

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,474,780 B2
APPLICATION NO. : 14/987791
DATED : October 25, 2016
INVENTOR(S) : Jorge Alsina-Fernandez et al.

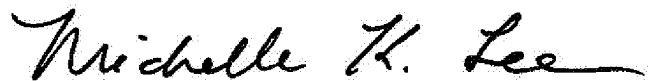
Page 1 of 1

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

In Claim 15, after "NH2" insert --.--

Signed and Sealed this
Seventh Day of March, 2017



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

PATENT
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U. S. Patent No. : 9,474,780

Issued : 25 October 2016

First Applicant : LOIZOS, Nick, et al

Serial No. : 14/987,791

Application Date : 05 January 2016

US Nat'l Entry Date :
(if applicable):

Entitled : GIP AND GLP-1 CO-AGONIST COMPOUNDS

Docket No. : X20448

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 C.F.R. 1.323

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

Sir:

The patentee of the above-identified patent respectfully requests issuance of a Certificate of Correction to correct certain errors in U.S. Patent Number 9,474,780. A copy of USPTO Form PTO/SB/44 on which the errors are specified is attached.

There was an inadvertent typographical error.

The Office invited to contact the undersigned Attorney by telephone if there are any outstanding issues regarding this Request, in order to attempt to resolve such issues without further delay.

9,474,780

Respectfully submitted,

/Alejandro Martinez/
Alejandro Martinez
Attorney for Applicant
Registration No. 58,163
Phone: 908-203-6835

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288
25 January 2017

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 1 of 1

PATENT NO. : 9474780

APPLICATION NO.: 14/987,791

ISSUE DATE : 10/25/2016

INVENTOR(S) : Jorge Alsina-Fernandez, Robert Chad Cummins, Tamer Coskun,
Krister B Bokvist

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:

In Claim 15, after "NH2" insert --.--

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

Eli Lilly and Company
P.O. Box 6288
Indianapolis, Indiana 46206-6288

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. 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 1.0 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: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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 disclosure of these records is required by the Freedom of Information Act.
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 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.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/987,791	10/25/2016	9474780	X20448	4253

25885 7590 10/05/2016
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

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):

Eli Lilly and Company, Indianapolis, IN;
Bengt Krister Bokvist, Carmel, IN;
Tamer Coskun, Indianapolis, IN;
Robert Chadwick Cummins, Carmel, IN;
Jorge Alsina-Fernandez, Indianapolis, IN;

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.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/987,791	01/05/2016	Bengt Krister Bokvist	X20448	4253

25885	7590	09/21/2016
ELI LILLY & COMPANY		
PATENT DIVISION		
P.O. BOX 6288		
INDIANAPOLIS, IN 46206-6288		

EXAMINER	
BRADLEY, CHRISTINA	

ART UNIT	PAPER NUMBER
1675	

NOTIFICATION DATE	DELIVERY MODE
09/21/2016	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):

patents@lilly.com

Response to Rule 312 Communication	Application No. 14/987,791	Applicant(s)
	Examiner	Art Unit

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

1. ☒ The amendment filed on 14 September 2016 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.

Trevon Couch

/Publishing Division/

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Type or print name of person signing certification

Signature

Date

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant: Bengt Krister Bokvist Group Art Unit:
Serial No.: 14/987791 Examiner:
Application Date: January 5, 2016 Conf No.: 4253
US Nat'l Entry
Date (if applicable):
For: GIP AND GLP-1 CO-AGONIST COMPOUNDS
Docket No.: X20448

RESPONSE AND AMENDMENT UNDER 37 C.F.R. 1.121

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

Sir:

Introductory Comments:

In response to the Notice of File Corrected Application Papers of 18-August-2016 (copy included herewith), please amend the above-identified application as follows:

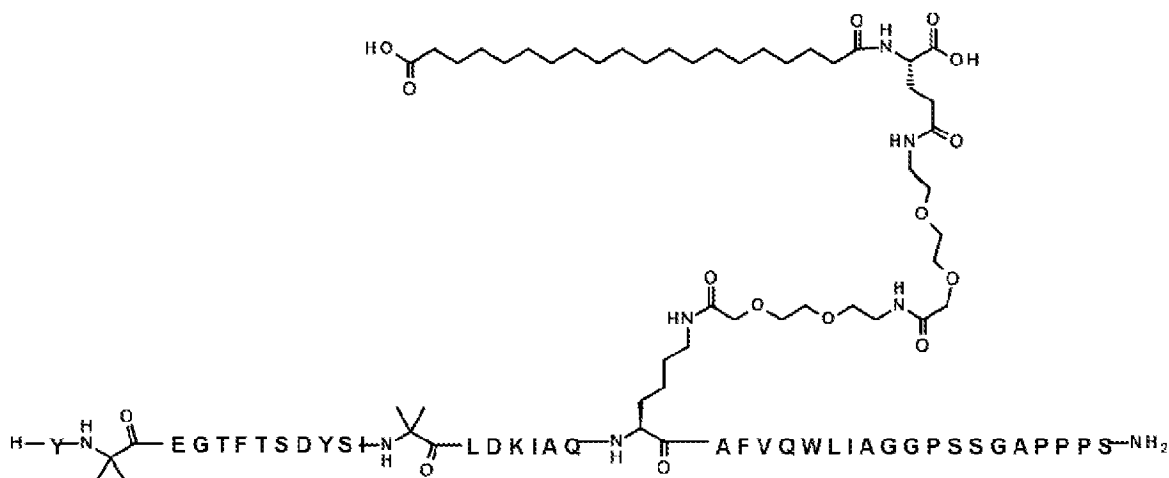
No fees are believed due in connection with this submission. However, in the event Applicants have overlooked the need for any fee, Applicants hereby petition therefor and authorize that any charges be made to Deposit Account No. 05-0840, Eli Lilly and Company, associated with Customer No. 25885.

Amendments to the Specification begin on page 2 of this paper.

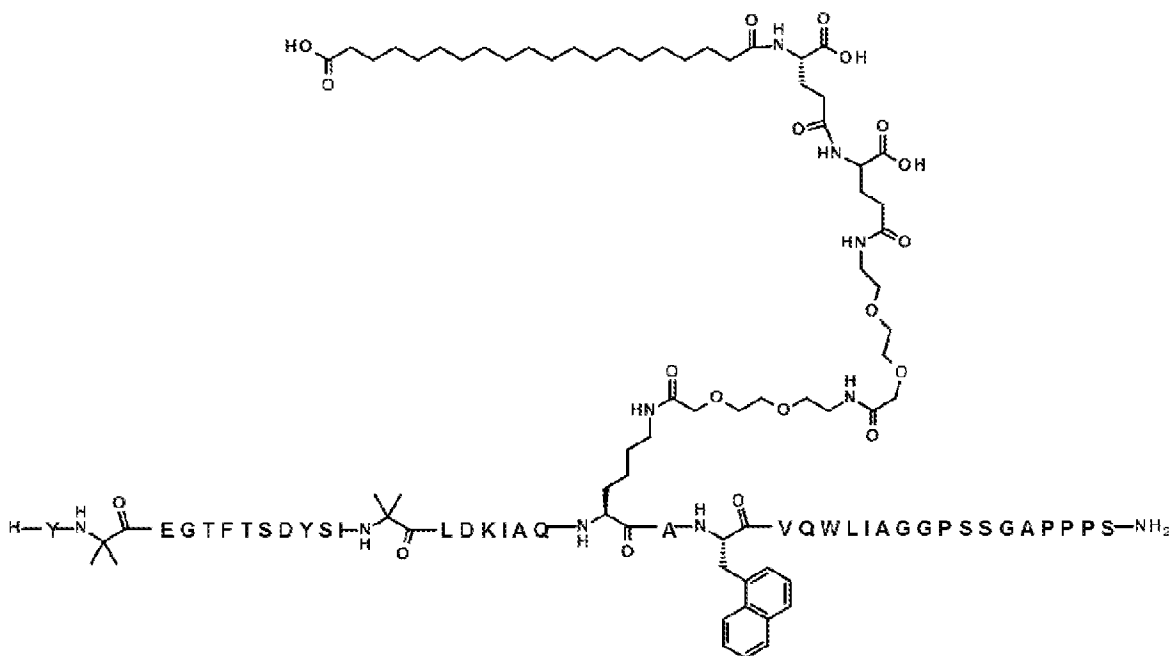
Remarks/Arguments begin on page 3 of this paper.

Amendments to the Specification

Please replace the chemical structure found on page 12, following line 10 (which reads “trifluoroacetate salt”) with the following chemical structure:



Please replace the chemical structure found on page 14, following line 3 (which reads “trifluoroacetate salt”) with the following chemical structure:



Remarks

Applicants thank the Examiner for indicating that the application has been accorded an Allowance Date and is being prepared for issuance. The Examiner has identified informalities in the application and has requested that Applicants provide legible text for pages 12 and 14 of the specification.

Applicants have reproduced the chemical structures found on pages 12 and 14 which Applicants believe address the Examiner's concerns. Support for the clearer representation of the chemical formula on page 12 can be found in SEQ ID NO: 3. Support for the clearer representation of the chemical formula on page 14 can be found in SEQ ID NO: 4. Applicants submit no new matter has been introduced and respectfully request removal of the objection.

If any questions concerning this application should arise, the Examiner is encouraged to telephone the undersigned at (317) 277-4260.

Respectfully submitted,

/Alejandro Martinez/

Alejandro Martinez
Attorney/Agent for Applicant(s)
Registration No. 58,163
Phone: 317-277-4260

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

September 14, 2016



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/987,791	01/05/2016	Bengt Krister Bokvist	X20448	4253

25885	7590	08/18/2016
ELI LILLY & COMPANY		
PATENT DIVISION		
P.O. BOX 6288		
INDIANAPOLIS, IN 46206-6288		

EXAMINER
BRADLEY, CHRISTINA

ART UNIT	PAPER NUMBER
1675	

NOTIFICATION DATE	DELIVERY MODE
08/18/2016	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):

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United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Application No. : 14987791
Applicant : Bokvist
Filing Date : 01/05/2016
Date Mailed : 08/18/2016

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given two (2) months from the mail date of this Notice within which to respond. This time period for reply is extendable under 37 CFR 1.136(a) for only TWO additional MONTHS.

The informalities requiring correction are indicated in the attachment(s). If the informality pertains to the abstract, specification (including claims) or drawings, the informality must be corrected with an amendment in compliance with 37 CFR 1.121 (or, if the application is a reissue application, 37 CFR 1.173). Such an amendment may be filed after payment of the issue fee if limited to correction of informalities noted herein. See Waiver of 37 CFR 1.312 for Documents Required by the Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004). In addition, if the informality is not corrected until after payment of the issue fee, for purposes of 35 U.S.C. 154(b)(1)(iv), "all outstanding requirements" will be considered to have been satisfied when the informality has been corrected. A failure to respond within the above-identified time period will result in the application being ABANDONED.

See attachment(s).

*A copy of this notice **MUST** be returned with the reply. Please address response to
"Mail Stop Issue Fee, Commissioner for Patents,
P.O. Box 1450, Alexandria, VA 22313-1450".*

/Stephanie Smart/
Publication Branch
Office of Data Management
(571) 272-4200

**IDENTIFICATION OF APPLICATION DEFICIENCIES
IN APPLICATION FILED ON OR AFTER SEPTEMBER 16, 2012**

- ☒ Applicant must provide legible text for the following item(s).
- ☒ Specification filed 01/05/2016, page(s) pages 12 and 14.
- ☐ Claims filed , claim(s) .
- ☐ Other: .
- ☐ Applicant must provide missing information on the following page(s) of the specification by amending the specification to add the missing text. No new matter may be added.
Page/line no(s).
- ☐ The specification refers to one or more applications by attorney docket number and does not show the U.S. application number(s). Applicant must supply the U.S. application number in place of each attorney docket number.
Page/line no(s).
- ☐ Applicant must provide an Abstract of the Disclosure.
- ☐ The Application Data Sheet (ADS dated) does not supply the inventor's city and/or does not supply the inventor's U.S. state and/or does not supply the inventor's country. Applicant must submit a signed application data sheet that corrects this deficiency. To be in compliance with 37 CFR 1.76, the corrected application data sheet must identify the information being changed by using underlining for additions and strikethroughs or brackets for deletions.
- ☐ The Application Data Sheet (ADS dated) was not properly signed. Applicant must submit an application data sheet that is properly signed in accordance with 37 CFR 1.76(e) and 1.33(b). If the unsigned application data sheet shows foreign priority information or domestic benefit information, and if the Office does not show foreign priority information or domestic benefit information on the filing receipt, applicant may need to file a petition under 37 CFR 1.55 or 1.78 for delayed claim for priority or benefit if the claim for priority or benefit has not been filed in accordance with the time periods set forth in 37 CFR 1.55 or 1.78.
- ☐ Other:

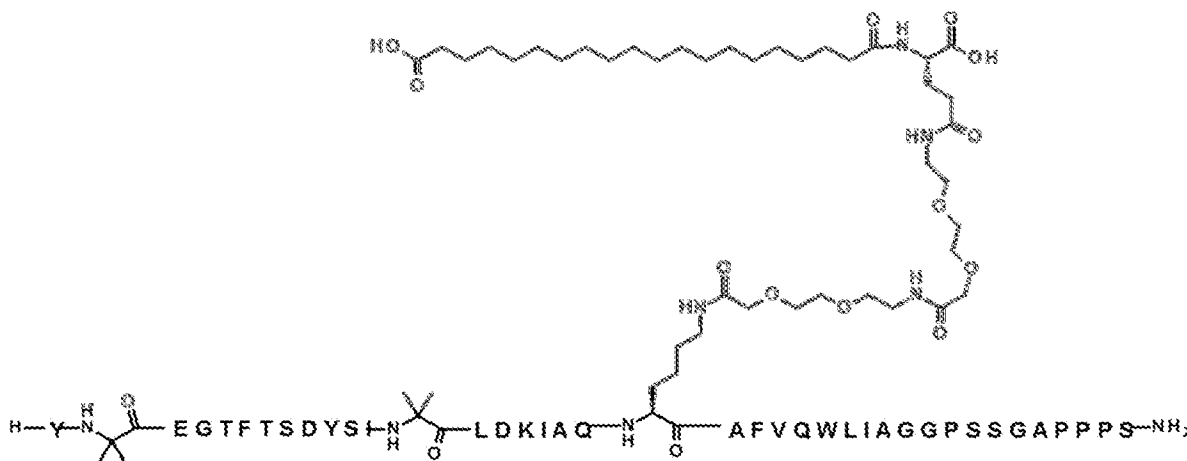
of ordinary skill in the art. It is understood that these Examples are not intended to be limiting to the scope of the invention in any way.

EXAMPLE 1

YX₁EGTFTSDYSIX₂LDKIAQKAFVQWLIAGGPSSGAPPPS

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₈-CO₂H; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 3)

trifluoroacetate salt



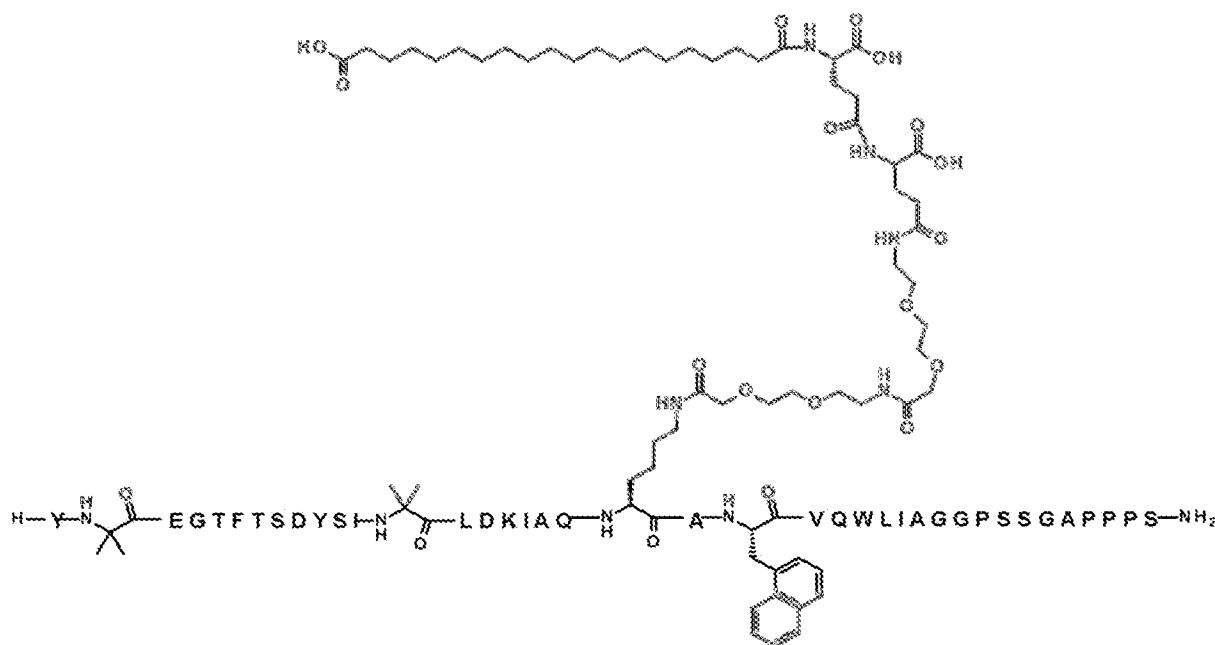
The above structure contains the standard single letter amino acid code with exception of residues Aib₂, Aib₁₃ and K₂₀ where the structures of these amino acid residues have been expanded.

The peptide according to SEQ ID NO: 3 of the present invention is generated by solid-phase peptide synthesis using a Fmoc/t-Bu strategy carried out on a Symphony automated peptide synthesizer (PTI Protein Technologies Inc.) starting from RAPP AM-Rink Amide resin and with couplings using 6 equivalents of amino acid activated with diisopropylcarbodiimide (DIC) and hydroxybenzotriazole (HOBt) (1:1:1 molar ratio) in dimethylformamide (DMF) for 90 min at 25°C.

