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Im Auftrag

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Compstatin Analogues And Their Medical Uses

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COMPSTATIN ANALOGUES AND THEIR MEDICAL USES

Field of the Invention

The present invention relates to activation of the complement cascade in the body, and more particularly to compstatin analogues that are capable of binding to C3 protein and inhibiting complement activation. The present invention also relates to the medical uses of the compstatin analogues, in particular for the treatment of conditions characterized by unwanted activation of the complement cascade, such as autoimmune and inflammatory diseases.

Background of the Invention

The human complement system is a powerful player in the defense against pathogenic organisms and the mediation of immune responses. Complement can be activated through three different pathways: the classical, lectin and alternative pathways. The major activation event that is shared by all three pathways is the proteolytic cleavage of the central protein of the complement system, C3, into its activation products C3a and C3b by C3 convertases. Generation of these fragments leads to the opsonization of pathogenic cells by C3b and iC3b, a process that renders them susceptible to phagocytosis or clearance, and to the activation of immune cells through an interaction with complement receptors (Markiewski & Lambris, 2007, Am. J. Pathol., 171: 715-727). Deposition of C3b on target cells also induces the formation of new convertase complexes and thereby initiates a self-amplification loop. An ensemble of plasma and cell surface-bound proteins carefully regulates complement activation to prevent host cells from self-attack by the complement cascade. However, excessive activation or inappropriate regulation of complement can lead to a number of pathologic conditions, ranging from autoimmune to inflammatory diseases (Holers, 2003, Clin. Immunol., 107: 140-51; Markiewski & Lambris, 2007, supra; Ricklin & Lambris, 2007, Nat. Biotechnol., 25: 1265-75; Sahu et al., 2000, J. Immunol., 165: 2491-9). The development of therapeutic complement inhibitors is therefore highly desirable. In this context, C3 and C3b have emerged as promising targets because their central role in the cascade allows for the simultaneous inhibition of the initiation, amplification, and downstream activation of complement (Ricklin & Lambris, 2007, supra).

Human compstatin was first identified as a 27 amino acid peptide and was the first non-host-derived complement inhibitor that was shown to be capable of blocking all three activation pathways (Sahu et al., 1996, J. Immunol., 157: 884-91; U.S. Patent No: 6,319,897). It has been shown that it is possible to truncate compstatin without loss of activity to a 13 amino acid peptide. However, attempts to further truncate this peptide led to loss of activity. The sequence of the 13 amino acid truncated compstatin peptide is Ile^{1}-Cys^{2}-Val^{3}-Val^{4}-Gln^{5}-Asp^{6}-

Trp^7-Gly^8-His^9-His^{10}-Arg^{11}-Cys^{12}-Thr^{13}-NH_2, where Cys^2 and Cys^{12} are disulfide bonded. This cyclic tridecapeptide binds to C3 (and fragments of C3), thereby inhibiting the activation of the downstream complement cascade and preventing the cleavage of native C3 by the C3 convertases. Its high inhibitory efficacy was confirmed by a series of studies using experimental models that pointed to its potential as a therapeutic agent (Fiane et al, 1999a, Xenotransplantation, 6: 52-65; Fiane et al,, 1999b, Transplant Proc., 31:934- 935; Nilsson et al., 1998, Blood, 92: 1661-1667; Ricklin & Lambris, 2008, Adv. Exp. Med..Biol., 632: 273-292; Schmidt et al., 2003, J. Biomed. Mater. Res., A66: 491-499; Soulika et al., 2000, Clin. Immunol., 96: 212-221).

Progressive optimization of the 13 amino acid compstatin peptide has led to analogues with improved biological activity (Ricklin & Lambris, 2008, supra; WO 2004/026328; WO 2007/062249, WO 2013/036778, WO 2014/100407).

Earlier structure-activity studies have identified the cyclic nature of the compstatin peptide and the presence of both a β-turn and hydrophobic cluster as key features of the molecule (Morikis et al., 1998, Protein Sci., 7: 619-627; WO 99/13899; Morikis et al., 2002, J. Biol. Chem., 277:14942-14953; Ricklin & Lambris, 2008, supra). Hydrophobic residues at positions 4 and 7 were found to be of particular importance, and their modification with unnatural amino acids generated an analogue with 264-fold improved activity over the original compstatin peptide (Katragadda et al., 2006, J. Med. Chem., 49: 4616-4622; WO 2007/062249). Further attempts to optimize compstatin for use in the treatment of eye disorders are described in WO 2007/044668.

While previous optimization steps have been based on combinatorial screening studies, solution structures, and computational models (Chiu et al., 2008, Chem. Biol. Drug Des., 72: 249-256; Mulakala et al., 2007, Bioorg. Med. Chem., 15: 1638-1644; Ricklin & Lambris, 2008, supra), the publication of a co-crystal structure of compstatin complexed with the complement fragment C3c (Janssen et al., 2007, J. Biol. Chem., 282: 29241-29247; WO 2008/153963) provided a basis for initiating rational optimization. The crystal structure revealed a shallow binding site at the interface of macroglobulin (MG) domains 4 and 5 of C3c and showed that 9 of the 13 amino acids were directly involved in the binding, either through hydrogen bonds or hydrophobic effects. As compared to the structure of the compstatin peptide in solution (Morikis et al., 1998, supra), the bound form of compstatin experienced a conformational change, with a shift in the location of the β-turn from residues 5-8 to 8-11 (Janssen et al., 2007, supra; WO 2008/153963).

In view of its therapeutic potential in AMD, C3G, PNH and other diseases, it remains a problem in the art to further optimize compstatin analogues, for example to achieve an even greater activity and/or to modulate other pharmacokinetic properties, such as increased solubility.

Summary of the Invention

Broadly, the present invention is based on work to develop a new family of compstatin analogues having improved binding and complement-inhibiting activity as compared to the 13 amino acid compstatin peptide (ICVVQDWGHHRCT (cyclic C2-C12)). In some cases, these compstatin analogues additionally possess useful physicochemical properties, such as increased solubility. In particular, the present inventors found that introducing an isoleucine residue at position 3 in place of the wild type valine residue led to compstatin peptides with improved binding and complement-inhibiting activity. The present inventors further discovered that the introduction of isoleucine at position 3 was compatible with other modifications, for example modifications that are capable of increasing solubility, such as the introduction of charged or polar amino acids at position 9 and/or the introduction of N-and/or C-terminal sequences. Example of such additional modifications include the replacement of Ile at position 1 with Trp, Phe or Sar, replacement of Val at position 4 with Trp, a Trp analogue (as described herein); replacement of His at position 9 with Ala, Glu, Asp, Lys or Ser; replacement of Arg at position 11 with Ser; replacement of Trp at position 13 with The, Glu, Sar or Ile. Preferred compstatin peptides including one or more of these modifications have improved solubility, for example as compared to the 13 amino acid compstatin peptide (ICVVQDWGHHRCT (cyclic C2-C12)). Further examples of these compstatin peptides combine modification at position 9 with extensions to the N-terminal and/or C-terminus of the peptide.

Accordingly, in one aspect, the present invention provides a compstatin analogue represented by Formula I:

Y1-R1-X1-C-I-X2-Q-X3-W-X4-X5-H-X6-C-X7-R2-Y2,

wherein:

Y1 is hydrogen or acetyl;

X1 is I, Y, F or Sar;

X2 is W, F, V, Y, 1MeTrp, D-Trp, N-Me-Trp, 1-For-Trp, 1-Nal, 2-Nal, 5MeTrp, Bpa or 2Igl;

X3 is E or D;

X4 is G or Sar;

X5 is H, A, E, D, K, R or S;

X6 is R or S;

X7 is T, S, E, F, H, K, Sar, G, I, D, N-Me-Ile or N-Me-Thr;

Y2 is NH_2 or OH;

R1 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof; and

R2 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof;

wherein the compstatin analogue has a disulphide bond between the cysteine residues at positions 2 and 12;

or a pharmaceutically acceptable salt and/or solvate thereof.

In a further aspect, the present invention provides a compstatin analogue represented by formula:

Y1-R1-X1-C-I-X2-Q-D-W-X4-X5-H-X6-C-X7-R2-Y2,

wherein:

Y1 is hydrogen or acetyl;

X1 is I, Y, F or Sar;

X2 is W, V, Y, 2-Nal, 1-Nal or 1MeTrp;

X4 is G or Sar;

X5 is A, E, D, K or S;

X6 is R or S;

X7 is T, S, E, I, Sar, K, G or N-Me-Ile;

Y2 is NH_2 or OH;

R1 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof; and

R2 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof;

wherein the compstatin analogue has a disulphide bond between the cysteine residues at positions 2 and 12;

or a pharmaceutically acceptable salt and/or solvate thereof.

In a further aspect, the present invention provides a compstatin analogue represented by the formula:

Y1-R1-X1-C-I-X2-Q-D-W-G-X5-H-X6-C-X7-R2-Y2,

wherein:

Y1 is hydrogen or acetyl;

X1 is I, Y, F or Sar;

X2 is W, V, Y, 1-Nal, 2-Nal or 1MeTrp;

X5 is A, E, D, K or S;

X6 is R or S;

X7 is T,I, S, E, K or Sar;

Y2 is NH_2 or OH;

R1 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof; and

R2 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof;

wherein the compstatin analogue has a disulphide bond between the cysteine residues at positions 2 and 12;

or a pharmaceutically acceptable salt and/or solvate thereof.

In a further aspect, the present invention provides a compstatin analogue represented by the formula:

Y1-R1-X1-C-I-X2-Q-D-W-G-X5-H-R-C-X7-R2-Y2,

wherein:

Y1 is hydrogen or acetyl;

X1 is I, Y, F or Sar;

X2 is W, V, 1-Nal, 2-Nal or 1MeTrp;

X5 is A, E, D, K or S;

X7 is T, S, E or Sar;

Y2 is NH_2 or OH;

R1 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof; and

R2 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof;

wherein the compstatin analogue has a disulphide bond between the cysteine residues at positions 2 and 12;

or a pharmaceutically acceptable salt and/or solvate thereof.

In a further aspect R1 is selected from ESSA, AKGE, ASSE, ASES, GSAE, ESSE, ESGA, SEG, GES, ESS, EGSA, ESE, EGE, ESA, SAE, SGA, YLEA, GSA, KEK, EKG, ES, AS, SE, SA or E; and/or R2 is selected from GAES, EYGS, EGYA, EAGS, EAKS, EKSA, EGGS, EGGA,ESSG, ESAG, GEES, AEES, ESEG, AEGS, ESGS, SEGA, SEG, ESG, EAG, GAE, EGEA, EGE, EA, E, GE, EG, EKE or EKP.

In a further aspect R1 is selected from ESSA, ASES, ESGA, SEG, GES, ESS, EGSA, ESE, EGE, ESA, SAE, SGA, KEK, EKG, ES, SE, SA or E; and/or R2 is selected from GAES, EAGS, EGGS, EGGA,ESAG, ESEG, AEGS, ESGS, SEGA, SEG, ESG, EAG, GAE, EGEA, EGE, EA, E, GE, EG, EKE or EKP.

Preferred classes of compstatin analogues and exemplified compounds are discussed further below.

In a further aspect, the present invention provides a composition comprising a compstatin analogue of the present invention, or a pharmaceutically acceptable salt or solvate thereof, in admixture with a carrier. In some instances, the composition is a pharmaceutical composition and the carrier is a pharmaceutically acceptable carrier.

In a further aspect, the present invention provides a pharmaceutical composition comprising a compstatin analogue of the present invention, or a pharmaceutically acceptable salt or solvate thereof, in admixture with a pharmaceutically acceptable carrier, excipient or vehicle.

In a further aspect, the present invention provides a compstatin analogue of the present invention for use in therapy.

In a further aspect, the present invention provides a compstatin analogue of the present invention for use in a method of inhibiting complement activation. By way of example, inhibiting complement activation includes one or more biological activities selected from (1) binding to C3 protein, (2) binding to C3b protein and/or (3) inhibiting the cleavage of native C3 by C3 convertases. Examples of disease or condition that may be treated using the compstatin analogues of the present invention are discussed below.

In a further aspect, the present invention provides a compstatin analogue of the present invention for use in a method of inhibiting complement activation that occurs during cell or organ transplantation.

