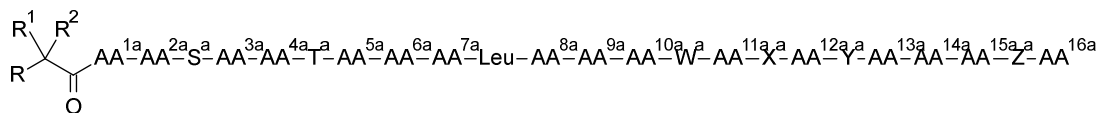


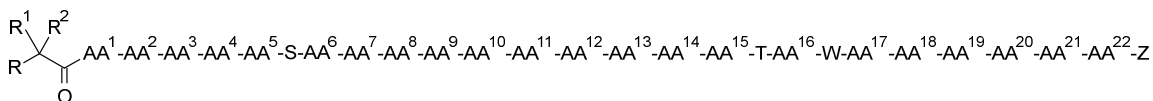
Claims

1. A compound comprising the sequence of formula (1a) or formula (1b):



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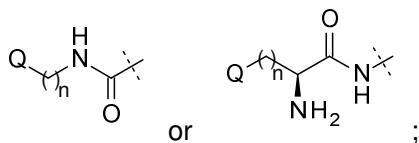
(1a); or



(1b)

wherein;

R is selected from:



10

Q is phenyl or a monocyclic heteroaryl ring each of which may be optionally substituted with one or more R^q groups;

R^q is selected from halogen, hydroxyl, amino or C₁₋₆ alkyl having an alkyl chain optionally containing one or more heteroatoms selected from O, N, or S;

15

n is 1 to 3;

R¹ and R² are independently selected from hydrogen or a C₁₋₆ alkyl group, or together with the carbon to which they are attached join to form a C₃₋₈ cycloalkyl or a heterocycl group;

S is the sequence -Glu-Nle-;

20

T is the sequence -Phe-Ile-;

W is the sequence -Trp-Leu-Ile-;

Z is absent or is -Pro-;

AA¹ is -NHCHR³CO-; wherein R³ is selected from -(CH₂)_yCONH₂, -(CH₂)_yCOOH or -(CH₂)_ytetrazolyl; where y is 1 or 2;

25

AA² is -Gly-, -DAla-, -Lys- optionally joined to AA⁵ via a lactam bridge or -Glu- optionally joined to AA⁵ via a lactam bridge;

AA³ is -Ser-Phe- or -Ser-2-F-α-Me-Phe-;

AA⁴ is -Ser- or -Glu- optionally joined to AA⁶ via a lactam bridge;

AA⁵ is -Asp- optionally joined to AA² via a lactam bridge or -Lys- optionally joined to

30

AA² or AA⁷ via a lactam bridge;

AA⁶ is -D-Phe-, -D-α-Me-Phe- or -Lys- optionally joined to AA¹⁰ via a lactam bridge;