Extended couplings (4h each) for Pro₃₁, Trp₂₅, Gln₂₄, Val₂₃, Phe₂₂, Lys₂₀, Gly₄, Glu₃ and Aib₂ are necessary to improve the quality of the crude peptide. A Fmoc-

ethoxy]-acetyl)₂-(γGlu)₂-CO-(CH₂)₁₈-CO₂H; X₃ is 1-Nal; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 4)

trifluoroacetate salt



The above structure contains the standard single letter amino acid code with exception of residues Aib2, Aib13, K20 and 1-Nal22 where the structures of these amino acid residues have been expanded.

The peptide according to SEQ ID NO: 4 of the present invention is synthesized similarly as described above in Example 1. The following conditions are used for the coupling of Fmoc-1Nal-OH at position 22: Fmoc-1Nal-OH (6 equiv), PyBOP (6 equiv), and DIEA (12 equiv) in DMF for 4 h at 25°C.

EXAMPLE 3

YX₁EGTFTSDYSIX₂LDKIAQKAFVQWLIAGGPSSGAPPPS

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₆-CO₂H; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 5)

trifluoroacetate salt

Electronic Acknowledgement Receipt

EFS ID:	26919032
Application Number:	14987791
International Application Number:	
Confirmation Number:	4253
Title of Invention:	GIP AND GLP-1 CO-AGONIST COMPOUNDS
First Named Inventor/Applicant Name:	Bengt Krister Bokvist
Customer Number:	25885
Filer:	Alejandro Martinez./Linda Durbin
Filer Authorized By:	Alejandro Martinez.
Attorney Docket Number:	X20448
Receipt Date:	14-SEP-2016
Filing Date:	05-JAN-2016
Time Stamp:	11:07:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
------------------------	----

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment after Notice of Allowance (Rule 312)	X20448Response.pdf	1056795	no	6
			d8674342c436b4904f70b30853c80f6fd03e1f6a		

Warnings:

17 of 141

Information:					
2	Specification	X20448Specificationp12.pdf	90353	no	1
			a0e95a58d6637e12b7db3fee7166a720e7ff3c6b		
Warnings:					
Information:					
3	Specification	X20448Specificationp14.pdf	101362	no	1
			1d4143b525c53443f232bca8b776cf14bbe d31c9		
Warnings:					
Information:					
Total Files Size (in bytes):			1248510		
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. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> 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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See attachment(s).

*A copy of this notice **MUST** be returned with the reply. Please address response to
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/Stephanie Smart/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 14987791

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- ☒ Specification filed 01/05/2016, page(s) pages 12 and 14.
- ☐ Claims filed , claim(s) .
- ☐ Other: .
- ☐ Applicant must provide missing information on the following page(s) of the specification by amending the specification to add the missing text. No new matter may be added.
Page/line no(s).
- ☐ The specification refers to one or more applications by attorney docket number and does not show the U.S. application number(s). Applicant must supply the U.S. application number in place of each attorney docket number.
Page/line no(s).
- ☐ Applicant must provide an Abstract of the Disclosure.
- ☐ The Application Data Sheet (ADS dated) does not supply the inventor's city and/or does not supply the inventor's U.S. state and/or does not supply the inventor's country. Applicant must submit a signed application data sheet that corrects this deficiency. To be in compliance with 37 CFR 1.76, the corrected application data sheet must identify the information being changed by using underlining for additions and strikethroughs or brackets for deletions..
- ☐ The Application Data Sheet (ADS dated) was not properly signed. Applicant must submit an application data sheet that is properly signed in accordance with 37 CFR 1.76(e) and 1.33(b). If the unsigned application data sheet shows foreign priority information or domestic benefit information, and if the Office does not show foreign priority information or domestic benefit information on the filing receipt, applicant may need to file a petition under 37 CFR 1.55 or 1.78 for delayed claim for priority or benefit if the claim for priority or benefit has not been filed in accordance with the time periods set forth in 37 CFR 1.55 or 1.78.
- ☐ Other:



UNITED STATES PATENT AND TRADEMARK OFFICE

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NOTICE OF ALLOWANCE AND FEE(S) DUE

25885 7590 07/28/2016
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER

BRADLEY, CHRISTINA

ART UNIT

PAPER NUMBER

1675

DATE MAILED: 07/28/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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14/987,791

01/05/2016

Bengt Krister Bokvist

X20448

4253

TITLE OF INVENTION: GIP AND GLP-1 CO-AGONIST COMPOUNDS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$960	\$0	\$0	\$960	10/28/2016

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.

25885 7590 07/28/2016
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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.
14/987,791	01/05/2016	Bengt Krister Bokvist	X20448	4253

TITLE OF INVENTION: GIP AND GLP-1 CO-AGONIST COMPOUNDS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$960	\$0	\$0	\$960	10/28/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
BRADLEY, CHRISTINA	1675	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 credits 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 forms 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: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/987,791	01/05/2016	Bengt Krister Bokvist	X20448	4253

25885 7590 07/28/2016
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INDIANAPOLIS, IN 46206-6288

EXAMINER

BRADLEY, CHRISTINA

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

1675

DATE MAILED: 07/28/2016

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

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

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.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B 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. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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 disclosure of these records is required by the Freedom of Information Act.
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 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.

Notice of Allowability	Application No. 14/987,791	Applicant(s) BOKVIST ET AL.	
	Examiner CHRISTINA BRADLEY	Art Unit 1675	AIA (First Inventor to File) Status Yes

-- 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 the claims filed January 5, 2016.
☐ 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 1-18. 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. _____.
 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: _____.

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 _____ | 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 _____. | |

/CHRISTINA BRADLEY/
Primary Examiner, Art Unit 1675

REASONS FOR ALLOWANCE

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

The following is an examiner's statement of reasons for allowance: The instant claims recite a peptide with the amino acid sequence Y-Aib-EGTFTSDYSI-Aib-LDKIAQKA[Phe or 1-Nal]VQWLIAGGPSSGAPPPS, wherein the lysine at position 20 is conjugated to ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁₋₂-CO-(CH₂)₁₀₋₂₀-CO₂H. The peptides have GIP and GLP1 agonist activity.

The closest prior art of Just et al. (US 2015/0299281 A1; WO 2013/164483) teaches GIP-GLP1 dual acting receptor agonists, which are closely related to the instantly claimed compounds. The genus of GIP-GLP1 co-agonists taught in the prior art (Formula I, para. [0044]) differs from the compounds claimed in this application at position 24. The prior art defines position 24 as Asn, Glu, Arg, or Lys, whereas the instant claims require position 24 to be Gln. Just et al. do not teach or suggest substituting Gln for the amino acids at position 24.

Just et al. teach that the GIP-GLP1 co-agonists can be conjugated with a lipophilic substituent to one or more of amino acid positions 16, 17, 19, 20, 24, 27, 28, 30 and 32 (para. [0111]), but do not teach the specific lipophilic substituent recited in the instant application.

In order to arrive at the instantly claimed compounds, one of ordinary skill in the art would have to substitute Gln at position 24 and a moiety of ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁₋₂-CO-(CH₂)₁₀₋₂₀-CO₂H as the lipophilic substituent. There is no teaching or suggestion in Just et al. to do so. Even if there were, it would require hindsight reasoning to

Art Unit: 1675

make the compounds claimed in this application because all of the preferred embodiments and species disclosed in Just et al. differ from the instant compounds at additional positions. In other words, although with the exception of the amino acid at position 24 and the lipophilic substituent, the broad genus of Just et al. encompasses the claimed compounds, the preferred embodiments, sub-genera, and species have several more differences.

For example, position 17 in Just et al. is preferably lysine, not isoleucine. In addition, position 27 in Just et al. is preferably Leu, Glu, or Val, not isoleucine. In addition, position 29 in Just et al. is preferably Gln or Ala, not Gly. See Formulae II(b), II(c), and II(d) and the species of Table 2 of Just et al. In addition, most of the species disclosed in Just et al. lack the GPSSGAPPPS sequence at positions 30-39 (see Tables 1 and 2). In addition, the species in Just et al. that are conjugated to a lipophilic substituent, are conjugated to hexadecanoyl-isoGlu at lysine 17, not at lysine 20 (see Table 2).

Therefore, in order to make the instantly claimed compounds one of ordinary skill in the art would have to choose options for positions 17, 27, 29, and 30-39, and for the site of lipophilic conjugation that are different from those preferred and reduced to practice in Just et al. Then, one of ordinary skill in the art would have to substitute a Gln at position 24 and a moiety of $([2-(2\text{-Amino-ethoxy})\text{-ethoxy}]\text{-acetyl})_2\text{-(}\gamma\text{Glu)}_{1-2}\text{-CO-(CH}_2\text{)}_{10-20}\text{-CO}_2\text{H}$ for the lipophilic substituent, but not make any other changes. To do so would require hindsight reasoning. Thus, the claimed compounds are both novel and unobvious over Just et al. With respect to the method claim, since the products are both novel and unobvious, methods of using these products are also both novel and unobvious.

Art Unit: 1675

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 CHRISTINA BRADLEY whose telephone number is (571)272-9044. The examiner can normally be reached on Monday through Friday from 5:30 A.M. to 3:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Alstrum-Acevedo can be reached on (571) 272-5548. 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.

/CHRISTINA BRADLEY/
Primary Examiner, Art Unit 1675

cmb

Application/Control Number: 14/987,791

Page 5

Art Unit: 1675

Notice of References Cited	Application/Control No. 14/987,791		Applicant(s)/Patent Under Reexamination BOKVIST ET AL.	
	Examiner CHRISTINA BRADLEY		Art Unit 1675	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2015/0299281 A1	10-2015	JUST; Rasmus	C07K14/605	514/7.2
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
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FOREIGN PATENT DOCUMENTS

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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Doc code: IDS

PTO/SB/08a (01-10)

Doc description: Information Disclosure Statement (IDS) Filed

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

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	14987791
	Filing Date	2016-01-05
	First Named Inventor	Bengt Kister Bokvist
	Art Unit	
	Examiner Name	Chavanne, Franz
	Attorney Docket Number	X20448

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14987791
Filing Date	2016-01-05
First Named Inventor	Bengt Kister Bokvist
Art Unit	
Examiner Name	Chavanne, Franz
Attorney Docket Number	X20448

1

GREEN B D ET AL: "STRUCTURALLY MODIFIED ANALOGUES OF GLUCAGON-LIKE PEPTIDE-1 (GLP-1) AND GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE (GIP) AS FUTURE ANTIDIABETIC AGENTS", CURRENT PHARMACEUTICAL DESIGN, BENTHAM SCIENCE PUBLISHERS, NL, vol. 10, no. 29, 1 January 2004 (2004-01-01), pages 3651-3662, XP009068381, ISSN: 1381-6128, DOI:10.2174/1381612043382774

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

EXAMINER SIGNATURE

Examiner Signature	/CHRISTINA BRADLEY/	Date Considered	07/17/2016
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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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14987791
Filing Date	2016-01-05
First Named Inventor	Bengt Kister Bokvist
Art Unit	
Examiner Name	Chavanne, Franz
Attorney Docket Number	X20448

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	/Alejandro Martinez/	Date (YYYY-MM-DD)	2016-05-13
Name/Print	Alejandro Martinez	Registration Number	58,163

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.

Doc code: IDS

PTO/SB/08a (01-10)

Doc description: Information Disclosure Statement (IDS) Filed

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

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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

Application Number 14987791

Filing Date 2016-01-05

First Named Inventor Bengt Krister Bokvist

Art Unit

Examiner Name

Attorney Docket Number X20448

U.S.PATENTS

Remove

Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	8541368	B2	2013-09-24	Lau, et al	

If you wish to add additional U.S. Patent citation information please click the Add button.

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U.S.PATENT APPLICATION PUBLICATIONS

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Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²ⁱ	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1	2013164483	WO	A1	2013-07-11	Just, et al		
	2	2012167744	WO	A1	2012-12-13	Ma, et al		
	3	2013192129	WO	A1	2013-12-27	Dimarchi, Richard D.		

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

Application Number		14987791
Filing Date		2016-01-05
First Named Inventor	Bengt Krister Bokvist	
Art Unit		
Examiner Name		
Attorney Docket Number	X20448	

4	2012088379	WO	A2	2012-06-28	Vignati, et al		
5	2010029159	WO	A1	2010-03-18	Christensen, et al		
6	2010071807	WO	A1	2010-06-24	Dimarchi,et al		
7	2012088116	WO	A1	2012-06-28	Dimarchi,et al		
8	2012138941	WO	A1	2012-10-11	Shandler, et al		
9	2011094337	WO	A1	2011-08-04	Dimarchi,et al		
10	2014096148	WO	A1	2014-06-24	Haack, et al		
11	2014060512	WO	A1	2014-04-24	Reslow, et al		
12	2012171994	WO	A1	2012-12-20	Hoeg-Jensen, et al		

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NON-PATENT LITERATURE DOCUMENTS

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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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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number		14987791
Filing Date		2016-01-05
First Named Inventor	Bengt Krister Bokvist	
Art Unit		
Examiner Name		
Attorney Docket Number	X20448	

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

EXAMINER SIGNATURE

Examiner Signature	/CHRISTINA BRADLEY/	Date Considered	07/17/2016
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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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Application Number	14987791
Filing Date	2016-01-05
First Named Inventor	Bengt Krister Bokvist
Art Unit	
Examiner Name	
Attorney Docket Number	X20448

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Signature	/Alejandro Martinez/	Date (YYYY-MM-DD)	2016-04-28
Name/Print	Alejandro Martinez	Registration Number	58,163

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BIB DATA SHEET

CONFIRMATION NO. 4253

SERIAL NUMBER 14/987,791	FILING or 371(c) DATE 01/05/2016 RULE	CLASS 514	GROUP ART UNIT 1675	ATTORNEY DOCKET NO. X20448	
APPLICANTS Eli Lilly and Company, Indianapolis, IN; INVENTORS Bengt Krister Bokvist, Carmel, IN; Tamer Coskun, Indianapolis, IN; Robert Chadwick Cummins, Carmel, IN; Jorge Alsina-Fernandez, Indianapolis, IN; ** CONTINUING DATA ***** This appln claims benefit of 62/101,488 01/09/2015 ** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 01/22/2016					
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and /CHRISTINA BRADLEY/ Acknowledged Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY IN	SHEETS DRAWINGS 0	TOTAL CLAIMS 18	INDEPENDENT CLAIMS 1
ADDRESS ELI LILLY & COMPANY PATENT DIVISION P.O. BOX 6288 INDIANAPOLIS, IN 46206-6288 UNITED STATES					
TITLE GIP AND GLP-1 CO-AGONIST COMPOUNDS					
FILING FEE RECEIVED 1600	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:		☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit		

Issue Classification 	Application/Control No. 14987791	Applicant(s)/Patent Under Reexamination BOKVIST ET AL.	
	Examiner CHRISTINA BRADLEY	Art Unit 1675	

CPC						
Symbol					Type	Version
A61K		38	/	16	F	2013-01-01
C07K		14	/	001	I	2013-01-01
A61K		45	/	06	I	2013-01-01
C07K		14	/	605	I	2013-01-01
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CPC Combination Sets				
Symbol	Type	Set	Ranking	Version

NONE		Total Claims Allowed:	
		18	
(Assistant Examiner) /CHRISTINA BRADLEY/ Primary Examiner.Art Unit 1675	(Date) 07/17/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	("8541368").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/07/17 09:00
L2	1	("20150299281").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/07/17 09:14
L3	7	((("BOKVIST") near3 ("Bengt"))).INV.	EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:29
L4	14	((("BOKVIST") near3 ("Bengt"))).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/07/17 09:29
L5	4	((("COSKUN") near3 ("Tamer"))).INV.	EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:29
L6	21	((("COSKUN") near3 ("Tamer"))).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/07/17 09:29
L7	12	((("CUMMINS") near3 ("Robert"))).INV.	EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:29
L8	84	((("CUMMINS") near3 ("Robert"))).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/07/17 09:29
L9	9	((("ALSINA-FERNANDEZ") near3 ("Jorge"))).INV.	EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:29
L10	21	((("ALSINA-FERNANDEZ") near3 ("Jorge"))).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/07/17 09:29
L11	1958	a61k38/26.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:31
L14	29821	glp\$	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:32
L15	15506	glucagon like peptide	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:32
L16	11454	glp	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:32
L17	1062	glucose-dependent insulinotropic polypeptide	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:32
L18	145	I1 or I2 or I3 or I4 or I5 or I6 or I7 or I8 or I9 or I10	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:33
L19	7	I18 and I11	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:33
L20	5	I18 and (I14 or I15) and (I16 or I17)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:33
L21	890	co-agonist	US-PGPUB; USPAT; USOCR; EPO; JPO;	ADJ	ON	2016/07/17 09:34

			DERWENT			
L22	184	coagonist	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:34
L23	141	(I21 or I22) and (I14 or I15) and (I16 or I17)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:34
L24	101	(I21 or I22) with (I14 or I15) with (I16 or I17)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:34
L25	94050	acylation	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:36
L26	79623	acylated	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:36
L27	70	I24 and (I25 or I26)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:36
L28	1209247	dual	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:36
L29	571567	fusion	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:36
L30	323	(I21 or I22 or I28 or I29) with (I14 or I15) with (I16 or I17)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:37
L31	123	I30 and (I25 or I26)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2016/07/17 09:37

7/ 17/ 2016 9:43:37 AM
C:\ Users\ cbradley\ Documents\ EAST\ Workspaces\ 14 987791.wsp

Search Notes 	Application/Control No. 14987791	Applicant(s)/Patent Under Reexamination BOKVIST ET AL.
	Examiner CHRISTINA BRADLEY	Art Unit 1675

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
ABSS: SEQ ID NOs 2-11 - see SCORE	4/19/2016; 7/12/2016	CMB
Commercial database structure and text search - see SCORE	7/14/2016	STIC
East - see transcript	7/17/2016	CMB
Palm inventor search	7/17/2016	CMB

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
	ABSS: SEQ ID NOs 2-11 - see SCORE	7/12/2016	CMB

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ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS IN 46206-6288

MAILED

JUL 07 2016

INTERNATIONAL PATENT LEGAL ADM.

