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(54) **GLP2 RECEPTOR AGONISTS AND METHODS OF USE**

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§ 371 (c)(1),
(2) Date: **Jun. 3, 2022**

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A61K 47/60	(2006.01)
A61P 25/28	(2006.01)
A61P 25/16	(2006.01)

(52) **U.S. Cl.**

CPC ***C07K 14/605*** (2013.01); ***A61K 47/542*** (2017.08); ***A61K 47/60*** (2017.08); ***A61P 25/28*** (2018.01); ***A61P 25/16*** (2018.01)

(57) **ABSTRACT**

Peptide conjugates comprising a peptide that modulates the GLP-2 receptor are provided. The peptide conjugates may be used for treating conditions responsive to modulation of the GLP-2 receptor. Further provided are stapled GLP-2 peptide conjugates.

Specification includes a Sequence Listing.

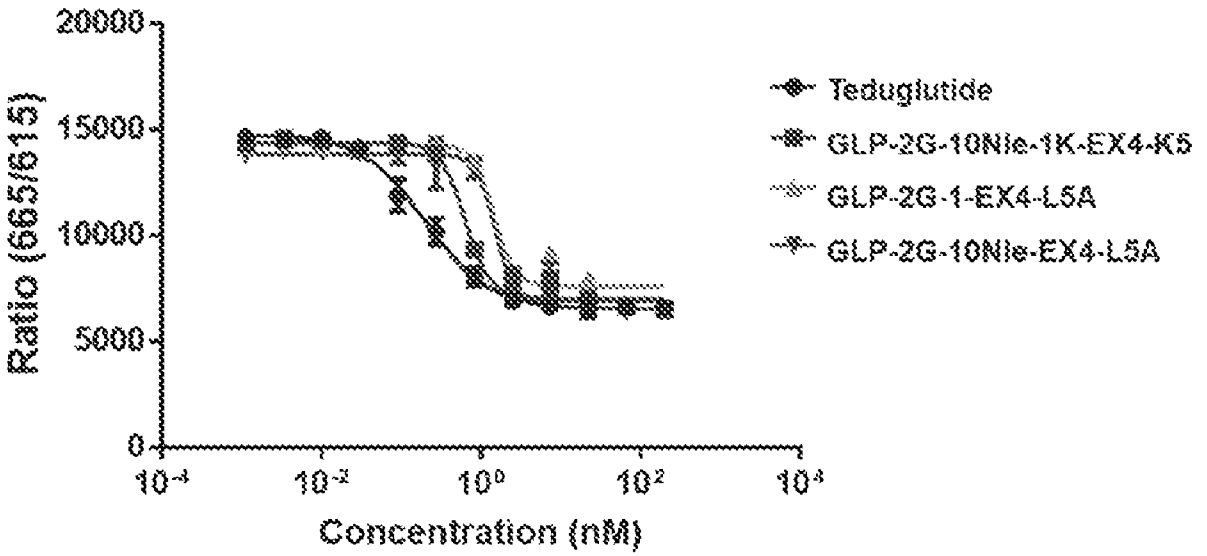


FIG. 1A

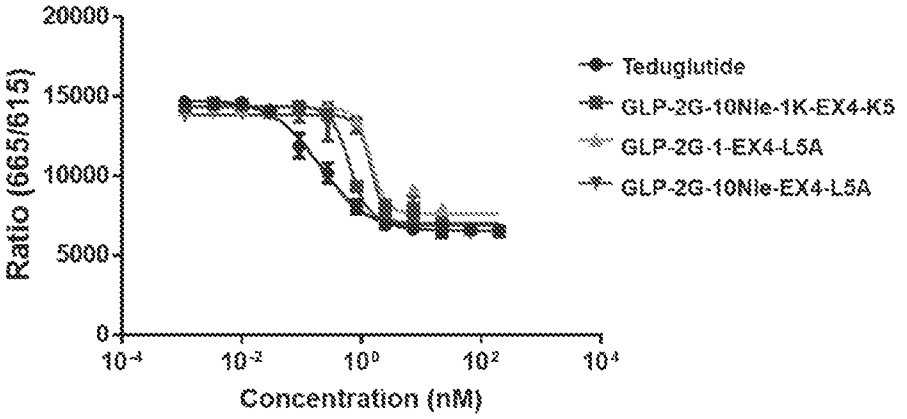

20000
15000
10000
5000
0
Ratio (665/615)
10^{-4}
10^{-2}
10^{0}
10^{2}
10^{4}
Concentration (nM)
Teduglutide
GLP-2G-10Nle-1K-EX4-K5
GLP-2G-1-EX4-L5A
GLP-2G-10Nle-EX4-L5A

FIG. 1B

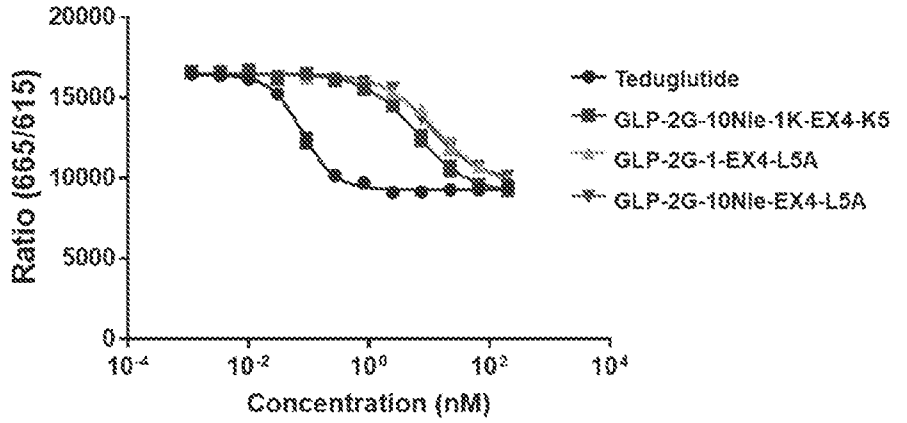

20000
15000
10000
5000
0
Ratio (665/615)
10^{-4}
10^{-2}
10^{0}
10^{2}
10^{4}
Concentration (nM)
Teduglutide
GLP-2G-10Nle-1K-EX4-K5
GLP-2G-1-EX4-L5A
GLP-2G-10Nle-EX4-L5A

FIG. 2

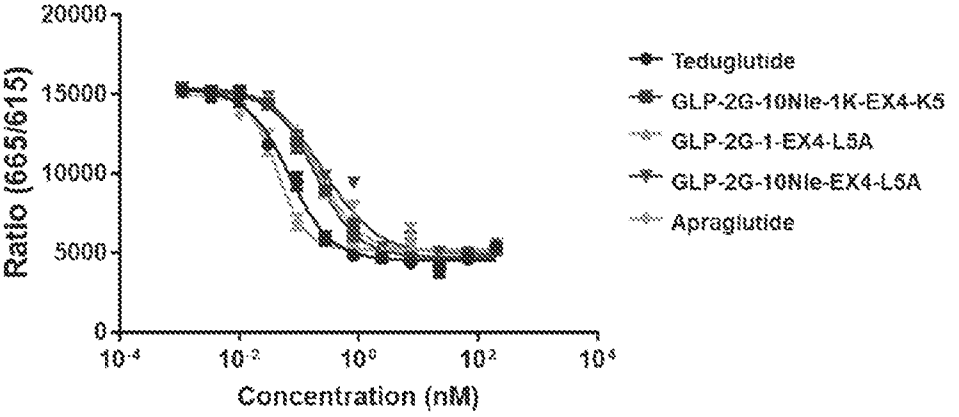

20000
15000
10000
5000
0
Ratio (665/615)
10^{-4}
10^{-2}
10^{0}
10^{2}
10^{4}
Concentration (nM)
Teduglutide
GLP-2G-10Nle-1K-EX4-K5
GLP-2G-1-EX4-L5A
GLP-2G-10Nle-EX4-L5A
Apraglutide

FIG. 3

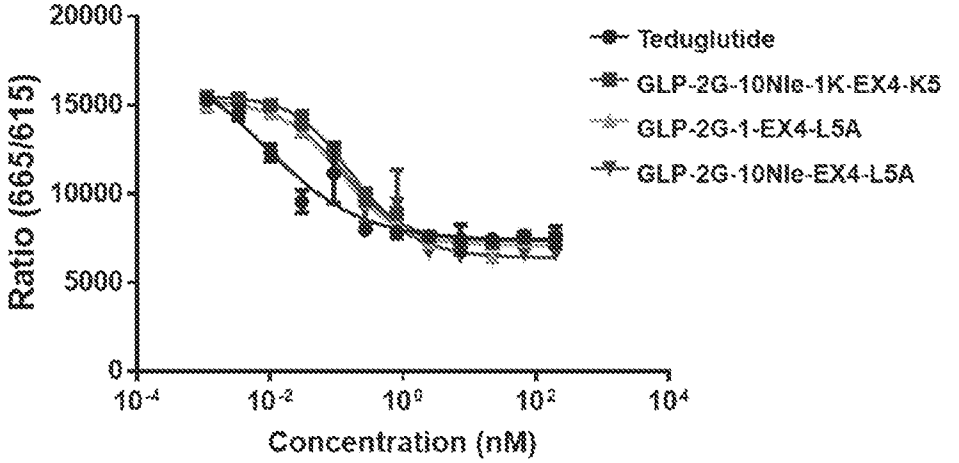

20000
15000
10000
5000
0
Ratio (665/615)
10^{-4}
10^{-2}
10^{0}
10^{2}
10^{4}
Concentration (nM)
Teduglutide
GLP-2G-10Nle-1K-EX4-K5
GLP-2G-1-EX4-L5A
GLP-2G-10Nle-EX4-L5A

FIG. 4A

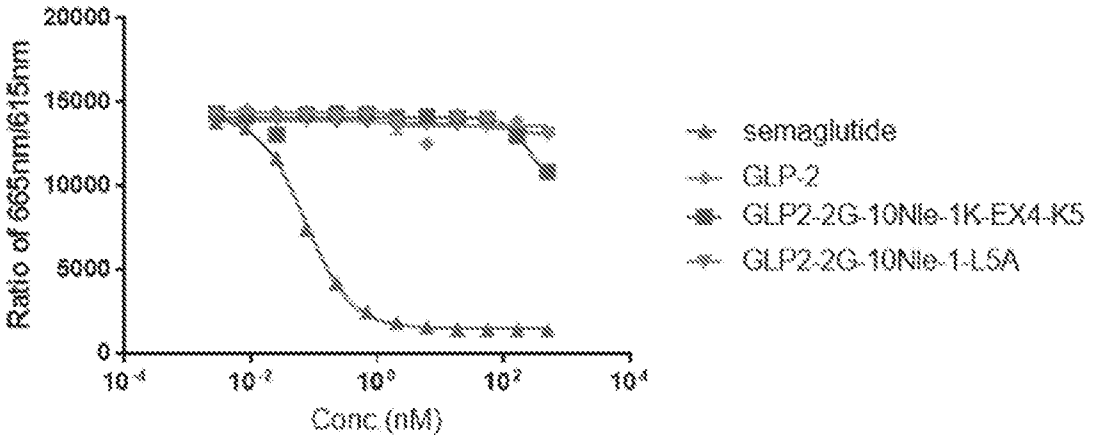

Ratio of 665nm/615nm
20000
15000
10000
5000
0
10^{-4}
10^{-2}
10^{0}
10^{2}
10^{4}
Conc.(nM)
semaglutide
GLP-2
GLP2-2G-10Nle-1K-EX4-K5
GLP2-2G-10Nle-1-L5A

FIG. 4B

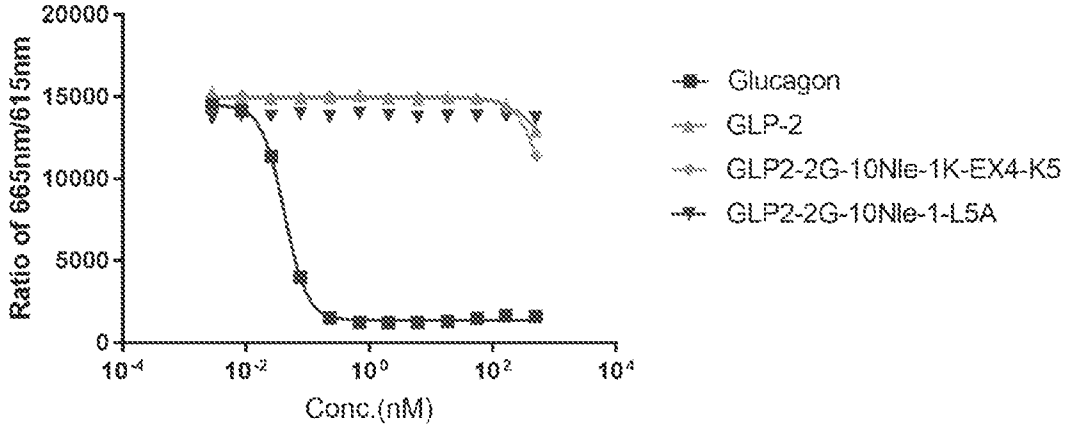

Ratio of 665nm/615nm
20000
15000
10000
5000
0
10^{-4}
10^{-2}
10^{0}
10^{2}
10^{4}
Conc.(nM)
Glucagon
GLP-2
GLP2-2G-10Nle-1K-EX4-K5
GLP2-2G-10Nle-1-L5A

FIG. 4C

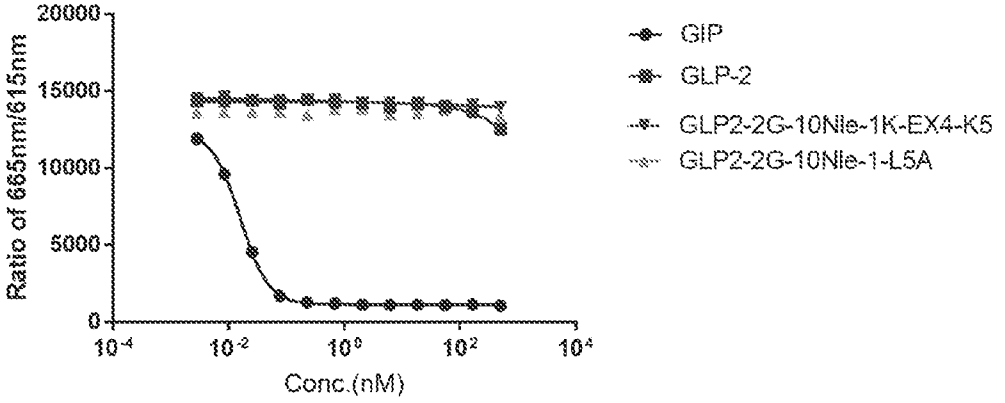

Ratio of 665nm/615nm
20000
15000
10000
5000
0
10^{-4}
10^{-2}
10^{0}
10^{2}
10^{4}
Conc.(nM)
GIP
GLP-2
GLP2-2G-10Nle-1K-EX4-K5
GLP2-2G-10Nle-1-L5A

FIG. 5A

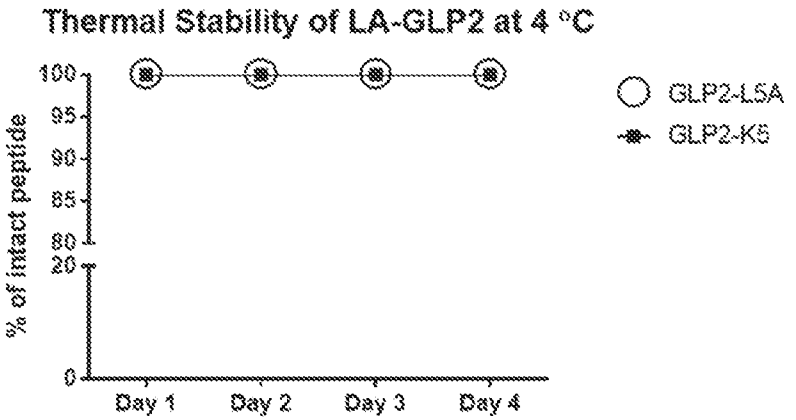

Thermal Stability of LA-GLP2 at 4 °C
% of intact peptide
100
95
90
85
80
20
0
Day 1
Day 2
Day 3
Day 4
GLP2-L5A
GLP2-K5

FIG. 5B

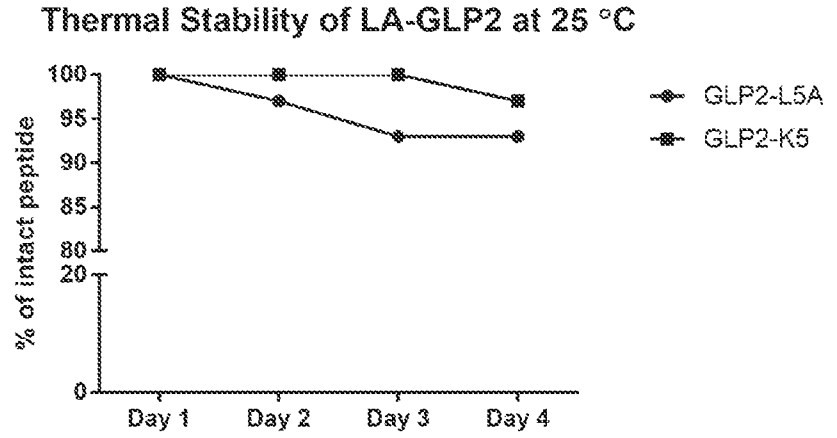

Thermal Stability of LA-GLP2 at 25 °C
% of intact peptide
100
95
90
85
80
20
0
Day 1
Day 2
Day 3
Day 4
GLP2-L5A
GLP2-K5

FIG. 5C

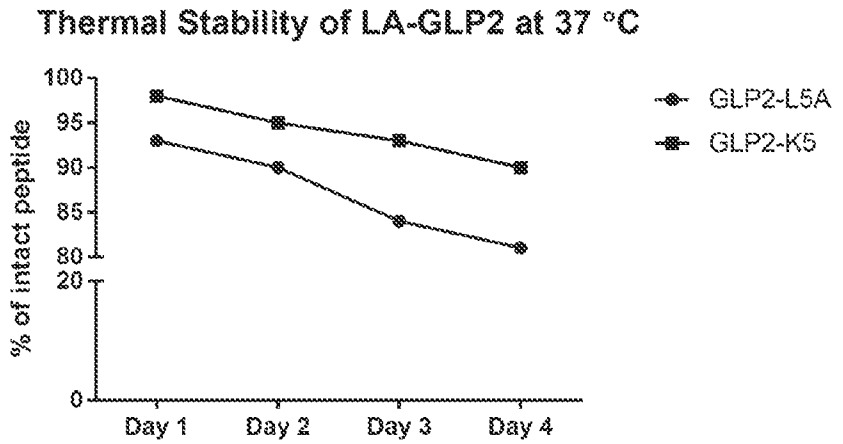

Thermal Stability of LA-GLP2 at 37 °C
% of intact peptide
100
95
90
85
80
20
0
Day 1
Day 2
Day 3
Day 4
GLP2-L5A
GLP2-K5

FIG. 5D

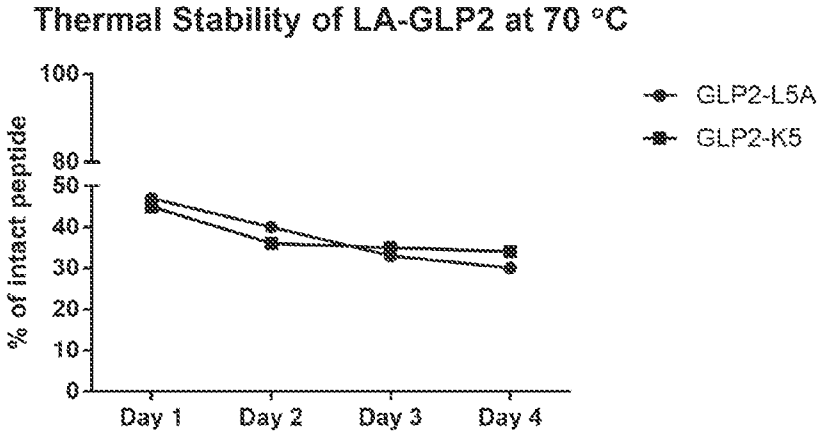

Thermal Stability of LA-GLP2 at 70 °C
% of intact peptide
100
80
50
40
30
20
10
0
Day 1
Day 2
Day 3
Day 4
GLP2-L5A
GLP2-K5

FIG. 6A

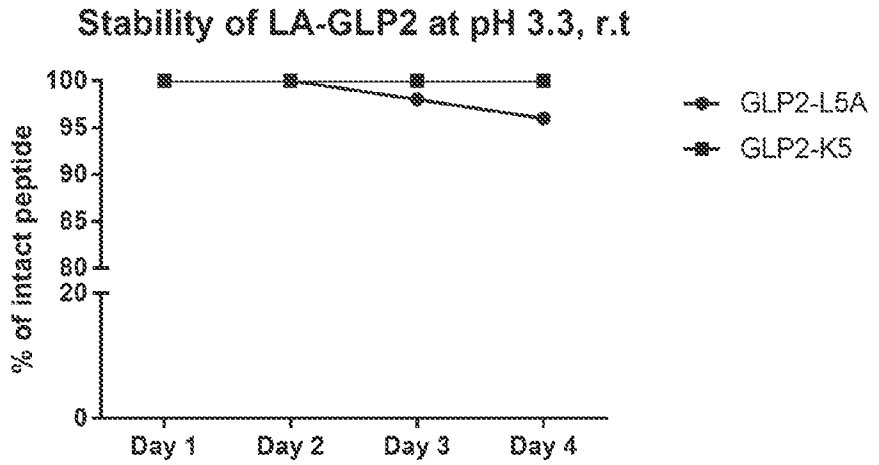

Stability of LA-GLP2 at pH 3.3, r.t
% of intact peptide
100
95
90
85
80
20
0
Day 1
Day 2
Day 3
Day 4
GLP2-L5A
GLP2-K5

FIG. 6B

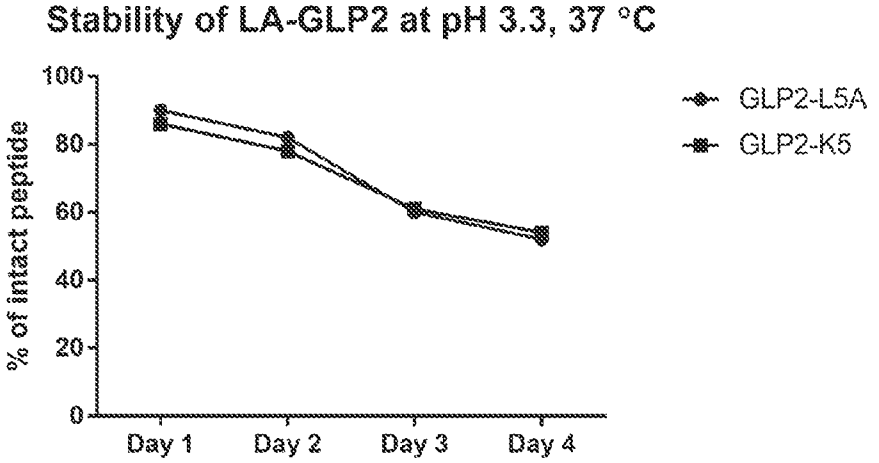

Stability of LA-GLP2 at pH 3.3, 37 °C
% of intact peptide
100
80
60
40
20
0
Day 1
Day 2
Day 3
Day 4
GLP2-L5A
GLP2-K5

FIG. 6C

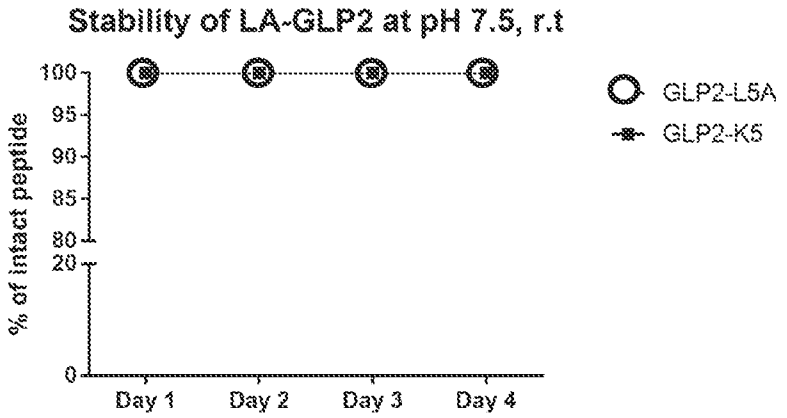

Stability of LA-GLP2 at pH 7.5, r.t
% of intact peptide
100
95
90
85
80
20
0
Day 1
Day 2
Day 3
Day 4
GLP2-L5A
GLP2-K5

FIG. 6D

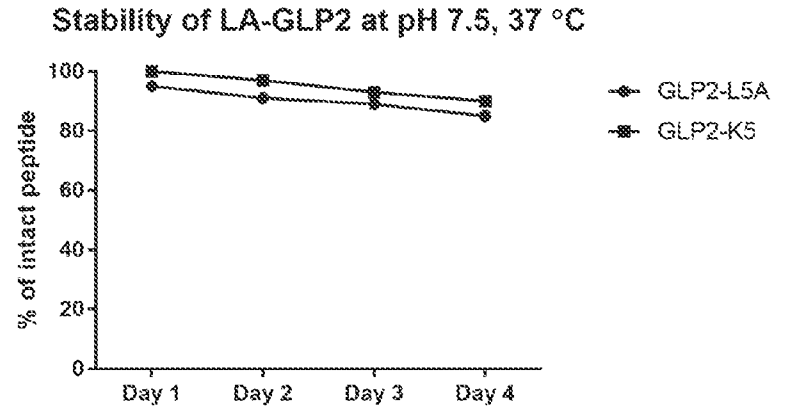

Stability of LA-GLP2 at pH 7.5, 37 °C
% of intact peptide
100
80
60
40
20
0
Day 1
Day 2
Day 3
Day 4
GLP2-L5A
GLP2-K5

FIG. 6E

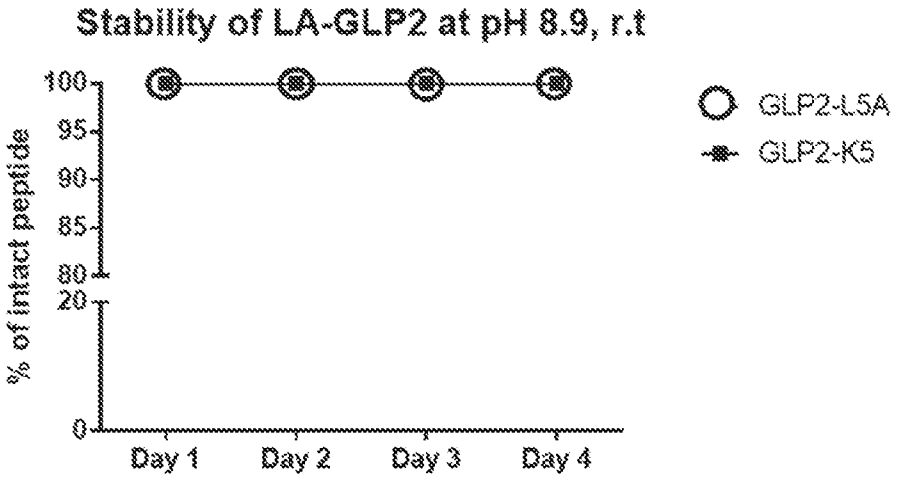

Stability of LA-GLP2 at pH 8.9, r.t
% of intact peptide
100
95
90
85
80
20
0
Day 1
Day 2
Day 3
Day 4
GLP2-L5A
GLP2-K5

FIG. 6F

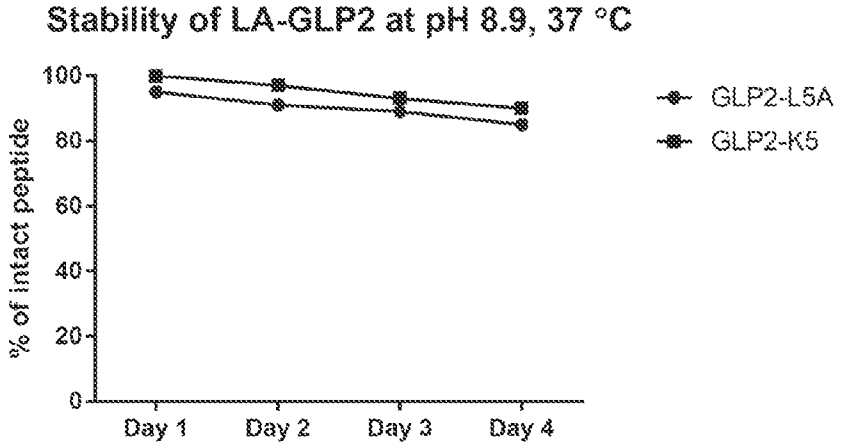

Stability of LA-GLP2 at pH 8.9, 37 °C
% of intact peptide
100
80
60
40
20
0
Day 1
Day 2
Day 3
Day 4
GLP2-L5A
GLP2-K5

FIG. 7A

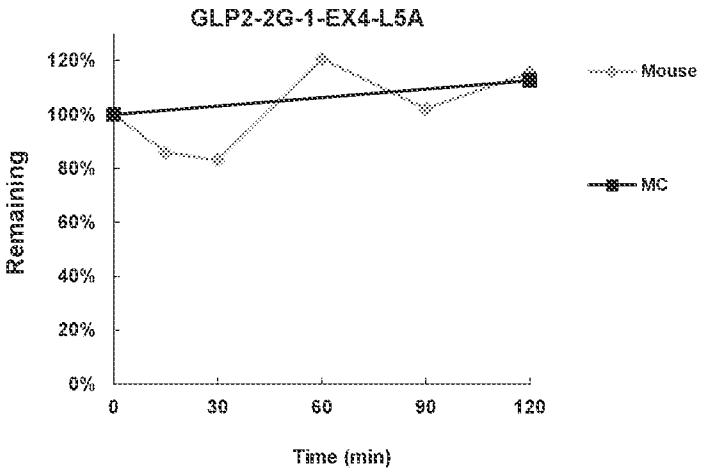


FIG. 7B

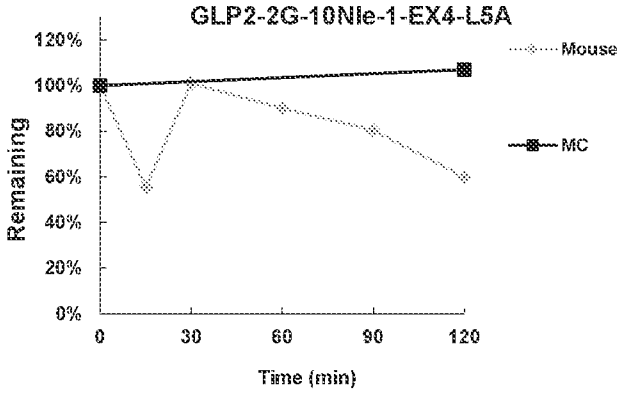


FIG. 7C

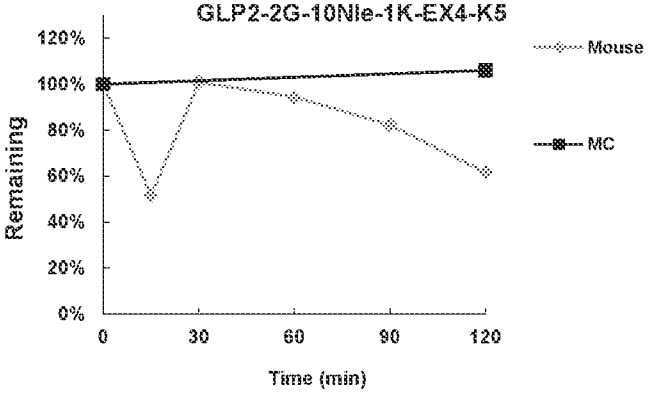


FIG. 8

Mean Plasma concentration of GLP2-Met-L5A after IV bolus1 and SC2 dosing

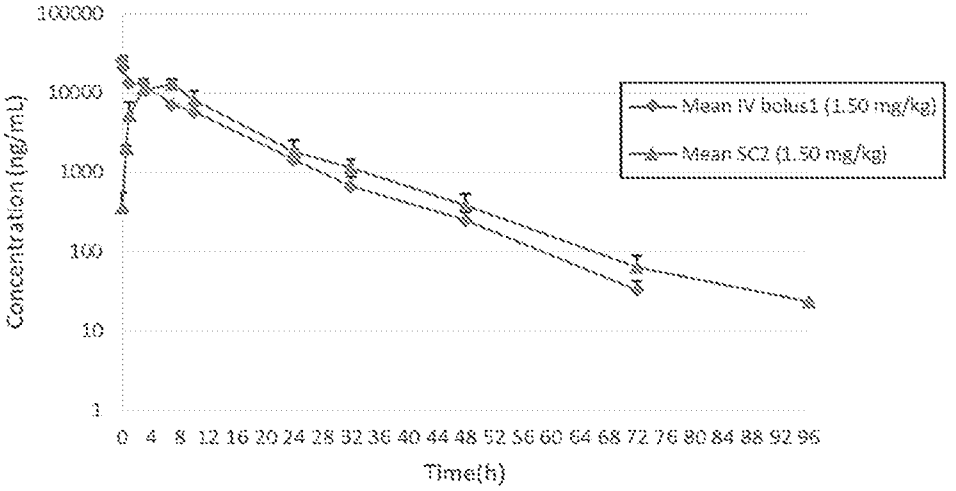


FIG. 9

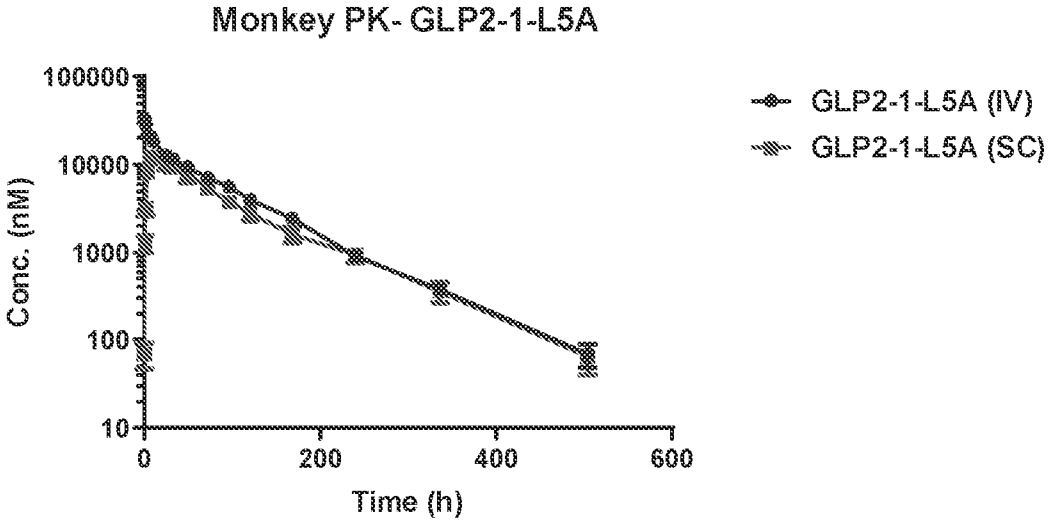


FIG. 10

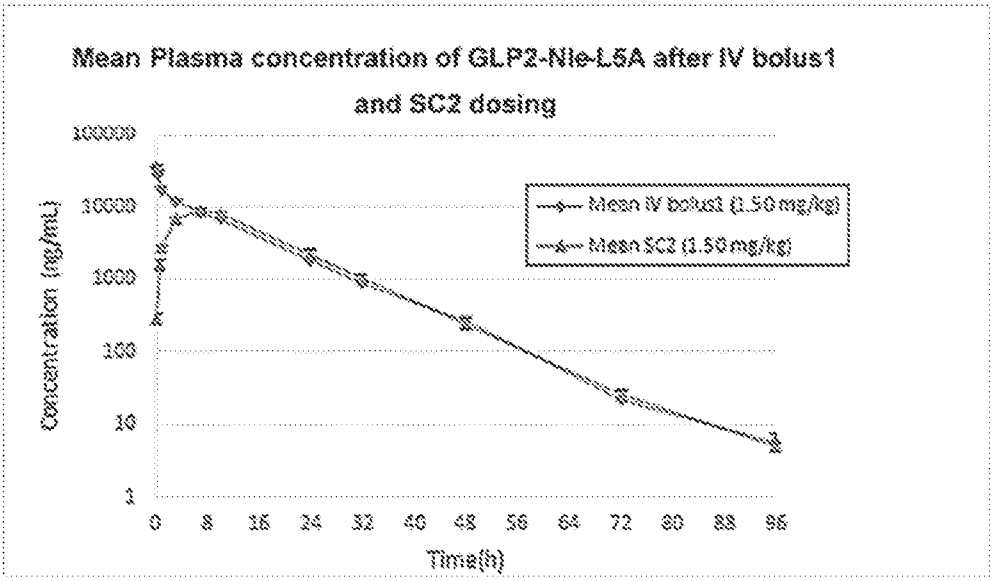

Mean Plasma concentration of GLP2-Nle-L5A after IV bolus1 and SC2 dosing
Concentration (ng/mL)
100000
10000
1000
100
10
1
0
8
16
24
32
40
48
56
64
72
80
88
96
Time(h)
Mean IV bolus1 (1.50 mg/kg)
Mean SC2 (1.50 mg/kg)

FIG. 11

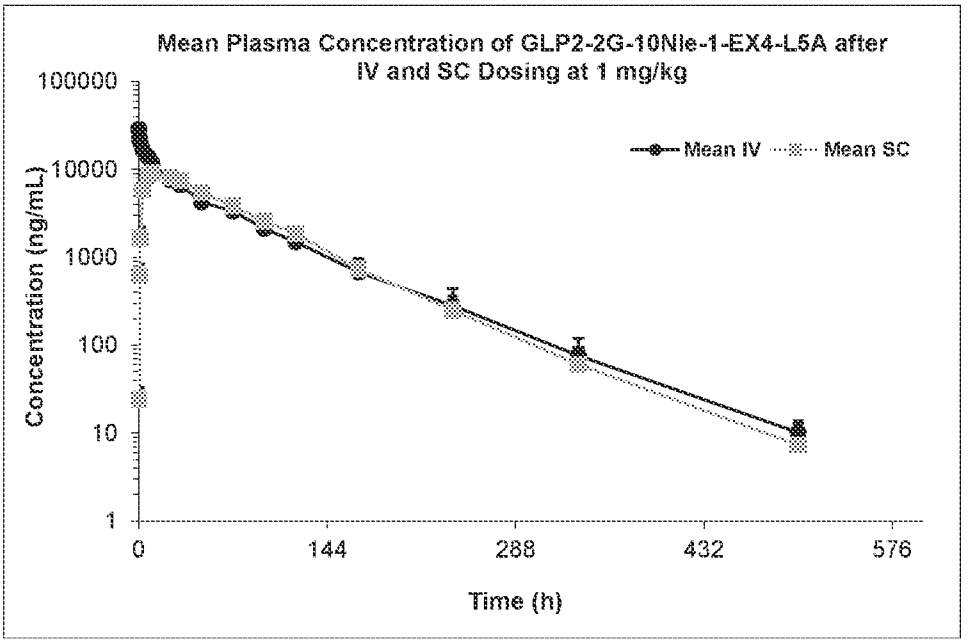

Mean Plasma Concentration of GLP2-2G-10Nle-1-EX4-L5A after IV and SC Dosing at 1 mg/kg
Concentration (ng/mL)
100000
10000
1000
100
10
1
0
144
288
432
576
Time (h)
Mean IV
Mean SC

FIG. 12

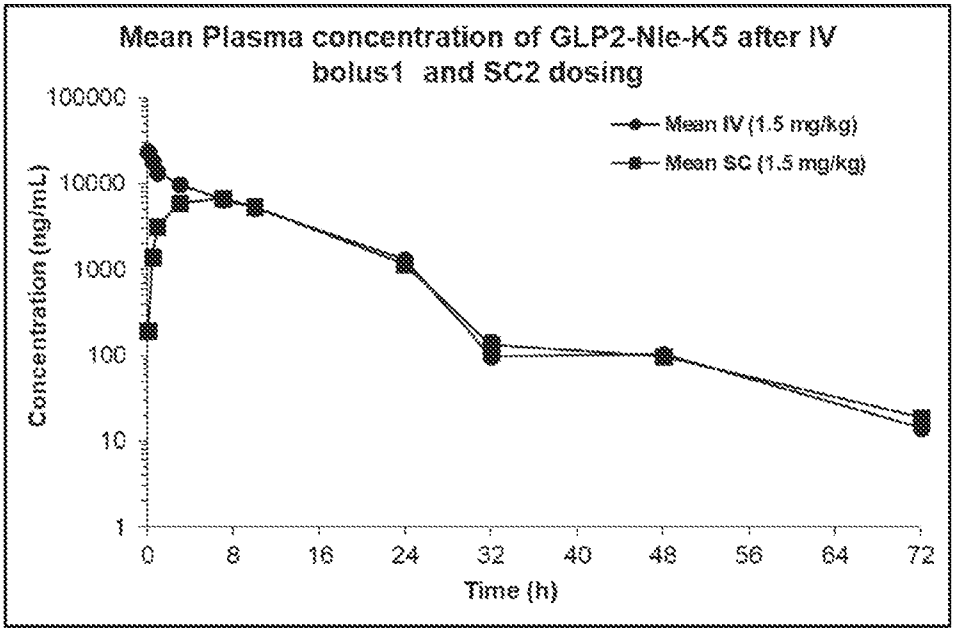

Mean Plasma concentration of GLP2-Nle-K5 after IV bolus1 and SC2 dosing
Mean IV (1.5 mg/kg)
Mean SC (1.5 mg/kg)
Concentration (ng/mL)
100000
10000
1000
100
10
1
0
8
16
24
32
40
48
56
64
72
Time (h)

FIG. 13

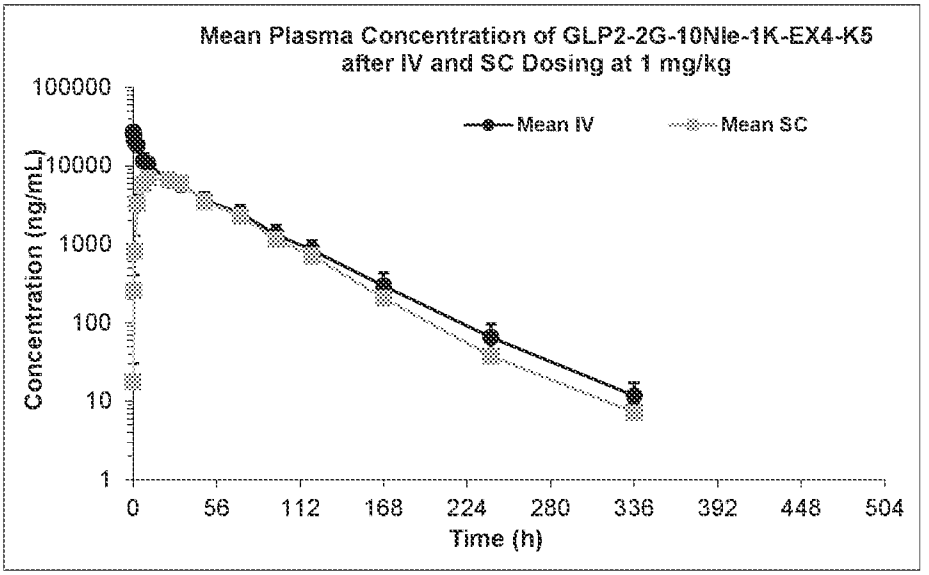

Mean Plasma Concentration of GLP2-2G-10Nle-1K-EX4-K5 after IV and SC Dosing at 1 mg/kg
Mean IV
Mean SC
Concentration (ng/mL)
100000
10000
1000
100
10
1
0
56
112
168
224
280
336
392
448
504
Time (h)

FIG. 14A

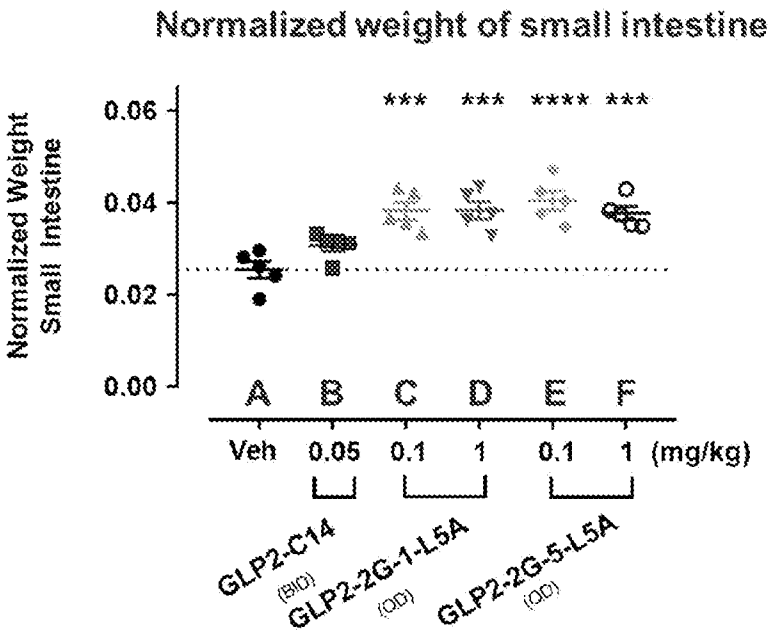


FIG. 14B

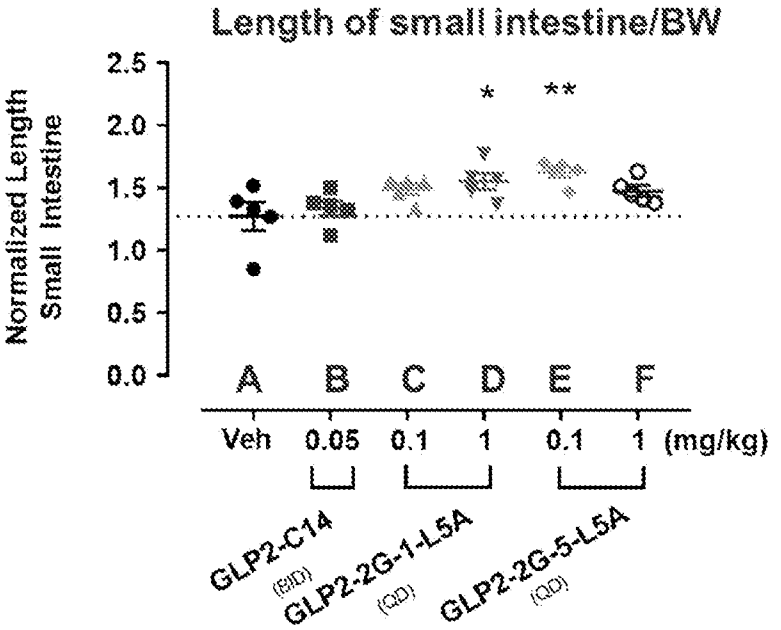


FIG. 14C

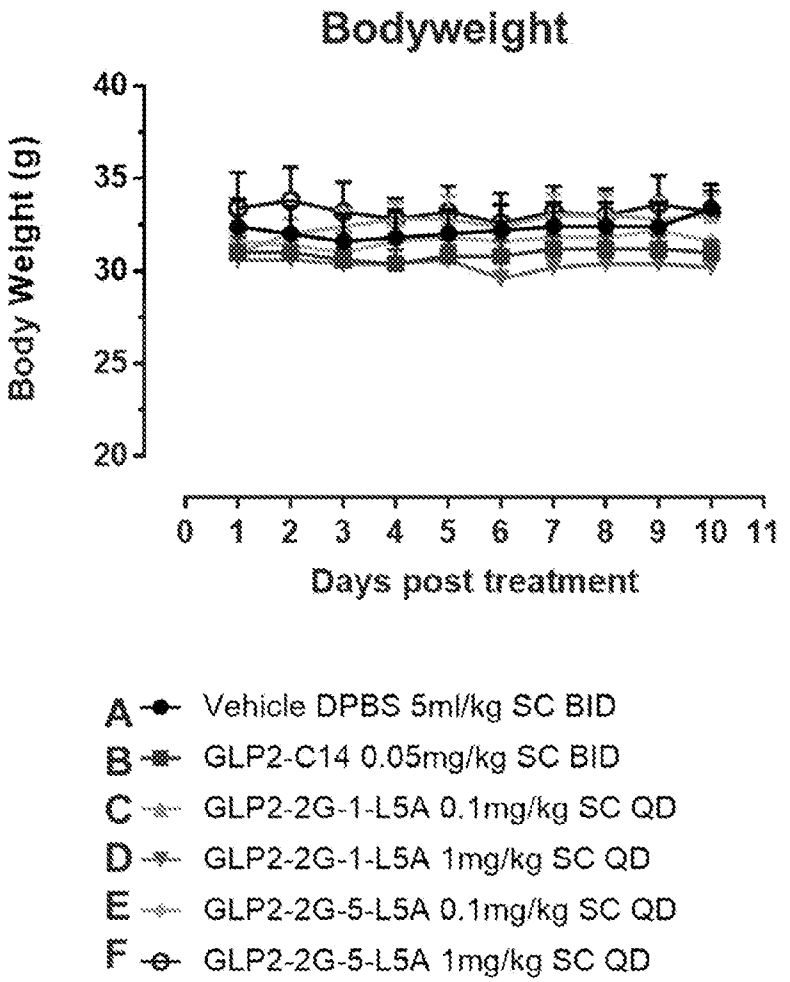

Bodyweight
Body Weight (g)
40
35
30
25
20
0 1 2 3 4 5 6 7 8 9 10 11
Days post treatment
A Vehicle DPBS 5ml/kg SC BID
B GLP2-C14 0.05mg/kg SC BID
C GLP2-2G-1-L5A 0.1mg/kg SC QD
D GLP2-2G-1-L5A 1mg/kg SC QD
E GLP2-2G-5-L5A 0.1mg/kg SC QD
F GLP2-2G-5-L5A 1mg/kg SC QD

FIG. 15A

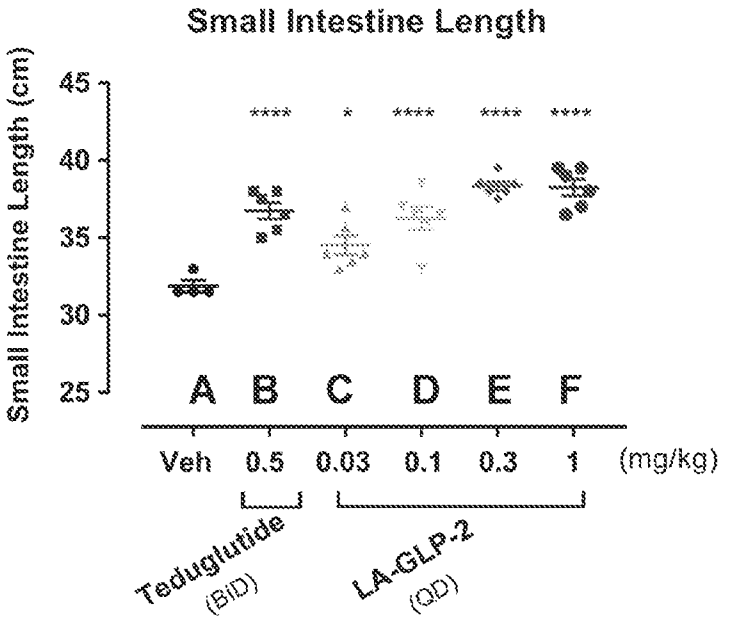


FIG. 15B

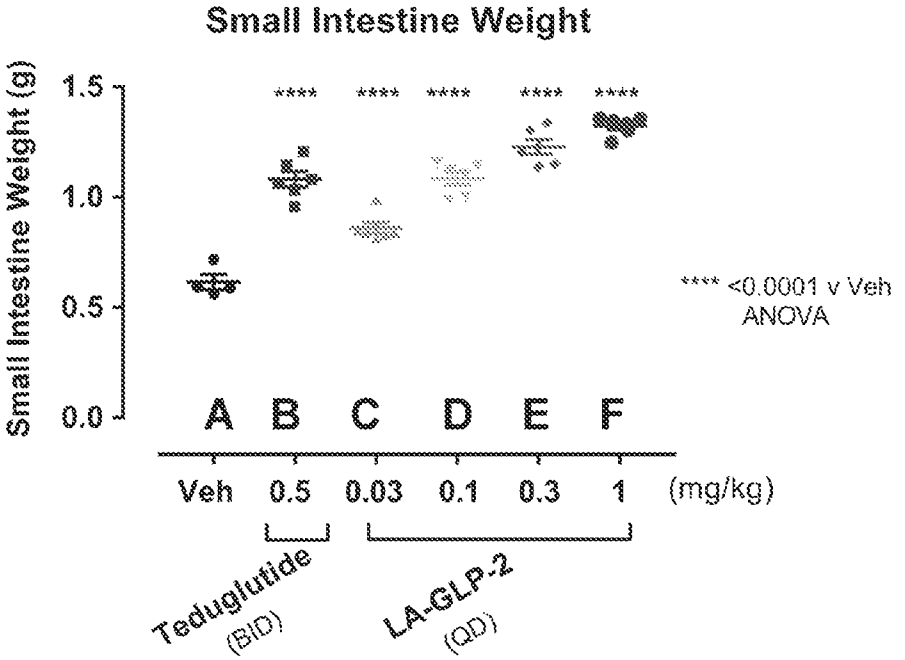


FIG. 15C

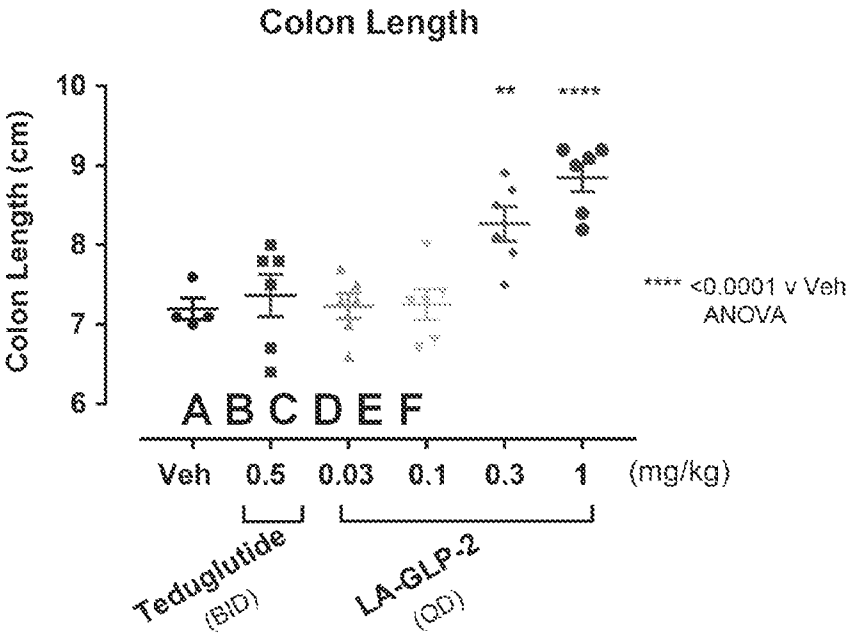


FIG. 15D

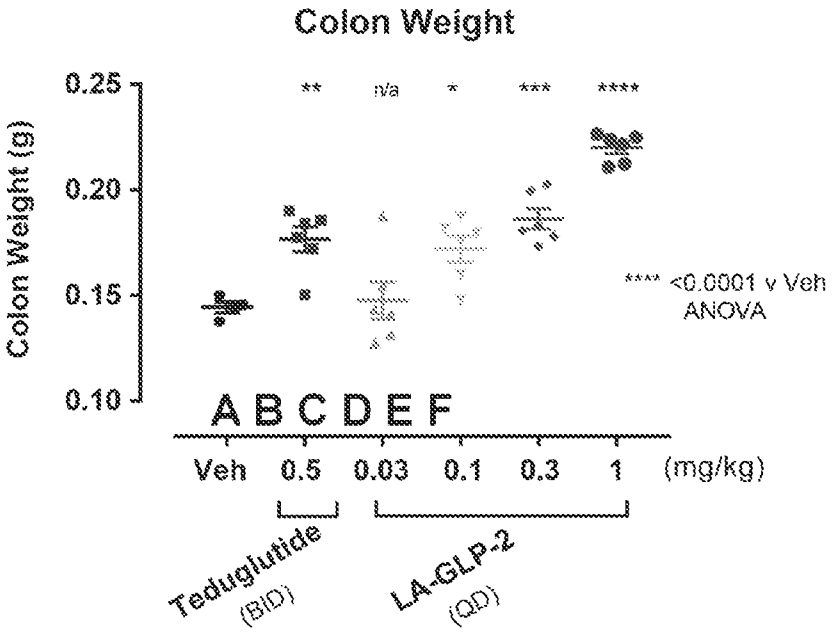


FIG. 16A

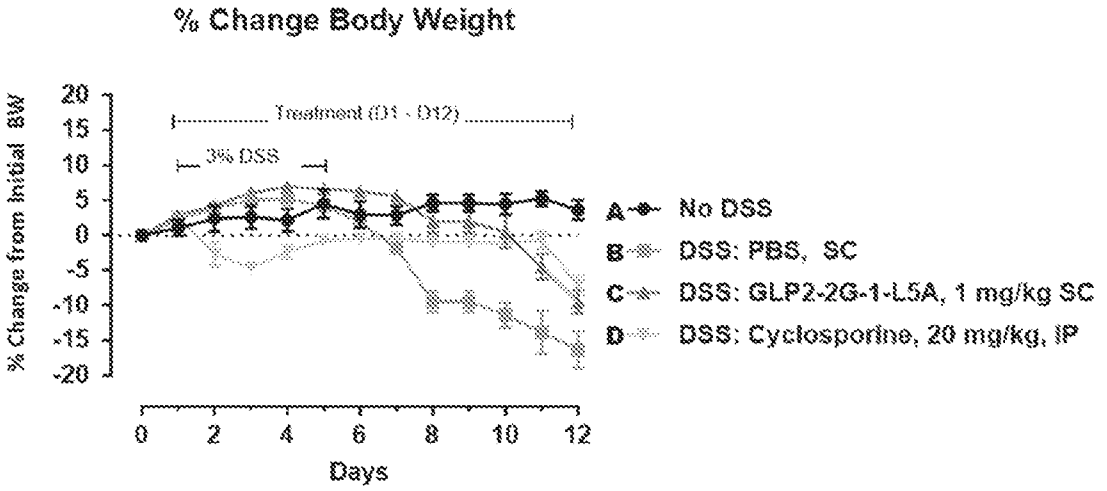


FIG. 16B

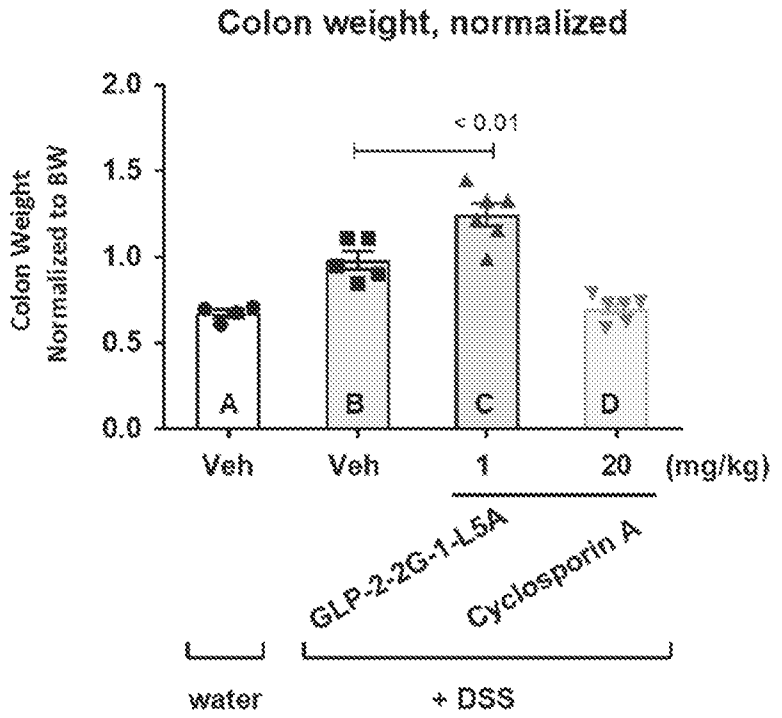


FIG. 16C

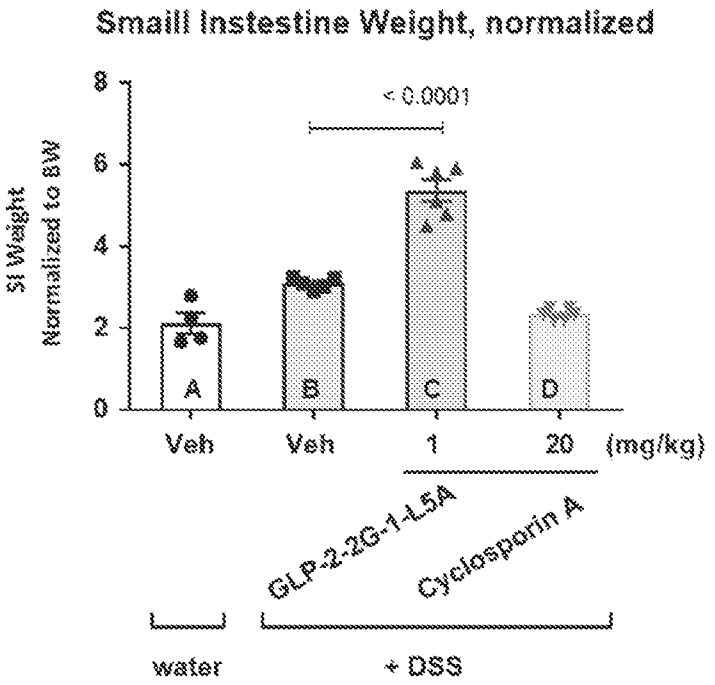


FIG. 16D

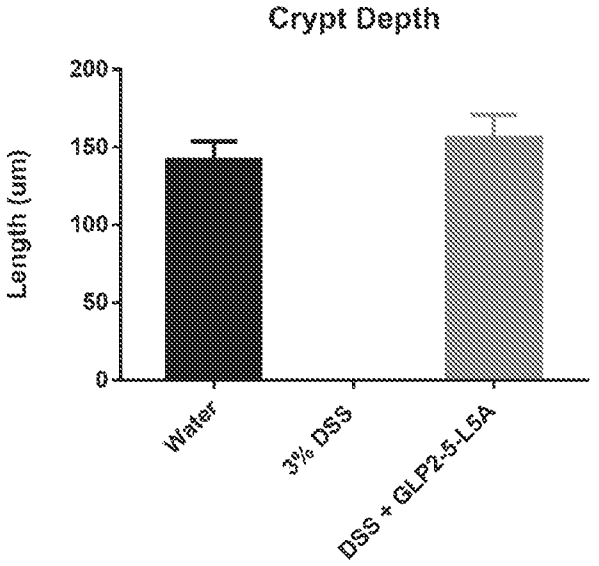


FIG. 16E

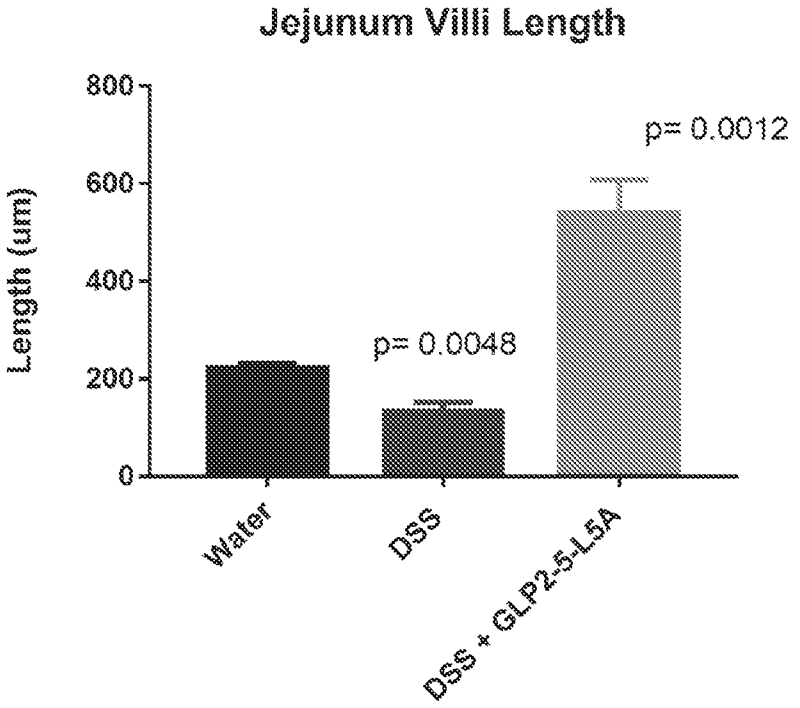

Jejunum Villi Length
Length (um)
800
600
400
200
0
p= 0.0012
p= 0.0048
Water
DSS
DSS + GLP2-5-L5A

