

POLYPEPTIDE FOR REPAIRING MUCOSAL DAMAGE OR SKIN WOUNDS AND USE THEREOF

Technical Field

Provided is a novel polypeptide for repairing mucosal damage or skin wounds and the use thereof. The polypeptide provided herein has no homology with any known polypeptides, can exist stably both *in vivo* and *in vitro*, and has the effect of regulating the proliferation and differentiation of stem cells to repair mucosal damage or skin injury. In addition, Provided is the use of the novel polypeptide in repairing mucosal damage or skin wounds by regulating the proliferation and differentiation of stem cells and in preventing, alleviating or treating a gastrointestinal disease.

Background Art

Skin wounds and/or mucosal damage are common pathological characteristics of many diseases. Skin wounds or skin injury refers to damage to normal skin (tissue) caused by external injury-causing factors such as surgery, external forces, heat, electric current, chemicals and low temperatures and internal factors in the body such as local blood supply disturbance. Skin injury is often accompanied by the destruction of skin integrity and loss of a certain amount of normal tissues; in addition, the normal function of the skin is impaired. It is also referred to as a wound or trauma. At present, proteins/polypeptide drugs, including basic fibroblast growth factor, epidermal growth factor, platelet growth factor, granulocyte-macrophage colony-stimulating factor, growth hormone, etc., have obvious wound healing, skin care, anti-wrinkle, and anti-aging effects. However, these proteins/polypeptide drugs have relatively long amino acid sequences, leading to the disadvantages of high preparation cost and poor stability, so the application thereof is limited to some extent.

Human mucosa refers to the inner layers of the respiratory system, digestive system, genitourinary system and other cavities or cystic muscular organs. It is the second largest barrier in the human body after skin and includes the oral cavity, pharynx, trachea, esophagus, stomach, intestine, vagina, bladder, etc. The tube walls or bladder walls of these organs all have the same stratification rules and also have characteristics that are compatible with the functions thereof. The embryonic origins, tissue structures, pathological processes, clinical manifestations, prognosis etc. thereof all have common characteristics.

Chronic gastritis is a chronic inflammation of gastric mucosa, which is a common and frequently occurring disease in gastroenterology. Clinically, chronic inflammation of gastric mucosa caused by various causes (i.e., manifested as infiltration of monocytes and lymphocytes in pathology) and (or) glandular atrophic lesions are called chronic gastritis. Chronic atrophic gastritis (CAG), which is characterized by atrophy of gastric mucosa epithelium and glands, has a hidden onset, long course, non-specific symptoms, is difficult to cure, accounts for 11-31% among chronic gastritis, and it is common in middle-aged and elderly people. The onset thereof is associated with age and has nothing to do with gender. The disease has a slow onset, a lingering tendency, slow recovery, and treatment difficulties. Chronic atrophic gastritis is an important stage in the occurrence and development of gastric cancer and is regarded as a gastric precancerous lesion. In 1978, the World Health Organization (WHO) classified CAG as a precancerous state, which is often accompanied by precancerous lesions such as pseudopyloric metaplasia and intestinal metaplasia or atypical hyperplasia phase. Especially for those with diffuse intestinal metaplasia or atypical hyperplasia, canceration is more likely to occur. Most professionals in the field agree with the development mode of chronic superficial gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and intestinal gastric cancer. Therefore, early accurate diagnosis and treatment are of great significance to patients with chronic atrophic gastritis. At present, modern medicine mainly treats this disease by means of symptom improvement and surgical intervention, and there is yet no good strategy for gland atrophy and intestinal metaplasia. CAG is an important stage for the transformation of chronic gastritis into gastric cancer. Active treatment of CAG

is of far-reaching significance to prevent its canceration and reduce the incidence of gastric cancer. Seeking for an effective method for treating atrophic gastritis is one of the important measures to better prevent gastric cancer.

Clinically, mucosal tissue injuries may lead to gastrointestinal diseases such as chronic gastritis and digestive tract ulcers. There are two different mechanisms for mucosal epithelium repair, i.e., restitution and regeneration or renewal (Cur. Med. Chem., 2008, 15, 3133-3144). Restitution or recovery generally begins within a few minutes after injury, and superficial lesions are quickly repaired by cell migration. Regeneration refers to continuous regeneration through differentiation and proliferation of stem cells and progenitor cells, which lasts for several days to several months.

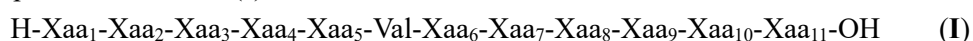
Epidermal growth factor (EGF) is a polypeptide composed of 53 amino acid residues, which widely exists in various tissues, organs and body fluids and can promote epithelial cell proliferation to protect the skin. Epidermal growth factor mainly promotes the proliferation and growth of skin tissue cells, so that new cells can replace aging cells, thus having anti-aging, skin care and health care functions, etc. Epidermal growth factor has been reported to have the function of repairing wounds. When skin wounds need to be disinfected and debrided, disinfectants containing iodine or hydrogen peroxide will be used, and as a result, EGF is unstable under this condition. Growth factors are related to healing from gastrointestinal anastomosis (J. Surgical Res. 2014; 17:202-210); however, when EGF is orally administered through the gastrointestinal tract, it degrades after entering the body and cannot achieve therapeutic effects.

Therefore, there is a need for a peptide substance which is stable *in vivo* and *in vitro* and can treat skin and/or mucosal damage, especially gastrointestinal mucosal damage.

Summary of the Invention

In order to overcome the deficiencies and defects in the prior art, an object of the present invention is to provide a novel class of polypeptides.

In a first aspect, Provided is a compound of Formula (I) or a physiologically compatible salt thereof, wherein the compound of Formula (I) is as follows:



wherein

Xaa₁ is Pro, Gly, Ala or absent;

Xaa₂ is Ala, Leu, Ile, Gly, Cys, Ser or absent;

Xaa₃ is Ala, Pro, Gly, Leu, Ile, Cys, Ser or absent;

Xaa₄ is Glu, Gln, Asp, Asn, Leu, Ile, Val or absent;

Xaa₅ is Pro, Gly, Ala, Val or absent;

Xaa₆ is Pro, Gly or Ala;

Xaa₇ is Leu, Phe, Val, Ala, Tyr, Glu, Lys, Asp, Ile, Met or absent;

Xaa₈ is Val, Leu, Gln, Ile, Met or absent;

Xaa₉ is Lys, Arg, His, Asp, Val or absent;

Xaa₁₀ is Glu, Gln, Asp, Asn or absent; and

Xaa₁₁ is Glu, Asp, Asn, Gln or absent,

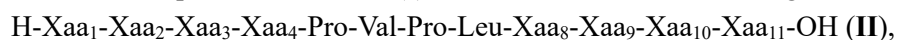
provided that at most 9 of Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀ and Xaa₁₁ are absent.

In one embodiment, Xaa₅ is Pro.

In one embodiment, Xaa₆ is Pro.

In one embodiment, Xaa₇ is Leu.

In one embodiment, the compound of Formula (I) has a structure of the following Formula (II):



wherein

Xaa₁ is Pro, Gly, Ala or absent;
Xaa₂ is Ala, Leu, Ile, Gly, Cys, Ser or absent;
Xaa₃ is Ala, Pro, Gly, Leu, Ile, Cys, Ser or absent;
Xaa₄ is Glu, Gln, Asp, Asn, Leu, Ile, Val or absent;
Xaa₈ is Val, Leu, Gln, Ile, Met or absent;
Xaa₉ is Lys, Arg, His, Asp, Val or absent;
Xaa₁₀ is Glu, Gln, Asp, Asn or absent; and
Xaa₁₁ is Glu, Asp, Asn, Gln or absent.

In one embodiment, Xaa₁ in Formula (I) or (II) is Pro or absent; preferably Pro.

In one embodiment, Xaa₂ in Formula (I) or (II) is Ala or absent; preferably Ala.

In one embodiment, Xaa₃ in Formula (I) or (II) is Ala, Gly or absent; preferably Ala.

In one embodiment, Xaa₄ in Formula (I) or (II) is Glu, Gln, Asp or absent; preferably Glu, Asp or Gln.

In one embodiment, Xaa₈ in Formula (I) or (II) is Val or absent; preferably Val.

In one embodiment, Xaa₉ in Formula (I) or (II) is Lys, Arg or absent; preferably Lys or absent.

In one embodiment, Xaa₁₀ in Formula (I) or (II) is Glu, Gln or absent; preferably Gln.

In one embodiment, Xaa₁₁ in Formula (I) or (II) is Asp or absent; preferably Asp.

In one embodiment, one of Xaa₁, Xaa₂, Xaa₃ and Xaa₄ in Formula (I) or (II) is absent; or two of Xaa₁, Xaa₂, Xaa₃ and Xaa₄ in Formula (I) or (II) are absent; or three of Xaa₁, Xaa₂, Xaa₃ and Xaa₄ in Formula (I) or (II) are absent; or all of Xaa₁, Xaa₂, Xaa₃ and Xaa₄ in Formula (I) or (II) are absent.

In one embodiment, one of Xaa₈, Xaa₉, Xaa₁₀ and Xaa₁₁ in Formula (I) or (II) is absent; or two of Xaa₈, Xaa₉, Xaa₁₀ and Xaa₁₁ in Formula (I) or (II) are absent; or three of Xaa₈, Xaa₉, Xaa₁₀ and Xaa₁₁ in Formula (I) or (II) are absent; or all of Xaa₈, Xaa₉, Xaa₁₀ and Xaa₁₁ in Formula (I) or (II) are absent.

In one embodiment, the compound is selected from any one of Compounds 1-73 of the present invention.

In one embodiment, the compound is selected from:

Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 1);
Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys (Compound 3);
Pro-Ala-Ala-Gln-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 10);
Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu (Compound 26);
Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 27);
Ala-Glu-Pro-Val-Pro-Leu (Compound 30);
Glu-Pro-Val-Pro-Leu (Compound 31);
Pro-Val-Pro-Leu (Compound 32);
Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 28);
Pro-Ala-Ala-Asp-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 11);
Pro-Ala-Gly-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 48);
Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Glu-Asp (Compound 57); or
Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 38).

For convenience, when the compound of the present invention is described in the present application, H on the left side and OH on the right side are omitted.

In one embodiment, the compound is Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 1).

In a second aspect, Provided is a method for repairing mucosal damage, the method comprising administering the compound of the present invention or a physiologically compatible salt thereof to a subject or bringing the mucosal damage into contact with the compound of the present invention or the physiologically compatible salt thereof. In one embodiment, the repair is carried out by regulating the

proliferation and differentiation of stem cells.

In one embodiment, the mucosal damage is mucosal damage in a cavity such as the digestive system or respiratory system.

The mucosal damage of the digestive system is related to oral, esophageal and gastrointestinal diseases, and oral diseases include oral ulcer, stomatitis, gingivitis, periodontitis, etc.; the esophageal diseases include esophagitis, esophageal ulcer, etc.; and the gastrointestinal diseases include, without limitation, chronic gastritis, chronic atrophic gastritis, acute gastritis, gastroduodenal ulcer, functional gastrointestinal diseases, dyspepsia, precancerous lesions, digestive system tumors, gastrointestinal bleeding, gastroesophageal reflux disease, acute and chronic enteritis, ulcerative colitis, Crohn's disease, and mucosal injuries caused by radiotherapy and/or chemotherapy.

In a preferred embodiment, the digestive tract mucosa includes gastric mucosa and intestinal mucosa. In a preferred embodiment, chronic gastritis includes chronic atrophic gastritis. In a preferred embodiment, the mucosal damage is gastric mucosal damage caused by an irritant substance or a drug or by a stress state. The irritant substance is, for example, hydrochloric acid, ethanol or alcohol, etc., and the drug is, for example, the non-steroidal anti-inflammatory drug aspirin or indomethacin, etc.

Provided is a method for preventing, alleviating or treating a digestive tract disease or eliminating inflammatory edema, the method comprising administering the compound of the present invention or a physiologically compatible salt thereof to a subject. The digestive tract disease includes those associated with oral, esophageal and gastrointestinal diseases, and the oral diseases include oral ulcer, stomatitis, gingivitis, periodontitis, etc.; the esophageal diseases include esophagitis, esophageal ulcer, etc.; and the gastrointestinal diseases include, without limitation, chronic gastritis, chronic atrophic gastritis, acute gastritis, gastroduodenal ulcer, functional gastrointestinal diseases, dyspepsia, precancerous lesions, digestive system tumors, gastrointestinal bleeding, gastroesophageal reflux disease, acute and chronic enteritis, ulcerative colitis, Crohn's disease, and mucosal injuries caused by radiotherapy and/or chemotherapy. In one embodiment, the prevention, alleviation or treatment of digestive tract disease is carried out by regulating the proliferation and differentiation of stem cells. The method can prevent, alleviate or treat a gastrointestinal disease by means of the protective effect of the compound of the present invention or a physiologically compatible salt thereof on digestive tract mucosae such as gastric mucosa or intestinal mucosa or by repairing the injury of digestive tract mucosae such as gastric mucosa or intestinal mucosa.

