Template- fixed beta-hairpin peptidomimetics with protease inhibitory activity

The present invention provides template-fixed β-hairpin peptidomimetics incorporating a template-fixed chain of 11 α-amino acid residues which, depending on their position in the chain, are Gly, or Pro, or Pro(4NHCOPhe), or are of certain types, as defined hereinbelow. These template-fixed β-hairpin peptidomimetics are useful as inhibitors of protease enzymes. They are especially valuable as inhibitors of various serine proteases such as human cathepsin G, elastase, or tryptase. In addition the present invention provides an efficient process by which these compounds can, if desired, be made in library-format.

The β-hairpin peptidomimetics of the invention show improved efficacy, oral bioavailability, improved half-life and most importantly a high selectivity ratio among different serine proteases which depends on the proper choice of certain types of α-amino acid residues and their position in said chain. In addition these β-hairpin peptidomimetics show a low hemolysis on red blood cells and low cytotoxicity.

WO-A-2004096839 and WO-A-2004096838 describe compounds which are useful as antagonists of the chemokine receptor CXCR4 (also named LCR1, Fusin, LESTR), originally isolated from bovine brain and later from human leukocytes, belonging to the family of seven transmembrane GTP-binding protein-coupled receptors (GPCRs). WO-A-2004033489, WO-A-2004018503, WO-A-2002070547 describe compounds which show antimicrobial activity and WO-A-2003054000 describes compounds inhibiting proteases. The properties of the compounds of these disclosures depend primarily on the nature of the chains(s) of α-amino acid residues connected with the template.

Inhibitors of proteases are emerging with promising therapeutic uses in the treatment of diseases such as cancers (R. P. Beckett, A. Davidson, A. H. Drummond, M. Whittaker, *Drug Disc. Today* **1996**, *1*, 16-26; L. L. Johnson, R. Dyer, D. J. Hupe, *Curr. Opin. Chem. Biol.* **1998**, *2*, 466-71; D. Leung, G. Abbenante, and D. P. Fairlie, *J. Med. Chem.* **2000**, *43*, 305-341, T. Rockway, *Expert Opin. Ther. Patents* **2003**, *13*, 773-786), parasitic, fungal, and viral infections [e.g. schistosomiasis (M. M. Becker, S. A. Harrop, J. P. Dalton, B. H. Kalinna, D. P. McManus, D. P. Brindley, *J. Biol. Chem.* **1995**, *270*, 24496-501); *C. albicans* (C. Abad-Zapetero, R. Goldman, S. W. Muchmore, C. Hutchins, K.

Stewart, J. Navaza, C. D. Payne, T. L. Ray, *Protein Sci.* **1996**, *5*, 640-52), HIV (A. Wlodawer, J. W. Erickson, *Annu. Rev. Biochem.* **1993**, *62*, 543-85; P. L. Darke, J. R. Huff, *Adv. Pharmacol.* **1994**, *5*, 399-454), hepatitis (J. L. Kim, K. A. Morgenstern, , C. Lin, T. Fox, M. D. Dwyer, J. A. Landro, S. P. Chambers , W. Markland, C. A. Lepre, E. T. O'Malley, S. L. Harbeson, C. M. Rice, M. A. Murcko, P. R. Caron, J. A. Thomson, *Cell*, **1996**, *87*, 343-55; R. A. Love, H. E. Parge, J. A. Wickersham, Z. Hostomsky, N. Habuka, E. W. Moomaw, T. Adachi, Z. Hostomska, *Cell*, **1996**, *87*, 331-342), herpes (W. Gibson, M. R. Hall, Drug. Des. Discov. 1997, 15, 39-47)], and inflammatory, immunological, respiratory (P. R. Bernstein, P. D. Edwards, J. C. Williams, *Prog. Med. Chem.* **1994**, *31*, 59-120; T. E. Hugli, Trends Biotechnol. **1996**, *14*, 409-12,), cardiovascular (M. T. Stubbs, W. A. Bode, *Thromb. Res.* **1993**, *69*, 1-58; H. Fukami et al, *Current Pharmaceutical Design* **1998**, *4*, 439-453), and neurodegenerative defects including Alzheimer's disease (R. Vassar, B. D. Bennett, S. Babu-Kahn, S. Kahn, E. A. Mendiaz, *Science*, **1999**, *286*, 735-41), angiogenesis (Kaatinen M et al, *Atherosklerosis* **1996**, *123* 1-2, 123-131) and multiple sclerosis (Ibrahim MZ et al, *J. Neuroimmunol* **1996**, *70*, 131-138.

As most proteases bind their substrates in extended or β-strand conformations, good inhibitors must thus be able to mimick such a conformation. β-Hairpin mimetics are thus ideally suited to lock peptide sequences in an extended conformation.

Among proteases, serine proteases constitute important therapeutic targets. Serine proteases are classified by their substrate specificity, particularly by the type of residue found at P1, as either trypsin-like (positively charged residues Lys/Arg preferred at P1), elastase-like (small hydrophobic residues Ala/Val at P1), or chymotrypsin-like (large hydrophobic residues Phe/Tyr/Leu at P1). Serine proteases for which protease-inhibitor X-ray crystal data is available on the PDB data base (PDB: www.rcsb.org/pdb) include trypsin, α-chymotrypsin, γ-chymotrypsin, human neutrophil elastase, thrombin, subtilisin, human cytomegalovirus, proteinase A, achromobacter, human cathepsin G, glutamic acid-specific protease, carbopeptidase D, blood coagulation factorVIIa, porcine factor 1XA, mesentericopeptidase, HCV protease, and thermitase. Other serine proteases which are of therapeutic interest include tryptase, complement convertase, hepatitis C-NS3 protease. Inhibitors of thrombin (e.g. J. L. Metha, L. Y. Chen, W. W. Nichols, C. Mattsson, D. Gustaffson, T. G. P. Saldeen, *J. Cardiovasc. Pharmacol.* **1998**, *31*, 345-51; C. Lila, P. Gloanec, L. Cadet, Y. Herve, J. Fournier, F. Leborgne, T. J. Verbeuren, G.

DeNanteuil, *Synth. Comm.* **1998**, *28*, 4419-29) and factor Xa (e.g. J. P. Vacca, *Annu. Rep. Med. Chem.* **1998**, *33*, 81-90) are in clinical evaluation as anti-thrombotics, inhibitors of elastase (J. R. Williams, R. C. Falcone, C. Knee, R. L. Stein, A. M. Strimpler, B. Reaves, R. E. Giles, R. D. Krell, *Am. Rev. Respir. Dis.* **1991**, *144*, 875-83) are in clinical trials for emphysema and other pulmonary diseases whereas tryptase inhibitors are currently in phase II clinical trials for asthma (C. Seife, *Science* **1997**, *277*, 1602-3), urokinase inhibitors for breast cancer, and chymase inhibitors for heart related diseases. Finally, cathepsin *G* and elastase are intimately involved in the modulation of activities of cytokines and their receptors. Particularly at sites of inflammation, high concentration of cathepsin G, elastase and proteinase 3 are released from infiltrating polymorphonuclear cells in close temporal correlation to elevated levels of inflammatory cytokines, strongly indicating that these proteases are involved in the control of cytokine bioactivity and availability (U. Bank, S. Ansorge, *J. Leukoc. Biol.* **2001**, *69*, 177-90). Thus inhibitors of elastase and cathepsin G constitute valuable targets for novel drug candidates particularly for chronic obstructive pulmonary disease (Ohbayashi H, *Epert Opin. Investig. Drugs* **2002**, *11*, 965-980).

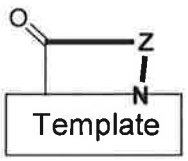
Of the many occurring proteinaceous serine protease inhibitors, one is a 14 amino acid cyclic peptide from sunflower seeds, termed sunflower trypsin inhibitor (**SFTI-1**) (S. Luckett, R. Santiago Garcia, J. J. Barker, A. V. Konarev, P. R. Shewry, A. R. Clarke, R. L. Brady, *J. Mol. Biol.* **1999**, *290*, 525-533; Y.-Q. Long, S.-L. Lee, C.-Y. Lin, I. J. Enyedy, S. Wang, P. Li, R. B. Dickson, P. P. Roller, *Biorg. & Med. Chem. Lett.* **2001**, *11*, 2515-2519), which shows both sequence and conformational similarity with the trypsin-reactive loop of the Bowman-Birk family of serine protease inhibitors. The inhibitor adopts a β-hairpin conformation when bound to the active site of bovine β-trypsin. **SFTI-1** inhibited β-trypsin (K_i<0.1nM), cathepsin G (K_i ~0.15nM), elastase (K_i~105μM), chymotrypsin (K_i~7.4μM) and thrombin (K_i~136mM).

We illustrate here an approach to inhibitor design which involves transplanting the β-hairpin loop from the naturally occurring peptide onto a hairpin-inducing template. Based on the well defined 3D-structure of the β-hairpin mimetics, libraries of compounds can be designed which ultimately can lead to novel inhibitors showing different specificity profiles towards several classes of proteases.

Template-bound hairpin mimetic peptides have been described in the literature (D, Obrecht, M. Altorfer, J. A. Robinson, *Adv. Med. Chem.* **1999**, *4*, 1-68; J. A. Robinson, *Syn. Lett.* **2000**, *4*, 429-441), and serine proteinase-inhibiting template-fixed peptidomimetics and methods for their synthesis have been described in International Patent Application WO2003/054000 A1 and in Descours A, Moehle K., Renard A, Robinson J. *ChemBioChem* **2002**, 3, 318-323 but the previously disclosed molecules do not exhibit high selectivity and particularly high potency. However, the ability to generate β-hairpin peptidomimetics using combinatorial and parallel synthesis methods has now been established (L. Jiang, K. Moehle, B. Dhanapal, D. Obrecht, J. A. Robinson, *Helv. Chim. Acta.* **2000**, *83*, 3097-3112).

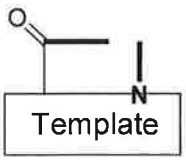
These methods allow the synthesis and screening of large hairpin mimetic libraries, which in turn considerably facilitates structure-activity studies, and hence the discovery of new molecules with highly potent and selective serine protease inhibitory activity, oral bioavailability, low hemolytic activity to human red blood cells and low cytotoxicity.

The β-hairpin peptidomimetics of the present invention are compounds of the general formula

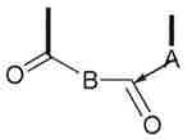


(I)

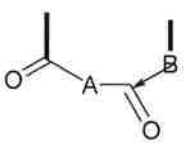
wherein



is a group of one of the formulae

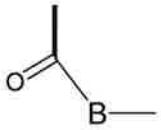


(a1)



(a2)

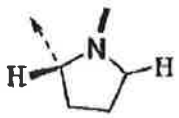
wherein



is Ala; Arg; Asn; Cys; Gln; Gly; His; Ile; Leu; Lys; Met; Phe; Pro; Pro(5RPhe), Ser; Thr; Trp; Tyr; Val; Cit; Orn; tBuA; Sar; t-BuG; 4AmPhe; 3AmPhe; 2AmPhe; Phe(mC(NH_2)=NH); Phe(pC(NH_2)=NH); Phe(mNHC (NH_2)=NH); Phe(pNHC (NH_2)=NH); Phg; Cha; C_4al; C_5al; Nle; 2-Nal; 1-Nal; 4Cl-Phe; 3Cl-Phe; 2Cl-Phe; 3,4Cl_2Phe; 4F-Phe; 3F-Phe; 2F-Phe; Tic; Thi; Tza; Mso; AcLys; Dpr; A_2Bu; Dbu; Abu; Aha; Aib; Y(Bzl); Bip; S(Bzl); T(Bzl); hCha; hCys; hSer, hArg; hPhe; Bpa; Pip; OctG; MePhe; MeNle; MeAla; MeIle; MeVal; or MeLeu;



is a group of the formula



A5

Z is a chain of 11 α-amino acid residues, the positions of said amino acid residues in said chain being counted starting from the N-terminal amino acid, whereby these amino acid residues in positions 1 to 11 are:

- P1: Nle, Ile, Aoc, hLeu, Chg, OctG, hPhe, 4AmPhe, Cha, Phe, Tyr, 2Cl-Phe, Trp, 1-Nal, Leu, Cha, or Arg;
- P2: Cys, Glu, Nle, Thr, or Gln ;
- P3: Thr, Ala or Abu;
- P4: Lys, Nle, Ala, Abu, or Thr;
- P5: Ser, AlloThr, or Dpr;
- P6: Ile, C5al, Leu, Nle, Aoc, OctG, Cha, hLeu, hPhe, Chg, t-BuA, Glu, or Asp;
- P7: Pro;
- P8: Pro, Ala, or Pro(4NHCOPhe);
- P9: Tyr, Phe, Ile, Nle, Cha, Gln, Arg, Lys, His, Thr, or Ala;
- P10: Cys, Arg, Nle, Gln, Lys, Met, Thr, or Ser;
- P11: Tyr, Gln, Arg, Ser, Nle, 2-Nal, 2Cl-Phe, Cha, Phg, Tyr, Phe, Asp, Asn, or Thr; and
- Cys, if present at P2 and P10, may form a disulfide bridge.

with the further proviso that if the template is $^{D}Pro^{L}Pro$, the amino acid residues in positions P1 to P6 and P8 to P11 are other than

- P1: Arg
- P2: Cys, linked with Cys in position P10 by a disulfide bridge
- P3: Thr
- P4: Lys
- P5: Ser
- P6: Ile
- P8: Pro
- P9: Ile
- P10: Cys, linked with Cys in position P2 by a disulfide bridge; and
- P11: Phe

and pharmaceutically acceptable salts thereof.

In accordance with the present invention these β-hairpin peptidomimetics can be prepared by a process which comprises

(a) coupling an appropriately functionalized solid support with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position 5, 6 or 7, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

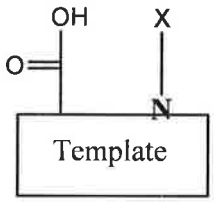
(b) removing the N-protecting group from the product thus obtained;

(c) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position nearer the N-terminal amino acid residue, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(d) removing the N-protecting group from the product thus obtained;

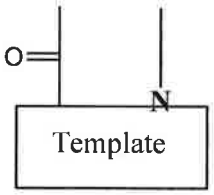
(e) repeating steps (c) and (d) until the N-terminal amino acid residue has been introduced;

(f) coupling the product thus obtained with a compound of the general formula

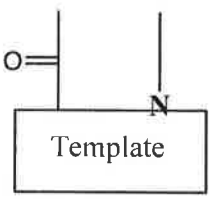


II

wherein



is as defined above and X is an N-protecting group or, alternatively, if



is to be group (a1) or (a2), above,

(fa) coupling the product obtained in step (e) with an appropriately N-protected derivative of an amino acid of the general formula

HOOC-B-H **III** or HOOC-A-H **IV**

wherein B and A are as defined above , any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(fb) removing the N-protecting group from the product thus obtained; and

(fc) coupling the product thus obtained with an appropriately N-protected derivative of an amino acid of the above general formula IV and, respectively, III, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(g) removing the N-protecting group from the product obtained in step (f) or (fc);

(h) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position 11, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(i) removing the N-protecting group from the product thus obtained;

(j) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position farther away from position 11, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(k) removing the N-protecting group from the product thus obtained;

(l) repeating steps (j) and (k) until all amino acid residues have been introduced;

(m) if desired, selectively deprotecting one or several protected functional group(s) present in the molecule and appropriately substituting the reactive group(s) thus liberated;

(n) if desired, forming an interstrand linkage between side-chains of appropriate amino acid residues at positions 2 and 10;

(o) detaching the product thus obtained from the solid support;

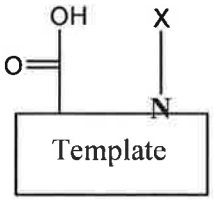
(p) cyclizing the product cleaved from the solid support;

(q) removing any protecting groups present on functional groups of any members of the chain of amino acid residues and, if desired, any protecting group(s) which may in addition be present in the molecule; and

(r) if desired, converting the product thus obtained into a pharmaceutically acceptable salt or converting a pharmaceutically acceptable, or unacceptable, salt thus obtained into the corresponding free compound of formula I or into a different, pharmaceutically acceptable, salt.