In a further aspect, the present invention provides a method of inhibiting complement activation for treating a subject in need thereof, the method comprising administering to the subject a compstatin analogue of the present invention thereby to inhibit complement activation in the subject. Examples of disease or condition that may be treated using the compstatin analogues of the present invention are discussed below.

In a further aspect, the present invention provides an *ex vivo* method of inhibiting complement activation during extracorporeal shunting of a physiological fluid, the method comprising contacting the physiological fluid with a compstatin of the present invention, thereby to inhibiting complement activation.

In a further aspect, the present invention provides the use of a compstatin analogue of the present invention in the preparation of a medicament for inhibiting complement activation. Examples of disease or condition that may be treated using the compstatin analogues of the present invention are discussed below.

Embodiments of the present invention will now be described by way of example and not limitation.

Detailed Description

"and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. For example "A and/or B" is to be taken as specific disclosure of each of (i) A, (ii) B and (iii) A and B, just as if each is set out individually herein.

Unless context dictates otherwise, the descriptions and definitions of the features set out above are not limited to any particular aspect or embodiment of the invention and apply equally to all aspects and embodiments which are described.

Various publications, including patents, published applications, technical articles and scholarly articles are cited throughout the specification. Each of these cited publications is incorporated by reference herein, in its entirety.

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, molecular biology, cell and cancer biology, immunology, microbiology, pharmacology, and protein and nucleic acid chemistry, described herein, are those well known and commonly used in the art.

Each embodiment of the invention described herein may be taken alone or in combination with one or more other embodiments of the invention.

Unless specified otherwise, the following definitions are provided for specific terms which are used in the present written description.

Definitions

Throughout this specification, the word "comprise", and grammatical variants thereof, such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or component, or group of integers or components, but not the exclusion of any other integer or component, or group of integers or components.

The singular forms "a," "an," and "the" include the plurals unless the context clearly dictates otherwise.

The term "including" is used to mean "including but not limited to". "Including" and "including but not limited to" may be used interchangeably.

The terms "patient", "subject" and "individual" may be used interchangeably. A subject may be a mammal, including a human or a non-human mammal, such as a non-human primate (e.g. ape, Old World monkey or New World monkey), livestock animal (e.g. bovine or porcine), companion animal (e.g. canine or feline) or laboratory animal such as a rodent (e.g. mouse or rat).

Throughout the present description and claims the conventional three-letter and one-letter codes for naturally occurring amino acids are used, i.e. A (Ala), G (Gly), L (Leu), I (Ile), V (Val), F (Phe), W (Trp), S (Ser), T (Thr), Y (Tyr), N (Asn), Q (Gln), D (Asp), E (Glu), K (Lys), R (Arg), H (His), M (Met), C (Cys) and P (Pro); as well as generally accepted three-letter codes for other α-amino acids, such as norleucine (Nle), sarcosine (Sar), α-aminoisobutyric acid (Aib), 2,3-diaminopropanoic acid (Dap), 2,4-diaminobutanoic acid (Dab) and 2,5-

diaminopentanoic acid (ornithine; Orn), 1-methyl-tryptophan(1MeTrp), 1-formyl-tryptophan (1-ForTrp), 1-naphathalin (1-Nal), 2-naphathalin (2-Nal), 5-methyl-tryptophan (5MeTrp), p-Benzoyl-phenylalanine (Bpa) 2-indanylglycine (2Igl). Other α-amino acids may be shown in square brackets "[ ]" (e.g. "[Nle]") when used in a general formula or sequence in the present specification, especially when the rest of the formula or sequence is shown using the single letter code. The 20 "naturally occurring" amino acids listed above are those which are encoded by the standard genetic code, and may also be referred to as "proteinogenic" amino acids.

Unless otherwise specified, amino acid residues in peptides of the invention are of the L-configuration. However, in some instances, D-configuration amino acids may be incorporated. In the present context, an amino acid code written with a small letter represents the D-configuration of said amino acid, e.g. "k" represents the D-configuration of lysine (K).

A "H" (or "Hy-") moiety at the N-terminus of the sequence in question indicates a hydrogen atom (i.e. R^1 = hydrogen), corresponding to the presence of a free primary or secondary amino group at the N-terminus, while an "-OH" or an "$-NH_2$" moiety at the C-terminus of the sequence (i.e. R^2 = OH or NH_2) indicate the presence of a carboxy (COOH) group or an amido ($CONH_2$) group at the C-terminus of the molecule.

Percent (%) amino acid sequence identity with respect to a reference sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. % identity values may be determined by WU-BLAST-2 (Altschul et al., Methods in Enzymology, 266:460-480 (1996)). WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable parameters are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11. A % amino acid sequence identity value is determined by the number of matching identical residues as determined by WU-BLAST-2, divided by the total number of residues of the reference sequence (gaps introduced by WU-BLAST-2 into the reference sequence to maximize the alignment score being ignored), multiplied by 100.

A conservative substitution may be defined as a substitution within an amino acid class and/or a substitution that scores positive in the BLOSUM62 matrix. According to one classification, the amino acid classes are acidic, basic, uncharged polar and non-polar,

wherein acidic amino acids are Asp and Glu; basic amino acids are Arg, Lys and His; uncharged polar amino acids are Asn, Gln, Ser, Thr and Tyr; and non-polar amino acids are Ala, Gly, Val, Leu, Ile, Pro, Phe, Met, Trp and Cys.

According to another classification, the amino acid classes are small hydrophilic, acid/acid amide/hydrophilic, basic, small hydrophobic and aromatic, wherein small hydrophilic amino acids are Ser, Thr, Pro, Ala and Gly; acid/acidamide/hydrophilic amino acids are Asn, Asp, Glu and Gln; basic amino acids are His, Arg and Lys; small hydrophobic amino acids are Met, Ile, Leu and Val; and aromatic amino acids are Phe, Tyr and Trp.

Substitutions which score positive in the BLOSUM62 matrix are as follows:

Original Residue	C	S	T	P	A	G	N	D	E	Q	H	R	K	M	I	L	V	F	Y	W
Substitution	-	T A N	S	-	S	-	S D H	N E	D Q K	E R K	N Y	Q K	E Q R	I L V	M L V	M I V	M I L	Y W	H F W	F Y

Various terms relating to the methods and other aspects of the present invention are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definition provided herein. The term "about" as used herein when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of ±20% or ±10%, in some embodiments ±5%, in some embodiments ±1%, and in some embodiments ±0.1% from the specified value, as such variations are appropriate to make and used the disclosed compounds and compositions.

The term "full length compstatin" as used herein refers to a 27 amino acid peptide having the sequence IC(1)VVQDWGHHRC(1)TAGHMANLTSHASAI, wherein C(1) denotes the cysteine residue linked by a disulphide bond. As described above, a truncated form of full length compstatin, the tridecapeptide Ile^{1}-Cys^{2}-Val^{3}-Val^{4}-Gln^{5}-Asp^{6}-Trp^{7}-Gly^{8}-His^{9}-His^{10}-Arg^{11}-Cys^{12}-Thr^{13}-NH_2 linked by a disulphide bond between the cysteine residues at positions 2 and 12 retains the activity of the full length peptide and is referred to herein as "Ac-compstatin"

The term "compstatin analogue" refers to a modified Ac-compstatin comprising substitutions of natural and unnatural amino acids, or amino acid analogs, as well as modifications within or between various amino acids, as described in greater detail herein. When referring to the position of amino acids or analogs within Ac-compstatin or compstatin analogs, the positions

are numbered from 1 (Ile in compstatin) to 13 (Thr in compstatin). For example, the Gly residue occupies "position 8." As used to describe the compstatin analogue peptides of the present invention "C(1)" denotes a disulphide bond between the respective cysteine residues in the compstatin analogue.

The terms "pharmaceutically active" and "biologically active" refer to the ability of the compounds of the invention to bind C3 or fragments thereof and inhibit complement activation. The biological activities of compstatin analogs may be measured by one or more of several art-recognized assays, as described in greater detail herein.

As used herein, "L-amino acid" refers to any of the naturally occurring levorotatory alpha-amino acids normally present in proteins or the alkyl esters of those alpha-amino acids. The term D-amino acid" refers to dextrorotatory alpha-amino acids. Unless specified otherwise, all amino acids referred to herein are L-amino acids.

"Hydrophobic" or "non-polar" are used synonymously herein, and refer to any inter- or intra-molecular interaction not characterized by a dipole.

As used herein, "pharmaceutically-acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically-acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Thus, the term "acid addition salt" refers to the corresponding salt derivative of a parent compound that has been prepared by the addition of an acid. The pharmaceutically-acceptable salts include the conventional salts or the quaternary ammonium salts of the parent compound formed, for example, from inorganic or organic acids. For example, such conventional salts include, but are not limited to, those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like. Certain acidic or basic compounds of the present invention may exist as zwitterions. All forms of the compounds, including free acid, free base, and zwitterions, are contemplated to be within the scope of the present invention.

Compstatin Analogues

Ac-Compstatin, a 13 amino acid peptides is known to bind to C3 and preventing C3 convertase-mediated cleavage. Since its discovery by phage display, modification to the 13 amino acids Ac-Compstatin sequence has been carried out in an effort to find analogues with increased biological activity. However, in the core sequence between the two cysteines residues at positions 2 and 12, alanine scanning experiments have produced analogues showing only modest improvements in biological activity, with few modifications being tolerated. The modifications include changing the valine at position 4 to tryptophan, or a tryptophan analogue, that leads to an increase in biological activity and changing the histidine at position 9 to alanine or analogs thereof.

In particular, previous attempts to introduce modifications to the valine residue at position 3, replacing it with glycine, alanine, D-valine or leucine have been shown to lead to a decrease in biological activity. In contrast to these prior art findings, the present inventors surprisingly found that a change of valine to isoleucine is well tolerated and provide improvements in biological activity, see Table 1 and Table 2.

Table 1: Position 3 exchange from valine to isoleucine. The rest of the amino acid sequence of Comp 4W9A is similar to Comp 1. Activity measured by classical pathway (CP) hemolysis as explained in the method section.

Comp no	CP hemolysis IC50 (nM)	1	2	3	4	5	6	7	8	9	10	11	12	13	
1	150	Ac	I	C(1)	I	W	Q	D	W	G	A	H	R	C(1)	T	NH_2
4W9A	220				**V**											

Without wishing to be bound by any specific theory, the present inventors reasoned that this modification might be combined with introduction of one or more polar or charged amino acids in the core sequence and may be used as an approach to increase the ability of the compstatin peptides to solubilize. Initially, glutamic acid or serine at position 9 were combined with valine 3 and led to a decrease in activity compared to the reference sequence 4W9A. However, when these changes are combined with the introduction of isoleucine at position 3, a surprising increase in biological activity is observed, in particular for the combination of isoleucine at position 3 and glutamic acid at position 9, see Table 2. This observation correlates with improved binding to C3 as measured by surface plasmon resonance (SPR), see Table 3.

Table 2 : Direct comparison of valine 3 to isoleucine 3 in combination with modification at position 9, 11 and/or 13. The rest of the amino acid sequences of the valine 3 compounds are are similar to Comp 2, 6, 3, 15, 19, 20, 21, 28 and 24 respectively. Activity measured by classical pathway (CP) hemolysis as explained in the method section.