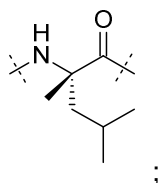
- AA⁷ is -Asp- optionally joined to AA⁵ via a lactam bridge, -Glu- optionally joined to AA¹⁰ via a lactam bridge or -Lys- optionally joined to AA¹⁰ via a lactam bridge;
- AA⁸ is -Ile or - α -Me-Leu-;
- AA⁹ is -Leu-Asp- or -Leu-ACPC-;
- 5 AA¹⁰ is -Asp- optionally joined to AA⁷ or AA¹⁴ via a lactam bridge, -Glu- optionally joined to AA⁷ or AA¹⁴ via a lactam bridge or -Lys- optionally joined to AA⁷ via a lactam bridge;
- AA¹¹ is -LysR- where LysR is an N-substituted Lysine residue, -Glu- optionally joined to AA¹⁴ via a lactam bridge or -Lys- optionally joined to AA¹⁵ via a lactam bridge;
- AA¹² is -Ala- or -AIB-;
- 10 AA¹³ is -Ala- or -AIB-;
- AA¹⁴ is -AIB- or is -Lys- optionally joined to AA¹⁰ or AA¹¹ via a lactam bridge;
- AA¹⁵ is -Asp- optionally joined to AA¹¹ via a lactam bridge or -Glu- optionally joined to AA¹⁶ via a lactam bridge;
- AA¹⁶ is -Asn-, -ACPC-, -Lys- optionally joined to AA¹⁷ via a lactam bridge or -Glu- optionally joined to AA¹⁷ via a lactam bridge;
- 15 AA¹⁷ is -Gln-, -ACPC-, -Lys- optionally joined to AA¹⁶ via a lactam bridge or -Glu- optionally joined to AA¹⁶ via a lactam bridge;
- AA¹⁸ is -Thr-, -Lys- optionally joined to AA²² via a lactam bridge or -Glu- optionally joined to AA²² via a lactam bridge;
- 20 AA¹⁹ is -Pro-, -PIPALA-, -Lys- or -Glu- optionally joined to AA²² via a lactam bridge;
- AA²⁰ is absent or is -Ile-, - α -Me-Leu- or -Pro-;
- AA²¹ is absent or is -Thr-;
- AA²² is absent or is -Lys- optionally joined to AA¹⁸ or AA¹⁹ via a lactam bridge or -Glu- optionally joined to AA¹⁸ via a lactam bridge;
- 25 S^a is the sequence -Ser-Phe-;
- T^a is the sequence -Glu-Nle-;
- W^a is the sequence -Ala-Ala-;
- X^a is the sequence -Asp-Phe-Ile-;
- Y^a is the sequence -Trp-Leu-Ile-;
- 30 Z^a is absent or is the sequence -Ile-Thr-;
- AA^{1a} is -NHCHR³CO-; wherein R³ is selected from -(CH₂)_yCONH₂, -(CH₂)_yCOOH or -(CH₂)_ytetrazolyl; where y is 1 or 2;
- AA^{2a} is -Gly-, -DAla-, -Lys- optionally joined to AA^{4a} via a lactam bridge or -Glu- optionally joined to AA^{4a} via a lactam bridge;
- 35 AA^{3a} is -Ser- or is -Glu- optionally joined to AA^{5a} via a lactam bridge;

AA^{4a} is -Asp- optionally joined to AA^{2a} via a lactam bridge, or -Lys- optionally joined to AA^{2a} or AA^{6a} via a lactam bridge;

AA^{5a} is -DPhe-, -Asp- optionally joined to AA^{8a} via a lactam bridge or -Lys- optionally joined to AA^{3a} via a lactam bridge;

5 AA^{6a} is -Thr-, -Asp- optionally joined to AA^{4a} or AA^{9a} via a lactam bridge, -Glu- optionally joined to AA^{9a} via a lactam bridge or -Lys- optionally joined to AA^{9a} via a lactam bridge;

AA^{7a} is -Ile- or an α -methyl Leucine residue of formula:



AA^{8a} is -Asp- or is -Lys- optionally joined to AA^{5a} via a lactam bridge;

10 AA^{9a} is -Leu-, -Lys- optionally joined to AA^{6a} or AA^{11a} via a lactam bridge, -Asp- optionally joined to AA^{6a} or AA^{11a} via a lactam bridge or -Glu- optionally joined to AA^{11a} via a lactam bridge;

AA^{10a} is -Lys- or is -Glu- optionally joined to AA^{11a} via a lactam bridge;

15 AA^{11a} is -Aib-, -Lys- optionally joined to AA^{9a} or AA^{10a} via a lactam bridge, -Glu- optionally joined to AA^{9a} via a lactam bridge or -Asp- optionally joined to AA^{9a} via a lactam bridge;

AA^{12a} is -Asn-, -Glu- optionally joined to AA^{13a} via a lactam bridge or -Lys- optionally joined to AA^{13a} via a lactam bridge;

20 AA^{13a} is -Gln-, -Asp- optionally joined to AA^{12a} via a lactam bridge or -Lys- optionally joined to AA^{12a} via a lactam bridge;

AA^{14a} is -Thr- or is -Lys- optionally joined to AA^{16a} via a lactam bridge;

