lys, or is absent;

Xaa₃₈ is Lys, Ser, amide, or is absent; and

where U is a spacer selected from



where n is 12, 13, 14, 15, 16, 17, or 18,

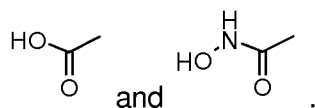
l is 12, 13, 14, 15, 16, 17, or 18,

m is 0, 1, 2, 3, 4, 5, or 6,

s is 0, 1, 2, or 3,

p is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23; and

where B is an acidic group selected from



33.(New) A GLP-1 analog according to claim 32, wherein

Xaa₇ is His or desamino-histidine;

Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys or Aib;

Xaa₁₆ is Val;

Xaa₁₈ is Ser;

Xaa₁₉ is Tyr;

Xaa₂₀ is Leu;

Xaa₂₂ is Gly, Glu or Aib;

Xaa₂₃ is Gln or Glu;

Xaa₂₅ is Ala;
Xaa₂₇ is Glu;
Xaa₃₀ is Ala or Glu;
Xaa₃₃ is Val;
Xaa₃₄ is Lys or Arg;
Xaa₃₅ is Gly or Aib;
Xaa₃₆ is Arg or Lys
Xaa₃₇ is Gly, amide or is absent; and
Xaa₃₈ is absent.

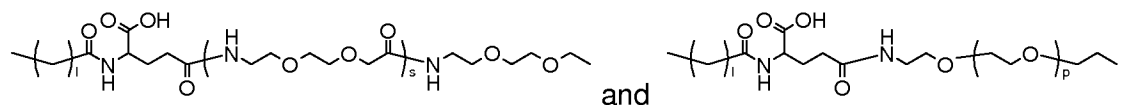
34.(New) A GLP-1 analog according to claim 33, wherein

Xaa₇ is His
Xaa₈ is Gly, or Aib;
Xaa₁₆ is Val;
Xaa₁₈ is Ser;
Xaa₁₉ is Tyr;
Xaa₂₀ is Leu;
Xaa₂₂ is Glu or Aib;
Xaa₂₃ is Gln;
Xaa₂₅ is Ala;
Xaa₂₇ is Glu;
Xaa₃₀ is Ala;
Xaa₃₃ is Val;
Xaa₃₄ is Lys or Arg;
Xaa₃₅ is Gly or Aib;
Xaa₃₆ is Arg
Xaa₃₇ is Gly and
Xaa₃₈ is absent.

35.(New) A GLP-1 analog according to claim 32, wherein said GLP-1 analog comprises Aib⁸ or Gly⁸ in position 8 of the GLP-1(7-37) sequence .

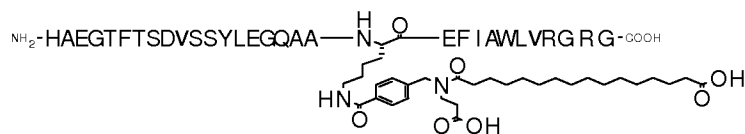
- 36.(New) A GLP-1 analog according to claim 35, wherein said GLP-1 analog comprises Aib⁸;
37. (New) A GLP-1 analog according to claim 32, wherein said GLP-1 analog comprises no more than six amino acid residues which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1).
38. (New) A GLP-1 analog according to claim 32, wherein said GLP-1 analog comprises no more than 3 amino acid residues which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1).
39. (New) A GLP-1 analog according to claim 32, wherein said GLP-1 analog comprises only one lysine residue.
40. (New) A GLP-1 analog according to claim 32, which is
Aib⁸,Arg³⁴-GLP-1(7-37) or
Aib^{8,22},Arg³⁴-GLP-1(7-37).

41. (New) A compound according to claim 32, wherein U is a spacer selected from

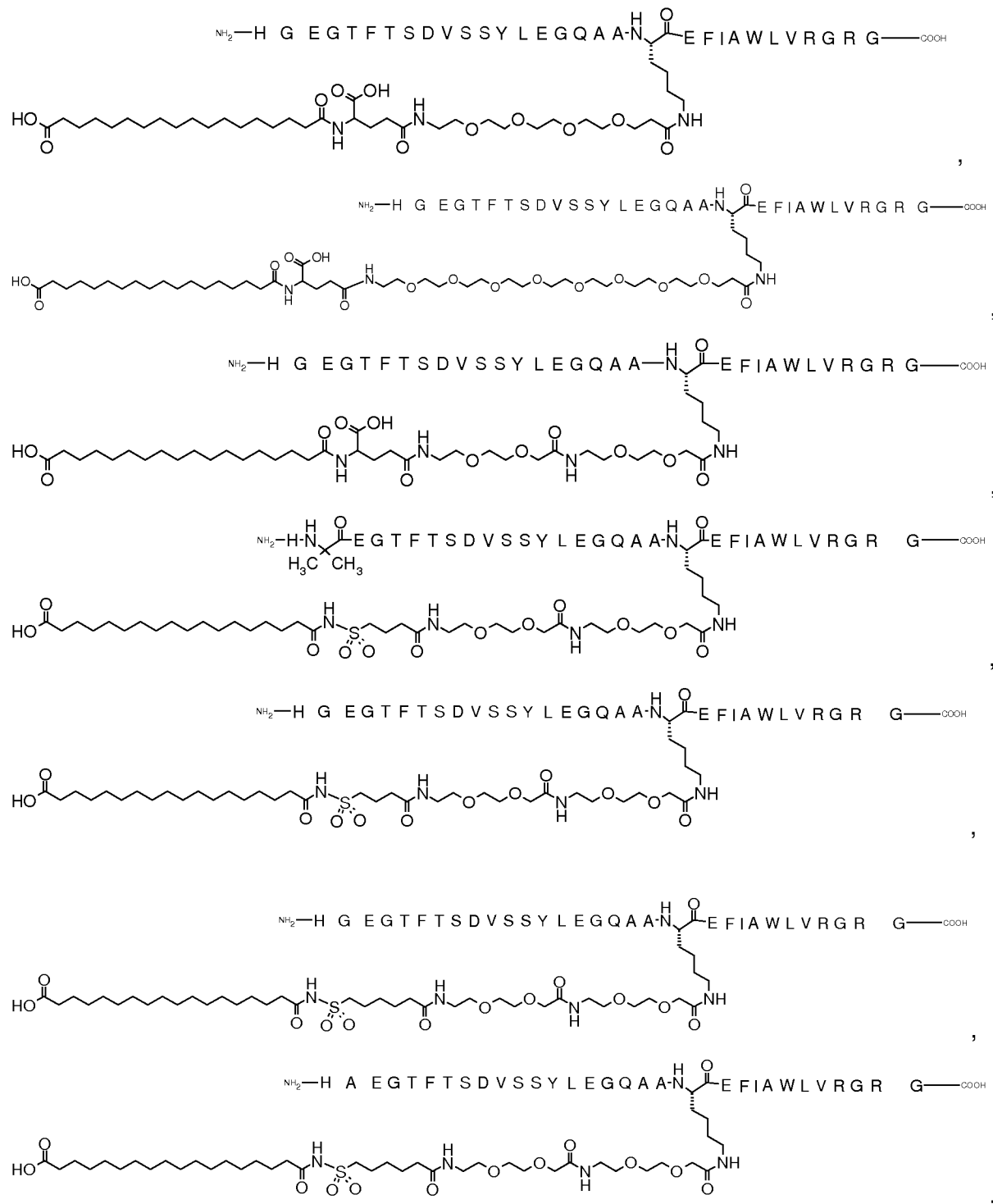


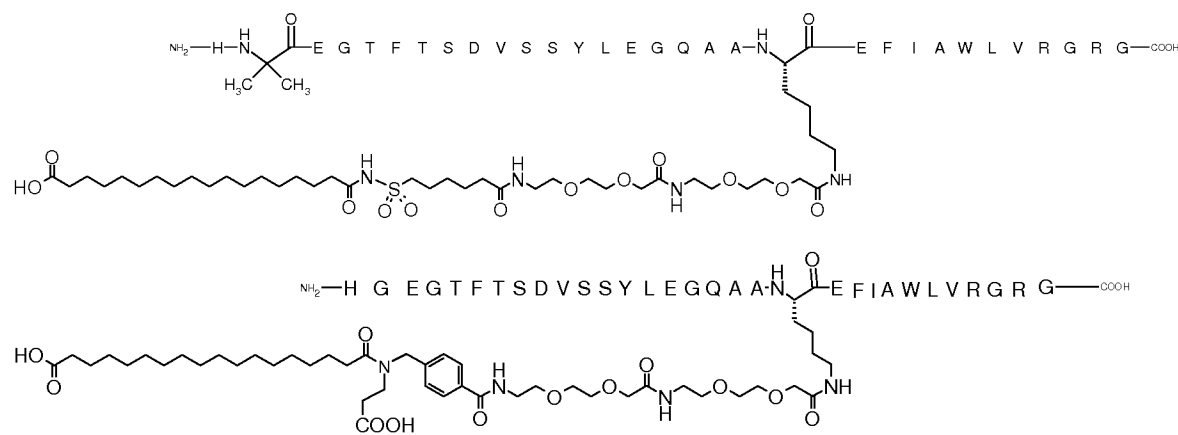
42. (New) A compound according to claim 41, wherein B is 

43. (New) A compound according to claim 32 selected from the following:

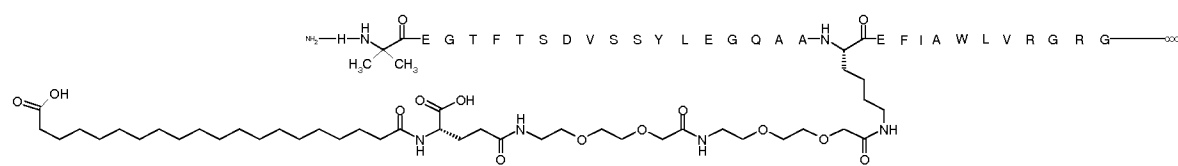


N- ϵ^{26} -(4-[[N-(2-carboxyethyl)-N-(15-carboxypentadecanoyl)amino]methyl]benzoyl)[Arg34]GLP-1-(7-37),





and



44. (New) A pharmaceutical composition comprising a compound according to claim 32, and a pharmaceutically acceptable excipient.

45. (New) A pharmaceutical composition comprising a compound according to claim 43, and a pharmaceutically acceptable excipient.

46. (New) A method for treating hyperglycemia, type 2 diabetes in a subject, said method comprising administering to a subject in need of such treatment an effective amount of a GLP-1 analog according to claim 32.

47. (New) A method for treating hyperglycemia, type 2 diabetes in a subject, said method comprising administering to a subject in need of such treatment an effective amount of a GLP-1 analog according to claim 43.

REMARKS

Claims 1-31 have been cancelled without prejudice. Claims 32-47 have been added. The added claims find support in the specification and claims as originally filed. No new matter is added. Applicants reserve the right to file continuation application(s) to the subject matter of cancelled and non-elected claims.

In the Office Action mailed December 31, 2012, the Examiner has required restriction between:

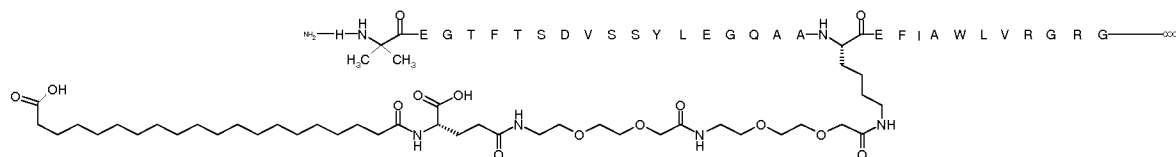
Group I: Claims 1 – 26, drawn to a GLP-1 analog having a modification of at least one non-proteogenic amino acid residue in position 7 and/or 8 relative to the sequence GLP-1(7 – 37)(SEQ ID NO:1) where said analog is acylated with a moiety to the lysine residue in position 26, and where said moiety comprises at least two acidic groups, wherein one acidic group is attached terminally, classified, e.g. in class 514, subclass 7.2;

Group II: Claims 27 – 29, drawn to a method for increasing the time of action in a patient of a GLP-1 analog, classified, e.g. in class 530, subclass 308.

Applicants respectfully wish to point out to the Examiner that claims 30 and 31 were not placed in either of the two groups the Examiner requested restriction to. As claim 30 is a composition claim and 31 is a method claim, Applicants believe that claim 30 would be included in Group I along with claim 29 that was placed in Group II and claim 31 would be included in Group II. If Applicants' understanding is mistaken, Applicants respectfully request clarification from the Examiner.

In addition to requiring Applicants to elect a single group of claims for continued prosecution on the merits, the Examiner also required Applicants to elect a single species of compound if Group I or II is elected and a single disease to be treated if Group II is elected.

In response to these requirements, Applicants hereby elect the claims of Group I (formerly originally filed claims 1-26 and 29-30, now cancelled, and now new claims 32-45) and the compound of Example 5 as the species:



N- ϵ^{26} -[2-(2-[2-(2-[2-(4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.

Elected claims 32-45 read on the elected species.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 14-1447, under Order No. 7140.214-US from which the undersigned is authorized to draw.

Dated: February 28, 2013

Respectfully submitted,

Electronic signature:

/Richard W. Bork, Reg. No. 36,459/

Richard W. Bork

Registration No.: 36,459

NOVO NORDISK INC

100 College Rd. W

Princeton, New Jersey 08540

(609) 987-5800

Attorney For Applicant

Electronic Acknowledgement Receipt

EFS ID:	15077072
Application Number:	13412283
International Application Number:	
Confirmation Number:	9438
Title of Invention:	Acylated GLP-1 Compounds
First Named Inventor/Applicant Name:	Jesper Lau
Customer Number:	23650
Filer:	Richard W. Bork/Csaba Attila Szakolczai
Filer Authorized By:	Richard W. Bork
Attorney Docket Number:	7140.214-US
Receipt Date:	28-FEB-2013
Filing Date:	05-MAR-2012
Time Stamp:	14:15:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 150
RAM confirmation Number	683
Deposit Account	141447
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

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Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response to Election / Restriction Filed	Response_to_Restriction_Requirement_without_Traverse_1.pdf	67372 6a5906a87100528c8ddd62bef33a65e0a4f9b49d	no	9

Warnings:

Information:

2	Extension of Time	Petition_for_Extension_of_Time_Under_37_CFR_1136a_PTO_SB-22_2.pdf	27202 4f83d504f492329448734b26ea734ae985329dfd	no	1
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Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	30270 53107f73dd8cba0c9c368afc59da354579a6343e	no	2
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Warnings:

Information:

Total Files Size (in bytes):

124844

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/412,283	03/05/2012	Jesper Lau	7140.214-US	9438

23650 7590 12/31/2012
NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER

CORDERO GARCIA, MARCELA M

ART UNIT	PAPER NUMBER
----------	--------------

1654

NOTIFICATION DATE	DELIVERY MODE
-------------------	---------------

12/31/2012

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nnipatent@novonordisk.com
KSHL@novonordisk.com
KISW@novonordisk.com

Office Action Summary	Application No. 13/412,283	Applicant(s) LAU ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 March 2012.
- 2a) ☐ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 5) ☒ Claim(s) 1-31 is/are pending in the application.
- 5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☐ Claim(s) ____ is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☒ Claim(s) 1-31 are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☐ Notice of References Cited (PTO-892) | 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date ____. | 4) ☐ Other: ____. |

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-26, drawn to a GLP-1 analog having a modification of at least one non-proteogenic amino acid residue in positions 7 and/or 8 relative to the sequence GLP-1(7-37) (SEQ ID NO:1) where said analog is acylated with a moiety to the lysine residue in position 26, and where said moiety comprises at least two acidic groups, wherein one acidic group is attached terminally, classified, e.g., in class 514, subclass 7.2.
- II. Claims 27-29, drawn to a method for increasing the time of action in a patient of a GLP-1 analog, classified, e.g., in class 530, subclass 308.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II-III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the GLP-1 analogs may also be used in a method of determination of mass spectrometric fragmentation patterns of peptides comprising acidic residues attached terminally.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above

and there would be a serious search and/or examination burden if restriction were not required because at least the following reason(s) apply:

A reference that would anticipate and/or make obvious one of the inventions would not necessarily anticipate and/or make obvious the other invention.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

In addition, this application contains claims directed to the following patentably distinct species: the many and multiple GLP-1 analogs encompassed by the instant claims and the many and multiple diseases to be treated (e.g., hyperglycemia, diabetes type 2). The species are independent or distinct because each GLP-1 analog has a different chemical and molecular composition. Further, each disease has a different etiology and patient population. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, [i.e., if Group I or II is elected: elect a single and specific GLP-1 analog with all substituents fully assigned; for Group II: elect also a disease to be treated] for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-31 are generic.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply:

A reference that would anticipate and/or make obvious one of the species would not necessarily anticipate and/or make obvious other species.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or a grouping of patentably indistinct species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species, including any claims subsequently added. An argument

that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note

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that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCELA M CORDERO GARCIA/
Primary Examiner, Art Unit 1654

MMCG 12/2012

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		13412283	
	Filing Date		2012-03-05	
	First Named Inventor	Jesper Lau		
	Art Unit	1654		
	Examiner Name	M. M. Cordero Garcia		
	Attorney Docket Number	7140.214-US		

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	2	2003/013573	WO	A1	2003-02-20	Epix Medical Inc et al.		☐

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Richard W. Bork, Reg. No. 36,459/	Date (YYYY-MM-DD)	2012-09-04
Name/Print	Richard W. Bork	Registration Number	36459

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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	1	5545618		1996-08-13	Buckley et al.	
	2	6268343		2001-07-31	Knudsen et al.	
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	1	20070203058	A1	2007-08-30	Lau et al.	
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Examiner Name	M. M. Cordero Garcia
Attorney Docket Number	7140.214-US

4	20010011071	A1	2001-08-02	KNUDSEN et al.	
5	20090156478		2009-06-18	Lau et al.	

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	1	1329458	EP	A2	2003-07-23	Zealand Pharma As		☐
	2	2000-500505	JP	A	2000-01-18			☒
	3	06/097538	WO	A1	2006-09-21	Novo Nordisk As et al.		☐
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10	03/087139	WO	A2	2003-10-23	Lilly Co Eli et al.		☐
11	03/002136	WO		2003-01-09	NOVO NORDISK A/S		☐
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13	0151071	WO		2001-07-19	NOVO NORDISK		☐
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	30	05102171.5	EP		2005-03-18	Novo Nordisk A/S		☐
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	32	91/11457	WO	A1	1991-08-08	Buckley Douglas I et al.		☐
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	1	BERENDSEN, 1998, "A Glimpse Of The Holy Grail?" Science 282:642-643	☐
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5	HODGSON et al., 2004, "The Synthesis Of Peptides And Proteins Containing Non-Natural Amino Acids," Chemical Reviews 33(7):422-430	☐
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10	OSTROVSKY, 1975, "Comparative Characteristics Of The Hydrophobic Nature Of Certain Proteins By Their Interaction With 2-P Toluidino," Ukrayins'kyi Biokhimichnyi Zhurnal 47(6):701-707	☒
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16	VOET et al., 1995, Biochemistry 2nd ed., John Wiley & Sons, Inc., pp. 235-241	☐
17	WALLACE, 1995, "Peptide Ligation And Semisynthesis," Current Opinion In Biotechnology 6(4):403-410	☐
18	ZOBEL et al., 2003, "Phosphate Ester Serum Albumin Affinity Tags Greatly Improve Peptide Half-Life In Vivo," Bioorganic & Medicinal Chemistry Letters 13:1513-1515	☐
19	KNUDSEN, L.B. et al., "Potent Derivatives of Glucagon-Like Peptide-1 With Pharmacokinetic Properties Suitable for Once Daily Administration", Journal of Medicinal Chemistry, 2000 Vol. 43, pp. 1664-9	☐
20	DEACON, C.F. et al., " Dipeptidyl peptidase IV resistant analogues of glucagon-like peptide-1 which have extended metabolic stability and improved biological activity." 1998, Diabetologia, Vol. 41, pp. 271-8	☐
21	KURTZHALS, P, ET AL., "ALBUMIN BINDING OF INSULINS ACYLATED WITH FATTY ACIDS: CHARACTERIZATION OF THE LIGAND-PROTEIN INTERACTION AND CORRELATION BETWEEN BINDING AFFINITY AND TIMING OF THE INSULIN EFFECT IN VIVO," BIOCHEM J, 1995, VOL. 312, PAGES 725-731	☐
22	SOLTERO ET AL., "THE ORAL DELIVERY OF PROTEIN AND PEPTIDE DRUGS," INNOVATIONS IN PHARMACEUTICAL TECHNOLOGY, 2001, VOL. 1, NO. 9, PAGES 106-110	☐
23	WATANABE ET AL., "STRUCTURE-ACTIVITY RELATIONSHIPS OF GLUCAGON-LIKE PEPTIDE-1 (7-36) AMIDE: INSULINOTROPIC ACTIVITIES IN PERFUSED RAT PANCREASES, AND RECEPTOR BINDING AND CYCLIC AMP PRODUCTION IN RINm5F CELLS," JOURNAL OF ENDOCRINOLOGY, 1994, VOL. 140, PAGES 45-52	☐
24	Inflammatory Bowel Disease from e-Medicine, pp. 1.24, Accessed 9/24/2008	☐
25	Ngo JT et al., "Computational Complexity, Protein Structure Prediction, and the Levinthal Paradox," The Protein Folding Problem and Tertiary Structure Prediction, K. Merc Jr. and S. LeGrand Edition, 1994, pp. 491-495	☐
26	Residue definition from www.dictionary.com, pp. 1-6, Accessed 5/5/09	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	13412283
Filing Date	2012-03-05
First Named Inventor	Jesper Lau
Art Unit	1654
Examiner Name	M. M. Cordero Garcia
Attorney Docket Number	7140.214-US

27	Small Bowel Syndrome from e-Medicine, pp. 1-21, Accessed 9/24/2008	☐
28	GREEN, BRIAN D. ET AL BIOLOGICAL CHEMISTRY. DEGRADATION, RECEPTOR BINDING, INSULIN... 2004 385 2 169-177	☐
29	Greenwald JOURNAL OF THE CONTROLLED RELEASE PEG DRUGS: AN OVERVIEW 2001 74 - 159-171	☐
30	Ji, J. et al. BIOMATERIALS STEARYL POLY (ETHYLENE OXIDE) GRAFTED SURFACES FOR PREFERENTIAL ADSORPTION OF ALBUMIN. 2001 22 - 3015-3023	☐
31	Knudsen, L.B. JOURNAL OF MEDICINAL CHEMISTRY GLUCAGON-LIKE PEPTIDE-1 2004 47 - 4128-4134	☐
32	Simonovsky et al. JOURNAL OF BIOMATERIALS SCIENCE, POLYMER EDITION POLY(ETHER URETHANE)S INCORPORATING LONG ALKYL SIDE-CHAINS WITH TERMINAL CARBOXYL GROUPS AS FATTY ACID MIMICS: SYNTHESIS, STRUCTURAL CHARACTERIZATION AND PROTEIN ADSORPTION 2005 16 12 1463-1483	☐
33	Soltero and Ekwuribe INNOVATIONS IN PHARMACEUTICAL TECHNOLOGY THE ORAL DELIVERY OF PROTEIN AND PEPTIDE DRUGS. 2001 1 - 106-110	☐
34	Still, J. Gordon, DIABETES/METABOLISM RESEARCH REVIEWS, DEVELOPMENT OF ORAL INSULIN: PROGRESS AND CURRENT STATUS, 2002, Vol. 18, Suppl 1, pp S29 - S37	☐
35	VERONESE F. M BIOMATERIALS PEPTIDE AND PROTEIN PEGYLATION: A REVIEW OF PORBLEMS AND SOLUTIONS 2001 22 5 405-417	☐
36	English abstract of JP 2004535442	☐
37	English abstract of RU 2006107600	☐

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	Filing Date	2012-03-05
	First Named Inventor	Jesper Lau
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	Examiner Name	M. M. Cordero Garcia
	Attorney Docket Number	7140.214-US

38	English abstract of JP 2010116407	☐
39	English abstract of JP 2004528014	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	
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***EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

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STATEMENT BY APPLICANT**
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Application Number	13412283
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Art Unit	1654
Examiner Name	M. M. Cordero Garcia
Attorney Docket Number	7140.214-US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Richard W. Bork, Reg. No. 36,459/	Date (YYYY-MM-DD)	2012-08-27
Name/Print	Richard W. Bork	Registration Number	36459

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

STATEMENT UNDER 37 CFR 3.73(b)Applicant/Patent Owner: Jesper LauApplication No./Patent No.: 13/412,283Filed/Issue Date: March 5, 2012Titled: Acylated GLP-1 CompoundsNovo Nordisk A/S

(Name of Assignee)

, a

Corporation

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;
2. ☐ an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or
3. ☐ an assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above by virtue of either:

- A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 020070 ,
Frame 0420 , or for which a copy thereof is attached.

OR

- B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

2. From: _____ To: _____

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Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

- ☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Richard W. Bork, Reg. No. 36,459/

Signature

August 3, 2012

Date

Richard W. Bork

Printed or Typed Name

Attorney for Assignee

Title

APPLICATION DATA SHEET**Application Information**

Application Type::	Continuation of US Application No. 11/908,834, filed September 17, 2007
Subject Matter::	Utility
Sequence submission?::	Electronic
Title::	Acylated GLP-1 Compounds
Attorney Docket Number::	7140.214-US
Pages in Specification::	73 (including abstract)
Request for Early Publication?::	No
Small Entity?::	No
Request for Non-Publication?::	No

Applicant Information

Applicant Authority Type::	Inventor
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City of mailing address::	Bagsværd
Country of mailing address::	Denmark
Postal or Zip Code of mailing address::	DK-2880

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Country of Residence::	Denmark
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City of mailing address::	Bagsværd
Country of mailing address::	Denmark
Postal or Zip Code of mailing address::	DK-2880
Applicant Authority Type::	Inventor
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Country of Residence::	Denmark
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Country of Residence::	Denmark
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City of mailing address::	Bagsværd
Country of mailing address::	Denmark
Postal or Zip Code of mailing address::	DK-2880
Applicant Authority Type::	Inventor
Primary Citizenship Country::	Denmark
Status::	Full Capacity
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Middle Name::	Kruse
Family Name::	Hansen
City of Residence::	Herlev
Country of Residence::	Denmark
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City of mailing address::	Bagsværd
Country of mailing address::	Denmark
Postal or Zip Code of mailing address::	DK-2880

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Primary Citizenship Country::	Denmark
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Country of mailing address::	Denmark
Postal or Zip Code of mailing address::	DK-2880

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E-Mail Address::	NNIPATENT@Novonordisk.com KISW@Novonordisk.com KSHL@Novonordisk.com

Representative Information

Representative Customer Number::	23650
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Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	is a Continuation of	11/908,834	09/17/07
	which is a 371 National Stage Filing of	PCT/EP2006/060855	03/20/06
	and Claims Priority under 35 U.S.C. § 119 of	60/664,497	03/23/05

Foreign Priority Information

Country::	Application number::	Filing Date::	Priority Claimed::
EP	05102171.5	03/18/05	Yes

Assignee Information

Assignee name::	Novo Nordisk A/S
Street of mailing address::	Novo Allé
City of mailing address::	Bagsværd
Country of mailing address::	Denmark
Postal or Zip Code of mailing address::	DK-2880

Declaration for Utility or Design Patent Application (37 CFR 1.63)☐

Declaration Submitted with Initial Filing or

☒

Declaration Submitted after Initial Filing

(surcharge (37 CFR 1.16(e)) required)

DECLARATION FOR PATENT APPLICATION

Attorney Docket Number:

7140.204-US

As a below named inventor, I hereby declare that:

My residence and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Acylated GLP-1 Compounds

The specification of which (check only one item below):

[] is attached hereto

[X] was filed as United States application

Application No. 11/908,834on September 17, 2007

and was amended

on September 17, 2007

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

PRIORITY CLAIMS

Pursuant to 37 CFR 1.63(c), Applicants hereby list any priority claims on an Application Data Sheet submitted herewith in accordance with 37 CFR 1.76.