FIG. 17A

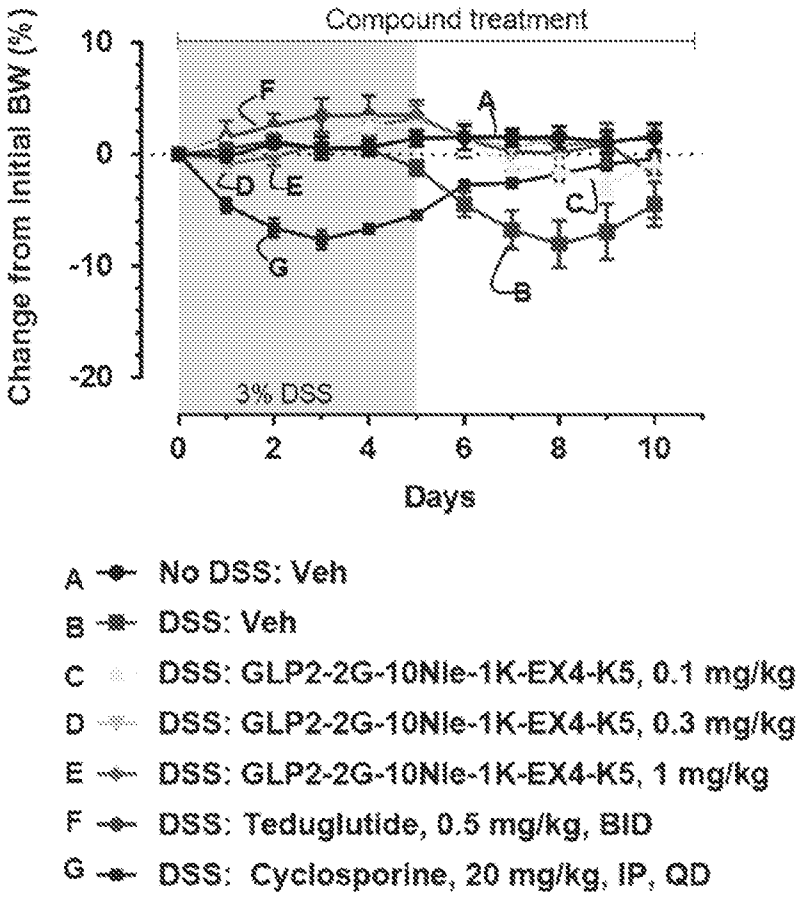


FIG. 17B

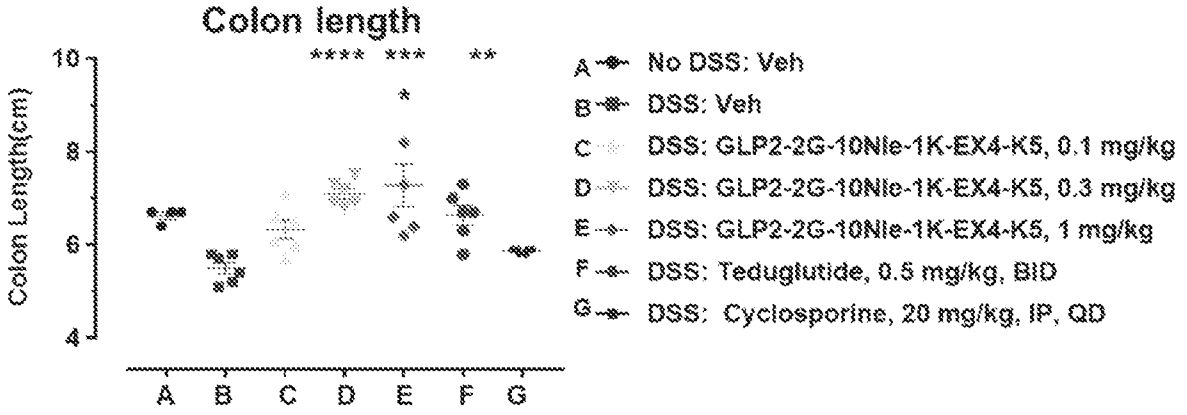


FIG. 17C

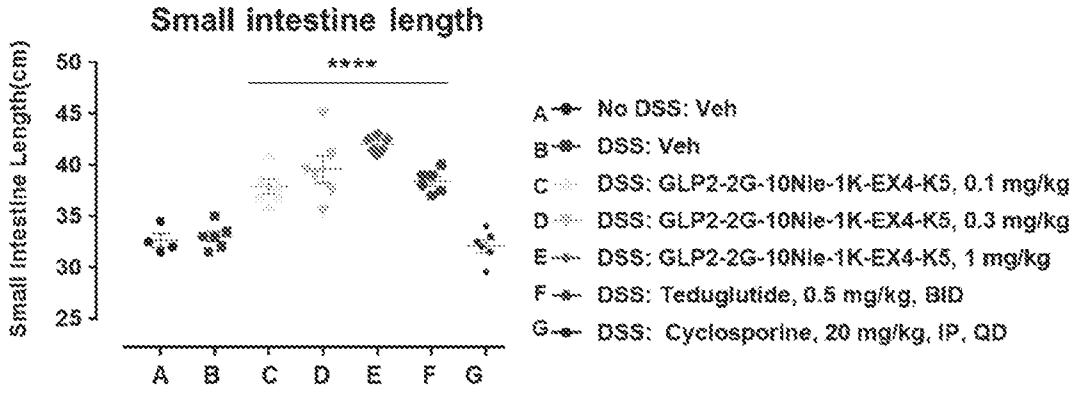


FIG. 17D

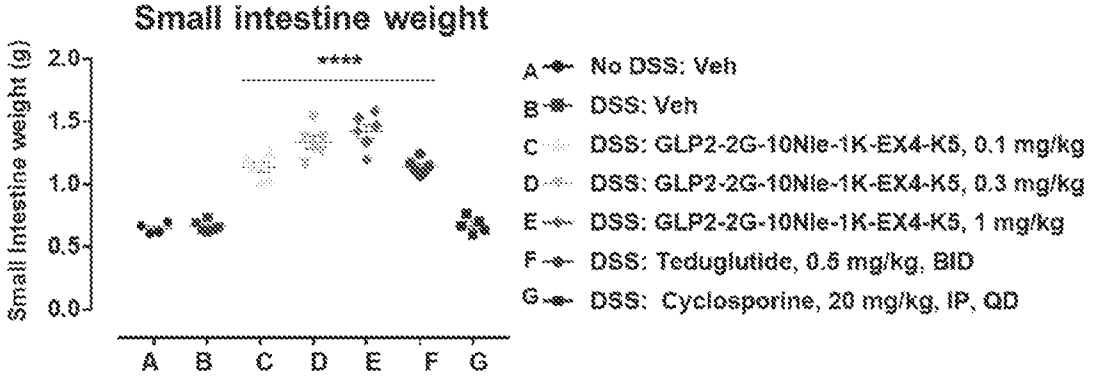


FIG. 17E

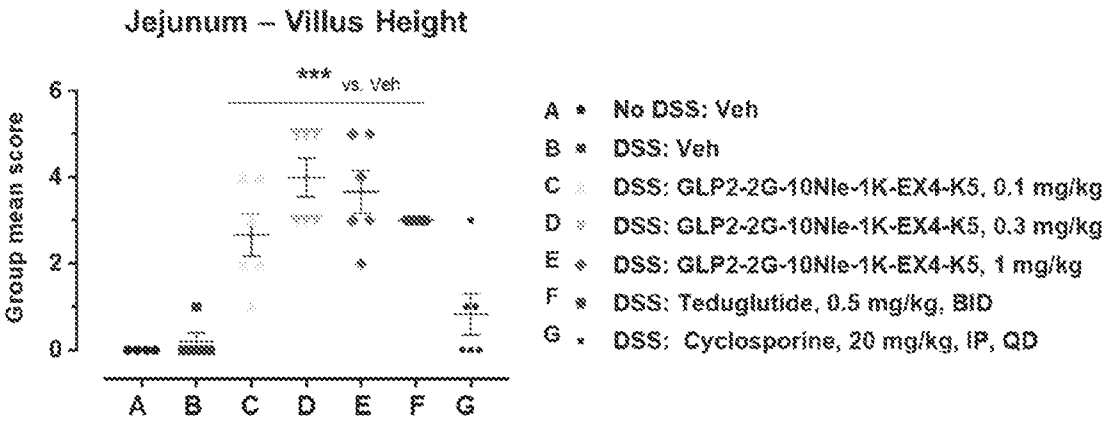


FIG. 17F

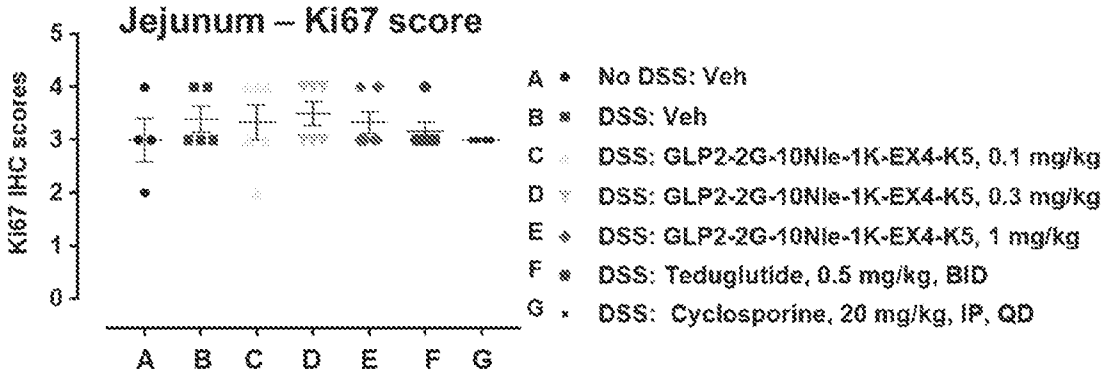


FIG. 17G

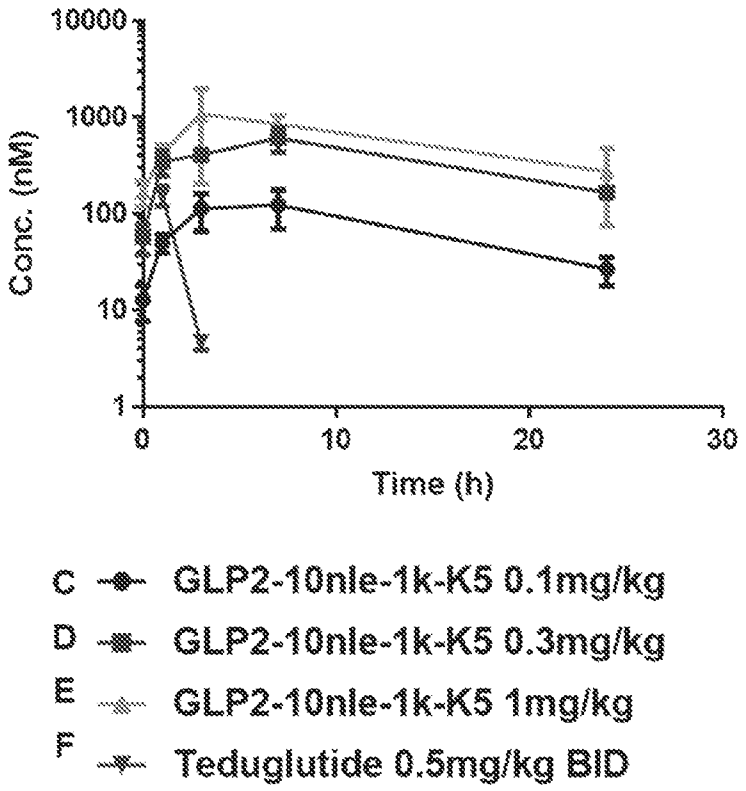

10000
1000
100
10
1
Conc. (nM)
0
10
20
30
Time (h)
C GLP2-10nle-1k-K5 0.1mg/kg
D GLP2-10nle-1k-K5 0.3mg/kg
E GLP2-10nle-1k-K5 1mg/kg
F Teduglutide 0.5mg/kg BID

FIG. 18A

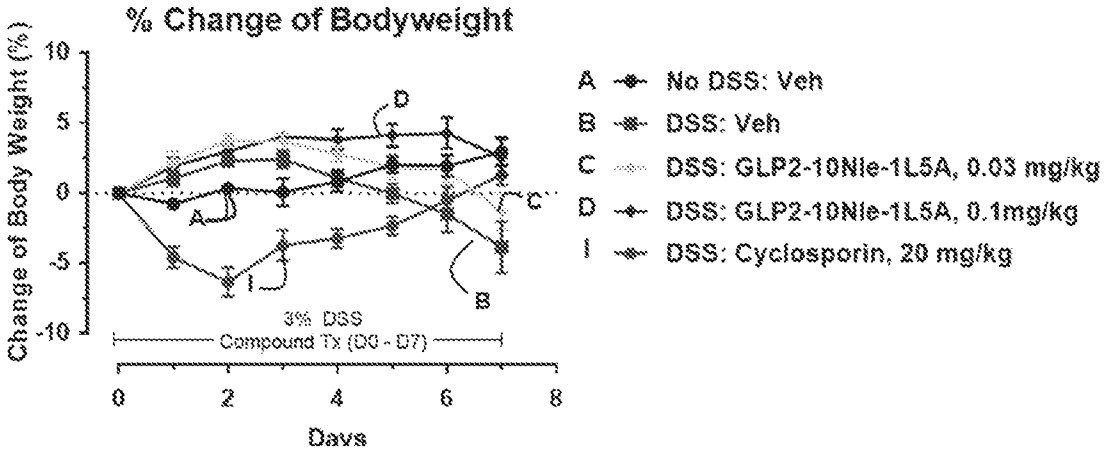


FIG. 18B

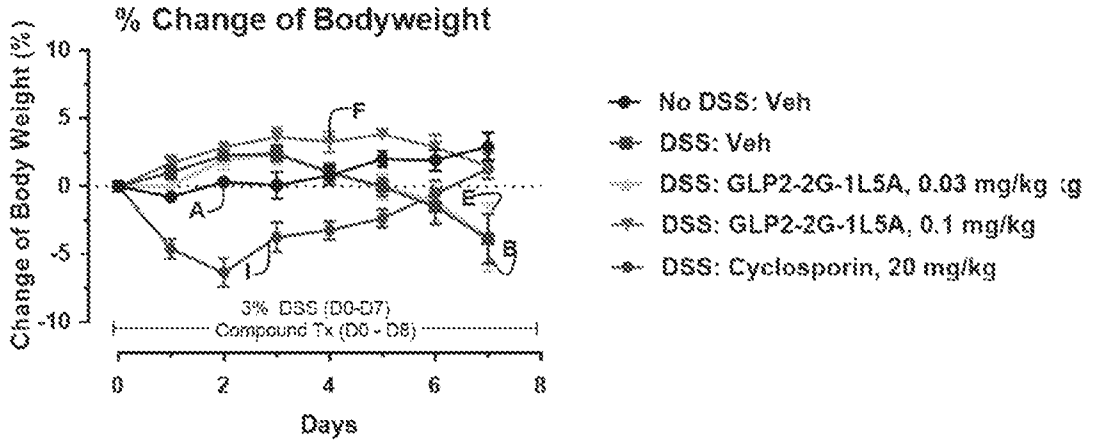


FIG. 18C

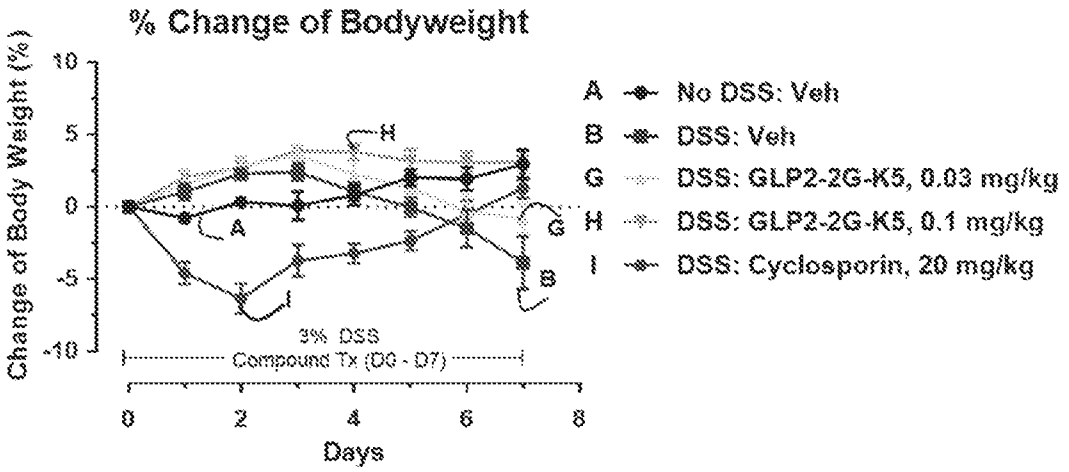


FIG. 18D

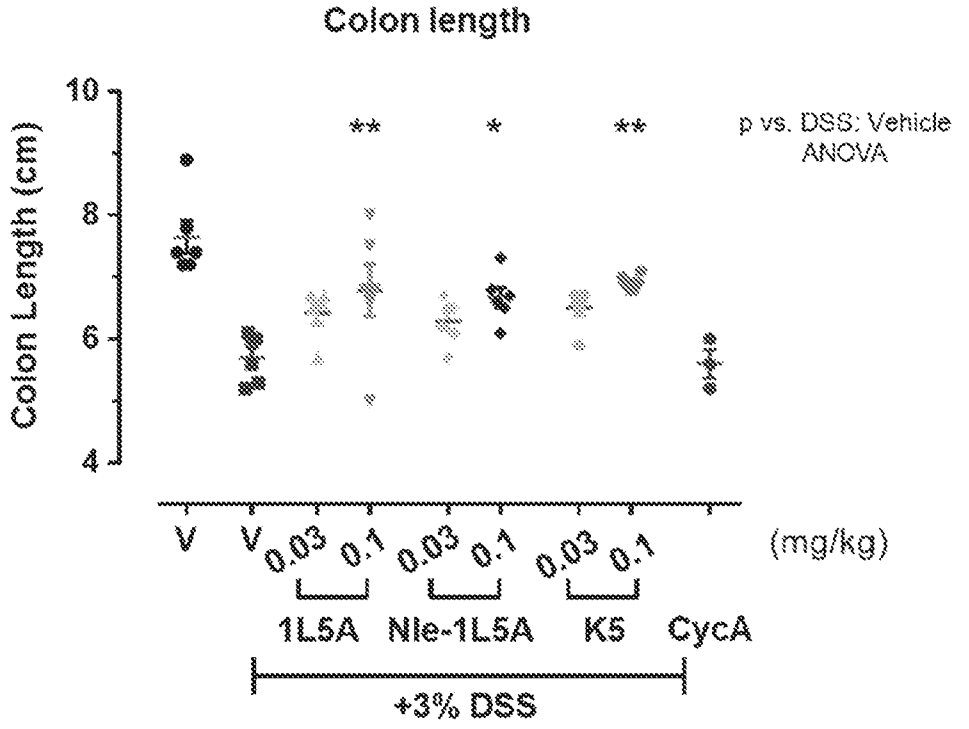


FIG. 18E

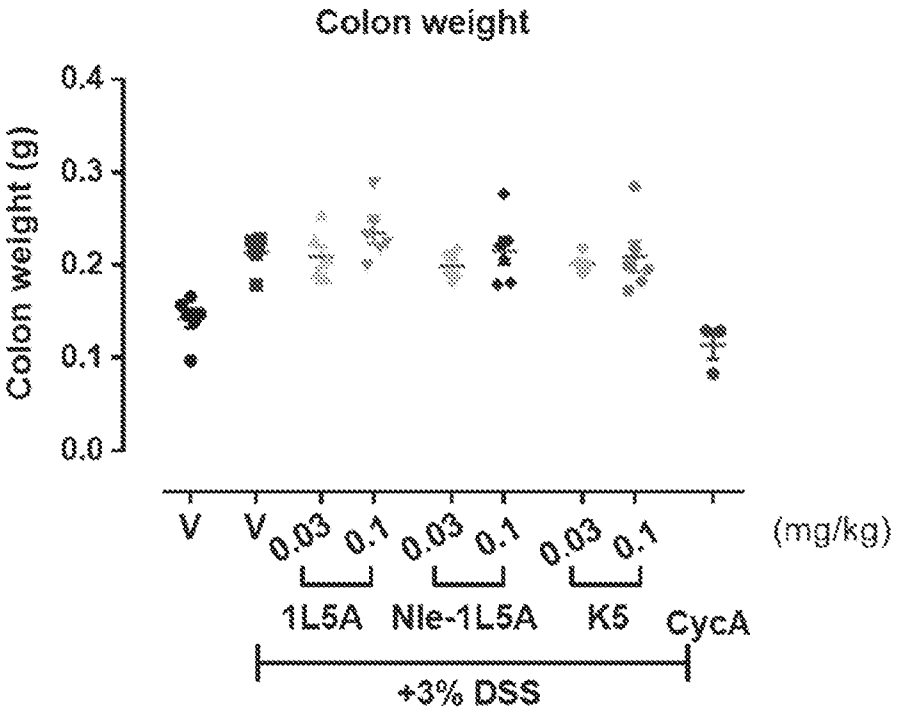


FIG. 18F

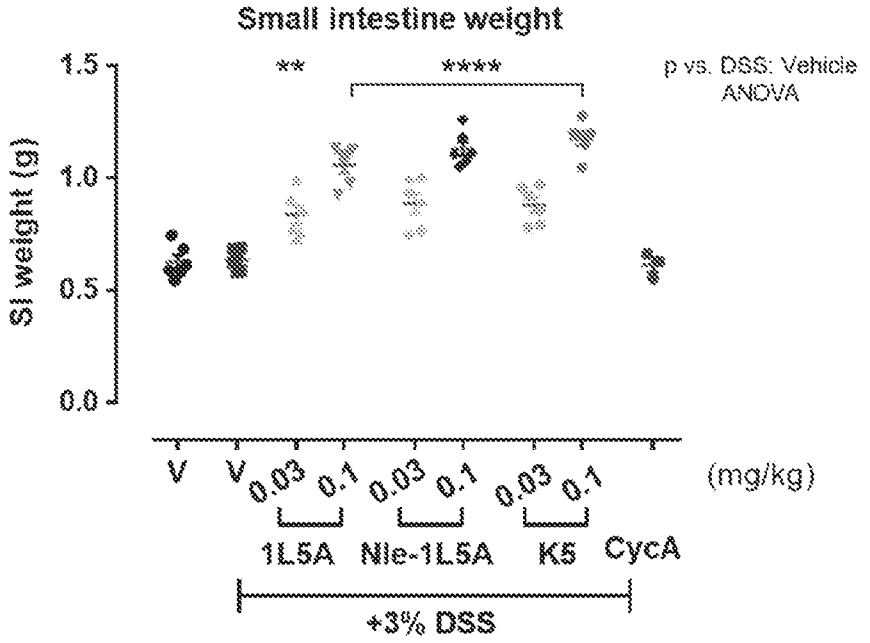


FIG. 18G

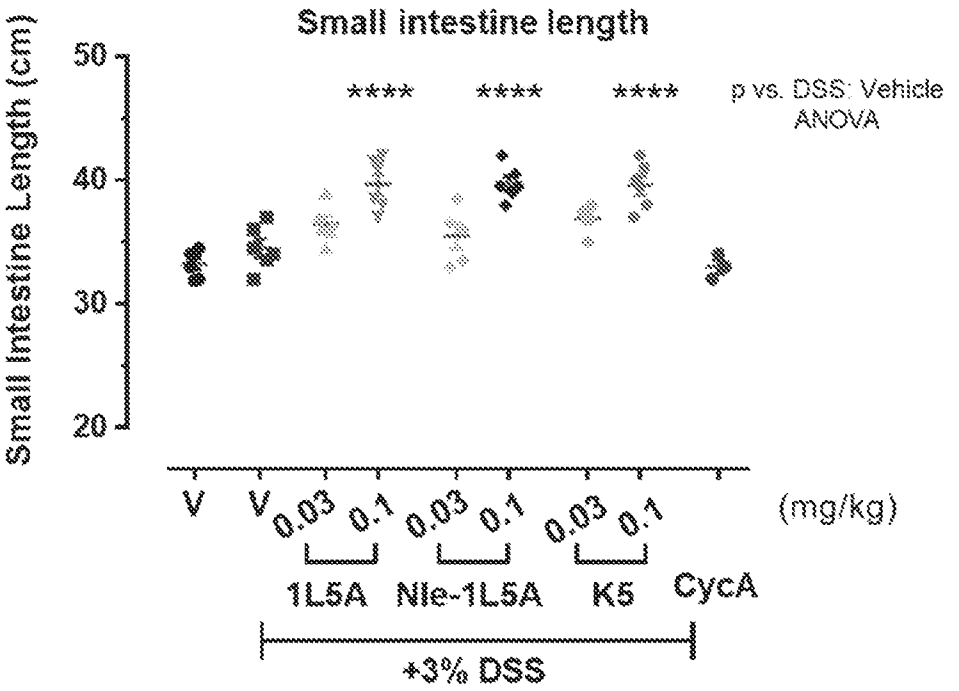


FIG. 18H

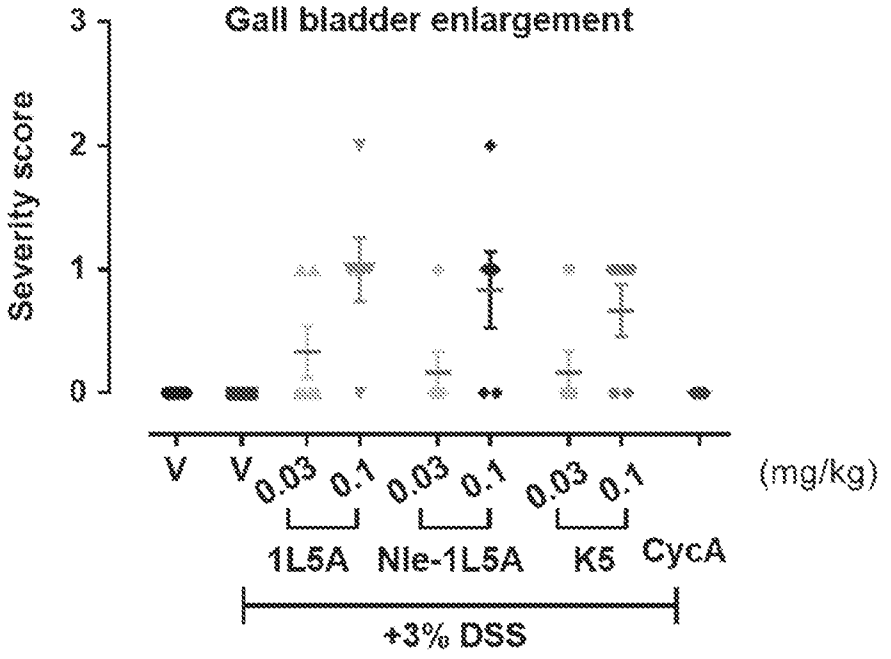


FIG. 18I

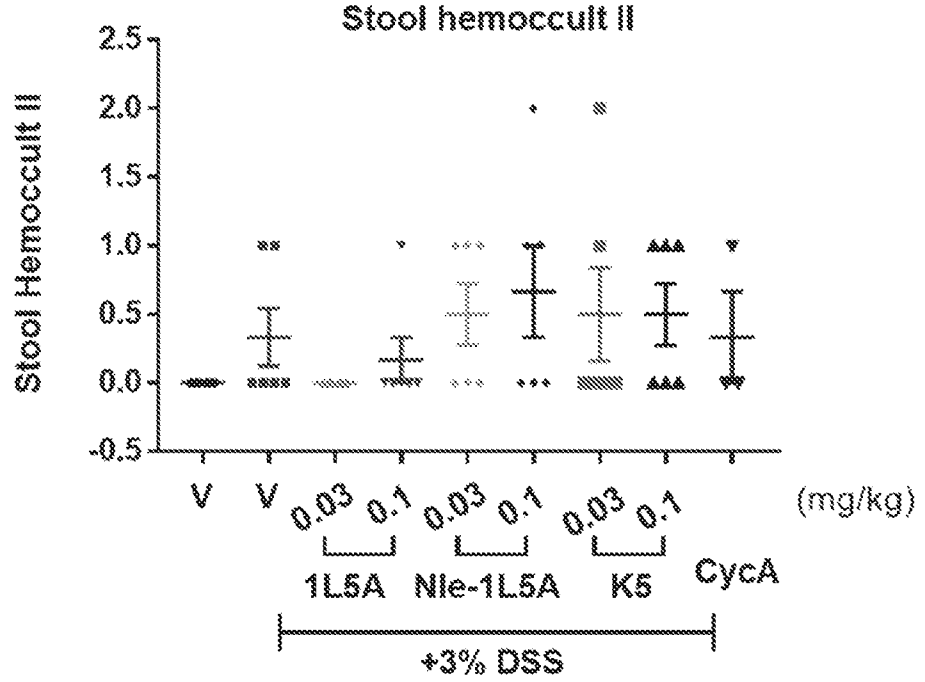


FIG. 18J

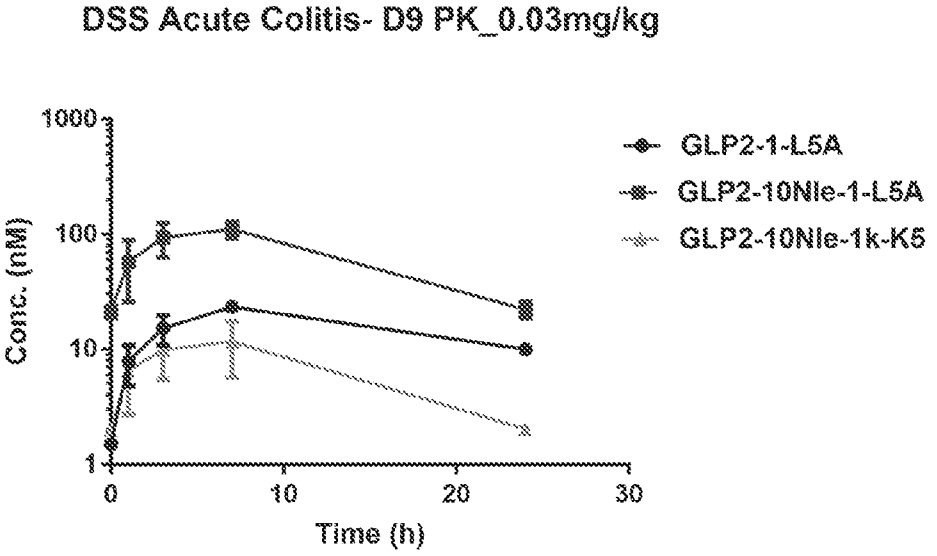


FIG. 18K

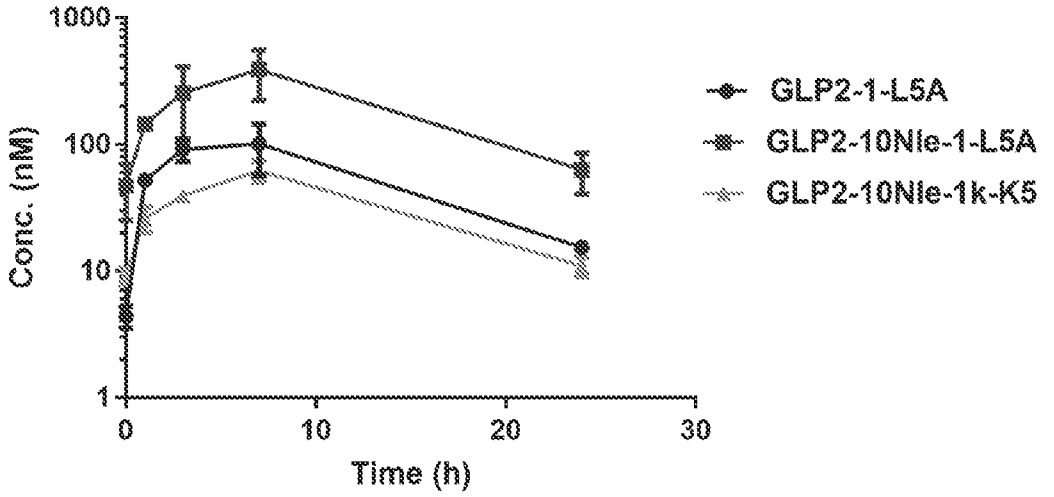


FIG. 18L

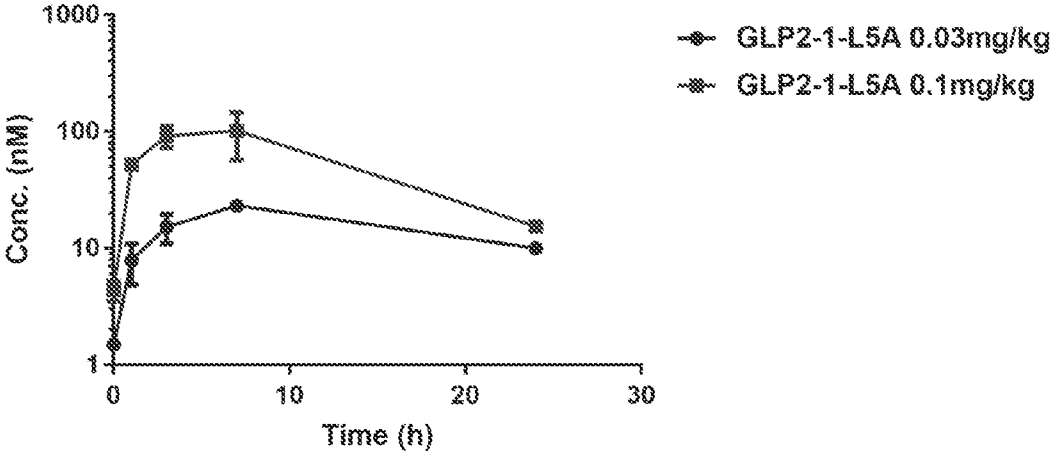


FIG. 18M

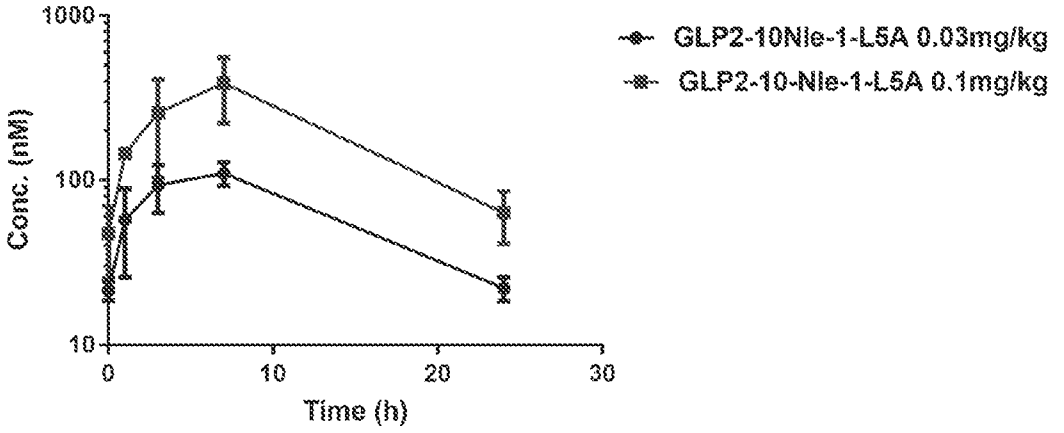


FIG.18N

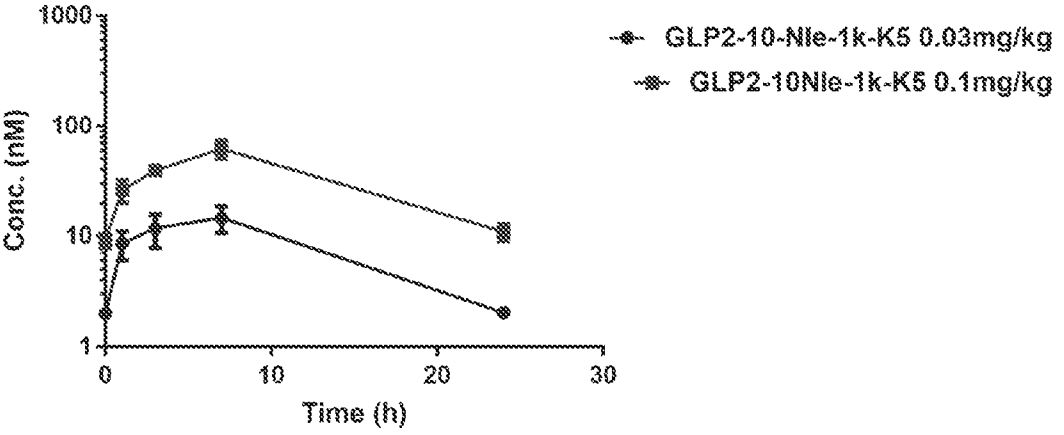


FIG.19A

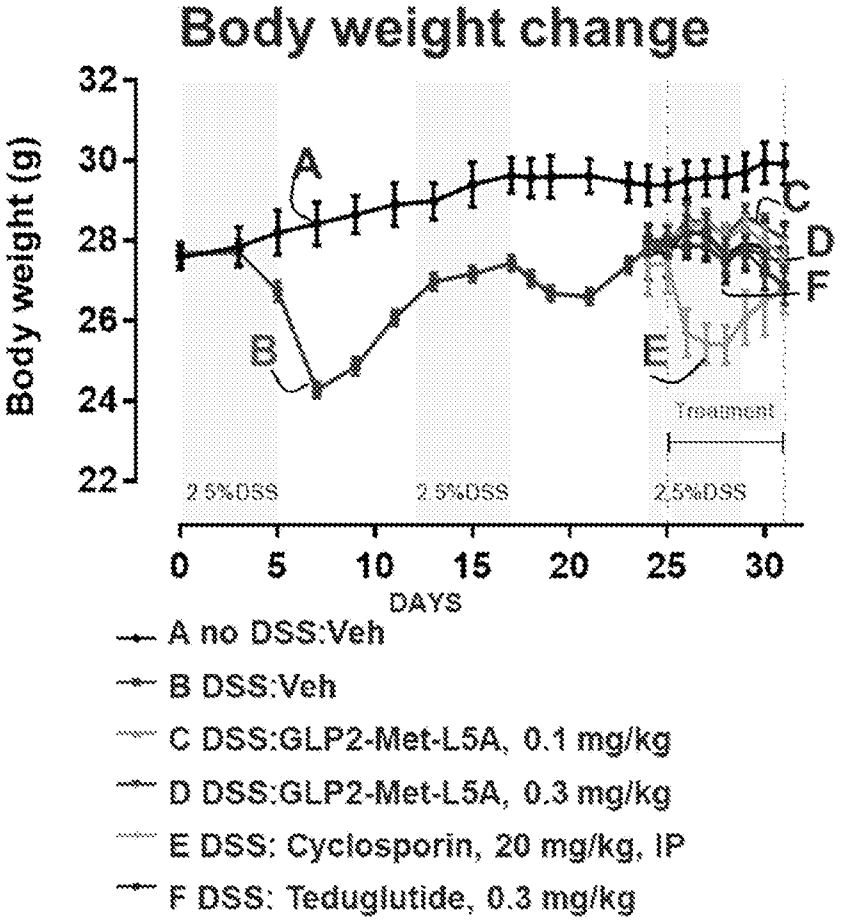

Body weight change
Body weight (g)
32
30
28
26
24
22
A
B
C
D
E
F
Treatment
2.5%DSS
2.5%DSS
2.5%DSS
0
5
10
15
20
25
30
DAYS
A no DSS:Veh
B DSS:Veh
C DSS:GLP2-Met-L5A, 0.1 mg/kg
D DSS:GLP2-Met-L5A, 0.3 mg/kg
E DSS: Cyclosporin, 20 mg/kg, IP
F DSS: Teduglutide, 0.3 mg/kg

FIG. 19B

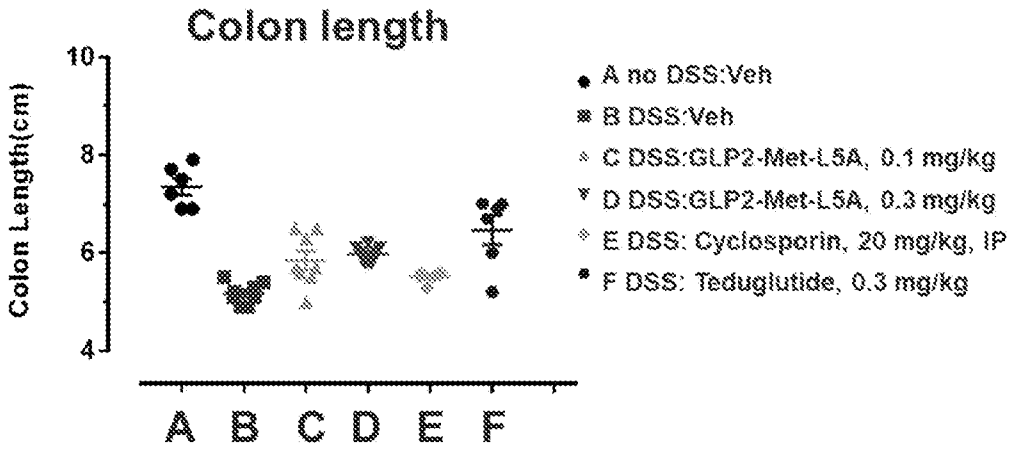


FIG. 19C

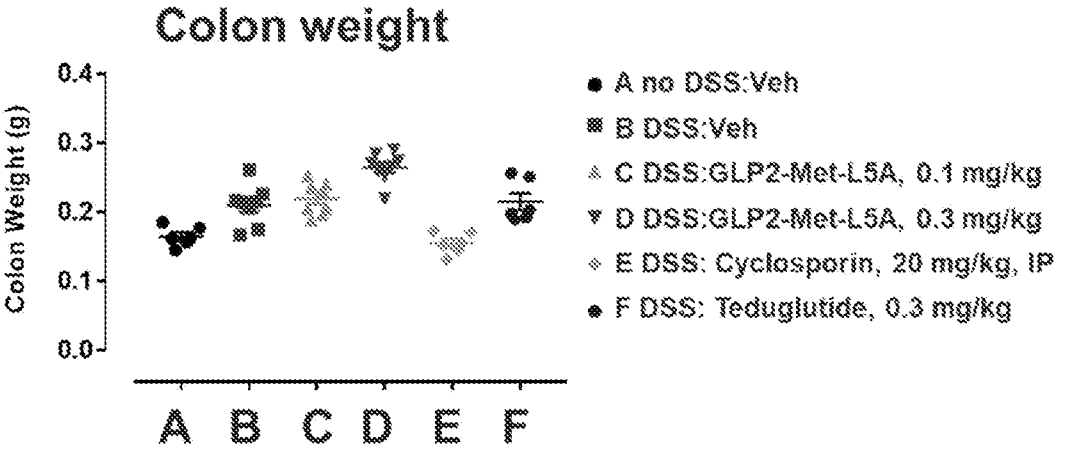


FIG. 19D

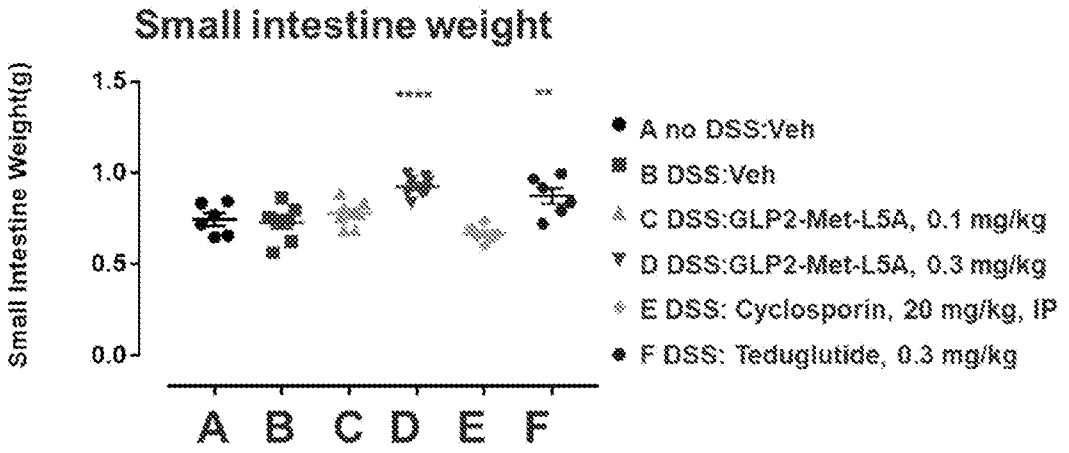

Small intestine weight
Small Intestine Weight(g)
1.5
1.0
0.5
0.0
****
**
A
B
C
D
E
F
A no DSS:Veh
B DSS:Veh
C DSS:GLP2-Met-L5A, 0.1 mg/kg
D DSS:GLP2-Met-L5A, 0.3 mg/kg
E DSS: Cyclosporin, 20 mg/kg, IP
F DSS: Teduglutide, 0.3 mg/kg

FIG.20A

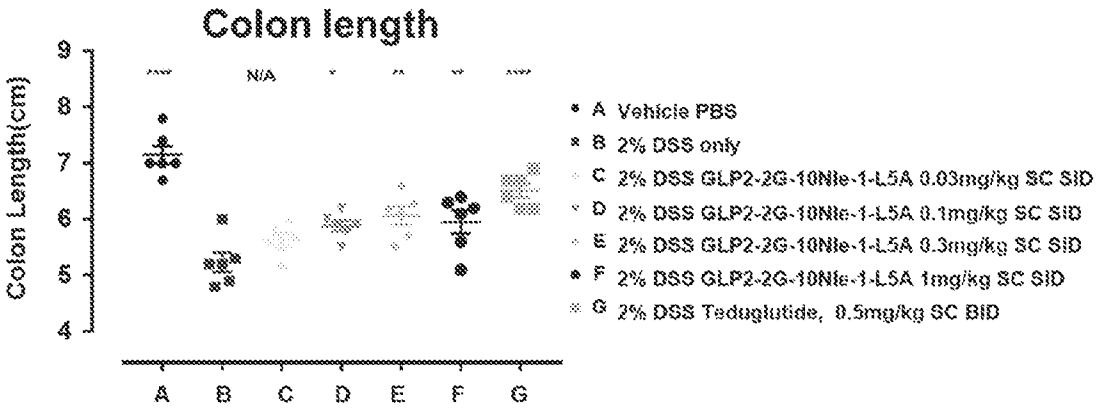


FIG. 20B

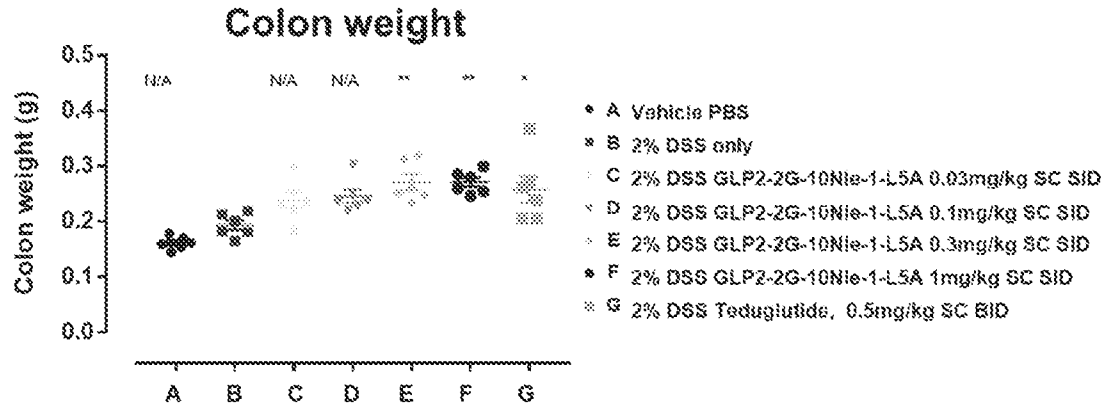


FIG. 20C

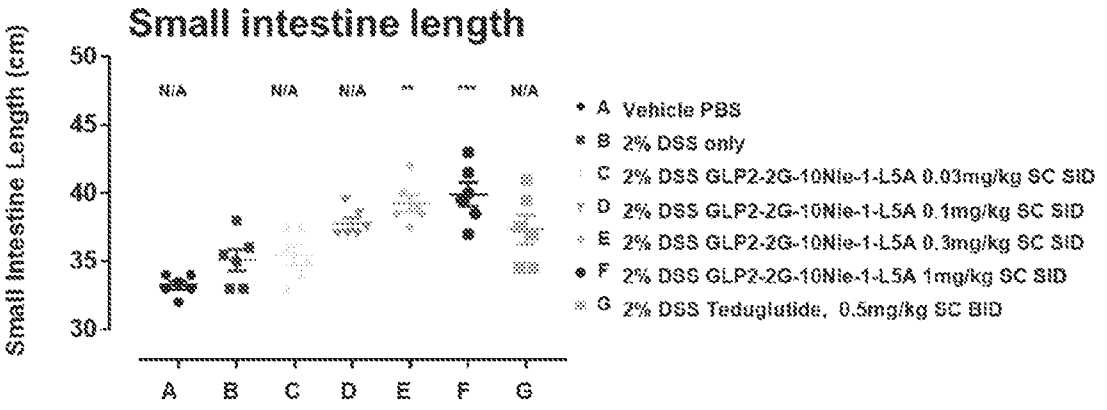

Small intestine length
Small Intestine Length (cm)
50
45
40
35
30
N/A
N/A
N/A
**
***
N/A
A
B
C
D
E
F
G
A Vehicle PBS
B 2% DSS only
C 2% DSS GLP2-2G-10Nle-1-L5A 0.03mg/kg SC SID
D 2% DSS GLP2-2G-10Nle-1-L5A 0.1mg/kg SC SID
E 2% DSS GLP2-2G-10Nle-1-L5A 0.3mg/kg SC SID
F 2% DSS GLP2-2G-10Nle-1-L5A 1mg/kg SC SID
G 2% DSS Teduglutide, 0.5mg/kg SC BID

FIG. 21A

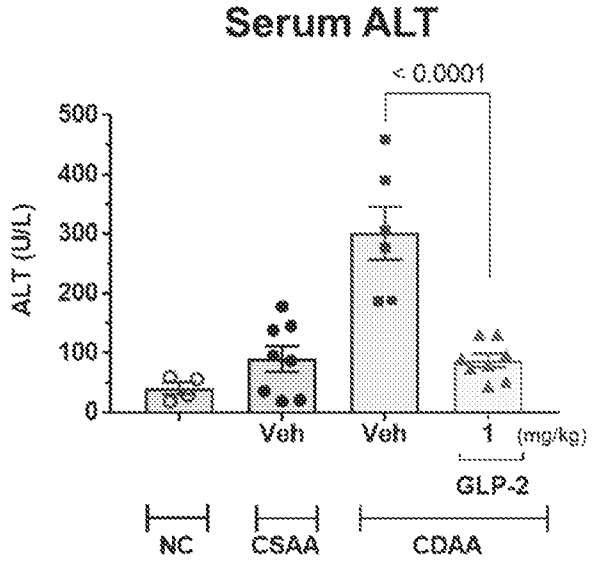


FIG. 21B

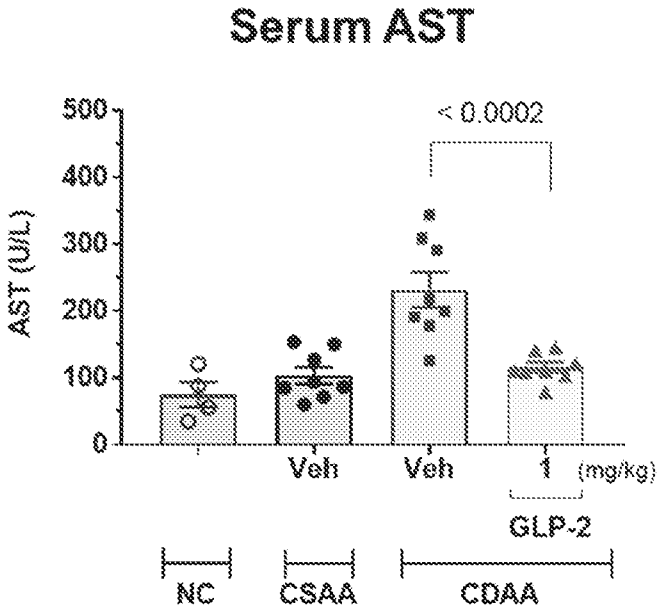


FIG. 21C

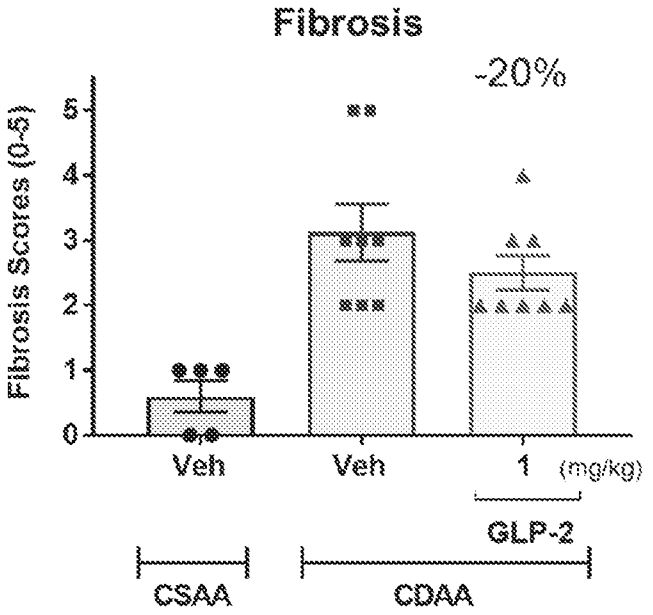


FIG. 21D

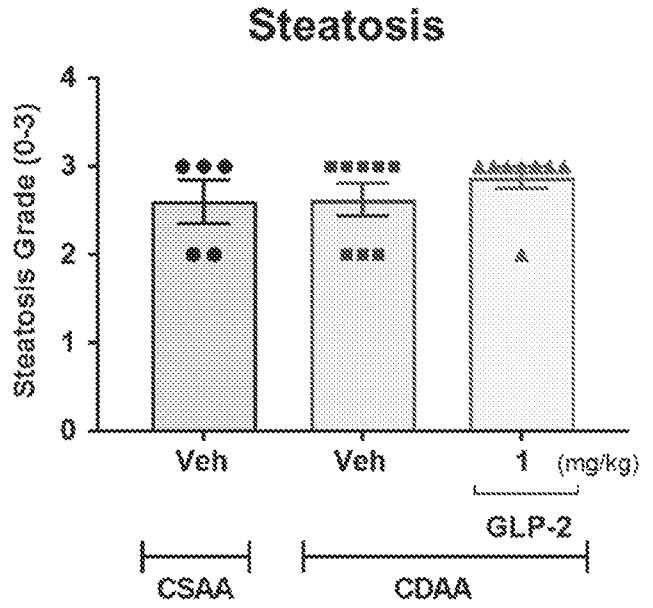


FIG. 21E

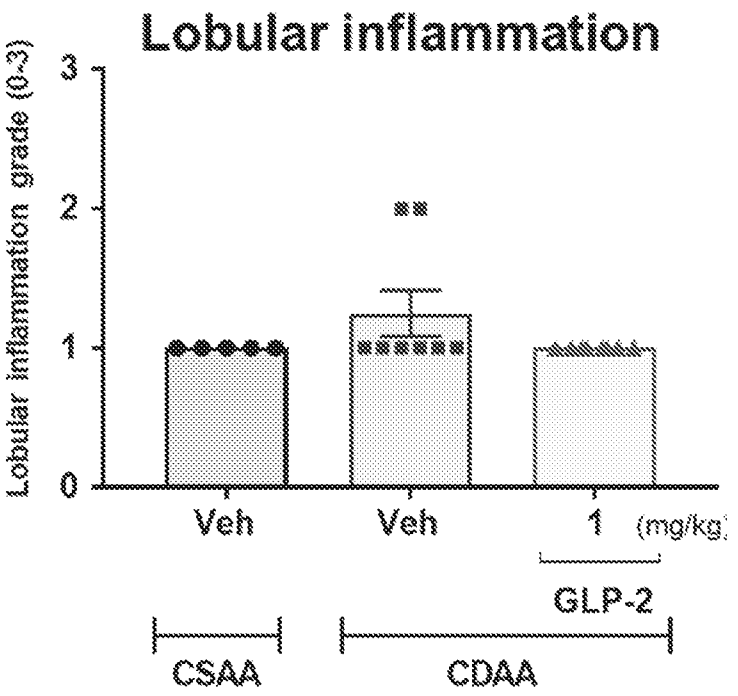

Lobular inflammation
Lobular inflammation grade (0-3)
3
2
1
0
Veh
Veh
1
(mg/kg)
GLP-2
CSAA
CDAA

FIG. 22A

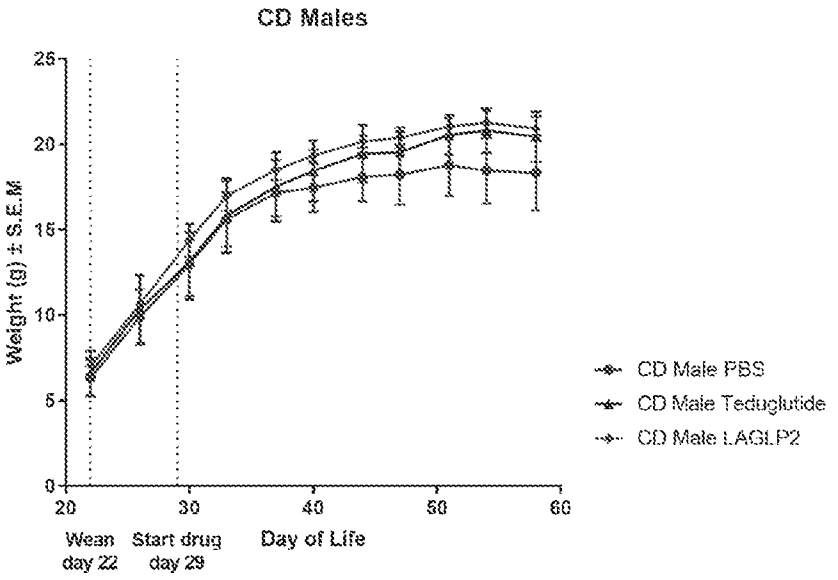


FIG. 22B

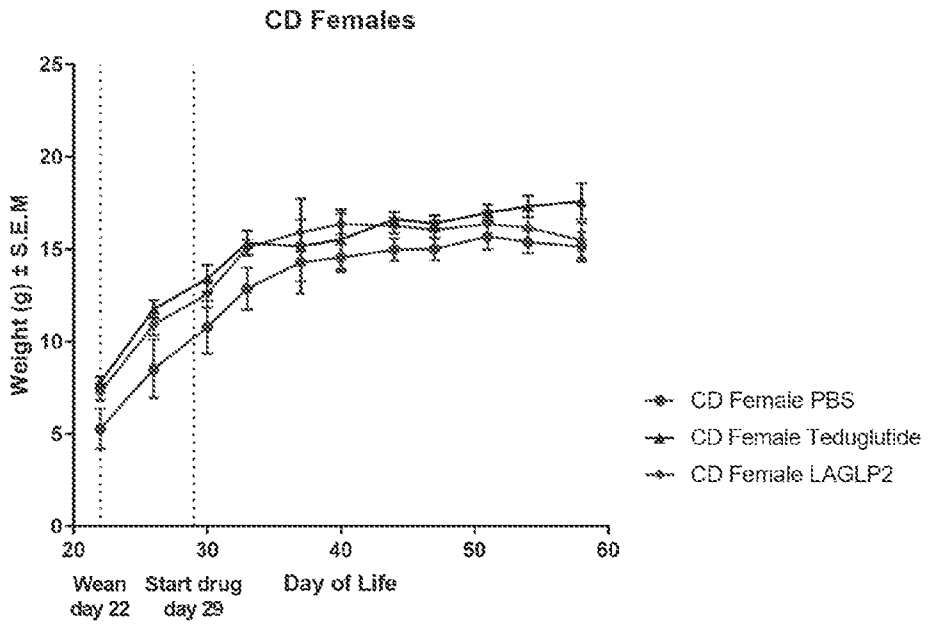


FIG. 22C

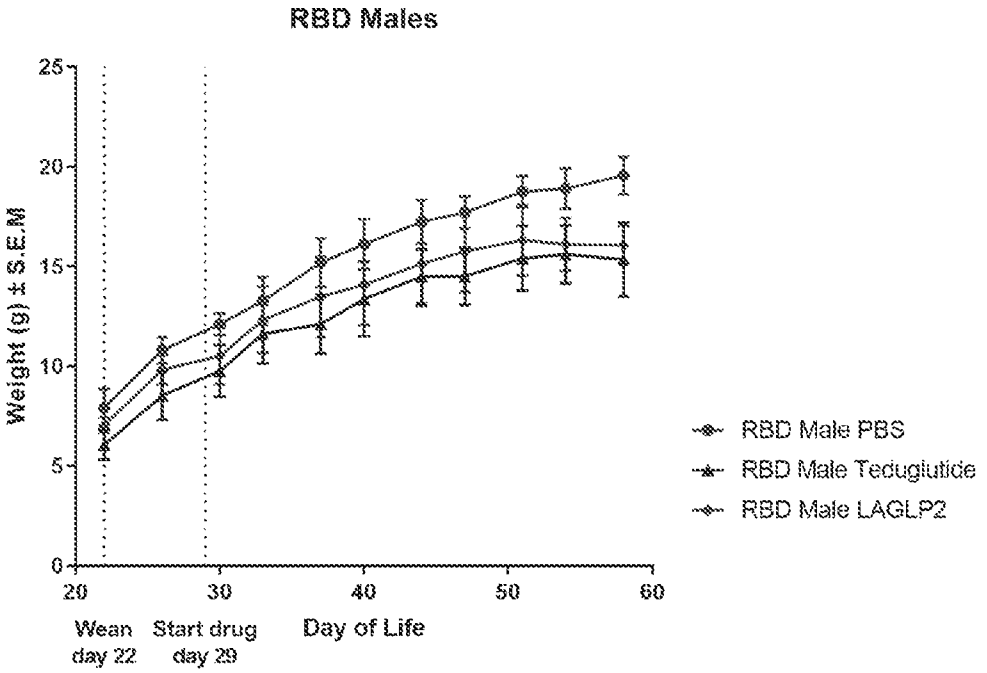


FIG. 22D

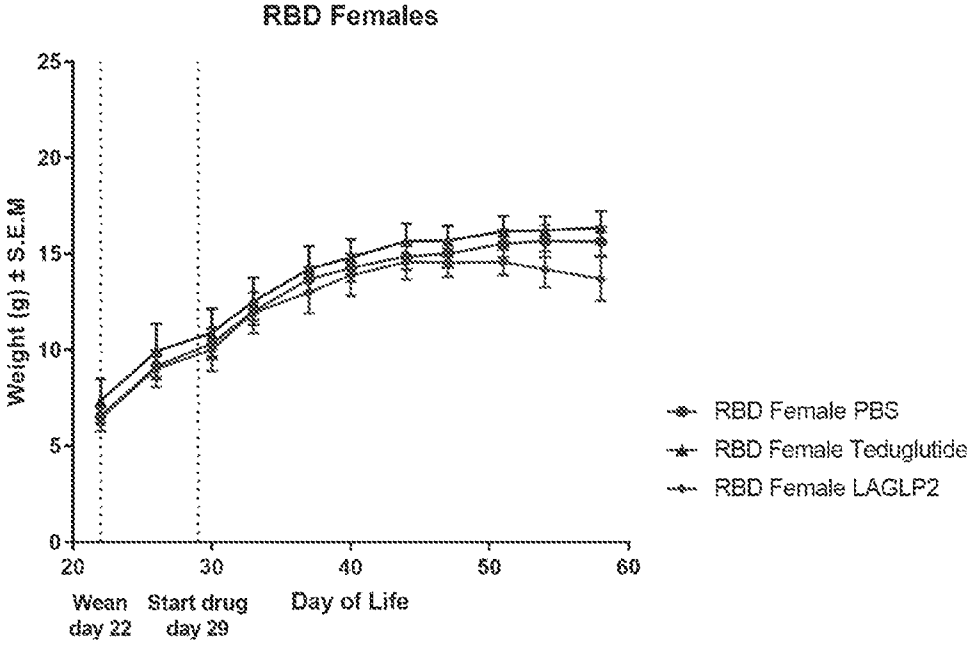


FIG. 22E

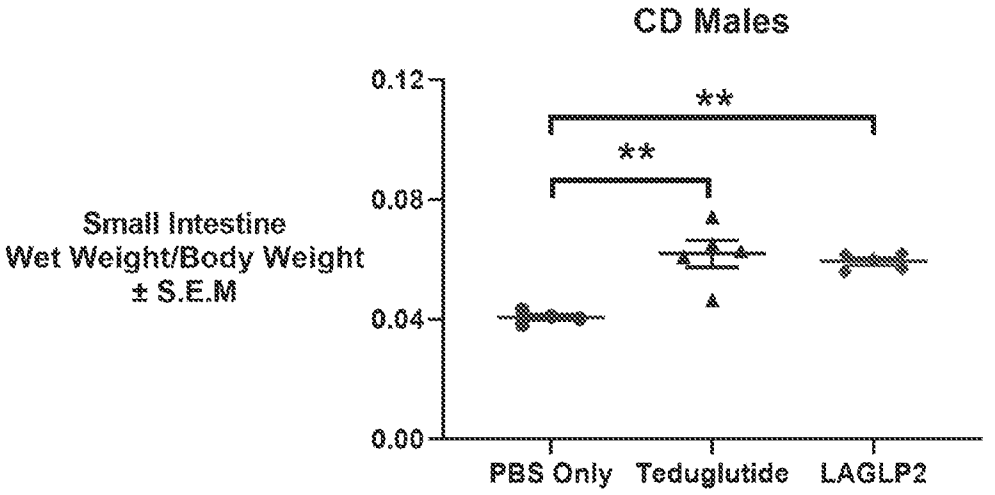
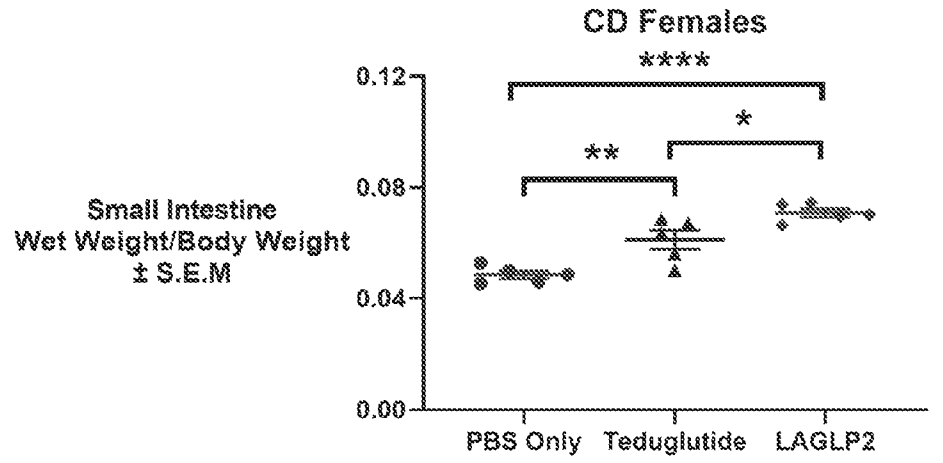


FIG. 22F



GLP2 RECEPTOR AGONISTS AND METHODS OF USE

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application Ser. No. 62/943,667 filed Dec. 4, 2019 and U.S. Provisional Application Ser. No. 62/994,791 filed Mar. 25, 2020; which are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] The development of therapeutic agents is often hampered by short half-lives. The biological half-life of an agent is the time it takes for the agent to lose half of its pharmacologic, physiologic, or radiologic activity. As a result, patients are often administered higher dosages of a therapeutic agent more frequently, which can lead to reduced compliance, higher costs and greater risk of side effects. Accordingly, there is a need for generation of therapeutic agents with extended half-lives.

SUMMARY OF THE INVENTION

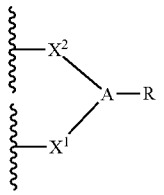
[0003] Disclosed herein is a peptide conjugate comprising:

[0004] a) a peptide that modulates the GLP-2 receptor; and

[0005] b) a staple attached to the peptide at a first amino acid and a second amino acid.