Comp no	CP hemolysis IC50 (nM)			1	2	3	4	5	6	7	8	9	10	11	12	13		
2	94	Ac		I	C(1)	**I**	W	Q	D	W	G	**E**	H	R	C(1)	T		NH_2
	310					**V**												
6	140	Ac		I	C(1)	**I**	W	Q	D	W	G	**S**	H	R	C(1)	T		NH_2
	360					**V**												
3	69	Ac	ESSA	I	C(1)	**I**	W	Q	D	W	G	**E**	H	R	C(1)	T		NH_2
	300					**V**												
46	51	Ac	ESSA	I	C(1)	**I**	W	Q	D	W	G	**A**	H	R	C(1)	T		NH_2
15	47	Ac		I	C(1)	**I**	W	Q	D	W	G	**E**	H	R	C(1)	T	GAES	NH_2
	210					**V**												
47	50	AC		I	C(1)	**I**	W	Q	D	W	G	**A**	H	R	C(1)	T	GAES	NH_2
19	140	Ac		I	C(1)	**I**	W	Q	D	W	G	**A**	H	**S**	C(1)	T		NH_2
	>1000					**V**												
20	59	Ac		I	C(1)	**I**	W	Q	D	W	G	**E**	H	**S**	C(1)	T		NH_2
	540					**V**												
21	77	Ac		I	C(1)	**I**	W	Q	D	W	G	**E**	H	R	C(1)	**S**		NH_2
	180					**V**												
28	88	Ac	EGSA	I	C(1)	**I**	W	Q	D	W	G	**E**	H	R	C(1)	**Sar**	E	NH_2
	330					**V**												
24	89	Ac		I	C(1)	**I**	W	Q	D	W	G	**E**	H	R	C(1)	**T**	EGE	NH_2
	240					**V**												

Table 3: Binding affinity of Compstatin analogues to immobilized C3 determined by a surface plasmon resonance (SPR) assay. The rest of the amino acid sequences of the valine 3 compounds are are similar to Comp 2, 15 and 21 respectively.

Comp no	SPR Kd (nM)		1	2	3	4	5	6	7	8	9	10	11	12	13		
2	16	Ac	I	C(1)	**I**	W	Q	D	W	G	**E**	H	R	C(1)	T		NH_2
	130				**V**												
15	14	Ac	I	C(1)	**I**	W	Q	D	W	G	**E**	H	R	C(1)	T	GAES	NH_2
	230				**V**												
21	16	Ac	I	C(1)	**I**	W	Q	D	W	G	**E**	H	R	C(1)	**S**		NH_2
	160				**V**												

In a further series of experiments to validate these findings, compstatin peptides with glutamic acid at position 9 are combined with different conservative substitutions in position 3, again showing that the peptides with isoleucine at position 3 are most active, see Table 4.

Table 4: Validating Position 3. Activity measured by classical pathway (CP) hemolysis as explained in the method section.

Ac-IC(1)**X**WQDWGEHRC(1)T-NH2

Comp no	Position 3 (X)	IC50, CP hemolysis (nM)
-	Valine	310
2	Isoleucine	94
-	Leucine	500
-	Norvaline	>1000
-	Norleucine	480
-	Phenylalanine	>10000
-	Beta-Homo-Isoleucine	>10000

Taken together, these experiments show that replacing the valine residue at position 3 with isoleucine provides compstatin peptides having increased biological activity and improved binding to C3. Furthermore, the experiments surprisingly demonstrate that these changes can be readily combined with other modifications in the core sequence of the compstatin analogues and with addition of N and C-terminal sequences, for example for improving the solubility of the compstatin peptides, e.g. at higher concentrations.

Lipophilic substituents

One or more of the amino acid side chains in a compound employed in the context of the

invention may be conjugated to a lipophilic substituent Z^1. Without wishing to be bound by theory, we believe that a lipophilic substituent binds albumin in the blood stream, thus shielding the compounds employed in the context of the invention from enzymatic degradation, which can enhance the half-life of the compounds. The lipophilic substituent may also modulate the potency of the compound.

In certain embodiments, only one amino acid side chain is conjugated to a lipophilic substituent. In other embodiments, two amino acid side chains are each conjugated to a lipophilic substituent. In yet further embodiments, three or even more amino acid side chains are each conjugated to a lipophilic substituent. When a compound contains two or more lipophilic substituents, they may be the same or different substituents.

The lipophilic substituent Z^1 may be covalently bonded to an atom in the amino acid side chain, or alternatively may be conjugated to the amino acid side chain by one or more spacers Z^2.

The term "conjugated" is used here to describe the covalent attachment of one identifiable chemical moiety to another, and the structural relationship between such moieties. It should not be taken to imply any particular method of synthesis. The one or more spacers Z^2, when present, are used to provide a spacing between the compound and the lipophilic moiety.

A lipophilic substituent may be attached to an amino acid side chain or to a spacer via an ester, a sulphonyl ester, a thioester, an amide or a sulphonamide. Accordingly, it will be understood that a lipophilic substituent may include an acyl group, a sulphonyl group, an N atom, an O atom or an S atom which forms part of the ester, sulphonyl ester, thioester, amide or sulphonamide. Preferably, an acyl group in the lipophilic substituent forms part of an amide or ester with the amino acid side chain or the spacer. The lipophilic substituent may include a hydrocarbon chain having 10 to 24 carbon (C) atoms, e.g. 10 to 22 C atoms, e.g. 10 to 20 C atoms. Preferably, it has at least 11 C atoms, and preferably it has 18 C atoms or fewer. For example, the hydrocarbon chain may contain 12, 13, 14, 15, 16, 17 or 18 carbon atoms. The hydrocarbon chain may be linear or branched and may be saturated or unsaturated. From the discussion above, it will be understood that the hydrocarbon chain is preferably substituted with a moiety which forms part of the attachment to the amino acid side chain or the spacer, for example an acyl group, a sulphonyl group, an N atom, an O atom or an S atom. Most preferably, the hydrocarbon chain is substituted with an acyl group, and accordingly the hydrocarbon chain may be part of an alkanoyl group, for example a dodecanoyl, 2-butyloctanoyl, tetradecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl or

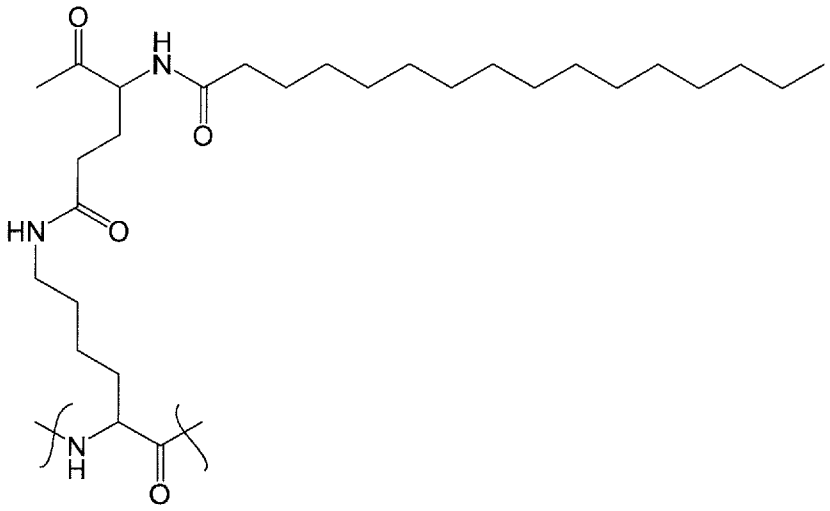
eicosanoyl group. Alternatively, Z^1 groups are derived from long-chain saturated α,ω-dicarboxylic acids of formula HOOC–$(CH_2)_{12-22}$–COOH, preferably from long-chain saturated α,ω-dicarboxylic acids having an even number of carbon atoms in the aliphatic chain. For example, Z^1 may be:

13-carboxytridecanoyl, i.e. HOOC–$(CH_2)_{12}$–(CO)–;
15-carboxypentadecanoyl, i.e. HOOC–$(CH_2)_{14}$–(CO)–;
17-carboxyheptadecanoyl, i.e. HOOC–$(CH_2)_{16}$–(CO)–;
19-carboxynonadecanoyl, i.e. HOOC–$(CH_2)_{18}$–(CO)–; or
21-carboxyheneicosanoyl, i.e. HOOC–$(CH_2)_{20}$–(CO)–

As mentioned above, the lipophilic substituent Z^1 may be conjugated to the amino acid side chain by one or more spacers Z^2. When present, the spacer is attached to the lipophilic substituent and to the amino acid side chain. The spacer may be attached to the lipophilic substituent and to the amino acid side chain independently by an ester, a sulphonyl ester, a thioester, an amide or a sulphonamide. Accordingly, it may include two moieties independently selected from acyl, sulphonyl, an N atom, an O atom or an S atom. The spacer may consist of a linear C_{1-10} hydrocarbon chain or more preferably a linear C_{1-5} hydrocarbon chain. Furthermore the spacer can be substituted with one or more substituents selected from C_{1-6} alkyl, C_{1-6} alkyl amine, C_{1-6} alkyl hydroxy and C_{1-6} alkyl carboxy.

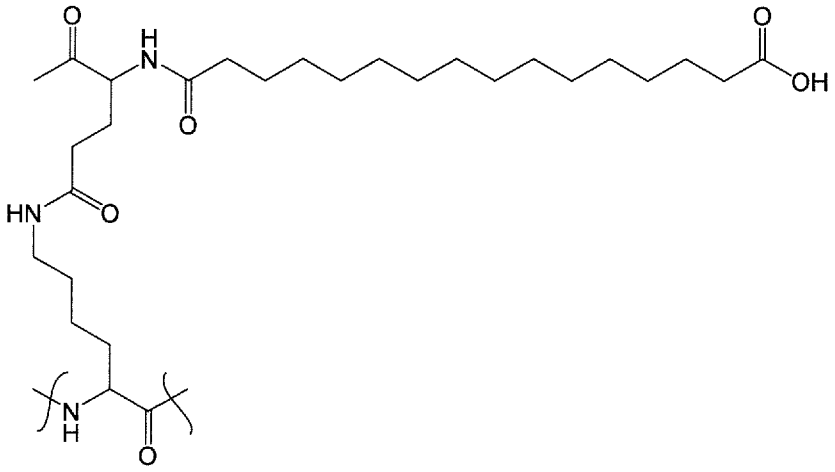
The spacer may be, for example, a residue of any naturally occurring or unnatural amino acid. For example, the spacer may be a residue of Gly, Pro, Ala, Val, Leu, Ile, Met, Cys, Phe, Tyr, Trp, His, Lys, Arg, Gln, Asn, α-Glu, γ-Glu, ε-Lys, Asp, Ser, Thr, Gaba, Aib, β-Ala (i.e., 3-aminopropanoyl), 4-aminobutanoyl, 5-aminopentanoyl, 6-aminohexanoyl, 7-aminoheptanoyl, 8-aminooctanoyl, 9- aminononanoyl, 10-aminodecanoyl or 8-amino-3,6-dioxaoctanoyl. In certain embodiments, the spacer is a residue of Glu, γ-Glu, ε-Lys, β-Ala (i.e., 3-aminopropanoyl), 4-aminobutanoyl, 8- aminooctanoyl or 8-amino-3,6-dioxaoctanoyl. In the present invention, γ-Glu and isoGlu are used interchangeably. The amino acid side chain to which the lipophilic substituent is conjugated may be a side chain of a Glu, Lys, Ser, Cys, Dbu, Dpr or Orn residue. For example, it may be a side chain of a Lys, Glu or Cys residue. Where two or more side chains carry a lipophilic substituent, they may be independently selected from those residues. Thus, the amino acid side chain includes an carboxy, hydroxyl, thiol, amide or amine group, for forming an ester, a sulphonyl ester, a thioester, an amide, or a sulphonamide with the spacer or lipophilic substituent.

An example of a lipophilic substituent comprising a lipophilic moiety Z^1 and spacer Z^2 is shown in the formula below:



Here, the side chain of a Lys residue is covalently attached to a γ-Glu spacer (Z^2) via an amide linkage. A hexadecanoyl group (Z^1) is covalently attached to the γ -Glu spacer via an amide linkage. This combination of lipophilic moiety and spacer, conjugated to a Lys residue, may be referred to by the short-hand notation K(Hexadecanoyl-γ-Glu), *e.g.*, when shown in formulae of specific compounds. γ-Glu can also be referred to as isoGlu, and a hexadecanoyl group as a palmitoyl group. Thus it will be apparent that the notation (Hexadecanoyl-γ-Glu) is equivalent to the notations (isoGlu(Palm)) or (isoGlu(Palmitoyl)) as used for example in PCT/GB2008/004121.

Alternative Z^1 groups are derived from long-chain saturated α,ω-dicarboxylic acids of formula $HOOC–(CH_2)_{12-22}–COOH$ as examplified below



Here, the side chain of a Lys residue is covalently attached to a γ-Glu spacer (Z^2) via an amide linkage. A 15-carboxypentadecanoyl group (Z^1) is covalently attached to the γ -Glu spacer via an amide linkage. This combination of lipophilic moiety and spacer, conjugated to a Lys residue, may be referred to by the short-hand notation K(15-carboxypentadecanoyl-γ-

Glu), *e.g.*, when shown in formulae of specific compounds. γ-Glu can also be referred to as isoGlu.