Send Correspondence to: Customer Number 23650**Direct Telephone Calls To:** Intellectual Property Department:
(609) 987-5800**1 Full Name of Inventor (Last Name First):**

LAU, Jesper

Country of Citizenship:

Denmark

2 Full Name of Inventor (Last Name First):

DÖRWALD, Florencio Zaragoza

Country of Citizenship:

Germany

3 Full Name of Inventor (Last Name First):

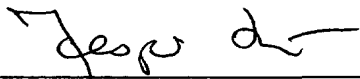
STEPHENSEN, Henrik

Country of Citizenship:

Denmark

Declaration	Attorney Docket No.: 7140.204-US
4 Full Name of Inventor (Last Name First): BLOCH, Paw	
Country of Citizenship: Denmark	
5 Full Name of Inventor (Last Name First): HANSEN, Thomas Kruse	
Country of Citizenship: Denmark	
6 Full Name of Inventor (Last Name First): MADSEN, Kjeld	
Country of Citizenship: Denmark	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 1 	Signature of Inventor 2 	Signature of Inventor 3 
Date 4/9 - 2008	Date	Date 4/9 - 2008
Signature of Inventor 4 	Signature of Inventor 5 	Signature of Inventor 6
Date 4/9 - 2008	Date	Date

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Signature of Inventor 1	Signature of Inventor 2 <i>F. Zaragoza</i>	Signature of Inventor 3
Date	Date <i>5. Sep 2008</i>	Date
Signature of Inventor 4	Signature of Inventor 5	Signature of Inventor 6
Date	Date	Date

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Date	Date	Date
Signature of Inventor 4	Signature of Inventor 5	Signature of Inventor 6
Date	Date 09/09/2008	Date

Declaration for Utility or Design Patent Application (37 CFR 1.63)☐**Declaration Submitted with Initial Filing or**☒**Declaration Submitted after Initial Filing**

(surcharge (37 CFR 1.16(e)) required)

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and was amended

on **September 17, 2007**

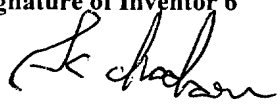
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Declaration		Attorney Docket No.: 7140.204-US
4	Full Name of Inventor (Last Name First): BLOCH, Paw	
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.		
Signature of Inventor 1		Signature of Inventor 2
Date		Date
Signature of Inventor 4		Signature of Inventor 5
Date		Date
		 08-SEP-2008

Electronic Acknowledgement Receipt

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Application Number:	13412283
International Application Number:	
Confirmation Number:	9438
Title of Invention:	Acylated GLP-1 Compounds
First Named Inventor/Applicant Name:	Jesper Lau
Customer Number:	23650
Filer:	Richard W. Bork/Lori Klewin
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		7140214US_Appln.pdf	451694	yes	73
			ab747b4d7bf2788dc8e67995261636069f339859		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	63	
	Claims		64	72	
	Abstract		73	73	
Warnings:					
Information:					
2	Transmittal of New Application	7140214US_AppTrans.pdf	76586	no	1
			9894953529495ab3ce362090d2fa3ce6ae43aa0a		
Warnings:					
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3	Miscellaneous Incoming Letter	7140214US_Hakim.pdf	95639	no	1
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Warnings:					
Information:					
4	Miscellaneous Incoming Letter	7140214US_SeqTrans.pdf	76842	no	1
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Warnings:					
Information:					
5	Sequence Listing (Text File)	SeqList2_ST25.txt	28513	no	0
Warnings:					
Information:					
6	Application Data Sheet	7140214US_ADS.pdf	77524	no	5
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Warnings:					
Information:					
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7	Oath or Declaration filed	7140214US_Declaration.pdf	349880 fbc72197668b67a96af68989bd8b4ef582d d0758	no	8
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	37881 ebe001d1867bf32c4015793cf73e39da577 1790c	no	2
Warnings:					
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Total Files Size (in bytes):			1194559		
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ACYLATED GLP-1 COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation of copending US Application No. 11/908,834, filed
5 September 17, 2007, which is a 35 U.S.C. § 371 national stage application of International
Patent Application PCT/ EP2006/060855 (published as WO 2006/097537), filed March 20,
2006, which claimed priority of European Patent Application 05102171.5, filed March 18,
2005; this application further claims priority under 35 U.S.C. § 119 of U.S. Provisional
Application 60/664,497, filed March 23, 2005.

10

FIELD OF THE INVENTION

This invention relates to the field of therapeutic peptides, i.e. to new protracted GLP-1
15 compounds.

BACKGROUND OF THE INVENTION

A range of different approaches have been used for modifying the structure of glucagon-like
20 peptide 1 (GLP-1) compounds in order to provide a longer duration of action in vivo.

WO 96/29342 discloses peptide hormone derivatives wherein the parent peptide hormone
has been modified by introducing a lipophilic substituent in the C-terminal amino acid residue
or in the N-terminal amino acid residue.

WO 98/08871 discloses GLP-1 derivatives wherein at least one amino acid residue of the
25 parent peptide has a lipophilic substituent attached.

WO 99/43708 discloses GLP-1(7-35) and GLP-1(7-36) derivatives which have a lipophilic
substituent attached to the C-terminal amino acid residue.

WO 00/34331 discloses acylated GLP-1 analogs.

WO 00/69911 discloses activated insulinotropic peptides to be injected into patients where
30 they are supposed to react with blood components to form conjugates and thereby allegedly
providing longer duration of action in vivo.

WO 02/46227 discloses GLP-1 and exendin-4 analogs fused to human serum albumin in
order to extend in vivo half-life.

35 Many diabetes patients particularly in the type 2 diabetes segment are subject to so-called
“needle-phobia”, i.e. a substantial fear of injecting themselves. In the type 2 diabetes

segment most patients are treated with oral hypoglycaemic agents, and since GLP-1 compounds are expected to be the first injectable product these patients will be administered, the fear of injections may become a serious obstacle for the widespread use of the clinically very promising GLP-1 compounds. Thus, there is a need to develop new GLP-1 compounds which can be administered less than once daily, e.g. once every second or third day preferably once weekly, while retaining an acceptable clinical profile.

SUMMARY OF THE INVENTION

10 The invention provides a GLP-1 analog having a modification of at least one non-proteogenic amino acid residue in positions 7 and/or 8 relative to the sequence GLP-1(7-37) (SEQ ID No 1), which is acylated with a moiety to the lysine residue in position 26, and where said moiety comprises at least two acidic groups, wherein one acidic group is attached terminally.

15 The present invention also provides pharmaceutical compositions comprising a compound according to the present invention and the use of compounds according to the present invention for preparing medicaments for treating disease.

The invention provides a method for increasing the time of action in a patient of a GLP-1 analog, characterised in acylating said GLP-1 analog with a moiety B-U' as disclosed in any of the preceding claims, on the lysine residue in position 26 of said GLP-1 analog.

DESCRIPTION OF THE INVENTION

25 In the present specification, the following terms have the indicated meaning :

The term "polypeptide" and "peptide" as used herein means a compound composed of at least five constituent amino acids connected by peptide bonds. The constituent amino acids may be from the group of the amino acids encoded by the genetic code and they may be natural amino acids which are not encoded by the genetic code, as well as synthetic amino acids. Natural amino acids which are not encoded by the genetic code are e.g., γ -carboxyglutamate, ornithine, phosphoserine, D-alanine and D-glutamine. Synthetic amino acids comprise amino acids manufactured by chemical synthesis, i.e. D-isomers of the amino acids encoded by the genetic code such as D-alanine and D-leucine, Aib (α -aminoisobutyric acid), Abu (α -aminobutyric acid), Tle (tert-butylglycine), β -alanine, 3-aminomethyl benzoic acid, anthranilic acid.

The 22 proteogenic amino acids are:

Alanine, Arginine, Asparagine, Aspartic acid, Cysteine, Cystine, Glutamine, Glutamic acid, Glycine, Histidine, Hydroxyproline, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine.

Thus a non-proteogenic amino acid is a moiety which can be incorporated into a peptide via peptide bonds but is not a proteogenic amino acid. Examples are γ -carboxyglutamate, ornithine, phosphoserine, the D-amino acids such as D-alanine and D-glutamine, Synthetic non-proteogenic amino acids comprise amino acids manufactured by chemical synthesis, i.e. D-isomers of the amino acids encoded by the genetic code such as D-alanine and D-leucine, Aib (α -aminoisobutyric acid), Abu (α -aminobutyric acid), Tle (tert-butylglycine), 3-aminomethyl benzoic acid, anthranilic acid, des-amino-Histidine, the beta analogs of amino acids such as β -alanine etc. D-histidine, desamino-histidine, 2-amino-histidine, β -hydroxy-histidine, homohistidine, N^{ac}-acetyl-histidine, α -fluoromethyl-histidine, α -methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

The term "analogue" as used herein referring to a polypeptide means a modified peptide wherein one or more amino acid residues of the peptide have been substituted by other amino acid residues and/or wherein one or more amino acid residues have been deleted from the peptide and/or wherein one or more amino acid residues have been deleted from the peptide and or wherein one or more amino acid residues have been added to the peptide. Such addition or deletion of amino acid residues can take place at the N-terminal of the peptide and/or at the C-terminal of the peptide. A simple system is often used to describe analogues : For example [Arg³⁴]GLP-1(7-37)Lys designates a GLP-1(7-37) analogue wherein the naturally occurring lysine at position 34 has been substituted with arginine and wherein a lysine has been added to the terminal amino acid residue, i.e. to the Gly³⁷. All amino acids for which the optical isomer is not stated is to be understood to mean the L-isomer. In embodiments of the invention a maximum of 17 amino acids have been modified. In embodiments of the invention a maximum of 15 amino acids have been modified. In embodiments of the invention a maximum of 10 amino acids have been modified. In embodiments of the invention a maximum of 8 amino acids have been modified. In embodiments of the invention a maximum of 7 amino acids have been modified. In embodiments of the invention a maximum of 6 amino acids have been modified. In embodiments of the invention a maximum of 5 amino acids have been modified. In embodiments of the invention a maximum of 4 amino acids have been modified. In embodiments of the invention a maximum of 3 amino acids have been modified. In

embodiments of the invention a maximum of 2 amino acids have been modified. In
embodiments of the invention 1 amino acid has been modified.

The term "derivative" as used herein in relation to a peptide means a chemically modified
peptide or an analogue thereof, wherein at least one substituent is not present in the
5 unmodified peptide or an analogue thereof, i.e. a peptide which has been covalently
modified. Typical modifications are amides, carbohydrates, alkyl groups, acyl groups, esters
and the like. An example of a derivative of GLP-1(7-37) is N^{ε26}-((4S)-4-(hexadecanoylamino)-
carboxy-butanoyl)[Arg³⁴, Lys²⁶]GLP-1-(7-37).

The term "GLP-1 peptide" as used herein means GLP-1(7-37) (SEQ ID No 1), a
10 GLP-1(7-37) analogue, a GLP-1(7-37) derivative or a derivative of a GLP-1(7-37) analogue.
In one embodiment the GLP-1 peptide is an insulinotropic agent.

The term "insulinotropic agent" as used herein means a compound which is an
agonist of the human GLP-1 receptor, i.e. a compound which stimulates the formation of
cAMP in a suitable medium containing the human GLP-1 receptor (one such medium
15 disclosed below). The potency of an insulinotropic agent is determined by calculating the
EC₅₀ value from the dose-response curve as described below.

Baby hamster kidney (BHK) cells expressing the cloned human GLP-1 receptor
(BHK- 467-12A) were grown in DMEM media with the addition of 100 IU/mL penicillin, 100
µg/mL streptomycin, 5% fetal calf serum and 0.5 mg/mL Geneticin G-418 (Life
20 Technologies). The cells were washed twice in phosphate buffered saline and harvested with
Versene. Plasma membranes were prepared from the cells by homogenisation with an
Ultraturrax in buffer 1 (20 mM HEPES-Na, 10 mM EDTA, pH 7.4). The homogenate was
centrifuged at 48,000 x g for 15 min at 4°C. The pellet was suspended by homogenization in
buffer 2 (20 mM HEPES-Na, 0.1 mM EDTA, pH 7.4), then centrifuged at 48,000 x g for 15
25 min at 4°C. The washing procedure was repeated one more time. The final pellet was
suspended in buffer 2 and used immediately for assays or stored at -80°C.

The functional receptor assay was carried out by measuring cyclic AMP (cAMP) as
a response to stimulation by the insulinotropic agent. cAMP formed was quantified by the
AlphaScreen™ cAMP Kit (Perkin Elmer Life Sciences). Incubations were carried out in half-
30 area 96-well microtiter plates in a total volume of 50 µL buffer 3 (50 mM Tris-HCl, 5 mM
HEPES, 10 mM MgCl₂, pH 7.4) and with the following additions: 1 mM ATP, 1 µM GTP, 0.5
mM 3-isobutyl-1-methylxanthine (IBMX), 0.01 % Tween-20, 0.1% BSA, 6 µg membrane
preparation, 15 µg/mL acceptor beads, 20µg/mL donor beads preincubated with 6 nM
biotinyl-cAMP. Compounds to be tested for agonist activity were dissolved and diluted in
35 buffer 3. GTP was freshly prepared for each experiment. The plate was incubated in the dark

with slow agitation for three hours at room temperature followed by counting in the Fusion™ instrument (Perkin Elmer Life Sciences). Concentration-response curves were plotted for the individual compounds and EC₅₀ values estimated using a four-parameter logistic model with Prism v. 4.0 (GraphPad, Carlsbad, CA).

5 The term “DPP-IV protected” as used herein referring to a polypeptide means a polypeptide which has been chemically modified in order to render said compound resistant to the plasma peptidase dipeptidyl aminopeptidase-4 (DPP-IV). The DPP-IV enzyme in plasma is known to be involved in the degradation of several peptide hormones, e.g. GLP-1, GLP-2, Exendin-4 etc. Thus, a considerable effort is being made to develop analogues and derivatives
10 of the polypeptides susceptible to DPP-IV mediated hydrolysis in order to reduce the rate of degradation by DPP-IV. In one embodiment a DPP-IV protected peptide is more resistant to DPP-IV than GLP-1(7-37) or Exendin-4(1-39).

Resistance of a peptide to degradation by dipeptidyl aminopeptidase IV is determined by the following degradation assay :

15 Aliquots of the peptide (5 nmol) are incubated at 37 °C with 1 µL of purified dipeptidyl aminopeptidase IV corresponding to an enzymatic activity of 5 mU for 10-180 minutes in 100 µL of 0.1 M triethylamine-HCl buffer, pH 7.4. Enzymatic reactions are terminated by the addition of 5 µL of 10% trifluoroacetic acid, and the peptide degradation products are separated and quantified using HPLC analysis. One method for performing this analysis is :
20 The mixtures are applied onto a Vydac C18 widepore (30 nm pores, 5 µm particles) 250 x 4.6 mm column and eluted at a flow rate of 1 ml/min with linear stepwise gradients of acetonitrile in 0.1% trifluoroacetic acid (0% acetonitrile for 3 min, 0-24% acetonitrile for 17 min, 24-48% acetonitrile for 1 min) according to Siegel et al., Regul. Pept. 1999;79:93-102 and Mentlein et al. Eur. J. Biochem. 1993;214:829-35. Peptides and their degradation
25 products may be monitored by their absorbance at 220 nm (peptide bonds) or 280 nm (aromatic amino acids), and are quantified by integration of their peak areas related to those of standards. The rate of hydrolysis of a peptide by dipeptidyl aminopeptidase IV is estimated at incubation times which result in less than 10% of the peptide being hydrolysed.

30 The term “C₁₋₆-alkyl” as used herein means a saturated, branched, straight or cyclic hydrocarbon group having from 1 to 6 carbon atoms. Representative examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, n-hexyl, isohexyl, cyclohexane and the like.

The term “pharmaceutically acceptable” as used herein means suited for normal pharmaceutical applications, i.e. giving rise to no adverse events in patients etc.

35

The term "excipient" as used herein means the chemical compounds which are normally added to pharmaceutical compositions, e.g. buffers, tonicity agents, preservatives and the like.

The term "effective amount" as used herein means a dosage which is sufficient to be effective for the treatment of the patient compared with no treatment.

The term "pharmaceutical composition" as used herein means a product comprising an active compound or a salt thereof together with pharmaceutical excipients such as buffer, preservative, and optionally a tonicity modifier and/or a stabilizer. Thus a pharmaceutical composition is also known in the art as a pharmaceutical formulation.

The term "treatment of a disease" as used herein means the management and care of a patient having developed the disease, condition or disorder. The purpose of treatment is to combat the disease, condition or disorder. Treatment includes the administration of the active compounds to eliminate or control the disease, condition or disorder as well as to alleviate the symptoms or complications associated with the disease, condition or disorder.

In another aspect the present invention relates to an acylated GLP-1 analogue that can bind to albumin and the GLP-1 receptor simultaneously.

In another aspect the present invention relates to an acylated GLP-1 analogue that bind to the GLP-1 receptor with an affinity below 100nM, preferable below 30 nM in the presence of 2% albumin.

In another aspect the present invention relates to an acylated GLP-1 analogue which affinity to the GLP-1 receptor is only partly decreased when comparing the affinity in the presence of very low concentration (e.g. 0.005% to 0.2%) of human albumin to the affinity in the presence of 2% human albumin. The shift in binding affinity under these conditions is less than 50 fold, preferable below 30 fold and more preferable below 10 fold.

The term "albumin binding moiety" as used herein means a residue which binds non-covalently to human serum albumin. The albumin binding residue attached to the therapeutic polypeptide typically has an affinity below 10 μ M to human serum albumin and preferably below 1 μ M. A range of albumin binding residues are known among linear and branched lipophilic moieties containing 4-40 carbon atoms having a distal acidic group.

The term "hydrophilic linker" as used herein means a spacer that separates a peptide and an albumin binding residue with a chemical moiety which comprises at least 5 non-hydrogen atoms where 30-50% of these are either N or O.

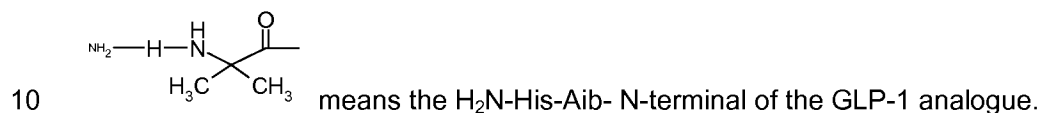
The term "acidic groups" as used herein means organic chemical groups which are fully or partly negatively charged at physiological pH. The pKa value of such groups is below 7, preferable below 5. This includes but is not limited to carboxylic acids, sulphonic acids,

phosphoric acids or heterocyclic ring systems which are fully or partly negatively charged at physiological pH.

In the below structural formula II the moiety U is a di-radical may be attached to the terminal groups B and the aminogroup of the lysine amino acid in the peptide in two different ways. In
5 embodiments of the invention the U in formula II is attached with the group B attached at the end of the alkyl chain and the peptide at the other end.

In the formulas below the terminal bonds from the attached groups are to be regarded as attachment bonds and not ending in methylene groups unless stated.

In the formulas below



In an embodiment the invention provides a GLP-1 analog acylated with a lipophilic albumin binding moiety containing at least two free acidic chemical groups attached via a non natural amino acid linker to the lysine residue in position 26.

15 In an embodiment, the term free acidic chemical groups is to be understood as having the same meaning as "acidic groups" as used herein.

In an embodiment the invention provides an acylated GLP-1 analog where said GLP-1 analog is stabilised against DPP-IV by modification of at least one amino acid residue in positions 7 and 8 relative to the sequence GLP-1(7-37) (SEQ ID No 1), and where said
20 acylation is a diacid attached to the lysine residue in position 26 optionally via a non natural amino acid hydrophilic linker.

In an embodiment of the invention a GLP-1 analog having a modification of at least one non-proteogenic amino acid residue in positions 7 and/or 8 relative to the sequence GLP-1(7-37) (SEQ ID No 1), which is acylated with a moiety to the lysine residue in position 26, and
25 where said moiety comprises at least two acidic groups, wherein one acidic group is attached terminally.

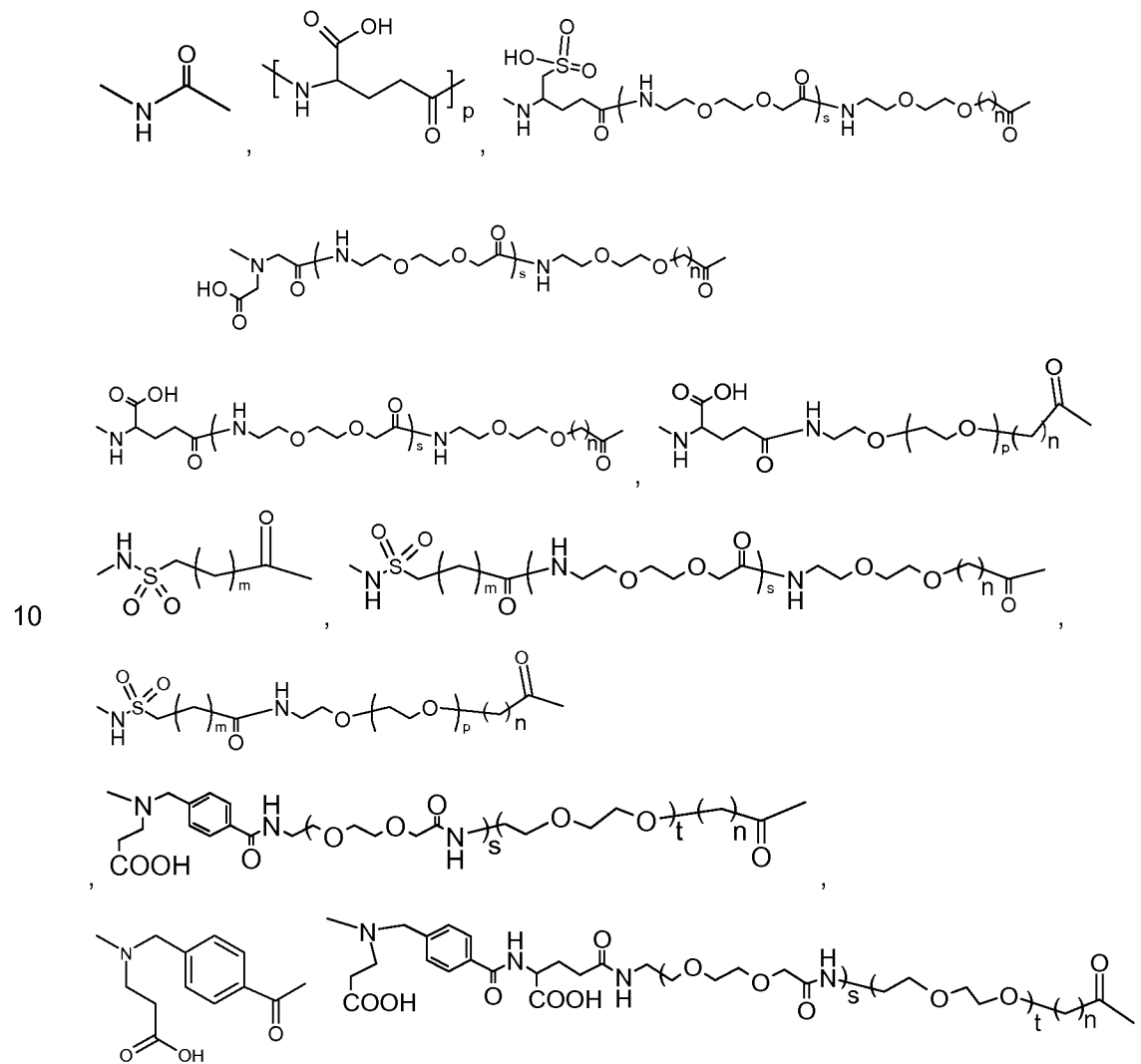
An embodiment provides a GLP-1 analog according to the above embodiment, wherein the moiety attached in position 26 comprises a hydrophilic linker.

An embodiment provides a GLP-1 analog according to the above embodiments, wherein the
30 hydrophilic linker comprises at least 5 non-hydrogen atoms where 30-50% of these are either N or O.

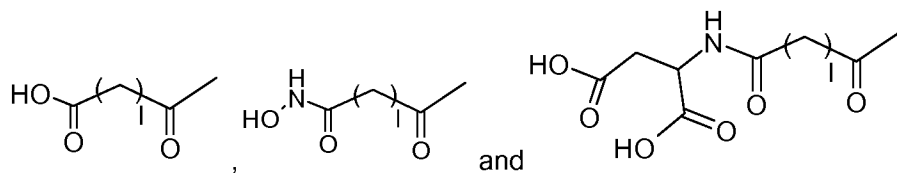
An embodiment provides a GLP-1 analog according to any of the above embodiments, wherein the moiety attached in position 26 comprises an albumin binding moiety separated from the peptide by the hydrophilic linker.

An embodiment provides a GLP-1 analog according to the above embodiment, wherein the albumin binding moiety is a linear or branched lipophilic moiety containing 4-40 carbon atoms having a distal acidic group.

