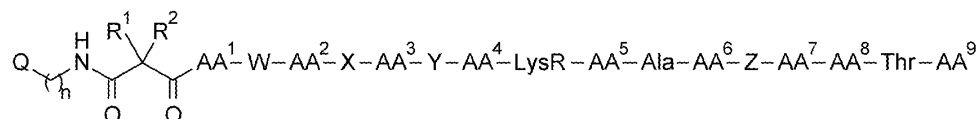


Claims

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



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(1)

wherein;

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;

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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;

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W is a sequence -Gly-Ser-, -Ala-Ser- or -DAla-Ser-;

X is a sequence -Ser-Asp-Glu-Nle-DPhe-Thr- or -Ser-Asp-Glu-Nle-Asn-Thr-;

Y is a sequence -Leu-Asp-;

Z is a sequence -Asp-Phe-Ile-Asn-Trp-Leu-Ile-Gln-Thr-;

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

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AA² is -NHCR^{4a}R^{4b}CO-; wherein R^{4a} is hydrogen or a C₁₋₃ alkyl group; and R^{4b} is a benzyl group optionally substituted with one or more halogen groups, C₁₋₃ alkyl groups or C₁₋₃ alkoxy groups;

AA³ is -Aib- or -Ile-;

AA⁴ is -NHCR^{5a}R^{5b}CO-; wherein R^{5a} is hydrogen or a C₁₋₃ alkyl group; and R^{5b} is an optionally substituted C₁₋₆ alkyl group, or -(CH₂)_xCONH₂; where x is 1 or 2;

25

AA⁵ is -Ala- or -Aib-;

AA⁶ is -Lys-, -Aib- or a group -LysR-;

AA⁷ is -Lys- or -Arg-;

AA⁸ is -NHCR^{6a}R^{6b}CO-; wherein R^{6a} is hydrogen or a C₁₋₃ alkyl group; and R^{6b} is an optionally substituted C₁₋₆ alkyl group;

AA⁹ is -NHCR^{7a}R^{7b}CO-; wherein R^{7a} is hydrogen or a C₁₋₃ alkyl group; and R^{7b} is - (CH₂)_zCOOH, or a benzyl group optionally substituted with one or more halogen groups, C₁₋₃ alkyl groups or C₁₋₃ alkoxy groups; where z is 1 or 2;

LysR is an N-substituted Lysine residue;

wherein the AA⁹ 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;

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

2. The compound according to claim 1, wherein Q is:



3. The compound according to claim 1 or claim 2, wherein n is 2.

4. The compound as defined in any one of claims 1 to 3, wherein R¹ and R² are independently selected from hydrogen or a C₁₋₆ alkyl group.

5. The compound according to claim 4, wherein R¹ and R² are both methyl.

6. The compound according to any one of claims 1 to 5, wherein R³ represents -CH₂tetrazolyl.

7. The compound according to any one of claims 1 to 6, wherein R^{4a} is hydrogen or methyl.

8. The compound according to claim 7, wherein R^{4b} is benzyl optionally substituted with fluorine.

9. The compound according to any one of claims 1 to 8, wherein R^{5a} is hydrogen or methyl.

10. The compound according to claim 9, wherein R^{5b} is isobutyl or $-\text{CH}_2\text{CONH}_2$.

11. The compound according to any one of claims 1 to 10, wherein R^{6a} is hydrogen or methyl.

12. The compound according to claim 11, wherein R^{6b} is isobutyl or *sec*-butyl.

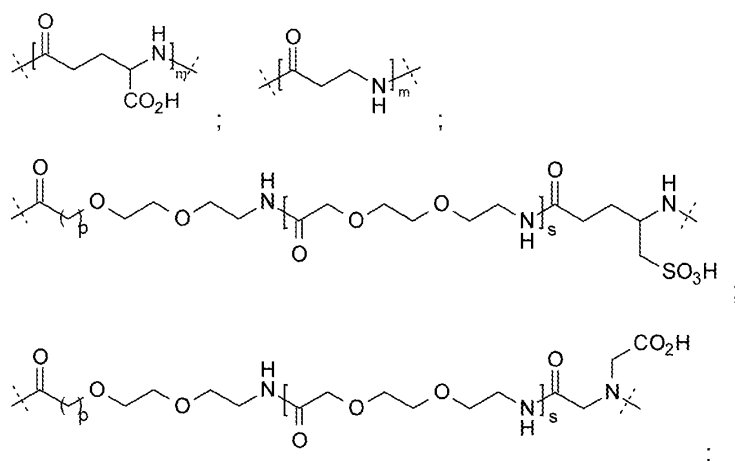
13. The compound according to any one of claims 1 to 12, wherein R^{7a} is hydrogen or methyl.