Provided is a method for repairing a mucosal or skin wound, the method comprising administering the compound of the present invention or a physiologically compatible salt thereof to a subject. In one embodiment, the repair of the mucosal or skin wounds surface includes the regulation of the proliferation and differentiation of stem cells.

In the above method of the present invention, the compound of the present invention or a physiologically compatible salt thereof is administered orally, by injection, subcutaneously, etc.

In a third aspect, Provided is a method for repairing skin wound, the method comprising bringing the skin wounds into contact with the compound of the present invention or a physiologically compatible salt thereof. In a preferred embodiment, the skin wounds is related to, but not limited to, epidermal inflammation, mechanical and surgical wound, burns and scalds, ulcers, fistulas, bedsores, and skin injuries caused by radiotherapy and/or chemotherapy. In one embodiment, the skin wounds refers to damage to normal skin caused by external injury-causing factors such as surgery, external forces, heat, electric current, chemicals and low temperatures and internal factors in the body such as local blood supply disturbance. In one embodiment, the skin wounds is often accompanied by the destruction of skin integrity and loss of a certain amount of normal tissues. In another embodiment, the skin wounds include the impairment of the normal function of the skin. In one embodiment, the recovery of the skin wounds is carried out by regulating the proliferation and differentiation of stem cells.

Provided is a method for promoting the proliferation of HaCAT cells, the method comprising bringing the cells into contact with the compound of the present invention or a physiologically compatible salt thereof.

In a fourth aspect, Provided is a method for regenerating an injured blood vessel, the method comprising bringing the injured blood vessel into contact with the compound of the present invention or a physiologically compatible salt thereof. In a preferred embodiment, the injured blood vessel includes blood vessel injuries caused by digestive tract mucosa injury and skin wounds.

In a fifth aspect, Provided is a pharmaceutical composition, a food composition, a health care or cosmetic composition, or commodity composition, said composition comprising the compound of the present invention or a physiologically compatible salt thereof and a physiologically acceptable carrier. In one embodiment, the physiologically acceptable carrier includes a pharmaceutically acceptable carrier or a cosmetically acceptable carrier. The composition for a medicament, a food product, a health care product or a cosmetic product, or a daily product can be prepared according to a conventional technique of pharmaceuticals or cosmetics, including mixing the compound of the present invention, which acts as an active ingredient, with a carrier, and preparing the mixture into the desired dosage form according to a conventional technique. According to requirements, the composition of the present invention can be formulated into an oral preparation, a mucosal preparation, an injection preparation, an inhalation preparation and a topical preparation.

The polypeptide Provided has no homology with known polypeptides, which facilitates artificial polypeptide synthesis to obtain a high-purity polypeptide. Compared with epidermal growth factor polypeptides, the polypeptide Provided is stable *in vivo* because it only consists of at most 12 amino acid residues. Moreover, the polypeptide Provided can promote the proliferation and differentiation of stem cells, particularly the proliferation and differentiation of gastric organoids, participate in and regulate the proliferation and differentiation of gastric epithelial stem cells, so as to repair the injury of gastrointestinal stem cells and epidermal stem cells, and has the effects of significantly alleviating the pathological development of gastrointestinal diseases such as chronic gastritis and digestive tract ulcers, eliminating inflammatory edema, promoting the repair of digestive tract mucosa injury and skin wound, shortening the wound healing time, modulating immune functions, etc. In addition, the polypeptide Provided, when applied to a skin wounds surface of the body surface, can function even after the skin wounds surface is sterilized by an iodine preparation or hydrogen peroxide, or can stably exist even in an artificial gastric juice, an artificial intestinal juice, etc., whereas the epidermal growth factor, when applied to the skin of the body surface, will be structurally destroyed and cannot function after disinfection with an iodine preparation or hydrogen peroxide.

Brief Description of the Drawings

Fig. 1 shows a schematic diagram of the steps of the solid-phase synthesis of a polypeptide.

Fig. 2 shows the anti-ulcer effect of Compound 1 on ethanol-induced gastric ulcer in mice.

Fig. 3 shows the results of Compound 1 on promoting the proliferation and differentiation of gastric organoids.

Fig. 4 shows the results of Compound 1 promoting the differentiation of gastric organoids.

Fig. 5 shows the therapeutic effect of Compound 1 on mice with chronic atrophic gastritis.

Fig. 6 shows the effect of Compound 1 on gastric epithelial stem cells in rats with chronic atrophic gastritis.

Fig. 7 shows the therapeutic effect of Compound 1 on rats with chronic atrophic gastritis.

Fig. 8 shows the proliferation-promoting effect of Compound 1 on HaCAT cells.

Fig. 9 shows a schematic diagram of the analysis site of the subintestinal vascular area of zebrafish.

Fig. 10 shows a typical diagram of the area of the subintestinal vascular area of zebrafish treated with

the compound of the present invention.

Fig. 11 shows the number of subintestinal vascular branches of zebrafish treated with the compound of the present invention.

Detailed Description of Embodiments

The term “physiologically compatible salt” refers to a salt form that is physiologically compatible (i.e., pharmacologically acceptable) and substantially non-toxic to an individual to whom the compound of the present invention is to be administered. Physiologically compatible salts of the compound of the present invention include conventional and stoichiometric acid addition salts or base addition salts formed from suitable, non-toxic organic or inorganic acids or inorganic bases.

The term “subject” refers to an animal, preferably a mammal, most preferably a human. Specifically, the term “subject” relates to a mammal or human with skin wounds and/or mucosal damage. It should be understood by those skilled in the art that the repair of skin wounds and/or mucosal damage in the present invention can be applied for cosmetic purposes (i.e., non-therapeutic purposes) and therapeutic purposes. To this end, the term “skin injury” in the present application further includes skin injuries to be repaired for cosmetic purposes, such as wrinkles (e.g., wrinkles caused by ultraviolet radiation), skin lines, cracks, lumps, large pores (e.g., those related to accessory structures such as sweat ducts, sebaceous glands or hair follicles), or unevenness or roughness, loss of skin elasticity (loss and/or inactivation of functional skin elastin), sagging (including dropsy of eyes and jaw), loss of skin hardness, loss of skin firmness, loss of recovery ability after skin deformation, discoloration (including dark circles under eyes), macula and blisters, sallow complexion, hyperpigmented skin areas such as senile plaques and freckles, cutin, abnormal differentiation, excessive keratinization, degenerated elastic tissues, destructed collagen, and other tissue changes in skin keratin, dermis, epidermis, skin vascular systems (such as telangiectasia or multi-branched blood vessels) and subcutaneous tissues, especially those close to the skin.

The following is a description of the present invention in conjunction with specific trials and is not a limitation on the scope of protection of the present invention.

Table 1 English names or abbreviations of reagents and solvents used in writing

English name or abbreviation	Chinese name
HBTU	Benzotriazole- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
Methanol	Methanol
Tert-Butyl methyl ether	Tert-Butyl methyl ether
Ethanol	Ethanol
AA	Amino acid

Example 1: Chemical Synthesis of Polypeptide

A polypeptide compound was synthesized by a conventional solid-phase synthesis method via multiple cyclic processes of resin swelling, substitution, deprotection, washing, amino acid dissolution, amino acid activation and condensation processes, washing, and further deprotection, and finally cleavage and side chain deprotection.

The schematic diagram of the steps of the solid-phase synthesis of the polypeptide was shown in Fig. 1. In Fig. 1, Cl-2-Cl-Resin represented 2-chlorotrityl chloride resin; Fmoc-Aa(n) represented an amino acid with 9-fluorenylmethoxycarbonyl; DIPEA was N,N-diisopropylethylamine; DCM was dichloromethane; PIP was piperidine; DMF was N,N-dimethylformamide; HOBt was 1-hydroxybenzotriazole; DIC was N,N'-diisopropyl carbodiimide; TFA was trifluoroacetic acid; and TIPS was triisopropylsilane.

Hereinafter, taking Compound 1 (Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp) as an example, a method for the synthesis and purification of Compound 1 was shown, the method comprising step 1. preparation of fully protected peptide resin; 2. cutting and deprotection; and 3. purification (salt exchange)

and freeze-drying.

1. Preparation of fully protected peptide resin

(1) Resin swelling: 2.0192 g of 2-Chlorotriyl Chloride Resin ($S = 0.73$ mmol/g) was weighed, added to a synthesis tube with a sieve plate, swelled with 40 ml of dichloromethane for 30 min, and subjected to suction filtration to remove dichloromethane.

(2) Preparation of Fmoc-Asp(OtBu)-Resin: Based on a molar ratio of 1 : 1.5 : 1.65 of resin to Fmoc-Asp(OtBu)-OH to DIPEA, Fmoc-Asp(OtBu)-OH and DIPEA were respectively weighed, dissolved in 20 ml of dichloromethane and added to the synthesis tube. Bubbling with N_2 and shaking were performed at room temperature for 1-3 hours, and 2 ml of methanol was directly added to the reaction solution, followed by blocking for 30 min. It was then washed 4 times separately with dimethylformamide, 25 ml each time, and the resin was dried by draining.

(3) Removal of Fmoc protecting group: 20 ml of a 20% piperidine-DMF (v/v) solution was added to the reactor, the reaction was bubbled with N_2 for 20 min, and draining was performed; and it was then washed with dimethylformamide 6 times, 25 ml each time, 3 min each time, and after draining, the results of Fmoc removal were detected by ninhydrin method.

(4) Amino acid pre-activation: 4.38 mmol of Fmoc-protected amino acid, 5.26 mmol of HOBt, 4.60 mmol of DIC were added to a 250 ml round bottom flask, dissolved in 20 ml of 1 : 1 DCM-DMF (v/v), and pre-activated in an ice bath at -5°C to 0°C under stirring for 30-60 min.

(5) Amino acid connection: the activated protected amino acid solution was poured into the reactor, and an appropriate amount of DCM was supplemented to clean the tools. After the reaction was bubbled with N_2 at room temperature for 1-3 hours, ninhydrin method was used to detect whether the amino acid connection was complete and if so, draining was performed. The resin was washed with dimethylformamide 4 times, 25ml each time, 3 min each time, and draining was performed. The amount of each amino acid and condensing agent and the specific reaction time were shown in Table 2.

(6) After the condensation of the first amino acid was complete, steps (3) to (5) were repeated to extend the peptide chain according to the amino acid sequence until the coupling of the last amino acid was completed.

(7) The resin peptide was washed with dichloromethane 6 times, 25 ml each time, 3 min each time, and draining was performed.

Table 2 Amounts of amino acids and condensing agent

Amino acid name	AA/eq	Amino acid amount/g	HOBt/g	DIPEA/g	DIC/g
Fmoc-L-Asp(OtBu)-OH	2.19	0.90	0	0.31	0
Fmoc-L-Gln(Trt)-OH	4.38	2.67	0.71	0.57	0.58
Fmoc-L-Lys(Boc)-OH	4.38	2.05	0.71	0.57	0.58
Fmoc-L-Val-OH	4.38	1.49	0.71	0.57	0.58
Fmoc-L-Leu-OH	4.38	1.55	0.71	0.57	0.58
Fmoc-L-Pro-OH	4.38	1.48	0.71	0.57	1.16
Fmoc-L-Val-OH	4.38	1.49	0.71	0.57	0.58
Fmoc-L-Pro-OH	4.38	1.48	0.71	0.57	1.16
Fmoc-L-Glu(OtBu)-OH $\cdot$ H $_2$ O	4.38	1.94	0.71	0.57	1.16
Fmoc-L-Ala-OH $\cdot$ H $_2$ O	4.38	1.44	0.71	0.57	1.16
Fmoc-L-Ala-OH $\cdot$ H $_2$ O	4.38	1.44	0.71	0.57	1.16
Fmoc-L-Pro-OH	4.38	1.48	0.71	0.57	1.16

Step 2. Cleavage and deprotection

(1) 50 ml of a cleaving agent (TFA : TIPS : H₂O = 95 : 2.5 : 2.5, v/v) was added to the synthesis tube in step 1, and the reaction was bubbled with N₂ for 1.5-3 hours.

(2) After the cleavage reaction was complete, the cleavage agent was suction-filtered into a 250 ml round bottom flask. After vacuum concentration to one third of the original volume of the cleavage agent, add 10 folds of the existing volume of methyl tert-butyl ether was added, and the mixture was stirred for 30 min. The resulting mixed solvent was filtered and washed three times separately with 30 ml of methyl tert-butyl ether, and the resulting crude peptide product was put into a sand core funnel and dried with N₂ in a fume hood, so that the solvent was volatilized until the crude peptide became powder. The obtained crude peptide was 1.87 g and had a crude yield of 85.1%.

Step 3. Purification (salt exchange) and freeze-drying

Using the following chromatographic parameter condition A, the crude peptide obtained in step 2 was purified by HPLC. Specifically, the crude peptide obtained in step 2 was dissolved with water and/or acetonitrile, and filtered by a 0.45 µm filter membrane; sample injection was performed; gradient elution was performed with an acetonitrile-water mobile phase; a peptide eluent of interest was collected; and finally, rotary evaporation concentration was performed.