5 wherein the acylated moiety is B-U', where U' is selected from



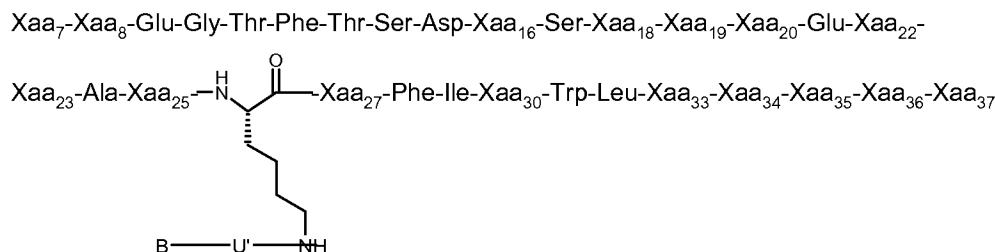
15 m is 0, 1, 2, 3, 4, 5, or 6,
n is 1, 2 or 3
s is 0, 1, 2, or 3,
t is 0, 1, 2, 3, or 4
p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;
and where B is an acidic group selected from



where I is 12, 13, 14, 15, 16, 17, 18, 19 or 20;

An embodiment provides a GLP-1 analog according to any of the above embodiments, which

5 is a compound of formula I (SEQ ID No. 2) :



Formula I

wherein

10 Xaa₇ is L-histidine, imidazopropionyl, α-hydroxy-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^α-acetyl-histidine, N^α-formyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine

Xaa₈ is Ala, Gly, Val, Leu, Ile, Thr, Ser, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

15 Xaa₁₆ is Val or Leu;

Xaa₁₈ is Ser, Lys or Arg;

Xaa₁₉ is Tyr or Gln;

Xaa₂₀ is Leu or Met;

20 Xaa₂₂ is Gly, Glu or Aib;

Xaa₂₃ is Gln, Glu, Lys or Arg;

Xaa₂₅ is Ala or Val;

Xaa₂₇ is Glu or Leu;

Xaa₃₀ is Ala, Glu or Arg;

25 Xaa₃₃ is Val or Lys;

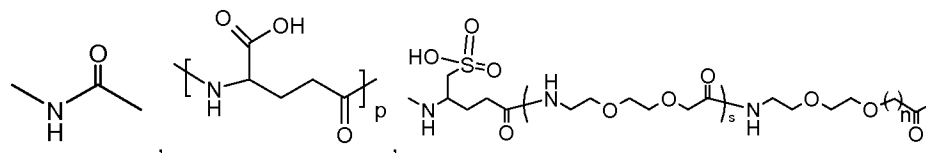
Xaa₃₄ is Lys, Glu, Asn or Arg;

Xaa₃₅ is Gly or Aib;

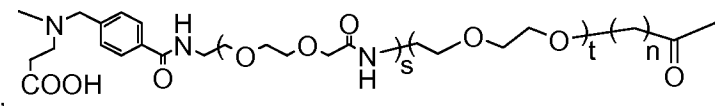
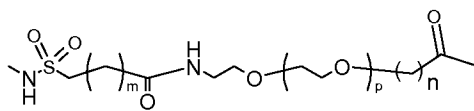
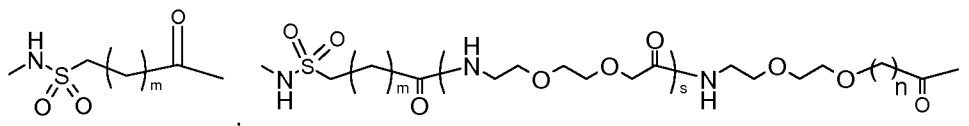
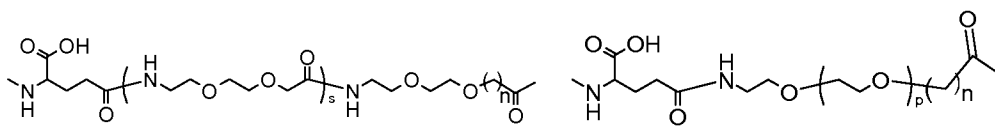
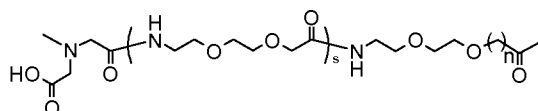
Xaa₃₆ is Arg, Gly or Lys, or is absent;

Xaa₃₇ is Gly, Ala, Glu, Pro, Lys, or is absent;

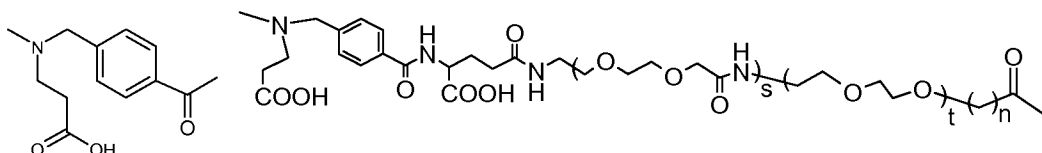
and B and U' together is the acylated moiety, where U' is selected from



5



10



m is 0, 1, 2, 3, 4, 5, or 6,

n is 1, 2 or 3

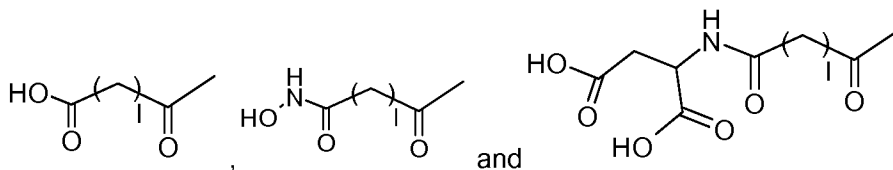
s is 0, 1, 2, or 3,

t is 0, 1, 2, 3, or 4

15

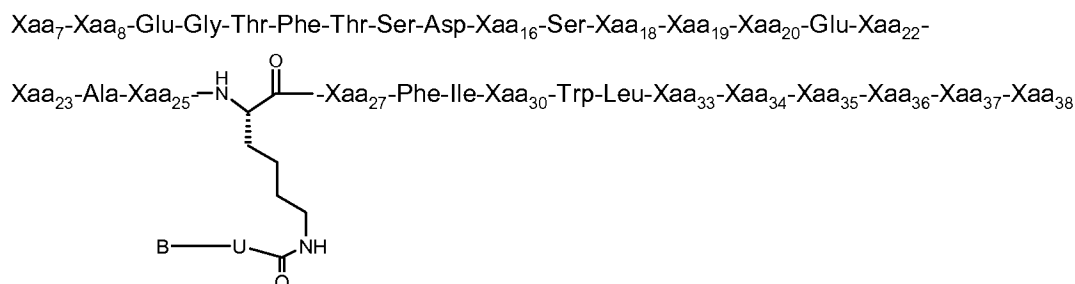
p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

and where B is an acidic group selected from



where l is 12, 13, 14, 15, 16, 17, 18, 19 or 20;

In an embodiment the invention provides a compound which is a compound of formula II (SEQ ID No. 3) :



5

Formula II

The formula II is identical to formula I as stated in an embodiment above, where the moiety B-U is replaced by B-U'. The difference being only the incorporation of the carboxy group in the U' relative to U, which is without the attaching carboxy group.

In formula II each of the Xaa's has the following meaning:

Xaa₇ is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^α-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

15 Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa₁₆ is Val or Leu;

Xaa₁₈ is Ser, Lys or Arg;

20 Xaa₁₉ is Tyr or Gln;

Xaa₂₀ is Leu or Met;

Xaa₂₂ is Gly, Glu or Aib;

Xaa₂₃ is Gln, Glu, Lys or Arg;

Xaa₂₅ is Ala or Val;

25 Xaa₂₇ is Glu or Leu;

Xaa₃₀ is Ala, Glu or Arg;

Xaa₃₃ is Val or Lys;

Xaa₃₄ is Lys, Glu, Asn or Arg;

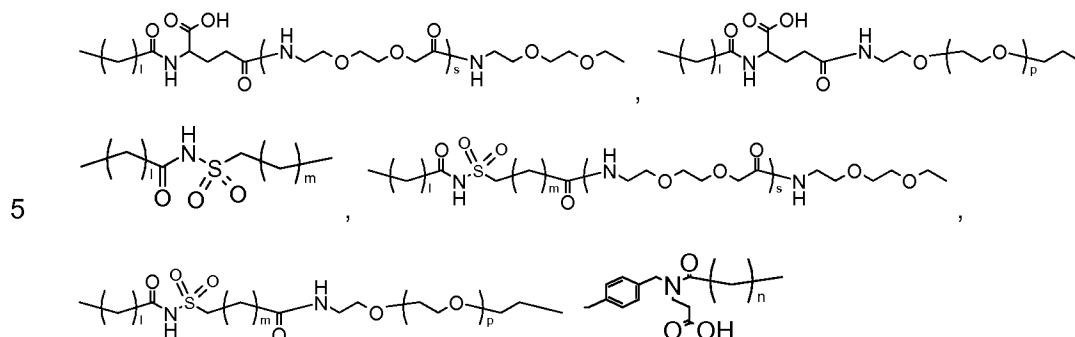
Xaa₃₅ is Gly or Aib;

30 Xaa₃₆ is Arg, Gly or Lys, or is absent;

Xaa₃₇ is Gly, Ala, Glu, Pro, Lys, or is absent;

Xaa₃₈ is Lys, Ser, amide or is absent;

and where U is a spacer selected from



where n is 12, 13, 14, 15, 16, 17 or 18

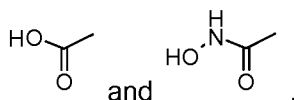
l is 12, 13, 14, 15, 16, 17 or 18,

m is 0, 1, 2, 3, 4, 5, or 6,

10 s is 0, 1, 2, or 3,

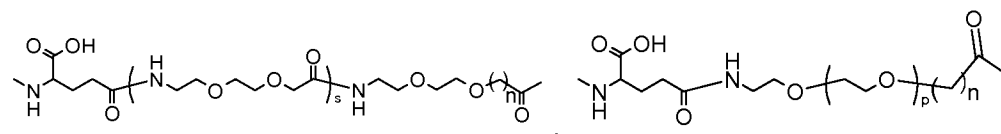
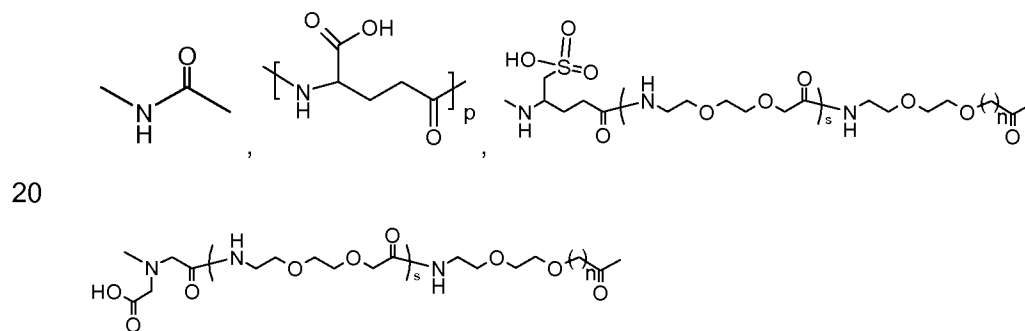
p is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

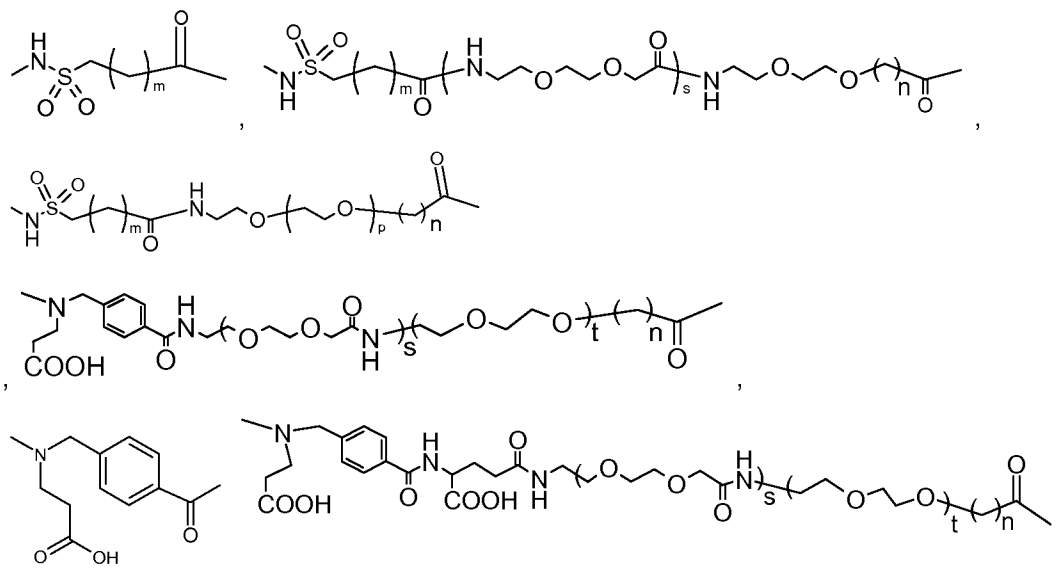
and where B is an acidic group selected from



15 In the embodiments below when referring to U' in formula I it is to be understood as also referring to formula II and U, with the only difference being the carboxy group.

An embodiment provides a GLP-1 analog according to the embodiments above, wherein U' is selected from





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m is 2, 3, 4 or 5,

n is 1 or 2

s is 0, 1, or 2,

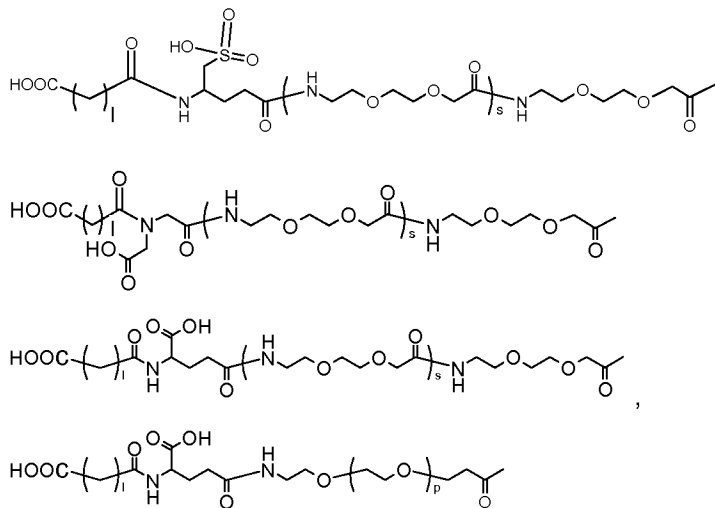
t is 0, 1, 2, or 3

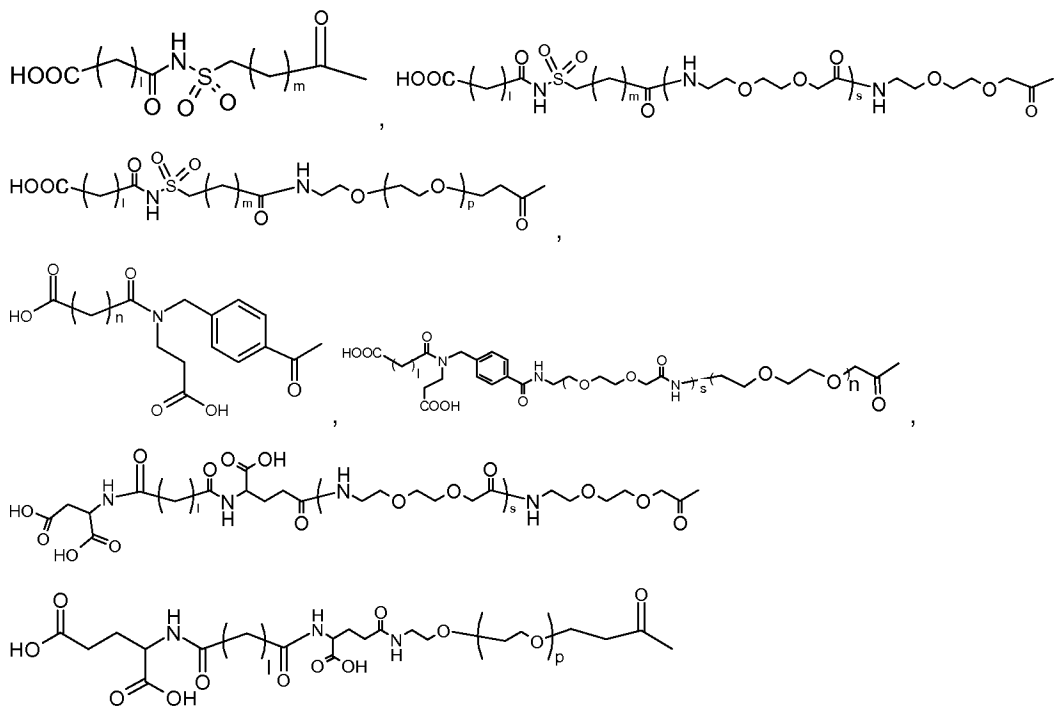
10

p is 1, 2, 3, 4, 7, 11 or 23

An embodiment provides a GLP-1 analog according to the embodiments above, wherein B-U'- is

15





where l is 14, 15, 16, 17, 18, 19 or 20;

p is 1, 2, 3, 4, 7, 8, 9, 10, 11 or 12.

s is 0, 1 or 2

t is 0 or 1;

An embodiment according to the above wherein

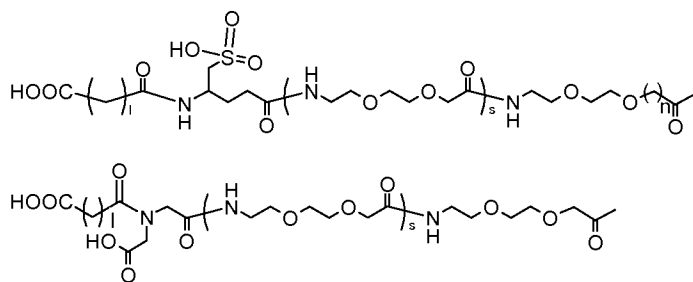
where l is 14, 15, 16, 17 or 18

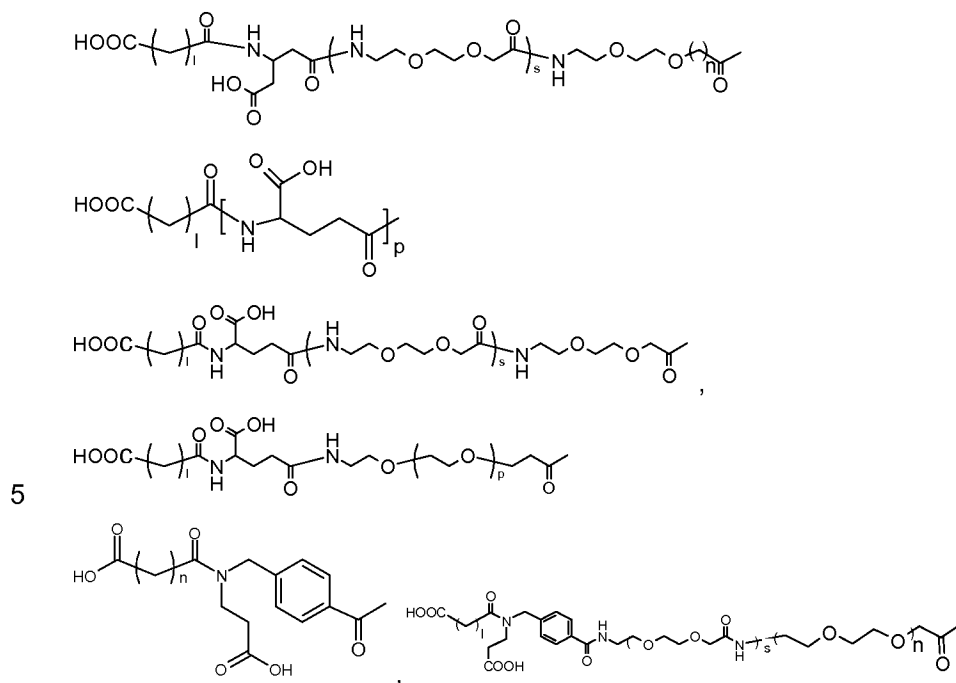
p is 1, 2, 3, 4 or 11;

s is 0, 1 or 2;

t is 0 or 1;

An embodiment provides a GLP-1 analog according to the embodiment above, wherein B-U' is





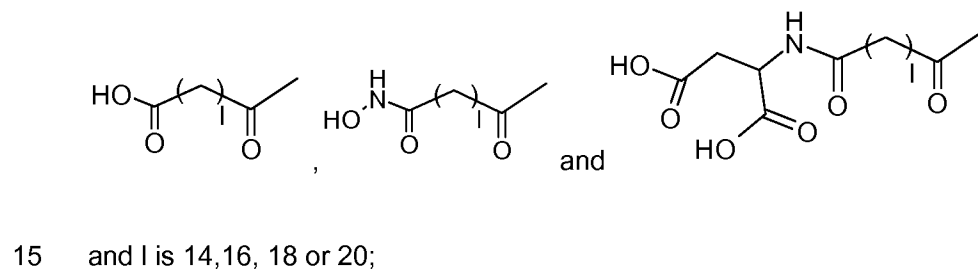
where I is 14, 15, 16, 17, 18, 19 or 20;

p is 1, 2, 3, or 4.

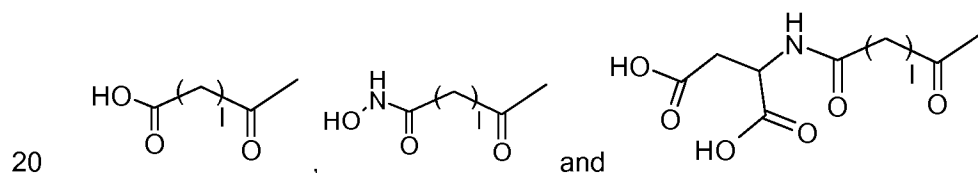
s is 0, 1 or 2

10 n is 0, 1 or 2

An embodiment according to any of the above embodiments is wherein B is



An embodiment provides a GLP-1 analog according to any of the embodiments above,
wherein B is



where l is 14, 15, or 16.

An embodiment provides a GLP-1 analog according to any of the embodiments above, wherein s is 1.

- 5 An embodiment provides a GLP-1 analog according to any of the embodiments above, wherein n is 1.

An embodiment provides a GLP-1 analog according any of the embodiments above, wherein l is 14, 15 or 16; In embodiments l is 17, 18, 19 or 20. In embodiments l is 15, 16 or 17. In embodiments l is 18, 19 or 20. In embodiments l is 14. In embodiments l is 16. In

- 10 embodiments l is 18. In embodiments l is 20.

An embodiment provides a GLP-1 analog according to any of the embodiments above, wherein p is 1.

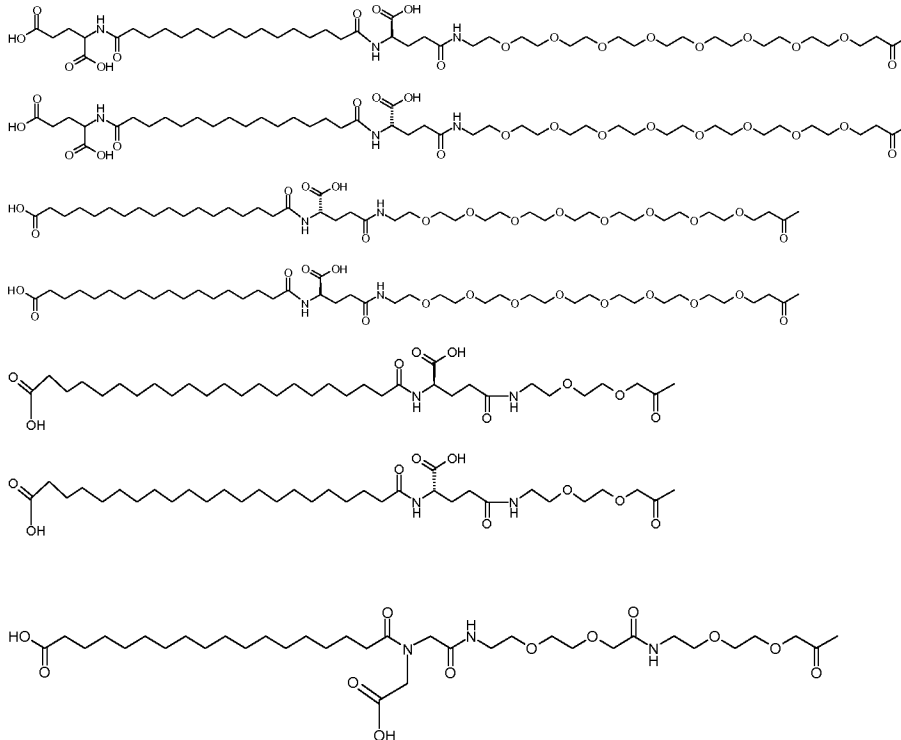
An embodiment provides a GLP-1 analog according to any of the embodiments above, wherein p is 2.

- 15 An embodiment provides a GLP-1 analog according to any of the embodiments above, wherein p is 3.

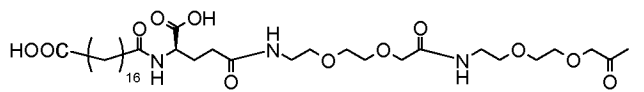
An embodiment provides a GLP-1 analog according to any of the embodiments above, wherein p is 4.

An embodiment provides a GLP-1 analog according to any of the embodiments above,

- 20 wherein B-U' is

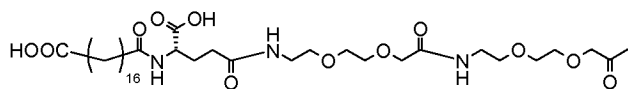


An embodiment provides a GLP-1 analog according to any of the embodiments above,
wherein B-U' is



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An embodiment provides a GLP-1 analog according to any of the embodiments above,
wherein B-U' is



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An embodiment provides a GLP-1 analog according to formula I above, wherein

Xaa₇ is His or desamino-histidine;

Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys or Aib;

Xaa₁₆ is Val;

15 Xaa₁₈ is Ser;

Xaa₁₉ is Tyr;

Xaa₂₀ is Leu;

Xaa₂₂ is Gly, Glu or Aib;

Xaa₂₃ is Gln or Glu;

20 Xaa₂₅ is Ala;

Xaa₂₇ is Glu;

Xaa₃₀ is Ala or Glu;

Xaa₃₃ is Val;

Xaa₃₄ is Lys or Arg;

25 Xaa₃₅ is Gly or Aib;

Xaa₃₆ is Arg or Lys

Xaa₃₇ is Gly, amide or is absent;

An embodiment provides a GLP-1 analog according to formula I above, wherein

30 Xaa₇ is His

Xaa₈ is Gly, or Aib;

Xaa₁₆ is Val;

Xaa₁₈ is Ser;

- Xaa₁₉ is Tyr;
Xaa₂₀ is Leu;
Xaa₂₂ is Glu or Aib;
Xaa₂₃ is Gln;
5 Xaa₂₅ is Ala;
Xaa₂₇ is Glu;
Xaa₃₀ is Ala;
Xaa₃₃ is Val;
Xaa₃₄ is Lys or Arg;
10 Xaa₃₅ is Gly or Aib;
Xaa₃₆ is Arg
Xaa₃₇ is Gly
- 15 An embodiment provides a GLP-1 analog according to any one of the above embodiments, wherein said GLP-1 analog comprises a modification of the N-terminal L-histidine in position 7 of the GLP-1(7-37) sequence.
- 20 An embodiment provides a GLP-1 analog according to the embodiment above, wherein said GLP-1 analog comprises imidazopropionyl⁷, α -hydroxy-histidine⁷ or N-methyl-histidine⁷, D-histidine⁷, desamino-histidine⁷, 2-amino-histidine⁷, β -hydroxy-histidine⁷, homohistidine⁷, N ^{α} -acetyl-histidine⁷, α -fluoromethyl-histidine⁷, α -methyl-histidine⁷, 3-pyridylalanine⁷, 2-pyridylalanine⁷ or 4-pyridylalanine⁷.
- 25 An embodiment provides a GLP-1 analog according to any one of the embodiments above, wherein said GLP-1 analog comprises a substitution of the L-alanine in position 8 of the GLP-1(7-37) sequence for another amino acid residue.
- 30 An embodiment provides a GLP-1 analog according to the embodiment above, wherein said GLP-1 analog comprises Aib⁸, Gly⁸, Val⁸, Ile⁸, Leu⁸, Ser⁸, Thr⁸, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid.
- 35 An embodiment provides a GLP-1 analog according to any of the the embodiment above, wherein said GLP-1 analog comprises Aib⁸;

In one embodiment of the invention said GLP-1 analog is Aib⁸,Arg³⁴-GLP-1(7-37) or Aib^{8,22},Arg³⁴-GLP-1(7-37).