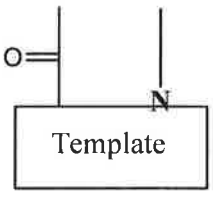
Alternatively, the peptidomimetics of the present invention can be prepared by

(a') coupling an appropriately functionalized solid support with a compound of the general formula

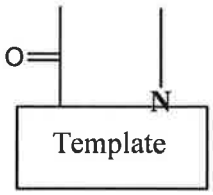


II

wherein



is as defined above and X is an N-protecting group or, alternatively, if



is to be group (a1) or (a2), above,

(a'a) coupling said appropriately functionalized solid support with an appropriately N-protected derivative of an amino acid of the general formula

HOOC-B-H **III** or HOOC-A-H **IV**

wherein B and A are as defined above , any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(a'b) removing the N-protecting group from the product thus obtained; and

(a'c) coupling the product thus obtained with an appropriately N-protected derivative of an amino acid of the above general formula IV and, respectively, III, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(b') removing the N-protecting group from the product obtained in step (a'), or (a'c);

(c') coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position 11, any functional

group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(d') removing the N-protecting group from the product thus obtained;

(e') coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position farther away from position 11, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(f') removing the N-protecting group from the product thus obtained;

(g') repeating steps (e') and (f') until all amino acid residues have been introduced;

(h') if desired, selectively deprotecting one or several protected functional group(s) present in the molecule and appropriately substituting the reactive group(s) thus liberated;

(i') if desired forming an interstrand linkage between side-chains of appropriate amino acid residues at positions 2 and 10;

(j') detaching the product thus obtained from the solid support;

(k') cyclizing the product cleaved from the solid support;

(l') removing any protecting groups present on functional groups of any members of the chain of amino acid residues and, if desired, any protecting group(s) which may in addition be present in the molecule; and

(m') if desired, converting the product thus obtained into a pharmaceutically acceptable salt or converting a pharmaceutically acceptable, or unacceptable, salt thus obtained into the corresponding free compound of formula I or into a different, pharmaceutically acceptable, salt.

The peptidomimetics of the present invention can also be enantiomers of the compounds of formula I. These enantiomers can be prepared by a modification of the above processes in which enantiomers of all chiral starting materials are used.

The structural element -**A**-CO- designates amino acid building blocks which in combination with the structural element -**B**-CO- form templates **(a1)** and **(a2)**. Templates (a1) and (a2) constitute building blocks which have an N-terminus and a C-terminus oriented in space in such a way that the distance between those two groups may lie between 4.0-5.5A. The peptide chain **Z** is linked to the C-terminus and the N-terminus of the templates (a1) and (a2) via the corresponding N- and C-termini so that the template and the chain form a cyclic structure such as that depicted in formula **I.** In a case as here where the distance between the N- and C- termini of the template lies between 4.0-5.5A the template will induce the H-bond network necessary for the formation of a β-hairpin conformation in the peptide chain **Z.** Thus template and peptide chain form a β-hairpin mimetic.

The β-hairpin conformation is highly relevant for the serine protease inhibitory activity of the β-hairpin mimetics of the present invention. The β-hairpin stabilizing conformational properties of the templates (a1) and (a2) play a key role not only for the selective inhibitory activity but also for the synthesis process defined hereinabove, as incorporation of the templates at the beginning or near the middle of the linear protected peptide precursors enhances cyclization yields significantly.

For example, ^{D}Pro-^{L}Pro constitutes the prototype of templates **(a1)** and ^{L}Pro-^{D}Pro constitutes the prototype of template (**a2**).

It will be appreciated that building block -A-Co- in which **A** has (D)-configuration, is carrying H at the α-position to the N-terminus. It will be recognized by those skilled in the art, that A is shown in (D)-configuration which corresponds to the (R)-configuration.

The building block -**B-CO**- within templates **(a1)**, and **(a2)** designates an L-amino acid residue. Most preferred are

Ala	L-Alanine
Arg	L-Arginine

Asn	L-Asparagine
Cys	L-Cysteine
Gln	L-Glutamine
Gly	Glycine
His	L-Histidine
Ile	L-Isoleucine
Leu	L-Leucine
Lys	L-Lysine
Met	L-Methionine
Phe	L-Phenylalanine
Pro	L-Proline
Pro(5RPhe)	(2S,5R)-5-phenylpyrrrolidine-2-carbocyclic acid
Ser	L-Serine
Thr	L-Threonine
Trp	L-Tryptophan
Tyr	L-Tyrosine
Val	L-Valine
Cit	L-Citrulline
Orn	L-Ornithine
tBuA	L-t-Butylalanine
Sar	Sarcosine
t-BuG	L-tert.-Butylglycine
4AmPhe	L-para-Aminophenylalanine
3AmPhe	L-meta-Aminophenylalanine
2AmPhe	L-ortho-Aminophenylalanine
Phe(mC(NH_2)=NH)	L-meta-Amidinophenylalanine
Phe(pC(NH_2)=NH)	L-para-Amidinophenylalanine
Phe(mNHC (NH_2)=NH)	L-meta-Guanidinophenylalanine
Phe(pNHC (NH_2)=NH)	L-para-Guanidinophenylalanine
Phg	L-Phenylglycine
Cha	L-Cyclohexylalanine
C_4al	L-3-Cyclobutylalanine
C_5al	L-3-Cyclopentylalanine
Nle	L-Norleucine
2-Nal	L-2-Naphthylalanine

1-Nal	L-1-Naphthylalanine
4Cl-Phe	L-4-Chlorophenylalanine
3Cl-Phe	L-3-Chlorophenylalanine
2Cl-Phe	L-2-Chlorophenylalanine
$3,4Cl_2$.Phe	L-3,4-Dichlorophenylalanine
4F-Phe	L-4-Fluorophenylalanine
3F-Phe	L-3-Fluorophenylalanine
2F-Phe	L-2-Fluorophenylalanine
Tic	L-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
Thi	L-β-2-Thienylalanine
Tza	L-2-Thiazolylalanine
Mso	L-Methionine sulfoxide
AcLys	L-N-Acetyllysine
Dpr	L-2,3-Diaminopropionic acid
A_2Bu	L-2,4-Diaminobutyric acid
Dbu	(S)-2,3-Diaminobutyric acid
Abu	γ-Aminobutyric acid (GABA)
Aha	ε-Aminohexanoic acid
Aib	α-Aminoisobutyric acid
Y(Bzl)	L-O-Benzyltyrosine
Bip	L-Biphenylalanine
S(Bzl)	L-O-Benzylserine
T(Bzl)	L-O-Benzylthreonine
hCha	L-Homo-cyclohexylalanine
hCys	L-Homo-cysteine
hSer	L-Homo-serine
hArg	L-Homo-arginine
hPhe	L-Homo-phenylalanine
Bpa	L-4-Benzoylphenylalanine
Pip	L-Pipecolic acid
OctG	L-Octylglycine
MePhe	L-N-Methylphenylalanine
MeNle	L-N-Methylnorleucine
MeAla	L-N-Methylalanine

MeIle	L-N-Methylisoleucine
MeVal	L-N-Methvaline
MeLeu	L-N-Methylleucine

Side chains of preferably (L)-amino acids at opposite positions of the β-strand region can form an interstrand linkage, the most widely known linkage is the disulfide bridge formed by cysteines and homo-cysteines positioned at opposite positions of the β-strand. Various methods are known to form disulfide linkages including those described by: J. P. Tam et al. *Synthesis* **1979**, 955-957; Stewart et al. , *Solid Phase Peptide Synthesis*, 2d Ed., Pierce Chemical Company, III., **1984**; Ahmed et al. J. Biol. Chem. 1975, 250, 8477-8482; and Pennington et al., *Peptides*, pages 164-166, Giralt and Andreu, Eds., ESCOM Leiden, The Netherlands, **1990**. Most advantageously, for the scope of the present invention, disulfide linkages can be prepared using acetamidomethyl (Acm)- protective groups for cysteine.

Positions for an interstrand linkage are positions P2 and P10, taken together. Such interstrand linkages are known to stabilize the β-hairpin conformations and thus constitute an important structural element for the design of β-hairpin mimetics.

Most preferred amino acid residues in chain Z are those derived from natural α-amino acids. Hereinafter follows a list of amino acids which, or the residues of which, are suitable for the purposes of the present invention, the abbreviations corresponding to generally adopted usual practice:

three letter code		one letter code
Ala	L-Alanine	A
Arg	L-Arginine	R
Asn	L-Asparagine	N
Asp	L-Aspartic acid	D
Cys	L-Cysteine	C
Glu	L-Glutamic acid	E
Gln	L-Glutamine	Q
His	L-Histidine	H
Ile	L-Isoleucine	I
Leu	L-Leucine	L
Lys	L-Lysine	K
Met	L-Methionine	M
Phe	L-Phenylalanine	F
Pro	L-Proline	P
Ser	L-Serine	S

Thr	L-Threonine	T
Trp	L-Tryptophan	W
Tyr	L-Tyrosine	Y

Other α-amino acids which, or the residues of which, are suitable for the purposes of the present invention include:

tBuA	L-t-Butylalanine
4AmPhe	L-para-Aminophenylalanine
Phg	L-Phenylglycine
Cha	L-Cyclohexylalanine
C_5al	L-3-Cyclopentylalanine
Nle	L-Norleucine
2-Nal	L-2-Naphthylalanine
1-Nal	L-1-Naphthylalanine
2Cl-Phe	L-2-Chlorophenylalanine
Dpr	2,3-Diaminopropionic acid
hPhe	L-Homo-phenylalanine
OctG	L-Octylglycine
Pro(4NHCOPhe)	(2S)-4-benzamidino-pyrrolidine-2-carboxylic acid
Aoc	2-(S)-Aminooctanoic acid

Generally, the peptidic chain **Z** within the β-hairpin mimetics of the invention comprises 11 amino acid residues. The positions P1 to P11 of each amino acid residue in the chain **Z** are unequivocally defined as follows: P1 represents the first amino acid in the chain **Z** that is coupled with its N-terminus to the C-terminus of group -**B**-CO- in template **(a1)**, or of group -**A**-CO- in template **(a2)**; and P11 represents the last amino acid in the chain **Z** that is coupled with its C-terminus to the N-terminus of group -**A**-CO- in template **(a1)**, or of group –**B**-CO- in template **(a2)**.

The α-amino acid residues in positions 1 to 11 are most preferably:

- P1: Nle, Ile, Aoc, hLeu, Chg, OctG, hPhe, 4AmPhe, Cha, Phe, Tyr, 2Cl-Phe, Trp, 1-Nal, Leu, Cha, or Arg;
- P2: Cys, Glu, Nle, Thr, or Gln ;
- P3: Thr, Ala or Abu;
- P4: Lys, Nle, Ala, Abu, or Thr;

- P5: Ser, AlloThr, or Dpr;
- P6: Ile, eC5al, Leu, Nle, Aoc, OctG, Cha, hLeu, hPhe, Chg, t-BuA, Glu, or Asp;
- P7: Pro;
- P8: Pro, Ala, or Pro(4NHCOPhe);
- P9: Tyr, Phe, Ile, Nle, Cha, Gln, Arg, Lys, His, Thr, or Ala;
- P10: Cys, Arg, Nle, Gln, Lys, Met, Thr, or Ser;
- P11: Tyr, Gln, Arg, Ser, Nle, 2-Nal, 2Cl-Phe, Cha, Phg, Tyr, Phe, Asp, Asn, or Thr; and
- Cys, if present at P2 and P10, may form a disulfide bridge.

with the proviso that if template is ^{D}Pro-^{L}Prothe amino acid residues in positions P1 to P6 and P8 to P11 are other than

- P1: Arg
- P2: Cys, linked with Cys in position P10 by a disulfide bridge
- P3: Thr
- P4 Lys
- P5 Ser
- P6 Ile
- P8 Pro
- P9 Ile
- P10 Cys, linked with Cys in position P2 by a disulfide bridge; and
- P11 Phe.

For inhibitors of Cathepsin G, the α-amino acid residues in positions 1 to 11 are most preferably

- P1: Phe, hPhe, 4AmPhe, Nle, Chg, Ile, Tyr, Trp, 2Cl-Phe, 1-Nal, or Cha;
- P2: Cys, Glu, or Nle;
- P3: Thr;
- P4: Lys, or Nle;
- P5: Ser, AlloThr, or Dpr;
- P6: Asp, or Glu;
- P7: Pro;
- P8: Pro;
- P9: Ile, Nle, Cha, Gln, Tyr, or Ala;
- P10: Cys, Arg, or Nle;
- P11: Thr, Asp, Ser, Tyr, Phe, Asn, or Arg; and
- Cys, if present at P2 and P10, may form a disulfide bridge.

For inhibitors of Elastase, the α-amino acid residues in positions 1 to 11 are most preferably:

- P1: Ile, Nle, Aoc, hLeu, Chg, OctG, or hPhe;
- P2: Cys, Glu, Thr, or Gln;
- P3: Thr, Ala, or Abu;
- P4: Ala, Thr, or Abu;
- P5: Ser;
- P6: OctG, Ile, Cha, Leu, eC5al, Nle, Aoc, Chg, tBuA, or hLeu;
- P7: Pro;
- P8: Pro, or Pro(4NHCOPhe);
- P9: Gln, Tyr, Ile, or Phe;
- P10: Cys, Lys, Gln, Thr, Met, or Arg;
- P11: Tyr, Ser, Arg, Gln, Nle, 2-Nal, 2Cl-Phe, Phe, Cha, or Phg; and
- Cys, if present at P2 and P10, may form a disulfide bridge.

For inhibitors of Tryptase the α-amino acid residues in positions 1 to 11 of the chain Z are most preferably:

- P1: Cha, Tyr , or Trp
- P2: Cys
- P3: Thr
- P4: Lys
- P5: Ser
- P6: Leu
- P7: Pro
- P8: Pro
- P9: Lys
- P10: Cys
- P11: Arg; and

the Cys residues present at P2 and P10 may form a disulfide bridge.

Particularly preferred β-peptidomimetics of the invention include those described in Examples **5, 19, 20, 22, 23, 38, 39, 40,** and **75** as inhibitors of cathepsin G; Examples **91, 153, 154, 155, 156, 157, 158, 159, 160, 161 177,** and **178** as inhibitors of elastase; and Examples **193, 194,** and **195** as inhibitors of Tryptase.

The processes of the invention can advantageously be carried out as parallel array syntheses to yield libraries of template-fixed β-hairpin peptidomimetics of the above general formula **I**. Such parallel syntheses allow one to obtain arrays of numerous (normally 24 to 192, typically 96) compounds of general formula I in high yields and defined purities, minimizing the formation of dimeric and polymeric by-products. The proper choice of the functionalized solid-support (i.e. solid support plus linker molecule), templates and site of cyclization play thereby key roles.

The functionalized solid support is conveniently derived from polystyrene crosslinked with, preferably 1-5%, divinylbenzene; polystyrene coated with polyethyleneglycol spacers (Tentagel^{R}); and polyacrylamide resins (see also Obrecht, D.; Villalgordo, J.-M, "Solid- Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries", *Tetrahedron Organic Chemistry Series*, Vol. 17, Pergamon, Elsevier Science, **1998**).