The skilled person will be well aware of suitable techniques for preparing the compounds employed in the context of the invention. For examples of suitable chemistry, see WO98/08871, WO00/55184, WO00/55119, Madsen et al., J. Med. Chem. 50:6126-32 (2007), and Knudsen et al., J. Med Chem. 43:1664-1669 (2000), incorporated herein by reference. In some embodiments, the compstatin analogue has a lipophilic substituent as described above conjugated to an amino acid at one or more of positions corresponding to positions 1, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 13 of the compstatin analogue.

In a specific embodiment, the compstatin analogue has a lipophilic substituent as described above conjugated to an amino acid at one or more of positions corresponding to positions 1,13, R1 and R2 as described in the formula of the compstatin analogue.

In one embodiment the compstatin analogues comprises one of the following sequences
IC(1)IWQDWGAHRC(1)T
IC(1)IWQDWGEHRC(1)T
ESSAIC(1)IWQDWGEHRC(1)T
IC(1)I[1MeTrp]QDWGEHRC(1)T
IC(1)IWQDWGKHRC(1)T
IC(1)IWQDWGSHRC(1)T
IC(1)IWQKWGEHRC(1)T
IC(1)IWQKWGAHRC(1)TGAES
YC(1)IWQDWGEHRC(1)T
ESSAYC(1)IWQDWGEHRC(1)T
[Sar]C(1)IWQDWGEHRC(1)T
IC(1)IWQDWGAHRC(1)E
IC(1)IWQDWGEHRC(1)[Sar]
ESSAIC(1)IWQDWGEHRC(1)TGAES
IC(1)IWQDWGEHRC(1)TGAES
IC(1)IWQEWGEHRC(1)T
IC(1)IWQDWGDHRC(1)T
IC(1)IWQDWGRHRC(1)T
IC(1)IWQDWGAHSC(1)T
IC(1)IWQDWGEHSC(1)T
IC(1)IWQDWGEHRC(1)S

IC(1)IWQDWGEHRC(1)E

FC(1)IWQDWGEHRC(1)T

IC(1)IWQDWGEHRC(1)TEGE

IC(1)IWQDWGEHRC(1)TEA

IC(1)IWQDWGEHRC(1)TE

IC(1)IWQDWGEHRC(1)EGE

EGSAIC(1)IWQDWGEHRC(1)[Sar]E

EGSAIC(1)IWQDWGEHRC(1)T

EGEIC(1)IWQDWGEHRC(1)T

ESEIC(1)IWQDWGEHRC(1)T

SEIC(1)IWQDWGEHRC(1)TEA

EIC(1)IWQDWGEHRC(1)TE

EIC(1)IWQDWGEHRC(1)TEGE

EGEIC(1)IWQDWGEHRC(1)EGE

ESEIC(1)IWQDWGEHRC(1)EGE

KEKIC(1)IWQDWGEHRC(1)TEKE

EKGIC(1)IWQDWGEHRC(1)TEKP

IC(1)IWQDWGEHRC(1)TEGK

GSAIC(1)IWQDWGEHRC(1)[Sar]E

SAIC(1)IWQDWGEHRC(1)[Sar]E

SAIC(1)IWQDWGEHRC(1)TEG

FC(1)IWQDWGEHRC(1)TGAE

EGSAIC(1)IWQDWGEHRC(1)[Sar]EGE

EGSAFC(1)IWQDWGEHRC(1)[Sar]E

ESSAIC(1)IWQDWGAHRC(1)T

IC(1)IWQDWGAHRC(1)TGAES

In another embodiment the compstatin analogues comprises one of the following sequences

[Ac]-IC(1)IWQDWGAHRC(1)T-[NH2] (Compound 1)

[Ac]-IC(1)IWQDWGEHRC(1)T-[NH2]] (Compound 2)

[Ac]-ESSAIC(1)IWQDWGEHRC(1)T-[NH2] (Compound 3)

[Ac]-IC(1)I[1-Me-Trp]QDWGEHRC(1)T-[NH2] (Compound 4)

[Ac]-IC(1)IWQDWGKHRC(1)T-[NH2] (Compound 5)

[Ac]-IC(1)IWQDWGSHRC(1)T-[NH2] (Compound 6)

[Ac]-IC(1)IWQKWGEHRC(1)T-[NH2] (Compound 7)

[Ac]-IC(1)IWQKWGAHRC(1)TGAES-[NH2] (Compound 8)

[Ac]-YC(1)IWQDWGEHRC(1)T-[NH2] (Compound 9)

[Ac]-ESSAYC(1)IWQDWGEHRC(1)T-[NH2] (Compound 10)

[Ac]-[Sar]C(1)IWQDWGEHRC(1)T-[NH2] (Compound 11)

[Ac]-IC(1)IWQDWGAHRC(1)E-[NH2] (Compound 12)

[Ac]-IC(1)IWQDWGEHRC(1)[Sar]-[NH2] (Compound 13)

[Ac]-ESSAIC(1)IWQDWGEHRC(1)TGAES-[NH2] (Compound 14)

[Ac]-IC(1)IWQDWGEHRC(1)TGAES-[NH2] (Compound 15)

[Ac]-IC(1)IWQEWGEHRC(1)T-[NH2] (Compound 16)

[Ac]-IC(1)IWQDWGDHRC(1)T-[NH2] (Compound 17)

[Ac]-IC(1)IWQDWGRHRC(1)T-[NH2] (Compound 18)

[Ac]-IC(1)IWQDWGAHSC(1)T-[NH2] (Compound 19)

[Ac]-IC(1)IWQDWGEHSC(1)T-[NH2] (Compound 20)

[Ac]-IC(1)IWQDWGEHRC(1)S-[NH2] (Compound 21)

[Ac]-IC(1)IWQDWGEHRC(1)E-[NH2] (Compound 22)

[Ac]-FC(1)IWQDWGEHRC(1)T-[NH2] (Compound 23)

[Ac]-IC(1)IWQDWGEHRC(1)TEGE-[NH2] (Compound 24)

[Ac]-IC(1)IWQDWGEHRC(1)TEA-[NH2] (Compound 25)

[Ac]-IC(1)IWQDWGEHRC(1)TE-[NH2] (Compound 26)

[Ac]-IC(1)IWQDWGEHRC(1)EGE-[NH2] (Compound 27)

[Ac]-EGSAIC(1)IWQDWGEHRC(1)[Sar]E-[NH2] (Compound 28)

[Ac]-EGSAIC(1)IWQDWGEHRC(1)T-[NH2] (Compound 29)

[Ac]-EGEIC(1)IWQDWGEHRC(1)T-[NH2] (Compound 30)

[Ac]-ESEIC(1)IWQDWGEHRC(1)T-[NH2] (Compound 31)

[Ac]-SEIC(1)IWQDWGEHRC(1)TEA-[NH2] (Compound 32)

[Ac]-EIC(1)IWQDWGEHRC(1)TE-[NH2] (Compound 33)

[Ac]-EIC(1)IWQDWGEHRC(1)TEGE-[NH2] (Compound 34)

[Ac]-EGEIC(1)IWQDWGEHRC(1)EGE-[NH2] (Compound 35)

[Ac]-ESEIC(1)IWQDWGEHRC(1)EGE-[NH2] (Compound 36)

[Ac]-KEKIC(1)IWQDWGEHRC(1)TEKE-[NH2] (Compound 37)

[Ac]-EKGIC(1)IWQDWGEHRC(1)TEKP-[NH2] (Compound 38)

[Ac]-IC(1)IWQDWGEHRC(1)TEGK-[NH2] (Compound 39)

[Ac]-GSAIC(1)IWQDWGEHRC(1)[Sar]E-[NH2] (Compound 40)

[Ac]-SAIC(1)IWQDWGEHRC(1)[Sar]E-[NH2] (Compound 41)

[Ac]-SAIC(1)IWQDWGEHRC(1)TEG-[NH2] (Compound 42)

[Ac]-FC(1)IWQDWGEHRC(1)TGAE-[NH2] (Compound 43)

[Ac]-EGSAIC(1)IWQDWGEHRC(1)[Sar]EGE-[NH2] (Compound 44)

[Ac]-EGSAFC(1)IWQDWGEHRC(1)[Sar]E-[NH2] (Compound 45)

[Ac]-ESSAIC(1)IWQDWGAHRC(1)T-[NH2] (Compound 46)

[Ac]-IC(1)IWQDWGAHRC(1)TGAES-[NH2] (Compound 47)

In accordance with the present invention, information about the biological and physico-chemical characteristics of Ac-compstatin binding to C3 have been employed to design compstatin analogues with significantly improved activity compared to the parent compstatin analogues. Preferably, the compstatin analogs have at least 30-fold greater activity than Ac-compstatin. In other embodiments, the analogs have 40-, 50-, 60-, 70-, 80-, 90-, 100-, 110-, 120-, 130-, 140-, 150-fold or greater activity than Ac-compstatin, as compared utilizing the assays described in the examples.

Compstatin analogues made in the prior art have been shown to possess improved activity as compared with the parent peptide, i.e., up to about 99-fold (Mallik, B. et al, 2005, supra; WO 2004/026328), and up to about 264-fold (Katragadda et al., 2006, supra; WO2007/062249).

The activity of the compstatin analogues may be determined with reference to one or more biological activities selected from (1) binding to C3 protein, (2) binding to C3b protein, (3) inhibiting the cleavage of native C3 by C3 convertases, and (4) inhibiting the activation of the complement system. Preferably, the *in vitro* effect of the compounds of the present invention were assessed by measuring their inhibitory effect of the classical complement pathway in a haemolysis assay, e.g. using the assay described in Example 2.

Synthesis of Compstatin Analogues

It is preferred to synthesize compstatin analogues of the present invention by means of solid-phase or liquid-phase peptide synthesis methodology. In this context, reference may be made to WO 98/11125 and, among many others, Fields, G.B. et al., 2002, "Principles and practice of solid-phase peptide synthesis". In: Synthetic Peptides (2nd Edition), and the Examples herein.

In accordance with the present invention, a compstatin analogue of the invention may be synthesized or produced in a number of ways, including for example, a method which comprises:

(a) synthesizing the compstatin analogues by means of solid-phase or liquid-phase peptide synthesis methodology and recovering the synthesized compstatin analogues thus obtained; or

(b) expressing a precursor peptide sequence from a nucleic acid construct that encodes the precursor peptide, recovering the expression product, and modifying the precursor peptide to yield a compound of the invention.

The precursor peptide may be modified by introduction of one or more non-proteinogenic amino acids, e.g. Aib, Orn, Dap, or Dab, or by the introduction of an appropriate terminal groups R1 and/or R2.

Expression is typically performed from a nucleic acid encoding the precursor peptide, which may be performed in a cell or a cell-free expression system comprising such a nucleic acid.

It is preferred to synthesize the analogues of the invention by means of solid-phase or liquid-phase peptide synthesis. In this context, reference is made to WO 98/11125 and, among many others, Fields, GB et al., 2002, "Principles and practice of solid-phase peptide synthesis". In: Synthetic Peptides (2nd Edition), and the Examples herein.

For recombinant expression, the nucleic acid fragments encoding the precursor peptide will normally be inserted in suitable vectors to form cloning or expression vectors. The vectors can, depending on purpose and type of application, be in the form of plasmids, phages, cosmids, mini-chromosomes, or virus, but also naked DNA which is only expressed transiently in certain cells is an important vector. Preferred cloning and expression vectors (plasmid vectors) are capable of autonomous replication, thereby enabling high copy-numbers for the purposes of high-level expression or high-level replication for subsequent cloning.

In general outline, an expression vector comprises the following features in the 5'→3' direction and in operable linkage: a promoter for driving expression of the nucleic acid fragment, optionally a nucleic acid sequence encoding a leader peptide enabling secretion (to the extracellular phase or, where applicable, into the periplasma), the nucleic acid fragment encoding the precursor peptide, and optionally a nucleic acid sequence encoding a terminator. They may comprise additional features such as selectable markers and origins of replication. When operating with expression vectors in producer strains or cell lines it may be preferred that the vector is capable of integrating into the host cell genome. The skilled person is very familiar with suitable vectors and is able to design one according to their specific requirements.