In re Application of
ELI LILLY AND COMPANY
Application No.: 14/987,791
Filing or 371(c) Date: 05 January 2016
Attorney Docket No.: X20448
For: GIP AND GLP-1 CO-AGONIST
COMPOUNDS

: DECISION ON REQUEST TO
: PARTICIPATE IN THE PATENT
: PROSECUTION HIGHWAY
: PROGRAM AND PETITION
: TO MAKE SPECIAL UNDER
: 37 CFR 1.102(a)

This is a decision on the request to participate in the Patent Prosecution Highway (PPH) program and the petition under 37 CFR 1.102(a), filed 13 May 2016, to make the above-identified application special.

The request and petition are **GRANTED**.

DISCUSSION

A grantable request to participate in the PPH pilot program and petition to make special require:

1. The U.S. application for which participation in the Global/IP5 PPH pilot program is requested must have the same earliest date, whether this is the priority date or filing date, as that of a corresponding national or regional application filed with another Global/IP5 PPH participating office or a corresponding PCT international application for which one of the Global/IP5 PPH participating offices was the International Searching Authority (ISA) or the International Preliminary Examining Authority (IPEA).
2. Applicant must:
 - a. Ensure all the claims in the U.S. application must sufficiently correspond or be amended to sufficiently correspond to the allowable/patentable claim(s) in the corresponding Office of Earlier Examination (OEE) application and
 - b. Submit a claims correspondence table in English;
3. Examination of the U.S. application has not begun;
4. Applicant must submit:

- a. Documentation of prior office action:
 - i. a copy of the office action(s) just prior to the "Decision to Grant a Patent" from each of the Global/IP5 PPH participating office application(s) containing the allowable/patentable claim(s) or
 - ii. if the allowable/patentable claims(s) are from a "Notification of Reasons for Refusal" then the Notification of Reasons for Refusal or
 - iii. if the Global/IP5 PPH participating office application is a first action allowance then no office action from the Global/IP5 PPH participating office is necessary should be indicated on the request/petition form or
 - iv. the latest work product in the international phase of the OEE PCT application;
 - b. An English language translation of the Global/IP5 PPH participating office action or work product from (4)(a)(i)-(ii) or (iv) above;
5. Applicant must submit:
- a. An IDS listing the documents cited by the Global/IP5 PPH participating office examiner in the Global/IP5 PPH participating office action or work product (unless already submitted in this application)
 - b. Copies of the documents except U.S. patents or U.S. patent application publications (unless already submitted in this application);

The request to participate in the PPH pilot program and petition comply with the above requirements. Accordingly, the above-identified application has been accorded "special" status.

Telephone inquiries concerning this decision should be directed to Deborah Porter at (571) 272-9323.

Additional information concerning the examination or status of the application is accessible in the PAIR system at <http://www.uspto.gov/ebc/index.html>.

This application will be forwarded to the examiner for action on the merits commensurate with this decision once this application's formality reviews have been completed.

/RichardMRoss/

Richard M. Ross
Attorney Advisor
International Patent Legal Administration

REQUEST FOR PARTICIPATION IN THE GLOBAL/IP5 PATENT PROSECUTION HIGHWAY (PPH) PILOT PROGRAM IN THE USPTO

Application No.:	14987791	First Named Inventor:	Bengt Kister Bokvist
Filing Date:	05-Jan-16	Attorney Docket No.:	X20448
Title of the Invention:	GIP AND GLP-1 CO-AGONIST COMPOUNDS		
THIS REQUEST FOR PARTICIPATION IN THE PPH PILOT PROGRAM ALONG WITH THE REQUIRED DOCUMENTS MUST BE SUBMITTED VIA EFS-WEB. INFORMATION REGARDING EFS-WEB IS AVAILABLE AT HTTP://WWW.USPTO.GOV/PATENTS-APPLICATION-PROCESS/FILING-ONLINE/ABOUT-EFS-WEB.			
APPLICANT HEREBY REQUESTS PARTICIPATION IN THE PATENT PROSECUTION HIGHWAY (PPH) PILOT PROGRAM AND PETITIONS TO MAKE THE ABOVE-IDENTIFIED APPLICATION SPECIAL UNDER THE PPH PILOT PROGRAM.			
Office of earlier examination (OEE): European Patent Office OEE application number: <u>PCT/US2016/012124</u> Both the OEE application and the above-identified U.S. application have the following earliest date (filing or priority date): <u>09-01-2015</u> Type of OEE work product relied upon: Written Opinion of the International Searching Authority (WO/ISA) Mailing date of OEE work product: <u>25-04-2016</u>			
Supporting Documents One or more of the required documents below may be available electronically from the Dossier Access System or PATENTSCOPE (see https://www.jpo.go.jp/pph-portal/filewrapper.htm). If the applicant requests the USPTO to attempt to obtain a document electronically and such attempt is unsuccessful, the applicant will be required to supply the document. Accordingly, to avoid dismissal of the initial PPH request and potential denial of participation in the PPH program, the applicant should verify that the document is actually available via the Dossier Access System or PATENTSCOPE before requesting retrieval. If the applicant is unable to verify availability, then the applicant should submit the document with the PPH request.			
1. OEE Work Product and Translation A copy of the OEE work product and translation if not already in English: ☒ Attached ☐ Previously submitted ☐ Not required because the decision to grant a patent was the first office action ☐ Applicant requests the USPTO to attempt to obtain the document(s) from the Dossier Access System or PATENTSCOPE			
2. References Cited in OEE Work Product A listing of references cited in the OEE work product and document copies (except U.S. patents and U.S. published patent applications): ☒ Attached ☐ Previously Submitted ☐ Not required because no references were cited in the OEE work product ☐ Applicant requests the USPTO to attempt to obtain the document(s) from the Dossier Access System or PATENTSCOPE			

[Page 1 of 2]

This collection of information is required by 35 U.S.C. 119, 37 CFR 1.55, and 37 CFR 1.102(d). 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 1.11 and 1.14. This collection is estimated to take 2 hours 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.

REQUEST FOR PARTICIPATION IN THE GLOBAL/IP5 PPH PILOT PROGRAM IN THE USPTO

(continued)

Application No.: 14987791

First Named Inventor: Bengt Kister Bokvist

3. Claims Correspondence Certification Statement

All of the claims in this application sufficiently correspond to the patentable/allowable claims in the OEE application.

4. Claims Correspondence Table

Claims in US Application	Patentable Claims in OEE Application	Explanation regarding the correspondence
1	1	same subject matter
2	2	same subject matter
3	3	same subject matter
4	4	subset of subject matter
5	5	same subject matter
6	6	same subject matter
7	7	subset of subject matter
8	8	subset of subject matter
9	9	subset of subject matter
10	10	same subject matter
11	11	same subject matter
12	14	subset of subject matter
13	15	subset of subject matter
14	16	subset of subject matter
15	12	same subject matter
16	14	subset of subject matter
17	15	subset of subject matter
18	16	subset of subject matter

Signature /Alejandro Martinez/

Date 5-13-2016

Name (Print/Typed) Alejandro Martinez

Registration Number 58,163

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 disclosure of these records is required by the Freedom of Information Act.
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 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.

PATENT COOPERATION TREATY

RECEIVED

APR 27 2016

ELI LILLY AND COMPANY
PATENT DIVISION

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

Martinez, Alejandro
Eli Lilly and Company
P.O. Box 6288
Indianapolis, IN 46206-6288
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year)		25 April 2016 (25-04-2016)
Applicant's or agent's file reference X20448	FOR FURTHER ACTION	See paragraphs 1 and 4 below
International application No. PCT/US2016/012124	International filing date (day/month/year)	5 January 2016 (05-01-2016)
Applicant ELI LILLY AND COMPANY		

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

How? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to any protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices. In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within 19 months from the priority date, the applicant may request that a supplementary international search be carried out by a different International Searching Authority that offers this service (Rule 45bis.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority	Authorized officer
 European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	TOUSSAINT, Marie-Paule Tel: +49 (0)89 2399-4514

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference X20448	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2016/012124	International filing date (day/month/year) 5 January 2016 (05-01-2016)	(Earliest) Priority Date (day/month/year) 9 January 2015 (09-01-2015)
Applicant ELI LILLY AND COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☒ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/012124

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/012124

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K14/575 C07K14/605 A61K38/26
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, Sequence Search, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/164483 A1 (ZEALAND PHARMA AS [DK]) 7 November 2013 (2013-11-07) abstract paragraphs [0005] - [0020], [0078] sequences 4, 30	1-19
A	WO 2012/088379 A2 (MARCADIA BIOTECH INC [US]; VIGNATI LOUIS [US]; DIMARCHI RICHARD D [US]) 28 June 2012 (2012-06-28) abstract paragraphs [0008] - [0013] sequence 115	1-19
	----- -/--	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 April 2016

Date of mailing of the international search report

25/04/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Chavanne, Franz

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/012124

(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GREEN B D ET AL: "STRUCTURALLY MODIFIED ANALOGUES OF GLUCAGON-LIKE PEPTIDE-1 (GLP-1) AND GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE (GIP) AS FUTURE ANTIDIABETIC AGENTS", CURRENT PHARMACEUTICAL DESIGN, BENTHAM SCIENCE PUBLISHERS, NL, vol. 10, no. 29, 1 January 2004 (2004-01-01), pages 3651-3662, XP009068381, ISSN: 1381-6128, DOI: 10.2174/1381612043382774 the whole document -----	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2016/012124

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013164483 A1	07-11-2013	AR 090937 A1	17-12-2014
		AU 2013255751 A1	18-12-2014
		CA 2872314 A1	07-11-2013
		CN 104470948 A	25-03-2015
		EA 201491918 A1	30-07-2015
		EP 2844669 A1	11-03-2015
		HK 1208232 A1	26-02-2016
		JP 2015517459 A	22-06-2015
		KR 20150003910 A	09-01-2015
		PH 12014502452 A1	02-02-2015
		SG 11201407137P A	27-11-2014
		TW 201348252 A	01-12-2013
		US 2015299281 A1	22-10-2015
		WO 2013164483 A1	07-11-2013

WO 2012088379 A2	28-06-2012	AR 084558 A1	22-05-2013
		AU 2011348202 A1	04-07-2013
		CA 2822617 A1	28-06-2012
		CN 103402536 A	20-11-2013
		EP 2654774 A2	30-10-2013
		JP 2014501762 A	23-01-2014
		KR 20140020851 A	19-02-2014
		NZ 611878 A	27-02-2015
		RU 2013133803 A	27-01-2015
		SG 191252 A1	31-07-2013
		US 2014018291 A1	16-01-2014
		WO 2012088379 A2	28-06-2012

Information on Search Strategy - Pilot phase (see OJ 2015, A86)

The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number

PCT/US2016/012124

TITLE: GIP AND GLP-1 CO-AGONIST COMPOUNDS

APPLICANT: ELI LILLY AND COMPANY

IPC CLASSIFICATION: C07K14/575, C07K14/605, A61K38/26

EXAMINER: Chavanne, Franz

CONSULTED DATABASES: BIOSIS, DOSYS, EMBASE, EPODOC, MEDLINE, NPL, WPI

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: C07K14/575, A61K38/26, C07K14/605

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:

GIP/GLP-1 co-agonist. Shown in vitro binding and functional potency to both human GLP-1 and GIP receptors. Dose dependent increase of insulin secretion, for example after glucose injection. Low risk of clinical immunogenicity

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2016/012124

International filing date (day/month/year)
05.01.2016

Priority date (day/month/year)
09.01.2015

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/575 C07K14/605 A61K38/26

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Chavanne, Franz

Telephone No. +49 89 2399-0



WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2016/012124

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2016/012124

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-19</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-19</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-19</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1 The claimed compound has been neither described nor suggested in the prior art. The subject-matter of claims 1-19 seems, thus, novel and inventive (Article 33(2)(3) PCT).

Re Item VIII

Certain observations on the international application

- 1 For the assessment of the present claims 15 and 16 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment.
- 2 Claim 16 refers to a method. Claim 16 has been formulated as a dependent claim of claim 13. However, claim 13 is a product claim. It seems that claim 16 shall be formulated as a dependent claim of claim 15 (Article 6 PCT).
- 3 Claim 19 refers to the claimed compound of claims 1-13. Claim 19 further mentions that this compound is in simultaneous, separate or sequential combination with one or more agents. However, this does not correspond to technical features defining the compound itself but rather to indications concerning the therapeutic used thereof. It seems that claim 19 shall be formulated as dependent claim from independent claims 17 and 18 (Article 6 PCT).

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WE CLAIM:

1. A compound of the Formula:
 $\text{YX}_1\text{EGTFTSDYSIX}_2\text{LDKIAQKAX}_3\text{VQWLIAGGPSSGAPPPS};$
 wherein
 X_1 is Aib;
 X_2 is Aib;
 K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γ Glu)_a-CO-(CH₂)_b-CO₂H wherein a is 1 to 2 and b is 10 to 20;
 X_3 is Phe or 1-Nal;
 and the C-terminal amino acid is optionally amidated as a C-terminal primary amide (SEQ ID NO: 11),
 or a pharmaceutically acceptable salt thereof.
2. The compound of Claim 1, wherein X_3 is Phe.
3. The compound of Claim 1, wherein X_3 is 1-Nal.
4. The compound of any one of Claims 1-3, wherein b is 14 to 18.
5. The compound of Claim 4, wherein b is 16 to 18.
6. The compound of Claim 5, wherein b is 18.
7. The compound of any one of Claims 1-6, wherein a is 1.
8. The compound of any one of Claims 1-6, wherein a is 2.
9. The compound of any one of Claims 1-8, wherein the C-terminal amino acid is amidated as a C-terminal primary amide.
10. The compound of Claim 1, wherein
 X_1 is Aib
 X_2 is Aib;
 K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γ Glu)₁-CO-(CH₂)₁₈-CO₂H;
 X_3 is Phe;

and the C-terminal amino acid is amidated as a C-terminal primary amide
(SEQ ID NO: 3),

or a pharmaceutically acceptable salt thereof.

11. The compound of Claim 1, wherein

X₁ is Aib

X₂ is Aib;

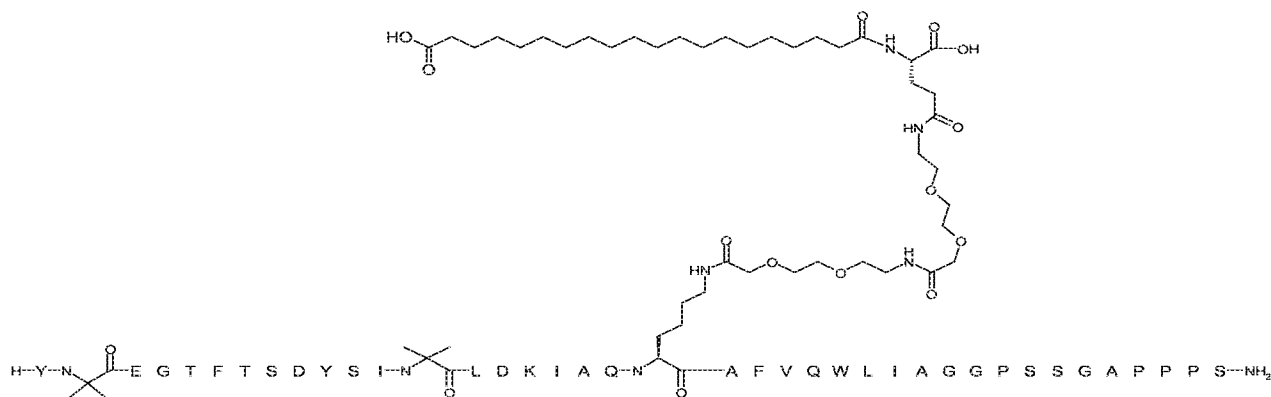
K at position 20 is chemically modified through conjugation to the
epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-
ethoxy]-acetyl)₂-(γGlu)₂-CO-(CH₂)₁₈-CO₂H;

X₃ is 1-Nal;

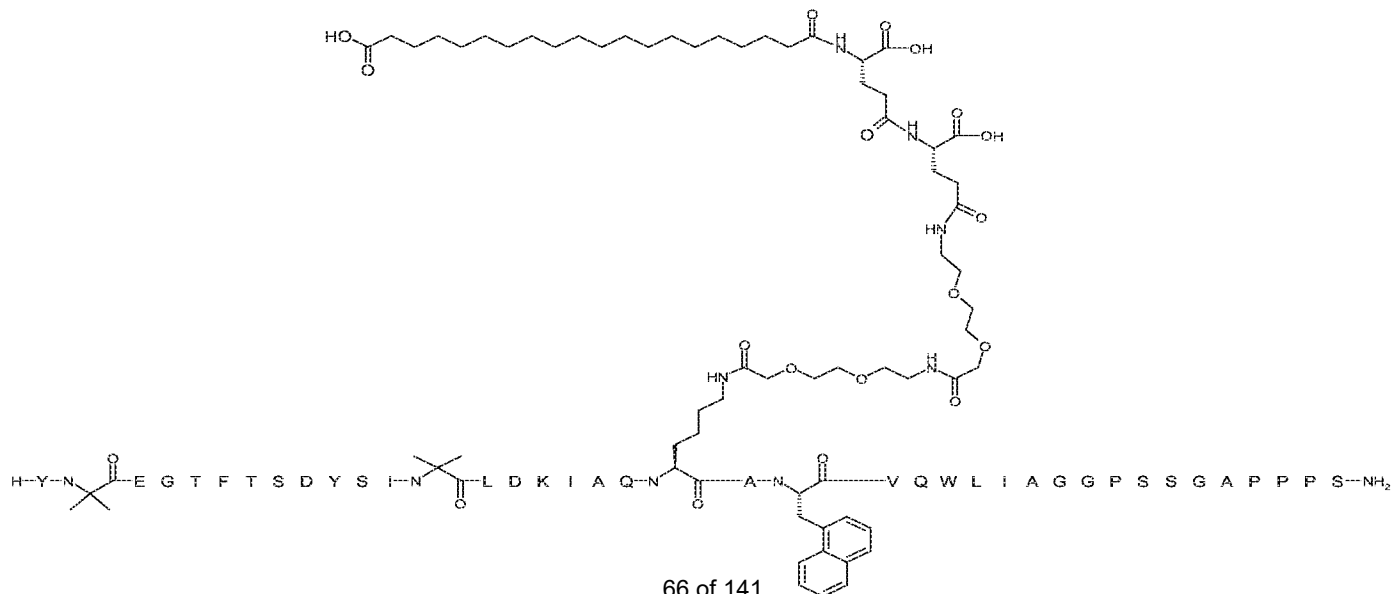
and the C-terminal amino acid is amidated as a C-terminal primary amide
(SEQ ID NO: 4),

or a pharmaceutically acceptable salt thereof.