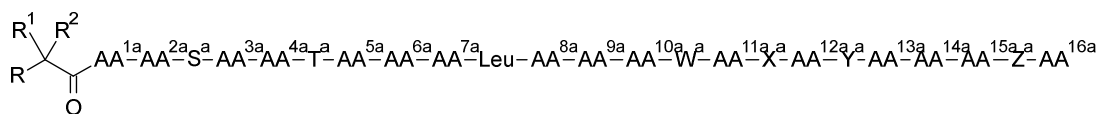
AA^{15a} is -Lys- optionally joined to AA^{16a} via a lactam bridge or -Glu- optionally joined to AA^{16a} via a lactam bridge;

25 AA^{16a} is absent or is -Asp-, -Phe-, -Lys- optionally joined to AA^{15a} via a lactam bridge or -Glu- optionally joined to AA^{14a} or AA^{15a} via a lactam bridge;

wherein the C-terminus is a carboxyl group or a carboxamide group, or is adjoined to any natural or non-natural amino acid sequence or any other moiety, functional group or groups, and wherein the compound contains one, two, three, four or five lactam bridges;

30 or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof.

2. The compound according to claim 1 according to formula (1a):

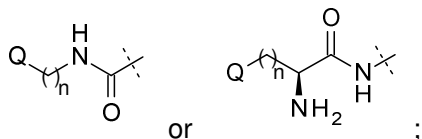


(1a)

wherein;

5

R is selected from:



Q is phenyl or a monocyclic heteroaryl ring each of which may be optionally substituted with one or more R^q groups;

10 R^q is selected from halogen, hydroxyl, amino or C₁₋₆ alkyl having an alkyl chain optionally containing one or more heteroatoms selected from O, N, or S;

n is 1 to 3;

R¹ and R² are independently selected from hydrogen or a C₁₋₆ alkyl group, or together with the carbon to which they are attached join to form a C₃₋₈ cycloalkyl or a heterocyclyl group;

15

S^a is the sequence -Ser-Phe-;

T^a is the sequence -Glu-Nle-;

W^a is the sequence -Ala-Ala-;

X^a is the sequence -Asp-Phe-Ile-;

Y^a is the sequence -Trp-Leu-Ile-;

20

Z^a is absent or is the sequence -Ile-Thr-;

AA^{1a} is -NHCHR³CO-; wherein R³ is selected from -(CH₂)_yCONH₂, -(CH₂)_yCOOH or -(CH₂)_ytetrazolyl; where y is 1 or 2;

AA^{2a} is -Gly-, -DAla-, -Lys- optionally joined to AA^{4a} via a lactam bridge or -Glu- optionally joined to AA^{4a} via a lactam bridge;

25

AA^{3a} is -Ser- or is -Glu- optionally joined to AA^{5a} via a lactam bridge;

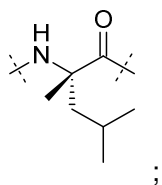
AA^{4a} is -Asp- optionally joined to AA^{2a} via a lactam bridge, or -Lys- optionally joined to AA^{2a} or AA^{6a} via a lactam bridge;

AA^{5a} is -DPhe-, -Asp- optionally joined to AA^{8a} via a lactam bridge or -Lys- optionally joined to AA^{3a} via a lactam bridge;

30

AA^{6a} is -Thr-, -Asp- optionally joined to AA^{4a} or AA^{9a} via a lactam bridge, -Glu- optionally joined to AA^{9a} via a lactam bridge or -Lys- optionally joined to AA^{9a} via a lactam bridge;

AA^{7a} is -Ile- or an α-methyl Leucine residue of formula:



AA^{8a} is -Asp- or is -Lys- optionally joined to AA^{5a} via a lactam bridge;

AA^{9a} is -Leu-, -Lys- optionally joined to AA^{6a} or AA^{11a} via a lactam bridge, -Asp- optionally joined to AA^{6a} or AA^{11a} via a lactam bridge or -Glu- optionally joined to AA^{11a} via a lactam bridge;

AA^{10a} is -Lys- or is -Glu- optionally joined to AA^{11a} via a lactam bridge;

AA^{11a} is -Aib-, -Lys- optionally joined to AA^{9a} or AA^{10a} via a lactam bridge, -Glu- optionally joined to AA^{9a} via a lactam bridge or -Asp- optionally joined to AA^{9a} via a lactam bridge;