The vectors of the invention are used to transform host cells to produce the precursor peptide. Such transformed cells can be cultured cells or cell lines used for propagation of the nucleic acid fragments and vectors, and/or used for recombinant production of the precursor peptides.

Preferred transformed cells are micro-organisms such as bacteria [such as the species *Escherichia* (e.g. *E. coli*), *Bacillus* (e.g. *Bacillus subtilis*), Salmonella, or *Mycobacterium* (preferably non-pathogenic, e.g. *M. bovis* BCG), yeasts (e.g., Saccharomyces cerevisiae and Pichia pastoris), and protozoans. Alternatively, the transformed cells may be derived from a multicellular organism, i.e. it may be fungal cell, an insect cell, an algal cell, a plant cell, or an animal cell such as a mammalian cell. For the purposes of cloning and/or optimised expression it is preferred that the transformed cell is capable of replicating the nucleic acid fragment of the invention. Cells expressing the nucleic fragment can be used for small-scale or large-scale preparation of the peptides of the invention.

When producing the precursor peptide by means of transformed cells, it is convenient, although far from essential, that the expression product is secreted into the culture medium.

Medical Conditions

In a broad aspect, the present invention provides compstatin analogues of the present invention for use as a medicament or for use in therapy.

The compstatin analogues described herein have biological activities of binding to C3 protein and/or inhibiting complement activation. Generally, the compstatin analogues of the present invention may be used for the treatment or prevention conditions associated with excessive or unwanted activation of the complement system. Complement can be activated through three different pathways: the classical, lectin and alternative pathways. The major activation event that is shared by all three pathways is the proteolytic cleavage of the central protein of the complement system, C3, into its activation products C3a and C3b by C3 convertases. Generation of these fragments leads to the opsonization of pathogenic cells by C3b and iC3b, a process that renders them susceptible to phagocytosis or clearance, and to the activation of immune cells through an interaction with complement receptors (Markiewski & Lambris, 2007, Am. J. Pathol., 171: 715-727). Deposition of C3b on target cells also induces the formation of new convertase complexes and thereby initiates a self-amplification loop. An ensemble of plasma and cell surface-bound proteins carefully regulates complement activation to prevent host cells from self-attack by the complement cascade. The 13 amino acid cyclic tridecapeptide used as a reference point for the design of the compstatin analogues of the present invention inhibits complement activation by binding to C3 and/or C3b, preventing the cleavage of native C3 by the C3 convertases. Without wishing to be bound by any particular theory, the present inventors believe that the compstatin analogues of the present invention also function in this way and may share one or more biological activities selected from (1) binding to C3 protein, (2) binding to C3b protein, (3) inhibiting the cleavage of native C3 by

C3 convertases, and/or (4) inhibiting the activation of the complement system. The biological activity of the compstatin analogues of the present invention may be determined *in vitro* by measuring their inhibitory effect of the classical complement pathway in a haemolysis assay, for example using a protocol set out in the examples below.

Excessive activation or inappropriate regulation of complement can lead to a number of pathologic conditions, ranging from autoimmune diseases to inflammatory diseases (Holers, 2003, Clin. Immunol., 107: 140-51; Markiewski & Lambris, 2007, supra; Ricklin & Lambris, 2007, Nat. Biotechnol., 25: 1265-75; Sahu et al., 2000, J. Immunol., 165: 2491-9). These conditions include: (1) inhibiting complement activation to facilitate treatment of diseases or conditions including age-related macular degeneration, periodontitis, diabetic retinopathy, glaucoma, uveitis, rheumatoid arthritis, spinal cord injury, stroke, multiple sclerosis, Parkinson's disease, Alzheimer's disease, cancer, and respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), allergic inflammation, emphysema, bronchitis, bronchiecstasis, cystic fibrosis, tuberculosis, pneumonia, respiratory distress syndrome (RDS - neonatal and adult), rhinitis and sinusitis; bacterial infections such as sepsis, ischemia-reperfusion injury in various tissues, myocardial infarction, anaphylaxis, paroxysmal nocturnal hemoglobinuria, autoimmune hemolytic anemia, psoriasis, hidradentitis suppurativa, myasthenia gravis, systemic lupus erythematosus, CHAPLE syndrome, C3 glomeropathy, atypical hemolytic uremic syndrome, Crohn´s disease, antiphospholipid syndrome, or (2) inhibiting complement activation that occurs during cell or organ transplantation, or in the use of artificial organs or implants (e.g., by coating or otherwise treating the cells, organs, artificial organs or implants with a peptide of the invention); or (3) inhibiting complement activation that occurs during extracorporeal shunting of physiological fluids (blood, urine) (e.g., by coating the tubing through which the fluids are shunted with a compstatin analogue of the present invention).

Pharmaceutical Compositions and Administration

In a further aspect, the present invention relates to a composition comprising a compstatin analogue according to the invention, or a pharmaceutically acceptable salt or solvate thereof, together with a carrier. In one embodiment of the invention, the composition is a pharmaceutical composition and the carrier is a pharmaceutically acceptable carrier. The present invention also relates to a pharmaceutical composition comprising a compstatin analogue according to the invention, or a salt and/or solvate thereof, together with a carrier, excipient or vehicle. Accordingly, the compstatin analogue of the present invention, or salts or solvates thereof, especially pharmaceutically acceptable salts and/or solvates thereof, may be formulated as compositions or pharmaceutical compositions prepared for storage or

administration, and which comprise a therapeutically effective amount of a compstatin analogue of the present invention, or a salt or solvate thereof.

Suitable salts formed with bases include metal salts, such as alkali metal or alkaline earth metal salts.

In one embodiment, a pharmaceutical composition of the invention is one wherein the compstatin analogue is in the form of a pharmaceutically acceptable acid addition salt.

As will be apparent to one skilled in the medical art, a "therapeutically effective amount" of a compstatin analogue compound or pharmaceutical composition thereof of the present invention will vary depending upon, inter alia, the age, weight and/or gender of the subject (patient) to be treated. Other factors that may be of relevance include the physical characteristics of the specific patient under consideration, the patient's diet, the nature of any concurrent medication, the particular compound(s) employed, the particular mode of administration, the desired pharmacological effect(s) and the particular therapeutic indication. Because these factors and their relationship in determining this amount are well known in the medical arts, the determination of therapeutically effective dosage levels, the amount necessary to achieve the desired result of treating and/or preventing and/or remedying malabsorption and/or low-grade inflammation described herein, as well as other medical indications disclosed herein, will be within the ambit of the skilled person.

As used herein, the term "a therapeutically effective amount" refers to an amount which reduces symptoms of a given condition or pathology, and preferably which normalizes physiological responses in an individual with that condition or pathology. Reduction of symptoms or normalization of physiological responses can be determined using methods routine in the art and may vary with a given condition or pathology. In one aspect, a therapeutically effective amount of one or more compstatin analogues, or pharmaceutical compositions thereof, is an amount which restores a measurable physiological parameter to substantially the same value (preferably to within 30%, more preferably to within 20%, and still more preferably to within 10% of the value) of the parameter in an individual without the condition or pathology in question.

In one embodiment of the invention, administration of a compound or pharmaceutical composition of the present invention is commenced at lower dosage levels, with dosage levels being increased until the desired effect of preventing/treating the relevant medical indication is achieved. This would define a therapeutically effective amount. For the

compstatin analogues of the present invention, alone or as part of a pharmaceutical composition, such human doses of the active compstatin analogue may be between about 0.01 pmol/kg and 500 µmol/kg body weight, between about 0.01 pmol/kg and 300 µmol/kg body weight, between 0.01 pmol/kg and 100 µmol/kg body weight, between 0.1 pmol/kg and 50 µmol/kg body weight, between 1 pmol/kg and 10 µmol/kg body weight, between 5 pmol/kg and 5 µmol/kg body weight, between 10 pmol/kg and 1 µmol/kg body weight, between 50 pmol/kg and 0.1 µmol/kg body weight, between 100 pmol/kg and 0.01 µmol/kg body weight, between 0.001 µmol/kg and 0.5 µmol/kg body weight, between 0.05 µmol/kg and 0.1 µmol/kg body weight.

The therapeutic dosing and regimen most appropriate for patient treatment will of course vary with the disease or condition to be treated, and according to the patient's weight and other parameters. Without wishing to be bound by any particular theory, it is expected that doses, in the mg/kg range, and shorter or longer duration or frequency of treatment may produce therapeutically useful results, such as a statistically significant inhibition of the alternative and classical complement pathways. The dosage sizes and dosing regimen most appropriate for human use may be guided by the results obtained by the present invention, and may be confirmed in properly designed clinical trials.

An effective dosage and treatment protocol may be determined by conventional means, starting with a low dose in laboratory animals and then increasing the dosage while monitoring the effects, and systematically varying the dosage regimen as well. Numerous factors may be taken into consideration by a clinician when determining an optimal dosage for a given subject.

For local delivery to the eye, the pharmaceutically acceptable compositions may be formulated in isotonic, pH adjusted sterile saline or water, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum or as eyedrops. Methods of local administration to the eye include, e.g., choroidal injection, transscleral injection or placing a scleral patch, selective arterial catheterization, eyedrops or eye ointments, intraocular administration including transretinal , subconjunctival bulbar, intravitreous injection, suprachoroidal injection, subtenon injection, scleral pocket and scleral cutdown injection, by osmotic pump, etc. The agent can also be alternatively administered intravascularly, such as intravenously (IV) or intraarterially. In choroidal injection and scleral patching, the clinician uses a local approach to the eye after initiation of appropriate anesthesia, including painkillers and ophthalmoplegics. A needle containing the therapeutic

compound is directed into the subject's choroid or sclera and inserted under sterile conditions. When the needle is properly positioned the compound is injected into either or both of the choroid or sclera. When using either of these methods, the clinician can choose a sustained release or longer acting formulation. Thus, the procedure can be repeated only every several months or several years, depending on the subject's tolerance of the treatment and response.

The following examples are provided to describe the invention in greater detail. They are intended to illustrate, not to limit, the invention.

Example 1: Synthesis of Compstatin Analogues

General Peptide Synthesis

List of abbreviations and suppliers			
	Abbreviation	**Name**	**Brand / Supplier**
Resins			
		TentaGel™ PHB AA(Proct)-Fmoc	Rapp Polymere
		TentaGel™ SRAM	Rapp Polymere
Amino acids			
		Pseudoprolines (E.g. YS, FS, FT)	Jupiter Bioscience Ltd.
		Fmoc-L-AA-OH	Senn Chemicals AG
Coupling reagents			
	Oxyma Pure	Ethyl cyanoglyoxylate-2-oxime	Chem Impex international
	DIC	Diisopropylcarbodiimide	Fluka / Sigma Aldrich Co.
	HATU	N-[(dimethylamino)-1H-1,2,3-triazol[4,5-b]pyridine-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide	ChemPep Inc.
	HOBt	Hydroxybenzotriazole	Sigma-Aldrich Co.
Solvents reagents			
	Boc_2O	Di-tert-butyl pyrocarbonate	Advanced ChemTech
	DCM	Dichloromethane	Prolabo (VWR)
	DIPEA	Diisopropylethylamine	Fluka / Sigma Aldrich Co.

	DMF	N,N-dimethylformamide	Taminco
	Et_2O	Diethyl ether	Prolabo (VWR)
	EtOH	Ethanol	CCS Healthcare AB
	HCOOH	Formic acid (HPLC grade)	Sigma-Aldrich Co.
	H_2O	Water, Milli-Q water	Millipore
	MeCN	Acetonitrile (HPLC)	Sigma-Aldrich Co.
	NMP	N-methylpyrrolidone	Sigma-Aldrich Co.
		Piperidine	Jubliant Life Sciences Ltd.
	TFA	Trifluoroacetic acid (HPLC)	Chemicals Raw Materials Ltd.
	TIS	Triisopropylsilane	Sigma-Aldrich Co.
	MeOH	Methanol	Sigma-Aldrich Co.