5 An embodiment provides a GLP-1 analog according to any of the above embodiments, wherein said GLP-1 analog comprises no more than fifteen amino acid residues which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1),

10 An embodiment provides a GLP-1 analog according to the embodiment above, wherein no more than ten amino acid residues which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1).

15 An embodiment provides a GLP-1 analog according to the embodiment above, wherein said GLP-1 analog comprises no more than six amino acid residues which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1).

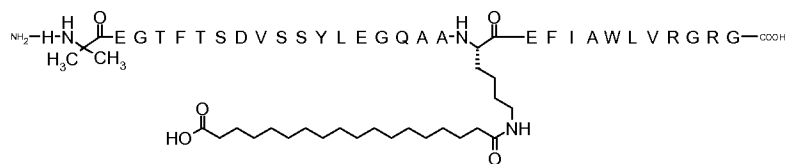
An embodiment provides a GLP-1 analog according to any of the above embodiments, wherein said GLP-1 analog comprises no more than 3 amino acid residues which are not encoded by the genetic code.

20 An embodiment provides a GLP-1 analog according to any of the above embodiments, wherein said GLP-1 analog comprises only one lysine residue.

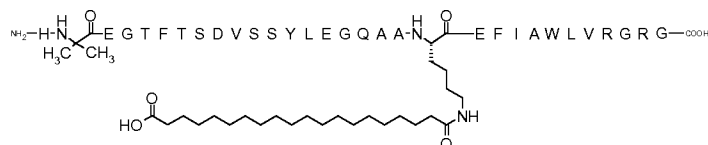
An embodiment provides a GLP-1 analog according to any of the above embodiments, which is

25 Aib⁸,Arg³⁴-GLP-1(7-37)
Aib^{8,22},Arg³⁴-GLP-1(7-37).
Arg³⁴-GLP-1(7-37).
[3-(4-Imidazolyl)Propionyl⁷,Arg³⁴]GLP-1-(7-37)peptide
Gly⁸,Arg³⁴-GLP-1(7-37)
30 Aib⁸,Arg³⁴, Pro³⁷-GLP-1(7-37)
Aib^{8,22,27,30,35},Arg³⁴,Pro³⁷- GLP-1 (7-37)amide,
all of which are substituted by B-U' in position 26.

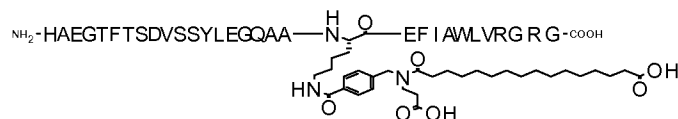
35 An embodiment provides a GLP-1 analog according to any one of the preceding embodiments, which is selected from



N-ε²⁶-(17-carboxyheptadecanoyl)-[Aib8,Arg34]GLP-1-(7-37)-peptide,

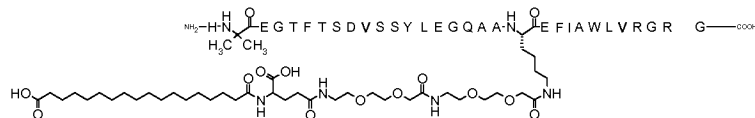


N-ε²⁶-(19-carboxynonadecanoyl)-[Aib8,Arg34]GLP-1-(7-37)-peptide,



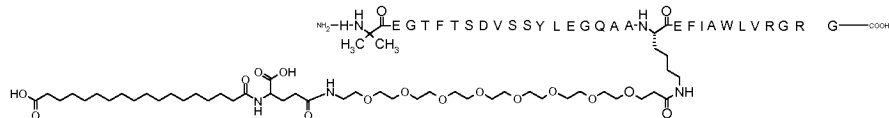
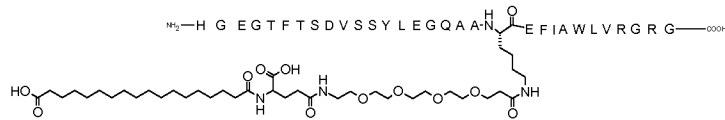
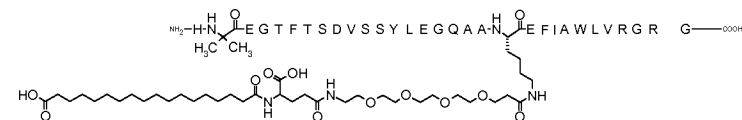
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N-ε²⁶-(4-[[N-(2-carboxyethyl)-N-(15-carboxypentadecanoyl)amino]methyl]benzoyl)[Arg34]GLP-1-(7-37),

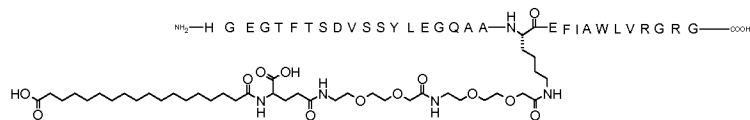
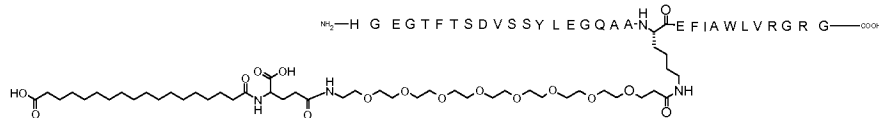


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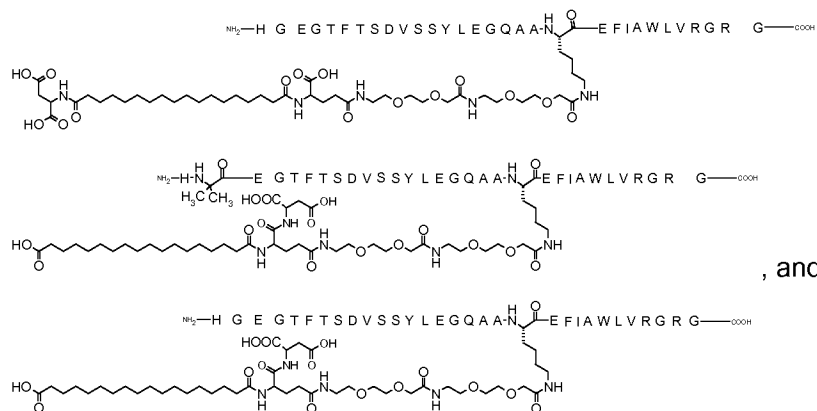
N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide,



15







- 5 An embodiment provides a method for increasing the time of action in a patient of a GLP-1 analog, characterised in acylating said GLP-1 analog with a moiety B-U as disclosed in any of the preceding embodiments, on the lysine residue in position 26 of said GLP-1 analog.

- 10 An embodiment provides a method for increasing the time of action in a patient of a GLP-1 analog to more than about 40 hours, characterised in modifying at least one of the amino acid residues in positions 7 and 8 of a GLP-1(7-37) peptide or an analog thereof, and acylating said GLP-1 analog with a moiety B-U'- as disclosed in any of the preceding embodiments on the lysine residue in position 26 of said GLP-1 analog.

- 15 An embodiment provides a pharmaceutical composition comprising a compound according to any one the embodiments above, and a pharmaceutically acceptable excipient.

An embodiment provides a pharmaceutical composition according to the embodiment above, which is suited for parenteral administration.

20

An embodiment provides the use of a compound according to any one of the embodiments above for the preparation of a medicament.

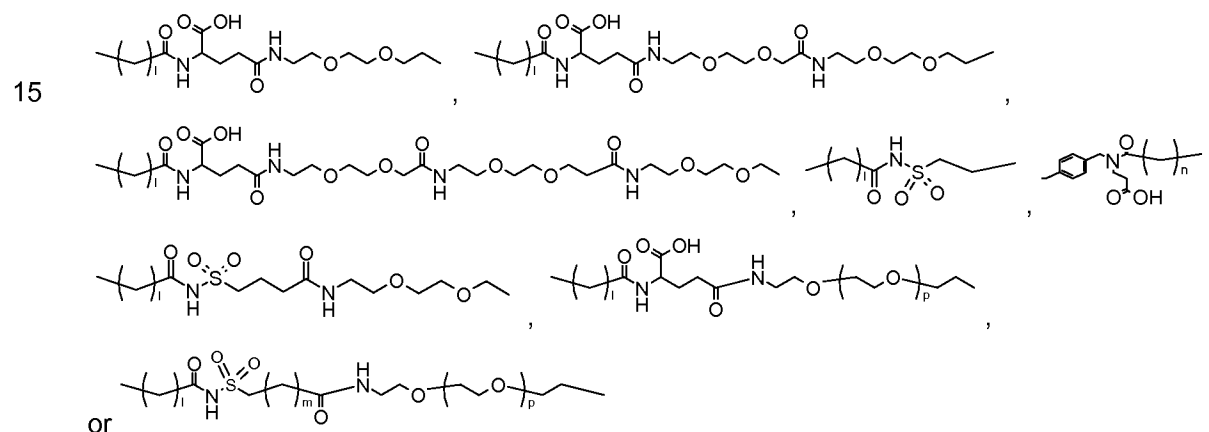
- 25 An embodiment provides the use of a compound according to any one of the embodiments above for the preparation of a medicament for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, hypertension, syndrome X, dyslipidemia, cognitive disorders, atherosclerosis, myocardial infarction, coronary heart disease and other cardiovascular disorders, stroke, inflammatory bowel syndrome, dyspepsia and gastric ulcers.

30

An embodiment provides the use of a compound according to any one of the embodiments above for the preparation of a medicament for delaying or preventing disease progression in type 2 diabetes.

- 5 An embodiment provides the use of a compound according to any one of the embodiments above for the preparation of a medicament for decreasing food intake, decreasing β -cell apoptosis, increasing β -cell function and β -cell mass, and/or for restoring glucose sensitivity to β -cells.
- 10 In an embodiment the invention provides a compound according to the embodiments above, wherein said GLP-1 analog is Aib⁸,Arg³⁴-GLP-1(7-37) or Aib^{8,22},Arg³⁴-GLP-1(7-37) attached to a linker B-U';

In an embodiment of Formula II, B-U represents



- 20
- where l is 14, 15 or 16;
n is 15, 16, 17 or 18;
p is 3, 7, 11 or 24.

- 25 In embodiments the invention provides a compound according to any one of the embodiments above, wherein said diacid comprises a dicarboxylic acid.

- 30 In embodiments the invention provides a compound according to any one of the embodiments above, wherein the acylation group comprises a straight-chain or branched alkane α,ω -dicarboxylic acid.

In embodiments the invention provides compound according to the embodiment above, wherein the acylation group comprises the structure $\text{HOOC}-(\text{CH}_2)_n\text{CO}-$, wherein n is 12 to 20.

5 In embodiments the invention provides a compound according to the embodiment above, wherein the acylation group comprises a structure selected from $\text{HOOC}-(\text{CH}_2)_{14}\text{CO}-$, $\text{HOOC}-(\text{CH}_2)_{15}\text{CO}-$, $\text{HOOC}-(\text{CH}_2)_{16}\text{CO}-$, $\text{HOOC}-(\text{CH}_2)_{17}\text{CO}-$, and $\text{HOOC}-(\text{CH}_2)_{18}\text{CO}-$.

10 In embodiments the invention provides a compound according to the embodiment above, wherein the acylation group comprises the structure $\text{HOOC}-(\text{CH}_2)_{16}\text{CO}-$.

Another object of the present invention is to provide a pharmaceutical formulation comprising a compound according to the present invention which is present in a concentration from 0.1 mg/ml to 25 mg/ml, and wherein said formulation has a pH from 3.0 to 9.0. The formulation may further comprise a buffer system, preservative(s), tonicity agent(s), chelating agent(s),
15 stabilizers and surfactants. In one embodiment of the invention the pharmaceutical formulation is an aqueous formulation, i.e. formulation comprising water. Such formulation is typically a solution or a suspension. In a further embodiment of the invention the pharmaceutical formulation is an aqueous solution. The term "aqueous formulation" is defined as a formulation comprising at least 50 %w/w water. Likewise, the term "aqueous
20 solution" is defined as a solution comprising at least 50 %w/w water, and the term "aqueous suspension" is defined as a suspension comprising at least 50 %w/w water.

In another embodiment the pharmaceutical formulation is a freeze-dried formulation, whereto the physician or the patient adds solvents and/or diluents prior to use.

25 In another embodiment the pharmaceutical formulation is a dried formulation (e.g. freeze-dried or spray-dried) ready for use without any prior dissolution.

In a further aspect the invention relates to a pharmaceutical formulation comprising an aqueous solution of a compound according to the present invention, and a buffer, wherein said compound is present in a concentration from 0.1 mg/ml or above, and wherein said formulation has a pH from about 3.0 to about 9.0.

30 In another embodiment of the invention the pH of the formulation is from about 7.0 to about 9.5. In another embodiment of the invention the pH of the formulation is from about 3.0 to about 7.0. In another embodiment of the invention the pH of the formulation is from about 5.0 to about 7.5. In another embodiment of the invention the pH of the formulation is from about 7.5 to about 9.0. In another embodiment of the invention the pH of the formulation is from
35 about 7.5 to about 8.5. In another embodiment of the invention the pH of the formulation is from about 6.0 to about 7.5. In another embodiment of the invention the pH of the formulation

is from about 6.0 to about 7.0. In another embodiment the pharmaceutical formulation is from 8.0 to 8.5.

In a further embodiment of the invention the buffer is selected from the group consisting of sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, and tris(hydroxymethyl)-aminomethan, bicine, tricine, malic acid, succinate, maleic acid, fumaric acid, tartaric acid, aspartic acid or mixtures thereof. Each one of these specific buffers constitutes an alternative embodiment of the invention.

In a further embodiment of the invention the formulation further comprises a pharmaceutically acceptable preservative. In a further embodiment of the invention the preservative is selected from the group consisting of phenol, o-cresol, m-cresol, p-cresol, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, 2-phenoxyethanol, butyl p-hydroxybenzoate, 2-phenylethanol, benzyl alcohol, chlorobutanol, and thiomerosal, bronopol, benzoic acid, imidurea, chlorohexidine, sodium dehydroacetate, chlorocresol, ethyl p-hydroxybenzoate, benzethonium chloride, chlorphenesine (3p-chlorphenoxypropane-1,2-diol) or mixtures thereof. In an embodiment the preservative is phenol or m-cresol. In a further embodiment of the invention the preservative is present in a concentration from 0.1 mg/ml to 20 mg/ml. In a further embodiment of the invention the preservative is present in a concentration from 0.1 mg/ml to 5 mg/ml. In a further embodiment of the invention the preservative is present in a concentration from 5 mg/ml to 10 mg/ml. In a further embodiment of the invention the preservative is present in a concentration from 10 mg/ml to 20 mg/ml. Each one of these specific preservatives constitutes an alternative embodiment of the invention. The use of a preservative in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

In a further embodiment of the invention the formulation further comprises an isotonic agent. In a further embodiment of the invention the isotonic agent is selected from the group consisting of a salt (e.g. sodium chloride), a sugar or sugar alcohol, an amino acid (e.g. L-glycine, L-histidine, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine), an alditol (e.g. glycerol (glycerine), 1,2-propanediol (propyleneglycol), 1,3-propanediol, 1,3-butanediol) polyethyleneglycol (e.g. PEG400), or mixtures thereof. In an embodiment the isotonicity agent is propyleneglycol. Any sugar such as mono-, di-, or polysaccharides, or water-soluble glucans, including for example fructose, glucose, mannose, sorbose, xylose,

maltose, lactose, sucrose, trehalose, dextran, pullulan, dextrin, cyclodextrin, soluble starch, hydroxyethyl starch and carboxymethylcellulose-Na may be used. In one embodiment the sugar additive is sucrose. Sugar alcohol is defined as a C4-C8 hydrocarbon having at least one -OH group and includes, for example, mannitol, sorbitol, inositol, galactitol, dulcitol, xylitol, and arabitol. In one embodiment the sugar alcohol additive is mannitol. The sugars or sugar alcohols mentioned above may be used individually or in combination. There is no fixed limit to the amount used, as long as the sugar or sugar alcohol is soluble in the liquid preparation and does not adversely effect the stabilizing effects achieved using the methods of the invention. In one embodiment, the sugar or sugar alcohol concentration is between about 1 mg/ml and about 150 mg/ml. In a further embodiment of the invention the isotonic agent is present in a concentration from 1 mg/ml to 50 mg/ml. In a further embodiment of the invention the isotonic agent is present in a concentration from 1 mg/ml to 7 mg/ml. In an embodiment of the invention the isotonic agent is present in a concentration from 5 mg/ml to 7 mg/ml. In a further embodiment of the invention the isotonic agent is present in a concentration from 8 mg/ml to 24 mg/ml. In a further embodiment of the invention the isotonic agent is present in a concentration from 25 mg/ml to 50 mg/ml. Each one of these specific isotonic agents constitutes an alternative embodiment of the invention. The use of an isotonic agent in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

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In a further embodiment of the invention the formulation further comprises a chelating agent. In a further embodiment of the invention the chelating agent is selected from salts of ethylenediaminetetraacetic acid (EDTA), citric acid, and aspartic acid, and mixtures thereof. In a further embodiment of the invention the chelating agent is present in a concentration from 0.1mg/ml to 5mg/ml. In a further embodiment of the invention the chelating agent is present in a concentration from 0.1mg/ml to 2mg/ml. In a further embodiment of the invention the chelating agent is present in a concentration from 2mg/ml to 5mg/ml. Each one of these specific chelating agents constitutes an alternative embodiment of the invention. The use of a chelating agent in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

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In a further embodiment of the invention the formulation further comprises a stabilizer. The use of a stabilizer in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

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More particularly, compositions of the invention are stabilized liquid pharmaceutical compositions whose therapeutically active components include a polypeptide that possibly exhibits aggregate formation during storage in liquid pharmaceutical formulations. By "aggregate formation" is intended a physical interaction between the polypeptide molecules that results in formation of oligomers, which may remain soluble, or large visible aggregates that precipitate from the solution. By "during storage" is intended a liquid pharmaceutical composition or formulation once prepared, is not immediately administered to a subject. Rather, following preparation, it is packaged for storage, either in a liquid form, in a frozen state, or in a dried form for later reconstitution into a liquid form or other form suitable for administration to a subject. By "dried form" is intended the liquid pharmaceutical composition or formulation is dried either by freeze drying (i.e., lyophilization; see, for example, Williams and Polli (1984) J. Parenteral Sci. Technol. 38:48-59), spray drying (see Masters (1991) in Spray-Drying Handbook (5th ed; Longman Scientific and Technical, Essex, U.K.), pp. 491-676; Broadhead et al. (1992) Drug Devel. Ind. Pharm. 18:1169-1206; and Mumenthaler et al. (1994) Pharm. Res. 11:12-20), or air drying (Carpenter and Crowe (1988) Cryobiology 25:459-470; and Roser (1991) Biopharm. 4:47-53). Aggregate formation by a polypeptide during storage of a liquid pharmaceutical composition can adversely affect biological activity of that polypeptide, resulting in loss of therapeutic efficacy of the pharmaceutical composition. Furthermore, aggregate formation may cause other problems such as blockage of tubing, membranes, or pumps when the polypeptide-containing pharmaceutical composition is administered using an infusion system.

The pharmaceutical compositions of the invention may further comprise an amount of an amino acid base sufficient to decrease aggregate formation by the polypeptide during storage of the composition. By "amino acid base" is intended an amino acid or a combination of amino acids, where any given amino acid is present either in its free base form or in its salt form. Where a combination of amino acids is used, all of the amino acids may be present in their free base forms, all may be present in their salt forms, or some may be present in their free base forms while others are present in their salt forms. In one embodiment, amino acids to use in preparing the compositions of the invention are those carrying a charged side chain, such as arginine, lysine, aspartic acid, and glutamic acid. Any stereoisomer (i.e., L, D, or a mixture thereof) of a particular amino acid (e.g. methionine, histidine, imidazole, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine and mixtures thereof) or combinations of these stereoisomers, may be present in the pharmaceutical compositions of the invention so long as the particular amino acid is present either in its free base form or its salt form. In one embodiment the L-stereoisomer is used. Compositions of the invention may also be formulated with analogues of these amino acids. By "amino acid analogue" is intended a

derivative of the naturally occurring amino acid that brings about the desired effect of decreasing aggregate formation by the polypeptide during storage of the liquid pharmaceutical compositions of the invention. Suitable arginine analogues include, for example, aminoguanidine, ornithine and N-monoethyl L-arginine, suitable methionine analogues include ethionine and buthionine and suitable cysteine analogues include S-methyl-L cysteine. As with the other amino acids, the amino acid analogues are incorporated into the compositions in either their free base form or their salt form. In a further embodiment of the invention the amino acids or amino acid analogues are used in a concentration, which is sufficient to prevent or delay aggregation of the protein.

10 In a further embodiment of the invention methionine (or other sulphuric amino acids or amino acid analogous) may be added to inhibit oxidation of methionine residues to methionine sulfoxide when the polypeptide acting as the therapeutic agent is a polypeptide comprising at least one methionine residue susceptible to such oxidation. By "inhibit" is intended minimal accumulation of methionine oxidized species over time. Inhibiting methionine oxidation

15 results in greater retention of the polypeptide in its proper molecular form. Any stereoisomer of methionine (L or D) or combinations thereof can be used. The amount to be added should be an amount sufficient to inhibit oxidation of the methionine residues such that the amount of methionine sulfoxide is acceptable to regulatory agencies. Typically, this means that the composition contains no more than about 10% to about 30% methionine sulfoxide.

20 Generally, this can be achieved by adding methionine such that the ratio of methionine added to methionine residues ranges from about 1:1 to about 1000:1, such as 10:1 to about 100:1.

In a further embodiment of the invention the formulation further comprises a stabilizer selected from the group of high molecular weight polymers or low molecular compounds. In a

25 further embodiment of the invention the stabilizer is selected from polyethylene glycol (e.g. PEG 3350), polyvinyl alcohol (PVA), polyvinylpyrrolidone, carboxy-/hydroxycellulose or derivatives thereof (e.g. HPC, HPC-SL, HPC-L and HPMC), cyclodextrins, sulphur-containing substances as monothioglycerol, thioglycolic acid and 2-methylthioethanol, and different salts (e.g. sodium chloride). Each one of these specific stabilizers constitutes an alternative

30 embodiment of the invention.

The pharmaceutical compositions may also comprise additional stabilizing agents, which further enhance stability of a therapeutically active polypeptide therein. Stabilizing agents of particular interest to the present invention include, but are not limited to, methionine and EDTA, which protect the polypeptide against methionine oxidation, and a

35 nonionic surfactant, which protects the polypeptide against aggregation associated with freeze-thawing or mechanical shearing.

In a further embodiment of the invention the formulation further comprises a surfactant. In another embodiment of the invention the pharmaceutical composition comprises two different surfactants. The term "Surfactant" as used herein refers to any molecules or ions that are
5 comprised of a water-soluble (hydrophilic) part, the head, and a fat-soluble (lipophilic) segment. Surfactants accumulate preferably at interfaces, which the hydrophilic part is orientated towards the water (hydrophilic phase) and the lipophilic part towards the oil- or hydrophobic phase (*i.e.* glass, air, oil etc.). The concentration at which surfactants begin to form micelles is known as the critical micelle concentration or CMC. Furthermore, surfactants
10 lower the surface tension of a liquid. Surfactants are also known as amphipathic compounds. The term "Detergent" is a synonym used for surfactants in general.

Anionic surfactants may be selected from the group of: Chenodeoxycholic acid, Chenodeoxycholic acid sodium salt, Cholic acid, Dehydrocholic acid, Deoxycholic acid, Deoxycholic acid methyl ester, Digitonin, Digitoxigenin, N,N-Dimethyldodecylamine N-oxide,
15 Docusate sodium, Glycochenodeoxycholic acid sodium, Glycocholic acid hydrate, Glycodeoxycholic acid monohydrate, Glycodeoxycholic acid sodium salt, Glycodeoxycholic acid sodium salt, Glycolithocholic acid 3-sulfate disodium salt, Glycolithocholic acid ethyl ester, N-Lauroylsarcosine sodium salt, N-Lauroylsarcosine sodium salt, N-Lauroylsarcosine, N-Lauroylsarcosine, Lithium dodecyl sulfate, Lugol, 1-Octanesulfonic acid sodium salt, 1-
20 Octanesulfonic acid sodium salt, Sodium 1-butanefulfonate, Sodium 1-decanesulfonate, Sodium 1-dodecanesulfonate, Sodium 1-heptanesulfonate, Sodium 1-heptanesulfonate, Sodium 1-nonanesulfonate, Sodium 1-propanesulfonate monohydrate, Sodium 2-bromoethanesulfonate, Sodium cholate hydrate, ox or sheep bile, Sodium cholate hydrate, Sodium choleate, Sodium deoxycholate, Sodium dodecyl sulfate, Sodium dodecyl sulfate,
25 Sodium hexanesulfonate, Sodium octyl sulfate, Sodium pentanesulfonate, Sodium taurocholate, Taurochenodeoxycholic acid sodium salt, Taurodeoxycholic acid sodium salt monohydrate, Taurolithocholic acid 3-sulfate disodium salt, Tauroursodeoxycholic acid sodium salt, Trizma[®] dodecyl sulfate, DSS (docusate sodium, CAS registry no [577-11-7]), docusate calcium, CAS registry no [128-49-4]), docusate potassium, CAS registry no [7491-
30 09-0]), SDS (sodium dodecyl sulfate or sodium lauryl sulfate), Dodecylphosphocholine (FOS-Choline-12), Decylphosphocholine (FOS-Choline-10), Nonylphosphocholine (FOS-Choline-9), dipalmitoyl phosphatidic acid, sodium caprylate, and/or Ursodeoxycholic acid.

Cationic surfactants may be selected from the group of: Alkyltrimethylammonium bromide
35 Benzalkonium chloride, Benzalkonium chloride, Benzyltrimethylhexadecylammonium chloride, Benzyltrimethyltetradecylammonium chloride,

Benzyltrimethylammonium tetrachloroiodate, Dimethyldioctadecylammonium bromide, Dodecylethyldimethylammonium bromide, Dodecyltrimethylammonium bromide, Dodecyltrimethylammonium bromide, Ethylhexadecyldimethylammonium bromide, Hexadecyltrimethylammonium bromide, Hexadecyltrimethylammonium bromide,
5 Polyoxyethylene(10)-N-tallow-1,3-diaminopropane, Thonzonium bromide, and/or Trimethyl(tetradecyl)ammonium bromide.