[0006] In some embodiments, the staple is of Formula (I):

Formula (I)



wherein

[0007] A is an optionally substituted alkylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted —NR^3-alkylene-NR^3—, or —N—;

[0008] X^1 and X^2 are independently a bond, —C(═O)—, -alkylene-C(═O)—, —C(═O)-alkylene, or -alkylene-C(═O)NR^3—, -alkylene-C(═O)NR^3-alkylene-;

[0009] wherein X^1 is attached to a first amino acid of the peptide, and X^2 is attached to a second amino acid of the peptide;

[0010] R is hydrogen or -$(L)_s$-Y;

[0011] each L is independently —$(CR^1R^2)_v$—, -alkylene-O—, —O-alkylene-, —C(═O)-alkylene-, -alkylene-C(═O)—, —NR^3-alkylene-, -alkylene-NR^3—, —S-alkylene-, -alkylene-S—, —S(═O)-alkylene-, -alkylene-S(═O)—, —$S(═O)_2$-alkylene, -alkylene-$S(═O)_2$—, —C(═O)—, —C(═O)NR^3—, —NR^3C(═O)—, —NR^3C(═O)NR^3—, —NR^3C(═O)NR^3-alkylene-, —NR^3C(═O)-alkylene-NR^3—, -alkylene-C(═O)NR^3—, —C(═O)NR^3-alkylene-, -alkylene-NR^3C(═O)—, or —NR^3C(═O)-alkylene-;

[0012] v is 2-20;

[0013] each R^1 or R^2 is independently hydrogen, halogen, —CN, —OR^a, —SR^a, —S(═O)R^b, —NO_2, —NR^cR^d, —$S(═O)_2R^d$, —$NR^aS(═O)_2R^d$, —$S(═O)_2NR^cR^d$, —C(═O)R^b, —OC(═O)R^b, —CO_2R^a, —OCO_2R^a, —C(═O)NR^cR^d, —OC(═O)NR^cR^d, —$NR^aC(═O)NR^cR^d$, —$NR^aC(═O)R^b$, —$NR^aC(═O)OR^a$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_5 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OR^a, or —NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OR^a, —NR^cR^d,

[0014] or R^1 and R^2 are taken together to form a C_1-C_6 cycloalkyl or C_1-C_6 heterocycloalkyl;

[0015] each R^3 is independently hydrogen, —S(═O)R^b, —$S(═O)_2R^a$, —$S(═O)_2NR^cR^d$, —C(═O)R^b, —CO_2R^a, —C(═O)NR^cR^d, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OR^a, or —NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OR^a, or —NR^cR^d;

[0016] Y is hydrogen, C_1-C_6 alkyl, —CO_2H, —CO_2(C_1-C_6 alkyl), —CO_2NH_2, —$CO_2N(alkyl)_2$, or —CO_2NH(alkyl); and

[0017] s is 0-20;

[0018] R^a is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

[0019] R^b is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

[0020] each R^c and R^d is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

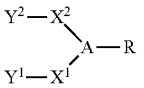
[0021] or R^c and R^d, together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl

is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2.

[0022] Also disclosed herein is a pharmaceutical composition comprising a peptide conjugate described herein and a pharmaceutically acceptable excipient.

[0023] Also disclosed herein is a method for treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a composition comprising a therapeutically effective amount of a peptide conjugate described herein.

[0024] Also described herein is a staple of Formula:

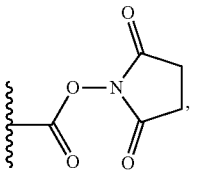


wherein

[0025] A is an optionally substituted alkylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted —NR^3-alkylene-NR^3—, or —N—;

[0026] X^1 and X^2 are independently a bond, —C(═O)—, -alkylene-C(═O)—, —C(═O)-alkylene, -alkylene-C(═O)NR^3—, or -alkylene-C(═O)NR^3-alkylene-;

[0027] Y^1 and Y^2 are independently halogen, —COOH,



or are independently the —S— of a sulfhydryl-containing amino acid or —CONH— wherein the —NH— is part of an amine-containing amino acid in a peptide that modulates the GLP-2 receptor;

[0028] R is hydrogen or -$(L)_s$-Y;

[0029] each L is independently —$(CR^1R^2)_v$—, -alkylene-O—, —O-alkylene-, —C(═O)-alkylene-, -alkylene-C(═O)—, —NR^3-alkylene-, -alkylene-NR^3—, —S-alkylene-, -alkylene-S—, —S(═O)-alkylene-, -alkylene-S(═O)—, —$S(═O)_2$-alkylene, -alkylene-$S(═O)_2$—, —C(═O)—, —C(═O)NR^3—, —NR^3C(═O)—, —NR^3C(═O)NR^3—, —NR^3C(═O)NR^3-alkylene-, —NR^3C(═O)-alkylene-NR^3—, -alkylene-C(═O)NR^3—, —C(═O)NR^3-alkylene-, -alkylene-NR^3C(═O)—, or —NR^3C(═O)-alkylene-;

[0030] v is 2-20;

[0031] each R^1 or R^2 is independently hydrogen, halogen, —CN, —OR^a, —SR^a, —S(═O)R^b, —NO_2, —NR^cR^d, —$S(═O)_2R^a$, —$NR^aS(═O)_2R^d$, —$S(═O)_2NR^cR^d$, —C(═O)R^b, —OC(═O)R^b, —CO_2R^a, —OCO_2R^a, —C(═O)NR^cR^d, —OC(═O)NR^cR^d, —$NR^aC(═O)NR^cR^d$, —$NR^aC(═O)R^b$, —$NR^aC(═O)OR^a$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_5 cycloalkyl, C_2-C_5 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OR^a, or —NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OW, —NR^cR^d,

[0032] or R^1 and R^2 are taken together to form a C_1-C_6 cycloalkyl or C_1-C_6 heterocycloalkyl;

[0033] each R^3 is independently hydrogen, —S(═O)R^b, —$S(═O)_2R^a$, —$S(═O)_2NR^cR^d$, —C(═O)R^b, —CO_2R^a, —C(═O)NR^cR^d, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OR^a, or —NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OR^a, or —NR^cR^d;

[0034] Y is hydrogen, C_1-C_6 alkyl, —CO_2H, —CO_2(C_1-C_6 alkyl), —CO_2NH_2, —$CO_2N(alkyl)_2$, or —CO_2NH(alkyl); and

[0035] s is 0-20;

[0036] R^a is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

[0037] R^b is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

[0038] each R^c and R^d is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

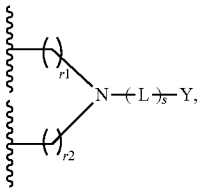
[0039] or R^c and R^d, together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2.

[0040] In some embodiments, A is optionally substituted alkylene. In some embodiments, A is —$(CH_2)_t$—, wherein t is 1-12. In some embodiments, A is optionally substituted arylene. In some embodiments, A is —NR^3-alkylene-NR^3—. In some embodiments, A is —N—.

[0041] In some embodiments, X^1 and X^2 are —C(═O)—. In some embodiments, X^1 and X^2 are -alkylene-C(═O)—. In some embodiments, X^1 and X^2 are —CH_2—C(═O)—. In some embodiments, X^1 and X^2 are independently -alkylene-

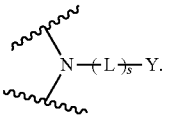
C(=O)NR^3—. In some embodiments, X^1 and X^2 are independently —CH$_2$—C(=O)NR^3—. In some embodiments, X^1 and X^2 are independently -alkylene-C(=O)NR^3-alkylene-. In some embodiments, X^1 and X^2 are independently —CH$_2$—C(=O)NR^3—CH$_2$CH$_2$—.

[0042] In some embodiments, >A-R has the following structure:

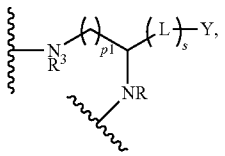


[0043] wherein r1 and r2 are each independently 0-4.

[0044] In some embodiments, >A-R has the following structure:

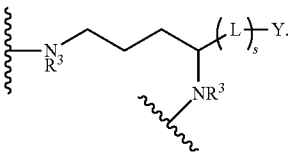


[0045] In some embodiments, >A-R has the following structure:

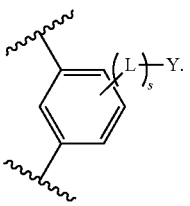


[0046] wherein p1 is 1-5.

[0047] In some embodiments, >A-R has the following structure:



[0048] In some embodiments, >A-R has the following structure:



[0049] In some embodiments, s is 1-15. In some embodiments, s is 1-10. In some embodiments, s is 5-15. In some embodiments, s is 5-10.

[0050] In some embodiments, Y is hydrogen or —CO$_2$H.

[0051] In some embodiments, each L is independently —(CR^{1}R^2)$_v$—, -alkylene-O—, —C(=O)—, —C(=O)NR^3—, —NR^{3}C(=O)—, -alkylene-C(=O)NR^3—, or -alkylene-NR^{3}C(=O)—; and v is 2-20.

[0052] In some embodiments, Y^1 and Y^2 are halogen. In some embodiments, Y^1 and Y^2 are —COOH. In some embodiments, Y^1 and Y^2 are the —S— of two sulfhydryl-containing amino acids in a peptide that modulates the GLP-2 receptor.

[0053] In some embodiments, Y^1 and Y^2 are the —S— of two sulfhydryl-containing amino acids in a peptide

[0054] In some embodiments, Y^1 and Y^2 are —CONH— wherein the —NH— is part of two amine-containing amino acids in a peptide that modulates the GLP-2 receptor.

[0055] In some embodiments, Y^1 and Y^2—CONH— wherein the —NH— is part of two amine-containing amino acids in a peptide that modulates the GLP-2 receptor which are 7 amino acids apart.

BRIEF DESCRIPTION OF FIGURES

[0056] FIG. **1**A depicts a concentration-response curve of teduglutide and the long-acting GLP2R agonists to the human GLP2R with no serum added.

[0057] FIG. **1**B depicts a concentration-response curve of teduglutide and the long-acting GLP2R agonists to the human GLP2R with serum added.

[0058] FIG. **2** depicts a concentration-response curve of teduglutide, the long-acting GLP2R agonists, and apraglutide to the mouse GLP2R.

[0059] FIG. **3** depicts a concentration-response curve of teduglutide and the long-acting GLP2R agonists to the cyno monkey GLP2R.

[0060] FIG. **4**A depicts a concentration-response curve of teduglutide and the long-acting GLP2R agonists to GLP1R.

[0061] FIG. **4**B depicts a concentration-response curve of teduglutide and the long-acting GLP2R agonists to GCGR.

[0062] FIG. **4**C depicts a concentration-response curve of teduglutide and the long-acting GLP2R agonists to GIPR.

[0063] FIG. **5**A depicts the thermal stability of GLP2-2G-10Nle-1K-Ex4-K5 (GLP2-K5) and GLP2-2G-1-EX4-L5A (GLP2-L5A) over 4 days at 4° C.

[0064] FIG. **5**B depicts the thermal stability of GLP2-2G-10Nle-1K-Ex4-K5 (GLP2-K5) and GLP2-2G-1-EX4-L5A (GLP2-L5A) over 4 days at 25° C.

[0065] FIG. **5**C depicts the thermal stability of GLP2-2G-10Nle-1K-Ex4-K5 (GLP2-K5) and GLP2-2G-1-EX4-L5A (GLP2-L5A) over 4 days at 37° C.

[0066] FIG. **5**D depicts the thermal stability of GLP2-2G-10Nle-1K-Ex4-K5 (GLP2-K5) and GLP2-2G-1-EX4-L5A (GLP2-L5A) over 4 days at 70° C.

[0067] FIG. **6**A depicts the stability of GLP2-2G-10Nle-1K-Ex4-K5 (GLP2-K5) and GLP2-2G-1-EX4-L5A (GLP2-L5A) over 4 days at a pH of 3.3 and a temperature of 4° C.

[0068] FIG. **6**B depicts the stability of GLP2-2G-10Nle-1K-Ex4-K5 (GLP2-K5) and GLP2-2G-1-EX4-L5A (GLP2-L5A) over 4 days at a pH of 3.3 at room temperature.

[0069] FIG. **6**C depicts the stability of GLP2-2G-10Nle-1K-Ex4-K5 (GLP2-K5) and GLP2-2G-1-EX4-L5A (GLP2-L5A) over 4 days at a pH of 37.5 and a temperature of 4° C.

[0070] FIG. **6**D depicts the stability of GLP2-2G-10Nle-1K-Ex4-K5 (GLP2-K5) and GLP2-2G-1-EX4-L5A (GLP2-L5A) over 4 days at a pH of 37.5 at room temperature.

[0071] FIG. **6**E depicts the stability of GLP2-2G-10Nle-1K-Ex4-K5 (GLP2-K5) and GLP2-2G-1-EX4-L5A (GLP2-L5A) over 4 days at a pH of 8.9 and a temperature of 4° C.

[0072] FIG. **6**F depicts the stability of GLP2-2G-10Nle-1K-Ex4-K5 (GLP2-K5) and GLP2-2G-1-EX4-L5A (GLP2-L5A) over 4 days at a pH of 8.9 at room temperature.

[0073] FIG. **7**A depicts the hepatic stability of long-acting GLP2-2G-1-EX4-L5A over 120 minutes.

[0074] FIG. **7**B depicts the hepatic stability of long-acting GLP2-2G-10Nle-1-EX4-L5A over 120 minutes.

[0075] FIG. **7**C depicts the hepatic stability of long-acting GLP2-2G-10Nle-1K-EX4-K5 over 120 minutes.

[0076] FIG. **8** depicts the mean plasma concentration of GLP2-2G-1-EX4-L5A over 96 hours in mice.

[0077] FIG. **9** depicts the mean plasma concentration of GLP2-2G-1-EX4-L5A over 504 hours in cyno monkeys.

[0078] FIG. **10** depicts the mean plasma concentration of GLP2-2G-10Nle-1-EX4-L5A over 96 hours in mice.

[0079] FIG. **11** depicts the mean plasma concentration of GLP2-2G-10Nle-1-EX4-L5A over 504 hours in cyno monkeys.

[0080] FIG. **12** depicts the mean plasma concentration of GLP2-2G-10Nle-1K-EX4-K5 over 96 hours in mice.

[0081] FIG. **13** depicts the mean plasma concentration of GLP2-2G-10Nle-1K-EX4-K5 over 504 hours in cyno monkeys.

[0082] FIG. **14**A depicts the normalized length of the small intestine in wildtype mice that received no treatment, GLP2-2G-1-L5A (GLP2-2G-1-EX4-L5A) and GLP2-2G-5-L5A (GLP2-2G-10Nle-1-EX4-L5A).

[0083] FIG. **14**B depicts the normalized length of the small intestine in wildtype mice that received no treatment, GLP2-2G-1-L5A (GLP2-2G-1-EX4-L5A) and GLP2-2G-5-L5A (GLP2-2G-10Nle-1-EX4-L5A).

[0084] FIG. **14**C depicts the bodyweight over 11 days of wildtype mice that received no treatment, GLP2-2G-1-L5A (GLP2-2G-1-EX4) and GLP2-2G-5-L5A (GLP2-2G-10Nle-1-EX4).

[0085] FIG. **15**A depicts the length of the small intestine in wildtype mice treated with GLP2-2G-10Nle-1K-EX4-K5 and untreated wildtype mice.

[0086] FIG. **15**B depicts the weight of the small intestine in wildtype mice treated with GLP2-2G-10Nle-1K-EX4-K5 and untreated wildtype mice.

[0087] FIG. **15**C depicts the length of the colon in wildtype mice treated with GLP2-2G-10Nle-1K-EX4-K5 and untreated wildtype mice.

[0088] FIG. **15**D depicts the weight of the colon in wildtype mice treated with GLP2-2G-10Nle-1K-EX4-K5 and untreated wildtype mice.

[0089] FIG. **16**A depicts the body weight over 12 days of mice with induced acute colitis that received no treatment, that were treated with GLP2-2G-1-L5A (GLP2-2G-1-EX4-L5), and with cyclosporin A.

[0090] FIG. **16**B depicts the normalized colon weight of mice with induced acute colitis that received no treatment, that were treated with GLP2-2G-1-L5A (GLP2-2G-1-EX4-L5), and with cyclosporin A.

[0091] FIG. **16**C depicts the normalized small intestine weight of mice with induced acute colitis that received no treatment, that were treated with GLP2-2G-1-L5A (GLP2-2G-1-EX4-L5), and with cyclosporin A.

[0092] FIG. **16**D depicts the crypt depth in the colon of wildtype mice and mice with induced acute colitis that received no treatment and that were treated with GLP2-2G-1-L5A (GLP2-2G-1-EX4-L5).

[0093] FIG. **16**E depicts the jejunum villi length of wildtype mice and mice with induced acute colitis that received no treatment and that were treated with GLP2-2G-1-L5A (GLP2-2G-1-EX4-L5).

[0094] FIG. **17**A depicts the body weight over 10 days of mice with induced acute colitis that received no treatment, GLP2-2G-10Nle-1K-EX4-K5, teduglutide, and cyclosporin A.

[0095] FIG. **17**B depicts the colon length of mice with induced acute colitis that received no treatment, GLP2-2G-10Nle-1K-EX4-K5, teduglutide, and cyclosporin A.

[0096] FIG. **17**C depicts the small intestine length of mice with induced acute colitis that received no treatment, GLP2-2G-10Nle-1K-EX4-K5, teduglutide, and cyclosporin A.

[0097] FIG. **17**D depicts the small intestine weight of mice with induced acute colitis that received no treatment, GLP2-2G-10Nle-1K-EX4-K5, teduglutide, and cyclosporin A.

[0098] FIG. **17**E depicts the height of the jejunum villi of mice with induced acute colitis that received no treatment, GLP2-2G-10Nle-1K-EX4-K5, teduglutide, and cyclosporin A.

[0099] FIG. **17**F depicts the proliferation index in the jejunum of mice with induced acute colitis that received no treatment, GLP2-2G-10Nle-1K-EX4-K5, teduglutide, and cyclosporin A.

[0100] FIG. **17**G depicts the pharmacokinetics of GLP2-2G-10Nle-1K-EX4-K5 and teduglutide in the mouse.

[0101] FIG. **18**A depicts the change in percent of bodyweight over 8 days of mice with induced acute colitis that received no treatment, GLP2-2G-10Nle-L5A, and cyclosporin A.

[0102] FIG. **18**B depicts the change in percent of bodyweight over 8 days of mice with induced acute colitis that received no treatment, GLP2-2G-1-EX4-L5A, and cyclosporin A.

[0103] FIG. **18**C depicts the change in percent of bodyweight over 8 days of mice with induced acute colitis that received no treatment, GLP2-2G-10Nle-1K-EX4-K5, cyclosporin A.

[0104] FIG. **18**D depicts the colon length of mice with induced acute colitis that received no treatment, that were treated with different long-acting GLP2R agonists, and cyclosporin A.

[0105] FIG. **18**E depicts the colon weight of mice with induced acute colitis that received no treatment, long-acting GLP2R agonists, and cyclosporin A.

[0106] FIG. **18**F depicts the small intestine length of mice with induced acute colitis that received no treatment, different long-acting GLP2R agonists, cyclosporin A.

[0107] FIG. **18**G depicts the small intestine weight of mice with induced acute colitis that received no treatment, different long-acting GLP2R agonists, and cyclosporin A.

[0108] FIG. **18**H depicts the gall bladder enlargement of mice with induced acute colitis that received no treatment, different long-acting GLP2R agonists, cyclosporin A.

[0109] FIG. **18**I depicts the amount of occult blood in the stool of mice with induced acute colitis that received no treatment, different long-acting GLP2R agonists, cyclosporin A.

[0110] FIG. **18**J depicts the pharmacokinetics of the long-acting GLP2R agonists at the 0.03 mg/kg dose.

[0111] FIG. **18**K depicts the pharmacokinetics of the long-acting GLP2R agonists at the 0.1 mg/kg dose.

[0112] FIG. **18**L depicts the pharmacokinetics of GLP2-2G-10Nle-L5A at both doses in an acute colitis mouse model.

[0113] FIG. **18**M depicts the pharmacokinetics of GLP2-2G-1-EX4-L5A at both doses in an acute colitis mouse model.

[0114] FIG. **18**N depicts the pharmacokinetics of GLP2-2G-10Nle-1K-EX4-K5 at both doses in an acute colitis mouse model.

[0115] FIG. **19**A depicts the absolute change in body-weight of mice with induced chronic colitis that received no treatment, that were treated with GLP2-2G-1-EX4-L5A, that were treated with cyclosporin, and that were treated with teduglutide.

[0116] FIG. **19**B depicts the colon length of mice with induced chronic colitis that received no treatment, GLP2-2G-1-EX4-L5A, cyclosporin, and teduglutide.

[0117] FIG. **19**C depicts the colon weight of mice with induced chronic colitis that received no treatment, GLP2-2G-1-EX4-L5A, cyclosporin, and teduglutide.

[0118] FIG. **19**D depicts the small intestine weight of mice with induced chronic colitis that received no treatment, GLP2-2G-1-EX4-L5A, cyclosporin, and teduglutide.

[0119] FIG. **20**A depicts the colon length of mice with induced chronic colitis that received no treatment, GLP2-2G-10Nle-1-EX4-L5A, cyclosporin, and teduglutide.

[0120] FIG. **20**B depicts the colon weight of mice with induced chronic colitis that received no treatment, GLP2-2G-10Nle-1-EX4-L5A, cyclosporin, and teduglutide.

[0121] FIG. **20**C depicts the small intestine length of mice with induced chronic colitis that received no treatment, GLP2-2G-10Nle-1-EX4-L5A, cyclosporin, and teduglutide.

[0122] FIG. **21**A depicts serum levels of ALT in choline deficient mice that were untreated and that received GLP2-2G-5-EX4-L5A treatment, and in mice fed a normal diet.

[0123] FIG. **21**B depicts serum levels of AST in choline deficient mice that were untreated and that received GLP2-2G-5-EX4-L5A treatment, and in mice fed a normal diet.

[0124] FIG. **21**C depicts fibrosis scores in choline deficient mice that were untreated and that received GLP2-2G-5-EX4-L5A treatment, and in mice fed a normal diet.

[0125] FIG. **21**D depicts steatosis in choline deficient mice that were untreated and that received GLP2-2G-5-EX4-L5A treatment, and in mice fed a normal diet.

[0126] FIG. **21**E depicts lobular inflammation in choline deficient mice that were untreated and that received GLP2-2G-5-EX4-L5A treatment, and in mice fed a normal diet.

[0127] FIG. **22**A depicts the body weight of male mice weaned to a conventional diet that received no treatment, teduglutide, or GLP2-2G-10Nle-1K-EX4-K5.

[0128] FIG. **22**B depicts the body weight of female mice weaned to a conventional diet that received no treatment, teduglutide, or GLP2-2G-10Nle-1K-EX4-K5.

[0129] FIG. **22**C depicts the body weight of male mice weaned to a deficient diet that received no treatment, teduglutide, or GLP2-2G-10Nle-1K-EX4-K5.

[0130] FIG. **22**D depicts the body weight of female mice weaned to a deficient diet that received no treatment, teduglutide, or GLP2-2G-10Nle-1K-EX4-K5.

[0131] FIG. **22**E depicts the normalized small intestine weight of male mice weaned to a conventional diet that received no treatment, teduglutide, or GLP2-2G-10Nle-1K-EX4-K5.

[0132] FIG. **22**F depicts the normalized small intestine weight of female mice weaned to a conventional diet that received no treatment, teduglutide, or GLP2-2G-10Nle-1K-EX4-K5.

DETAILED DESCRIPTION OF THE INVENTION

[0133] Glucagon-like peptide 2 (GLP-2) is a hormone secreted from gut endocrine cells. GLP-2 stimulates intestinal growth, increases nutrient absorption and blood flow, decreases gut permeability and motility, and reduces epithelial cell apoptosis and inflammation. Due to the intestinotrophic effects of GLP-2, GLP-2 and related analogs may be useful for the treatment of GI disorders. In humans, the short plasma half-life of native GLP-2 requires higher doses and frequent injections or infusions to achieve a clinical efficacy, which can negatively affect patient compliance. Approaches have been utilized to extend the half-life of GLP-2, including PEGylation and fusion to polypeptides to increase molecular weight and hydrodynamic radius, and decrease the clearance rate through renal filtration. However, resulting analogs have suffered from reduced in vitro potency and, as a result, require higher doses to be effective in vivo.

Peptide Conjugates

[0134] In one aspect, disclosed herein are peptide conjugates comprising a peptide that modulates the GLP-2 receptor. In exemplary cases, the peptide that modulates the GLP-2 receptor comprises two amino acids connected by a staple. Non-limiting examples of amino acids for use in conjugation include cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, homolysine, other sulfhydryl containing amino acids, or other amine containing amino acids. For a peptide that modulates the GLP-2 receptor comprising two amino acids connected by a staple, the two amino acids are about or at least about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or more amino acids apart. For example, the first amino acid has position i, and the second amino acid has position i+7, i+11, i+13, i+15, or i+16. For example, the first amino acid has a position i in the peptide and the second amino acid has a position i+n in the peptide, wherein n is 4-16. For example, the first amino acid has a position i in the peptide and the second amino acid has a position i+7 in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position i+11 in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position i+15 in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position i+16 in the peptide.

Peptide that Modulates the GLP-2 Receptor

[0135] In one aspect, provided herein are peptide conjugates comprising a peptide that modulates the GLP-2 recep-

tor. In some embodiments, a peptide that modulates the GLP-2 receptor is a GLP-2 receptor agonist.

[0136] The binding affinity of the peptide conjugate as described herein may be within about 5% of the binding affinity of an unmodified form of the GLP-2 peptide (e.g., the unconjugated GLP-2 peptide). The binding affinity of the peptide conjugate as described herein may be within about 10% of the binding affinity of an unmodified form of the GLP-2 peptide. The binding affinity of the peptide conjugate as described herein may be within about 15% of the binding affinity of an unmodified form of the GLP-2 peptide. The binding affinity of the peptide conjugate as described herein may be within about 20% of the binding affinity of an unmodified form of the GLP-2 peptide.

[0137] The peptide that modulates the GLP-2 receptor may comprise at least a portion of a wild-type GLP-2 peptide and may comprise one or more amino acid mutations. The one or more amino acid mutations may comprise a deletion, substitution, addition or a combination thereof. The one or more amino acid mutations may comprise adding one or more amino acid residues to a wild-type GLP-2 peptide. The one or more amino acid mutations may comprise deletion of one or more amino acid residues of the wild-type GLP-2 peptide. The one or more amino acid mutations may comprise substitution of one or more amino acid residues of the wild-type GLP-2 peptide. The one or more amino acid mutations may comprise substituting one or more amino acid residues of the wild-type GLP-2 peptide with one or more cysteine, lysine or other sulfhydryl or amine containing residues. The one or more amino acid mutations may comprise substituting one or more amino acid residues of the wild-type GLP-2 peptide with one or more D-amino acid residues. The one or more amino acid residues of the GLP-2 wild-type peptide may comprise one or more alanines, methionines, arginines, serines, threonines, and tyrosines.

[0138] The peptide that modulates the GLP-2 receptor may be modified with, for example, acetylation, phosphorylation, and methylation. The peptide modification may comprise a chemical modification. Peptide modifications may occur on the N-terminus of the peptide. Peptide modifications may comprise acetyling the amino group at the N-terminus of the peptide. Alternatively, or additionally, peptide modifications may occur on the C-terminus of the peptide. Peptide modifications may occur at one or more internal amino acids of the peptide. Peptide modifications may comprise replacing the carboxyl group at the C-terminus of the peptide. Peptide modifications may comprise modifying the carboxyl group at the C-terminus of the peptide. The carboxyl group at the C-terminus of the peptide may be modified to produce an amide group. The carboxyl group at the C-terminus of the peptide may be modified to produce an amine group.

[0139] Non-limiting examples of a peptide that modulates the GLP-2 receptor are shown in Table 1.

[0140] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of any one of SEQ ID NOs: 1-40. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to any one of SEQ ID NOs: 1-40. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to any one of SEQ ID NOS: 1-40.

[0141] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of any one of SEQ ID NOs: 1-9. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to any one of SEQ ID NOs: 1-9. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to any one of SEQ ID NOS: 1-9.

[0142] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 1. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 1. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 1.

[0143] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 2. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 2. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 2.

[0144] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 3. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 3. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 3.

[0145] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 4. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%,

90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 4. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 4.

[0146] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 5. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 5. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 5.

[0147] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 6. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 6. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 6.

[0148] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 7. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 7. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 7.

[0149] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 8. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 8. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 8.

[0150] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 9. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 9. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 9.

[0151] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of any one of SEQ ID NOs: 10-20. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to any one of SEQ ID NOs: 10-20. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to any one of SEQ ID NOS: 10-20.

[0152] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 10. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 10. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 10.

[0153] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 11. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 11. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 11.

[0154] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 12. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 12. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 12.

[0155] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 13. In some cases, the peptide that modulates

the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 13. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 13.

[0156] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 14. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 14. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 14.

[0157] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 15. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 15. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 15.

[0158] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 16. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 16. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 16.

[0159] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 17. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 17. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 17.

[0160] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 18. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 18. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 18.

[0161] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 19. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 19. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 19.

[0162] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 20. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 20. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 20.

[0163] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of any one of SEQ ID NOs: 21-29. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to any one of SEQ ID NOs: 21-29. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to any one of SEQ ID NOS: 21-29.

[0164] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 21. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 21. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 21.

[0165] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 2. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 22. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 22.

[0166] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 23. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 23. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 23.

[0167] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 24. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 24. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 24.

[0168] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 25. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 25. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 25.

[0169] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 26. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 26. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 26.

[0170] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 27. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 27. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 27.

[0171] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 28. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 28. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 28.

[0172] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 29. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 29. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 29.

[0173] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of any one of SEQ ID NOs: 30-40. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to any one of SEQ ID NOs: 30-40. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to any one of SEQ ID NOS: 30-40.

[0174] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 30. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 30. In some embodiments, the

peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 30.

[0175] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 31. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 31. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 31.

[0176] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 32. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 32. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 32.

[0177] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 33. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 33. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 33.

[0178] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 34. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 34. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 34.

[0179] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 35. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 35. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 35.

[0180] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 36. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 36. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 36.

[0181] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 37. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 37. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 37.

[0182] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 38. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 38. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 38.

[0183] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 39. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 39. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 39.

[0184] In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence of SEQ ID NO: 40. In some cases, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, 90%, about 91%, about 92%, about 93%, about 94%,

about 95%, about 96%, about 97%, about 98%, or about 99% identical to SEQ ID NO: 40. In some embodiments, the peptide that modulates the GLP-2 receptor comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to SEQ ID NO: 40.

TABLE 1

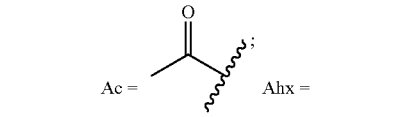
SEQ ID Table

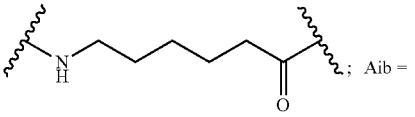
SEQ ID NO.	Name	Sequence
1	GLP2-2G-1-EX4	HGDGSFSDEMNTILDNCAARDFICWLIQTKITDPSS GAPPPS
2	GLP2-2G-10Nle-1-EX4	HGDGSFSDE(Nle)NTILDNCAARDFICWLIQTKITDP SSGAPPPS
3	GLP2-2G-10L-1-EX4	HGDGSFSDELNTILDNCAARDFICWLIQTKITDPSS GAPPPS
4	GLP2-2G-10I-1-EX4	HGDGSFSDEINTILDNCAARDFICWLIQTKITDPSSG APPPS
5	GLP2-2G-10Aib-1-EX4	HGDGSFSDE(Aib)NTILDNCAARDFICWLIQTKITDP SSGAPPPS
6	GLP2-2G-10Nva-1-EX4	HGDGSFSDE(Nva)NTILDNCAARDFICWLIQTKITDP SSGAPPPS
7	GLP2-2G-10V-1-EX4	HGDGSFSDEVNTILDNCAARDFICWLIQTKITDPSS GAPPPS
8	GLP2-2G-5-EX4	HGDGSFSDCMNTILDCLAARDFINWLIQTKITDPSS GAPPPS
9	GLP2-2G-6-EX4	HGDGSFSDEMCTILDNLCARDFINWLIQTKITDPSS GAPPPS
10	GLP2-2G-10Nle-1K-EX4	HGDGSFSDE(Nle)NTILDNKAARDFIKWLIQTKITDP SSGAPPPS
11	GLP2-2G-10Nle-11f-1K-EX4	HGDGSFSDE(Nle)(D-Phe)TILDNKAARDFIKWLIQTKITDPSSGAPPPS
12	GLP2-2G-10Nle-12S-13L-1K-EX4	HGDGSFSDE(Nle)NSLLDNKAARDFIKWLIQTKITD PSSGAPPPS
13	GLP2-2G-10Nle-13A-14Nle-1K-EX4	HGDGSFSDE(Nle)NTA(Nle)DNKAARDFIKWLIQTKI TDPSSGAPPPS
14	GLP2-2G-10Nle-13Nle-14Nle-1K-EX4	HGDGSFSDE(Nle)NT(Nle)(Nle)DNKAARDFIKWLIQ TKITDPSSGAPPPS
15	GLP2-2G-10Nle-11A-13A-14Nle-16A-1K-EX4	HGDGSFSDE(Nle)ATA(Nle)DAKAARDFIKWLIQTKI TDPSSGAPPPS
16	GLP2-2G-1K-EX4	HGDGSFSDEMNTILDNKAARDFIKWLIQTKITDPSS GAPPPS
17	GLP2-2G-11f-1K-EX4	HGDGSFSDEM(D-Phe)TILDNKAARDFIKWLIQTKITDPSSGAPPPS
18	GLP2-2G-5K-EX4	HGDGSFSDKMNTILDKLAARDFINWLIQTKITDPSS GAPPPS
19	GLP2-2G-10Nle-5K-EX4	HGDGSFSDK(Nle)NTILDKLAARDFINWLIQTKITDP SSGAPPPS
20	GLP2-2G-10m-EX4	HGDGSFSDEMNTILDN(Orn)AARDFI(Orn)WLIQTKI TDPSSGAPPPS
21		HGDGSFSDEMNTILDNCAARDFICWLIQTKITD
22		HGDGSFSDE(Nle)NTILDNCAARDFICWLIQTKITD
23		HGDGSFSDELNTILDNCAARDFICWLIQTKITD
24		HGDGSFSDEINTILDNCAARDFICWLIQTKITD

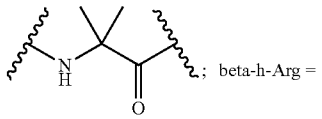
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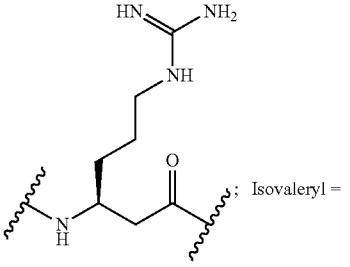
SEQ ID Table

SEQ ID NO.	Name	Sequence
25		HGDGSFSDE(Aib)NTILDNCAARDFICWLIQTKITD
26		HGDGSFSDE(Nva)NTILDNCAARDFICWLIQTKITD
27		HGDGSFSDEVNTILDNCAARDFICWLIQTKITD
28		HGDGSFSDCMNTILDCLAARDFINWLIQTKITD
29		HGDGSFSDEMCTILDNLCARDFINWLIQTKITD
30		HGDGSFSDE(Nle)NTILDNKAARDFIKWLIQTKITD
31		HGDGSFSDE(Nle)(D-Phe)TILDNKAARDFIKWLIQTKITD
32		HGDGSFSDE(Nle)NSLLDNKAARDFIKWLIQTKITD
33		HGDGSFSDE(Nle)NTA(Nle)DNKAARDFIKWLIQTKITD
34		HGDGSFSDE(Nle)NT(Nle)(Nle)DNKAARDFIKWLIQTKITD
35		HGDGSFSDE(Nle)ATA(Nle)DAKAARDFIKWLIQTKITD
36		HGDGSFSDEMNTILDNKAARDFIKWLIQTKITD
37		HGDGSFSDEM(D-Phe)TILDNKAARDFIKWLIQTKITD
38		HGDGSFSDKMNTILDKLAARDFINWLIQTKITD
39		HGDGSFSDK(Nle)NTILDKLAARDFINWLIQTKITD
40		HGDGSFSDEMNTILDN(Orn)AARDFI(Orn)WLIQTKITD

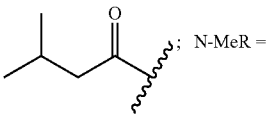


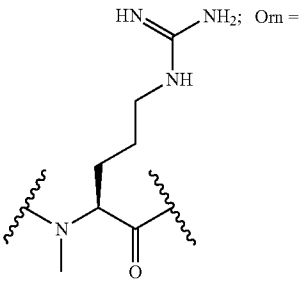


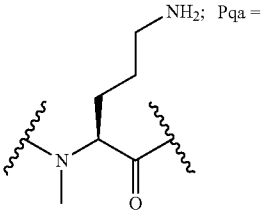




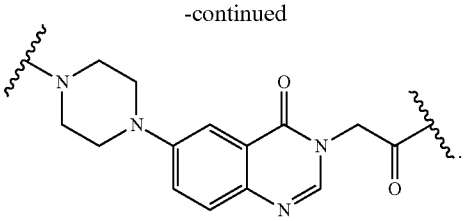
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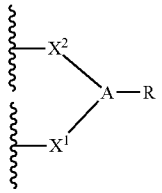


Staples

[0185] Disclosed herein are peptide conjugates comprising a staple.

[0186] In some embodiments, the staple attached to the peptide is of Formula (I):

Formula (I)



wherein

[0187] A is an optionally substituted alkylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted —NR^3-alkylene-NR^3—, or —N—;

[0188] X^1 and X^2 are independently a bond, —C(═O)—, -alkylene-C(═O)—, —C(═O)-alkylene-, -alkylene-C(═O)NR^3—, -alkylene-NR^3C(═O)—, —C(═O)NR^3-alkylene-, —NR^3C(═O)-alkylene-, -alkylene-C(═O)NR^3-alkylene-, or -alkylene-NR^3C(═O)-alkylene-;

[0189] wherein X^1 is attached to a first amino acid of the peptide, and X^2 is attached to a second amino acid of the peptide;

[0190] R is hydrogen or —X^3-$(L)_s$-Y;

[0191] X^3 is bond, —C(═O)—, -alkylene-C(═O)—, —C(═O)-alkylene, -alkylene-C(═O)NR^3—, or -alkylene-C(═O)NR^3-alkylene-;

[0192] each L is independently —$(CR^1R^2)_v$—, -alkylene-O—, —O-alkylene-, —C(═O)-alkylene-, -alkylene-C(═O)—, —NR^3-alkylene-, -alkylene-NR^3—, —S-alkylene-, -alkylene-S—, —S(═O)-alkylene-, -alkylene-S(═O)—, —$S(═O)_2$-alkylene, -alkylene-$S(═O)_2$—, —C(═O)—, —C(═O)NR^3—, —NR^3C(═O)—, —NR^3C(═O)NR^3—, —NR^3C(═O)NR^3-alkylene-, —NR^3C(═O)-alkylene-NR^3—, -alkylene-C(═O)NR^3—, —C(═O)NR^3-alkylene-, -alkylene-NR^3C(═O)—, or —NR^3C(═O)-alkylene-;

[0193] v is 2-20;

[0194] each R^1 or R^2 is independently hydrogen, halogen, —CN, —OR^a, —SR^a, —S(═O)R^b, —NO_2, —NR^cR^d, —$S(═O)_2R^a$, —$NR^aS(═O)_2R^d$, —$S(═O)_2NR^cR^d$, —C(═O)R^b, —OC(═O)R^b, —CO_2R^a, —OCO_2R^a, —C(═O)NR^cR^d, —OC(═O)NR^cR^d, —$NR^aC(═O)NR^cR^d$, —$NR^aC(═O)R^b$, —$NR^aC(═O)OR^a$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OR^a, or —NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OR^a, —NR^cR^d;

[0195] or R^1 and R^2 are taken together to form a C_1-C_6 cycloalkyl or C_1-C_6 heterocycloalkyl;

[0196] each R^3 is independently hydrogen, —S(═O)R^b, —$S(═O)_2R^a$, —$S(═O)_2NR^cR^d$, —C(═O)R^b, —CO_2R^a, —C(═O)NR^cR^d, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OR^a, or —NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OR^a, or —NR^cR^d;

[0197] Y is hydrogen, C_1-C_6 alkyl, —CO_2H, —CO_2(C_1-C_6 alkyl), —CO_2NH_2, —$CO_2N(alkyl)_2$, or —CO_2NH(alkyl); and

[0198] s is 0-20;

[0199] R^a is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

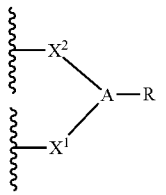
[0200] R^b is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

[0201] each R^c and R^d is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

[0202] or R^c and R^d, together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2.

[0203] In some embodiments, the staple attached to the peptide is of Formula (I):

Formula (I)



wherein

[0204] A is an optionally substituted alkylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted —NR^3-alkylene-NR^3—, or —N—;

[0205] X^1 and X^2 are independently a bond, —C(═O)—, -alkylene-C(═O)—, —C(═O)-alkylene, -alkylene-C(═O)NR^3—, or -alkylene-C(═O)NR^3-alkylene-;

[0206] wherein X^1 is attached to a first amino acid of the peptide, and X^2 is attached to a second amino acid of the peptide;

[0207] R is hydrogen or —X^3-$(L)_s$-Y;

[0208] X^3 is bond, —C(═O)—, -alkylene-C(═O)—, —C(═O)-alkylene, -alkylene-C(═O)NR^3—, or -alkylene-C(═O)NR^3-alkylene-;

[0209] each L is independently —$(CR^1R^2)_v$—, -alkylene-O—, —O-alkylene-, —C(═O)-alkylene-, -alkylene-C(═O)—, —NR^3-alkylene-, -alkylene-NR^3—, —S-alkylene-, -alkylene-S—, —S(═O)-alkylene-, -alkylene-S(═O)—, —S(═O)$_2$-alkylene, -alkylene-S(═O)$_2$—, —C(═O)—, —C(═O)NR^3—, —NR^3C(═O)—, —NR^3C(═O)NR^3—, —NR^3C(═O)NR^3-alkylene-, —NR^3C(═O)-alkylene-NR^3—, -alkylene-C(═O)NR^3—, —C(═O)NR^3-alkylene-, -alkylene-NR^3C(═O)—, or —NR^3C(═O)-alkylene-;

[0210] v is 2-20;

[0211] each R^1 or R^2 is independently hydrogen, halogen, —CN, —OR^a, —SR^a, —S(═O)R^b, —NO_2, —NR^cR^d, —S(═O)$_2R^a$, —$NR^aS(═O)_2R^d$, —S(═O)$_2NR^cR^d$, —C(═O)R^b, —OC(═O)R^b, —CO_2R^a, —OCO_2R^a, —C(═O)NR^cR^d, —OC(═O)NR^cR^d, —$NR^aC(═O)NR^cR^d$, —$NR^aC(═O)R^b$, —$NR^aC(═O)OR^a$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_5 cycloalkyl, C_2-C_5 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OW, or —NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OR^a, —NR^cR^d;

[0212] or R^1 and R^2 are taken together to form a C_1-C_6 cycloalkyl or C_1-C_6 heterocycloalkyl;

[0213] each R^3 is independently hydrogen, —S(═O)R^b, —S(═O)$_2R^a$, —S(═O)$_2NR^cR^d$, —C(═O)R^b, —CO_2R^a, —C(═O)NR^cR^d, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OR^a, or —NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OR^a, or —NR^cR^d;

[0214] Y is hydrogen, C_1-C_6 alkyl, —CO_2H, —CO_2(C_1-C_6 alkyl), —CO_2NH_2, —$CO_2N(alkyl)_2$, or —CO_2NH(alkyl); and

[0215] s is 0-20;

[0216] R^a is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

[0217] R^b is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

[0218] each R^c and R^d is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

[0219] or R^c and R^d, together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2.

[0220] In some embodiments, A is optionally substituted alkylene. In some embodiments, A is —$(CH_2)_t$—, wherein t is 1-12. In some embodiments, A is —$(CH_2)_t$—, wherein t is 1-10. In some embodiments, A is —$(CH_2)_t$—, wherein t is 1-8. In some embodiments, A is —$(CH_2)_t$—, wherein t is 1-6. In some embodiments, A is —$(CH_2)_t$—, wherein t is 1-4.

[0221] In some embodiments, A is optionally substituted arylene. In some embodiments, A is arylene optionally substituted with halogen, alkyl, or haloalkyl. In some embodiments, A is arylene.

[0222] In some embodiments, A is —NR^3-alkylene-NR^3—.

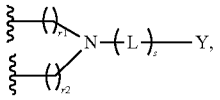
[0223] In some embodiments, A is —N—.

[0224] In some embodiments, X^1 and X^2 are identical. In some embodiments, X^1 and X^2 are different.

[0225] In some embodiments, X^1 and X^2 are —C(═O)—. In some embodiments, X^1 and X^2 are independently -alkylene-C(═O)— or —C(═O)alkylene-. In some embodiments, X^1 and X^2 are independently —CH_2—C(═O)— or —C(═O)—CH_2—. In some embodiments, X^1 and X^2 are independently -alkylene-C(═O)NR^3— or —C(═O)NR^3-alkylene-. In some embodiments, X^1 and X^2 are independently —CH_2—C(═O)NR^3— or —C(═O)NR^3—CH_2—. In some embodiments, X^1 and X^2 are independently -alkylene-C(═O)NR^3-alkylene- or -alkylene-NR^3C(═O)-alkylene-. In some embodiments, X^1 and X^2 are independently —CH_2—C(═O)NR^3—CH_2CH_2— or —CH_2—NR^3C(═O)—CH_2CH_2—. In some embodiments, X^1 and X^2 are independently —CH_2—C(═O)NH—CH_2CH_2— or —CH_2—NHC(═O)—CH_2CH_2—.

[0226] In some embodiments, each R^3 is independently hydrogen or C_1-C_6 alkyl. In some embodiments, each R^3 is hydrogen.

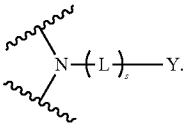
[0227] In some embodiments, >A-R has the following structure:



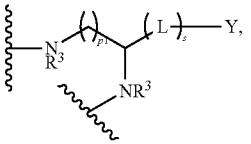
wherein r1 and r2 are each independently 0-4.

[0228] In some embodiments, r1 and r2 are each independently 0-2. In some embodiments, r1 and r2 are each 0. In some embodiments, r1 and r2 are each 1. In some embodiments, r1 and r2 are each 3.

[0229] In some embodiments, >A-R has the following structure:



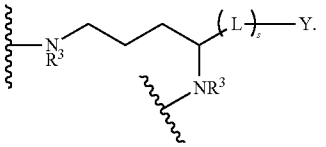
[0230] In some embodiments, >A-R has the following structure:



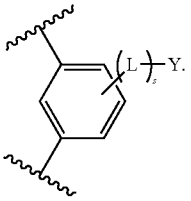
wherein p1 is 1-5.

[0231] In some embodiments, p1 is 1-3. In some embodiments, p1 is 1-2. In some embodiments, p1 is 1. In some embodiments, p1 is 2. In some embodiments, p1 is 3. In some embodiments, p1 is 4. In some embodiments, p1 is 5.

[0232] In some embodiments, >A-R has the following structure:



[0233] In some embodiments, >A-R has the following structure:



[0234] In some embodiments, s is 1-15. In some embodiments, s is 1-10. In some embodiments, s is 5-15. In some embodiments, s is 5-10. In some embodiments, s is 5-20.

[0235] In some embodiments, Y is hydrogen or $—CO_2H$. In some embodiments, Y is hydrogen. In some embodiments, Y is $—CO_2H$.

[0236] In some embodiments, each L is independently $—(CR^1R^2)_v—$, -alkylene-O—, —C(═O)—, —C(═O)NR^3—, —NR^{3}C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^{3}C(═O)—; and v is 2-20.

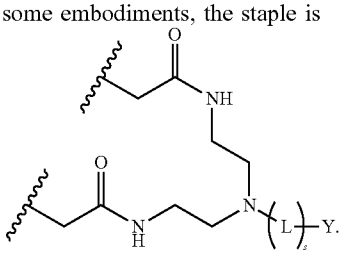
[0237] In some embodiments, each L is independently $—(CR^1R^2)_v—$, -alkylene-O—, —C(═O)—, —C(═O)NR^3—, —NR^{3}C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^{3}C(═O)—; and v is 2-16.

[0238] In some embodiments, v is 2-16. In some embodiments, v is 2-5. In some embodiments, v is 5-16. In some embodiments, v is 5 or 16. In some embodiments, v is 2 or 16.

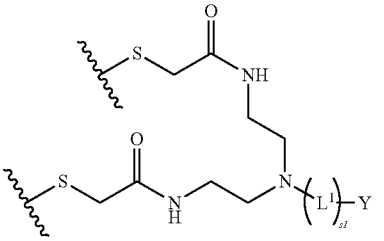
[0239] In some embodiments, each R^1 or R^2 is independently hydrogen, halogen, —CN, —OW, $—NR^cR^d$, $—C(═O)R^b$, $—CO_2R^a$, $—C(═O)NR^cR^d$, or C_1-C_6 alkyl.

[0240] In some embodiments, each R^1 or R^2 is independently hydrogen, halogen, $—CO_2R^a$, $—C(═O)NR^cR^d$, or C_1-C_6 alkyl. In some embodiments, each R^1 or R^2 is independently hydrogen, $—CO_2R^a$, or $—C(═O)NR^cR^d$. In some embodiments, each R^1 or R^2 is independently hydrogen or $—CO_2R^a$.

[0241] In some embodiments, the staple is

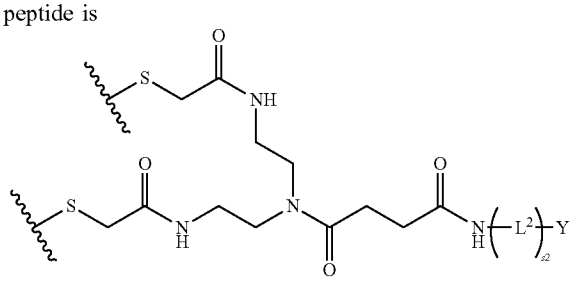


[0242] In some embodiments, the staple attached to the peptide is



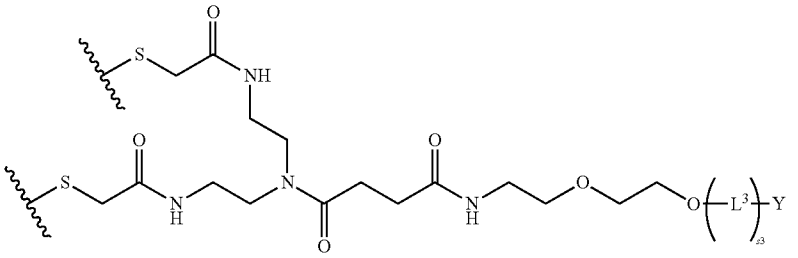
wherein each L^1 is independently $—(CR^1R^2)_v—$, -alkylene-O—, —O-alkylene-, —C(═O)NR^3—, —NR^{3}C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^{3}C(═O)—; v is 2-20; and s1 is 1-15.

[0243] In some embodiments, the staple attached to the peptide is



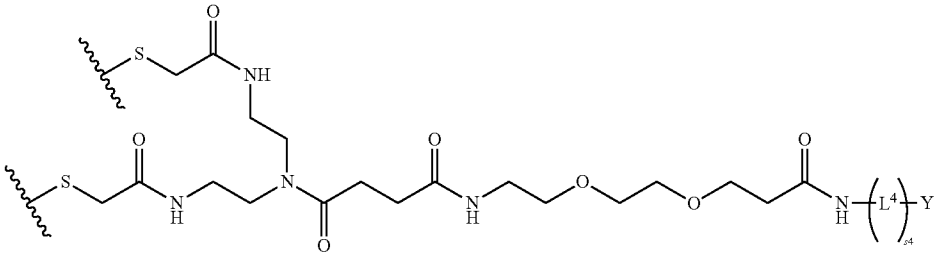
wherein each L^2 is independently $—(CR^1R^2)_v—$, -alkylene-O—, —O-alkylene-, —C(═O)NR^3—, —NR^{3}C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^{3}C(═O)—; v is 2-20; and s2 is 1-15.

[0244] In some embodiments, the staple attached to the peptide is



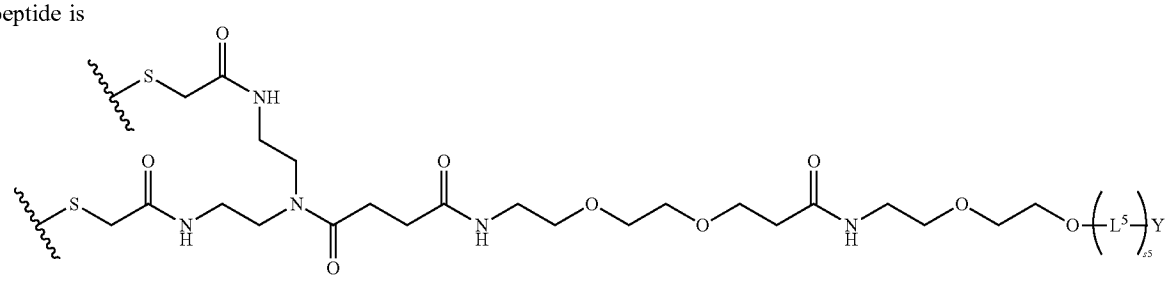
wherein each L^3 is independently —$(CR^1R^2)_v$—, -alkylene-O—, —O-alkylene-, —$C(=O)NR^3$—, —$NR^3C(=O)$—, -alkylene-$C(=O)NR^3$—, or -alkylene-$NR^3C(=O)$—; v is 2-20; and s3 is 1-15.

[0245] In some embodiments, the staple attached to the peptide is



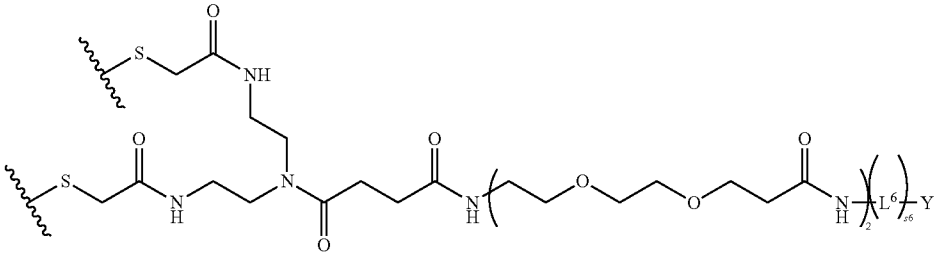
wherein each L^4 is independently —$(CR^1R^2)_v$—, -alkylene-O—, —O-alkylene-, —$C(=O)NR^3$—, —$NR^3C(=O)$—, -alkylene-$C(=O)NR^3$—, or -alkylene-$NR^3C(=O)$—; v is 2-20; and s4 is 1-15.

[0246] In some embodiments, the staple attached to the peptide is



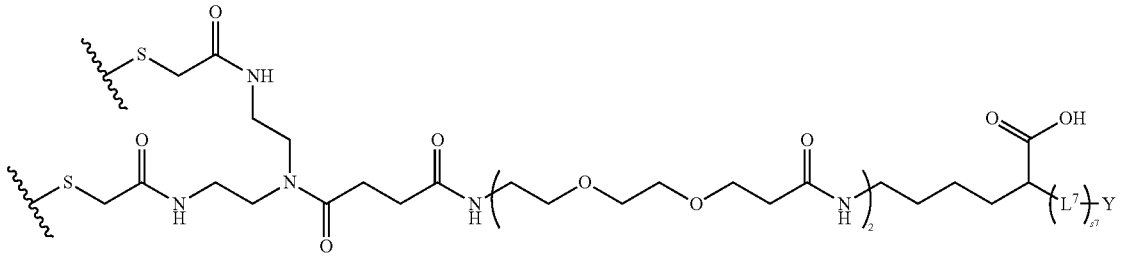
wherein each L^5 is independently —$(CR^1R^2)_v$—, —$C(=O)NR^3$—, —$NR^3C(=O)$—, -alkylene-$C(=O)NR^3$—, or -alkylene-$NR^3C(=O)$—; v is 2-20; and s5 is 1-10.

[0247] In some embodiments, the staple attached to the peptide is



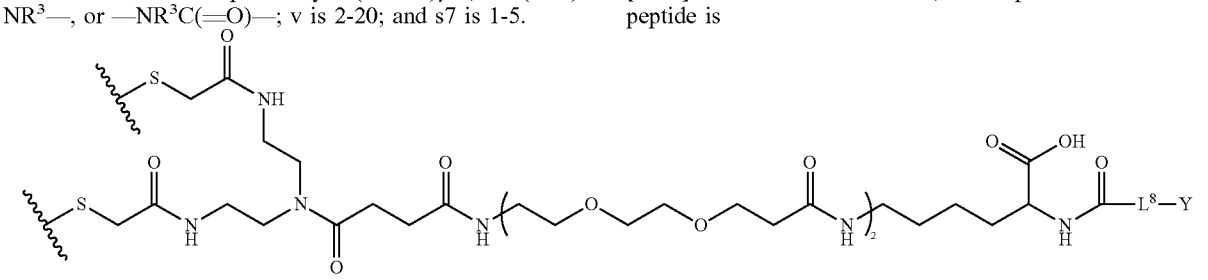
wherein each L^6 is independently —$(CR^1R^2)_v$—, —C(═O)NR^3—, —NR^3C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^3C(═O)—; v is 2-20; and s6 is 1-5.

[0248] In some embodiments, the staple attached to the peptide is



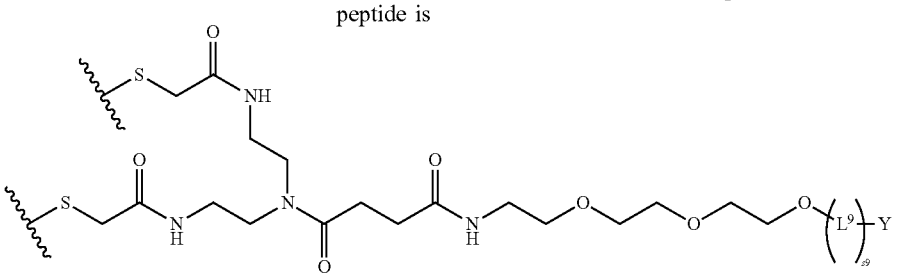
wherein each L^7 is independently —$(CR^1R^2)_v$—, —C(═O)NR^3—, or —NR^3C(═O)—; v is 2-20; and s7 is 1-5.

[0249] In some embodiments, the staple attached to the peptide is



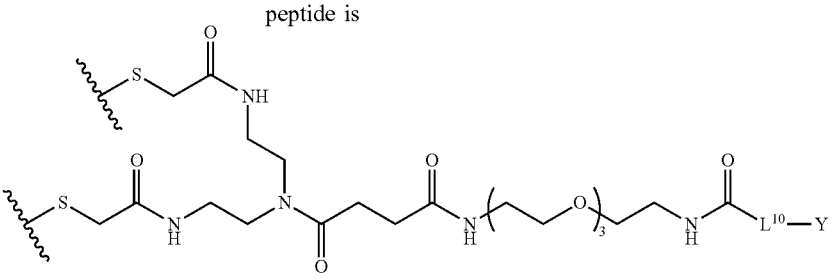
wherein L^8 is —$(CR^1R^2)_v$— and v is 10-20.

[0250] In some embodiments, the staple attached to the peptide is



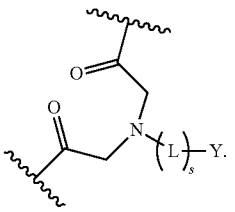
wherein each L^9 is independently —$(CR^1R^2)_v$—, —C(═O)NR^3—, —NR^3C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^3C(═O)—; v is 2-20; and s9 is 1-5.

[0251] In some embodiments, the staple attached to the peptide is

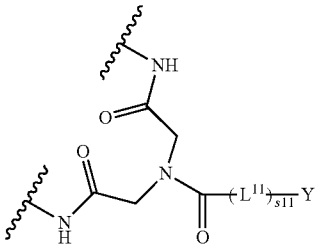


wherein L^{10} is —$(CR^1R^2)_v$— and v is 10-20.

[0252] In some embodiments, the staple attached to the peptide is

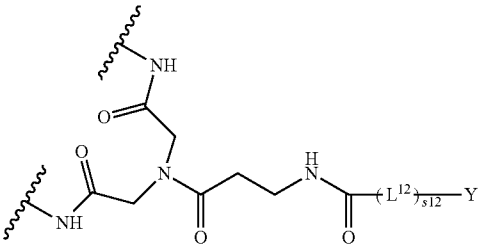


[0253] In some embodiments, the staple attached to the peptide is



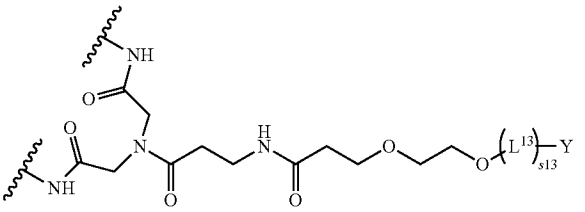
wherein each L^{11} is independently —$(CR^1R^2)_v$—, -alkylene-O—, —O-alkylene-, —C(═O)NR^3—, —NR^3C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^3C(═O)—; v is 2-20; and s11 is 1-15.

[0254] In some embodiments, the staple attached to the peptide is



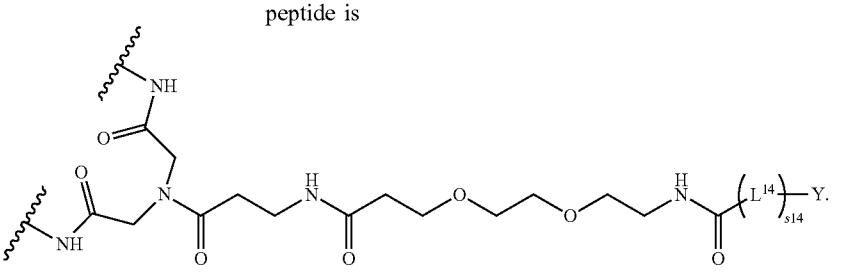
wherein each L^{12} is independently —$(CR^1R^2)_v$—, -alkylene-O—, —O-alkylene-, —C(═O)NR^3—, —NR^3C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^3C(═O)—; v is 2-20; and s12 is 1-15.

[0255] In some embodiments, the staple attached to the peptide is



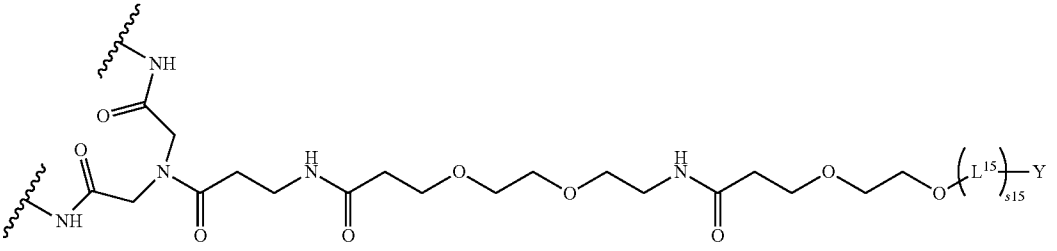
wherein each L^{13} is independently —$(CR^1R^2)_v$—, -alkylene-O—, —O-alkylene-, —C(═O)NR^3—, —NR^3C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^3C(═O)—; v is 2-20; and s13 is 1-15.

[0256] In some embodiments, the staple attached to the peptide is



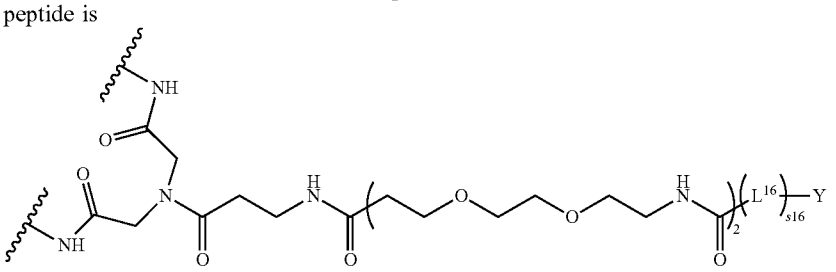
wherein each L^{14} is independently —$(CR^1R^2)_v$—, -alkylene-O—, —O-alkylene-, —C(═O)NR^3—, —NR^3C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^3C(═O)—; v is 2-20; and s14 is 1-15.

[0257] In some embodiments, the staple attached to the peptide is



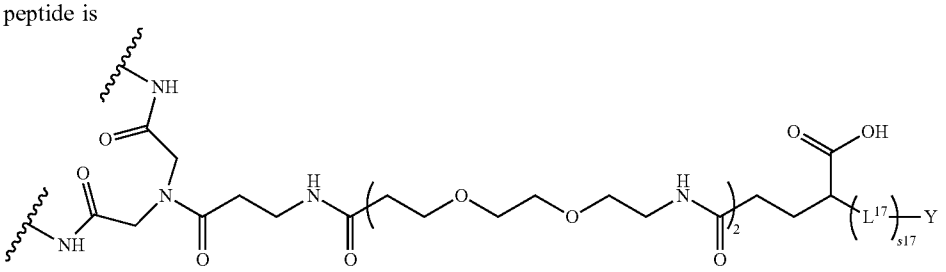
wherein each L^{15} is independently —$(CR^1R^2)_v$—, —C(═O)NR^3—, —NR^3C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^3C(═O)—; v is 2-20; and s15 is 1-10.

[0258] In some embodiments, the staple attached to the peptide is



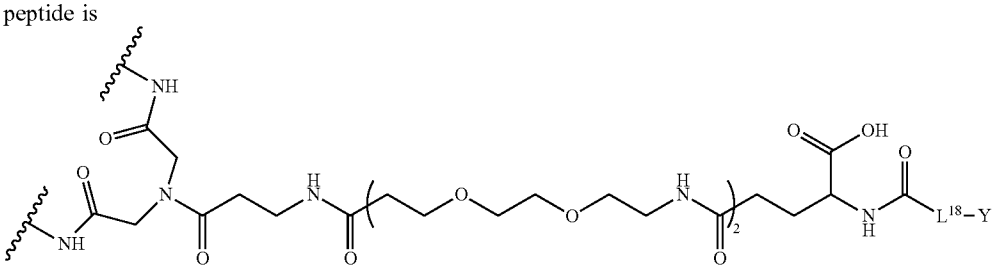
wherein each L^{16} is independently —$(CR^1R^2)_v$—, —C(═O)NR^3—, or —NR^3C(═O)—; v is 2-20; and s16 is 1-5.

[0259] In some embodiments, the staple attached to the peptide is



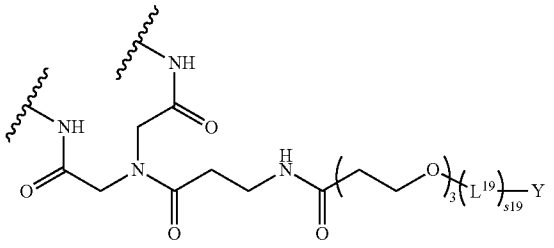
wherein each L^{17} is independently —$(CR^1R^2)_v$—, —C(═O)NR^3—, or —NR^3C(═O)—; v is 2-20; and s17 is 1-5.

