CLAIMS

1. A GLP-1 receptor-amylin receptor co-agonist comprising a polypeptide (R1) according to Formula I:

Z1-Z2-Z3,

comprising 1-3 lysine (Lys, K) residues and no disulfide bridge; wherein:

- Z1 is a GLP-1 receptor agonist peptide comprising a maximum of 9 amino acid modifications relative to SEQ ID NO: 1, and

Z1 has Formula II (SEQ ID NO: 255):

Xaa1-Xaa2-Glu-Gly-Thr-Phe-Thr-Ser-Xaa9-Xaa10-Ser-Xaa12-Tyr-Leu-Glu-Xaa16-Xaa17-Ala-Xaa19-Xaa20-Xaa21-Phe-Ile-Xaa24-Xaa25-Leu-Val-Xaa28-Xaa29-Xaa30-Xaa31;

wherein

Xaa1 is His (H) or Imp,

Xaa2 is Aib, Ala (A), Gly (G) or Trp (W),

Xaa9 is Asp (D) or Lys (K),

Xaa10 is Lys (K) or Val (V),

Xaa12 is Lys (K), Arg (R) or Ser (S),

Xaa16 is Glu (E), Gly (G) or Lys (K),

Xaa17 is Gln (Q) or Lys (K),

Xaa19 is Ala (A) or Val (V),

Xaa20 is Lys (K) or Arg (R),

Xaa21 is Glu (E) or Lys (K),

Xaa24 is Ala (A) or Glu (E),

Xaa25 is Lys (K) or Trp (W),

Xaa28 is Lys (K) or Arg (R),

Xaa29 is Lys (K) or Gly (G),

Xaa30 is Ala (A), Gly (G), Lys (K), Arg (R) or absent,

Xaa31 is Ala (A), Lys (K), Gly (G), Gln (Q) or absent;

- Z2 is a peptide linker;
- Z3 is an amylin receptor agonist peptide comprising a C-terminal amide and a maximum of 7 amino acid modifications relative to SEQ ID NO: 79, and

Z3 has Formula III (SEQ ID NO: 256):

Xaa1-Xaa2-Xaa3-Leu-Ser-Thr-Xaa7-Ala-Leu-Gly-Arg-Leu-Ser-Xaa14-Glu-Leu-His-Xaa18-Leu-Xaa20-Thr-Leu-Xaa23-Arg-Thr-Glu-Thr-Gly-Xaa29-Gly-Ser-Pro,

wherein:

Xaa1 is Ala (A) or is absent,

Xaa2 is Lys (K) or Ser (S),

Xaa3 is Glu (E) or Arg (R),

Xaa7 is Ala (A) or Glu (E),

Xaa14 is Ala (A), or Lys (K),

Xaa18 is Glu (E), Lys (K) or Gln (Q),

Xaa20 is Ala (A), or Lys (K),

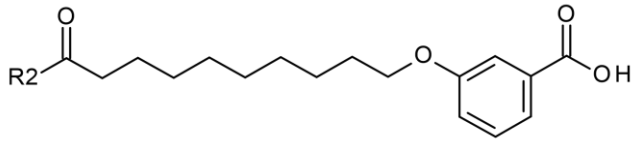
Xaa23 is Lys (K) or Pro (P),

Xaa29 is Ser (S) or Lys (K);

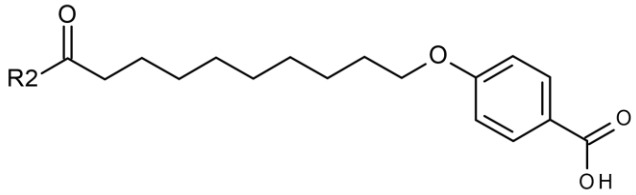
and further comprising 1-3 protraction moieties (R2-R3), attached to the polypeptide (R1) via said 1-3 lysine (Lys, K) residues,

wherein R2 is a linker, and

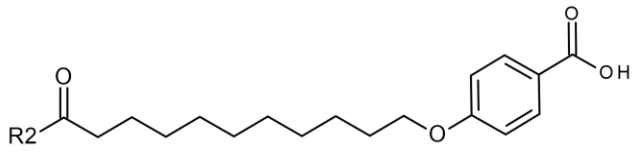
wherein R3 is selected from the group consisting of:



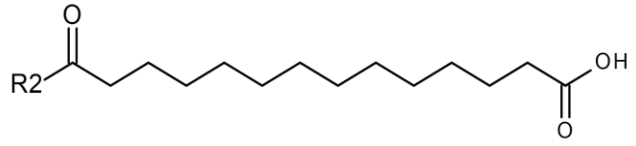
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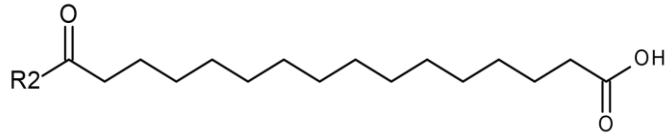
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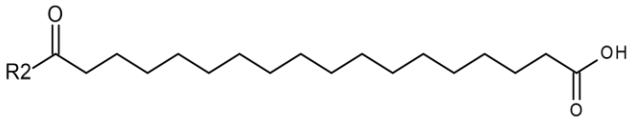
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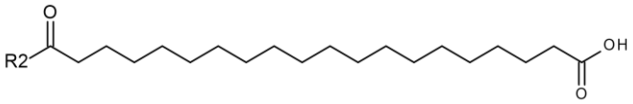
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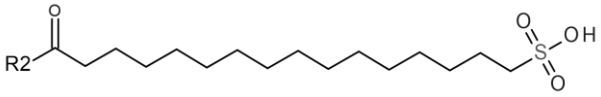
;



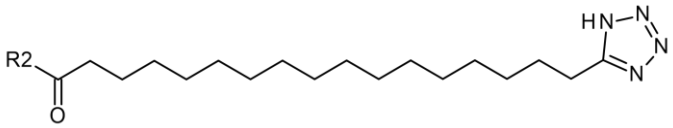
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; and



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2. The GLP-1 receptor-amylin receptor co-agonist according to claim 1, wherein the GLP-1 receptor agonist peptide (Z1) comprises 0-3 lysine (Lys, K) residues at any one, or combination of, positions 9, 10, 12, 16, 20, 21, 25, 28, 29, 30 and/or 31, relative to SEQ ID NO: 255.

3. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, wherein the GLP-1 receptor agonist peptide (Z1) comprises 2 lysine (Lys, K) residues at positions:

- 12 and either 21, 30 or 31, or
- 21 and either 30 or 31;

relative to SEQ ID NO: 255.

4. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, wherein the GLP-1 receptor agonist peptide (Z1) comprises 1 lysine residue (Lys, K) at any one of positions 12, 20, 21, 28, 30 or 31.

5. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, wherein the peptide linker (Z2) comprises 0-3 lysine (Lys, K) residues.

6. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, wherein the amylin receptor agonist peptide (Z3) comprises 0-3 lysine

(Lys, K) residues at any one of positions 2, 14, 18, 20, 23 and/or 29, relative to SEQ ID NO: 256.

7. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, wherein the amylin receptor agonist peptide (Z3) is a polypeptide represented by SEQ ID NO: 79.

8. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, comprising one to two C14-C20 diacids.

9. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, comprising a polypeptide represented by any one of SEQ ID NOs 117-236.

10. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, comprising a polypeptide represented by SEQ ID NO: 153.

11. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, which is any one of the following compounds:

Compound 0007
Compound 0009
Compound 0010
Compound 0019
Compound 0025
Compound 0035
Compound 0039
Compound 0040
Compound 0042
Compound 0044
Compound 0045
Compound 0051
Compound 0052
Compound 0056
Compound 0057
Compound 0071

Compound 0072
Compound 0073
Compound 0074
Compound 0075
Compound 0076
Compound 0077
Compound 0083
Compound 0084
Compound 0085
Compound 0086
Compound 0087
Compound 0089
Compound 0090
Compound 0092
Compound 0093
Compound 0094
Compound 0095
Compound 0096
Compound 0097
Compound 0098
Compound 0099
Compound 0100
Compound 0101
Compound 0102
Compound 0103
Compound 0105
Compound 0106
Compound 0109
Compound 0110
Compound 0111
Compound 0114
Compound 0115
Compound 0116
Compound 0120
Compound 0124

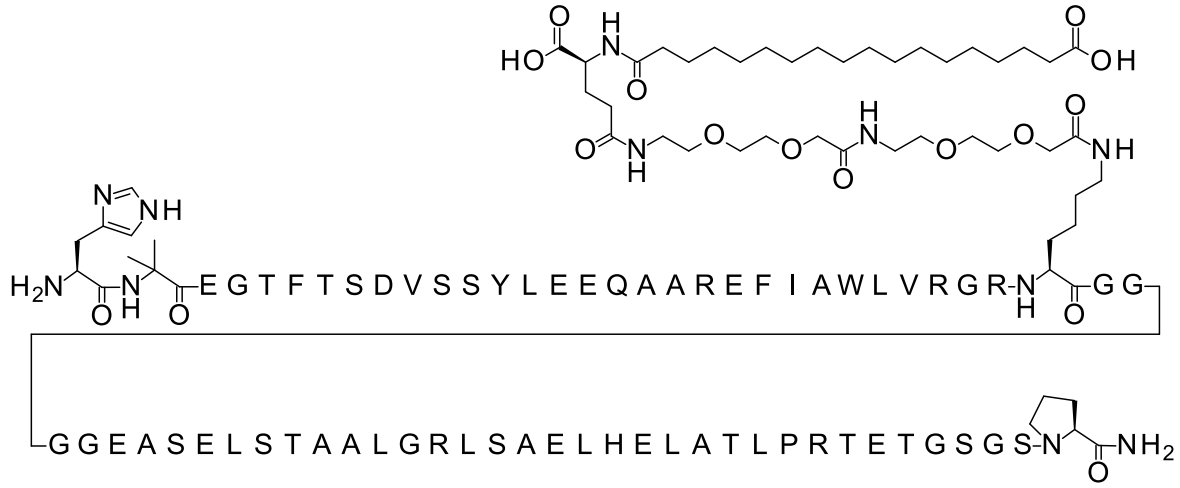
Compound 0125
Compound 0127
Compound 0128
Compound 0129
Compound 0131
Compound 0132
Compound 0141
Compound 0142
Compound 0144
Compound 0145
Compound 0146
Compound 0147
Compound 0151
Compound 0156
Compound 0157
Compound 0159
Compound 0160
Compound 0179
Compound 0180
Compound 0191
Compound 0202
Compound 0231
Compound 0232
Compound 0233
Compound 0234
Compound 0235
Compound 0254
Compound 0255
Compound 0259
Compound 0260
Compound 0261
Compound 0263
Compound 0264
Compound 0265
Compound 0266

Compound 0267
Compound 0268
Compound 0269
Compound 0270
Compound 0271
Compound 0272
Compound 0273
Compound 0280
Compound 0281
Compound 0284
Compound 0285
Compound 0292
Compound 0294
Compound 0295
Compound 0296
Compound 0297
Compound 0299
Compound 0396
Compound 0397
Compound 0411
Compound 0414
Compound 0415
Compound 0416
Compound 0417
Compound 0431
Compound 0433
Compound 0434
Compound 0435
Compound 0436
Compound 0437
Compound 0438
Compound 0439
Compound 0440
Compound 0472
Compound 0473

Compound 0474
Compound 0475
Compound 0482
Compound 0483
Compound 0484
Compound 0502
Compound 0503
Compound 0504
Compound 0506
Compound 0509
Compound 0511
Compound 0512
Compound 0516
Compound 0518
Compound 0528
Compound 0529
Compound 0539
Compound 0552
Compound 0560
Compound 0561
Compound 0562
Compound 0564
Compound 0565
Compound 0575
Compound 0576
Compound 0577
Compound 0578
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Compound 0631
Compound 0632
Compound 0633
Compound 0634