12. The compound of Claim 1, wherein the Formula is:



13. The compound of Claim 1, wherein the Formula is:



14. A pharmaceutical composition comprising the compound of any one of Claims 1-13 with a pharmaceutically acceptable carrier, diluent, or excipient.
15. A method of treating type 2 diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of the compound of any one of Claims 1-13.
16. The method of Claim 13, further comprising administering simultaneously, separately, or sequentially in combination with an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.
17. The compound of any one of Claims 1-13, for use in therapy.
18. The compound of any one of Claims 1-13, for use in the treatment of type 2 diabetes mellitus.
19. The compound of any one of Claims 1-13 in simultaneous, separate, or sequential combination with one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		14987791
	Filing Date		2016-01-05
	First Named Inventor	Bengt Kister Bokvist	
	Art Unit		
	Examiner Name	Chavanne, Franz	
	Attorney Docket Number	X20448	

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	Filing Date		2016-01-05
	First Named Inventor	Bengt Kister Bokvist	
	Art Unit		
	Examiner Name	Chavanne, Franz	
	Attorney Docket Number	X20448	

1	GREEN B D ET AL: "STRUCTURALLY MODIFIED ANALOGUES OF GLUCAGON-LIKE PEPTIDE-1 (GLP-1) AND GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE (GIP) AS FUTURE ANTIDIABETIC AGENTS", CURRENT PHARMACEUTICAL DESIGN, BENTHAM SCIENCE PUBLISHERS, NL, vol. 10, no. 29, 1 January 2004 (2004-01-01), pages 3651-3662, XP009068381, ISSN: 1381-6128, DOI:10.2174/1381612043382774
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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	14987791
Filing Date	2016-01-05
First Named Inventor	Bengt Kister Bokvist
Art Unit	
Examiner Name	Chavanne, Franz
Attorney Docket Number	X20448

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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	/Alejandro Martinez/	Date (YYYY-MM-DD)	2016-05-13
Name/Print	Alejandro Martinez	Registration Number	58,163

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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.
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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		14987791
	Filing Date		2016-01-05
	First Named Inventor	Bengt Krister Bokvist	
	Art Unit		
	Examiner Name		
	Attorney Docket Number		X20448

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	1	8541368	B2	2013-09-24	Lau, et al	

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	1	2013164483	WO	A1	2013-07-11	Just, et al		
	2	2012167744	WO	A1	2012-12-13	Ma, et al		
	3	2013192129	WO	A1	2013-12-27	Dimarchi, Richard D.		

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First Named Inventor	Bengt Krister Bokvist	
Art Unit		
Examiner Name		
Attorney Docket Number	X20448	

4	2012088379	WO	A2	2012-06-28	Vignati, et al		
5	2010029159	WO	A1	2010-03-18	Christensen, et al		
6	2010071807	WO	A1	2010-06-24	Dimarchi,et al		
7	2012088116	WO	A1	2012-06-28	Dimarchi,et al		
8	2012138941	WO	A1	2012-10-11	Shandler, et al		
9	2011094337	WO	A1	2011-08-04	Dimarchi,et al		
10	2014096148	WO	A1	2014-06-24	Haack, et al		
11	2014060512	WO	A1	2014-04-24	Reslow, et al		
12	2012171994	WO	A1	2012-12-20	Hoeg-Jensen, et al		

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	Filing Date		2016-01-05
	First Named Inventor	Bengt Krister Bokvist	
	Art Unit		
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Signature	/Alejandro Martinez/	Date (YYYY-MM-DD)	2016-04-28
Name/Print	Alejandro Martinez	Registration Number	58,163

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Document Date: 01/05/2016

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UTILITY PATENT APPLICATION TRANSMITTAL <i>(Only for new nonprovisional applications under 37 CFR 1.53(b))</i>		Attorney Docket No. X20448	
		First Named Inventor Bengt Krister BOKVIST	
		Title GIP AND GLP-1 CO-AGONIST COMPOUNDS	
		Express Mail Label No.	

APPLICATION ELEMENTS <i>See MPEP chapter 600 concerning utility patent application contents.</i>	Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
1. ☐ Fee Transmittal Form (PTO/SB/17 or equivalent) 2. ☐ Applicant asserts small entity status. See 37 CFR 1.27 3. ☐ Applicant certifies micro entity status. See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent. 4. ☒ Specification [Total Pages <u>45</u>] Both the claims and abstract must start on a new page. (See MPEP § 608.01(a) for information on the preferred arrangement) 5. ☐ Drawing(s) (35 U.S.C. 113) [Total Sheets _____] 6. Inventor's Oath or Declaration [Total Pages <u>4</u>] (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e)) a. ☒ Newly executed (original or copy) b. ☐ A copy from a prior application (37 CFR 1.63(d)) 7. ☒ Application Data Sheet * See note below. See 37 CFR 1.76 (PTO/AIA/14 or equivalent) 8. CD-ROM or CD-R in duplicate, large table, or Computer Program (Appendix) ☐ Landscape Table on CD 9. Nucleotide and/or Amino Acid Sequence Submission (if applicable, items a. – c. are required) a. ☒ Computer Readable Form (CRF) b. ☐ Specification Sequence Listing on: i. ☐ CD-ROM or CD-R (2 copies); or ii. ☐ Paper c. ☐ Statements verifying identity of above copies	ACCOMPANYING APPLICATION PAPERS 10. ☐ Assignment Papers (cover sheet & document(s)) Name of Assignee _____ 11. ☐ 37 CFR 3.73(c) Statement ☐ Power of Attorney (when there is an assignee) 12. ☐ English Translation Document (if applicable) 13. ☐ Information Disclosure Statement (PTO/SB/08 or PTO-1449) ☐ Copies of citations attached 14. ☐ Preliminary Amendment 15. ☐ Return Receipt Postcard (MPEP § 503) (Should be specifically itemized) 16. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed) 17. ☐ Nonpublication Request Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent. 18. ☐ Other: _____ _____ _____ _____

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
 (2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

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Signature	/Alejandro Martinez/	Date	January 5, 2016
Name (Print/Type)	Alejandro Martinez	Registration No. (Attorney/Agent)	58163

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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.
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).
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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 inspection or an issued patent.
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	X20448
		Application Number	
Title of Invention	GIP AND GLP-1 CO-AGONIST COMPOUNDS		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
--------------------------	---

Inventor Information:

Inventor	1				Remove	
Legal Name						
Prefix	Given Name	Middle Name	Family Name	Suffix		
	Bengt	Krister	Bokvist			
Residence Information (Select One) • US Residency Non US Residency Active US Military Service						
City	Carmel	State/Province	IN	Country of Residence	US	
Mailing Address of Inventor:						
Address 1	c/o Eli Lilly and Company					
Address 2	P.O. Box 6288					
City	Indianapolis	State/Province	IN			
Postal Code	46206-6288	Country	US			
Inventor	2				Remove	
Legal Name						
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	Tamer		Coskun			
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City	Indianapolis	State/Province	IN	Country of Residence	US	
Mailing Address of Inventor:						
Address 1	c/o Eli Lilly and Company					
Address 2	P.O. Box 6288					
City	Indianapolis	State/Province	IN			
Postal Code	46206-6288	Country	US			
Inventor	3				Remove	
Legal Name						
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	Robert	Chadwick	Cummins			
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	X20448
		Application Number	
Title of Invention	GIP AND GLP-1 CO-AGONIST COMPOUNDS		

City	Carmel	State/Province	IN	Country of Residence	US
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Mailing Address of Inventor:

Address 1	c/o Eli Lilly and Company				
Address 2	P.O. Box 6288				
City	Indianapolis	State/Province	IN		
Postal Code	46206-6288	Country	US		
Inventor	4				Remove
Legal Name					

Prefix	Given Name	Middle Name	Family Name	Suffix	
	Jorge		Alsina-Fernandez		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Indianapolis	State/Province	IN	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Eli Lilly and Company				
Address 2	P.O. Box 6288				
City	Indianapolis	State/Province	IN		
Postal Code	46206-6288	Country	US		
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. Add					

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Customer Number	25885		
Email Address	patents@lilly.com	Add Email	Remove Email

Application Information:

Title of the Invention	GIP AND GLP-1 CO-AGONIST COMPOUNDS		
Attorney Docket Number	X20448	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

Filing By Reference :

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	X20448
		Application Number	
Title of Invention	GIP AND GLP-1 CO-AGONIST COMPOUNDS		

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For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

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☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

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When referring to the current application, please leave the application number blank.

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Claims benefit of provisional	62/101488	2015-01-09

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	X20448
		Application Number	
Title of Invention	GIP AND GLP-1 CO-AGONIST COMPOUNDS		

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

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Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ⁱ (if applicable)
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Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013. NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	X20448
		Application Number	
Title of Invention	GIP AND GLP-1 CO-AGONIST COMPOUNDS		

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

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Applicant Information:

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Applicant	1		Remove
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.			
Clear			
☒ Assignee	Legal Representative under 35 U.S.C. 117		Joint Inventor
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest	
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:			
Name of the Deceased or Legally Incapacitated Inventor :			
If the Applicant is an Organization check here. ☒			
Organization Name	Eli Lilly and Company		
Mailing Address Information For Applicant:			
Address 1	P.O. Box 6288		
Address 2			
City	Indianapolis	State/Province	IN
Country	US	Postal Code	46206-6288
Phone Number	317-277-4260	Fax Number	317-276-3861

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	X20448
		Application Number	
Title of Invention	GIP AND GLP-1 CO-AGONIST COMPOUNDS		
Email Address	patents@lilly.com		
Additional Applicant Data may be generated within this form by selecting the Add button.			Add

Assignee Information including Non-Applicant Assignee Information:

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Assignee	1			
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Signature	/Alejandro Martinez/		Date (YYYY-MM-DD)	2016-01-05
First Name	Alejandro	Last Name	Martinez	Registration Number
				58163
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	X20448
		Application Number	
Title of Invention	GIP AND GLP-1 CO-AGONIST COMPOUNDS		

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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.

GIP AND GLP-1 CO-AGONIST COMPOUNDS

The present invention relates to the field of medicine. More particularly, the present invention relates to dual incretin peptide mimetic compounds that agonize
5 receptors for both human glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), and may be useful for treating type 2 diabetes mellitus (T2D).

T2D is the most common form of diabetes accounting for approximately 90% of all diabetes. T2D is characterized by high blood glucose levels caused by insulin-
10 resistance. The current standard of care for T2D includes diet and exercise along with available oral and injectable glucose lowering drugs. Nonetheless, many patients with T2D still remain inadequately controlled. Currently marketed incretin mimetics or dipeptidyl peptidase IV (DPP-IV) inhibitors only utilize a single established mechanism of action for glycemic control. A compound for T2D is needed that utilizes a dual
15 mechanism of action.

GIP is a 42-amino acid gastrointestinal regulatory peptide that plays a physiological role in glucose homeostasis by stimulating insulin secretion from pancreatic beta cells in the presence of glucose and protecting pancreatic beta cells. GLP-1 is a 37-amino acid peptide that stimulates insulin secretion, protects pancreatic beta cells, and
20 inhibits glucagon secretion, gastric emptying and food intake which leads to weight loss. GIP and GLP-1 are known as incretins; incretin receptor signaling exerts physiologically relevant action critical for glucose homeostasis. In normal physiology, GIP and GLP-1 are secreted from the gut following a meal, and these incretins enhance the physiological response to food including sensation of satiety, insulin secretion, and nutrient disposal.
25 T2D patients have impaired incretin responses.

Dosing of GLP-1 analogues has been found to be limited by adverse effects, such as nausea and vomiting, and as a consequence dosing most often cannot reach full efficacy for glycemic control and weight loss. GIP alone has very modest glucose-lowering ability in type 2 diabetic humans. Both native GIP and GLP-1 are inactivated

rapidly by the ubiquitous protease, DPP IV, and therefore, can only be used for short-term metabolic control.

Glucagon is a 29-amino acid peptide produced by the pancreas, and when bound to glucagon receptor, signals the liver to release glucose leading to an increase in blood glucose. GLP-2, a peptide that like GLP-1 is produced from processing of proglucagon, is known to be associated with cellular proliferation in the gut. Thus, stimulation of glucagon and GLP-2 receptors should be minimized during chronic treatment of T2D patients in order to maximize glucose lowering and reduce potential long term carcinogenic risks.

10 Certain GIP analogs have been described as exhibiting both GIP and GLP-1 activity in WO 2013/164483, WO 2014/192284, and WO 2011/119657.

DPP IV is in the exopeptidase class of proteolytic enzymes. The introduction of non-natural amino acids in a sequence can increase the proteolytic stability of any given peptide. While use of non-natural amino acids can help with the stability of peptides against DPP IV proteolysis and other forms of degradation, it was discovered by Applicants as part of the present invention that non-natural amino acids can have unexpected effects on the balance of agonist activity between GIP and GLP-1. Non-natural amino acids also increase the likelihood that a peptide may be seen as foreign and set off undesirable immune reactions, such as human immunogenicity and injection site reactions.

20 Fatty acids, through their albumin binding motifs, can improve the pharmacokinetics of a peptide by extending the half-life, for example. While use of fatty acids can improve peptide half-life, it was discovered by Applicants as part of the present invention that the length, composition, and placement of the fatty acid chain and the linker between the peptide and the fatty acid chain can have unexpected effects on the balancing of the GIP and GLP-1 agonist activity.

25 Tolerability of certain GLP-1 analogues has been found to prevent a dose of the GLP-1 analogue that reaches better efficacy for glycemic control and weight loss. The most common side effects assigned to GLP-1 analogues are nausea and vomiting but some compounds may also impact heart rate. The HPA axis is part of a physiological

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stress response and GLP-1 has been found to stimulate the HPA axis in rats resulting in increased corticosterone levels providing a potential link to adverse events such as increased heart rate. As part of the present invention, Applicants unexpectedly found that a compound of the present invention did not lead to elevated corticosterone levels like
5 seen with semaglutide in a rat model and so possibly can be dosed to higher efficacy levels than GLP-1R-selective agents.

There remains a need to provide a compound that is a balanced co-agonist of GIP and GLP-1 receptors, but is selective against related glucagon and GLP-2 receptors. Also, there remains a need to provide a compound with balanced co-agonist activity of
10 GIP and GLP-1 receptors which may provide weight loss given activity found in animal models. Additionally, there remains a need to provide a compound with balanced co-agonist activity of GIP and GLP-1 receptors that delivers adequate stability against DPP IV and other forms of degradation, but while still maintaining a low immunogenicity potential. Also, there remains a need to provide a compound with balanced co-agonist
15 activity of GIP and GLP-1 receptors that supports potential once-weekly dosing in humans.

Accordingly, certain compounds of the present invention have lower potential for immunogenicity and injection site reactions than certain GIP-GLP-1 co-agonist compounds in the art. Certain compounds of the present invention have potential for
20 producing weight loss in patients based on animal energy expenditure data. Furthermore, certain compounds of the present invention have a balanced co-agonist activity against GIP and GLP-1 receptors and selectivity against both glucagon and GLP-2 receptors, low immunogenicity potential, and pharmacokinetic (PK) characteristics that support once-weekly dosing in humans.

25 Accordingly, an embodiment of the present invention provides a compound of Formula I:

YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPPS;

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-
30 ethoxy]-acetyl)₂-(γGlu)_a-CO-(CH₂)_b-CO₂H wherein a is 1 to 2 and b is 10 to 20; X₃ is Phe

or 1-Nal; and the C-terminal amino acid is optionally amidated as a C-terminal primary amide (SEQ ID NO: 11), or a pharmaceutically acceptable salt thereof.

In a further embodiment, the present invention provides a compound of Formula I, wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γ Glu)_a-CO-(CH₂)_b-CO₂H wherein a is 1 to 2 and b is 10 to 18; X_3 is Phe; and the C-terminal amino acid is optionally amidated as a C-terminal primary amide, or a pharmaceutically acceptable salt thereof.

In a further embodiment, the present invention provides a compound of Formula I, wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γ Glu)_a-CO-(CH₂)_b-CO₂H wherein a is 1 to 2 and b is 10 to 18; X_3 is 1-Nal; and the C-terminal amino acid is optionally amidated as a C-terminal primary amide, or a pharmaceutically acceptable salt thereof.

In a further embodiment, the present invention provides a compound of Formula I, wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γ Glu)_a-CO-(CH₂)_b-CO₂H wherein a is 1 to 2 and b is 14 to 18; X_3 is Phe or 1-Nal; and the C-terminal amino acid is optionally amidated as a C-terminal primary amide, or a pharmaceutically acceptable salt thereof. In a further embodiment, the present invention provides a compound wherein b is 16 to 18. Additionally, the present invention provides a compound wherein b is 18.

In a further embodiment, the present invention provides a compound of Formula I, wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γ Glu)_a-CO-(CH₂)_b-CO₂H wherein a is 1 and b is 10 to 18; X_3 is Phe or 1-Nal; and the C-terminal amino acid is optionally amidated as a C-terminal primary amide, or a pharmaceutically acceptable salt thereof.

In a further embodiment, the present invention provides a compound of Formula I, wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation

to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)_a-CO-(CH₂)_b-CO₂H wherein a is 2 and b is 10 to 18; X₃ is Phe or 1-Nal; and the C-terminal amino acid is optionally amidated as a C-terminal primary amide, or a pharmaceutically acceptable salt thereof.

5 In a further embodiment, the present invention provides a compound of Formula I, wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)_a-CO-(CH₂)_b-CO₂H wherein a is 1 to 2 and b is 10 to 18; X₃ is Phe or 1-Nal; and the C-terminal amino acid is amidated as a C-terminal primary amide, or a
10 pharmaceutically acceptable salt thereof.