Chromatographic parameter condition A:

Chromatographic column: YMC-Actus Triart C18 30*250 mm;

Eluent A: 0.1% (v/v) TFA/H₂O;

Eluent B: acetonitrile;

Flow rate: 25 ml/min;

Ultraviolet detection wavelength: 220 nm;

Table 3 Gradient elution conditions

Time, min	Eluent A (%)	Eluent B (%)
0	90	10
30	75	25

Next, the product obtained in the previous step was subjected to salt exchange by HPLC method using the following chromatographic parameter condition B, whereby the final peptide Compound 1 was obtained. Specifically, 95% A1 + 5% B balanced chromatographic column was used; sample injection was then performed; next, 95% A2 + 5% B balanced chromatographic column was used; gradient elution was performed with A1 and B; a peptide eluent of interest was collected; and finally, rotary evaporation concentration and freeze-drying were performed to obtain Compound 1 (purification yield 73.3%, purity 100%). The structure of Compound 1 was confirmed by MS and ¹H-NMR.

Chromatographic parameter condition B:

Chromatographic column: YMC-Actus Triart C18 30*250 mm

Eluent A1: 0.1 M acetic acid

Eluent A2: 0.025 M acetic acid + 0.1 M ammonium acetate

Eluent B: acetonitrile

Flow rate: 25 ml/min

Ultraviolet detection wavelength: 220 nm

Table 4 Gradient elution conditions

Time, min	Eluent A1 (%)	Eluent B (%)
0	95	5
5	95	5
35	70	30

Other compounds were synthesized in a similar way to the synthesis of Compound 1. The results were shown in Table 5 and the other parts of the description.

Table 5 Synthesized compounds

No.	Compound sequence	Amount of crude product (g)	Yield (after purification)	Purity	MS
1	Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	1.87	73.3%	100%	1263.70, 632.50 (double charge), and 422.10 (triple charge)
2	Gly-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.07	N/A	100.0%	612.60 (double charge)
3	Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys	1.62	33.8%	99.8%	511.00 (double charge)
4	Pro-Ala-Ala-Glu-Gly-Val-Pro-Leu-Val-Lys-Gln-Asp	2.00	56.8%	97.9%	612.60 (double charge)
5	Pro-Ala-Ala-Glu-Pro-Val-Gly-Leu-Val-Lys-Gln-Asp	1.50	42.3%	99.2%	612.50 (double charge)
6	Pro-Ala-Ala-Glu-Pro-Val-Gly-Ala-Val-Lys-Gln-Asp	1.78	38.1%	100.0%	591.50 (double charge)
7	Pro-Ala-Ala-Glu-Pro-Val-Gly-Val-Val-Lys-Gln-Asp	1.50	46.5%	100.0%	605.50 (double charge)
8	Pro-Ala-Ala-Glu-Gly-Val-Gly-Leu-Val-Lys-Gln-Asp	2.15	14.4%	100.0%	592.50 (double charge)
9	Pro-Ala-Ala-Glu-Gly-Val-Gly-Leu	2.12	67.9%	98.9%	713.40
10	Pro-Ala-Ala-Gln-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.36	57.4%	100.0%	632.00 (double charge)
11	Pro-Ala-Ala-Asp-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.39	52.9%	99.6%	625.50 (double charge)
12	Pro-Ala-Ala-Glu-Pro-Val-Pro-Phe-Val-Lys-Gln-Asp	2.95	78.3%	100.0%	649.5 (double charge) and 433.4 (triple charge)
13	Pro-Ala-Ala-Glu-Pro-Val-Pro-Tyr-Val-Lys-Gln-Asp	2.66	38.4%	100.0%	657.4 (double charge) and 438.8 (triple charge)
14	Pro-Ala-Ala-Glu-Pro-Val-Gly-Leu-Val-Lys	1.92	53.5%	100.0%	490.9 (double charge)
15	Pro-Ala-Ala-Glu-Pro-Val-Gly-Val-Val-Lys	1.81	56.9%	100.0%	483.8 (double charge)
16	Pro-Ala-Ala-Glu-Pro-Val-Ala-Leu-Val-Lys	1.98	60.1%	100.0%	497.8 (double charge)
17	Pro-Ala-Ala-Glu-Pro-Val-Ala-Val-Val-Lys	2.04	57.3%	100.0%	490.9 (double charge)
18	Pro-Ala-Ala-Glu-Ala-Val-Pro-Leu-Val-Lys-Gln-Asp	2.15	52.0%	100.0%	619.5 (double charge)
19	Pro-Ala-Ala-Glu-Pro-Val-Ala-Leu-Val-Lys-Gln-Asp	1.92	37.7%	100.0%	619.4 (double charge)
20	Pro-Ala-Ala-Glu-Ala-Val-Ala-Leu-Val-Lys-Gln-Asp	1.96	19.1%	99.7%	606.50 (double charge)
21	Ala-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.58	61.6%	100.0%	619.50 (double charge)
22	Pro-Ala-Ala-Glu-Pro-Val-Pro-Phe-Val-Lys	2.11	53.8%	100.0%	527.8 (double charge)
23	Pro-Ala-Ala-Glu-Pro-Val-Pro-Tyr-Val-Lys	2.05	51.1%	100.0%	535.8 (double charge)
24	Pro-Ala-Ala-Glu-Pro-Val-Gly-Phe-Val-Lys	1.81	55.5%	100.0%	507.9 (double charge)
25	Pro-Ala-Ala-Glu-Pro-Val-Ala-Phe-Val-Lys	1.81	59.0%	100.0%	514.8 (double charge)
26	Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu	1.57	60.3%	100.0%	793.4 and 397.3 (double charge)
27	Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.52	48.3%	100.0%	548.5 (double charge)
28	Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.05	43.6%	100.0%	448.40 (double charge)
29	Pro-Ala-Ala-Glu-Pro-Val-Pro	1.62	55.4%	100.0%	680.40
30	Ala-Glu-Pro-Val-Pro-Leu	2.70	71.7%	100.0%	625.10
31	Glu-Pro-Val-Pro-Leu	1.82	52.2%	97.9%	554.40
32	Pro-Val-Pro-Leu	N/A	46.4%	100.0%	425.30
33	Ala-Ala-Glu-Pro-Val-Pro-Leu	3.02	60.3%	100.0%	696.40
34	Pro-Ala-Ala-Glu-Pro-Val	2.50	94.3%	100.0%	583.40
35	Pro-Ala-Ala-Glu-Pro	2.05	59.3%	99.2%	484.30

36	Pro-Ala-Ala-Glu	2.53	65.3%	100.0%	387.30
37	Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.54	N/A	100.0%	584.10 (double charge)
38	Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.48	56.0%	94.1%	513.00 (double charge)
39	Val-Pro-Leu-Val-Lys-Gln-Asp	1.95	57.9%	100.0%	399.90 (double charge)
40	Pro-Leu-Val-Lys-Gln-Asp	1.82	49.8%	100.0%	350.30 (double charge)
41	Pro-Ala-Ala-Glu-Pro-Val-Pro-Ile-Val-Lys	2.04	58.5%	99.6%	511.00 (double charge)
42	Pro-Ala-Ala-Glu-Pro-Val-Pro-Val-Val-Lys	2.22	56.7%	98.7%	504.00 (double charge)
43	Pro-Ala-Ala-Glu-Pro-Val-Pro-Met-Val-Lys	2.22	48.8%	98.6%	520.10 (double charge)
44	Ala-Glu-Pro-Val-Pro	2.37	47.8%	100.0%	512.40
45	Ala-Glu-Pro-Val	0.43	57.8%	100.0%	415.30
46	Pro-Ala-Ala-Asn-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.58	57.5%	100.0%	625.10 (double charge)
47	Pro-Ala-Ala-Leu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.68	57.9%	100.0%	624.50 (double charge)
48	Pro-Ala-Gly-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.74	56.7%	100.0%	625.50 (double charge)
49	Pro-Ala-Pro-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.92	22.2%	100.0%	645.40 (double charge)
50	Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asn	3.10	48.4%	100.0%	632.10 (double charge)
51	Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Val-Gln-Asp	2.71	53.9%	100.0%	618.00 (double charge)
52	Pro-Ala-Ala-Glu-Pro-Val-Pro-Val-Val-Lys-Gln-Asp	3.13	57.1%	100.0%	625.60 (double charge)
53	Pro-Ala-Ala-Glu-Pro-Val-Pro-Ile-Val-Lys-Gln-Asp	3.25	53.5%	100.0%	632.60 (double charge)
54	Pro-Ala-Ala-Glu-Pro-Val-Pro-Met-Val-Lys-Gln-Asp	1.82	59.4%	100.0%	641.60 (double charge)
55	Pro-Leu-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.34	62.7%	100.0%	653.60 (double charge)
56	Pro-Ile-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	3.22	41.9%	100.0%	653.60 (double charge)
57	Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Glu-Asp	2.38	61.3%	100.0%	633.10 (double charge)
58	Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Asn-Asp	3.10	57.7%	100.0%	625.60 (double charge)
59	Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Asp-Asp	2.66	51.7%	99.5%	626.10 (double charge)
60	Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Glu	1.91	80.8%	99.5%	639.60 (double charge)
61	Pro-Ala-Leu-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.14	64.7%	100.0%	653.60 (double charge)
62	Pro-Ala-Ile-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	1.93	72.1%	100.0%	653.60 (double charge)
63	Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Leu-Lys-Gln-Asp	2.21	61.8%	100.0%	639.60 (double charge)
64	Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Ile-Lys-Gln-Asp	2.53	57.2%	100.0%	639.60 (double charge)
65	Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Met-Lys-Gln-Asp	3.17	33.3%	100.0%	648.50 (double charge)
66	Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Arg-Gln-Asp	1.35	49.8%	100.0%	646.60 (double charge)
67	Pro-Ala-Ala-Val-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.24	54.4%	100.0%	617.60 (double charge)
68	Val-Pro-Leu-Val-Lys-Gln-Asp	1.68	53.3%	100.0%	399.90 (double charge)
69	Gly-Ala-Ala-Val-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	1.66	58.9%	100.0%	597.60 (double charge)
70	Gly-Ala-Gly-Val-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp	2.42	45.0%	100.0%	590.60 (double charge)
71	Gly-Ala-Gly-Val-Gly-Val-Pro-Leu-Val-Lys-Gln-Asp	1.94	54.5%	100.0%	570.50 (double charge)
72	Pro-Ala-Ala-Glu-Pro-Val-Ala-Phe-Val-Lys-Gln-Asp	3.20	43.3%	100.0%	636.60 (double charge)
73	Val-Pro-Leu-Val	2.37	58.3%	100.0%	427.40

Note: Double charge represented 1/2 target peak in the mass spectrum, and triple charge represented 1/3 target peak in the mass spectrum; N/A represented having difficulties in weighing, and no actual weight was considered.

Compound 1: Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp acetate

¹H NMR (600 MHz, DMSO) δ 8.27 (d, J = 7.6 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.99 (d, J = 7.4 Hz, 1H), 7.94 (dd, J = 16.7, 8.0 Hz, 2H), 7.58 (d, J = 6.3 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.16 (s, 1H), 6.70 (s, 1H), 4.48 (dd, J = 13.3, 7.9 Hz, 1H), 4.39 (dd, J = 8.2,

4.2 Hz, 1H), 4.35 - 4.21 (m, 6H), 4.18 - 4.03 (m, 3H), 3.71 - 3.47 (m, 5H), 2.93 - 2.69 (m, 4H), 2.45 - 2.32 (m, 2H), 2.25 (t, $J = 7.7$ Hz, 2H), 2.08 (t, $J = 7.9$ Hz, 2H), 2.01 - 1.93 (m, 3H), 1.93 - 1.84 (m, 14H, AcOH), 1.84 - 1.76 (m, 3H), 1.75 - 1.57 (m, 8H), 1.54 - 1.39 (m, 5H), 1.36 - 1.27 (m, 2H), 1.21 - 1.10 (m, 6H), 0.91 - 0.74 (m, 18H).

Compound 3: Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys acetate

^1H NMR (600 MHz, DMSO) δ 8.22 - 8.13 (m, 2H), 8.10 (s, 1H), 7.98 (d, $J = 7.6$ Hz, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 7.72 (s, 1H), 7.59 (s, 1H), 4.52 - 4.43 (m, 1H), 4.39 - 4.19 (m, 6H), 4.12 - 4.04 (m, 1H), 3.89 (d, $J = 5.9$ Hz, 1H), 3.67 - 3.46 (m, 6H), 2.85 (dt, $J = 10.2, 6.8$ Hz, 1H), 2.80 - 2.73 (m, 1H), 2.69 (s, 2H), 2.21 (t, $J = 7.4$ Hz, 2H), 2.03 - 1.76 (m, 14H, AcOH), 1.73 (d, $J = 5.5$ Hz, 1H), 1.70 - 1.61 (m, 4H), 1.61 - 1.52 (m, 3H), 1.47 (s, 4H), 1.26 (s, 2H), 1.20 - 1.12 (m, 6H), 0.91 - 0.83 (m, 9H), 0.83 - 0.77 (m, 9H).