Nonionic surfactants may be selected from the group of: BigCHAP, Bis(polyethylene glycol bis[imidazolyl carbonyl]), block copolymers as polyethyleneoxide/polypropyleneoxide block copolymers such as poloxamers, poloxamer
10 188 and poloxamer 407, Brij[®] 35, Brij[®] 56, Brij[®] 72, Brij[®] 76, Brij[®] 92V, Brij[®] 97, Brij[®] 58P, Cremophor[®] EL, Decaethylene glycol monododecyl ether, N-Decanoyl-N-methylglucamine, n-Dodecanoyl-N-methylglucamide, alkyl-polyglucosides, ethoxylated castor oil, Heptaethylene glycol monodecyl ether, Heptaethylene glycol monododecyl ether, Heptaethylene glycol monotetradecyl ether, Hexaethylene glycol monododecyl ether,
15 Hexaethylene glycol monohexadecyl ether, Hexaethylene glycol monooctadecyl ether, Hexaethylene glycol monotetradecyl ether, Igepal CA-630, Igepal CA-630, Methyl-6-O-(N-heptylcarbamoyl)-beta-D-glucopyranoside, Nonaethylene glycol monododecyl ether, N-Nonanoyl-N-methylglucamine, N-Nonanoyl-N-methylglucamine, Octaethylene glycol monodecyl ether, Octaethylene glycol monododecyl ether, Octaethylene glycol
20 monohexadecyl ether, Octaethylene glycol monooctadecyl ether, Octaethylene glycol monotetradecyl ether, Octyl-β-D-glucopyranoside, Pentaethylene glycol monodecyl ether, Pentaethylene glycol monododecyl ether, Pentaethylene glycol monohexadecyl ether, Pentaethylene glycol monooctadecyl ether, Pentaethylene glycol monooctyl ether, Polyethylene glycol diglycidyl ether, Polyethylene
25 glycol ether W-1, Polyoxyethylene 10 tridecyl ether, Polyoxyethylene 100 stearate, Polyoxyethylene 20 isohexadecyl ether, Polyoxyethylene 20 oleyl ether, Polyoxyethylene 40 stearate, Polyoxyethylene 50 stearate, Polyoxyethylene 8 stearate, Polyoxyethylene bis(imidazolyl carbonyl), Polyoxyethylene 25 propylene glycol stearate, Saponin from Quillaja bark, Span[®] 20, Span[®] 40, Span[®] 60, Span[®] 65, Span[®] 80, Span[®] 85, Tergitol, Type 15-S-12,
30 Tergitol, Type 15-S-30, Tergitol, Type 15-S-5, Tergitol, Type 15-S-7, Tergitol, Type 15-S-9, Tergitol, Type NP-10, Tergitol, Type NP-4, Tergitol, Type NP-40, Tergitol, Type NP-7, Tergitol, Type NP-9, Tetradecyl-β-D-maltoside, Tetraethylene glycol monodecyl ether, Tetraethylene glycol monododecyl ether, Tetraethylene glycol monotetradecyl ether, Triethylene glycol monodecyl ether, Triethylene glycol monododecyl ether, Triethylene glycol
35 monohexadecyl ether, Triethylene glycol monooctyl ether, Triethylene glycol monotetradecyl ether, Triton CF-21, Triton CF-32, Triton DF-12, Triton DF-16, Triton GR-5M, Triton QS-15,

Triton QS-44, Triton X-100, Triton X-102, Triton X-15, Triton X-151, Triton X-200, Triton X-207, Triton[®] X-100, Triton[®] X-114, Triton[®] X-165 solution, Triton[®] X-305 solution, Triton[®] X-405, Triton[®] X-45, Triton[®] X-705-70, TWEEN[®] 20, TWEEN[®] 40, TWEEN[®] 60, TWEEN[®] 6, TWEEN[®] 65, TWEEN[®] 80, TWEEN[®] 81, TWEEN[®] 85, Tyloxapol, sphingophospholipids (sphingomyelin), and sphingoglycolipids (ceramides, gangliosides), phospholipids, and/or n-Undecyl β -D-glucopyranoside. '

Zwitterionic surfactants may be selected from the group of: CHAPS, CHAPSO, 3-(Decyldimethylammonio)propanesulfonate inner salt, 3-(Dodecyldimethylammonio)propanesulfonate inner salt, 3-(Dodecyldimethylammonio)propanesulfonate inner salt, 3-(N,N-Dimethylmyristylammonio)propanesulfonate, 3-(N,N-Dimethyloctadecylammonio)propanesulfonate, 3-(N,N-Dimethyloctylammonio)propanesulfonate inner salt, 3-(N,N-Dimethylpalmitylammonio)propanesulfonate, N-alkyl-N,N-dimethylammonio-1-propanesulfonates, 3-cholamido-1-propyldimethylammonio-1-propanesulfonate, Dodecylphosphocholine, myristoyl lysophosphatidylcholine, Zwittergent 3-12 (N-dodecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate), Zwittergent 3-10 (3-(Decyldimethylammonio)propanesulfonate inner salt), Zwittergent 3-08 (3-(Octyldimethylammonio)propanesulfonate), glycerophospholipids (lecithins, cephalins, phosphatidyl serine), glyceroglycolipids (galactopyranoside), alkyl, alkoxyl (alkyl ester), alkoxy (alkyl ether)- derivatives of lysophosphatidyl and phosphatidylcholines, e.g. lauroyl and myristoyl derivatives of lysophosphatidylcholine, dipalmitoylphosphatidylcholine, and modifications of the polar head group, that is cholines, ethanolamines, phosphatidic acid, serines, threonines, glycerol, inositol, lysophosphatidylserine and lysophosphatidylthreonine, acylcarnitines and derivatives, N^{beta}-acylated derivatives of lysine, arginine or histidine, or side-chain acylated derivatives of lysine or arginine, N^{beta}-acylated derivatives of dipeptides comprising any combination of lysine, arginine or histidine and a neutral or acidic amino acid, N^{beta}-acylated derivative of a tripeptide comprising any combination of a neutral amino acid and two charged amino acids, or the surfactant may be selected from the group of imidazoline derivatives, long-chain fatty acids and salts thereof C₆-C₁₂ (eg. oleic acid and caprylic acid), N-Hexadecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate, anionic (alkyl-aryl-sulphonates) monovalent surfactants, palmitoyl lysophosphatidyl-L-serine, lysophospholipids (e.g. 1-acyl-sn-glycero-3-phosphate esters of ethanolamine, choline, serine or threonine), or mixtures thereof.

The term "alkyl-polyglucosides" as used herein relates to an straight or branched C₅₋₂₀-alkyl, -alkenyl or -alkynyl chain which is substituted by one or more glucoside moieties such as maltoside, saccharide etc. Embodiments of these alkyl-polyglucosides include C₆₋₁₈-alkyl-polyglucosides. Specific embodiments of these alkyl-polyglucosides includes the even

numbered carbon-chains such as C₆, C₈, C₁₀, C₁₂, C₁₄, C₁₆, C₁₈ and C₂₀ alkyl chain. Specific
embodiments of the glucoside moieties include pyranoside, glucopyranoside, maltoside,
maltotrioside and sucrose. In embodiments of the invention less than 6 glucosid moieties are
attached to the alkyl group. In embodiments of the invention less than 5 glucosid moieties
5 are attached to the alkyl group. In embodiments of the invention less than 4 glucosid
moieties are attached to the alkyl group. In embodiments of the invention less than 3
glucosid moieties are attached to the alkyl group. In embodiments of the invention less than
2 glucosid moieties are attached to the alkyl group. Specific embodiments of alkyl-
polyglucosides are alkyl glucosides such n-decyl β -D-glucopyranoside, decyl β -D-
10 maltopyranoside, dodecyl β -D-glucopyranoside, n-dodecyl β -D-maltoside, n-dodecyl β -D-
maltoside, n-dodecyl β -D-maltoside, tetradecyl β -D-glucopyranoside, decyl β -D-maltoside,
hexadecyl β -D-maltoside, decyl β -D-maltotrioside, dodecyl β -D-maltotrioside, tetradecyl β -D-
maltotrioside, hexadecyl β -D-maltotrioside, n-dodecyl-sucrose, n-decyl-sucrose, sucrose
monocaprato, sucrose monolaurate, sucrose monomyristate, and sucrose monopalmitate.

15 The use of a surfactant in pharmaceutical compositions is well-known to the skilled
person. For convenience reference is made to Remington: *The Science and Practice of
Pharmacy*, 19th edition, 1995.

In a further embodiment of the invention the formulation further comprises protease inhibitors
such as EDTA (ethylenediamine tetraacetic acid) and benzamidineHCl, but other
20 commercially available protease inhibitors may also be used. The use of a protease inhibitor
is particular useful in pharmaceutical compositions comprising zymogens of proteases in
order to inhibit autocatalysis.

It is possible that other ingredients may be present in the peptide pharmaceutical
25 formulation of the present invention. Such additional ingredients may include wetting agents,
emulsifiers, antioxidants, bulking agents, tonicity modifiers, chelating agents, metal ions,
oleaginous vehicles, proteins (e.g., human serum albumin, gelatine or proteins) and a
zwitterion (e.g., an amino acid such as betaine, taurine, arginine, glycine, lysine and
histidine). Such additional ingredients, of course, should not adversely affect the overall
30 stability of the pharmaceutical formulation of the present invention.

Pharmaceutical compositions containing a compound according to the present invention may
be administered to a patient in need of such treatment at several sites, for example, at topical
sites, for example, skin and mucosal sites, at sites which bypass absorption, for example,
35 administration in an artery, in a vein, in the heart, and at sites which involve absorption, for
example, administration in the skin, under the skin, in a muscle or in the abdomen.

Administration of pharmaceutical compositions according to the invention may be through several routes of administration, for example, lingual, sublingual, buccal, in the mouth, oral, in the stomach and intestine, nasal, pulmonary, for example, through the bronchioles and alveoli or a combination thereof, epidermal, dermal, transdermal, vaginal, rectal, ocular, for
5 examples through the conjunctiva, uretal, and parenteral to patients in need of such a treatment.

Compositions of the current invention may be administered in several dosage forms, for example, as solutions, suspensions, emulsions, microemulsions, multiple emulsion, foams, salves, pastes, plasters, ointments, tablets, coated tablets, rinses, capsules, for example,
10 hard gelatine capsules and soft gelatine capsules, suppositories, rectal capsules, drops, gels, sprays, powder, aerosols, inhalants, eye drops, ophthalmic ointments, ophthalmic rinses, vaginal pessaries, vaginal rings, vaginal ointments, injection solution, in situ transforming solutions, for example in situ gelling, in situ setting, in situ precipitating, in situ crystallization, infusion solution, and implants.

15 Compositions of the invention may further be compounded in, or attached to, for example through covalent, hydrophobic and electrostatic interactions, a drug carrier, drug delivery system and advanced drug delivery system in order to further enhance stability of the compound of the present invention, increase bioavailability, increase solubility, decrease adverse effects, achieve chronotherapy well known to those skilled in the art, and increase
20 patient compliance or any combination thereof. Examples of carriers, drug delivery systems and advanced drug delivery systems include, but are not limited to, polymers, for example cellulose and derivatives, polysaccharides, for example dextran and derivatives, starch and derivatives, poly(vinyl alcohol), acrylate and methacrylate polymers, polylactic and polyglycolic acid and block co-polymers thereof, polyethylene glycols, carrier proteins, for
25 example albumin, gels, for example, thermogelling systems, for example block co-polymeric systems well known to those skilled in the art, micelles, liposomes, microspheres, nanoparticulates, liquid crystals and dispersions thereof, L2 phase and dispersions thereof, well known to those skilled in the art of phase behaviour in lipid-water systems, polymeric micelles, multiple emulsions, self-emulsifying, self-microemulsifying, cyclodextrins and
30 derivatives thereof, and dendrimers.

Compositions of the current invention are useful in the formulation of solids, semisolids, powder and solutions for pulmonary administration of compounds of the present invention, using, for example a metered dose inhaler, dry powder inhaler and a nebulizer, all being devices well known to those skilled in the art.

35 Compositions of the current invention are specifically useful in the formulation of controlled, sustained, protracting, retarded, and slow release drug delivery systems. More specifically,

but not limited to, compositions are useful in formulation of parenteral controlled release and sustained release systems (both systems leading to a many-fold reduction in number of administrations), well known to those skilled in the art. Even more preferably, are controlled release and sustained release systems administered subcutaneous. Without limiting the scope of the invention, examples of useful controlled release system and compositions are hydrogels, oleaginous gels, liquid crystals, polymeric micelles, microspheres, nanoparticles, Methods to produce controlled release systems useful for compositions of the current invention include, but are not limited to, crystallization, condensation, co-crystallization, precipitation, co-precipitation, emulsification, dispersion, high pressure homogenisation, encapsulation, spray drying, microencapsulating, coacervation, phase separation, solvent evaporation to produce microspheres, extrusion and supercritical fluid processes. General reference is made to Handbook of Pharmaceutical Controlled Release (Wise, D.L., ed. Marcel Dekker, New York, 2000) and Drug and the Pharmaceutical Sciences vol. 99: Protein Formulation and Delivery (MacNally, E.J., ed. Marcel Dekker, New York, 2000). Parenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump. A further option is a composition which may be a solution or suspension or a powder for the administration of the compound of the present invention in the form of a nasal or pulmonal liquid or powder spray. As a still further option, the pharmaceutical compositions containing the compound of the invention can also be adapted to transdermal administration, e.g. by needle-free injection or from a patch, optionally an iontophoretic patch, or transmucosal, e.g. buccal, administration.

The compounds of the present invention can be administered via the pulmonary route in a vehicle, as a solution, suspension or dry powder using any of known types of devices suitable for pulmonary drug delivery. Examples of these comprise, but are not limited to, the three general types of aerosol-generating for pulmonary drug delivery, and may include jet or ultrasonic nebulizers, metered-dose inhalers, or dry powder inhalers (Cf. Yu J, Chien YW. Pulmonary drug delivery: Physiologic and mechanistic aspects. Crit Rev Ther Drug Carr Sys 14(4) (1997) 395-453).

Based on standardised testing methodology, the aerodynamic diameter (d_a) of a particle is defined as the geometric equivalent diameter of a reference standard spherical particle of unit density (1 g/cm^3). In the simplest case, for spherical particles, d_a is related to a reference diameter (d) as a function of the square root of the density ratio as described by:

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Modifications to this relationship occur for non-spherical particles (cf. Edwards DA, Ben-Jebria A, Langer R. Recent advances in pulmonary drug delivery using large, porous inhaled particles. J Appl Physiol 84(2) (1998) 379-385). The terms "MMAD" and "MMEAD" are well-described and known to the art (cf. Edwards DA, Ben-Jebria A, Langer R and represents a
5 measure of the median value of an aerodynamic particle size distribution. Recent advances in pulmonary drug delivery using large, porous inhaled particles. J Appl Physiol 84(2) (1998) 379-385). Mass median aerodynamic diameter (MMAD) and mass median effective aerodynamic diameter (MMEAD) are used inter-changeably, are statistical parameters, and empirically describe the size of aerosol particles in relation to their potential to deposit in the
10 lungs, independent of actual shape, size, or density (cf. Edwards DA, Ben-Jebria A, Langer R. Recent advances in pulmonary drug delivery using large, porous inhaled particles. J Appl Physiol 84(2) (1998) 379-385). MMAD is normally calculated from the measurement made with impactors, an instrument that measures the particle inertial behaviour in air.

In a further embodiment, the formulation could be aerosolized by any known aerosolisation
15 technology, such as nebulisation, to achieve a MMAD of aerosol particles less than 10 μm , more preferably between 1-5 μm , and most preferably between 1-3 μm . The preferred particle size is based on the most effective size for delivery of drug to the deep lung, where protein is optimally absorbed (cf. Edwards DA, Ben-Jebria A, Langer A, Recent advances in pulmonary drug delivery using large, porous inhaled particles. J Appl Physiol 84(2) (1998)
20 379-385).

Deep lung deposition of the pulmonal formulations comprising the compound of the present invention may optional be further optimized by using modifications of the inhalation techniques, for example, but not limited to: slow inhalation flow (eg. 30 L/min), breath holding and timing of actuation.

25 The term "stabilized formulation" refers to a formulation with increased physical stability, increased chemical stability or increased physical and chemical stability.

The term "physical stability" of the protein formulation as used herein refers to the
30 tendency of the protein to form biologically inactive and/or insoluble aggregates of the protein as a result of exposure of the protein to thermo-mechanical stresses and/or interaction with interfaces and surfaces that are destabilizing, such as hydrophobic surfaces and interfaces. Physical stability of the aqueous protein formulations is evaluated by means of visual inspection and/or turbidity measurements after exposing the formulation filled in suitable
35 containers (e.g. cartridges or vials) to mechanical/physical stress (e.g. agitation) at different temperatures for various time periods. Visual inspection of the formulations is performed in a

sharp focused light with a dark background. The turbidity of the formulation is characterized by a visual score ranking the degree of turbidity for instance on a scale from 0 to 3 (a formulation showing no turbidity corresponds to a visual score 0, and a formulation showing visual turbidity in daylight corresponds to visual score 3). A formulation is classified physical
5 unstable with respect to protein aggregation, when it shows visual turbidity in daylight. Alternatively, the turbidity of the formulation can be evaluated by simple turbidity measurements well-known to the skilled person. Physical stability of the aqueous protein formulations can also be evaluated by using a spectroscopic agent or probe of the conformational status of the protein. The probe is preferably a small molecule that
10 preferentially binds to a non-native conformer of the protein. One example of a small molecular spectroscopic probe of protein structure is Thioflavin T. Thioflavin T is a fluorescent dye that has been widely used for the detection of amyloid fibrils. In the presence of fibrils, and perhaps other protein configurations as well, Thioflavin T gives rise to a new excitation maximum at about 450 nm and enhanced emission at about 482 nm when bound
15 to a fibril protein form. Unbound Thioflavin T is essentially non-fluorescent at the wavelengths.

Other small molecules can be used as probes of the changes in protein structure from native to non-native states. For instance the "hydrophobic patch" probes that bind preferentially to exposed hydrophobic patches of a protein. The hydrophobic patches are generally buried
20 within the tertiary structure of a protein in its native state, but become exposed as a protein begins to unfold or denature. Examples of these small molecular, spectroscopic probes are aromatic, hydrophobic dyes, such as anthracene, acridine, phenanthroline or the like. Other spectroscopic probes are metal-amino acid complexes, such as cobalt metal complexes of hydrophobic amino acids, such as phenylalanine, leucine, isoleucine, methionine, and valine,
25 or the like.

The term "chemical stability" of the protein formulation as used herein refers to chemical covalent changes in the protein structure leading to formation of chemical degradation products with potential less biological potency and/or potential increased immunogenic
30 properties compared to the native protein structure. Various chemical degradation products can be formed depending on the type and nature of the native protein and the environment to which the protein is exposed. Elimination of chemical degradation can most probably not be completely avoided and increasing amounts of chemical degradation products is often seen during storage and use of the protein formulation as well-known by the person skilled in the
35 art. Most proteins are prone to deamidation, a process in which the side chain amide group in glutamyl or asparagyl residues is hydrolysed to form a free carboxylic acid. Other

degradations pathways involves formation of high molecular weight transformation products where two or more protein molecules are covalently bound to each other through transamidation and/or disulfide interactions leading to formation of covalently bound dimer, oligomer and polymer degradation products (*Stability of Protein Pharmaceuticals*, Ahern. T.J. & Manning M.C., Plenum Press, New York 1992). Oxidation (of for instance methionine residues) can be mentioned as another variant of chemical degradation. The chemical stability of the protein formulation can be evaluated by measuring the amount of the chemical degradation products at various time-points after exposure to different environmental conditions (the formation of degradation products can often be accelerated by for instance increasing temperature). The amount of each individual degradation product is often determined by separation of the degradation products depending on molecule size and/or charge using various chromatography techniques (e.g. SEC-HPLC and/or RP-HPLC).

Hence, as outlined above, a “stabilized formulation” refers to a formulation with increased physical stability, increased chemical stability or increased physical and chemical stability. In general, a formulation must be stable during use and storage (in compliance with recommended use and storage conditions) until the expiration date is reached.

In one embodiment of the invention the pharmaceutical formulation comprising the compound of the present invention is stable for more than 6 weeks of usage and for more than 3 years of storage.

In another embodiment of the invention the pharmaceutical formulation comprising the compound of the present invention is stable for more than 4 weeks of usage and for more than 3 years of storage.

In a further embodiment of the invention the pharmaceutical formulation comprising the compound of the present invention is stable for more than 4 weeks of usage and for more than two years of storage.

In an even further embodiment of the invention the pharmaceutical formulation comprising the compound of the present invention is stable for more than 2 weeks of usage and for more than two years of storage.

In another aspect the present invention relates to the use of a compound according to the invention for the preparation of a medicament.

In one embodiment a compound according to the invention is used for the preparation of a medicament for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, hypertension, syndrome X, dyslipidemia, cognitive

disorders, atherosclerosis, myocardial infarction, stroke, coronary heart disease and other cardiovascular disorders, inflammatory bowel syndrome, dyspepsia and gastric ulcers.

In another embodiment a compound according to the invention is used for the preparation of a medicament for delaying or preventing disease progression in type 2 diabetes.

5 In another embodiment a compound according to the invention is used for the preparation of a medicament for decreasing food intake, decreasing β -cell apoptosis, increasing β -cell function and β -cell mass, and/or for restoring glucose sensitivity to β -cells.

The treatment with a compound according to the present invention may also be
10 combined with a second or more pharmacologically active substances, e.g. selected from antidiabetic agents, antiobesity agents, appetite regulating agents, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders
15 resulting from or associated with obesity. Examples of these pharmacologically active substances are : Insulin, sulphonylureas, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake
20 modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents as HMG CoA inhibitors (statins), Gastric Inhibitory Polypeptides (GIP analogs), compounds lowering food intake, RXR agonists and agents acting on the ATP-dependent potassium
channel of the β -cells; Cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol, dextrothyroxine, neteglinide, repaglinide; β -blockers such
as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin
25 converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, alatriopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α -blockers such as
doxazosin, urapidil, prazosin and terazosin; CART (cocaine amphetamine regulated
transcript) agonists, NPY (neuropeptide Y) antagonists, PYY agonist, PYY2 agonists, PYY4
agonists, mixed PYY2/PYY4 agonists, MC4 (melanocortin 4) agonists, orexin antagonists,
30 TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β 3 agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone)
antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and
noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT
35 (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyrotropin releasing hormone) agonists, UCP 2 or 3

(uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, RXR (retinoid X receptor) modulators, TR β agonists; histamine H3 antagonists, Gastric Inhibitory Polypeptide agonists or antagonists (GIP analogs), gastrin and gastrin analogs.

5 The treatment with a compound according to this invention may also be combined with surgery- a surgery that influence the glucose levels and/or lipid homeostasis such as gastric banding or gastric bypass.

 It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or
10 more further pharmacologically active substances are considered to be within the scope of the present invention.

 The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any
15 combination thereof, be material for realising the invention in diverse forms thereof.

EXAMPLES

Abbreviations used:

20 r.t: Room temperature
 DIPEA: diisopropylethylamine
 H₂O: water
 CH₃CN: acetonitrile
 DMF: NN dimethylformamide
25 HBTU: 2-(1H-Benzotriazol-1-yl)-1,1,3,3 tetramethyluronium hexafluorophosphate
 Fmoc: 9 H-fluoren-9-ylmethoxycarbonyl
 Boc: tert butyloxycarbonyl
 OtBu: tert butyl ester
 tBu: tert butyl
30 Trt: triphenylmethyl
 Pmc: 2,2,5,7,8-Pentamethyl-chroman-6-sulfonyl
 Dde: 1-(4,4-Dimethyl-2,6-dioxocyclohexylidene)ethyl
 ivDde: 1-(4,4-Dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl
 Mtt: 4-methyltrityl
35 Mmt: 4-methoxytrityl
 DCM: dichloromethane

TIS: triisopropylsilane)
TFA: trifluoroacetic acid
Et₂O: diethylether
NMP: 1-Methyl-pyrrolidin-2-one
DIPEA: Diisopropylethylamine
HOAt: 1-Hydroxy-7-azabenzotriazole
HOBt: 1-Hydroxybenzotriazole
DIC: Diisopropylcarbodiimide

10 **A: Synthesis of resin bound peptide.**

The protected peptidyl resin was synthesized according to the Fmoc strategy on an Applied Biosystems 433 peptide synthesizer in 0.25 mmol or 1.0 mmol scale using the manufacturer supplied FastMoc UV protocols which employ HBTU (2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) or HATU (O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) mediated couplings in NMP (N-methyl pyrrolidone), and UV monitoring of the deprotection of the Fmoc protection group. The starting resin used for the synthesis of the GLP-1 peptide amides was Rink-Amide resin and either Wang or chlorotriyl resin was used for GLP-1 peptides with a carboxy C-terminal. The protected amino acid derivatives used were standard Fmoc-amino acids (supplied from e.g. Anaspec, or Novabiochem) supplied in preweighed cartridges suitable for the ABI433A synthesizer with the exception of unnatural aminoacids such as Fmoc-Aib-OH (Fmoc-aminoisobutyric acid). The N terminal amino acid was Boc protected at the alpha amino group (e.g. Boc-His(Boc)OH was used for peptides with His at the N-terminal). The epsilon amino group of lysine in position 26 was either protected with Mtt, Mmt, Dde, ivDde, or Boc, depending on the route for attachment of the albumin binding moiety and spacer. The synthesis of the peptides may in some cases be improved by the use of dipeptides protected on the dipeptide amide bond with a group that can be cleaved under acidic conditions such but not limited to 2-Fmoc-oxy-4-methoxybenzyl or 2,4,6-trimethoxybenzyl. In cases where a serine or a threonine is present in the peptide, the use of pseudoproline dipeptides may be used (see e.g. catalogue from Novobiochem 2002/2003 or newer version, or W.R. Sampson (1999), J. Pep. Sci. 5, 403.

Procedure for removal of ivDde or Dde-protection.

35 The resin (0.25 mmol) was placed in a manual shaker/filtration apparatus and treated with 2% hydrazine in N-methyl pyrrolidone (20 ml, 2x12 min) to remove the Dde or

ivDde group and wash with N-methyl pyrrolidone (4x20 ml).

Procedure for removal of Mtt or Mmt-protection.

- 5 The resin (0.25 mmol) was placed in a manual shaker/filtration apparatus and treated with 2% TFA and 2-3% TIS in DCM (20 ml, 5-10 min repeated 6-12 times) to remove the Mtt or Mmt group and wash with DCM (2x20 ml), 10%MeOH and 5% DIPEA in DCM (2x20ml) and N-methyl pyrrolidone (4x20 ml).

Procedure for attachment of sidechains to Lysine residue.

- 10 The albumin binding residue (B-U- sidechain of formula I) can be attached to the GLP-1 peptide either by acylation to resin bound peptide or acylation in solution to the unprotected peptide using standard acylating reagent such as but not limited to DIC, HOBt/DIC, HOAt/DIC, or HBTU.

- 15 Attachment to resin bound peptide:

Route I

- Activated (active ester or symmetric anhydride) albumin binding residue (B-U- sidechain of formula I) such as octadecanedioic acid mono-(2,5-dioxo-pyrrolidin-1-yl) ester (Ebashi *et al.* EP511600, 4 molar equivalents relative to resin bound peptide) was dissolved in NMP (25
20 mL), added to the resin and shaken overnight at room temperature. The reaction mixture was filtered and the resin was washed extensively with NMP, dichloromethane, 2-propanol, methanol and diethyl ether.

Route II

- 25 The albumin binding residue (B-U- sidechain of formula I) was dissolved in N-methyl pyrrolidone/methylene chloride (1:1, 10 ml). The activating reagent such as hydroxybenzotriazole (HOBt) (4 molar equivalents relative to resin) and diisopropylcarbodiimide (4 molar equivalents relative to resin) was added and the solution was stirred for 15 min. The solution was added to the resin and diisopropylethylamine (4
30 molar equivalents relative to resin) was added. The resin was shaken 2 to 24 hours at room temperature. The resin was washed with N-methyl pyrrolidone (2x20 ml), N-methyl pyrrolidone/Methylene chloride (1:1) (2x20ml) and methylene chloride (2x20 ml).