In an embodiment, the present invention provides a compound of the Formula:

YX₁EGTFTSDYSIX₂LDKIAQKAFVQWLIAGGPSSGAPPPS;

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₈-CO₂H; and the C-terminal amino acid is amidated
15 as a C-terminal primary amide (SEQ ID NO: 3), or a pharmaceutically acceptable salt thereof.

In an embodiment, the present invention provides a compound of the Formula:

YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPPS;

20 wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₂-CO-(CH₂)₁₈-CO₂H; X₃ is 1-Nal; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 4), or a pharmaceutically acceptable salt thereof.

25 In an embodiment, the present invention provides a compound of the Formula:

YX₁EGTFTSDYSIX₂LDKIAQKAFVQWLIAGGPSSGAPPPS;

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₆-CO₂H; and the C-terminal amino acid is amidated

as a C-terminal primary amide (SEQ ID NO: 5), or a pharmaceutically acceptable salt thereof.

In an embodiment, the present invention provides a compound of the Formula:

$\text{YX}_1\text{EGTFTSDYSIX}_2\text{LDKIAQKAFVQWLIAGGPSSGAPPPS}$;

5 wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl) $_2$ -(γ Glu) $_2$ -CO-(CH $_2$) $_{16}$ -CO $_2$ H; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 6), or a pharmaceutically acceptable salt thereof.

10 In an embodiment, the present invention provides a compound of the Formula:

$\text{YX}_1\text{EGTFTSDYSIX}_2\text{LDKIAQKAFVQWLIAGGPSSGAPPPS}$

wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl) $_2$ -(γ Glu) $_2$ -CO-(CH $_2$) $_{18}$ -CO $_2$ H; and the C-terminal amino acid is amidated
15 as a C-terminal primary amide (SEQ ID NO: 7), or a pharmaceutically acceptable salt thereof.

In an embodiment, the present invention provides a compound of the Formula:

$\text{YX}_1\text{EGTFTSDYSIX}_2\text{LDKIAQKAX}_3\text{VQWLIAGGPSSGAPPPS}$

wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through
20 conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl) $_2$ -(γ Glu) $_1$ -CO-(CH $_2$) $_{16}$ -CO $_2$ H; X_3 is 1-Nal; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 8), or a pharmaceutically acceptable salt thereof.

In an embodiment, the present invention provides a compound of the Formula:

25 $\text{YX}_1\text{EGTFTSDYSIX}_2\text{LDKIAQKAX}_3\text{VQWLIAGGPSSGAPPPS}$

wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl) $_2$ -(γ Glu) $_2$ -CO-(CH $_2$) $_{16}$ -CO $_2$ H; X_3 is 1-Nal; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 9), or a pharmaceutically
30 acceptable salt thereof.

In an embodiment, the present invention provides a compound of the Formula:

YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPPS

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₈-CO₂H; X₃ is 1-Nal; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 10), or a pharmaceutically acceptable salt thereof.

In an embodiment, the present invention provides a composition comprising a compound of the present invention with a pharmaceutically acceptable carrier, diluent, or excipient.

In an embodiment, the present invention provides a method of treating type 2 diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of a compound of the present invention. In a further embodiment, the present invention provides a method of treating type 2 diabetes mellitus further comprising administering simultaneously, separately, or sequentially in combination with an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.

In an embodiment, the present invention provides a method to improve glycemic control in adults with type 2 diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of a compound of the present invention as an adjunct to diet and exercise. In an embodiment, the present invention provides a method for chronic weight management in adults with an initial body mass index ≥ 27 and type 2 diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of a compound of the present invention as an adjunct to a reduced-calorie diet and increased physical activity.

In an embodiment, the present invention provides a method to treat metabolic syndrome, comprising administering to a patient in need thereof, an effective amount of a compound of the present invention. In a further embodiment, the present invention provides a method to treat dyslipidemia, obesity, and/or hepatic steatosis associated with insulin resistance and diabetes, comprising administering to a patient in need thereof, an

effective amount of a compound of the present invention. Additionally, the present invention provides a method to treat frailty or increase bone strength, comprising administering to a patient in need thereof, an effective amount of a compound of the present invention.

5 In an embodiment, the present invention provides a compound of the present invention for use in therapy. In a further embodiment, the present invention provides a compound of the present invention for use in the treatment of type 2 diabetes mellitus. In a further embodiment, the present invention provides a compound of the present invention in simultaneous, separate, or sequential combination with one or more agents
10 selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters for use in the treatment of type 2 diabetes mellitus.

 In an embodiment, the present invention provides a compound of the present invention for use in glycemic control in adults with type 2 diabetes mellitus as an adjunct
15 to diet and exercise. In an embodiment, the present invention provides a compound of the present invention for use in chronic weight management in adults with an initial body mass index ≥ 27 and type 2 diabetes mellitus as an adjunct to a reduced-calorie diet and increased physical activity.

 In an embodiment, the present invention provides the use of a compound of the
20 present invention for the manufacture of a medicament for the treatment of type 2 diabetes mellitus. In a further embodiment, the present invention provides the use of a compound of the present invention in simultaneous, separate, or sequential combination with one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters for the manufacture
25 of a medicament for the treatment of type 2 diabetes mellitus.

 The present invention provides compounds that display a balanced GIP and GLP-1 activity. Balanced activity against GIP and GLP-1 as used herein refers to a compound that has affinity for GIP receptors and GLP-1 receptors in an *in vitro* binding assay at a molar ratio that is close to 1:1, such as 1:1 GLP-1/GIP, 2:1 GLP-1/GIP, 3:2 GLP-1/GIP,
30 1:2 GLP-1/GIP, or 2:3 GLP-1/GIP.

The present invention provides compounds that display selectivity for GIP and GLP-1 receptors versus receptors for glucagon and GLP-2. The term “selectivity” or “selective against” when used herein to reference GIP and GLP-1 activity in comparison to glucagon activity, refers to a compound that displays 1000-, 500-, or about 100-fold
5 higher potency for GIP and GLP-1 over glucagon when the data is normalized from the respective *in vitro* binding assays. The term “selectivity” or “selective against” when used herein to reference GIP and GLP-1 activity in comparison to GLP-2 activity, refers to a compound that displays 250-, 200-, 100-, or about 50-fold higher potency for GIP and GLP-1 over GLP-2 when the data is normalized from the respective *in vitro*
10 functional assays.

The present invention provides a method for treatment of type 2 diabetes in a patient comprising administering to a patient in need of such treatment an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof. The present invention also provides a method for treatment of type 2 diabetes in
15 a patient comprising administering to a patient in need of such treatment an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, wherein the administration is subcutaneous. The present invention also provides a method of treatment of type 2 diabetes in a patient comprising administering to a patient in need of such treatment an effective amount of a compound of the present invention, or
20 a pharmaceutically acceptable salt thereof, and simultaneously, separately, or sequentially an effective amount of one or more other active ingredients. In one embodiment, the other active ingredient or ingredients is currently available oral glucose lowering drugs from a class of drugs that is considered prior to administration the standard of care as determined by industry guidelines such as the American Diabetes Association.

25 The compounds of the present invention utilize a fatty acid chemically conjugated to the epsilon-amino group of a lysine side-chain. The fatty acid is conjugated to the epsilon-amino group of a lysine side-chain through a linker. The linker comprises [2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)_a wherein a is 1 to 2. The fatty acid and the gamma-glutamic acid in the linker act as albumin binders, and provide the potential to
30 generate long-acting compounds. Compounds of the present invention comprise a lysine

at position 20 that is chemically modified through conjugation to the epsilon-amino group of the K side-chain with $([2-(2\text{-Amino-ethoxy})\text{-ethoxy}]\text{-acetyl})_2\text{-(}\gamma\text{Glu)}_a\text{-CO-(CH}_2)_b\text{-CO}_2\text{H}$ wherein a is 1 to 2 and b is 10 to 20. As shown in the chemical structures of Examples 1 and 2, the first unit of $[2-(2\text{-Amino-ethoxy})\text{-ethoxy}]\text{-acetyl}$ is linked to the
5 epsilon-amino group of the lysine side-chain. The second unit of $[2-(2\text{-Amino-ethoxy})\text{-ethoxy}]\text{-acetyl}$ is then attached to the amino-group of the first unit of $[2-(2\text{-Amino-ethoxy})\text{-ethoxy}]\text{-acetyl}$. Then, the first unit of γGlu is attached to the amino-group of the second unit of $[2-(2\text{-Amino-ethoxy})\text{-ethoxy}]\text{-acetyl}$ through the γ -carboxyl group of the side-chain. When $a = 2$, the second unit of γGlu is attached to the α -amino-group of the
10 first unit of γGlu through the γ -carboxyl group of the side-chain. Finally, the symmetrical fatty acid is attached to the α -amino-group of the first (when $a = 1$) or second (when $a = 2$) unit of γGlu .

The compounds of the invention are preferably formulated as pharmaceutical compositions administered by parenteral routes (*e.g.*, subcutaneous, intravenous,
15 intraperitoneal, intramuscular, or transdermal). Such pharmaceutical compositions and processes for preparing same are well known in the art. (See, *e.g.*, Remington: The Science and Practice of Pharmacy (D.B. Troy, Editor, 21st Edition, Lippincott, Williams & Wilkins, 2006). The preferred route of administration is subcutaneous.

The compounds of the present invention may react with any of a number of
20 inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable salts and common methodology for preparing them are well known in the art. See, *e.g.*, P. Stahl, *et al.* Handbook of Pharmaceutical Salts: Properties, Selection and Use, 2nd Revised Edition (Wiley-VCH, 2011); S.M. Berge, *et al.*,
"Pharmaceutical Salts," Journal of Pharmaceutical Sciences, Vol. 66, No. 1, January
25 1977. Pharmaceutically acceptable salts of the present invention include trifluoroacetate, hydrochloride, and acetate salts.

As used herein, the term "effective amount" refers to the amount or dose of compound of the present invention, or a pharmaceutically acceptable salt thereof which, upon single or multiple dose administration to the patient, provides the desired effect in
30 the patient under diagnosis or treatment. An effective amount can be readily determined

by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount for a patient, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and
5 general health; the specific disease or disorder involved; the degree of or involvement or the severity of the disease or disorder; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

10 As used herein, the term “treating” or “to treat” includes restraining, slowing, stopping, or reversing the progression or severity of an existing symptom or disorder.

As used herein, “semaglutide” refers to a chemically synthesized GLP-1 analogue that has the peptide backbone and overall compound structure of that found in CAS Registry Number 910463-68-2.

15 Certain compounds of the present invention are generally effective over a wide dosage range. For example, dosages for once-weekly dosing may fall within the range of about 0.05 to about 30 mg per person per week. Certain compounds of the present invention may be dosed daily. Additionally, certain compounds of the present invention may be dosed once-weekly.

20 The amino acid sequences of the present invention contain the standard single letter or three letter codes for the twenty naturally occurring amino acids. Additionally, “Aib” is alpha amino isobutyric acid, and “1-Nal” is 1-Naphthylalanine.

The present invention also encompasses novel intermediates and processes useful for the synthesis of compounds of the present invention, or a pharmaceutically acceptable
25 salt thereof. The intermediates and compounds of the present invention may be prepared by a variety of procedures known in the art. In particular, the process using chemical synthesis is illustrated in the Examples below. The specific synthetic steps for each of the routes described may be combined in different ways to prepare compounds of the present invention, or salts thereof. The reagents and starting materials are readily available to one

-12-

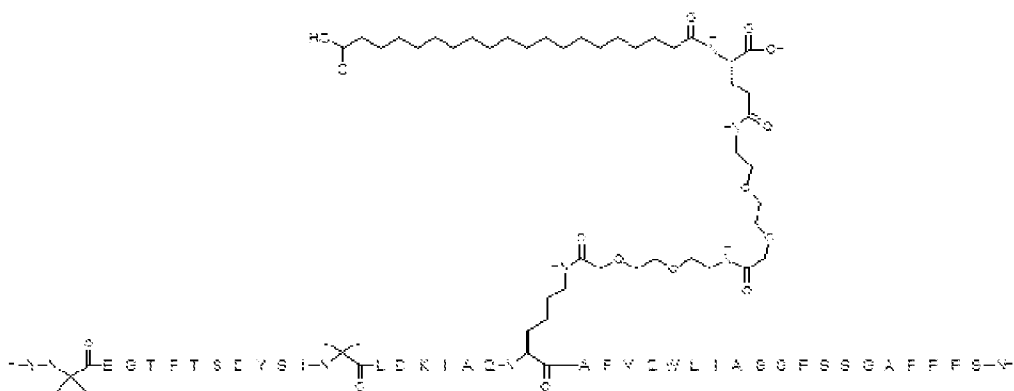
of ordinary skill in the art. It is understood that these Examples are not intended to be limiting to the scope of the invention in any way.

EXAMPLE 1

5 YX₁EGTFTSDYSIX₂LDKIAQKAFVQWLIAGGPSSGAPPPS

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₈-CO₂H; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 3)

10 trifluoroacetate salt



The above structure contains the standard single letter amino acid code with exception of residues Aib2, Aib13 and K20 where the structures of these amino acid residues have been expanded.

The peptide according to SEQ ID NO: 3 of the present invention is generated by solid-phase peptide synthesis using a Fmoc/t-Bu strategy carried out on a Symphony automated peptide synthesizer (PTI Protein Technologies Inc.) starting from RAPP AM-Rink Amide resin and with couplings using 6 equivalents of amino acid activated with diisopropylcarbodiimide (DIC) and hydroxybenzotriazole (HOBt) (1:1:1 molar ratio) in dimethylformamide (DMF) for 90 min at 25°C.

Extended couplings (4h each) for Pro31, Trp25, Gln24, Val23, Phe22, Lys20, Gly4, Glu3 and Aib2 are necessary to improve the quality of the crude peptide. A Fmoc-

Lys(Alloc)-OH building block is used for Lys20 coupling (orthogonal protecting group) to allow for site specific attachment of the fatty acid moiety later on in the synthetic process. The following conditions are used for the coupling of Fmoc-Ile-OH at position 12: Fmoc-Ile-OH (6 equiv), PyBOP (6 equiv), and DIEA (12 equiv) in DMF for 24 h at 25°C. The N-terminal residue is incorporated as Boc-Tyr(tBu)-OH using DIC-HOBt protocols as described above.

After finishing the elongation of the peptide-resin described above, the Alloc protecting group present in Lys20 is removed using catalytic amounts of $\text{Pd}(\text{PPh}_3)_4$ in the presence of PhSiH_3 as a scavenger. Additional coupling/deprotection cycles using a Fmoc/t-Bu strategy to extend the Lys20 side-chain involved Fmoc-NH-PEG₂-CH₂COOH (ChemPep Catalog#280102), Fmoc-Glu(OH)-OtBu (ChemPep Catalog#100703) and HOOC-(CH₂)₁₈-COOtBu. In all couplings, 3 equivalents of the building block are used with PyBOP (3 equiv) and DIEA (6 equiv) in DMF for 4h at 25°C.

Concomitant cleavage from the resin and side chain protecting group removal are carried out in a solution containing trifluoroacetic acid (TFA): triisopropylsilane : 1,2-ethanedithiol: water : thioanisole 90:4:2:2:2 (v/v) for 2 h at 25°C followed by precipitation with cold ether. Crude peptide is purified to > 99% purity (15-20% purified yield) by reversed-phase HPLC chromatography with water / acetonitrile (containing 0.05% v/v TFA) gradient on a C18 column, where suitable fractions are pooled and lyophilized.

In a synthesis performed essentially as described above, the purity of Example 1 was examined by analytical reversed-phase HPLC, and identity was confirmed using LC/MS (observed: $\text{M}+3\text{H}^+/3 = 1605.2$; Calculated $\text{M}+3\text{H}^+/3 = 1605.5$; observed: $\text{M}+4\text{H}^+/4 = 1204.3$; Calculated $\text{M}+4\text{H}^+/4 = 1204.4$).

EXAMPLE 2

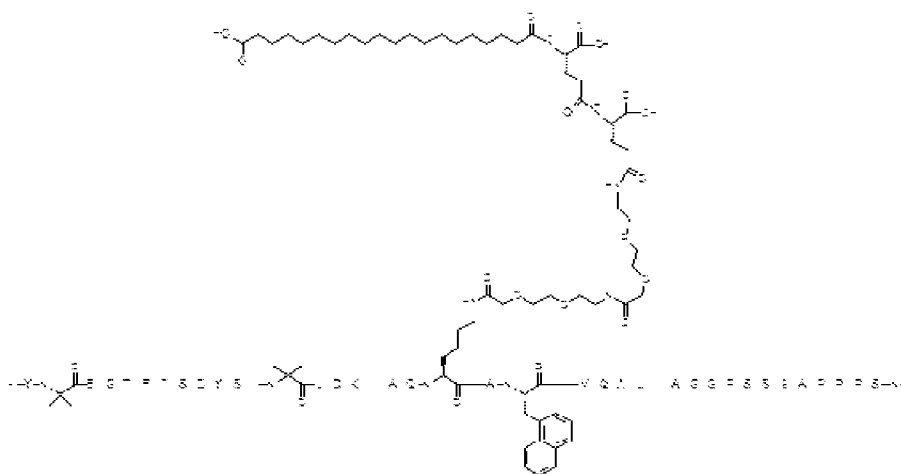
YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPPS

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-

-14-

ethoxy]-acetyl)₂-(γGlu)₂-CO-(CH₂)₁₈-CO₂H; X₃ is 1-Nal; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 4)

trifluoroacetate salt



5

The above structure contains the standard single letter amino acid code with exception of residues Aib₂, Aib₁₃, K₂₀ and 1-Nal₂₂ where the structures of these amino acid residues have been expanded.

The peptide according to SEQ ID NO: 4 of the present invention is synthesized similarly as described above in Example 1. The following conditions are used for the coupling of Fmoc-1Nal-OH at position 22: Fmoc-1Nal-OH (6 equiv), PyBOP (6 equiv), and DIEA (12 equiv) in DMF for 4 h at 25°C.

EXAMPLE 3

15 YX₁EGTFTSDYSIX₂LDKIAQKAFVQWLIAGGPSSGAPPPS

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₆-CO₂H; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 5)

20

trifluoroacetate salt

The compound according to SEQ ID NO: 5 of the present invention is synthesized similarly as described above for Example 1.