[0260] In some embodiments, the staple attached to the peptide is



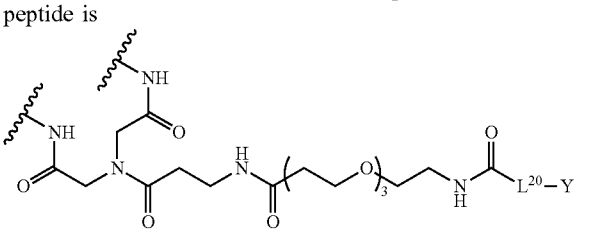
wherein L^{18} is —$(CR^1R^2)_v$— and v is 10-20.

[0261] In some embodiments, the staple attached to the peptide is



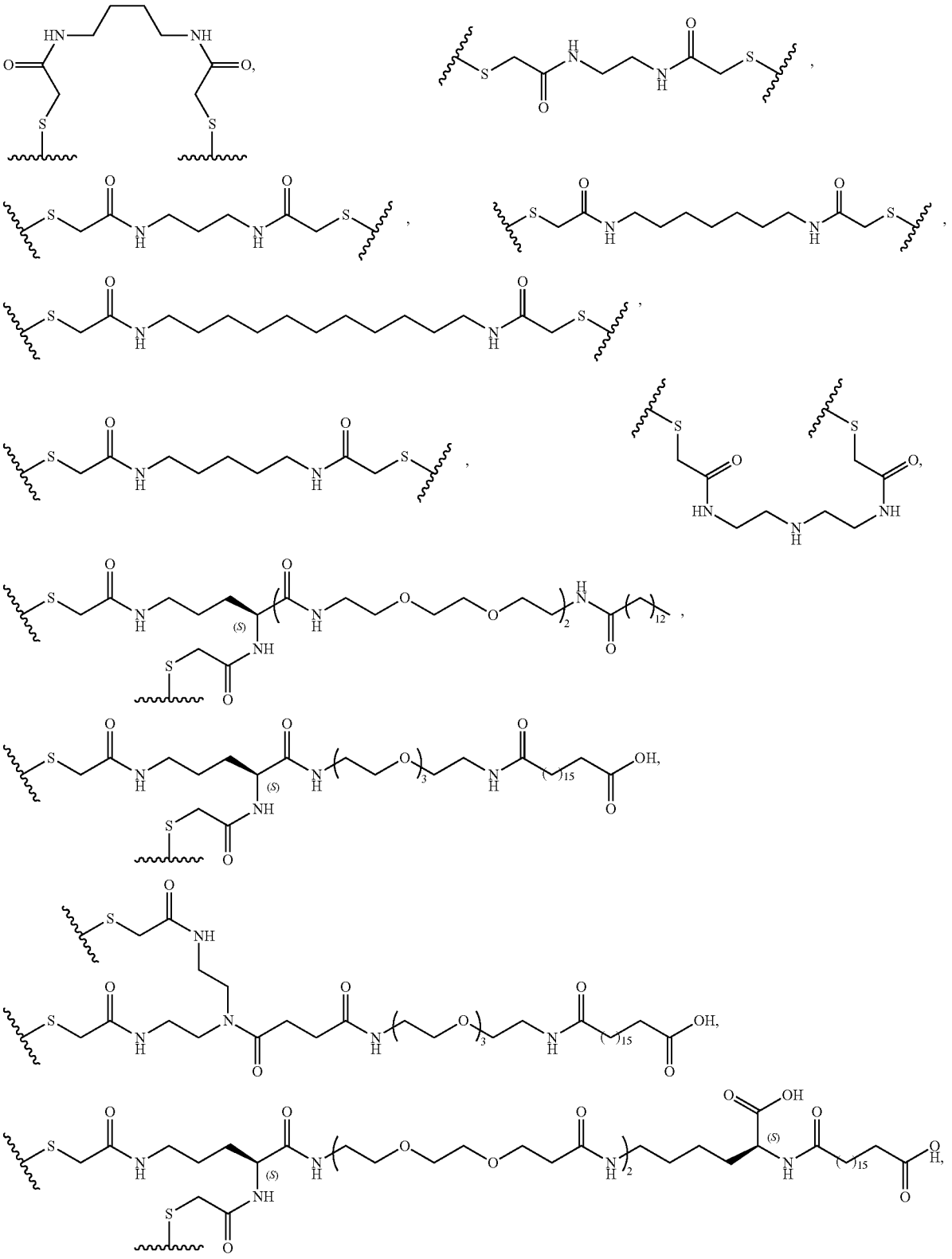
wherein each L^{19} is independently —$(CR^1R^2)_v$—, —C(═O)NR^3—, —NR^3C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^3C(═O)—; v is 2-20; and s19 is 1-5.

[0262] In some embodiments, the staple attached to the peptide is

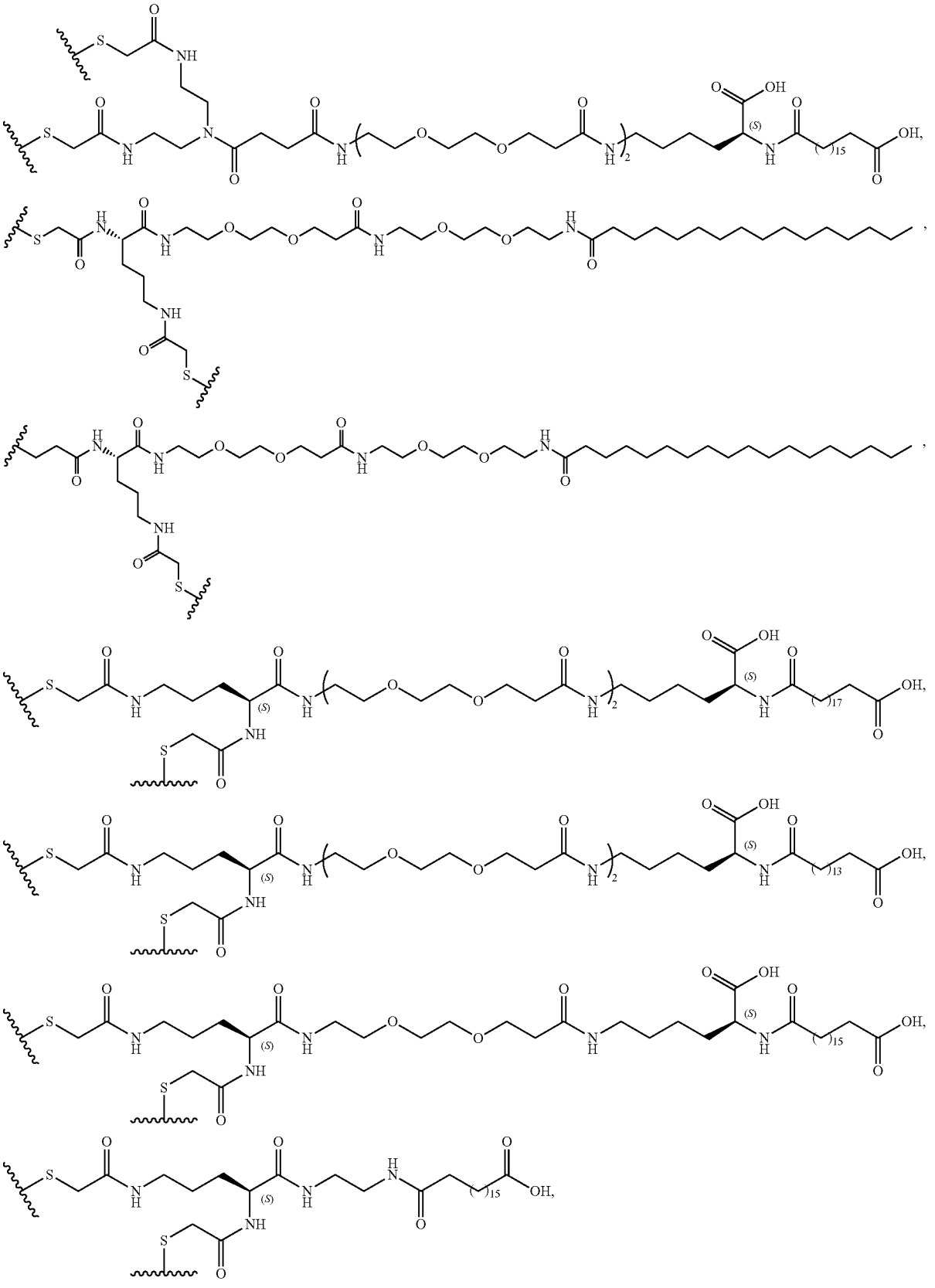


wherein L^{20} is —$(CR^1R^2)_v$— and v is 10-20.

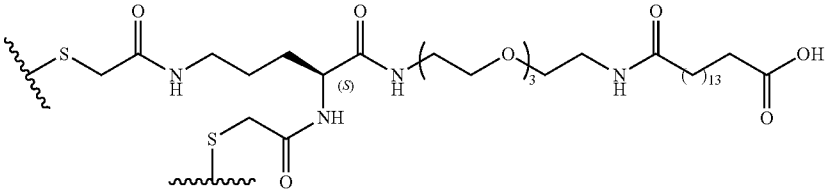
[0263] In some embodiments, the staple attached to the peptide is:

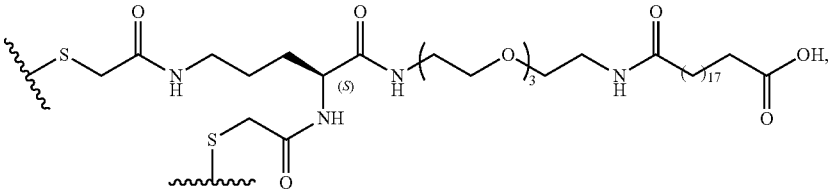


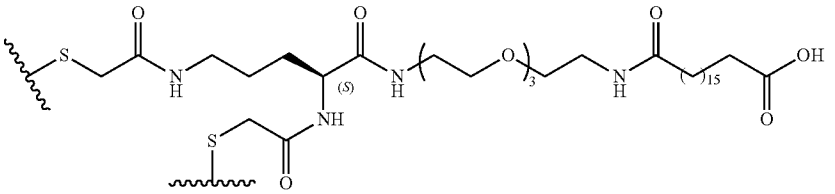
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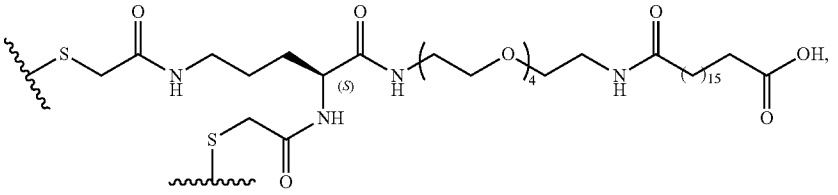


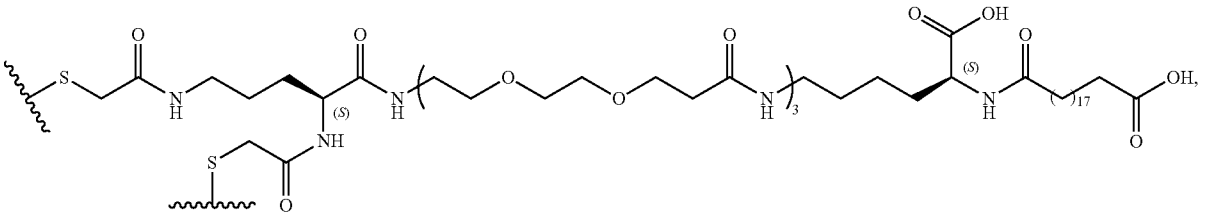
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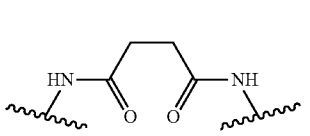


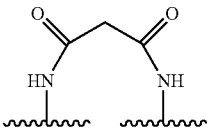


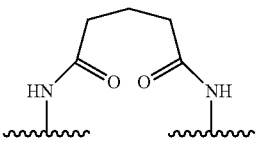


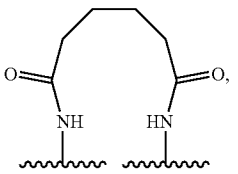


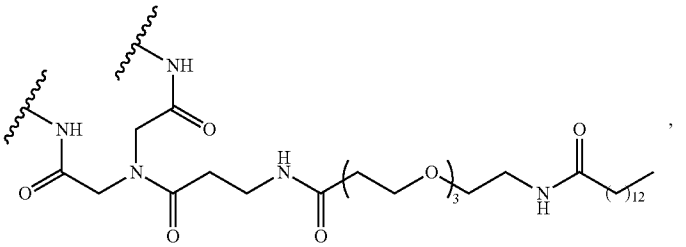


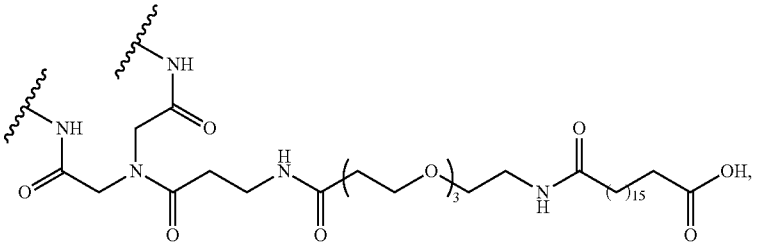




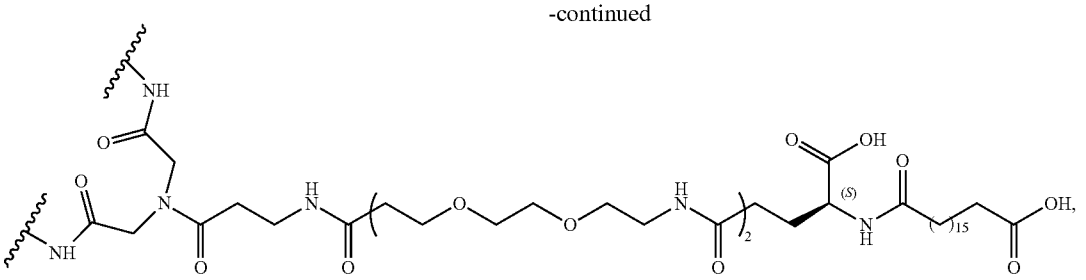


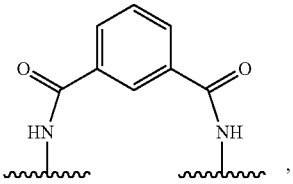




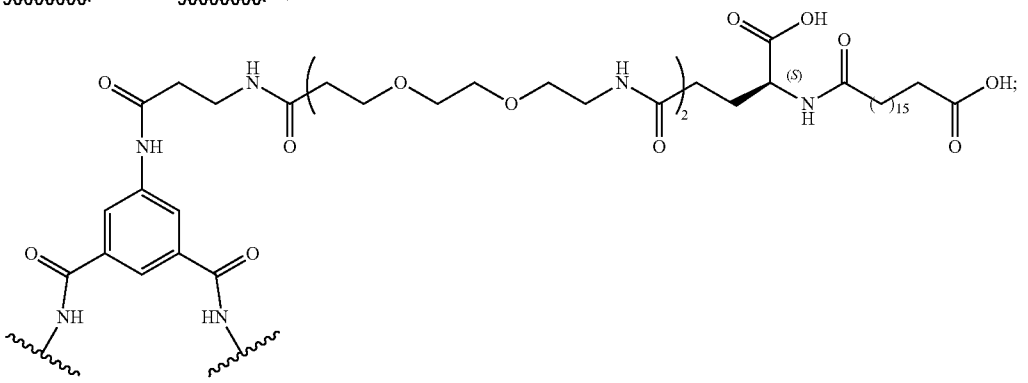


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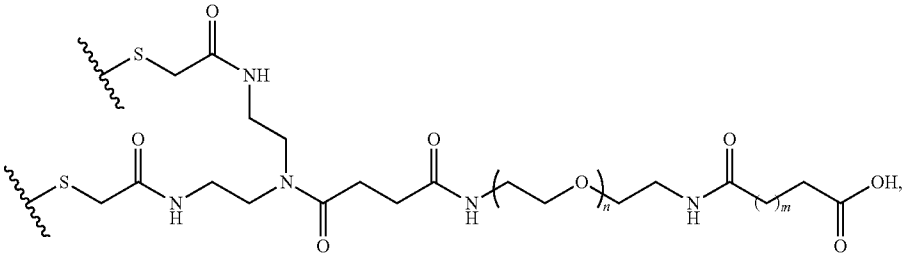


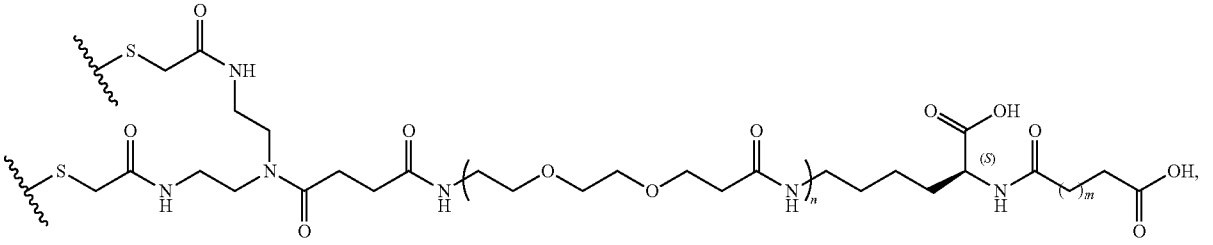
, or



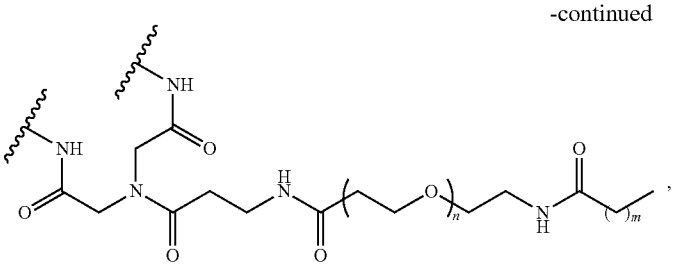
the "≀-S" being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue and the "≀-NH" being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

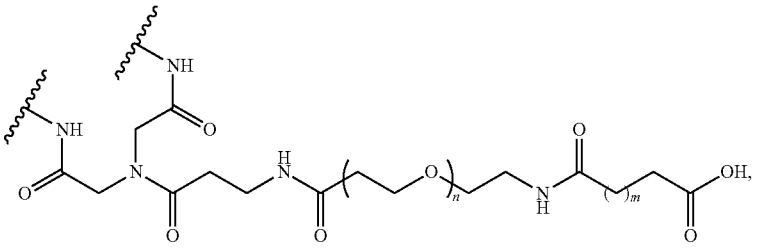
[0264] In some embodiments, the staple attached to the peptide is:



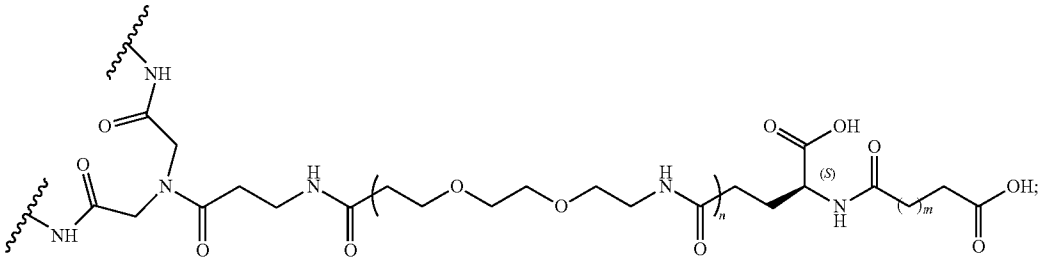


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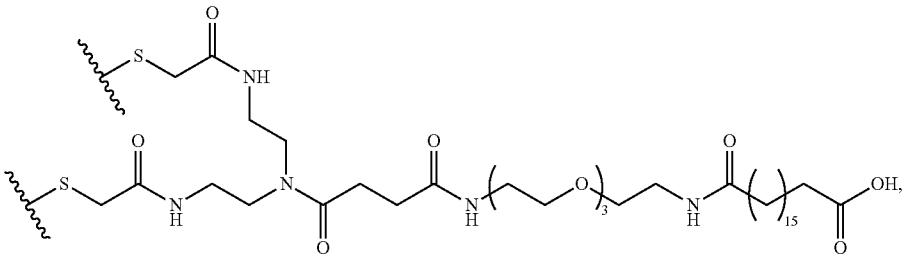


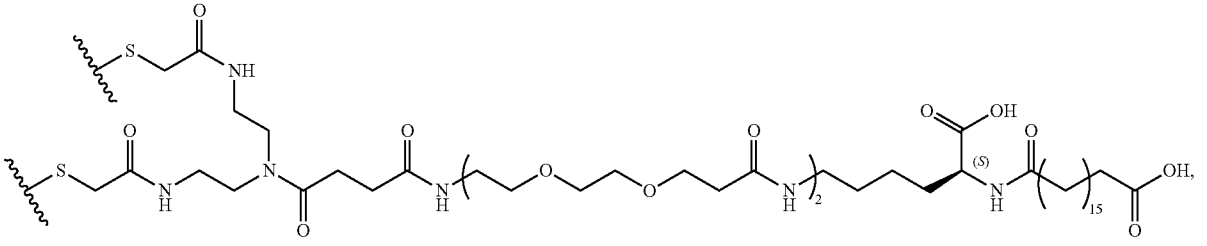
or



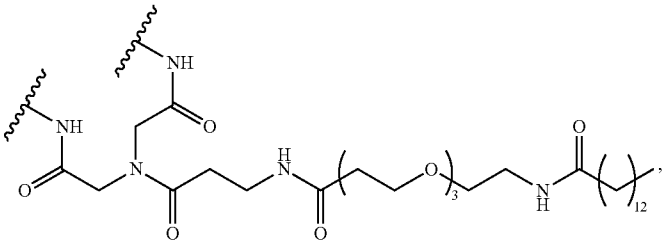
wherein n is 1-4 and m is 6-20; the "≀-S" being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue and the "≀-NH" being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

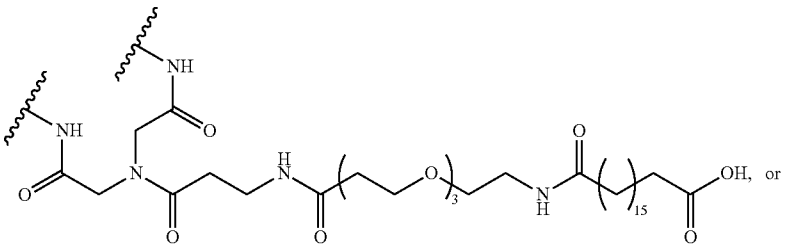
[0265] In some embodiments, the staple attached to the peptide is:

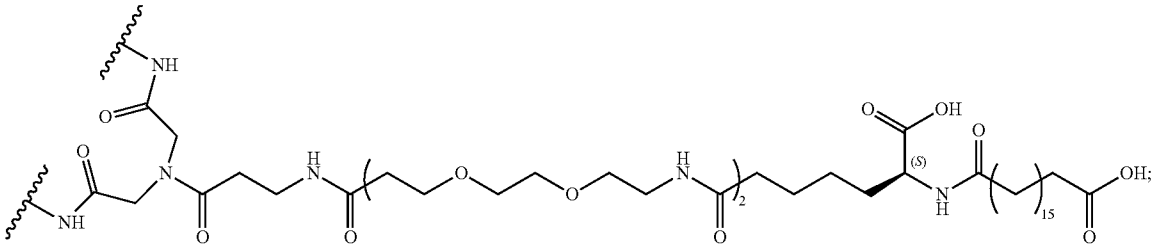




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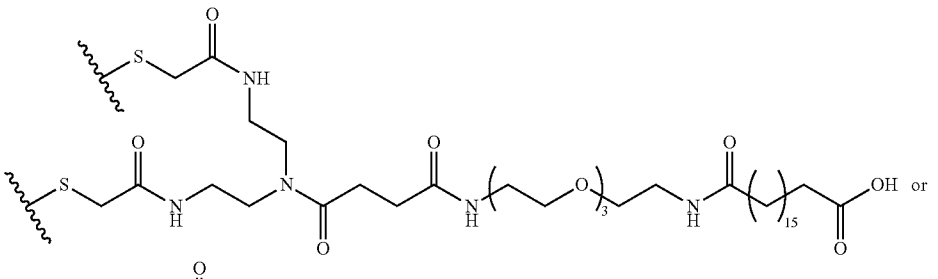


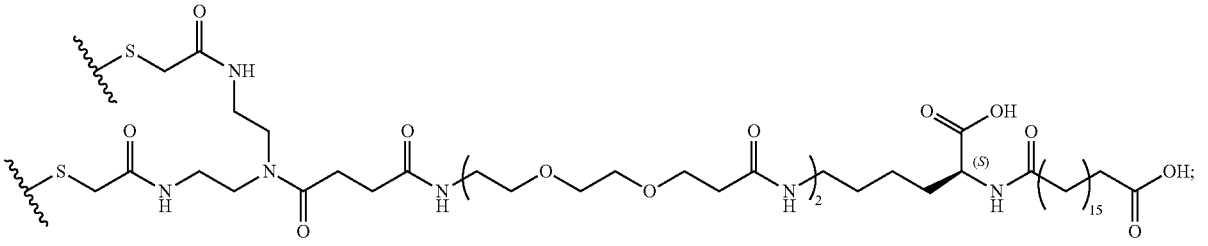




the "≀-S" being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue and the "≀-NH" being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

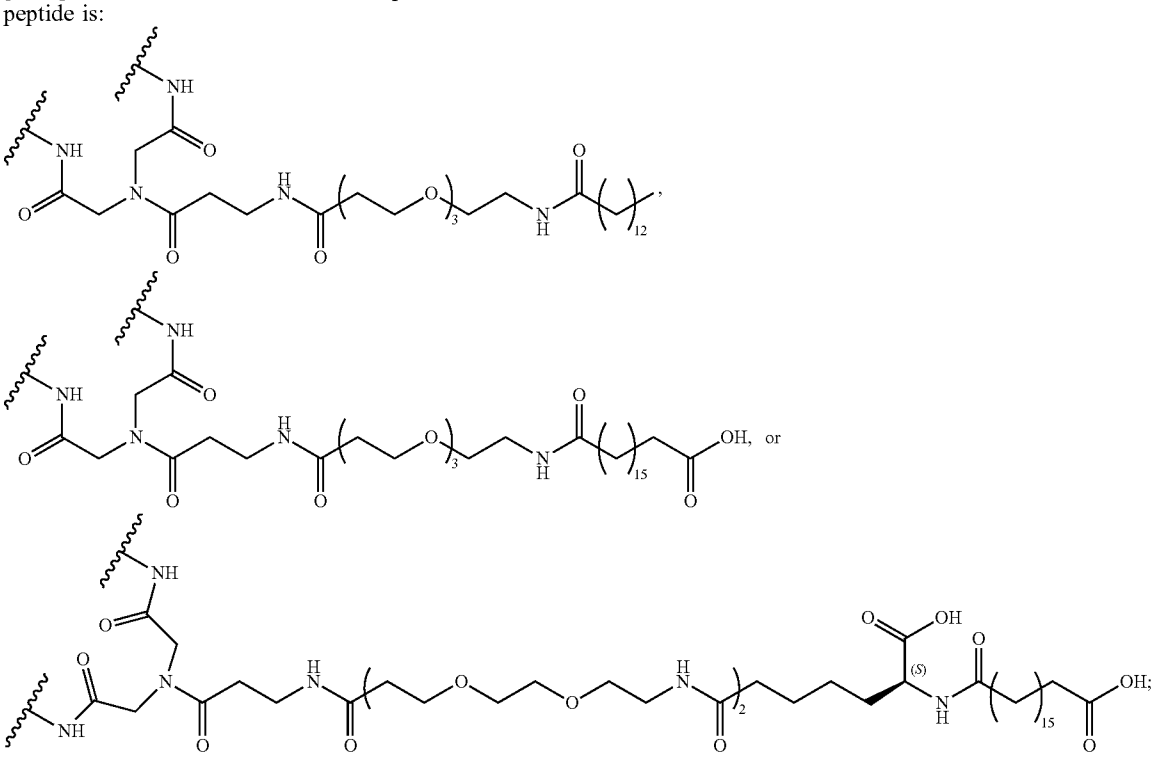
[0266] In some embodiments, the staple attached to the peptide is:





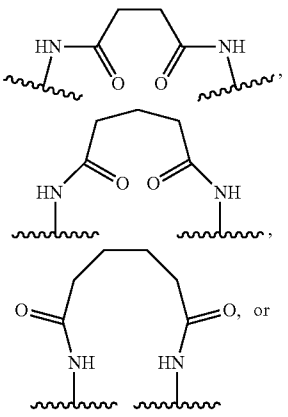
the "≀-S" being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue.

[0267] In some embodiments, the staple attached to the peptide is:

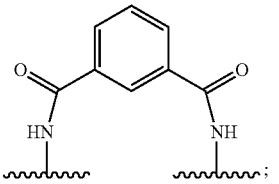


the "≀-NH" being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

[0268] In some embodiments, the staple attached to the peptide is:

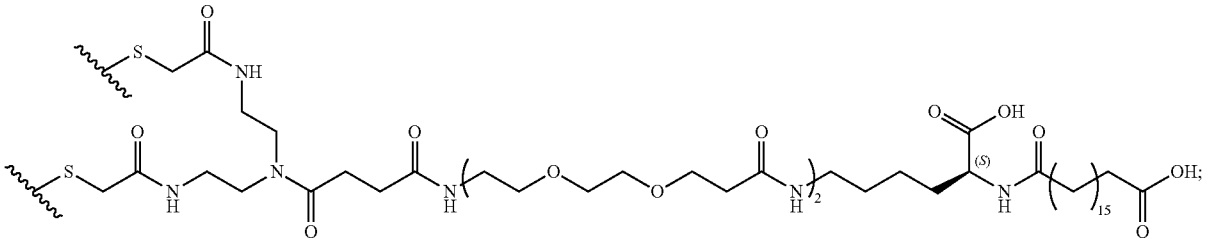


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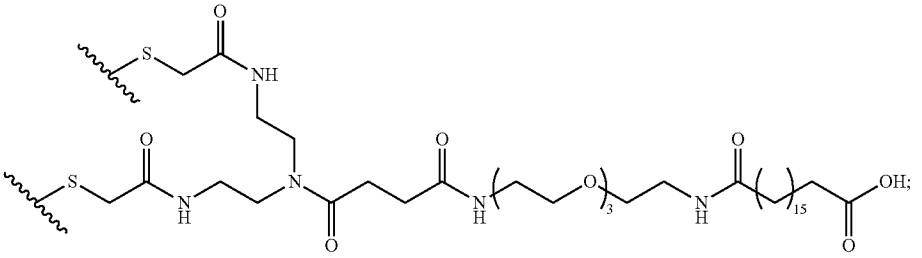
the "≀-NH" being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

[0269] In some embodiments, the staple attached to the peptide is:



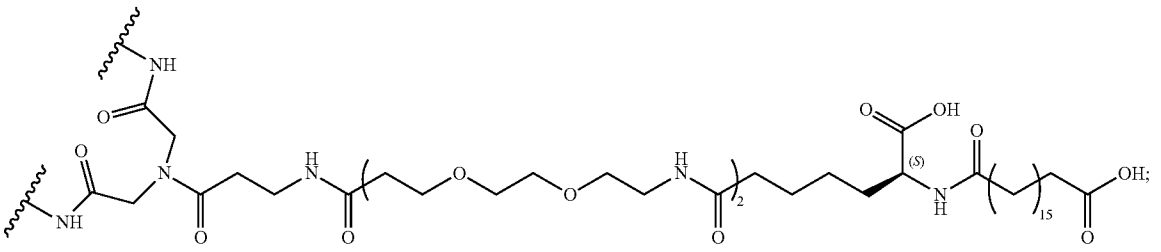
the "≀-S" being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue.

[0270] In some embodiments, the staple attached to the peptide is:



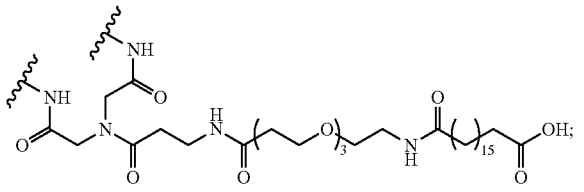
the "≀-S" being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue.

[0271] In some embodiments, the staple attached to the peptide is:



the "≀-NH" being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

[0272] In some embodiments, the staple attached to the peptide is:

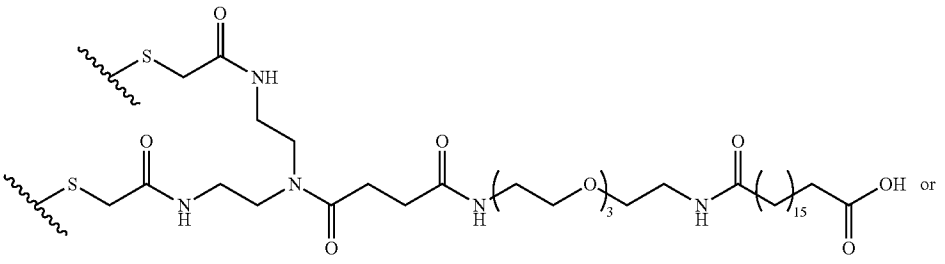


the "≀-NH" being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

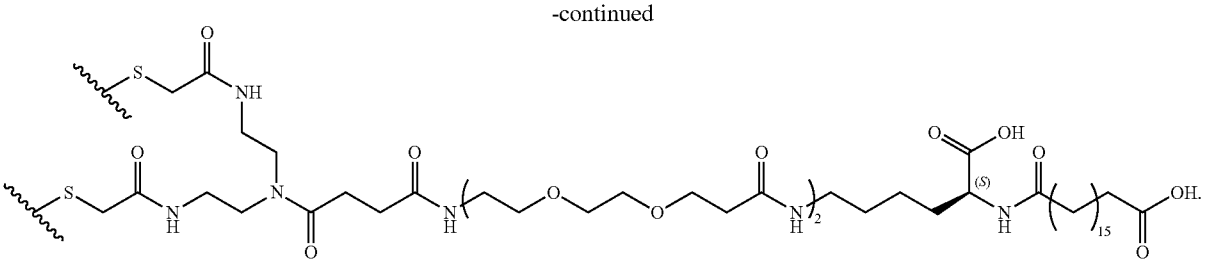
[0273] In some embodiments the peptide conjugate comprises:

[0274] a) a peptide that modulates the GLP-2 receptor comprising a sequence that is any one of SEQ ID NOs: 1-9; and

[0275] b) a staple attached to the peptide at a first cysteine and a second cysteine having the following structure ("S" being part of the cysteine residue):

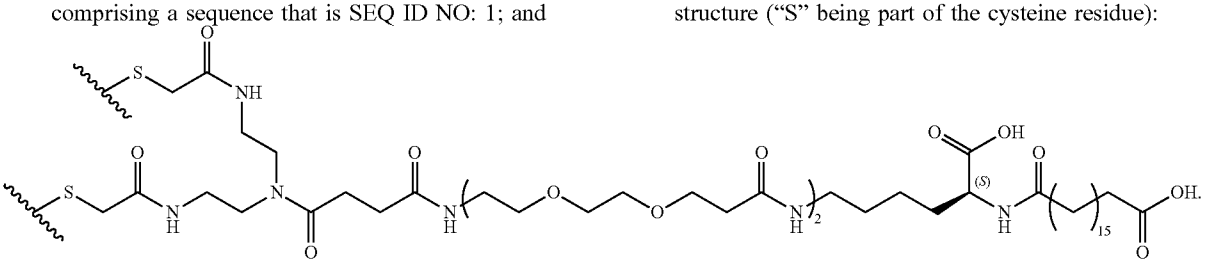


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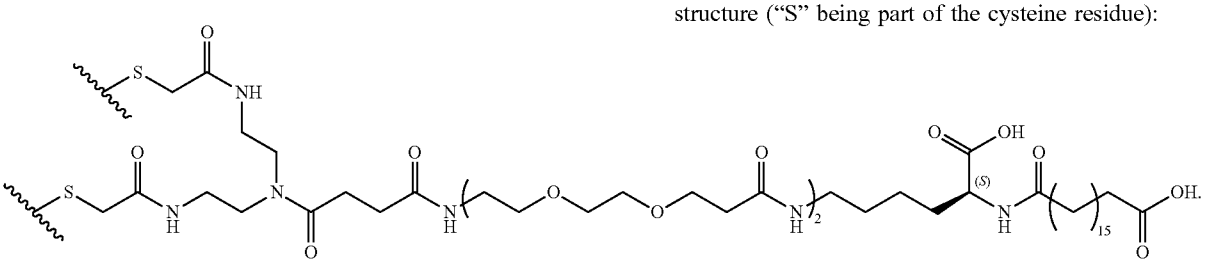


[0276] In some embodiments the peptide conjugate comprises:

[0277] a) a peptide that modulates the GLP-2 receptor comprising a sequence that is SEQ ID NO: 1; and



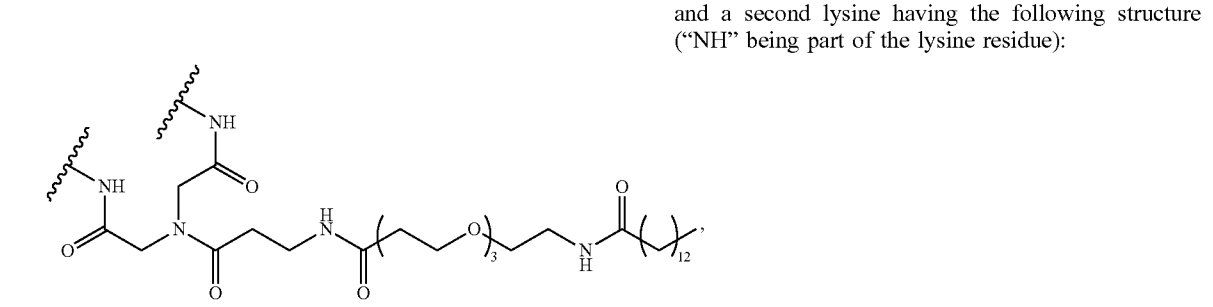
[0278] b) a staple attached to the peptide at a first cysteine and a second cysteine having the following structure ("S" being part of the cysteine residue):



[0279] In some embodiments the peptide conjugate comprises:

[0280] a) a peptide that modulates the GLP-2 receptor comprising a sequence that is SEQ ID NO: 2; and

[0281] b) a staple attached to the peptide at a first cysteine and a second cysteine having the following structure ("S" being part of the cysteine residue):

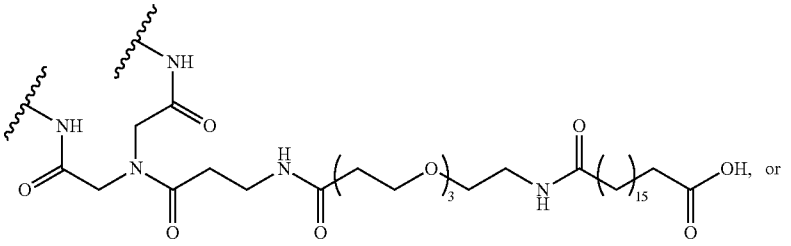


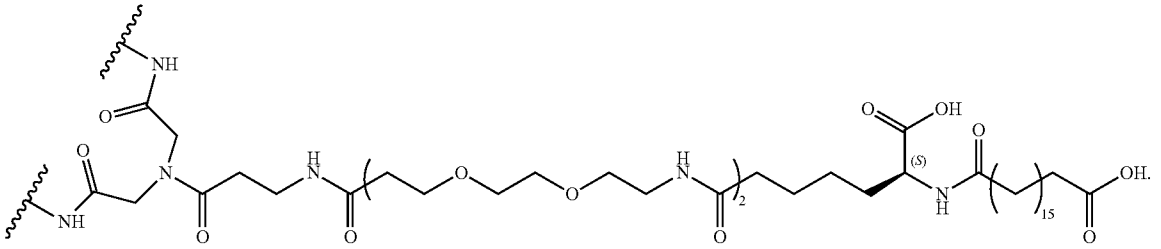
[0282] In some embodiments the peptide conjugate comprises:

[0283] a) a peptide that modulates the GLP-2 receptor comprising a sequence that is any one of SEQ ID NOs: 10-20; and

[0284] b) a staple attached to the peptide at a first lysine and a second lysine having the following structure ("NH" being part of the lysine residue):

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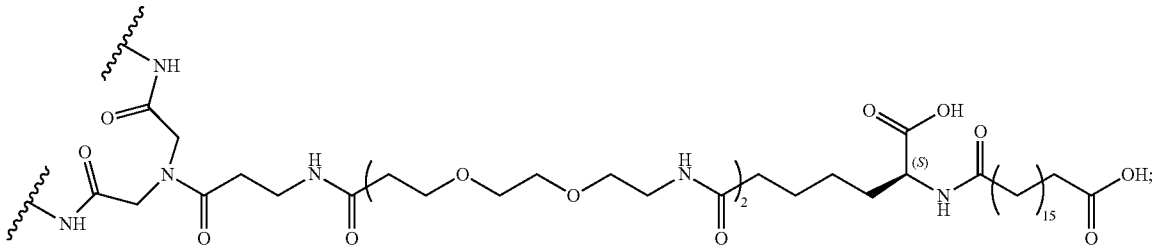




[0285] In some embodiments the peptide conjugate comprises:

[0286] a) a peptide that modulates the GLP-2 receptor comprising a sequence that is SEQ ID NO: 10; and

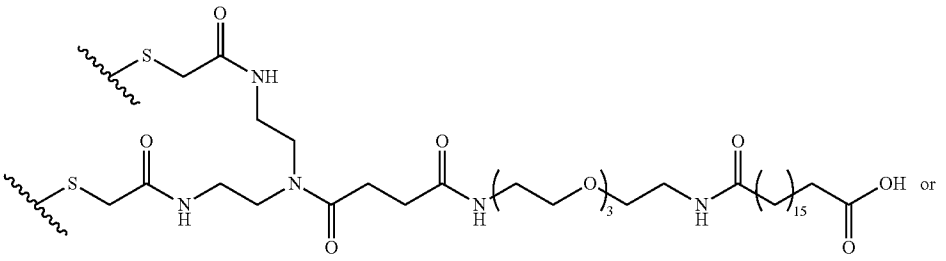
[0287] b) a staple attached to the peptide at a first lysine and a second lysine having the following structure ("NH" being part of the lysine residue):



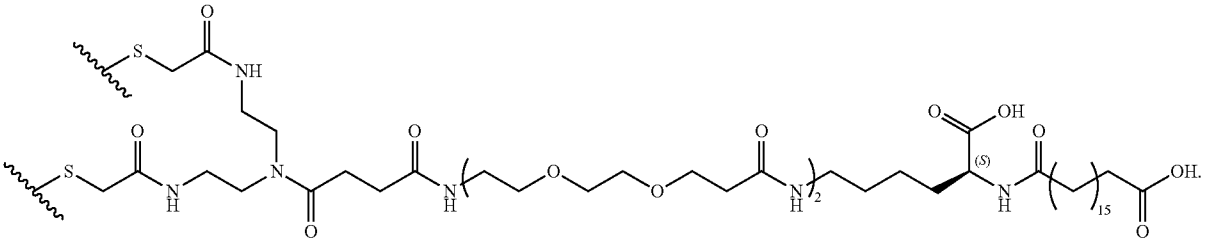
[0288] In some embodiments the peptide conjugate comprises:

[0289] a) a peptide that modulates the GLP-2 receptor comprising a sequence that is any one of SEQ ID NOs: 21-29; and

[0290] b) a staple attached to the peptide at a first cysteine and a second cysteine having the following structure ("S" being part of the cysteine residue):



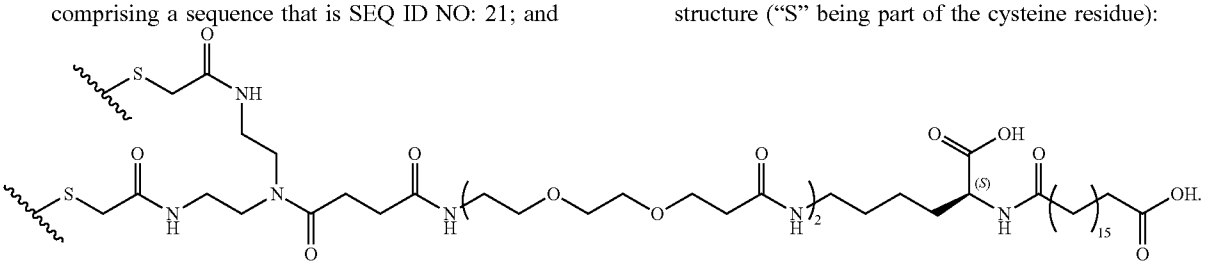
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[0291] In some embodiments the peptide conjugate comprises:

[0292] a) a peptide that modulates the GLP-2 receptor comprising a sequence that is SEQ ID NO: 21; and

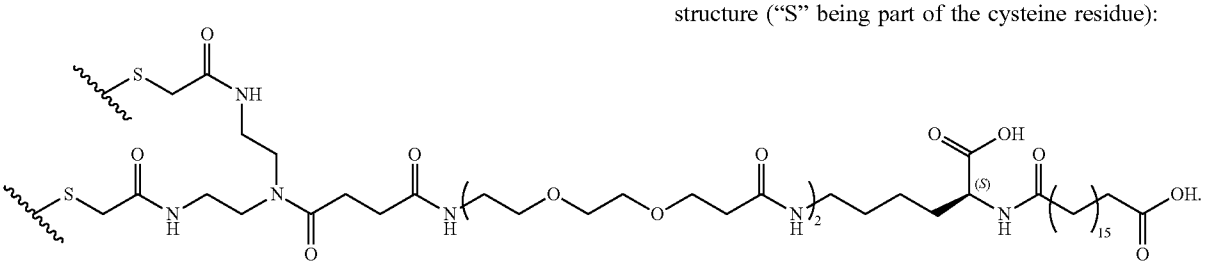
[0293] b) a staple attached to the peptide at a first cysteine and a second cysteine having the following structure ("S" being part of the cysteine residue):



[0294] In some embodiments the peptide conjugate comprises:

[0295] a) a peptide that modulates the GLP-2 receptor comprising a sequence that is SEQ ID NO: 22; and

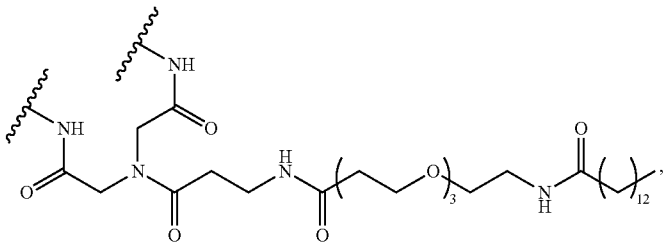
[0296] b) a staple attached to the peptide at a first cysteine and a second cysteine having the following structure ("S" being part of the cysteine residue):



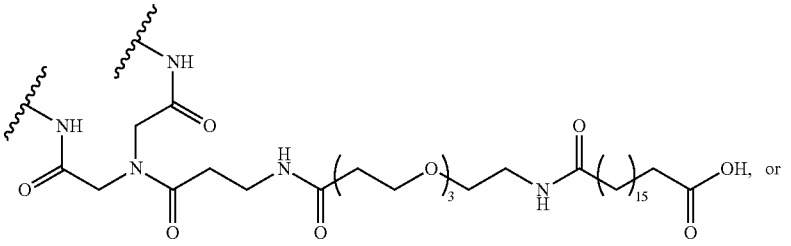
[0297] In some embodiments the peptide conjugate comprises:

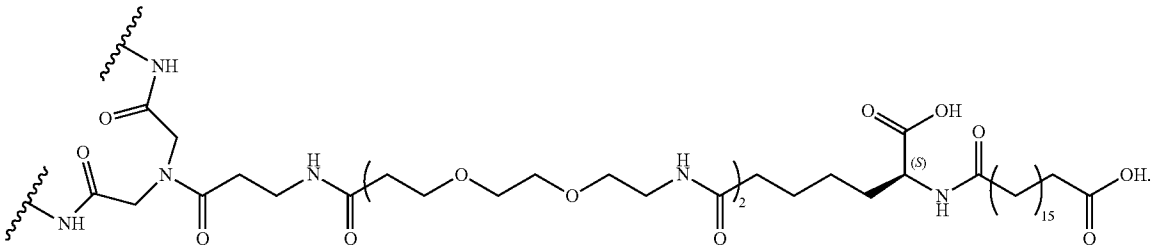
[0298] a) a peptide that modulates the GLP-2 receptor comprising a sequence that is any one of SEQ ID NOs: 30-40; and

[0299] b) a staple attached to the peptide at a first lysine and a second lysine having the following structure ("NH" being part of the lysine residue):



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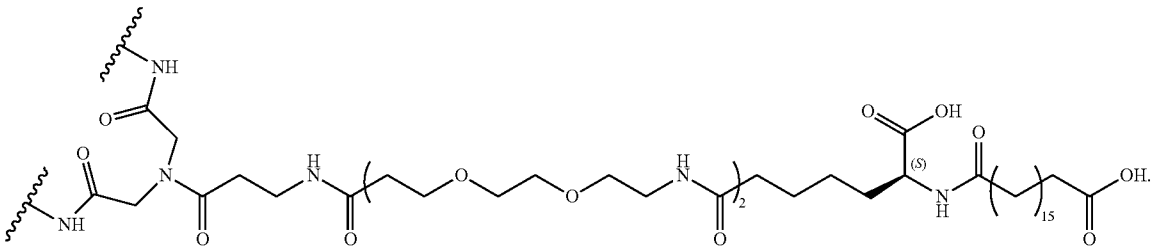




[0300] In some embodiments the peptide conjugate comprises:

[0301] a) a peptide that modulates the GLP-2 receptor comprising a sequence that is SEQ ID NO: 30; and

[0302] b) a staple attached to the peptide at a first lysine and a second lysine having the following structure ("NH" being part of the lysine residue):



Pharmacokinetics

[0303] Mechanisms by which peptide conjugates positively influence pharmacokinetic or pharmacodynamic behavior include, but are not limited to, (i) preventing or mitigating in vivo proteolytic degradation or other activity-diminishing chemical modification of the peptide that modulates the GLP-2 receptor; (ii) improving half-life or other pharmacokinetic properties by reducing renal filtration, decreasing receptor-mediated clearance or increasing bioavailability; (iii) reducing toxicity; (iv) improving solubility; and/or (v) increasing biological activity and/or target selectivity of the peptide or unmodified peptide.

[0304] Peptide conjugates may enhance one or more pharmacokinetic properties of a peptide that modulates the GLP-2 receptor when attached to the peptide. Peptide conjugates disclosed herein may enhance the one or more pharmacokinetic properties of the peptide that modulates the GLP-2 receptor by at least about 200% as measured by pharmacodynamics when compared to the peptide or unmodified peptide alone. Peptide conjugates disclosed herein may enhance the one or more pharmacokinetic properties of the therapeutic agent by at least about 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000% as measured by pharmacodynamics when compared to the peptide or unmodified peptide alone.

[0305] The pharmacokinetic properties may comprise a half-life. The half-life of the peptide conjugate may be at least about two-fold longer compared to the half-life of the unmodified peptide alone. The half-life of the peptide conjugate disclosed herein may be at least about 3-fold, 4-fold, 5-fold, or 10-fold longer compared to the half-life of the therapeutic agent or unmodified therapeutic peptide alone. The half-life of a peptide conjugate disclosed herein may be at least about 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 30-, 35-, 40-, 45-, or 50-fold longer compared to the half-life of the unmodified peptide alone.

[0306] In some embodiments, the half-life of the peptide conjugate is at least about 2-fold greater than the half-life of an unmodified form of the peptide. In some embodiments, the half-life of the peptide conjugate is at least about 5-fold greater than the half-life of an unmodified form of the peptide. In some embodiments, the half-life of the peptide conjugate is at least about 10-fold greater than the half-life of an unmodified form of the peptide.

[0307] In addition, a peptide conjugate as described herein may have a positive effect on terms of increasing manufacturability, and/or reducing immunogenicity of the peptide, compared to an unconjugated form of the unmodified therapeutic peptide.

Therapeutic Use

[0308] In one aspect, peptide conjugates disclosed herein are useful for treating, alleviating, inhibiting and/or preventing one or more diseases and/or conditions. The disease and/or condition may be a chronic disease or condition. Alternatively, the disease and/or condition is an acute disease or condition. The disease or condition may be recurrent, refractory, accelerated, or in remission. The disease or condition may affect one or more cell types. The one or more diseases and/or conditions may be an autoimmune disease, inflammatory disease, or metabolic disease.

[0309] Disclosed herein are methods for treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein. The disease or condition may be diabetes or obesity, or a medical condition associated with diabetes or obesity. The disease or condition may be non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or cardiovascular disease. The disease or condition may be an autoimmune disorder. The disease or condition may be Crohn's disease or ulcerative colitis. The disease or condition may be short bowel syndrome (SBS). The disease or condition may be inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), or psoriasis. The disease or condition may be Alzheimer's disease, Parkinson's disease or Huntington's disease. The PLC may be administered with one or more additional therapeutic agents. Disclosed herein are methods of treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a composition disclosed herein comprising one or more peptide conjugates.

[0310] Provided herein is a method of preventing or treating a metabolic disease or condition in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein. The metabolic disease or condition may be diabetes. The metabolic disease or condition may be obesity. The metabolic disease or condition may be glycogen storage disease, phenylketonuria, maple syrup urine disease, glutaric acidemia type 1, Carbamoyl phosphate synthetase I deficiency, alcaptonuria, Medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD), acute intermittent porphyria, Lesch-Nyhan syndrome, lipoid congenital adrenal hyperplasia, congenital adrenal hyperplasia, POMPC deficiency, LEPR deficiency, Bardet Biedl syndrome, Alstrome syndrome, Prader-Willi Syndrome, Kearns-Sayre syndrome, Zellweger syndrome, Gaucher's disease, or Niemann Pick disease.

[0311] Provided herein is a method of preventing or treating NAFLD, NASH, or cardiovascular disease in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein.

[0312] Provided herein is a method of preventing or treating short bowel syndrome (SBS) in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein.

[0313] Provided herein is a method of preventing or treating inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), or psoriasis in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein.

[0314] Provided herein is a method of preventing or treating Crohn's disease or ulcerative colitis in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein.

[0315] Provided herein is a method of preventing or treating a sleep disorder.

[0316] Provided herein is a method of preventing or treating absence seizure.

[0317] Provided herein is a method of preventing or treating chronic kidney disease (for example complication of diabetes). Provided herein is a method of preventing or treating diabetic heart disease.

[0318] Provided herein is a method of preventing or treating cardiovascular events.

[0319] Provided herein is a method of preventing or treating Alzheimer's disease, Parkinson's disease or Huntington's disease in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein.

[0320] Provided herein is a method of preventing or treating stomach and bowel-related disorders, such as the treatment of neonatals with compromised intestine function, osteoporosis, and DPP-IV (dipeptidylpeptidase-IV) mediated conditions. By way of example, the stomach and bowel-related disorders include ulcers, gastritis, digestion disorders, malabsorption syndromes, short-gut syndrome, cul-de-sac syndrome, inflammatory bowel disease, celiac sprue (for example arising from gluten induced enteropathy or celiac disease), tropical sprue, hypogammaglobulinemia sprue, enteritis, regional enteritis (Crohn's disease), ulcerative colitis, irritable bowel syndrome associated with diarrhea, Small intestine damage and short bowel syndrome.

[0321] Provided herein is a method of preventing or treating radiation enteritis, infectious or post-infectious enteritis, and small intestinal damage due to toxic or other chemotherapeutic agents. This may require administration of the peptide conjugate prior to, concurrently with or following a course of chemotherapy or radiation therapy in order to reduce side effects of chemotherapy such as diarrhea, abdominal cramping and vomiting, and reduce the consequent structural and functional damage of the intestinal epithelium resulting from the chemotherapy or radiation therapy.

[0322] Provided herein is a method of preventing or treating malnutrition, for example conditions such as the wasting syndrome cachexia and anorexia.

[0323] Provided herein is a method of preventing or treating a disease or condition which benefits from a modulator of a GLP-2 receptor in a subject in need thereof comprising administering to the subject a peptide conjugate described herein.

Combinations

[0324] Disclosed herein are pharmaceutical compositions comprising a peptide conjugate described herein and one or more additional therapeutic agents.

[0325] The additional therapeutic agents may comprise one or more other diabetes drugs, DPP4 inhibitors, SGLT2 inhibitors, hypoglycemic drugs and biguanidine drugs, insulin secretogogues and sulfonyl urea drugs, TZD drugs, insulin and insulin analogs, FGF21 and analogs, leptin or leptin analogs, amylin and amylin analogs, an anti-inflammatory drug, cyclosporine A or FK506, 5-ASA, or a statin, or any combination thereof. The additional therapeutic agent may be aspirin.

[0326] The additional therapeutic agents may comprise a therapeutic incretin or derivative thereof. Non-limiting

examples of incretins or derivatives thereof include GLP-1, glucagon, oxyntomodulin, exendin-4, GLP-2, GIP, and combinations thereof.

Compositions

[0327] Disclosed herein are pharmaceutical compositions comprising a peptide conjugate described herein and a pharmaceutically acceptable excipients or vehicles. Pharmaceutically acceptable excipients or vehicles may include carriers, excipients, diluents, antioxidants, preservatives, coloring, flavoring and diluting agents, emulsifying agents, suspending agents, solvents, fillers, bulking agents, buffers, delivery vehicles, tonicity agents, cosolvents, wetting agents, complexing agents, buffering agents, antimicrobials, and surfactants.

[0328] Neutral buffered saline or saline mixed with serum albumin are exemplary appropriate carriers. The pharmaceutical compositions may include antioxidants such as ascorbic acid; low molecular weight polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as Tween, pluronics, or polyethylene glycol (PEG). Also by way of example, suitable tonicity enhancing agents include alkali metal halides (preferably sodium or potassium chloride), mannitol, sorbitol, and the like. Suitable preservatives include benzalkonium chloride, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid and the like. Hydrogen peroxide also may be used as preservative. Suitable cosolvents include glycerin, propylene glycol, and PEG. Suitable complexing agents include caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxy-propyl-beta-cyclodextrin. Suitable surfactants or wetting agents include sorbitan esters, polysorbates such as polysorbate 80, tromethamine, lecithin, cholesterol, tyloxapal, and the like. The buffers may be conventional buffers such as acetate, borate, citrate, phosphate, bicarbonate, or Tris-HCl. Acetate buffer may be about pH 4-5.5, and Tris buffer can be about pH 7-8.5. Additional pharmaceutical agents are set forth in Remington's Pharmaceutical Sciences, 18th Edition, A. R. Gennaro, ed., Mack Publishing Company, 1990.

[0329] The composition may be in liquid form or in a lyophilized or freeze-dried form and may include one or more lyoprotectants, excipients, surfactants, high molecular weight structural additives and/or bulking agents. In one embodiment, a lyoprotectant is included, which is a non-reducing sugar such as sucrose, lactose or trehalose. The amount of lyoprotectant generally included is such that, upon reconstitution, the resulting formulation will be isotonic, although hypertonic or slightly hypotonic formulations also may be suitable. In addition, the amount of lyoprotectant should be sufficient to prevent an unacceptable amount of degradation and/or aggregation of the protein upon lyophilization. Exemplary lyoprotectant concentrations for sugars (e.g., sucrose, lactose, trehalose) in the pre-lyophilized formulation are from about 10 mM to about 400 mM. In another embodiment, a surfactant is included, such as for example, nonionic surfactants and ionic surfactants such as polysorbates (e.g., polysorbate 20, polysorbate 80); poloxamers (e.g., poloxamer 188); poly(ethylene glycol) phenyl ethers (e.g., Triton); sodium dodecyl sulfate (SDS); sodium laurel sulfate; sodium octyl glycoside; lauryl-, myristyl-, linoleyl-, or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl- or stearyl-sarcosine; linoleyl, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocamidopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine (e.g., lauroamidopropyl); myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, or disodium methyl ofeyl-taurate; and the MONAQUAT™ series (Mona Industries, Inc., Paterson, N.J.), polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol (e.g., Pluronics, PF68 etc). Exemplary amounts of surfactant that may be present in the pre-lyophilized formulation are from about 0.001-0.5%. High molecular weight structural additives (e.g., fillers, binders) may include for example, acacia, albumin, alginic acid, calcium phosphate (dibasic), cellulose, carboxymethylcellulose, carboxymethylcellulose sodium, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, microcrystalline cellulose, dextran, dextrin, dextrates, sucrose, tylose, pregelatinized starch, calcium sulfate, amylose, glycine, bentonite, maltose, sorbitol, ethylcellulose, disodium hydrogen phosphate, disodium phosphate, disodium pyrosulfite, polyvinyl alcohol, gelatin, glucose, guar gum, liquid glucose, compressible sugar, magnesium aluminum silicate, maltodextrin, polyethylene oxide, polymethacrylates, povidone, sodium alginate, tragacanth microcrystalline cellulose, starch, and zein. Exemplary concentrations of high molecular weight structural additives are from 0.10% to 10% by weight. In other embodiments, a bulking agent (e.g., mannitol, glycine) may be included.

[0330] Compositions may be suitable for parenteral administration. Exemplary compositions are suitable for injection or infusion into an animal by any route available to the skilled worker, such as intraarticular, subcutaneous, intravenous, intramuscular, intraperitoneal, intracerebral (intraparenchymal), intracerebroventricular, intramuscular, intraocular, intraarterial, or intralesional routes. A parenteral formulation typically may be a sterile, pyrogen-free, isotonic aqueous solution, optionally containing pharmaceutically acceptable preservatives.

[0331] Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringers' dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers, such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present, such as, for example, anti-microbials, anti-oxidants, chelating agents, inert gases and the like. See generally, Remington's Pharmaceutical Science, 16th Ed., Mack Eds., 1980.

[0332] Pharmaceutical compositions described herein may be formulated for controlled or sustained delivery in a manner that provides local concentration of the product (e.g., bolus, depot effect) and/or increased stability or half-life in a particular local environment. The compositions can include the formulation of peptide conjugates, disclosed herein with particulate preparations of polymeric com-

pounds such as polylactic acid, polyglycolic acid, etc., as well as agents such as a biodegradable matrix, injectable microspheres, microcapsular particles, microcapsules, bioerodible particles beads, liposomes, and implantable delivery devices that provide for the controlled or sustained release of the active agent which then can be delivered as a depot injection. Techniques for formulating such sustained- or controlled-delivery means are known and a variety of polymers have been developed and used for the controlled release and delivery of drugs. Such polymers are typically biodegradable and biocompatible. Polymer hydrogels, including those formed by complexation of enantiomeric polymer or polypeptide segments, and hydrogels with temperature or pH sensitive properties, may be desirable for providing drug depot effect because of the mild and aqueous conditions involved in trapping bioactive protein agents (e.g., antibodies comprising an ultralong CDR3).

[0333] Suitable and/or preferred pharmaceutical formulations may be determined in view of the present disclosure and general knowledge of formulation technology, depending upon the intended route of administration, delivery format, and desired dosage. Regardless of the manner of administration, an effective dose may be calculated according to patient body weight, body surface area, or organ size. Further refinement of the calculations for determining the appropriate dosage for treatment involving each of the formulations described herein are routinely made in the art and is within the ambit of tasks routinely performed in the art. Appropriate dosages may be ascertained through use of appropriate dose-response data.

Definitions

[0334] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, "consist of" or "consist essentially of" the described features.

[0335] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0336] "Alkyl" refers to a straight or branched chain hydrocarbon monoradical, which may be fully saturated or unsaturated, having from one to about ten carbon atoms, or from one to six carbon atoms, wherein a sp3-hybridized carbon of the alkyl residue is attached to the rest of the molecule by a single bond. Examples of saturated hydrocarbon monoradical include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl, and the like. Whenever it appears herein, a numerical range such as "C_1-C_6 alkyl" means that the alkyl group consists of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, the alkyl is a C_1-C_{10} alkyl, a C_1-C_9 alkyl, a C_1-C_8 alkyl, a C_1-C_7 alkyl, a C_1-C_6 alkyl, a C_1-C_5 alkyl, a C_1-C_4 alkyl, a C_1-C_3 alkyl, a C_1-C_2 alkyl, or a C_1 alkyl. When the alkyl refers to an unsaturated straight or branched chain hydrocarbon monoradical it is known as an "alkenyl" or an "alkynyl". The alkenyl may be in either the cis or trans conformation about the double bond(s), and should be understood to include both isomers. Examples of alkenyls include, but are not limited to ethenyl (—CH═CH_2), 1-propenyl (—CH_2CH═CH_2), isopropenyl [—C(CH_3)═CH_2], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as "C_2-C_6 alkenyl" means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkenyl" where no numerical range is designated. In some embodiments, the alkenyl is a C_2-C_{10} alkenyl, a C_2-C_9 alkenyl, a C_2-C_8 alkenyl, a C_2-C_7 alkenyl, a C_2-C_6 alkenyl, a C_2-C_5 alkenyl, a C_2-C_4 alkenyl, a C_2-C_3 alkenyl, or a C_2 alkenyl. Examples of alkynyl include, but are not limited to ethynyl, 2-propynyl, 2- and the like. Whenever it appears herein, a numerical range such as "C_2-C_6 alkynyl" means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkynyl" where no numerical range is designated. In some embodiments, the alkynyl is a C_2-C_{10} alkynyl, a C_2-C_9 alkynyl, a C_2-C_8 alkynyl, a C_2-C_7 alkynyl, a C_2-C_6 alkynyl, a C_2-C_5 alkynyl, a C_2-C_4 alkynyl, a C_2-C_3 alkynyl, or a C_2 alkynyl. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with oxo, halogen, —CN, —CF_3, —OH, —OMe, —NH_2, or —NO_2. In some embodiments, the alkyl is optionally substituted with oxo, halogen, —CN, —CF_3, —OH, or —OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[0337] "Alkylene" refers to a straight or branched divalent hydrocarbon chain. Whenever it appears herein, a numerical range such as "C_1-C_6 alkylene" means that the alkylene consists of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkylene" where no numerical range is designated. In some embodiments, the alkylene is a C_1-C_{10} alkylene, a C_1-C_9

alkylene, a C_1-C_8 alkylene, a C_1-C_7 alkylene, a C_1-C_6 alkylene, a C_1-C_5 alkylene, a C_1-C_4 alkylene, a C_1-C_3 alkylene, a C_1-C_2 alkylene, or a C_1 alkylene. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkylene is optionally substituted with oxo, halogen, —CN, —CF_3, —OH, —OMe, —NH_2, or —NO_2. In some embodiments, an alkylene is optionally substituted with oxo, halogen, —CN, —CF_3, —OH, or —OMe. In some embodiments, the alkylene is optionally substituted with halogen.