The solid support is functionalized by means of a linker, i.e. a bifunctional spacer molecule which contains on one end an anchoring group for attachment to the solid support and on the other end a selectively cleavable functional group used for the subsequent chemical transformations and cleavage procedures. For the purposes of the present invention two types of linkers are used:

Type 1 linkers are designed to release the amide group under acidic conditions (Rink H, *Tetrahedron Lett.* **1987**, *28*, 3783-3790). Linkers of this kind form amides of the carboxyl group of the amino acids; examples of resins functionalized by such linker structures include 4-[(((2,4-dimethoxyphenyl)Fmoc-aminomethyl)phenoxyacetamido) aminomethyl] PS resin, 4-[(((2,4-dimethoxyphenyl)Fmoc-aminomethyl)phenoxyacetamido) aminomethyl] -4-methylbenzydrylamine PS resin (Rink amide MBHA PS Resin), and 4-[(((2,4-dimethoxyphenyl)Fmoc-aminomethyl)phenoxyacetamido) aminomethyl] benzhydrylamine PS-resin (Rink amide BHA PS resin). Preferably, the support is derived from polystyrene crosslinked with, most preferably 1-5%, divinylbenzene and functionalized by means of the 4- (((2,4-dimethoxyphenyl)Fmoc-aminomethyl)phenoxyacetamido) linker.

Type 2 linkers are designed to eventually release the carboxyl group under acidic conditions. Linkers of this kind form acid-labile esters with the carboxyl group of the amino acids, usually acid-labile benzyl, benzhydryl and trityl esters; examples of such linker structures include 2-methoxy-4-hydroxymethylphenoxy (Sasrin^{R} linker), 4-(2,4-dimethoxyphenyl-hydroxymethyl)-phenoxy (Rink linker), 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid (HMPB linker), trityl and 2-chlorotrityl. Preferably, the support is derived from polystyrene crosslinked with, most preferably 1-5%, divinylbenzene and functionalized by means of the 2-chlorotrityl linker.

When carried out as parallel array syntheses the processes of the invention can be advantageously carried out as described herein below but it will be immediately apparent to those skilled in the art how these procedures will have to be modified in case it is desired to synthesize one single compound of the above formula I.

A number of reaction vessels (normally 24 to 192, typically 96) equal to the total number of compounds to be synthesized by the parallel method are loaded with 25 to 1000 mg, preferably 100 mg, of the appropriate functionalized solid support which is preferably derived from polystyrene cross-linked with 1 to 3% of divinylbenzene, or from Tentagel resin.

The solvent to be used must be capable of swelling the resin and includes, but is not limited to, dichloromethane (DCM), dimethylformamide (DMF), N-methylpyrrolidone (NMP), dioxane, toluene, tetrahydrofuran (THF), ethanol (EtOH), trifluoroethanol (TFE), isopropylalcohol and the like. Solvent mixtures containing as at least one component a polar solvent (e. g. 20% TFE/DCM, 35% THF/NMP) are beneficial for ensuring high reactivity and solvation of the resin-bound peptide chains (Fields, G. B., Fields, C. G., *J. Am. Chem. Soc.* **1991**, *113*, 4202-4207).

With the development of various linkers that release the C-terminal carboxylic acid group under mild acidic conditions, not affecting acid-labile groups protecting functional groups in the side chain(s), considerable progresses have been made in the synthesis of protected peptide fragments. The 2-methoxy-4-hydroxybenzylalcohol-derived linker (Sasrin^R linker, Mergler et al., *Tetrahedron Lett.* **1988**, 29 4005-4008) is cleavable with diluted trifluoroacetic acid (0.5-1% TFA in DCM) and is stable to Fmoc deprotection conditions during the peptide synthesis, Boc/tBu-based additional protecting groups being compatible with this protection scheme. Other linkers which are suitable for the processes of the invention include the super acid labile 4-(2,4-dimethoxyphenyl-hydroxymethyl)-phenoxy linker (Rink linker, Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787-3790), where the removal of the peptide requires 10% acetic acid in DCM or 0.2% trifluoroacetic acid in DCM; the 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid-derived linker (HMPB-linker, Flörsheimer & Riniker, *Peptides* **1991**,1990 131) which is also cleaved with 1%TFA/DCM in order to yield a peptide fragment containing all acid labile side-chain protective groups; and, in addition, the 2-chlorotritylchloride linker (Barlos et al.,

Tetrahedron Lett. **1989**, *30*, 3943-3946), which allows the peptide detachment using a mixture of glacial acetic acid/trifluoroethanol/DCM (1:2:7) for 30 min.

Suitable protecting groups for amino acids and, respectively, for their residues are, for example,

- for the amino group (as is present e. g. also in the side-chain of lysine)

Cbz	benzyloxycarbonyl
Boc	tert.-butyloxycarbonyl
Fmoc	9-fluorenylmethoxycarbonyl
Alloc	allyloxycarbonyl
Teoc	trimethylsilylethoxycarbonyl
Tcc	trichloroethoxycarbonyl
Nps	o-nitrophenylsulfonyl;
Trt	triphenymethyl or trityl

- for the carboxyl group (as is present e. g. also in the side-chain of aspartic and glutamic acid) by conversion into esters with the alcohol components

tBu	tert.-butyl
Bn	benzyl
Me	methyl
Ph	phenyl
Pac	Phenacyl
	Allyl
Tse	trimethylsilylethyl
Tce	trichloroethyl;

- for the guanidino group (as is present e. g. in the side-chain of arginine)

Pmc	2,2,5,7,8-pentamethylchroman-6-sulfonyl
Ts	tosyl (i. e. p-toluenesulfonyl)
Cbz	benzyloxycarbonyl
Pbf	pentamethyldihydrobenzofuran-5-sulfonyl

- for the hydroxy group (as is present e. g. in the side-chain of threonine and serine)

tBu	tert.-butyl
Bn	benzyl
Trt	trityl

- and for the mercapto group (as is present e. g. in the side-chain of cysteine)

Acm	acetamidomethyl
tBu	tert.-butyl
Bn	benzyl
Trt	trityl
Mtr	4-methoxytrityl.

The 9-fluorenylmethoxycarbonyl- (Fmoc)-protected amino acid derivatives are preferably used as the building blocks for the construction of the template-fixed β-hairpin loop mimetics of formula I. For the deprotection, i. e. cleaving off of the Fmoc group, 20% piperidine in DMF or 2% DBU/2% piperidine in DMF can be used.

The quantity of the reactant, i. e. of the amino acid derivative, is usually 1 to 20 equivalents based on the milliequivalents per gram (meq/g) loading of the functionalized solid support (typically 0.1 to 2.85 meq/g for polystyrene resins) originally weighed into the reaction tube. Additional equivalents of reactants can be used, if required, to drive the reaction to completion in a reasonable time. The reaction tubes, in combination with the holder block and the manifold, are reinserted into the reservoir block and the apparatus is fastened together. Gas flow through the manifold is initiated to provide a controlled environment, for example, nitrogen, argon, air and the like. The gas flow may also be heated or chilled prior to flow through the manifold. Heating or cooling of the reaction wells is achieved by heating the reaction block or cooling externally with isopropanol/dry ice and the like to bring about the desired synthetic reactions. Agitation is achieved by shaking or magnetic stirring (within the reaction tube). The preferred workstations (without, however, being limited thereto) are Labsource's Combi-chem station and MultiSyn Tech's-Syro synthesizer.

Amide bond formation requires the activation of the α-carboxyl group for the acylation step. When this activation is being carried out by means of the commonly used

carbodiimides such as dicyclohexylcarbodiimide (DCC, Sheehan & Hess, *J. Am. Chem. Soc.* **1955,** *77*, 1067-1068) or diisopropylcarbodiimide (DIC, Sarantakis et al *Biochem. Biophys. Res. Commun.* **1976,** *73*, 336-342), the resulting dicyclohexylurea and diisopropylurea is insoluble and, respectively, soluble in the solvents generally used. In a variation of the carbodiimide method 1-hydroxybenzotriazole (HOBt, König & Geiger, *Chem. Ber* **1970**, *103*, 788-798) is included as an additive to the coupling mixture. HOBt prevents dehydration, suppresses racemization of the activated amino acids and acts as a catalyst to improve the sluggish coupling reactions. Certain phosphonium reagents have been used as direct coupling reagents, such as benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP, Castro et al., *Tetrahedron Lett.* **1975**, *14,* 1219-1222; *Synthesis*, **1976**, 751-752), or benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexaflurophoshate (Py-BOP, Coste et al., *Tetrahedron Lett.* **1990**, *31*, 205-208), or 2-(1H-benzotriazol-1-yl-)1,1,3,3-tetramethyluronium terafluoroborate (TBTU), or hexafluorophosphate (HBTU, Knorr et al., *Tetrahedron Lett.* **1989**, *30*, 1927-1930); these phosphonium reagents are also suitable for in situ formation of HOBt esters with the protected amino acid derivatives. More recently diphenoxyphosphoryl azide (DPPA) or O-(7-aza-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TATU) or O-(7-aza-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU)/7-aza-1-hydroxy benzotriazole (HOAt, Carpino et al., *Tetrahedron Lett.* **1994**, *35*, 2279-2281) have also been used as coupling reagents.

Due to the fact that near-quantitative coupling reactions are essential, it is desirable to have experimental evidence for completion of the reactions. The ninhydrin test (Kaiser et al., *Anal. Biochemistry* **1970**, *34*, 595), where a positive colorimetric response to an aliquot of resin-bound peptide indicates qualitatively the presence of the primary amine, can easily and quickly be performed after each coupling step. Fmoc chemistry allows the spectrophotometric detection of the Fmoc chromophore when it is released with the base (Meienhofer et al., *Int. J. Peptide Protein Res.* **1979**, *13*, 35-42).

The resin-bound intermediate within each reaction tube is washed free of excess of retained reagents, of solvents, and of by-products by repetitive exposure to pure solvent(s) by one of the two following methods:

1) The reaction wells are filled with solvent (preferably 5 ml), the reaction tubes, in combination with the holder block and manifold, are immersed and agitated for 5 to 300 minutes, preferably 15 minutes, and drained by gravity followed by gas pressure applied through the manifold inlet (while closing the outlet) to expel the solvent;

2) The manifold is removed from the holder block, aliquots of solvent (preferably 5 ml) are dispensed through the top of the reaction tubes and drained by gravity through a filter into a receiving vessel such as a test tube or vial.

Both of the above washing procedures are repeated up to about 50 times (preferably about 10 times), monitoring the efficiency of reagent, solvent, and by-product removal by methods such as TLC, GC, or inspection of the washings.

The above described procedure of reacting the resin-bound compound with reagents within the reaction wells followed by removal of excess reagents, by-products, and solvents is repeated with each successive transformation until the final resin-bound fully protected linear peptide has been obtained.

Before this fully protected linear peptide is detached from the solid support, it is possible, if desired, to selectively deprotect one or several protected functional group(s) present in the molecule and to appropriately substitute the reactive group(s) thus liberated. To this effect, the functional group(s) in question must initially be protected by a protecting group which can be selectively removed without affecting the remaining protecting groups present. Alloc (allyloxycarbonyl) is an example for such an amino protecting group which can be selectively removed, e.g. by means of Pd° and phenylsilane in CH_2Cl_2, without affecting the remaining protecting groups, such as Fmoc, present in the molecule. The reactive group thus liberated can then be treated with an agent suitable for introducing the desired substituent. Thus, for example, an amino group can be acylated by means of an acylating agent corresponding to the acyl substituent to be introduced.

Before this fully protected linear peptide is detached from the solid support, it is also possible, if desired, to form an interstrand linkages between side-chains of appropriate amino acid residues at positions 2 and 10.

Interstrand linkages and their formation have been discussed above, in connection with the explanations above which can, for example, be disulfide bridges formed by cysteine and homocysteine residues at opposite positions of the β-strand; or lactam bridges formed by glutamic and aspartic acid residues linking ornithine and, respectively, lysine residues, or by glutamic acid residues linking 2,4-diaminobutyric acid residues located at opposite β-strand positions by amide bond formation. The formation of such interstrand linkages can be effected by methods well known in the art.

For the formation of disulfide bridges preferably a solution of 10 equivalents of iodine solution is applied in DMF or in a mixture of CH_2Cl_2 /MeOH for 1.5 h which is repeated for another 3h with a fresh iodine solution after filtering of the iodine solution, or in a mixture of DMSO and acetic acid solution, buffered with 5% with $NaHCO_3$ to pH 5-6 for 4h, or in water adjusted to pH 8 with ammonium hydroxide solution by stirring for 24h, or in ammonium acetate buffer adjusted to pH 8 in the presence of air, or in a solution of NMP and tri-n- butylphosphine (preferably 50 eq.).

Detachment of the fully protected linear peptide from the solid support is achieved by immersion of the reaction tubes, in combination with the holder block and manifold, in reaction wells containing a solution of the cleavage reagent (preferably 3 to 5 ml). Gas flow, temperature control, agitation, and reaction monitoring are implemented as described above and as desired to effect the detachment reaction. The reaction tubes, in combination with the holder block and manifold, are disassembled from the reservoir block and raised above the solution level but below the upper lip of the reaction wells, and gas pressure is applied through the manifold inlet (while closing the outlet) to efficiently expel the final product solution into the reservoir wells. The resin remaining in the reaction tubes is then washed 2 to 5 times as above with 3 to 5 ml of an appropriate solvent to extract (wash out) as much of the detached product as possible. The product

solutions thus obtained are combined, taking care to avoid cross-mixing. The individual solutions/extracts are then manipulated as needed to isolate the final compounds. Typical manipulations include, but are not limited to, evaporation, concentration, liquid/liquid extraction, acidification, basification, neutralization or additional reactions in solution.

The solutions containing fully protected linear peptide derivatives which have been cleaved off from the solid support and neutralized with a base, are evaporated. Cyclization is then effected in solution using solvents such as DCM, DMF, dioxane, THF and the like. Various coupling reagents which were mentioned earlier can be used for the cyclization. The duration of the cyclization is about 6-48 hours, preferably about 16 hours. The progress of the reaction is followed, e. g. by RP-HPLC (Reverse Phase High Performance Liquid Chromatography). Then the solvent is removed by evaporation, the fully protected cyclic peptide derivative is dissolved in a solvent which is not miscible with water, such as DCM, and the solution is extracted with water or a mixture of water-miscible solvents, in order to remove any excess of the coupling reagent.

Finally, the fully protected peptide derivative is treated with 95% TFA, 2.5% H_2O, 2.5% TIS or another combination of scavengers for effecting the cleavage of protecting groups. The cleavage reaction time is commonly 30 minutes to 12 hours, preferably about 2.5 hours. The volatiles are evaporated to dryness and the crude peptide is dissolved in 20% AcOH in water and extracted with isopropyl ether or other solvents which are suitable therefor. The aqueous layer is collected and evaporated to dryness, and the fully deprotected cyclic peptide derivative of formula I is obtained as end-product.

Alternatively the detachment, cyclization and complete deprotection of the fully protected peptide from the solid support can be achieved manually in glass vessels.

Depending on its purity, this peptide derivative can be used directly for biological assays, or it has to be further purified, for example by preparative HPLC.

As mentioned earlier, it is thereafter possible, if desired, to convert a fully deprotected product of formula I thus obtained into a pharmaceutically acceptable salt or to convert a pharmaceutically acceptable, or unacceptable, salt thus obtained into the corresponding free compound of formula I or into a different, pharmaceutically acceptable, salt. Any of these operations can be carried out by methods well known in the art.

The template starting materials of formula II used in the processes of the invention, pre-starting materials therefor, and the preparation of these starting and pre-starting materials are described in International Application PCT/EP02/01711 of the same applicants, published as WO 02/070547 A1.

