

NEW MULTI-FUNCTIONAL OLIGOPEPTIDES**Field of the Invention**

5 This invention relates to new peptides, the use of such peptides in human medicine, as pharmaceutically-active ingredients or otherwise, and to pharmaceutical compositions comprising them. In particular, the invention relates to the use of those peptides and compositions in the treatment of various conditions including inflammation.

10 **Background and Prior Art**

Inflammation is typically characterized as a localised tissue response to e.g. invasion of microorganisms, certain antigens, damaged cells or physical and/or chemical factors. The inflammatory response is normally a protective mechanism which serves to destroy, dilute
15 or sequester both the injurious agent and the injured tissue, as well as to initiate tissue healing.

Inflammation may result from physical trauma, infection, some chronic diseases (e.g. psoriasis and autoimmune diseases, such as rheumatoid arthritis) and/or chemical and/or
20 physiological reactions to external stimuli (e.g. as part of an allergic response). A complex series of events may be involved, in which inflammatory mediators increase blood flow and dilation of local blood vessels, resulting in redness and heat, the exudation of fluids, often resulting in localised swelling, leukocytic migration into the inflamed area, and pain.

25 Many conditions/disorders are characterized by, and/or are caused by, abnormal, tissue-damaging inflammation. Such conditions are typically characterized by activation of immune defence mechanisms, resulting in an effect that is more harmful than beneficial to the host, and are generally associated with varying degrees of tissue redness or hyperemia, swelling, hyperthermia, pain, itching, cell death, tissue destruction, cell proliferation and/or
30 loss of function. Examples include inflammatory bowel diseases, rheumatoid arthritis, multiple sclerosis, psoriasis, glomerulonephritis and transplant rejection.

Typically, a complex series of events results in inflammatory changes such as increased blood flow through dilation of local blood vessels, resulting in redness and heat, the
35 extravasation of leukocytes and plasma, often resulting in localised swelling, activation of sensory nerves (resulting in pain in some tissues) and loss of function. These inflammatory changes are triggered by a cascade of cellular and biochemical events involving cells like neutrophils, monocytes, macrophages and lymphocytes together with inflammatory

mediators such as vasoactive amines, cytokines, complement factors and reactive oxygen species.

Amongst other things, inflammation plays a key role in the wound healing process.

5 Wounds and burns can therefore be classified as conditions with which inflammation is associated. Traditional thinking in the art is that anti-inflammatory drugs should not be applied directly to open wounds, as this would be detrimental to the progress of wound healing.

10 Fibrosis is defined by the excessive accumulation of fibrous connective tissue (components of the extracellular matrix (ECM) such as collagen and fibronectin) in and around inflamed or damaged tissue. Although collagen deposition is typically a reversible part of wound healing, it can often evolve into a progressively irreversible fibrotic response if tissue injury is severe, or if the wound-healing response itself becomes dysregulated. Furthermore,
15 fibrogenesis is known to be a major cause of morbidity and mortality in many chronic inflammatory diseases, as well as end-stage liver disease, kidney disease, idiopathic pulmonary fibrosis (IPF) and heart failure. It is also a pathological feature of many chronic autoimmune diseases, such as scleroderma, rheumatoid arthritis, Crohn's disease, ulcerative colitis, myelofibrosis and systemic lupus erythematosus. Fibrosis may also
20 influence the pathogenesis of many progressive myopathies, metastasis and graft rejection.

Mussel adhesive protein (MAP), also known as *Mytilus edulis* foot protein (mefp), is a protein that is secreted by marine shellfish species, such as *Mytilus edulis*, *Mytilus coruscus* and *Perna viridis*. Eleven identified separate adhesive protein subtypes have been derived
25 from mussels, including the collagens pre-COL-P, pre-COL-D and pre-COL-NG; the mussel feet matrix proteins PTMP (proximal thread matrix protein) and DTMP (distal thread matrix protein); and mfp proteins mfp-2 (sometimes referred to as 'mefp-2', hereinafter used interchangeably), mfp-3/mefp-3, mfp-4/mefp-4, mfp-5/mefp-5, mfp-6/mefp-6 and, most preferably mfp-1/mefp-1 (see, for example, Zhu et al., *Advances in Marine Science*, **2014**,
30 32, 560-568 and Gao et al., *Journal of Anhui Agr. Sci.*, **2011**, 39, 19860-19862).

A significant portion of mefp-1 consists of 70 to 90 tandem repeats of the decapeptide: Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 61; see Waite, *Int. J. Adhesion and Adhesives*, **1987**, 7, 9-14). This decapeptide sequence may be isolated as a low
35 molecular weight derivative of naturally-occurring MAPs, or may be synthesized, for example as described by Yamamoto in *J. Chem. Soc., Perkin Trans.*, **1987**, 1, 613-618. See also Dalsin et al., *J. Am. Chem. Soc.*, **2003**, 125, 4253-4258.

Analogues of the decapeptide, notably Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 2) have also been disclosed. See, for example, US 5,616,311 and WO 96/39128, as well as international patent applications WO 2019/007355 A1, WO 2019/228307 A1, WO 2021/047648 A1, WO 2011/110061 A1 and WO 2021/110064 A1.

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Japanese patent application JP 2003238589 A discloses certain di- and tripeptides as angiotensin converting enzyme inhibitors.

The use of lysine amino acid residues to prepare multi antigen peptides has been disclosed in, for example, Tam Proc. Natl. Acad., Sci. USA, **1988**, 85, 5409-5413, Rao et al., J. Am. Chem. Soc., **1994**, 116, 6975-6976, US 5,229,490 and WO 2010/038220. See also international patent application WO 2021/110064 A1.

The use of peptide-based scaffolds as drug delivery vehicles has been disclosed. See, for example, Brokx et al, J. Control. Release, **2002**, 78, 115-123.

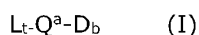
The use of lipid-peptide conjugates, such as palmitoyl tetrapeptide-7, palmitoyl tripeptide-1 and other palmitoyl oligopeptides, in anti-aging cosmetic products has been disclosed in, for example, MS Ferreira. Cosmetics. **2000**, 7, 91. See also Kamysz et al, which discloses palmitoyl tripeptides as antimicrobial agents.

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There is a clear need for new and/or improved medicines that may be used in the treatment of inflammation and conditions characterised thereby.

25 Disclosure of the Invention

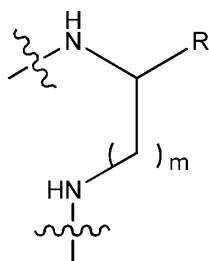
According to a first aspect of the invention, there is provided a compound of Formula I,



wherein:

30 Q^a represents Z or A-Q-B;

Q is a structural fragment of Formula II,

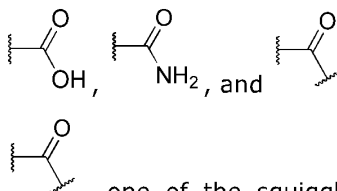


(II)

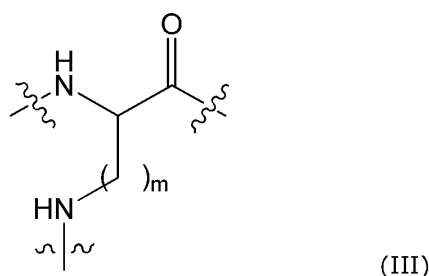
wherein:

the squiggly lines represent points of attachment of Q to A and/or B;

R is selected from the group consisting of:

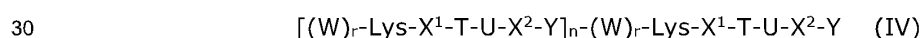


- 5 wherein, when R represents , one of the squiggly lines represents a point of attachment to the rest of the Q fragment, and the other squiggly line represents a point of attachment to a Z group;
- m represents an integer 1 to 4;
- A and B independently represent Z or A¹-Q¹-B¹;
- 10 A¹ and B¹ independently represent Z or A²-Q²-B²;
- A² and B² independently represent Z or Z-Q³-Z;
- Q¹, Q² and Q³ independently represent structural fragments of Formula III,



wherein:

- 15 the squiggly lines adjacent to the NH groups represent the points of attachment of Q¹, Q² and Q³ to A¹ and/or B¹, A² and/or B², and Z, respectively;
- the squiggly line adjacent to the C=O group represents the point of attachment of Q¹, Q² and Q³ to Q, Q¹ and Q², respectively;
- m is as defined above;
- 20 each L independently represents one or more lipids selected from the group consisting of vitamin A, vitamin E, cholesterol and a fatty acid comprising one or more carboxylic acid groups, 1 to 50 carbons, and/or one or more cyclic rings, is linear or branched, saturated or unsaturated with between 1 and 10 carbon-carbon double bonds and/or substituted by between 1 to 10 -OH groups, or a derivative of any of these lipids;
- 25 t represents an integer selected from 1 to 32;
- D represents montelukast;
- b represents an integer selected from 0 to 16;
- on each occasion that it is employed above, Z represents a structural fragment Formula IV,



(SEQ ID No: 1)

wherein:

n represents an integer selected from 0 to 4;

on each occasion that it is employed, r independently represents 0 or 1;

5 on each occasion that it is employed, W independently represents a 1 or 2 amino acid sequence selected from one or more of the group Ser, Lys, Ala, DOPA and a 3,4-dihydrocinnamic acid (HCA) residue, provided that, when present, the HCA residue is located at the N-terminus of Z;

X¹ independently represents Pro, Hyp or diHyp;

10 T independently represents Ser or pSer;

U independently represents Tyr, pTyr, DOPA, Hyp, or Pro;

X² independently represents Thr, Ser, Pro, Hyp or diHyp;

Y independently represents a 1 to 5 (such as 1 to 4) amino acid sequence selected from one or more of the group Lys, Ala, Pro, Hyp, diHyp, Thr, pThr, DOPA, Tyr, which sequences

15 is optionally terminated by dopamine (or, more properly, 'a dopamine fragment');

if present, each D is covalently bonded to Z through an amide bond between respective carboxylic acid residues thereof and one or more NH₂ residues of Z; and

each of the L residues are covalently bonded to Z through an amide bond between respective carboxylic acid residues of L and one or more NH₂ residues of Z and/or through

20 an ester bond between respective -OH residues of L and one or more carboxylic acid residues of Z,

as well as regioisomers, stereoisomers, and pharmaceutically- or cosmetically-acceptable salts of said compound, which compounds, regioisomers, stereoisomers and salts are referred to together hereinafter as 'the compounds of the invention'.

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The skilled person will be able to determine whether the Z peptide attaches to the rest of the molecule through the N- or C- terminus. For the avoidance of doubt, Z attaches to the rest of the molecule by forming an amide bond.

30 As such, when Z attaches to R when R is , Z attaches through the N-terminus.

Preferred compounds of the invention include those in which the lipid is selected from the group consisting of palmitic acid, stearic acid, oleic acid, octadecanedioic acid, docosahexaenoic acid and leukotriene B4 (LTB4), or a derivative of any of these.

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Further preferred compounds of the invention also include those in which the lipid is a polyunsaturated fatty acid, or a derivative thereof. In such embodiments, the derivative may be a specialized pro-resolving mediator (SPM).

- 5 Further preferred compounds of the invention also include those in which the lipid is a derivative of a fatty acid, such as a glycerolipid, glycerophospholipid, sphingolipid or saccharolipid.

- Further preferred compounds of the invention also include those in which the lipid is
10 palmitic acid, or a derivative thereof. In such embodiments, the derivative may be phosphatidylserine, or more preferably, the derivative is 1,2-dipalmitoyl-sn-glycero-3-phospho-L-serine, and most preferably, the derivative is 1,2-dipalmitoyl-sn-glycero-3-phospho-L-serine (DPPS). In such embodiments, the derivative may be
15 phosphatidylethanolamine, or more preferably, the derivative is 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine (DPPE).

- Further preferred compounds of the invention also include those in which the lipid is stearic acid, or a derivative thereof. In such embodiments, the derivative may be 1,2-distearoyl-sn-glycero-3-phospho-L-serine.

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- Further preferred compounds of the invention also include those in which the lipid is oleic acid, or a derivative thereof. In such embodiments, the derivative may be 1,2-dioleoyl-sn-glycero-3-phospho-L-serine.

- 25 Further preferred compounds of the invention also include those in which the lipid is palmitoylethanolamide (PEA).

- Further preferred compounds of the invention also include those in which the lipid is selected from the group consisting of vitamin E, vitamin A, and cholesterol, or a derivative
30 of any of these. In such embodiments, the derivative of cholesterol may be cholesterol-acetic acid.

- Further preferred compounds of the invention also include those in which the lipid is a fatty acid comprising 1 to 50 carbons, and/or one or more cyclic rings, is linear or branched,
35 saturated or unsaturated with between 1 and 10 carbon-carbon double bonds and/or substituted by between 1 to 10 -OH groups, or a derivative thereof. In such embodiments, the fatty acid may have 6 to 24 carbons, such as 6 to 18 carbons. In other embodiments, the fatty acid may have 1 to 6 carbon-carbon double bonds, such as 1 to 5 carbon-carbon

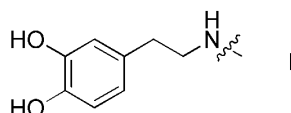
double bonds. In other embodiments, the fatty acid may have 1 to 5 -OH groups, such as 1 to 2 -OH groups. In other embodiments, the fatty acid may have 1 to 10 cyclic rings, such as 1 to 8 cyclic rings.

- 5 Further preferred compounds of the invention also include those in which:
t represents an integer selected from 1 to 8; or, more preferably
t represents an integer selected from 1 to 4.

Further preferred compounds of the invention also include those in which:

- 10 b represents an integer selected from 0 to 4; or, more preferably
b represents 1.

As used herein, the terms 'dopamine' and 'dopamine fragment' refer to a structural fragment of formula I,

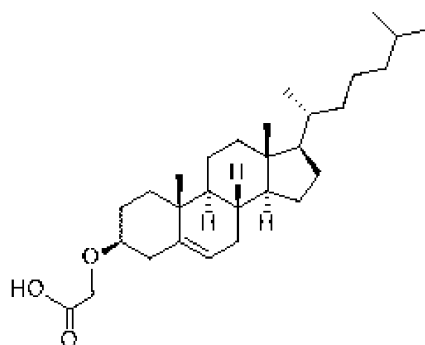


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wherein the squiggly line represents the point of attachment to Y.

- As used herein, Palm represents palmitic acid, Stea represents stearic acid, dopamine is
20 as defined hereinbefore, Olei represents oleic acid, DHA represents docosahexaenoic acid,
DPPS represents 1,2-dipalmitoyl-sn-glycero-3-phospho-L-serine, LTB4 represents
leukotriene B4 and PEA represents palmitoylethanolamide.

- As used herein, Pro represents proline, Ala represents alanine, Ser represents serine, Tyr
25 represents tyrosine, Hyp represents hydroxyproline (including 3-hydroxyproline (3Hyp)
and 4-hydroxyproline (4Hyp)), diHyp represents dihydroxyproline (including 3,4-
dihydroxyproline (3,4diHyp), trans-2,3-cis-3,4-dihydroxyproline, 3,5-dihydroxyproline
(3,5diHyp) and 4,5-dihydroxyproline (4,5diHyp)), Thr represents threonine, Lys represents
lysine, Ala represents alanine, DOPA represents 3,4-dihydroxyphenylalanine, Orn
30 represents ornithine, Chol-Ac represents cholesterol-acetic acid:



(which may form an amide bond by being attached to any free amine group, including the N-terminus of an amino acid sequence, Z), and Dap represents diaminopropionic acid. 3,4-Dihydrocinnamic acid (HCA) residues are essentially DOPA residues but without the -NH₂ group in the 2- or α-carbon position relative to the carboxylic acid that is attached to the N-terminal amino acid (whether Lys or Ala).

On each occasion that they are employed, Q, Q¹, Q² and Q³ may each be covalently bonded to zero, one or two Z groups through an amide bond between respective carboxylic acid residues of Z and one or more NH₂ residues of Q, Q¹, Q² and Q³.

In this respect, preferred compounds of the invention include those in which: one of A or B represents Z and the other represents A¹-Q¹-B¹; or, more preferably, A and B both represent Z, or both represent A¹-Q¹-B¹, in which, in each case, Q¹ preferably represents a Lys fragment and Z is as hereinbefore defined.

Further preferred compounds of the invention also include those in which: one of A¹ and B¹ represents Z and the other represents A²-Q²-B²; or, more preferably, A¹ and B¹ both represent Z, or both represent A²-Q²-B², in which, in each case, Q² preferably represents a Lys fragment, and Z is as hereinbefore defined.

Further preferred compounds of the invention also include those in which: one of A² and B² represents Z and the other represents Z-Q³-Z; or, more preferably, A² and B² both represent Z, or both represent or Z-Q³-Z, in which, in each case, Q³ preferably represents a Lys fragment, and Z is as hereinbefore defined.

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More preferred compounds of the invention include those in which:

A¹ and B¹ both represent Z; or
A² and B² both represent Z.

Further preferred compounds of the invention are those in which m represents 1, 3 or,
5 more preferably 4, such that one or more of Q, Q¹, Q² and Q³ represent Lys or, more properly, 'a Lys fragment', in accordance with what are defined above as 'the structural fragments of formulae II and III' (as appropriate).

Particularly preferred compounds of the invention include those in which:

10 Q^a represents Z; in which
n is 0, 1 or 4, preferably n is 1 or, more preferably, n is 0.

Compounds of the invention that may be mentioned include those in which an amino acid residue at the N-terminus of a Z component is optionally, covalently bonded to montelukast.

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Further compounds of the invention that may be mentioned include those in which:
R represents



t represents an integer selected from 1 to 4; and/or

20 b is 0 or 1.

Compounds of the invention that may be mentioned include those in which:

on each occasion that it is employed, W represents a 1 or 2 amino acid sequence, in which the amino acids are selected from one or more of the group Lys, Ala, DOPA and HCA;

25 T represents Ser;

U represents Tyr or DOPA;

X² represents Ser, Pro, Hyp or diHyp;

Y represents a 1 to 5 (e.g. a 1 to 4) amino acid sequence, in which the amino acids are selected from one or more of the group Lys, Ala, Pro, Hyp, diHyp, Thr, DOPA and Tyr.

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Compounds of the invention that may be mentioned include those in which:

1 or 2 of the amino acids in W represents Ser;

T represents pSer;

U represents pTyr, Hyp, or Pro;

35 X² represents Thr;

1 to 5 (such as 1 to 4) of the amino acids in Y is pThr;

Y is optionally terminated by dopamine.

Preferred compounds of the invention include those in which:

X¹ represents Hyp or, more preferably, Pro;

T represents Ser;

5 U represents Tyr or DOPA;

X² represents Hyp;

W, if present, represents HCA-, HCA-Ala-, Lys-Ala-, DOPA-, DOPA-Ala- or, preferably, Ala;
and/or

Y represents a 5, preferably a 3, more preferably a 2 or, most preferably, a 4 amino acid
10 sequence, in which the amino acids are selected from one or more of the group Lys, Hyp,
Thr, DOPA and Tyr, optionally terminated by a dopamine fragment.

Preferred compounds of the invention also include those in which Y represents a 4 amino
acid sequence selected from the group -Pro-Y¹-Y²-Lys- or, more preferably,
15 -Hyp-Y¹-Y²-Lys- and -Thr-Y¹-Y²-Lys-, wherein Y¹ and Y² are each independently selected
from the group Pro, Ala or, more preferably, Hyp, Thr, DOPA and Tyr, optionally terminated
by a dopamine fragment.

When Y represents a 2 amino acid sequence, preferred compounds of the invention include
20 those in which the amino acid sequence defined by Y is selected from the group -Tyr-Pro-,
preferably -Thr-Lys- and, more preferably, -DOPA-Lys- and -Tyr-Lys-, optionally
terminated by a dopamine fragment.

Further preferred compounds of the invention include those in which the amino acid
25 sequence defined by Y is selected from the group:

-Thr-Tyr-Hyp-;
-Thr-DOPA-Hyp-;
-Hyp-Thr-DOPA-;
-Hyp-pThr-DOPA-;
30 -Hyp-Thr-Tyr-;
-Hyp-Thr-Tyr-Hyp;
-Hyp-Thr-DOPA-Hyp-;
-Hyp-pThr-DOPA-Hyp-;
-Thr-Tyr-Lys-Hyp-;
35 -Thr-DOPA-Lys-Hyp-; preferably,
-Pro-Thr-DOPA-Lys-;
-Pro-Thr-Tyr-Lys-;
-Thr-Tyr-Pro-Lys-;

- Thr-DOPA-Pro-Lys-;
- Tyr-Hyp-Lys-;
- Tyr-Pro-Lys-;
- DOPA-Hyp-Lys-;
- 5 -Hyp-Thr-Ala-Lys-;
- Thr-Ala-Hyp-Lys-;
- Thr-Tyr-Lys-;
- Thr-Lys-; and, more preferably,
- Hyp-Thr-Tyr-Lys-;
- 10 -Hyp-Thr-DOPA-Lys-;
- Thr-Tyr-Hyp-Lys-;
- Thr-DOPA-Hyp-Lys-;
- DOPA-Lys-; and
- Tyr-Lys-,
- 15 each of which is optionally terminated by a dopamine fragment.

Compounds of the invention that may be mentioned include those in which W represents Ala.

- 20 In this respect, further compounds of the invention that may be mentioned include those wherein Z is selected from the group:
- Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 9);
 - Ala-Lys-Pro-Ser-Tyr-Hyp-Thr (SEQ ID No: 21)
 - Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-Hyp (SEQ ID No: 22)
 - 25 Ala-Lys-Pro-Ser-Tyr-DiHyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 23)
 - Ala-Lys-Pro-Ser-Tyr-DiHyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 24)
 - Ala-Lys-Hyp-Ser-Tyr-DiHyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 25)
 - Ala-Lys-Hyp-Ser-Tyr-DiHyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 26)
 - Ala-Lys-Hyp-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 27)
 - 30 Ala-Lys-Hyp-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 28)
 - Ala-Lys-Pro-Ser-Tyr-Hyp-DOPA-Hyp-Lys (SEQ ID No: 29)
 - Ala-Lys-Pro-Ser-Tyr-Hyp-Tyr-Hyp-Lys (SEQ ID No: 30)
 - Ala-Lys-Hyp-Ser-Tyr-Hyp-Thr-DOPA-Hyp (SEQ ID No: 31)
 - Ala-Lys-Hyp-Ser-Tyr-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 32)
 - 35 Ala-Lys-Hyp-Ser-Tyr-Hyp-Thr-DOPA-Lys-Hyp (SEQ ID No: 33)
 - Ala-Lys-Hyp-Ser-Tyr-Hyp-Thr-Tyr-Hyp (SEQ ID No: 34)
 - Ala-Lys-Hyp-Ser-Tyr-Hyp-Thr-Tyr-Hyp-Lys (SEQ ID No: 35)
 - Ala-Lys-Hyp-Ser-Tyr-Hyp-Thr-Tyr-Lys-Hyp (SEQ ID No: 36)

- Ala-Lys-Pro-pSer-Tyr-Hyp-Hyp-Thr-DOPA (SEQ ID No: 37)
Ala-Lys-Pro-pSer-Tyr-Hyp-Hyp-Thr-DOPA-Hyp (SEQ ID No: 38)
Ala-Lys-Pro-pSer-Tyr-Hyp-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 39)
Ala-Lys-Pro-pSer-Tyr-Hyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 40)
5 Ala-Lys-Pro-pSer-Tyr-Hyp-Hyp-Thr-Tyr (SEQ ID No: 41)
Ala-Lys-Pro-pSer-Tyr-Hyp-Hyp-Thr-Tyr-Hyp (SEQ ID No: 42)
Ala-Lys-Pro-pSer-Tyr-Hyp-Hyp-Thr-Tyr-Hyp-Lys (SEQ ID No: 43)
Ala-Lys-Pro-pSer-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 44)
Ala-Lys-Pro-pSer-Tyr-Hyp-Thr-DOPA-Hyp (SEQ ID No: 45)
10 Ala-Lys-Pro-pSer-Tyr-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 46)
Ala-Lys-Pro-pSer-Tyr-Hyp-Thr-Tyr-Hyp (SEQ ID No: 47)
Ala-Lys-Pro-pSer-Tyr-Hyp-Thr-Tyr-Hyp-Lys (SEQ ID No: 48)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp (SEQ ID No: 49)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-pThr-DOPA (SEQ ID No: 50)
15 Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-pThr-DOPA-Hyp (SEQ ID No: 51)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-pThr-DOPA-Hyp-Lys (SEQ ID No: 52)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-pThr-DOPA-Lys (SEQ ID No: 53)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-pThr-Tyr (SEQ ID No: 54)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-pThr-Tyr-Hyp (SEQ ID No: 55)
20 Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-pThr-Tyr-Hyp-Lys (SEQ ID No: 56)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-pThr-Tyr-Lys (SEQ ID No: 57)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA (SEQ ID No: 58)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Hyp (SEQ ID No: 59)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 60)
25 Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 61)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys-DOPA (SEQ ID No: 62)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr (SEQ ID No: 63)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Hyp (SEQ ID No: 64)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Hyp-Lys (SEQ ID No: 65)
30 Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 2)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys-DOPA (SEQ ID No: 66)
Ala-Lys-Pro-Ser-Tyr-Hyp-Pro-Thr-DOPA-Lys (SEQ ID No: 67)
Ala-Lys-Pro-Ser-Tyr-Hyp-Pro-Thr-Tyr-Lys (SEQ ID No: 68)
Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-DOPA-Hyp (SEQ ID No: 69)
35 Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-DOPA-Hyp-Lys-DOPA (SEQ ID No: 70)
Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-DOPA-Lys-Hyp (SEQ ID No: 71)
Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-DOPA-Lys (SEQ ID No: 72)
Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-Hyp-Lys (SEQ ID No: 11)

- Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-Hyp-Lys-DOPA (SEQ ID No: 73)
Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-Lys-Hyp (SEQ ID No: 74)
Ala-Lys-Pro-Ser-Tyr-Pro-Hyp-Thr-DOPA-Lys (SEQ ID No: 75)
Ala-Lys-Pro-Ser-Tyr-Pro-Hyp-Thr-Tyr-Lys (SEQ ID No: 76)
5 Ala-Lys-Pro-Ser-Tyr-Pro-Pro-Thr-DOPA-Lys (SEQ ID No: 77)
Ala-Lys-Pro-Ser-Tyr-Pro-Thr-DOPA-Pro-Lys (SEQ ID No: 78)
Ala-Lys-Pro-Ser-Tyr-Pro-Thr-Tyr-Pro-Lys (SEQ ID No: 79)
Ala-Lys-Pro-Ser-Tyr-Ser-Hyp-Thr-Tyr-Lys-Ala-Lys-Pro-Ser-Tyr-Ser-Hyp-Thr-Tyr-Lys (SEQ ID No: 80)
10 Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 81)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 82)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys-
15 Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 83)
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 84)
20 Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 85)
Ala-Lys-Pro-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 116).
- 25 Preferred compounds of the invention that may be mentioned include those wherein Z is selected from the group:
Ala-Lys-Pro-Ser-Tyr-DiHyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 24);
Ala-Lys-Hyp-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 28);
Ala-Lys-Pro-pSer-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 44);
30 Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-pThr-Tyr-Lys (SEQ ID No: 57);
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 61);
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr (SEQ ID No: 63);
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Hyp (SEQ ID No: 64);
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys-DOPA (SEQ ID No: 66);
35 Ala-Lys-Pro-Ser-Tyr-Hyp-Pro-Thr-Tyr-Lys (SEQ ID No: 68);
Ala-Lys-Pro-Ser-Tyr-Pro-Hyp-Thr-Tyr-Lys (SEQ ID No: 76);
Ala-Lys-Pro-Ser-Tyr-Hyp-DOPA-Hyp-Lys (SEQ ID No: 29);
Ala-Lys-Hyp-Ser-Tyr-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 32);

- Ala-Lys-Pro-pSer-Tyr-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 46);
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 60);
Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-DOPA-Hyp-Lys-DOPA (SEQ ID No: 70);
Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-Hyp (SEQ ID No: 22);
- 5 Ala-Lys-Hyp-Ser-Tyr-Hyp-Thr-Tyr-Hyp-Lys (SEQ ID No: 35);
Ala-Lys-Pro-pSer-Tyr-Hyp-Thr-Tyr-Hyp-Lys (SEQ ID No: 48);
Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-Hyp-Lys-DOPA (SEQ ID No: 73); and
Ala-Lys-Pro-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 116).
- 10 More preferred compounds of the invention that may be mentioned include those wherein
Z is selected from the group:
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 2);
Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 9);
Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-Hyp-Lys (SEQ ID No: 11); and
- 15 Ala-Lys-Pro-Ser-DOPA-Hyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 12).