Compound 4: Pro-Ala-Ala-Glu-Gly-Val-Pro-Leu-Val-Lys-Gln-Asp acetate

^1H NMR (600 MHz, D_2O) δ 4.45 - 4.16 (m, 10H), 4.04 (d, $J = 8.1$ Hz, 1H), 3.93 - 3.76 (m, 3H), 3.67 - 3.58 (m, 1H), 3.42 - 3.28 (m, 2H), 2.94 (t, $J = 7.4$ Hz, 2H), 2.72 (qd, $J = 16.4, 6.0$ Hz, 2H), 2.45 - 2.27 (m, 5H), 2.27 - 2.16 (m, 1H), 2.11 - 1.86 (m, 17H, AcOH), 1.84 - 1.47 (m, 8H), 1.45 - 1.25 (m, 8H), 0.91 (d, $J = 6.8$ Hz, 3H), 0.89 - 0.73 (m, 15H).

Compound 5: Pro-Ala-Ala-Glu-Pro-Val-Gly-Leu-Val-Lys-Gln-Asp acetate

^1H NMR (600 MHz, $\text{D}_2\text{O} + \text{D}_3\text{COD}$) δ 4.66 - 4.62 (m, 2H), 4.40 (dd, $J = 8.1, 5.9$ Hz, 1H), 4.35 - 4.21 (m, 6H), 4.03 - 3.98 (m, 2H), 3.92 - 3.81 (m, 2H), 3.78 - 3.71 (m, 1H), 3.62 (dt, $J = 10.3, 7.1$ Hz, 1H), 3.39 - 3.30 (m, 2H), 2.96 - 2.87 (m, 4H), 2.51 - 2.35 (m, 3H), 2.32 (t, $J = 7.6$ Hz, 2H), 2.26 - 2.19 (m, 1H), 2.10 - 1.91 (m, 14H, AcOH), 1.91 - 1.78 (m, 2H), 1.78 - 1.71 (m, 1H), 1.70 - 1.58 (m, 3H), 1.53 (d, $J = 3.6$ Hz, 3H), 1.42 - 1.34 (m, 2H), 1.33 (d, $J = 7.2$ Hz, 3H), 1.30 (d, $J = 7.2$ Hz, 3H), 0.94 - 0.88 (m, 6H), 0.88 - 0.83 (m, 9H), 0.82 - 0.79 (m, 3H).

Compound 8: Pro-Ala-Ala-Glu-Gly-Val-Gly-Leu-Val-Lys-Gln-Asp acetate

^1H NMR (600 MHz, DMSO) δ 8.30 - 8.24 (m, 3H), 8.15 (d, $J = 7.3$ Hz, 1H), 8.11 - 8.03 (m, 2H), 7.94 (d, $J = 7.4$ Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.80 (t, $J = 9.4$ Hz, 2H), 7.59 (d, $J = 6.4$ Hz, 1H), 7.17 (s, 1H), 6.70 (s, 1H), 4.44 - 3.99 (m, 10H), 3.82 - 3.57 (m, 7H), 2.94 - 2.69 (m, 5H), 2.47 - 2.41 (m, 1H), 2.41 - 2.32 (m, 1H), 2.21 (t, $J = 7.9$ Hz, 2H), 2.08 (t, $J = 7.9$ Hz, 2H), 2.03 - 1.79 (m, 11H, AcOH), 1.78 - 1.26 (m, 14H), 1.19 (dd, $J = 6.9, 4.7$ Hz, 6H), 0.87 - 0.76 (m, 18H).

Compound 9: Pro-Ala-Ala-Glu-Gly-Val-Gly-Leu

^1H NMR (600 MHz, DMSO) δ 8.43 (d, $J = 7.6$ Hz, 1H), 8.29 - 8.23 (m, 2H), 8.22 - 8.14 (m, 2H), 7.81 (d, $J = 8.5$ Hz, 1H), 7.75 (d, $J = 7.9$ Hz, 1H), 4.32 - 4.08 (m, 5H), 3.78 - 3.69 (m, 4H), 3.63 (dd, $J = 16.4, 5.6$ Hz, 1H), 2.98 - 2.86 (m, 2H), 2.22 (t, $J = 7.9$ Hz, 2H), 2.07 - 1.92 (m, 2H), 1.92 - 1.86 (m, 1H), 1.79 - 1.64 (m, 4H), 1.62 - 1.54 (m, 1H), 1.50 - 1.40 (m, 2H), 1.19 (dd, $J = 7.0, 1.3$ Hz, 6H), 0.86 - 0.78 (m, 12H).

Compound 10: Pro-Ala-Ala-Gln-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp acetate

^1H NMR (600 MHz, DMSO) δ 8.28 (d, $J = 7.7$ Hz, 1H), 8.14 (d, $J = 7.8$ Hz, 1H), 8.07 (d, $J = 7.4$ Hz, 1H), 8.04 (d, $J = 8.0$ Hz, 1H), 8.00 (d, $J = 7.3$ Hz, 1H), 7.95 (t, 2H), 7.58 (d, $J = 6.3$ Hz, 1H), 7.50 (d, $J = 8.7$ Hz, 1H), 7.17 (d, $J = 15.3$ Hz, 2H), 6.76 (s, 1H), 6.70 (s, 1H), 4.45 (q, $J = 13.6, 7.9$ Hz, 1H), 4.39 (dd, $J = 8.3, 4.1$ Hz, 1H), 4.33 - 4.20 (m, 6H), 4.20 - 4.09 (m, 2H), 4.09 - 4.02 (m, 1H), 3.69 - 3.47 (m, 5H), 2.86 (dt, $J = 10.2, 6.7$ Hz, 1H), 2.80 - 2.62 (m, 3H), 2.46 - 2.40 (m, 1H), 2.37 (dd, $J = 15.5, 2.7$ Hz, 1H), 2.14 - 2.03 (m, 4H), 2.02 - 1.76 (m, 16H, AcOH), 1.75 - 1.39 (m, 13H), 1.39 - 1.22 (m, 2H), 1.22 - 1.11 (m, 6H), 1.00 - 0.68 (m, 18H).

Compound 11: Pro-Ala-Ala-Asp-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp acetate

^1H NMR (600 MHz, DMSO) δ 8.26 (d, $J = 7.6$ Hz, 1H), 8.19 (d, $J = 7.7$ Hz, 1H), 8.09 (d, $J = 7.7$ Hz, 1H), 8.04 (d, $J = 7.5$ Hz, 1H), 7.96 (t, $J = 7.4$ Hz, 2H), 7.87 (d, $J = 7.0$ Hz, 1H), 7.60 (d, $J = 6.4$ Hz, 1H), 7.37 (d, $J = 8.9$ Hz, 1H), 7.17 (s, 1H), 6.70 (s, 1H), 4.70 (q, $J = 14.2, 7.0$ Hz, 1H), 4.37 - 4.21 (m, 7H), 4.16 - 4.10 (m, 2H), 4.09 - 4.03 (m, 1H), 3.74 - 3.67 (m, 2H), 3.68 - 3.59 (m, 4H), 3.49 - 3.45 (m, 1H), 2.99 - 2.84

(m, 3H), 2.80 - 2.71 (m, 2H), 2.63 (dd, $J = 16.5, 7.5$ Hz, 1H), 2.46 - 2.25 (m, 4H), 2.07 (t, $J = 7.9$ Hz, 2H), 2.05 - 1.76 (m, 20H, AcOH), 1.74 - 1.58 (m, 6H), 1.56 - 1.42 (m, 5H), 1.32 (d, $J = 8.0$ Hz, 2H), 1.18 (d, $J = 7.0$ Hz, 3H), 1.14 (d, $J = 7.1$ Hz, 3H), 0.88 - 0.74 (m, 18H).

Compound 12: Pro-Ala-Ala-Glu-Pro-Val-Pro-Phe-Val-Lys-Gln-Asp acetate

^1H NMR (600 MHz, DMSO) δ 8.29 (d, $J = 7.5$ Hz, 1H), 8.17 (d, $J = 7.7$ Hz, 1H), 8.09 (d, $J = 7.4$ Hz, 1H), 8.03 (d, $J = 7.2$ Hz, 1H), 7.96 (d, $J = 7.6$ Hz, 1H), 7.90 (d, $J = 8.7$ Hz, 1H), 7.86 (d, $J = 7.9$ Hz, 1H), 7.73 (d, $J = 8.5$ Hz, 1H), 7.58 (d, $J = 6.4$ Hz, 1H), 7.25 - 7.19 (m, 4H), 7.18 - 7.12 (m, 2H), 6.71 (s, 1H), 4.54 - 4.44 (m, 2H), 4.37 (q, $J = 8.3$ Hz, 1H), 4.33 - 4.21 (m, 5H), 4.19 - 4.10 (m, 2H), 4.09 - 4.02 (m, 1H), 3.64 - 3.53 (m, 5H), 3.51 - 3.45 (m, 2H), 3.00 (dd, $J = 9.6$ Hz, 1H), 2.89 - 2.82 (m, 2H), 2.80 - 2.71 (m, 3H), 2.46 - 2.36 (m, 2H), 2.24 (t, $J = 7.4$ Hz, 2H), 2.08 (t, $J = 8.0$ Hz, 2H), 2.00 - 1.70 (m, 18H, AcOH), 1.69 - 1.64 (m, 2H), 1.63 - 1.56 (m, 2H), 1.55 - 1.47 (m, 3H), 1.34 (s, 2H), 1.16 (t, $J = 6.9$ Hz, 6H), 0.87 - 0.76 (m, 12H).

Compound 26: Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu acetate

^1H NMR (600 MHz, DMSO) δ 8.25 (s, 1H), 8.09 (d, $J = 7.5$ Hz, 1H), 7.94 (d, $J = 7.6$ Hz, 1H), 7.89 (d, $J = 8.3$ Hz, 2H), 4.53 - 4.46 (m, 1H), 4.39 (dd, $J = 8.3, 4.2$ Hz, 1H), 4.34 (dd, $J = 8.4, 3.8$ Hz, 1H), 4.31 - 4.19 (m, 3H), 4.13 (dd, $J = 15.1, 7.7$ Hz, 1H), 3.71 - 3.49 (m, 5H), 2.94 - 2.77 (m, 2H), 2.33 - 2.20 (m, 2H), 2.06 - 1.77 (m, 13H, AcOH), 1.77 - 1.56 (m, 6H), 1.46 (t, $J = 7.3$ Hz, 2H), 1.25 - 1.11 (m, 6H), 0.95 - 0.76 (m, 12H).

Compound 27: Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp acetate

^1H NMR (600 MHz, D_2O) δ 4.61 (dd, $J = 9.6, 4.4$ Hz, 1H), 4.44 - 4.22 (m, 8H), 4.09 - 3.99 (m, 2H), 3.85 - 3.72 (m, 2H), 3.69 - 3.57 (m, 2H), 2.94 (t, $J = 7.4$ Hz, 2H), 2.79 - 2.63 (m, 2H), 2.43 - 2.16 (m, 7H), 2.09 - 1.74 (m, 19H, AcOH), 1.73 - 1.47 (m, 7H), 1.48 - 1.13 (m, 6H), 1.00 - 0.79 (m, 21H).

Compound 28: Pro-Val-Pro-Leu-Val-Lys-Gln-Asp acetate

^1H NMR (600 MHz, DMSO) δ 8.28 (d, $J = 7.8$ Hz, 1H), 8.13 - 7.87 (m, 3H), 7.57 (d, $J = 6.4$ Hz, 1H), 7.50 (d, $J = 8.7$ Hz, 1H), 7.15 (s, 1H), 6.69 (s, 1H), 4.40 - 4.31 (m, 2H), 4.29 - 4.21 (m, 2H), 4.19 - 4.02 (m, 3H), 3.67 - 3.60 (m, 1H), 3.59 - 3.53 (m, 2H), 2.92 - 2.85 (m, 1H), 2.80 - 2.70 (m, 3H), 2.47 - 2.38 (m, 1H), 2.38 - 2.31 (m, 1H), 2.08 (t, $J = 7.9$ Hz, 2H), 2.04 - 1.76 (m, 14H, AcOH), 1.74 - 1.41 (m, 11H), 1.41 - 1.14 (m, 2H), 0.91 - 0.74 (m, 18H).

Compound 30: Ala-Glu-Pro-Val-Pro-Leu acetate

^1H NMR (600 MHz, DMSO) δ 8.29 (d, $J = 7.1$ Hz, 1H), 7.89 (d, $J = 8.6$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 4.54 (d, $J = 5.4$ Hz, 1H), 4.42 - 4.38 (m, 1H), 4.37 - 4.28 (m, 2H), 4.09 (dd, $J = 14.2, 8.5$ Hz, 1H), 3.66 - 3.46 (m, 5H), 2.28 (t, $J = 7.4$ Hz, 2H), 2.13 - 1.71 (m, 16H, AcOH), 1.71 - 1.58 (m, 2H), 1.53 - 1.32 (m, 2H), 1.18 (d, $J = 6.9$ Hz, 3H), 0.90 - 0.83 (m, 9H), 0.80 (d, $J = 6.6$ Hz, 3H).