The β-hairpin peptidomimetics of the invention can be used in a wide range of applications where inflammatory diseases or pulmanory diseases or infections or immunological diseases or cardiovascular diseases or neurodegenerative diseases are mediated or resulting from serine protease activity, or where cancer is mediated or resulting from serine protease activity. For the control or prevention of a given illness or disease amenable to treatment with protease inhibitors, the β-hairpin peptidomimetics may be administered per se or may be applied as an appropriate formulation together with carriers, diluents or excipients well known in the art.

When used to treat or prevent diseases such as pulmonary emphysema, rheumatoid arthritis, osteoarthritis, atherosklerosis, psoriaris, cystic fibrosis, multiple sclerosis, adult respiratory distress syndrome, pancreatitis, asthma, allergic rhinitis, inflammatory dermatoses, postangioplasty restenosis, cardiac hypertrophy, heart failure or cancer such as, but not limited to, breast cancer, or cancer related to angiogenesis or metastasis, the β-hairpin peptidomimetics can be administered singly, as mixtures of several β-hairpin peptidomimetics, in combination with other anti-inflammatory agents, or antimicrobial agents or anti-cancer agents and/or in combination with other pharmaceutically active agents. The β-hairpin peptidomimetics can be administered per se or as pharmaceutical compositions.

Pharmaceutical compositions comprising β-hairpin peptidomimetics of the invention may be manufactured by means of conventional mixing, dissolving, granulating, coated tablet-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Pharmaceutical compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxilliaries which facilitate processing of the active β-hairpin peptidomimetics into preparations which can be used pharmaceutically. Proper formulation depends upon the method of administration chosen.

For topical administration the β-hairpin peptidomimetics of the invention may be formulated as solutions, gels, ointments, creams, suspensions, etc. as are well-known in the art.

Systemic formulations include those designed for administration by injection, e.g. subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal, oral or pulmonary administration.

For injections, the β-hairpin peptidomimetics of the invention may be formulated in adequate solutions, preferably in physiologically compatible buffers such as Hink's solution, Ringer's solution, or physiological saline buffer. The solutions may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the β-hairpin peptidomimetics of the invention may be in powder form for combination with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation as known in the art.

For oral administration, the β-hairpin peptidomimetics of the invention can be readily formulated by combining them with pharmaceutically acceptable carriers well known in the art. Such carriers enable the β-hairpin peptidomimetics of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions etc., for oral ingestion by a patient to be treated. For oral formulations such as, for example, powders, capsules and tablets, suitable excipients include fillers such as sugars, e. g. lactose, sucrose, mannitol and sorbitol; cellulose preparations such as maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP); granulating agents; and binding agents. If desired, desintegrating agents may be added, such as cross-linked polyvinylpyrrolidones, agar, or alginic acid or a salt thereof, such as sodium alginate. If desired, solid dosage forms may be sugar-coated or enteric-coated using standard techniques.

For oral liquid preparations such as, for example, suspensions, elixirs and solutions, suitable carriers, excipients or diluents include water, glycols, oils, alcohols, etc. In addition, flavoring agents, preservatives, coloring agents and the like may be added.

For buccal administration, the composition may take the form of tablets, lozenges, etc., formulated as usual.

For administration by inhalation, the β-hairpin peptidomimetics of the invention are conveniently delivered in form of an aerosol spray from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluromethane, carbon dioxide or another suitable gas. In the case of a pressurized aerosol the dose unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the β-hairpin peptidomimetics of the invention and a suitable powder base such as lactose or starch.

The compounds may also be formulated in rectal or vaginal compositions such as suppositories together with appropriate suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the β-hairpin peptidomimetics of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (e.g. subcutaneously or intramuscularly) or by intramuscular injection. For the manufacture of such depot preparations the β-hairpin peptidomimetics of the invention may be formulated with suitable polymeric or hydrophobic materials (e.g. as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble salts.

In addition, other pharmaceutical delivery systems may be employed such as liposomes and emulsions well known in the art. Certain organic solvents such as dimethylsulfoxide may also be employed. Additionally, the β-hairpin peptidomimetics of the invention may be delivered using a sustained-release system, such as semipermeable matrices of solid polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic agent, additional strategies for protein stabilization may be employed.

As the β-hairpin pepdidomimetics of the invention may contain charged residues, they may be included in any of the above-described formulations as such or as pharmaceutically acceptable salts. Pharmaceutically acceptable salts tend to be more soluble in aqueous and other protic solvents than are the corresponding free forms.

The β-hairpin peptidomimetics of the invention, or compositions thereof, will generally be used in an amount effective to achieve the intended purpose. It is to be understood that the amount used will depend on a particular application.

For topical administration to treat or prevent diseases amenable to treatment with beta hairpin mimetics a therapeutically effective dose can be determined using, for example, the in vitro assays provided in the examples. The treatment may be applied while the disease is visible, or even when it is not visible. An ordinary skilled expert will be able to determine therapeutically effective amounts to treat topical diseases without undue experimentation.

For systemic administration, a therapeutically effective dose can be estimated initially from in vitro assays. For example, a dose can be formulated in animal models to achieve a circulating β-hairpin peptidomimetic concentration range that includes the IC_{50} as determined in the cell culture. Such information can be used to more accurately determine useful doses in humans.

Initial dosages can also be determined from in vivo data, e.g. animal models, using techniques that are well known in the art. One having ordinary skill in the art could readily optimize administration to humans based on animal data.

Dosage amounts for applications as serine protease inhibitory agents may be adjusted individually to provide plasma levels of the β-hairpin peptidomimetics of the invention which are sufficient to maintain the therapeutic effect. Therapeutically effective serum levels may be achieved by administering multiple doses each day.

In cases of local administration or selective uptake, the effective local concentration of the β-hairpin peptidomimetics of the invention may not be related to plasma concentration. One having the ordinary skill in the art will be able to optimize therapeutically effective local dosages without undue experimentation.

The amount of β-hairpin peptidomimetics administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgement of the prescribing physician.

Normally, a therapeutically effective dose of the β-hairpin peptidomimetics described herein will provide therapeutic benefit without causing substantial toxicity.

Toxicity of the β-hairpin peptidomimetics of the invention can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the LD_{50} (the dose lethal to 50% of the population) or the LD_{100} (the dose lethal to 100% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a dosage range that is not toxic for use in humans. The dosage of the β-hairpin peptidomimetics of the invention lies preferably within a range of circulating concentrations that include the effective dose with little or no toxicity. The dosage may vary within the range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dose can be chosen by the individual physician in view of the patient's condition (see, e.g. Fingl et al. **1975**, In : *The Pharmacological Basis of Therapeutics*, Ch.1, p.1).

The following Examples illustrate the invention in more detail but are not intended to limit its scope in any way. The following abbreviations are used in these Examples:

HBTU: 1-benzotriazol-1-yl-tetramethylurounium hexafluorophosphate (Knorr et al. *Tetrahedron Lett.* **1989**, *30*, 1927-1930);

HOBt: 1-hydroxybenzotriazole;

DIEA: diisopropylethylamine;

HOAT: 7-aza-1-hydroxybenzotriazole;

HATU: O-(7-aza-benzotriazole-1-yl)-N,N,N',N'-tetramethyluronoium hexafluorophosphate (Carpino et al. *Tetrahedron Lett.* **1994**, *35*, 2279-2281).

Examples

1. Peptide synthesis

Examples 1 - 46, 48, 51 - 63, 65 – 67, 70, 71, 74 – 114, 122 – 125, 129, 131 – 162, 164, 166, 167, 169, 170, 172, 173, 175, 177 – 182, 184 – 189, and 191 – 196 illustrate the invention and examples 47, 49, 50, 64, 68, 69, 72, 73, 115 – 121, 126 – 128, 130, 163, 165, 168, 171, 174, 176, 183, and 190 are present for the sake of completeness of the disclosure.

Coupling of the first protected amino acid residue to the resin

0.5 g of 2-chlorotritylchloride resin (Barlos et al. *Tetrahedron Lett.* **1989**, *30*, 3943-3946) (0.83 mMol/g, 0.415 mmol) was filled into a dried flask. The resin was suspended in CH_2Cl_2 (2.5 ml) and allowed to swell at room temperature under constant stirring for 30 min. The resin was treated with 0.415 mMol (1eq) of the first suitably protected amino acid residue (see below) and 284 µl (4eq) of diisopropylethylamine (DIEA) in CH_2Cl_2 (2.5 ml), the mixture was shaken at 25°C for 4 hours. The resin colour changed to purple and the solution remained yellowish. The resin was shaken (CH_2Cl_2 /MeOH/DIEA : 17/2/1), 30 ml for 30 min; then washed in the following order with CH_2Cl_2 (1x), DMF (1x), CH_2Cl_2 (1x), MeOH (1x), CH_2Cl_2(1x), MeOH (1x), CH_2Cl_2 (2x), Et_2O (2x) and dried under vacuum for 6 hours.
Loading was typically 0.6-0.7 mMol/g.

The following preloaded resins were prepared: Fmoc-Pro-2-chlorotritylresin, Fmoc-Asp (OtBu)-2-chlorotritylresin, Fmoc-Pro(5RPhe)-2-chlorotritylresin, Fmoc-Leu-2-chlorotritylresin, Fmoc-Glu(OtBu)-2-chlorotritylresin, Fmoc-Asp(OtBu) -2-chlorotritylresin,. Fmoc-Phe-2-chlorotritylresin, Fmoc-Gln(Trt)-2-chlorotritylresin, Fmoc-Ser (OtBu) -2-chlorotritylresin, Fmoc-Val-2-chlorotritylresin, Fmoc-Thr(OtBu) -2-chlorotritylresin and Fmoc-Ile-2-chlorotritylresin.

Synthesis of the fully protected peptide fragment

The synthesis was carried out using a Syro-peptide synthesizer (Multisyntech) using 24 to 96 reaction vessels. In each vessel were placed 60 mg (weight of the resin before loading) of the above resin. The following reaction cycles were programmed and carried out:

Step	Reagent	Time
1	CH_2Cl_2, wash and swell (manual)	3 x 1 min.
2	DMF, wash and swell	1 x 5 min
3	40 % piperidine/DMF	1 x 5 min.
4	DMF, wash	5 x 2 min.
5	5 equiv. Fmoc amino acid/DMF	
	+ 5 eq. HBTU	
	+ 5 eq. HOBt	
	+ 5 eq. DIEA	1 x 120 min.
6	DMF, wash	4 x 2 min.
7	CH_2Cl_2, wash (at the end of the synthesis)	3 x 2 min.

Steps **3** to **6** are repeated to add each amino-acid.

After the synthesis of the fully protected peptide fragment had been terminated, then subsequently either Procedure A or Procedure B , as described hereinbelow, was adopted, depending on whether not interstrand linkages (i. e. disulfide β-strand linkages) were to be formed.

Procedure A: Cyclization and work up of backbone cyclized peptides

Cleavage of the fully protected peptide fragment

After completion of the synthesis, the resin was suspended in 1 ml (0.39 mMol) of 1% TFA in CH_2Cl_2 (*v/v*) for 3 minutes, filtered and the filtrate was neutralized with 1ml (1.17 mMol, 3 eq.) of 20% DIEA in CH_2Cl_2 (*v/v*). This procedure was repeated twice to ensure completion of the cleavage. An aliquot (200 µL) of the filtrate was fully deprotected with 0.5ml of the cleavage mixture containing 95% trifluoroacetic acid (TFA), 2.5% water and 2.5% triisopropylsilane (TIS) and analysed by reverse phase-LC MS to monitor the efficiency of the linear peptide synthesis.

Cyclization of the linear peptide

The fully protected linear peptide was dissolved in DMF (8 ml, conc. 10 mg/ml). Two eq. of HATU (0.72 mMol) in 1ml of DMF and 4 eq. of DIEA (1.44 mMol) in 1ml of DMF were added, and the mixture was stirred at room temperature for 16 h. The volatile was evaporated to dryness. The crude cyclised peptide was dissolved in 7 ml of CH_2Cl_2 and extracted with 10% acetonitrile in water (4.5 ml) three times. The CH_2Cl_2 layer was evaporated to dryness.

Deprotection and purification of the cyclic peptide

The cyclic peptide obtained was dissolved in 3 ml of the cleavage mixture containing 95% trifluoroacetic acid (TFA), 2.5% water and 2.5% triisopropylsilane (TIS). The mixture was left to stand at 20°C for 2.5 hours and then concentrated under vacuum. The crude peptide was dissolved in 20% AcOH in water (7 ml) and extracted with diisopropylether (4 ml) three times. The aqueous layer was collected and evaporated to dryness, and the residue was purified by preparative reverse phase LC-MS.

After lyophilisation the products were obtained as white powders and analysed by LC-MS. The analytical data comprising purity after preparative HPLC and ESI-MS are shown in Table 1.

Analytical method:

Analytical HPLC retention times (RT, in minutes) were determined using an Jupiter Proteo 90A, 150 x 2.0 mm, (cod. 00F4396-B0 - Phenomenex) with the following solvents **A** (H_2O + 0.1% TFA) and **B** (CH_3CN + 0.1% TFA) and the gradient: 0 min: 95%A, 5%B; 20 min: 40%A 60%B; 21-23 min: 0%A, 100%B; 23.1-30 min: 95% A, 5%B.

Procedure B: Cyclization and work up of backbone cyclized peptides having disulfide β-strand linkages

Formation of disulfide β-strand linkage

After completion of the synthesis, the resin was swelled in 3 ml of dry DMF for 1 h. Then 10 eq. of iodine solution in DMF (6 ml) were added to the reactor, followed by stirring for 1.5 h. The resin was filtered and a fresh solution of iodine (10 eq.) in DMF (6 ml) was added, followed by stirring for another 3 h. The resin was filtered and washed with DMF (3x) and CH_2Cl_2 (3x).

Backbone cyclization, cleavage and purification of the peptide

After formation of the disulfide β-strand linkage, the resin was suspended in 1 ml (0.39 mMol) of 1% TFA in CH_2Cl_2 (*v/v*) for 3 minutes and filtered, and the filtrate was neutralized with 1ml (1.17 mMol, 3eq.) of 20% DIEA in CH_2Cl_2 (*v/v*). This procedure was repeated twice to ensure completion of the cleavage. The resin was washed with 2ml of CH_2Cl_2. The CH_2Cl_2 layer was evaporated to dryness.

The fully protected linear peptide was solubilised in 8 ml of dry DMF. Then 2 eq. of HATU in dry DMF (1ml) and 4 eq. of DIPEA in dry DMF (1 ml) were added to the peptide, followed by stirring for 16 h. The volatiles were evaporated to dryness. The crude cyclised peptide was dissolved in 7 ml of CH_2Cl_2 and extracted with 10% acetonitrile in water (4.5 ml) three times. The CH_2Cl_2 layer was evaporated to dryness. To deprotect the peptide fully, 3 ml of cleavage cocktail TFA:TIS:H_2O (95:2.5:2.5) were added, and the mixture was kept for 2.5 h. The volatile was evaporated to dryness and the crude peptide was dissolved in 20% AcOH in water (7 ml) and extracted with diisopropyl ether (4 ml) for three times. The aqueous layer was collected and evaporated to dryness, and the residue was purified by preparative reverse phase LC-MS.

After lyophilisation the products were obtained as white powders and analysed by ESI-MS analytical method as described above. The analytical data comprising purity after preparative HPLC and ESI-MS are shown in Table 1.