EXAMPLE 4

5 YX₁EGTFTSDYSIX₂LDKIAQKAFVQWLIAGGPSSGAPPPS

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₂-CO-(CH₂)₁₆-CO₂H; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 6)

10 trifluoroacetate salt

The compound according to SEQ ID NO: 6 of the present invention is synthesized similarly as described above for Example 1.

EXAMPLE 5

15

YX₁EGTFTSDYSIX₂LDKIAQKAFVQWLIAGGPSSGAPPPS

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₂-CO-(CH₂)₁₈-CO₂H; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 7)

20 trifluoroacetate salt

The compound according to SEQ ID NO: 7 of the present invention is synthesized similarly as described above for Example 1.

25

EXAMPLE 6

YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPPS

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-

-16-

ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₆-CO₂H; X₃ is 1-Nal; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 8)

trifluoroacetate salt

5 The compound according to SEQ ID NO: 8 of the present invention is synthesized similarly as described above for Example 1.

EXAMPLE 7

YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPPS

10 wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₂-CO-(CH₂)₁₆-CO₂H; X₃ is 1-Nal; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 9)

trifluoroacetate salt

15

 The compound according to SEQ ID NO: 9 of the present invention is synthesized similarly as described above for Example 1.

EXAMPLE 8

20 YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPPS

 wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₈-CO₂H; X₃ is 1-Nal; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 10)

25

trifluoroacetate salt

 The compound according to SEQ ID NO: 10 of the present invention is synthesized similarly as described above for Example 1.

30

ASSAYS

Provided below are the conditions and data for Examples in several assays: *in vitro* function and selectivity, immunogenicity profiling, pharmacokinetics, and *in vivo* type 2 diabetes models.

5

In vitro function and selectivity

***In vitro* binding potency to human GLP-1 and GIP Receptors**

The *in vitro* binding potency of compounds of the present invention to human GIP and GLP-1 receptors is evaluated by measuring the binding affinities, as K_i , using crude
10 cellular membranes obtained from clonal cell lines over-expressing either the human GLP1R cDNA or human GIP-R cDNA.

The human glucose-dependent insulinotropic polypeptide receptor binding assay uses hGIP-R (Usdin,T.B., Gruber,C., Modi,W. and Bonner,T.I., GenBank: AAA84418.1) cloned into pcDNA3.1 (Promega)-NeoR plasmid. The hGIP-R-pcDNA3.1/Neo plasmid
15 is transfected into Chinese Hamster Ovary cells, CHO-S, for suspension cultures and selected in the presence of 500 μ g/mL Geneticin (Invitrogen).

Crude plasma membranes are prepared using cells from suspension culture. The cells are lysed on ice in hypotonic buffer containing 25 mM Tris HCl, pH 7.5, 1 mM $MgCl_2$, DNase1, 20 μ /mL, and Roche Complete™ Inhibitors without EDTA. The cell
20 suspension is homogenized with a glass dounce homogenizer using a Teflon® pestle for 25 strokes. The homogenate is centrifuged at 4°C at 1800 x g for 15 minutes. The supernatant is collected and the pellet resuspended in hypotonic buffer and re-homogenized. The mixture is centrifuged at 1800 x g for 15 minutes. The second supernatant is combined with the first supernatant. The combined supernatants are re-
25 centrifuged at 1800 x g for 15 minutes to clarify. The clarified supernatant is transferred to high speed tubes and centrifuged at 25,000 x g for 30 minutes at 4°C. The membrane pellet is resuspended in homogenization buffer and stored as frozen aliquots at -80 °C freezer until use.

GIP is radioiodinated by the I-125-lactoperoxidase procedure (Markalonis, J.J.,
30 *Biochem. J.* 113:299 (1969)) and purified by reversed phase HPLC (Perkin-Elmer Life

and Analytical Sciences NEX-402). The specific activity is 2200 Ci/mmol. K_D determination is performed by homologous competition using cold hGIP instead of saturation binding. The receptor binding assay is carried out using a Scintillation Proximity Assay (SPA) with wheat germ agglutinin (WGA) beads (Perkin Elmer Life and Analytical Sciences) previously blocked with 1% fatty acid free BSA (Gibco, 7.5% BSA). The binding buffer contains 25 mM HEPES, pH 7.4, 2.5 mM CaCl_2 , 1 mM MgCl_2 , 0.1% fatty acid free BSA, 0.003% Tween20, and Roche Complete™ Inhibitors without EDTA. hGIP and the compounds of the present invention are dissolved in 100% DMSO and stored at -20°C . The compounds are serially diluted into binding buffer. Next, 10 μL diluted compound or 100% DMSO is transferred into Corning® 3632 clear bottom assay plates containing 40 μL assay binding buffer or cold GIP (NSB at 0.1 μM final). Then, 90 μL membranes (3 $\mu\text{g}/\text{well}$), 50 μL [^{125}I] GIP (Perkin Elmer Life and Analytical Sciences at 0.15 nM final in reaction), and 50 μL of WGA beads (150 $\mu\text{g}/\text{well}$) is added, sealed, and mixed on a plate shaker for 1 minute. Plates are read with a MicroBeta® scintillation counter after 12 hours of settling time at room temperature.

Results are calculated as a percentage of specific I-125-GIP binding in the presence of compound. The Absolute IC_{50} concentration is derived by non-linear regression of percent specific binding of I-125-GIP versus the concentration of compound added. The IC_{50} concentration is converted to K_i using the Cheng-Prusoff equation.

The GLP-1 receptor binding assay uses cloned human glucagon-like peptide 1 receptor (hGLP-1R) (Graziano MP, Hey PJ, Borkowski D, Chicchi GG, Strader CD, *Biochem Biophys Res Commun.* 196(1): 141-6, 1993) isolated from 293HEK membranes. The hGLP-1R cDNA is subcloned into the expression plasmid pHD (Trans-activated expression of fully gamma-carboxylated recombinant human protein C, an antithrombotic factor. Grinnell, B.W., Berg, D.T., Walls, J. and Yan, S.B. *Bio/Technology* 5: 1189-1192, 1987). This plasmid DNA is transfected into 293HEK cells and selected with 200 $\mu\text{g}/\text{mL}$ Hygromycin.

Crude plasma membranes are prepared using cells from suspension culture. The cells are lysed on ice in hypotonic buffer containing 25 mM Tris HCl, pH 7.5, 1 mM MgCl_2 , DNase1, 20 $\mu\text{g}/\text{mL}$, and Roche Complete™ Inhibitors without EDTA. The cell

suspension is homogenized with a glass dounce homogenizer using a Teflon® pestle for 25 strokes. The homogenate is centrifuged at 4°C at 1800 x g for 15 minutes. The supernatant is collected and the pellet resuspended in hypotonic buffer and re-homogenized. The mixture is centrifuged at 1800 x g for 15 minutes. The second
5 supernatant is combined with the first supernatant. The combined supernatants are recentrifuged at 1800 x g for 15 minutes to clarify. The clarified supernatant is transferred to high speed tubes and centrifuged at 25000 x g for 30 minutes at 4°C. The membrane pellet is resuspended in homogenization buffer and stored as frozen aliquots at -80 °C freezer until use.

10 Glucagon-like peptide 1 (GLP-1) is radioiodinated by the I-125-lactoperoxidase procedure and purified by reversed phase HPLC at Perkin-Elmer Life and Analytical Sciences (NEX308). The specific activity is 2200 Ci/mmol. K_D determination is performed by homologous competition instead of saturation binding due to high propanol content in the I-125 GLP-1 material. The K_D is estimated to be 0.329 nM and is used to
15 calculate K_i values for all compounds tested.

The receptor binding assay is carried out using a Scintillation Proximity Assay (SPA) with wheat germ agglutinin (WGA) beads previously blocked with 1% fatty acid free BSA (Gibco). The binding buffer contains 25 mM HEPES, pH 7.4, 2.5 mM CaCl_2 , 1 mM MgCl_2 , 0.1% fatty acid free BSA, 0.003% Tween20, and Roche Complete™

20 Inhibitors without EDTA. Glucagon-like peptide 1 is dissolved in 100% DMSO at 1 mg/mL and stored frozen at -20 °C in 30 μL aliquots. The glucagon-like peptide 1 aliquot is diluted and used in binding assays within an hour. The peptide analog is dissolved in 100% DMSO and serially diluted in 100% DMSO. Next, 10 μL diluted compounds of the present invention or 100% DMSO are transferred into Corning® 3632
25 clear bottom assay plates containing 40 μL assay binding buffer or cold glucagon (NSB at 1 μM final). Then, 90 μL membranes (0.5 $\mu\text{g}/\text{well}$), 50 μL I-125 Glucagon-like peptide 1 (0.15 nM final in reaction), and 50 μL of WGA beads (150 $\mu\text{g}/\text{well}$) is added, sealed, and mixed on a plate shaker for 1 minute. Plates are read with a PerkinElmer Life and Analytical Sciences Trilux MicroBeta® scintillation counter after 12 hours of settling
30 time at room temperature.

Results are calculated as a percentage of specific I-125-Glucagon-like peptide 1 binding in the presence of compounds. The Absolute IC₅₀ concentration of compound is derived by non-linear regression of percent specific binding of I-125-Glucagon-like peptide 1 versus the concentration of compound added. The IC₅₀ concentration is converted to Ki using the Cheng-Prusoff equation.

In experiments performed essentially as described in this assay, certain compounds of the present invention display an hGLP-1R/hGIPR ratio of approximately 0.5-4.0 (Table 1). The molar binding ratio is normalized to the corresponding molar ratio of a mixture of native GIP and GLP-1. This normalization factor is 4.53 based on binding data for GIP (Ki=0.175 nM) and GLP-1 (Ki=0.793 nM). The value of 1.48 demonstrates the balanced co-agonist activity of Example 1.

Table 1: Receptor Binding Affinity, Ki, nM (SEM, n)

Compound	Human GIP-R	Human GLP-1R	Absolute ratio of hGLP-1R/hGIP-R	Molar ratio of hGLP-1R/hGIP-R
Example 1	34.4 (5.0, n=8)	232 (40, n=8)	6.7	1.48
GIP, 1-42	0.175 (0.022, n=8)	>175 (n=14)	>1000	
GLP-1, 7-36-NH ₂	>100 (n=15)	0.793 (0.099, n=8)	<0.008	
Example 3	26.7 (2.3, n=17)	427 (33, n=17)	16	3.53
Example 6	44.2 (3.6, n=14)	365 (28, n=14)	8.3	1.83
Example 7	46.1 (5.9, n=11)	352 (39, n=11)	7.6	1.68
Example 8	67.5 (9.9, n=6)	307 (35, n=6)	4.5	0.99
Example 4	40.7 (5.1, n=7)	714 (76, n=7)	17.5	3.86
Example 2	63.9 (11.8, n=8)	344 (60, n=8)	5.4	1.19
Example 5	17.8 (3.0, n=5)	158 (32, n=5)	8.9	1.96

Means are expressed as geometric means with the standard error of the mean (SEM) and the number of replicates (n) indicated in parenthesis. A qualifier (>) indicates data did not reach 50% inhibition and the K_i is calculated using the highest concentration tested in the assay.

5

Functional hGIP-R, hGLP-1R, and hGCGR assays.

The *in vitro* functional activity towards human GIP, GLP-1, and glucagon receptors for compounds of the present invention are determined in HEK-293 clonal cell lines expressing these receptors. Each receptor over-expressing cell line is treated with compounds of the present invention in DMEM (Gibco Cat# 31053) supplemented with 1X GlutaMAXTM (Gibco Cat# 35050), 0.25% FBS, 0.05% fraction V BSA, 250 μ M IBMX and 20 mM HEPES in a 40 μ l assay volume. After an incubation of 60 minutes at room temperature, the resulting increase in intracellular cAMP is quantitatively determined using the CisBio cAMP Dynamic 2 HTRF Assay Kit (Bedford, MA). Briefly, cAMP levels within the cell are detected by adding the cAMP-d2 conjugate in cell lysis buffer (20 μ l) followed by the antibody anti-cAMP-Eu³⁺-Cryptate, also in cell lysis buffer (20 μ l). The resulting competitive assay is incubated for at least 60 minutes at room temperature, then detected using a PerkinElmer Envision® instrument with excitation at 320 nm and emission at 665 nm and 620 nm. Envision units (emission at 665nm/620nm*10,000) are inversely proportional to the amount of cAMP present and are converted to nM cAMP per well using a cAMP standard curve. The amount of cAMP generated (nM) in each well is converted to a percent of the maximal response observed with either human GIP(1-42)NH₂, human GLP-1(7-36)NH₂, or human glucagon controls. A relative EC₅₀ value and percent top (E_{max}) is derived by non-linear regression analysis using the percent maximal response versus the concentration of the compound of the present invention, fitted to a four-parameter logistic equation.

25

In experiments performed essentially as described in this assay, certain compounds of the present invention demonstrate activity against human GIP and GLP-1 receptors, while also demonstrating selectivity over the glucagon receptor. In Table 2,

functional potency against the receptors is shown for the native hGIP(1-42)NH₂, hGLP-1(7-36)NH₂, and hGlucagon controls, and certain compounds of the present invention.

Table 2. Functional Potency (EC₅₀) against human GIP, GLP-1, and glucagon receptors.

Compound	Human GIP-R		Human GLP-1R		Human GCGR	
	EC ₅₀ , nM±SEM (n)	E _{max} , %	EC ₅₀ , nM±SEM (n)	E _{max} , %	EC ₅₀ , nM±SEM, (n)	E _{max} , %
Example 1	11.0±0.9 (17)	97.9±3.0	71.2±7.2 (17)	85.2±4.4	>1000 (13)	ND
Example 3	3.15±0.34 (14)	106±3	33.9±3.2 (14)	96.2±6.2	>1000 (10)	ND
Example 6	4.40±0.71 (13)	106±3	28.4±4.2 (13)	104±4	>1000 (9)	ND
Example 7	8.07±0.70 (17)	106±3	35.5±2.6 (17)	97.2±3.4	>1000 (13)	ND
Example 8	21.1±2.7 (14)	108±4	57.9±6.8 (13)	88.4±2.3	>1000 (10)	ND
Example 4	3.76±0.83 (6)	102±3	66.9±14.9 (6)	100±5	>1000 (2)	ND
Example 2	17.5±2.0 (13)	94.7±2.0	75.7±6.0 (13)	98.2±5.5	>1000 (9)	ND
Example 5	8.76±0.86 (10)	105±2	70.9±9.7 (10)	105±4	>1000 (10)	ND
hGLP-1(7-36)NH ₂			0.176 ±0.015 (17)	102±2		
hGIP(1-	0.135	100±1				

-23-

42)NH ₂	±0.010 (17)					
hGlucagon					0.0208 ±0.0024 (13)	115±2

Means for EC₅₀ are expressed as geometric means +/- standard error of the mean (SEM) with the number of replicates (n) indicated in parenthesis. Means for E_{max} are expressed as the arithmetic mean +/- standard error. ND signifies that agonist activity was not detected. A qualifier (>) indicates that an EC₅₀ could not be determined. All values shown are to three significant digits

Functional activation of hGIP-R cells to generate intracellular cAMP in incretin-secreting cell lines

The functional activity of hGIP-R for compounds of the present invention are demonstrated by the ability of the compounds to generate intracellular cAMP in GLUTag cells, a stable immortalized relatively differentiated murine enteroendocrine cell line that expresses the proglucagon gene and secretes the glucagon-like peptides in a regulated manner. The cells are maintained at 37°C, 5% CO₂, 95% humidity in DMEM medium supplemented with 5.5 mM glucose, 10% FBS, and 2 mM glutamine. Prior to assay, cells are trypsinized, pelleted, and seeded into 96-well tissue culture assay plates at a density of 20,000 cells/well. Cells are allowed to attach and are incubated for 48 hours at 37°C, 5% CO₂. On the day of the assay, media is decanted from cells and 50 µl EBSS Buffer (0.1% BSA, 2 mM glucose and 0.25 mM IBMX) containing a range of compound concentrations (0.001 – 3 µM) is added to cells. The plate is incubated at 37°C for one hour and cAMP levels determined using Cisbio Dynamic 2 cAMP HTRF kit (Bedford, MA). 25 µl of anti-cAMP cryptate and 25 µl cAMP d2 is added to each well and plates incubated for one hour at room temperature. Plates are read at 620nm and 665nm on a Tecan Genios Pro. Results are calculated from the 665nm/620nm ratio multiplied by 10000, and converted to nM cAMP per well using a cAMP standard curve. Data is analyzed with GraphPad using a 4-parameter non-linear logistic algorithm.

In experiments performed essentially as described in this assay, certain compounds of the present invention show a dose-dependent, enhanced cAMP accumulation of GLUtag cells (Table 3). The native GLP-1 control fails to induce any changes in cAMP at all concentrations tested and indicates that this cell system
5 exclusively expresses the GIP receptor; therefore, certain compounds of the present invention can be shown to exert an effect through the GIP receptor.

Table 3: EC50 in GLUtag cells.

Compound	Average EC50, nM (n)
Example 3	1610 (1)
Example 7	2746 (1)
Example 4	2186 (1)
Example 2	2918 (1)
Example 1	1494 (2)
Native GIP	11.62 (3)

10 **Measurement of Intracellular cAMP in HEK293 Cells Transiently Expressing the Human GLP-2 Receptor**

The functional activity of hGLP-2R in the presence of compounds of the present invention is demonstrated by measuring intracellular cAMP in HEK293 cells. These cells are passaged in complete medium, transfected in suspension with Promega Fugene6
15 reagent and human full-length GLP-2R cDNA in pcDNA3.1 expression vector, and allowed to adhere to tissue culture flasks in a humidified 37°C 5% CO₂ environment. Following approximately 48 hours of propagation, cells are lifted, strained, and cryopreserved with controlled rate freezing and 10% DMSO as a cryoprotectant. In subsequent assays, a single assay-ready vial from the same cell freeze is thawed to
20 minimize inter-assay variation. On the day of the cellular assay, freezing medium is exchanged with Invitrogen 31053 DMEM containing 0.5% FBS.