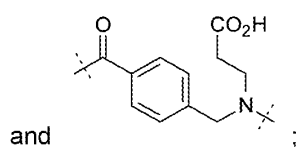
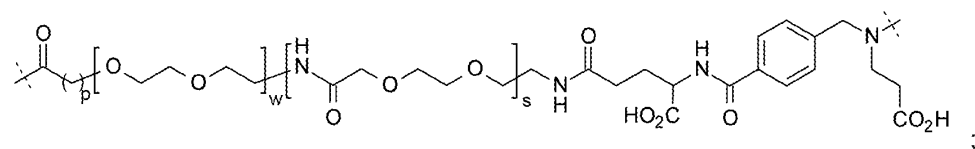
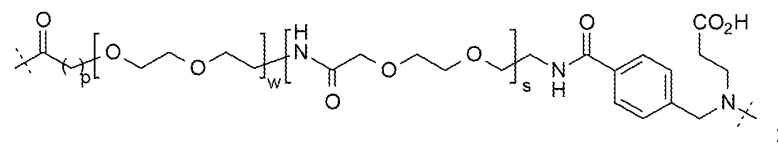
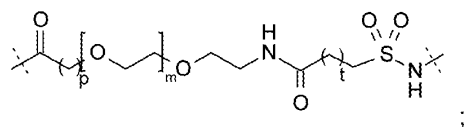
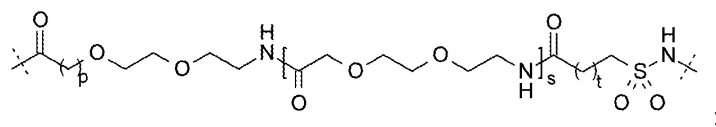
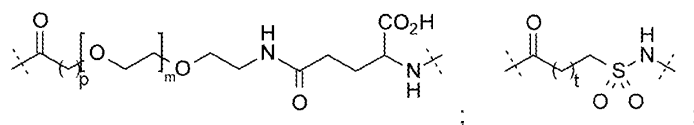
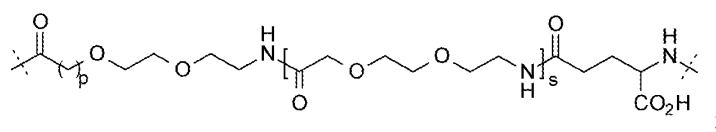
14. The compound according to claim 13, wherein R^{7b} is benzyl or $-\text{CH}_2\text{COOH}$.

15. The compound according to any one of claims 1 to 14, wherein LysR is an N-substituted Lysine residue, wherein the N-substituent is selected from: $-\text{CO}(\text{CH}_2)_q\text{CH}_3$; $-\text{CO}(\text{CH}_2)_q\text{CO}_2\text{H}$; $-\text{CO}(\text{CH}_2)_q\text{CHCH}_2$; $-\text{COO}(\text{CH}_2)_q\text{CH}_3$; $-\text{COO}(\text{CH}_2)_q\text{CO}_2\text{H}$ and $-\text{COO}(\text{CH}_2)_q\text{CHCH}_2$; where q is 1 to 22.