Examples 1-45, 52-63, 65-67, 70-71, 75-114, 129, 131-162 and **179-196** are shown in *Table 1*. The peptides were synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptides were synthesized on solid support according to the procedure described above in the following sequence: Resin-Pro-^{D}Pro-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. **Ex. 1-6, 9-45, 52-63, 65-67, 70-71, 75-103 112-114, 129, 131, 133, 136-138, 140-141, 143-146, 148-153, 155, 157-162** and **179-196** were cleaved from the resin, subjected to the disulfide bridge formation, cyclized, deprotected and purified as indicated in procedure B. **Ex. 82, 123, 149, 159, 161** and **178** were cleaved from the resin as indicated in procedure B. The disulfide bridges were formed using the following procedure:

The crude product was solubilised in a ammonium acetate buffer 0.1M (pH adjusted to 8) (concentration: 1mg of crude product per ml). The mixture was stirred at room

temperature in presence of air. The reaction was monitored by reverse phase LC-MS. After reaction completion, the solution was evaporated to dryness and the residue purified by preparative reverse phase LC-MS.

The cyclisation of the backbone was perfomed as indicated in procedure A. The deprotection was performed using the following procedure:
To deprotect the peptide fully, 5 ml of cleavage cocktail TFA:H_2O:Phenol:Thioanisol: Ethanedithiol (82.5:5:5:5:2.5) were added, and the mixture was kept for 5h at room temperature. The peptide was precipitated by addition of cold diethylether (10ml). After centrifugation, the supernatant phase was removed. The precipitate was washed three times with 5 ml of diethylether and was purified by preparative reverse phase LC-MS.

After lyophilisation the products were obtained as white powders and analysed by ESI-MS analytical method as described above.

Ex. 7, 8, 104-111, 132, 134, 135, 139, 142, 147, 154 and **156** were cleaved from the resin, cyclized, deprotected and purified as indicated in procedure A.

HPLC-retention times (minutes) were determined using the analytical method as described above:
Ex. 1 (15.37), **Ex. 2** (11.54), **Ex. 3** (7.82), **Ex. 4** (8.62), **Ex. 5** (16.51), **Ex. 6** (13.67), **Ex. 7** (3.61), **Ex. 8** (4.11), **Ex. 9** (5.82), **Ex. 10** (7.98), **Ex. 11** (8.38), **Ex. 12** (6.80), **Ex. 13** (7.41), **Ex. 14** (6.20), **Ex. 15** (8.68), **Ex. 16** (9.82); **Ex. 17** (5.59), **Ex. 20** (7.32), **Ex. 21** (8.66), **Ex. 22** (8.68), **Ex. 23** (12.66), **Ex. 24** (8.67), **Ex. 25** (7.53), **Ex. 26** (9.02), **Ex. 27** (8.06), **Ex. 28** (9.62), **Ex. 29** (8.78), **Ex. 30** (10.49), **Ex. 31** (5.50), **Ex. 32** (7.45), **Ex. 33** (8.39), **Ex. 34** (10.16), **Ex. 35** (9.04), **Ex. 36** (10.98), **Ex. 37** (7.56), **Ex. 38** (9.29), **Ex. 39** (8.32), **Ex. 40** (10.11), **Ex. 41** (7.23), **Ex. 42** (8.83), **Ex. 43** (7.92), **Ex. 44** (9.87), **Ex. 45** (8.26), **Ex. 52** (6.20), **Ex. 53** (8.68), **Ex 54** (9.82), **Ex. 55** (5.59), **Ex. 56** (6.06), **Ex. 57** (6.47), **Ex. 58** (7.32), **Ex. 59** (8.68), **Ex. 60** (10.66), **Ex. 61** (8.54), **Ex. 62** (9.83), **Ex. 63** (16.54), **Ex. 65** (15.71), **Ex. 66** (17.50), **Ex. 67** (15.87), **Ex. 70** (12.87), **Ex. 71** (13.48), **Ex. 75** (14.22), **Ex. 76** (4.47), **Ex. 77** (5.15), **Ex. 78** (10.93), **Ex. 79** (10.70), **Ex. 80** (12.09), **Ex. 81** (11.63), **Ex. 82** (5.71), **Ex. 83** (5.45), **Ex. 84** (11.14), **Ex. 85** (10.90), **Ex. 86** (13.78), **Ex. 87** (13.98), **Ex. 88** (14.35), **Ex. 89** (15.21), **Ex. 90** (14.72), **Ex. 91** (11.97), **Ex. 92** (11.77), **Ex. 93** (15.25), **Ex. 94** (14.61), **Ex. 95** (20.46), **Ex. 96** (15.08), **Ex. 97** (20.78), **Ex. 98** (18.28), **Ex. 99** (14.62), **Ex. 100** (13.90), **Ex. 101** (13.76), **Ex. 102**

(20.53), **Ex. 103** (14.14), **Ex. 104** (11.60), **Ex. 105** (11.90), **Ex. 106** (11.63), **Ex. 107** (11.78), **Ex. 108** (13.03), **Ex. 109** (15.22), **Ex. 110** (12.40), **Ex. 111** (12.10), **Ex. 112** (5.49), **Ex. 113** (5.67), **Ex. 114** (5.55), **Ex. 129** (17.22), **Ex. 131** (11.97), **Ex. 132** (13.56), **Ex. 133** (14.57), **Ex. 134** (14.72), **Ex. 135** (17.53), **Ex. 136** (18.28), **Ex. 137** (14.72), **Ex. 138** (14.35), **Ex. 139** (15.40), **Ex. 140** (11.14), **Ex. 141** (5.71), **Ex. 142** (13.97), **Ex. 143** (13.94), **Ex. 144** (15.08), **Ex. 145** (20.87), **Ex. 146** (17.91), **Ex. 147** (17.11), **Ex. 148** (7.83), **Ex. 149** (16.22), **Ex. 150** (20.09), **Ex. 151** (20.72), **Ex. 152** (21.38), **Ex. 153** (17.97), **Ex. 154** (16.58), **Ex. 155** (19.46), **Ex. 156** (15.66), **Ex. 157** (22.04), **Ex. 158** (15.65), **Ex. 159** (17.89), **Ex. 160** (18.72), **Ex. 161** (19.91), **Ex. 162** (17.79), **Ex. 179** (4.25), **Ex. 180** (11.43), **Ex. 181** (12.30), **Ex. 182** (12.83), **Ex. 183** (10.51), **Ex. 184** (12.12), **Ex. 185** (10.14), **Ex. 186** (10.09), **Ex. 187** (10.14), **Ex. 188** (10.65), **Ex. 189** (10.73), **Ex. 190** (10.10), **Ex. 191** (10.17), **Ex. 192** (10.19), **Ex. 193** (11.02), **Ex. 194** (9.92), **Ex. 195** (10.74), **Ex. 196** (9.94).

Example 46 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Pro-^{D}Asp(OtBu)-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 46 (8.94).

Example 47 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Asp which was grafted to the resin. Starting resin was Fmoc-Asp(OtBu)-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin- Asp(OtBu)-^{D}Pro-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method as described above:

Ex. 47 (7.29).

Example 48 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro(5RPhe) which was grafted to the resin. Starting resin was Fmoc-Pro(5RPhe)-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Pro(5RPhe)-^{D}Pro-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical described above: **Ex.48** (10.07).

Example 49 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Pro-^{D}Ala-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex.49 (8.09);

Example 50 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin- Pro-^{D}Ile-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical described above: **Ex.50** (9.78).

Example 51 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Leu which was grafted to the resin. Starting resin was Fmoc-Leu-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid

support according to procedure described above in the following sequence: Resin-Leu-^{D}Pro-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex.51 (8.94);

Example 64 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Glu which was grafted to the resin. Starting resin was Fmoc-Glu(OtBut)-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Glu(OtBu)-^{D}Pro-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex.64 (13.17).

Example 68 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Asp which was grafted to the resin. Starting resin was Fmoc-Asp(OtBu)-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Asp(OtBu)-^{D}Ala-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 68 (12.44).

Example 69 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin Pro-^{D}Asn(Trt)-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was

formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 69 (12.97).

Example 72 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Pro-^{D}Thr(OtBu)-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 72 (13.34).

Example 73 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Pro-^{D}Ile-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 73 (9.78).

Example 74 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Leu which was grafted to the resin. Starting resin was Fmoc-Leu-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Leu-^{D}Pro-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 74 (8.94).

Example 115 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Pro-^{D}Asp(OtBu)-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 115 (4.82).

Example 116 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Pro-^{D}Phe-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 116 (5.98).

Example 117 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Pro-^{D}Arg(Trt)-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 117 (4.48).

Example 118 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Pro-^{D}Ser(OtBu)-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 118 (4.73).

Example 119 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Pro-^{D}Val-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 119 (5.47).

Example 120 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Pro-^{D}Pic-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the gradient method 1 described above:

Ex. 120 (5.48).

Example 121 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Asp which was grafted to the resin. Starting resin was Fmoc-Asp(OtBu)-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Asp(OtBu)-^{D}Pro-P11-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 121 (4.56).

Examples 122 and **167** are shown in *Table 1*. The peptides were synthesized starting with the amino acid Phe which was grafted to the resin. Starting resin was Fmoc-Phe-2-chlorotrityl resin, which was prepared as described above. The linear peptides were synthesized on solid support according to procedure described above in the following sequence: Resin-Phe-^{D}Pro-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 122 (5.75); **167** (5.75).

Examples 123, 164, 169, 170, 172, 173, 175, 177 and **178** are shown in *Table 1*. The peptides were synthesized starting with the amino acid Gln which was grafted to the resin. Starting resin was Fmoc-Gln(Trt)-2-chlorotrityl resin, which was prepared as described above. The linear peptides were synthesized on solid support according to procedure described above in the following sequence: Resin-Gln(Trt)-^{D}Pro-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 123 (4.35), **164** (13.20), **169** (16.81), **170** (14.57), **172** (16.78), **173** (13.57), **175** (15.94), **177** (16.78), **178** (17.45).

Example 124 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Ser which was grafted to the resin. Starting resin was Fmoc-Ser(OtBu)-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Ser(OtBu)-^{D}Pro-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 124 (4.46).

Example 125 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Val which was grafted to the resin. Starting resin was Fmoc-Val-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Val-^{D}Pro-P11-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 125 (18.42).

Example 126 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Thr which was grafted to the resin. Starting resin was Fmoc-Thr(OtBu)-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Thr(OtBu)-^{D}Thr(OtBu)-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 126 (4.35).

Examples 127, 163, 165 and **174** are shown in *Table 1*. The peptides were synthesized starting with the amino acid Glu which was grafted to the resin. Starting resin was Fmoc-

Glu(OtBu)-2-chlorotrityl resin, which was prepared as described above. The linear peptides were synthesized on solid support according to procedure described above in the following sequence: Resin-Glu(OtBu)-^{D}Lys(Boc)-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.
HPLC-retention time (minutes) was determined using the analytical method described above:
Ex. 127 (4.11), **163** (14.93), **165** (14.40), **174** (12.73).

Example 128 is shown in *Table 1*. The peptide is synthesized starting with the amino acid Thr which was grafted to the resin. Starting resin was Fmoc-Thr(OtBu)-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Thr(OtBu)-^{D}Phe-P11-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.
HPLC-retention time (minutes) was determined using the gradient method 1 described above:
Ex. 128 (5.26).

Example 130 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Pro which was grafted to the resin. Starting resin was Fmoc-Pro-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Pro-^{D}Ala-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.
HPLC-retention time (minutes) was determined using the analytical method described above:
Ex.130 (14.79).

Example 166 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Ile which was grafted to the resin. Starting resin was Fmoc-Ile-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Ile-

^{D}Phe-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 166 (16.80).

Example 168 is shown in *Table 1*. The peptide was synthesized starting with the amino acid Asp which was grafted to the resin. Starting resin was Fmoc-Asp(OtBu)-2-chlorotrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-Asp(OtBu)-^{D}Pro-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical described above:

Ex. 168 (4.56).

Examples 171 and **176** are shown in *Table 1*. The peptides were synthesized starting with the amino acid Gln which was grafted to the resin. Starting resin was Fmoc-Gln(Trt)-2-chlorotrityl resin, which was prepared as described above. The linear peptides were synthesized on solid support according to procedure described above in the following sequence: Resin-Gln(Trt)-^{D}Gln(Trt)-P11-P10-P9-P8-P7-P6-P5-P4-P3-P2-P1. Thereafter the disulfide bridge was formed, and the peptide was cleaved from the resin, cyclized, deprotected and purified as indicated in procedure B.

HPLC-retention time (minutes) was determined using the analytical method described above:

Ex. 171 (15.40), **176** (13.67).

Table 1: Examples

Example	Sequ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	Template	Purity%[a)]	[M+ H]
1	SEQ ID NO: 1	Phe	Cys	Thr	Lys	Ser	Glu	Pro	Pro	Ile	Cys	Thr	$^{D}Pro^{L}Pro$	95	1385.7
2	SEQ ID NO: 2	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Asp	$^{D}Pro^{L}Pro$	93	1399.5
3	SEQ ID NO: 3	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Asn	$^{D}Pro^{L}Pro$	95	1398.5
4	SEQ ID NO: 4	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Pro$	95	1371.1
5	SEQ ID NO: 5	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1447.5
6	SEQ ID NO: 6	Tyr	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Thr	$^{D}Pro^{L}Pro$	95	1401.7
7	SEQ ID NO: 7	Arg	Glu	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Arg	Phe	$^{D}Pro^{L}Pro$	95	1521.2
8	SEQ ID NO: 8	Arg	Nle	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Nle	Phe	$^{D}Pro^{L}Pro$	95	1462.4
9	SEQ ID NO: 9	4AmPhe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Pro$	92	1386.9
10	SEQ ID NO: 10	Nle	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Pro$	93	1337.8
11	SEQ ID NO: 11	Chg	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Pro$	95	1363.8
12	SEQ ID NO: 12	Chg	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Arg	$^{D}Pro^{L}Pro$	95	1432.7
13	SEQ ID NO: 13	2Cl-Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Arg	$^{D}Pro^{L}Pro$	95	1474.5
14	SEQ ID NO: 14	Ile	Cys	Thr	Lys	Ser	Asp	Pro	Ala	Ile	Cys	Arg	$^{D}Pro^{L}Pro$	93	1380.5
15	SEQ ID NO: 15	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Nle	Cys	Ser	$^{D}Pro^{L}Pro$	95	1371.8
16	SEQ ID NO: 16	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Cha	Cys	Ser	$^{D}Pro^{L}Pro$	95	1411.6
17	SEQ ID NO: 17	Ile	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Gln	Cys	Arg	$^{D}Pro^{L}Pro$	95	1421.6
18	SEQ ID NO: 18	Ile	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Tyr	Cys	Arg	$^{D}Pro^{L}Pro$	89	1456.6
19	SEQ ID NO: 19	Ile	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Nle	Cys	Arg	$^{D}Pro^{L}Pro$	95	1476.6
20	SEQ ID NO: 20	Ile	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Cha	Cys	Arg	$^{D}Pro^{L}Pro$	95	1446.5
21	SEQ ID NO: 21	Phe	Cys	Thr	Lys	Ser	Glu	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Pro$	95	1385.8
22	SEQ ID NO: 22	Ile	Cys	Thr	Nle	Ser	Asp	Pro	Pro	Ile	Cys	Arg	$^{D}Pro^{L}Pro$	95	1391.6
23	SEQ ID NO: 23	Phe	Cys	Thr	Nle	Ser	Asp	Pro	Pro	Ile	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1432.7
24	SEQ ID NO: 24	Phe	Cys	Thr	Lys	AlloThr	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Pro$	95	1385.7
25	SEQ ID NO: 25	Phe	Cys	Thr	Lys	Dpr	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Pro$	95	1370.9
26	SEQ ID NO: 26	Tyr	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1463.8
27	SEQ ID NO: 27	hPhe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Asn	$^{D}Pro^{L}Pro$	95	1412.6
28	SEQ ID NO: 28	hPhe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Thr	$^{D}Pro^{L}Pro$	95	1399.7