[0338] "Alkoxy" refers to a radical of the formula —OR_a where R_a is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkoxy is optionally substituted with oxo, halogen, —CN, —CF_3, —OH, —OMe, —NH_2, or —NO_2. In some embodiments, an alkoxy is optionally substituted with oxo, halogen, —CN, —CF_3, —OH, or —OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

[0339] "Aryl" refers to a radical derived from a hydrocarbon ring system comprising hydrogen, 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl. Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. In some embodiments, the aryl is phenyl. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an aryl is optionally substituted with halogen, methyl, ethyl, —CN, —CF_3, —OH, —OMe, —NH_2, or —NO_2. In some embodiments, an aryl is optionally substituted with halogen, methyl, ethyl, —CN, —CF_3, —OH, or —OMe. In some embodiments, the aryl is optionally substituted with halogen.

[0340] "Cycloalkyl" refers to a stable, partially or fully saturated, monocyclic or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (C_3-C_{15} cycloalkyl), from three to ten carbon atoms (C_3-C_{10} cycloalkyl), from three to eight carbon atoms (C_3-C_8 cycloalkyl), from three to six carbon atoms (C_3-C_6 cycloalkyl), from three to five carbon atoms (C_3-C_5 cycloalkyl), or three to four carbon atoms (C_3-C_4 cycloalkyl). In some embodiments, the cycloalkyl is a 3- to 6-membered cycloalkyl. In some embodiments, the cycloalkyl is a 5- to 6-membered cycloalkyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls or carbocycles include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, —CN, —CF_3, —OH, —OMe, —NH_2, or —NO_2. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, —CN, —CF_3, —OH, or —OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

[0341] "Halo" or "halogen" refers to bromo, chloro, fluoro, or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0342] "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0343] "Heterocycloalkyl" refers to a stable 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from nitrogen, oxygen, phosphorous, and sulfur. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (C_2-C_{15} heterocycloalkyl), from two to ten carbon atoms (C_2-C_{10} heterocycloalkyl), from two to eight carbon atoms (C_2-C_8 heterocycloalkyl), from two to six carbon atoms (C_2-C_6 heterocycloalkyl), from two to five carbon atoms (C_2-C_5 heterocycloalkyl), or two to four carbon atoms (C_2-C_4 heterocycloalkyl). In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkyl. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidinyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl,

and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). Partially saturated heterocycloalkyls include, for example dihydropyrrolyl or tetrahydropyridine. Unless stated otherwise specifically in the specification, a heterocycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, —CN, —CF_3, —OH, —OMe, —NH_2, or —NO_2. In some embodiments, a heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, —CN, —CF_3, —OH, or —OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

[0344] "Heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g. —NH—, —N(alkyl)-), sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1-C_6 heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen (e.g. —NH—, —N(alkyl)-), sulfur, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Unless stated otherwise specifically in the specification, a heteroalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, —CN, —CF_3, —OH, —OMe, —NH_2, or —NO_2. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, —CN, —CF_3, —OH, or —OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[0345] "Heteroaryl" refers to a 5- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. In some embodiments, the heteroaryl is a 6-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl is optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroaryl is optionally substituted with halogen, methyl, ethyl, —CN, —CF_3, —OH, —OMe, —NH_2, or —NO_2. In some embodiments, a heteroaryl is optionally substituted with halogen, methyl, ethyl, —CN, —CF_3, —OH, or —OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

[0346] The term "percent identity" refers to a comparison between two nucleic acid or amino acid sequences. Such comparisons are measured using any number of alignment methods known in the art, including but not limited to global (e.g., Needleman-Wunsch algorithm) or local alignments (e.g., Smith-Waterman, Sellers, or other algorithm). Percent identity often refers to the percentage of matching positions of two sequences for a contiguous section of positions, wherein the two sequences are aligned in such a way to maximize matching positions and minimize gaps of non-matching positions. In some instances, alignments are conducted wherein there are no gaps between the two sequences. In some instances, the alignment results in less than 5% gaps, less than 3% gaps, or less than 1% gaps. Additional methods of sequence comparison or alignment are also consistent with the disclosure.

[0347] The term "homology," as used herein, may be to calculations of "homology" or "percent homology" between two or more amino acid sequences that can be determined by aligning the sequences for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first sequence). The amino acids at corresponding positions may then be compared, and the percent identity between the two sequences may be a function of the number of identical positions shared by the sequences (i.e., % homology=# of identical positions/total # of positions×100). For example, a position in the first sequence may be occupied by the same amino acid as the corresponding position in the second sequence, then the molecules are identical at that position. The percent homology between the two sequences may be a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. In some embodiments, the length of a sequence aligned for comparison purposes may be at least about: 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,

98%, or 95%, of the length of the reference sequence. A BLAST® search may determine homology between two sequences. The homology can be between the entire lengths of two sequences or between fractions of the entire lengths of two sequences. The two sequences can be peptide sequences, amino acid sequences, or fragments thereof. The actual comparison of the two sequences can be accomplished by well-known methods, for example, using a mathematical algorithm. A non-limiting example of such a mathematical algorithm may be described in Karlin, S. and Altschul, S., Proc. Natl. Acad. Sci. USA, 90-5873-5877 (1993). Such an algorithm may be incorporated into the NBLAST and XBLAST programs (version 2.0), as described in Altschul, S. et al., Nucleic Acids Res., 25:3389-3402 (1997). When utilizing BLAST and Gapped BLAST programs, any relevant parameters of the respective programs (e.g., NBLAST) can be used. For example, parameters for sequence comparison can be set at score=100, word length=12, or can be varied (e.g., W=5 or W=20). Other examples include the algorithm of Myers and Miller, CABIOS (1989), ADVANCE, ADAM, BLAT, and FASTA. In another embodiment, the percent identity between two amino acid sequences can be accomplished using, for example, the GAP program in the GCG software package (Accelrys, Cambridge, UK).

[0348] "Pharmaceutically acceptable" refers to approved or approvable by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, including humans.

[0349] "Pharmaceutically acceptable salt" refers to a salt of a compound that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound.

[0350] "Pharmaceutically acceptable excipient, carrier or adjuvant" refers to an excipient, carrier or adjuvant that may be administered to a subject, together with at least one antibody of the present disclosure, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

[0351] "Pharmaceutically acceptable vehicle" refers to a diluent, adjuvant, excipient, or carrier with which at least one antibody of the present disclosure is administered.

[0352] Terms such as "treating" or "treatment" or "to treat" or "alleviating" or "to alleviate" may refer to: 1) therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder; and/or 2) prophylactic or preventative measures that prevent and/or slow the development of a targeted pathologic condition or disorder. "Treatment" refers to clinical intervention in an attempt to alter the natural course of the individual or cell being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include preventing occurrence or recurrence of disease, alleviation of symptoms, and diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. Thus those in need of treatment may include those already with the disorder; those prone to have the disorder; and those in whom the disorder is to be prevented.

[0353] "Amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function similarly to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, gamma-carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, e.g., an alpha carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs can have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions similarly to a naturally occurring amino acid.

[0354] "Disorder" or "disease" refers to a condition that would benefit from treatment with a substance/molecule (e.g., a peptide conjugate as disclosed herein) or method disclosed herein. This includes chronic and acute disorders or diseases including those pathological conditions which predispose the mammal to the disorder in question.

[0355] "Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, rodents (e.g., mice and rats), and monkeys; domestic and farm animals; and zoo, sports, laboratory, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. In some embodiments, the mammal is selected from a human, rodent, or monkey.

[0356] "Unmodified peptide" refers to either an unmodified sequence (wild type peptide) or a modified sequence without a staple.

EXAMPLES

[0357] Peptides were synthesized by standard solid-phase peptide synthesis (SPPS) techniques and purified via HPLC (as described).

[0358] Unless otherwise noted, all reagents were purchased from commercial suppliers (Sigma Aldrich, Fisher, Oakwood) and used without further purification. Peptides were purchased from Cellmano Biotech Limited (Hefei), InnoPep (San Diego), Shanghai Apeptide Co. (Shanghai) or Shanghai Dechi Biosciences Co. (Shanghai). All reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon. All solvents used were of HPLC grade. Reactions were monitored by LC-MS or by thin-layer chromatography (TLC) on Merck 50×100 mm silica gel 60 aluminum sheets stained using an aqueous solution of KMnO4.

[0359] Flash chromatography purifications were performed on silica gel prepacked columns (40 μm, RediSep® Rf from Teledyne Isco) on a CombiFlash® Rf (Teledyne Isco). Purified final compounds were eluted as single and symmetrical peaks (thereby confirming a purity of ≥95%).

[0360] Semi-preparative chromatography were performed on a Shimadzu HPLC with a Phenomenex Luna column (C18, 100 Å pore size, 10 μm particle size, 250×10.0 mm, flow: 4 mL/min) or on an Agilent 1200 HPLC with a Phenomenex Luna column (C18, 100 Å pore size, 5 μm particle size, 150×21.2 mm, flow: 20 mL/min).

[0361] ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 system in d_6-DMSO, $CDCl_3$ or CD_3OD. Chemical shifts are given in parts per million (ppm) with tetramethylsilane as an internal standard. Abbreviations are used as follows: s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, m=multiplet, dd=doublet of doublets, br=broad. Coupling constants (J values) are given in hertz (Hz). Low resolution mass spectra were recorded on a Waters Acquity UPLC with a Phemomenex Luna Omega C18 column (C18, 100 Å pore size, 1.6 μm particle size, 50×2.1 mm, flow: 0.4 mL/min). Solvents: A—H_2O+0.1% formic acid, B—MeCN+0.1% formic acid, gradient: 0-1 min 10-90% B, 1-1.6 min 90% B, 1.6-1.7 min 90-10% B, 1.7-2 min 10% B.

[0362] High resolution mass spectra (HRMS) were recorded on an Agilent 1200 Series Accurate Mass Time-of-Flight (TOF) with an Aeris Widepore column (XB-C8, 3.6 μm particle size, 150×2.1 mm, flow: 0.5 mL/min). Solvents: A—H_2O+0.1% formic acid, B—MeCN+0.1% formic acid, gradient: 0-2 min 5% B, 2-12 min 5-60% B, 12-13 min 60-80% B, 13-14 min 80-20% B, 14-15 min 20-80% B, 15-16 min 80-20% B, 16-17 min 20-95% B, 17-20 min 95% B, 20-21 min 95-5% B.

General Protocol A for Loading of Chlorotrityl Chloride Resin

[0363] Fmoc-Lys(ivDde)-OH (60 mg, 100 μmol) was coupled to 2-chlorotrityl chloride resin (Novabiochem) (100 mg, 80 μmol) by mixing the amino acid, resin, and DIEA (70 μL, 400 μmol) in 5 mL of DMF and stirring for 30 min. The resin was then washed with DMF (3×), DCM (3×) and treated with CH_3OH/DCM/DIEA (8:1:1) for 10 min to cap the unreacted trityl chloride sites, dried under vacuum and stored in a desiccator.

General Protocol B for Deprotection of Fmoc Protecting Group

[0364] To the resin was added piperidine in DMF (20%). The mixture was shaken for 5 min and drained. Fresh 20% piperidine was added and this time the mixture was shaken for 15 min. Positive ninhydrin and/or TNBS test was observed. The resin was then washed with DMF (3×), DCM (3×).

General Protocol C for Deprotection of ivDde Protecting Group

[0365] After washing with DMF and DCM, the resin was treated with 2% hydrazine in DMF (5 mL, 2×15 min). Positive ninhydrin and/or TNBS test was observed. The resin was then washed with DMF (3×), DCM (3×).

General Protocol D for Peptide Coupling

[0366] The resin was treated with the carboxylic acid derivative specified (3 eq) using coupling reagent HATU (3.3 eq), and DIEA (3.3 eq) in DMF (5 mL) for 2 h or repeated until a negative ninhydrin and/or TNBS test was observed. The resin was then washed with DMF (3×), DCM (3×).

General Protocol E for On-Resin Bromoacetylation

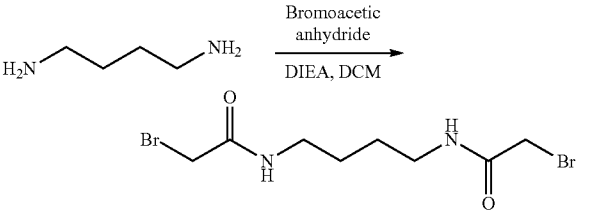
[0367] The resin was then treated with bromoacetic anhydride (2.4 eq), and DIEA (2.6 eq) in 200 mL of DCM for 30 min.

General Protocol F for Cleavage of Peptides from Chlorotrityl Resin

[0368] The resin was washed with DCM (3×), the product was cleaved from the resin using 5 mL of 10% TFA in DCM containing 10% H_2O and 10% triisopropylsilane for 1 h.

Example 1: Synthesis of L1

[0369]

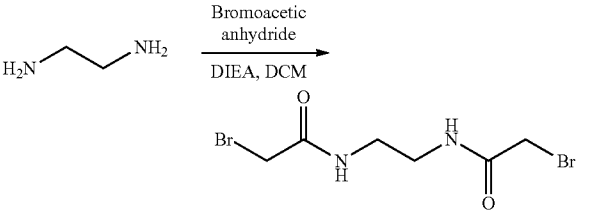


L1

[0370] To a solution of 1,4-diaminobutane (80 μL, 0.795 mmol, 1 eq) in DCM (10 mL) at 0° C. were added DIEA (276 μL, 1.59 mmol, 2 eq) followed by bromoacetic anhydride (413 g, 1.59 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded L1 as a white solid (162 mg, 0.49 mmol, 61%). MS (ES^+) m/z 331.0 ($[M+H]^+$). ^{1}H NMR (400 MHz, methanol-d_4) δ 3.94 (s, 4H), 3.40-3.30 (m, 4H), 1.68 (p, J=3.5 Hz, 4H).

Example 2: Synthesis of LIB

[0371]

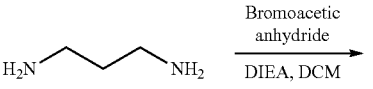


L1B

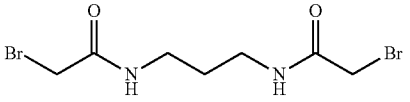
[0372] To a solution of 1,2-ethylenediamine (30 μL, 0.448 mmol, 1 eq) in DCM (5 mL) at 0° C. were added DIEA (172 μL, 0.985 mmol, 2.2 eq) followed by bromoacetic anhydride (233 mg, 0.897 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel provided LIB as a white solid (43.9 mg, 0.145 mmol, 32%). MS (ES^+) m/z 302.55 ($[M+H]^+$), 304.54 ($[M+H]^+$). ^{1}H NMR (400 MHz, methanol-d_4) δ 2.49 (s, 4H), 2.06 (s, 4H).

Example 3: Synthesis of L1C

[0373]



-continued

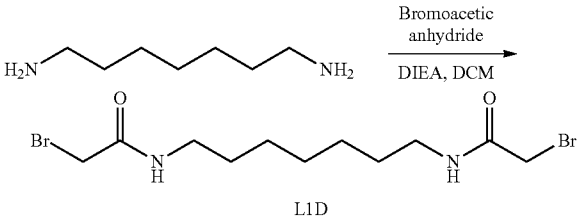


L1C

[0374] To a solution of 1,3-diaminopropane (30 μL, 0.359 mmol, 1 eq) in DCM (5 mL) at 0° C. were added DIEA (138 μL, 0.789 mmol, 2.2 eq) followed by bromoacetic anhydride (186 mg, 0.718 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded L1C as a white solid (60.8 mg, 0.19 mmol, 53%). MS (ES^+) m/z 316.32 ($[M+H]^+$), 318.6 ($[M+H]^+$). ^1H NMR (400 MHz, methanol-d_4) δ 3.86 (s, 4H), 3.27 (t, J=6.8 Hz, 4H), 1.74 (p, J=6.8 Hz, 2H).

Example 4: Synthesis of LID

[0375]

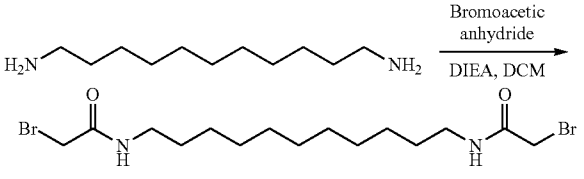


L1D

[0376] To a solution of 1,7-diaminohexane (65 mg, 0.499 mmol, 1 eq) in DCM (15 mL) at 0° C. were added DIEA (208 μL, 1.197 mmol, 2.4 eq) followed by bromoacetic anhydride (259 mg, 0.998 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded LID as a white solid (120 mg, 0.322 mmol, 64%). MS (ES^+) m/z 372.71 ($[M+H]^+$), 374.70 ($[M+3H]^+$). ^1H NMR (400 MHz, chloroform-d) δ 6.55 (s, 2H), 3.91 (s, 4H), 3.30 (q, J=7.1 Hz, 4H), 1.56 (p, J=7.1 Hz, 4H), 1.45-1.29 (m, 6H).

Example 5: Synthesis of LIE

[0377]

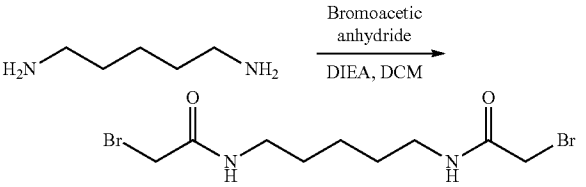


L1E

[0378] To a solution of 1,11-diaminoundecane (48 mg, 0.257 mmol, 1 eq) in DCM (10 mL) at 0° C. were added DIEA (108 μL, 0.616 mmol, 2.4 eq) followed by bromoacetic anhydride (134 mg, 0.515 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded LIE as a white solid (62.3 mg, 0.145 mmol, 56%). MS (ES^+) m/z 428.33 ($[M+H]^+$). ^1H NMR (400 MHz, chloroform-d) δ 6.53 (s, 2H), 3.91 (s, 4H), 3.30 (q, J=6.8 Hz, 4H), 1.57 (q, J=7.2 Hz, 4H), 1.42-1.20 (m, 14H).

Example 6: Synthesis of L1F

[0379]

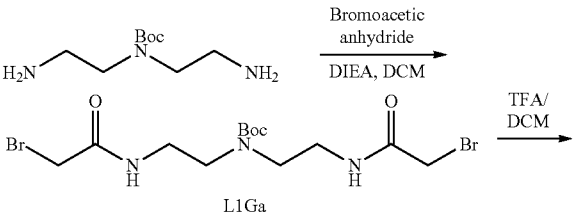


L1F

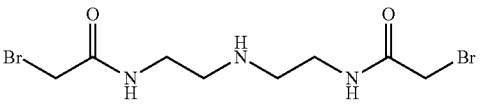
[0380] To a solution of cadaverine (48 mg, 0.257 mmol, 1 eq) in DCM (20 mL) at 0° C. were added DIEA (284 μL, 1.63 mmol, 2.4 eq) followed by bromoacetic anhydride (353 mg, 1.36 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded L1F as a white solid (156 mg, 0.453 mmol, 66%). MS (ES^+) m/z 344.65 ($[M+H]^+$), 346.64 ($[M+H]^+$). ^1H NMR (400 MHz, methanol-d_4) δ 3.83 (s, 4H), 3.23 (q, J=6.8 Hz, 4H), 1.57 (p, J=7.2 Hz, 4H), 1.44-1.33 (m, 2H).

Example 7: Synthesis of L1G

[0381]



L1Ga



L1G

Intermediate L1Ga

[0382] To a solution of tert-butyl bis(2-aminoethyl)carbamate (167 mg, 0.82 mmol, 1 eq) in DCM (20 mL) at 0° C. were added DIEA (342 μL, 11.96 mmol, 2.4 eq) followed by bromoacetic anhydride (426 mg, 1.64 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded L1Ga as a white solid (289 mg, 0.65

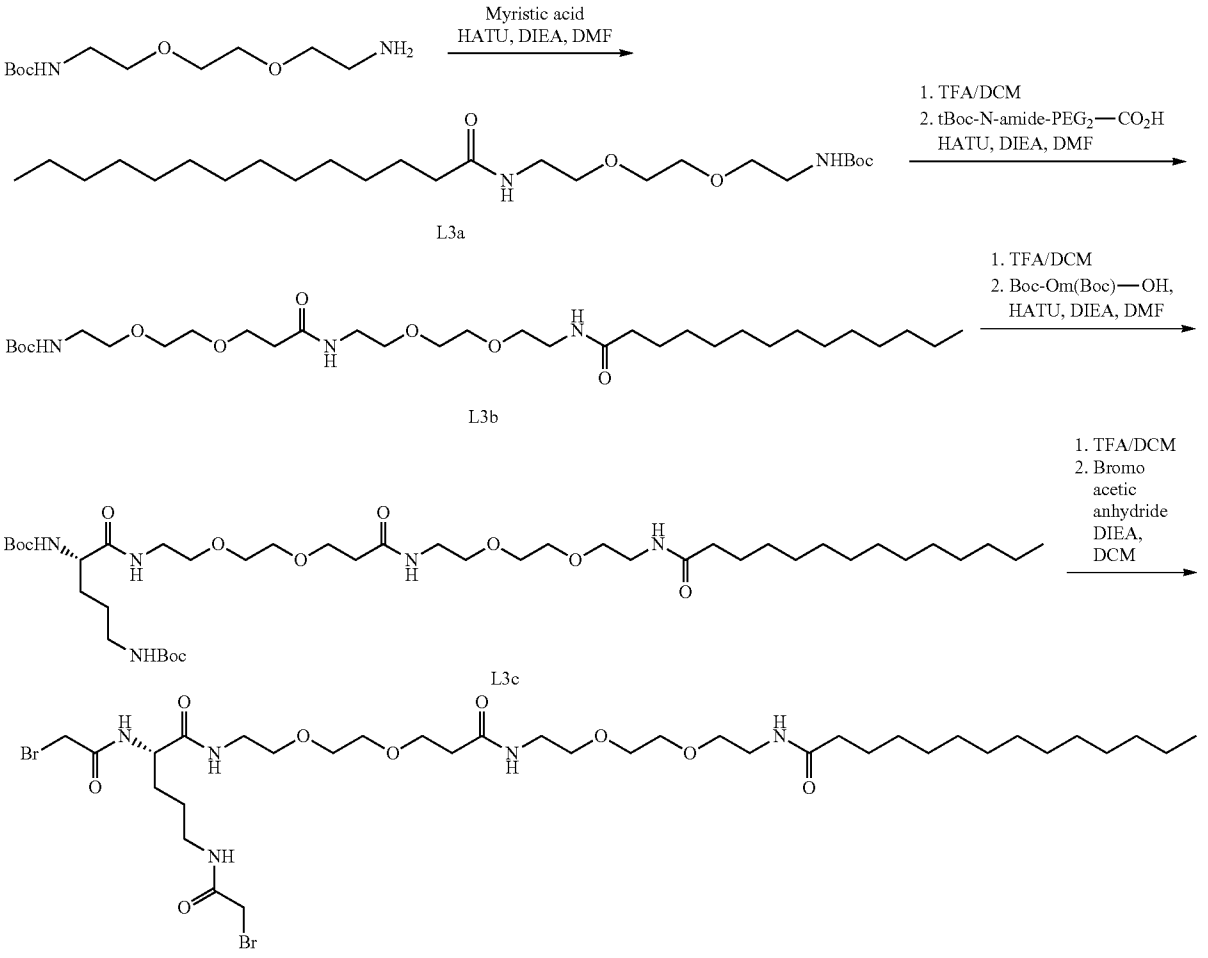
mmol, 79%). MS (ES^+) m/z 445.71 ($[M+H]^+$), 447.7 ($[M+H]^+$). ^1H NMR (400 MHz, methanol-d_4) δ 3.85 (s, 4H), 3.39 (s, 9H), 1.50 (s, 10H).

L1G

[0383] Compound L1Ga (20 mg) was dissolved in TFA/DCM (1:1, v/v, 2 mL), agitated 30 min at RT and evaporated (co-evaporation with hexane) to obtain compound L1G as an oil. The product was directly used in further steps. MS (ES^+) m/z 345.2 ($[M+H]^+$).

Example 8: Synthesis of L3

[0384]



Intermediate L3a

[0385] Myristic acid (184 mg, 0.805 mmol, 1 eq) was dissolved in 4 mL of DMF. HATU (321 mg, 0.845 mmol, 1.1 eq) and DIEA (154 μL, 0.885 mmol, 1.1 eq) were added followed by the addition of Boc-NH-PEG_2-COOH (200 mg, 0.805 mmol, 1 eq). The reaction mixture was then stirred for 1.5 h, and the solvent was removed. The product was dissolved in EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L3a as a white solid (254 mg, 0.55 mmol, 69%). ^1H NMR (400 MHz, chloroform-d) δ 3.66-3.54 (m, 8H), 3.49 (q, J=5.2 Hz, 2H), 3.35 (d, J=6.1 Hz, 2H), 2.20 (t, J=7.7 Hz, 2H), 1.63-1.58 (m, 2H), 1.47 (s, 8H), 1.33-1.24 (m, 21H), 0.90 (t, J=6.9 Hz, 3H). t_R=2.21 min (Agilent). MS (ES^+) m/z 459.6 ($[M+H]^+$)

Intermediate L3b

[0386] A solution of compound L3a (242 mg, 0.527 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane. To a solution of BocNH-PEG_2-CO_2H (146 mg, 0.527 mol, 1 eq) dissolved in DMF (5 mL) was added HATU (224 mg, 0.59 mmol, 1.1 eq). Deprotected compound L3a and DIEA (183 μL, 1.05 mmol, 2 eq) in DMF were added to the reaction mixture. The reaction mixture was agitated for 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on

silica gel provided the desired compound L3b as an oil (129 mg, 0.209 mmol, 40%). ^{1}H NMR (400 MHz, chloroform-d) δ 6.76 (s, 1H), 6.19 (s, 1H), 5.29 (s, 1H), 3.76 (t, J=5.8 Hz, 2H), 3.69-3.62 (m, 8H), 3.57 (dt, J=12.3, 5.0 Hz, 6H), 3.48 (dt, J=10.4, 5.5 Hz, 4H), 3.33 (s, 2H), 2.51 (t, J=5.8 Hz, 2H), 2.20 (t, J=7.0 Hz, 2H), 1.90-1.75 (m, 4H), 1.64 (p, J=7.3 Hz, 2H), 1.46 (s, 9H), 1.33-1.22 (m, 17H).

Intermediate L3c

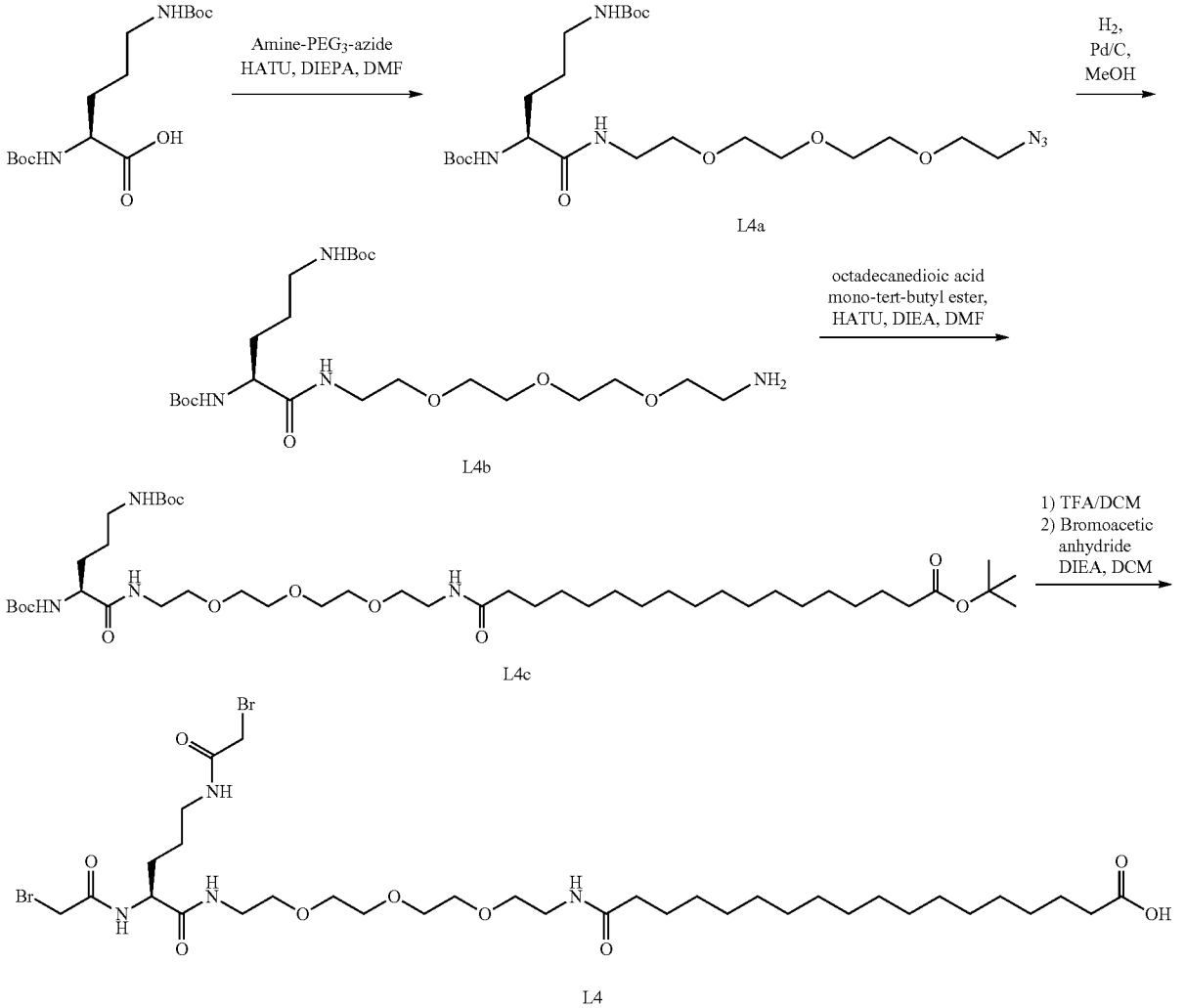
[0387] A solution of Compound L3b (129 mg, 0.209 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane. To a solution of Boc-Orn(Boc)-OH (69 mg, 0.209 mmol, 1 eq) dissolved in DMF (5 mL) was added HATU (88 mg, 0.23 mmol 1.1 eq). Deprotected compound L3b and DIEA (73 μL, 0.419 mmol, 2 eq) in DMF were added to the reaction mixture. The reaction mixture was agitated 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L3c as an oil (137 mg, 0.164 mmol, 78%). t_R=4.07 min (Agilent). MS (ES^+) m/z 832.9 ($[M+H]^+$). ^{1}H NMR (400 MHz, chloroform-d) δ 7.12 (s, 1H), 6.80 (s, 1H), 6.30 (s, 1H), 4.87 (s, 1H), 3.85-3.73 (m, 2H), 3.68-3.61 (m, 7H), 3.58 (p, J=6.1, 5.5 Hz, 7H), 3.53-3.36 (m, 6H), 3.29-3.00 (m, 2H), 2.51 (t, J=5.8 Hz, 2H), 2.20 (t, J=7.7 Hz, 2H), 2.00-1.74 (m, 6H), 1.71-1.51 (m, 5H), 1.45 (s, 18H), 1.35-1.22 (m, 21H).

L3

[0388] A solution of Compound L3c (137 mg, 0.165 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 10 mL of DCM and cooled at 0° C. DIEA (115 μL, 0.66 mmol, 4 eq) was added followed by bromoacetic anhydride (85.8 g, 0.33 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded L3 as a white solid (56 mg, 0.064 mmol, 39%). t_R=3.4 min (Agilent). MS (ES^+) m/z 872.4 ($[M+H]^+$), 874.3 ($[M+H]^+$).

Example 9: Synthesis of L4

[0389]



Intermediate L4a

[0390] To a solution of Boc-Orn(Boc)-OH (595 mg, 1.79 mmol, 1 eq) dissolved in DMF (5 mL) was added HATU (750 mg, 1.79 mmol 1.1 eq), DIEA (343 μL, 1.97 mmol, 1.1 eq) and amine-PEG_3-N_3 (391 mg, 1.79 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 16 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L4a as an oil (558 mg, 1.05 mmol, 58%). MS (ES^+) m/z 533.13 ($[M+H]^+$). ^1H NMR (400 MHz, chloroform-d) δ 6.82 (s, 1H), 5.25 (d, J=8.3 Hz, 1H), 4.75 (s, 1H), 4.19 (s, 1H), 3.76-3.60 (m, 10H), 3.57 (t, J=5.1 Hz, 2H), 3.43 (t, J=4.6 Hz, 2H), 3.30-3.19 (m, 1H), 3.18-3.03 (m, 1H), 1.85 (s, 4H), 1.68-1.49 (m, 2H), 1.45 (s, 18H).

Intermediate L4b

[0391] To a solution of compound L4a (548 mg, 1.02 mmol, 1 eq) in anhydrous MeOH (10 mL) and under argon was added Pd/C (10.9 mg, 0.102 mmol, 0.1 eq) and argon was replaced with H_2. The reaction mixture was agitated for 6 h at RT, filtrated on celite and evaporated to afford compound L4b as an oil (516 mg, 1.02 mmol, quant). The product was used without any further purification.

Intermediate L4c

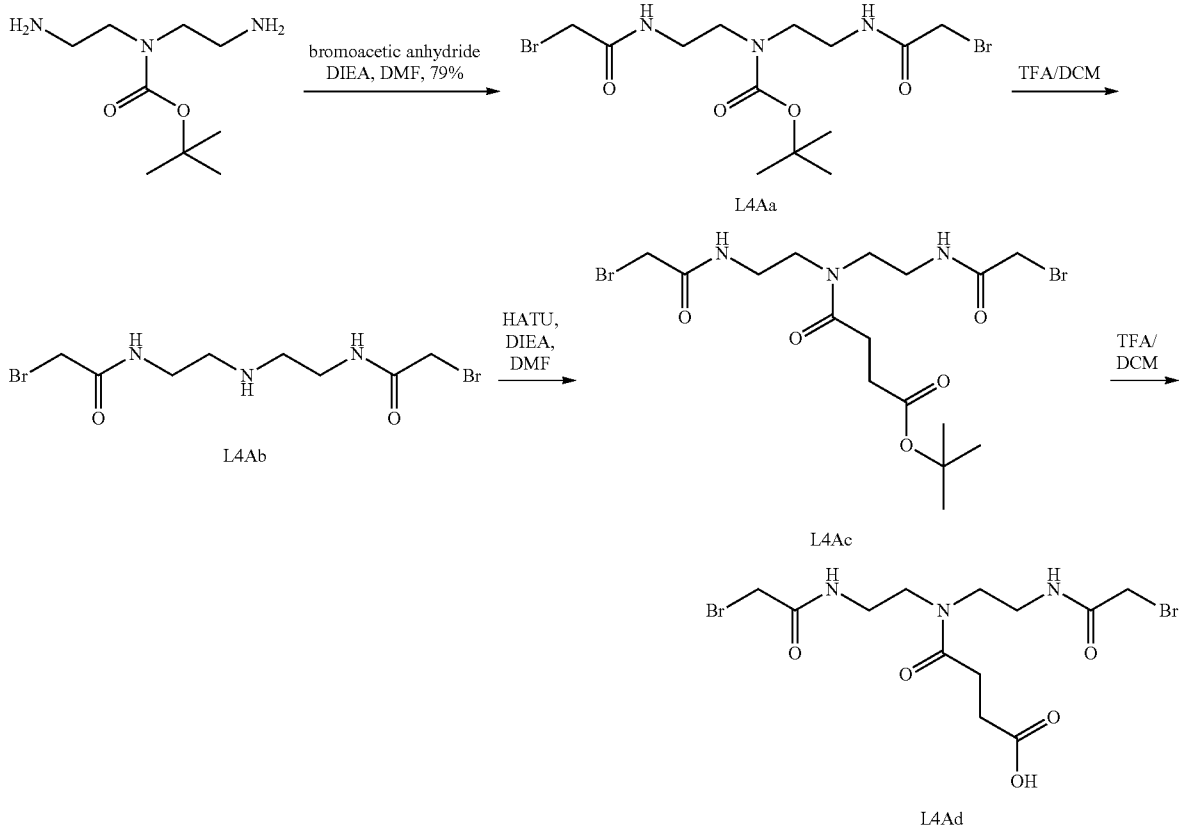
[0392] To a solution of octadecanedioic acid mono tert-butyl ester (370 mg, 1.02 mmol, 1 eq) dissolved in DMF (5 mL) was added HATU (387 mg, 1.02 mmol 1.1 eq), DIEA (186 μL, 1.07 mmol, 2 eq) and compound L4b (516 mg, 1.02 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 3 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L4c as an oil (697 mg, 0.81 mmol, 79%). ^1H NMR (400 MHz, chloroform-d) δ 6.94 (s, 1H), 6.42 (s, 1H), 4.81 (s, 1H), 4.20 (s, 1H), 3.65 (d, J=6.7 Hz, 8H), 3.59 (dt, J=9.7, 5.1 Hz, 4H), 3.51-3.35 (m, 4H), 3.31-3.18 (m, 1H), 3.17-3.06 (m, 1H), 2.20 (q, J=8.0 Hz, 4H), 1.87 (s, 4H), 1.71-1.53 (m, 6H), 1.45 (s, 26H), 1.26 (s, 24H).

L4

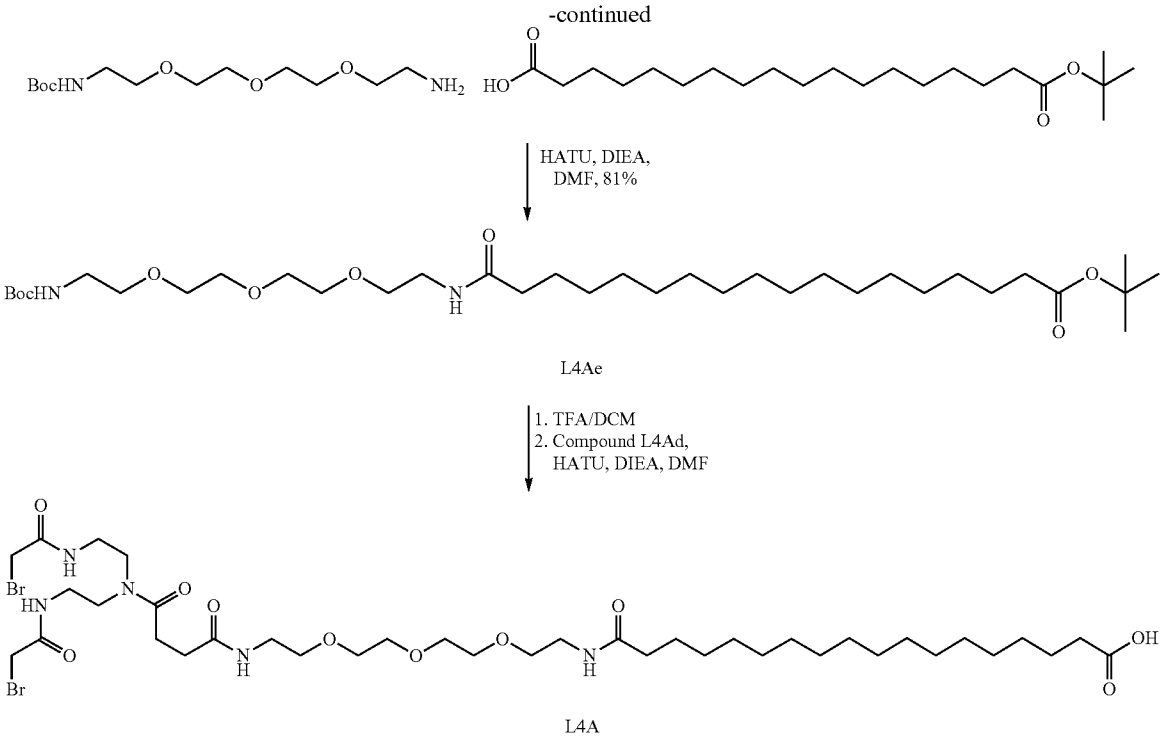
[0393] A solution of L4c (422 mg, 0.49 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 20 mL of DCM and cooled at 0° C. DIEA (327 μL, 1.96 mmol, 4 eq) was added followed by bromoacetic anhydride (254 mg, 0.98 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded L4 as a white solid (53 mg, 0.063 mmol, 12%). MS (ES^+) m/z 845.08 ($[M+H]^+$), 847.07 ($[M+H]^+$)^1H NMR (400 MHz, methanol-d_4) δ 3.68-3.60 (m, 8H), 3.54 (td, J=5.4, 3.4 Hz, 4H), 3.43-3.35 (m, 4H), 3.30-3.16 (m, 2H), 2.27 (t, J=7.5 Hz, 2H), 2.17 (t, J=7.6 Hz, 2H), 1.86-1.73 (m, 1H), 1.72-1.45 (m, 8H), 1.37-1.19 (m, 28H).

Example 10: Synthesis of L4A

[0394]



-continued



Intermediate L4Aa

[0395] To a solution of tert-butyl bis(2-aminoethyl)carbamate (500 mg, 2.45 mmol, 1 eq) and DIEA (1.02 mL, 5.88 mmol, 2 eq) in DCM (20 mL) at 0° C. was added dropwise bromoacetic anhydride (1.31 g, 5.04 mmol, 2.05 eq in 1 mL DCM). The reaction mixture was agitated 30 min at 0° C., 2 h at RT and evaporated in vacuo. Purification by flash chromatography afforded the product as an oil (883 mg, 81%). ^{1}H NMR (400 MHz, methanol-d_4) δ 1.50 (s, 9H), 3.39 (s, 8H), 3.85 (s, 4H). t_R=1.04 min. MS (ES$^+$) m/z 445.71/447.70 ([M+H]$^+$).

Intermediate L4Ab

[0396] A solution of compound L4Aa (1 eq) in DCM/TFA (1:1, v/v) was agitated at RT for 30 min and concentrated in vacuo (co-evaporated with heptane). Compound L4Ab was used directly in further steps without purification. t_R=0.58 min. MS (ES$^+$) m/z 345.65/347.67 ([M+H]$^+$).

Intermediate L4Ac

[0397] To a solution of mono-tert-butyl succinate (1.05 eq) in DMF was added HATU (1.05 eq). The reaction mixture was agitated at RT for 5 min. Compound L4Ab and DIEA (4 eq) were dissolved in DMF (1 mL) and added to the reaction mixture. The reaction was agitated overnight at RT and diluted with AcOEt. The organic phase was washed with HCl 1N, a solution of saturated $NaHCO_3$, dried over $MgSO_4$ and evaporated. Purification by flash chromatography afforded the product as an oil. t_R=1.07 min. MS (ES$^+$) m/z 501.52/503.80 ([M+H]$^+$).

Intermediate L4Ad

[0398] A solution of compound L4Ac (1 eq) in DCM/TFA (1:1, v/v) was agitated at RT for 30 min and concentrated in vacuo (co-evaporated with heptane). Compound L4Ad was used directly in further steps without purification. t_R=0.57 min. MS (ES$^+$) m/z 445.71/447.73 ([M+H]$^+$).

Intermediate L4Ae

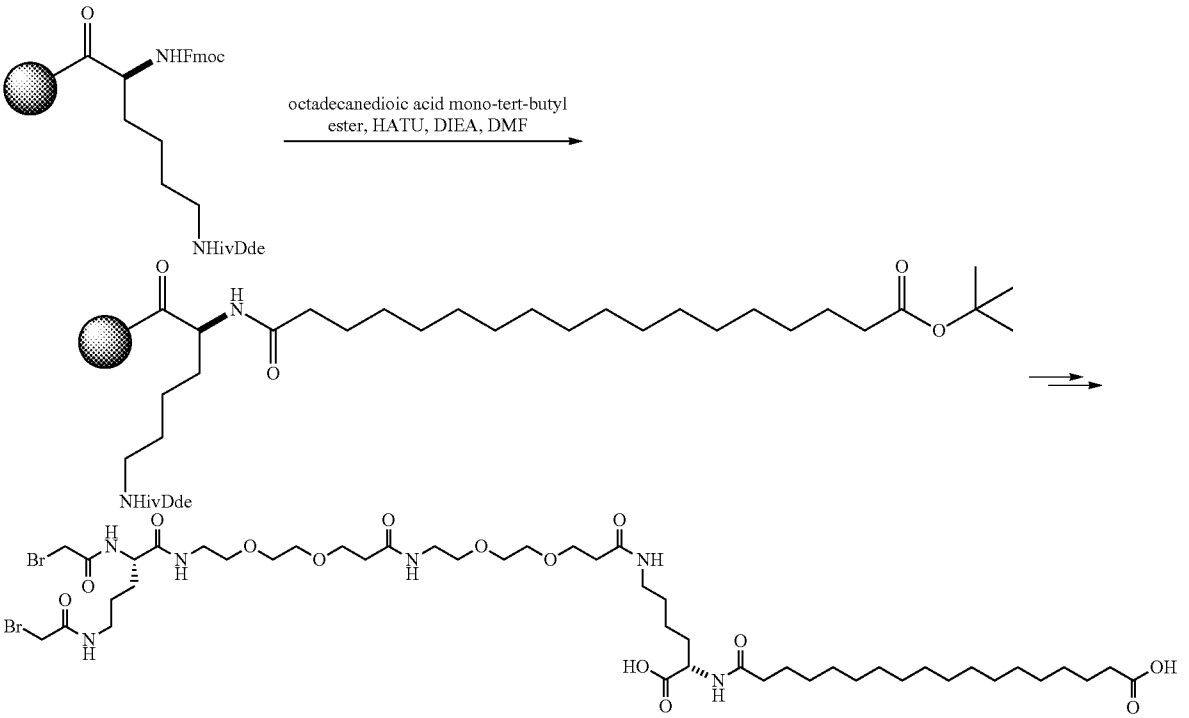
[0399] Octadecanedioic acid mono-tert-butyl ester acid (200 mg, 0.54 mmol, 1 eq) was dissolved in 5 mL of DMF. HATU (225 mg, 0.59 mmol, 1.1 eq) and DIEA (103 μL, 0.59 mmol, 1.1 eq) were added followed by the addition of Boc-NH-PEG$_3$-NH$_2$ (157.8 g, 0.54 mmol, 1 eq). The reaction mixture was then stirred for 3 h, and the solvent was removed. The product was dissolved in EtOAc. The organic layer was successively washed with sat. $NaHCO_3$, 1M HCl, brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired product L4Ae as a white solid (281 mg, 0.43 mmol, 81%). MS (ES$^+$) m/z 645.5 ([M+H]$^+$). ^{1}H NMR (400 MHz, chloroform-d) δ 3.76-3.61 (m, 8H), 3.63-3.54 (m, 4H), 3.48 (q, J=5.1 Hz, 2H), 3.34 (s, 2H), 2.20 (dt, J=9.8, 7.6 Hz, 4H), 1.67-1.55 (m, 4H), 1.49-1.44 (m, 17H), 1.30 (s, 6H), 1.30-1.24 (m, 19H).

L4A

[0400] A solution of compound L4Ae in DCM was treated with TFA for 30 min. The mixture was concentrated, co-evaporated with heptane, dissolved in DMF and added to a solution of compound L4Ad, HATU and DIEA in DMF. The reaction mixture was agitated 3 h and purified by semi-preparative HPLC to provide the desired product L4A.

Example 11: Synthesis of L5

[0401]



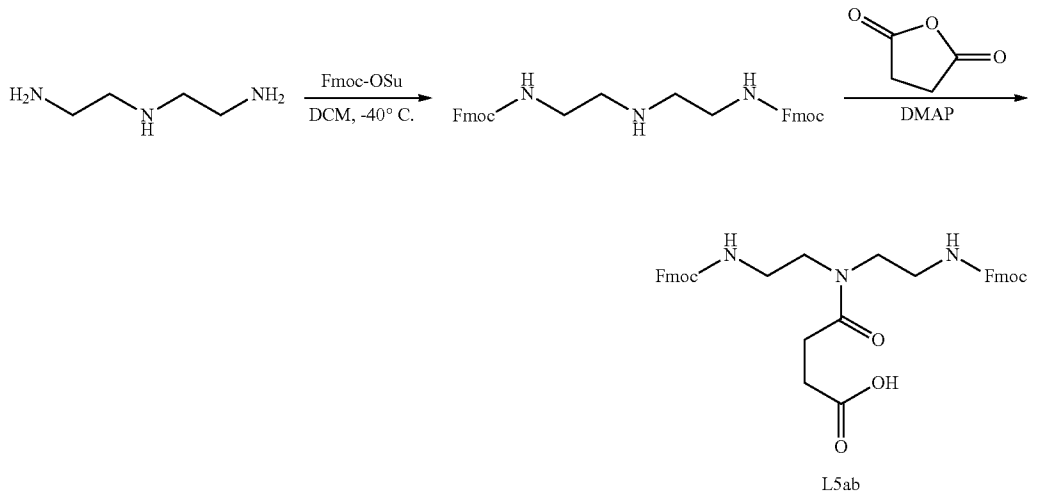
L5

General Protocol A, B, D (octadecanedioic acid mono-tert butyl ester), C, D (Fmoc-PEG_2-propionic acid), B, D (Fmoc-PEG_2-propionic acid), B, D (Fmoc-Orn(Fmoc)-OH), B, E, F

[0402] The crude was purified by semi-preparative HPLC with mass detection to afford the product L5 as a white solid (73 mg, 0.065 mmol, 11%). ^{1}H NMR (400 MHz, methanol-d_4) δ 4.36 (td, J=8.9, 5.1 Hz, 2H), 3.89 (q, J=11.4 Hz, 2H), 3.82 (s, 2H), 3.74 (t, J=6.2 Hz, 2H), 3.60 (s, 4H), 3.54 (t, J=5.5 Hz, 2H), 3.37 (q, J=5.2 Hz, 2H), 3.29-3.11 (m, 5H), 2.44 (t, J=6.2 Hz, 2H), 2.26 (dt, J=12.3, 7.5 Hz, 4H), 1.89-1.77 (m, 2H), 1.76-1.49 (m, 10H), 1.48-1.38 (m, 2H), 1.37-1.25 (m, 25H).

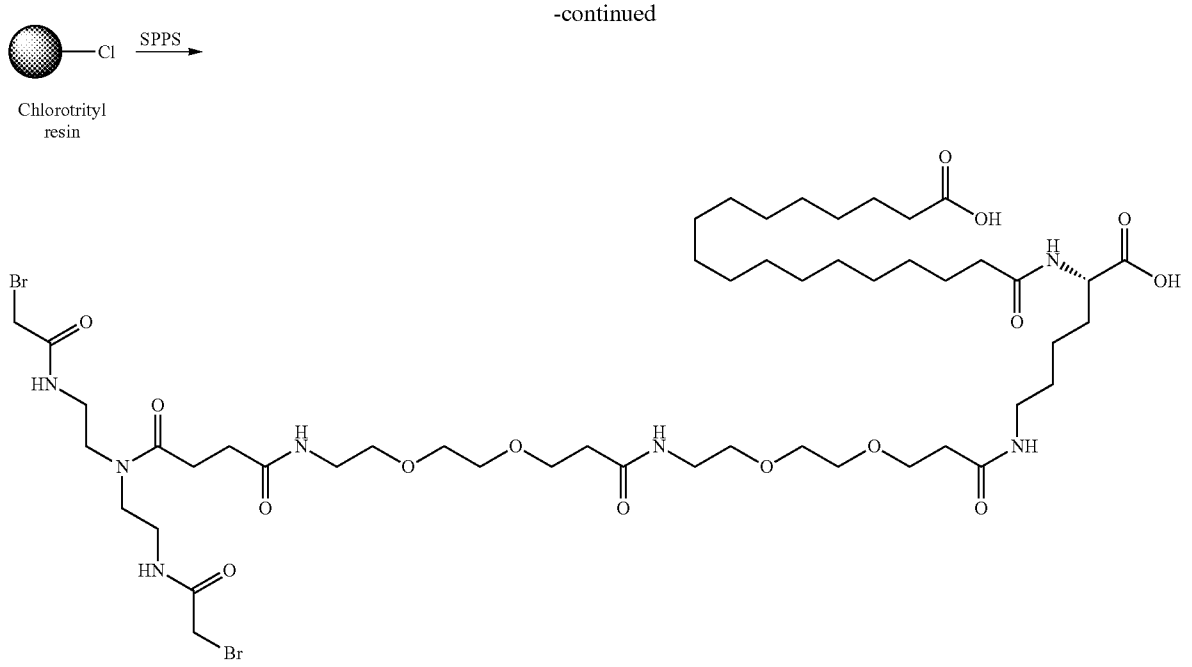
Example 12: Synthesis of L5A

[0403]



L5ab

-continued



L5A

Intermediate L5Aa

[0404] A solution of Fmoc-OSu (131 g, 388 mmol) in DCM (200 mL) was added dropwise to a solution of diethylenetriamine (20 g, 194 mmol) in DCM (200 mL) at −40° C. under N_2, stirred for 2 h. LCMS showed the reaction was complete. The crude product in solution was not purified and used for the next step directly. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J=7.6 Hz, 4H), 7.68 (d, J=7.6 Hz, 4H), 7.43-7.24 (m, 10H), 4.30 (d, J=6.4 Hz, 4H), 4.21 (d, J=6.4 Hz, 2H), 3.06 (d, J=5.6 Hz, 4H), 2.57 (d, J=7.6 Hz, 4H). MS (ES^+) m/z 548.2 ($[M+H]^+$).

Intermediate L5Ab

[0405] To a solution of compound L5Aa (106 g, 194 mmol) in DCM (400 mL) was added DMAP (4.74 g, 38.8 mmol) and tetrahydrofuran-2,5-dione (67.9 g, 678 mmol), stirred at 25° C. for 14 h. LCMS showed the reaction was complete. To the reaction mixture was added 1 N HCl until pH=5-6, stirred for 15 min, the organic phase was separated, then the organic phase was washed with water and saturated NaCl (500 mL) and the aqueous phase was extracted with DCM (500 mL) twice. The combined DCM was dried over anhydrous Na_2SO_4, concentrated under vacuum. The crude product was purified by column chromatography on silica gel using DCM/MeOH (80:0-5:1) as eluent to give compound L5Ab (57.6 g, 45% yield) as a white solid powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (s, 1H), 7.87 (d, J=7.5 Hz, 4H), 7.66 (d, J=7.0 Hz, 4H), 7.23-7.48 (m, 10H), 4.24-4.33 (m, 4H), 4.14-4.22 (m, 2H), 3.27 (s, 4H), 2.95-3.19 (m, 4H), 2.37-2.44 (m, 4H). MS (ES^+) m/z 648.2 ($[M+H]^+$).

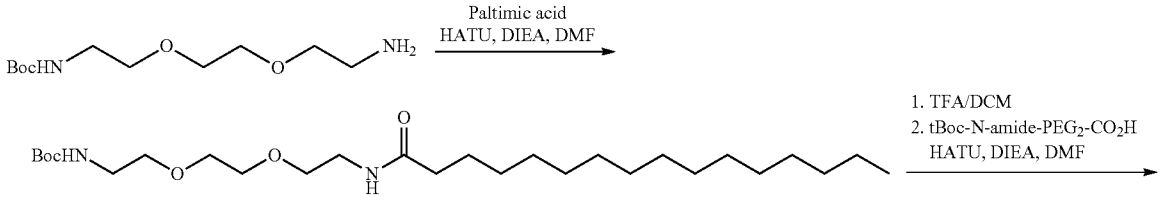
L5A

General Protocol A, B, D (octadecanedioic acid mono-tert butyl ester), C, D (Fmoc-PEG_2-propionic acid), B, D (Fmoc-PEG_2-propionic acid), B, D (compound L5Ab), B, E, F

[0406] The crude was purified by HPLC to afford the product L5A as a white solid (5.2 g, 11% yield). MS (ES^+) m/z 1188.5 ([M+H]*).

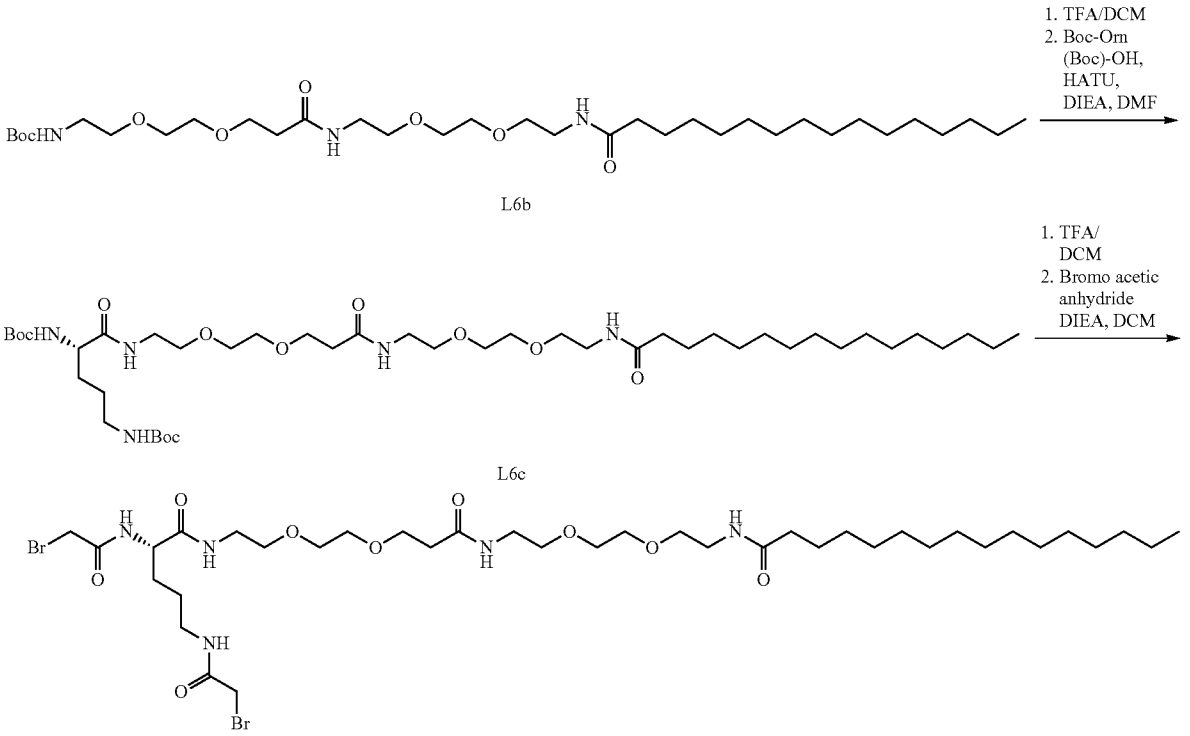
Example 13: Synthesis of L6

[0407]



L6a

-continued



Intermediate L6a

[0408] Palmitic acid (235 mg, 0.919 mmol, 1.05 eq) was dissolved in 4 mL of DMF. HATU (349 mg, 0.919 mmol, 1.05 eq) and DIEA (167 μL, 0.963 mmol, 1.1 eq) were added followed by the addition of Boc-NH-PEG_2-NH_2 (200 mg, 0.875 mmol, 1 eq). The reaction mixture was then stirred for 2 h, and the solvent was removed. The product was dissolved in EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, HCl and brine, dried over Na_2SO_4, filtered, and concentrated to provide the desired compound L6a as a white solid (412 mg, 0.84 mmol, 97%). ^{1}H NMR (400 MHz, chloroform-d) δ 6.17 (s, 1H), 5.07 (s, 1H), 3.58 (s, 4H), 3.53 (t, J=5.0 Hz, 3H), 3.43 (q, J=5.3 Hz, 2H), 3.36-3.21 (m, 2H), 2.15 (t, J=7.5 Hz, 2H), 1.66-1.54 (m, 2H), 1.32-1.15 (m, 26H), 0.84 (t, J=6.6 Hz, 3H).

Intermediate L6b

[0409] A solution of compound L6a (412 mg, 0.84 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane. To a solution of BocNH-PEG_2-CO_2H (258 mg, 0.931 mmol, 1.1 eq) dissolved in DMF (5 mL) was added HATU (353 mg, 0.931 mmol, 1.1 eq). Deprotected compound L6a and DIEA (294 μL, 1.69 mmol, 2 eq) in DMF were added to the reaction mixture. The reaction mixture was agitated 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, HCl and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L6b as an oil (329 mg, 0.51 mmol, 60%). ^{1}H NMR (400 MHz, chloroform-d) δ 6.79 (s, 1H), 6.28 (s, 1H), 5.28 (s, 1H), 3.68 (t, J=5.8 Hz, 2H), 3.61-3.44 (m, 14H), 3.38 (p, J=5.6 Hz, 4H), 3.24 (q, J=5.5 Hz, 2H), 2.42 (t, J=5.8 Hz, 2H), 2.11 (t, J=7.9 Hz, 2H), 1.55 (p, J=7.2 Hz, 2H), 1.38 (s, 9H), 1.32-1.10 (m, 24H), 0.81 (t, J=6.7 Hz, 3H).

Intermediate L6c

[0410] A solution of compound L6b (329 mg, 0.51 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane. To a solution of Boc-Orn(Boc)-OH (186 mg, 0.56 mmol, 1.1 eq) dissolved in DMF (5 mL) was added HATU (213 mg, 0.56 mmol 1.1 eq). Deprotected compound L6b and DIEA (177 μL, 1.02 mmol, 2 eq) in DMF were added to the reaction mixture. The reaction mixture was agitated 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with sat. $NaHCO_3$, 1M HCl and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L6c as an oil (326 mg, 0.37 mmol, 94%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.18 (s, 1H), 6.92 (s, 1H), 6.48 (s, 1H), 5.61 (d, J=8.4 Hz, 1H), 5.08 (t, J=5.9 Hz, 1H), 4.13 (s, 1H), 3.73-3.65 (m, 2H), 3.59-3.44 (m, 14H), 3.42-3.29 (m, 8H), 3.19-2.86 (m, 2H), 2.42 (t, J=5.9 Hz, 2H), 2.10 (d, J=7.3 Hz, 2H), 1.78-1.63 (m, 1H), 1.60-1.40 (m, 5H), 1.35 (s, 18H), 1.26-1.09 (m, 22H), 0.80 (t, J=6.7 Hz, 3H).

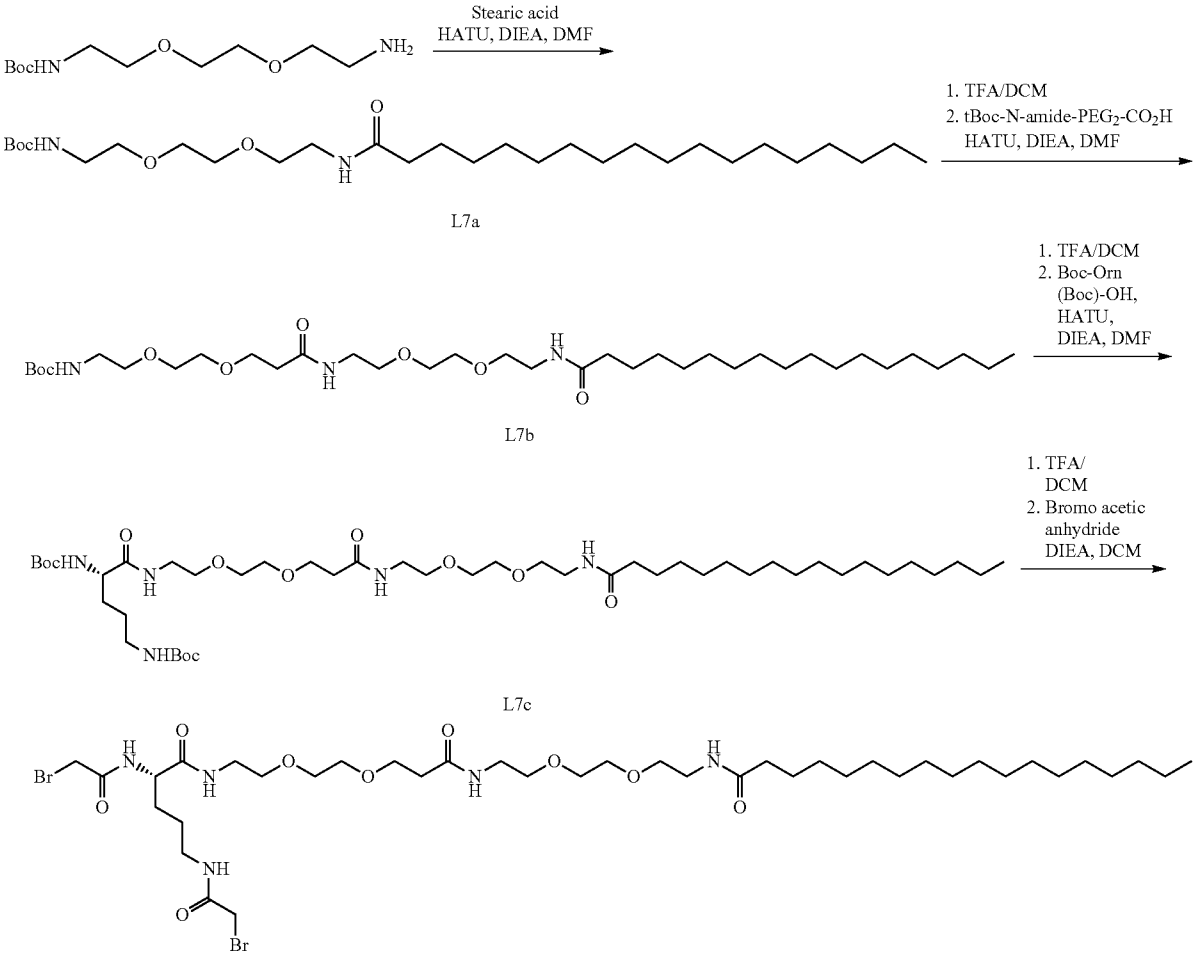
L6

[0411] A solution of compound L6c (100 mg, 0.116 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 10 mL of DCM and cooled at 0° C. DIEA (80.8 μL, 0.46 mmol, 4 eq) was added followed by

bromoacetic anhydride (61.9 mg, 0.238 mmol, 2.05 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded L6 as a white solid (50.1 mg, 0.055 mmol, 40%). ^{1}H NMR (400 MHz, methanol-d_4) δ 4.39 (dd, J=8.4, 5.5 Hz, 1H), 3.91 (q, J=11.4 Hz, 2H), 3.84 (s, 2H), 3.76 (t, J=6.2 Hz, 2H), 3.63 (d, J=7.1 Hz, 8H), 3.57 (q, J=5.5 Hz, 6H), 3.43-3.36 (m, 6H), 3.25 (t, J=13.9, 6.8 Hz, 2H), 2.49 (t, J=6.2 Hz, 2H), 2.21 (t, J=7.5 Hz, 2H), 1.91-1.79 (m, 1H), 1.75-1.53 (m, 5H), 1.42-1.25 (m, 24H), 0.92 (t, J=6.7 Hz, 3H).