Apparatus and synthetic strategy

Peptides were synthesized batchwise on a peptide synthesiser, such as a CEM Liberty Peptide Synthesizer or a Symphony X Synthesizer, according to solid phase peptide synthetic procedures using 9-fluorenylmethyloxycarbonyl (Fmoc) as N-α-amino protecting group and suitable common protection groups for side-chain functionalities.

As polymeric support based resins, such as e.g. TentaGel™, was used. The synthesizer was loaded with resin that prior to usage was swelled in DMF.

Coupling

CEM Liberty Peptide Synthesizer

A solution of Fmoc-protected amino acid (4 equiv.) was added to the resin together with a coupling reagent solution (4 equiv.) and a solution of base (8 equiv.). The mixture was either heated by the microwave unit to 70-75°C and coupled for 5 minutes or coupled with no heat for 60 minutes. During the coupling nitrogen was bubbled through the mixture.

Symphony X Synthesizer

The coupling solutions were transferred to the reaction vessels in the following order: amino acid (4 equiv.), HATU (4 equiv.) and DIPEA (8 equiv.). The coupling time was 10 min at room temperature (RT) unless otherwise stated. The resin was washed with DMF (5 x 0,5 min). In case of repeated couplings the coupling time was in all cases 45 min at RT.

Deprotection

CEM Liberty Peptide Synthesizer

The Fmoc group was deprotected using piperidine in DMF or other suitable solvents. The deprotection solution was added to the reaction vessel and the mixture was heated for 30 sec. reaching approx. 40°C. The reaction vessel was drained and fresh deprotection solution

was added and subsequently heated to 70-75°C for 3 min. After draining the reaction vessel the resin was washed with DMF or other suitable solvents.

Symphony X Synthesizer

Fmoc deprotection was performed for 2,5 minutes using 40% piperidine in DMF and repeated using the same conditions. The resin was washed with DMF (5 x 0,5 min).

Cleavage

The dried peptide resin was treated with TFA and suitable scavengers for approximately 2 hours. The volume of the filtrate was reduced and the crude peptide was precipitated after addition of diethylether. The crude peptide precipitate was washed several times with diethylether and finally dried.

HPLC purification of the crude peptide

The crude peptide was purified by preparative reverse phase HPLC using a conventional HPLC apparatus, such as a Gilson GX-281 with 331/332 pump combination, for binary gradient application equipped with a column, such as 5 x 25 cm Gemini NX 5u C18 110A column, and a fraction collector using a flow 20-40 ml/min with a suitable gradient of buffer A (0.1% Fomic acid, aq.) or A (0.1% TFA, aq.) and buffer B (0.1% Formic acid, 90% MeCN, aq.) or B (0.1% TFA, 90% MeCN, aq.). Fractions were analyzed by analytical HPLC and MS and selected fractions were pooled and lyophilized. The final product was characterized by HPLC and MS.

Oxidation

Following purification and lyophilisation of the crude linear peptide, the peptide was redissolved in 0.1% TFA in water, acetonitrile and acetic acids until a clear solution. The concentration of the peptide solution was kept at approx. 1-2 mg/ml depending on the peptides ability to solubilize. The peptide solution was stirred, while a solution of iodine in methanol (approx. 1.5 equiv.) was added drop-wise until the peptide solution obtain an orange colour. After 10-15 minutes, the oxidation was finished and excess iodine was reduced with a solution of ascorbic acid in water (1 equiv.) until a colourless peptide solution. The peptide solution was diluted with water before preparative HPLC purification.

Analytical HPLC

Final purities were determined by analytic HPLC (Agilent 1100/1200 series) equipped with auto sampler, degasser, 20 µl flow cell and Chromeleon software. The HPLC was operated with a flow of 1.2 ml/min at 40°C using an analytical column, such as Kinetex 2.6 µm XB-C18

100A 100x4,6 mm column. The compound was detected and quantified at 215 nm. Buffers A (0.1% TFA, aq.) and buffer B (0.1% TFA, 90% MeCN, aq.).

Mass spectroscopy

Final MS analysis were determined on a conventional mass spectroscopy, e.g. Waters Xevo G2 TOF, equipped with electrospray detector with lock-mass calibration and MassLynx software. It was operated in positive mode using direct injection and a cone voltage of 15V (1 TOF), 30 V (2 TOF) or 45 V (3 TOF) as specified on the chomatogram. Precision was 5 ppm with a typical resolution of 15,000-20,000.

Synthesis of compound shown in Comp No 24:

Ac-IC(1)IWQDWGEHRC(1)TEGE-NH_2

Solid phase peptide synthesis was performed on a Symphony X Synthesizer using standard Fmoc chemistry. TentaGel S RAM (2,51 g; 0.23 mmol/g) was swelled in DMF (20 ml) prior to use and the Fmoc-group was deprotected according to the procedure described above.

Coupling

Suitable protected Fmoc-amino acids according to the sequence were coupled as described above using HATU as coupling reagent. All couplings were performed at R.T.

Deprotection

Fmoc deprotection was performed according to the procedure described above.

Cleavage of the peptide from the solid support

The peptide-resin was washed with EtOH (3 x 10 ml) and Et2O (3 x 10 ml) and dried to constant weight at room temperature (r.t.). The peptide was cleaved from the resin by treatment with TFA/TIS/H_2O (95/2,5/2,5; 60 ml, 2 h; r.t.). The volume of the filtrate was reduced and the crude peptide was precipitated after addition of diethylether. The crude peptide precipitate was washed several times with diethylether and finally dried to constant weight at room temperature yield 760 mg crude peptide product (purity ~30%).

HPLC purification of the crude linear peptide

The crude peptide was purified by preparative reverse phase HPLC using a Gilson GX-281with 331/332 pump combination for binary gradient application equipped with a *5 x 25 cm Gemini NX 5u C18* 110A, column and a fraction collector and run at 35 ml/min with a gradient of buffer A (0.1% TFA, aq.) and buffer B (0.1% TFA, 90% MeCN, aq.) gradient from 20%B to

45%B in 47 min. Fractions were analyzed by analytical HPLC and MS and relevant fractions were pooled and lyophilized to yield 190 mg, with a purity of 85% as characterized by HPLC and MS as described above. Calculated monoisotopic MW = 2001.58 found 2001.81.

Oxidation of the crude linear peptide

The 190 mg purified linear peptide was dissolved in 220 ml 0.1% TFA in water (65%) and acetonitrile (35%) until a clear solution. The peptide solution was stirred, while a solution of iodine in methanol (2.2 mL, approx. 1.5 equiv. iodine) was added drop-wise until the peptide solution obtain an orange colour. The reaction was followed by analytic HPLC but already after 10-15 minutes, the oxidation was finished. Excess iodine was reduced with a solution of ascorbic acid in water (220 μL, approx.1 equiv.) until a colourless peptide solution. The peptide solution was reduced slightly by rota evaporation before purification on preparative HPLC.

HPLC purification of the oxidized peptide

The crude peptide was purified by preparative reverse phase HPLC using a Gilson GX-281with 331/332 pump combination for binary gradient application equipped with a *5 x 25 cm Gemini NX 5u C18* 110A, column and a fraction collector and run at 35 ml/min with a gradient of buffer A (0.1% TFA, aq.) and buffer B (0.1% TFA, 90% MeCN, aq.) gradient from 20%B to 45%B in 47 min. Fractions were analyzed by analytical HPLC and MS and relevant fractions were pooled and lyophilized to yield 138 mg, with a purity of 92% as characterized by HPLC and MS as described above. Calculated monoisotopic MW = 1999,83 found 1999,54.

Table 5: Synthesized compounds:

Compound Number	**Sequence**
Compstatin 1-13	H-IC(1)VVQDWGHHRC(1)T-[NH2]
Ac-compstatin	[Ac]-IC(1)VVQDWGHHRC(1)T-[NH2]
4W9A	[Ac]-IC(1)VWQDWGAHRC(1)T-[NH2]
1	[Ac]-IC(1)IWQDWGAHRC(1)T-[NH2]
2	[Ac]-IC(1)IWQDWGEHRC(1)T-[NH2]
3	[Ac]-ESSAIC(1)IWQDWGEHRC(1)T-[NH2]
4	[Ac]-IC(1)I[1-Me-Trp]QDWGEHRC(1)T-[NH2]
5	[Ac]-IC(1)IWQDWGKHRC(1)T-[NH2]
6	[Ac]-IC(1)IWQDWGSHRC(1)T-[NH2]
7	[Ac]-IC(1)IWQKWGEHRC(1)T-[NH2]
8	[Ac]-IC(1)IWQKWGAHRC(1)TGAES-[NH2]

9	[Ac]-YC(1)IWQDWGEHRC(1)T-[NH2]
10	[Ac]-ESSAYC(1)IWQDWGEHRC(1)T-[NH2]
11	[Ac]-[Sar]C(1)IWQDWGEHRC(1)T-[NH2]
12	[Ac]-IC(1)IWQDWGAHRC(1)E-[NH2]
13	[Ac]-IC(1)IWQDWGEHRC(1)[Sar]-[NH2]
14	[Ac]-ESSAIC(1)IWQDWGEHRC(1)TGAES-[NH2]
15	[Ac]-IC(1)IWQDWGEHRC(1)TGAES-[NH2]
16	[Ac]-IC(1)IWQEWGEHRC(1)T-[NH2]
17	[Ac]-IC(1)IWQDWGDHRC(1)T-[NH2]
18	[Ac]-IC(1)IWQDWGRHRC(1)T-[NH2]
19	[Ac]-IC(1)IWQDWGAHSC(1)T-[NH2]
20	[Ac]-IC(1)IWQDWGEHSC(1)T-[NH2]
21	[Ac]-IC(1)IWQDWGEHRC(1)S-[NH2]
22	[Ac]-IC(1)IWQDWGEHRC(1)E-[NH2]
23	[Ac]-FC(1)IWQDWGEHRC(1)T-[NH2]
24	[Ac]-IC(1)IWQDWGEHRC(1)TEGE-[NH2]
25	[Ac]-IC(1)IWQDWGEHRC(1)TEA-[NH2]
26	[Ac]-IC(1)IWQDWGEHRC(1)TE-[NH2]
27	[Ac]-IC(1)IWQDWGEHRC(1)EGE-[NH2]
28	[Ac]-EGSAIC(1)IWQDWGEHRC(1)[Sar]E-[NH2]
29	[Ac]-EGSAIC(1)IWQDWGEHRC(1)T-[NH2]
30	[Ac]-EGEIC(1)IWQDWGEHRC(1)T-[NH2]
31	[Ac]-ESEIC(1)IWQDWGEHRC(1)T-[NH2]
32	[Ac]-SEIC(1)IWQDWGEHRC(1)TEA-[NH2]
33	[Ac]-EIC(1)IWQDWGEHRC(1)TE-[NH2]
34	[Ac]-EIC(1)IWQDWGEHRC(1)TEGE-[NH2]
35	[Ac]-EGEIC(1)IWQDWGEHRC(1)EGE-[NH2]
36	[Ac]-ESEIC(1)IWQDWGEHRC(1)EGE-[NH2]
37	[Ac]-KEKIC(1)IWQDWGEHRC(1)TEKE-[NH2]
38	[Ac]-EKGIC(1)IWQDWGEHRC(1)TEKP-[NH2]
39	[Ac]-IC(1)IWQDWGEHRC(1)TEGK-[NH2]
40	[Ac]-GSAIC(1)IWQDWGEHRC(1)[Sar]E-[NH2]
41	[Ac]-SAIC(1)IWQDWGEHRC(1)[Sar]E-[NH2]
42	[Ac]-SAIC(1)IWQDWGEHRC(1)TEG-[NH2]
43	[Ac]-FC(1)IWQDWGEHRC(1)TGAE-[NH2]
44	[Ac]-EGSAIC(1)IWQDWGEHRC(1)[Sar]EGE-[NH2]

45	[Ac]-EGSAFC(1)IWQDWGEHRC(1)[Sar]E-[NH2]
46	[Ac]-ESSAIC(1)IWQDWGAHRC(1)T-[NH2]
47	[Ac]-IC(1)IWQDWGAHRC(1)TGAES-[NH2]

Example 2: *In vitro* haemolysis assay

Method

The *in vitro* effect of the compounds of the present invention was assessed by measuring their inhibitory effect of the classical complement pathway in a haemolysis assay.