Table 1 continued, Examples

Example	Sequ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	Template	Purity%[a)]	[M+ H]
29	SEQ ID NO: 29	hPhe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Asp	$^{D}Pro^{L}Pro$	95	1413.6
30	SEQ ID NO: 30	hPhe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1461.7
31	SEQ ID NO: 31	4AmPhe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Asn	$^{D}Pro^{L}Pro$	91	1413.8
32	SEQ ID NO: 32	4AmPhe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Tyr	$^{D}Pro^{L}Pro$	93	1462.7
33	SEQ ID NO: 33	Cha	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Asn	$^{D}Pro^{L}Pro$	94	1404.8
34	SEQ ID NO: 34	Cha	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Thr	$^{D}Pro^{L}Pro$	95	1391.7
35	SEQ ID NO: 35	Cha	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Asp	$^{D}Pro^{L}Pro$	95	1405.8
36	SEQ ID NO: 36	Cha	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1453.8
37	SEQ ID NO: 37	Chg	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Asn	$^{D}Pro^{L}Pro$	95	1390.7
38	SEQ ID NO: 38	Chg	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Thr	$^{D}Pro^{L}Pro$	95	1377.6
39	SEQ ID NO: 39	Chg	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Asp	$^{D}Pro^{L}Pro$	95	1391.6
40	SEQ ID NO: 40	Chg	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1439.6
41	SEQ ID NO: 41	Nle	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Asn	$^{D}Pro^{L}Pro$	95	1364.7
42	SEQ ID NO: 42	Nle	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Thr	$^{D}Pro^{L}Pro$	93	1351.7
43	SEQ ID NO: 43	Nle	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Asp	$^{D}Pro^{L}Pro$	95	1365.7
44	SEQ ID NO: 44	Nle	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1413.6
45	SEQ ID NO: 45	2Cl-Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Asn	$^{D}Pro^{L}Pro$	95	1432.6
46	SEQ ID NO: 46	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Asp^{L}Pro$	95	1389.6
47	SEQ ID NO: 47	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Asp$	95	1389.6
48	SEQ ID NO: 48	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Pro(5RPhe)$	95	1447.5
49	SEQ ID NO: 49	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Ala^{L}Pro$	95	1345.6
50	SEQ ID NO: 50	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Ile^{L}Pro$	94	1387.9
51	SEQ ID NO: 51	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Leu$	94	1395.7
52	SEQ ID NO: 52	Ile	Cys	Thr	Lys	Ser	Asp	Pro	Ala	Ile	Cys	Arg	$^{D}Pro^{L}Pro$	93	1380.7
53	SEQ ID NO: 53	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Nle	Cys	Ser	$^{D}Pro^{L}Pro$	95	1371.8
54	SEQ ID NO: 54	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Cha	Cys	Ser	$^{D}Pro^{L}Pro$	95	1411.6
55	SEQ ID NO: 55	Ile	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Gln	Cys	Arg	$^{D}Pro^{L}Pro$	95	1421.6
56	SEQ ID NO: 56	Ile	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Tyr	Cys	Arg	$^{D}Pro^{L}Pro$	89	1456.5
57	SEQ ID NO: 57	Ile	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Nle	Cys	Arg	$^{D}Pro^{L}Pro$	94	1406.6
58	SEQ ID NO: 58	Ile	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Cha	Cys	Arg	$^{D}Pro^{L}Pro$	95	1446.5
59	SEQ ID NO: 59	Ile	Cys	Thr	Nle	Ser	Asp	Pro	Pro	Ile	Cys	Arg	$^{D}Pro^{L}Pro$	95	1391.6
60	SEQ ID NO: 60	Phe	Cys	Thr	Nle	Ser	Asp	Pro	Pro	Ile	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1432.7
61	SEQ ID NO: 61	Trp	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Pro$	95	1410.9

Table 1 continued, Examples

Example	Sequ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	Template	Purity%[a)]	[M+ H]
62	SEQ ID NO: 62	1-Nal	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Pro$	95	1421.9
63	SEQ ID NO: 63	Chg	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Nle	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1439.
64	SEQ ID NO: 64	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Glu$	95	1403.8
65	SEQ ID NO: 65	Chg	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Tyr	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1489.5
66	SEQ ID NO: 66	Chg	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Cha	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1479.6
67	SEQ ID NO: 67	Chg	Cys	Thr	Lys	AlloThr	Asp	Pro	Pro	Tyr	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1503.6
68	SEQ ID NO: 68	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Ala^{L}Asp$	95	1363.6
69	SEQ ID NO: 69	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Asn^{L}Pro$	90	1388.8
70	SEQ ID NO: 70	4AmPhe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Cha	Cys	Asn	$^{D}Pro^{L}Pro$	92	1454.5
71	SEQ ID NO: 71	Chg	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Cha	Cys	Arg	$^{D}Pro^{L}Pro$	95	1472.6
72	SEQ ID NO: 72	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Thr^{L}Pro$	95	1375.6
73	SEQ ID NO: 73	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Ile^{L}Pro$	94	1387.9
74	SEQ ID NO: 74	Phe	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Ser	$^{D}Pro^{L}Leu$	94	1387.9
75	SEQ ID NO: 75	Arg	Cys	Thr	Lys	Ser	Asp	Pro	Pro	Ile	Cys	Phe	$^{D}Pro^{L}Pro$	95	1440.5
76	SEQ ID NO: 76	Ile	Cys	Thr	Ala	Ser	Leu	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1369.3
77	SEQ ID NO: 77	Nle	Cys	Thr	Thr	Ser	Ile	Pro	Pro	Tyr	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1434.3
78	SEQ ID NO: 78	Nle	Cys	Thr	Abu	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1383.6
79	SEQ ID NO: 79	Nle	Cys	Thr	Ala	Ser	Nle	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1369.8
80	SEQ ID NO: 80	Nle	Cys	Thr	Ala	Ser	Aoc	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1397.6
81	SEQ ID NO: 81	Nle	Cys	Thr	Ala	Ser	OctG	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1425.6
82	SEQ ID NO: 82	Nle	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1409.5
83	SEQ ID NO: 83	Nle	Cys	Thr	Ala	Ser	hLeu	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1383.6
84	SEQ ID NO: 84	Nle	Cys	Thr	Ala	Ser	Chg	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1395.7
85	SEQ ID NO: 85	Nle	Cys	Thr	Ala	Ser	t-BuA	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1383.6
86	SEQ ID NO: 86	Nle	Cys	Ala	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1340.1
87	SEQ ID NO: 87	Nle	Cys	Abu	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1354.0
88	SEQ ID NO: 88	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro(4NHCOPhe)	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1488.6
89	SEQ ID NO: 89	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Phe	Cys	Tyr	$^{D}Pro^{L}Pro$	88	1388.7
90	SEQ ID NO: 90	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Phe	$^{D}Pro^{L}Pro$	95	1353.6
91	SEQ ID NO: 91	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Gln	$^{D}Pro^{L}Pro$	95	1334.5
92	SEQ ID NO: 92	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Arg	$^{D}Pro^{L}Pro$	56	1362.6
93	SEQ ID NO: 93	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Ser	$^{D}Pro^{L}Pro$	95	1293.7

Table 1 continued, Examples

Example	Sequ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	Template	Purity%[a)]	[M+ H]
94	SEQ ID NO: 94	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Nle	$^{D}Pro^{L}Pro$	95	1319.5
95	SEQ ID NO: 95	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	2-Nal	$^{D}Pro^{L}Pro$	94	1404.0
96	SEQ ID NO: 96	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	2Cl-Phe	$^{D}Pro^{L}Pro$	94	1387.8
97	SEQ ID NO: 97	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Cha	$^{D}Pro^{L}Pro$	95	1359.8
98	SEQ ID NO: 98	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Phg	$^{D}Pro^{L}Pro$	95	1359.9
99	SEQ ID NO: 99	Aoc	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	93	1397.4
100	SEQ ID NO: 100	hLeu	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1383.4
101	SEQ ID NO: 101	Chg	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	87	1395.6
102	SEQ ID NO: 102	OctG	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1425.5
103	SEQ ID NO: 103	hPhe	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1417.5
104	SEQ ID NO: 104	Nle	Glu	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Lys	Tyr	$^{D}Pro^{L}Pro$	95	1422.8
105	SEQ ID NO: 105	Nle	Glu	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Arg	Tyr	$^{D}Pro^{L}Pro$	95	1450.9
106	SEQ ID NO: 106	Nle	Thr	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Lys	Tyr	$^{D}Pro^{L}Pro$	95	1394.7
107	SEQ ID NO: 107	Nle	Gln	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Arg	Tyr	$^{D}Pro^{L}Pro$	90	1449.8
108	SEQ ID NO: 108	Nle	Thr	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Met	Tyr	$^{D}Pro^{L}Pro$	96	1397.7
109	SEQ ID NO: 109	Nle	Gln	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Thr	Tyr	$^{D}Pro^{L}Pro$	95	1394.7
110	SEQ ID NO: 110	Nle	Thr	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Gln	Tyr	$^{D}Pro^{L}Pro$	81	1394.6
111	SEQ ID NO: 111	Nle	Gln	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Ser	Tyr	$^{D}Pro^{L}Pro$	95	1380.7
112	SEQ ID NO: 112	Nle	Cys	Thr	Ala	Ser	C5al	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Pro$	85	1413.8
113	SEQ ID NO: 113	Nle	Cys	Thr	Ala	Ser	Leu	Pro	Pro	Tyr	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1404.7
114	SEQ ID NO: 114	Ile	Cys	Thr	Ala	Ser	Leu	Pro	Pro	Tyr	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1404.7
115	SEQ ID NO: 115	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Asp^{L}Pro$	95	1387.8
116	SEQ ID NO: 116	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Phe^{L}Pro$	95	1419.9
117	SEQ ID NO: 117	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Arg^{L}Pro$	95	1428.6
118	SEQ ID NO: 118	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Ser^{L}Pro$	95	1359.9
119	SEQ ID NO: 119	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Val^{L}Pro$	95	1371.8
120	SEQ ID NO: 120	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Pip^{L}Pro$	95	1383.7
121	SEQ ID NO: 121	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Asp$	95	1387.9
122	SEQ ID NO: 122	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	$^{D}Pro^{L}Phe$	95	1419.9

Table 1 continued, Examples

Example	Sequ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	Template	Purity%[a)]	[M+ H]
123	SEQ ID NO: 123	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Gln	95	1400.6
124	SEQ ID NO: 124	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Ser	95	1359.5
125	SEQ ID NO: 125	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Val	95	1371.8
126	SEQ ID NO: 126	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Thr^{L}Thr	95	1377.4
127	SEQ ID NO: 127	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Lys^{L}Glu	95	1433.5
128	SEQ ID NO: 128	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Phe^{L}Thr	95	1423.5
129	SEQ ID NO: 129	Nle	Cys	Thr	Ala	Ser	OctG	Pro	Pro	Gln	Cys	Gln	^{D}Pro^{L}Pro	91	1390.4
130	SEQ ID NO: 130	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Ala^{L}Pro	95	1343.5
131	SEQ ID NO: 131	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Gln	^{D}Pro^{L}Pro	95	1334.5
132	SEQ ID NO:132	hPhe	Glu	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Lys	Tyr	^{D}Pro^{L}Pro	95	1470.6
133	SEQ ID NO:133	Nle	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	Gln	^{D}Pro^{L}Pro	95	1440.5
134	SEQ ID NO: 134	hPhe	Thr	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Gln	Tyr	^{D}Pro^{L}Pro	95	1442.5
135	SEQ ID NO: 135	Nle	Thr	Thr	Ala	Ser	OctG	Pro	Pro	Gln	Gln	Tyr	^{D}Pro^{L}Pro	88	1450.7
136	SEQ ID NO: 136	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Phg	^{D}Pro^{L}Pro	95	1339.9
137	SEQ ID NO: 137	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Phe	^{D}Pro^{L}Pro	95	1353.6
138	SEQ ID NO: 138	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro(4NHCOPhe)	Gln	Cys	Tyr	^{D}Pro^{L}Pro	95	1488.6
139	SEQ ID NO: 139	Nle	Thr	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Gln	Tyr	^{D}Pro^{L}Pro	95	1434.8
140	SEQ ID NO: 140	Nle	Cys	Thr	Ala	Ser	Chg	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Pro	95	1395.7
141	SEQ ID NO: 141	Nle	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Pro	95	1409.5
142	SEQ ID NO: 142	hPhe	Gln	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Thr	Tyr	^{D}Pro^{L}Pro	91	1406.5
143	SEQ ID NO: 143	hPhe	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Gln	^{D}Pro^{L}Pro	94	1383.5
144	SEQ ID NO: 144	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	2Cl-Phe	^{D}Pro^{L}Pro	94	1387.8
145	SEQ ID NO: 145	OctG	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Phe	^{D}Pro^{L}Pro	95	1409.4
146	SEQ ID NO: 146	hPhe	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Phe	^{D}Pro^{L}Pro	95	1401.5
147	SEQ ID NO: 147	OctG	Thr	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Gln	Tyr	^{D}Pro^{L}Pro	95	1450.9
148	SEQ ID NO: 148	OctG	Cys	Thr	Ala	Ser	OctG	Pro	Pro	Gln	Cys	Gln	^{D}Pro^{L}Pro	95	1446.6
149	SEQ ID NO: 149	OctG	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Gln	^{D}Pro^{L}Pro	95	1390.4
150	SEQ ID NO: 150	OctG	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Pro	95	1465.6
151	SEQ ID NO: 151	OctG	Cys	Thr	Ala	Ser	OctG	Pro	Pro(4NHCOPhe)	Gln	Cys	Gln	^{D}Pro^{L}Pro	94	1565.7
152	SEQ ID NO: 152	hPhe	Cys	Thr	Ala	Ser	OctG	Pro	Pro	Gln	Cys	Phe	^{D}Pro^{L}Pro	95	1457.6
153	SEQ ID NO: 153	hPhe	Cys	Thr	Ala	Ser	OctG	Pro	Pro	Gln	Cys	Gln	^{D}Pro^{L}Pro	95	1438.5
154	SEQ ID NO: 154	OctG	Gln	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Thr	Tyr	^{D}Pro^{L}Pro	93	1450.9
155	SEQ ID NO: 155	hPhe	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	Phe	^{D}Pro^{L}Pro	90	1441.5