16. The compound according to any one of claims 1 to 14, wherein LysR is an N-substituted Lysine residue, wherein the N-substituent is a group $-\text{L}-\text{G}$;

wherein L is selected from the group consisting of:

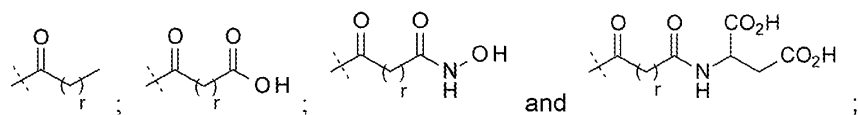




and

and G is selected from the group consisting of:

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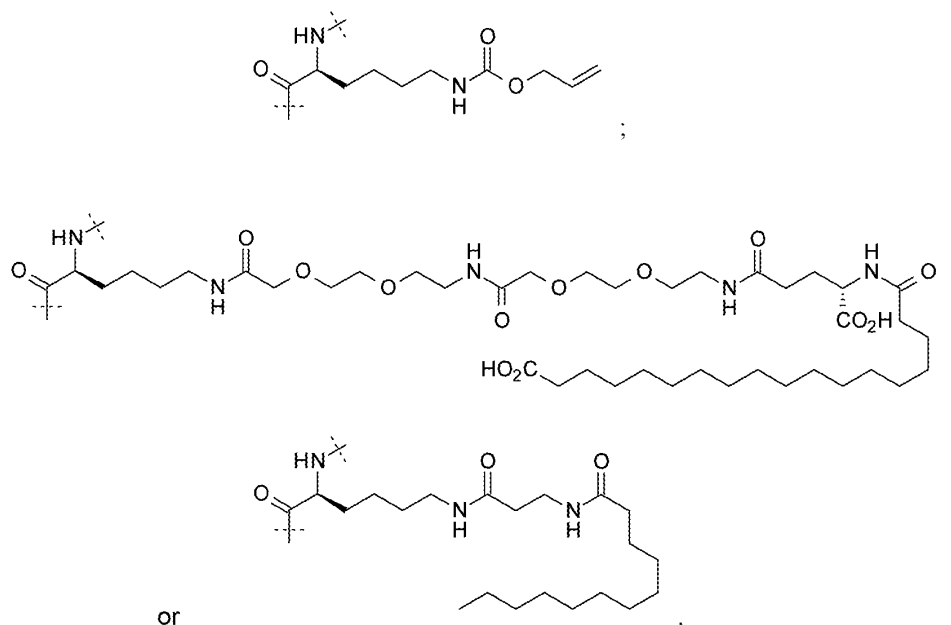
where m is 1 to 23;

p is 1 to 3;

r is 1 to 20;
s is 0 to 3;
t is 0 to 4;
and w is 0 to 4.

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17. The compound according to claim 15, wherein LysR is selected from:



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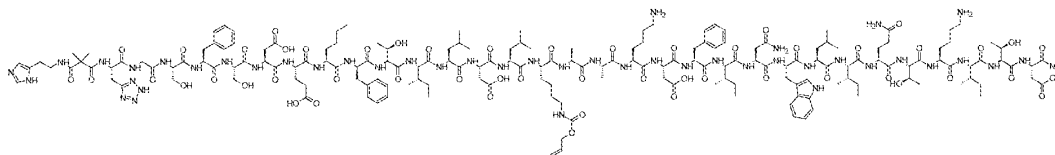
18. The compound according to any one of claims 1 to 17, wherein the AA⁹ C-terminus is a carboxamide group.

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19. The compound according to claim 1 which is selected from any one of Examples 1 to 23.

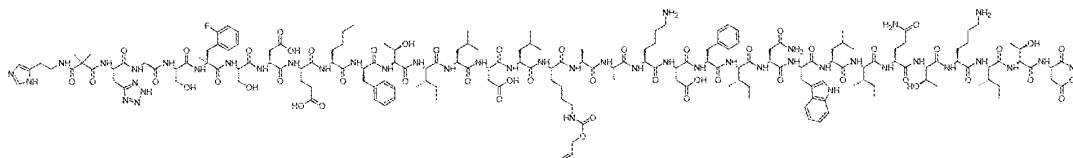
20. The compound according to claim 1 which is selected from:

Example 1:



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or Example 3:



or a tautomer, salt or zwitterion thereof.

21. The compound according to any one of claims 1 to 20 having GLP-1 and/or GLP-2 receptor agonist activity.
22. The compound according to claim 21 having higher GLP-2 receptor agonist activity compared to GLP-1 receptor agonist activity.
23. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 22 and a pharmaceutically acceptable excipient.
24. The compound or composition according to any one of claims 1 to 23 for use in 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) or congenital diarrheal diseases.

25. The use according to claim 24, wherein the disorder is Tufting enteropathy.