Briefly, compounds of the present invention and reference compounds were dissolved in DMSO and diluted in Tris/Casein Assay Buffer (10 mM Tris, 145 mM NaCl, 0.5 mM MgCl2, 0.15 mM CaCl2, and 0.1 % W/V Casein, adjusted to pH 7.4) as 9-point serial dilutions in a 96 well plate. Sensitized sheep red blood cells (RBC) coated with rabbit anti-sheep erythrocyte antiserum (Complement Technology, Inc., TX, USA) were washed in Tris/Casein Assay Buffer. 50 µl from each well of diluted compound was added to a 96-well plate containing 50 µl diluted human serum (Complement Technology, Inc., TX, USA) and incubated for 15 minutes at room temperature. The serum dilution factor was optimized for every serum batch to obtain 70-90% of maximal haemolysis using the protocol. Then 50 µl sensitized sheep red blood cells were added to all wells (10^7 per well).

After 30 minutes of incubation at 37 °C with gentle agitation, the reaction was stopped by addition of 50 µl Tris STOP Buffer per well (10 mM EDTA, 10 mM Tris, 145 mM NaCl adjusted to pH 7.4). The RBCs were then removed by centrifugation and the resulting supernatant measured for hemolysis by absorbance at 405 nm.

The response was normalized relative to a positive and negative control (vehicle) to calculate the IC50 from the concentration response curve using the 4-parameter logistic (4PL) nonlinear model for curve fitting. All values are based on n=>2 independent determinations.

Table 6: *in vitro* analysis of inhibition of hemolysis

Comp No	**IC50[nM]**
Compstatin	>5µM
Ac-compstatin	>5µM
4W9A	220
1	150
2	94
3	69
4	50
5	130

6	140
7	850
8	410
9	60
10	67
11	86
12	54
13	47
14	81
15	47
16	100
17	47
18	66
19	140
20	59
21	77
22	50
23	37
24	89
25	47
26	50
27	79
28	88
29	52
30	66
31	93
32	72
33	93
34	110
35	320
36	150
37	130
38	250
39	98
40	150
41	150
42	130
43	39
44	110
45	37
46	51
47	50

Example 3: Solubility test

Materials and method

Compound solubility at 10 mg/mL

The solubility of compounds was assessed by measuring light scattering over a pH interval from pH 4 to pH 7.5.

Compounds were dissolved in a stock solution of 20 mg/mL at pH 2.5. These stock solutions were diluted 1:1 with 200 mM buffered solution to reach a final solution of 10 mg/mL compound in 100 mM buffer. The 5 investigated conditions were (1) acetate pH 4.0, (2) acetate pH 5.0, (3) phosphate pH 6.0, (4) phosphate pH 7 and (5) phosphate pH 7.5.

These samples were equilibrated for 15 minutes at ambient temperature, before evaluating solubility by visual inspection and absorbance measurements in a microplate reader.

Visual inspection

Visual inspection included manually checking the 96 well plate for wells that are clear or non-clear. In addition to this a picture of the 96 well plate is taken.

Microplate reader and light scattering

Absorbance was measured at four wavelengths: 280 nm, 325 nm, 340 nm and 360 nm in an UV transparent 96 well microplate in a SpectraMax 190 microplate reader. The compounds do not absorb at 325-360 nm and signal at these wavelengths are therefore an expression of light scattering, which reflects the presence of visible or sub-visible particles that are detected as increased signal.

The light scattering was normalized to the signal from pure buffer solutions (100 mM) and compound solubility was evaluated as good (+) or poor (-). The criteria for this was a combination of visual inspection and light scattering not exceeding 0.1 AU, where values below 0.1 AU are good.

Solubility of Comp No 24: (Sequence Ac-IC(1)IWQDWGEHRC(1)TEGE-NH_2)

Stock solution

Comp No 24 was carefully weighed out and dissolved in pH 2.5 H_2O-Cl. The stock solution was equilibrated 15 minutes at ambient temperature, at which point no visible particles were present. 200 mM buffer stock solutions were prepared for each pH condition.

Solubility assay:

The formulations for solubility testing were made by mixing 50 µL Comp No 24 stock solution

and 50 μL buffer stock solution with gentle mixing by pipetting the solution a couple of times. This was done for each buffer/pH condition in a UV transparent 96 well microplate (Corning 96 well REF 3635). Reference samples without Comp No 24 were made by mixing 50 μL pH 2.5 H_2O-Cl and 50 μL buffer stock solution. The plate was covered with a lid and left 15 minutes at ambient temperature before assessing solubility.

Measuring solubility:

Solubility was assessed by visual inspection of each formulation and a picture taken in a photo box. Light scattering was measured at 280 nm, 325 nm, 340 nm and 360 nm in a SpectraMax 190 microplate reader.

The visual inspection revealed that condition 1, 2 and 3 were cloudy and condition 2 additionally contained visible precipitates. The absorbance measurement confirmed the visual evaluation with condition 1, 2 and 3 all exceeding 0.1 AU threshold. Condition 4 and 5 were thus deemed good conditions for solubility of 10 mg/mL Comp No 24 .

Table 7: Table of most soluble compounds, as tested at 10 mg/mL. + denotes solubility at the given condition, as determined by UV absorbance being less than 0.1 AU at 340 nm and the sample being clear when manually inspected. - denotes lack of solubility at the given condition, as UV absorbance at 340 nm exceeds 0.1 AU.

	Buffer & pH				
Comp No	Acetate pH 4	Acetate pH 5	Phosphate pH 6	Phosphate pH 7	Phosphate pH 7.5
1	+	-	-	-	-
3	+	-	-	+	+
14	+	-	-	+	+
15	+	-	-	+	+
24	-	-	-	+	+
27	-	-	-	+	+
28	+	+	+	+	+
30	-	-	-	+	+
31	+	+	+	+	+
32	-	-	-	+	+
33	-	-	+	+	+
36	-	-	-	+	+

Example 4: Affinity measurements by surface plasmon resonance
Method

Surface plasmon resonance (SPR) was used to characterize peptides with respect to their binding affinity (Kd) for C3. Human C3b (Complement tech cat #A114) was immobilised on individual flow cells of CM5 sensor chips (GE Healthcare) using standard amine coupling to a density of approximately 3000 resonance units (RU) in a buffer consisting of 10 mM phosphate pH 7.4, 150 mM NaCl, 0.05% Tween20.

For interaction experiments a multi-cycle experiment approach was used and performed using a BiacoreT200™ instrument (GE Healthcare) at 25C. Peptides were injected in increasing concentration series (6-8 different concentrations) for 60-120 s at a flow rate of 30 µL/min in a buffer consisting of 10 mM Tris buffer at pH 7.4, with 150 mM NaCl and 0.05% Tween20. This was followed by a dissociation period for up to 10 min. The C3 surface was regenerated between runs by a 45 s injection of 3 M $MgCl_2$.

Sensorgrams were double-referenced (reference surface, blanks) prior to analysis of the kinetic profiles by globally fitting data to a 1:1 Langmuir binding model to obtain association and dissociation rates for calculation of the equilibrium dissociation constant Kd. Each peptide was tested at in a least 3 independent experiments.

Table 8: Compstatin analogues binding affinities for C3 as determined by a surface plasmon resonance assay with immobilized C3

Comp. no.	Kd [nM]	N
2	16	3
4	1.5	3
15	14	3
20	37	3
21	16	3
23	2.9	3
24	28	5
28	44	3
29	21	3
43	3.3	3

Claims:

1. A compstatin analogue represented by the formula:

Y1-R1-X1-C-I-X2-Q-X3-W-X4-X5-H-X6-C-X7-R2-Y2,

wherein:

Y1 is hydrogen or acetyl;

X1 is I, Y, F or Sar;

X2 is W, F, V, Y, 1MeTrp, D-Trp, N-Me-Trp, 1-For-Trp, 1-Nal, 2-Nal, 5MeTrp, Bpa or 2Igl;

X3 is E, K or D;

X4 is G or Sar;

X5 is H, A, E, D, K, R or S;

X6 is R or S;

X7 is T, S, E, F, H, K, Sar, G, I, D, N-Me-Ile or N-Me-Thr;

Y2 is NH_2 or OH;

R1 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof; and

R2 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof;

wherein the compstatin analogue has a disulphide bond between the cysteine residues at positions 2 and 12;

or a pharmaceutically acceptable salt and/or solvate thereof.

2. The compstatin analogue of claim 1, which is represented by the formula:

Y1-R1-X1-C-I-X2-Q-D-W-X4-X5-H-X6-C-X7-R2-Y2,

wherein:

Y1 is hydrogen or acetyl;

X1 is I, Y, F or Sar;

X2 is W, V, Y, 2-Nal, 1-Nal or 1MeTrp;

X4 is G or Sar;

X5 is A, E, D, K or S;

X6 is R or S;

X7 is T, S, E, I, Sar, K, G or N-Me-Ile;

Y2 is NH_2 or OH;

R1 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof; and

R2 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof;

wherein the compstatin analogue has a disulphide bond between the cysteine residues at positions 2 and 12;

or a pharmaceutically acceptable salt and/or solvate thereof.

3. The compstatin analogue of claim 1 or claim 2 which is represented by the formula:

Y1-R1-X1-C-I-X2-Q-D-W-G-X5-H-X6-C-X7-R2-Y2,

wherein:

Y1 is hydrogen or acetyl;

X1 is I, Y, F or Sar;

X2 is W, V, Y, 1-Nal, 2-Nal or 1MeTrp;

X5 is A, E, D, K or S;

X6 is R or S;

X7 is T, I, S, E, K or Sar;

Y2 is NH_2 or OH;

R1 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof; and

R2 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof;

wherein the compstatin analogue has a disulphide bond between the cysteine residues at positions 2 and 12;

or a pharmaceutically acceptable salt and/or solvate thereof.

4. The compstatin analogue of any one of claims 1 to 3 which is represented by the formula:

Y1-R1-X1-C-I-X2-Q-D-W-G-X5-H-R-C-X7-R2-Y2,

wherein:
Y1 is hydrogen or acetyl;

X1 is I, Y, F or Sar;

X2 is W, V, Y, 1-Nal, 2-Nal or 1MeTrp;

X5 is A, E, D, K or S;

X7 is T, S, E or Sar;

Y2 is NH_2 or OH;

R1 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof; and

R2 is absent or is a sequence of 1 to 6 amino acid residues selected from A, E, G, L, K, F, P, S, T, W, R, V or Sar, or a corresponding D form thereof;

wherein the compstatin analogue has a disulphide bond between the cysteine residues at positions 2 and 12;

or a pharmaceutically acceptable salt and/or solvate thereof.

5. The compstatin analogue of any one of the preceding claims, wherein R1 is selected from ESSA, AKGE, ASSE, ASES, GSAE, ESSE, ESGA, SEG, GES, ESS, EGSA, ESE, EGE, ESA, SAE, SGA, YLEA, GSA, KEK, EKG, ES, AS, SE, SA or E; and/or R2 is selected from GAES, EYGS, EGYA, EAGS, EAKS, EKSA, EGGS, EGGA,ESSG, ESAG, GEES, AEES, ESEG, AEGS, ESGS, SEGA, SEG, ESG, EAG, GAE, EGEA, EGE, EA, E, GE, EG, EKE or EKP.

6. The compstatin analogue of any one of the preceding claims, wherein R1 is selected from ESSA, ASES, ESGA, SEG, GES, ESS, EGSA, ESE, EGE, ESA, SAE, SGA, KEK, EKG, ES, SE, SA or E; and/or R2 is selected from GAES, EAGS, EGGS, EGGA,ESAG, ESEG, AEGS, ESGS, SEGA, SEG, ESG, EAG, GAE, EGEA, EGE, EA, E, GE, EG, EKE or EKP.