Table 1 continued, Examples

Example	Sequ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	Template	Purity%[a)]	[M+ H]
156	SEQ ID NO: 156	OctG	Glu	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Lys	Tyr	^{D}Pro^{L}Pro	95	1478.7
157	SEQ ID NO: 157	OctG	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	Phe	^{D}Pro^{L}Pro	95	1449.8
158	SEQ ID NO: 158	hPhe	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	Gln	^{D}Pro^{L}Pro	94	1422.7
159	SEQ ID NO: 159	OctG	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	Gln	^{D}Pro^{L}Pro	93	1430.0
160	SEQ ID NO: 160	OctG	Cys	Thr	Ala	Ser	Cha	Pro	Pro(4NHCOPhe)	Gln	Cys	Gln	^{D}Pro^{L}Pro	95	1549.6
161	SEQ ID NO: 161	hPhe	Cys	Thr	Ala	Ser	OctG	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Pro	95	1473.4
162	SEQ ID NO: 162	hPhe	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Pro	95	1457.3
163	SEQ ID NO: 163	Nle	Cys	Thr	Ala	Ser	OctG	Pro	Pro	Gln	Cys	Tyr	^{D}Lys^{L}Glu	95	1374.4
164	SEQ ID NO: 164	Nle	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	Gln	^{D}Pro^{L}Gln	95	1405.5
165	SEQ ID NO: 165	OctG	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Lys^{L}Glu	95	1488.0
166	SEQ ID NO: 166	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Ile	95	1385.6
167	SEQ ID NO: 167	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Phe	95	1419.9
168	SEQ ID NO: 168	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Asp	95	1387.9
169	SEQ ID NO: 169	Nle	Cys	Thr	Ala	Ser	OctG	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Gln	95	1456.5
170	SEQ ID NO: 170	Nle	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Gln	95	1440.5
171	SEQ ID NO: 171	Nle	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	Cha	^{D}Gln^{L}Gln	95	1461.0
172	SEQ ID NO: 172	Nle	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	Cha	^{D}Pro^{L}Gln	95	1430.6
173	SEQ ID NO: 173	hPhe	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Gln	95	1448.6
174	SEQ ID NO: 174	hPhe	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Lys^{L}Glu	95	1480.0
175	SEQ ID NO: 175	Nle	Cys	Thr	Ala	Ser	Cha	Pro	Pro	Gln	Cys	2Cl-Phe	^{D}Pro^{L}Gln	95	1458.5
176	SEQ ID NO: 176	Nle	Cys	Thr	Ala	Ser	Cha	Pro	Pro(4NHCOPhe)	Gln	Cys	Gln	^{D}Gln^{L}Gln	95	1555.5
177	SEQ ID NO: 177	OctG	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Gln	95	1430.6
178	SEQ ID NO: 178	OctG	Cys	Thr	Ala	Ser	OctG	Pro	Pro	Gln	Cys	Gln	^{D}Pro^{L}Gln	95	1477.6
179	SEQ ID NO: 179	Nle	Cys	Thr	Ala	Ser	Ile	Pro	Pro	Gln	Cys	Tyr	^{D}Pro^{L}Pro	90	1369.7
180	SEQ ID NO: 180	Ile	Cys	Thr	Lys	Ser	Leu	Pro	Pro	Ile	Cys	Arg	^{D}Pro^{L}Pro	94	1404.8
181	SEQ ID NO: 181	Ile	Cys	Thr	Lys	Ser	hPhe	Pro	Pro	Ile	Cys	Arg	^{D}Pro^{L}Pro	92	1452.6
182	SEQ ID NO: 182	Ile	Cys	Thr	Lys	Ser	Cha	Pro	Pro	Ile	Cys	Arg	^{D}Pro^{L}Pro	95	1444.6
183	SEQ ID NO: 183	Ile	Cys	Thr	Lys	Ser	Tyr	Pro	Pro	Ile	Cys	Arg	^{D}Pro^{L}Pro	91	1454.5
184	SEQ ID NO: 184	Phe	Cys	Thr	Lys	Ser	Leu	Pro	Pro	Ile	Cys	Arg	^{D}Pro^{L}Pro	95	1438.6

Table 1 continued, Examples

Example	Sequ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	Template	Purity%[a)]	[M+ H]
185	SEQ ID NO: 185	Ile	Cys	Thr	Lys	Ser	Leu	Pro	Pro	Arg	Cys	Arg	$^{D}Pro^{L}Pro$	95	1447.5
186	SEQ ID NO: 186	Ile	Cys	Thr	Lys	Ser	Leu	Pro	Pro	Lys	Cys	Arg	$^{D}Pro^{L}Pro$	95	1419.9
187	SEQ ID NO: 187	Ile	Cys	Thr	Lys	Ser	Leu	Pro	Pro	His	Cys	Arg	$^{D}Pro^{L}Pro$	95	1428.6
188	SEQ ID NO: 188	Ile	Cys	Thr	Lys	Ser	Leu	Pro	Pro	Gln	Cys	Arg	$^{D}Pro^{L}Pro$	95	1419.8
189	SEQ ID NO: 189	Ile	Cys	Thr	Lys	Ser	Leu	Pro	Pro	Thr	Cys	Arg	$^{D}Pro^{L}Pro$	95	1392.4
190	SEQ ID NO: 190	Ile	Cys	Thr	Lys	Ser	Leu	Pro	Pro	Arg	Cys	Lys	$^{D}Pro^{L}Pro$	95	1420.1
191	SEQ ID NO: 191	Leu	Cys	Thr	Lys	Ser	Leu	Pro	Pro	Lys	Cys	Arg	$^{D}Pro^{L}Pro$	95	1420.0
192	SEQ ID NO: 192	Nle	Cys	Thr	Lys	Ser	Leu	Pro	Pro	Lys	Cys	Arg	$^{D}Pro^{L}Pro$	95	1420.0
193	SEQ ID NO: 193	Cha	Cys	Thr	Lys	Ser	Leu	Pro	Pro	Lys	Cys	Arg	$^{D}Pro^{L}Pro$	95	1459.7
194	SEQ ID NO: 194	Tyr	Cys	Thr	Lys	Ser	Leu	Pro	Pro	Lys	Cys	Arg	$^{D}Pro^{L}Pro$	95	1469.6
195	SEQ ID NO: 195	Trp	Cys	Thr	Lys	Ser	Leu	Pro	Pro	Lys	Cys	Arg	$^{D}Pro^{L}Pro$	92	1492.6
196	SEQ ID NO: 196	Arg	Cys	Thr	Lys	Ser	Leu	Pro	Pro	Lys	Cys	Tyr	$^{D}Pro^{L}Pro$	95	1469.6

a) %-purity of compounds after prep. HPLC
Cys in pos. 2 and 10 in Ex. 1-6, 9-103, 112-131, 133, 136-138, 140-141, 143-146, 148-153, 155, 157-196 form a disulfide bridge

2. Biological methods

2.1. Preparation of the peptide samples.

Lyophilized peptides were weighed on a Microbalance (Mettler MT5) and dissolved in sterile water to a final concentration of 1 mM unless stated otherwise. Stock solutions were kept at +4°C, light protected.

2.2. Enzymatic assays

Enzyme and substrate conditions were as indicated **Table 2.**

Kinetic measurements were made in a total reaction volume of 100 µl in 96 well flat bottomed plates (Greiner) on a Genios plate reader (Tecan). The enzyme was combined with the peptides (inhibitors) in a buffer containing 100mM HEPES (pH 7.5), 50mM $CaCl_2$, 0.025% Tween-20, 5% DMSO, and 1 mM of the substrate. The rate of substrate hydrolysis was measured by monitoring the change in absorbance at 405 nm over 30 minutes to verify linearity of the reaction curve. The average rate from minute 1 through minute 10 was used for all calculations. Initial calculations of background subtraction, average rate, duplicate averaging and % inhibition were made using the Magellan software (version 5) from Tecan. IC50% calculations were made using Grafit (version 5.0.10) from Erithacus Software by fitting inhibition data from 6 different inhibitor concentrations to a 4-parameter equation:

$$y = \frac{100\%}{1+\left(\frac{x}{IC_{50}}\right)^{s}}$$

In this equation s is the slope factor, x is the inhibitor concentration and y is % inhibition at a given concentration of the inhibitor.

K_m/K_i determination

The K_m for the serine protease substrate was determined from a Lineweaver-Burke plot (Grafit v5). The K_i values for inhibitors were calculated using the formula $K_i = IC50\%/(1+([substrate]/K_m))$.

Increasing concentrations of substrate were reacted with the enzyme and the rate of each reaction (ABS/mSec) was plotted vs. substrate concentration. The reciprocal plot (Lineweaver-Burke) was also plotted to give K_m and V_{max} (inset) (see ref. 1 below).

Table 2

Enzyme/ Supplier	**Enzyme concentration in assay**	**Substrate/ Supplier**	**Substrate concentration in assay (mM)**
Elastase from human neutrophils/ Serva	0.6 mU/reaction	N-Met-Ala-Pro-Val-p-nitroanilide /Sigma	1
CathepsinG, from human neutrophils CAS nr. 107200-92-0 Calbiochem	1 mU/ reaction	N-Succinyl-Ala-Pro-Phe-p-nitroanilide Sigma	1
Trypsin, Iodination grade, from human pancreas, CAS nr. 9002-07-7 Calbiochem	1 mU/reaction	N-Benzoyl-Arg-p-nitroanilide Sigma	0.32
Chymase, from human skin Calbiochem	9 mU/reaction	N-Succinyl-Ala-Pro-Phe-p-nitroanilide Sigma	1.5
Thrombin, from Human Plasma, high activity, CAS nr. 9002-04-4 Calbiochem	100 mU/reaction	Benzoyl-Phe-Val-Arg-p-nitroanilide Calbiochem	0.5
Chymotrypsin, from human pancreas CAS nr 9004-07-3 Calbiochem	1.6 microM/ reaction	N-Succinyl-Ala-Pro-Phe-p-nitroanilide Sigma	1
Coagulation Factor Xa, from uman plasma, CAS nr. 9002-05-5 Calbiochem	0.4mU/reaction	Methoxycarbonyl-D-Nle-Gly-Arg-p-nitroanilid Roche	2
Tryptase, from human lung Calbiochem	12.5mU/reaction	N-Benzoyl-Arg-p-nitroanilide Sigma	1.28
Urokinase from human urine/ Sigma Aldrich CAS nr. 9039-53-6	250mU/reaction	Pyroglu-Gly-Arg- p-nitroanilide x HCl Endotell	0.5

Enzyme/ Supplier	Enzyme concentration in assay	Substrate/ Supplier	Substrate Concentration in assay (mM)
Kallikrein, from human plasma, CAS Nr 9001-01-8 Calbiochem	0.34 microgram /reaction	N-Benzoyl-Pro-Phe-Arg-p-nitroanilide Sigma	1
Plasmin from human plasma, CAS nr. 9001-90-5 Sigma-Aldrich	2 mU/reaction	D-Val-Leu-Lys-p-Nitroanilide Sigma	5

2.3. Cytotoxicity assay

The cytotoxicity of the peptides to HELA cells (Acc57) and COS-7 cells (CRL-1651) was determined using the MTT reduction assay [see ref. 2 and 3, below]. Briefly the method was as follows: HELA cells and COS-7 cells were seeded at $7.0x10^3$ and, respectively, $4.5x10^3$ cells per well and grown in 96-well microtiter plates for 24 hours at 37°C at 5% CO_2. At this point, time zero (Tz) was determined by MTT reduction (see below).The supernatant of the remaining wells was discarded, and fresh medium and the peptides in serial dilutions of 12.5, 25 and 50 µM were pipetted into the wells. Each peptide concentration was assayed in triplicate. Incubation of the cells was continued for 48 hours at 37°C at 5% CO_2. Wells were then washed once with phosphate buffered saline (PBS) and subsequently 100 µl MTT reagent (0.5 mg/ml in medium RPMI1640 and, respectively, DMEM) were added to the wells. This was incubated at 37°C for 2 hours and subsequently the medium was aspirated and 100 µl isopropanol were added to each well. The absorbance at 595 nm of the solubilized product was measured (OD_{595}peptide). For each concentration averages were calculated from triplicates. The percentage of growth was calculated as follows: (OD_{595}peptide-OD_{595}Tz-OD_{595}Empty well) / (OD_{595}Tz-OD_{595}Empty well) x 100% and was plotted for each peptide concentration.

The LC 50 values (Lethal Concentration, defined as the concentration that kills 50% of the cells) were determined for each peptide by using the trend line function of EXCEL (Microsoft Office 2000) for the concentrations (50, 25, 12.5 and 0 µM), the corresponding growth percentages and the value -50, (=TREND(C50:C0,%50:%0,-50)).

The GI 50 (Growth Inhibition) concentrations were calculated for each peptide by using a trend line function for the concentrations (50, 25, 12.5 and 0 µg/ml), the corresponding percentages and the value 50, (=TREND (C_{50}:C_0,$\%_{50}$:$\%_0$,50).

2.4. Hemolysis

The peptides were tested for their hemolytic activity against human red blood cells (hRBC). Fresh hRBC were washed three times with phosphate buffered saline (PBS) by centrifugation for 10 min at 2000 x g. Peptides at a concentration of 100 µM were incubated with 20% v/v hRBC for 1 hour at 37°C. The final erythrocyte concentration was approximately $0.9x10^9$ cells per ml. A value of 0% and, respectively,. 100% cell lysis was determined by incubation of the hRBC in the presence of PBS alone and, respectively, 0.1% Triton X-100 in H_2O. The samples were centrifuged, the supernatant was 20-fold diluted in PBS buffer and the optical density (OD) of the sample at 540 nM was measured. The 100% lysis value ($OD_{540}H_20$) gave an OD_{540} of approximately 1.3-1.8. Percent hemolysis was calculated as follows: (OD_{540}peptide/$OD_{540}H_20$) x100%.

2.5 Plasma stability

405 µl of plasma/albumin solution were placed in a polypropylene (PP) tube and spiked with 45 µl of compound from a 100 mM solution B, derived from 135 µl of PBS and 15 µl of 1 mM peptide in PBS, pH 7.4. 150 µl aliquots were transferred into individual wells of the 10 kDa filter plate (Millipore MAPPB 1010 Biomax membrane). For "0 minutes controls": 270 µl of PBS were placed in a PP tube and 30 µl of stock solution B was added and vortexed. 150 µl of control solution were placed into one well of the filter plate and served as "filtered control".

Further 150 µl of control solution were placed directly into a receiver well (reserved for filtrate) and served as "not-filtered control". The entire plate including evaporation lid was incubated for 60 min at 37°C. Plasma samples (rat plasma: Harlan Sera lab UK, human plasma: Blutspendezentrum Zürich) were centrifuged at least for 2 h at 4300 rpm (3500 g) and 15°C in order to yield 100 µl filtrate. For "serum albumin"-samples (freshly prepared human albumin: Sigma A-4327, rat albumin: Sigma A-6272, all at 40 mg/ml concentration in PBS) approximately 1 hour of centrifugation was sufficient. The filtrates in the receiver PP plate were analysed by LC/MS as followes: Column: Jupiter C18 (Phenomenex), mobile phases: (A) 0.1% formic acid in water and (B) acetonitrile, gradient: 5%-100% (B) in 2 minutes, electrospray ionization, MRM detection (triple quadrupole). The peak areas were determined and triplicate values were averaged. The binding was expressed in percent of the (filtered and not-filtered time point 0 min) control 1 and 2 by: 100-(100 x T_{60}/T_0). The average from these values was then calculated.

2.6. Pharmacokinetic study (PK)

Pharmacokinetic study after single oral (gavage) and intravenous administration in rats

Pharmacokinetic study after single intravenous (i.v.) and oral (p.o., gavage) administration was performed for the compound of Example **75** ("**Ex. 75**"). 332 g (± 10 g) male Wistar mice obtained from RCC Ltd, Laboratory animal Services, CH-4414 Füllinsdorf, Switzerland were used in the study. The vehicle, physiological saline, was added to give a final concentration of 2.5 mg/ml of the compound. The volume was 2 ml/kg i.v. and 10 ml/kg p.o. and the peptide **Ex. 75** was injected to give a final intravenous dose of 5 mg/kg and an oral dose of 50 mg/kg. Blood samples (approx. 0.24 ml) were taken following the schedule below at different time points into heparinized tubes by automated blood sampling using the DiLab AccuSampler. When a problem occured during automated blood sampling, blood was sampled by retro-orbital bleeding under light isoflurane anesthesia. Samples where taken at the following time points: 0, 5 min (only i.v.), 15, 30 min and 1, 2, 4, 8, 16, 24 and 36 (only p.o.) hours and added to heparinized tubes. Plasma was removed from pelleted cells upon centrifugation and frozen at -80°C prior to HPLC-MS analysis.