Compound 31: Glu-Pro-Val-Pro-Leu acetate

^1H NMR (600 MHz, DMSO) δ 7.94 - 7.86 (m, 2H), 4.44 (dd, $J = 8.3, 4.5$ Hz, 1H), 4.37 - 4.27 (m, 2H), 4.13 (q, $J = 7.6$ Hz, 1H), 3.74 - 3.69 (m, 1H), 3.66 - 3.42 (m, 4H), 2.40 - 2.25 (m, 2H), 2.06 - 1.58 (m, 17H, AcOH), 1.46 (t, $J = 7.3$ Hz, 2H), 0.89 - 0.84 (m, 9H), 0.81 (d, $J = 6.5$ Hz, 3H).

Compound 32: Pro-Val-Pro-Leu acetate

^1H NMR (600 MHz, DMSO) δ 8.15 (d, $J = 9.0$ Hz, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 4.35 (dt, $J = 10.1, 5.2$ Hz, 2H), 4.22 - 4.02 (m, 1H), 3.67 - 3.59 (m, 2H), 3.56 (q, $J = 13.2, 9.3$ Hz, 1H), 2.96 - 2.88 (m, 1H), 2.86 - 2.76 (m, 1H), 2.05 - 1.59 (m, 11H, AcOH), 1.59 - 1.42 (m, 2H), 0.91 - 0.72 (m, 12H).

Compound 34: Pro-Ala-Ala-Glu-Pro-Val acetate

^1H NMR (600 MHz, DMSO) δ 8.01 (d, $J = 7.3$ Hz, 1H), 7.14 (d, $J = 7.8$ Hz, 1H), 4.49 (q, $J = 6.8$ Hz, 1H), 4.31 - 4.22 (m, 3H), 3.75 (dd, $J = 7.8, 4.7$ Hz, 1H), 3.70 - 3.61 (m, 2H), 2.88 - 2.81 (m, 1H), 2.81 - 2.75 (m, 1H), 2.27 - 2.13 (m, 2H), 2.01 - 1.64 (m, 18H, AcOH), 1.58 (p, $J = 6.9$ Hz, 2H), 1.17 (dd, $J = 10.2, 7.1$ Hz, 6H), 0.78 (dd, $J = 6.9, 3.5$ Hz, 6H).

Compound 35: Pro-Ala-Ala-Glu-Pro acetate

¹H NMR (600 MHz, DMSO) δ 8.28 (s, 1H), 8.12 (d, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 4.49 (dd, *J* = 13.7, 7.7 Hz, 1H), 4.35 - 4.13 (m, 3H), 3.76 - 3.50 (m, 3H), 2.97 - 2.79 (m, 2H), 2.33 - 2.18 (m, 2H), 2.16 - 1.77 (m, 10H, AcOH), 1.73 - 1.58 (m, 4H), 1.26 - 1.13 (m, 6H).

Compound 45: Ala-Glu-Pro-Val acetate

¹H NMR (600 MHz, DMSO) δ 8.36 (d, *J* = 7.4 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 4.65 - 4.53 (m, 1H), 4.35 (dd, *J* = 8.6, 3.4 Hz, 1H), 3.89 (dd, *J* = 7.9, 5.4 Hz, 1H), 3.74 - 3.53 (m, 3H), 2.38 - 2.19 (m, 2H), 2.05 - 1.64 (m, 10H, AcOH), 1.27 - 1.17 (m, 3H), 0.83 (d, *J* = 7.1 Hz, 6H).

Compound 48: Pro-Ala-Gly-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp acetate

¹H NMR (600 MHz, DMSO) δ 8.33 (d, *J* = 7.6 Hz, 1H), 8.27 (d, 1H), 8.21 (t, *J* = 5.8 Hz, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 8.05 - 7.97 (m, 2H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 6.4 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.16 (s, 1H), 6.70 (s, 1H), 4.53 - 4.47 (m, 1H), 4.38 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.35 - 4.20 (m, 5H), 4.18 - 4.09 (m, 2H), 4.06 (s, 1H), 3.75 - 3.50 (m, 8H), 2.93 - 2.69 (m, 5H), 2.45 - 2.41 (m, 1H), 2.41 - 2.30 (m, 1H), 2.25 (t, *J* = 7.3 Hz, 2H), 2.08 (t, *J* = 7.9 Hz, 2H), 2.01 - 1.76 (m, 15H, AcOH), 1.74 - 1.53 (m, 8H), 1.53 - 1.40 (m, 4H), 1.33 (d, *J* = 7.2 Hz, 2H), 1.20 (t, *J* = 9.0 Hz, 3H), 0.91 - 0.73 (m, 18H).

Compound 50: Pro-Ala-Ala-Glu-Pro-Val-Pro-leu-Val-Lys-Gln-Asn acetate

¹H NMR (600 MHz, DMSO) δ 8.49 (d, *J* = 7.8 Hz, 1H), 8.17 - 8.06 (m, 2H), 8.05 - 7.99 (m, 2H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.59 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 6.9 Hz, 1H), 7.10 (s, 1H), 6.68 (d, *J* = 15.7 Hz, 2H), 4.48 (d, *J* = 5.1 Hz, 1H), 4.39 (dd, *J* = 8.1, 4.3 Hz, 1H), 4.35 - 4.19 (m, 6H), 4.17 - 4.10 (m, 1H), 4.05 - 3.97 (m, 2H), 3.67 - 3.48 (m, 6H), 2.92 - 2.78 (m, 2H), 2.78 - 2.66 (m, 3H), 2.44 - 2.34 (m, 1H), 2.33 - 2.20 (m, 3H), 2.07 (t, *J* = 7.8 Hz, 2H), 2.01 - 1.76 (m, 15H, AcOH), 1.75 - 1.62 (m, 6H), 1.62 - 1.53 (m, 3H), 1.49 - 1.29 (m, 6H), 1.19 - 1.12 (m, 6H), 0.91 - 0.73 (m, 18H).

Compound 51: Pro-Ala-Ala-Glu-Pro-Val-Pro-leu-Val-Val-Gln-Asp acetate

¹H NMR (600 MHz, DMSO) δ 8.51 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 7.3 Hz, 1H), 8.03 - 7.96 (m, 2H), 7.95 - 7.89 (m, 2H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.75 - 7.69 (m, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.18 (s, 1H), 6.68 (s, 1H), 4.51 (d, *J* = 5.4 Hz, 1H), 4.40 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.35 - 4.12 (m, 10H), 4.01 - 3.95 (m, 1H), 3.69 - 3.51 (m, 4H), 3.09 (d, *J* = 6.4 Hz, 2H), 2.45 - 2.40 (m, 1H), 2.39 - 2.34 (m, 1H), 2.27 (dd, *J* = 13.4, 6.7 Hz, 2H), 2.21 - 2.13 (m, 1H), 2.06 (t, *J* = 8.0 Hz, 2H), 2.02 - 1.75 (m, 18H, AcOH), 1.75 - 1.58 (m, 5H), 1.44 (t, *J* = 7.3 Hz, 2H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.85 (dd, *J* = 6.5, 2.7 Hz, 6H), 0.83 - 0.77 (m, 15H).

Compound 52: Pro-Ala-Ala-Glu-Pro-Val-Pro-Val-Val-Lys-Gln-Asp acetate

¹H NMR (600 MHz, DMSO) δ 8.28 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 1H), 7.99 - 7.92 (m, 2H), 7.87 (dd, *J* = 16.4, 8.8 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 6.1 Hz, 1H), 7.17 (s, 1H), 6.70 (s, 1H), 4.50 - 4.45 (m, 1H), 4.44 - 4.35 (m, 2H), 4.32 - 4.21 (m, 4H), 4.18 - 4.10 (m, 3H), 4.08 - 3.99 (m, 1H), 3.66 - 3.49 (m, 6H), 2.90 - 2.82 (m, 1H), 2.82 - 2.72 (m, 3H), 2.46 - 2.30 (m, 2H), 2.27 - 2.23 (m, 1H), 2.07 (t, *J* = 7.9 Hz, 2H), 2.01 - 1.76 (m, 19H, AcOH), 1.75 - 1.60 (m, 5H), 1.60 - 1.45 (m, 5H), 1.39 - 1.25 (m, 2H), 1.20 - 1.10 (m, 6H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.86 - 0.76 (m, 15H).

Compound 56: Pro-Ile-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp acetate

¹H NMR (600 MHz, DMSO) δ 8.27 (d, *J* = 7.8 Hz, 1H), 8.17 (d, *J* = 7.3 Hz, 1H), 8.10 (d, *J* = 9.4 Hz, 1H), 8.05 - 7.97 (m, 2H), 7.92 (q, *J* = 13.5, 8.1 Hz, 2H), 7.57 (d, *J* = 6.3 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.16 (s, 1H), 6.70 (s, 1H), 4.54 - 4.45 (m, 1H), 4.39 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.35 - 4.22 (m, 5H), 4.21 - 4.09 (m, 3H), 4.10 - 4.00 (m, 1H), 3.67 - 3.48 (m, 6H), 3.41 - 3.16 (m, 4H), 2.95 - 2.86 (m, 1H), 2.81 - 2.68 (m, 3H), 2.47 - 2.41 (m, 1H), 2.41 - 2.32 (m, 1H), 2.25 (t, *J* = 7.6 Hz, 2H), 2.08 (t, *J* = 7.9 Hz, 2H), 2.02 - 1.75 (m, 19H, AcOH), 1.75 - 1.55 (m, 9H), 1.54 - 1.36 (m, 5H), 1.33 (d, *J* = 7.0 Hz, 2H), 1.15 (d, *J* = 7.1 Hz, 3H), 0.89 - 0.784 (m, 8H), 0.82 - 0.76 (m, 14H).

Compound 57: Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Glu-Asp acetate

¹H NMR (600 MHz, DMSO) δ 8.31 (d, *J* = 7.8 Hz, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 8.09 (d, *J* = 7.5 Hz,

1H), 8.03 (t, $J = 7.7$ Hz, 2H), 7.96 - 7.87 (m, 2H), 7.58 (d, $J = 6.3$ Hz, 1H), 7.49 (d, $J = 8.8$ Hz, 1H), 4.49 (q, $J = 5.3$ Hz, 1H), 4.39 (dd, $J = 8.2, 4.4$ Hz, 1H), 4.35 - 4.20 (m, 7H), 4.19 - 4.12 (m, 2H), 4.10 - 4.00 (m, 1H), 3.67 - 3.49 (m, 7H), 2.91 - 2.84 (m, 2H), 2.84 - 2.70 (m, 4H), 2.46 - 2.38 (m, 1H), 2.38 - 2.33 (m, 1H), 2.29 - 2.18 (m, 4H), 2.04 - 1.76 (m, 19H, AcOH), 1.76 - 1.55 (m, 8H), 1.55 - 1.41 (m, 5H), 1.32 (s, 2H), 1.21 - 1.11 (m, 6H), 0.94 - 0.73 (m, 18H).

Compound 58: Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Asn-Asp acetate

^1H NMR (600 MHz, DMSO) δ 8.28 (d, $J = 7.1$ Hz, 1H), 8.19 (d, $J = 7.7$ Hz, 1H), 8.09 (d, $J = 7.5$ Hz, 1H), 8.04 (d, $J = 7.7$ Hz, 1H), 8.00 - 7.89 (m, 3H), 7.50 (d, $J = 8.6$ Hz, 1H), 7.44 (d, $J = 6.0$ Hz, 1H), 7.30 (s, 1H), 6.80 (s, 1H), 4.56 - 4.46 (m, 2H), 4.38 (dd, $J = 8.1, 4.3$ Hz, 1H), 4.35 - 4.20 (m, 6H), 4.18 - 4.12 (m, 1H), 4.04 - 4.00 (m, 1H), 3.66 - 3.49 (m, 6H), 2.93 - 2.84 (m, 1H), 2.83 - 2.71 (m, 3H), 2.43 - 2.31 (m, 3H), 2.25 (t, $J = 8.0$ Hz, 2H), 2.04 - 1.57 (m, 26H, AcOH), 1.56 - 1.46 (m, 3H), 1.46 - 1.43 (m, 2H), 1.35 - 1.27 (m, 2H), 1.20 - 1.10 (m, 6H), 0.86 (dd, $J = 14.8, 7.9$ Hz, 9H), 0.81 - 0.76 (m, 9H).

Compound 60: Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Glu acetate

^1H NMR (600 MHz, DMSO) δ 8.51 (d, $J = 8.0$ Hz, 1H), 8.17 (d, $J = 7.8$ Hz, 1H), 8.10 (d, $J = 7.4$ Hz, 1H), 8.04 (d, $J = 6.2$ Hz, 2H), 7.96 (d, $J = 7.7$ Hz, 1H), 7.93 (d, $J = 8.5$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 1H), 7.34 (d, $J = 6.6$ Hz, 1H), 7.11 (s, 1H), 6.71 (s, 1H), 4.48 (d, $J = 5.4$ Hz, 1H), 4.39 (dd, $J = 8.1, 4.3$ Hz, 1H), 4.34 - 4.18 (m, 7H), 4.18 - 4.10 (m, 1H), 4.07 - 3.99 (m, 1H), 3.83 (q, $J = 12.8, 6.5$ Hz, 2H), 3.69 - 3.48 (m, 7H), 2.92 - 2.83 (m, 1H), 2.81 - 2.62 (m, 4H), 2.31 - 2.02 (m, 7H), 2.01 - 1.75 (m, 22H, AcOH), 1.74 - 1.25 (m, 16H), 1.20 - 1.11 (m, 6H), 0.91 - 0.83 (m, 9H), 0.81 - 0.76 (m, 9H).