Compounds of the invention that may be mentioned include those in which W is absent.

- In this respect, further compounds of the invention that may be mentioned include those
- 20 wherein Z is selected from the group:
Lys-Hyp-pSer-Tyr-Hyp-DOPA-Lys (SEQ ID No: 86);
Lys-Hyp-pSer-Tyr-Hyp-Tyr-Lys (SEQ ID No: 87);
Lys-Hyp-Ser-Tyr-Hyp-DOPA-Hyp-Lys (SEQ ID No: 88);
Lys-Hyp-Ser-Tyr-Hyp-Tyr-Hyp-Lys (SEQ ID No: 89);
- 25 Lys-Hyp-Ser-Tyr-Hyp-DOPA (SEQ ID No: 90);
Lys-Hyp-Ser-Tyr-Hyp-DOPA-Lys (SEQ ID No: 91);
Lys-Hyp-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 19);
Lys-Hyp-Ser-Tyr-Hyp-Tyr (SEQ ID No: 92);
Lys-Pro-pSer-Tyr-Hyp-DOPA-Lys (SEQ ID No: 93)
- 30 Lys-Pro-pSer-Tyr-Hyp-Tyr-Lys (SEQ ID No: 94);
Lys-Pro-Ser-Tyr-Hyp-DOPA-Hyp-Lys (SEQ ID No: 95);
Lys-Pro-Ser-Tyr-Hyp-Tyr-Hyp-Lys (SEQ ID No: 96);
Lys-Pro-Ser-Tyr-Hyp-Tyr (SEQ ID No: 97);
Lys-Pro-Ser-Tyr-Hyp-Thr (SEQ ID No: 98);
- 35 Lys-Pro-Ser-Tyr-Hyp-Thr-Lys (SEQ ID No: 99);
Lys-Pro-Ser-Tyr-Hyp-DOPA (SEQ ID No: 100);
Lys-Pro-Ser-Tyr-Hyp-DOPA-Lys (SEQ ID No: 14);
Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Hyp (SEQ ID No: 101);

- Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 102);
 Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Hyp (SEQ ID No: 103);
 Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Hyp-Lys (SEQ ID No: 104);
 Lys-Pro-Ser-Tyr-Hyp-Thr-DOPA-Hyp (SEQ ID No: 105);
 5 Lys-Pro-Ser-Tyr-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 106);
 Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-Hyp (SEQ ID No: 107);
 Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-Hyp-Lys (SEQ ID No: 108); and
 Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 16).
- 10 Preferred compounds of the invention that may be mentioned include those wherein Z is selected from the group:
 Lys-Hyp-Ser-Tyr-Hyp-DOPA-Lys (SEQ ID No: 91);
 Lys-Pro-pSer-Tyr-Hyp-DOPA-Lys (SEQ ID No: 93);
 Lys-Pro-Ser-Tyr-Hyp-DOPA (SEQ ID No: 100);
 15 Lys-Pro-pSer-Tyr-Hyp-Tyr-Lys (SEQ ID No: 94);
 Lys-Pro-Ser-Tyr-Hyp-Tyr (SEQ ID No: 97);
 Lys-Pro-Ser-Tyr-Hyp-Thr-Lys (SEQ ID No: 99);
 Lys-Hyp-pSer-Tyr-Hyp-Tyr-Lys (SEQ ID No: 87); and
 Lys-Hyp-Ser-Tyr-Hyp-Tyr (SEQ ID No: 92).
- 20 More preferred compounds of the invention that may be mentioned include those wherein Z is selected from the group:
 Lys-Pro-Ser-Tyr-Hyp-DOPA-Lys (SEQ ID No: 14);
 Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 16); and
 25 Lys-Hyp-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 19).
- Compounds of the invention that may be mentioned include those wherein the amino acid residue at the N-terminus of a Z component is optionally, covalently bonded to montelukast, forming an amide linkage with the carboxylic acid group in montelukast.
- 30 There is further provided an (optionally isolated) peptide compound Z (i.e. a compound that is equivalent to a compound of formula I as defined hereinbefore, but in which L and D are absent, and Q^a represents Z, as hereinbefore defined), in which:
 r and n both represent 0;
 35 X¹ represents Hyp or, more preferably, Pro;
 T represents pSer or, more preferably, Ser;
 U represents DOPA or, more preferably, Tyr;
 X² represents Hyp; and

Y represents a 1 to 5, preferably a 3, more preferably a 4 or, most preferably, a 2 amino acid sequence, in which the amino acids are selected from one or more of the group Lys, Hyp, Thr, DOPA and Tyr, optionally terminated by a dopamine fragment, as well as regioisomers, stereoisomers, and pharmaceutically- or cosmetically-acceptable salts of such peptide compounds.

Preferred peptide compounds Z include those of the following sequences:

Lys-Hyp-pSer-Tyr-Hyp-DOPA-Lys (SEQ ID No: 86);
 Lys-Hyp-pSer-Tyr-Hyp-Tyr-Lys (SEQ ID No: 87);
 10 Lys-Hyp-Ser-Tyr-Hyp-DOPA-Hyp-Lys (SEQ ID No: 88);
 Lys-Hyp-Ser-Tyr-Hyp-Tyr-Hyp-Lys (SEQ ID No: 89);
 Lys-Hyp-Ser-Tyr-Hyp-DOPA (SEQ ID No: 90);
 Lys-Hyp-Ser-Tyr-Hyp-DOPA-Lys (SEQ ID No: 91);
 Lys-Hyp-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 19);
 15 Lys-Hyp-Ser-Tyr-Hyp-Tyr (SEQ ID No: 92);
 Lys-Pro-pSer-Tyr-Hyp-DOPA-Lys (SEQ ID No: 93)
 Lys-Pro-pSer-Tyr-Hyp-Tyr-Lys (SEQ ID No: 94);
 Lys-Pro-Ser-Tyr-Hyp-DOPA-Hyp-Lys (SEQ ID No: 95);
 Lys-Pro-Ser-Tyr-Hyp-Tyr-Hyp-Lys (SEQ ID No: 96);
 20 Lys-Pro-Ser-Tyr-Hyp-Tyr (SEQ ID No: 97);
 Lys-Pro-Ser-Tyr-Hyp-Thr (SEQ ID No: 98);
 Lys-Pro-Ser-Tyr-Hyp-Thr-Lys (SEQ ID No: 99);
 Lys-Pro-Ser-Tyr-Hyp-DOPA (SEQ ID No: 100);
 Lys-Pro-Ser-Tyr-Hyp-DOPA-Lys (SEQ ID No: 14);
 25 Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Hyp (SEQ ID No: 101);
 Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 102);
 Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Hyp (SEQ ID No: 103);
 Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Hyp-Lys (SEQ ID No: 104);
 Lys-Pro-Ser-Tyr-Hyp-Thr-DOPA-Hyp (SEQ ID No: 105);
 30 Lys-Pro-Ser-Tyr-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 106);
 Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-Hyp (SEQ ID No: 107);
 Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-Hyp-Lys (SEQ ID No: 108); and
 Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 16),
 as well as regioisomers, stereoisomers, and pharmaceutically- or cosmetically-acceptable salts of such peptide compounds.

More preferred peptide may be selected from the group:

Lys-Hyp-Ser-Tyr-Hyp-DOPA-Lys (SEQ ID No: 91);

Lys-Pro-pSer-Tyr-Hyp-DOPA-Lys (SEQ ID No: 93);
Lys-Pro-Ser-Tyr-Hyp-DOPA (SEQ ID No: 100);
Lys-Pro-pSer-Tyr-Hyp-Tyr-Lys (SEQ ID No: 94);
Lys-Pro-Ser-Tyr-Hyp-Tyr (SEQ ID No: 97);
5 Lys-Pro-Ser-Tyr-Hyp-Thr-Lys (SEQ ID No: 99);
Lys-Hyp-pSer-Tyr-Hyp-Tyr-Lys (SEQ ID No: 87); and
Lys-Hyp-Ser-Tyr-Hyp-Tyr (SEQ ID No: 92),
as well as regioisomers, stereoisomers, and pharmaceutically- or cosmetically-acceptable
salts of such peptide compounds.

10

Especially preferred peptide compounds may be selected from the group:
Lys-Pro-Ser-Tyr-Hyp-DOPA-Lys (SEQ ID No: 14);
Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 16); and
Lys-Hyp-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 19),
15 as well as regioisomers, stereoisomers, and pharmaceutically- or cosmetically-acceptable
salts of such peptide compounds.
For the avoidance of doubt, compounds of the invention as hereinbefore defined are
referred to together hereinafter as 'compounds of the invention'.

20 Compounds of the invention, whether in the form of salts or otherwise, include
regioisomers within amino acids of the peptides (for example diHyp, Hyp and Tyr moieties),
as well as mixtures of such regioisomers. For example, included within the definition of
Tyr are, not only tyrosine (4-hydroxyphenylalanine), but also 2- and 3-
hydroxyphenylalanine. Included within the definition of Hyp are 4-hydroxyproline (4Hyp),
25 3-hydroxyproline (3Hyp) and 5-hydroxyproline (5Hyp). It is more preferred that Hyp
residues are 4-hydroxyproline. Similarly, included within the definition of diHyp are 3,4-
dihydroxyproline (3,4diHyp), 3,5-dihydroxyproline (3,5diHyp) and 4,5-dihydroxyproline
(4,5diHyp). It is more preferred that diHyp residues are 3,4-dihydroxyproline (3,4diHyp).

30 Also, in addition to the standard central carbon atom of the amino acids in the compounds
of the invention (which are normally but not exclusively in the L-configuration), certain
amino acids in the sequence comprise further chiral carbon atoms. All such stereoisomers
and mixtures (including racemic mixtures) thereof are included within the scope of the
invention. In this respect, included within the definition of Hyp are trans-4-hydroxy-L-
35 proline, cis-4-hydroxy-L-proline, trans-3-hydroxy-L-proline, cis-3-hydroxy-L-proline,
trans-5-hydroxy-L-proline and cis-5-hydroxy-L-proline, however we prefer that the Hyp
that is employed in compounds of the invention is 4-hydroxy-L-proline. Similarly,
corresponding definitions may be applied to diHyp, in which the two hydroxy groups can

also be cis or trans relative to each other. In any event, individual enantiomers of compounds of formula I that may form part of a compound of the invention are included within the scope of the invention.

5 Compounds of the invention may be in the form of salts. Salts that may be mentioned include pharmaceutically-acceptable and/or cosmetically-acceptable salts, such as pharmaceutically- and/or cosmetically-acceptable acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a compound of the invention with one or more equivalents of an appropriate acid or base,
10 optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. in vacuo, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of the compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

15 Preferred salts include, for example, acetate, hydrochloride, bisulfate, maleate, mesylate, tosylate, alkaline earth metal salts, such as calcium and magnesium, or alkali metal salts, such as sodium and potassium salts. Most preferably, compounds of the invention may be in the form of acetate salts.

20 Compounds of the invention may be prepared by way of conventional techniques, for example by way of standard amino acid coupling techniques, using standard coupling reagents and solvents, for example as described hereinafter. Compounds of the invention may be synthesised from available starting materials using appropriate reagents and reaction conditions. In this respect, the skilled person may refer to inter alia
25 "Comprehensive Organic Synthesis" by B. M. Trost and I. Fleming, Pergamon Press, 1991. Further references that may be employed include "Heterocyclic Chemistry" by J. A. Joule, K. Mills and G. F. Smith, 3rd edition, published by Chapman & Hall, "Comprehensive Heterocyclic Chemistry II" by A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon
30 Press, 1996 and "Science of Synthesis", Volumes 9-17 (Heteroarenes and Related Ring Systems), Georg Thieme Verlag, 2006.

Compounds of the invention may be isolated from their reaction mixtures and, if necessary, purified using conventional techniques as known to those skilled in the art. Thus, processes
35 for preparation of compounds of the invention as described herein may include, as a final step, isolation and optionally purification of the compound of the invention.

It will be appreciated by those skilled in the art that, in the processes described above and hereinafter, the functional groups of intermediate compounds may need to be protected by protecting groups. The protection and deprotection of functional groups may take place before or after a reaction.

5

Protecting groups may be applied and removed in accordance with techniques that are well-known to those skilled in the art and as described hereinafter. For example, protected compounds/intermediates described herein may be converted chemically to unprotected compounds using standard deprotection techniques. The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis. The use of protecting groups is fully described in 'Protective Groups in Organic Synthesis', 5th edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (2014), the contents of which are incorporated herein by reference.

10

Compounds of the invention are useful as human and animal medicine. They are therefore indicated as pharmaceuticals (and/or in veterinary science), although they may also be used as cosmetics and/or as part of a medical device.

15

Compounds of the invention may also possess pharmacological activity as such, certain pharmaceutically-acceptable (e.g. 'protected') derivatives of compounds of the invention may exist or may be prepared which may not possess such activity, but which may be administered and thereafter be metabolised or chemically transformed to form compounds of the invention. Such compounds (which may possess some pharmacological activity, provided that such activity is appreciably lower than that of the active compounds to which they are metabolised/transformed) may therefore be described as 'prodrugs' of compounds of the invention.

20

25

As used herein, references to prodrugs will include compounds that form a compound of the invention, in an experimentally-detectable amount, within a predetermined time, following administration. All prodrugs of the compounds of the invention are included within the scope of the invention.

30

When compounds of the invention possess pharmacological activity, they are particularly useful in the treatment of inflammation.

35

The term 'treatment of inflammation' includes the treatment of inflammation in any organ of the body (including soft tissue, joints, nerves, the vascular system, internal organs, especially mucosal surfaces, and particularly the skin), irrespective of the cause, and also

includes all such inflammatory disorders or conditions, and/or disorders or conditions characterized by inflammation (e.g. as a symptom).

5 Inflammatory disorders and/or conditions may be (and are typically) characterized by activation of immune defence mechanisms, resulting in an effect that is more harmful than beneficial to the host. Such conditions are generally associated with varying degrees of tissue redness or hyperemia, swelling, edema, hyperthermia, pain (including aching), exudation of body fluids, itching (pruritis), cell death and tissue destruction, cell proliferation, and/or loss of function.

10

Inflammatory conditions that may be mentioned include arteritis, diabetes mellitus, metabolic syndrome, rosacea, asthma and allergy, ankylosing spondylitis, chronic obstructive pulmonary disease, gouty arthritis, inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), multiple sclerosis, osteoarthritis, pancreatitis, 15 prostatitis, psoriatic arthritis, rheumatoid arthritis, tendinitis, bursitis, Sjögren's syndrome, systemic lupus erythematosus, uveitis, urticaria, vasculitis, mastocytosis, diabetic vascular complications, migraine, atherosclerosis and associated cardiovascular disorders. A disease state characterised by inflammation that may be mentioned is chronic obstructive pulmonary disease (COPD). A further disease state characterised by inflammation that 20 may be mentioned is inflammatory bowel diseases including Crohn's disease and, especially, ulcerative colitis. Other disease states characterized by inflammation that may be mentioned are gynaecological diseases, such as cervicitis, vaginitis (e.g. radiation vaginitis) and colpitis. Diseases that affect the gastrointestinal tract, such as gastrohelcosis (e.g. gastritis, gastric ulcer, stress-induced gastritis, gastric cancer and 25 other stomach mucosa diseases) as well as gastroesophageal reflux disease (GERD), constipation, and gastritis, inflammation associated with cancers and infections (e.g. viral infections, such as the common cold or influenza).

Inflammatory conditions that may be more especially mentioned include inflammations of 30 the skin or mucosa (including the oral, nasal, ocular, vaginal, cervical and/or anorectal mucosae, more particularly the oral or nasal mucosae), such as inflammation resulting from infections (such as viral and/or bacterial infections), or allergic/atopic conditions (such as rhinitis (e.g. allergic rhinitis), pharyngitis, periodontitis, gingivitis, xerophthalmia, conjunctivitis (e.g. allergic conjunctivitis), dermatitis, urticaria (hives) and food allergy); 35 and other inflammatory conditions, such as herpes, drug eruptions, polymorphous light eruptions, sunburn, early manifestations of skin cancers (erythema-like skin lesions), pathological hair loss (including following skin grafting), chemo rash, psoriasis, erythema

multiforme, folliculitis, eczema and external otitis. A disease state that may be mentioned is polymorphous light eruptions.

5 More particularly, compounds may be used to treat certain conditions characterized by inflammation, and/or with which inflammation is associated. Such conditions may include wounds (including abrasions (scratches), incisions (including operative incisions), lacerations, punctures, avulsions, bruising and scarring), and burns (including inflammation resulting from surgery following burns, such as skin grafting) and other conditions, such as hemorrhoids. Wounds may be acute or chronic, and/or may result
10 from one or more inflammatory disorders as defined herein.

Wounds of the skin or mucosa may arise from internal or external physical injury to the membrane surface, or may be caused by (i.e. be a symptom of) an underlying physiological disorder.

15 Physical (e.g. 'open') wounds may be caused by sharp objects (cuts, incisions, punctures) or blunt objects/mechanical forces (lacerations, abrasions, avulsions), physical blows (bruises), heat or chemicals (burns and blisters), UV light (sunburn), cold (chilblains or frostbite). Wounds may be superficial (damage only to the epidermis and/or dermis) or
20 may be full thickness wounds (damage below the epidermis and/or dermis). In serious cases, subcutaneous and/or submucosal tissues, such as muscles, bones, joints, and even internal organs, may be damaged.

Compounds of the invention may be used to relieve the pain (including aching) associated
25 with inflammation and/or wounding. In particular, compounds of the invention may be used to relieve procedural pain and/or non-procedural pain. The skilled person will understand that the term 'procedural pain' (i.e. operation pain) refers to acute pain that is associated with medical investigations and treatments conducted for the purpose of healthcare. The term 'non-procedural' refers to general pain that is associated with
30 inflammation and/or wounding (e.g. pain associated with dental ulcers, burns and/or scars), and is not a consequence of a particular medical intervention.

Compounds of the invention may be used to treat not only the inflammation, pain
(including aching) and/or pruritis (itching) associated with the wound itself and the healing
35 process, but also to prevent the exudation of body fluids from wounds, the risk of infection, and the prevention of physiological reactions that result from inflammation and/or wound healing processes, such as scarring and melanin pigmentation.

Scarring is a consequence of inflammation and/or wound healing and is a general term for the formation of fibrotic tissue that is a consequence of such inflammation/healing.

Compounds of the invention may also be useful in the suppression of the production of melanin pigmentation, which may or may not result from inflammation and/or wound healing. Compounds of the invention may also be useful in the suppression of disorders associated with melanin pigmentation, such as chloasma, freckles, melanosis, malar rash and other chromatosis, skin cancers with melanoma, and chromatosis that is caused by exposure to the sun or skin diseases like acne.

Wounds may also arise as a consequence of (e.g. inflammatory) diseases or disorders. Such wounds may include blistering and/or ulcers of the skin and mucosa. These are common conditions that are often long-lasting and difficult to treat. Skin tissues can often be damaged, removed, liquefied, infected and/or necrotic. Ulcers can lead to secondary consequences to health particularly if they become infected, are hard to heal and are costly to treat. They can also cause significant psychological stress and economic loss to patients, affecting both general well-being and quality of life.

In the alternative, inflammatory skin conditions or diseases in which compounds of the invention find particular utility include viral skin diseases such as herpes zoster, bacterial skin diseases, fungal skin diseases, skin diseases induced by animal, sexually transmitted skin diseases, skin diseases related to allergy, autoimmune skin diseases, neutrophilic dermatosis, erythematous popular and squamous dermatosis, connective tissue diseases, bullous skin disease, pigmentary skin diseases, skin appendage disorders, genodermatoses, skin diseases related to nutritional and metabolic disorders, skin tumours, psoriasis, acne, eczema and dermatitis, especially allergic/atopic dermatitis and neurodermatitis, as well as in the treatment of mucosal inflammation as characterized by rhinitis, especially allergic rhinitis, hemorrhoids, chronic obstructive pulmonary disease and ulcerative colitis, for example.

Psoriasis is a chronic, inflammatory skin disease with a tendency to recur (some patients never heal during their entire life). Clinical manifestations of psoriasis mainly include erythema and scales. It can occur over the whole body, but is more commonly observed on the scalp and limbs.

Acne is a follicular (pilosebaceous unit) chronic, inflammatory skin disease, the occurrence of which is closely related to main factors like hypersebatosis, blocked pilosebaceous ducts (including closed and open comedones), bacterial infection and inflammatory reactions,

that tends to occur during youth, characterized by multiform skin lesions on the face. The term acne thus includes regular acne and acne rosacea (i.e. copper nose).

Eczema is a skin inflammatory reaction with strong itching caused by a variety of internal and external factors. It has three phases, acute, sub-acute, and chronic. In the acute phase, there is a tendency for the production of exudates, while the chronic phase includes infiltration and hypertrophy. Skin lesions are often itchy and recur easily.

Dermatitis is a common skin disease characterized by coarseness, redness, itching, eczema, and dryness. Small lumps, refractory ulcers, and pigmented spots caused by dermatitis may, if not treated promptly, develop to basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. Dermatitis may be caused by various internal and external infectious or non-infectious factors, including substances (contact dermatitis) or allergy (allergic/atopic dermatitis). Also included is seborrheic dermatitis (seborrheic eczema), cicatricial alopecia and related diseases, and all forms of steroid-dependent dermatitis (including light-sensitive seborrheic; perioral dermatitis; rosacea-like dermatitis; rosacea such as steroid-rosacea, steroid-induced rosacea, iatrosacea, steroid dermatitis resembling rosacea, topical corticosteroid-induced rosacea-like dermatitis; and, more particularly, facial corticosteroid addictive dermatitis (FCAD) or facial corticosteroid-dependent dermatitis (FCDD), as characterized by flushing, erythema, telangiectasia, atrophy, papules and/or pustules in the facial area after long-term treatment with (including uncontrolled use, abuse or misuse of) topical corticosteroids; see, for example, Xiao et al., J. Dermatol., **2015**, 42, 697-702 and Lu et al., Clin. Exp. Dermatol., **2009**, 35, 618-621).

Rhinitis is irritation and inflammation of the mucous membrane inside the nose. Common symptoms of rhinitis include a stuffy nose, runny nose, sneezing and post-nasal drip. The most common kind of rhinitis is allergic rhinitis, caused by an allergen, such as pollen, dust, mould, or flakes of skin from certain animals. It has been surprisingly found that patients with allergic rhinitis who were treated with compounds of the invention experienced relief of eye itchiness, even when compounds of the invention were administered nasally (i.e. to the nasal mucosa).

Hemorrhoids are swellings caused by inflammation of the hemorrhoidal blood vessels found inside or around the rectum and the anus. Symptoms include bleeding (i.e. wounding) after the passage of a stool, prolapse of the hemorrhoid, mucus discharge and itchiness, soreness, redness and swelling in the area of the anus. Hemorrhoids are believed to be a consequence of an increase of pressure in the abdomen, for example, as a result of constipation or diarrhea.

Chronic obstructive pulmonary disease (COPD) is the name for a group of lung conditions that cause breathing difficulties, including emphysema (damage to the alveoli) and chronic bronchitis (long-term inflammation of the airways). COPD occurs when the lungs become inflamed, damaged and narrowed. The damage to the lungs is usually irreversible and results in an impairment of the flow of air into and out of the lungs. Symptoms of COPD include breathlessness, productive cough, frequent chest infections and persistent wheezing. The most common cause of the disease is smoking, although other risk factors include high levels of air pollution and occupational exposure to dust, chemicals and fumes.

10

Compounds of the invention may have positive effects in mitigating erythema, redness and swelling, edema, blisters, and bullous pemphigoid caused by various conditions including those mentioned generally and specifically herein, and may inhibit exudation of subcutaneous tissue fluid, and suppressing itching and pain caused by such inflammatory conditions.

15

Other inflammatory conditions that may be mentioned include:

(a) Mucosal inflammation, such as oral mucositis, aphthous ulcers, otitis media, laryngitis, tracheitis, esophagitis, gastritis, enteritis and enterocolitis (including bacillary dysentery, chronic amoebic dysentery, schistosomiasis, nonspecific ulcerative colitis and regional enteritis), cervicitis and endocervicitis, endometritis, inflammation caused by inhalation injury and the like, as well as mucosal inflammation associated with cancers, and infections (e.g. viral infections, such as the common cold or influenza), that affect mucosal surfaces, such as those in the oral cavity, the nasopharynx, the ear, the throat, the trachea, the gastrointestinal tract, the cervix, etc.

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(b) Orthopedic inflammation associated with, for example bone fractures, pyogenic infection of bones and joints, inflammation caused by rheumatic bone diseases, as well as pyogenic osteomyelitis (acute, chronic, localized, sclerotic, post-traumatic), pyogenic arthritis; bone tumors (osteoma, osteoid osteoma, chondroma), bone cysts, osteoclastoma, primary bone sarcoma (osteosarcoma, chondrosarcoma, osteofibrosarcoma, Ewing's sarcoma, non-Hodgkin's lymphoma, myeloma, chordoma), metastatic bone tumors, tumor-like lesions of bone (bone cyst, aneurysmal bone cyst, eosinophilic granuloma, fibrous dysplasia); and rheumatic arthritis.

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(c) Nerve inflammation, such as peripheral polyneuritis, facial neuritis, peripheral neuritis, subcutaneous neuritis, ulnar neuritis, intercostal neuritis, etc.

(d) Subcutaneous and submucosal soft tissue inflammation, such as myositis, ligamentitis, tendonitis, panniculitis capsulitis, lymphadenitis, bubonadentitis, tonsillitis, synovitis, fasciitis, and soft tissue inflammation caused by injuries, contusion or laceration of muscles, ligaments, fascia, tendons, membrana synovialis, fat, articular capsules, and lymphoid tissue.

(e) Vascular inflammation, such as allergic leukocytoclastic vasculitis, allergic cutaneous vasculitis, polyarteritis nodosa, thrombotic vasculitis, granulomatous vasculitis, lymphocytic vasculitis, vasculitis with abnormalities in blood composition, and rheumatic vasculitis, as well as vascular inflammation associated with vascular cancers caused by allergic leukocytoclastic vasculitis, polyarteritis nodosa, thrombotic vasculitis, granulomatous vasculitis, lymphocytic vasculitis, vasculitis with abnormalities in blood composition, and rheumatic vasculitis.

(f) Inflammation of the internal organs, such as the heart, stomach, intestine, lung, liver, spleen, kidney, pancreas, bladder, ovary, and prostate, including but not limited to pericarditis, myocarditis, endocarditis, pneumonia, hepatitis, splenitis, nephritis pancreatitis, cystitis (including interstitial cystitis), oophoritis, prostatitis and treatment of gastric ulcer.

(g) Inflammation of the eye and surrounding area, such as conjunctivitis, keratitis (e.g. acute epithelial keratitis, nummular keratitis, interstitial keratitis, disciform keratitis, neurotrophic keratitis, mucous plaque keratitis, herpes simplex keratitis, herpes zoster keratitis, bacterial keratitis, fungal keratitis acanthamoebic keratitis, onchocercal keratitis, superficial punctate keratitis, ulcerative keratitis, exposure keratitis photokeratitis and contact lens acute red eye), optic neuritis, maculopathy of the retina, retinopathy, etc.

(h) Inflammation of the gums and the oral cavity, such as periodontitis, gingivitis, dental ulcers, etc.

(i) Inflammation associated with rheumatism, such as rheumatic vasculitis, rheumatoid arthritis, rheumatic bone diseases, ankylosing spondylitis, bursitis, Crohn's disease, gout, infectious arthritis, juvenile idiopathic arthritis, osteoarthritis, osteoporosis, polymyalgia rheumatica, polymyositis, psoriatic arthritis, scleroderma, Sjögren's syndrome, spondyloarthropathies, systemic lupus erythematosus, tendinitis, etc.

Compounds of the invention may also be used in differentiation and regeneration of bone marrow cells and aplastic anemia (for example by systemic and topical administration).

Compounds of the invention may also be used in the treatment of renal diseases, including
5 end stage renal diseases and its complications, including uremic pruritus.

Compounds of the invention may also be used in the treatment of certain specific diseases of the digestive system, such as gastroesophageal reflux disease (GERD), which may be characterized by an acidic taste in the mouth, regurgitation, heartburn, pain with
10 swallowing and/or sore throat, increased salivation (water brash), nausea, chest pain, and coughing. GERD may cause injury of the esophagus, including reflux esophagitis (i.e. inflammation of the esophageal epithelium which may cause ulceration at or around the junction of the stomach and esophagus), esophageal strictures (i.e. the persistent narrowing of the esophagus caused by reflux-induced inflammation), Barrett's
15 esophagus (i.e. intestinal metaplasia (i.e. changes of epithelial cells from squamous to intestinal columnar epithelium of the distal esophagus) and/or esophageal adenocarcinoma (a form of cancer)).