AA^{12a} is -Asn-, -Glu- optionally joined to AA^{13a} via a lactam bridge or -Lys- optionally joined to AA^{13a} via a lactam bridge;

AA^{13a} is -Gln-, -Asp- optionally joined to AA^{12a} via a lactam bridge or -Lys- optionally joined to AA^{12a} via a lactam bridge;

AA^{14a} is -Thr- or is -Lys- optionally joined to AA^{16a} via a lactam bridge;

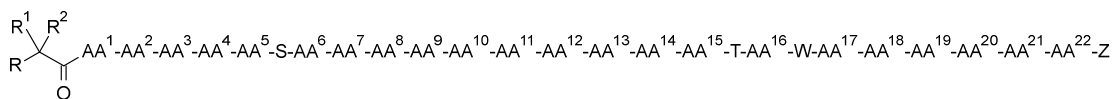
AA^{15a} is -Lys- optionally joined to AA^{16a} via a lactam bridge or -Glu- optionally joined to AA^{16a} via a lactam bridge;

AA^{16a} is absent or is -Asp-, -Phe-, -Lys- optionally joined to AA^{15a} via a lactam bridge or -Glu- optionally joined to AA^{14a} or AA^{15a} via a lactam bridge;

wherein the AA^{15a} or AA^{16a} C-terminus is a carboxyl group or a carboxamide group, or is adjoined to any natural or non-natural amino acid sequence or any other moiety, functional group or groups, and wherein the compound contains one or two lactam bridges;

or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof.

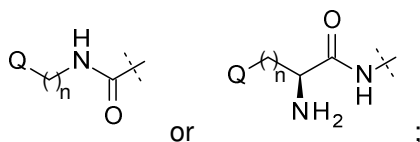
3. The compound according to claim 1 of formula (1b)



(1b)

wherein;

R is selected from:



Q is phenyl or a monocyclic heteroaryl ring each of which may be optionally substituted with one or more R^q groups;

R^q is selected from halogen, hydroxyl, amino or C_{1-6} alkyl having an alkyl chain optionally containing one or more heteroatoms selected from O, N, or S;

n is 1 to 3;

R^1 and R^2 are independently selected from hydrogen or a C_{1-6} alkyl group, or together with the carbon to which they are attached join to form a C_{3-8} cycloalkyl or a heterocyclyl group;

S is the sequence -Glu-Nle-;

T is the sequence -Phe-Ile-;

W is the sequence -Trp-Leu-Ile-;

Z is absent or is -Pro-;

AA^1 is -NHCHR³CO-; wherein R^3 is selected from $-(CH_2)_yCONH_2$, $-(CH_2)_yCOOH$ or $-(CH_2)_y$ tetrazolyl; where y is 1 or 2;

AA^2 is -Gly-, -DAla-, -Lys- optionally joined to AA^5 via a lactam bridge or -Glu- optionally joined to AA^5 via a lactam bridge;

AA^3 is -Ser-Phe or -Ser-2-F- α -Me-Phe-;

AA^4 is -Ser- or -Glu- optionally joined to AA^6 via a lactam bridge;

AA^5 is -Asp- optionally joined to AA^2 via a lactam bridge or -Lys- optionally joined to AA^2 or AA^7 via a lactam bridge;

AA^6 is -D-Phe-, -D- α -Me-Phe- or -Lys- optionally joined to AA^{10} via a lactam bridge;

AA^7 is -Asp- optionally joined to AA^5 via a lactam bridge, -Glu- optionally joined to AA^{10} via a lactam bridge or -Lys- optionally joined to AA^{10} via a lactam bridge;

AA^8 is -Ile or - α -Me-Leu-;

AA^9 is -Leu-Asp- or -Leu-ACPC-;

AA^{10} is -Asp- optionally joined to AA^7 or AA^{14} via a lactam bridge, -Glu- optionally joined to AA^7 or AA^{14} via a lactam bridge or -Lys- optionally joined to AA^7 via a lactam bridge;

AA^{11} is -LysR- where LysR is an N-substituted Lysine residue, -Glu- optionally joined to AA^{14} via a lactam bridge or -Lys- optionally joined to AA^{15} via a lactam bridge;