Example 14: Synthesis of L7

[0412]



Intermediate L7a

[0413] Stearic acid (261 mg, 0.919 mmol, 1.05 eq) was dissolved in 4 mL of DMF. HATU (349 mg, 0.919 mmol, 1.05 eq) and DIEA (167 μL, 0.963 mmol, 1.1 eq) were added followed by the addition of Boc-NH-PEG_2-NH_2 (200 mg, 0.875 mmol, 1 eq). The reaction mixture was then stirred for 2 h, and the solvent was removed. The product was dissolved in EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated to provide the desired compound L7a as a white solid (430 mg, 0.83 mmol, 95%). ^{1}H NMR (400 MHz, chloroform-d) δ 3.69-3.59 (m, 4H), 3.56 (t, J=5.1 Hz, 4H), 3.46 (q, J=5.2 Hz, 2H), 3.40-3.23 (m, 2H), 2.18 (t, J=7.6 Hz, 2H), 1.62 (t, J=7.3 Hz, 2H), 1.45 (s, 9H), 1.35-1.19 (m, 30H), 0.88 (t, J=6.7 Hz, 4H).

Intermediate L7b

[0414] A solution of compound L7a (426 mg, 0.87 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane. To a solution of BocNH-PEG_2-CO_2H (266 mg, 0.96 mmol, 1.1 eq) dissolved in DMF (5 mL) was added HATU (366 mg, 0.96 mmol, 1.1 eq). Deprotected compound L7a and DIEA (304 μL, 1.75 mmol, 2 eq) in DMF were added to the reaction mixture. The reaction mixture was agitated 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L7b as an oil (360 mg, 0.53 mmol, 61%). ^{1}H NMR (400 MHz, chloroform-d) δ 6.75 (s,

1H), 6.18 (s, 1H), 5.26 (s, 1H), 3.75 (t, J=5.8 Hz, 2H), 3.69-3.52 (m, 14H), 3.47 (p, J=5.4 Hz, 4H), 3.33 (q, J=5.5 Hz, 2H), 2.50 (t, J=5.8 Hz, 2H), 2.19 (t, J=7.5 Hz, 2H), 2.07 (s, 1H), 1.63 (p, J=7.3 Hz, 2H), 1.46 (s, 9H), 1.37-1.19 (m, 29H), 0.89 (t, J=6.7 Hz, 3H).

Intermediate L7c

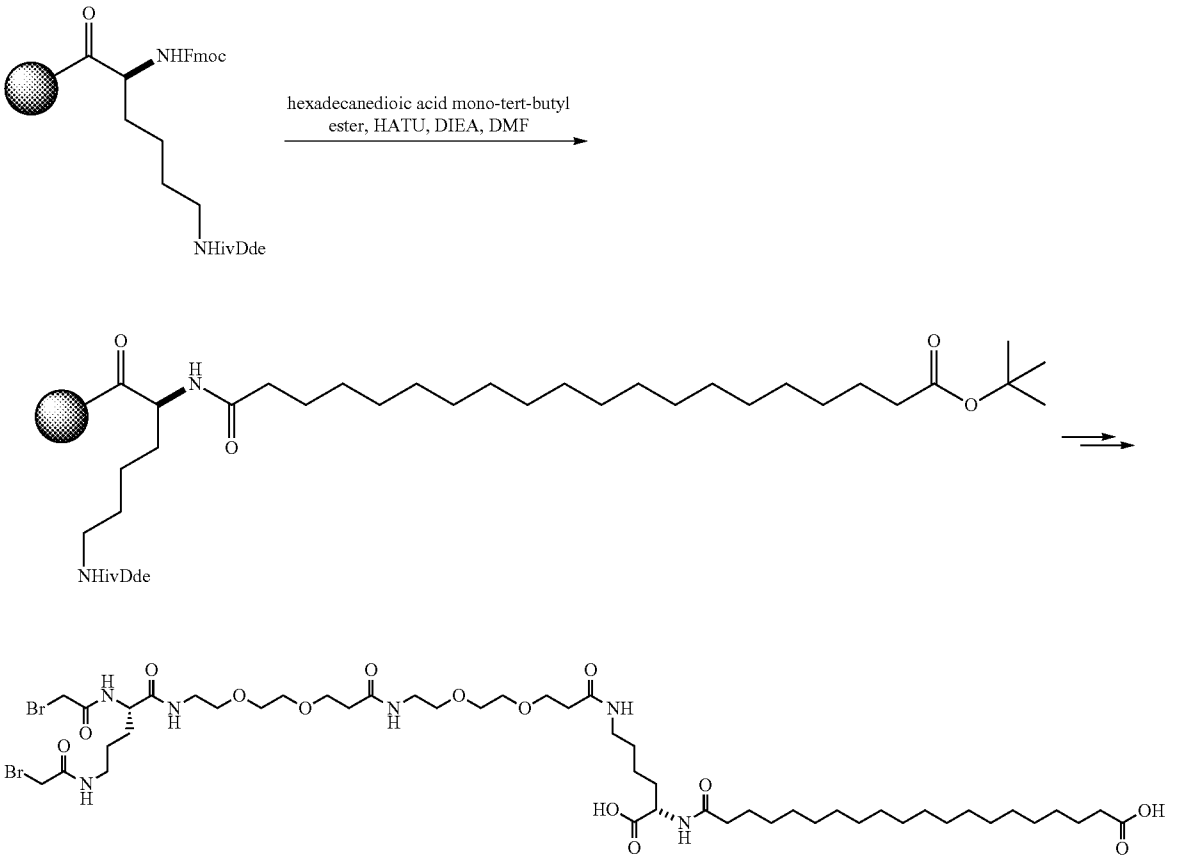
[0415] A solution of compound L7b (360 mg, 0.53 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane. To a solution of Boc-Orn(Boc)-OH (195 mg, 0.58 mmol, 1.1 eq) dissolved in DMF (5 mL) was added HATU (223 mg, 0.58 mmol 1.1 eq). Deprotected compound L7b and DIEA (186 μL, 1.07 mmol, 2 eq) in DMF were added to the reaction mixture. The reaction mixture was agitated 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L7c as an oil (373 mg, 0.42 mmol, 78%). ^1H NMR (400 MHz, chloroform-d) δ 7.14 (s, 1H), 6.84 (s, 1H), 6.35 (s, 1H), 5.53 (d, J=8.2 Hz, 1H), 5.05-4.88 (m, 1H), 4.20 (s, 1H), 3.82-3.69 (m, 2H), 3.65-3.31 (m, 22H), 3.23-3.00 (m, 2H), 2.48 (t, J=5.8 Hz, 2H), 2.17 (t, J=7.8 Hz, 2H), 1.87-1.72 (m, 1H), 1.67-1.48 (m, 5H), 1.42 (s, 18H), 1.34-1.14 (m, 29H), 0.87 (t, J=6.9 Hz, 3H).

L7

[0416] A solution of compound L7c (100 mg, 0.112 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 10 mL of DCM and cooled at 0° C. DIEA (78 μL, 0.44 mmol, 4 eq) was added followed by bromoacetic anhydride (62 mg, 0.24 mmol, 2.05 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. The product was dissolved in EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel afforded L7 as a white solid (95 mg, 0.10 mmol, 91%). MS (ES^+) m/z 931.31 ($[M+H]^+$), 933.25 ($[M+H]^+$). ^1H NMR (400 MHz, methanol-d_4) δ 4.39 (dd, J=8.5, 5.4 Hz, 1H), 3.91 (q, J=11.3 Hz, 2H), 3.84 (s, 2H), 3.76 (t, J=6.2 Hz, 2H), 3.63 (d, J=7.0 Hz, 8H), 3.57 (t, J=5.5 Hz, 6H), 3.42-3.35 (m, 6H), 3.31-3.13 (m, 4H), 2.49 (t, J=6.2 Hz, 2H), 2.20 (t, J=7.4 Hz, 2H), 1.91-1.79 (m, 1H), 1.75-1.56 (m, 6H), 1.39-1.26 (m, 26H), 0.92 (t, J=6.3 Hz, 3H).

Example 15: Synthesis of L8

[0417]



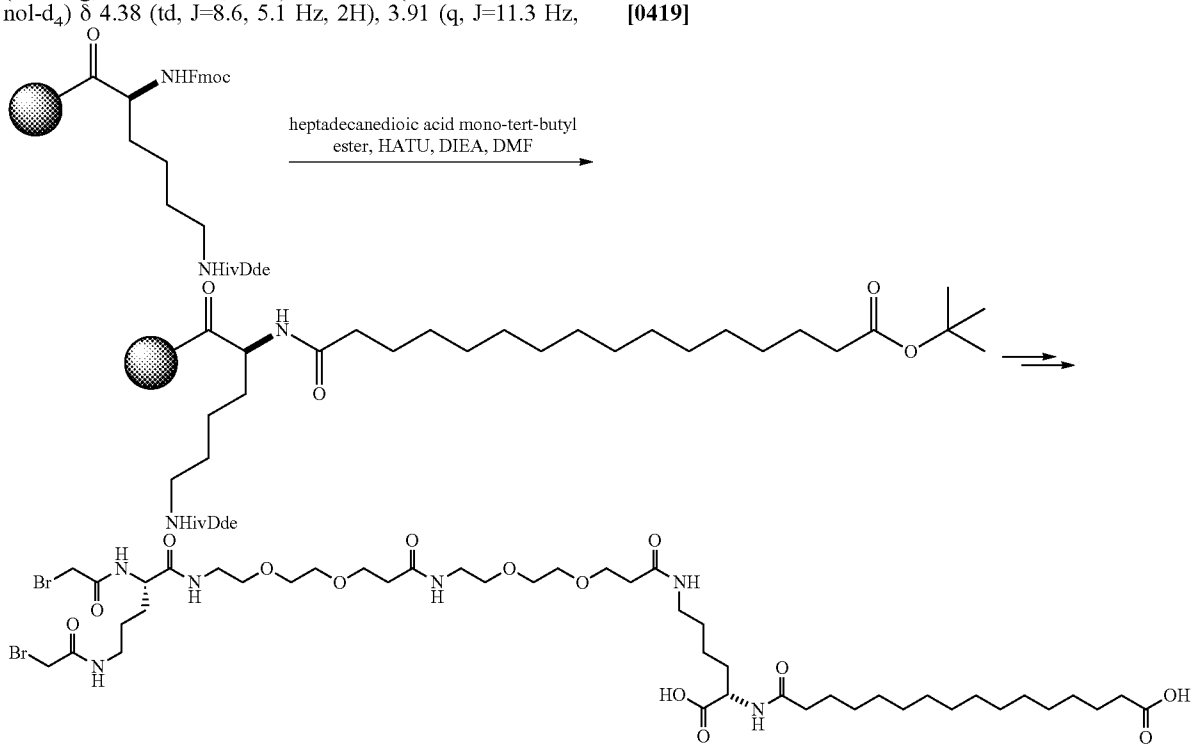
L8

General Protocol A, B, D (hexadecanedioic acid mono-tert butyl ester), C, D (Fmoc-PEG_2-propionic acid), B, D (Fmoc-PEG_2-propionic acid), B, D (Fmoc-Orn(Fmoc)-OH), B, E, F

[0418] The crude was purified by semi-preparative HPLC with mass detection to afford the product L8 as a white solid (42.6 mg, 0.038 mmol, 22%). ^{1}H NMR (400 MHz, methanol-d_4) δ 4.38 (td, J=8.6, 5.1 Hz, 2H), 3.91 (q, J=11.3 Hz, 2H), 3.84 (s, 2H), 3.76 (q, J=6.1 Hz, 4H), 3.65-3.59 (m, 8H), 3.56 (td, J=5.5, 1.7 Hz, 4H), 3.43-3.37 (m, 4H), 3.31-3.16 (m, 4H), 2.48 (dt, J=15.7, 6.2 Hz, 4H), 2.28 (dt, J=12.6, 7.5 Hz, 4H), 1.95-1.79 (m, 1H), 1.77-1.51 (m, 10H), 1.49-1.41 (m, 2H), 1.40-1.26 (m, 31H).

Example 16: Synthesis of L9

[0419]



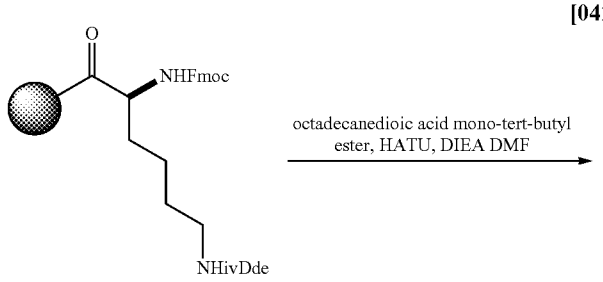
L9

General Protocol A, B, D (heptadecanedioic acid mono-tert butyl ester), C, D (Fmoc-PEG_2-propionic acid), B, D (Fmoc-PEG_2-propionic acid), B, D (Fmoc-Orn(Fmoc)-OH), B, E, F

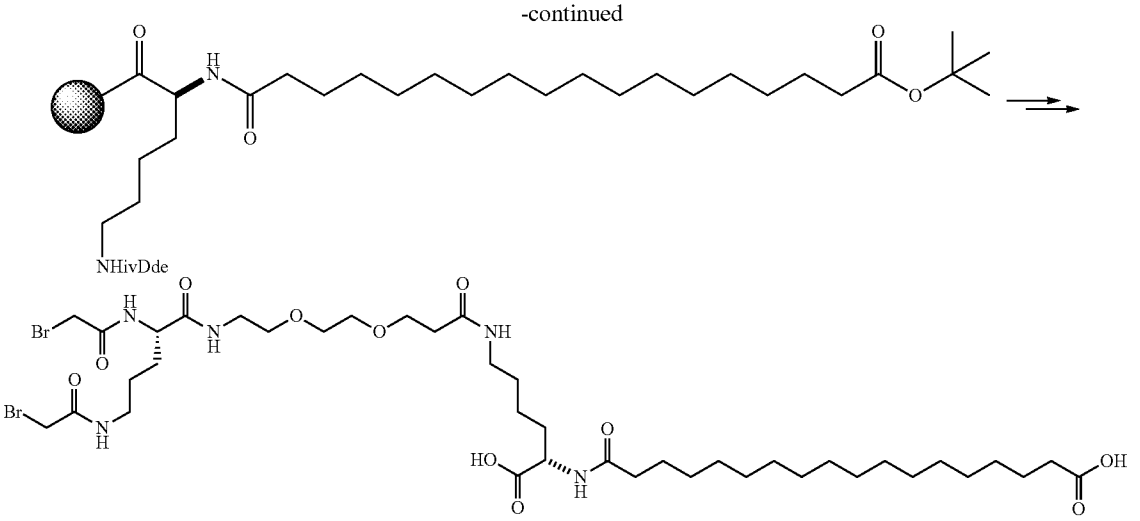
[0420] The crude was purified by semi-preparative HPLC with mass detection to afford the product L9 as a white solid (49 mg, 0.089 mmol, 9%). ^{1}H NMR (400 MHz, methanol-d_4) δ 4.45-4.33 (m, 2H), 3.92 (t, J=10.9 Hz, 2H), 3.85 (d, J=1.1 Hz, 2H), 3.77 (q, J=6.0 Hz, 4H), 3.63 (s, 8H), 3.57 (t, J=5.6 Hz, 4H), 3.40 (t, J=5.5 Hz, 4H), 3.25 (dq, J=22.7, 6.7 Hz, 4H), 2.48 (dt, J=15.6, 6.2 Hz, 4H), 2.29 (dt, J=13.2, 7.4 Hz, 4H), 1.95-1.79 (m, 2H), 1.80-1.50 (m, 10H), 1.51-1.41 (m, 2H), 1.40-1.27 (m, 20H).

Example 17: Synthesis of L12

[0421]



-continued



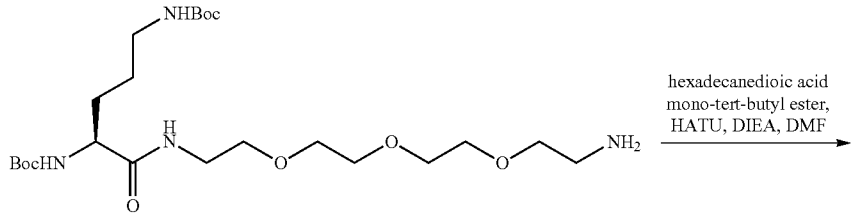
L12

General Protocol A, B, D (octadecanedioic acid), C, D (Fmoc-PEG_2-propionic acid), B, D (Fmoc-Orn(Fmoc)-OH), B, E, F

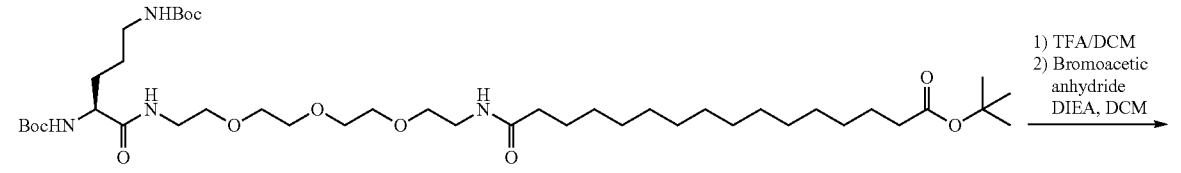
[0422] The crude was purified by semi-preparative HPLC with mass detection to afford the product L12 as a white solid (51.7 mg, 0.054 mmol, 3%). ^{1}H NMR (400 MHz, methanol-d_4) δ 4.39 (td, J=9.2, 5.1 Hz, 2H), 3.92 (qd, J=11.4, 1.2 Hz, 2H), 3.85 (s, 2H), 3.76 (t, J=6.2 Hz, 2H), 3.63 (s, 4H), 3.57 (t, J=5.5 Hz, 2H), 3.40 (q, J=5.1 Hz, 2H), 3.30-3.12 (m, 6H), 2.47 (t, J=6.1 Hz, 2H), 2.29 (dt, J=12.1, 7.4 Hz, 4H), 1.95-1.77 (m, 2H), 1.78-1.50 (m, 10H), 1.48-1.40 (m, 2H), 1.39-1.26 (m, 22H).

Example 18: Synthesis of L14

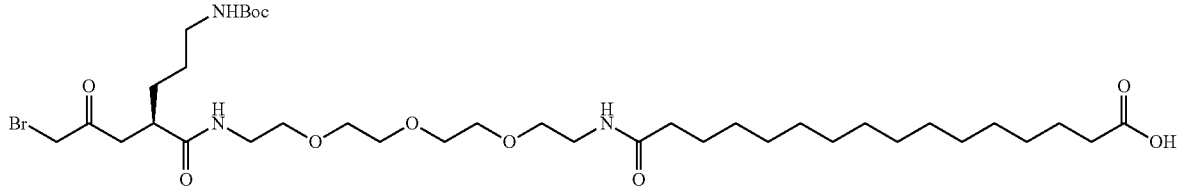
[0423]



L4b



L14a



L14

Intermediate L14a

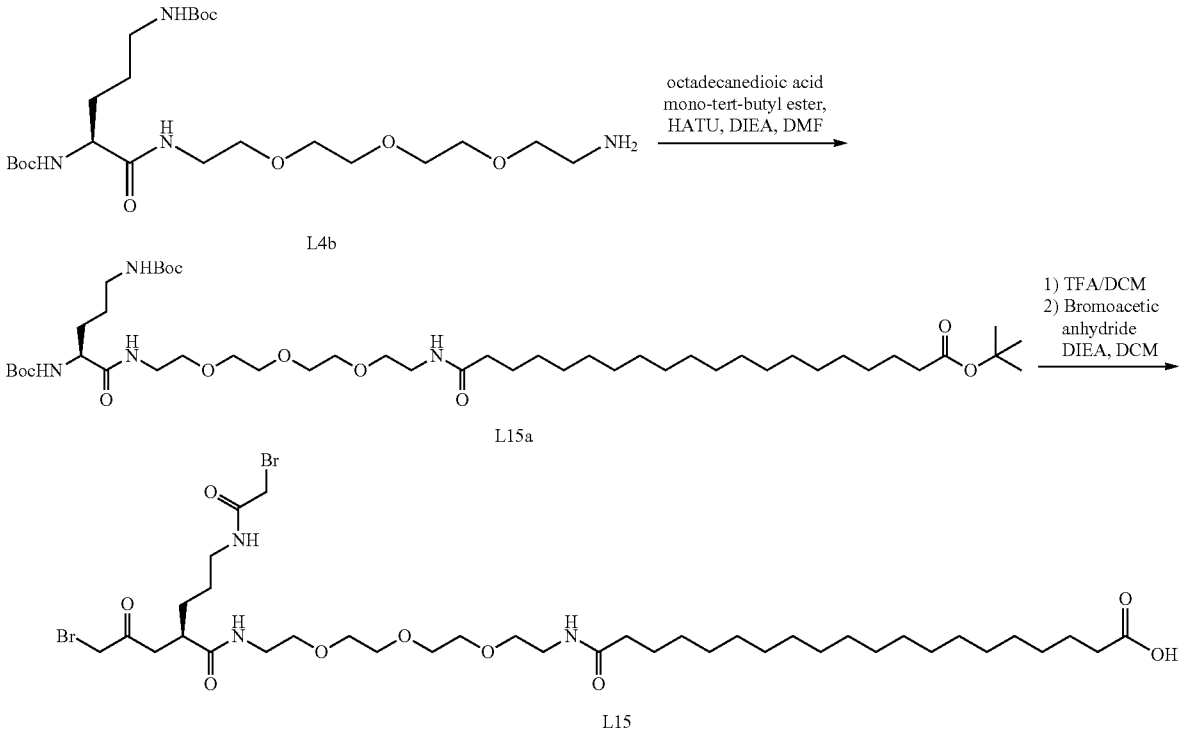
[0424] To a solution of hexadecanedioic acid mono tert-butyl ester (102 mg, 0.30 mmol, 1 eq) dissolved in DMF (5 mL) was added HATU (125 mg, 0.33 mmol 1.1 eq), DIEA (51 μL, 0.33 mmol, 1.1 eq) and compound L4b (151.9 mg, 0.3 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 3 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L14a as an oil (147 mg, 0.176 mmol, 59%). ^1H NMR (400 MHz, chloroform-d) δ 6.87 (s, 1H), 6.40 (s, 1H), 5.32 (s, 2H), 4.79 (s, 1H), 4.20 (s, 1H), 3.66 (d, J=7.0 Hz, 8H), 3.60 (dt, J=10.0, 5.1 Hz, 4H), 3.49-3.45 (m, 3H), 3.31-3.18 (m, 1H), 3.13-3.06 (m, 1H), 2.21 (td, J=7.8, 6.0 Hz, 4H), 1.88-1.78 (m, 1H), 1.66-1.53 (m, 7H), 1.51-1.42 (m, 27H), 1.36-1.19 (m, 20H).

L14

[0425] A solution of compound L14a (40 mg, 0.048 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 20 mL of DCM and cooled at 0° C. DIEA (34 μL, 0.1924 mmol, 4 eq) was added followed by bromoacetic anhydride (23.63 mg, 0.098 mmol, 2.05 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded L14 as a white solid (18.3 mg, 0.022 mmol, 46%). MS (ES^+) m/z 817.1 ($[M+H]^+$), 819.09 ($[M+H]^+$). ^1H NMR (400 MHz, methanol-d_4) δ 4.38 (dd, J=8.4, 5.5 Hz, 1H), 3.92 (q, J=11.2, 10.6 Hz, 2H), 3.84 (s, 2H), 3.69-3.61 (m, 8H), 3.56 (td, J=5.5, 2.6 Hz, 4H), 3.44-3.36 (m, 4H), 3.30-3.14 (m, 2H), 2.29 (t, J=7.4 Hz, 2H), 2.21 (t, J=7.5 Hz, 2H), 1.91-1.78 (m, 1H), 1.76-1.67 (m, 1H), 1.67-1.54 (m, 6H), 1.40-1.29 (m, 20H).

Example 19: Synthesis of L15

[0426]



Intermediate L15a

[0427] To a solution of 20-(tert-butoxy)-20-oxoicosanoic acid (360 mg, 0.90 mmol, 1.05 eq) dissolved in DMF (5 mL) was added HATU (343 mg, 0.90 mmol 1.05 eq), DIEA (300 μL, 1.71 mmol, 2 eq) and compound L4b (435 mg, 0.858 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 3 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L15a as an oil (555 mg, 0.625 mmol, 72%). ^1H NMR (400 MHz, chloroform-d) δ 6.87 (s, 1H), 6.40 (s, 1H), 4.79 (s, 1H), 4.21 (s, 1H), 3.76-3.53 (m, 15H), 3.47 (s, 5H), 3.32-3.05 (m, 3H), 2.29-2.17 (m, 4H), 1.90-1.76 (m, 4H), 1.69-1.53 (m, 2H), 1.52-1.41 (m, 33H), 1.36-1.20 (m, 29H).

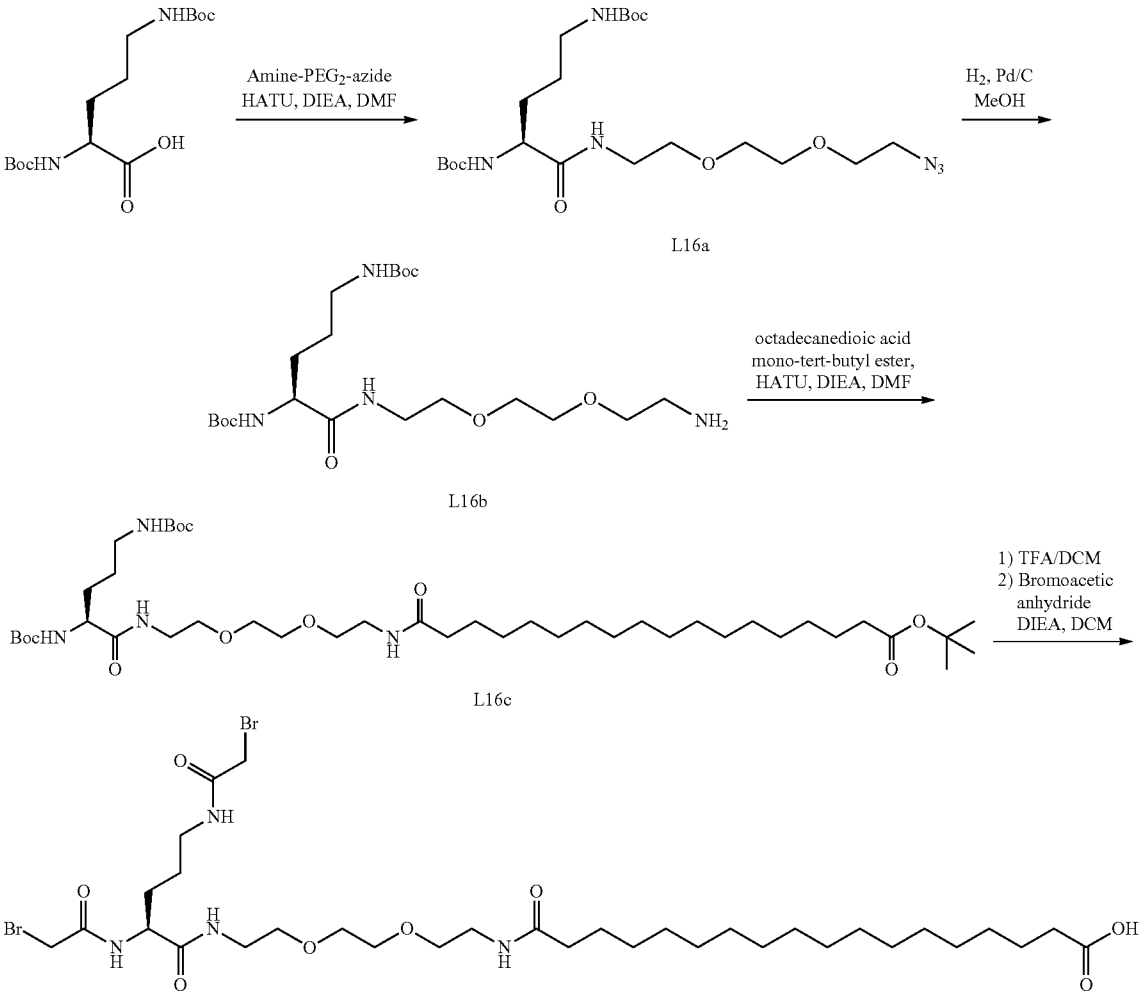
L15

[0428] A solution of compound L15a (100 mg, 0.112 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 20 mL of DCM and cooled at 0° C. DIEA (79 μL, 0.45 mmol, 4 eq) was added followed by bromoacetic anhydride (60 mg, 0.231 mmol, 2.05 eq)

dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded L15 as a white solid (17.5 mg, 0.02 mmol, 18%). MS (ES^+) m/z 873.21 ($[M+H]^+$), 875.20 ($[M+H]^+$)^{1}H NMR (400 MHz, methanol-d_4) δ 4.38 (dd, J=8.4, 5.5 Hz, 1H), 3.91 (q, J=11.4 Hz, 2H), 3.84 (s, 2H), 3.72-3.61 (m, 8H), 3.56 (td, J=5.5, 2.7 Hz, 4H), 3.44-3.35 (m, 5H), 3.30-3.17 (m, 2H), 2.29 (t, J=7.4 Hz, 2H), 2.21 (t, J=7.5 Hz, 2H), 1.92-1.77 (m, 1H), 1.75-1.53 (m, 7H), 1.40-1.27 (m, 27H).

Example 20: Synthesis of L16

[0429]



Intermediate L16a

[0430] To a solution of Boc-Orn(Boc)-OH (400 mg, 1.2 mmol, 1 eq) dissolved in DMF (10 mL) was added HATU (504 mg, 1.32 mmol 1.1 eq), DIEA (230 μL, 1.32 mmol, 1.1 eq) and amine-PEG_2-N_3 (210 mg, 1.20 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 4 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L16a as an oil (471 mg, 0.96 mmol, 80%). ^{1}H NMR (400 MHz, methanol-d_4) δ 4.01 (t, J=6.6 Hz, 1H), 3.71-3.60 (m, 6H), 3.55 (t, J=5.5 Hz, 2H), 3.41-3.37 (m, 3H), 3.04 (t, J=6.2 Hz, 2H), 1.78-1.66 (m, 1H), 1.62-1.48 (m, 3H), 1.48-1.39 (m, 18H).

Intermediate L16b

[0431] To a solution of compound L16a (471 mg, 0.9 mmol, 1 eq) in anhydrous MeOH (10 mL) and under argon was added Pd/C (10.2 mg, 0.09 mmol, 0.1 eq) and argon was replaced with H_2. The reaction mixture was agitated for 6 h at RT, filtrated on celite and evaporated to afford compound L16b as an oil (295.5 mg, 0.64 mmol, 71%). The product was used without any further purification. MS (ES^+) m/z 462.51 ($[M+H]^+$).

Intermediate L16c

[0432] To a solution of octadecanedioic acid mono tert-butyl ester (281 mg, 0.76 mmol, 1 eq) dissolved in DMF (5

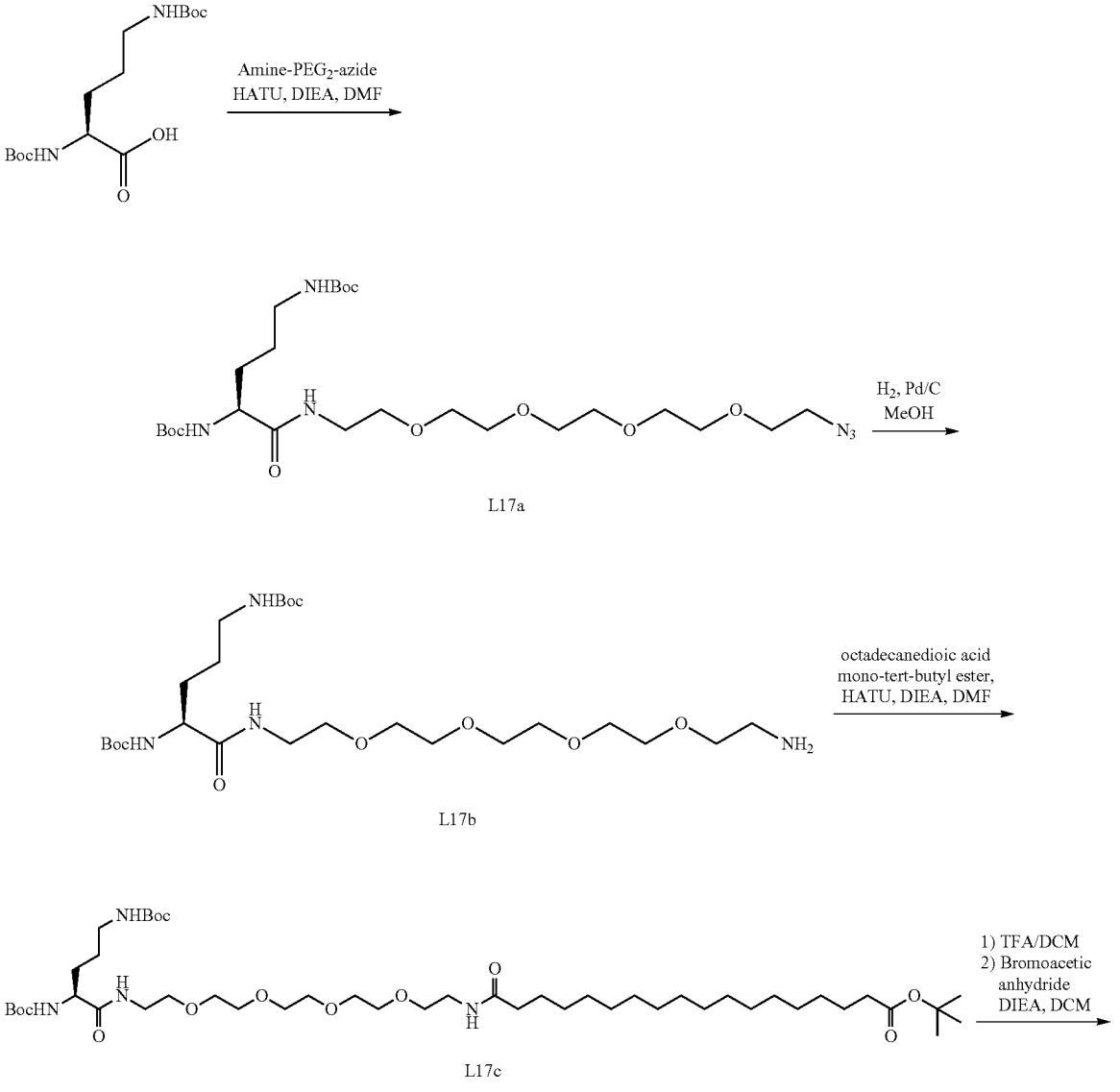
mL) was added HATU (288 mg, 0.76 mmol, 1 eq), DIEA (132 μL, 0.76 mmol, 1 eq) and compound L16b (351 mg, 0.76 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 3 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L16c as an oil (351 mg, 0.43 mmol, 57%). ^1H NMR (400 MHz, methanol-d_4) δ 3.61 (s, 4H), 3.54 (td, J=5.6, 2.3 Hz, 4H), 3.40-3.34 (m, 4H), 3.04 (t, J=6.6 Hz, 2H), 2.20 (td, J=7.6, 5.9 Hz, 4H), 1.77-1.68 (m, 2H), 1.64-1.48 (m, 2H), 1.48-1.42 (m, 28H), 1.35-1.26 (m, 26H).

L16

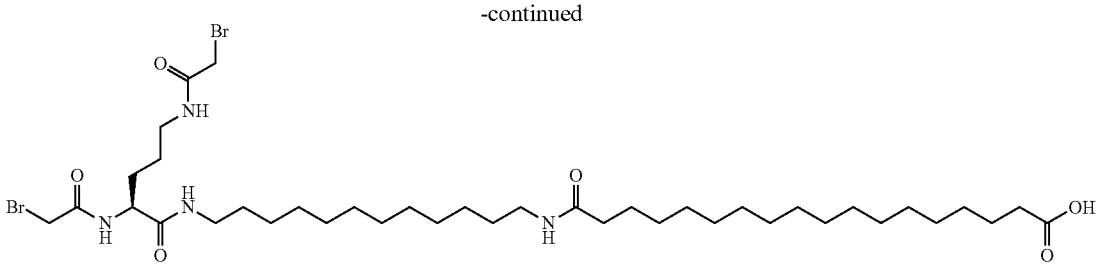
[0433] A solution of compound L16c (31 mg, 0.038 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 20 mL of DCM and cooled at 0° C. DIEA (27 μL, 0.152 mmol, 4 eq) was added followed by bromoacetic anhydride (21 mg, 0.078 mmol, 2.05 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded L16 as a white solid (12.6 mg, 0.015 mmol, 41%). MS (ES^+) m/z 801.13 ($[M+H]^+$), 803.12 ($[M+H]^+$). ^1H NMR (400 MHz, methanol-d_4) δ 4.37 (dd, J=8.5, 5.4 Hz, 1H), 3.91 (q, J=11.3 Hz, 2H), 3.84 (s, 2H), 3.63 (s, 4H), 3.57 (td, J=5.6, 2.6 Hz, 4H), 3.43-3.36 (m, 4H), 3.31-3.17 (m, 1H), 2.29 (t, J=7.4 Hz, 2H), 2.21 (t, J=7.5 Hz, 2H), 1.90-1.79 (m, 1H), 1.76-1.54 (m, 7H), 1.41-1.30 (m, 26H).

Example 21: Synthesis of L17

[0434]



-continued



L17

Intermediate L17a

[0435] To a solution of Boc-Orn(Boc)-OH (400 mg, 1.2 mmol, 1 eq) dissolved in DMF (10 mL) was added HATU (504 mg, 1.32 mmol 1.1 eq), DIEA (230 μL, 1.32 mmol, 1.1 eq) and amine-PEG_2-N_3 (316 mg, 1.20 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 4 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L17a as an oil (454 mg, 0.78 mmol, 66%). ^{1}H NMR (400 MHz, methanol-d_4) δ 4.04-3.97 (m, 1H), 3.71-3.58 (m, 14H), 3.54 (t, J=5.4 Hz, 2H), 3.37 (t, J=5.0 Hz, 4H), 3.04 (t, J=6.6 Hz, 2H), 1.75-1.67 (m, 1H), 1.62-1.48 (m, 3H), 1.48-1.41 (m, 18H).

Intermediate L17b

[0436] To a solution of compound L17a (454 mg, 0.9 mmol, 1 eq) in anhydrous MeOH (10 mL) and under argon was added Pd/C (8.3 mg, 0.078 mmol, 0.1 eq) and argon was replaced with H_2. The reaction mixture was agitated for 6 h at RT, filtrated on celite and evaporated to afford compound L17b as an oil (192 mg, 0.35 mmol, 45%). The product was used without any further purification.

Intermediate L17c

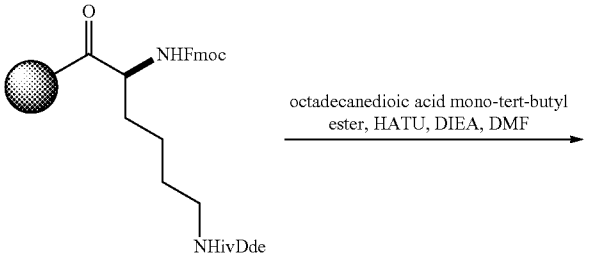
[0437] To a solution of octadecanedioic acid mono tert-butyl ester (225 mg, 0.61 mmol, 1 eq) dissolved in DMF (5 mL) was added HATU (231 mg, 0.61 mmol 1 eq), DIEA (106 μL, 0.61 mmol, 1 eq) and compound L17b (335 mg, 0.61 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound L17c as an oil (178 mg, 0.20 mmol, 32%). ^{1}H NMR (400 MHz, chloroform-d) δ 5.32 (s, 2H), 3.74-3.63 (m, 11H), 3.59 (dt, J=10.9, 5.0 Hz, 4H), 3.52-3.43 (m, 4H), 3.27-3.08 (m, 2H), 2.22 (d, J=7.6 Hz, 4H), 1.69-1.52 (m, 6H), 1.51-1.42 (m, 27H), 1.27 (s, 26H).

L17

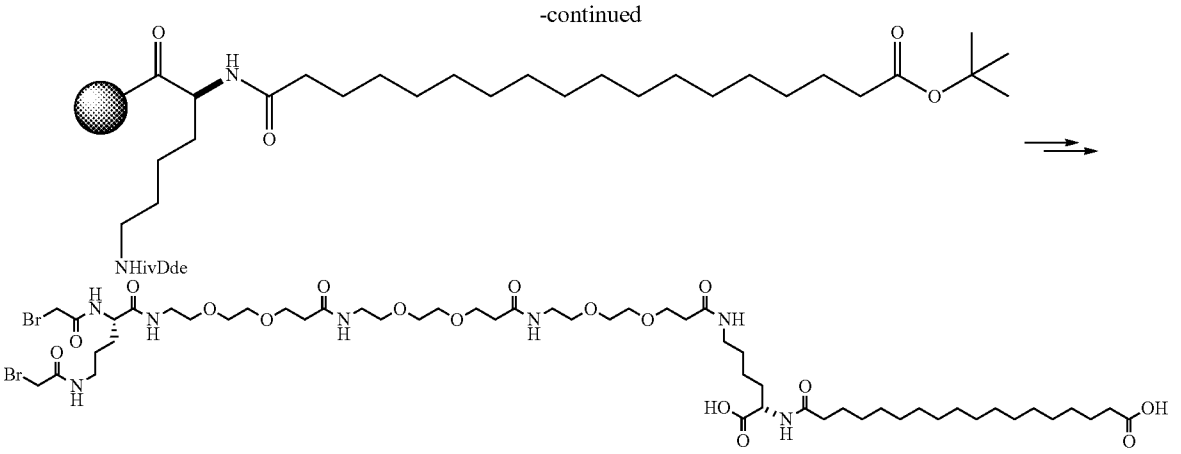
[0438] A solution of compound L17c (45.6 mg, 0.05 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 20 mL of DCM and cooled at 0° C. DIEA (36 μL, 0.202 mmol, 4 eq) was added followed by bromoacetic anhydride (27 mg, 0.103 mmol, 2.05 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0° C., 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded L17 as a white solid (14.9 mg, 0.017 mmol, 33%). MS (ES$^+$) m/z 889.18 ([M+H]$^+$), 891.17 ([M+H]$^+$)^{1}H NMR (400 MHz, methanol-d_4) δ 4.38 (dd, J=8.3, 5.5 Hz, 1H), 3.92 (q, J=11.3 Hz, 2H), 3.84 (s, 2H), 3.67-3.60 (m, 7H), 3.56 (td, J=5.5, 3.5 Hz, 4H), 3.45-3.35 (m, 5H), 3.32-3.15 (m, 3H), 2.29 (t, J=7.4 Hz, 2H), 2.21 (t, J=7.5 Hz, 2H), 1.90-1.76 (m, 1H), 1.74-1.57 (m, 7H), 1.41-1.26 (m, 25H).

Example 22: Synthesis of L18

[0439]



-continued



L18

General Protocol A, B, D (octadecanedioic acid), C, D (Fmoc-PEG_2-propionic acid), B, (Fmoc-PEG_2-propionic acid), B, (Fmoc-PEG_2-propionic acid), B, D (Fmoc-Orn(Fmoc)-OH), B, E, F

[0440] The crude was purified by semi-preparative HPLC with mass detection to afford the product L18 as a white solid (47 mg, 0.036 mmol, 10%). MS (ES^+) m/z 1276.39 ($[M+H]^+$), 1278.37 ($[M+H]^+$).

General Procedure for Bromoacetyl Peptide Stapling/Conjugation

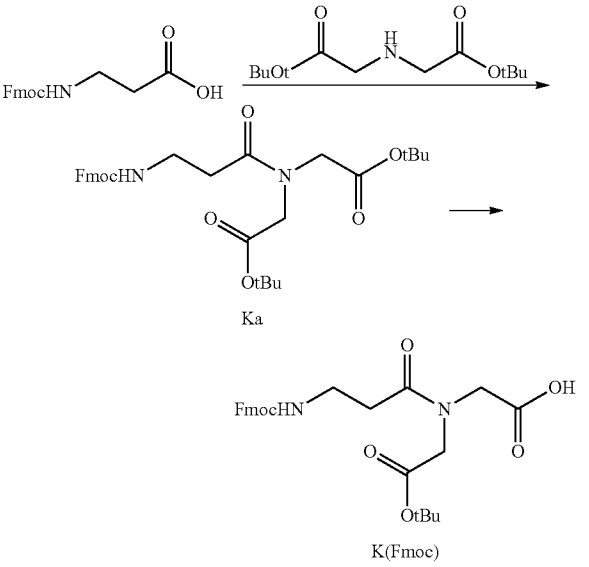
[0441] Peptides were dissolved at a concentration of 2 mM with 1.5 eq of bromoacetyl staple in 1:3 (v/v) MeCN/30 mM NH_4HCO_3 buffer (pH 8.5). The pH of the reaction mixture was readjusted with ammonium hydroxide to correct the drop in pH caused by the peptide TFA counterion. More MeCN was added for particularly insoluble peptides. The reaction was stirred at RT for 2-4 h, before acidification to pH 5 via dropwise addition of acetic acid. The resulting solution was lyophilized and purified by reversed-phase HPLC.

General Solid-Phase Protocols for Lactam Stapling

[0442] Peptide-resin bearing amine side chain orthogonal protection (Dde/Mmt) at each stapling position was swollen in DMF for 1 h. The Dde protecting group was removed from the first side chain via treatment with 2% hydrazine solution in DMF (2×15 min). Positive TNBS test was observed. The linker building block specified below was coupled as described and a negative TNBS test was observed. The solvent was exchanged for DCM and the Mint group was removed from the second side chain via treatment with 1% TFA in DCM containing 5% TIPS, 5×2 min. The resin was washed with DCM, 10% DIEA in DMF, DMF and a positive TNBS test was observed. The linker was cyclized and the PEG-fatty acid portion of the staple (if applicable) elongated as described below. The complete stapled peptide was cleaved from the resin using 95% TFA, 2.5% TIPS, 2.5% H_2O, 3 h. The peptide cleavage mixture was evaporated to an oil, triturated and washed with diethyl ether and purified via reversed-phase HPLC. A Dde/Alloc protection scheme can also be used for this approach, which requires the addition of allyl alcohol to the Dde deprotection cocktail as a scavenger to prevent concurrent reduction of the Alloc allyl moiety.

Synthesis of K(Fmoc) Linker

[0443]



Ka

K(Fmoc)

[0444] Intermediate Ka

[0445] Fmoc-β-Ala-OH (1.00 g, 3.21 mmol) and di-tert-butyl iminodiacetate (0.461 g, 2.68 mmol) were suspended in 100 mL DCM. HATU (1.02 g, 2.68 mmol) and DIEA (3.32 mL, 12.8 mmol) were added and the reaction was stirred at RT for 3.5 h. The solvent was evaporated and the residue dissolved in MeOH and purified via flash column chromatography on silica gel (hexane/EtOAc) to afford the product as a white solid (0.802 g, 56%). ^1H NMR (400 MHz, chloroform-d) δ 7.78 (d, J=7.4 Hz, 2H), 7.62 (d, J=7.4 Hz, 2H), 7.42 (t, J=7.4 Hz, 2H), 7.33 (t, J=7.4 Hz, 2H), 5.66 (t, J=5.7 Hz, 1H), 4.35 (d, J=7.3 Hz, 2H), 4.23 (t, J=7.3 Hz,

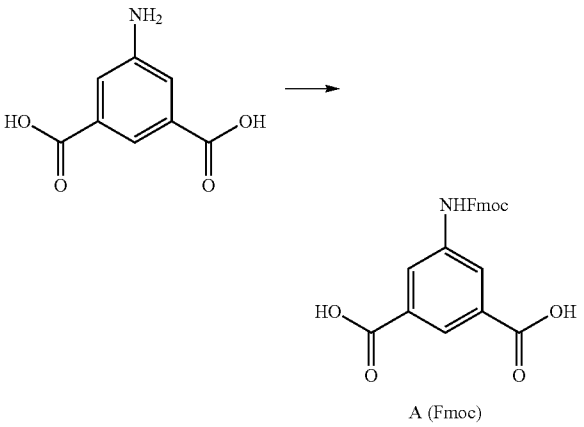
1H), 4.10 (s, 2H), 4.02 (s, 2H), 3.56 (q, J=5.7 Hz, 2H), 2.55 (t, J=5.7 Hz, 2H), 1.49 (s, 18H).

K(Fmoc) Linker

[0446] Compound Ka was treated with 20 mL 1:1 TFA/DCM for 2 h. The solvent was evaporated and the residue triturated and washed with diethyl ether to afford K(Fmoc) linker as a white solid (0.371 g, 58%). MS (ES^+) m/z 427.15 ($[M+H]^+$).

Synthesis of A(Fmoc) Linker

[0447]



A (Fmoc)

[0448] A solution of 5-Aminoisophthalic acid (1.00 g, 5.5 mmol) in 10 mL dioxane was added to a degassed solution of Na_2CO_3 (1.46 g, 5.5 mmol) in 15 mL water. The solution was cooled on ice and a solution of Fmoc chloride (1.42 g, 5.5 mmol) in 10 mL dioxane was then added dropwise with stirring over 15 min. The reaction was then stirred for 1 h and then 24 h at RT. The dioxane was removed under vacuum and the remaining aqueous solution acidified with 1M HCl. The resulting solid precipitate was then washed with diethyl ether (4×10 mL), redissolved in EtOAc, filtered, washed with brine, dried over Na_2SO_4 filtered and concentrated to give A (Fmoc) linker as a white solid (119 mg, 5%). ^1H NMR (500 MHz, DMSO-d_6) δ 13.24 (s, 2H), 10.12 (s, 1H), 8.33 (d, J=1.5 Hz, 2H), 8.12 (t, J=1.5 Hz, 1H), 7.91 (d, J=7.6 Hz, 2H), 7.76 (dd, J=7.6, 1.2 Hz, 2H), 7.43 (t, J=7.6 Hz, 2H), 7.36 (td, J=7.6, 1.2 Hz, 2H), 4.50 (d, J=6.8 Hz, 2H), 4.33 (t, J=6.8 Hz, 1H).

General Protocol G for 'A1' and 'K1' Series Simple Lactam Staples

[0449] For linker coupling the appropriate diacid building block (2 eq) was attached using HATU (4 eq) and DIEA (4 eq) in DMF, 1×2 h. The cyclization step was achieved using HATU (1 eq) and DIEA (2 eq) in DMF, 1×2 h.

General Protocol H for 'K' PEG-Fatty Acid Trifunctional Lactam Staples

[0450] For linker coupling the intramolecular symmetric anhydride of building block K(Fmoc) linker (2 eq) was preformed using DIC (2 eq) and catalytic DMAP in dry DCM for 10 min at RT. The peptide-resin solvent was exchanged for DCM and the anhydride was then added and agitated overnight. The resin was drained, washed with DCM and DMF. The linker was cyclized overnight via treatment with DIC (1 eq) and HOBt or HOAt (1 eq) in DMF, and a negative TNBS was observed. Remaining uncyclized linker was capped via treatment with 10% acetic anhydride in DMF (30 min). The linker Fmoc group was deprotected via treatment with 20% piperidine in DMF (2×10 min). A positive TNBS was observed. Subsequent staple PEG and fatty acid building blocks were attached sequentially to the linker free amine via standard coupling chemistry: building block (3 eq), HATU (3 eq) and DIEA (6 eq) in DMF, 1 h at RT, using 20% piperidine in DMF for deprotection cycles (5+10 min, RT).

General Protocol I for 'A' PEG-Fatty Acid Trifunctional Lactam Staples

[0451] For linker coupling the building block A(Fmoc) linker (2 eq) was attached using HATU (4 eq) and DIEA (4 eq) in DMF, 1×2 h. The cyclization step was achieved using HATU (1 eq) and DIEA (2 eq) in DMF, 1×2 h. Remaining uncyclized linker was capped via treatment with 10% acetic anhydride in DMF (30 min). The linker Fmoc group was deprotected via treatment with 20% piperidine in DMF (2×10 min). It was not possible to observe a positive TNBS test for the aniline nitrogen. Fmoc-R-Ala-OH (3 eq) was coupled using HATU (3 eq) and DIEA (6 eq) in DMF, 4×1 h at RT or as the symmetric anhydride using DIC/DMAP in DCM (2 h, RT). Subsequent staple PEG and fatty acid building blocks were attached sequentially to the linker free amine via standard coupling chemistry: building block (3 eq), HATU (3 eq) and DIEA (6 eq) in DMF, 1 h at RT, using 20% piperidine in DMF for deprotection cycles (5+10 min, RT).

[0452] In some embodiments, the peptide conjugate described herein comprises a staple of Table 2.

TABLE 2

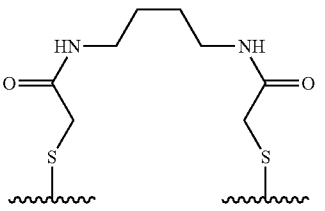
Ex.	ID	Structure
1	L1	

TABLE 2-continued

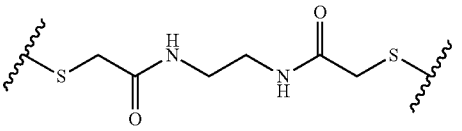
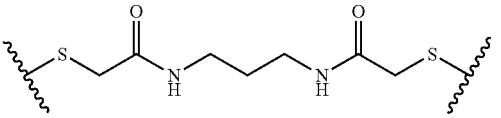
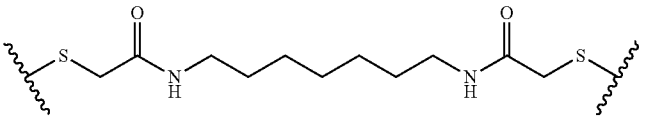
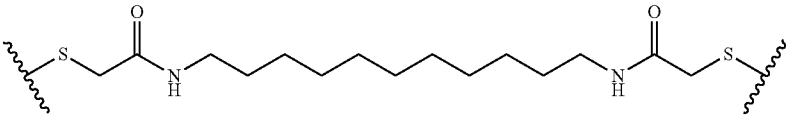
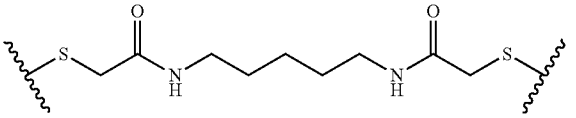
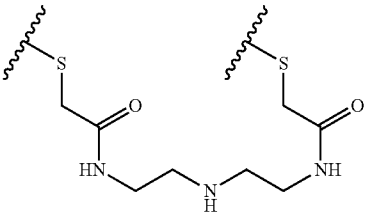
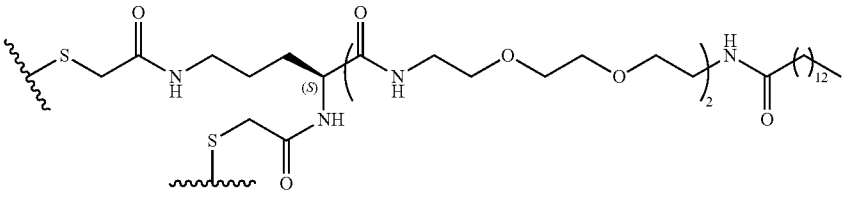
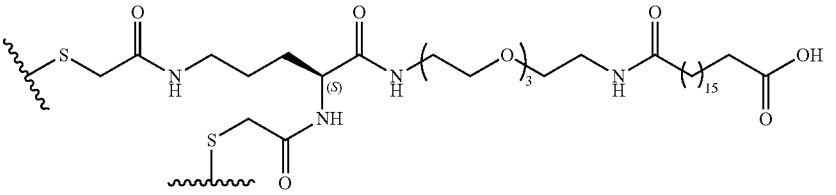
Ex.	ID	Structure
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4	L1D	
5	L1E	
6	L1F	
7	L1G	
8	L3	
9	L4	

TABLE 2-continued

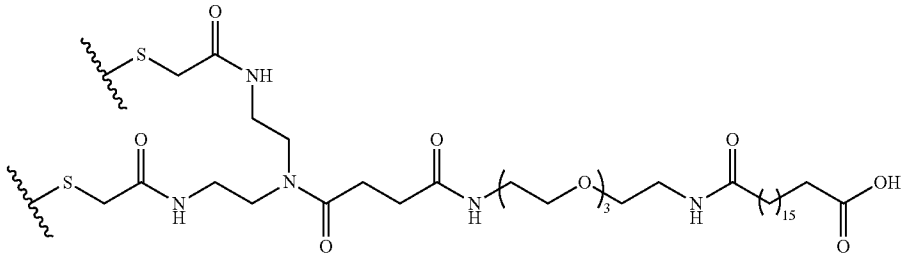
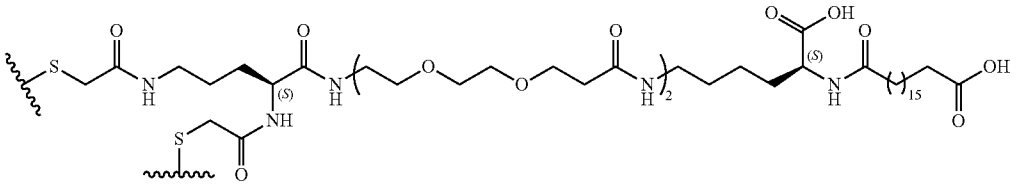
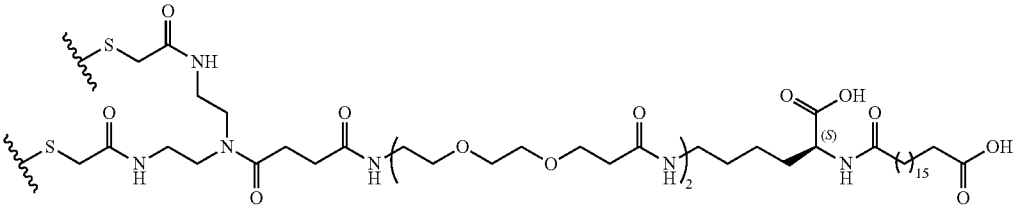
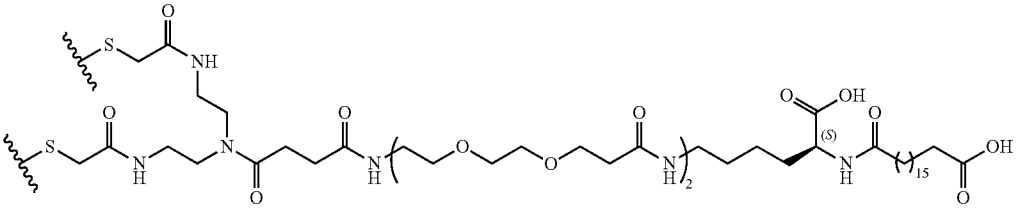
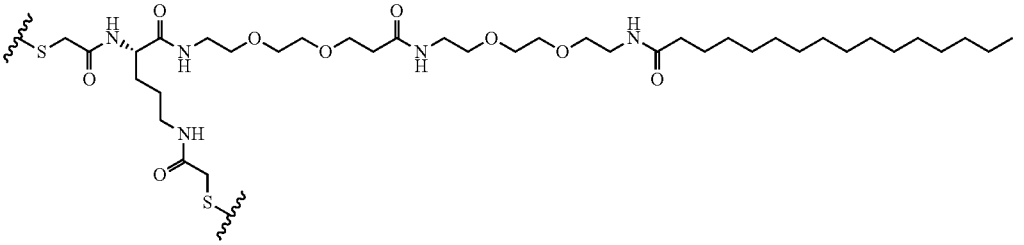
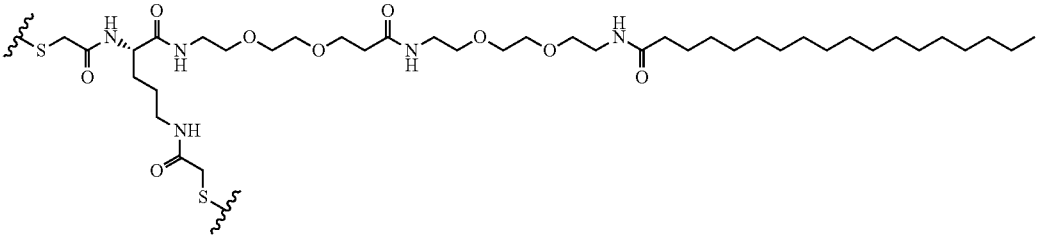
Ex.	ID	Structure
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11	L5	
12	L5A	
	C20L5A	
13	L6	
14	L7	

TABLE 2-continued

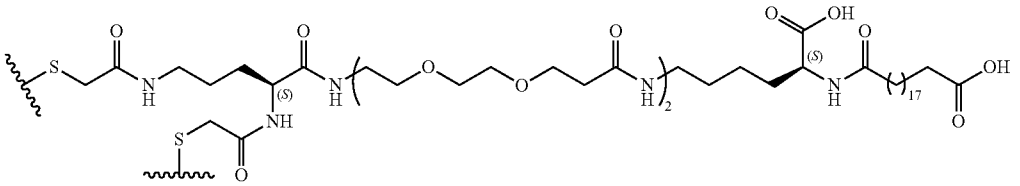
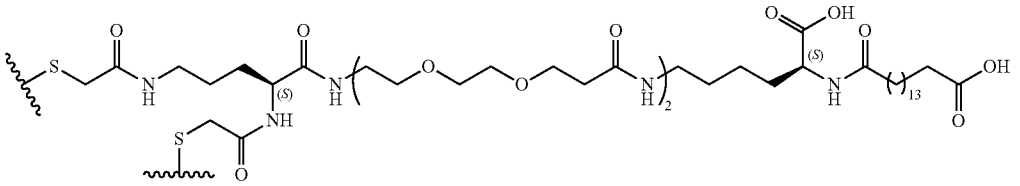
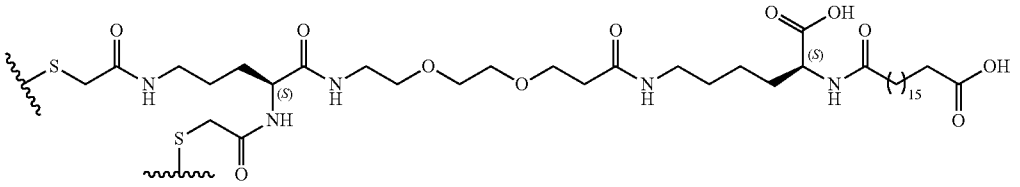
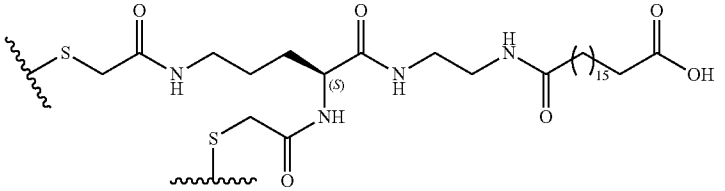
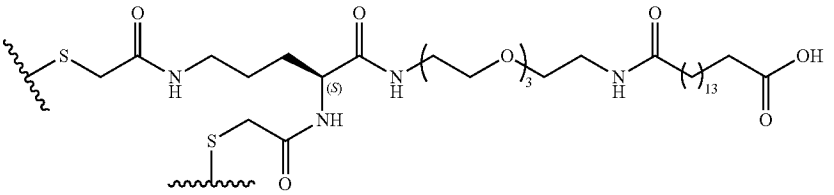
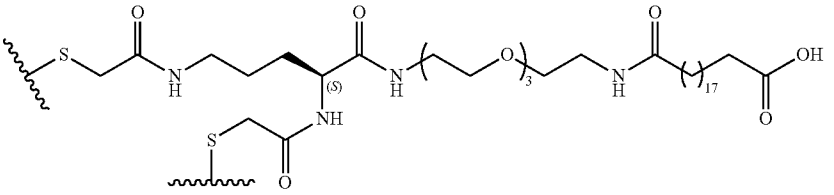
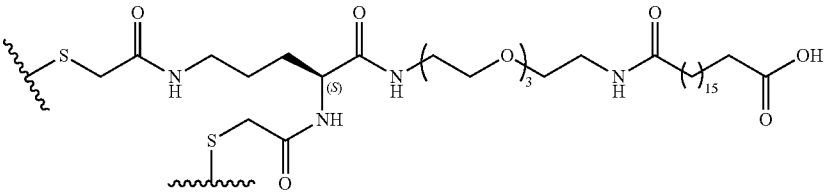
Ex.	ID	Structure
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16	L9	
17	L12	
	L13	
18	L14	
19	L15	
20	L16	

TABLE 2-continued

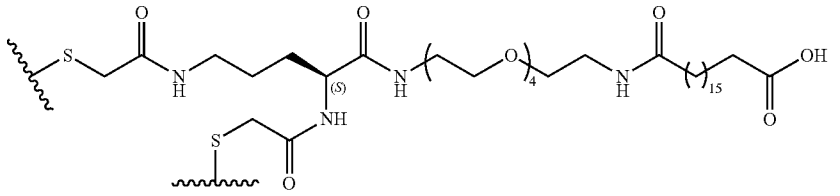
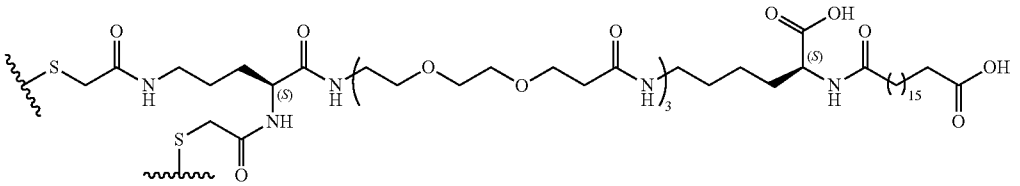
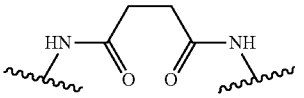
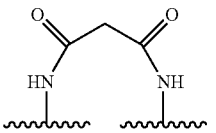
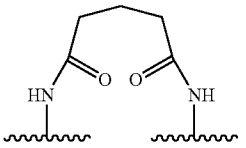
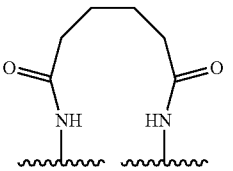
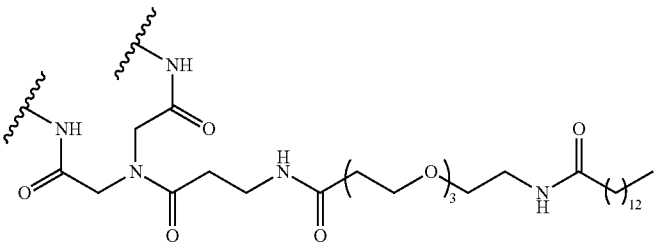
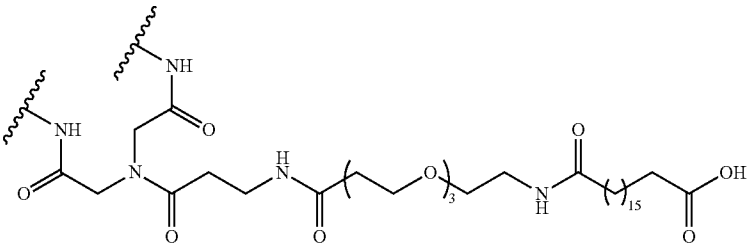
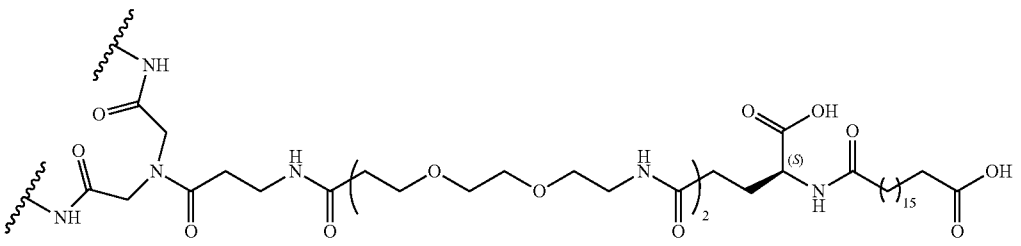
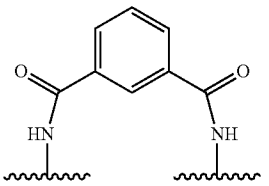
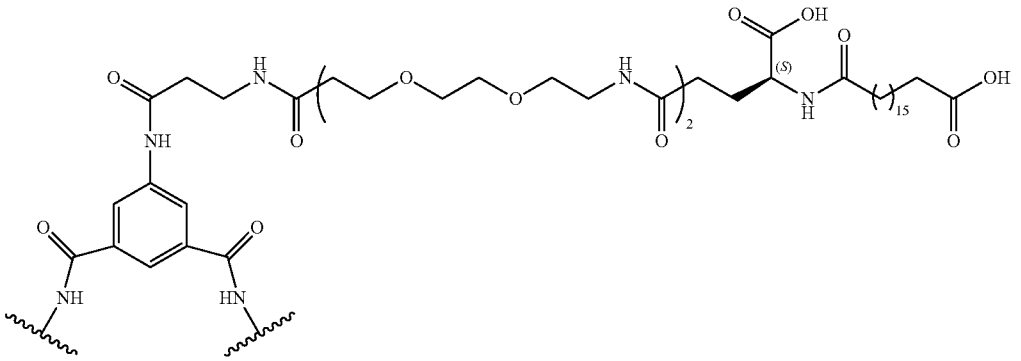
Ex.	ID	Structure
21	L17	
22	L18	
	K1	
	K1C	
	K1F	
	K1H	
	K3	
	K4	

TABLE 2-continued

Ex.	ID	Structure
	K5	
	A1	
	A5	

[0453] The "≀-S" being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue, and the "≀-NH" being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

[0454] In some embodiments, the peptide conjugate described herein is as shown in Table 3.