7. The compstatin analogue of any one of the preceding claims, wherein the compstatin analogue has the sequence:
IC(1)IWQDWGAHRC(1)T;
IC(1)IWQDWGEHRC(1)T;
ESSAIC(1)IWQDWGEHRC(1)T;
IC(1)I[1-Me-Trp]QDWGEHRC(1)T;

IC(1)IWQDWGKHRC(1)T;
IC(1)IWQDWGSHRC(1)T;
IC(1)IWQKWGEHRC(1)T;
IC(1)IWQKWGAHRC(1)TGAES;
YC(1)IWQDWGEHRC(1)T;
ESSAYC(1)IWQDWGEHRC(1)T;
[Sar]C(1)IWQDWGEHRC(1)T;
IC(1)IWQDWGAHRC(1)E;
IC(1)IWQDWGEHRC(1)[Sar];
ESSAIC(1)IWQDWGEHRC(1)TGAES;
IC(1)IWQDWGEHRC(1)TGAES;
IC(1)IWQEWGEHRC(1)T;
IC(1)IWQDWGDHRC(1)T;
IC(1)IWQDWGRHRC(1)T;
IC(1)IWQDWGAHSC(1)T;
IC(1)IWQDWGEHSC(1)T;
IC(1)IWQDWGEHRC(1)S;
IC(1)IWQDWGEHRC(1)E;
FC(1)IWQDWGEHRC(1)T;
IC(1)IWQDWGEHRC(1)TEGE;
IC(1)IWQDWGEHRC(1)TEA;
IC(1)IWQDWGEHRC(1)TE;
IC(1)IWQDWGEHRC(1)EGE;
EGSAIC(1)IWQDWGEHRC(1)[Sar]E;
EGSAIC(1)IWQDWGEHRC(1)T;
EGEIC(1)IWQDWGEHRC(1)T;
ESEIC(1)IWQDWGEHRC(1)T;
SEIC(1)IWQDWGEHRC(1)TEA;
EIC(1)IWQDWGEHRC(1)TE;
EIC(1)IWQDWGEHRC(1)TEGE;
EGEIC(1)IWQDWGEHRC(1)EGE;
ESEIC(1)IWQDWGEHRC(1)EGE;
KEKIC(1)IWQDWGEHRC(1)TEKE;
EKGIC(1)IWQDWGEHRC(1)TEKP;
IC(1)IWQDWGEHRC(1)TEGK;
GSAIC(1)IWQDWGEHRC(1)[Sar]E;
SAIC(1)IWQDWGEHRC(1)[Sar]E;

SAIC(1)IWQDWGEHRC(1)TEG;
FC(1)IWQDWGEHRC(1)TGAE;
EGSAIC(1)IWQDWGEHRC(1)[Sar]EGE;
EGSAFC(1)IWQDWGEHRC(1)[Sar]E;
ESSAIC(1)IWQDWGAHRC(1)T; or
IC(1)IWQDWGAHRC(1)TGAES;

or a pharmaceutically acceptable salt and/or solvate thereof;

wherein C(1) denotes a disulphide bond between the respective cysteine residues in the compstatin analogue.

8. The compstatin analogue of any onE of claims 1 to 7, wherein the compstatin analogue has the sequence:
[Ac]-IC(1)IWQDWGAHRC(1)T-[NH2] (Compound 1);
[Ac]-IC(1)IWQDWGEHRC(1)T-[NH2]] (Compound 2);
[Ac]-ESSAIC(1)IWQDWGEHRC(1)T-[NH2] (Compound 3);
[Ac]-IC(1)I[1-Me-Trp]QDWGEHRC(1)T-[NH2] (Compound 4);
[Ac]-IC(1)IWQDWGKHRC(1)T-[NH2] (Compound 5);
[Ac]-IC(1)IWQDWGSHRC(1)T-[NH2] (Compound 6);
[Ac]-IC(1)IWQKWGEHRC(1)T-[NH2] (Compound 7);
[Ac]-IC(1)IWQKWGAHRC(1)TGAES-[NH2] (Compound 8);
[Ac]-YC(1)IWQDWGEHRC(1)T-[NH2] (Compound 9);
[Ac]-ESSAYC(1)IWQDWGEHRC(1)T-[NH2] (Compound 10);
[Ac]-[Sar]C(1)IWQDWGEHRC(1)T-[NH2] (Compound 11);
[Ac]-IC(1)IWQDWGAHRC(1)E-[NH2] (Compound 12);
[Ac]-IC(1)IWQDWGEHRC(1)[Sar]-[NH2] (Compound 13);
[Ac]-ESSAIC(1)IWQDWGEHRC(1)TGAES-[NH2] (Compound 14);
[Ac]-IC(1)IWQDWGEHRC(1)TGAES-[NH2] (Compound 15);
[Ac]-IC(1)IWQEWGEHRC(1)T-[NH2] (Compound 16);
[Ac]-IC(1)IWQDWGDHRC(1)T-[NH2] (Compound 17);
[Ac]-IC(1)IWQDWGRHRC(1)T-[NH2] (Compound 18);
[Ac]-IC(1)IWQDWGAHSC(1)T-[NH2] (Compound 19);
[Ac]-IC(1)IWQDWGEHSC(1)T-[NH2] (Compound 20);
[Ac]-IC(1)IWQDWGEHRC(1)S-[NH2] (Compound 21);
[Ac]-IC(1)IWQDWGEHRC(1)E-[NH2] (Compound 22);
[Ac]-FC(1)IWQDWGEHRC(1)T-[NH2] (Compound 23);

[Ac]-IC(1)IWQDWGEHRC(1)TEGE-[NH2] (Compound 24);
[Ac]-IC(1)IWQDWGEHRC(1)TEA-[NH2] (Compound 25);
[Ac]-IC(1)IWQDWGEHRC(1)TE-[NH2] (Compound 26);
[Ac]-IC(1)IWQDWGEHRC(1)EGE-[NH2] (Compound 27);
[Ac]-EGSAIC(1)IWQDWGEHRC(1)[Sar]E-[NH2] (Compound 28);
[Ac]-EGSAIC(1)IWQDWGEHRC(1)T-[NH2] (Compound 29);
[Ac]-EGEIC(1)IWQDWGEHRC(1)T-[NH2] (Compound 30);
[Ac]-ESEIC(1)IWQDWGEHRC(1)T-[NH2] (Compound 31);
[Ac]-SEIC(1)IWQDWGEHRC(1)TEA-[NH2] (Compound 32);
[Ac]-EIC(1)IWQDWGEHRC(1)TE-[NH2] (Compound 33);
[Ac]-EIC(1)IWQDWGEHRC(1)TEGE-[NH2] (Compound 34);
[Ac]-EGEIC(1)IWQDWGEHRC(1)EGE-[NH2] (Compound 35);
[Ac]-ESEIC(1)IWQDWGEHRC(1)EGE-[NH2] (Compound 36);
[Ac]-KEKIC(1)IWQDWGEHRC(1)TEKE-[NH2] (Compound 37);
[Ac]-EKGIC(1)IWQDWGEHRC(1)TEKP-[NH2] (Compound 38);
[Ac]-IC(1)IWQDWGEHRC(1)TEGK-[NH2] (Compound 39);
[Ac]-GSAIC(1)IWQDWGEHRC(1)[Sar]E-[NH2] (Compound 40);
[Ac]-SAIC(1)IWQDWGEHRC(1)[Sar]E-[NH2] (Compound 41);
[Ac]-SAIC(1)IWQDWGEHRC(1)TEG-[NH2] ; (Compound 42);
[Ac]-FC(1)IWQDWGEHRC(1)TGAE-[NH2] (Compound 43);
[Ac]-EGSAIC(1)IWQDWGEHRC(1)[Sar]EGE-[NH2] (Compound 44);
[Ac]-EGSAFC(1)IWQDWGEHRC(1)[Sar]E-[NH2] (Compound 45);
[Ac]-ESSAIC(1)IWQDWGAHRC(1)T-[NH2] (Compound 46); or
[Ac]-IC(1)IWQDWGAHRC(1)TGAES-[NH2] (Compound 47);

or a pharmaceutically acceptable salt and/or solvate thereof,

wherein C(1) denotes a disulphide bond between the respective cysteine residues in the compstatin analogue.

9. A composition comprising a compstatin analogue according to any one of claims 1 to 8, or a pharmaceutically acceptable salt or solvate thereof, in admixture with a carrier.

10. A composition according to claim 9, wherein the composition is a pharmaceutical composition and the carrier is a pharmaceutically acceptable carrier.

11. A pharmaceutical composition comprising a compstatin analogue according to any one of claims 1 to 8, or a pharmaceutically acceptable salt or solvate thereof, in admixture with a pharmaceutically acceptable carrier, excipient or vehicle.

12. A compstatin analogue according to any one of claims 1 to 8 for use in therapy.

13. A compstatin analogue according to any one of claims 1 to 8 for use in a method of inhibiting complement activation.

14. The compstatin analogue according to claim 13, wherein inhibiting complement activation comprises more biological activities selected from (1) binding to C3 protein, (2) binding to C3b protein and/or (3) inhibiting the cleavage of native C3 by C3 convertases.

15. A compstatin analogue according to any one of claims 1 to 8 for use in a method of prophylaxis or treatment of age-related macular degeneration, diabetic retinopathy, glaucoma, uveitis, rheumatoid arthritis, spinal cord injury, stroke, multiple sclerosis, Parkinson's disease, Alzheimer's disease, cancer, and respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), allergic inflammation, emphysema, bronchitis, bronchiecstasis, cystic fibrosis, tuberculosis, pneumonia, respiratory distress syndrome, rhinitis and sinusitis; bacterial infections such as sepsis, ischemia-reperfusion injury, myocardial infarction, anaphylaxis, paroxysmal nocturnal haemoglobinuria, autoimmune haemolytic anemia, psoriasis, hidradentitis suppurativa, myasthenia gravis, systemic lupus erythematosus, CHAPLE syndrome, C3 glomeropathy, atypical haemolytic uremic syndrome, Crohn´s disease or antiphospholipid syndrome.

16. A compstatin analogue according to any one of claims 1 to 8 for use in a method of inhibiting complement activation that occurs during cell or organ transplantation.

17. A method of inhibiting complement activation for treating a subject in need thereof, the method comprising administering to the subject a compstatin analogue according to any one of claims 1 to 8 thereby to inhibit complement activation in the subject.

18. The method of claim 17, wherein the subject has age-related macular degeneration, diabetic retinopathy, glaucoma, uveitis, rheumatoid arthritis, spinal cord injury, stroke, multiple sclerosis, Parkinson's disease, Alzheimer's disease, cancer, and respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), allergic inflammation, emphysema, bronchitis, bronchiecstasis, cystic fibrosis, tuberculosis, pneumonia, respiratory

distress syndrome, rhinitis and sinusitis; bacterial infections such as sepsis, ischemia-reperfusion injury, myocardial infarction, anaphylaxis, paroxysmal nocturnal haemoglobinuria, autoimmune haemolytic anemia, psoriasis, hidradentitis suppurativa, myasthenia gravis, systemic lupus erythematosus, CHAPLE syndrome, C3 glomeropathy, atypical haemolytic uremic syndrome, Crohn´s disease or antiphospholipid syndrome, the method comprising administering to the subject a compstatin analogue according to any one of claims 1 to 8.

19. An *ex vivo* method of inhibiting complement activation during extracorporeal shunting of a physiological fluid, the method comprising contacting the physiological fluid with a compstatin analogue according to any one of claims 1 to 8 thereby to inhibiting complement activation.

20. Use of a compstatin analogue according to any one of claims 1 to 8 in the preparation of a medicament for inhibiting complement activation.

21. Use of a compstatin analogue according to any one of claims 1 to 8 in the preparation of a medicament for the treatment of age-related macular degeneration, diabetic retinopathy, glaucoma, peridontitis, uveitis, rheumatoid arthritis, spinal cord injury, stroke, multiple sclerosis, Parkinson's disease, Alzheimer's disease, cancer, and respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), allergic inflammation, emphysema, bronchitis, bronchiecstasis, cystic fibrosis, tuberculosis, pneumonia, respiratory distress syndrome, rhinitis and sinusitis; bacterial infections such as sepsis, ischemia-reperfusion injury, myocardial infarction, anaphylaxis, paroxysmal nocturnal haemoglobinuria, autoimmune haemolytic anemia, psoriasis, hidradentitis suppurativa, myasthenia gravis, systemic lupus erythematosus, CHAPLE syndrome, C3 glomeropathy, atypical haemolytic uremic syndrome, Crohn´s disease or antiphospholipid syndrome.