AA^{12} is -Ala- or -AIB-;

AA^{13} is -Ala- or -AIB-;

AA^{14} is -AIB- or is -Lys- optionally joined to AA^{10} or AA^{11} via a lactam bridge;

AA¹⁵ is -Asp- optionally joined to AA¹¹ via a lactam bridge or -Glu- optionally joined to AA¹⁶ via a lactam bridge;

AA¹⁶ is -Asn-, -ACPC-, -Lys- optionally joined to AA¹⁷ via a lactam bridge or -Glu- optionally joined to AA¹⁷ via a lactam bridge;

5 AA¹⁷ is -Gln-, -ACPC-, -Lys- optionally joined to AA¹⁶ via a lactam bridge or -Glu- optionally joined to AA¹⁶ via a lactam bridge;

AA¹⁸ is -Thr-, -Lys- optionally joined to AA²² via a lactam bridge or -Glu- optionally joined to AA²² via a lactam bridge;

AA¹⁹ is -Pro-, -PIPALA-, -Lys- or -Glu- optionally joined to AA²² via a lactam bridge;

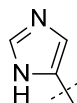
10 AA²⁰ is absent or is -Ile-, - α -Me-Leu- or -Pro-;

AA²¹ is absent or is -Thr-;

AA²² is absent or is -Lys- optionally joined to AA¹⁸ or AA¹⁹ via a lactam bridge or -Glu- optionally joined to AA¹⁸ via a lactam bridge;

15 wherein the C-terminus is a carboxyl group or a carboxamide group, or is adjoined to any natural or non-natural amino acid sequence or any other moiety, functional group or groups, and wherein the compound contains three, four or five lactam bridges;
or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof.

20 4. The compound according to any one of claims 1 to 3, wherein Q is:



25 5. The compound according to any one of claims 1 to 4, wherein n is 1 or 2.

6. The compound as defined in any one of claims 1 to 5, wherein R¹ and R² are independently selected from hydrogen or a C₁₋₆ alkyl group.

7. The compound according to claim 6, wherein R¹ and R² are both methyl.

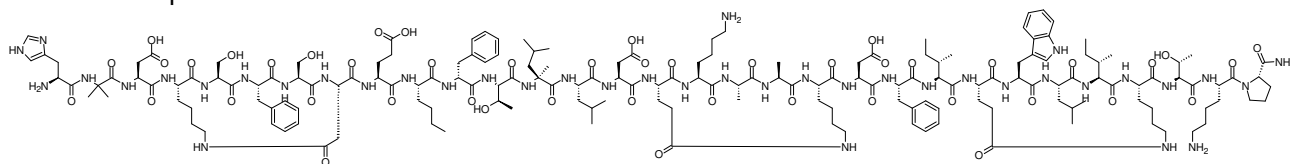
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8. The compound according to any one of claims 1 to 7, wherein R³ represents -CH₂tetrazolyl or CH₂COOH.

9. The compound according to any one of claims 1 to 8, wherein AA² is cyclised to AA⁵, and either AA¹⁰ is cyclised to one of AA⁶, AA⁷ or AA¹⁴ or AA¹¹ is cyclised to one of AA¹⁴ or AA¹⁵ and either AA¹⁶ is cyclised to AA¹⁷ or AA²² is cyclised to either AA¹⁸ or AA¹⁹.
- 5 10. The compound according to any one of claims 1 to 8, wherein AA¹⁶ is cyclised to AA¹⁷ and AA²² is cyclised to either AA¹⁸ or AA¹⁹.
11. The compound according to any one of claims 1 to 8, wherein AA^{2a} is -Gly- or -DAla-, AA^{3a} is -Ser-, AA^{4a} is -Asp-, AA^{5a} is -DPhe-, AA^{6a} is -Thr-, AA^{8a} is -Asp-, AA^{10a} is -Lys- and AA^{15a} is -Lys-.
- 10 12. The compound according to any one of claims 1 to 11, wherein AA^{9a} is -Leu-, -Glu- joined to AA^{11a} via a lactam bridge or -Lys- joined to AA^{11a} via a lactam bridge.
- 15 13. The compound according to any one of claims 1 to 12, wherein AA^{11a} is -Lys- optionally joined to AA^{9a} via a lactam bridge or -Glu- joined to AA^{9a} via a lactam bridge.
14. The compound according to any one of claims 1 to 13, wherein AA^{12a} is -Asn- or is -Glu- joined to AA^{13a} via a lactam bridge.
- 20 15. The compound according to any one of claims 1 to 14, wherein AA^{13a} is -Gln- or is -Lys- joined to AA^{12a} via a lactam bridge.
16. The compound according to any one of claims 1 to 15, wherein AA^{14a} is -Thr- or is -Lys- joined to AA^{16a} via a lactam bridge.
- 25 17. The compound according to any one of claims 1 to 16, wherein AA^{16a} is -Phe- or is -Glu- joined to AA^{14a} via a lactam bridge.
18. The compound according to any one of claims 1 to 17, wherein Z^a and AA^{16a} are absent.
19. The compound according to any one of claims 1 to 18, wherein the C-terminus is a carboxamide group.
- 35 20. The compound according to claim 1 which is selected from any one of Examples 1 to 117.