TABLE 3

Peptide Conjugates

Conjugate	Sequence	Conjugation position	Staple/ HEM
1	GLP2-2G-1-EX4 (SEQ ID NO. 1)	17, 24	L5A
2	GLP2-2G-10Nle-1-EX4 (SEQ ID NO. 2)	17, 24	L5A
3	GLP2-2G-10L-1-EX4 (SEQ ID NO. 3)	17, 24	L5A
4	GLP2-2G-10I-1-EX4 (SEQ ID NO. 4)	17, 24	L5A
5	GLP2-2G-10Aib-1-EX4 (SEQ ID NO. 5)	17, 24	L5A
6	GLP2-2G-10Nva-1-EX4 (SEQ ID NO. 6)	17, 24	L5A

TABLE 3-continued

Peptide Conjugates

Conjugate	Sequence	Conjugation position	Staple/ HEM
7	GLP2-2G-10V-1-EX4 (SEQ ID NO. 7)	17, 24	L5A
8	GLP2-2G-5-EX4 (SEQ ID NO. 8)	9, 16	L5A
9	GLP2-2G-5-EX4 (SEQ ID NO. 8)	9, 16	L4A
10	GLP2-2G-6-EX4 (SEQ ID NO. 9)	11, 18	L5A
11	GLP2-2G-10Nle-1K-EX4 (SEQ ID NO. 10)	17, 24	K5
12	GLP2-2G-10Nle-11f-1K-EX4 (SEQ ID NO. 11)	17, 24	K5
13	GLP2-2G-10Nle-12S-13L-1K-EX4 (SEQ ID NO. 12)	17, 24	K5
14	GLP2-2G-10Nle-13A-14Nle-1K-EX4 (SEQ ID NO. 13)	17, 24	K5
15	GLP2-2G-10Nle-13Nle-14Nle-1K-EX4 (SEQ ID NO. 14)	17, 24	K5
16	GLP2-2G-10Nle-11A-13A-14Nle-16A-1K-EX4 (SEQ ID NO. 15)	17, 24	K5
17	GLP2-2G-1K-EX4 (SEQ ID NO. 16)	17, 24	K5
18	GLP2-2G-11f-1K-EX4 (SEQ ID NO. 17)	17, 24	K5
19	GLP2-2G-1K-EX4 (SEQ ID NO. 16)	17, 24	K1
20	GLP2-2G-1K-EX4 (SEQ ID NO. 16)	17, 24	A1
21	GLP2-2G-1K-EX4 (SEQ ID NO. 16)	17, 24	K1F
22	GLP2-2G-1K-EX4 (SEQ ID NO. 16)	17, 24	K1H
23	GLP2-2G-5K-EX4 (SEQ ID NO. 18)	9, 16	K5
24	GLP2-2G-10Nle-5K-EX4 (SEQ ID NO. 19)	9, 16	K5
25	GLP2-2G-1Orn-EX4 (SEQ ID NO. 20)	17, 24	K5
26	HGDGSFSDEMNTILDNCA ARDFICWLIQTKITD (SEQ ID NO. 21)	17, 24	L5A
27	HGDGSFSDE(Nle)NTILDN CAARDFICWLIQTKITD (SEQ ID NO. 22)	17, 24	L5A

TABLE 3-continued

Peptide Conjugates

Conjugate	Sequence	Conjugation position	Staple/ HEM
28	HGDGSFSDELNTILDNCA ARDFICWLIQTKITD (SEQ ID NO. 23)	17, 24	L5A
29	HGDGSFSDEINTILDNCA ARDFICWLIQTKITD (SEQ ID NO. 24)	17, 24	L5A
30	HGDGSFSDE(Aib)NTILDN CAARDFICWLIQTKITD (SEQ ID NO. 25)	17, 24	L5A
31	HGDGSFSDE(Nva)NTILDN CAARDFICWLIQTKITD (SEQ ID NO. 26)	17, 24	L5A
32	HGDGSFSDEVNTILDNCA ARDFICWLIQTKITD (SEQ ID NO. 27)	17, 24	L5A
33	HGDGSFSDCMNTILDCLA ARDFINWLIQTKITD (SEQ ID NO. 28)	9, 16	L5A
34	HGDGSFSDCMNTILDCLA ARDFINWLIQTKITD (SEQ ID NO. 28)	9, 16	L4A
35	HGDGSFSDEMCTILDNLC ARDFINWLIQTKITD (SEQ ID NO. 29)	11, 18	L5A
36	HGDGSFSDE(Nle)NTILDN KAARDFIKWLIQTKITD (SEQ ID NO. 30)	17, 24	K5
37	HGDGSFSDE(Nle)(D-Phe)TILDNKAARDFIKWLI QTKITD (SEQ ID NO. 31)	17, 24	K5
38	HGDGSFSDE(Nle)NSLLDN KAARDFIKWLIQTKITD (SEQ ID NO. 32)	17, 24	K5
39	HGDGSFSDE(Nle)NTA(Nle) DNKAARDFIKWLIQTKIT D (SEQ ID NO. 33)	17, 24	K5
40	HGDGSFSDE(Nle)NT(Nle) (Nle)DNKAARDFIKWLIQT KITD (SEQ ID NO. 34)	17, 24	K5
41	HGDGSFSDE(Nle)ATA(Nle) DAKAARDFIKWLIQTKIT D (SEQ ID NO. 35)	17, 24	K5
42	HGDGSFSDEMNTILDNKA ARDFIKWLIQTKITD (SEQ ID NO. 36)	17, 24	K5
43	HGDGSFSDEM(D-Phe)TILDNKAARDFIKWLI QTKITD (SEQ ID NO. 37)	17, 24	K5
44	HGDGSFSDEMNTILDNKA ARDFIKWLIQTKITD (SEQ ID NO. 36)	17, 24	K1

TABLE 3-continued

Peptide Conjugates

Conjugate	Sequence	Conjugation position	Staple/ HEM
45	HGDGSFSDEMNTILDNKA ARDFIKWLIQTKITD (SEQ ID NO. 36)	17, 24	A1
46	HGDGSFSDEMNTILDNKA ARDFIKWLIQTKITD (SEQ ID NO. 36)	17, 24	K1F
47	HGDGSFSDEMNTILDNKA ARDFIKWLIQTKITD (SEQ ID NO. 36)	17, 24	K1H
48	HGDGSFSDKMNTILDKLA ARDFINWLIQTKITD (SEQ ID NO. 38)	9, 16	K5
49	HGDGSFSDK(Nle)NTILDK LAARDFINWLIQTKITD (SEQ ID NO. 39)	9, 16	K5
50	HGDGSFSDEMNTILDN(Orn) AARDFI(Orn)WLIQTKIT D (SEQ ID NO. 40)	17, 24	K5

Example A: In Vitro GLP-2 Receptor Activation Reporter Assay (Receptor-Mediated cAMP Synthesis)

[0455] Peptide activity and potency toward the GLP-2R activation were determined using a stable HEK293 cell line overexpressing cAMP response element (CRE) driven luciferase reporter and human GLP-2R in the presence of LP2 FBS. GLP2-2G (teduglutide) was used as a positive control.

[0456] HEK293-GLP-2R-CRE cells were seeded in 384-well plates at a density of 5000 cells per well and cultured for 18 h in DMEM with 10% FBS at 37° C. and 5% CO2. Cells were treated with peptides in a dose dependent manner for 16 h, and receptor activation was reported by luminescence intensities, using One-Glo (Promega, WI) luciferase reagent following manufacturer's instruction. The EC50 of each peptide was determined using GraphPad Prism 6 software (GraphPad, San Diego, Calif.). The assay was performed in triplicate, and the results were obtained in three independent experiments. The results are shown in Table 4 below.

TABLE 4

Conjugate	GLP-2R - cAMP 0% FBS/nM	GLP-2R - cAMP 10% FBS/nM
1	0.92	20.95
2	0.44	—
3	0.87	—
5	8.71	—
6	5.74	—
7	1.45	—
8	2.44	44.84
10	2.09	102.1
11	0.64	1.57
12	2.13	—
13	3.782	—

TABLE 4-continued

Conjugate	GLP-2R - cAMP 0% FBS/nM	GLP-2R - cAMP 10% FBS/nM
14	2.683	—
15	1.989	—
16	1.334	—
17	1.07	—
18	1.41	—
19	0.15	—
20	0.09	—
21	0.14	—
22	0.23	—
23	1.25	—
24	8.36	—
25	2.11	—

Example B: Pharmacokinetics of Peptides in Mice (Half-Life)

[0457] To determine the in vivo half-lives of GLP-2 agonists, pharmacokinetic (PK) studies were performed by iv or sc injection of the peptides at 10 nmol/kg in CD1 female mice (n=4 per group). Plasma levels of the peptides at various time points (5 min, 30 min, 1 h, 3 h, 7 h, and 24 h) were determined using the in vitro GLP-2R mediated cell based reporter assay. The estimated terminal half-lives after iv or sc administration is shown in Table 5 below.

[0458] Briefly, female CD-1 mice (n=4 per group) from Charles River Laboratory were fasted overnight and administrated with 100 μL of each peptide in phosphate buffered saline by intravenous (iv) or subcutaneous (sc) route. Food was provided to mice immediately after bleeding at 30 min. Blood was extracted into heparin tubes and centrifuged at 3000 g for 15 min. The resulting supernatant plasma were then stored at −80° C. for peptide concentration determination. The concentrations of peptides in plasma at each time point were determined by in vitro cell based activity assay.

HEK293-GLP-2R-CRE cells were treated with plasma samples at different time points (5 point dose response, starting from 1:10 to 1:100 dilution of each plasma sample) and incubated for 16 h in DMEM with 1000 FBS at 37° C. with 500 CO2, and the firefly luciferase activity was then measured. At the same time, the same peptides were used to obtain standard curves and parameters for Bottom, Top, EC50, and Hill slope. Relative light unit (RLU) for each plasma sample was used to calculate the peptide concentrations in plasma (nmol/L), using parameters derived from the standard curve (RLU=Bottom+(Top−Bottom)/(1+10((log EC50−Conc)Hill slope)). Peptide concentrations in plasma were obtained and plotted against time points to obtain in vivo half-life of each peptide, using WinNonLin Phoenix software (Pharsight Corp, St. Louis, Mo.).

TABLE 5

Conjugate	Mouse T½/h	Mouse CL/ (mL/h/kg)	Cyno T½/h	Cyno CL/ (mL/h/kg)
1	9.81 ± 0.94	9.47 ± 3.09	71.9 ± 7.02	0.66 ± 0.04
2	6.6 ± 0.26	68.4 ± 10.2	49.8 ± 4.72	1.39 ± 0.27
8	11.18 ± 1.96	6.43 ± 0.39	—	—
11	8.59 ± 0.45	6.06 ± 1.8	—	—
17	8.53 ± 0.044	14.4 ± 2.03	—	—

Example C: The In Vitro Potency of the Long-Acting GLP2R Agonists to Human GLP2R

[0459] This example assessed the potency of the long-acting GLP2s on GLP2R. A decrease in the 665/615 ratio indicated an increase in free cAMP due to increased GLP2R activity.

[0460] GLP2-2G (teduglutide) was used as a positive control. As concentrations of teduglutide increased, the ratio of 665/615 decreased, indicating increased activity of GLP2R, as depicted in FIG. **1**A. Varying the concentration of GLP2-2G-10Nle-1K-EX4-K5, GLP2-2G-1-EX4-L5A and GLP2-2G-10Nle-1-EX4-L5A produced similar activity levels when compared to teduglutide. From this data, IC_{50} values were calculated as seen in Table 6. When 10% fetal bovine serum was added to the assay, the teduglutide curve became steeper than the curve of the long-acting GP2R agonists, as depicted in FIG. **1**B. The resulting IC_{50} values were higher for all three long-acting GLP2R agonists, as listed in Table 6.

TABLE 6

IC_{50} values of long-acting GLP2R agonists

	IC_{50} [nM] (no serum)		IC_{50} [nM] (serum)	
	Average	STDEV	Average	STDEV
Teduglutide	0.23	0.03	0.14	0.06
GLP2-2G-10Nle-1K-EX4-K5	0.67	0.24	5.12	1.16
GLP2-2G-1-EX4-L5A	1.18	0.31	8.46	2.53
GLP2-2G-10Nle-EX4-L5A	1.25	0.28	7.9	2.09

Example D: The In Vitro Potency of the Long-Acting GLP2R Agonists on Mouse GLP2R

[0461] To determine the potency of the long-acting GLP2R agonists against mouse GLP2R. A decrease in the 665/615 ratio indicated an increase in free cAMP due to increased GLP2R activity.

[0462] The ratio of 665 fluorescence to 615 fluorescence was plotted against the concentration of the molecule, as depicted in FIG. **2**, and this data was used to calculate the IC_{50} values, listed in Table 7. Teduglutide (GLP2-2G) and apraglutide (a synthetic GLP-2 analog) were used as positive controls. The IC_{50} values of the long-acting GLP2R agonists were found to be in similar ranges as that of both teduglutide and apraglutide, indicating that the long-acting GLP2R agonists were relatively potent agonists to the mouse GLP2R.

TABLE 7

IC_{50} values of long-acting GLP2R agonists on mouse GLP2R

mGLP-2R	IC_{50} [nM]
Teduglutide	0.07
GLP2-2G-10Nle-1K-EX4-K5	0.19
GLP2-2G-1-EX4-L5A	0.21
GLP2-2G-10Nle-1-EX4-L5A	0.30
Apraglutide	0.04

Example E: The In Vitro Potency of the Long-Acting GLP2R Agonists on Cyno Monkey GLP2R

[0463] To determine the potency of the long-acting GLP2R agonists against cyno monkey GLP2R. The ratio of 665 to 615 was plotted against the concentration in nM, as depicted in FIG. **3**, in order to determine the potency of the long-acting GLP2R agonists on cyno monkey GLP2R. The EC_{50} was calculated using the data in FIG. **3** and the values are listed in Table 8. The EC50 value for the long-acting GLP2R agonists were within a range of 0.119 nM to 0.156 nM, indicating that the long-acting GLP2R agonists were relatively potent agonists to the cyno GLP2R.

TABLE 8

EC_{50} values in cyno monkeys

	EC_{50} [nM]
Teduglutide	0.009
GLP2-2G-1-EX4-L5A	0.147
GLP2-2G-10Nle-1K-EX4-K5	0.119
GLP2-2G-10Nle-1-EX4-L5A	0.156

Example F: The Long-Acting GLP2R Agonists were Highly Selective for GLP2R Over Other G-Protein Coupled Receptors

[0464] This example assessed the effect of the stabilized GLP2R agonists on other G-protein coupled receptors (GPCRs).

[0465] A decrease in the 665/615 ratio indicated an increase in free cAMP due to increased GLP2R activity.

[0466] Neither GLP2 nor either stabilized molecule tested (GLP2-2G-10Nle-1K-EX4-K5 or GLP2-2G-10Nle-1-L5A) produced any significant change in the activity levels of GLP-1R, when compared to the change produced by varying concentrations of semaglutide, a GLP-1R agonist, as depicted in FIG. **4**A. When the IC_{50} values were calculated, as listed in Table 9, the values were extremely high when compared to semaglutide, the positive control. This indi-

cated that extremely high concentrations of GLP2 and the long-acting GLP2R agonists were required before GLP-1R was activated.

TABLE 9

IC_{50}s of stabilized GLP2R agonists on other GPCRs

	IC_{50} [nM]		
molecule	GLP-1R	GCGR	GIPR
semaglutide	0.07	—	—
glucagon	—	0.04	—
GIP	—	—	0.02
GLP-2	>500	>500	>500
GLP2-2G-10Nle-1K-EX4-K5	243.30	>500	>500
GLP2-2G-10Nle-1-L5A	>500	>500	>500

[0467] The long-acting GLP2R agonists did not result in a change in GCGR activity levels over a range of concentrations between 10^{-2} and 10^{2} nm, as depicted in FIG. **4**B. However, increasing concentrations of glucagon impacted activity levels of GCGR. While glucagon had an IC_{50} of 0.04 indicating it affected the activity levels of GCGR at lower concentrations, the IC_{50} values for GLP2 and the long-acting GLP2R agonists were greater than 500, as listed in Table 9.

[0468] The long-acting GLP2R agonists also did not result in a change in GIPR activity levels over a range of concentrations between 10^{-2} and 10^{2} nm, as depicted in FIG. **4**C. However, increasing concentrations of GIP impacted activity levels of GIPR. The IC_{50} values were calculated, as listed in Table 9. GIP had an IC_{50} of 0.04 indicating it was relatively effective at affecting the activity levels of GIPR; however, the IC_{50} values for GLP2 and the long-acting GLP2R agonists were greater than 500.

[0469] Furthermore GLP2-2G-1-EX4-L5A and GLP2-2G-10Nle-1K-EX4-K5 were profiled against the gpcrMAX Panel by DiscoverRx. 168 GPCR targets were tested with an agonist and antagonist primary screen. The assays were performed utilizing the PathHunter beta-arrestin enzyme fragment complementation (EFC) technology. In agonist mode, no targets were identified with >30% activity except for GLP2. In antagonist mode: no targets were identified with >35% inhibition.

Example G: The Stability of the Long-Acting GLP2R Agonists at Different Temperatures

[0470] This example assessed the stability of the stabilized GLP2R agonists at different temperatures over extended periods of time.

[0471] GLP2-2G-1-EX4-L5A (GLP2-L5A) and GLP2-2G-10Nle-1K-EX4-L5A (GLP2-K5) are stable at 4° C. for 4 days, as depicted in FIG. **5**A. At 25° C. 3% oxidation was observed for GLP2-2G-1-EX4-L5A, while GLP2-2G-10Nle-1K-EX4-K5 stayed reasonably intact for 4 days, as depicted in FIG. **5**B. At 37° C., 11% oxidation was observed for GLP2-2G-1-EX4-L5A and a 4% increase in the +12 Da impurity at day 2. GLP2-2G-10Nle-1K-EX4-K5 had a higher percentage of intact peptide at 4 days than GLP2-2G-1-EX4-L5A, as depicted in FIG. **5**C. At 70° C. (forced degradation), many racemized products for both peptides were present. By 4 days at 70° C., the percent of intact peptides was less than 50% for both GLP2-2G-1-EX4-L5A and GLP2-2G-10Nle-1K-EX4-K5, as depicted in FIG. **5**D.

Example H: The Stability of the Long-Acting GLP2R Agonists in Different Solutions

[0472] The stability of the compounds in different solutions at 0 hours was measured, as listed in Table 10. For both GLP2-2G-1-EX4-L5A and GLP2-2G-10Nle-1-EX4-L5A, there was no detection of the target compound at 24 hours. For GLP2-2G-10Nle-1K-EX4-K5, there was good protection in the glutathione group at 24 hours. Overall, this showed that the most stable peptide was GLP2-2G-10Nle-1-EX4-L5A and the least stable peptide was GLP2-2G-1-EX4-L5A.

TABLE 10

Stability of compounds in different solutions at 0 hours

Conditions	GLP2-2G-1-EX4-L5A	GLP2-2G-10Nle-1-EX4-L5A	GLP2-2G-10Nle-1K-EX4-K5
Peptide in PBS	High purity	High purity	High purity
+3% H_2O_2	100% degradation of the peptide	100% degradation of the peptide	100% degradation of the peptide
+3% H_2O_2 + 10 mM Met	No protection (100% degradation of the peptide)	No protection (100% degradation of the peptide)	38% degradation of the peptide
+3% H_2O_2 + 100 mM Met	No protection (100% degradation of the peptide)	Good protection - no sign of degradation	Good protection - no sign of degradation
+3% H_2O_2 + 10 mM Glutathione	92% Met oxidation - issue with solubility	Good protection - no sign of degradation	Good protection - no sign of degradation
+3% H_2O_2 + 100 mM Glutathione	92% Met oxidation	Good protection - a little degradation	Good protection - a little degradation
+3% H_2O_2 + 0.27% m-cresol	No protection (100% degradation of the peptide)	No protection (100% degradation of the peptide)	No protection (100% degradation of the peptide)
+3% H_2O_2 + 1.2 mg/mL NaMBS	92% Met oxidation	Good protection - a little degradation	Good protection - a little degradation

Example E: The Long-Term Stability of the Thioether Peptides in Liquid and in Solid Forms

[0473] The long-term stability of the thioether peptides was tested in this example.

[0474] The stability of the thioether peptides was measured against wet air oxidation. Met oxidation was observed for GLP2-2G-1-EX4-L5A after 10 days, with 16% degradation observed. GLP2-2G-10Nle-1-EX4-L5A was more stable against wet air oxidation. This indicated that the thioether bridge was stable against oxidation for at least 10 days.

[0475] The powder was stored at 4 C as an HCl salt. There was no sign of Met oxidation for GLP2-2G-1-EX4-L5A (GLP2-L5A) after 4 months. Likewise, there was no sign of Met oxidation for GLP2-2G-1-EX4-L5A (GLP2-L5A) after 7 months.

Example F: The Stability of the Long-Acting GLP2R Agonists at Different pH Values

[0476] The stability of the peptides was measured across a range of pH values and temperatures.

[0477] At pH 3.3 at room temperature, GLP2-2G-1-EX4-L5A (GLP2-L5A) was 100% stable over 4 days. GLP2-2G-10Nle-1K-EX4-K5 was also stable, with 95% of peptides remaining intact by 5 days, as depicted in FIG. **6**A. GLP2-2G-10Nle-1K-EX4-K5 and GLP2-2G-1-EX4-L5A (GLP2-L5A) were less stable at a pH of 3.3 and a temperature of 37 degrees than they were at room temperature, as depicted in FIG. **6**B. At 37° C., GLP2-2G-10Nle-1K-EX4-K5 and GLP2-2G-1-EX4-L5A (GLP2-L5A) underwent major hydrolysis at pH 3.4 (−18 Da and −775 Da). Additionally, GLP2-2G-1-EX4-L5A (GLP2-L5A) was not soluble at pH 4.6.

[0478] Both GLP2-2G-10Nle-1K-EX4-K5 and GLP2-2G-1-EX4-L5A (GLP2-L5A) were 100% stable for 4 days at pH 7.5 at room temperature, as depicted in FIG. **6**C. At 37C, GLP2-2G-10Nle-1K-EX4-K5 underwent 1-% degradation and L5A underwent 1% degradation, as depicted in FIG. **6**D. Both GLP2-2G-10Nle-1K-EX4-K5 and GLP2-2G-1-EX4-L5A (GLP2-L5A) were 100% stable for 4 days at pH 8.9 at room temperature, as depicted in FIG. **6**E. At 37° C. and a pH of 8.9, GLP2-2G-10Nle-1K-EX4-K5 underwent 1-% degradation and GLP2-2G-1-EX4-L5A (GLP2-L5A) underwent 1% degradation, as depicted in FIG. **6**F.

Example G: The Stability of the Long-Acting GLP2R Agonists in Hepatocytes

[0479] The hepatocyte stability of the long-acting GLP2R agonists was measured over time. For GLP2-2G-1-EX4-L5A, both the mouse and the MC values were slightly over 100% after 120 minutes, as depicted in FIG. **7**A. However, for both GLP2-2G-10Nle-1-EX4-L5A and GLP2-2G-10Nle-1K-EX4-K5, while the mouse values increased to slightly over 100%, the MC values decreased to approximately 60% after 120 minutes, as depicted in FIGS. **7**B-**7**C.

[0480] The biological half-lives ($T_1/2$) and the intrinsic clearance (CLint) values were calculated for each peptide from the data, as listed in Table 11. GLP2-2G-1-EX4-L5A had the highest half-life and the lowest CLint in both hepatocytes and in the liver. GLP2-2G-10Nle-1-EX4-L5A had the lowest half-life and GLP2-2G-10Nle-1-EX4-L5A had the highest CLint values in both the hepatocytes and the liver.

TABLE 11

Half-lives and CLint values in hepatocytes

Peptide	$T_{1/2}$ (min)	CLint (hep) (μL/min/10^6)	CLint (liver) (mL/min/kg)
GLP2-2G-1-EX4-L5A	>289	<4.8	<57
GLP2-2G-10Nle-1-EX4-L5A	153	9.1	107.6
GLP2-2G-10Nle-1K-EX4-K5	178	7.8	92.7

Example H: GLP2-2G-1-EX4-L5A Exhibited an Extended In Vivo Half-Life in Mouse

[0481] Male C57BL/6 mice were dosed with GLP2-2G-1-EX4-L5A at 1.5 mg/kg in PBS (pH 7.5, clear solution) and the plasma concentration of agonists was tracked for 96 hours, as depicted in FIG. **8**. Plasma concentration was analyzed using a LC-MS assay with a lower limit of quantification of 20 ng/mL. These values were also used to calculate other pharmacokinetic properties of this compound in mice, both for administration of the drug via intravenous injection and subcutaneous injection, as depicted in Table 12. A long in vivo half-life of around 8.4 hours was observed, similar to the 8-hour half-life of semaglutide in rodents.

TABLE 12

Pharmacokinetics of GLP2-Met-L5A in mice

PK Parameters	Mean IV	PK Parameters	Mean SC
C_0 (ng/mL)	28956	C_{max} (ng/mL)	12933
$T_{1/2}$ (h)	8.37	T_{max} (h)	7.00
Vd_{ss} (L/kg)	0.0966	$T_{1/2}$ (h)	11.0
Cl (mL/min/kg)	0.152	T_{last} (h)	96.0
T_{last} (h)	72.0	$AUC_{0\text{-}last}$ (ng · h/mL)	183645
$AUC_{0\text{-}last}$ (ng · h/mL)	164199	$AUC_{0\text{-}inf}$ (ng · h/mL)	184007
$AUC_{0\text{-}inf}$ (ng · h/mL)	164585	$MRT_{0\text{-}last}$ (h)	13.7
$MRT_{0\text{-}last}$ (h)	10.4	$MRT_{0\text{-}inf}$ (h)	13.9
$MRT_{0\text{-}inf}$ (h)	10.6	AUC_{Extra} (%)	0.197
AUC_{Extra} (%)	0.235	$AUMC_{Extra}$ (%)	1.59
$AUMC_{Extra}$ (%)	1.86	Bioavailability (%)[a]	112

Example I: GLP2-2G-1-EX4-L5A Exhibited an Extended In Vivo Half-Life in Cyno Monkey

[0482] Male cyno monkeys were dosed with GLP2-2G-1-EX4-L5A at 1.0 mg/kg in PBS (pH 7.5, clear solution) and the plasma concentration of agonists tracked for 504 hours, as depicted in FIG. **9** Pharmacokinetic properties of GLP2-2G-1-EX4-L5A were analyzed for drug delivers via an IV and via a subcutaneous injection, as listed in Table 13. Plasma concentration was analyzed using a LC-MS assay with a lower limit of quantification of 10 ng/mL. A long in vivo half-life of approximately 70 hours was observed, longer than the approximately 50-hour half-life of semaglutide in monkey. This long in vivo half-life indicated that potential translation into once-weekly human dosing may be possible.

TABLE 13

Pharmacokinetic properties of GLP2-2G-1-EX4-L5A in cyno monkeys

PK Parameters	Mean IV	SD	PK Parameters	Mean SC	SD
C_0 (ng/mL)	34845	2087	C_{max} (ng/mL)	12100	1652
$T_{1/2}$ (h)	68.7	8.05	T_{max} (h)	9.00	1.73
Vd_{ss} (L/kg)	0.0551	0.00244	$T_{1/2}$ (h)	71.9	7.02
Cl (mL/min/kg)	0.0110	0.000748	T_{last} (h)	504	—
T_{last} (h)	504	—	$AUC_{0\text{-}last}$ (ng · h/mL)	1102126	157113
$AUC_{0\text{-}last}$ (ng · h/mL)	1507007	103313	$AUC_{0\text{-}inf}$ (ng · h/mL)	1109413	158218
$AUC_{0\text{-}inf}$ (ng · h/mL)	1514090	105816	$MRT_{0\text{-}last}$ (h)	90.0	4.40
$MRT_{0\text{-}last}$ (h)	80.8	2.53	$MRT_{0\text{-}inf}$ (h)	93.4	3.07
$MRT_{0\text{-}inf}$ (h)	83.2	3.31	AUC_{Extra} (%)	0.658	0.252
AUC_{Extra} (%)	0.462	0.147	$AUMC_{Extra}$ (%)	4.34	1.80
$AUMC_{Extra}$ (%)	3.33	1.01	Bioavailability (%)[a]	73.3	—

Example J: GLP2-2G-10Nle-1-EX4-L5A Exhibited a Long In Vivo Half-Life in Mice

[0483] Male C57BL/6 mice were dosed with GLP2-2G-10Nle-1-EX4-L5A at a concentration of 1.5 mg/kg in PBS (pH 7.5), either subcutaneously (SC) or intravenously (IV). The plasma concentration of agonists was tracked for 96 hours after administration of the drug, as depicted in FIG. **10**. Plasma concentration was analyzed using a LC-MS assay with a lower limit of quantification of 5 ng/mL. The pharmacokinetic properties of the drug in mice, including the half-life, was calculated from this data and values are listed in Table 14. A long in vivo half-life of approximately 8 hours was observed for this drug in mice.

TABLE 14

Pharmacokinetic properties of GLP2-2G-10Nle-1-EX4-L5A in mice

PK Parameters	Mean IV	PK Parameters	Mean SC
C_0 (ng/mL)	40492	C_{max} (ng/mL)	8963
$T_{1/2}$ (h)	8.07	T_{max} (h)	7.0
Vd_{ss} (L/kg)	0.0823	$T_{1/2}$ (h)	7.97
Cl (mL/min/kg)	0.129	T_{last} (h)	96
T_{last} (h)	96.0	$AUC_{0\text{-}last}$ (ng · h/mL)	153773
$AUC_{0\text{-}last}$	193243	$AUC_{0\text{-}inf}$	153830

TABLE 14-continued

Pharmacokinetic properties of GLP2-2G-10Nle-1-EX4-L5A in mice

PK Parameters	Mean IV	PK Parameters	Mean SC
(ng · h/mL)		(ng · h/mL)	
$AUC_{0\text{-}inf}$ (ng · h/mL)	193309	$MRT_{0\text{-}last}$ (h)	14.3
$MRT_{0\text{-}last}$ (h)	10.6	$MRT_{0\text{-}inf}$ (h)	14.3
$MRT_{0\text{-}inf}$ (h)	10.6	AUC_{Extra} (%)	0.0369
AUC_{Extra} (%)	0.034	$AUMC_{Extra}$ (%)	0.277
$AUMC_{Extra}$ (%)	0.345	Bioavailability (%)[a]	79.6

Example K: GLP2-2G-10Nle-1-EX4-L5A Exhibited an Extended Half-Life in Cyno Monkeys

[0484] Male cyno monkeys were dosed with GLP2-2G-10Nle-1-EX4-L5A at a concentration of 1.0 mg/kg in PBS (pH 7.5), either subcutaneously (SC) or intravenously (IV). The plasma concentration of agonists was tracked for 504 hours after administration of the drug, as depicted in FIG. **11**. Plasma concentration was analyzed using a LC-MS assay with a lower limit of quantification of 5 ng/mL. The pharmacokinetic properties of the drug in monkeys, including the half-life, was calculated from this data, and values are listed in Table 15. A long in vivo half-life of approximately 57 hours was observed for this drug in monkeys.

TABLE 15

Pharmacokinetic properties of GLP2-2G-10Nle-1-EX4-L5A in cyno monkeys

PK Parameters	Mean IV	SD	PK Parameters	Mean SC	SD
C_0 (ng/mL)	30072	203	C_{max} (ng/mL)	9313	783
$T_{1/2}$ (h)	57.2	7.89	T_{max} (h)	14.7	8.08
Vd_{ss} (L/kg)	0.0784	0.00189	$T_{1/2}$ (h)	49.8	4.72
Cl (mL/min/kg)	0.0231	0.00446	T_{last} (h)	504	—
T_{last} (h)	504	—	$AUC_{0\text{-}last}$ (ng · h/mL)	696366	72381
$AUC_{0\text{-}last}$ (ng · h/mL)	737816	129904	$AUC_{0\text{-}inf}$ (ng · h/mL)	696916	72842
$AUC_{0\text{-}inf}$ (ng · h/mL)	738632	130076	$MRT_{0\text{-}last}$ (h)	66.5	5.12
$MRT_{0\text{-}last}$ (h)	57.2	8.94	$MRT_{0\text{-}inf}$ (h)	66.9	5.41
$MRT_{0\text{-}inf}$ (h)	57.8	8.94	AUC_{Extra} (%)	0.0751	0.0576
AUC_{Extra} (%)	0.110	0.0165	$AUMC_{Extra}$ (%)	0.626	0.436
$AUMC_{Extra}$ (%)	1.14	0.247	Bioavailability (%)[a]	94.4	—

Example L: GLP2-2G-10Nle-1K-EX4-K5 Exhibited a Long In Vivo Half-Life in Mice

[0485] Male C57B3L/6 mice were dosed with GLP2-2G-10Nle-1K-EX4-K5 at a concentration of 1.5 mg/kg in PBS (pH 7.5), either subcutaneously (SC) or intravenously (IV). The plasma concertation of agonists was tracked for 72 hours after administration of the drug, as depicted in FIG. **12**. Plasma concentration was analyzed using a LC-MS assay with a lower limit of quantification of 5 ng/mL. The pharmacokinetic properties of the drug in mice, including the half-life, was calculated from this data, and values are listed in Table 16. A long in vivo half-life of approximately 7 hours was observed for this drug in mice.

TABLE 16

Pharmacokinetic properties of GLP2-2G-10Nle-1K-EX4-K5 in mice

PK Parameters	Mean IV	PK Parameters	Mean SC
C_0 (ng/mL)	24574	C_{max} (ng/mL)	6760
$T_{1/2}$ (h)	7.16	T_{max} (h)	7.0
Vd_{ss} (L/kg)	0.102	$T_{1/2}$ (h)	7.54
Cl (mL/min/kg)	0.173	T_{last} (h)	72.0
T_{last} (h)	72.0	$AUC_{0\text{-}last}$ (ng · h/mL)	104199
$AUC_{0\text{-}last}$ (ng · h/mL)	144060	$AUC_{0\text{-}inf}$ (ng · h/mL)	104404
$AUC_{0\text{-}inf}$ (ng · h/mL)	144210	$MRT_{0\text{-}last}$ (h)	12.3
$MRT_{0\text{-}last}$ (h)	9.71	$MRT_{0\text{-}inf}$ (h)	12.5
$MRT_{0\text{-}inf}$ (h)	9.79	AUC_{Extra} (%)	0.196
AUC_{Extra} (%)	0.104	$AUMC_{Extra}$ (%)	1.3
$AUMC_{Extra}$ (%)	0.875	Bioavailability (%)[a]	72.4

Example M: GLP2-2G-10Nle-1K-EX4-K5 Exhibited an Extended Half-Life in Cyno Monkeys

[0486] Male cyno monkeys were dosed with GLP2-2G-10Nle-1K-EX4-K5 at a concentration of 1.0 mg/kg in PBS (pH 7.5), either subcutaneously (SC) or intravenously (IV). The plasma concentration of agonists was tracked for 504 hours after administration of the drug, as depicted in FIG. **13**. Plasma concentration was analyzed using a LC-MS assay with a lower limit of quantification of 5 ng/mL. The pharmacokinetic properties of the drug in monkeys, including the half-life, was calculated from this data, as listed in Table 17. A long in vivo half-life of approximately 36 hours was observed for this drug in monkeys.

TABLE 17

Pharmacokinetic properties of GLP2-2G-10Nle-1K-EX4-K5 in cyno monkeys

PK Parameters	Mean IV	SD	PK Parameters	Mean SC	SD
C_0 (ng/mL)	27532	4270	C_{max} (ng/mL)	7037	626
$T_{1/2}$ (h)	35.7	1.09	T_{max} (h)	14.7	8.08
Vd_{ss} (L/kg)	0.0723	0.00438	$T_{1/2}$ (h)	31.0	2.5
Cl (mL/min/kg)	0.0294	0.00532	T_{last} (h)	336	—
T_{last} (h)	336	—	$AUC_{0\text{-}last}$ (ng · h/mL)	420263	21246
$AUC_{0\text{-}last}$ (ng · h/mL)	577542	97811	$AUC_{0\text{-}inf}$ (ng · h/mL)	420590	21369
$AUC_{0\text{-}inf}$ (ng · h/mL)	578146	98047	$MRT_{0\text{-}last}$ (h)	48.7	4.79
$MRT_{0\text{-}last}$ (h)	41.2	4.65	$MRT_{0\text{-}inf}$ (h)	48.9	4.88
$MRT_{0\text{-}inf}$ (h)	41.5	4.75	AUC_{Extra} (%)	0.0768	0.0257
AUC_{Extra} (%)	0.101	0.0367	$AUMC_{Extra}$ (%)	0.590	0.140
$AUMC_{Extra}$ (%)	0.932	0.271	Bioavailability (%)[a]	72.7	—

Example N: GLP2-L5A Produced Intestinotrophic Effects in Mice

[0487] 13 week old female CD1 mice were divided into 5 treatment groups as listed: A (Vehicle PBS, SC, QD), B (GLP-C14, 0.05 mg/kg, BID), C (GLP2-2G-1-EX4-L5A, 0.1 mg/kg, QD), D (GLP2-2G-1-EX4-L5A, 1 mg/kg, QD), E (GLP2-2G-10Nle-1-EX4-L5A, 0.1 mg/kg, QD), and F (GLP2-2G-10Nle-1-EX4-L5A, 1 mg/kg, QD). 5 mice were in each group. The mice were administered the relevant dose subcutaneously either daily (QD) or twice a day (BID) using DPBS as the vehicle in a volume of 5 mL/kg and then monitored daily for bodyweight,

[0488] At 10 days after administration of the dose, GI tract measurements were collected. These measurement included collecting terminal bleed; dissecting out the small intestine; and measuring the length and weight of the small intestine; recording the length and weight of the empty large intestine.

[0489] There was a significant increase in the weight of the small intestine in treated mice that received a dose of at least 0.1 mg/kg of either long-acting GLP2R agonist (groups C-F) when compared to untreated mice (group A), as depicted in FIG. **14**A. The length of the small intestine was increased in all mice that received long-acting GLP2R agBonist treatment when compared to untreated mice (group A), and significantly increased in mice that received a treatment of 0.1 mg/kg of GLP2-2G-5-L5A (group E), as depicted in FIG. **14**B. No treatment groups produced a significant change in bodyweight over 10 days, as depicted in FIG. **14**C.

Example O: GLP2-2G-10Nle-1-EX4-L5A was Effective in Treating a Mouse Model of Acute Colitis

[0490] This example assessed the intestinotrophic effects of GLP2-2G-10Nle-1-Ex4-L5A in mice.

[0491] 7-8 week old male C57B6 mice were grouped into 6 experimental groups: A (Vehicle PBS, QD); B (teduglutide, 0.5 mg/kg, BID); C (GLP2-2G-10Nle-1K-EX4-K5, 0.03 mg/kg, QD); D (GLP2-2G-10Nle-1K-EX4-K5, 0.1 mg/kg, QD); E (GLP2-2G-10Nle-1K-EX4-K5, 0.3 mg/kg, QD); and F (GLP2-2G-10Nle-1K-EX4-K5, 1 mg/kg, QD). Each treatment group contained 6 mice, except for group A, which contained 4. Mice were administered the treatment subcutaneously either once daily (QD) or twice daily (BID), using FPBS as a vehicle with a dosing volume of 5 mL/kg. Bodyweight was monitored daily and after 10 days of dosing, GI tract measurements were collected. These mea-

surement included collecting terminal bleed; dissecting out the small intestine; measuring the length and weight of the small intestine; and recording the length and weight of the empty large intestine.

[0492] As depicted in FIGS. **15**C-**15**D, all treatment groups (B-F) resulted in a significant increase in small intestine lengths and weights when compared to control groups. Even the lowest dose of GLP2-2G-10Nle-1K-EX4-K5, at 0.03 mg/kg (group C), produced significant effects on both measurements of the small intensive. Furthermore, the 0.1 mg/kg dose of GLP2-2G-10Nle-1-EX4-K5 (group D) showed comparable effects to treatment with teduglutide at 0.5 mg/kg (group B).

[0493] Mice that received high doses of GLP2-2G-10Nle-1-EX4-K5 (groups E-F), showed significant increases in the length of the colon when compared to untreated controls (group A). All treatment groups showed a significant increase in colon weight when compared to untreated controls. However, the mice in groups E and F treated with the highest doses of GLP2-2G-10Nle-1-EX4-K5 showed the greatest increase.

Example P: GLP2-2G-1-EX4-L5A was Effective in Treating a Mouse Model of Acute Colitis

[0494] Acute colitis was induced in mice by a single 5-day treatment course with 3% dextran sodium sulfate (DSS). Mice were divided into 4 treatments groups as listed: A (control mice that received no DSS), B (mice that received DSS and a subcutaneous injection of PBS), C (mice that received DSS and a 1 mg/kg subcutaneous treatment of GLP2-2G-1-EX4-L5), and D (mice that received DSS and a intraperitoneal treatment of 20 mg·kg of cyclosporin).

[0495] The body weight was measured over 12 days, as depicted in FIG. **16**A. Mice that received treatment for acute colitis (groups C and D) did not have as great of a decrease in bodyweight when compared to untreated mice with induced colitis (group B). Additionally, mice in group C treated with GLP2-2G-1-EX4-L5A showed a significant increase in both colonic and small intestinal weight, as depicted in FIGS. **16**B-**16**C, compared to untreated mice with induced acute colitis (group B). Mice that were treated with GLP2-2G-1-EX4-L5A also showed significant increases in the length of both the colon and the small intestine when compared to untreated controls with induced acute colitis (figure not shown). Treatment with GLP2-2G-1-EX4-L5A also improved the colon and small intestine histopathology in the DSS-induced colitis model. The histopathology of mice that received both DSS and L5A showed a similar crypt depth in the colon as mice that did not received DSS treatment, while mice that received only DSS had a significant reduction in crypt length, as depicted in FIG. **16**D. In the jejunal small intestine, the length of jejunum villi was greater in group C mice than in either group A or group B mice, as depicted in FIG. **16**E. There was a significant increase in the length of the jejunum villi when comparing mice treated with GLP2-2G-1-EX4-L5A to untreated mice. Additionally, the group C mice did not show the villous distortion and abscesses exhibited by the group B mice.

Example Q: GLP2-2G-10Nle-1K-EX4-K5 was Effective in Treating a Mouse Model of Acute Colitis

[0496] 8 week old male C57BL/6 mice were divided into 7 treatments groups as listed: A (control mice that received no DSS), B (mice that received DSS and a subcutaneous injection of PBS), C (mice that received DSS and a 0.1 mg/kg subcutaneous treatment of GLP2-2G-10Nle-1K-EX4-K5), D (mice that received DSS and a 0.3 mg/kg subcutaneous treatment of GLP2-2G-10Nle-1K-EX4-K5, E (mice that received DSS and a 1 mg/kg subcutaneous treatment of GLP2-2G-10Nle-1K-EX4-K5), F (mice that received DSS and a 0.5 mg/kg subcutaneous treatment of teduglutide), and G (mice that received DSS and a IP treatment of 20 mg·kg of cyclosporin). Each group contained 6 mice, except for group A, which contained 4.

[0497] Acute colitis was induced in the mice by a single 5-day treatment course with 3% dextran sodium sulfate (DSS), as depicted in FIG. **17**A. The animals were treated daily for 11 days with the appropriate dose per treatment group. The body weight was monitored daily. If animals lost more than 20% of their bodyweight, they were euthanized. On days 10-11, samples were collected for pharmacokinetic analysis at 0, 1, 3, 7 and 24 hours after the dose was administered. On day 11, animals were euthanized, and a necropsy was performed. The terminal bleed was collected into a heparinized collection tube and processed into plasma. The small intestine and colon were collected to measure weight and length. GI tissues were collected for histology.

[0498] When examining bodyweight over time, as depicted in FIG. **17**A, mice in group G treated with cyclosporine showed a greater percent decrease in bodyweight during the DSS treatment than mice in any other treatment groups, but bodyweight increased after DSS treatment ended. Mice that received DSS and no treatment (group B) showed the greatest percent decrease in bodyweight after DSS treatment had ended when compared to all other treatment groups. Mice that had been treated with either GLP2-2G-10Nle-1K-EX4-K5 (groups C-E) or with teduglutide (group F), along with mice that did not received DSS (group A) did not exhibit significant changes in bodyweight during this time.

[0499] Treatment with GLP2-2G-10Nle-1K-EX4-K5 protected the mice both from loss of bodyweight and restored colon shortening. As shown in FIG. **17**B, Colon length was significantly increased in mice that received high doses of GLP2-2G-10Nle-1K-EX4-K5 or teduglutide (groups D-F), compared to untreated groups (group B). There was no change in colon weight. In the small intestine, both the length and weight were significantly increased in groups that had received either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 (groups C-F) compared to untreated mice, as depicted in FIGS. **17**C-**17**D. The lowest dose of GLP2-2G-10Nle-1K-EX4-K5at 0.1 mg/ml (group C), showed comparable effects to teduglutide at 0.5 mg/kg BID.

[0500] Treatment with GLP2-2G-10Nle-1K-EX4-K5 also affected the histological features of the intestines. All teduglutide and GLP2-2G-10Nle-1K-EX4-K5 treatment groups (groups C-F) showed a significant increase in villus height compared to untreated mice (groups A-B), as seen in FIG. **17**E. The lowest dose of GLP2-2G-10Nle-1K-EX4-K5, 0.1 mg/kg, administered once daily, showed comparable intestinotrophic effects to Teduglutide at 0.5 mg/kg, administered twice daily. Furthermore, Ki67 staining showed that there was no increased proliferation in any of the treatment groups, as depicted in FIG. **17**F. This showed that there was no evidence of abnormal proliferation associated with GLP2-2G-10Nle-1K-EX4-K5 treatment.

[0501] The pharmacokinetic properties of treatment groups C-F are plotted in FIG. **17**G. Teduglutide was not detectable after 3 hours post treatment. However, all doses of GLP2-2G-10Nle-1K-EX4-K5 were detectable at up to 24 hours after treatment.

Example R: The Long-Acting GLP2R Agonists were Effective in Treating Acute Colitis

[0502] Mice were divided into 9 treatment groups as listed: A (Non-DSS: Vehicle), B (DSS: Vehicle (PBS)), C (DSS: GLP2-2G-1-EX4-L5A, 0.03 mg/kg), D (DSS: GLP2-2G-1-EX4-L5A, 0.1 mg/kg), E (DSS: GLP2-2G-10Nle-1-EX4-L5A, 0.03 mg/kg), F (DSS: GLP2-2G-10Nle-1-EX4-L5A, 0.1 mg/kg), G (DSS: GLP2-2G-10Nle-1K-EX4-K5, 0.03 mg/kg), H (DSS: GLP2-2G-10Nle-1K-EX4-K5, 0.1 mg/kg), and I (DSS: Cyclosporine A, 20 mg/kg, IP). Each group contain 6 C57BL/6 male mice aged 8 weeks. Mice were dosed with 3% DSS for 7 days and concurrently dosed with the appropriate treatment for 8 days to induce acute colitis. The animals were all dosed subcutaneously using a volume of 5 ml/kg and a vehicle of DPBS, with the except of group I, where the vehicle was olive oil. At days 6-7, pharmacokinetic samples were collected from groups C—H at 0, 1, 3, 7 and 24 hours after dosing. Measurements were taken at day 9. These measurement included collecting the terminal bleed; dissecting out the small intestine; measuring the length and weight of the small intestine; and recording the length and weight of the empty large intestine.

[0503] All long-acting GLP-2 agonists showed a dose-related protection from body weight loss compared to untreated animals, and this protection was significant at a dose of 0.1 mg/kg. As depicted in FIG. **18**A, animals treated with either dose of GLP2-2G-10Nle-1-Ex4-L5A (groups C, D) had a greater overall bodyweight than those who received no treatment (group B). As depicted in FIG. **18**B, animals treated with either dose of GLP2-2G-1-EX4-L5A (groups E,F) had a greater overall bodyweight than those who received no treatment (group B). As depicted in FIG. **18**C, animals treated with either dose of GLP2-2G-10Nle-1K-Ex4-K5A (groups G,H) had a greater overall bodyweight than those who received no treatment (group B). Furthermore, at a dose of 0.03 mg/kg, GLP2-2G-10Nle-1-Ex4-L5A and GLP2-2G-10Nle-1K-Ex4-K5 were more effective at protecting from bodyweight loss than GLP2-2G-1-EX4-L5A.

[0504] All 3 long acting-GLP-2 agonists increased colon length significantly in the acute DSS-induced colitis model at 0.1 mg/kg, as depicted in FIG. **18**D. Furthermore, there was a non-significant increasing trend on colon weight when comparing animals treated with long-acting GLP2 agonists to the untreated DSS animals, as depicted in FIG. **18**E. Furthermore, all 3 long-acting GLP2 agonists showed dose-related trophic effects on both the weight and length of the small intestine, as depicted in FIGS. **18**F-**18**G.

[0505] Treatment with GLP2R agonists also increased the size of the gall bladder, as depicted in FIG. **18**H. Additionally, the quantity of fecal occult blood was measured using a hemoccult II test, as depicted in FIG. **18**I. Several treatment parameters, such as both doses of 1L5A, decreased the hemoccult levels compared to the untreated DSS model mice.

[0506] The levels of the long-acting GLP2 agonists were measured over time. At doses of 0.03 mg/kg, the concentrations increased until 7 hours after administration but were still detectable at 24 hours after administration, as depicted in FIG. **18**J. At doses of 0.1 mg/kg, the concentrations increased until 7 hours after administration and were still detectable at 24 hours after administration, as depicted in FIG. **18**K. For both doses, GLP2-2G-1-EX4-L5A had the highest levels present, followed by GLP2-2G-10Nle-1-Ex4-L5A, then GLP2-2G-10Nle-1K-Ex4-K5. For all three drugs tested, the higher dose resulted in higher concentrations of the drug present at all tested time points, as depicted in FIGS. **18**L-**18**N.

[0507] Significant reduction of mRNA level for inflammatory cytokines was observed in colon tissues.

Example S: GLP2-2G-1-EX4-L5A was Effective in Treating Chronic Colitis

[0508] Chronic DSS-induced colitis was induced in C57BL/6 mice (male, age 10-12 weeks) by 3 cycles of administration of 2.5% DSS in drinking water for 5 consecutive days, followed by 7 days of recovery. Animals were treated daily for 7 days during the last DSS-induction cycle. Treatment was administered either subcutaneously (S) or intraperitoneally (IP) either once daily (QD) or twice daily (BID). Mice were treated according to their treatment groups as listed: A (Non-DSS: Vehicle, SC, QD (n=6)), B (DSS: Vehicle (PBS), SC, QD (n=8)), C (DSS: GLP2-2G-1-EX4-L5A, 0.1 mg/kg, SC, QD (n=8)), D (DSS: GLP2-2G-1-EX4-L5A, 0.3 mg/kg, SC, QD (n=8)), E (DSS: Cyclosporin, 20 mg/kg, IP (n=6)), and F (DSS: Teduglutide, 0.3 mg/kg, SC, QD (n=6).

[0509] Bodyweight was monitored 3 times a week. Pharmacokinetic collection occurred 3 and 4 days prior to necropsy. At day 33, a necropsy was performed, and measurements were taken. These measurement included collecting terminal bleed; dissecting out the small intestine; measuring the length and weight of the small intestine; and recording the length and weight of the empty large intestine.

[0510] GLP2-2G-1-EX4-L5A was effective in treating weight loss in a mouse model of chronic colitis. The mice which were treated with GLP2-2G-1-EX4-L5A or teduglutide (groups C, D and F) did not show the same loss in percent of bodyweight or in overall bodyweight as seen in untreated mice (group B), as depicted in FIG. **19**A. The protection from bodyweight loss was dose dependent, with the higher dose resulting in increased protection. Additionally, these effects were equivalent to teduglutide treatment at 0.3 mg/kg, QD.

[0511] GLP2-2G-1-EX4-L5A showed a dose-related restoration of colon length when compared to mice that received no treatment, as depicted in FIG. **19**B. Furthermore, when comparing the 0.3 mg/kg GLP2-2G-1-EX4-L5A treatment to the equivalent dose of teduglutide, the effects of GLP2-2G-1-EX4-L5A were less variable than the effects of teduglutide treatment. Colon weight was also affected by GLP2-2G-1-EX4-L5A and teduglutide treatment, as seen in FIG. **19**C. Mice treated with the low dose of GLP2-2G-1-EX4-L5A has a similar colon weight as those treated with teduglutide.

[0512] The higher dose of GLP2-2G-1-EX4-L5A showed a significant increase in small intestinal weight compared to mice that received no treatment, as depicted in FIG. **19**D. This effect was equivalent to the effect produced by teduglutide.

Example T: GLP2-2G-10Nle-1-Ex4-L5A was Effective in Treating a Mouse Model of Chronic Colitis

[0513] Chronic DSS-induced colitis was induced in C57BL/6 mice (male, age 10-12 weeks) by 3 cycles of administration of 2.5% DSS in drinking water for 5 consecutive days, followed by 7 days of recovery. Animals were treated daily for 7 days during the last DSS-induction cycle. Treatment was administered either subcutaneously (S) or intraperitoneally (IP) either once daily (QD) or twice daily (BID). Mice were treated according to their treatment groups as listed: A (Non-DSS: Vehicle, SC, QD (n=4)), B (DSS: Vehicle (PBS), SC, QD (n=6)), C (DSS: GLP2-2G-10Nle-1-L5A, 0.03 mg/kg, SC, QD (n=6)), D (DSS: GLP2-2G-10Nle-1-L5A, 0.1 mg/kg, SC, QD (n=6)), E (DSS: GLP2-2G-10Nle-1-L5A, 0.3 mg/kg, SC, QD (n=6)), F (DSS: GLP2-2G-10Nle-1-L5A, 1 mg/kg, SC, QD (n=6)), and G (DSS: Teduglutide, 0.5 mg/kg, SC, BID (n=6)).

[0514] Bodyweight was monitored 3 times a week. Pharmacokinetic collection occurred 3 and 4 days prior to necropsy. At day 33, a necropsy was performed, and measurements were taken. These measurement included collecting terminal bleed; dissecting out the small intestine; measuring the length and weight of the small intestine; and recording the length and weight of the empty large intestine.

[0515] Low doses of GLP2-2G-10Nle-1-Ex4-L5A showed modest effects on body weight loss. Treatment with doses of 0.03 mg/kg and 0.3 mg/kg was protective against bodyweight loss when compared to mice that received no treatment. (figure not shown).

[0516] GLP2-2G-10Nle-1-Ex4-L5A increased both colon length and weight in a chronic DSS-induced colitis model, as depicted in FIGS. **20**A-**20**B. Colon length was significantly increased in animals treated with GLP2-2G-10Nle-1-Ex4-L5A at doses of 0.1 mg/kg and higher, as well as animals treated with teduglutide (groups D-G), when compared to untreated animals (group B). Colon weight was increased in animals treated with GLP2-2G-10Nle-1-Ex4-L5A at doses of 0.3 mg/kg or higher, as well as in animals treated with teduglutide, compared to untreated animals.

[0517] GLP2-2G-10Nle-1-Ex4-L5A also significantly affected the small intestine weight and length. Treatment with GLP2-2G-10Nle-1-Ex4-L5A at doses of 0.1 mg/kg and higher, as well as treatment with teduglutide, resulted in significant increases in small intestine length compared to untreated mice models, as depicted in FIG. **20**C. Treatment with GLP2-2G-10Nle-1-Ex4-L5A at doses of 0.3 mg/kg or higher resulted in significant increases in small intestine weight compared with untreated mice (not depicted).

Example U: GLP-2-2G-5-L5A Treatment in a NASH Model

[0518] 5-week-old C57BL/6 mice were place on either a choline-deficient diet (CDAA, Dyets #518753) or an AA supplemented control diet (CSAA, Dyets #518754) for a total of 19 weeks. Mice were divided into 3 treatment groups, with 8 mice per group, as listed: a CSAA control diet, treated with vehicle only; a CDAA diet treated with vehicle (MCT, PO; saline, SC); and a CDAA diet treated with 1 mg/kg subcutaneously of GLP2-2G-5-EX4-L5A. After 15 weeks, the mice were treated with either vehicle or compounds for 4 weeks. Body weight was monitored weekly during the diet induction phase and 3 times a week during the treatment phase. After 19 weeks, the animals were euthanized, and terminal blood and liver samples were harvested for serum panels, histology, and gene expression.

[0519] Chronic treatment with GLP2-2G-5-EX4-L5A improved markers of liver function. In mice that had been fed a choline-deficient diet, there was a significant decrease in both serum ALT and serum AST compared to untreated mice on the same diet, as depicted in FIGS. **21**A-**21**B. Total serum bilirubin was also decreased in mice that had received GLP2-2G-5-EX4-L5A treatment compared to untreated mice with the same diet. The gall bladder was enlarged in 7/8 of GLP-2 treated mice. Treatment with GLP2-2G-5-EX4-L5A resulted in a 20% decrease in the liver fibrosis score, as depicted in FIG. **21**C. Collagen deposition/fibrosis was observed with picrosirius red and was graded for severity using the following scale: 0=absent; 1=minimal; 2=mild; 3=moderate; 4=marked; and 5=severe. There were no significant effects on body weight with this treatment, indicating that the treatment was tolerated.

[0520] The effects of this treatment on hepatic steatosis and inflammation were also analyzed. Steatosis was analyzed by the percent of hepatocyte vacuolization determined by crisp, round, non-staining lipid vacuoles and assigned a grade based on the listed scale: 0 indicates less than 5%; 1 indicates 5-33%; 2 indicates 33-66%; and 3 indicates greater than 66%. Treatment with GLP2-2G-5-EX4-L5A did not significantly affect the steatosis grade in the liver, as depicted in FIG. **21**D. Lobular inflammation was analyzed by assessment of inflammatory foci for infiltrates of neutrophils, lymphocytes and macrophages. Lobular inflammation was scored using the following scale: 0 indicates no foci; 1 indicates 2 foci/200× field; 2 indicates 2-4 foci/200× field; and 3 indicates more than 4 foci/200× field. Treatment with GLP-2-2G-5-L5A decreased the levels of lobular inflammation compared to untreated animals on the CDAA diet, as depicted in FIG. **21**E.

[0521] This example showed that treatment with GLP2-2G-5-EX4-L5A improved markers of liver injury and prevented worsening of liver fibrosis in a CDAA-NASH model.

Example V: Long-Acting GLP2 Agonists Treat a Mouse Model of Environmental Enteric Dysfunction (EED)

[0522] A weaning undernutrition model was used to assess the ability of GLP2-2G-10Nle-1K-EX4-K5 to treat environmental enteric dysfunction (EED). All dams were placed on an isocaloric Northeast Brazil (Regional Basic Diet—RBD), which was moderately deficient in protein, fat and minerals when their pups were 10 days old. At weaning (3 weeks of age), pups were placed on either a standard control diet (CD) or continued on RBD. At 4 weeks of age, weanlings were given drug or placebo (0.1 mg/kg formulated in PBS (vehicle)) once a day subcutaneously for 2-3 weeks. Bodyweight and food consumption were measured twice weekly. Stool was collected at weaning, 6 weeks of age, and 8 weeks of age for calorimetry and microbiome. Oral FITC-dextran was used as a measurement of barrier function. At 6 weeks of age, mice were euthanized, and jejunal tissue was collected for morphology, immunohistochemistry, and for chamber analysis of transmucosal resistance and permeability. There were trends towards greater weight gain in both male and female RBD mice weaned to CD and treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5, as depicted in FIG. **22**A-**22**B. However, male and female mice

weaned to RBD showed trends towards worsening weight when administered teduglutide or long-acting GLP2 agonist, as depicted in FIG. **22**C-**22**D.

[0523] Treatment with both teduglutide and long-acting GLP2 agonists had profound effects on intestinal wet weights and lengths. CD males treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 showed a significant increase in the small intestine wet body weight/body weight compared to untreated males, as depicted in FIG. **22**E. CD females treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 showed a significant increase in the small intestine wet body weight/body weight compared to untreated females, as depicted in FIG. **22**F. Furthermore, treatment with GLP2-2G-10Nle-1K-EX4-K5 also resulted in a significant increase when compared to treatment with teduglutide. RBD males treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 showed a significant increase in the small intestine wet body weight/body weight compared to untreated males. In RBD females, only animals treated with GLP2-2G-10Nle-1K-EX4-K5 showed a significant increase in the small intestine wet weight/bodyweight compared to that of untreated animals.

[0524] For both animals weaned to a CD diet and animals weaned to an RBD diet, treatment with either GLP2 or teduglutide resulted in a significant increase in the length of the small intestine when compared to that of untreated animals.

[0525] Treatment with GLP2-2G-10Nle-1K-EX4-K5 also had intestinotrophic effects on the animals. CD males treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 had significantly longer villus heights than untreated males. CD females treated with GLP2-2G-10Nle-1K-EX4-K5 also had significantly longer villus lengths than untreated females. The crypt depth of treated and untreated CD animals. Males treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 had longer crypt depths than untreated males.

[0526] The intestinal permeability was also measured in these mice, where the greater the FITC-dextran relative fluorescence, the greater the intestinal permeability. CD males treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 showed a trend towards decreased permeability in treated mice compared to untreated mice. CD females treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 showed a significant decreases in permeability when compared to untreated CD female mice. Treatment with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 did not significantly affect the permeability of either RBD females or RBD males when compared to untreated mice.

[0527] Untreated CD mice showed higher levels of intestinal permeability than untreated RBD mice. CD and RBD mice had similar overall levels of permeability when treated with teduglutide. Female might had slightly high levels of permeability when treated with GLP2-2G-10Nle-1K-EX4-K5 when compared to male mice on the same diet.

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Asp Pro Ser Ser Gly Ala Pro Pro Pro Ser
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35 40

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Asp Pro Ser Ser Gly Ala Pro Pro Pro Ser
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Asp

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Asp


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Asp


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Asp


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20 25 30

Asp

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Lys Ala Ala Arg Asp Phe Ile Lys Trp Leu Ile Gln Thr Lys Ile Thr
20 25 30

Asp

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His Gly Asp Gly Ser Phe Ser Asp Glu Leu Asn Ser Leu Leu Asp Asn
1 5 10 15

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Lys Ala Ala Arg Asp Phe Ile Lys Trp Leu Ile Gln Thr Lys Ile Thr
20 25 30

Asp

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His Gly Asp Gly Ser Phe Ser Asp Glu Leu Asn Thr Ala Leu Asp Asn
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Lys Ala Ala Arg Asp Phe Ile Lys Trp Leu Ile Gln Thr Lys Ile Thr
20 25 30

Asp

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Lys Ala Ala Arg Asp Phe Ile Lys Trp Leu Ile Gln Thr Lys Ile Thr
20 25 30

Asp

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Lys Ala Ala Arg Asp Phe Ile Lys Trp Leu Ile Gln Thr Lys Ile Thr
20 25 30

Asp

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20 25 30

Asp

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20 25 30

Asp

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Asp

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Asp

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His Gly Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp Asn
1 5 10 15

Xaa Ala Ala Arg Asp Phe Ile Xaa Trp Leu Ile Gln Thr Lys Ile Thr
20 25 30

Asp

What is claimed is:

1. A peptide conjugate comprising:

a) a peptide that modulates the GLP-2 receptor; and

b) a staple attached to the peptide at a first amino acid and a second amino acid.

2. The peptide conjugate of claim **1**, wherein the first amino acid and the second amino acid are independently an amine-containing amino acid or a sulfhydryl-containing amino acid.

3. The peptide conjugate of claim **1** or **2**, wherein the first amino acid and second amino acid is independently cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid.

4. The peptide conjugate of any one of claims **1-3**, wherein the first amino acid and second amino acid are cysteines.

5. The peptide conjugate of claim **1** or **2**, wherein the first amino acid and second amino acid is independently lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine.

6. The peptide conjugate of any one of claim **1** or **2** or **5**, wherein the first amino acid and second amino acid are lysines.

7. The peptide conjugate of any one of claim **1** or **2** or **5**, wherein the first amino acid and second amino acid are ornithine.

8. The peptide conjugate of any one of claims **1-7**, wherein the first amino acid has a position i in the peptide and the second amino acid has a position i+n in the peptide, wherein n is 4-16.

9. The peptide conjugate of any one of claims **1-8**, wherein the first amino acid has a position i in the peptide and the second amino acid has a position i+n in the peptide, wherein n is 4-10.