Compound 62: Pro-Ala-Ile-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp acetate

^1H NMR (600 MHz, DMSO) δ 8.31 - 8.23 (m, 1H), 8.20 (d, $J = 7.5$ Hz, 1H), 8.03 (d, $J = 7.7$ Hz, 2H), 7.99 (d, $J = 7.6$ Hz, 1H), 7.93 - 7.85 (m, 2H), 7.57 (d, $J = 6.6$ Hz, 1H), 7.51 (d, $J = 8.1$ Hz, 1H), 7.16 (s, 1H), 6.70 (s, 1H), 4.49 (d, $J = 5.5$ Hz, 1H), 4.41 - 4.20 (m, 6H), 4.19 - 4.00 (m, 5H), 3.71 - 3.61 (m, 2H), 3.61 - 3.47 (m, 4H), 2.91 - 2.73 (m, 4H), 2.45 - 2.39 (m, 1H), 2.39 - 2.29 (m, 1H), 2.24 (t, $J = 7.1$ Hz, 2H), 2.07 (t, $J = 7.9$ Hz, 2H), 2.02 - 1.76 (m, 20H, AcOH), 1.74 - 1.47 (m, 12H), 1.47 - 1.29 (m, 5H), 1.16 (d, $J = 6.9$ Hz, 3H), 1.04 (d, $J = 8.4$ Hz, 1H), 0.89 - 0.84 (m, 8H), 0.83 - 0.72 (m, 16H).

Compound 66: Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Arg -Gln-Asp acetate

^1H NMR (600 MHz, DMSO) δ 9.30 (s, 1H), 8.39 (d, $J = 8.7$ Hz, 1H), 8.19 (d, $J = 7.9$ Hz, 1H), 8.09 (d, $J = 7.4$ Hz, 1H), 8.03 (d, $J = 8.1$ Hz, 1H), 7.98 (d, $J = 7.0$ Hz, 1H), 7.96 - 7.89 (m, 3H), 7.52 (d, $J = 8.9$ Hz, 1H), 7.11 (s, 1H), 6.69 (s, 1H), 4.49 (d, $J = 5.3$ Hz, 1H), 4.39 (dd, $J = 8.2, 4.3$ Hz, 1H), 4.34 (d, $J = 4.3$ Hz, 1H), 4.31 - 4.21 (m, 5H), 4.20 - 4.10 (m, 3H), 3.68 - 3.49 (m, 6H), 3.13 (d, $J = 6.1$ Hz, 1H), 3.00 - 2.93 (m, 1H), 2.92 - 2.85 (m, 1H), 2.83 - 2.76 (m, 1H), 2.41 - 2.32 (m, 1H), 2.25 (t, $J = 8.2$ Hz, 2H), 2.09 - 2.03 (m, 2H), 2.02 - 1.76 (m, 20H, AcOH), 1.74 - 1.70 (m, 1H), 1.69 - 1.56 (m, 7H), 1.55 - 1.39 (m, 4H), 1.22 - 1.11 (m, 6H), 0.93 - 0.83 (m, 9H), 0.83 - 0.77 (m, 9H).

Compound 73: Val-Pro-Leu-Val acetate

^1H NMR (600 MHz, MeOD) δ 4.54 - 4.49 (m, 1H), 4.40 (dd, $J = 9.2, 6.0$ Hz, 1H), 4.18 (d, $J = 5.0$ Hz, 1H), 3.99 (d, $J = 5.3$ Hz, 1H), 3.69 (dd, $J = 10.7, 5.0$ Hz, 1H), 3.65 - 3.58 (m, 1H), 2.32 - 2.20 (m, 2H), 2.19 - 2.01 (m, 3H), 2.00 - 1.86 (m, 4H, AcOH), 1.85 - 1.75 (m, 1H), 1.69 - 1.54 (m, 2H), 1.12 (d, $J = 7.0$ Hz, 3H), 1.03 - 1.01 (m, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 0.93 - 0.89 (m, 9H).

Example 2: Anti-ulcer effect of polypeptide (Compound 1) on ethanol-induced gastric ulcer in mice

1. Experimental animal: SPF grade C57BL/6 mice, from Chengdu Yaokang Biotechnology Ltd, animal license number: SCXK (Chuan) 2020-034.

2. Method: After adaptive feeding, the mice were randomly divided into four groups with 10 mice in each group, namely, control group (normal group), model group (modeling with absolute ethanol), positive

drug group (teprenone 160 mg/kg) and compound 1 group (1 mg/kg). After the animals were grouped, the control group and model group were treated with pure water, and the other dosed groups were treated with the corresponding drugs once a day for 8 consecutive days. On the 7th day, after treatment, all the animals were fasted for 24 h with free access to water. On the 8th day, 30 min after administration, the mice in each group (except the control group) were given 0.15 mL of absolute ethanol by oral gavage; and after 1 h, the animals were sacrificed by excessive CO₂ inhalation, the gastric cardia was ligated, the pylorus was occluded, and the whole stomach was removed. 1 mL of 1% formaldehyde solution was injected into the gastric lumen, the cardia was ligated, and the stomach was taken out and immediately immersed in 1% formaldehyde solution for fixation of 25 min. The stomach was cut open along the greater curvature, the content of the stomach was cleaned off with normal saline, and the ulcer index was calculated after being laid flat. Calculation method for ulcer index: If the length of cord-like injury was greater than 1 mm, the length thereof was measured, with 1 point per millimeter; if the width thereof was greater than 1 mm, the score thereof was doubled according to the number of millimeters of the width; and if the length was less than 1 mm, a score of 0.5 was given, and the scores were added up to obtain the ulcer index of the animal.

3. Results:

In the mouse ethanol-induced gastric ulcer model, oral gavage of Compound 1 once a day for 8 consecutive days could significantly reduce the gastric ulcer index of mice, and the effect was greater than that of the positive drug group (Table 6). The results showed that Compound 1 had a significant effect on treating gastric ulcer. The experimental results were shown in Fig. 2.

Table 6. Effects of test drugs on the ulcer index of mice with ethanol-induced gastric ulcer (n=10, $\bar{x} \pm s$)

Group	Ulcer index
Control group	1.84 ± 1.62
Model group	35.32 ± 23.30 ^{##}
Teprenone group:	13.42 ± 7.61*
Compound 1 group	8.13 ± 4.17**

Note:., ^{##}P < 0.01, compared with the control group; and *P < 0.05, **P < 0.01, compared with the model group.

Example 3: Anti-ulcer effect of some polypeptide samples obtained from Example 1 on ethanol-induced gastric ulcer model in mice

1. Experimental animal: SPF grade C57BL/6 mice, from Chengdu Yaokang Shengwu Keji Youxian Gongsi, animal license number: SCXK (Chuan) 2020-034.

2. Method:

After adaptive feeding, all the animals were fasted for 24 h with free access to water after administration one day before the experiment. Before modeling, the experimental mice were randomly divided into groups: blank group (5 mice), model group (10 mice), and treatment groups (10 mice per group). Except for the blank group and the model group, which were given sterile water by gavage, the treatment groups were administered with different test compounds by gavage at a dose of 0.2 mg/kg, respectively. One hour after administration, the mice received 0.9 ml/kg absolute ethanol by oral gavage for modeling. After 1 h, the animals were sacrificed by cervical dislocation, the gastric cardia was ligated, the pylorus was occluded, and the whole stomach was removed. 1 mL of 1% formaldehyde solution was injected into the gastric lumen, the cardia was ligated, and the stomach was taken out and immediately immersed in

1% formaldehyde solution. After 30 min, the stomach tissue was taken out and cut open along the greater curvature. The content of the stomach was rinsed off with normal saline, the injury of gastric mucosa in mice were observed and measured after being laid flat, and the ulcer index and ulcer inhibition rate were calculated.

Calculation method for ulcer index: If the length of cord-like injury was greater than 1 mm, the length thereof was measured, with 1 point per millimeter; if the width thereof was greater than 1 mm, the score thereof was doubled according to the number of millimeters of the width; and if the length was less than 1 mm, a score of 0.5 was given, and the scores were added to obtain the ulcer index of the animal.

Ulcer inhibition rate = (ulcer index of model group - ulcer index of treatment group) / ulcer index of model group * 100%; and

Relative ulcer inhibition rate = (ulcer inhibition rate of test compound) / (ulcer inhibition rate of Compound 1).

3. Results: Table 7 showed the relative ulcer inhibition rates of the compounds of the present invention

Table 7 Anti-ulcer activity of single administration in ethanol-induced model in mice

No.	Anti-ulcer activity *	24	ND	49	ND
1	+++	25	ND	50	/
2	ND	26	+++	51	ND
3	+++	27	+++	52	ND
4	ND	28	+++	53	ND
5	ND	29	ND	54	ND
6	ND	30	+++	55	ND
7	ND	31	+++	56	-
8	+	32	+++	57	++
9	ND	33	ND	58	/
10	++++	34	/	59	ND
11	++	35	+	60	ND
12	/	36	ND	61	ND
13	ND	37	ND	62	ND
14	ND	38	+++	63	ND
15	ND	39	ND	64	+
16	ND	40	ND	65	ND
17	ND	41	ND	66	+
18	ND	42	ND	67	+
19	ND	43	ND	68	ND
20	ND	44	+	69	ND
21	ND	45	-	70	ND
22	ND	46	ND	71	ND
23	ND	47	ND	72	ND
		48	++	73	++

* Note:

The anti-ulcer effect of each compound was completed by several cohorts of experiments. For easy comparison, the anti-ulcer activity was expressed as the mean value of the relative ulcer inhibition rate

(Compound 1 was used as a control group in each cohort of experiments).

Relative ulcer inhibition rate = (ulcer inhibition rate of test compound) / (ulcer inhibition rate of Compound 1)

Relative ulcer inhibition rate > 1.20, denoted as “++++”;

relative ulcer inhibition rate 0.9-1.20, denoted as “+++”;

relative ulcer inhibition rate 0.6-0.9, denoted as “++”;

relative ulcer inhibition rate 0.3-0.6, denoted as “+”;

0 < relative ulcer inhibition rate < 0.3, denoted as “/” (very low activity);

relative ulcer inhibition rate < 0, denoted as “-”; and

ND represented no comparison with Compound 1.

Example 4: Effect of Compound 1 on mouse gastric organoid

Method: The gastric antrum epithelium of healthy wild-type mice was used for organoid culture. The epithelial layer of the gastric antrum of the mice was separated from the muscle layer under stereoscope, cut into small pieces about 0.5 mm in size, and digested with 2.5 mM EDTA/DPBS at 4°C for about 1 h. The digested gastric glandular epithelial cells were filtered and centrifuged, and the supernatant was discarded. The obtained cell pellet was resuspended in matrix gel and seeded in a culture dish followed by addition of organoid medium containing growth factors. In the control group, no test drug was added except growth factors. In the experimental group, Compound 1 was added under the same culture conditions as in the control group. The ball formation and organoid growth were observed and photographed at Day 1, Day 3, Day 5 and Day 7 with an inverted microscope, and the effect of Compound 1 on organoid growth was assessed.

Results: Compared with the control group, the growth rate of the organoids in the culture medium containing Compound 1 was obviously accelerated over time. Through the quantitative analysis of the diameter of each organoids, the results showed that the volume of the organoids treated with Compound 1 was significantly larger than that of the control group (see Fig. 3, * $p < 0.05$, compared with the control group), and the proliferation of the organoids could be significantly promoted (all the statistical data also showed significant difference). RNA was extracted from the organoids, and the transcription level of target genes was detected by real-time fluorescence quantitative PCR. It was discovered that the mRNA levels of the endocrine cell markers SST and Gastrin and the neck mucus cell marker TFF2 increased significantly (see Fig. 4). These results indicated that the polypeptide Compound 1 could promote the proliferation and differentiation of gastric organoid, indicating that Compound 1 participated in and regulated the proliferation and differentiation of gastric epithelial stem cells.

Example 5: Therapeutic effect of Compound 1 on chronic atrophic gastritis model in mice

Method: Chronic atrophic gastritis (Lgr5-GFP-CreERT mice) was induced by MNNG (N-methyl-N-nitro-N-nitrosoguanidine) combined with ranitidine. The mice were free to access to an aqueous solution containing MNNG (100 mg/ml), and at the same time, the mice were given ranitidine (8 mg/ml) aqueous solution at a dose of 150 mg/kg by gavage at a fixed time per day for 20 consecutive weeks. After 20 weeks of modeling, on the basis of drinking ordinary distilled water, the mice were given Compound 1 (5 mg/kg) daily by gavage. After 2 weeks of administration, the therapeutic effect of Compound 1 on chronic atrophic gastritis was observed.