Compounds of the invention may also be used in the treatment of certain specific diseases
20 of the respiratory system, such as pulmonary cystic fibrosis, interstitial pneumonia, including usual interstitial pneumonia, allergic pneumonia, asbestosis, emphysema, pulmonary heart disease, pulmonary embolism, etc. A specific disease state that may be mentioned in idiopathic pulmonary fibrosis (IPF).

IPF is a diffuse and fatal pulmonary interstitial disease with pathological features including
25 alveolar epithelial damage, massive proliferation of lung fibroblasts, excessive deposition of extracellular matrix, ultimately leading to irreversible lung tissue damage. In the latter stages of the disease, subjects with IPF experience respiratory failure and death. It has been found that compounds of the invention may find utility in the treatment of IPF and/or
30 alleviation of the symptoms associated with the disease.

Compounds of the invention are particularly useful in the treatment of the following lung and/or fibrotic conditions (whether otherwise mentioned herein or not): lung fibrosis, renal
35 fibrosis, liver fibrosis, silicosis, acute bronchitis, chronic bronchitis, tracheobronchitis, bronchial asthma, status asthmatics, bronchiectasis, upper respiratory tract infections (including the common cold and influenza), allergic airway inflammation, bacterial pneumonia, viral pneumonia, mycoplasma pneumonia, reckettsia, radiation pneumonia, pneumococcal (including staphylococcal, streptococcal and gram-negative bacillus)

pneumonia, pulmonary candidiasis (including aspergillosis, mucormycosis, histoplasmosis, actinomycosis and nocardiosis), pulmonary mycosis, cryptococcosis, lung abscesses, anaphylactic pneumonia, extrinsic allergic alveolitis, pulmonary eosinophilia (including Loeffler's syndrome and eosinophilosis), obstructive pulmonary emphysema, pulmonary edema, pulmonary tuberculosis, respiratory alkalosis/acidosis, acute lung injury, interstitial lung disease, empyema, lung fibroma and cor pulmonale.

Particular mucosal disorders and disease in which compounds of the invention find utility include anorectal diseases, such as diarrhea, hemorrhoids, abscesses, fistula, fissures, anal itching, anal sinusitis, warts and rectal prolapse; inflammatory bowel disease, including Crohn's disease and, particularly, ulcerative colitis; gynaecological diseases, such as cervicitis, vaginitis, pelvic pain and disorders; and dental diseases, such as paradentitis, for example.

Compounds of the invention may further possess an antioxidation effect, by increasing SOD (superoxide dismutase) production and reducing lipid oxidation. Compounds of the invention may therefore be considered to have antioxidant properties.

Compounds of the invention may also possess antipyretic properties that allow for the treatment of a fever and/or alleviate the symptoms thereof; for example, by reducing a subject's body temperature, which results in a reduction of fever. Compounds of the invention and formulations including them may therefore be considered to be antipyretics.

Compounds of the invention are especially useful in the treatment of:

- skin diseases, including acne, rosacea, dermatitis, seborrheic dermatitis, neurodermatitis, eczema, melanin pigmentation, scar (fibrosis), hair loss, seborrheic alopecia, alopecia cicatrisata and paronychia;
- oral diseases, including periodontitis, gingivitis, oral mucositis (including radiation-induced mucositis), hemodia and gingival recession;
- gynecological diseases, including vaginitis, vulvitis, leukoplakia of external genitalia, cervicitis, lateral incision of external genitalia and radiation vaginitis; and/or
- inflammatory Bowel Diseases (IBDs), including ulcerative colitis, proctitis, radiation proctitis, hemorrhoids and anal sinusitis.

According to a further aspect of the invention there is provided a method of treatment of inflammation, of an inflammatory disorder, and/or of a disorder/condition characterised by inflammation (for example as a symptom), which method comprises the administration of a compound of the invention or a salt thereof to a patient in need of such treatment.

For the avoidance of doubt, in the context of the present invention, the terms 'treatment', 'therapy' and 'therapy method' include the therapeutic, or palliative, treatment of patients in need of, as well as the prophylactic treatment and/or diagnosis of patients which are susceptible to, inflammation and/or inflammatory disorders.

Compounds of the invention may further possess antiviral properties that may allow for the treatment of a viral infection per se, that is treatment of a viral infection, or a viral disease, by interfering with the replication of the virus within a host, as opposed to the treatment of any symptoms of any viral infection or disease, such as pain and/or inflammation. Such antiviral properties may also allow for the prevention of the onset of such an infection or disease, the protection of cells in a host from (e.g. further) viral infection, prevention or arrest of the spread of viral infection or disease (within a single host, or from one host to a new host), or for the prevention of reactivation of a virus after latency in a host.

According to a further aspect of the invention there is provided a method of treatment of a viral infection, which method comprises the administration of a compound of the invention or a salt thereof to a patient in need of such treatment.

Viral infections that may be mentioned include those caused by viruses in the following families: adenoviridae (e.g. adenovirus), papillomaviridae (e.g. human papillomavirus), polyomaviridae (e.g. BK virus; JC virus), herpesviridae (e.g. herpes simplex, type 1; herpes simplex, type 2; varicella-zoster virus; Epstein-Barr virus; human cytomegalovirus; human herpes virus, type 8), poxviridae (e.g. smallpox), hepadnaviridae (e.g. hepatitis B virus), parvoviridae (e.g. parvovirus B19), astroviridae (e.g. human astrovirus), caliciviridae (e.g. norovirus; Norwalk virus), picornaviridae (e.g. coxsackievirus, hepatitis A virus; poliovirus; rhinovirus), coronaviridae (e.g. severe acute respiratory syndrome virus), flaviviridae (e.g. hepatitis C virus; yellow fever virus; dengue virus; West Nile virus; tick-borne encephalitis virus), retroviridae (e.g. human immunodeficiency virus; HIV), togaviridae (e.g. rubella virus), arenaviridae (e.g. Lassa virus), bunyaviridae (e.g. hantavirus; Crimean-Congo hemorrhagic fever virus; Hantaan virus), filoviridae (e.g. Ebola virus; Marburg virus; Ravn virus), orthomyxoviridae (e.g. influenza viruses, including influenza A virus (e.g. H1N1 and H3N2 viruses), influenza B virus or influenza C virus), paramyxoviridae (e.g. measles virus; mumps virus; parainfluenza virus, respiratory syncytial virus), rhabdoviridae (e.g. rabies virus), hepeviridae (e.g. hepatitis E virus), reoviridae (e.g. rotavirus; orbivirus; coltivirus; Banna virus), as well as viruses not assigned to families, such as hepatitis D virus.

Viruses that may be more specifically mentioned include herpes simplex, type 1 and herpes simplex, type 2 viruses, human papillomavirus, influenza virus and parainfluenza virus.

5 Compounds of the invention may further possess antibacterial and/or bacteriostatic properties that may allow for the treatment of a bacterial infection per se, that is treatment of a bacterial infection, or a bacterial disease, by interfering with bacterial growth or proliferation in a host, as opposed to the treatment of any symptoms of any bacterial infection or disease, such as pain and/or inflammation. Compounds of the invention may
10 therefore be considered to be bacteriocides and/or, preferably, bacteriostatic agents.

Such antibacterial properties may also allow for the prevention of the onset of such an infection or disease, the protection of cells in a host from (e.g. further) bacterial infection, prevention or arrest of the spread of bacterial infection or disease (within a single host, or
15 from one host to a new host), or for the prevention of reactivation of a bacterium after latency in a host.

According to a further aspect of the invention there is provided a method of treatment of a bacterial infection, which method comprises the administration of a compound of the invention or a salt thereof to a patient in need of such treatment.
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As disclosed herein, compounds of the invention may further possess anticancer properties that may allow for the treatment of a cancer per se, that is treatment of a cancer by interfering with the cancer as opposed to the treatment of any symptoms of the cancer, such as pain and/or inflammation. Such anticancer properties may also include the
25 prevention of the onset of such a disease e.g. by treating inflammation and thereby preventing such onset.

According to another aspect of the invention, there is provided a method of treatment of cancer, which method comprises the administration of a compound of the invention or a salt thereof to a patient in need of such treatment.
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Particular cancers that may be mentioned include oral cancer, a nasopharynx cancer, a middle ear cancer, a conjunctival cancer, a throat cancer, a tracheal cancer, an esophageal cancer, a gastric cancer, an intestinal cancer, a cervical cancer, an endometrial cancer, skin cancer and the like caused by oral mucositis (including severe oral mucositis), rhinitis, otitis media, conjunctivitis, pharyngitis, laryngitis, tracheitis, esophagitis, gastritis,
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enterocolitis, cervicitis, endometritis, erythema-like skin lesions and the like. A particular skin cancer that may be mentioned is basal cell carcinoma.

5 Fibrotic conditions of internal organs that may be mentioned include acute and/or severe internal fibrotic conditions characterised by the excessive accumulation of fibrous connective tissues (as described above) in and around inflamed or damaged tissues. Formulations of the invention may thus be useful in the treatment or prevention of fibrogenesis (as described above) and the morbidity and mortality that may be associated therewith. Thus, (e.g. acute and/or severe) fibrotic conditions of the internal organs that
10 may be treated with formulations of the invention include fibrosis of the liver, the kidneys, the lungs, the cardiovascular system, including the heart and the vascular system, the pancreas, the spleen, the central nervous system (nerve fibrosis), bone marrow fibrosis, the eyes, the vagina, the cervix, etc.

15 Inflammatory conditions of internal organs include any condition that is, or may develop into a condition that is, severe (i.e. one that requires intensive medical treatment), and in which some sort of inflammatory component is apparent, as may be characterised by detectable inflammation, and further in which morbidity is manifested (or is expected) and/or is life-threatening.

20 Inflammatory conditions that may be mentioned include one or more acute disorders or conditions of internal organs (i.e. one or more conditions that require, or may develop into a condition that requires, immediate medical interventions) that are characterized by inflammation (e.g. as a symptom), such as acute internal injuries, in one or more internal
25 organs (including any of the organs mentioned hereinbefore). By treating such acute inflammatory disorders, formulations of the invention may prevent or arrest the development of symptoms (acute or chronic) that are associated with such conditions, and also may arrest the progress of morbidity and/or mortality that is associated with such conditions.

30 Acute inflammatory conditions that may be mentioned thus include conditions such as peritonitis, pancreatitis, colitis, proctitis (including radiation proctitis), gastritis, duodenitis, pharyngitis, GERD, parodontitis and stomatitis. Particular acute inflammatory conditions that may be mentioned include acute injury to one or more internal organs (including any
35 of those mentioned hereinbefore), such as acute lung injury, inhalation injury (such as burns), acute respiratory distress syndrome (ARDS), severe acute respiratory syndrome (SARS), and multiple-organ inflammation, injury and/or failure.

Such conditions may be caused by internal or external trauma (e.g. injury or a burn), or by an infection by e.g. viruses, bacteria or fungi.

For example, proctitis (which includes eosinophilic, gonorrheal and/or ulcerative proctitis) may be caused by inflammatory bowel disease, infections, radiation (e.g. for cancer), drugs such as antibiotics, surgery or allergic conditions, such as food intolerances.

For example, multiple-organ inflammation, injury and/or failure may result from extensive and/or traumatic external injuries, including traumatic and/or extensive external burns. Traumatic external burns will be understood to include second-degree, and more particularly third-degree burns and fourth-degree, burns. Extensive external burns will be understood to include burns that affect at least about 10%, such as at least about 15%, including at least about 20% of a patient's body area. External (and internal) burns may result from exposure to heat, chemicals and the like.

Acute inflammatory and/or fibrotic conditions may also result from sepsis or septic shock, which can be caused by viral, bacterial or fungal infection. Furthermore, acute lung injury, ARDS and, particularly, SARS may be caused by viruses, such as coronaviruses, include the novel SARS coronavirus 2 (SARS-CoV-2).

Thus, in addition, one or more of the aforementioned (e.g. acute) inflammatory conditions may (indeed in some cases will likely) result in some form of internal tissue damage and/or dysfunction of relevant internal tissues. Relevant tissues thus include (e.g. mucosal) tissues, such as the respiratory epithelium. Such tissue damage may also give rise to one or more of the fibrotic conditions mentioned hereinbefore. For example, the SARS disease caused by the novel coronavirus SARS-CoV-2 (coronavirus disease 2019 or COVID-19) is known in many cases to result in fibrosis, which arise from one or more of a number of factors, including inflammation.

In this respect, compounds of the invention and salts thereof find particular utility in the treatment of relevant inflammatory and/or fibrotic conditions on the basis that such conditions are often characterized by one or more comorbidities. By conditions that are 'characterized by comorbidities', we include that the main condition in question results in (or from) one more further medical conditions, including (and indeed preferably) those mentioned hereinbefore, at the same time, which conditions may interact and/or overlap with each other in some way.

Thus, there are provided:

- methods of treatment of at least one inflammatory and/or fibrotic disorder or condition of one or more internal organs of a patient, which method comprises direct systemic parenteral administration of a compound of the invention, or a pharmaceutically-acceptable salt thereof, to a patient in need of such treatment;
- 5 • a method of treatment of two or more inflammatory and/or fibrotic disorders or conditions of one or more internal organs of a patient, which method comprises direct systemic parenteral administration of a compound of the invention, or a pharmaceutically-acceptable salt thereof, to a patient in need of such treatment; and
- 10 • a method of reduction in the incidence of morbidity and/or mortality that is or may be associated with one or more inflammatory and/or fibrotic disorders or conditions of one or more internal organs of a patient, which method comprises direct systemic parenteral administration of a compound of the invention, or a pharmaceutically-acceptable salt thereof, to a patient in need of such treatment.

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In addition, compounds of the invention may be used in the treatment of a condition characterized by immunosuppression, immunodeficiency disorders, in the treatment of a patient with a compromised immune system, and/or for the restoration of the normal function of the immune system of a patient.

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Conditions characterized by immunosuppression (or immunodeficiency disorders) include primary immunodeficiency disorders (PIDDs), which are typically rare, congenital disorders that are usually inherited. PIDDs thus include humoral immunodeficiency disorders, such as common variable immunodeficiency, selective immunoglobulin deficiency (e.g. IgA deficiency), transient hypogammaglobulinemia of infancy, X-linked agammaglobulinemia; cellular immunodeficiency disorders, such as chronic mucocutaneous candidiasis, DiGeorge syndrome, X-linked lymphoproliferative syndrome; combined humoral and cellular immunodeficiency disorders, such as ataxia-telangiectasia, hyperimmunoglobulinemia E syndrome, severe combined immunodeficiency, Wiskott-Aldrich syndrome; phagocytic immunodeficiencies, such as Chédiak-Higashi syndrome, chronic granulomatous disease, cyclic neutropenia, leukocyte adhesion defects; and complement deficiencies, such as complement component 1 (C1) inhibitor deficiency (or hereditary angioedema), C3 deficiency, C4 deficiency, as well as C5, C6, C7, C8, and/or C9 deficiencies.

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However, we prefer that the immunodeficiency disorders that is treated in accordance with the invention is a secondary immunodeficiency disorders (SIDD), which are more common than PIDDs and tend to develop later in life. SIDDs include immunodeficiency disorders

that are caused by a secondary factor, such as old age, malnutrition (e.g. undernutrition), a chronic disorder, one or more chemical agents (e.g. drugs) and/or (e.g. ionizing) radiation.

- 5 For the purposes of the present invention the term 'SIDD' may also include physical and/or mental stress, which stress may serve to compromise a patient's immune system.

Physical stress may be brought on by trauma (injury, infection, surgery), intense physical labour/over-exertion (e.g. over-training), environmental pollution (pesticides, herbicides,
10 toxins, heavy metals, inadequate light, radiation, noise, electromagnetic fields), illness (viral, bacterial, or fungal agents), fatigue, inadequate oxygen supply, hypoglycemia, hormonal and/or biochemical imbalances, dietary stress (nutritional deficiencies, food allergies and sensitivities, unhealthy eating habits), dehydration, substance abuse, dental challenges, and musculoskeletal misalignments/imbbalances.

15 Mental stress may include various forms of psychological and/or psychosocial stress, such as emotional stress (e.g. negative emotions, such as resentment, fear, frustration, sadness, anger, grief/bereavement); cognitive stress (information overload, worry, guilt, shame, jealousy, resistance, attachments, self-criticism, self-loathing, unworkable perfectionism,
20 anxiety, panic attacks, a sense of generally being not being in control); perceptual stress (beliefs, roles, attitudes, values, meaning and/or purpose); death/loss of loved ones; relationship difficulties (with partners, siblings, children, extended family, employers, co-workers); lack of social support (e.g. friends and/or isolation); financial stress (e.g. due to loss of employment, investments, savings, bankruptcy, home foreclosure, etc.).

25 Disorders that can cause immunodeficiency in patients include cancers; disorders of the blood, such as aplastic anaemia, leukaemia, multiple myeloma; sickle cell disease; Down's syndrome; infections such as viral infections, including varicella, cytomegalovirus, Epstein-Barr virus, HIV, measles and bacterial infections; diabetes mellitus; diseases of internal
30 organs, such as chronic kidney disease, nephrotic syndrome, chronic hepatitis, liver failure; systemic lupus erythematosus; alcoholism, chronic burns; and operations, such as removal of the spleen.

Drugs that can cause immunodeficiency in patients include antiseizure drugs, such as
35 lamotrigine, phenytoin, valproate; immunosuppressants, such as azathioprine, cyclosporine, everolimus, leflunomide, mycophenolate, mofetil, sirolimus, tacrolimus, tofacitinib; biologics, such as abatacept, adalimumab, anakinra, basiliximab, certolizumab, daclizumab, etanercept, golimumab, infliximab, ixekizumab, muromonab (OKT3),

- natalizumab, rituximab, secukinumab, tocilizumab, ustekinumab, vedolizumab; and, particularly, corticosteroids, such as naturally-occurring corticosteroids, including cortisol (hydrocortisone), aldosterone, corticosterone, cortisone, pregnenolone, progesterone, as well as naturally-occurring precursors and intermediates in corticosteroid biosynthesis, and
- 5 other derivatives of naturally-occurring corticosteroids, such as 11-deoxycortisol, 21-deoxycortisol, 11-dehydrocorticosterone, 11-deoxycorticosterone, 18-hydroxy-11-deoxycorticosterone, 18-hydroxycorticosterone, 21-deoxycortisone, 11 β -hydroxypregnenolone, 11 β ,17 α ,21-trihydroxypregnenolone, 17 α ,21-dihydroxypregnenolone, 17 α -hydroxypregnenolone, 21-hydroxypregnenolone, 11-
- 10 ketoprogesterone, 11 β -hydroxyprogesterone, 17 α -hydroxyprogesterone and 18-hydroxyprogesterone, and synthetic corticosteroids, including those of the hydrocortisone-type (Group A), such as cortisone acetate, hydrocortisone aceponate, hydrocortisone acetate, hydrocortisone buteprate, hydrocortisone butyrate, hydrocortisone valerate, tixocortol and tixocortol pivalate, prednisolone, methylprednisolone, prednisone,
- 15 chloroprednisone, cloprednol, difluprednate, fludrocortisone, fluocinolone, fluperolone, fluprednisolone, loteprednol, prednicarbate and triamcinolone; acetonides and related substances (Group B), such as amcinonide, budesonide, desonide, fluocinolone cetonide, fluocinonide, halcinonide, triamcinolone acetonide, ciclesonide, deflazacort, formocortal, fludroxycortide, flunisolide and fluocinolone acetonide, those of the (beta)methasone-type
- 20 (Group C), such as beclomethasone, betamethasone, betamethasone dipropionate and betamethasone valerate, dexamethasone, flucortolone, halometasone, mometasone and mometasone furoate, alclometasone and alclometasone dipropionate, clobetasol and clobetasol propionate, clobetasone and clobetasone butyrate, clocortolone, desoximetasone, diflorasone, difluocortolone, fluclorolone, flumetasone, fluocortin,
- 25 fluprednidene and fluprednidene acetate, fluticasone, fluticasone furoate and fluticasone propionate, meprednisone, paramethasone, prednylidene, rimexolone and ulobetasol; those of the progesterone-type, such as flugestone, fluorometholone, medrysone and prebediolone acetate, and progesterone derivatives (progestins), such as chlormadinone acetate, cyproterone acetate, medrogestone, medroxyprogesterone acetate, megestrol
- 30 acetate and segesterone acetate; as well as other corticosteroids, such as cortivazol and 6-methyl-11 β ,17 β -dihydroxy-17 α -(1-propynyl)androsta-1,4,6-trien-3-one. Particular corticosteroids that may be mentioned include cortisone, prednisone, prednisolone, methylprednisolone and dexamethasone.
- 35 Drugs that may cause immunodeficiency in patients that may particularly be mentioned however include chemotherapeutic treatments of cancers, such as alemtuzumab, busulfan, cyclophosphamide, melphalan.

Particular SIDDs that may be mentioned include those caused by radiation therapy that is employed to treat disorders such as cancer (i.e. radiation-induced immunosuppression).

5 Ionizing radiation not only suppresses the immune system in the manner described hereinbefore, but also can alter the functions of the immune system in irradiated organs in other ways. For example, increased levels in inflammatory mediators, such as NF- κ B and SMAD2/3, and cytokines, such as IL-1, IL-2, IL-6, IL-8, IL-33, tumor necrosis factor (TNF- α), transforming growth factor beta (TGF- β) and interferon gamma (IFN- γ) are associated with the release of prostaglandins and free radicals, including reactive oxygen
10 species (ROS) and nitric oxide (NO). Exposure to high doses of radiation that may occur during accidental exposure (e.g. as a consequence of a nuclear or a radiologic disaster) may result in inflammatory responses and/or wounding, which may continue for years afterwards and/or disrupt the functions of irradiated organs.

15 Compounds of the invention may be employed not only to provide an immunorestorative effect, but also to simultaneously promote wound recovery and/or healing. This is particularly useful in view of the fact that wounds that are associated with such a condition are difficult, if not impossible, to treat properly in view of the immunosuppressive effect induced by the radiation and the absence of a normal endogenous inflammatory response.

20 By providing the aforesaid immunorestorative effect, this enables the body's immune system and localised inflammatory response to become more effective and, in this respect, compounds of the invention may also be employed to provide an antiinflammatory effect, at the same time as promoting further wound healing, but in a manner that does not
25 compromise further the patient's immune system (in the manner that a corticosteroid would if it were employed to treat the inflammation).

According to a further aspect of the invention, there is provided the use of a compound of the invention or a pharmaceutically-acceptable salt thereof for the manufacture of a
30 medicament for the treatment of inflammation and/or of a condition characterized by inflammation or wounding, in a patient that has, or is vulnerable to, a condition characterized by immunosuppression, which includes the treatment of radiation-induced conditions characterized by inflammation and/or wounds.

35 Diseases (including those characterised by inflammation and/or wounds) that are radiation-induced per se, and/or may result from radiation-induced immunosuppression, include those that may arise following accidental exposure to radiation (commonly known as 'radiation poisoning'), or following deliberate and/or targeted exposure to radiation,

for example as a consequence of (e.g. ionizing) radiation therapy to treat a disease, such as cancer.

5 Radiation therapy is a type of e.g. cancer treatment that uses an external beam of intense energy to kill cancer cells. Radiation therapy most often uses X-rays, but protons or other types of energy also can be used. Radiation therapy may be used as a primary cancer treatment, in neoadjuvant therapy (shrinking a cancerous tumor before surgery), adjuvant therapy (preventing proliferation of cancer cells after surgery), to alleviate symptoms caused by advanced cancer, or two or more of the above in combination. Radiation therapy
10 may also be used in combination with other treatments, such as chemotherapy.

Disorders characterised by inflammation and/or wounding of the mucosa and/or skin that may result from exposure to radiation are often associated with the part of the body that is targeted/irradiated. For example:

- 15 • radiation-induced dermatitis and mucositis may occur in the skin or the mucosa, respectively, at locations that may be close to the part of the body that is irradiated. For example, radiation-induced oral mucositis may occur following irradiation of the head or neck;
- radiation-induced encephalitis may also occur following irradiation of the head or neck; and
- 20 • radiation pneumonitis and/or radiation esophagitis often result from radiation treatment of lung cancers, breast cancer, lymphomas, thymic tumours, or oesophageal cancer with radiation.

Radiation treatment that is aimed at the abdomen, pelvis or rectum (e.g. to treat cancer
25 of the cervix, the prostate, the bladder or the rectum) may result in one or more of radiation enteropathy (or radiation enteritis, including radiation colitis and radiation enterocolitis), radiation hepatitis, radiation myelitis, radiation vaginitis and, particularly, radiation proctitis.

30 In particular, radiation proctitis or radiation proctopathy is condition characterized by damage to the rectum after exposure to radiation during radiation therapy. Inflammation can be acute (acute radiation proctitis, as well as the related radiation colitis), or chronic (e.g. radiation associated vascular ectasias (RAVE) and chronic radiation proctopathy).

35 Initial symptoms of acute radiation proctitis include pelvic pain, diarrhoea and tenesmus but radiation damage to the rectum often causes incontinence and rectal bleeding, with severe cases leading to wounds, strictures and/or fistulae.

Thus, in the treatment of disorders induced by irradiation for e.g. cancer therapy, more particularly irradiation of the lower abdominal region, including disorders such as radiation proctitis as defined above, radiation colitis and radiation-induced dermatitis, compounds of the invention and salts thereof may be employed:

- 5 • to provide an immunorestorative effect at the same time as treating wounds and/or promoting recovery and/or healing of wounds that are associated with such a disorder; and/or
- to provide a more direct antiinflammatory effect without compromising the patient's immune system further, at the same time as being available to promote
10 further wound healing.

According to two further aspects of the invention there are provided:

- a method of treatment of a radiation-induced condition that is characterized by (i) immunosuppression, and (ii) inflammation and/or wounding; and
- 15 • a method of treating inflammation and/or wounds that are associated with a radiation-induced immunodeficiency disorder whilst simultaneously restoring the normal function of the immune system of a patient,

which methods comprise administering a compound of the invention or a pharmaceutically acceptable salt thereof to a patient in need thereof.

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The methods of treatment and uses described above are particularly useful when the disorder that is induced by irradiation for e.g. cancer therapy, result from irradiation of the lower abdominal region as described above.

- 25 There is further provided a method of reduction in the incidence of morbidity and/or mortality that is or may be associated with of radiation- (e.g. ionizing radiation- induced disorder) characterised by inflammation and/or wounding in a patient, which method comprises administration of a compound of the invention, or a pharmaceutically-acceptable salt thereof to a patient in need of such treatment.

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- Conditions that compounds of the invention find particular utility in include skin inflammation, physiological reactions that result from skin inflammation and/or wound healing processes, such as scarring and melanin pigmentation; scalp & hair follicle inflammation and fibrosis, include seborrheic dermatitis, conditions characterised by
35 pathological hair loss, including cicatricial alopecia and related conditions, such as seborrheic alopecia and fibrous alopecia; gastritis, gastric ulcer and stress-induced gastritis; GERD; IBDs including Crohn's disease, ulcerative colitis and or proctitis, radiation proctitis; arthritis; maculopathy of the retina (retinal macular degeneration); differentiation and

regeneration of bone marrow cells and aplastic anemia; stress; as well as IPF, ALI/ARDS, uremic pruritis, COPD, asthma, bronchitis (including chronic bronchitis), vasculitis, pancreatitis, multiple organ injury and/or viral infections.

- 5 In addition, compounds of the invention may be used in non-therapeutic, cosmetic treatments, such as anti-aging.

Therefore, a further aspect of the invention is the non-therapeutic use of the compounds of the invention in anti-aging, for example by promoting skin integrity in such a way that
10 the skin has the appearance of younger skin.

A further aspect of the invention is a cosmetic composition comprising a compound of the invention. Such a composition may provide antiaging properties.

- 15 'Patients' include reptilian, avian and, preferably, mammalian (particularly human) patients.

In accordance with the invention, compounds of the invention are preferably administered locally or systemically, for example orally, intravenously or intraarterially (including by intravascular and other perivascular devices/dosage forms (e.g. stents)), intramuscularly,
20 cutaneously, subcutaneously, transmucosally (e.g. sublingually or buccally), rectally, intravaginally, intradermally, transdermally, nasally, pulmonarily (e.g. tracheally or bronchially), for example by way of direct injection, or by way of any other parenteral route, preferably topically, or by any other parenteral route, in the form of a pharmaceutical preparation comprising the compound(s) in pharmaceutically acceptable
25 dosage form(s).

Administration by inhalation (e.g. nasally) is particularly useful when the condition to be treated is rhinitis or inflammation resulting from viral infections of the airways (e.g. upper respiratory tract infections, such as the common cold and influenza).