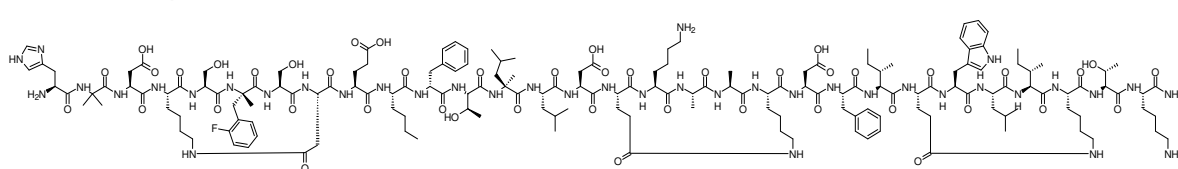
21. The compound according to claim 1 which is selected from the group consisting of:

Example 30:

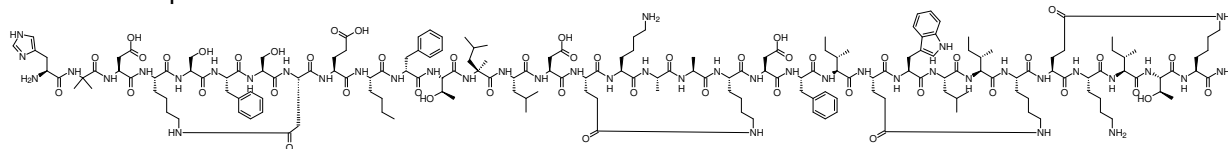


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Example 31:

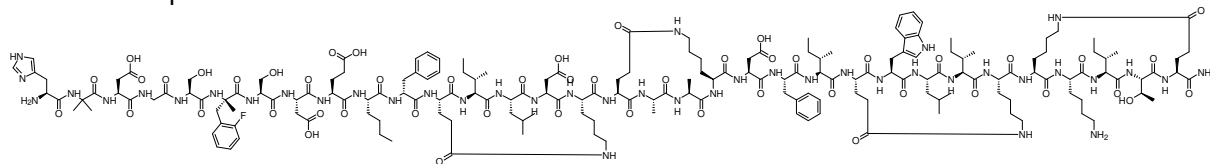


Example 46:

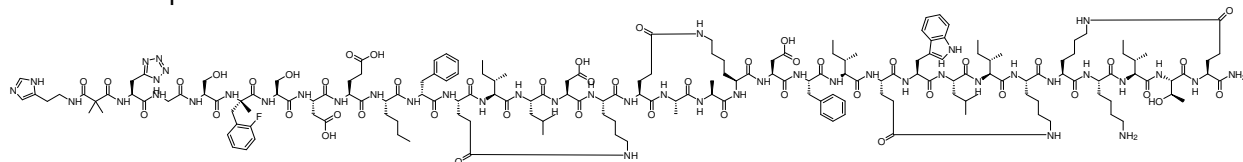


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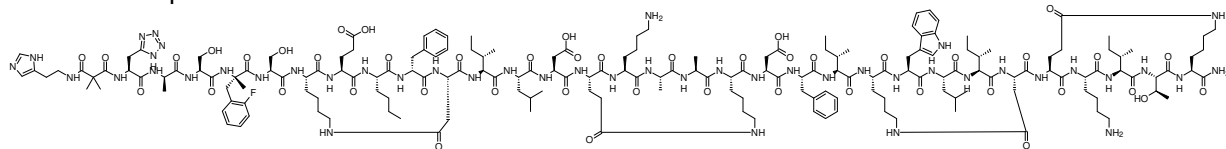
Example 48:



Example 52:

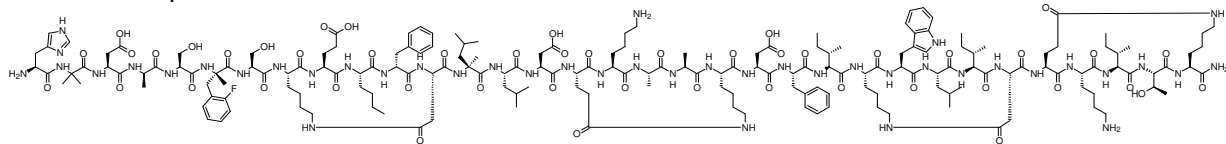


Example 55:



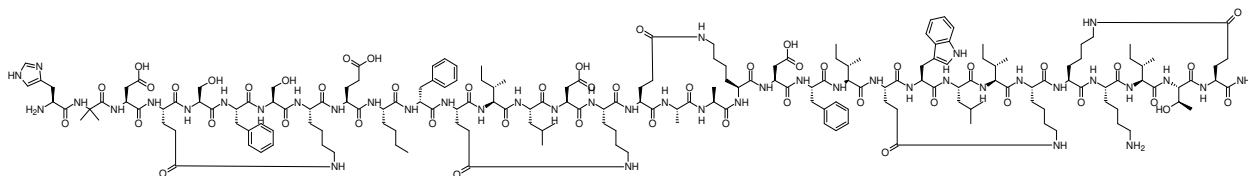
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Example 60:

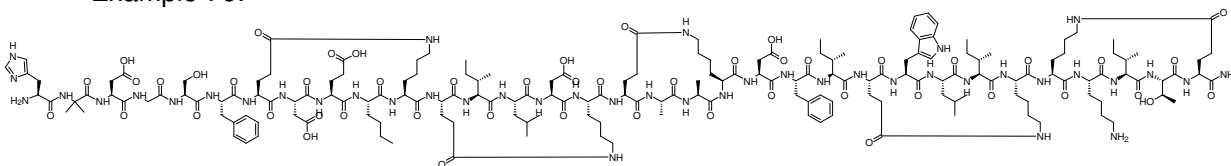


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Example 74:

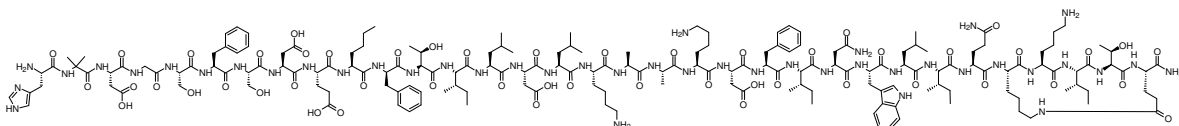


Example 76:

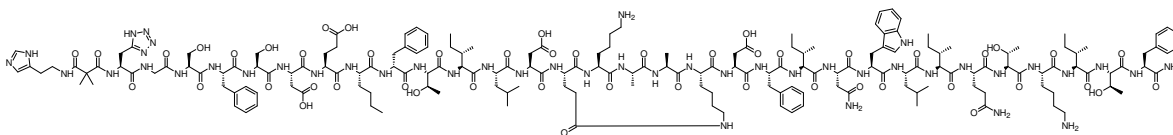


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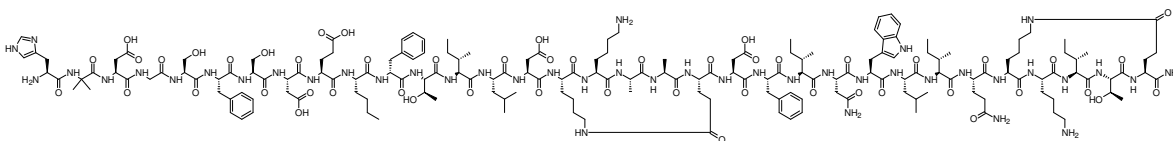
Example 93:



Example 96:

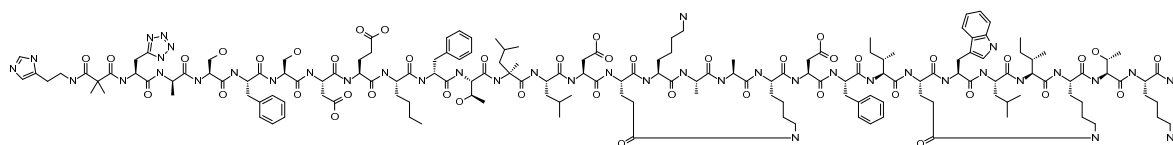


Example 115:



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Example 117:



or a tautomer, salt or zwitterion thereof.

15

22. The compound according to any one of claims 1 to 21 having GLP-1 and/or GLP-2 receptor agonist activity.

23. The compound according to claim 22 having higher GLP-2 receptor agonist activity compared to GLP-1 receptor agonist activity.

20

24. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 23 and a pharmaceutically acceptable excipient.

25. Use of the compound or composition according to any one of claims 1 to 24 for use in the manufacture of a medicament for the treatment of gastrointestinal and metabolic diseases, promoting intestinal recovery and nutritional status of patients with malabsorption disorders, intestinal failure, intestinal insufficiency, diarrheal diseases, chronic inflammatory bowel disorders, improve mucosal barrier function, ameliorate gut inflammation, inflammatory disorders, celiac disease, congenital and acquired digestion and malabsorption syndromes, chronic diarrhoeal diseases, conditions caused by mucosal damage (e.g. cancer treatment), hyperglycemia during enteral and parenteral nutrition therapy in patients with intestinal failure, insufficiency or malabsorption disorders, gastrointestinal injury, diarrheal diseases, intestinal insufficiency, intestinal failure, acid-induced intestinal injury, arginine deficiency, obesity, celiac disease, chemotherapy-induced enteritis, diabetes, obesity, fat malabsorption, steatorrhea, autoimmune diseases, food allergies, gastric ulcers, gastrointestinal barrier disorders, Parkinson's disease, sepsis, bacterial peritonitis, inflammatory bowel disease, chemotherapy-associated tissue damage, bowel trauma, bowel ischemia, mesenteric ischemia, short bowel syndrome, malnutrition, necrotizing enterocolitis, necrotizing pancreatitis, neonatal feeding intolerance, NSAID-induced gastrointestinal damage, nutritional insufficiency, total parenteral nutrition damage to gastrointestinal tract, neonatal nutritional insufficiency, radiation-induced enteritis, radiation-induced injury to the intestines, mucositis, pouchitis, ischemia, obesity, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), insulin resistance, hyperglycemia, insulin resistance, glucose intolerance, brush border enzyme deficiencies (congenital lactase deficiency, congenital sucrase-isomaltase deficiency, congenital maltase-glucoamylase-deficiency), defects of membrane carriers (glucose-galactose-malabsorption, fructose malabsorption, Fanconi-Bickel syndrome, Acrodermatitis enteropathica, Congenital chloride / sodium diarrhoea, Lysinuric protein intolerance, Primary biliary malabsorption, cystic fibrosis), enzyme deficiencies (hereditary pancreatitis, congenital pancreas lipase deficiency), lipid/lipoprotein metabolism defects (chylomicron retention disease, hypobetalipoproteinemia, abetalipoproteinemia), defects of enterocyte differentiation or cellular polarisation (Microvillous atrophy, Tufting enteropathy, Trichohepatoenteric syndrome, Familiar haemophagocytic lymphohistiocytosis type 5), defects of enteroendocrine cells (Congenital malabsorptive diarrhoea, anendocrinosis, protein-convertase 1/3 deficiency), congenital diarrheal diseases.

26. The use according to claim 25, wherein the disorder is Tufting enteropathy.