Results: The results of tissue staining showed that the gland structure in the corpus and antrum of model group was disordered, accompanied by a reduced number of parietal cells ($H^+-K^+-ATPase$ positive) and decreased height of the mucosal epithelium in the gastric antrum. After 2 weeks of treatment with Compound 1, compared with the model group, the structure of the gastric was recovered to normal, the

number of parietal cells increased significantly, and the height of the mucosa in the gastric antrum was substantially recovered to the normal state. The results were shown in Fig. 5. These results indicated that Compound 1 could promote the repair of chronic atrophic gastritis in mice.

In chronic atrophic gastritis, the epithelial repair process entails stem cells. We detected the change in the gastric epithelial stem cells (Lgr5⁺ and AQP5⁺) by immunofluorescence staining. The experimental results showed that compared with the control group, the number of stem cells in the model group decreased significantly; and compared with the model group, the number of proliferatively active stem cells (PCNA-positive Lgr5⁺ cells and Ki67-positive AQP5⁺ cells) in the Compound 1 treatment group also increased significantly, and all the statistical results had significant difference. The results were shown in Fig. 6.

Example 6: Therapeutic effect of Compound 1 on rats with chronic atrophic gastritis

1. Experimental animals

85 SPF grade SD rats, half male and half female, weighing 160-280 g, were provided by SPF (Beijing) Biotechnology Co., Ltd. with the license number: SCXK (Jing) 2016-0002.

2. Experimental method

85 SD rats were fed adaptively for one week and then randomly divided into a blank control group (10 rats) and a chronic atrophic gastritis model group (abbreviated as CAG group) (75 rats). The blank control group was given 5 ml/kg deionized water daily by gavage, with normal diet and free access to water. The CAG group was given 120 µg/mL MNNG (N-methyl-N-nitro-N-nitrosoguanidine) aqueous solution daily by gavage, at 5 ml/kg, with free access to 0.03% ranitidine feed, 2% sodium salicylate and water. After fasting for 18 hours every week from the 15th week, a hot starch paste (5 ml/kg, 60-70°C), instead of MNNG, was given by gavage. The rest treatment was the same as hereinbefore. From the 18th week, two male and two female rats in the model group were randomly selected every two weeks, the gastric mucosa was taken for pathological evaluation until the model was successful (reduction of intrinsic glands + intestinal metaplasia), and 19 rats died during the modeling process. At the 25th week of modeling, the CAG rats were randomly divided into three groups: a model group, a Compound 1 high-dose group (3 mg/kg) and a low-dose Compound 1 group (1 mg/kg). The normal control and model groups were given the same volume of normal saline by gavage daily, and each of the other groups was given the corresponding drug by gavage for 8 weeks.

During the experiment, the weight changes of the rats were recorded, the food intake and water consumption were measured every week, the activity status of the rats was observed, etc., at regular intervals every week. After 8 weeks of administration, the rats were fasted for 24 hours with free access to water and were anesthetized by intraperitoneal injection of 10% chloral hydrate at 3.5 ml/kg. The whole stomach was removed, then quickly cut open along the greater curvature, and rinsed with normal saline, and gastric mucosa tissues were taken from the whole lesser curvature and the near greater curvature up from the esophagus end down to the duodenum end, fixed in 10% neutral formalin solution, conventionally embedded with paraffin, sectioned and conventionally stained with HE, and the pathological results were analyzed.

All data were processed by SPSS23 software. The measurement data was subjected to normality test by Shapiro-Wilk test. If it conformed to normal distribution, it was expressed by the mean ± standard deviation ($\bar{X} \pm S$). The mean values were compared between multiple groups by One-way ANOVA. Those with equal variances were compared between groups by LSD method, while those without equal variances were compared between groups by Dunnett's T3 method. $P < 0.05$ indicated that the difference was statistically significant. If it did not conform to normal distribution, rank sum test was performed, Kruskal-Wallis test was used for comparison between multiple groups, and Mann-Whitney test was used for pairwise comparison between groups. The grade data was the same as in the test method of non-normal distribution. $P < 0.05$ indicated that the difference was statistically significant.

3. Results

3.1 General condition of rats

The rats in the normal group had smooth and dense body hair and white and shiny hair color. The degree of activity was relatively high, and the responsiveness to activities such as rearing cage movement and feeding with food and water, and sounds was high. The mental state was good, and the mood was stable during gavage, weighing and other operations. The body hair of the rats in the model group was withered, sparse and easy to fall off and had a dull and beige color. The rats had low mobility, liked to curl up and had low responsiveness to activities such as rearing cage movement and feeding with food and water, and the mental state thereof was sluggish. The rats were prone to mood swings and the behavior of biting and scratching the experiment operators during gavage, weighing and other operations. The low- and high-dose Compound 1 groups both improved the whole condition of the rats, e.g., in terms of mobility and responsiveness, to various extents.

3.2 Weight of rats

After 8 weeks of administration, there was no significant difference in the weights of the female rats in each group. Compared with the normal group, the weights of the male rats in the model group significantly decreased ($P < 0.05$); compared with the model group, the weights of the male rats in the low- and high-dose Compound 1 groups significantly increased ($P < 0.05$), and in each of the other groups, the difference in weight was not statistically significant, as shown in Table 8.

Table 8. Weight (g) in each group after 8 weeks of administration

Group	No. of animals	Weight of female rat (mean)	Weight of male rat (mean)
Blank control group	10	364	602
Model group	12	369	446 [#]
Compound 1, high	14	396	637 [*]
Compound 1, low	14	374	532 [*]

Note: [#] $P < 0.05$, compared with the normal group; and ^{*} $P < 0.05$, compared with the model group.

3.3 Pathological results

Microscopic observation of pathological sections of gastric mucosa in rats: The rats in the normal group had a clear structure of each layer in the mucosa, compact and orderly arrangement of glands, and no chronic inflammation in the mucosal layer; and the rats in the model group had inflammatory cell infiltration in gastric mucosa, mucosal muscle hyperplasia, various degrees of reduction of glands in lamina propria, sparse and irregular arrangement, dilation of some glands, no intestinal metaplasia, and dysplasia in few cases. The scores of inflammation and atrophy in the model group were significantly increased ($P < 0.05$); and compared with the model group, the low- and high-dose Compound 1 groups could significantly improve the degree of inflammation and atrophy of gastric mucosa in rats ($P < 0.05$). The results were shown in Fig. 7.

Example 7: Effect of Compound 1 on the proliferation of HaCAT cells

Method: HaCAT cells were adjusted to a concentration of 1.0×10^5 to 5.0×10^5 /mL for passaging and cultured at 37°C and 5% CO₂ for 24-36 hours for biological activity detection. The cells were digested by trypsin, collected, prepared into a concentration of 2.5×10^4 /mL with a serum-free medium, seeded in a 96-well cell culture plate with 100 μ L per well, i.e., 2500 cells/well, and cultured overnight at 37°C and 5% CO₂. 50 μ L of a compound solution formulated with the serum-free medium was further added to make the final concentration of Compound 1 0.4 μ g/mL. An EGF control group was performed in parallel by adding 50 μ L of a recombinant human epidermal growth factor (EGF) with a final concentration at 100 ng/mL. In the model control group, an equal volume of serum-free medium was added. After culturing at 37°C and 5% CO₂ for 72 hours, the proliferation of the HaCAT cell line was detected by the CellTiter-Glo® kit.

Results: As shown in Fig. 8, 0.4 µg/mL **Compound 1** had a significant proliferation-promoting effect on HaCAT cells, indicating that Compound 1 had a good effect on epidermal growth and skin injury repair. In Fig. 8, compared with the model control group, * represented $p < 0.05$, and ** represented $p < 0.01$.

Example 8: Repair effect of Compounds 1 and 26 on vascular injury in zebrafish

Method: The blood vessels of transgenic vascular green fluorescent zebrafish (Fli-1) were labeled by green fluorescent protein, which was clearly visible under a fluorescence microscope (Fig. 9, the dotted frame in Fig. 9 (yellow in the original picture) was the intestinal blood vessel at the analysis site, and the arrow (white in the original picture) pointed to subintestinal vascular branches), and it became a model organism for observing vascular change. Zebrafish Fli-1 was naturally mated in pairs for breeding. Zebrafish Fli-1 was randomly selected and placed in a 6-well plate one day after fertilization, with 30 fish per well (experimental group). The zebrafish in the normal control group were treated with standard dilution water, and each of the other experimental groups was induced with aqueous simvastatin for 3 hours to establish a zebrafish microvascular loss model. After 3 hours, the aqueous solutions in all the groups were replaced with standard dilution water, and simvastatin induction was terminated. The test drug groups were respectively given Compound 1 (500 ng/fish) or Compound 26 (500 ng/fish) by intravenous injection and treated at 28°C for 2 days. Ten zebrafish in each group were randomly selected and photographed under the fluorescence microscope. NIS-Elements D 3.20 advanced image processing software was used for analysis and data collection, and the number of subintestinal vascular branches was analyzed.

Results: In the model group, it could be seen that the number of subintestinal vascular branches decreased. Intravenous injection of **Compounds 1** and **26** could significantly reverse subintestinal microvascular loss caused by simvastatin and restore the number of subintestinal vascular branches of zebrafish. **Compounds 1** and **26** were shown to promote the repair of injured blood vessels (Figs. 10 and 11). In Fig. 11, compared with the model control group, ** $p < 0.01$ and *** $p < 0.001$.

Example 9: Gastric and intestinal stability test of some polypeptide samples

Method: 1 mg of each of the samples to be tested (Compounds 1, 26, 27 and 28 and EGF) were taken and dissolved in 1 ml of water. 100 µl of sample solution was taken, 900 µl of water was added, and they were uniformly mixed, as a control solution. 100 µl of each sample solution was taken, and 900 µl of artificial gastric juice (W), artificial intestinal juice (X), povidone-iodine solution (I), and hydrogen peroxide solution (O) were respectively added. The solution was placed in a constant temperature water bath at 37°C for 1 hour, and left to stand for cooling and filtering, as a test solution. The peak areas of the sample before and after treatment were respectively detected by high performance liquid chromatography, and the experimental results were compared based on the peak areas of the samples. The original solution without any treatment after being diluted with water was used as a control, and the changes in the peak areas (contents) of test solutions at corresponding positions were compared and counted.

Table 9: Gastric and intestinal stability test of polypeptide samples

No.	W Retained %	X Retained %	I Retained %	O Retained %
Compound 1	96	0	101	100
Compound 26	100	103	101	102
Compound 27	97	0	100	101
Compound 28	96	0	99	99
EGF	0	0	0	0

Note: W represented artificial gastric juice, X represented artificial intestinal juice, I represented povidone-iodine solution, and O represented hydrogen peroxide solution.

Results: As shown in Table 9, the four test products (**Compounds 1, 26, 27, and 28**) all retained 100% in the artificial gastric juice (**W**), povidone-iodine solution (**I**) and hydrogen peroxide solution (**O**), indicating that they were very stable; **Compound 26** was also extremely stable in artificial intestinal juice (**X**); EGF was not retained in both the gastric juice and intestinal juice, indicating that it was unstable in the gastric juice and intestinal juice, and where EGF was applied externally after disinfection with povidone-iodine solution and hydrogen peroxide solution, EGF was also destroyed.

Example 10: Effect of Compound 1 on aspirin-induced gastric ulcer in rats

Method: After adaptive feeding, SD rats were divided into three groups (10 rats in each group) by Excel-based complete randomization, namely, a control group, a model group, and a Compound 1 (0.3 mg/kg) group. After the animals were grouped, they were given corresponding treatments (the control group and the model group were given the same volume of purified water, and the Compound 1 group was given corresponding drug treatment) once a day for 8 consecutive days. On the 7th day after administration, all the animals were fasted for 24 h with free access to water. On the 8th day, except for the control group, the rats in the Compound 1 group and the model group were orally given 250 mg/kg aspirin solution for modeling 30 min after compound administration (or given water). 4 h after modeling, the animals were sacrificed, the cardia was ligated, the pylorus was occluded, and the whole stomach was removed. 8 mL of 1% formaldehyde solution was injected into the gastric lumen, the pylorus was ligated, and the stomach was taken out and immediately immersed in 1% formaldehyde solution for fixation. After 30 min, the stomach was cut open along the greater curvature, the content of the stomach was cleaned off with normal saline, and after the stomach was laid flat, the stomach was observed, and panoramic photos were taken to measure the ulcer area.

Results: Oral gavage of Compound 1 (0.3 mg/kg) once a day for 8 consecutive days had no obvious effects on the weight change of the aspirin-induced gastric ulcer model rats. Compound 1 reduced bleeding points in the stomach of the aspirin-induced gastric ulcer model rats and significantly reduced the area of gastric ulcer in the rats. Table 10 showed the effect of Compound 1 on aspirin-induced gastric ulcers in rats.

Table 10 Effect of Compound 1 on aspirin-induced gastric ulcer in rats.