Cells are counted for viability and equilibrated for approximately one to two hours at 37°C prior to treatment. Compounds of the present invention are solubilized in DMSO

and immediately diluted in DMEM medium containing 0.1% fraction V BSA and the non-specific phosphodiesterase inhibitor, IBMX. Duration of treatment is 30 minutes at 37°C. Final DMSO concentration does not exceed 1.1%, and final IBMX concentration is 250 μ M. Cyclic AMP is measured using the dynamic 2 assay with homogenous time-resolved fluorescence technology (Cisbio Bioassays, Bedford, MA). Respective cAMP concentrations are deduced from the ratio method of calculation and external standards. Sigmoidal dose-responses of tested compounds are examined using the four parameter logistic equation and compared to the native C₁₈-acylated ligand.

In experiments performed essentially as described in this assay, the C₁₈-acylated human GLP-2 control has an EC₅₀ value for receptor activation of 1.71 nM while certain compounds of the present invention have EC₅₀ values from approximately 100x to 1000x higher. The EC₅₀ values for certain compounds of the present invention demonstrate selectivity against the GLP-2 receptor.

Table 4: GLP-2R functional activity measurement in HEK293 cells.

Compound	Rel EC50 (nM)	n
GLP2-C ₁₈ -diacid	1.857	4
Example 3	199.3	4
Example 7	1,800	4
Example 4	405	2
Example 1	238	4
Example 2	1612	2

Rodent islet insulin secretion

To assess action of compounds of the present invention in a system representing physiological GLP-1R and GIP-R expression levels insulin secretion, compounds are tested for effects on insulin secretion from wild-type rodent islets.

After common bile duct cannulation in male C57Bl/6 mice (22-26 g) or male Sprague-Dawley rats (approx. 250 g), the pancreas is distended with Hank's buffer (3 ml for mice or 10 ml for rats, containing 2% BSA and 0.75 mg/ml Clzyme collagenase

(VitaCyte). Subsequently, tissues are digested in Hank's buffer at 37°C for 11–13 minutes (mice) or 14–16 minutes for rat pancreata. Purified islets (Histopaque-1100 gradient [Sigma-Aldrich], 18 min at 750x gravity) are cultured overnight in RPMI-1640 medium (Invitrogen) containing 10% FBS, 100 U/ml penicillin and 100 µg/ml streptomycin, and preconditioned by starvation in Earle's Balanced Salt Solution (EBSS) supplemented with 0.1% BSA and 2.8 mM glucose. Subsequently, islets are incubated in EBSS (Invitrogen) supplemented with 0.1% BSA, 2.8–11.2 mM glucose and increasing levels of compound (6 batches of 4 islets/condition). GLP-1(7-36)amide (30 nM) is used as a positive control. Insulin is measured over 90 minutes in supernatant using the MSD Insulin Assay (Meso Scale, Gaithersburg, MD).

Certain compounds of the present invention dose-dependently increase insulin secretion from both rat and mouse islets as depicted in Table 5.

Table 5. Rodent Islet Insulin Secretion

Rat islet insulin secretion		
Compound	Mean ED50 (nM)	N
Example 3	34.9	2
Example 1	15.5	3
Mouse islet insulin secretion		
Compound	Mean ED50 (nM)	N
Example 3	58.9	2
Example 6	51.4	1
Example 7	11.3	1
Example 4	3.5	1
Example 2	30.0	1
Example 1	47.2	2

15

Immunogenicity Profiling

The risk of immunogenicity for compounds of the present invention is assessed using *in silico* prediction programs, such as Epivax *in silico* analysis. The risk of immunogenicity for compounds of the present invention is also assessed by an *ex-vivo* method to measure cultured T cells responses (³H-thymidine uptake and IL-2 cytokine secretion) in the presence of compounds of the present invention.

20

With Epivax immune-informatic tools, an *in silico* assessment is performed on compounds of the present invention to predict an immune response following administration. The analysis utilizes the probability of a 9-mer frame to bind to a given human leukocyte antigen (HLA) allele and then detection of these Epi-
5 Bars. For Example 1, a EpiMatrix score of approximately +1.13 indicates a much lower potential to induce an immune response compared to native GIP peptide backbone with a EpiMatrix score of + 15.4. A GIP / GLP-1 co-agonist Example from WO 2011/119657 had a score of + 29.5.

A measure of predicted clinical immunogenicity is also examined for compounds
10 of the present invention by using the characterization of CD4+ T-cell proliferation and IL-2 cytokine secretion in a cohort of 50 healthy donors representative of the world HLA allotype population. Certain compounds of the present invention demonstrate a degree of T-cell stimulation and IL-2 secretion following exposure that does not exceed the threshold associated with known or positive immunogenic compounds, indicating a low
15 risk of producing clinical immunogenicity.

Pharmacokinetics

Pharmacokinetics in Cynomolgus Monkeys.

The *in vivo* pharmacokinetic properties for compounds of the present invention
20 are demonstrated using cynomolgus monkeys. The compounds are administered by a single intravenous or subcutaneous dose (0.2 mg/kg) in 20 mM citrate buffer (pH 7.0) at a volume of 0.21 ml/kg. Blood is collected from each animal at 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168, 204, 240, and 312 hours post-dosage. The plasma concentrations of compounds of the present invention are determined by a LC/MS method. Briefly, a
25 compound of the present invention is extracted from 100% Monkey plasma sample (50 µl) diluted with 1X PBS (150 µl) and mixed with N-butanol (400 µl). Three distinct liquid layers are formed with the compound located in the top layer. A volume of 200 µl is transferred to a v-bottom 96-well plate, dried down using heated Nitrogen gas and reconstituted with 100 µl of 30% acetonitrile/ 0.1% formic acid. 20 µl of the
30 reconstituted sample is injected onto a Supelco Analytical Discovery bio wide C5 3 µm

column. The column effluent is directed into a Thermo Q-Exactive mass spectrometer for detection and quantitation.

In experiments performed essentially as described for this assay, Example 1 reached a mean maximum plasma concentration approximately 8 hours post the subcutaneous dose. The mean half-life is 55 hours and the mean clearance is 0.73 mL/hr/kg. The bioavailability is approximately 83%. This data supports the potential of once-weekly dosing for Example 1. Data for other compounds of the present invention are summarized in Table 6.

Table 6: Mean Pharmacokinetic Parameters Following a Single Subcutaneous Dose of 0.2 mg/kg to Male Cynomolgus Monkeys

Compound	Mean $T_{1/2}$ (hr)	Mean T_{max} (hr)	Mean C_{max} (μ g/mL)	Mean AUC_{0-inf} (hr* μ g/mL)	Mean CL/F (mL/hr/kg)
Example 3	34	8	3.0	153	1.3
Example 7	31	6	2.9	136	1.5
Example 6	23	4	2.2	72.3	2.8
Example 8	23	10	1.0	42.8	4.7
Example 2	43	24	2.1	173	1.2

n = 2, AUC_{0-inf} = area under the curve from 0 to infinity, CL/F = clearance / bioavailability, T_{max} = time to maximum concentration, C_{max} = maximum plasma concentration, $T_{1/2}$ = half-life.

Dose potency projection

The intravenous glucose tolerance test (ivGTT) in the rat is used to estimate relative potency of compounds of the present invention in comparison to semaglutide. Single subcutaneous (SC) doses of 0.1-10 nmol/kg of each compound are administered to the rats and an ivGTT is administered to each rat 16 hours post-dosage. Exposure is measured at the time of the ivGTT, and for exposure response modeling, the insulin AUC in response to the ivGTT is used as the primary endpoint.

An E_{max} model is used to compare the exposure response profiles for Example 1 to semaglutide. In experiments performed essentially as described for this assay, exposure is essentially the same for Example 1 and semaglutide for the dose levels that had drug

levels above the limit of quantitation of the assay. Both data sets are fit simultaneously and E_0 and $E_{\max}$ values are constrained to be the same for both compounds. Only ED_{50} values are fit separately for the compounds. ED_{50} value for semaglutide is estimated as 0.6 +/- 0.2 nmol/kg. Potency of Example 1 is estimated as a relative potency to semaglutide, and is 1.7 +/- 0.6 times the potency of semaglutide. Adjusting for CL/F (apparent clearance) differences between the two molecules in monkeys and also for the difference in molecular weight, the projected mean human equivalent dose to 1 mg semaglutide is approximately 1.3 mg/week for Example 1.

10

Type 2 Diabetes

Rat in vivo insulin secretion following intravenous glucose (IVGTT)

Male Wistar rats (Harlan Labs, Indianapolis, IN) are randomized by body weight and dosed 1.5 ml/kg s.c. 16 hour prior to glucose administration and then fasted. Doses are vehicle, 0.1, 0.3, 1, 3 and 10 nmol/kg. Animals are weighed, and then anesthetized with sodium pentobarbital (Nembutal Sodium solution; Ovation Pharmaceuticals) dosed i.p. (65 mg/kg, 30 mg/ml). A time zero blood sample is collected into EDTA tubes after which glucose is administered (0.5 mg/kg, 5 ml/kg). Blood samples are collected at 2, 4, 6, 10, 20, and 30 minutes post glucose. Plasma glucose levels are determined using a Hitachi analyzer (Roche) and plasma insulin is measured by the MSD insulin assay (Meso Scale, Gaithersburg, MD).

As shown in Table 7, certain compounds of the present invention dose-dependently enhance insulin secretion following i.v. injection of glucose. The ED_{50} for insulin and the maximal increases in insulin secretion (measured as area under the insulin curve) are given in Table 7.

Table 7. Enhancement of insulin secretion in the rat IVGTT assay

Compound	ED_{50} (nmol/kg)	% max increase of insulin AUC
Example 3	1.00	314 +/- 38%
Example 3	1.42	219 +/- 19%
Example 6	2.58	289 +/- 4%
Example 7	4.33	335 +/- 35%

Example 7	1.10	278 +/- 26%
Example 8	6.13	324 +/- 30%
semaglutide	0.70	231 +/- 13%
Example 2	1.62	233 +/- 19%
Example 1	0.87	298 +/- 17%
Example 5	1.02	349 +/- 39%

Effect on weight loss, body composition and hepatic steatosis in diet-induced obese (DIO) mice

5 The effects on weight loss, body composition and hepatic steatosis in DIO mice for compounds of the present invention are evaluated in C57/BL6 DIO mice. These animals, although not diabetic, display insulin resistance, dyslipidemia, and hepatic steatosis, which are all characteristics of metabolic syndrome, after being placed on a high fat (60% Kcal from fat) diet for 12 weeks.

10 In this study, 23-24 week old male diet-induced obese (DIO) C57/BL6 male mice are used, with each weighing 41-49 g and having an initial fat mass ranging from 10.5-17.5 g. Animals are individually housed in a temperature-controlled (24°C) facility with a 12 hour light/dark cycle (lights on 22:00), and free access to food and water. After 2 weeks acclimation to the facility, the mice are randomized to treatment groups

15 (n=5/group) based on body weight so each group has similar starting mean body weight.

Vehicle control, compounds of the present invention (with dose ranging from 10 to 100 nmol/kg), or a long-acting GLP1 analogue semaglutide (30 nmol/kg), dissolved in vehicle (20 mM Citrate Buffer at pH 7.0), are administered by SC injection to *ad libitum* fed DIO mice 30-90 minutes prior to the onset of the dark cycle every three days for 15
20 days. SC injections are made on Day 1, 4, 7, 10, and 13. Daily body weight and food intake are measured throughout the study. Absolute changes in body weight are calculated by subtracting the body weight of the same animal prior to the first injection of compound. On days 0 and 14, total fat mass is measured by nuclear magnetic resonance (NMR) using an Echo Medical System (Houston, TX) instrument.

25 On Day 15, blood glucose is measured with Accu-Chek glucometer (Roche) from tail vein blood and then animals may be sacrificed and livers removed and frozen. Liver

triglycerides, determined from homogenates of livers collected at sacrifice, and plasma cholesterol are measured on a Hitachi Modular P clinical analyzer. Statistical comparisons between groups are done using one-way ANOVA followed by Dunnett's multiple comparison test. The ED₅₀ for weight loss lowering is determined in GraphPad Prism using the non-linear fit tool.

In experiments performed essentially as described in this assay, certain compounds of the present invention reduced body weight and fat mass in a dose-dependent manner (Table 8-13), and compared to semaglutide, may be 3-5x more efficacious in lowering body weight. The ED₅₀ of Example 1 in percent body weight loss is 5.422 nmol/kg (95% Confidence interval levels [nmol/kg] = 2.2 to 13.6). Reduced body weight is found to be primarily due to reduction in fat mass.

Table 8. Percent body weight or fat mass change in DIO mice.

Treatment	Dose (nmol/kg)	% Change from starting body weight	% Change from starting fat mass
Control	0	-3.14 ± 0.88	-4.84 ± 1.79
Semaglutide	10	-12.36 ± 1.00****	-18.21 ± 2.24**
Semaglutide	30	-14.20 ± 1.01****	-21.90 ± 2.07***
Semaglutide	100	-19.30 ± 1.38****	-33.51 ± 3.30***
Example 3	10	-13.38 ± 0.88****	-20.76 ± 2.42***
Example 3	30	-18.13 ± 1.44****	-30.90 ± 2.06****
Example 3	100	-25.84 ± 1.93****	-45.92 ± 2.15****
Example 6	10	-15.31 ± 1.25****	-24.75 ± 1.89****
Example 6	30	-21.62 ± 0.92****	-36.30 ± 2.47****
Example 6	100	-33.95 ± 1.93****	-64.64 ± 4.04****

p<0.01, *p<0.001, ****p<0.0001 from control group (One-Way ANOVA, Dunnett's). The results are expressed as Mean $\pm$ SEM of 5 mice per group.

Table 9. Percent body weight or fat mass change in DIO mice.

Treatment	Dose (nmol/kg)	% Change from starting body weight	% Change from starting fat mass
Control	0	-0.74 $\pm$ 1.49	3.04 $\pm$ 3.65
Semaglutide	30	-17.03 $\pm$ 0.98****	-35.94 $\pm$ 4.09****
Example 2	10	-23.27 $\pm$ 1.72****	-49.89 $\pm$ 5.62****
Example 2	30	33.07 $\pm$ 1.65****	-72.80 $\pm$ 4.04****
Example 2	100	-34.66 $\pm$ 1.80****	-76.20 $\pm$ 3.78****
Example 5	10	-23.42 $\pm$ 1.43****	-51.28 $\pm$ 1.89****
Example 5	30	-26.84 $\pm$ 3.14****	-62.77 $\pm$ 5.49****
Example 5	100	-37.86 $\pm$ 2.25****	-81.08 $\pm$ 1.68****
Example 1	10	-25.18 $\pm$.1.82****	-50.98 $\pm$ 2.87****
Example 1	30	-26.58 $\pm$ 2.49****	-59.98 $\pm$ 6.60****
Example 1	100	-38.14 $\pm$ 1.67****	-79.79 $\pm$ 3.10****

5

****p<0.0001 from control group (One-Way ANOVA, Dunnett's). The results are expressed as Mean $\pm$ SEM of 5 mice per group.

Table 10. Percent body weight or fat mass change in DIO mice.

Treatment	Dose (nmol/kg)	% Change from starting body weight	% Change from starting fat mass
Control	0	-2.43 $\pm$ 2.06	-1.49 $\pm$ 3.69

Example 6	10	-17.54 ± 1.17****	-34.30 ± 1.20****
Example 6	30	-19.52 ± 1.18****	-39.52 ± 3.18****
Example 6	100	-29.36 ± 2.62****	-56.66 ± 4.96****
Example 7	10	-15.08 ± 1.22****	-26.46 ± 2.31***
Example 7	30	-20.70 ± 1.95****	-43.49 ± 5.47****
Example 7	100	-24.36 ± 2.06****	-49.92 ± 3.40****
Example 8	10	-17.13 ± 0.81****	-34.20 ± 1.62****
Example 8	30	-25.27 ± 0.70****	-54.24 ± 2.35****
Example 8	100	-29.91 ± 2.03****	-65.23 ± 6.69****

****p<0.001 from control group (One-Way ANOVA, Dunnett's). The results are expressed as Mean ± SEM of 5 mice per group.

Table 11. Blood glucose, plasma cholesterol and plasma triglycerides in DIO mice.

Treatment	Dose (nmol/kg)	Blood Glucose (mg/dl)	Plasma Cholesterol (mg/dl)	Plasma Triglycerides (mg/dl)
Control	0	141.6 ± 5.59	303.2 ± 13.97	54.2 ± 11.14
Semaglutide	10	147.6 ± 6.13	226.8 ± 13.86**	27.36 ± 3.56*
Semaglutide	30	146.8 ± 8.43	229.8 ± 10.96**	27.9 ± 6.01*
Semaglutide	100	134.3 ± 9.22	218.4 ± 18.70**	36.46 ± 5.34
Example 3	10	109.5 ± 2.35***	213.2 ± 15.54***	30.38 ± 8.23
Example 3	30	107.6 ± 1.32***	177.4 ± 16.58****	21.32 ± 2.48**
Example 3	100	102.00 ± 0.50****	194.00 ± 14.40***	20.55 ± 4.60**
Example 6	10	105.8 ± 2.10***	198.4 ± 6.76****	20.78 ± 4.40**

Example 6	30	100.1 ± 3.29****	186.4 ± 17.04****	26.12 ± 6.85*
Example 6	100	103.6 ± 3.20****	151.4 ± 14.32****	17.26 ± 1.67***

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 from control group (One-Way ANOVA, Dunnett's). The results are expressed as Mean ± SEM of 5 mice per group.

Table 12. Blood glucose, plasma cholesterol and liver triglycerides in DIO mice.