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Pulmonary administration is particularly useful when the condition to be treated is COPD or IPF. Topical forms of administration may be enhanced by creating a spray comprising active ingredients, e.g. by using a powder aerosol or by way of an aqueous mist using an appropriate atomisation technique or apparatus, such as a nebulizer.

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Anorectal administration is particularly useful when the condition to be treated is hemorrhoids or ulcerative colitis, using an appropriate delivery means, such as a solution of foam to be injected or a suppository.

Administration to the lower gastrointestinal tract may also be achieved by parenteral, and particularly by peroral, delivery, by means of standard delayed- or extended-release coating techniques known to those skilled in the art. In particular, distinct parts of the upper or lower intestine may be targeted. For example, colonic administration can also be achieved by way of colon-targeted drug delivery means that are initially administered perorally or parenterally.

Compounds of the invention may in the alternative be administered by direct systemic parenteral administration. Such administration may be useful in methods of treatment of one or more of the aforementioned disorders or conditions of one or more internal organs of a patient.

Compounds of the invention are preferably administered by intradermal injection, by inhalation, or by topical administration (such as to the skin or mucosal surfaces, such as the oral mucosa, the ocular mucosa, the nasal mucosa, the vaginal mucosa, the rectal mucosa, the colonic mucosa, the oesophageal mucosa, to the throat, or to the dental periphery, the gingiva and/or the teeth).

Internal organs that may be mentioned include the stomach, the intestines, the pancreas, the liver, the spleen, the bladder, the vascular system, the ovaries, the prostate, preferably the heart and the kidneys and more preferably the lungs.

Standard delayed- or extended-release techniques known to those skilled in the art may be used for means of administration other than peroral, such as subcutaneous or intramuscular depot-forming technologies or via alternative means of parenteral administration.

Pharmaceutically-acceptable formulations for use in the above-mentioned routes of administration may thus comprise compounds of the invention in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier, which may be selected with due regard to the intended route of direct parenteral administration and standard pharmaceutical practice. Such pharmaceutically-acceptable carriers may be chemically inert to the active compounds and may have no detrimental side effects or toxicity under the conditions of use. Such pharmaceutically-acceptable carriers may also impart an immediate, or a modified, release of the compound of the invention.

Formulations for injection may thus be in the form of an aqueous formulation such as an a suspension and/or, more preferably a solution (e.g. an (optionally) buffered aqueous formulation (e.g. solution), such as a physiological saline-containing formulation (e.g. solution), a phosphate-containing formulation (e.g. solution), an acetate-containing
5 formulation (e.g. solution) or a borate-containing formulation (e.g. solution), or a freeze-dried powder that may be reconstituted with a vehicle, such as an aqueous vehicle prior to use (e.g. injection)).

Formulations for injection may include other suitable excipients known to those skilled in
10 the art, such as solvents (e.g. water), co-solvents, solubilizing agents (e.g. cyclodextrins), wetting agents, suspending agents, emulsifying agents, thickening agents, chelating agents, antioxidants, reducing agents, antimicrobial preservatives, bulking agents and/or protectants.

Formulations for injection are preferably buffered by standard techniques to
15 physiologically-acceptable pH values (e.g. pHs of between about 4.5 and about 9.5, e.g. about 6 and about 9, such as between about 6.5 and about 8.5) using buffers and/or pH modifiers as described herein, and/or may further comprise tonicity-modifying agents (such as sodium chloride).

20

The above notwithstanding, preferred modes of delivery of compounds of the invention include topically to the site of inflammation (e.g. the mucosa, including the oral and/or nasal mucosa, the lung, the anorectal area and/or the colon or, more preferably, the skin) in an appropriate (for example pharmaceutically- and topically-acceptable) vehicle suitable
25 for application to the skin and/or the appropriate mucosal surface, and/or a commercially-available formulation, but may also include oral, intravenous, cutaneous or subcutaneous, nasal, intramuscular, intraperitoneal, or pulmonary delivery.

Administration by injection is particularly useful for administering the compounds of the
30 invention, in the form of a solution of suspension into e.g. the dermis (e.g. intradermal injection), joint cavity or the eyes.

Administration by intradermal injection (e.g. intradermally) is particularly useful for administering the compound of the invention, in the form of a solution or suspension (e.g.
35 a dermal filler), into the dermis. This is particularly useful as a means of administration for melanin pigmentation therapy as described hereinbefore or for the use of the compounds of the invention in the treatment of, e.g. wrinkles.

Administration by injection is particularly useful to fill, e.g. the surgical site of the nasal cavity, the anal fistula, the space between the gingival and the root or the sinus. This is particularly useful for shaping support and/or lubrication.

- 5 Compounds of the invention will generally be administered in the form of one or more for example pharmaceutical formulations in admixture with a (e.g. pharmaceutically acceptable) adjuvant, diluent or carrier, which may be selected with due regard to the intended route of administration (e.g. topical to the relevant mucosa (including the lung) or, preferably, the skin) and standard pharmaceutical or other (e.g. cosmetic) practice.
- 10 Such pharmaceutically acceptable carriers may be chemically inert to the active compounds and may have no detrimental side effects or toxicity under the conditions of use. Such pharmaceutically acceptable carriers may also impart an immediate, or a modified, release of the compound of the invention.
- 15 Suitable pharmaceutical formulations may be commercially available or otherwise prepared according to techniques that are described in the literature, for example, Remington The Science and Practice of Pharmacy, 22nd edition, Pharmaceutical Press (2012) and Martindale – The Complete Drug Reference, 38th Edition, Pharmaceutical Press (2014) and the documents referred to therein, the relevant disclosures in all of which documents are
- 20 hereby incorporated by reference. Otherwise, the preparation of suitable formulations including compounds of the invention may be achieved non-inventively by the skilled person using routine techniques.

Compounds of the invention may be in the form of an aqueous formulation such as an

25 emulsion, a suspension and/or a solution (e.g. an (optionally) buffered aqueous formulation (e.g. solution), such as a physiological saline-containing formulation (e.g. solution), a phosphate-containing formulation (e.g. solution), an acetate-containing formulation (e.g. solution) or a borate-containing formulation (e.g. solution)), or a freeze-dried powder.

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Compounds of the invention may further and/or in the alternative be combined with appropriate excipients to prepare:

- gel formulations (for which suitable gel matrix materials include cellulose derivatives, carbomer and alginates, gummi tragacanthae, gelatin, pectin,
- 35 carrageenan, gellan gum, starch, Xanthan gum, cationic guar gum, agar, noncellulosic polysaccharides, saccharides such as glucose, glycerin, propanediol, vinyl polymers, acrylic resins, polyvinyl alcohol, carboxyvinyl polymer and, particularly, hyaluronic acid);

- lotions (for which suitable matrix materials include cellulose derivatives, glycerin, noncellulosic polysaccharides, polyethylene glycols of different molecular weights and propanediol);
- pastes or ointments (for which suitable paste matrix materials include glycerin, vaseline, paraffin, polyethylene glycols of different molecular weights, etc.);
- creams or foams (for which suitable excipients (e.g. foaming agents) include hydroxypropyl methyl cellulose, gelatin, polyethylene glycols of different molecular weights, sodium dodecyl sulfate, sodium fatty alcohol polyoxyethylene ether sulfonate, corn gluten powder and acrylamide);
- powder aerosols (for which suitable excipients include mannitol, glycine, dextrin, dextrose, sucrose, lactose, sorbitol and polysorbates, e.g. a dry powder inhalant); and/or
- liquid, for example, mouthwash, water (aerosol) sprays for oral use, inhalation, or facial use (for which suitable excipients include viscosity modifiers, such as hyaluronic acid, sugars, such as glucose and lactose, emulsifiers, buffering agents, alcohols, water, preservatives, sweeteners, flavours, etc.);
- injectable solutions or suspensions (which may be aqueous or otherwise and for which suitable excipients include solvents and co-solvents, solubilizing agents, wetting agents, suspending agents, emulsifying agents, thickening agents, chelating agents, antioxidants, reducing agents, antimicrobial preservatives, buffers and/or pH modifiers, bulking agents, protectants and tonicity-modifying agents), particular injectable solutions or suspensions that may be mentioned include dermal fillers (i.e. injectable fillers or soft-tissue fillers), particularly when the compound of the invention is combined with hyaluronic acid.
- oral tablets (for which suitable excipients include binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, celluloses or polyvinylpyrrolidone; fillers, such as lactose, sucrose, corn starch, calcium phosphate, sorbitol, or glycine; lubricants, such as magnesium stearate, talc, polyethylene glycol, or silica; and surfactants, such as sodium lauryl sulfate).

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Moisturizing agents, such as glycerol, glycerin, polyethylene glycol, trehalose, glycerol, petrolatum, paraffin oil, silicone oil, hyaluronic acid and salts (e.g. sodium and potassium salts) thereof, octanoic/caprylic triglyceride, and the like; and/or antioxidants, such as vitamins and glutathione; and/or pH modifiers, such as acids, bases and pH buffers, may also be included in such formulations, as appropriate. Furthermore, surfactants/emulsifiers, such as hexadecanol (cetyl alcohol), fatty acids (e.g. stearic acid), sodium dodecyl sulfate (sodium lauryl sulfate), sorbitan esters (e.g. sorbitan stearate, sorbitan oleate, etc.), monoacyl glycerides (such as glyceryl monostearate), polyethoxylated alcohols, polyvinyl

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alcohols, polyol esters, polyoxyethylene alkyl ethers (e.g. polyoxyethylene sorbitan monooleate), polyoxyethylene castor oil derivatives, ethoxylated fatty acid esters, polyoxylglycerides, lauryl dimethyl amine oxide, bile salts (e.g. sodium deoxycholate, sodium cholate), lipids (e.g. fatty acids, glycerolipids, glycerophospholipids, sphingolipids, sterols, prenols, saccharolipids, polyketides), phospholipids, N,N-dimethyldodecylamine-N-oxide, hexadecyltrimethyl-ammonium bromide, poloxamers, lecithin, sterols (e.g. cholesterol), sugar esters, polysorbates, and the like; preservatives, such as phenoxyethanol, ethylhexyl glycerin, and the like; and thickeners, such as acryloyldimethyltaurate/VP copolymer, may be included. In particular, stearic acid, glyceryl monostearate, hexadecanol, sorbitan stearate, cetyl alcohol, octanoic/capric glyceride etc. may be included, particularly in cream formulations.

Compounds of the invention, and (e.g. pharmaceutical) formulations (e.g. aqueous solutions, gels, creams, ointments, lotions, foams, pastes and/or dry powders as described above) including them, may further be combined with an appropriate matrix material to prepare a dressing or a therapeutic patch for application on a biological surface, such as the skin or a mucosal surface. Such formulations may thus be employed to impregnate a matrix material, such as gauze, non-woven cloth or silk paper. The therapeutic patch may alternatively be, for example, a band-aid, a facial mask, an eye mask, a hand mask, a foot mask, etc.

Vaseline may be employed for use in applying such dressings to wounds, but we have also found that ointments based on PEGs (e.g. PEG 400) may be combined with matrix materials to prepare dressings without the need to use Vaseline.

Compounds of the invention may also be used in combination with solid supports (such as nasal dressings (for example, to stop nasal bleeding), dermal scaffolds (for example, in wound healing) or artificial bones (for example, in the case of bone grafting/implantation).

Compounds of the invention may be administered for inhalation by way of suspension, a dry powder or a solution. Suitable inhalation devices include pressurized metered-dose inhalers (pMDIs), which may be hand- or breath-actuated and employed with or without a standard spacer device, dry powder inhalers (DPIs), which may be single-dose, multi-dose, and power-assisted, and soft mist inhalers (SMIs) or nebulizers, in which aerosol drug in a fine mist is delivered with slower velocity than a spray delivered using, for example, a pMDI.

In pMDIs, compounds of the invention may be administered as a pressurized suspension of micronized particles distributed in a propellant (e.g. HFA, along with excipients, such as mannitol, lactose, sorbitol, etc.), or as an ethanolic solutions, to deliver one or more metered dose of between about 20 and about 100 μ L with each actuation. Actuation may be effected by hand (e.g. pressing) or by inhalation (breath-actuation), involving a flow-triggered system driven by a spring.

In DPIs, compounds of the invention may be administered in the form of micronized drug particles (of a size between about 1 and about 5 μ m), either alone or blended with inactive excipient of larger particle size (e.g. mannitol), inside a capsule, which may be pre-loaded or manually loaded into the device. Inhalation from a DPI may de-aggregate the medication particles and disperse them within the airways.

In SMIs, compounds of the invention may be stored as a solution inside a cartridge, which is loaded into the device. A spring may release the dose into a micropump, such that the dose is released when a button is pressed, releasing jet streams of drug solution.

Various nebulizers may also be used to administer compounds of the invention in the form of a fine mist of aerosolized solution. Nebulizers may include breath-enhanced jet nebulizer (in which, with the assistance of a compressor, an air stream moves through jet causing drug solution to be aerosolized); breath-actuated jet nebulizers (in which, after a patient inhales, with the assistance of a compressor, an air stream moves through a tube causing the drug solution to be aerosolized); ultrasonic nebulizers (in which piezoelectric crystals vibrate causing aerosolization by heating causing nebulization); vibrating mesh nebulizers (in which piezoelectric crystals vibrate a mesh plate causing aerosolization to give very fine droplets without a significant change in temperature of the solution during nebulization).

According to a further aspect of the invention there is provided a process for the preparation of a pharmaceutical composition/formulation, as defined herein, which process comprises bringing into association a compound of the invention, as hereinbefore defined, with one or more pharmaceutically-acceptable excipient, as hereinbefore defined.

Compounds of the invention may also be combined in treatment with one or more growth factors selected from platelet-type growth factors (including platelet-derived growth factors, PDGFs); osteosarcoma-derived growth factors (ODGF), epidermal growth factors (EGFs), transforming growth factors (TGF α and TGF β), fibroblast growth factors (α FGF, β FGF), insulin-like growth factors (IGF-I, IGF-II), nerve growth factors (NGF), interleukin-

type growth factors (IL-1, IL-1, IL-3), erythropoietin (EPO), and colony stimulating factor (CSF).

5 According to a further aspect of the invention there is provided a (e.g. pharmaceutical) composition comprising a compound of the invention and one or more pharmaceutically-acceptable excipient, such as an adjuvant, diluent or carrier. Preferred formulations are suitable for application locally to e.g. the mucosa (including the oral and/or nasal mucosa, the lung, the anorectal area and/or the colon) or, more preferably, the skin and therefore comprise a topically-acceptable adjuvant, diluent or carrier.

10

There is, thus, further provided pharmaceutical compositions comprising compounds of the invention that are suitable for, adapted for, and/or packaged and presented for topical administration (e.g. to the mucosa, including the oral and/or nasal mucosa, the lung, the anorectal area and/or the colon, or, preferably, to the skin), as well as the use of such a
15 formulation in the treatment of a disorder including inflammation, an inflammatory disorder and/or a condition characterized by inflammation (e.g. as a symptom) by way of direct topical administration of that formulation (e.g. to the mucosa, including the oral and/or nasal mucosa, the lung, the anorectal area and/or the colon, or, preferably, to the skin).

20 In relation to this aspect of the invention, for the avoidance of doubt, topical formulations comprising compounds of the invention may be used in any and all conditions described herein, including treatments of inflammation, in the treatment of any and all inflammatory disorder(s), and/or in the treatment of any and all condition(s) characterized by inflammation, as hereinbefore mentioned, defined or described. Similarly, topical
25 formulations comprising compounds of the invention that may be mentioned include any and all of those mentioned, defined or described herein. Any and all of the relevant disclosures herein are hereby incorporated by reference in conjunction with this aspect of the invention.

30 Topical (e.g. liquid- or (e.g. aqueous) solution-based) formulations comprising compounds of the invention may be particularly useful in wound recovery, and may alleviate pain (including aching) and, particularly, pruritis/itching that is associated with the wound itself and the wound healing process. Such topical formulations comprising compounds of the invention may be particularly useful in the prevention and/or suppression of the exudation
35 of body fluids from wounds, particularly during the acute inflammation stage, for example during the first 48 hours, after a burn or wound has been inflicted. This prevents the risk of infection, and other physiological reactions. Such topical formulations comprising compounds of the invention may also be particularly useful in the prevention and/or

suppression of scarring and melanin pigmentation (*vide supra*), whether associated with wounds or otherwise.

Administration of compounds of the invention may be continuous or intermittent. The mode of administration may also be determined by the timing and frequency of administration, but is also dependent, in the case of the therapeutic treatment of inflammation, on the severity of the condition.

Depending on the disorder, and the patient, to be treated, as well as the route of administration, compounds of the invention may be administered at varying therapeutically effective doses to a patient in need thereof.

Similarly, the amount of compound of the invention in a formulation will depend on the severity of the condition, and on the patient, to be treated, but may be determined by the skilled person.

In any event, the medical practitioner, or other skilled person, will be able to determine routinely the actual dosage, which will be most suitable for an individual patient, depending on the severity of the condition and route of administration. The dosages mentioned herein are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Doses may be administered between once and four (e.g. three) times daily.

Appropriate concentrations of compounds of the invention in an aqueous solution product may be about 0.01 (e.g. about 0.1) to about 15.0 mg/mL, in all cases calculated as the free (non-salt) compound.

Appropriate topical doses of compounds of the invention are in the range of about 0.05 to about 50 $\mu\text{g}/\text{cm}^2$ of treated area, such as about 0.1 (e.g. about 0.5) to about 20 $\mu\text{g}/\text{cm}^2$ of treated area, including about 1 to about 10 $\mu\text{g}/\text{cm}^2$ of treated area, such as about 5 $\mu\text{g}/\text{cm}^2$ of treated area, in all cases calculated as the free (non-salt) compound.

Appropriate doses of compounds of the invention for nasal administration (e.g. by inhalation) are in the range of about 0.01 μg to about 2000 mg, for example between about 0.1 μg to about 500 mg, or between 1 μg to about 100 mg. Particular doses for nasal administration that may be mentioned include between about 10 μg to about 1 mg, particularly a dose of about 0.1 mg (i.e. about 100 μg). Nasal administration of about 0.1

mg per day of compounds of the invention has been found to be particularly effective in the treatment of conditions associated with inflammation of the nasal passages and mucosae, such as rhinitis (e.g. allergic rhinitis) and/or conditions associated with nasosinusitis surgery.

5

Appropriate doses of compounds of the invention for pulmonary administration (e.g. by inhalation) are in the range of about 0.01 µg to about 2000 mg, for example between about 0.1 µg to about 500 mg, or between 1 µg to about 100 mg. Particular doses for pulmonary administration that may be mentioned include between about 10 µg to about 10 mg, particularly a dose of about 0.6 mg (i.e. 60 µg) to 6 mg (e.g. for use in treating COPD or IPF).

10

We prefer that pH values of formulations comprising compounds of the invention are in the range of about 1.0 to about 9.0 (for example about 3.0 to about 8.0).

15

In any event, the dose administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response in the mammal over a reasonable timeframe (as described hereinbefore). One skilled in the art will recognize that the selection of the exact dose and composition and the most appropriate delivery regimen will also be influenced by inter alia the pharmacological properties of the formulation, the nature and severity of the condition being treated, and the physical condition and mental acuity of the recipient, as well as the age, condition, body weight, sex and response of the patient to be treated, and the stage/severity of the disease, as well as genetic differences between patients.

20

25

Compounds of the invention are useful in human and animal medicine. In this respect, and as described above, compounds of the invention that possess an appropriate degree of relevant pharmacological (or biological) activity per se may be used as human, and/or animal, medicines.

30

Certain compounds of invention, particularly compounds of formula I, may in addition and/or instead of possessing the aforementioned biological activity, possess adhesive properties.

35

These adhesive properties stem from the fact that the relevant W and/or U groups are capable of cross-linking with each other in order to form three-dimension networks.

Such compounds of the invention may adhere to a number of substrates including inorganic substrates, such as glass, metal and the like, as well as organic substrates, such as biological tissue.

5 In respect, such compounds of the invention may also be used as wound surface repair products, wound surface protecting products, medical biological adhesive products, medical coating products, industrial coating products (e.g. in corrosion prevention in ships, electronic apparatuses, pipelines and the like), biochemical reagents, medical products, sterilization products, culture vessels for cell culture and the like.

10

Such compounds of the invention may form a film over various skin and mucous wound surfaces such as burns, scalds, ulcers, chilblains, and bedsores to aid in recovery. Such compounds of the invention may also be used in surgery, e.g. in the closure of surgical incisions, adhesion of fractured bones, adhesion of mucous membranes, coatings of human
15 body implants such as artificial bones, cartilage brackets, periosteal, artificial joints, dental implants, plugging stents, spinal fusion devices, spinal spacers and organ patches.

According to a further aspect of the invention, there is provided a compound of formula I as an adhesive or a film-forming material.

20

As discussed hereinbefore, naturally occurring MAP is known for its adhesive properties, but it should be remembered that such adhesive properties may arise from the fact that that is a high molecular weight, linear peptide that can exist in multiple conformations, enabling inter- and intramolecular reactions/cross-linking of DOPA residues in molecules, and thereby adhesion. Conversely, compounds of the invention as defined above are not
25 linear polypeptides or proteins but are instead, for example multiply-branched lower molecular weight residues and it is a surprise to the applicant that similar properties (whether adhesive or biological) to naturally-occurring MAP are observed.

30 Such crosslinking may be carried out by a variety of chemicals (e.g. iodine vapour, glutaraldehyde, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride and N-hydroxysuccinimide (EDC/NHS), 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM), or other water soluble condensation agents) or enzymatic means (e.g. tyrosinase, or as described hereinafter).

35

Irrespective of the level of pharmacological activity that compounds of the invention may possess, they may in any event be (and/or may be further) combined with active pharmaceutical ingredients, either in combination therapy (as described hereinafter), or

by performing a function either as, or as part of, a pharmaceutically-acceptable excipient (e.g. an adjuvant, diluent or carrier), as part of a medical device, and/or as part of a drug-medical device combination.

5 Certain compounds of the invention may thus be described as novel multifunctional excipients, which may be used for a variety of applications in the pharmaceutical field. In this respect, such compounds of the invention include those that may be used as adhesives and/or as film-forming agents (as described hereinbefore). Furthermore, such compounds of the invention and/or different compounds of the invention may in the alternative, and/or
10 in addition, be used as release retarding polymers, as binders, as suspending agents, as gelling agents, as coating agents, as diluents or as carriers for active ingredients (drugs) of varying solubilities.

Compounds of the invention that are particularly useful as pharmaceutical excipients may
15 be adopted for large-scale production and may present no significant toxicity risk and may so be described and listed as 'Generally Recognized as Safe' (GRAS) by the US Food & Drug Administration (FDA).

Such compounds of the invention may also be employed as excipients in veterinary science,
20 as well as in cosmetics.

According to a further aspect of the invention, there is provided a pharmaceutical formulation comprising an active pharmaceutical ingredient in admixture with a pharmaceutically-acceptable excipient system (such as a pharmaceutically-acceptable
25 adjuvant, diluent or carrier system), which excipient system comprises one of more compounds of the invention.

Furthermore, compounds of the invention may be combined with active pharmaceutical ingredients, and may thus be employed as part of a drug-medical device combination,
30 which combination comprises one or more active pharmaceutical ingredients and one or more compounds of the invention, in which said one or more compounds of the invention constitute the medical device component of that combination.

When used as, or as part of, a medical device or the medical device part of a drug-medical
35 device combination, the skilled person will understand that the relevant compound of the invention will be employed in human or animal medicine, optionally in conjunction with an active pharmaceutical ingredient, in such a way as to affect the structure, and/or one or more functions, of a human or an animal body, and will achieve its primary intended

purposes without exerting a chemical action within or on said human or animal body (optionally in a manner that is not dependent upon the compound of the invention being metabolized for the achievement of any of its primary intended purposes).

- 5 In this respect, compounds of the invention may be combined with a multitude of known pharmaceutically-active ingredients and may be so combined irrespective of whether the compound of the invention is employed:
- as a separate pharmaceutically-active ingredient per se in combination therapy;
 - as, or as part of, a medical device;
 - 10 • as, or as the medical device part of, a drug-medical device combination; or
 - as a pharmaceutically-acceptable excipient.

Such patients may also (and/or may already) be receiving therapy based upon administration of one or more of such other, known pharmaceutically-active ingredients,
15 by which we mean receiving a prescribed dose of one or more of the active ingredients mentioned herein, prior to, in addition to, and/or following, treatment with a compound of the invention.

Pharmaceutically-active agents that may be co-administered with a compound of the invention include any agent, or drug, that is capable of producing some sort of physiological effect (whether in a therapeutic or prophylactic capacity against a particular disease state or condition) in a living subject, including, in particular, mammalian and especially human subjects (patients).

25 In addition, compounds of the invention such as those that may be crosslinked as hereinbefore described may be employed as pharmaceutical excipients and may be mixed with such pharmaceutically-active ingredients either before or after crosslinking and/or at least partial crosslinking, as hereinbefore described, in order to form a stable pharmaceutical composition in which a compound of the invention acts an excipient, such
30 as a carrier. When employed in this way, it may be found that compounds of the invention may affect, in a positive way, physical, chemical and/or biological properties of such active ingredients, including their physical and/or chemical stability and/or their metabolism following administration.

35 Pharmaceutically-active agents that may be used along with compounds of the invention may, for example, be selected from anti-inflammatory agents, pro-inflammatory agents, antibiotics, anti-bacterial and/or antiprotozoal agents, antiviral agents (e.g. protease inhibitors), anaesthetics and wound recovery drugs (e.g. growth factors).

Biologically-active agents may, for example, be selected from anti-inflammatory agents, pro-inflammatory agents, antibiotics, anti-bacterial and/or antiprotozoal agents, antiviral agents (e.g. protease inhibitors), anaesthetics and wound recovery drugs (e.g. growth factors).

Non-limiting examples of anti-inflammatory drugs which may be used also include those used in the treatment of rheumatic diseases and/or arthritis (such as cataflam, betamethasone, naproxen, cyclosporin, chondroitin, celecoxib, etodolac, meclofenamate, 10 salsalate, methylprednisolone, and piroxicam); osteoarthritis (such as sulindac, meloxicam, fenoprofen, etoricoxib, and nabumetone); inflammation and its symptoms, e.g. fever, pain, itchiness and/or swelling (such as mefenamic acid, indomethacin, aspirin, ketorolac, fluorometholone, loteprednol, hydrocortisone, fluorometholone, bromfenac, prednisolone acetate, indomethacin, and ibuprofen); allergies and their symptoms (such as pheniramine, 15 diphenhydramine, naphazoline, antazoline, prednisolone, lodoxamide, pemirolast, oxymetazoline, ketotifen, naphazoline, emestine fumarate, olopatadine, azelastine, tranilast, levocabastine, cortisone, ephedrine, cetirizine, levocetirizine, pseudophedrine, fexofenadine, terfenadine, loratadine, and alexis); respiratory diseases, including asthma and/or COPD (such as budesonide, ciclesonide, nedocromil, dexamethasone, ambroxol, 20 and pranlukast); skin diseases (such as mometasone, triamcinolone, desonide, sulfacetamide, tacrolimus, allantoin, and triamcinolone); mastocytosis (such as cromolyn); gout (such as diclofenac, and febuxostat); conjunctivitis (such as hydrobenzole, pranoprofen, and zinc sulfate); eye diseases (such as dextran 70, thyroxine/liothyronine, and ocular extractives), known or commercially-available pharmaceutically acceptable 25 salts of any of the foregoing, and combinations of any of the foregoing compounds and/or salts.

Antiinflammatory drugs that may be mentioned include endogenous (and/or exogenous) lipid-based pro-resolving, antiinflammatory molecules or mediators, such as lipoxins, 30 resolvins, and protectins. Pro-inflammatory agents that may be mentioned include prostaglandins (e.g. latanoprost, prostaglandin E1, and prostaglandin E2), and leukotrienes (e.g. Leukotriene B4).

Non-limiting examples of anti-bacterial drugs which may be used also include 35 chloramphenicol, ofloxacin, levofloxacin, tobramycin, norfloxacin, ciprofloxacin, lomefloxacin, lincomycin, fluconazole, enoxacin, furazolidone, nitrofurazone, rifampicin, micronomicin, gentamicin, cetylpyridinium, neomycin, roxithromycin, sulfadiazine silver, clarithromycin, clindamycin, metronidazole, azithromycin, mafenide, sulfamethoxazole,

paracetamol, chloramphenicol, pseudoephedrine, mupirocin, amoxicillin, amoxicillin/clavulanic acid, trimethoprim/sulfamethoxazole, cefalexin, moxifloxacin, known or commercially-available pharmaceutically acceptable salts of any of the foregoing, and combinations of any of the foregoing compounds and/or salts.