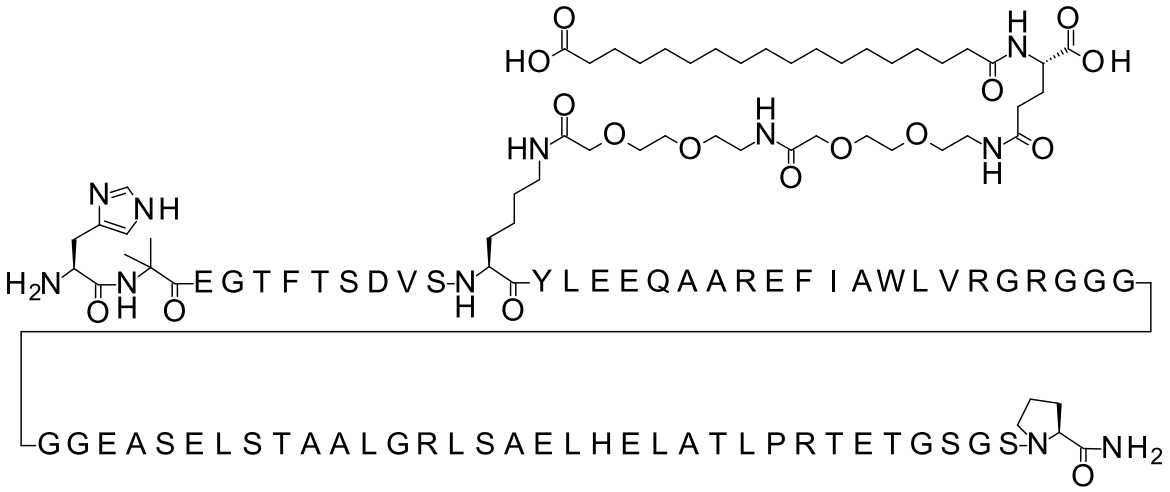
Compound 0635
Compound 0636
Compound 0637
Compound 0638
Compound 0639
Compound 0640
Compound 0648
Compound 0654
Compound 0655
Compound 0656
Compound 0657
Compound 0658
Compound 0659
Compound 0660
Compound 0661
Compound 0662
Compound 0663.

12. A GLP-1 receptor-amylin receptor co-agonist, which is H-Aib-EGTFTSDVSSYLEEQAAREFIAWLVRGR-K([2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl])-GGGGEASELSTAALGRLSAELHELATLPRTETGSGSP-amide (Compound 0111):