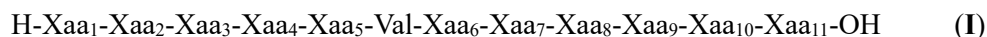
Group/dose	Ulcer area (mm ²)
Control group:	7.42 ± 7.32
Model group:	140.36 ± 82.40 ^{##}
Compound 1 group:	20.55 ± 10.45 ^{**}

Note: ^{##} $p < 0.01$, compared with the control group; and ^{**} $p < 0.01$, compared with the model group,

Although the above examples are disclosed in the present invention, the embodiments of the present invention are not limited to the above examples, and any other changes, modifications, substitutions, combinations, and simplifications that do not depart from the present invention should be equivalent replacements and are included in the scope of protection of the present invention.

WHAT IS CLAIMED IS:

1. A compound of Formula (I) or a physiologically compatible salt thereof, wherein the compound of Formula (I) is as follows:



wherein

- Xaa₁ is Pro, Gly, Ala or absent;
- Xaa₂ is Ala, Leu, Ile, Gly, Cys, Ser or absent;
- Xaa₃ is Ala, Pro, Gly, Leu, Ile, Cys, Ser or absent;
- Xaa₄ is Glu, Gln, Asp, Asn, Leu, Ile, Val or absent;
- Xaa₅ is Pro, Gly, Ala, Val or absent;
- Xaa₆ is Pro, Gly or Ala;
- Xaa₇ is Leu, Phe, Val, Ala, Tyr, Glu, Lys, Asp, Ile, Met or absent;
- Xaa₈ is Val, Leu, Gln, Ile, Met or absent;
- Xaa₉ is Lys, Arg, His, Asp, Val or absent;
- Xaa₁₀ is Glu, Gln, Asp, Asn or absent; and
- Xaa₁₁ is Glu, Asp, Asn, Gln or absent,

provided that at most 9 of Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀ and Xaa₁₁ are absent.

- 2. The compound or physiologically compatible salt thereof according to claim 1, wherein Xaa₅ is Pro.
 - 3. The compound or physiologically compatible salt thereof according to claim 1, wherein Xaa₆ is Pro.
 - 4. The compound or physiologically compatible salt thereof according to claim 1, wherein Xaa₇ is Leu.
 - 5. The compound or physiologically compatible salt thereof according to any one of claims 1 to 5,
- wherein the compound of formula (I) has a structure of the following Formula (II),



wherein

- Xaa₁ is Pro, Gly, Ala or absent;
- Xaa₂ is Ala, Leu, Ile, Gly, Cys, Ser or absent;
- Xaa₃ is Ala, Pro, Gly, Leu, Ile, Cys, Ser or absent;
- Xaa₄ is Glu, Gln, Asp, Asn, Leu, Ile, Val or absent;
- Xaa₈ is Val, Leu, Gln, Ile, Met or absent;
- Xaa₉ is Lys, Arg, His, Asp, Val or absent;
- Xaa₁₀ is Glu, Gln, Asp, Asn or absent; and
- Xaa₁₁ is Glu, Asp, Asn, Gln or absent.

6. The compound or physiologically compatible salt thereof according to any one of claims 1 to 5, wherein Xaa₁ in Formula (I) or (II) is Pro or absent; preferably Pro.

7. The compound or physiologically compatible salt thereof according to any one of claims 1 to 6, wherein Xaa₂ in Formula (I) or (II) is Ala or absent; preferably Ala.

8. The compound or physiologically compatible salt thereof according to any one of claims 1 to 7, wherein Xaa₃ in Formula (I) or (II) is Ala, Gly or absent; preferably Ala.

9. The compound or physiologically compatible salt thereof according to any one of claims 1 to 8, wherein Xaa₄ in Formula (I) or (II) is Glu, Gln, Asp or absent; preferably Glu or Gln.

10. The compound or physiologically compatible salt thereof according to any one of claims 1 to 9, wherein Xaa₈ in Formula (I) or (II) is Val or absent; preferably Val.

11. The compound or physiologically compatible salt thereof according to any one of claims 1 to 10, wherein Xaa₉ in Formula (I) or (II) is Lys, Arg or absent; preferably Lys or absent.

12. The compound or physiologically compatible salt thereof according to any one of claims 1 to 11, wherein Xaa₁₀ in Formula (I) or (II) is Glu, Gln or absent; preferably Gln.

13. The compound or physiologically compatible salt thereof according to any one of claims 1 to 12, wherein Xaa₁₁ in Formula (I) or (II) is Asp or absent; preferably Asp.

14. The compound or physiologically compatible salt thereof according to any one of claims 1 to 13, wherein one of Xaa₁, Xaa₂, Xaa₃ and Xaa₄ in Formula (I) or (II) is absent; or two of Xaa₁, Xaa₂, Xaa₃ and Xaa₄ in Formula (I) or (II) are absent; or three of Xaa₁, Xaa₂, Xaa₃ and Xaa₄ in Formula (I) or (II) are absent; or all of Xaa₁, Xaa₂, Xaa₃ and Xaa₄ in Formula (I) or (II) are absent.

15. The compound or physiologically compatible salt thereof according to any one of claims 1 to 14, wherein one of Xaa₈, Xaa₉, Xaa₁₀ and Xaa₁₁ in Formula (I) or (II) is absent; or two of Xaa₈, Xaa₉, Xaa₁₀ and Xaa₁₁ in Formula (I) or (II) are absent; or three of Xaa₈, Xaa₉, Xaa₁₀ and Xaa₁₁ in Formula (I) or (II) are absent; or all of Xaa₈, Xaa₉, Xaa₁₀ and Xaa₁₁ in Formula (I) or (II) are absent.

16. The compound or physiologically compatible salt thereof according to claim 1, wherein the compound is selected from:

Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 1)

Gly-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 2)

Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys (Compound 3)

Pro-Ala-Ala-Glu-Gly-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 4)

Pro-Ala-Ala-Glu-Pro-Val-Gly-Leu-Val-Lys-Gln-Asp (Compound 5)

Pro-Ala-Ala-Glu-Pro-Val-Gly-Ala-Val-Lys-Gln-Asp (Compound 6)

Pro-Ala-Ala-Glu-Pro-Val-Gly-Val-Val-Lys-Gln-Asp (Compound 7)

Pro-Ala-Ala-Glu-Gly-Val-Gly-Leu-Val-Lys-Gln-Asp (Compound 8)

Pro-Ala-Ala-Glu-Gly-Val-Gly-Leu (Compound 9)

Pro-Ala-Ala-Gln-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 10)

Pro-Ala-Ala-Asp-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 11)

Pro-Ala-Ala-Glu-Pro-Val-Pro-Phe-Val-Lys-Gln-Asp (Compound 12)

Pro-Ala-Ala-Glu-Pro-Val-Pro-Tyr-Val-Lys-Gln-Asp (Compound 13)

Pro-Ala-Ala-Glu-Pro-Val-Gly-Leu-Val-Lys (Compound 14)

Pro-Ala-Ala-Glu-Pro-Val-Gly-Val-Val-Lys (Compound 15)

Pro-Ala-Ala-Glu-Pro-Val-Ala-Leu-Val-Lys (Compound 16)

Pro-Ala-Ala-Glu-Pro-Val-Ala-Val-Val-Lys (Compound 17)

Pro-Ala-Ala-Glu-Ala-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 18)

Pro-Ala-Ala-Glu-Pro-Val-Ala-Leu-Val-Lys-Gln-Asp (Compound 19)

Pro-Ala-Ala-Glu-Ala-Val-Ala-Leu-Val-Lys-Gln-Asp (Compound 20)

Ala-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 21)

Pro-Ala-Ala-Glu-Pro-Val-Pro-Phe-Val-Lys (Compound 22)

Pro-Ala-Ala-Glu-Pro-Val-Pro-Tyr-Val-Lys (Compound 23)

Pro-Ala-Ala-Glu-Pro-Val-Gly-Phe-Val-Lys (Compound 24)

Pro-Ala-Ala-Glu-Pro-Val-Ala-Phe-Val-Lys (Compound 25)

Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu (Compound 26)

Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 27)

Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 28)

Pro-Ala-Ala-Glu-Pro-Val-Pro (Compound 29)

Ala-Glu-Pro-Val-Pro-Leu (Compound 30)

Glu-Pro-Val-Pro-Leu (Compound 31)

Pro-Val-Pro-Leu (Compound 32)

Ala-Ala-Glu-Pro-Val-Pro-Leu (Compound 33)

Pro-Ala-Ala-Glu-Pro-Val (Compound 34)

Pro-Ala-Ala-Glu-Pro (Compound 35)
 Pro-Ala-Ala-Glu (Compound 36)
 Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 37)
 Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 38)
 Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 39)
 Pro-Leu-Val-Lys-Gln-Asp (Compound 40)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Ile-Val-Lys (Compound 41)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Val-Val-Lys (Compound 42)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Met-Val-Lys (Compound 43)
 Ala-Glu-Pro-Val-Pro (Compound 44)
 Ala-Glu-Pro-Val (Compound 45)
 Pro-Ala-Ala-Asn-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 46)
 Pro-Ala-Ala-Leu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 47)
 Pro-Ala-Gly-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 48)
 Pro-Ala-Pro-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 49)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-leu-Val-Lys-Gln-Asn (Compound 50)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-leu-Val-Val-Gln-Asp (Compound 51)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Val-Val-Lys-Gln-Asp (Compound 52)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Ile-Val-Lys-Gln-Asp (Compound 53)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Met-Val-Lys-Gln-Asp (Compound 54)
 Pro-Leu-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 55)
 Pro-Ile-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 56)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Glu-Asp (Compound 57)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Asn-Asp (Compound 58)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Asp-Asp (Compound 59)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Glu (Compound 60)
 Pro-Ala-Leu-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 61)
 Pro-Ala-Ile-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 62)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Leu-Lys-Gln-Asp (Compound 63)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Ile-Lys-Gln-Asp (Compound 64)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Met-Lys-Gln-Asp (Compound 65)
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Arg-Gln-Asp (Compound 66)
 Pro-Ala-Ala-Val-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 67)
 Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 68)
 Gly-Ala-Ala-Val-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 69)
 Gly-Ala-Gly-Val-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 70)
 Gly-Ala-Gly-Val-Gly-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 71)
 Pro-Ala-Ala-Glu-Pro-Val-Ala-Phe-Val-Lys-Gln-Asp (Compound 72)
 Val-Pro-Leu-Val (Compound 73).

17. The compound or physiologically compatible salt thereof according to claim 6, wherein the compound is selected from:

Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 1);
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys (Compound 3);
 Pro-Ala-Ala-Gln-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 10);
 Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu (Compound 26);
 Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 27);

Ala-Glu-Pro-Val-Pro-Leu (Compound 30);
Glu-Pro-Val-Pro-Leu (Compound 31);
Pro-Val-Pro-Leu (Compound 32);
Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 28);
Pro-Ala-Ala-Asp-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 11);
Pro-Ala-Gly-Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 48);
Pro-Ala-Ala-Glu-Pro-Val-Pro-Leu-Val-Lys-Glu-Asp (Compound 57); or
Glu-Pro-Val-Pro-Leu-Val-Lys-Gln-Asp (Compound 38).

18. Use of the compound or physiologically compatible salt thereof according to any one of claims 1 to 17 in the preparation of a medicament for repairing skin wounds or mucosal damage.

19. Use of the compound or physiologically compatible salt thereof according to any one of claims 1 to 17 in the preparation of a medicament for regulating the proliferation and differentiation of stem cells.

20. The use according to claim 18, wherein the mucosal damage is mucosal damage in a cavity such as the digestive system or respiratory system.

21. The use according to claim 20, wherein the mucosal damage of the digestive system is related to oral, esophageal, and gastrointestinal diseases, and the oral diseases include oral ulcer, stomatitis, gingivitis, periodontitis, etc.; the esophageal diseases include esophagitis, esophageal ulcer, etc.; the gastrointestinal diseases include chronic gastritis, chronic atrophic gastritis, acute gastritis, gastroduodenal ulcer, functional gastrointestinal diseases, dyspepsia, precancerous lesions, digestive system tumors, gastrointestinal bleeding, gastroesophageal reflux disease, acute and chronic enteritis, ulcerative colitis, Crohn's disease, and mucosal injuries caused by radiotherapy and/or chemotherapy; and the skin wounds is related to diseases such as epidermal inflammation, mechanical and surgical wound, burns and scalds, ulcers, fistulas, bedsores, and skin injuries caused by radiotherapy and/or chemotherapy.

22. The use according to claim 20, wherein the mucosal damage of the digestive system is mucosal damage caused by an irritant substance or a drug or by a stress state.

23. Use of the compound or physiologically compatible salt thereof according to any one of claims 1 to 17 in the preparation of a medicament for preventing, alleviating or treating a gastrointestinal disease or eliminating inflammatory edema.

24. A pharmaceutical composition, a food composition, a health care or cosmetic composition or commodity composition, said composition comprising the compound or a physiologically compatible salt thereof according to any one of claims 1 to 17 and a physiologically acceptable carrier.