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Non-limiting examples of antiviral drugs which may be used also include tobramycin ribavirin, acyclovir, moroxydine, foscarnet, ganciclovir, idoxuridine, trifluridine, brivudine, vidarabine, entecavir, telbivudine, foscarnet, zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine, nevirapine, delavirdine, efavirenz, etravirine, rilpivirine, saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, ritonavir, atazanavir, fosamprenavir, tipranavir, darunavir, telaprevir, boceprevir, simeprevir, asunaprevir, raltegravir, elvitegravir, dolutegravir, rsv-igiv, palivizumab, docosanol, enfuvirtide, maraviroc, vzig, varizig, acyclovir, ganciclovir, famciclovir, valacyclovir, penciclovir, valganciclovir, cidofovir, tenofovir disoproxil fumarate, adefovir dipivoxil, fomivirsen, podofilox, imiquimod, sinecatechins, interferon- α 2b (recombinant, human), known or commercially-available pharmaceutically acceptable salts of any of the foregoing, and combinations of any of the foregoing compounds and/or salts.

Non-limiting examples of anaesthetics which may be used also include articaine, dextropropoxyphene, sevoflurane, cophenylcaine, lidocaine, prilocaine, pramoxine, benzocaine, dibucaine, diclonine, tetracaine, bupivacaine and known or commercially-available pharmaceutically acceptable salts of any of the foregoing, and combinations of any of the foregoing compounds and/or salts.

Non-limiting examples of wound recovery drugs which may be used also include basic fibroblast growth factor (recombinant, human; recombinant, bovine), epidermal growth factor (recombinant, human; yeast), rhEGF (I), acidic fibroblast growth factor (recombinant, human), granulocyte macrophage stimulating factor (recombinant, human), sulfadiazine silver, sulfadiazine zinc, fusidic acid, bacitracin, chlorhexidine, silver nitrate, triethanolamine, ethacridine, retinoids, calf blood deproteinized extract, carraghenates, amiotide and known or commercially-available pharmaceutically acceptable salts of any of the foregoing, and combinations of any of the foregoing compounds and/or salts.

Such pharmaceutically-active ingredients include those that may be administered topically, e.g. to the skin or to a mucosal surface along with a compound of the invention. In this respect, preferred active ingredients from the above list include cyclosporin, chondroitin, loteprednol, fluorometholone, bromfenac, prednisolone acetate, indomethacin, oxymetazoline, ketotifen, naphazoline, emestine fumarate, olopatadine, azelastine,

- tranilast, levocabastine, cortisone, ephedrine, cetirizine, pseudoephedrine, levocetirizine, fexofenadine, terfenadine, loratadine, alexis, dexamethasone, ambroxol), sulfacetamide, tacrolimus, allantoin, triamcinolone, cromolyn, nedocromil, diclofenac, hydrobenzole, pranoprofen, zinc sulfate, dextran 70, thyroxine/liothyronine, ocular extractives,
- 5 chloramphenicol, ofloxacin, levofloxacin, tobramycin, norfloxacin, ciprofloxacin, lomefloxacin, lincomycin, fluconazole, enoxacin, furazolidone, nitrofurazone, rifampicin, micronomicin, gentamicin, cetylpyridinium, neomycin, roxithromycin, sulfadiazine silver, clarithromycin, sulfamethoxazole, chloramphenicol, tobramycin ribavirin, acyclovir, moroxydine, foscarnet, ganciclovir, interferon- α 2b (recombinant, human), articaine,
- 10 dextropropoxyphene, sevoflurane, cophenylcaine, lidocaine, prilocaine, pramoxine, benzocaine, dibucaine, diclonine, tetracaine, bupivacaine, basic fibroblast growth factor (recombinant, human; recombinant, bovine), epidermal growth factor (recombinant, human; yeast), rhEFG (I), acidic fibroblast growth factor (recombinant, human), granulocyte macrophage stimulating factor (recombinant, human), sulfadiazine silver,
- 15 sulfadiazine zinc, fusidic acid, bacitracin, chlorhexidine, silver nitrate, triethanolamine, ethacridine, retinoids, calf blood deproteinized extract, carraghenates, amiotide, and known or commercially-available pharmaceutically acceptable salts of any of the foregoing, and combinations of any of the foregoing compounds and/or salts.
- 20 Other pharmaceutically-active ingredients that may be co-administered with a compound of the invention include those that may be administered to treat one or of the gastrointestinal disorders mentioned hereinbefore.

- Non-limiting examples of gastrointestinal drugs include oxalazine (olsalazine),
- 25 sulfasalazine, domperidone, erythromycin, berberine, dexamethasone, cefuroxime axetil, levofloxacin, mesalazine, belladonna, sulfobenzidine, azathioprine, sulfasalazine, live bacillus (such as clostridium butyricum, licheniformis, cereus), probiotics (such as bifidobacterium) tegafur, nifuratel, amoxicillin, ampicillin, nystatin, allicin, cefadroxil, dyclonine, carmofur, fluorouracil, mosapride, sodium carbosulfan, thrombin, pantoprazole,
- 30 cimetidine, cisapride, ethylenediamine diacetamine, nimustine, famotidine, barium sulfate, aminocaproic acid, roxatidine acetate, vincristine, azasetron, lentinan, bismuth salts (e.g. aluminate, potassium citrate) in combination with e.g. magnesium salts, magnesium trisilicate, bicarbonate, vitamin U, aluminium hydroxide, belladonna extract, famotidine and calcium carbonate, magnesium hydroxide, hydrotalcite, proton pump inhibitors (such
- 35 as omeprazole, lansoprazole, rabeprazole, pantoprazole, dexlansoprazole or esomeprazole), glycine, trypsin, allantoin aluminium hydroxide, sodium L-glutamine gualenate, rebampette, rotundine, quxipite, lafutidine, thymus protein, hericium erinaceus, irsogladine maleate, nizatidine, L-glutamine and sodium azulene sulfonate (sodium

gualenate), ranitidine, bismuth citrate, lactobacillin, bisacordine, dimethylsiloxane, live clostridium butyricum, loperamide hydrochloride, dibazol, secnidazole, zinc acephate, montmorillonite, tegafur/gimeracil/oteracil, famotidine, oteracil, doxifluridine, capecitabine and known or commercially-available pharmaceutically acceptable salts of any of the foregoing.

Pharmaceutically-active ingredients that may be mentioned for use in combination with compounds of the invention include active ingredients that are useful in the treatment of inflammation and/or inflammatory disorders (other anti-inflammatory agents).

Anti-inflammatory agents that may be used in combination with compounds of the invention in the treatment of inflammation include therapeutic agents that are useful in the treatment of inflammation and/or of diseases characterized by inflammation as one of its symptoms, including those described hereinbefore. Depending on the condition to be treated, such anti-inflammatory agents may include NSAIDs (e.g. aspirin), aminosalysates (e.g. 5-aminosalicylic acid (mesalazine)), leukotriene receptor antagonists (e.g. montelukast, pranlukast, and zafirlukast), corticosteroids, analgesics and certain enzymes, such as trypsin, for example as described hereinafter. Compounds of the invention may also be combined with leukotrienes (e.g. cysteinyl leukotrienes, and leukotriene B₄).

Other preferred agents that may be combined with compounds of the invention include LTB₄ (to treat wounds and burns), NSAIDS (e.g. aspirin) or montelukast (to treat inflammation generally) and trypsin (to treat inflammation of the mucosa associated with e.g. viral infections).

Compounds of the invention may also be combined with other therapeutic agents which, when administered, are known to give rise to inflammation as a side-effect.

Conjugates of the invention may also be combined with stem cells (e.g. totipotent (omnipotent), pluripotent (such as embryonic or induced pluripotent stem cells), multipotent (such as mesenchymal stem cells), oligopotent (such as hematopoietic stem cells), or unipotent (such as muscle stem cells)).

Other known pharmaceutically-active ingredients may also be administered in combination with compounds of the invention in numerous ways.

For example, compounds of the invention may be 'combined' with the (or with the other) pharmaceutically-active ingredients (or 'therapeutic agents') for administration together in

the same (e.g. pharmaceutical) formulation, or administration separately (simultaneously or sequentially) in different (e.g. pharmaceutical) formulations.

Thus, such combination products provide for the administration of compounds of the invention in conjunction with the (or with the other) therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises a compound of the invention, and at least one comprises the (or the other) therapeutic agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including a compound of the invention and the (or the other) therapeutic agent).

Thus, there is further provided:

(1) a (e.g. pharmaceutical) formulation including a compound of the invention; another pharmaceutically-active ingredient; and, optionally, a pharmaceutically-acceptable inactive excipient (e.g. adjuvant, diluent or carrier), which formulation is hereinafter referred to as a 'combined preparation'; and

(2) a kit of parts comprising components:
(A) a compound of the invention, optionally in the form of an (e.g. pharmaceutical) formulation in admixture with a pharmaceutically-acceptable inactive excipient (e.g. adjuvant, diluent or carrier); and
(B) another pharmaceutically-active ingredient, optionally in the form of a (e.g. pharmaceutical) formulation in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,
which components (A) and (B) are each provided in a form that is suitable for administration in conjunction with the other.

In a further aspect of the invention, there is provided a process for the preparation of a combined preparation (1) as hereinbefore defined, which process comprises bringing into association a compound of the invention, the other pharmaceutically-active ingredient, and at least one (e.g. pharmaceutically-acceptable) excipient.

In a further aspect of the invention, there is provided a process for the preparation of a kit-of-parts (2) as hereinbefore defined, which process comprises bringing into association components (A) and (B). As used herein, references to bringing into association will mean that the two components are rendered suitable for administration in conjunction with each other.

Thus, in relation to the process for the preparation of a kit-of-parts as hereinbefore defined, by bringing the two components 'into association with' each other, we include that the two components of the kit-of-parts may be:

- 5 (i) provided separately (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or
(ii) packaged and presented together as separate components of a 'combination pack' for use in conjunction with each other in combination therapy.

- 10 Thus, there is further provided a kit of parts comprising:
(I) one of components (A) and (B) as defined herein; together with
(II) instructions to use that component in conjunction with the other of the two components.

- In relation to kits of parts described above, although the compound of the invention may
15 be provided in the form of an (e.g. pharmaceutical) formulation, in admixture with one or more additional pharmaceutically-acceptable excipients (e.g. adjuvants, diluents or carriers), when the compound of the invention is provided with a view to it primarily performing its function as a medical device or as an excipient, it may not be provided along with such additional pharmaceutically-acceptable excipients. In any event, it is preferred
20 that the (other) pharmaceutically-active ingredient of the kit of parts is provided in the form of a pharmaceutical formulation in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

- The kits of parts described herein may comprise more than one (e.g. formulation including
25 an) appropriate quantity/dose of a compound of the invention, and/or more than one (e.g. formulation including an) appropriate quantity/dose of the other pharmaceutically-active ingredient, in order to provide for repeat dosing. If more than one formulation comprising or quantity/dose of either of the foregoing is present, such may be the same, or may be different in terms of the dose of either compound, chemical composition(s) and/or physical
30 form(s).

- With respect to the kits of parts as described herein, by 'administration in conjunction with', we include that respective components are administered, sequentially, separately and/or simultaneously, over the course of treatment of the relevant condition.

- 35 Thus, in respect of the combination product according to the invention, the term 'administration in conjunction with' includes that the two components of the combination product (compound of the invention and other pharmaceutically-active ingredient) are

administered (optionally repeatedly), either together, or sufficiently closely in time, to enable a beneficial effect for the patient, that is greater, over the course of the treatment of the relevant condition, than if either the compound of the invention, or (e.g. a formulation comprising) the other agent, are administered (optionally repeatedly) alone, 5 in the absence of the other component, over the same course of treatment. Determination of whether a combination provides a greater beneficial effect in respect of, and over the course of treatment of, a particular condition will depend upon the condition to be treated or prevented, but may be achieved routinely by the skilled person.

10 Further, in the context of a kit of parts according to the invention, the term 'in conjunction with' includes that one or other of the two components may be administered (optionally repeatedly) prior to, after, and/or at the same time as, administration of the other component. When used in this context, the terms 'administered simultaneously' and 'administered at the same time as' include that individual quantities/doses of the relevant 15 compound of the invention and other active pharmaceutical ingredient are administered within 48 hours (e.g. 24 hours) of each other.

In relation to combined preparations and kits of parts described above, it is preferred that the other pharmaceutically-active ingredient is an anti-inflammatory agent, or agent 20 known to give rise to inflammation as a side-effect, as hereinbefore described.

Wherever the word 'about' is employed herein, for example in the context of amounts, such as concentrations and/or doses of active ingredients and/or compounds of the invention, molecular weights or pHs, it will be appreciated that such variables are 25 approximate and as such may vary by $\pm 10\%$, for example $\pm 5\%$ and preferably $\pm 2\%$ (e.g. $\pm 1\%$) from the numbers specified herein. In this respect, the term 'about 10%' means e.g. $\pm 10\%$ about the number 10, i.e. between 9% and 11%.

Compounds of the invention have the advantage that they have a wide variety of uses, 30 including:

- as biologically-active agents in variety of conditions characterised by inflammation, whether that condition is an organic inflammatory disease per se or is associated with, or is characterised by, inflammation (e.g. a wound or a burn), and/or in surgical and/or cosmetic applications as described hereinbefore
- 35 • in combination with active pharmaceutical ingredients, either in combination therapy, or by performing a more inert function either as, or as part of:
 - a pharmaceutically-acceptable excipient (e.g. an adjuvant, diluent or carrier),

- o a medical device, and/or
- o the medical device part of a drug-medical device combination.

The compounds, uses and methods described herein may also have the advantage that, in the treatment of the conditions mentioned hereinbefore, they may be more convenient for the physician and/or patient than, be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, or that it/they may have other useful pharmacological properties over, similar compounds or methods (treatments) known in the prior art, whether for use in the treatment of any of the aforementioned conditions, including inflammation, inflammatory disorders, or disorders characterised by inflammation as a symptom (including wounds), or otherwise.

Brief Description of the Figures

Figure 1 shows the results of ear swelling in a mouse model treated with xylene and test Compounds A, B and C.

Figure 2 shows the results of ear swelling in a mouse model treated with xylene and test Compounds D, E, F, G and H.

Figure 3 shows the results of ear swelling in a mouse model treated with xylene, test Compounds E, I, J and palmitic acid + DMSO.

Figure 4 shows the results of ear swelling in a mouse model treated with xylene and test Compound E.

Figure 5 shows the results for radiation oral mucositis scores in a hamster model treated with test Compound E.

Figure 6 shows the results of mechanical pain threshold in an SD rat model treated with test Compound E and lidocaine.

Figure 7 shows the results for 5-FU induced oral mucositis scores in an SD rat model treated with test Compound E.

Figure 8 shows the results of a human subject with rosacea treated with test Compound E.

Figure 9 shows the results of the severity of esophagitis in GERD rat model treated with test Compounds K, L and M.

Examples

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Example 1

Palm-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 3)

10 Fmoc-Lys(Boc)-Wang resin (9.32 g, 3mmol; GL Biochem, Shanghai, China) was loaded into a glass reaction column.

Methylene chloride (DCM, 200 mL; Shandong Jinling Chemical Industry Co. Ltd., Shandong, China) was added to the column and allowed to soak the resin for about half an hour. The DCM was then removed by vacuum filtration.

15

The resin was washed 3 times with N,N-dimethylformamide (DMF, 200 mL; Shandong Shitaifeng Fertilizer Industry Co. Ltd., Shandong, China).

20 A 20% piperidine solution in DMF (200 mL; Shandong Shitaifeng Fertilizer Industry Co. Ltd., Shandong, China) was added as deprotection solution and reacted for 20 minutes. The solution was then removed by vacuum filtration and the column was washed with DMF six times.

25 Fmoc-Tyr(tBu)-OH (4.14 g, 9 mmol; GL Biochem, Shanghai, China) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU, 2.89 g, 9 mmol; GL Biochem, Shanghai, China) were added to the resin. DMF (150 mL) was added to the reaction column, followed by N,N-diisopropylethylamine (DIPEA, 2.33 g, 9 mmol; Suzhou Highfine Biotech Co. Ltd., Jiangsu, China). A Kaiser Test was carried out with few of the resin after reacting for 30 minutes, a yellow color of the solution and colorless gel indicated
30 that the reaction was complete. The solvent was removed by vacuum filtration.

The above coupling steps were repeated to couple the remaining amino acids in the same amounts (by mols): Fmoc-Thr(tBu)-OH, Fmoc-4-Hyp(tBu)-OH, Fmoc-4-Hyp(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Pro-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH
35 and palmitic acid.

After the palmitic acid was coupled, the resin was washed three times, each time with the following solvents, DMF (200 mL), DCM (200 mL) and methanol (200 mL; Xilong Scientific Co., Ltd., Guangdong, China). The resin was dried under vacuum for about 2 hours.

130.0 mL (i.e. 10 mL per gram of the dried resin) of lysate, which comprised of 95% trifluoroacetic acid (TFA, Macklin, Shanghai, China), 2.5% water and 2.5% triisopropylsilane (Tis, Macklin, Shanghai, China), were added to immerse the resin-
5 bounded peptide-containing compound. After cleavage for about 2 hours, the solid support was removed by filtration and the filtrate was collected under reduced pressure. The filtrate was precipitated with 1300 mL (i.e. 10 mL per ml of the filtrate) of diethyl ether (Xilong Scientific Co., Ltd., Guangdong, China) and the sediment was collected by filtration. The sediment was dried by vacuum for about 2 hours, yielding 4.51 g of crude title
10 compound.

The crude product was firstly analysed as a 1 mg/mL sample in pure water and detected using a Shimadzu LCMS-8050 system (Shimadzu, Japan). The analysis column was an Agilent ZORBAX Eclipse SB-C18 (4.6 × 250 mm, 5 µm column; detection: UV at 220 nm;
15 solvent A: 0.1% TFA in MeCN, solvent B: 0.1% TFA in water, with a linear gradient from 5%-90% solvent A concentration in 50 minutes; flow rate 1.0 mL/min; sample volume: 10 µL).

The target peak was eluted at 35.232 minutes and had the expected molecular weight,
20 (MS: m/z 1421.7), with a purity of 64.564%.

4.5 g of crude product was then dissolved in 90 mL of pure water and purified using NP7010C semi-preparation equipment (Hanbon Sci. & Tech. Co., Ltd., Jiangsu, China). The preparation column model was a Dubhe-C18 model (Hanbon Sci. & Tech. Co., Ltd.,
25 Jiangsu, China) (50*250 mm, 100Å column; detection: UV at 220 nm). The appropriate gradient for elution was calculated from LCMS detection step (Solvent A: 0.1% TFA in MeCN, solvent B: 0.1% TFA in water, with a linear gradient from 50%-80% solvent A concentration in 30 minutes; flow rate 60.0 mL/min;). Fractions were collected and analyzed using a Shimadzu LC-20 HPLC system (Shimadzu, Japan) (column as above,
30 except with a linear gradient from 50%-75% solvent A concentration in 25 minutes).

Fractions with a purity of higher than 90% were then mixed together for an anion exchange step. This was achieved using a NP7010C semi-preparation equipment (preparation column model: Dubhe-C18 model, as above). The fractions were diluted one time with
35 pure water and loaded to the column directly, after that the column was washed with 3.2% of ammonium acetate in pure water for about 20 minutes followed by pure water for another 10 minutes at the flow rate of 60 mL/min, then eluted with the following gradient (Solvent A: 0.1% HAc in MeCN, solvent B: 0.1% HAc in water, with a linear gradient from

50%-80% solvent A concentration in 30 minutes; flow rate 60.0 mL/min). Fractions were collected and analyzed using Shimadzu LC-20 HPLC system (column and conditions as above). Fractions with a purity of higher than 95% were mixed and freeze-dried to give 1.64 g of the purified title compound.

5

Example 2

Stearyl-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 4)

The title compound was prepared using essentially the same process as that described in Example 1 above, except that stearic acid was used instead of palmitic acid in the same amounts (by mols) in the last coupling step.

Repeating essentially the same procedure gave a further batch of crude title compound (yield 4.37 g). Analysis showed a target peak that was eluted at 36.231 minutes with the expected molecular weight, (MS: m/z 1449.8) with a purity of 60.287%.

4.3 g of the crude product was then purified as described in Example 1 above to give 1.52 g of pure title compound after freeze-drying.

Example 3

Palm-Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 10)

The title compound was prepared using essentially the same process as that described in Example 1 above except that the coupling steps were carried out by the following sequence in the same amounts (by mols): Fmoc-4-Hyp(tBu)-OH, Fmoc-DOPA(Acetonide)-OH, Fmoc-Thr(tBu)-OH, Fmoc-4-Hyp(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Pro-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH and palmitic acid.

Repeating essentially the same procedure gave a further batch of crude title compound (yield 4.56 g). Analysis showed a target peak that was eluted at 30.746 minutes with the expected molecular weight, (MS: m/z 1437.7) with a purity of 65.128%.

4.5 g of the crude product was then purified as described in Example 1 above to give 1.57 g of pure title compound after freeze-drying.

35

Example 4

Palm-Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-Hyp-Lys-Dopamine (SEQ ID No: 109)

The title compound was synthesized from Lys as the first amino acid with Fmoc-Lys(Boc)-Wang resin, using almost the same process as described in Example 1 above. Fmoc-4-Hyp(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-4-Hyp(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Pro-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH and palmitic acid were coupled in the same process as described in Example 1 above.

After palmitic acid was coupled on the resin, the resin was washed three times, each time with the following solvents, DMF (200 mL), DCM (200 mL) and methanol (200 mL). Then the resin was dried by vacuum for about 2 hours.

120.0 mL (i.e. 10 mL per gram of the dried resin) of lysate, which comprised of 2% trifluoroacetic acid (TFA) in DCM, was added to immerse the resin-bounded peptide-containing compound. After cleavage for about 2 hours, the solid support was removed by filtration and the filtrate was collected under reduced pressure. Then the filtrate was concentrated by rotary distillation under reduced pressure. After all solvents were removed, DMF (100 mL) was added to the flask to dissolve the solid, dopamine hydrochloride (1.71g, 9 mmol; Aladdin, Shanghai, China), TBTU (2.89 g), and DIPEA (2.33 g) were added to the reaction solution. After 30 minutes of the reaction, the reaction was completed. Precipitation of the final solution was carried out by adding 1200 mL (i.e. 10 mL per mL of the final solution) of saturated citric acid (Aladdin, Shanghai, China) in water solution and the sediment was collected by filtration. The sediment was then added to 120 mL (i.e. 10 mL per gram of the solid) of lysate, which comprised of 95% trifluoroacetic acid (TFA), 2.5% water and 2.5% triisopropylsilane (Tis) to dissolve the peptide-containing solid. The side chains were deprotected during cleavage. After cleavage for about 2 hours, the solution was precipitated with 1200 mL (i.e. 10 mL per mL of the filtrate) of diethyl ether and the sediment was collected by filtration. The sediment was dried by vacuum for about 2 hours. Finally, 4.25g of crude title compound was obtained.

Repeating essentially the same procedure gave a further batch of crude title compound (yield 4.38 g). Analysis showed a target peak that was eluted at 32.173 minutes with the expected molecular weight, (MS: m/z 1556.9) with a purity of 55.395%.

4.3 g of the crude product was then purified as described in Example 1 above to give 1.39 g of pure title compound after freeze-drying.

35

Example 5

Olei-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 5)

The title compound was prepared using essentially the same process as that described in Example 1 above, except that oleic acid was used instead of palmitic acid in the same amounts (by mols) in the last coupling step.

- 5 Repeating essentially the same procedure gave a further batch of crude title compound (yield 4.41 g). Analysis showed a target peak that was eluted at 35.877 minutes with the expected molecular weight, (MS: m/z 1447.8) with a purity of 61.737%.

4.4 g of the crude product was then purified as described in Example 1 above to give 1.55
10 g of pure title compound after freeze-drying.

Example 6

Olei-Ala-Lys-Pro-Ser-DOPA-Hyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 13)

- 15 The title compound was prepared using essentially the same process as that described in Example 5 above, except that Fmoc-DOPA(Acetonide)-OH was used instead of Fmoc-Tyr(tBu)-OH in the same amounts (by mols) in the corresponding coupling step.

Repeating essentially the same procedure gave a further batch of crude title compound
20 (yield 4.53 g). Analysis showed a target peak that was eluted at 35.124 minutes with the expected molecular weight, (MS: m/z 1479.8) with a purity of 62.522%.

4.5 g of the crude product was then purified as described in Example 1 above to give 1.52
25 g of pure title compound after freeze-drying.

Example 7

- 30 DHA-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 6)

The title compound was prepared using essentially the same process as that described in Example 1 above, except that docosahexaenoic acid was used instead of palmitic acid in the same amounts (by mols) in the last coupling step.

- 35 Repeating essentially the same procedure gave a further batch of crude title compound (yield 4.47 g). Analysis showed a target peak that was eluted at 35.877 minutes with the expected molecular weight, (MS: m/z 1493.8) with a purity of 63.228%.

4.4 g of the crude product was then purified as described in Example 1 above to give 1.57 g of pure title compound after freeze-drying.

Example 8 (Compound E)

5 Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)

The title compound was synthesized using essentially the same procedure as that described in Example 1 above, except that the appropriate amino acids were used as in the relevant peptide coupling sequences.

10

Repeating essentially the same procedure gave a further batch of crude title compound (yield 3.59 g). Analysis showed a target peak that was eluted at 29.947 minutes with the expected molecular weight, (MS: m/z 1136.4) with a purity of 70.223%.

15 3.5 g of the crude product was then purified as described in Example 1 above to give 1.21 g of pure title compound after freeze-drying.

Example 9

Olei-Lys-Pro-Ser-Tyr-Hyp-DOPA-Lys (SEQ ID No: 15)

20

The title compound was synthesized using essentially the same procedure as that described in Example 6 above, except that the appropriate amino acids and fatty acids were used in the relevant peptide coupling sequences.

25 Repeating essentially the same procedure gave a further batch of crude title compound (yield 3.65 g). Analysis showed a target peak that was eluted at 30.093 minutes with the expected molecular weight, (MS: m/z 1178.6) with a purity of 71.943%.

30 3.6 g of the crude product was then purified as described in Example 1 above to give 1.25 g of pure title compound after freeze-drying.

Example 10 (Compound N)

DPPS-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 7)

35 The title compound was prepared using essentially the same process as that described in Example 1 above, except that Fmoc-DPPS-OH was used instead of palmitic acid in the same amounts (by mols) in the last coupling step. After Fmoc-DPPS-OH was coupled on the resin, a deprotection step was carried out to remove the Fmoc protection on DPPS.

The resin was washed 3 times with DMF (200 mL each time). A 20% piperidine solution in DMF (200 mL) was added as a deprotection solution and reacted for 20 minutes and then removed by vacuum. Then, the remaining steps were carried out according to essentially the same as described in Example 1.

5

Repeating essentially the same procedure gave a further batch of crude title compound (yield 5.77 g). Analysis showed a target peak that was eluted at 48.284 minutes with the expected molecular weight, (MS: m/z 1814.2) with a purity of 53.933%.

10 5.7 g of the crude product was then purified as described in Example 1 above to give 1.79 g of pure title compound after freeze-drying.

Example 11 (Compound O)

LTB4-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 8)

15

The title compound was prepared using essentially the same process as that described in Example 1 above, except that LTB4 was used instead of palmitic acid in the same amounts (by mols) in the last coupling step.

20 Repeating essentially the same procedure gave a further batch of crude title compound (yield 4.39 g). Analysis showed a target peak that was eluted at 33.877 minutes with the expected molecular weight, (MS: m/z 1501.8) with a purity of 57.847%.

25 4.3 g of the crude product was then purified as described in Example 1 above to give 1.38 g of pure title compound after freeze-drying.

Example 12 (Compound M)

30 Montelukast-Ala-lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys(Palm) (SEQ ID No: 2)

Fmoc-Lys(Boc)-Wang resin (9.15 g, GL Biochem, Shanghai, China) was loaded into a glass reaction column.

35 Methylene chloride (DCM, 200 mL; Shandong Jinling Chemical Industry Co. Ltd., Shandong, China) was added to the column and allowed to soak the resin for about half an hour. The DCM was then removed by vacuum filtration.

200mL of 30% trifluoroacetic acid (TFA, Macklin Biochemical Co. Ltd., Shanghai, China) solution in DCM was added to the column and reacted with the resin for about half an hour to remove the Boc protection group on Lys. Then, TFA solution in DCM was then removed by vacuum filtration.

5

The resin was washed 6 times with N,N-dimethylformamide (DMF, 200 mL; Shandong Shitaifeng Fertilizer Industry Co Ltd, Shandong, China).