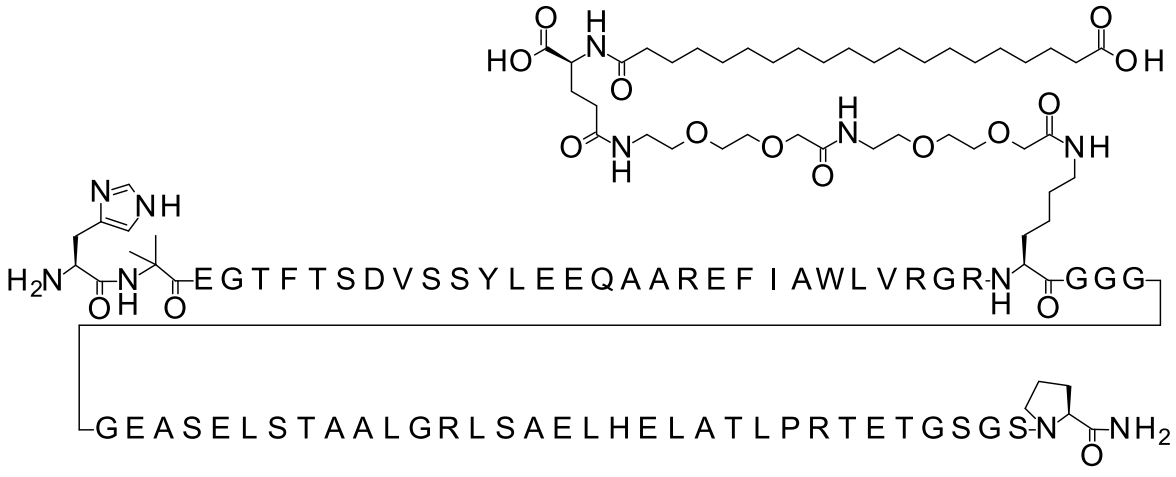
or

H-Aib-EGTFTSDVS-K([2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl])-YLEEQAAREFIAWLVRGRGGGGGEASELSTAALGRLSAELHELATLPRTETGSGSP-amide (Compound 0640):



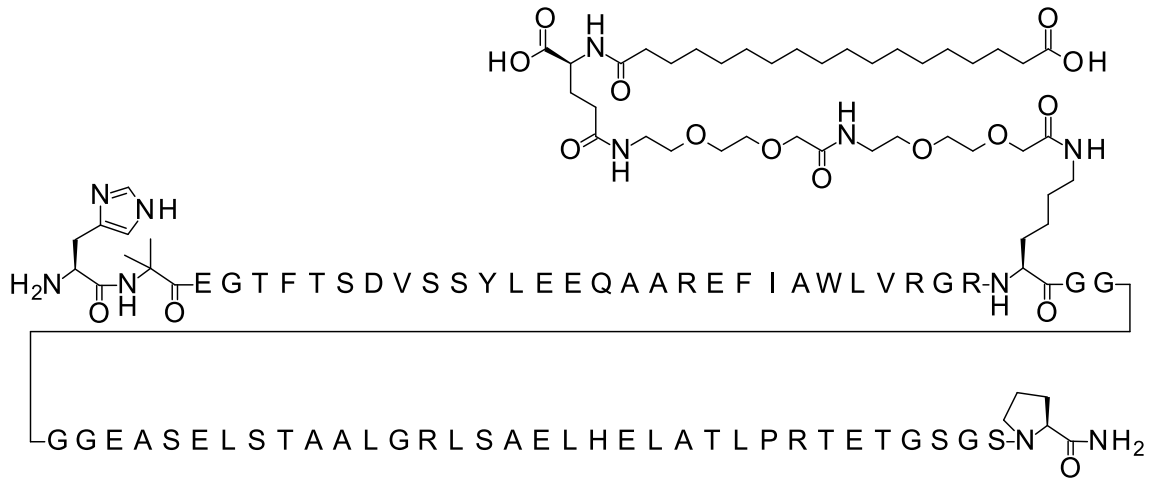
or

H-Aib-EGTFTSDVSSYLEEQAAREFIAWLVRGR-K([2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(19-carboxynonadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl])-GGGGEASELSTAALGRLSAELHELATLPRTETGSGSP-amide (Compound 0502):



13. The GLP-1 receptor-amylin receptor co-agonist according to claim 12, which is H-Aib-EGTFTSDVSSYLEEQAAREFIAWLVRGR-K([2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acety

l])-GGGGEASELSTAALGRLSAELHELATLPRTETGSGSP-amide (Compound 0111):



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14. A pharmaceutical formulation comprising a GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims.

15. Use of the GLP-1 receptor-amylin receptor co-agonist according to any one of claims 1- 13, or the pharmaceutical formulation according to claim 14, in the manufacture of a medicament for the treatment of a subject with any one or more of:

a) obesity, optionally in the presence of at least one weight-related comorbidity;

b) diabetes, optionally in the presence of at least one weight-related comorbidity;

c) cardiovascular disease;

d) non-alcoholic steatohepatitis; and/or

e) cognitive impairment, such as that caused by Alzheimer’s disease.

16. The use according to claim 15 for the treatment of a subject with obesity with an initial body mass index (BMI) of 27 or more, or the treatment of a subject with diabetes.