10. The peptide conjugate of any one of claims **1-9**, wherein the first amino acid has a position i in the peptide and the second amino acid has a position i+n in the peptide, wherein n is 6-8.

11. The peptide conjugate of any one of claims **1-10**, wherein the first amino acid has a position i in the peptide and the second amino acid has a position i+7 in the peptide.

12. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 80% identity to any one of SEQ ID NOs: 1-9, 21-29.

13. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 90% identity to any one of SEQ ID NOs: 1-9, 21-29.

14. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 95% identity to any one of SEQ ID NOs: 1-9, 21-29.

15. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 99% identity to any one of SEQ ID NOs: 1-9, 21-29.

16. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence that is anyone of SEQ ID NOs: 1-9, 21-29.

17. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 80% identity to SEQ ID NO: 1 or 21.

18. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 90% identity to SEQ ID NO: 1 or 21.

19. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 95% identity to SEQ ID NO: 1 or 21.

20. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 99% identity to SEQ ID NO: 1 or 21.

21. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence that is SEQ ID NO: 1 or 21.

22. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 80% identity to SEQ ID NO: 2 or 22.

23. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 90% identity to SEQ ID NO: 2 or 22.

24. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 95% identity to SEQ ID NO: 2 or 22.

25. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 99% identity to SEQ ID NO: 2 or 22.

26. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence that is SEQ ID NO: 2 or 22.

27. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 80% identity to any one of SEQ ID NOs: 10-20, 30-40.

28. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 90% identity to any one of SEQ ID NOs: 10-20, 30-40.

29. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 95% identity to any one of SEQ ID NOs: 10-20, 30-40.

30. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 99% identity to any one of SEQ ID NOs: 10-20, 30-40.

31. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence that is any one of SEQ ID NOs: 10-20, 30-40.

32. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 80% identity to SEQ ID NO: 10 or 30.

33. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 90% identity to SEQ ID NO: 10 or 30.

34. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 95% identity to SEQ ID NO: 10 or 30.

35. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence having at least about 99% identity to SEQ ID NO: 10 or 30.

36. The peptide conjugate of any one of claims **1-11**, wherein the peptide comprises a sequence that is SEQ ID NO: 10 or 30.

37. The peptide conjugate of any one of claims **1-36**, wherein the half-life of the peptide conjugate is at least about 2-fold greater than the half-life of an unmodified form of the peptide.

38. The peptide conjugate of any one of claims **1-36**, wherein the half-life of the peptide conjugate is at least about 5-fold greater than the half-life of an unmodified form of the peptide.

39. The peptide conjugate of any one of claims **1-36**, wherein the half-life of the peptide conjugate is at least about 10-fold greater than the half-life of an unmodified form of the peptide.

40. The peptide conjugate of any one of claims **1-36**, wherein the binding affinity of the peptide conjugate is within about 5% of the binding affinity of an unmodified form of the peptide.

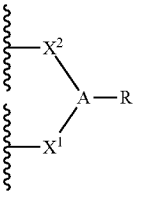
41. The peptide conjugate of any one of claims **1-36**, wherein the binding affinity of the peptide conjugate is within about 10% of the binding affinity of an unmodified form of the peptide.

42. The peptide conjugate of any one of claims **1-36**, wherein the binding affinity of the peptide conjugate is within about 15% of the binding affinity of an unmodified form of the peptide.

43. The peptide conjugate of any one of claims **1-36**, wherein the binding affinity of the peptide conjugate is within about 20% of the binding affinity of an unmodified form of the peptide.

44. The peptide conjugate of any one of claims **1-43**, wherein the staple is of Formula (I):

Formula (I)



wherein

A is an optionally substituted alkylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted —NR^3-alkylene-NR^3—, or —N—;

X^1 and X^2 are independently a bond, —C(═O)—, -alkylene-C(═O)—, —C(═O)-alkylene-, -alkylene-C(═O)NR^3—, -alkylene-NR^3C(═O)—, —C(═O)

NR^3-alkylene-, —$NR^3C(=O)$-alkylene-, -alkylene-$C(=O)NR^3$-alkylene-, or -alkylene-$NR^3C(=O)$-alkylene-;

wherein X^1 is attached to a first amino acid of the peptide, and X^2 is attached to a second amino acid of the peptide;

R is hydrogen or $-(L)_s-Y$;

each L is independently —$(CR^1R^2)_v$—, -alkylene-O—, —O-alkylene-, —C(=O)-alkylene-, -alkylene-C(=O)—, —NR^3-alkylene-, -alkylene-NR^3—, —S-alkylene-, -alkylene-S—, —S(=O)-alkylene-, -alkylene-S(=O)—, —$S(=O)_2$-alkylene, -alkylene-$S(=O)_2$—, —C(=O)—, —$C(=O)NR^3$—, —$NR^3C(=O)$—, —$NR^3C(=O)NR^3$—, —$NR^3C(=O)NR^3$-alkylene-, —$NR^3C(=O)$-alkylene-NR^3—, -alkylene-$C(=O)NR^3$—, —$C(=O)NR^3$-alkylene-, -alkylene-$NR^3C(=O)$—, or —$NR^3C(=O)$-alkylene-;

v is 2-20;

each R^1 or R^2 is independently hydrogen, halogen, —CN, —OR^a, —SR^a, —$S(=O)R^b$, —NO_2, —NR^cR^d, —$S(=O)_2R^a$, —$NR^aS(=O)_2R^d$, —$S(=O)_2NR^cR^d$, —$C(=O)R^b$, —$OC(=O)R^b$, —CO_2R^a, —OCO_2R^a, —$C(=O)NR^cR^d$, —$OC(=O)NR^cR^d$, —$NR^aC(=O)NR^cR^d$, —$NR^aC(=O)R^b$, —$NR^aC(=O)OR^a$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OR^a, or —NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OR^a, —NR^cR^d,

or R^1 and R^2 are taken together to form a C_1-C_6 cycloalkyl or C_1-C_6 heterocycloalkyl;

each R^3 is independently hydrogen, —$S(=O)R^b$, —$S(=O)_2R^a$, —$S(=O)_2NR^cR^d$, —$C(=O)R^b$, —CO_2R^a, —$C(=O)NR^cR^d$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OR^a, or —NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OR^a, or —NR^cR^d;

Y is hydrogen, C_1-C_6 alkyl, —CO_2H, —$CO_2(C_1$-C_6 alkyl), —CO_2NH_2, —$CO_2N(alkyl)_2$, or —CO_2NH(alkyl); and

s is 0-20;

R^a is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

R^b is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

each R^c and R^d is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

or R^c and R^d, together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2.

45. The peptide conjugate of claim **44**, wherein A is optionally substituted alkylene.

46. The peptide conjugate of claim **44** or **45**, wherein A is —$(CH_2)_t$—, wherein t is 1-12.

47. The peptide conjugate of claim **44**, wherein A is optionally substituted arylene.

48. The peptide conjugate of claim **44**, wherein A is —NR^3-alkylene-NR^3—.

49. The peptide conjugate of claim **44**, wherein A is —N—.

50. The peptide conjugate of any one of claims **44-49**, wherein X^1 and X^2 are —C(=O)—.

51. The peptide conjugate of any one of claims **44-49**, wherein X^1 and X^2 are -alkylene-C(=O)—.

52. The peptide conjugate of any one of claims **44-49**, wherein X^1 and X^2 are —CH_2—C(=O)—.

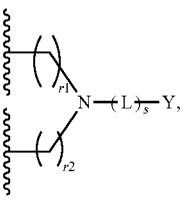
53. The peptide conjugate of any one of claims **44-49**, wherein X^1 and X^2 are independently -alkylene-C(=O)NR^3—.

54. The peptide conjugate of any one of claims **44-49**, wherein X^1 and X^2 are independently —CH_2—C(=O)NR^3—.

55. The peptide conjugate of any one of claims **44-49**, wherein X^1 and X^2 are independently -alkylene-C(=O)NR^3-alkylene-.

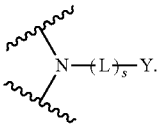
56. The peptide conjugate of any one of claims **44-49**, wherein X^1 and X^2 are independently —CH_2—C(=O)NR^3—CH_2CH_2—.

57. The peptide conjugate of any one of claims **44-56**, wherein >A-R has the following structure:

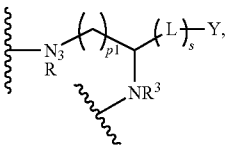


wherein r1 and r2 are each independently 0-4.

58. The peptide conjugate of any one of claims **44-56**, wherein >A-R has the following structure:

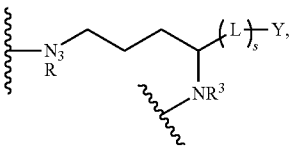


59. The peptide conjugate of any one of claims **44-56**, wherein >A-R has the following structure:

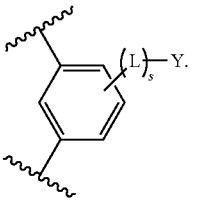


wherein p1 is 1-5.

60. The peptide conjugate of any one of claims **44-56**, wherein >A-R has the following structure:



61. The peptide conjugate of any one of claims **44-56**, wherein >A-R has the following structure:



62. The peptide conjugate of any one of claims **44-61**, wherein s is 1-15.

63. The peptide conjugate of any one of claims **44-62**, wherein s is 1-10.

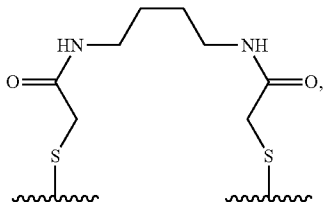
64. The peptide conjugate of any one of claims **44-62**, wherein s is 5-15.

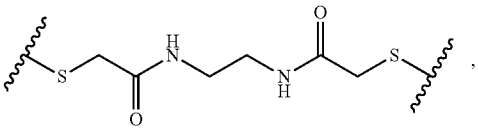
65. The peptide conjugate of any one of claims **44-62**, wherein s is 5-10.

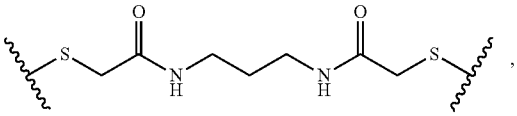
66. The peptide conjugate of any one of claims **44-65**, wherein Y is hydrogen or —CO_2H.

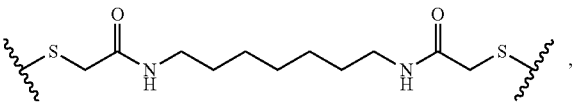
67. The peptide conjugate of any one of claims **44-66**, wherein each L is independently —$(CR^1R^2)_v$—, -alkylene-O—, —C(═O)—, —C(═O)NR^3—, —NR^3C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^3C(═O)—; and v is 2-20.

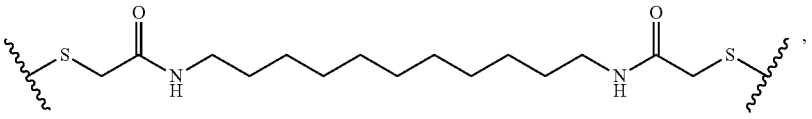
68. The peptide conjugate of claim **1**, wherein the peptide conjugate comprises the structure:

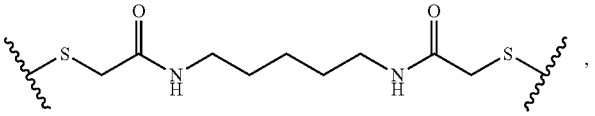


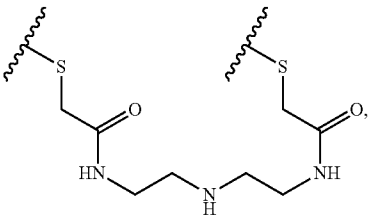




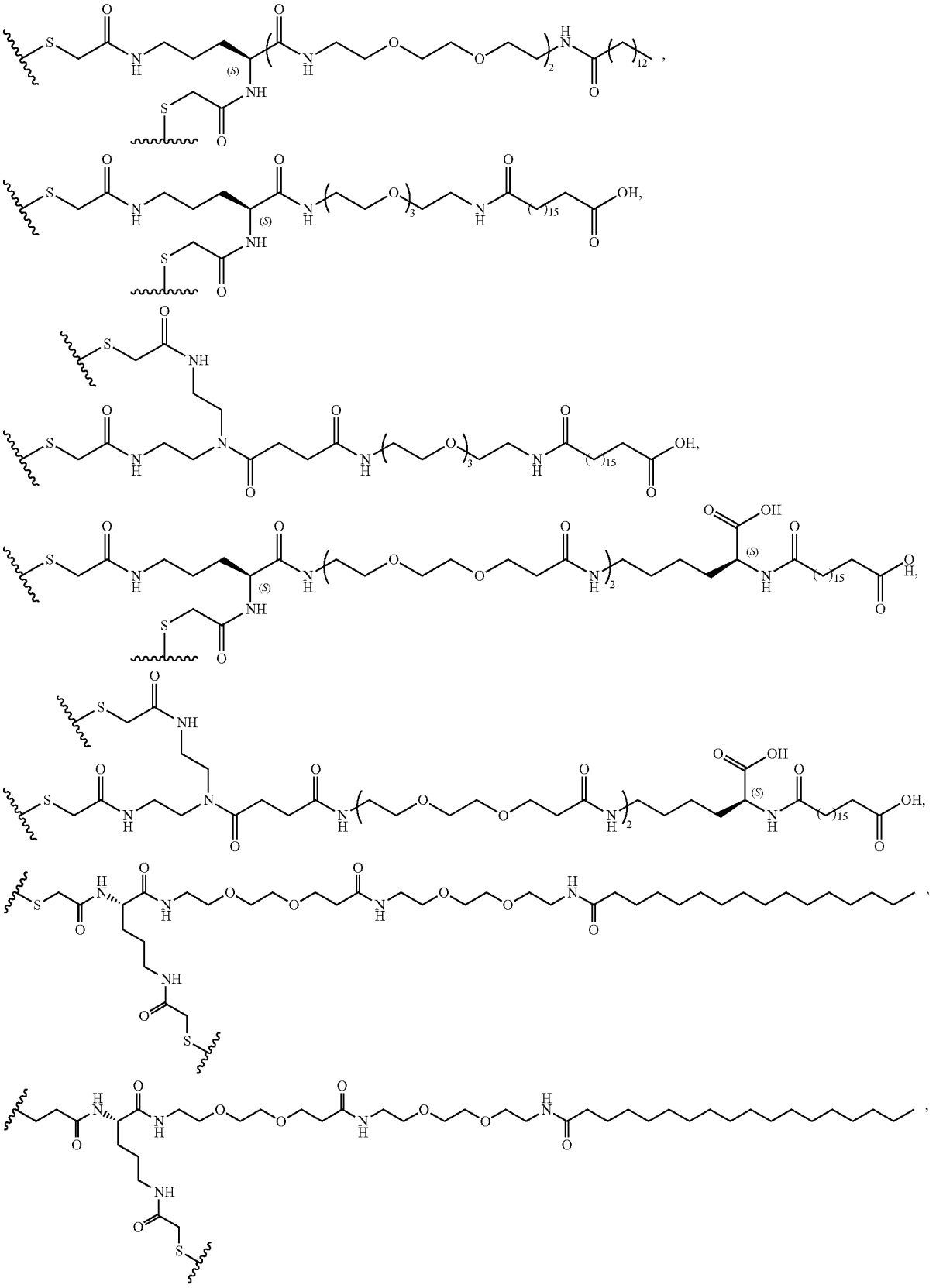




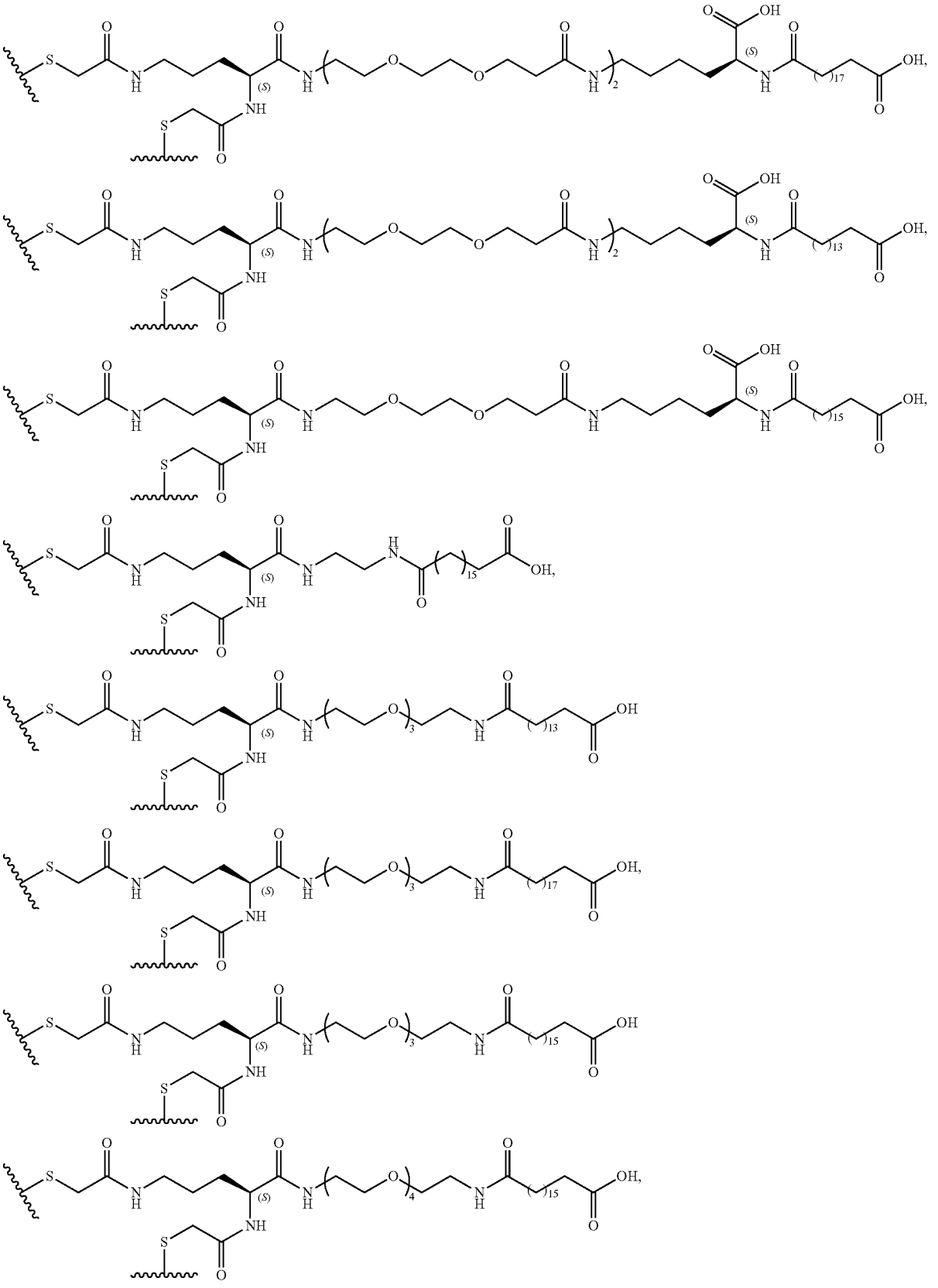




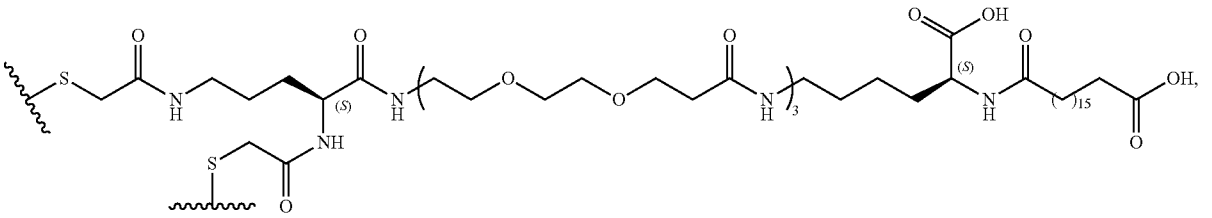
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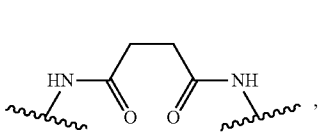


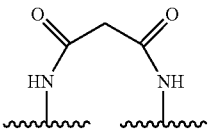
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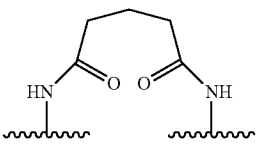


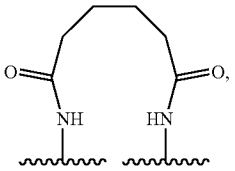
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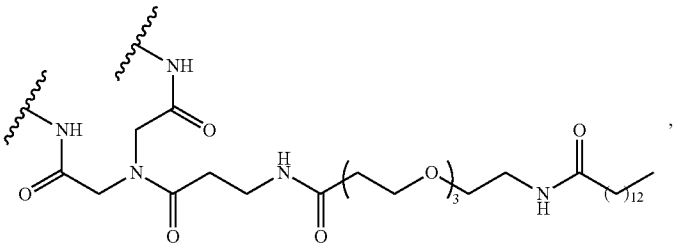


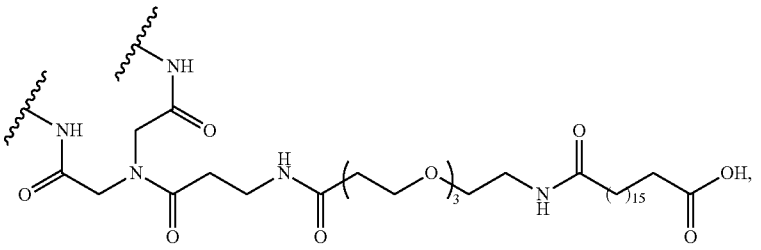


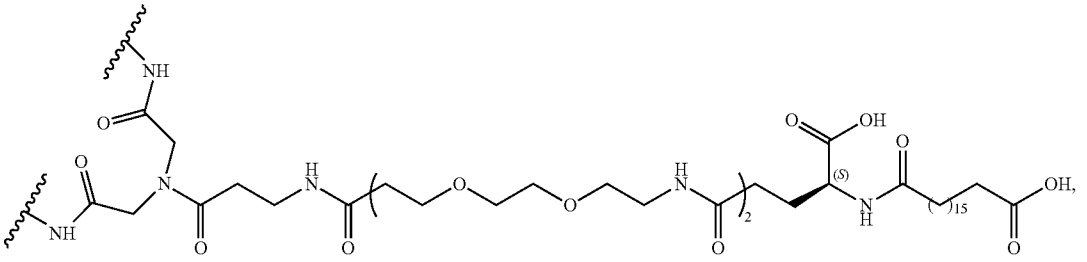


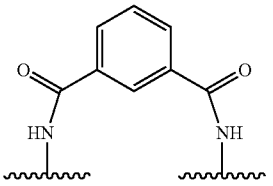






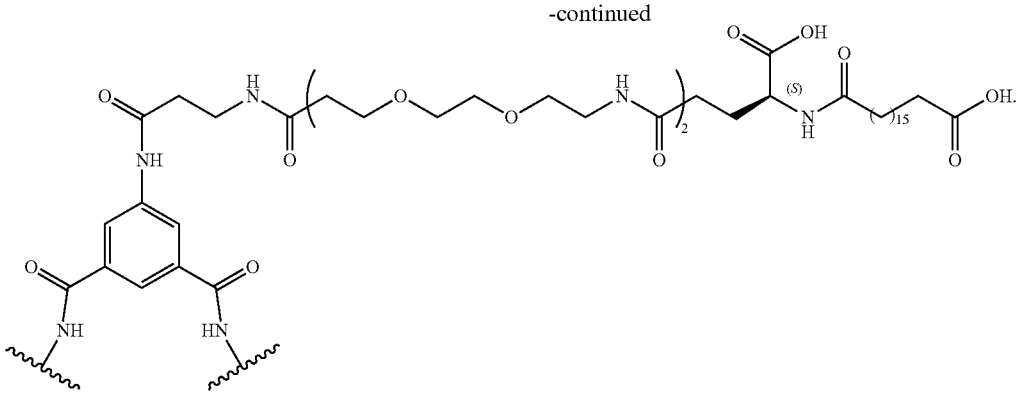




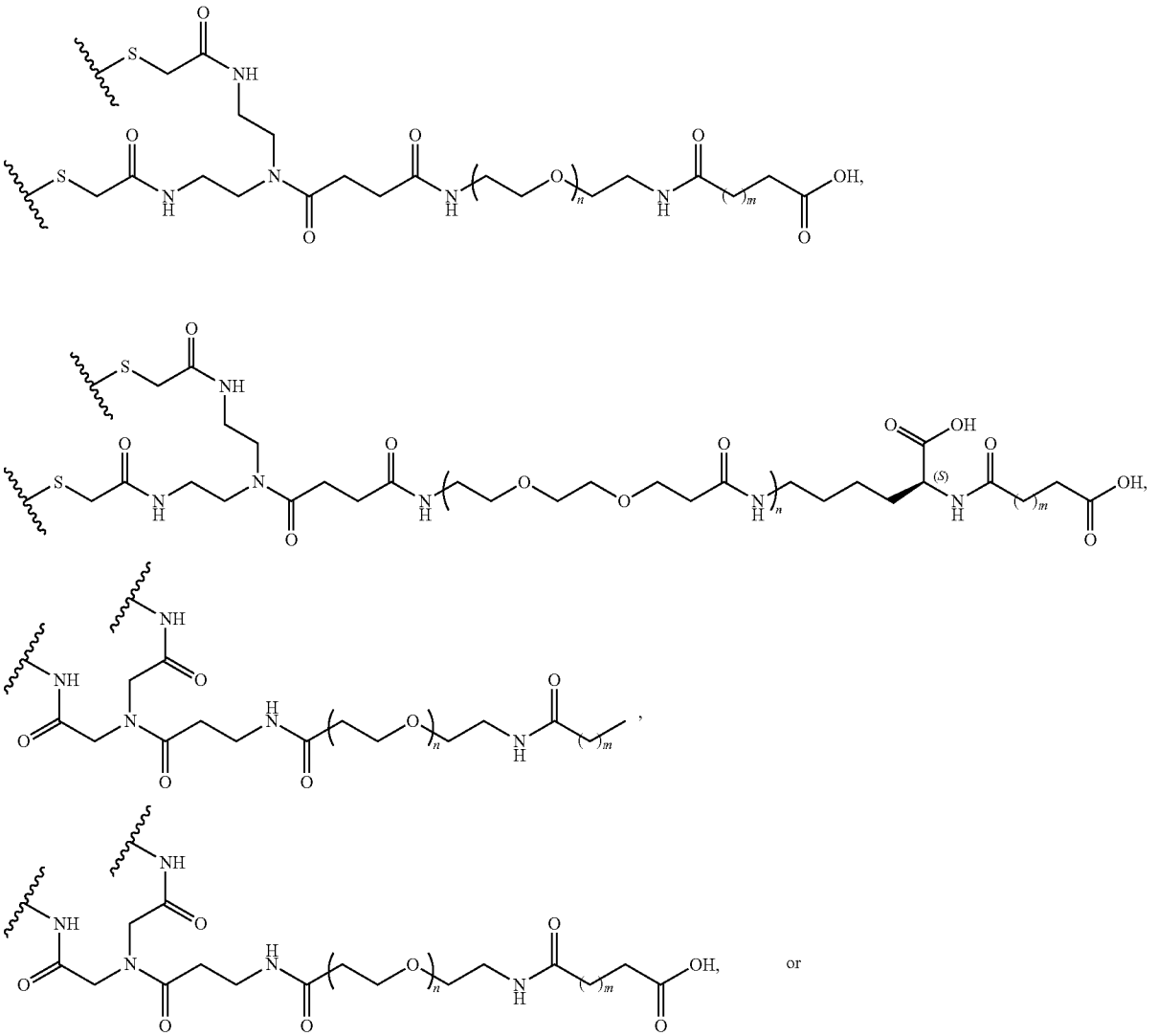


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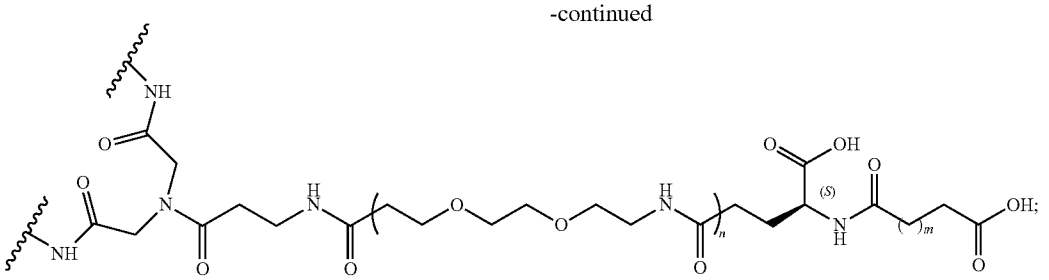
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69. The peptide conjugate of claim **1**, wherein the peptide conjugate comprises the structure:

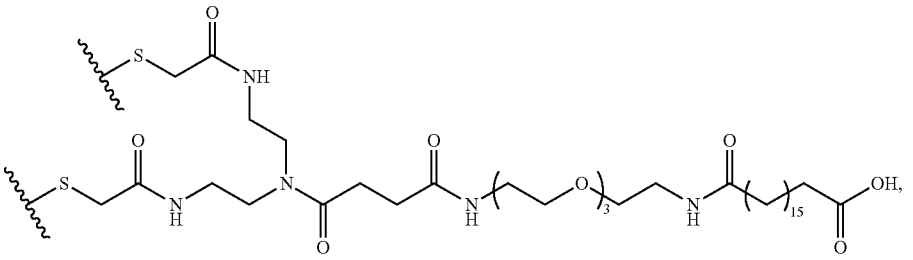


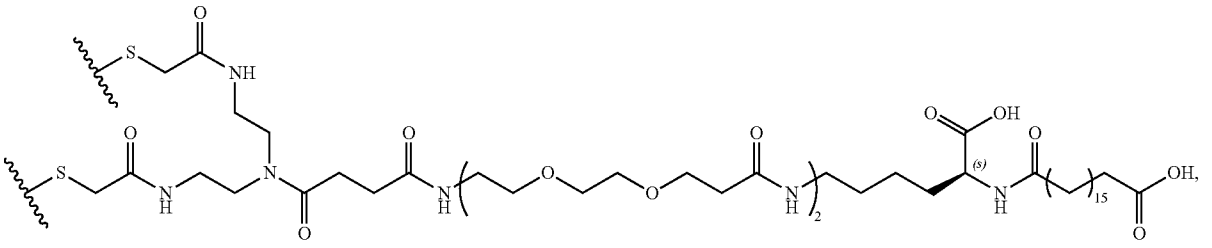
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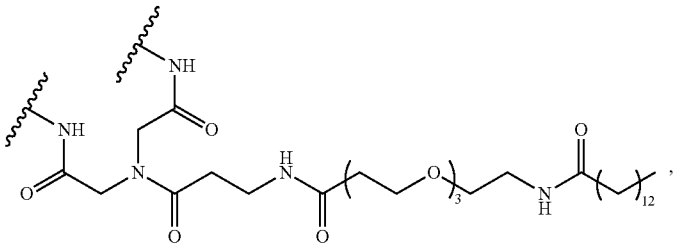


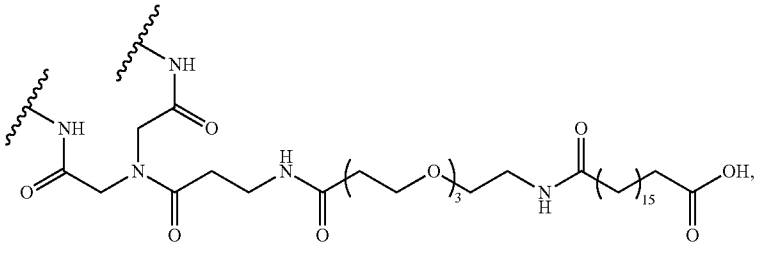
wherein n is 1-4 and m is 6-20.

70. The peptide conjugate of claim **1**, wherein the peptide conjugate comprises the structure:



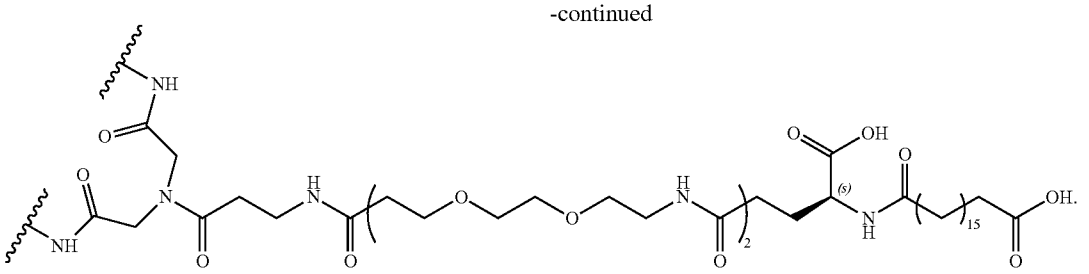




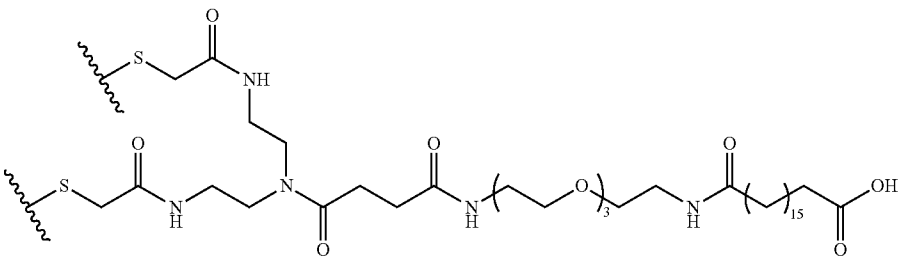


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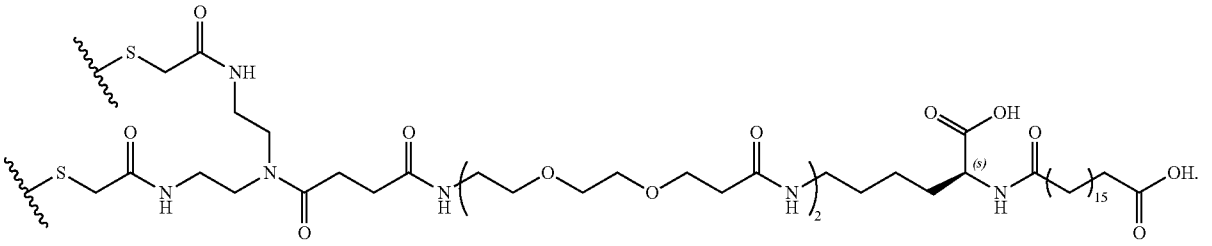
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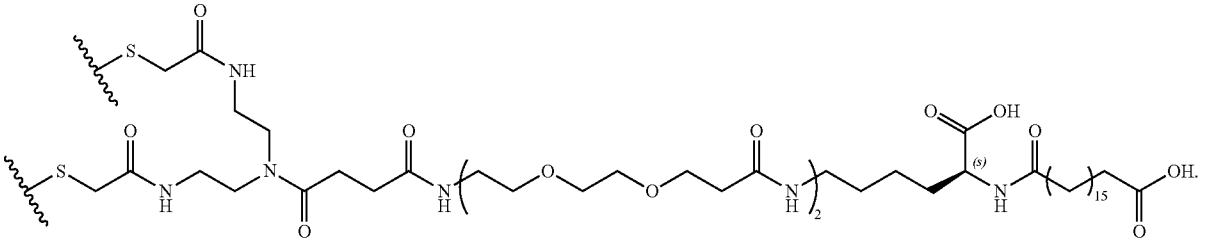
71. The peptide conjugate of claim **1**, wherein the peptide conjugate comprises the structure:



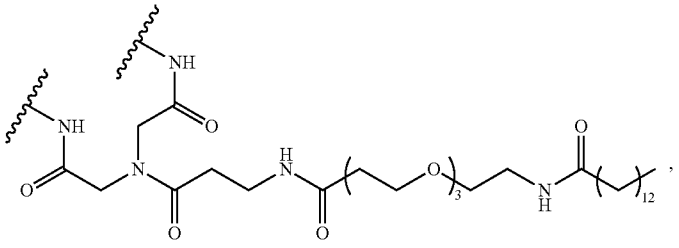
or



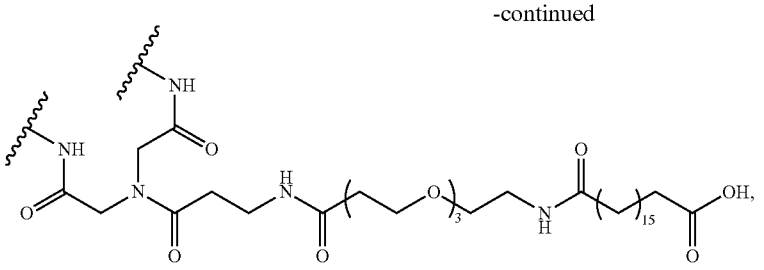
72. The peptide conjugate of claim **1**, wherein the peptide conjugate comprises the structure:



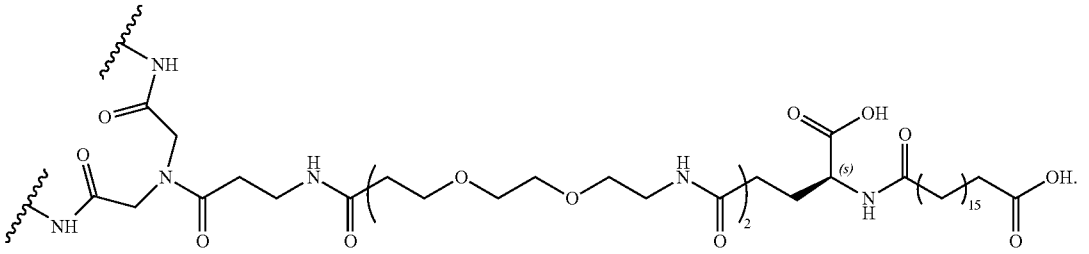
73. The peptide conjugate of claim **1**, wherein the peptide conjugate comprises the structure:



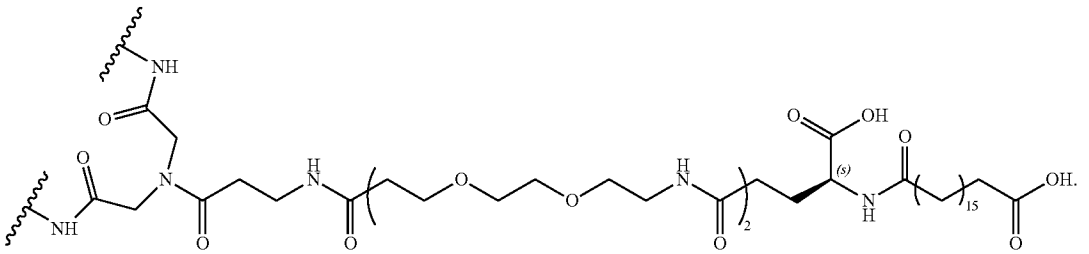
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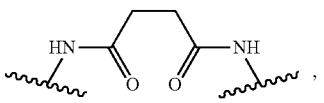
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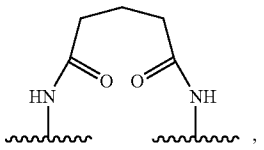


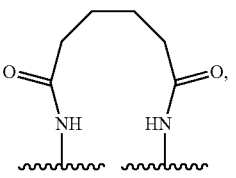
74. The peptide conjugate of claim **1**, wherein the peptide conjugate comprises the structure:



75. The peptide conjugate of claim **1**, wherein the peptide conjugate comprises the structure:

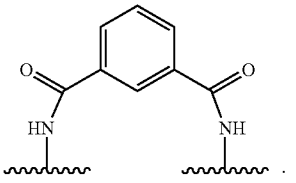






or

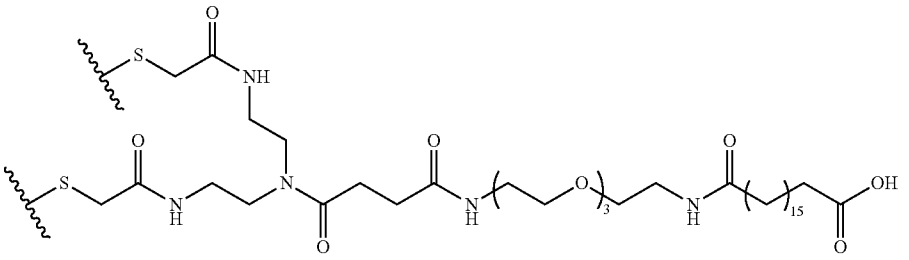
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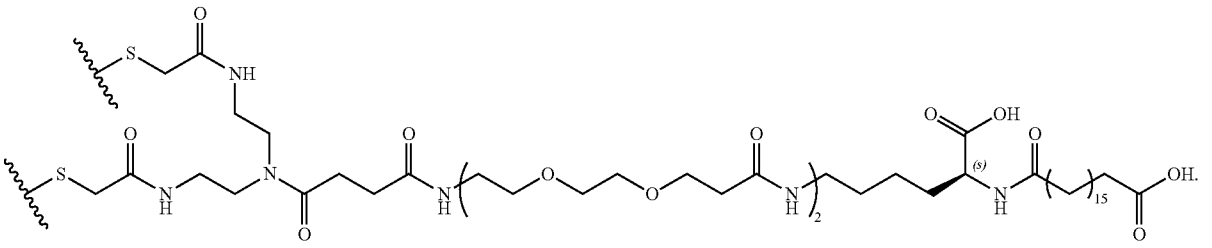
76. The peptide conjugate of claim **1**, wherein the peptide conjugate comprises:

a) a peptide that modulates the GLP-2 receptor comprising a sequence that is any one of SEQ ID NOs: 1-9, 21-29; and

b) a staple attached to the peptide at a first cysteine and a second cysteine having the following structure ("S" being part of the cysteine residue):



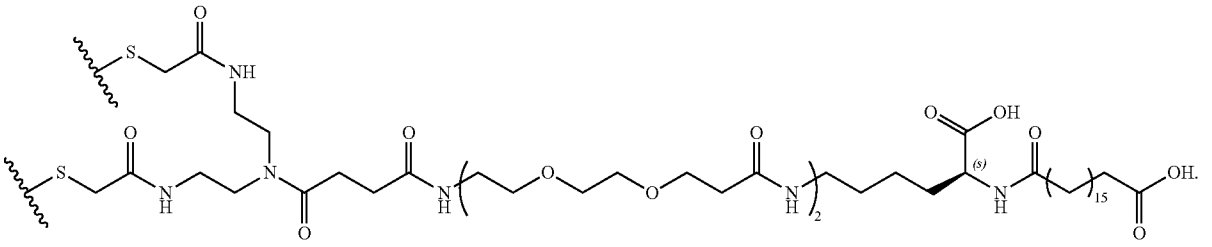
or



77. The peptide conjugate of claim **1**, wherein the peptide conjugate comprises:

a) a peptide that modulates the GLP-2 receptor comprising a sequence that is SEQ ID NO: 1 or 21; and

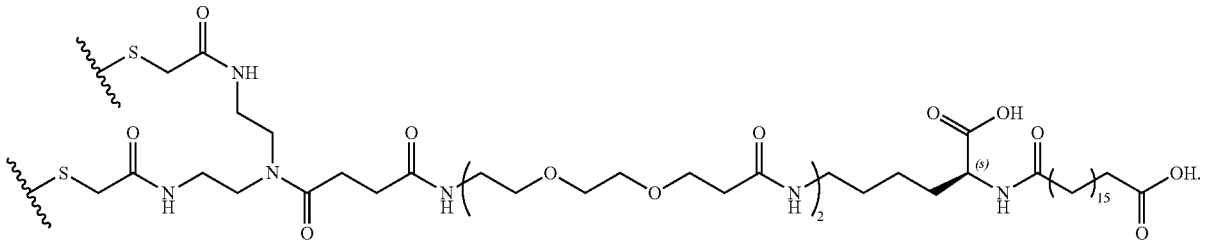
b) a staple attached to the peptide at a first cysteine and a second cysteine having the following structure ("S" being part of the cysteine residue):



78. The peptide conjugate of claim **1**, wherein the peptide conjugate comprises:

a) a peptide that modulates the GLP-2 receptor comprising a sequence that is SEQ ID NO: 2 or 22; and

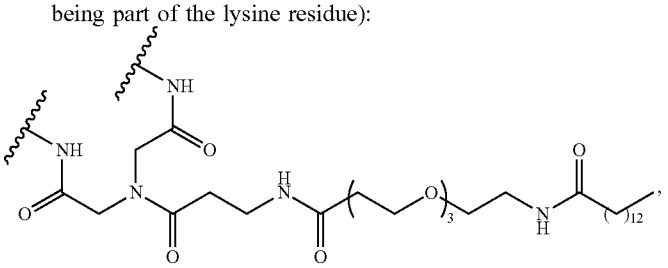
b) a staple attached to the peptide at a first cysteine and a second cysteine having the following structure ("S" being part of the cysteine residue):

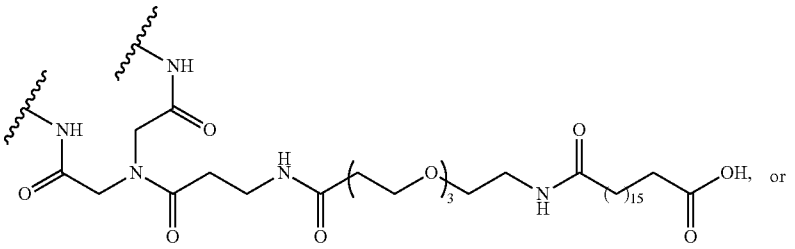


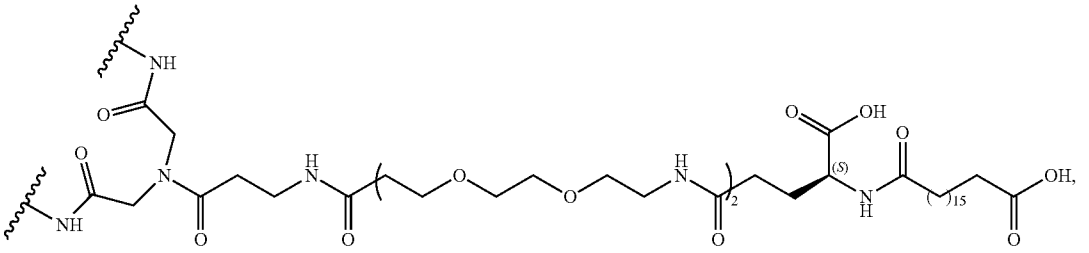
79. The peptide conjugate of claim **1**, wherein the peptide conjugate comprises:

a) a peptide that modulates the GLP-2 receptor comprising a sequence that is any one of SEQ ID NOs: 10-20, 30-40; and

b) a staple attached to the peptide at a first lysine and a second lysine having the following structure ("NH" being part of the lysine residue):



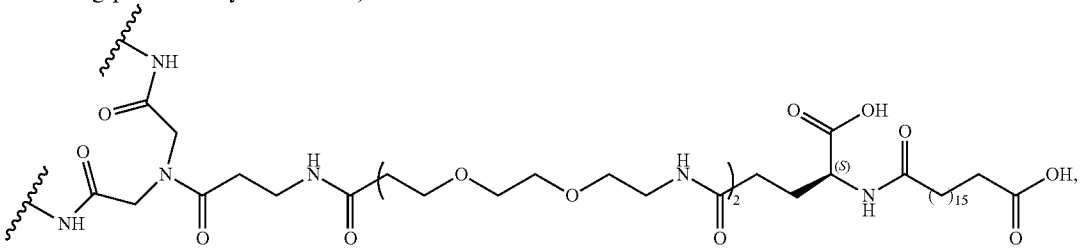




80. The peptide conjugate of claim **1**, wherein the peptide conjugate comprises:

a) a peptide that modulates the GLP-2 receptor comprising a sequence that is SEQ ID NO: 10 or 30; and

b) a staple attached to the peptide at a first lysine and a second lysine having the following structure ("NH" being part of the lysine residue):



81. A pharmaceutical composition comprising the peptide conjugate of any one of claims **1-80** and a pharmaceutically acceptable excipient.

82. A method for treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a composition comprising a therapeutically effective amount of the peptide conjugate of any one of claims **1-80**.

83. The method of claim **81**, wherein the disease or condition is diabetes or obesity, or a medical condition associated with diabetes or obesity.

84. The method of claim **82**, wherein the disease or condition is non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or cardiovascular disease.

85. The method of claim **82**, wherein the disease or condition is a gastrointestinal (GI) disorder.

86. The method of claim **85**, wherein the gastrointestinal (GI) disorder is short bowel syndrome (SBS), inflammatory bowel syndrome (IBS), or inflammatory bowel diseases (IBD).

87. The method of claim **86**, wherein the inflammatory bowel diseases (IBD) is Crohn's disease.

88. The method of claim **86**, wherein the inflammatory bowel diseases (IBD) is ulcerative colitis.

89. The method of claim **82**, wherein the disease or condition is psoriasis.

90. The method of claim **82**, wherein the disease or condition is Alzheimer's disease, Parkinson's disease, or Huntington's disease.

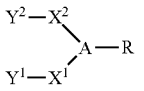
91. The method of claim **82**, wherein the subject in need thereof is undergoing chemotherapy.

92. The method of claim **82**, wherein the subject in need thereof has radiation-induced GI mucositis.

93. The method of claim **82**, wherein the subject in need thereof has chemotherapy-induced diarrhea (CID).

94. The method of claim **82**, wherein the subject in need thereof has total parenteral nutrition (TPN) induced intestinal atrophy.

95. A staple of Formula:

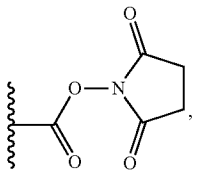


wherein

A is an optionally substituted alkylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted —NR^3-alkylene-NR^3—, or —N—;

X^1 and X^2 are independently a bond, —C(═O)—, -alkylene-C(═O)—, —C(═O)-alkylene, -alkylene-C(═O)NR^3—, or -alkylene-C(═O)NR^3-alkylene-;

Y^1 and Y^2 are independently halogen, —COOH,



or are independently the —S— of a sulfhydryl-containing amino acid or —CONH— wherein the —NH— is part of an amine-containing amino acid in a peptide that modulates the GLP-2 receptor;

R is hydrogen or -$(L)_s$-Y;

each L is independently —$(CR^1R^2)_v$—, -alkylene-O—, —O-alkylene-, —C(═O)-alkylene-, -alkylene-C(═O)—, —NR^3-alkylene-, -alkylene-NR^3—, —S-alkylene-, -alkylene-S—, —S(═O)-alkylene-, -alkylene-S(═O)—, —$S(═O)_2$-alkylene, -alkylene-$S(═O)_2$—, —C(═O)—, —C(═O)NR^3—, —NR^3C(═O)—, —NR^3C(═O)NR^3—, —NR^3C(═O)NR^3-alkylene-, —NR^3C(═O)-alkylene-NR^3—, -alkylene-C(═O)NR^3—, —C(═O)NR^3-alkylene-, -alkylene-NR^3C(═O)—, or —NR^3C(═O)-alkylene-;

v is 2-20;

each R^1 or R^2 is independently hydrogen, halogen, —CN, —OR^a, —SR^a, —S(═O)R^b, —NO_2, —NR^cR^d, —$S(═O)_2R^a$, —$NR^aS(═O)_2R^d$, —$S(═O)_2NR^cR^d$, —C(═O)R^b, —OC(═O)R^b, —CO_2R^a, —OCO_2R^a, —C(═O)NR^cR^d, —OC(═O)NR^cR^d, —$NR^aC(═O)NR^cR^d$, —$NR^aC(═O)R^b$, —$NR^aC(═O)OR^a$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_5 cycloalkyl, C_2-C_5 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OR^a, or —NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OR^a, —NR^cR^d,

or R^1 and R^2 are taken together to form a C_1-C_6 cycloalkyl or C_1-C_6 heterocycloalkyl;

each R^3 is independently hydrogen, —S(═O)R^b, —$S(═O)_2R^a$, —$S(═O)_2NR^cR^d$, —C(═O)R^b, —CO_2R^a, —C(═O)NR^cR^d, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OR^a, or —NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OR^a, or —NR^cR^d;

Y is hydrogen, C_1-C_6 alkyl, —CO_2H, —CO_2(C_1-C_6 alkyl), —CO_2NH_2, —$CO_2N(alkyl)_2$, or —CO_2NH(alkyl); and

s is 0-20;

R^a is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

R^b is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

each R^c and R^d is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, —OH, —OMe, or —NH_2; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2;

or R^c and R^d, together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, —OH, —OMe, or —NH_2.

96. The staple of claim **95**, wherein A is optionally substituted alkylene.

97. The staple of claim **95** or **96**, wherein A is —$(CH_2)_t$—, wherein t is 1-12.

98. The staple of claim **95**, wherein A is optionally substituted arylene.

99. The staple of claim **95**, wherein A is —NR^3-alkylene-NR^3—.

100. The staple of claim **95**, wherein A is —N—.

101. The staple of any one of claims **95-100**, wherein X^1 and X^2 are —C(═O)—.

102. The staple of any one of claims **95-100**, wherein X^1 and X^2 are -alkylene-C(═O)—.

103. The staple of any one of claims **95-100**, wherein X^1 and X^2 are —CH_2—C(═O)—.

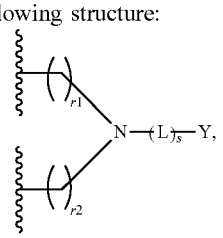
104. The staple of any one of claims **95-100**, wherein X^1 and X^2 are independently -alkylene-C(═O)NR^3—.

105. The staple of any one of claims **95-100**, wherein X^1 and X^2 are independently —CH_2—C(═O)NR^3—.

106. The staple of any one of claims **95-100**, wherein X^1 and X^2 are independently -alkylene-C(═O)NR^3-alkylene-.

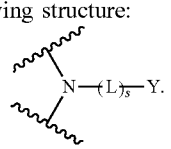
107. The staple of any one of claims **95-100**, wherein X^1 and X^2 are independently —CH_2—C(═O)NR^3—CH_2CH_2—.

108. The staple of any one of claims **95-107**, wherein >A-R has the following structure:

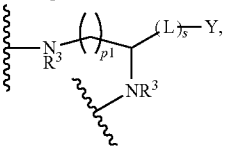


wherein r1 and r2 are each independently 0-4.

109. The staple of any one of claims **95-107**, wherein >A-R has the following structure:

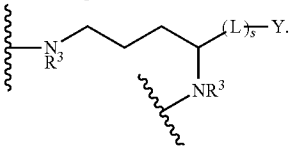


110. The staple of any one of claims **95-107**, wherein >A-R has the following structure:

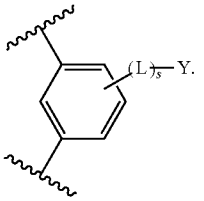


wherein p1 is 1-5.

111. The staple of any one of claims **95-107**, wherein >A-R has the following structure:



112. The staple of any one of claims **95-107**, wherein >A-R has the following structure:



113. The staple of any one of claims **95-112**, wherein s is 1-15.

114. The staple of any one of claims **95-113**, wherein s is 1-10.

115. The staple of any one of claims **95-113**, wherein s is 5-15.

116. The staple of any one of claims **95-113**, wherein s is 5-10.

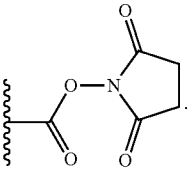
117. The staple of any one of claims **95-116**, wherein Y is hydrogen or —C_2H.

118. The staple of any one of claims **95-117**, wherein each L is independently —$(CR^1R^2)_v$—, -alkylene-O—, —C(═O)—, —C(═O)NR^3—, —NR^3C(═O)—, -alkylene-C(═O)NR^3—, or -alkylene-NR^3C(═O)—; and v is 2-20.

119. The staple of claim **94-118**, wherein Y^1 and Y^2 are halogen.

120. The staple of claim **94-118**, wherein Y^1 and Y^2 are —COOH.

121. The staple of claim **95-118**, wherein Y^1 and Y^2 are



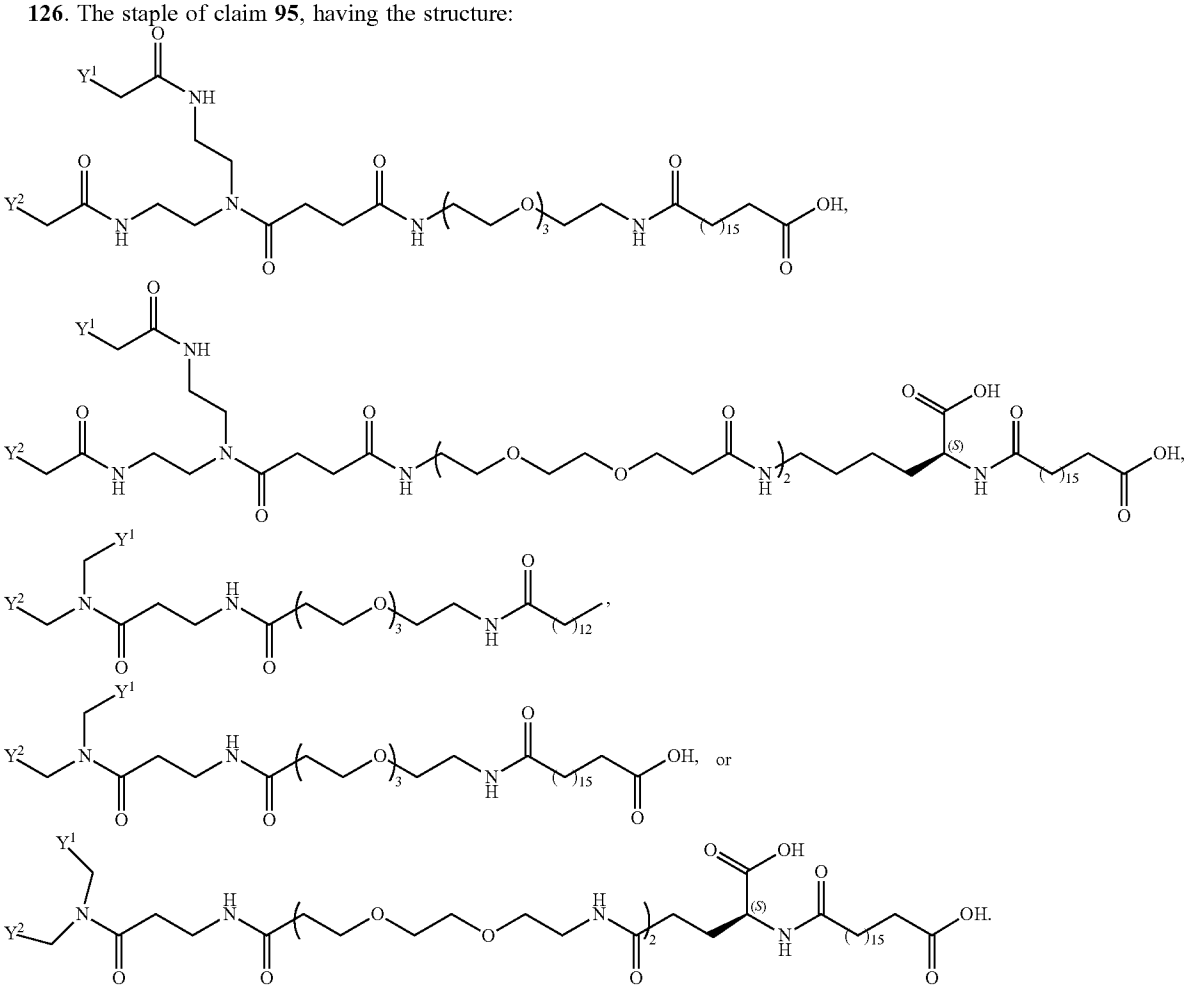
122. The staple of claim **95-118**, wherein Y^1 and Y^2 are the —S— of two sulfhydryl-containing amino acids in a peptide that modulates the GLP-2 receptor.

123. The staple of claim **95-118**, wherein Y^1 and Y^2 are the —S— of two sulfhydryl-containing amino acids in a peptide that modulates the GLP-2 receptor which are 7 amino acid apart.

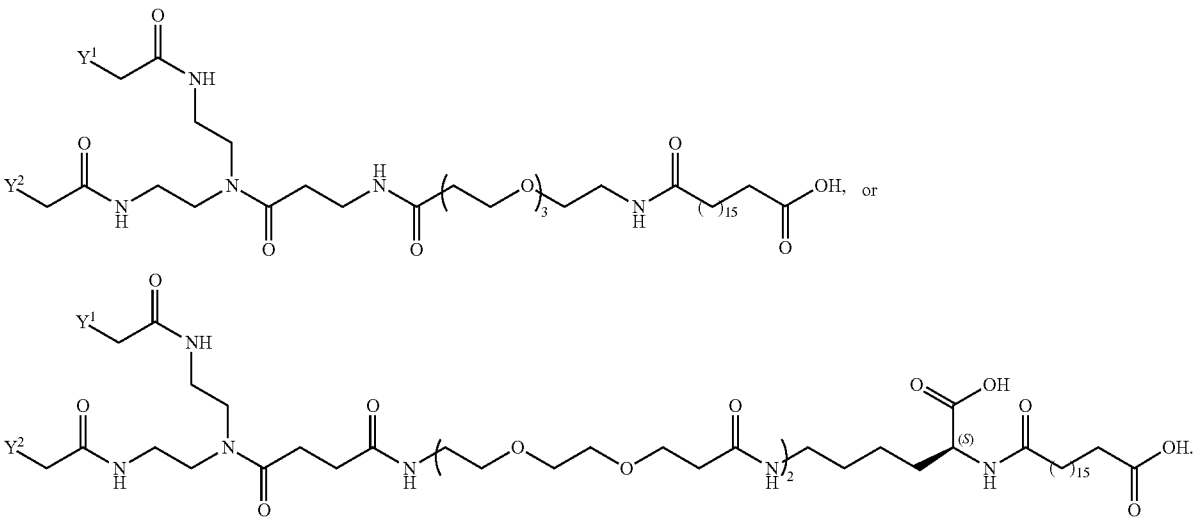
124. The staple of claim **95-118**, wherein Y^1 and Y^2 are —CONH— wherein the —NH— is part of two amine-containing amino acids in a peptide that modulates the GLP-2 receptor.

125. The staple of claim **95-118**, wherein Y^1 and Y^2 —CONH— wherein the —NH— is part of two amine-containing amino acids in a peptide that modulates the GLP-2 receptor which are 7 amino acids apart.

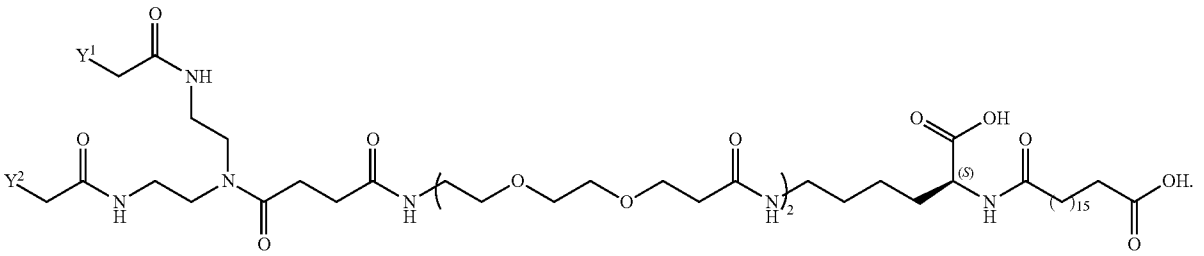
126. The staple of claim **95**, having the structure:



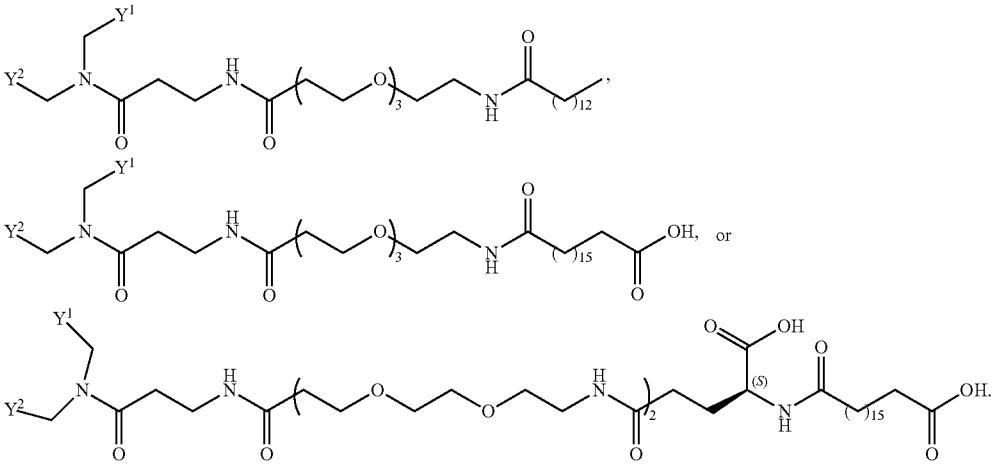
127. The staple of claim **95**, having the structure:



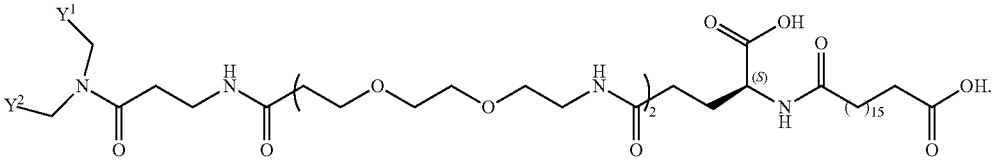
128. The staple of claim **95**, having the structure:



129. The staple of claim **95**, having the structure:



130. The staple of claim **95**, having the structure:



131. A peptide sequence that is SEQ ID NO: 1.
132. A peptide sequence that is SEQ ID NO: 2.
133. A peptide sequence that is SEQ ID NO: 3.
134. A peptide sequence that is SEQ ID NO: 4.
135. A peptide sequence that is SEQ ID NO: 5.
136. A peptide sequence that is SEQ ID NO: 6.
137. A peptide sequence that is SEQ ID NO: 7.
138. A peptide sequence that is SEQ ID NO: 8.
139. A peptide sequence that is SEQ ID NO: 9.
140. A peptide sequence that is SEQ ID NO: 10.
141. A peptide sequence that is SEQ ID NO: 11.
142. A peptide sequence that is SEQ ID NO: 12.
143. A peptide sequence that is SEQ ID NO: 13.
144. A peptide sequence that is SEQ ID NO: 14.
145. A peptide sequence that is SEQ ID NO: 15.
146. A peptide sequence that is SEQ ID NO: 16.
147. A peptide sequence that is SEQ ID NO: 17.
148. A peptide sequence that is SEQ ID NO: 18.
149. A peptide sequence that is SEQ ID NO: 19.
150. A peptide sequence that is SEQ ID NO: 20.

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