Palmitic acid (2.31 g, 9 mmol; Macklin Biochemical Co. Ltd., Shanghai, China) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU, 2.89 g; GL Biochem, Shanghai, China) were added to the resin. DMF (150 mL) was added to the reaction column, followed by N,N-diisopropylethylamine (DIPEA, 2.33 g; Suzhou Highfine Biotech Co. Ltd, Jiangsu, China). A Kaiser Test was carried out with few of the resin after 30 minutes reaction, a yellow color of the solution and colorless gel indicated that the reaction was complete. The solvent was removed by vacuum filtration.

15

After palmitic acid was coupled to the side chain of the Lysine resin, the other amino acids were coupled essentially in the same steps and sequence as described in Example 1 above. Fmoc-Tyr(tBu)-OH was coupled first, followed by Fmoc-Thr(tBu)-OH, Fmoc-4-Hyp(tBu)-OH, Fmoc-4-Hyp(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Pro-OH, Fmoc-Lys(Boc)-OH and Fmoc-Ala-OH, except montelukast sodium was used instead of palmitic acid in the last coupling step. The amounts of amino acids, montelukast sodium, TBTU and DIPEA in these coupling steps were also in the same amount (by mol) compared with Example 1.

25

After Montelukast sodium was coupled, repeating essentially the same procedure gave a further batch of crude title compound (yield 5.86 g). Analysis showed a target peak that was eluted at 43.848 minutes with the expected molecular weight, (MS: m/z 2011.9) with a purity of 52.432%.

30

5.8 g of the crude product was then purified as described in Example 1 above to give 1.63 g of pure title compound after freeze-drying.

Example 13

35 Olei-Ala-Iys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys(Palm) (SEQ ID No: 2)

The title compound was prepared using essentially the same process as that described in Example 10 above, except that oleic acid was used instead of montelukast sodium in the same amounts (by mols) in the last coupling step.

- 5 Repeating essentially the same procedure gave a further batch of crude title compound (yield 4.37 g). Analysis showed a target peak that was eluted at 46.129 minutes with the expected molecular weight, (MS: m/z 1686.2) with a purity of 51.237%.

- 4.3 g of the crude product was then purified as described in Example 1 above to give 1.51
10 g of pure title compound after freeze-drying.

Example 14

Palm-Lys-Hyp-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 20)

- 15 The title compound was synthesized using essentially the same procedure as that described in Example 8 above, except that the appropriate amino acids were used as in the relevant peptide coupling sequences.

- Repeating essentially the same procedure gave a further batch of crude title compound
20 (yield 3.51 g). Analysis showed a target peak that was eluted at 28.847 minutes with the expected molecular weight, (MS: m/z 1152.5) with a purity of 68.983%.

- 3.5 g of the crude product was then purified as described in Example 1 above to give 1.16
25 g of pure title compound after freeze-drying.

Example 15

DPPS-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 18)

- The title compound was synthesized using essentially the same procedure as that described in Example 10 above, except that the appropriate amino acids were used as in the relevant
35 peptide coupling sequences.

Repeating essentially the same procedure gave a further batch of crude title compound (yield 5.03 g). Analysis showed a target peak that was eluted at 43.288 minutes with the expected molecular weight, (MS: m/z 1616.0) with a purity of 65.039%.

- 5 5.0 g of the crude product was then purified as described in Example 1 above to give 2.1 g of pure title compound after freeze-drying.

Example 16

Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys(Chol-Ac)-NH₂ (SEQ ID No: 110)

10

The title compound was synthesized using essentially the same procedure as that described in Example 12 above, except that Fmoc-Lys(Boc)-AM resin (6.98 g, USUN pharma, Jiangsu, China) was used as the starting material compared with Example 12. After the side chain of Fmoc-Lys(Boc)-AM resin was deprotected, cholesterol-acetic acid (self-synthesized) was
15 connected to the side chain of Fmoc-Lys-AM resin. The appropriate amino acids were used as in the relevant peptide coupling sequences compared with Example 12, to obtain the title compound.

- 20 Repeating essentially the same procedure gave a further batch of crude title compound (yield 3.84 g). Analysis showed a target peak that was eluted at 37.822 minutes with the expected molecular weight, (MS: m/z 1323.7) with a purity of 61.438%.

- 3.8 g of the crude product was then purified as described in Example 1 above to give 1.3 g of pure title compound after freeze-drying.

25

Example 17

Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys-PEA (SEQ ID No: 111)

- 30 The title compound was synthesized from Lysine as the first amino acid with Fmoc-Lys(Boc)-CTC resin (7.23 g, USUN pharma, Jiangsu, China) as the solid support.

- The peptide sequence Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 16) was synthesized using essentially the same procedure as that described in Example 1 above, except that the appropriate amino acids (Boc-Lys(Boc)-OH was used in the last coupling step) were
35 used as in the relevant peptide coupling sequences compared with Example 1.

After Boc-Lys(Boc)-OH was coupled on the resin, the resin was washed three times each time with the following solvents, DMF (200 mL), DCM (200 mL) and methanol (200 mL). The resin was dried by vacuum for about 2 hours.

5 100.0 mL (i.e. 10 mL per gram of the dried resin) of lysate, which comprised of 2% trifluoroacetic acid (TFA) in DCM, was added to immerse the resin-bounded peptide-containing compound. After cleavage for about 2 hours, the solid support was removed by filtration and the filtrate was collected under reduced pressure. The filtrate was concentrated by rotary distillation under reduced pressure. After all solvents were removed,
10 PEA (1.8g, CAS: 544-31-0; Macklin, Shanghai, China) was added, followed by pyridine (100 mL), to the flask to dissolve the solids, then phosphorus oxychloride (0.3ml, Adamas-beta Co. Ltd., Shanghai, China) was added to the reaction solution. After 3 hours of the reaction, the reaction was completed. Precipitation of the final solution was carried out by adding 1000 mL (i.e. 10 mL per ml of the final solution) of saturated citric acid (Aladdin,
15 Shanghai, China) water solution and the sediment was collected by filtration. 100 mL (i.e. 10 mL per gram of the solid) of lysate, which comprised of 95% trifluoroacetic acid (TFA), 2.5% water and 2.5% triisopropylsilane (Tis) was added to the sediment to dissolve the peptide-containing solid. The side chains were deprotected during cleavage. After cleavage for about 2 hours, the solution was precipitated with 1000 mL (i.e. 10 mL per ml
20 of the filtrate) of diethyl ether and the sediment was collected by filtration. The sediment was dried by vacuum for about 2 hours. Finally, 3.87g of crude title compound was obtained.

Analysis showed a target peak that was eluted at 30.449 minutes with the expected
25 molecular weight, (MS: m/z 1179.5) with a purity of 58.323%.

3.8 g of the crude product was then purified as described in Example 1 above to give 1.2 g of pure title compound after freeze-drying.

30

Example 18 (Compound K)

35 (Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys)₂-Lys (SEQ ID No: 113)

Fmoc-Lys(Fmoc)-Wang resin (10.23 g, 3mmol; GL Biochem, Shanghai, China) was loaded into a glass reaction column. Methylene chloride (DCM, 200 mL; Shandong Jinling

Chemical Industry Co. Ltd., Shandong, China) was added to the column and allowed to soak the resin for about half an hour. DCM was removed by vacuum filtration. The resin was washed 3 times with N,N-dimethylformamide (DMF, 200 mL; Shandong Shitaifeng Fertilizer Industry Co. Ltd., Shandong, China).

5

A 20% piperidine solution in DMF (200 mL; Shandong Shitaifeng Fertilizer Industry Co. Ltd., Shandong, China) was added as deprotection solution and allowed to react for 20 minutes. The solution was removed by vacuum filtration and the column was washed with DMF six times.

10

Fmoc-Lys(Boc)-OH (8.43 g, 18 mmol; GL Biochem, Shanghai, China) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylammonium tetrafluoroborate (TBTU, 5.78 g, 18 mmol; GL Biochem, Shanghai, China) were added to the resin. DMF (150 mL) was added to the reaction column, followed by N,N-diisopropylethylamine (DIPEA, 4.66 g, 18 mmol; Suzhou Highfine Biotech Co. Ltd., Jiangsu, China). A Kaiser Test was carried out with some of the resin after reacting for 30 minutes, in which a yellow color of the solution and colorless gel indicated that the reaction was complete. The solvent was removed by vacuum filtration.

15

The title compound was prepared using essentially the same process as that described in Example 8 above, except that the amount of the amino acids, palmitic acid and the condensation agents (TBTU and DIPEA) was doubled (by mols).

20

Repeating essentially the same procedure gave a further batch of crude title compound (yield 6.68 g). Analysis showed a target peak that was eluted at 30.665 minutes with the expected molecular weight, (MS: m/z 2383.1) with a purity of 57.542%.

25

6.6 g of the crude product was then purified as described in Example 1 above to give 2.76 g of pure title compound after freeze-drying.

30

Example 19 (Compound P)

(Palm-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys)₂-Lys (SEQ ID No: 114)

35

The title compound was synthesized using essentially the same procedure as that described in Example 18 above, except that the appropriate amino acids were used as in the relevant peptide coupling sequences.

Repeating essentially the same procedure gave a further batch of crude title compound (yield 8.53 g). Analysis showed a target peak that was eluted at 32.192 minutes with the expected molecular weight, (MS: m/z 2953.7) with a purity of 52.821%.

5

8.5 g of the crude product was then purified as described in Example 1 above to give 3.2 g of pure title compound after freeze-drying.

Example 20 (Compound L)

10 Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys(Palm)-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys(Palm) (SEQ ID No: 115)

Fmoc-Lys(Dde)-Wang resin (9.97 g, 3mmol; GL Biochem, Shanghai, China) was loaded into a glass reaction column.

15 Methylene chloride (DCM, 200 mL; Shandong Jinling Chemical Industry Co. Ltd., Shandong, China) was added to the column and allowed to soak the resin for about half an hour. DCM was removed by vacuum filtration.

Side-chain coupling steps:

20 1. Resin wash: The resin was washed 3 times with N,N-dimethylformamide (DMF, 200 mL; Shandong Shitaifeng Fertilizer Industry Co. Ltd., Shandong, China).

2. De-protection: A 5% Hydrazine monohydrate (Merck KGaA, Darmstadt, Germany) solution in DMF (200 mL) was added as deprotection solution and reacted for 20 minutes. The solution was removed by vacuum filtration and the column was washed

25 with DMF six times.

3. Coupling: Palmitic acid (2.31 g, 9mmol; Merck KGaA, Darmstadt, Germany) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU, 2.89 g, 9mmol; GL Biochem, Shanghai, China) were added to the resin. DMF (150 mL) was added to the reaction column, followed by N,N-diisopropylethylamine (DIPEA, 2.33 g,

30 9mmol; Suzhou Highfine Biotech Co. Ltd., Jiangsu, China). A Kaiser Test was carried out with few of the resin after 30 minutes reaction, a yellow color of the solution and colorless gel indicated that the reaction was complete. The solvent was removed by vacuum filtration.

35 After the Side-chain palmitic acid was coupled, the amino acids were coupled to the resin.

Amino acids coupling steps:

1. Resin wash: The resin was washed 3 times with N,N-dimethylformamide (DMF, 200 mL;

Shandong Shitaifeng Fertilizer Industry Co. Ltd., Shandong, China).

2. De-protection: A 20% piperidine (Shandong Shitaifeng Fertilizer Industry Co. Ltd., Shandong, China) solution in DMF (DBLK, 200 mL) was added as deprotection solution and reacted for 20 minutes. The solution was removed by vacuum filtration and the gel was washed with DMF six times.
3. Coupling: Fmoc-Tyr(tBu)-OH (4.14 g, 9 mmol; GL Biochem, Shanghai, China) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU, 2.89 g, 9mmol; GL Biochem, Shanghai, China) were added to the resin. DMF (150 mL) was added to the reaction column, followed by N,N-diisopropylethylamine (DIPEA, 2.33 g, 9 mmol; Suzhou Highfine Biotech Co. Ltd., Jiangsu, China). A Kaiser Test was carried out with some of the resin after 30 minutes of reacting, a yellow color of the solution and colorless gel indicated that the reaction was complete. The solvent was removed by vacuum filtration.
- The above coupling steps were repeated to couple the following amino acids in the same amounts (by mols): Fmoc-4-Hyp(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Pro-OH, Fmoc-Lys(Boc)-OH and then Fmoc-Lys(Dde)-OH.

After Fmoc-Lys(Dde)-OH was coupled, the Dde side-chain protecting group was removed, followed by coupling of Palmitic acid to the side chain using essentially the same method as above.

After Palmitic acid was coupled to the side chain of the de-protected Lysine residue, further coupling steps were repeated to couple the following amino acids in the same amounts (by mols): Fmoc-4-Hyp(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Pro-OH and then Boc-Lys(Boc)-OH, using essentially the same method as above.

After Boc-Lys(Boc)-OH was coupled, the resin was washed three times each with the following solvents, DMF (200 mL each time), DCM (200 mL each time) and methanol (200 mL each time; Xilong Scientific Co., Ltd., Guangdong, China). The resin was dried under vacuum for about 2 hours.

MS: m/z 2254.9

- Repeating essentially the same procedure as Example 1 gave a further batch of crude title compound (yield 6.3 g). Analysis showed a target peak that was eluted at 31.282 minutes with the expected molecular weight (MS: m/z 2254.9). The purity was 50.872%.

6.3 g of the crude product was then purified as described in Example 1 above to give 2.01 g of pure title compound after freeze-drying.

Example 21

5 Compound E Cream - 1: Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)

The Compound E cream contained a mixture of the following substances in Table 1 below. Ingredients of phase A were mixed, heated to 85°C, and stirred for 30 minutes at 85 °C. Phase B was added, the mixture homogenized for 5 minutes, then stirred to cool down.
10 When the temperature dropped to 45 °C, the raw materials of phase C were added and the mixture homogenized for 1 minute. Phase D was added and the mixture homogenized for 3-5 minutes until the system was uniform to obtain the Compound E Cream - 1.

Table 1

15

Phase	Brand name	INCI name	Amount (%)
A1	Pure water	AQUA	71.95
A2	Glycerin	GLYCERIN	1.7
A3	1,3-butylene glycol	BUTYLENE GLYCOL	3
A4	Betaine	BETAINE	0.2
A5	EDTA-2NA	DISODIUM EDTA	0.05
A6	AVC	AMMONIUM ACRYLOYLDIMETHYLAURATE/VP COPOLYMER	0.4
A7	HA(150W)	SODIUM HYALURONATE	0.08
B1	A165	GLYCERYLSTEARATE	0.4
		PEG-100STEARATE	
B2	olive800	CETEARETH-6 OLIVATE	1.47
B3	RH-201-2	DIMETHICONE	2.57
B4	DC200/100	DIMETHICONE	2.53
B5	DC200/350	DIMETHICONE	1.3
B6	BUTYROSPERMUM PARKII (SHEA) BUTTER	BUTYROSPERMUM PARKII (SHEA) BUTTER	0.25
B7	L70	TOCOPHEROL	0.1
		HELIANTHUS ANNUUS (SUNFLOWER) SEED OIL	

B8	PHYTOSTERYL ISOSTEARATE	PHYTOSTERYL ISOSTEARATE	0.1
		PHYTOSTERO LS	
B9	ININ	ISONONYL ISONONANOATE	4.3
B10	Lanolin	LANOLIN	1
B11	CHE	CETYL ETHYLHEXANOATE	4
C1	Compound E		0.1
	Pure water	AQUA	1
C2	BHC	BUTYLENE GLYCOL	1
		1,2-HEXANEDIOL	
		CAPRYLHYDROXAMIC ACID	
C3	PL-429	TETRAHYDRO PIPERINE	0.5
		INOSITOL	
		HYDROXYPROPYL CYCLODEXTRIN	
		POLYLYSINE	
		BETAINE	
		HYDROLYZED CHITIN	
		GLYCERIN	
		BUTYLENE GLYCOL	
		AQUA	
D1	SKG-19	DIMETHICONE	2
		DIMETHICONE/VINYL	
		DIMETHICONE CROSSPOLYMER	
			100

Example 22

Compound E Oral Spray: Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)

- 5 The Compound E oral spray contained a mixture of the following substances in Table 2 below. The ingredients of phase A were mixed, heated to 85 °C, and stirred for 30 minutes at 85 °C. When the temperature dropped to 45 °C, the pre-mixed raw materials of phase B were added. The mixture was stirred for 3-5 minutes until phase B was dissolved and the system was uniform to obtain the Compound E Oral Spray.

10

Table 2

Phase	Brand name	INCI name	Amount (%)
-------	------------	-----------	------------

A1	Pure water	AQUA	92.355
A2	Glycerin	GLYCERIN	5.3
A3	Citric Acid (1%)	CITRIC ACID	0.77
B1	Sucralose (10%)	SUCRALOSE	0.175
B2	Compound E		0.1
B3	Potassium sorbate	POTASSIUM SORBATE	0.2
B4	Menthol	MENTHOLUM	0.1
B5	C0-40	PEG-40 Hydrogenated Castor Oil Lucsei	1
			100

Example 23

Compound E Facial Spray – 1: Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)

- 5 The Compound E Facial Spray - 1 contained a mixture of the following substances in Table 3 below. The ingredients of phase A were mixed and heated to 85 °C and stirred for 30 minutes at 85 °C. When the temperature dropped to 45 °C phase B was added. The mixture was stirred for 3-5 minutes until phase B was dissolved and the system was uniform to obtain the Compound E Facial Spray - 1.

10

Table 3

Phase	Brand name	INCI name	Amount (%)
A1	Pure water	AQUA	98.6
A2	PL-429	TETRAHYDRO PIPERINE	0.5
		INOSITOL	
		HYDROXYPR OPYL CYCLODEXTRI N	
		POLYLYSINE	
		BETAINE	
		HYDROLYZED CHITIN	
		GLYCERIN	
		BUTYLENE GLYCOL	
		AQUA	
A3	PHL	1,2-HEXANEDIOL	0.8
		1,3-PROPANEDIOL	
		CAPRYLHYDROXAMIC ACID	

B	Compound E		0.1
			100

Example 24

Compound E Facial Spray – 2: Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)

- 5 The Compound E Facial Spray - 2 contained a mixture of the following substances in Table 4 below. The ingredients of phase A were mixed and heated to 85 °C. The mixture was stirred for 30 minutes at 85 °C. When the temperature dropped to 45 °C, phase B was added and stirred for 3-5 minutes until phase B was dissolved and the system was uniform to obtain the Compound E Facial Spray - 2.

10

Table 4

Phase	Brand name	INCI name	Amount (%)
A1	Pure water	AQUA	92.1
A2	Betaine	BETAINE	0.2
A3	Glycerin	GLYCERIN	1.8
A4	E-20	METHYL GLUCETH-20	0.5
A5	PEG-32	PEG-32	0.5
B1	SymCalmin	PENTYLENE GLYCOL	0.1
		BUTYLENE GLYCOL	
		HYDROXYPHENYL PROPAMIDOBENZOIC ACID	
		ASCORBYL PALMITATE	
B2	PL-429	TETRAHYDRO PIPERINE	0.5
		INOSITOL	
		HYDROXYPR OPYL CYCLODEXTRIN	
		POLYLYSINE	
		BETAINE	
		HYDROLYZED CHITIN	
		GLYCERIN	
		BUTYLENE GLYCOL	
B3	PHL	AQUA	0.8
		1,2-HEXANEDIOL	
		1,3-PROPANEDIOL	
		CAPRYLHYDROXAMIC ACID	

B4	ROSA FLOWER WATER	ROSA RUGOSA FLOWER WATER	3.4
B5	Compound E		0.1
			100

Example 25

Compound E Mouthwash - 1: Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)

- 5 The Compound E mouthwash contained a mixture of the following substances in Table 5 below. The ingredients of phase A were mixed and heated to 85 °C and stirred for 30 minutes at 85 °C. When the temperature dropped to 45 °C, phase B was added and stirred for 3-5 minutes until phase B was dissolved the system was uniform to obtain the Compound E Mouthwash - 1.

10

Table 5

Phase	Brand name	INCI name	Amount (%)
A1	Pure water	AQUA	90.84
A2	Sorbitol (70%)	SORBITOL	6.0
A3	Citric Acid (1%)	CITRIC ACID	0.5
B1	NB371	ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	2.0
B3	Sucralose (10%)	SUCRALOSE	0.03
B4	Compound E		0.1
B5	Menthol	MENTHOLUM	0.03
	C0-40	PEG-40 Hydrogenated Castor Oil Lucsei	0.3
B6	Potassium sorbate	POTASSIUM SORBATE	0.2
			100

15

Example 26

Compound E Cream - 2: Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)

20

The Compound E Cream – 2 and its placebo sample contained a mixture of the following substances in Tables 6 and 7 below, respectively. The ingredients of phase A were mixed, heated to 80 °C, and stirred for 30 minutes at 80 °C. The ingredients of phase B were

mixed, heated to 80 °C and stirred for 30 minutes at 80 °C. The solution of phase B was transferred to the solution of phase A and homogenized for 5 minutes. The sample was allowed to cool until the system was uniform to obtain the Compound E Cream – 1 or its placebo sample.

5

Table 6

Phase	Material	Amount (%)
A1	Tefose 63	10.0
A2	Stearyl alcohol	1.5
A3	Cetyl alcohol	1.5
A4	Liquid paraffin	10.0
A5	Methylparaben	0.1
B1	Pure water	76.8
B2	Compound E	0.1
		100

Table 7

10

Phase	Material	Amount (%)
A1	Tefose 63	10.0
A2	Stearyl alcohol	1.5
A3	Cetyl alcohol	1.5
A4	Liquid paraffin	10.0
A5	Methylparaben	0.1
B1	Pure water	76.9
		100

15

Example 27

Compound E Hair Care Essence: Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)

The Compound E Hair Care Essence and its placebo sample contained the following substances in Table 8 and 9 below, respectively. The ingredients of phase A were mixed,

20

heated to 80 °C and stirred for 30 minutes at 80 °C. The sample was allowed to cool until the system was uniform to obtain the Compound E Hair Care Essence or its placebo sample.

Table 8

5

Phase	Brand name	INCI name	Amount (%)
A1	Pure water	AQUA	99.89
A2	Benzalkonium chloride	BENZALKONIUM CHLORIDE	0.01
A3	Compound E		0.1
			100

Table 9

Phase	Brand name	INCI name	Amount (%)
A1	Pure water	AQUA	99.99
A2	Benzalkonium chloride	BENZALKONIUM CHLORIDE	0.01
			100

10 Example 28

Compound E Mouthwash – 2: Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)

The Compound E Mouthwash - 2 and its placebo sample contained a mixture of the following substances in Tables 10 and 11 below, respectively. The ingredients of phase A were mixed, heated to 80 °C and stirred for 30 minutes at 80 °C. The sample was allowed to cool until the system was uniform to obtain the Compound E Mouthwash – 2 or its placebo sample.

15

Table 10

20

Phase	Brand name	INCI name	Amount (%)
A1	Pure water	AQUA	99.89
A2	Cetylpyridinium Chloride	CETYLPYRIDINIUM CHLORIDE	0.05
A3	Menthol	MENTHOLUM	0.01
A4	Sucralose	SUCRALOSE	0.02
A5	Compound E		0.03
			100

Table 11

Phase	Brand name	INCI name	Amount (%)
A1	Pure water	AQUA	99.92
A2	Cetylpyridinium Chloride	CETYLPIRIDINIUM CHLORIDE	0.05
A3	Menthol	MENTHOLUM	0.01
A4	Sucralose	SUCRALOSE	0.02
			100

Example 29

Compound E Foam: Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)

Formula - 1: The Compound E Foam Formula - 1 contained a mixture of the following substances in Table 12 below. The ingredients of phase A were mixed and stirred for 30 minutes until the system was uniform to obtain the Compound E Foam Formula - 1.

Table 12

Phase	Material	Amount (%)
A1	Tween-80	3.0
A2	Hydroxypropyl methyl cellulose (HPMC)	0.5
A3	Glycerin	5.0
A4	Benzil alcohol	1.0
A5	Pure water	90.4
A6	Compound E	0.1
		100

Formula - 2: The Compound E Foam Formula - 2 contained a mixture of the following substances in Table 13 below. The ingredients of phase A were mixed and stirred for 30 minutes until the system was uniform. Sodium hydroxide was added to adjust the pH of the solution to 6.5-7.0 while stirring to obtain the Compound E Foam Formula - 2.

Table 13

Phase	Material	Amount (%)
A1	Tween-80	3.0
A2	Hydroxypropyl methyl cellulose (HPMC)	0.5

A3	Glycerin	5.0
A4	Benzil alcohol	1.0
A5	Pure water	90.4
A6	Compound E	0.1
B1	Sodium hydroxide	
		100

Formula - 3: The Compound E Foam Formula – 3 contained a mixture of the following substances in Table 14 below. The procedures for preparing the Compound E Foam Formula – 3 were the same as that described for Formula – 2.

5

Table 14

Phase	Material	Amount (%)
A1	Tween-80	3.0
A2	Hydroxypropyl methyl cellulose (HPMC)	0.5
A3	Glycerin	5.0
A4	Benzil alcohol	1.0
A5	Glucosamine	1.5
A6	Maluca honey	1.0
A7	Pure water	87.9
A8	Compound E	0.1
B1	Sodium hydroxide	
		100

Example 30

10 Compound E Gel: Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)

The preparation of the Compound E Gel contained a mixture of the following substances in Table 15 below. The ingredients of phase A were mixed, heated to 80 °C and stirred for 30 minutes at 80 °C. The sample was allowed to cool until the system was uniform to obtain the Compound E Gel.

15

Table 15

Phase	Brand name	INCI name	Amount (%)
A1	Pure water	AQUA	81.23

A2	Propanediol	PROPYLENE GLYCOL	13.40
A3	Glycerin	GLYCERIN	2.60
A4	Carbomer 940	KABOMUER	0.67
A5	Carbomer 941	KABOMUER	0.13
A6	Triethanolamine	TRIETHANOLAMINE	0.80
A7	4-Hydroxyacetophenone	HYDROXYACETOPHENONE	0.50
A8	1,2-Hexanediol	HEXANEDIOL	0.50
A9	Sodium Hyaluronate (1.5M Da)	SODIUM HYALURONATE	0.07
A10	Compound E		0.10
			100

Example 31

Ear Swelling Mouse Model

- 5
- Test compounds:
Compound A: Palm-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 3)
Compound B: Stea-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 4)
Compound C: Palm-Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 10)
- 10
- 25, 6 to 8 week old, healthy male BALB/c mice with average body weights of 18-25 g (Hangzhou Ziyuan Experimental Animal Technology Co., Ltd. Hangzhou, China) were housed and cared for about 1 week prior to the experiment. The housing conditions were at 25-27 °C, 74% humidity, 12h dark-light cycle, and the mice had free access to food and water. These mice were randomly divided into 5 groups (5 mice in each group) as described in Table 16 below.
- 15

Table 16

Group	Drug concentration	Drug administration on right ear	Total amount of dose (µg/mouse)
Model	/	xylene	/
Dex cream (Dexamethasone)	0.75 mg/g	xylene + Dex cream	0.03
Compound A	1.5 mg/ml	xylene + Compound A	60
Compound B	1.5 mg/ml	xylene + Compound B	60
Compound C	1.5 mg/ml	xylene + Compound C	60

The left ear of each mouse was used as the autologous control and the right ear of each mouse was treated with a different treatment: 20 µl of xylene (Shanghai Aladdin Bio-Chem Technology Co., LTD, Shanghai, China) was applied to the right ear of each mouse, both the inside and outside. The ear started to swell after about 4 mins. Then 40 µl of drugs
 5 was applied to the right ear in each group. The mice were placed back in the cages.

Dexamethasone Acetate Cream (0.75 mg/g, China resources group) was purchased on the local drug store. Compounds A-C were synthesized by the Chinese Peptide Company as described above. 15 mg of each compound (powder) was dissolved in 10 ml of normal
 10 saline to make a solution of 1.5 mg/ml. The resultant solution was applied to the mice accordingly.

The mice were sacrificed by cervical dislocation after 40 mins. The left and right ears were cut off. A skin pouch (Electron Microscopy Sciences, P.O. Box 550, 1560 Industry Road,
 15 Hatfield, PA 19440) with a diameter of 8 mm was used to take a piece of ear from the same site on both ears. The weights were recorded and used to calculate the rate of swelling, shown in Table 17 below and in Figure 1.

Swollen rate (%) = (right ear weight - left ear weight) / left ear weight × 100%

20 Table 17

Group	Model	DEX	Compound A	Compound B	Compound C
Swollen rate (%)	81.03	33.33	45.29	53.59	45.70
SD (%)	25.08	21.83	17.88	13.52	20.32

The results showed that all three compounds could significantly reduce the xylene induced ear swelling in the mouse model. The effect was a little weaker than that of the
 25 Dexamethasone.