Treatment	Dose (nmol/kg)	Blood Glucose (mg/dl)	Plasma Cholesterol (mg/dl)	Liver Triglycerides (mg/g tissue)
Control	0	144.30 ± 8.16	233.6 ± 12.99	206.65 ± 29.47
Semaglutide	30	136.3 ± 3.81	161.0 ± 13.92***	67.63 ± 23.40****
Example 2	10	110.8 ± 3.87**	121.8 ± 13.64****	60.77 ± 13.24****
Example 2	30	110.8 ± 3.20**	114.00 ± 9.70****	65.78 ± 17.07****
Example 2	100	113.2 ± 4.86**	109.4 ± 8.83****	56.74 ± 17.76****
Example 5	10	111.00 ± 6.56**	126.6 ± 9.67****	48.30 ± 8.14****
Example 5	30	104.5 ± 5.30***	108.2 ± 13.84****	39.60 ± 4.71****
Example 5	100	105.3 ± 6.16***	108.6 ± 4.83****	67.96 ± 13.53****
Example 1	10	102.3 ± 5.59****	120.6 ± 8.55****	60.74 ± 5.33****
Example 1	30	110.7 ± 5.85**	118.2 ± 10.11****	45.24 ± 5.87****

Example 1	100	106.7 ± 7.33***	107.6 ± 10.43****	66.98 ± 17.29****
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*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 from control group (One-Way ANOVA, Dunnett's). The results are expressed as Mean ± SEM of 5 mice per group.

Table 13. Blood glucose and plasma cholesterol in DIO mice.

Treatment	Dose (nmol/kg)	Blood Glucose (mg/dl)	Plasma Cholesterol (mg/dl)
Control	0	152.4 ± 3.63	243.6 ± 13.12
Example 6	10	121.4 ± 2.74***	167.8 ± 15.59****
Example 6	30	121.9 ± 6.65**	159.8 ± 9.99****
Example 6	100	116.1 ± 4.67****	144.2 ± 7.12****
Example 7	10	113.6 ± 4.16****	161.8 ± 6.2****
Example 7	30	114.7 ± 4.70****	153.6 ± 13.47****
Example 7	100	114 ± 2.36****	145.4 ± 9.48****
Example 8	10	114.7 ± 4.61****	158.8 ± 7.57****
Example 8	30	117.1 ± 8.26***	139.4 ± 6.83****
Example 8	100	125.4 ± 6.30**	127.8 ± 6.34****

5 *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 from control group (One-Way ANOVA, Dunnett's). The results are expressed as Mean ± SEM of 5 mice per group.

The effect on energy metabolism in DIO mice

10 The effects on energy metabolism in DIO mice for compounds of the present invention are evaluated in 26 week old C57/B16 DIO male mice, weighing 43-50 g. Mice are individually housed in a temperature-controlled (24°C) facility with a 12 hour light/dark cycle (lights on 22:00), and with free access to food TD95217 (Teklad) and

water. After 2 weeks acclimation to the facility, mice are randomized to treatment groups (n=6/group) based on body weight so each group has similar starting mean body weight. Animals are placed in a PhenoMaster/LabMaster calorimeter (TSE Systems, Chesterfield, MO) for 3 days of acclimation. Vehicle control (20 mM citrate buffer at pH 7.0, 10 ml/kg), compounds of the present invention, or a long-acting GLP1 analogue, semaglutide, (30 nmol/kg) are subcutaneously administered to *ad libitum* fed DIO mice 30-90 minutes prior to the onset of the dark cycle every three days for 22 days. Heat and respiratory quotient (RER) are measured by indirect calorimetry as described using an open-circuit calorimetry system. RER is the ratio of the volume of CO₂ produced (VCO₂) to the volume of O₂ consumed (VO₂). Heat is calculated with full body weight considered:

$$VO_2 = \text{FlowML} * (V_1 + V_2) / N_2\text{Ref} * \text{Animal weight} * 100)$$

$$VCO_2 = \text{FlowML} * dCO_2 / \text{Animal weight} * 100)$$

$$\text{Heat} = (CVO_2 * VO_2 + CVCO_2 * VCO_2) / 1000;$$

$$\text{where } CVO_2 = 3.941; CVCO_2 = 1.106$$

15

In experiments performed essentially as described in this assay, mice treated with Example 1 significantly increased their metabolic rate 10 to 15 % compared to the control group, starting from week 2, and sustained the effect throughout the treatment period. Semaglutide, however, had no effect on metabolic rate. The increase in metabolic rate for Example 1 partially accounts for the additional weight loss observed with Example 1 treatment in comparison with semaglutide treatment.

20

The effect on gastric emptying in DIO mice

The effects on gastric emptying in DIO mice for compounds of the present invention are evaluated in 23 week old diet-induced obese (DIO) male mice (Harlan). The mice are fasted for 16-17 hours. During the start of fasting period the mice are dosed subcutaneously with vehicle control (20 mM citrate buffer at pH 7.0); escalating doses of compounds of the present invention (3, 10, 30 and 100 nmol/kg), or a long-acting GLP1 analogue, semaglutide, (30 nmol/kg). The next day, mice are administered 0.5 ml (0.5 gram) of freshly prepared semi-liquid diet (2 minutes apart) by oral gavage. Water is

30

removed at this time to prevent dilution of administered diet. Two hours after diet administration, mice are euthanized two minutes apart by CO₂ gas. The stomach is removed while clamped at both cardiac and pyloric openings, then clamps removed and the full stomach weighed in a weigh boat. The stomach is then incised and contents removed. The stomach is washed and dried and re-weighed to assess food contents in stomach. The % gastric emptying equals 100 x (1 - (food remaining in stomach/food orally administered)).

In experiments performed essentially as described in this assay, Example 1 slowed the gastric emptying rate of the semi-liquid diet in a dose dependent manner. The maximum inhibition of gastric emptying was observed at a dose of 10 nmol/kg +/- dose (Table 14).

Table 14. Gastric emptying of a semi-liquid diet in lean C57/BL6 DIO mice.

<i>Treatment</i>	<i>Dose (nmol/kg)</i>	<i>Percent Gastric Emptying (Mean ± SEM)</i>
Vehicle (n=5)	0	69.50 +/- 6.60
Semaglutide (n=5)	30	30.56 +/- 7.53**
Example 1 (n=4)	3	49.11 +/- 8.52
Example 1 (n=5)	10	9.76 +/- 7.69****
Example 1 (n=5)	30	26.53 +/- 8.14**
Example 1 (n=5)	100	18.45 +/- 6.87***

Statistical comparisons between groups are done by using one-way ANOVA followed by Dunnett's multiple comparison test. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 from control group. The results are expressed as mean +/- SEM of 4-5 mice per group.

Plasma Corticosterone Measurements in Sprague Dawley Rats

As suggested in certain published studies, elevated plasma corticosterone levels are an indicator of possible reduced tolerability for GIP and GLP-1 analogues. Plasma corticosterone levels are evaluated using Sprague Dawley Rats (Harlan, Indianapolis), weighing approximately 220 g and acclimated for at least 72 hours before handling. The

rats are then dosed with vehicle (20 mM citrate buffer, pH 7), semaglutide (10 nmol/kg), or compounds of the present invention at 3, 10 or 30 nmol/kg s.c. with 8 rats per dose group. The rats are decapitated 16 hours later. Blood is collected into EDTA tubes on ice, then centrifuged 5 minutes at 8000 RPM in a Eppendorf 5402 tabletop centrifuge.

5 Plasma is stored at -80°C until analysis.

For corticosterone analysis, corticosterone standards (Sigma, 27840) are prepared by serial dilutions in HPLC-grade methanol, H₂O and the addition of 5% charcoal stripped rat serum (Bioreclamation, RATSRLM-STRPD-HEV). Rat plasma samples are diluted with PBS, precipitated with cold methanol, incubated for 20 minutes at -20° C, and then centrifuged at 14,000 RPM with an Eppendorf 5417R at 4°C. Supernatants are extracted, evaporated under a stream of N₂ gas, and reconstituted in MeOH/H₂O (1:1) solution. Samples are analyzed on the LC/MS equipped with a XSelect CSH C18 3.5 µm HPLC column (2.1 mm x 30 mm) (Waters #186005254).

15 In experiments performed essentially as described for this assay, Example 1 demonstrated no increase in plasma corticosterone levels at any of the doses tested while semaglutide had an approximately 4x increase over control.

Table 15: Plasma corticosterone analysis in Sprague Dawley Rats

Compound	Corticosterone (ng/ml)	
	Mean	SEM
Vehicle	60.78	8.41
10 nmol/kg Semaglutide	274.57	42.06
3 nmol/kg Example 1	52.21	19.39
10 nmol/kg Example 1	32.46	9.78
30 nmol/kg Example 1	31.35	5.86

Amino Acid Sequences

SEQ ID NO: 1 (Human GIP)

YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ

5 SEQ ID NO: 2 (Human GLP-1)

HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR

SEQ ID NO: 3

YX₁EGTFTSDYSIX₂LDKIAQKAFVQWLIAGGPSSGAPPPS

10 wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₈-CO₂H; and the C-terminal amino acid is amidated as a C-terminal primary amide.

15 SEQ ID NO: 4

YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPPS

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₂-CO-(CH₂)₁₈-CO₂H; X₃ is 1-Nal; and the C-terminal amino acid
20 is amidated as a C-terminal primary amide.

SEQ ID NO: 5

YX₁EGTFTSDYSIX₂LDKIAQKAFVQWLIAGGPSSGAPPPS

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through
25 conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₆-CO₂H; and the C-terminal amino acid is amidated as a C-terminal primary amide.

SEQ ID NO: 6

30 YX₁EGTFTSDYSIX₂LDKIAQKAFVQWLIAGGPSSGAPPPS

wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl) $_2$ -(γ Glu) $_2$ -CO-(CH $_2$) $_{16}$ -CO $_2$ H; and the C-terminal amino acid is amidated as a C-terminal primary amide.

5

SEQ ID NO: 7

YX $_1$ EGTFTSDYSIX $_2$ LDKIAQKAFVQWLIAGGPSSGAPPPS

wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl) $_2$ -(γ Glu) $_2$ -CO-(CH $_2$) $_{18}$ -CO $_2$ H; and the C-terminal amino acid is amidated as a C-terminal primary amide.

10

SEQ ID NO: 8

YX $_1$ EGTFTSDYSIX $_2$ LDKIAQKAX $_3$ VQWLIAGGPSSGAPPPS

wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl) $_2$ -(γ Glu) $_1$ -CO-(CH $_2$) $_{16}$ -CO $_2$ H; X_3 is 1-Nal; and the C-terminal amino acid is amidated as a C-terminal primary amide.

15

20 SEQ ID NO: 9

YX $_1$ EGTFTSDYSIX $_2$ LDKIAQKAX $_3$ VQWLIAGGPSSGAPPPS

wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl) $_2$ -(γ Glu) $_2$ -CO-(CH $_2$) $_{16}$ -CO $_2$ H; X_3 is 1-Nal; and the C-terminal amino acid is amidated as a C-terminal primary amide.

25

SEQ ID NO: 10

YX $_1$ EGTFTSDYSIX $_2$ LDKIAQKAX $_3$ VQWLIAGGPSSGAPPPS

wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-

30

ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₈-CO₂H; X₃ is 1-Nal; and the C-terminal amino acid is amidated as a C-terminal primary amide.

SEQ ID NO: 11

5 YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPPS

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)_a-CO-(CH₂)_b-CO₂H wherein a is 1 to 2 and b is 10 to 20; X₃ is Phe or 1-Nal; and the C-terminal amino acid is optionally amidated as a C-terminal primary

10 amide.

WE CLAIM:

1. A compound of Formula:
5 YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPPS;
wherein
X₁ is Aib;
X₂ is Aib;
K at position 20 is chemically modified through conjugation to the
10 epsilon-amino group of the K side-chain with ([2-(2-Amino-
ethoxy)-ethoxy]-acetyl)₂-(γGlu)_a-CO-(CH₂)_b-CO₂H wherein a is 1
to 2 and b is 10 to 20;
X₃ is Phe or 1-Nal;
and the C-terminal amino acid is optionally amidated as a C-
15 terminal primary amide (SEQ ID NO: 11),
or a pharmaceutically acceptable salt thereof.
2. The compound of Claim 1, wherein X₃ is Phe.
3. The compound of Claim 1, wherein X₃ is 1-Nal.
4. The compound of Claim 2, wherein b is 14 to 18.
- 20 5. The compound of Claim 4, wherein b is 16 to 18.
6. The compound of Claim 5, wherein b is 18.
7. The compound of Claim 4, wherein a is 1.
8. The compound of Claim 4, wherein a is 2.
9. The compound of Claim 4, wherein the C-terminal amino acid is amidated
25 as a C-terminal primary amide.
10. The compound of Claim 1, wherein
X₁ is Aib
X₂ is Aib;

K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₈-CO₂H;

X₃ is Phe;

5 and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 3),

or a pharmaceutically acceptable salt thereof.

11. The compound of Claim 1, wherein

X₁ is Aib

10 X₂ is Aib;

K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₂-CO-(CH₂)₁₈-CO₂H;

X₃ is 1-Nal;

15 and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 4),

or a pharmaceutically acceptable salt thereof.

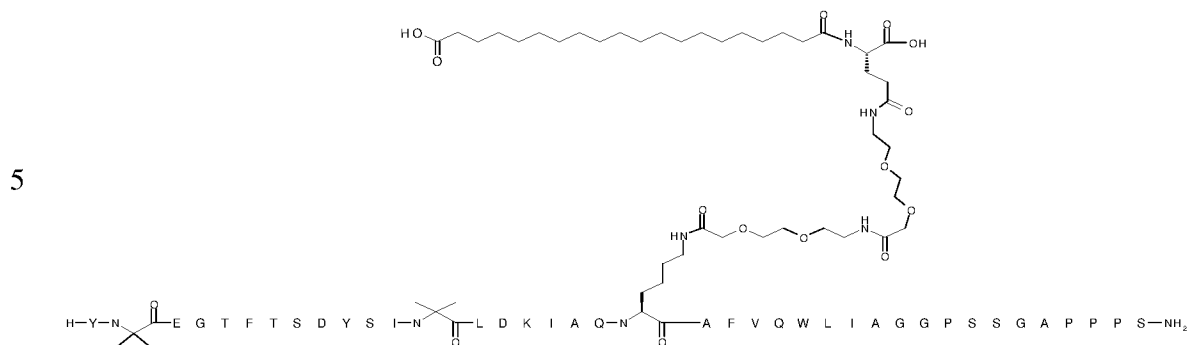
12. A pharmaceutical composition comprising the compound of Claim 10 with a pharmaceutically acceptable carrier, diluent, or excipient.

20 13. A method of treating type 2 diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of the compound of Claim 10.

25 14. The method of Claim 13, further comprising administering simultaneously, separately, or sequentially in combination with an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.

30

15. The compound of Claim 1, wherein the Formula is



- 10
16. A pharmaceutical composition comprising the compound of Claim 15 with a pharmaceutically acceptable carrier, diluent, or excipient.
17. A method of treating type 2 diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of the compound of Claim 15.
- 15
18. The method of Claim 17, further comprising administering simultaneously, separately, or sequentially in combination with an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.

ABSTRACT

5 The present invention relates to dual incretin peptide mimetic compounds that
agonize receptors for both human glucose-dependent insulintropic polypeptide (GIP)
and glucagon-like peptide-1 (GLP-1), and may be useful for treating type 2 diabetes
mellitus (T2D).

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of
Invention

GIP AND GLP-1 CO-AGONIST COMPOUNDS

As the below named inventor, I hereby declare that:

This declaration
is directed to:



The attached application, or



United States application or PCT international application number _____

filed on _____

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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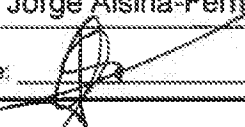
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LEGAL NAME OF INVENTOR

Inventor: Jorge Alsina-Fernandez

Date (Optional): Nov 09, 2015

Signature: 

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LEGAL NAME OF INVENTOR

Inventor: Robert Chadwick Cummins

Date (Optional): Nov. 9, 2015

Signature: Robert Chadwick Cummins

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LEGAL NAME OF INVENTOR

Inventor: Tamer Coskun

Date (Optional):

November 9, 2015

Signature:

Tamer Coskun

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Invention****GIP AND GLP-1 CO-AGONIST COMPOUNDS**

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This declaration
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United States application or PCT international application number _____

filed on _____.

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LEGAL NAME OF INVENTORInventor: Bengt Krister BokvistDate (Optional): Nov 9, 2015Signature: *Bengt Bokvist*

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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Application Number:				
Filing Date:				
Title of Invention:	GIP AND GLP-1 CO-AGONIST COMPOUNDS			
First Named Inventor/Applicant Name:	Bengt Krister Bokvist			
Filer:	Alejandro Martinez./Linda Durbin			
Attorney Docket Number:	X20448			
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1600

Electronic Acknowledgement Receipt

EFS ID:	24523542
Application Number:	14987791
International Application Number:	
Confirmation Number:	4253
Title of Invention:	GIP AND GLP-1 CO-AGONIST COMPOUNDS
First Named Inventor/Applicant Name:	Bengt Krister Bokvist
Customer Number:	25885
Filer:	Alejandro Martinez./Linda Durbin
Filer Authorized By:	Alejandro Martinez.
Attorney Docket Number:	X20448
Receipt Date:	05-JAN-2016
Filing Date:	
Time Stamp:	08:01:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 1600
RAM confirmation Number	9028
Deposit Account	050840
Authorized User	MARTINEZ, ALEJANDRO

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 CFR 1.16 (National application filing, search, and examination fees)

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	X20448ApplicationTransmittal.pdf	276633	no	2
			ea1b3d395fe7426401f0da7ce8225849dac1dc97		
Warnings:					
Information:					
2	Application Data Sheet	X20448ApplicationDataSheet.pdf	1561272	no	8
			d5367a42a7d3189e6d9e83c4bbc9fdd4f12d1604		
Warnings:					
Information:					
3		X20448Specification.pdf	249004	yes	45
			7ab5100d8343cafdbe35f10a26e98cd9ecd5d1f2		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	38	
	Sequence Listing		39	41	
	Claims		42	44	
	Abstract		45	45	
Warnings:					
Information:					
4	Oath or Declaration filed	X20448Declarations.pdf	2736587	no	4
			6235048e88b0c68d86c6ca82bace9ef77bfd9e8f		
Warnings:					
Information:					
5	Sequence Listing (Text File)	X20448SequenceListing.txt	12458	no	0
Warnings:					
Information:					

6	Fee Worksheet (SB06)	fee-info.pdf	35363	no	2
			ef55dc62c317f85045936e0a896ff8a1100907b8		
Warnings:					
Information:					
Total Files Size (in bytes):				4871317	
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