Route III

- 35 Activated (active ester or symmetric anhydride) albumin binding residue (B-U- sidechain of formula I) such as octadecanedioic acid mono-(2,5-dioxo-pyrrolidin-1-yl) ester (Ebashi *et al.*

EP511600, 1-1.5 molar equivalents relative to the GLP-1 peptide was dissolved in an organic solvent such as acetonitrile, THF, DMF, DMSO or in a mixture of water/organic solvent (1-2 ml) and added to a solution of the peptide in water (10-20ml) together with 10 molar equivalents of DIPEA. In case of protecting groups on the albumin binding residue such as
5 tert.-butyl, the reaction mixture was lyophilized O/N and the isolated crude peptide deprotected afterwards – in case of a *tert*-butyl group the peptide was dissolved in a mixture of trifluoroacetic acid, water and triisopropylsilane (90:5:5). After for 30min the mixture was, evaporated in vacuo and the finale petide purified by preparative HPLC.

10 Procedure for removal of Fmoc-protection: The resin (0.25 mmol) was placed in a filter flask in a manual shaking apparatus and treated with N-methyl pyrrolidone/methylene chloride (1:1) (2x20 ml) and with N-methyl pyrrolidone (1x20 ml), a solution of 20% piperidine in N-methyl pyrrolidone (3x20 ml, 10 min each). The resin was washed with N-methyl pyrrolidone (2x20 ml), N-methyl pyrrolidone/Methylene chloride (1:1) (2x20ml) and methylene
15 chloride (2x20 ml).

Procedure for cleaving the peptide off the resin:

The peptide was cleaved from the resin by stirring for 180 min at room temperature with a mixture of trifluoroacetic acid, water and triisopropylsilane (95:2.5:2.5 to 92:4:4). The
20 cleavage mixture was filtered and the filtrate was concentrated to an oil by a stream of nitrogen. The crude peptide was precipitated from this oil with 45 ml diethyl ether and washed 1 to 3 times with 45 ml diethyl ether.

Purification: The crude peptide was purified by semipreparative HPLC on a 20 mm x 250 mm
25 column packed with either 5 μ or 7 μ C-18 silica. Depending on the peptide one or two purification systems were used.

TFA: After drying the crude peptide was dissolved in 5 ml 50% acetic acid H₂O and diluted to 20 ml with H₂O and injected on the column which then was eluted with a gradient of 40-60 % CH₃CN in 0.1% TFA 10 ml/min during 50 min at 40 °C. The peptide containing fractions were
30 collected. The purified peptide was lyophilized after dilution of the eluate with water.

Ammonium sulphate: The column was equilibrated with 40% CH₃CN in 0.05M (NH₄)₂SO₄, which was adjusted to pH 2.5 with concentrated H₂SO₄. After drying the crude peptide was dissolved in 5 ml 50% acetic acid H₂O and diluted to 20 ml with H₂O and injected on the column which then was eluted with a gradient of 40% - 60% CH₃CN in 0.05M (NH₄)₂SO₄, pH
35 2.5 at 10 ml/min during 50 min at 40 °C. The peptide containing fractions were collected and diluted with 3 volumes of H₂O and passed through a Sep-Pak® C18 cartridge (Waters part.

#51910) which has been equilibrated with 0.1% TFA. It was then eluted with 70% CH₃CN containing 0.1% TFA and the purified peptide was isolated by lyophilisation after dilution of the eluate with water.

The final product obtained was characterised by analytical RP-HPLC (retention time) and by
5 LCMS

The RP-HPLC analysis was performed using UV detection at 214 nm and a Vydac 218TP54 4.6mm x 250mm 5 μ C-18 silica column (The Separations Group, Hesperia, USA) which was eluted at 1 ml/min at 42 °C. Two different elution conditions were used:

A1: Equilibration of the column with in a buffer consisting of 0.1M (NH₄)₂SO₄, which was
10 adjusted to pH 2.5 with concentrated H₂SO₄ and elution by a gradient of 0% to 60% CH₃CN in the same buffer during 50 min.

B1: Equilibration of the column with 0.1% TFA / H₂O and elution by a gradient of 0% CH₃CN / 0.1% TFA / H₂O to 60% CH₃CN / 0.1% TFA / H₂O during 50 min.

B6: Equilibration of the column with 0.1% TFA / H₂O and elution by a gradient of 0% CH₃CN
15 / 0.1% TFA / H₂O to 90% CH₃CN / 0.1% TFA / H₂O during 50 min.

Alternative the RP-HPLC analysis was performed using UV detection at 214 nm and a Symmetry300, 3.6mm x 150mm, 3.5 μ C-18 silica column (Waters) which was eluted at 1 ml/min at 42 °C.

B4: Equilibration of the column with 0.05% TFA / H₂O and elution by a gradient of 5%
20 CH₃CN / 0.05% TFA / H₂O to 95% CH₃CN / 0.05% TFA / H₂O during 15 min.

The following instrumentation was used:

LCMS was performed on a setup consisting of Sciex API 100 Single quadrupole mass spectrometer, Perkin Elmer Series 200 Quard pump ,Perkin Elmer Series 200 autosampler,
25 Applied Biosystems 785A UV detector, Sedex 75 evaporative light scattering detector

The instrument control and data acquisition were done by the Sciex Sample control software running on a Windows 2000 computer.

30 The HPLC pump is connected to two eluent reservoirs containing:

A: 0.05% Trifluoro acetic acid in water

B: 0.05% Trifluoro acetic acid in acetonitrile

The analysis is performed at room temperature by injecting an appropriate volume of the
35 sample (preferably 20 μ l) onto the column which is eluted with a gradient of acetonitrile.

The HPLC conditions, detector settings and mass spectrometer settings used are giving in the following table.

Column : Waters Xterra MS C-18 X 3 mm id 5 μ m

5 Gradient : 5% - 90 % acetonitrile linear during 7.5 min at 1.5ml/min

Detection : 210 nm (analogue output from DAD)

ELS (analogue output from ELS), 40 °C

MS ionisation mode API-ES

10

Alternatively LCMS was performed on a setup consisting of Hewlett Packard series 1100 G1312A Bin Pump, Hewlett Packard series 1100 Column compartment, Hewlett Packard series 1100 G1315A DAD diode array detector, Hewlett Packard series 1100 MSD and

15 Sedere 75 Evaporative Light Scattering detector controlled by HP Chemstation software. The HPLC pump is connected to two eluent reservoirs containing:

A: 10mM NH₄OH in water

B: 10mM NH₄OH in 90% acetonitrile

The analysis was performed at 23° C by injecting an appropriate volume of the sample

20 (preferably 20 μ l) onto the column which is eluted with a gradient of A and B.

The HPLC conditions, detector settings and mass spectrometer settings used are giving in the following table.

Column Waters Xterra MS C-18 X 3 mm id 5 μ m

Gradient 5% - 100% acetonitrile linear during 6.5 min at 1.5ml/min

25 Detection 210 nm (analogue output from DAD)

ELS (analogue output from ELS)

MS ionisation mode API-ES. Scan 100-1000 amu step 0.1 amu

Radioligand binding to plasma membranes expressing the human GLP-1 receptor

30

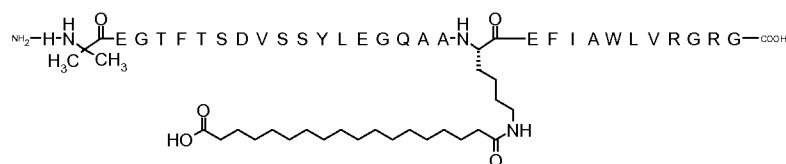
The binding assay was performed with purified plasma membranes containing the human GLP-1 receptor. The plasma membranes containing the receptors were purified from stably expressing BHK tk-ts 13 cells. The membranes were diluted in Assay Buffer (50 mM HEPES, 5 mM EGTA, 5 mM MgCl₂, 0.005% Tween 20, pH=7.4) to a final concentration of

35 0.2 mg/ml of protein and distributed to 96-well microtiter plates precoated with 0.3 % PEI. Membranes in the presence of 0.05 nM [¹²⁵I]GLP-1, unlabelled ligands in increasing

concentrations and different HSA concentrations (0.005%, 0.05%, and 2%) were incubated 2 hr at 30°C. After incubation, unbound ligands were separated from bound ligands by filtration through a vacuum-manifold followed by 2X100 µl washing with ice cold assaybuffer. The filters were dried overnight at RT, punched out and quantified in a γ-counter.

5

Example 1



N-ε²⁶ (17-carboxyheptadecanoyl)-[Aib8,Arg34]GLP-1-(7-37)-peptide

A resin (Fmoc-Gly-NovaSyn TGT, 0.22 mmol/g Novabiochem 0.25 mmole) was used to produce the primary sequence on an ABI433A machine according to manufacturers guidelines. All protecting groups were acid labile with the exception of the residue used in position 26 (FmocLys(ivDde)-OH, Novabiochem) allowing specific deprotection of this lysine rather than any other lysine.

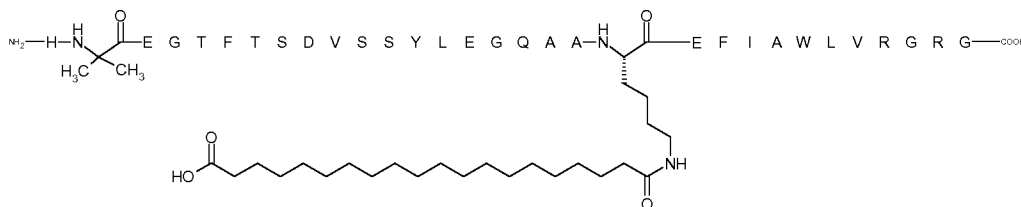
15 Procedure

The resin (0.09 mmole) was placed in a manual shaker/filtration apparatus and treated with 4% hydrazine in N-methyl pyrrolidone in (4x10 min. 4x4 ml) to remove the ivDde group. The resin was washed with N-methyl pyrrolidone (3x4 ml). Octadecanedioic acid mono-(2,5-dioxo-pyrrolidone-1-yl)ester) (4 molar equivalents relative to resin) was dissolved in DMF (4ml). The solution was added to the resin and diisopropylethylamine (8 molar equivalents relative to resin) was added. The resin was shaken 24 hours at room temperature. The resin was washed with N-methyl pyrrolidone (4x4 ml) and DCM (4x4ml). The peptide was cleaved from the resin by stirring for 180 min at room temperature with a mixture of trifluoroacetic acid, water and triisopropylsilane (92.5:5.0:2.5 4 ml). The cleavage mixture was filtered and the crude peptide was precipitated from 40 ml diethyl ether and washed 3 times with 45 ml diethyl ether. The crude peptide was purified by preparative HPLC on a 20 mm x 250 mm column packed with 7µ C-18 silica. The crude peptide was dissolved in 5 ml 50% acetic acid in water and diluted to 20 ml with H₂O and injected on the column which then was eluted with a gradient of 25-65 % (CH₃CN in water with 0.1% TFA) 20 ml/min during 40 min at RT. The peptide containing fractions were collected. The purified peptide was lyophilized after dilution of the eluate with water.

HPLC (method B4): RT= 9.94 min (91%)

LCMS: m/z = 1232 (MH₃³⁺) Calculated for (MH₃³⁺) = 1232

Example 2



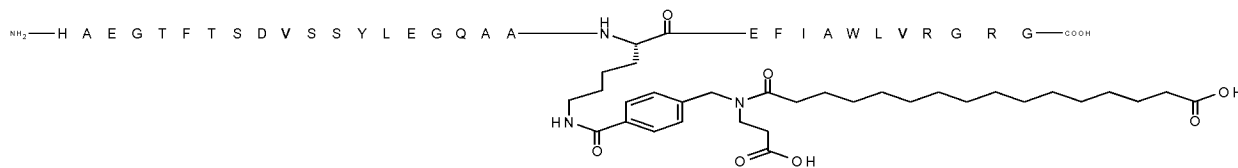
5 N-ε²⁶-(19-carboxynonadecanoyl)-[Aib8,Arg34]GLP-1-(7-37)-peptide

Prepared as in Example 1 and in accordance with "synthetic methods".

HPLC (method B4): RT= 10.42 min (91%)

LCMS: m/z = 1242 (MH₃³⁺), Calculated for (MH₃³⁺) = 1242

10 Example 3



N-ε²⁶-(4-([N-(2-carboxyethyl)-N-(15-

15 carboxypentadecanoyl)amino]methyl)benzoyl[Arg34]GLP-1-(7-37)-peptide

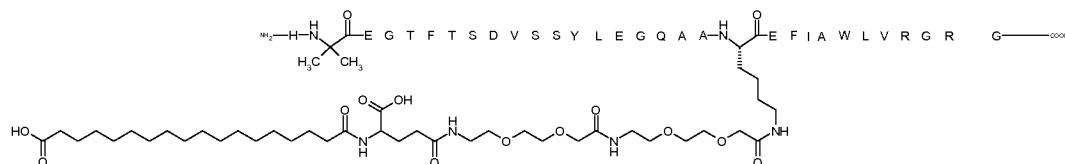
To a solution of 4-(N-(2-(*tert*-butoxycarbonyl)ethyl)-N-(15-(*tert*-butoxycarbonyl)pentadecanoyl)aminomethyl)benzoic acid (36 mg, 60 μmol) in THF (1 ml) were added DIPEA (7 μl) and O-(1-succinimidy)-N,N,N',N'-tetramethyluronium hexafluorophosphate (TSTU, 17 mg, 56 μl). After stirring for 1 h at room temperature, the mixture was diluted with THF (1 ml), and 1 ml of the resulting solution was added to a solution of [Arg34]GLP-1-(7-37) peptide (approx 100 mg) and DIPEA (103 μl) in water (5 ml). After 0.5 h more of the THF-solution of acylating agent (0.4 ml) was added. After stirring at room temperature for a total of 1.5 h the reaction mixture was filtered and applied to a preparative HPLC (gradient elution with 35-55% MeCN/55-35% water/10% water with 1% TFA). Fractions containing the desired product were combined and lyophilized. The product was then treated with 25 ml of a mixture of TFA and water (95/5 vol) for 15 min at room temperature, concentrated, and purified once more by HPLC. 15.4 mg of the title compound was obtained.

30 HPLC (method B4): RT = 9.41 min (99%)

LCMS: $m/z = 1287$ (MH_3^{3+}). Calculated for (MH_3^{3+}): 1287

Example 4

- 5 N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.

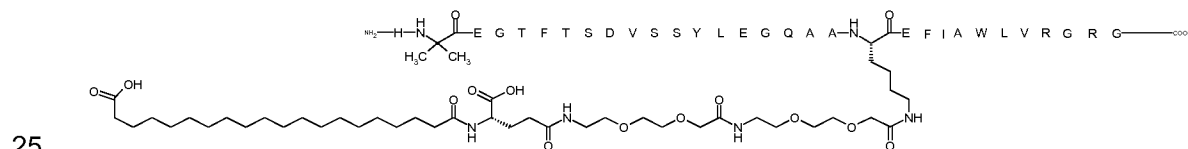


- [Aib8,Arg34]GLP-1-(7-37)-peptide was prepared by standard Fmoc-solid phase peptide synthesis and purified by preparative HPLC. [Aib8,Arg34]GLP-1-(7-37)-peptide was dissolved in water (15ml) and DIPEA (50ul) was added. 17-((S)-1-tert-Butoxycarbonyl-3-{2-[2-({2-[2-(2,5-dioxopyrrolidin-1-yloxy)carbonylmethoxy]ethoxy}ethylcarbamoyl)methoxy)ethoxy}ethylcarbamoyl)propylcarbamoyl)heptadecanoic acid tert-butyl ester (21 mg) was dissolved in acetonitrile/water 2:1 (1.5 ml) and added in small portions. The reaction was monitored by HPLC. When no more [Aib8,Arg34]GLP-1-(7-37)-peptide was found the reaction mixture was lyophilized O/N. To the isolated compound was added 10 ml of 90% TFA / 5% TIS/ 5% water and the reaction mixture was standing for 2 hours, evaporated *in vacuo*, and co-evaporated with heptane. The residual oil was dissolved in 15ml of water containing 1% of NH₃-aq and purified by preparative HPLC to give the title compound.

HPLC (method B4): RT = 9.60 min (100%)

LCMS: $m/z = 1372$ (MH_3^{3+}). Calculated for (MH_3^{3+}): 1372

Example 5



- 25 N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.

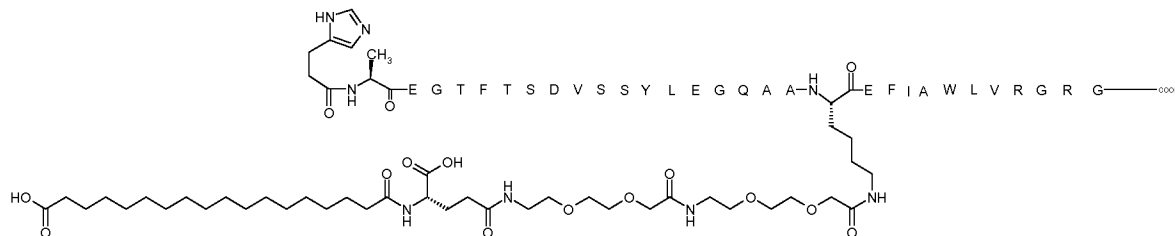
- The peptide was prepared according to: A. Synthesis of resin bound peptide in 0.25 mMol scale on a Fmoc-Gly-Wang resin (0.66 mmol/g Novabiochem) was used to produce the primary sequence on an ABI433A machine according to manufacturers guidelines. All

protecting groups were acid labile with the exception of the residue used in position 26 (FmocLys(Mtt)-OH, Novabiochem) which is super acid labile, allowing specific deprotection of this lysine rather than any other lysine.

Procedure for removal of Mtt-protection. The resin (0.25 mmol) was placed in a manual shaker/filtration apparatus and treated with 2% TFA, 3% TIS in DCM (20 ml, 5-10 min repeated 6-12 times) to remove the Mtt group and wash with DMF. Synthesis was continued with Procedure for attachment of sidechains to Lysine residue, following Route II, with the appropriate Procedure for removal of Fmoc-protection. Final deprotection, HPLC-purification and analysis by HPLC and LC-MS according to the procedures.

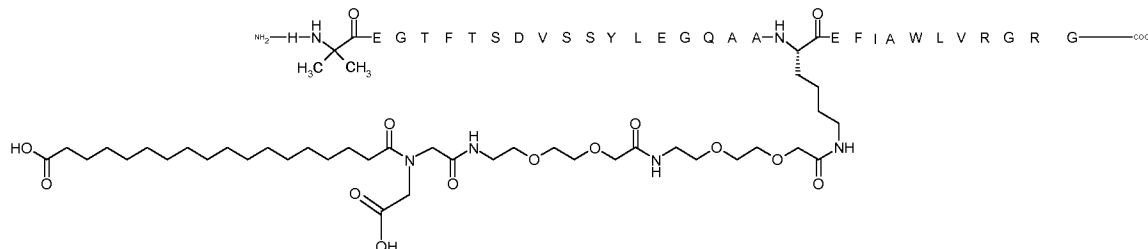
- 10 HPLC (method B6): RT = 34.56 min (100%)
LCMS: m/z = 1381.8 (MH_3^{3+}). Calculated for ($M+H^+$): 4142.7

Example 6



- 15 N- ϵ^{26} -[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy]acetyl][3-(4-Imidazolyl)Propionyl7,Arg34]GLP-1-(7-37)peptide
Prepared as in Example 5 and in accordance with "synthetic methods".
20 HPLC (method B6): RT = 32.89 min (100%)
LCMS: m/z = 1362.3 (MH_3^{3+}). Calculated for ($M+H^+$): 4085.6

Example 7



25

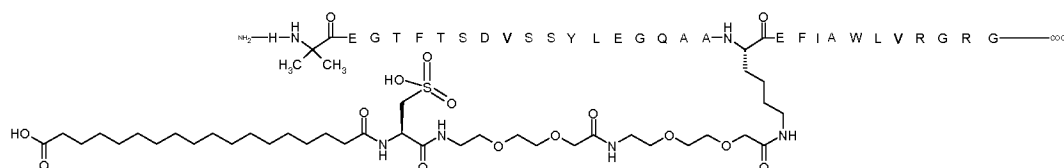
N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-(Carboxymethyl-amino)acetyl]amino)ethoxy]ethoxy]acetyl]amino)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide

Prepared as in Example 5 and in accordance with "synthetic methods".

5 HPLC (method B6): RT = 32.67 min (100%)

LCMS: m/z = 1367.3 (MH₃³⁺). Calculated for (M+H⁺): 4100.6

Example 8



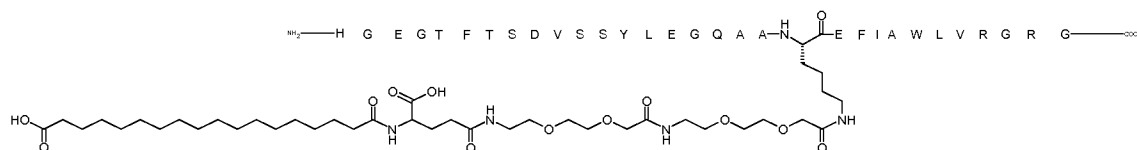
10 N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-3(S)-Sulfopropionylamino]ethoxy]ethoxy]acetyl]amino)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide

Prepared as in Example 5 and in accordance with "synthetic methods".

HPLC (method B6): RT = 32.04 min (100%)

15 LCMS: m/z = 1379.8 (MH₃³⁺). Calculated for (M+H⁺): 4136.7

Example 9



20 N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy]ethoxy]acetyl]amino)ethoxy]ethoxy]acetyl][Gly8,Arg34]GLP-1-(7-37)peptide.

[Gly8,Arg34]GLP-1(7-37) peptide starting from 150 mg 2-chlorotrityl chloride resin (1.4 mmol/g) was prepared by Fmoc-solid phase peptide synthesis using Apex396 from Advanced Chemtech. The Lys residue at position 26 was protected as Lys(ivDde) while the functional side-chains for the other amino acids were protected with standard acid labile protecting groups. The Lys residue was deprotected with 3% hydrazine/3% piperidine in NMP for 1 hr. Then, the two units of 8-amino-3,6-dioxaoctanoic acid, γ-glutamic acid and octadecanedioic acid were coupled to the resin attached peptide using DIC/HOAt. The

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30

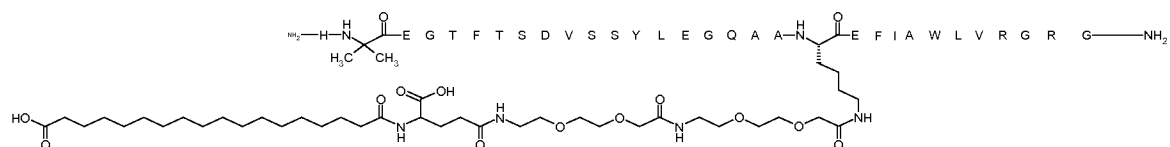
peptide was finally deprotected and cleaved from the resin with TFA/TIS/H₂O/thioanisol (90/5/3/2). The peptide was isolated by LC-MS.

HPLC: Elutes at 46% acetonitrile

MALDI: 4087 (MH⁺)

5

Example 10



N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-

10 carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)-amide

[Aib8,34]GLP-1(7-37) amide starting from 200 mg Tentagel RAM S resin (0.26 mmol/g) was prepared by Fmoc-solid phase peptide synthesis using Apex396 from Advanced Chemtech.

The Lys residue at position 26 was protected as Lys(ivDde) while the functional side-chains

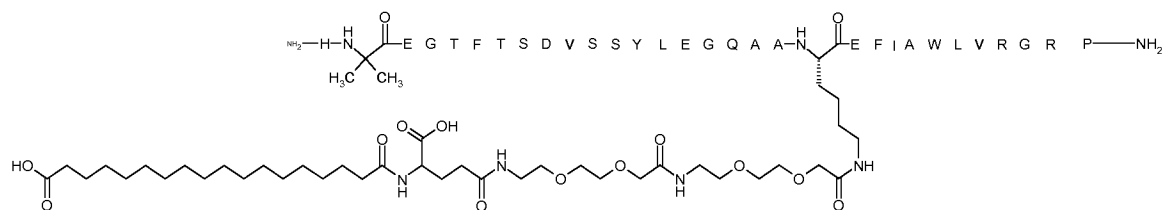
15 for the other amino acids were protected with standard acid labile protecting groups. The Lys residue was deprotected with 3% hydrazine/3% piperidine in NMP for 1 hr. Then, the two units of,8-amino-3,6-dioxaoctanoic acid, γ-glutamic acid octadecanedioic acid were coupled to the resin attached peptide using DIC/HOAt. The peptide was finally deprotected and cleaved from the resin with TFA/TIS/H₂O/thioanisol (90/5/3/2). The peptide was isolated by

20 LC-MS.

HPLC: Elutes at 49% acetonitrile

MALDI: 4114 (MH⁺)

Example 11



25

N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-

carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy]acetyl][Aib8,Arg34,Pro37]GLP-1-(7-37)amide

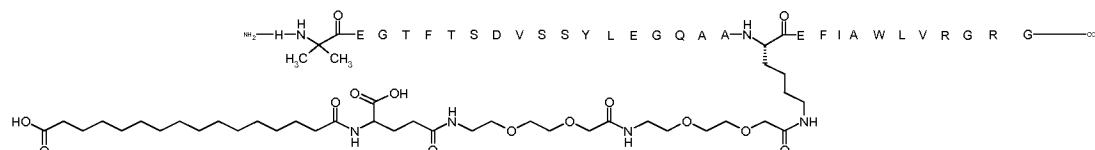
The peptide was prepared on a Rink amide resin (0.70 mmol/g Novabiochem) and else as in Example 5 and in accordance with "synthetic methods".

HPLC (method B6): RT = 32.13 min (100%). (method A1): RT = 44.33 min (98.4%)

LCMS: m/z = 1385.3 (MH_3^{3+}). Calculated for ($M+H^+$): 4153.8

5

Example 12



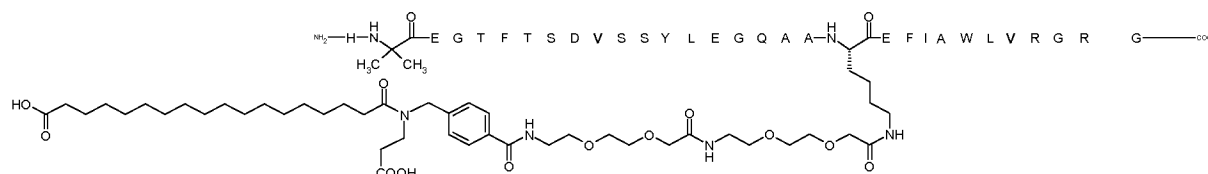
Aib⁸,Lys²⁶(N-ε²⁶-{2-(2-(2-(2-[2-(2-(4-(pentadecanoylamino)-4-carboxybutyrylamino)ethoxy)ethoxy)acetyl)ethoxy)ethoxy)acetyl})),Arg³⁴)GLP-1 H(7-37)-OH

10

HPLC (method B6): RT= 30.41 min

LCMS: m/z = 1362.9 (MH_3^{3+}) Calculated for (M^+) = 4085.61

Example 13



N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-[[N-(2-carboxyethyl)-N-(17-carboxyheptadecanoyl)amino]methyl]benzoyl)amino]ethoxy)ethoxy]acetyl)amino]ethoxy]ethoxy]acetyl[[Aib8,Arg34]GLP-1(7-37)]

20

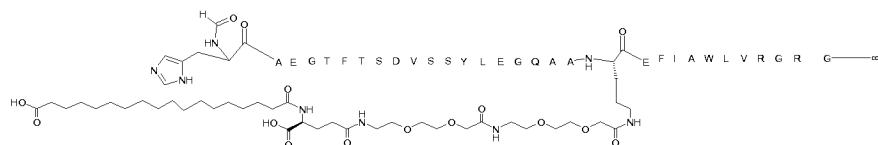
[Aib8,Arg34]GLP-1(7-37) peptide starting from 150 mg 2-chlorotrityl chloride resin (1.4 mmol/g) was prepared by Fmoc-solid phase peptide synthesis using Apex396 from Advanced Chemtech. The Lys residue at position 26 was protected as Lys(ivDde) while the functional side-chains for the other amino acids were protected with standard acid labile protecting groups. The Lys residue was deprotected with 3% hydrazine/3% piperidine in NMP for 1 hr. The two units of 8-amino-3,6-dioxaoctanoic acid and 4{[(2-tert-butoxycarbonyl-ethyl)-(17-tert-butoxycarbonyl-heptadecanoyl)-amino]-methyl}-benzoic acid were coupled to the resin attached peptide using DIC/HOAt. The peptide was finally deprotected and cleaved from the resin with TFA/TIS/H₂O/thioanisol (90/5/3/2). The peptide was isolated by preparative LC-MS.