Example 32

Ear Swelling Mouse Model

30 Test compounds:

Compound D: DHA-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 6)

Compound E: Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)

Compound F: Olei-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 5)

Compound G: Olei-Ala-Lys-Pro-Ser-DOPA-Hyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 13)

Compound H: DPPS-Ala-Lys-Pro-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 112)

The experimental procedure and recording of results were the same as that described in Example 31 above. Ear swelling was induced by xylene in mice. 35 mice were divided into 7 groups as described in Table 18 below, and the results are shown in Table 19 below and in Figure 2.

Table 18

Group	Drug concentration	Drug administration on right ear	Total amount of dose ($\mu\text{g}/\text{mouse}$)
Model	/	xylene	/
Dex cream (Dexamethasone)	0.75 mg/g	xylene + Dex cream	0.03
Compound D	1.5 mg/ml	xylene + Compound D	60
Compound E	1.5 mg/ml	xylene + Compound E	60
Compound F	1.5 mg/ml	xylene + Compound F	60
Compound G	1.5 mg/ml	xylene + Compound G	60
Compound H	1.5 mg/ml	xylene + Compound H	60

Table 19

Group	Model	Dex	Compound D	Compound E	Compound F	Compound G	Compound H
Swollen rate (%)	94.11	42.74	69.49	51.92	72.79	69.56	62.98
SD (%)	21.82	12.37	11.24	12.21	9.99	18.14	31.49

The results showed that all five compounds were effective in reducing the swelling rate in the mouse model treated with xylene, however not to the extent of treatment with dexamethasone.

Example 33

20 Ear Swelling Mouse Model

Test compounds:

Compound E: Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)
Compound I: Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 16)
Compound J: Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 2)
Palmitic acid + DMSO

5

The experimental procedure and recording of results were the same as that described in Example 31 above. Ear swelling was induced by xylene in mice. 35 mice were divided into 7 groups as described in Table 20 below and the results are shown in Table 21 below and in Figure 3.

10

Table 20

Group	Drug concentration	Drug administration on right ear
Model	/	Normal saline
Dex cream (Dexamethasone)	0.75 mg/g	xylene + Dex cream
Compound E	1 mg/ml	xylene + Compound E
Compound I	1 mg/ml	xylene + Compound I
Compound J	1 mg/ml	xylene + Compound J
Palmitic acid + DMSO	0.3 mg/ml	xylene + palmitic acid + DMSO

Table 21

15

Group	Model	Dex	Compound E	Compound I	Compound J	Palmitic acid + DMSO
Swollen rate (%)	82.09	38.56	46.86	54.29	64.67	49.88
SD (%)	13.62	18.09	11.96	3.91	9.23	11.71

Example 34
Ear Swelling Mouse Model

20

Test compound:
Compound E: Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 17)

The experimental procedure and recording of results were the same as that described in Example 31 above. Ear swelling was induced by xylene in mice. The mice were divided

into 8 groups as described in Table 22 below and the results are shown in Table 23 below and in Figure 4.

Table 22

5

Group	Drug Concentration	Drug administration on right ear
Model	/	Normal saline
Dex	0.75 mg/g	Dexamethasone cream
Compound E	0.1 mg/ml	Compound E
Compound E	0.3 mg/ml	Compound E
Compound E	1.0 mg/ml	Compound E
Compound E	1.5 mg/ml	Compound E
Compound E	3.0 mg/ml	Compound E
Compound E	10 mg/ml	Compound E

Table 23

Group	Swollen rate (%)	SD
Model	79.49	16.42
Dex	32.75	9.80
Compound E (0.1 mg/ml)	68.30	5.42
Compound E (0.3 mg/ml)	64.10	6.54
Compound E (1.0 mg/ml)	50.77	24.08
Compound E (1.5 mg/ml)	43.85	9.26
Compound E (3.0 mg/ml)	34.95	22.30
Compound E (10 mg/ml)	46.04	10.70

- 10 The results showed that Compound E was effective as an anti-inflammatory in the mouse ear swelling model and provides guidance for future clinical anti-inflammatory use. Compound E also has good dose dependence in anti-inflammation.

15

Example 35
Pain Relief in Radiation-induced Oral Mucositis

Two patients were undergoing radiotherapy treatment on the head and neck. Both patients experienced severe oral mucositis, diagnosed as grade 4 (most severe level) and oral mucosal ulcers. The patients also experienced high levels of pain and difficulties in eating. The patients were suggested to use 1 mg/ml x 5 ml Compound E solution three times a day as mouth rinse. After 5 days, both patients reported very positive feedback. The VAS score for pain was reduced from 8 to 1 for one patient, and 7 to 3 for the other patient. The latter patient also reported that the mucous in his mouth, which was caused by infection and inflammatory exudate, was reduced significantly. It has therefore, been shown that Compound E is effective for the treatment of oral mucositis.

10

Example 36Itch Relief in Neurodermatitis

A 28-year-old male was presented with a skin lesion with a constant itch and scaling on his left elbow. It was diagnosed as neurodermatitis a year ago. The patient had previously used glucocorticoids to treat the lesion, but its effects were temporary. The itch became worse when he was stressed. The patient tried 3 mg/ml of Compound E solution spray. After 1 spray on the lesion, the itching symptom was completely relieved after about 30 mins. The patient reported that the itching symptom had stopped during the day following administration.

20

Example 37Radiation Mucositis in Golden Hamster Model

32, 6 to 8 week old, healthy, male LVG Syrian Golden Hamsters with average body weights of 93-101 g (Beijing Chairs river Experimental Animal Technology Co., Ltd) were housed and cared for about 1 week prior to the experiment. Housing conditions: 25-27 °C, 74% humidity, 12h dark-light cycle, free access to food and water. The hamsters were randomly divided into 4 groups (8 hamsters in each group) as described in Table 24 below.

30 Table 24

Group	Test sample	Dose (mg/animal)	Concentration (mg/mL)	Volume (mL/animal)	Administration
Model	Placebo	-	-	0.2	Local oral administration BID
Compound E (low dose)	Compound E	0.02	0.1	0.2	

Compound E (medium dose)	Compound E	0.06	0.3	0.2	
Compound E (high dose)	Compound E	0.2	1	0.2	

After anesthesia, the left cheek pouch of the animal was pulled out and fixed on a self-made fixation device and exposed to radiation. The remaining parts of body were shielded by 3.5 mm thick lead. Radiation dose was 40 Gy (Precision X-ray Inc., X-RAD 320). The animals were put back into the cage after waking them up. Photos were taken and evaluated every two days. Evaluation was done according to Sonis' scoring criteria (0-Pouch was completely healthy with no erythema or vasodilation; 1-Erythema and vasodilation, but mucosa was intact; 2-Severe erythema with superficial mucosal erosion; 3-Formation of mucosal ulceration with a cumulative size of about 25% of the pouch's surface area; 4-Ulceration with a cumulative size of about 50% of the pouch's surface area; 5-Contiguous ulceration involving almost the entire surface area of the pouch mucosa). The results are shown in Table 25 below and in Figure 5.

Table 25

Group Day	Model	Compound E Low dose	Compound E Medium dose	Compound E High dose
Pre	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
Day 7	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
Day 9	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
Day 11	0.75±0.46	0.5±0.53	0.5±0.53	0.38±0.52
Day 13	1.50±0.53	1.38±0.52	1.38±0.52	1.38±0.52
Day 15	2.50±0.53	2.13±0.35	2.13±0.64	2.38±0.52
Day 17	3.25±0.46	3.13±0.35	3.13±0.35	3.13±0.35
Day 19	4.00±0.00	3.38±0.74	3.63±0.52	3.13±0.35**
Day 21	3.75±0.46	3.00±0.53*	3.00±0.00**	2.63±0.74**
Day 23	3.25±0.46	2.75±0.46*	2.63±0.52*	2.25±0.46**
Day 25	2.88±0.64	2.13±0.35*	1.88±0.35**	1.63±0.52**
Day 27	2.50±0.93	1.75±0.46*	1.50±0.76*	1.00±0.53**
Day 29	2.00±0.93	1.00±0.53**	0.88±0.83**	0.50±0.53**

Note: The data in the table were expressed as mean ± standard deviation (Mean ± SD), and 8 animals were used for statistical analysis in each group. * P<0.05, ** P<0.01 represent the comparison results between each treatment group and the model control group.

Compound E was shown to improve mucositis according to the Sonis' scoring criteria and SOM duration in radiation induced mucositis in hamsters. Compound E showed good dose dependence in this model. It was therefore shown that Compound E may alleviate patient symptoms associated with mucositis in clinical practice.

Example 38

Pain Relief in Sprague Dawley (SD) Rats

48, 7 to 8 week old, healthy male SD rats (Beijing Chairs river Experimental Animal Technology Co., Ltd) with average body weights of 180-220 g were housed and cared for about 1 week prior to the experiment. Housing conditions: 25-27 °C, 74% humidity, 12h dark-light cycle, free access to food and water. These rats were randomly divided into 6 groups (8 rats in each group) as described in Table 26 below and the results are shown in Figure 6.

Table 26

Group	Dose (mg/animal)	Concentration (mg/mL)	Volume (μL)	Administration
Normal Control	-	-	20	Local administration of medication to the affected area
Model Control	-	-	20	
Compound E	0.003/0.02/0.3	0.3/1/3	20	
Lidocaine	0.2	10	20	

All animals were trained in advance to allow rats to adapt to external stimuli. Then the oral mucosa ulcer was induced by acetic acid (Sigma-Aldrich). Von Frey filaments (Danmic Aesthesio) (0.008 g, 0.04 g, 0.02 g, 0.04 g, 0.07 g, 0.16 g, 0.4 g, 0.6 g, 1.0 g, 1.4 g, 2.0 g, 4.0 g) were used to stimulate the rat's ulcer area for mechanical pain threshold value measurement. Each level of stimulation was given continuously for 5 times with a 15 second interval between each test, until there were 3 or more positive reactions under a certain level of stimulation. The value was recorded as the mechanical pain threshold value. To prevent damage to the mucosa of rats and affect subsequent testing, the maximum detection intensity of von Frey was set to 4.0 g.

Compound E was shown to relieve acetic acid induced pain in SD rats and showed a pain relief effect equivalent to lidocaine. Compound E showed good dose dependence in this model. It has therefore been shown that Compound E may alleviate symptoms associated with ulcers of the oral mucosa in patients.

Example 39

5-FU Induced Oral Mucositis in SD Rats

40, 7 to 8 week old, healthy male SD rats with average body weights of 180-220 g (Hangzhou Ziyuan Experimental Animal Technology Co., Ltd. Hangzhou, China) were housed and cared for about 1 week prior to the experiment. Housing conditions: 25-27 °C, 74% humidity, 12h dark-light cycle, free access to food and water. The rats were randomly divided into 5 groups (8 in each group) as described in Table 27 below.

Table 27

Group	Dose (mg/animal)	Concentration (mg/mL)	Volume (μL)	Administration
Normal control	-	-	20	Local administration of medication to the affected area. BID
Model control	-	-	20	
Compound E	0.006/0.02/0.06	0.3/1/3	20	

Three days before injection of test compounds, rats were intraperitoneally injected with 5-FU (MCE, China), with a dosage of 50 mg/kg and a dosage volume of 2 ml/kg. One day before injection of test compounds, rats were intraperitoneally injected with further 5-FU followed by inhalation of 2.5% isoflurane (Sigma-Aldrich) to anesthetize the animals.

The animals were placed in the right supine position and the upper and lower jaws of the rats were opened using a self-made mouthpiece to expose the right cheek mucosa. 6 mm filter paper was placed on the right cheek mucosa, and 80% acetic acid (5μL, Sigma-Aldrich) was dripped onto the filter paper. After maintaining contact for 20 seconds, the filter paper was removed and the residual liquid on the cheek mucosa was wiped with a cotton swab. The sham surgery group used the same method but with 5 μL saline dripped onto the filter paper.

After 24h of treatment with acetic acid, the ulcer scores in all animals except those in the sham group were assessed and re-grouped accordingly. The animals were treated according to the study plan described in Table 27, and assessed using the following criteria every day: 0-Normal mucosal appearance, without erythema or congestion; 1-The oral mucosa has erythema or congestion, but the mucosa is intact; 2-Large area erythema of

oral mucosa with punctate diffuse ulcers; 3-Oral mucosal flake ulcer covering an area less than 1/4 of the cheek mucosal area (+); 4-Oral mucosal ulcer covering an area less than 1/2 of the buccal mucosa (++) ; 5-Buccal mucosal ulcers larger than half of the area (+++).

- 5 The results (Figure 7) show that Compound E improved the 5-FU and acetic acid induced mucositis score in SD rats and accelerated the recovery of the ulcers in mucosa. Compound E showed good dose dependence in this model. It has therefore been shown that Compound E may alleviate patient symptoms associated with mucositis in clinical practice.

10 Example 40

Wound Healing Effect - cell scratch assay in HaCaT

- Once the cell laying rate reached 40%-60% in a 96 well plate, the following were added: 200 μ L culture medium containing 10% PBS (Sigma) was added to each well in the control group; 200 μ L culture medium containing 10% DMSO was added to each well in the positive control group; 200 μ L culture medium containing corresponding concentration samples was added to each well of the sample group; and 200 μ L cell culture medium was added to the zero group without cell inoculation. After administration, the 96 well plate was placed in a culture incubator (37 °C, 5% CO₂) for cultivation. After 24 hours of cell incubation, the supernatant was discarded and MTT working solution (0.5 mg/mL) was added. The 96 well plate was incubated at 37 °C in the dark for 2 hours. After incubation, the supernatant was discarded and 100 μ L of DMSO was added to each well. The OD value was read at 490 nm.

- The results showed that Compound E presented no cytotoxicity in its efficacious dose.

- 25 200 μ L Pipette gun hangs were used on a 24 well plate covered with cells and marked "damage". The cells were washed with PBS three times to remove the scratched cells. After treatment with Compound E at concentrations of 0.001%, 0.004%, and 0.008% (m/V), the cell healing rate of the human skin immortalized keratinocytes (HaCaT) (ATCC) significantly increased ($p < 0.01$), indicating that Compound E is effective in cell repair. It has therefore been shown that Compound E effectively promotes cell healing in vitro, which corresponds to the in vivo results, and that Compound E could effectively promote healing in clinical practice.

35 Example 41

No Immunosuppression Effect – in vitro Peripheral Blood Mononuclear Cells (PBMC) Study

PBMC were resuscitated and stained with Celltrace. The T cell concentration was adjusted to 0.1M per well (50 μ L) using the 1640 full culture medium. 50ul of LPS (Sigma-Aldrich) was added to the cells four times. 100 μ L of blank culture medium/Compound E or dexamethasone of different concentrations/culture medium containing 0.4% DMSO+highest concentration was added to the corresponding holes separately. The LPS group was incubated for 24 hours. The cell supernatant was collected to detect the secretion of relevant inflammatory factors. Flow cytometry was used to detect cell proliferation and viability.

The results showed that under the conditions of this experiment, Compound E does not have an immunosuppressive effect. Compared to dexamethasone, Compound E did not cause an immunosuppressive effect and is therefore safer for clinical use by reducing the risk of infection.

Example 42
in vitro Anti-inflammatory Effect in Keratinocytes

The culture medium was added to the blank control group; a culture medium containing LPS (Sigma-Aldrich) was added to the model control group; a culture medium containing LPS and dexamethasone was added to the positive control group; and a culture medium containing LPS and a certain concentration of Compound E was added to the sample group. The groups were exposed for 24 hours. After incubation, the cell supernatant was collected and stored in a -80 $^{\circ}$ C ultra-low temperature freezer. The content of IL-1 α , IL-6, IL-8, and TNF- α was measured according to the instructions of the ELISA kit (R&D Systems).

The results showed that Compound E effectively reduced inflammatory factors in keratinocytes and therefore, indicates that Compound E could be useful in alleviating inflammation associated with clinical skin diseases.

Example 43
in vitro Anti-inflammatory Effect in Macrophages

The culture medium was added to the blank control group; a culture medium containing LPS (Sigma-Aldrich) was added to the model control group added; a culture medium containing LPS and dexamethasone was added to the positive control group; and a culture medium containing LPS and a certain concentration of Compound E was added to the sample group. The groups were exposed for 24 hours. After incubation, the cell supernatant was collected and stored in a -80 $^{\circ}$ C ultra-low temperature freezer. The levels

of IL-6, TNF- α , and NO were measured according to the instructions of the ELISA kit (R&D Systems).

The results showed that Compound E effectively reduced inflammatory factors in macrophages and therefore, indicates that Compound E could be useful alleviating inflammation associated with clinical diseases.

Example 44

in vitro Oil Control of Sebaceous Gland Cells

10

2 mL of the cell culture medium was added to the blank control group; 2 mL of cell culture medium containing linoleic acid (MCE, China) was added to the model group; 2 mL of cell culture medium containing linoleic acid and retinoic acid was added to the positive control group; and 2 mL of cell culture medium containing linoleic acid and test concentration samples was added to the sample group. The groups were incubated in a carbon dioxide incubator for 48 hours. After incubation, the supernatant was discarded, 1 mL of PBS was added dropwise to clean the cell layer, 500 μ L of paraformaldehyde was added to fix at room temperature for 5 minutes, the cell layer was washed twice with 1 mL of PBS, 500 μ L of Nile Red dye was added, and incubated at 37 $^{\circ}$ C in the dark for 15 minutes. The cell layer was washed twice with 1 mL PBS and the cells were observed under an inverted phase contrast fluorescence microscope and photos were recorded.

The results showed that Compound E was effective in controlling the oil content of sebaceous gland cells. It has therefore, been shown that Compound E may effectively reduce oil secretion in the patient's skin for clinical use.

Example 45

Acute Oral Toxicity in Institute for Cancer Research (ICR) mice

30

The animals (Beijing Chairs River Experimental Animal Technology Co., Ltd) were divided into two cages, male and female, with 5 animals in each cage. Before the experiment, animals were fasted overnight and there were no restrictions on drinking water. Using a maximum limit experiment, animals were weighed and administered the toxin by gavage, at a capacity of 2 mL/100g and a dose of 5000 mg/kg body weight. The animals were poisoned once in 24 hours. After being poisoned, the animals were fasted for 3h-4h. After being poisoned, the abnormal situation of the animals was observed every day, and autopsies were performed on the dead animals during the observation period and the

animals were euthanized at the end of the observation period. The tissues and organs were observed for abnormalities with the naked eye and histopathological examination was conducted when necessary. The results are shown in Table 28 below.

5 Table 28

Toxicity data of Compound E in ICR mice								
Sex	Dose (mg/ kg)	Weight (g)				Toxic Manifest ations	Mortality	Autopsy Abnormalitie s
		D0	D1	D7	D14			
F	5000	19.1	19.7	25.2	33.3	-	0	-
M	5000	19.4	20.1	26.3	35.6	-	0	-

The results show that the LD50 of Compound E is more than 5000 mg/kg in ICR mice, and according to the acute oral toxicity grading, it is non-toxic. It has therefore, been shown
10 that Compound E is safe at a very high dose in ICR mice, and based on previous animal data, Compound E also has good safety in a clinical setting.

Example 46

Acute Percutaneous Toxicity in SD rats

15

The animals (Beijing Chairs River Experimental Animal Technology Co., Ltd) were divided into two cages, male and female, with 5 animals in each cage. The test area was approximately 30-40cm². Before the experiment, the animals were acclimated to the experimental animal room environment for 3 days to ensure that the enrolled animals were
20 healthy and had no skin damage. About 24 hours before the experiment, the fur on the back of the animal's trunk in the area to be contaminated was cut off. When removing the fur, it was ensured that the skin was not damaged. The experiment adopted a maximum limit test, with a toxic dose of 2180 mg/kg; After weighing the animal, the test substance was moistened with water and applied evenly to the contaminated area of the animal's
25 back skin. The skin was covered with a thin film and fixed with non-irritating adhesive tape. The skin was closed and covered from contact for 24 hours. After poisoning, the residual test substance was removed with warm water. After being poisoned, the abnormal situation of the animals was observed every day, and autopsies on the dead animals were performed during the observation period and the animals euthanized after the observation period.
30 The tissue was observed with the naked eye for abnormalities, and if necessary,

histopathological examination was performed. The observation time was 14 days. The weight of active objects was recorded during the observation period at 0 days, 1 day, 7 days, and 14 days (D0-14). The results are shown in Table 29 below.

5 Table 29

Acute Percutaneous Toxicity Results								
Sex	Dose	Weight (g)				Toxic Manifestations	Mortality	Autopsy Abnormalities
		D0	D1	D7	D14			
F	2180 mg/kg	203.8	204.7	210.2	216.6	-	0	-
M	2810 mg/kg	206.6	207.5	214.1	219.9	-	0	-

The results show that the LD50 dose of Compound E in SD rats is more than or equal to 2180 mg/kg, indicating slight toxicity. It has therefore, been shown that Compound E is safe at a high dose in SD rats, and based on previous animal data, Compound E has good safety in clinical use.

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Example 47

Human Acne Efficacy of Compound E

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Compound E was applied to adult subjects for 28 consecutive days under normal conditions according to the instructions to evaluate whether the product showed efficacy in acne reduction, oil control, moisturizing, repair, and soothing, and whether it was gentle (non-irritating) and suitable for sensitive skin. A total of 32 Chinese adult males and females with sensitive skin, including 7 males and 25 females, aged from 19 to 43 years old (mean age 27.91±6.82) were used and all met the inclusion and exclusion criteria. A fingertip unit of Compound E was used twice a day for a total of 28 days. The dosage of cream is based on the fingertip unit (FTU), and 1 fingertip unit refers to the amount of cream from the index finger to the first interphalangeal joint squeezed from 5 mm open tube (approximately 0.5g).

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25

An image capture was taken with VISIA 7 to analyze the skin color, redness area and porphyrin with IPP. An image capture was taken to analyze acne volume with Antera 3D (Miravex Limited, Ireland). Skin hydration was measured with Corneometer®CM825 (Courage+Khazaka electronic GmbH,Germany). Skin transepidermal waterloss was

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measured with Tewameter ®TM HEX 5 (Courage+Khazaka electronic GmbH,Germany). Skin sebum was measured with Sebumeter SM 815 (Courage+Khazaka electronic GmbH,Germany). A dermatologist assessment and self-assessment was taken.

- 5 The results are shown in Tables 30 and 31 below.

Table 30

Item	Change value			Change rate		
	D3	D7	D28	D3	D7	D28
Whiteheads	-2.75	-3.75	-5.44	-29.83%	-40.68%	-58.98%
Blackheads	-0.91	-0.94	-0.94	-96.67%	-	-
					100.00%	100.00%
Non-inflammatory lesions	-3.66	-4.69	-6.38	-36.00%	-46.15%	-62.77%
Papules	-0.25	-0.25	-0.28	-88.89%	-88.89%	-
						100.00%
Pustules	-0.16	-0.47	-0.88	-12.50%	-37.50%	-70.00%
Nodules	-0.38	-0.63	-0.78	-38.71%	-64.52%	-80.65%
Inflammatory lesions	-0.78	-1.34	-1.94	-31.25%	-53.75%	-77.50%
Non-inflammatory and inflammatory lesions	-4.44	-6.03	-8.31	-35.06%	-47.65%	-65.68%
Overall healthy appearance	0.00	-0.03	-0.53	0.00%	-1.00%	-17.00%
PIH-PIE	-0.05	-0.08	-0.42	-1.46%	-2.43%	-13.11%
Redness	0.00	-0.13	-0.72	0.00%	-4.00%	-23.00%

- 10 Table 31

Efficacy indicators	Compound E vs baseline
Whitehead	Days 3, 7, 28 had statistical differences
Blackhead	Days 3, 7, 28 had statistical differences
Papules	Days 3, 7, 28 had statistical differences
Abscess	Day 28 had statistical differences

Nodules	Days 7, 28 had statistical differences
Acne volume	Days 3, 7, 28 had statistical differences
Skin redness	Redness area on Days 3, 7, 28 had statistical differences
Porphyrin	No statistical differences
Skin oil content	Day 28 had statistical differences
Skin stratum corneum moisture content	Day 7, 28 had statistical differences
Transdermal moisture loss rate	Day 28 had statistical differences

Of the 32 Chinese male and female subjects with sensitive skin, the results showed that under the evaluation conditions, the product has anti-acne, oil controlling, moisturizing, repairing, and soothing effects, and is mild (non-irritating) and suitable for sensitive skin.

- 5 It has therefore, been shown that Compound E could effectively alleviate acne and has significant skin benefits for patients using it.

Example 48

Human Gingivitis Efficacy of Compound E (ongoing)

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The aim of the clinical study was to test the efficacy of Compound E as a novel raw material for use in a Gum-protecting peptide mouthwash and for the control of gingivitis. Seventy subjects with gingivitis aged 18 to 60 years were included in this study, with an estimated number of ≥ 60 subjects completing the whole study, i.e. ≥ 30 per group.

15

The Inclusion criteria was: 1) Good general condition and no systemic diseases; 2) Aged 18 to 60 years, male or female; 3) Having more than 20 intact teeth, no large restorations at the gingival margin, untreated cavities and severe gingival recession and severe periodontal diseases; 4) Modified Quigley-Hein plaque index ≥ 1.5 ; 5) Loe-Silness gingival index ≥ 2.0 , bleeding index ≥ 2.0 .

20

Clinical Evaluation Criteria and Methods:

1) Plaque index (PI): 0 = No plaque; 1 = Separate flecks of plaque at the cervical margin of the tooth; 2 = A thin, continuous band of plaque (up to 1 mm wide) at the cervical margin; 3 = A band of plaque wider than 1 mm but covering less than 1/3 of crown; 4 =

25

Plaque covering at least 1/3 but less than 2/3 of crown; 5 = Plaque covering 2/3 or more of crown.

2) Gingival index (GI): 0 = Normal gingiva; 1 = Mild inflammation, slight change in color, slight edema, no bleeding on probing; 2 = Moderate inflammation, glazing gingiva, redness, edema, hyperplasia, or bleeding on probing; 3 = Severe inflammation, marked redness, edema, tendency toward spontaneous bleeding.

3) Bleeding index: 0 = Healthy looking gingiva, no inflammation and bleeding; 1 = Inflammatory changes in color, no bleeding on probing; 2 = Spot bleeding after probing; 3 = Bleeding spreads towards the marginal gingiva after probing; 4 = Bleeding fills and spills over the sulcus; 5 = Spontaneous bleeding.

The test product was the mouthwash composed of the following ingredients: 0.05% ammonium chloride, 0.02% galactose trichloride, 0.01% water-soluble menthol, 0.03% Compound E and water for injection. The placebo was the same formulation without Compound E. The pH of the mouthwash was 6.0.

All subjects were provided with soft toothbrushes, toothpaste and randomized into the test product group or placebo group. After baseline data collection, the subjects were instructed to apply toothpaste to the entire length of the brush head and brush for 3 minutes by using the designated toothpaste and toothbrush twice a day, once in the morning and once in the evening after meals. They were instructed to then use 10 ml of mouthwash 30 seconds after brushing, rinse thoroughly and spit out the mouthwash and refrain from eating or drinking for 30 minutes. The efficacy was evaluated after 1 month. The plaque index, gingival index (GI), bleeding index were evaluated by dentists. The efficacy was expressed as the mean index scores of each group.

The results showed that the Plaque index, gingival index (GI) and bleeding index in the Compound E group were lower than that in placebo group after 1 month of treatment (test vs placebo were 1.22 ± 0.76 vs 1.87 ± 0.60 ; 1.42 ± 0.8 vs 1.77 ± 0.95 ; 1.69 ± 0.12 vs 2.19 ± 0.59).

It has therefore, been shown that Compound E is effective in alleviating gingivitis and has significant benefits for patients using it.

Example 49

Efficacy on Seborrheic Dermatitis of the Scalp of Compound E

The test product was prepared as described in Example 27 above. 66 healthy subjects aged 25 to 60 years were included in the study, with an estimated number of ≥ 60 subjects completing the whole study, i.e. ≥ 30 per group.

- 5 The Inclusion criteria was: 1) Hair length $\geq 3\text{cm}$, 2) No severe hair loss, with hair roots covering at least 70% of the scalp, 3) Dandruff level ≥ 3 points, 4) Self perceived itching and redness on the scalp.

10 The test subjects were randomly divided into the test group and placebo group. After 2 weeks wash off period, when the subjects washed their hair every two days using the provided shampoo, they started to use the test product, Compound E Hair Care Essence or the placebo. The test product was applied evenly to the scalp using a scalp applicator in a dry hair state, once a day, 3 ml each time. If the product was used after washing hair, it was necessary to dry the hair before use.

15 The efficacies were evaluated after 28 days. Evaluation included the measurement of scalp skin oil content (Sebumeter SM815, Courage+Khazaka electronic GmbH, Germany), stratum corneum moisture content (Corneometer CM825, Courage+Khazaka electronic GmbH, Germany), and transdermal water diversion loss rate (Tewameter, 20 Courage+Khazaka electronic GmbH, Germany) by laboratory technicians. General scalp condition, itching, dandruff, dryness and redness were evaluated by a dermatologist.

The results show that Compound E could effectively control the secretion of oil, increase the water contain and repair the skin barrier in the scalp. It could also relieve itching, 25 reduce the severity dandruff, reduce the dryness and redness of scalp (Table 32 below).

Table 32

Parameter	Rate of change	Significant difference compared with D0	Improved subjects (improved rate %)
Skin hydration	28.56%	significant	30 (100%)
Skin trans epidermal water loss	-15.35%	significant	30 (100%)
Skin sebum	-28.26%	significant	30 (100%)

- 30 It has therefore, been shown that Compound E is effective in relieving symptoms related to seborrheic dermatitis and has significant benefits for patients using it.

Example 50Acne Rosacea Treatment

- 5 A 31-year-old female was diagnosed with rosacea. The patient had small pink or red bumps on her face. Redness (blushing) appeared around her mouth, and she felt warm, hot, itchiness or pain. A burning or stinging feeling could be felt when using water or skincare products. She used Compound E cream (as described in Example 26) twice daily for 7 days. The redness and itchiness were relieved, and the bumps disappeared (Figure 8).

10

Example 51Gastroesophageal Reflux (GERD) in Rats

Test compounds:

- 15 Compound K: (Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys)₂-Lys (SEQ ID No: 113)
Compound L: Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys(Palm)-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys(Palm)
(SEQ ID No: 115)
Compound M: Montelukast-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys(Palm) (SEQ ID No: 2)

20

Twenty SPF grade, male Wistar rats, weighing 280-350 g were provided by Zhejiang Charles River Experimental Animal Technology Co., Ltd., Certificate No.: 20211103Aaz0600000356.

- 25 Before surgery, the rats were housed and cared for about for 1 week prior to the experiment. The housing temperature was 25-27°C with 74% humidity, with alternating 12-hour periods of light and darkness, and free access to food and water.

- The rats were randomly divided into 5 groups, with 4 rats in each group. The groups were
30 as follows: sham group, model group, compound K, L and M groups. The rats were anesthetized with 2% isoflurane inhalation and placed into a supine position. The surgical area was shaved with a hair clipper and the skin was disinfected with iodophor. A 2 cm incision was made along the midline of the abdomen, 0.5 cm below the xiphoid to open the abdominal cavity and expose the surgical field. The connective tissues were separated
35 and cut between the liver and the stomach. The vessel bundle was ligated and cut between the spleen and the fundus to completely free up the fundus. The fundus was turned slightly to the left, exposing the left side of the gastroesophageal junction in the field. A 5 mm

longitudinal incision was made on the muscle along the distal esophagus using a pair of sharp scissors to expose the gastroesophageal junction.

The dorsal side of the esophagus was gently separated from the blood vessels behind the esophagus. A small cotton tip was passed between the esophagus and blood vessels. Two 5 mm longitudinal incisions were made on each of the gastroesophageal junction and the proximal end of duodenum adjacent to the pylorus with sharp operating scissors. For the incision on the duodenum, blood vessels were avoided and placed on the anti-mesenteric border. The incisions were anastomosed with accurate mucosal to mucosal opposition using interrupted 8-0 Prolene sutures. 3-4 sutures were placed on the dorsal side and 2-3 sutures on the front side. The abdominal cavity was washed with normal saline and the abdominal wall and the skin was closed. The surgery was performed for each rat except for those in sham surgery group. After anesthesia and laparotomy, the lower esophagus, duodenum, and gastric fundus were separated in the sham surgery group, without incision.

Postoperative fasting and water deprivation was done for 30 hours, the rats were given glucose injection via tail vein infusion, 8 ml/animal, once a day, for 2 consecutive days. The rats were given intramuscular injection of 50000 IU of penicillin once a day to prevent infection, continuously administered for 3 days. 1 week after the operation, different interventions were given to the rats by gavage, according to Table 33 below.

Table 33

Group	Intervention	Dose	Volume	Concentration
Sham	Normal saline	/	2 ml	/
Model	Normal saline	/	2 ml	/
Test 1	Compound K	10 mg/kg	2 ml	50 mg/ml
Test 2	Compound L	10 mg/kg	2 ml	50 mg/ml
Test 3	Compound M	10 mg/kg	2 ml	50 mg/ml

500 mg of Compounds K, L and M (GL Biochem, Shanghai, China) were fully suspended in 10 ml 0.5% CMC-Na (Sodium Carboxymethyl Cellulose, Chemical Reagent Co., Ltd. China) solution respectively, to obtain a 50 mg/ml concentration of the three testing solutions.

The interventions were given once daily for 2 weeks. The body weights were measured every three days. After two weeks of interventions, the animals were scarified, and the chest cavities were opened. The esophagus was peeled off and longitudinally cut open, to

expose the anastomotic site. The severity of esophagitis was evaluated according to the scoring criteria in Table 34 below.

Table 34

5

Erosion (mm)	1 or less	1 to 2	2 to 3	More than 3
Score	1	2	3	4

The results for the severity of esophagitis are shown in Figure 9, showing that montelukast and pranlukast could reduce the severity of esophagitis in a GERD model in rats.

10 Example 52

PK Study: Instrument Assisted Transdermal Administration

Test samples:

Compound E: 1mg Compound E dissolved in 1 ml normal saline to make a 1 mg/ml solution.

- 15 Compound E + PL429: PL429 (Guangzhou Jizhou Trading Co., Ltd) is a transdermal enhancer. 0.5% PL429 was added into the above solution.

27 SPF grade, male SD rats, weighing 250-300 g were provided by Zhejiang Charles River Experimental Animal Technology Co., Ltd., and were housed and cared for about 1 week prior to the experiment. The housing temperature was 25-27 °C with 74% humidity and a 12h dark-light cycle and had free access to food and water. The rats were randomly divided into 3 groups as described in Table 35 below, 9 rats in each group with 3 sample collection points in each group.

25 Table 35

Group	Concentration (mg/mL)	Dose (mg)	Dose (mg/cm ²)	Administered Amount (mL/g)	Sample Collection
Compound E	1	0.2	0.02	0.2	0.25h, 0.5h, 1h after administration. 3 rats for each collection.
Compound E + PL429					
Compound E + instrument					

The instrument used was a high pressure transdermal nutrition supplement instrument (Guangzhou Tuonasi Beauty Instrument Co., Ltd, China).

- 5 The hair on the administration site (left back skin of the spine) was shaved with an area of 4.0 cm². The area of the administration was 3 cm² which was marked. The administration was on the intact skin (without any damage).

- Sample processing: Approximately 200 µL of the whole blood was collected from the carotid arteries of each group of animals at each time point and injected into an EP tube containing EDTA-K anticoagulant. Immediately, it was manually shaken and placed in wet ice. The samples were centrifuged at 1800g, 4 °C for 10 minutes. Within 2 hours, the plasma was separated and stored at -80 °C. At the same time, the skin tissue from the administration site was collected. Before collecting the tissue samples, site was cleaned with normal saline and the water was dried. After collection, the samples were stored at -80 °C for further analysis.

The results are shown in Table 36 below.

20 Table 36

Compound E concentration in plasma (ng/mL)			
Group/Time	0.25h	0.5h	1h
Compound E	7.37	7.03	0.84
Compound E + PL429	11.60	3.10	4.60
Compound E + Instrument	12.70	8.02	5.30
Compound E concentration in skin (ng/mL)			
Group/Time	0.25h	0.5h	1h
Compound E	19633	20433	28267
Compound E + PL429	18700	20433	19677
Compound E + Instrument	25867	27692	20653

- The results show that a major amount of Compound E had remained in skin tissue after topically applying on the skin. Neither transdermal enhancer nor the instrument could significantly increase the plasm exposure. But the instrument could enhance local concentration. This is shows a beneficial property for the topical application of Compound E.

Example 53Skin pigmentation: instrument assisted transdermal administration-1

Test sample:

- 5 Compound E: 1 mg of Compound E dissolved in 1 ml of normal saline to make a 1 mg/ml solution.

Instrument:

- 10 Dermashine pro (Huons Meditech, Republic of Korea), an automatic mesotherapy injector using vacuum pressure. It has been used for replenishing moisture and nutrition to the skin.

- A 56-year-old woman was presented with pigment deposition on her checks after a beach trip. During her staying on the beach, the subject was exposed to the sun, causing
15 reddening of the skin. After a few days, pigmentation was present. The subject went to a beauty salon for treatment. The subject was treated with Compound E by Dermashine injection to the whole face. The solution was filtrated by a 0.22 μ m Minisart®High Flow filter (Sartorius, Germany). A total of 3 ml of solution was injected. The treatment was repeated after 2 weeks. A week after the second injection, the pigmentation disappeared,
20 and the dullness and roughness of the skin had improved significantly.

Example 54Skin pigmentation: instrument assisted transdermal administration-2

- 25 Test sample:

Compound K: (Palm-Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys)₂-Lys (SEQ ID No: 113) was dissolved in normal saline to make a 1 mg/ml solution.

- A 32-year-old woman was presented with pigmentation on both of her checks after giving
30 birth to a baby girl. 6 months after the birth, she sought treatment for her face. The subject went to a beauty salon and was recommended to use a non-invasive treatment with the above-mentioned solution. A High-pressure transdermal nutrition supplement instrument (Guangzhou Tuonasi Beauty Instrument Co., Ltd, China) was used to enhance the absorption of the solution. The treatment was conducted every week. After two months,
35 the skin became tight and flawless.

Example 55LPS induced lung injury in rats

Test compounds:

Compound N: DPPS-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 7)

Compound O: LTB4-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 8)

5 Compound M: Montelukast-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys(Palm) (SEQ ID No: 2)

A total of 67 male SD rats were randomly assigned into a normal control group (10 rats) and a model group (57 rats) for the first grouping according to animal weight. The animals
10 in the normal control group were intraperitoneal injected and intra-trachea nebulized with sodium chloride injection. The animals in the model group were intraperitoneal injected and intra-trachea nebulized with lipopolysaccharide (LPS) to induce the model of acute lung injury (intraperitoneal injection of 2 mg/kg on Day 0, intra-trachea nebulization of 4 mg/kg on Day 1, with an interval of about 16 hours). On Day 1, after the LPS was nebulized
15 into the trachea of the animals, the animals in the model group were randomly assigned again into: vehicle control group according to weight; test article Compound N group (0.5 mg/kg); test article Compound O group (0.5 mg/kg); test article Compound M group (0.5 mg/kg); and positive control group (2.5 mg/kg). The normal control group was no longer grouped again. Both the normal control group and the vehicle control group were given
20 intravenous injection of 0.9% sodium chloride injection; the test article Compound N, Compound O and Compound M groups were given intravenous injection of the corresponding dose once daily for 1 day; and animals in the positive control group were intraperitoneally injected with dexamethasone sodium phosphate injection once daily for 1 day. On Day 2, the animals were anesthetized and euthanized, and the lung lavage fluid
25 test and lung weight index test were performed.

The bronchoalveolar lavage fluid (BALF): Compared with the corresponding indicators of animals in the vehicle control group, showed that the mean values of WBC, Neut, Lymph and Mono of animals in test article Compound N, Compound O and Compound M groups
30 and positive control group were significantly reduced. The maximum decreases in WBC were about 62%, 74%, 84% and 87%, respectively, with statistical differences. The maximum decreases of Neut were about 73%, 79%, 92% and 93%, respectively, with statistical differences. The maximum decreases of Lymph were about 65%, 76%, 82% and 84%, respectively, with statistical differences. The maximum decrease of Mono were about
35 71%, 85%, 88% and 91%, respectively, with statistical differences.

Total protein: Compared with the total protein in BALF of animals in the vehicle control group, the mean values of total protein of the animals in the test article Compound N,

Compound O and Compound M groups, and positive control group showed a significant decrease. The maximum decreases of total protein were about 68%, 72%, 77% and 56%, respectively, with statistical differences.

5 Lung weight index: Compared with the lung weight index of animals in the vehicle control group, the mean values of lung weight index of the animals in the test article Compound N, Compound O and Compound M groups, and positive control group showed a significant decrease. The maximum decreases of lung weight index were about 20%, 23%, 25%, and 29%, respectively, with statistical differences.

10

Inflammatory factors: Compared with the serum and BALF, inflammatory factors (Ang-2, LTD4) of animals in the vehicle control group, the test article Compound N, Compound O and Compound M groups, and positive control group significantly decreased. The maximum decrease of Ang-2 in the serum was about 25%, 31%, 40% and 46%, respectively. The maximum decrease of Ang-2 indicators in the BALF was about 25%, 27%, 37% and 55%, respectively, with statistical differences in the positive control group. The maximum decrease of LTD4 indicators in the serum was about 35%, 32%, 37% and 32%, respectively. The maximum decrease of LTD4 in BALF was about 5%, 15%, 10% and 25%, respectively.

20

In summary, under the conditions of this study, the test articles that were administered Compound N, O and M intravenously once a day at doses of 0.5 mg/kg reduced the total white blood cell count, neutrophil count, total protein, lung weight index, Ang-2 and LTD4 in serum and BALF indicators in acute lung injury model rats, indicating that the compounds are effective in treating acute lung injury.

25

Example 56

Compound P Foam: (Palm-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys)₂-Lys (SEQ ID No: 114)

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The preparation of the Compound P Foam contained a mixture of the following substances in Table 37 below.

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Table 37

Phase	Material	Amount (%)
-------	----------	------------

A1	Tween-80	3.0
A2	Hydroxypropyl methyl cellulose (HPMC)	0.5
A3	Glycerin	5.0
A4	Benzyl alcohol	1.0
A5	Pure water	90.4
A6	Compound P	0.1
B1	Sodium hydroxide	

The ingredients of phase A were mixed and stirred for 30 minutes, until the system was uniform. Sodium hydroxide was added to adjust the pH of the solution to 6.5.0 while stirring to obtain the Compound P Foam.

5

This foam is intended to be used as an anti-inflammatory for the repairing of vaginal mucosa damages caused by disorders and operation.

Example 57

10 Compound P Gel: (Palm-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys)₂-Lys (SEQ ID No: 114)

The preparation of the Compound P Gel contained a mixture of the following substances in Table 38 below.

15 Table 38

Phase	Brand name	INCI name	Amount (%)
A1	Pure water	AQUA	81.23
A2	Propanediol	PROPYLENE GLYCOL	13.40
A3	Glycerin	GLYCERIN	2.60
A4	Carbomer 940	KABOMUER	0.67
A5	Carbomer 941	KABOMUER	0.13
A6	Triethanolamine	TRIETHANOLAMINE	0.80
A7	4-Hydroxyacetophenone	HYDROXYACETOPHENONE	0.50
A8	1,2-Hexanediol	HEXANEDIOL	0.50
A9	Sodium Hyaluronate (1.5M Da)	SODIUM HYALURONATE	0.07
A10	Compound P		0.10

The ingredients of phase A were mixed, heated to 80 °C and stirred for 30 minutes at 80°C. The sample was allowed to cool down until the system was uniform to obtain the Compound P Gel.

- 5 This gel is intended to be used as anti-inflammatory in the repairing of colorectal mucosa damages caused by disorders and operation.

Example 58

Compound P Tablet: (Palm-Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys)₂-Lys (SEQ ID No:

10 114)

The preparation of the Compound P Tablet contained a mixture of the following substances in Table 39 below.

15 Table 39

Phase	Material	Amount (%)
A1	β -cyclodextrin	6.0
A2	Mannitol	20.0
A3	Citric acid	3.0
A4	Polyvinylpyrrolidone cross-linked	7.0
A5	Starch	62.9
A6	Compound P	0.1
B1	50% Ethyl Alcohol	Q.S.
C1	Magnesium stearate	1.0

The ingredients of phase A were sieved through a 100-mesh sieve. The pharmaceutic adjuvants were added to the Compound P in sequence and mixed evenly. 50% ethyl alcohol was used as a wetting agent while adding the pharmaceutic adjuvants, and the mixture was stirred continuously to make it evenly wetted. The humidity of the material was adjusted to make a soft material that could be kneaded into a ball by hand and dispersed when lightly pressed. The prepared soft material was sieved through a 20-mesh standard sieve to obtain wet granules.

25

The prepared wet granules were evenly spread on a tray with a granule layer thickness of 2 cm to 3 cm. The granules were dried at 55°C for 1 h, turning the granules over every 15 min to speed up the drying process and ensure uniform drying until the moisture content was below 3%.

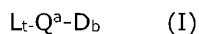
The dried granules were sieved again, sized, mixed with a certain amount of lubricant magnesium stearate, and put into a tablet press for tableting to obtain the Compound P Tablet.

5

This tablet is intended for use as an anti-inflammatory and the repairing of gastrointestinal tract mucosa damages caused by disorders and operation.

Claims

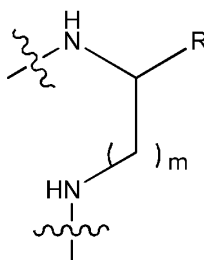
1. A compound of Formula I,



5 wherein:

Q^a represents Z or A-Q-B;

Q is a structural fragment of Formula II,

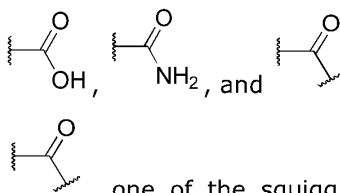


(II)

wherein:

10 the squiggly lines represent points of attachment of Q to A and/or B;

R is selected from the group consisting of:



wherein, when R represents , one of the squiggly lines represents a point of attachment to the rest of the Q fragment, and the other squiggly line represents a point of

15 attachment to a Z group;

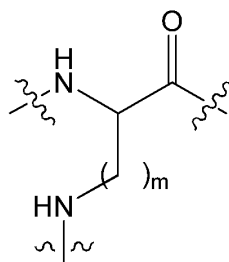
m represents an integer 1 to 4;

A and B independently represent Z or $A^1-Q^1-B^1$;

A^1 and B^1 independently represent Z or $A^2-Q^2-B^2$;

A^2 and B^2 independently represent Z or $Z-Q^3-Z$;

20 Q^1 , Q^2 and Q^3 independently represent structural fragments of Formula III,



(III)

wherein:

the squiggly lines adjacent to the NH groups represent the points of attachment of Q^1 , Q^2 and Q^3 to A^1 and/or B^1 , A^2 and/or B^2 , and Z, respectively;

the squiggly line adjacent to the C=O group represents the point of attachment of Q¹, Q² and Q³ to Q, Q¹ and Q², respectively;

m is as defined above;

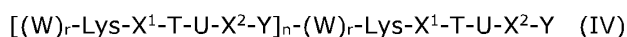
each L independently represents one or more lipids selected from the group consisting of vitamin A, vitamin E, cholesterol and a fatty acid comprising one or more carboxylic acid groups, 1 to 50 carbons, and/or one or more cyclic rings, is linear or branched, saturated or unsaturated with between 1 and 10 carbon-carbon double bonds and/or substituted by between 1 to 10 -OH groups, or a derivative of any of these lipids;

t represents an integer selected from 1 to 32;

10 D represents montelukast;

b represents an integer selected from 0 to 16;

on each occasion that it is employed above, Z represents a structural fragment Formula IV,



15 (SEQ ID No: 1)

wherein:

n represents an integer selected from 0 to 4;

on each occasion that it is employed, r independently represents 0 or 1;

on each occasion that it is employed, W independently represents a 1 or 2 amino acid sequence selected from one or more of the group Ser, Lys, Ala, DOPA and a 3,4-dihydrocinnamic acid (HCA) residue, provided that, when present, the HCA residue is located at the N-terminus of Z;

X¹ independently represents Pro, Hyp or diHyp;

T independently represents Ser or pSer;

25 U independently represents Tyr, pTyr, DOPA, Hyp, or Pro;

X² independently represents Thr, Ser, Pro, Hyp or diHyp;

Y independently represents a 1 to 5 (such as 1 to 4) amino acid sequence selected from one or more of the group Lys, Ala, Pro, Hyp, diHyp, Thr, pThr, DOPA, Tyr, which sequences is optionally terminated by dopamine (or, more properly, 'a dopamine fragment');

30 if present, each D is covalently bonded to Z through an amide bond between respective carboxylic acid residues thereof and one or more NH₂ residues of Z; and

each of the L residues are covalently bonded to Z through an amide bond between respective carboxylic acid residues of L and one or more NH₂ residues of Z and/or through an ester bond between respective -OH residues of L and one or more carboxylic acid residues of Z,

35 as well as regioisomers, stereoisomers, and pharmaceutically- or cosmetically-acceptable salts of said compound.

2. A compound as claimed in Claim 1, wherein the lipid is selected from the group consisting of palmitic acid, stearic acid, oleic acid, octadecanedioic acid, docosahexaenoic acid and leukotriene B₄, or a derivative of any of these.
- 5 3. A compound as claimed in Claim 2, wherein the lipid is palmitic acid, or a derivative thereof.
4. A compound as claimed in Claim 3, wherein the derivative is palmitoylethanolamide (PEA).
- 10 5. A compound as claimed in Claim 3, wherein the derivative is a phosphatidylserine.
6. A compound as claimed in Claim 3, wherein the derivative is 1,2-dipalmitoyl-sn-glycero-3-phospho-L-serine, phosphatidylethanolamine, or 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine.
- 15 7. A compound as claimed in Claim 3, wherein the derivative is 1,2-dipalmitoyl-sn-glycero-3-phospho-L-serine.
- 20 8. A compound as claimed in Claim 2, wherein the lipid is stearic acid, or a derivative thereof.
9. A compound as claimed in Claim 8, wherein the derivative is 1,2-distearoyl-sn-glycero-3-phospho-L-serine.
- 25 10. A compound as claimed in Claim 2, wherein the lipid is oleic acid, or a derivative thereof.
11. A compound as claimed in Claim 10, wherein the derivative is 1,2-dioleoyl-sn-glycero-3-phospho-L-serine.
- 30 12. A compound as claimed in Claim 1, wherein the lipid is selected from the group consisting of vitamin E, vitamin A and cholesterol, or a derivative of any of these.
13. A compound as claimed in Claim 12, wherein the derivative of cholesterol is cholesterol-acetic acid.
14. A compound as claimed in any one of the preceding claims wherein Q^a represents Z.

15. A compound as claimed in any one of the preceding claims, wherein n represents 0.
16. A compound as claimed in any one of the preceding claims, wherein W, if present,
5 represents Ala.
17. A compound as claimed in any one of the preceding claims wherein X¹ represents Pro.
- 10 18. A compound as claimed in any one of the preceding claims wherein T represents Ser.
19. A compound as claimed in any one of the preceding claims wherein U represents Tyr or DOPA.
- 15 20. A compound as claimed in any one of the preceding claims wherein X² represents Hyp.
21. A compound as claimed in any one of the preceding claims, wherein Y represents a
20 4 amino acid sequence, in which the amino acids are selected from one or more of the group Lys, Hyp, Thr, DOPA and Tyr, optionally terminated by a dopamine fragment.
22. A compound as claimed in Claim 21, wherein the amino acid sequence defined by Y is selected from the group:
- 25 -Hyp-Thr-Tyr-Lys-;
-Hyp-Thr-DOPA-Lys-;
-Thr-Tyr-Hyp-Lys-;
-Thr-DOPA-Hyp-Lys-;
-DOPA-Lys-; and
30 -Tyr-Lys-,
each of which is optionally terminated by a dopamine fragment.
23. A compound as claimed in Claim 22, wherein Z is selected from the group:
Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys (SEQ ID No: 2);
35 Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-DOPA-Hyp-Lys (SEQ ID No: 9);
Ala-Lys-Pro-Ser-Tyr-Hyp-Thr-Tyr-Hyp-Lys (SEQ ID No: 11);
Ala-Lys-Pro-Ser-DOPA-Hyp-Hyp-Thr-DOPA-Lys (SEQ ID No: 12);
Lys-Pro-Ser-Tyr-Hyp-DOPA-Lys (SEQ ID No: 14);
Lys-Pro-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 16); and

Lys-Hyp-Ser-Tyr-Hyp-Tyr-Lys (SEQ ID No: 19).

24. A compound as defined in any of the preceding claims, for use in human or animal medicine.

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25. A compound as defined in any one of Claims 1 to 23, for use as a pharmaceutical.

26. A pharmaceutical formulation comprising a compound as defined in any one of Claims 1 to 25.

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27. A pharmaceutical formulation as claimed in Claim 26, which further comprises a pharmaceutically- or cosmetically-acceptable, adjuvant, diluent or carrier.

28. A pharmaceutical formulation as claimed in Claim 26 or Claim 27 that is suitable for, adapted for, and/or packaged and presented for, topical administration, wherein the pharmaceutically- or cosmetically-acceptable adjuvant, diluent or carrier is a topical adjuvant, diluent or carrier.

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29. A pharmaceutical formulation as claimed in any one of Claims 26 to 28, which is in the form of a gel, a spray, a cream, an ointment or a dry powder.

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30. A pharmaceutical formulation as claimed in any one of Claims 26 to 29, which further includes a, or a further, pharmaceutically-active ingredient.

31. A kit of parts comprising components:

(A) a compound as defined in any one of Claims 1 to 23 or a pharmaceutical formulation as defined in any one of Claims 26 to 30; and

(B) a pharmaceutical formulation including a, or a further, pharmaceutically-active ingredient in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (A) and (B) are each provided in a form that is suitable for administration in conjunction with the other.

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32. A pharmaceutical formulation as claimed in Claim 30, or a kit of parts as claimed in Claim 31 wherein the pharmaceutically-active ingredient is an anti-inflammatory agent, a pro-inflammatory agent, an antibiotic, an anti-bacterial and/or antiprotozoal agent, an antiviral agent, an anaesthetic and/or a wound recovery drug.

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33. A pharmaceutical formulation or a kit of parts as claimed in Claim 32, wherein the pharmaceutically-active ingredient is an anti-inflammatory agent.
34. A compound as defined in any one of Claims 1 to 23, a formulation as claimed in
5 any one of Claims 26 to 30, 32 or 33, or a kit of parts as claimed in any one of Claim 31 to 33, for use in the treatment of inflammation, an inflammatory disorder, and/or of a disorder characterised by inflammation.
35. The use of a compound as defined in any one of Claims 1 to 23, a formulation as
10 claimed in any one of Claims 26 to 30, 32 or 33, or a kit of parts as claimed in any one of Claim 31 to 33, for the manufacture a medicament for the treatment of inflammation, an inflammatory disorder, and/or of a disorder characterised by inflammation.
36. A method of treatment of inflammation, an inflammatory disorder, and/or of a
15 disorder characterised by inflammation, which method comprises the administration of a compound as defined in any one of Claims 1 to 23, a formulation as claimed in any one of Claims 26 to 30, 32 or 33, or a kit of parts as claimed in any one of Claim 31 to 33, to a patient in need of such treatment.
- 20 37. A compound, formulation or kit of parts for use as claimed in Claim 34, a use as claimed in Claim 35, or a method as claimed in Claim 36, wherein the disorder characterised by inflammation is, or results in, a wound or a burn.
38. A compound, formulation or kit of parts for use, use or method as claimed in Claim
25 37, wherein the disorder resulting in a wound is haemorrhoids or ulcerative colitis.
39. A compound, formulation or kit of parts for use, use or method as claimed in any
one of Claims 24 to 38 (as appropriate), wherein the compound(s) or salt thereof is administered topically in the form of a topical formulation.
- 30 40. A compound, formulation or kit of parts for use, use or method as claimed in Claim 39 wherein the relevant condition is treated by way of direct topical administration to the skin.
- 35 41. A compound, formulation or kit of parts for use, use or method as claimed in Claim 39, wherein the relevant condition is treated by way of direct topical administration to a mucosal surface.

42. A compound, a formulation, or a kit of parts, for use, a use or a method as claimed in any one of Claims 24 to 41 (as appropriate), wherein the compound(s) is/are administered by oral, intravenous, cutaneous or subcutaneous, nasal, intramuscular, intraperitoneal, pulmonary or anorectal delivery.

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43. A compound, a formulation, or a kit of parts, for use, a use or a method as claimed in any one of Claims 30 to 42 (as appropriate), wherein the compound as defined in any of Claim 1 to 23 functions as an excipient, as a medical device, or as a medical device component of a drug-medical device combination.