30

HPLC: Elutes at 52% acetonitrile

MALDI: 4191 (MH⁺)

Example 14

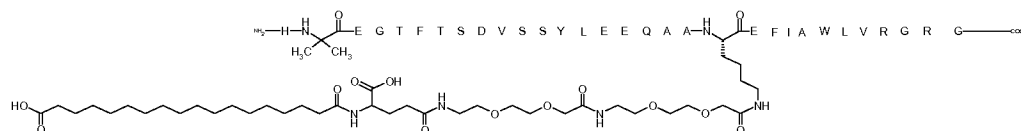


- 5 N- α^7 -formyl, N- ϵ^{26} -[2-(2-[2-(2-[2-(4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)amino)ethoxy]ethoxy]acetyl][Arg³⁴]GLP-1-(7-37)-peptide

HPLC (method B6): RT= 32,6 min

- 10 LCMS: m/z = 1377.3 (MH₃³⁺) Calculated for (M⁺) = 4128.0

Example 15



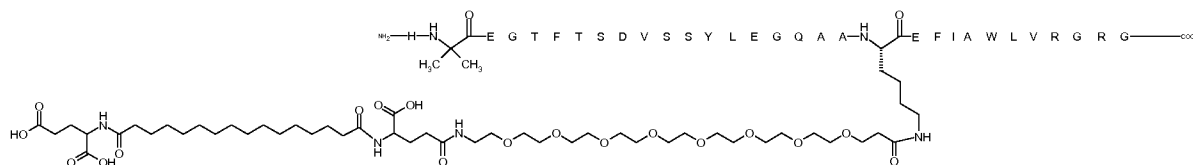
- 15 N- ϵ^{26} -[2-(2-[2-(2-[2-(4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)amino)ethoxy]ethoxy]acetyl][Aib8,Glu22,Arg34]GLP-1-(7-37)peptide.

- [Aib8,Glu22,Arg34]GLP-1(7-37) peptide starting from 150 mg Fmoc-Gly-Wang resin (0.66mmol/g) was prepared by Fmoc-solid phase peptide synthesis using Apex396 from Advanced Chemtech. The Lys residue at position 26 was protected as Lys(Mtt) while the functional side-chains for the other amino acids were protected with standard acid labile protecting groups. The Lys residue was deprotected with 2% TFA/2% TIS in DCM for 4 x 5 min. The two units of 8-amino-3,6-dioxaoctanoic acid, γ -glutamic and octadecanoic acid tert-butyl ester were coupled to the resin attached peptide using DIC/HOAt. The peptide was finally deprotected and cleaved from the resin with TFA/TIS/H₂O/thioanisol (90/5/3/2). The peptide was isolated by LC-MS.

HPLC: Elutes at 50% acetonitrile

MALDI: 4187 (MH⁺)

Example 16


$$N-\varepsilon^{26}\{3-[2-(2-\{2-[2-(2-\{2-[2-(2-[4-(15-(N-(S)-1,3-$$

5 dicarboxypropyl)carbamoyl)pentadecanoylamino)-(S)-4-

carboxybutyrylamino]ethoxy)ethoxy}ethoxy)ethoxy}ethoxy}ethoxy)ethoxy]propionyl}[Ala
b8.Arg341GLP-1-(7-37)-peptide

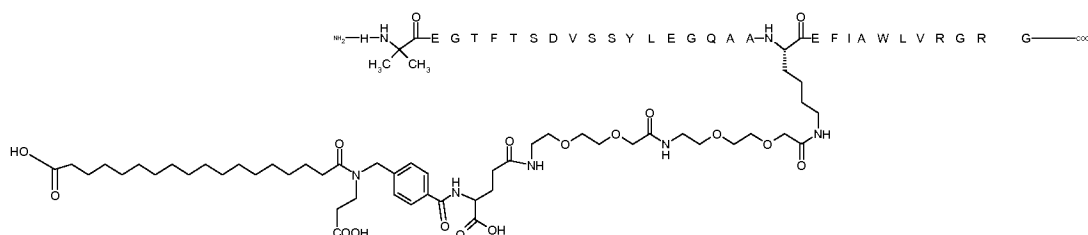
Method and analysis

Prepared as in Example 3 and in accordance with "synthetic methods".

10 HPLC (method B4): RT = 10.29 min (92%)

LCMS: $m/z = 1450$ (MH_3^{3+}). Calculated for (MH_3^{3+}): 1450

Example 17



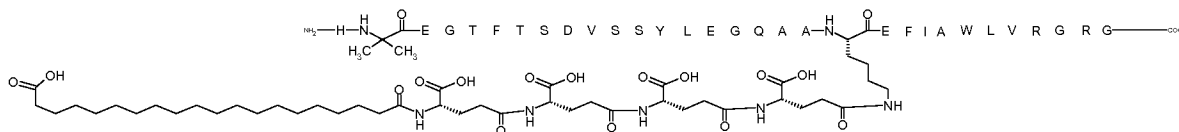
15 N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-[[N-(2-carboxyethyl)-N-(17-carboxyheptadecanoyl)amino]methyl]benzoyl)amino](4(S)-carboxybutyrylamino)ethoxy)ethoxy]acetyl)amino)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1(7-37)

[Aib8,Arg34]GLP-1(7-37) peptide starting from 150 mg Fmoc-Gly Wang resin (0.66mmol/g) was prepared by Fmoc-solid phase peptide synthesis using Apex396 from Advanced Chemtech. The Lys residue at position 26 was protected as Lys(Mtt) while the functional side-chains for the other amino acids were protected with standard acid labile protecting groups. The Lys residue was deprotected with 2% TFA/2% TIS in DCM for 4 x 5 min. The two units of 8-amino-3,6-dioxaoctanoic acid, γ -glutamic acid and 4[[[2-tert-butoxycarbonyl-ethyl)-(17-tert-butoxycarbonyl-heptadecanoyl)-amino]-methyl]-benzoic acid were coupled to the resin attached peptide using DIC/HOAt. The peptide was finally deprotected and cleaved from the resin with TFA/TIS/H₂O/thioanisole (90/5/3/2). The peptide was isolated by preparative HPLC.

was prepared by Fmoc-solid phase peptide synthesis using Apex396 from Advanced Chemtech. The Lys residue at position 26 was protected as Lys(Mtt) while the functional side-chains for the other amino acids were protected with standard acid labile protecting groups. The Lys residue was deprotected with 2% TFA/2% TIS in DCM for 4 x 5 min. The two units of 8-amino-3,6-dioxaoctanoic acid, γ -glutamic acid and 4{[(2-tert-butoxycarbonyl-ethyl)-(17-tert-butoxycarbonyl-heptadecanoyl)-amino]-methyl}-benzoic acid were coupled to the resin attached peptide using DIC/HOAt. The peptide was finally deprotected and cleaved from the resin with TFA/TIS/H₂O/thioanisole (90/5/3/2). The peptide was isolated by preparative HPLC.

MALDI: 4320 (MH+)

Example 18



5

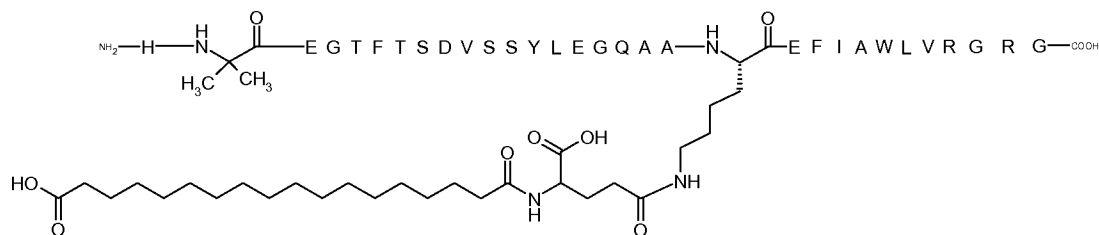
N-ε²⁶-{(S)-4-carboxy-4-((S)-4-carboxy-4-((S)-4-carboxy-4-((S)-4-carboxy-4-(19-carboxynonadecanoylamino)butyrylamino)butyrylamino)butyrylamino)butyrylamino}[Aib8,Arg34]GLP-1-(7-37)

10 The peptide was synthesized using Fmoc chemistry on a Liberty Microwave Peptide Synthesizer (CEM Corporation). The synthesis was performed on a Gly-Wang resin (Novabiochem) with a loading of 0.66 mmol/g using 4 fold excess of amino acids and DIC/HOAt for coupling. The N-terminal histidine was Boc-protected and the lysine to be modified was Mtt-protected. After synthesis of the peptide backbone, the Mtt group was
15 removed with 3% TFA in DCM and the side chain was built on the Liberty using standard peptide synthesis protocols. In the last step the fatty diacid was added as a mono-t-butyl-ester.

After cleavage with TFA/TIS/water (95:2.5:2.5), the peptide was dissolved in 50% acetonitrile by addition of DIPEA and purified on a Waters LC-MS system using a 7.8 x 300 mm X-Terra Prep MS C18 10 μ m column running at room temperature. After 5 minutes at 30% CH₃CN, 0.08% TFA, 4 ml/min, the column was eluted with a linear gradient of 30 to 70% CH₃CN over 40 minutes. The fractions containing the desired compound were collected and the concentration of the peptide in the eluate was determined by measurement of the UV absorption at 280 nm assuming molar extinction coefficients of 1280 and 3690 for tyrosine and tryptophan respectively. The identity and purity was confirmed by MALDI. After the concentration determination the eluate was aliquotted into vials containing the desired amount and dried by vacuum centrifugation.

30 HPLC: Elutes at 52% acetonitrile
MALDI: 4239 (MH⁺)

Example 19



N-ε²⁶-4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyryl-[Aib8,Arg34]GLP-1-(7-37)-peptide

5 Method and analysis

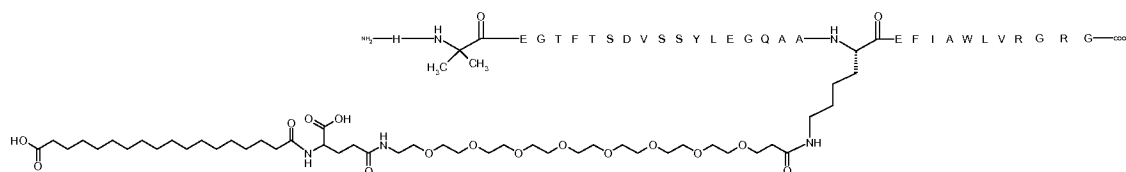
Prepared as in Example 4 and in accordance with "synthetic methods".

HPLC (method B4): Rt = 9.64 min (97 %)

LCMS: m/z = 1276 (MH₃³⁺), Calculated for (MH₃³⁺) 1276

10

Example 20



N-ε²⁶-{3-[2-(2-{2-[2-(2-{2-[2-(2-[4-(17-carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]

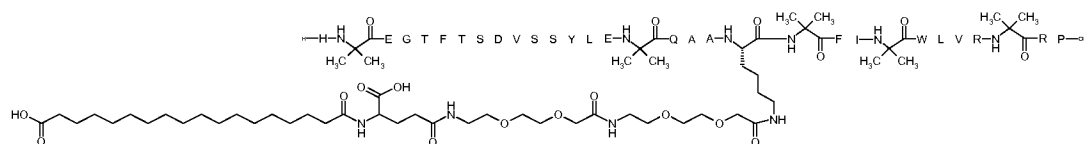
15 ethoxy)ethoxy]ethoxy}ethoxy)ethoxy]ethoxy]ethoxy]ethoxy]propionyl}[Aib8,Arg34]GLP-1-(7-37)-peptide.

LCMS*: m/z = 1417 (MH₃³⁺), Calculated for (MH₃³⁺) 1417

*HPLC (Eluted at 0.5 mL/min at 42°C by a linear gradient from 5 ---->80% acetonitrile, 85----

20 214 on a Symmetry300, 5μm, 3.9 mm x 150 mm C-18 silica column.)method B4): Rt = 32.09 min (95 %)

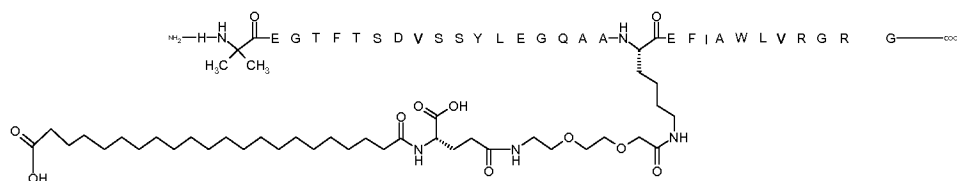
Example 21



N- ϵ^{26} -[2-(2-(2-(2-[2-(2-(4-(17-carboxyheptadecanoylamino)-4-carboxybutyrylamino)ethoxy)ethoxy]acetyl)ethoxy)ethoxy)acetyl)]-[Aib^{8,22,27,30,35},Arg³⁴,Pro³⁷,Lys²⁶] GLP-1 (7-37)amide

- 5 HPLC (method B6): RT= 35.0 min
LCMS: m/z = 1394.0 (MH₃³⁺) Calculated for (M⁺) = 4180.0

Example 22

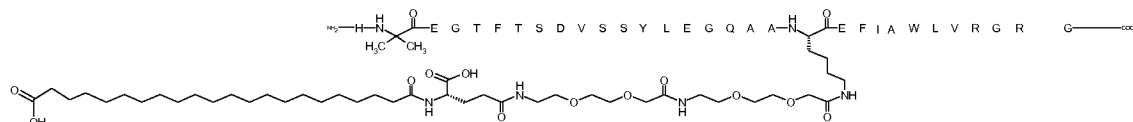


- 10 N- ϵ^{26} -[2-(2-[2-[4-(21-Carboxyuneicosanoylamino)-4(S)-carboxybutyrylamino]ethoxy]ethoxy)acetyl)]-[Aib⁸,Arg³⁴]GLP-1-(7-37)
Prepared using the same method as in Example 19.

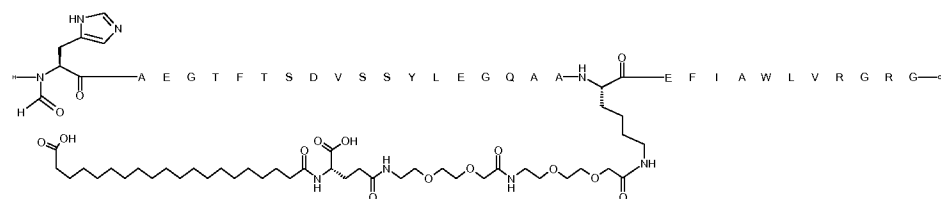
HPLC: Elutes at 53.4% acetonitrile

- 15 MALDI: 4025 (MH⁺)

Other compounds of this invention include:

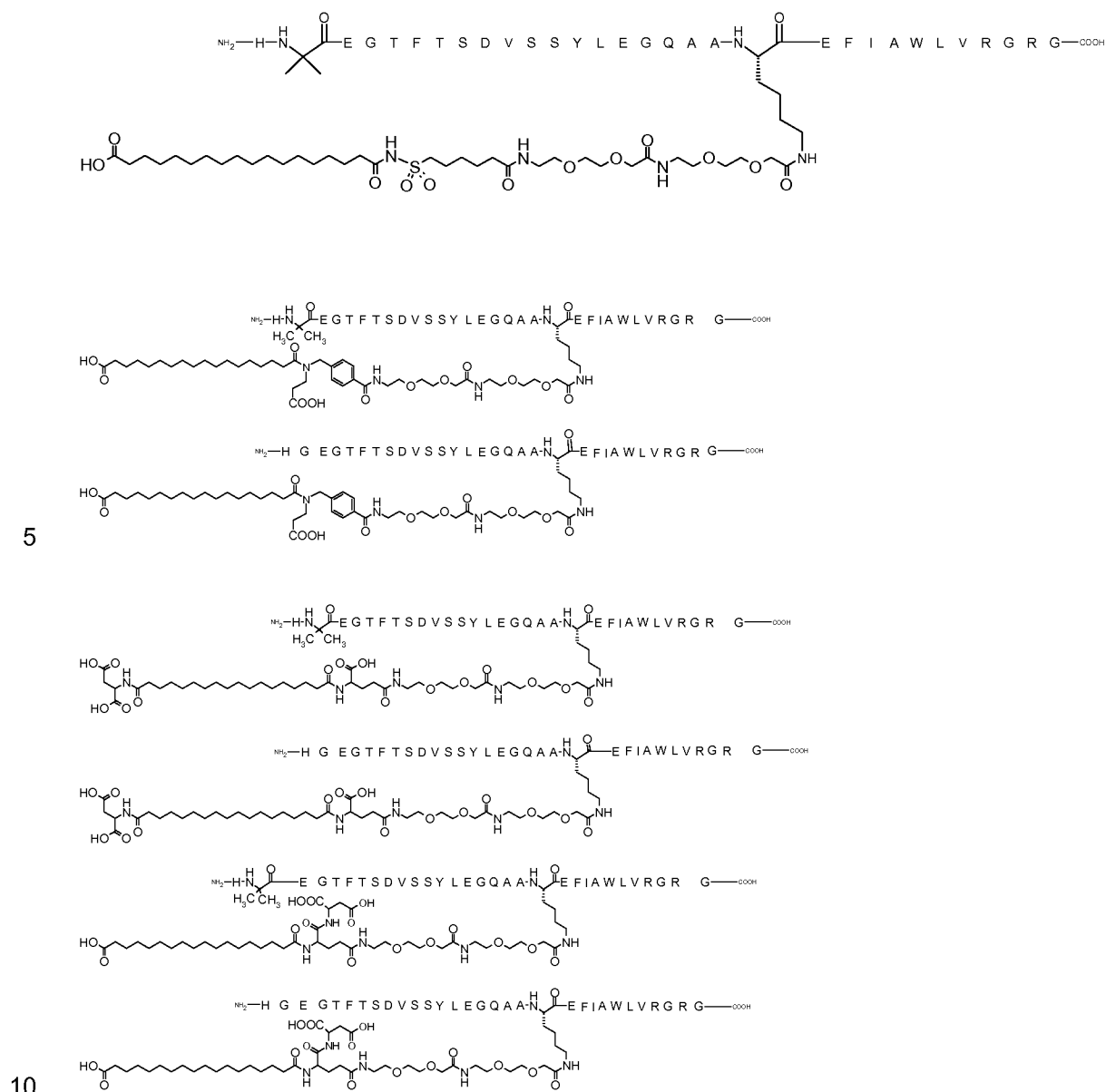


- 20 N- ϵ^{26} -[2-(2-[2-(2-[2-(2-[4-(21-Carboxyuneicosanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)ethoxy]ethoxy)acetyl)]-[Aib⁸,Arg³⁴]GLP-1-(7-37)peptide.



- 25 N- α 1-formyl-N- ϵ^{26} -[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)ethoxy]ethoxy)acetyl)]-[Arg³⁴]GLP-1-(7-37)peptide.





Pharmacodynamic study using db/db mice

- 15 In one aspect of this invention the GLP-1 agonists have a duration of action of at least 24hrs after dosing of 30nmol/kg to db/db mice
- The efficacy and duration of action are measured in db/db mice.
- Male db/db mice are shipped from Taconic, Denmark at the age of 8-10 weeks. From the time of arrival, the mice are housed under standard conditions but at 24 °C. The mice are
- 20 kept 10 per cage until experimentation with free access to standard chow (Altromin,

Brogaarden APS., Denmark) and tap water at a normal day: light cycle (light on at 6 am). The mice are used for 1 experiment per week for 3 weeks. After this, the mice are euthanized.

5 After an acclimatisation period of 1 week, the blood glucose is measured by sampling from the tail tip capillary. In brief, 5 µl blood is sampled in heparinised glass capillary tubes and immediately suspended in 250 µl EBIO buffer solution (Eppendorf, Germany) in an 1.5 ml Eppendorf tube. The blood glucose concentration is measured by the glucose oxidase method at the EBIO Plus Auto analyser (Eppendorf, Germany).

10 The cut of value for blood glucose is 10 mM. When evaluating the mice, it is essential, that all 42 mice entering the experiment have blood glucose values above 10 mM, but also that the inter-mice variance is small. Therefore, if many mice are not severely diabetic, whereas some are, the start up of experiments should be postponed one week and new basal blood glucose measurements be made.

15 Based on the basal blood glucose values, the mice are allocated to 7 groups of n=6 with matching group mean blood glucose values.

On the day of testing the basal blood glucose morning values are assessed as described above and the basal body weight of each mouse is assessed. A time 0, the compound is dosed subcutaneously in the scruff of the neck (dosing volume app. 300 µl/50 g mouse).

20 The blood glucose values are followed up to 48 hours (time 1, 3, 6, 24 and 48 h) and the terminal body weight is assessed.

All data are entered into Graphpad Prism where mean blood glucose and mean delta body weights are calculated.

25 One aspect of this invention is to prepare GLP-1 analogues/derivatives with extended plasma half-lives that are suitable for once weekly administration. The pharmacokinetic properties can be evaluated in mini pigs or domestic pigs as described below

Pharmacokinetic screening of once weekly GLP-1 analogues

30 Pharmacokinetic screening of GLP-1 analogues for identification of suitable once weekly candidates were performed on candidates that according to the project screenings plan were shown to be sufficiently potent with respect to glucose lowering potential in a diabetic mouse model (db/db mice) and subsequently had a time of duration of 48 hours or more in the db/db mouse model.

Primary screening

The first part of the pharmacokinetic screening consisted of a single dose subcutaneous administration of 2 nmol/kg to three minipigs weighing 8-12 kg. Blood samples were drawn from each animal at predose, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96 and 120 hours post-injection. All blood samples were stabilised with a special stabilisation buffer consisting of:
5 EDTA (di-sodium) 0.18 M, Aprotinin 15000 KIE/ml, Val-Pyr 0.30 mM, pH adjusted to 7.4 in order to prevent enzymatic degradation of the GLP-1 analogues. Plasma was collected from each stabilised blood samples by centrifugation (4°C, 10 min., 1270 G (4000 rpm), and analysed for the content of GLP-1 analogue by ELISA assays. Three different ELISA assays were used for the plasma analysis: "The "Total assay" using the antibody combination
10 F1/Ra2135 detecting both the N-terminally intact 7-37GLP-1 molecule and the N-terminal enzymatically degraded 9-37GLP-1 molecule with a limit of detection (LOD) of 35 pM and a dynamic analytical range of 35-30000 pM. The "Intact assay" using the antibody combination F1/Mab26.1. This assay was detecting the N-terminally intact 7-37GLP-1 molecule only. The LOD was 35 pM and a dynamic analytical range of 35-30000 pM. The "Aib-intact assay"
15 using the antibody combination F1/GLP162-3F15. This assay was detecting the Aib stabilised N-terminal of the GLP-1 molecule enabling detection of stabilised GLP-1 analogues. The LOD was 45 pM and the dynamic analytical range 45-30000 pM.

All plasma concentration-time profiles were analysed pharmacokinetically by a non-compartmental analysis. The following pharmacokinetic parameters were calculated if data
20 permitted: t_{max} , C_{max} , AUC, AUC/Dose, AUC%Extrapol, λ_z , $t_{1/2}$, CL/F, V_z/F and MRT.

Secondary screening

A second part of the pharmacokinetic screening was conducted on those compounds with an initial terminal half-life of 60-70 hours or more. This screening consisted of a single dose intravenous and subcutaneous administration of 2 nmol/kg to six minipigs for each route of
25 administration. The blood sampling schedule was extended from 0-120 hours to 0-432 and 0-504 hours after intravenous and subcutaneous administration respectively. This was done in order to increase the precision and accuracy of the pharmacokinetic parameter estimates, especially the terminal half-life, AUC and the derived parameters clearance and volume of distribution, and to estimate the bioavailability after subcutaneous administration.

30 GLP-1 (AIB8- INTACT) ASSAY

The assay was a two-site assay with simultaneous incubation of the analyte with catcher and detector antibody. A ready to use chemiluminescent substrate was used to maximize signal. The assay neither recognizes endogen GLP-1 (7-37) nor the DPPIV cleaved GLP-1 (9-37).

Reference plasma for GLP-1 assays

0-plasma was prepared from pooled EDTA plasma without Valine Pyrrolidide and Aprotinin from fasting animals. The pooled EDTA plasma was incubated at 37°C for 4 hours to remove traces of GLP-1 and after incubation Valine Pyrrolidide and Aprotinin were added.

5 Buffers

Coating buffer

PBS was used as coating buffer: 10mM sodium phosphate and 145mM sodium chloride adjusted to pH 7.4.

Washing buffer

10 PBS with 0.05% (v/v) Tween 20

Assay buffer

PBS with 0.05% (v/v) Tween 20, 10g/L BSA and 10mg/L anti-TNP.

Streptavidin buffer

Washing buffer with an additional 0.5M NaCl.

15 Substrate

Ready to use substrate SuperSignal ELISA Femto (Pierce, cat.no. 37075).

Standards

Standards were prepared from a 25 μ M stock solution of 0113-0000-0217. The peptide was serially diluted into reference plasma to make standards with final concentrations of 30000-
20 10000-3333-1111-370-123-41 and 0 pM. Standards were stored in Micronic tubes in 100 μ L aliquots at -20°C.

Assay procedure

Crystal 2000 Microplates (black) were coated with monoclonal antibody GLPb1-7F1, 100 μ L of 5 μ g/mL in PBS overnight at 4°C.

25 Plates were washed 5 times with washing buffer in an automated plate washer (SkanWasher, Skatron) and allowed to stand for at least 30min. with washing buffer to block remaining sites.

20 μ L of sample or standard was added to each well in duplicate immediately followed by 100 μ L GLP162-3F15 biotinylated, 1 μ g/mL in assay buffer. Plates were incubated for 2 hours
30 at room temperature on a plate shaker followed by 5 wash cycles as previously described.

100 μ L of streptavidin-peroxidase solution (KPL, code 14-30-00, 1:20000 in streptavidin buffer) was added to each well and incubated for 1 hour at room temperature on a plate shaker. Plates were washed as previously described and after emptying 100 μ L of SuperSignal femto was added. Plates were put on a shaker for 1 minute and measured in
35 Orion Luminometer (Berthold). Data were transferred to MultiCalc and standard curves

calculated using the weighted 4PL method. Sample concentrations were calculated from the standard curve.

GLP-1 (TOTAL) ASSAY

The assay was a two-site assay with simultaneous incubation of the analyte with catcher and
5 detector antibody. The assay recognizes N-terminally cleaved GLP-1 up to GLP-1(12-37).

Buffers

Coating buffer

PBS was used as coating buffer: 10mM sodium phosphate and 145mM sodium chloride
adjusted to pH 7.4.

10 Washing buffer

PBS with 0.05% (v/v) Tween 20

Assay buffer

PBS with 0.05% (v/v) Tween 20, 10g/L BSA and 10mg/L anti-TNP.

Streptavidin buffer

15 Washing buffer with an additional 0.5M NaCl.

Substrate

Ready-to-use substrate TMB (KemEnTec code 4380A)

Stop buffer

4 M H₃PO₄

20 Standards

Standards were prepared from a 25 µM stock solution of 0113-0000-0217. The peptide was
serially diluted into reference plasma to make standards with final concentrations of 30000-
10000-3333-1111-370-123-41 and 0 pM. Standards were stored in Micronic tubes in 100µL
aliquots at -20°C.

25 Assay procedure

Maxisorp microtiter plates (NUNC) were coated with monoclonal antibody GLPb1-7F1,
100µL of 5 µg/mL in PBS overnight at 4°C.

Plates were washed 5 times with washing buffer in an automated plate washer
(SkanWasher, Skatron) and allowed to stand for at least 30min. with washing buffer to block
30 remaining sites.

20µL of sample or standard was added to each well immediately followed by 100µL Ra2135-
biotinylated, 1µg/mL in assay buffer. Plates were incubated for 2 hours at room temperature
on a plate shaker followed by 5 wash cycles as previously described.

100µL of streptavidin-peroxidase solution (Amersham Biosciences code RPN4401V, 1:8000 in
35 assay buffer) was added to each well and incubated for 1 hour at room temperature on a

plate shaker. Plates were washed as previously described and after emptying 100 μ L of TMB was added and after 5 minutes stopped with 100 μ L H₃PO₄ .

Plates were measured in Victor Multilabel Reader (Wallac). Data were transferred to MultiCalc and standard curves calculated using the weighted 4PL method. Sample

5 concentrations were calculated from the standard curve.

The in-life experimental procedures, plasma analysis and pharmacokinetic analysis were identical to that described under the primary screening.

10 **Pharmaceutical formulation:**

A compound of the invention may be formulated as:

Compound of example 4 6,25 mg/ml

Propyleneglycol 14,0 mg/ml

Phenol 5.5 mg/ml

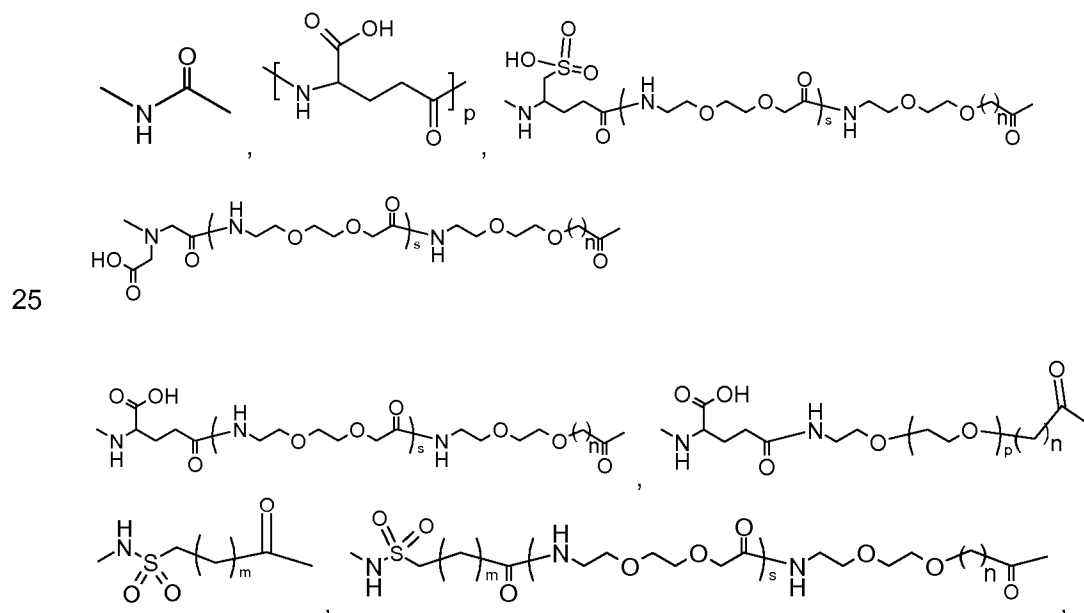
15 Phosphate Buffer pH 8.15

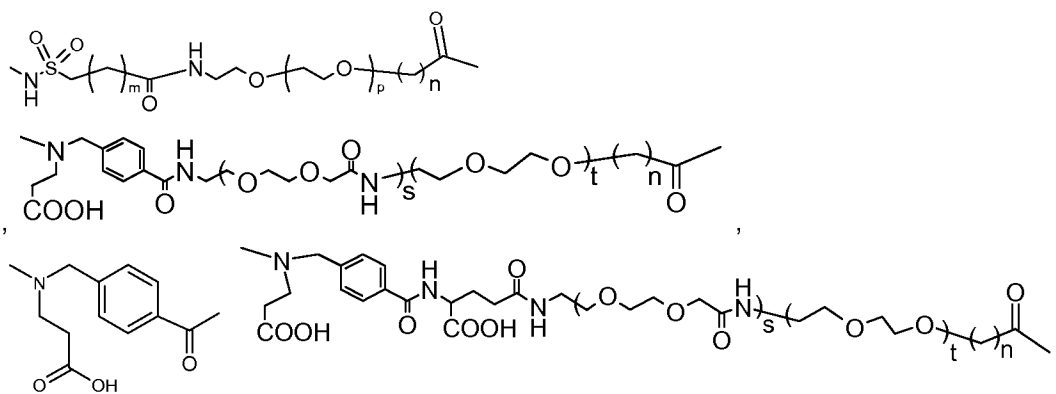
Optionally the compound is treated with heat and/or base before formulation as described in PCT/ EP2005/055946.

20

Claims

1. A GLP-1 analog having a modification of at least one non-proteogenic amino acid residue in positions 7 and/or 8 relative to the sequence GLP-1(7-37) (SEQ ID No 1), where
5 said analog is acylated with a moiety to the lysine residue in position 26, and where said moiety comprises at least two acidic groups, wherein one acidic group is attached terminally.
2. A GLP-1 analog according to claim 1, wherein the moiety attached in position 26 comprises a hydrophilic linker.
3. A GLP-1 analog according to claim 2, wherein the hydrophilic linker comprises at least
10 5 non-hydrogen atoms where 30-50% of said non-hydrogen atoms are either N or O.
4. A GLP-1 analog according to claim 1, wherein the moiety attached in position 26
15 comprises an albumin binding moiety separated from the peptide by the hydrophilic linker.
5. A GLP-1 analog according to claim 4 wherein the albumin binding moiety is a linear or branched lipophilic moiety containing 4-40 carbon atoms having a distal acidic group.
6. A GLP-1 analog according to claim 1, wherein the acylated moiety is B-U',
20 where U' is selected from





m is 0, 1, 2, 3, 4, 5, or 6,

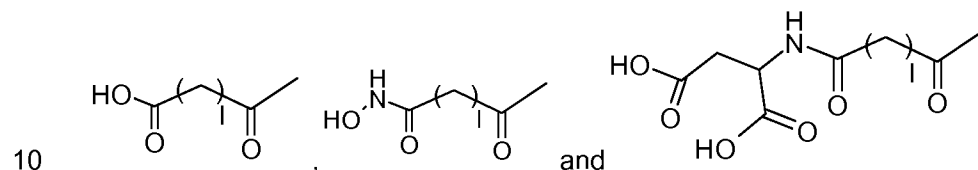
n is 1, 2 or 3

s is 0, 1, 2, or 3,

t is 0, 1, 2, 3, or 4

p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

and where B is an acidic group selected from



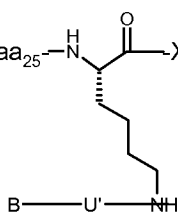
where l is 12, 13, 14, 15, 16, 17, 18, 19 or 20

7. A GLP-1 analog which is a compound of formula I (SEQ ID No. 2):

15

Xaa₇-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa₁₆-Ser-Xaa₁₈-Xaa₁₉-Xaa₂₀-Glu-Xaa₂₂-

Xaa₂₃-Ala-Xaa₂₅-NH-CH(CH₂CH₂CH₂CH₂NH-B)-C(=O)-Xaa₂₇-Phe-Ile-Xaa₃₀-Trp-Leu-Xaa₃₃-Xaa₃₄-Xaa₃₅-Xaa₃₆-Xaa₃₇



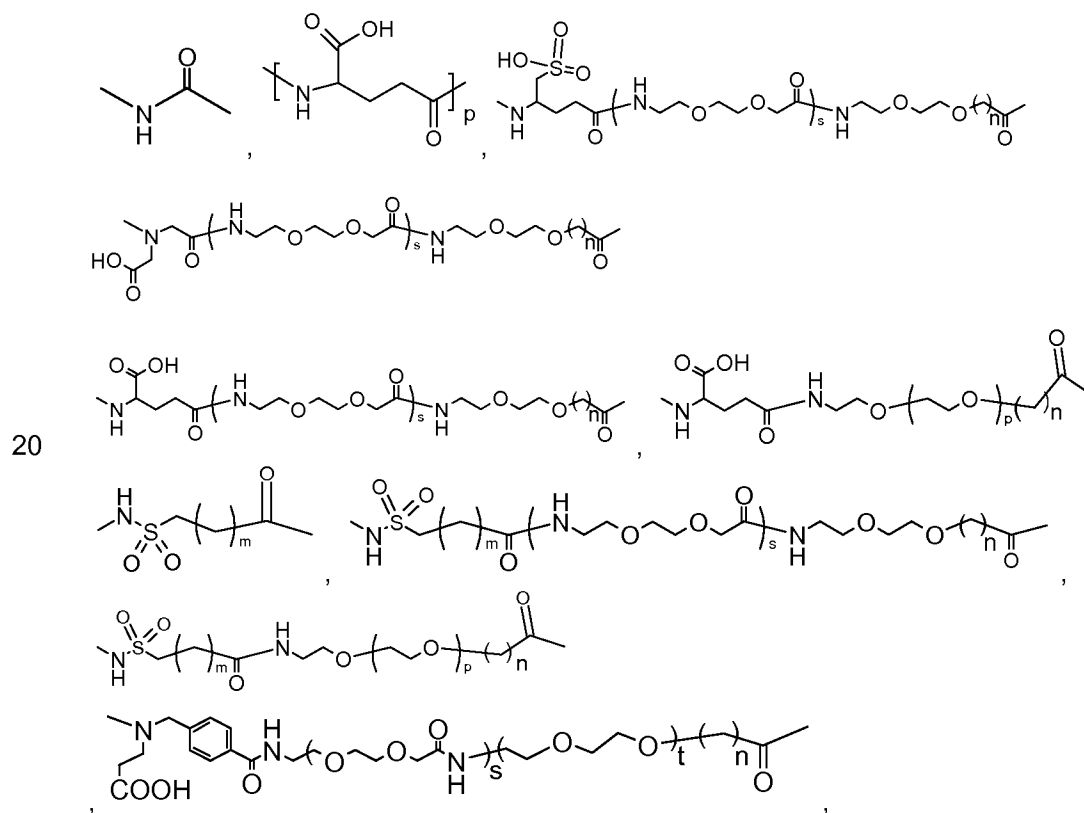
Formula I

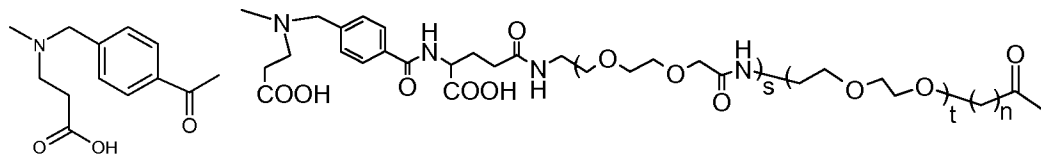
wherein

Xaa₇ is L-histidine, imidazopropionyl, α-hydroxy-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^α-acetyl-histidine, N^α-formyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine

Xaa₈ is Ala, Gly, Val, Leu, Ile, Thr, Ser, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

- Xaa₁₆ is Val or Leu;
Xaa₁₈ is Ser, Lys or Arg;
Xaa₁₉ is Tyr or Gln;
Xaa₂₀ is Leu or Met;
5 Xaa₂₂ is Gly, Glu or Aib;
Xaa₂₃ is Gln, Glu, Lys or Arg;
Xaa₂₅ is Ala or Val;
Xaa₂₇ is Glu or Leu;
Xaa₃₀ is Ala, Glu or Arg;
10 Xaa₃₃ is Val or Lys;
Xaa₃₄ is Lys, Glu, Asn or Arg;
Xaa₃₅ is Gly or Aib;
Xaa₃₆ is Arg, Gly or Lys, or is absent;
Xaa₃₇ is Gly, Ala, Glu, Pro, Lys, or is absent;
15 and B and U' together is the acylated moiety, where U' is selected from





m is 0, 1, 2, 3, 4, 5, or 6,

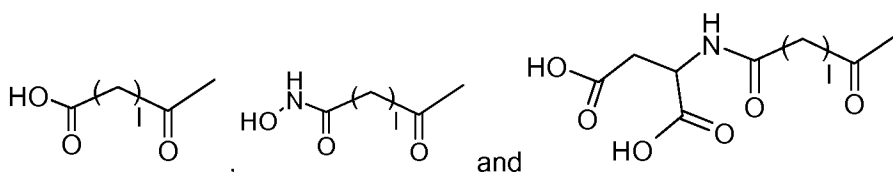
n is 1, 2 or 3

s is 0, 1, 2, or 3,

5 t is 0, 1, 2, 3, or 4

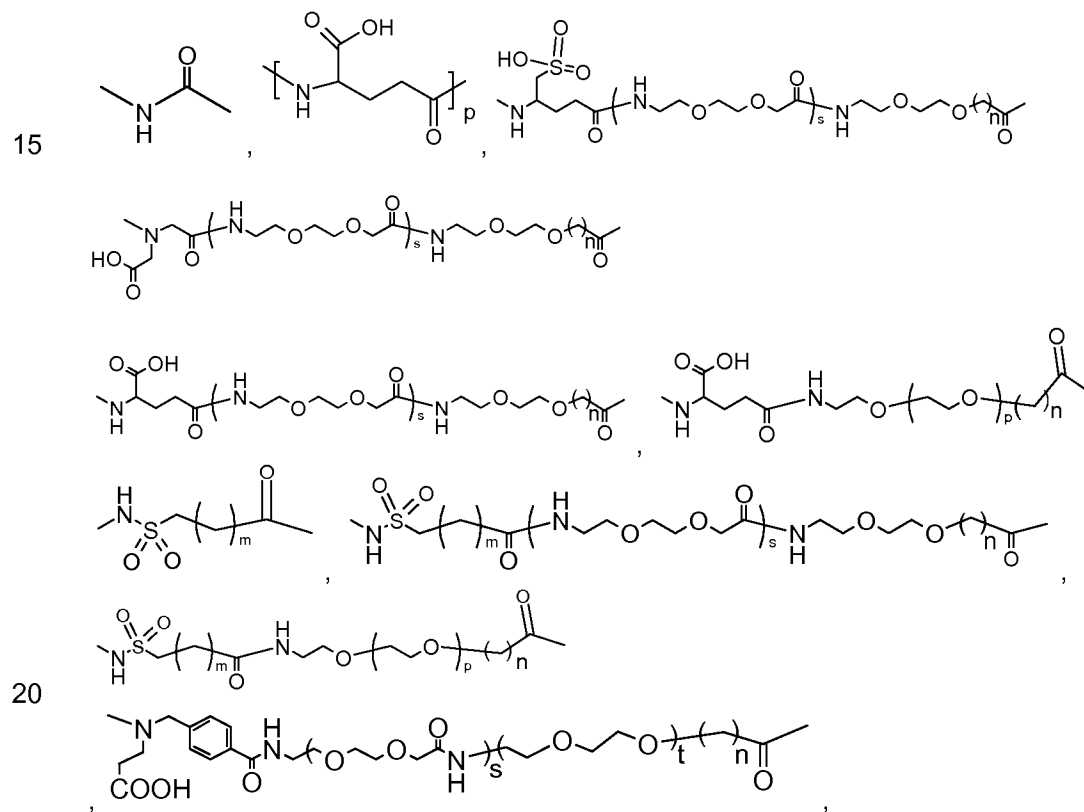
p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

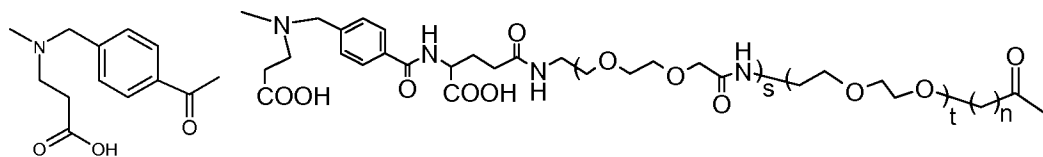
and where B is an acidic group selected from



10 where l is 12, 13, 14, 15, 16, 17, 18, 19 or 20;

8. A GLP-1 analog according to claim 6, wherein U' is selected from





m is 2, 3, 4 or 5,

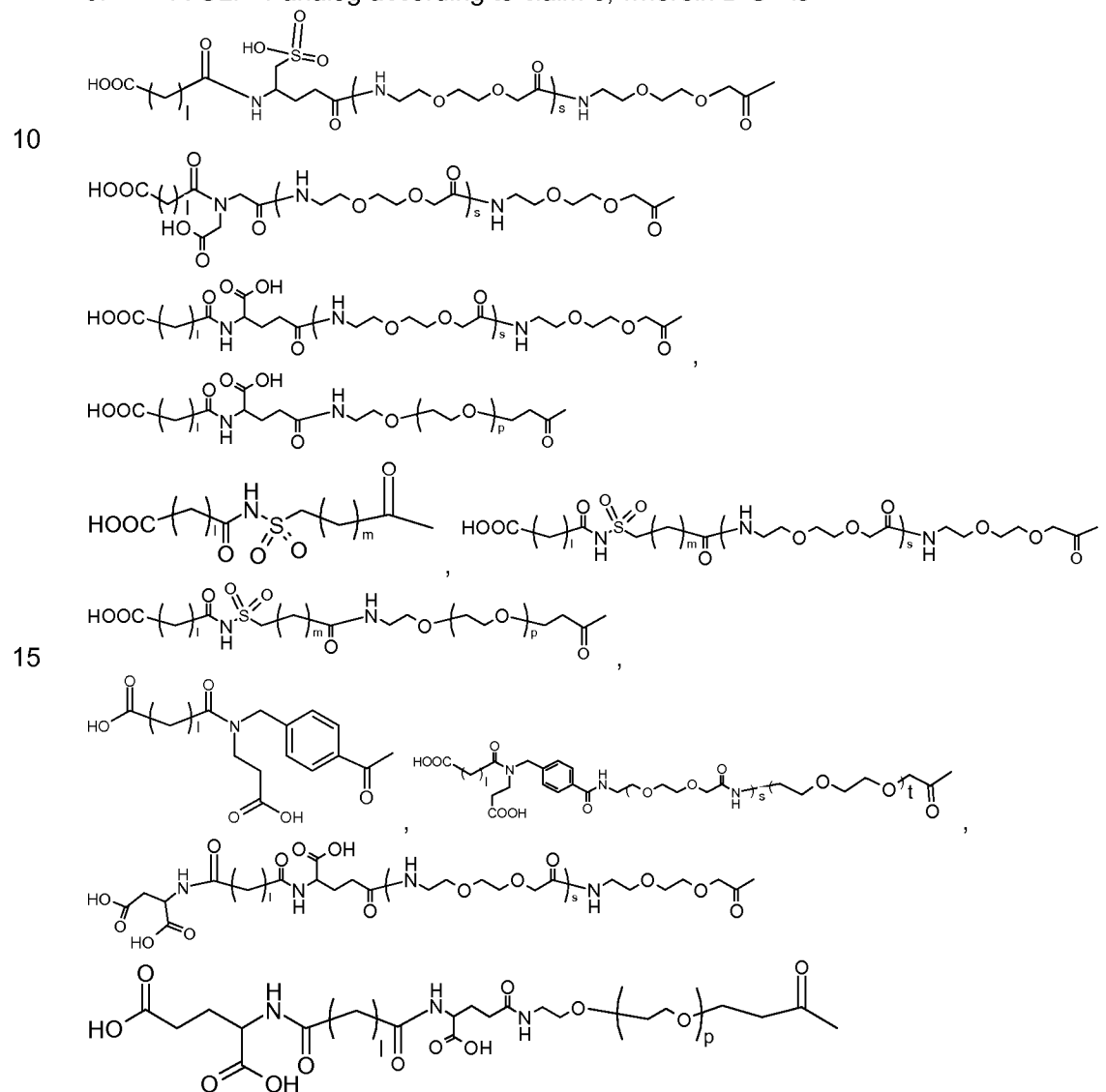
n is 1 or 2

5 s is 0, 1, or 2,

t is 0, 1, 2, or 3

p is 1, 2, 3, 4, 7, 11 or 23

9. A GLP-1 analog according to claim 6, wherein B-U'- is



where l is 14, 15, 16, 17, 18, 19 or 20;

20 p is 1, 2, 3, 4, 7, 8, 9, 10, 11 or 12.

s is 0, 1 or 2

t is 0 or 1;

m is 2, 3 or 4;

- 5 10. A GLP-1 analog according to claim 9, wherein
where l is 14, 15, 16, 17 or 18
p is 1, 2, 3, 4 or 11;
s is 0, 1 or 2;
t is 0 or 1;

10

11. A GLP-1 analog according to claim 6, wherein s is 1.

12. A GLP-1 analog according to claim 6, wherein l is 16

- 15 13. A GLP-1 analog according to claim 6, wherein p is 3 or 4.

14. A GLP-1 analog according to claim 6, wherein n is 1.

15. A GLP-1 analog according to claim 7, wherein

- 20 Xaa₇ is His or desamino-histidine;
Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys or Aib;
Xaa₁₆ is Val;
Xaa₁₈ is Ser;
Xaa₁₉ is Tyr;
25 Xaa₂₀ is Leu;
Xaa₂₂ is Gly, Glu or Aib;
Xaa₂₃ is Gln or Glu;
Xaa₂₅ is Ala;
Xaa₂₇ is Glu;
30 Xaa₃₀ is Ala or Glu;
Xaa₃₃ is Val;
Xaa₃₄ is Lys or Arg;
Xaa₃₅ is Gly or Aib;
Xaa₃₆ is Arg or Lys
35 Xaa₃₇ is Gly, amide or is absent;

16. A GLP-1 analog according to claim 15, wherein

Xaa₇ is His

Xaa₈ is Gly, or Aib;

- Xaa₁₆ is Val;
Xaa₁₈ is Ser;
Xaa₁₉ is Tyr;
Xaa₂₀ is Leu;
5 Xaa₂₂ is Glu or Aib;
Xaa₂₃ is Gln;
Xaa₂₅ is Ala;
Xaa₂₇ is Glu;
Xaa₃₀ is Ala;
10 Xaa₃₃ is Val;
Xaa₃₄ is Lys or Arg;
Xaa₃₅ is Gly or Aib;
Xaa₃₆ is Arg;
Xaa₃₇ is Gly
15
17. A GLP-1 analog according to claim 1, wherein said GLP-1 analog comprises a modification of the N-terminal L-histidine in position 7 of the GLP-1(7-37) sequence.
18. A GLP-1 analog according to claim 17, wherein said GLP-1 analog comprises
20 imidazopropionyl⁷, α-hydroxy-histidine⁷ or N-methyl-histidine⁷, D-histidine⁷, desamino-histidine⁷, 2-amino-histidine⁷, β-hydroxy-histidine⁷, homohistidine⁷, N^α-acetyl-histidine⁷, α-fluoromethyl-histidine⁷, α-methyl-histidine⁷, 3-pyridylalanine⁷, 2-pyridylalanine⁷ or 4-pyridylalanine⁷.
19. A GLP-1 analog according to claim 1, wherein said GLP-1 analog comprises a substitution of the L-alanine in position 8 of the GLP-1(7-37) sequence for another amino acid residue.
20. A GLP-1 analog according to claim 19, wherein said GLP-1 analog comprises Aib⁸,
30 Gly⁸, Val⁸, Ile⁸, Leu⁸, Ser⁸, Thr⁸, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid.
21. A GLP-1 analog according to claim 20, wherein said GLP-1 analog comprises Aib⁸;
35
22. A GLP-1 analog according to claim 21, wherein no more than ten amino acid residues

which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1).

23. A GLP-1 analog according to claim 22, wherein said GLP-1 analog comprises no more than six amino acid residues which have been exchanged, added or deleted as compared to
5 GLP-1(7-37) (SEQ ID No. 1).

24. A GLP-1 analog according to claim 1, wherein said GLP-1 analog comprises no more than 3 amino acid residues which are not encoded by the genetic code.

10 25. A GLP-1 analog according to claim 1, wherein said GLP-1 analog comprises only one lysine residue.

26. A GLP-1 analog according to claim 1, which is
Aib⁸,Arg³⁴-GLP-1(7-37)
15 Aib^{8,22},Arg³⁴-GLP-1(7-37).
Arg³⁴-GLP-1(7-37).
[3-(4-Imidazolyl)Propionyl⁷,Arg³⁴]GLP-1-(7-37)peptide
Gly⁸,Arg³⁴-GLP-1(7-37)
Aib⁸,Arg³⁴, Pro³⁷-GLP-1(7-37)
20 Aib^{8,22,27,30,35},Arg³⁴,Pro³⁷- GLP-1 (7-37)amide,
all of which are substituted by B-U' in position 26.

27. A method for increasing the time of action in a patient of a GLP-1 analog, said
25 method comprising acylating said GLP-1 analog with a moiety B-U' as disclosed in claim 6,
on the lysine residue in position 26 of said GLP-1 analog.

28. A method for increasing the time of action in a patient of a GLP-1 analog to more than about 40 hours, said method comprising modifying at least one of the amino acid residues in
30 positions 7 and 8 of a GLP-1(7-37) peptide or an analog thereof, and acylating said GLP-1
analog with a moiety B-U'- as disclosed in claim 6 on the lysine residue in position 26 of said
GLP-1 analog.

29. A pharmaceutical composition comprising a compound according to claim 1, and a
35 pharmaceutically acceptable excipient.

30. The pharmaceutical composition according to claim 29, which is suited for parenteral administration.

31. A method for treating hyperglycemia, type 2 diabetes in a subject, said method
5 comprising administering to a subject in need of such treatment an effective amount of a GLP-1
analog according to claim 1.

ABSTRACT

Protracted GLP-1 compounds and therapeutic uses thereof.