Preparation of the plasma calibration samples

"Blank" rat plasma from untreated animals was used. Aliquots of plasma of 0.1 ml each were spiked with 50 ng of propranolol (Internal Standard, IS), (sample preparation by solid phase extraction on OASIS® HLB cartridges (Waters)) and with known amounts of **Ex. 75** in order to obtain 9 plasma calibration samples in the range 5 – 2000 ng/ml. The OASIS® HLB cartridges were conditioned with 1 ml of methanol and then with 1 ml of 1% NH_3 in water. Samples were then diluted with 400 µl of 1% NH_3 in water and loaded. The plate was washed with 1 ml of methanol/1% NH_3 in water 5/95. Elution was performed using 1 ml of 0.1% TFA in methanol.

The plate containing eluates was introduced into the concentrator system and taken to dryness. The residues were dissolved in 100 µl of formic acid 0.1%/acetonitrile, 95/5 (v/v) and analysed in the HPLC/MS on a reverse phase analytical column (Jupiter C18, 50 x 2.0 mm, 5 µm, Phenomenex), using gradient elution (mobile phases A: 0.1% formic acid in water, B: Acetonitrile; from 5%B to 100%B in 2 min.).

Preparation of plasma samples

From each sample 100 µl of plasma were taken for the extraction. If the volume was less than 100 µl the appropriate amount of "blank" mouse plasma was added in order to keep

the matrix identical to the calibration curve. Samples were then spiked with IS and processed as described for the calibration curve.

Pharmacokinetic evaluation

PK analysis was performed on pooled data (generally n=2 or 3) using the software PK solutions 2.0™ (Summit Research Service, Montrose, CO 81401 USA). The area under the curve AUC was calculated by the linear trapezoidal rule. $AUC_{(t-\infty)}$ was estimated as Ct/b (b: elimination rate constant). $AUC_{(t-\infty)}$ is the sum of $AUC_{(0-t)}$ and $AUC_{(t-\infty)}$. Elimination half-life was calculated by the linear regression on at least three data points during the elimination phase. The time intervals selected for the half-life determinations were evaluated by the correlation coefficient (r^2), which should be at least above 0.85 and most optimally above 0.96. In case of i.v. administration the initial concentration at t_{zero} was determined by extrapolation of the curve through the first two time points. Finally bioavailability after i.p. administration was calculated from the normalised $AUC_{(0-\infty)}$ ratio after i.p. *versus* i.v. administration.

3.0 Results

The results of the experiments described under 2.2 - 2.5, above, are indicated in Table 3 herein below.

Table 3

Ex	Cathepsin G IC50 (nmol)	Elastase IC50 (nmol)	Trypsin at 100 μM %	Chymo-trypsin at 100 μM %	Chymase at 100 μM %	Thrombin at 100 μM %	FXa at 100 μM %	Urokinase at 100 μM %	Tryptase At 100 μM %	Cytotoxicity LC_{50}/ GI_{50} *Hela cells*	Hemo-lysis at 100 μM %
1	86	>100000	92.6	7.8	0	1.1	5.7	5.7	0	nd	0
2	84	>100000	92	2.9	0	9.2	5.3	0.9	39.6	nd	nd
3	51	>100000	92	0	1	0	4	4	68	100	0
4	91	>100000	96	1.8	0	0	2.4	5.4	0	100	0
5	56	>100000	92	3	0	0.5	0.2	5.7	74	nd	0
6	?	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
7	91	1.5 at 100 μM %	41	12	13.4	0	11.7	1.1	1.5	100	0.2
8	126	0.8 at 100 μM %	74.2	5.6	71.7	nd	nd	nd	nd	nd	nd
9	105	4.1 at 100 μM %	88.1	nd	nd	nd	nd	nd	nd	nd	nd
10	75	0.3 at 100 μM %	89.9	nd	9.4	nd	nd	nd	nd	nd	nd
11	95	19 at 100 μM %	6.5	73.6	12.1	nd	nd	nd	nd	nd	nd
12	90	37038	97	28	12	11	5	12	59.3	59.3	nd
13	100	8.2 at 100 μM %	95.0	nd	19.9	nd	nd	nd	nd	nd	nd
14	52	>100000	88	0	42.3	8.7	6	5.4	84.2	100	0
15	56.0	>100000	95.0	54.2	12.7	nd	nd	nd	nd	100	0
16	66	>100000	90.0	17.9	12.9	nd	nd	3.2	nd	94	0.1

Table 3 continued

Ex	Cathepsin G IC50 (nmol)	Elastase IC50 (nmol)	Trypsin at 100 μM %	Chymo-trypsin at 100 μM %	Chymase at 100 μM %	Thrombin at 100 μM %	FXa at 100 μM %	Urokinase at 100 μM %	Tryptase at 100 μM %	Cytotoxicity LC_{50}/ GI_{50} *Hela cells*	Hemo-lysis at 100 μM %
17	55	>100000	90.0	16	27.6	0	nd	nd	90.4	94	0.1
18	47	>100000	84	25	32.5	0	nd	nd	88.3	100	0
19	41	>100000	94.0	0	26.9	11	32	4	85.2	100	0
20	48	>100000	97.0	0	44.1	28	25	6.7	nd	100	0
21	97	16.4	95.6	2.6	5	nd	nd	nd	nd	nd	nd
22	55	>100000	84.	0	98.8	nd	nd	5.7	3.8	8	0
23	38	>100000	90	4	60	0	11	9	29	51	0
24	71	>100000	97	1.0	1.2	3.5	30	5.1	0	99	nd
25	102	3.2 at 100μM %	89.3	nd	10.0	nd	nd	nd	nd	nd	nd
26	49	>100000	84	2.2	0	3	6	3.1	66.4	nd	nd
27	48	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
28	39	>100000	95	32	0	12	6	1	0	nd	nd
29	42	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
30	39	49900	98	49	0	2	3	9	nd	nd	nd
31	34	>100000	98	15	12	10	8	15	76	nd	nd
32	52	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
33	45	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
34	56	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
35	54	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd

Table 3 continued

Ex	Cathe-psin G IC50 (nmol)	Elastase IC50 (nmol)	Trypsin at 100 μM %	Chymo-trypsin at 100 μM %	Chymase at 100 μM %	Thrombin at 100 μM %	FXa at 100 μM %	Urokinase at 100 μM %	Tryptase at 100 μM %	Cytotoxicity LC_{50}/ GI_{50} *Hela cells*	Hemolysis at 100 μM %
36	41	nd	Nd	nd	nd	nd	nd	0	73.3	83	0
37	35	nd	nd	nd	nd	nd	nd	5	56	92	0.1
38	31	>100000	96	4	1	0	0	1	11	100	0
39	38	>100000	94	7	0	2	0	2	34	98	0
40	25	>44862	94	19	8	1	3	10	33	97	0.1
41	49	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
42	46	nd	nd	nd	nd	nd	nd	7	0	87	0
43	77	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
44	31	>10000	100	24	3	9	9	14	50	67	0.1
45	47	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
46	87.5	>100000	95	0	10.2	6.9	12.2	5.8	44.1	nd	nd
47	64	>10000	87	1	8.2	0	9.3	6.3	0	100	0
48	83	>100000	93	3	nd	nd	nd	nd	nd	nd	nd
49	82	>10000	96	0	0	7.9	nd	6.2	30.5	nd	nd
50	89	>100000	94	0	nd	nd	nd	nd	nd	nd	nd
51	91	>100000	nd	nd	nd	nd	nd	nd	nd	nd	nd
52	52	>100000	86	0	42.3	8.7	6	5.4	84.2	100	0
53	56	>100000	95	54	12.7	nd	nd	nd	nd	63	0
54	66	>100000	90	18	12.9	nd	nd	3.2	nd	nd	nd
55	55	>100000	90	16	27.6	nd	nd	nd	90.4	94	0.1
56	47	>100000	84	25	32.5	0	nd	nd	88.3	100	0

Table 3 continued

Ex	Cathe-psin G IC50 (nmol)	Elastase IC50 (nmol)	Trypsin at 100 μM %	Chymo-trypsin at 100 μM %	Chymase at 100 μM %	Thrombin at 100 μM %	FXa at 100 μM %	Urokinase at 100 μM %	Tryptase at 100 μM %	Cyto-toxicity LC_{50}/ GI_{50} *Hela cells*	Hemo-lysis at 100 μM %
57	41	>100000	94	0	26.9	11	32	4	82.2	0	0
58	47.5	>100000	97	0	44.1	28	25	6.7	nd	100	0
59	55	>100000	84	0	98.8	nd	nd	5.7	3.8	8	0
60	38	>100000	90	4	60	0	11	9	29.4	51	0
61	72	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
62	69	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
63	41	>100000	96	11	7	1	0	0	50	87	0
64	45	>100000	87	0	0	2.3	0	3	0	59	0
65	47	nd	nd	nd	nd	nd	nd	1	57	84	0
66	48	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
67	48	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
68	59	>100000	84.2	4.3	0	5.4	8.6	4.6	21.3	nd	nd
69	68	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
70	69	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
71	70	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
72	87	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
73	89	>100000	94	0	nd	nd	nd	nd	nd	nd	Nd
74	91	>100000	86	>100000	nd	nd	nd	nd	nd	nd	nd
75	86	69.1 at 100 μM %	92.6	7.8 at 100 μM %	0	1.1	5.7	5.7	0	nd	nd
76	nd	71	nd	nd	nd	nd	nd	nd	nd	nd	nd

Table 3 continued

Ex	Cathepsin G IC50 (nmol)	Elastase IC50 (nmol)	Trypsin at 100 μM %	Chymo-trypsin at IC50 (nmol)	Chymase at 100 μM %	Thrombin at 100 μM %	FXa at 100 μM %	Urokinase at 100 μM %	Tryptase at 100 μM %	Cyto-toxicity LC_{50}/ GI_{50} *Hela cells*	Hemo-lysis at 100 μM %
77	nd	68	nd	nd	nd	nd	nd	nd	nd	nd	nd
78	nd	29	nd	<4000	nd	nd	nd	nd	nd	61	nd
79	nd	66	nd	nd	nd	nd	nd	nd	nd	nd	nd
80	nd	35	nd	>20000	nd	nd	nd	nd	nd	12	nd
81	61.3 at 100 μM %	28	100000	100000	nd	13.1	8.7	nd	nd	58	nd
82	nd	18	nd	72.9	nd	nd	15.3	nd	44.5	nd	nd
83	nd	43	nd	100000	nd	nd	nd	nd	nd	12	nd
84	20195	18	10.8	17103	0	20.6	13.3	10.4	4.2	9	nd
85	nd	28	0	>20000	nd	12.6	25.6	nd	nd	nd	nd
86	47 at 100 μM %	26	0	>100000	0	10.7	24.8	nd	0	nd	nd
87	nd	37	nd	106977	nd	nd	nd	nd	nd	65	nd
88	>100000	18	6.4	4309	0	0.2	3	96	0.6	73	nd
89	nd	43	nd	nd	nd	nd	nd	nd	nd	51	nd
90	66975	21	5.2	33074	0	0	5.5	3.5	5	96	nd
91	45 at 100 μM %	28	0	48108	4.7	13.5	19.4	nd	nd	79	nd
92	nd	43	nd	nd	nd	nd	nd	nd	nd	93	nd
93	nd	41	nd	nd	nd	nd	nd	nd	5.6	100	nd
94	nd	50	nd	nd	nd	nd	nd	nd	nd	nd	nd
95	38677	24	8.9	33729	0	0	11.3	10.3	0	89	nd

Table 3 continued

Ex	Cathepsin G IC50 (nmol)	Elastase IC50 (nmol)	Trypsin at 100 μM %	Chymo-trypsin at IC50 (nmol)	Chymase at 100 μM %	Thrombin at 100 μM %	FXa at 100 μM %	Urokinase at 100 μM %	Tryptase at 100 μM %	Cytotoxicity LC_{50}/ GI_{50} *Hela cells*	Hemo-lysis at 100 μM %
96	21175	15	7.5	15433	0	3.6	0	6.2	0	52	nd
97	>100000	24	9.5	77431	0	11.6	4.8	11.9	0	100	nd
98	>100000	21	0	38820	0	5.2	0	0	0	78	nd
99	85196	16	30.5	8558	0	0	0	17.4	0	58	nd
100	nd	35	nd	nd	nd	nd	nd	nd	nd	83	nd
101	nd	49	nd	nd	nd	nd	nd	nd	nd	nd	nd
102	>100000	13	0	4975	0	1.7	0	0.5	0	55	nd
103	>100000	18	6.4	4309	0	10.2	3	9.6	0.6	47	nd
104	53.5 at 100 μM %	34	0	3.1 at 100 μM %	0	7.7	6.2	0	0	nd	nd
105	nd	34	nd	nd	nd	nd	nd	nd	nd	nd	nd
106	nd	49	nd	nd	nd	nd	nd	nd	nd	nd	nd
107	nd	51	nd	nd	nd	nd	nd	nd	nd	nd	nd
108	nd	31	nd	nd	nd	nd	nd	nd	nd	nd	nd
109	54.1 at 100 μM %	33	0	13.8	0.1	0	5.6	nd	nd	nd	nd
110	nd	38	nd	nd	nd	nd	nd	nd	nd	nd	nd
111	nd	46	nd	nd	nd	nd	nd	nd	nd	nd	nd
112	nd	39	nd	nd	nd	nd	nd	nd	nd	33	nd
113	nd	35	nd	nd	nd	nd	nd	nd	nd	nd	nd
114	nd	47	nd	nd	nd	nd	nd	nd	nd	34	nd
115	nd	38	nd	27751	nd	nd	nd	nd	nd	51	nd
116	nd	46	0	39710	nd	nd	nd	nd	nd	nd	nd
117	nd	33	nd	nd	nd	nd	nd	nd	nd	29	nd
118	nd	43	nd	nd	nd	nd	nd	nd	nd	nd	nd
119	nd	45	nd	nd	nd	nd	nd	nd	nd	nd	nd

Table 3 continued

Ex	Cathepsin G IC50 (nmol)	Elastase IC50 (nmol)	Trypsin at 100 μM %	Chymotrypsin at 100 μM %	Chymase at 100 μM %	Thrombin at 100 μM %	FXa at 100 μM %	Urokinase at 100 μM %	Tryptase at 100 μM %	Cytotoxicity LC_{50}/ GI_{50} *Hela cells*	Hemolysis at 100 μM %
120	nd	29	nd	nd	nd	nd	nd	nd	nd	38	nd
121	11155	18	12.8	27526, IC50 (nmol)	1.2	0	5.6	5.7	4.6	49	nd
122	35134	18	19	58000, IC50 (nmol)	6.4	0	19.6	11.1	0.2	29	nd
123	35203	14	7.9	14995, IC50 (nmol)	0	2.7	0	7.6	nd	nd	nd
124	nd	40	nd	nd	nd	nd	nd	nd	nd	40	nd
125	18269	15	28.3	>20000, IC50 (nmol)	4.8	0	0	nd	nd	37	nd
126	nd	36	nd	nd	nd	nd	nd	nd	nd	nd	nd
127	64 at 100 μM %	29	0	47.2	1.9	3.7	13.3	nd	0	nd	nd
128	nd	40	nd	nd	nd	nd	nd	nd	nd	nd	nd
129	nd	30	nd	nd	nd	nd	nd	nd	nd	nd	nd
130	nd	29	nd	nd	<4000	nd	nd	nd	nd	nd	nd
131	45	28	0	nd	46108	nd	nd	nd	nd	nd	nd
132	nd	26	nd	nd	nd	nd	nd	nd	nd	nd	nd
133	nd	26	nd	nd	nd	nd	nd	nd	nd	nd	nd
134	nd	23	nd	nd	nd	nd	nd	nd	nd	nd	nd
135	nd	23	nd	nd	nd	nd	nd	nd	nd	nd	nd
136	>100000	21	0	67.9	0	5.2	0	0	0	nd	nd
137	66975	21	5.2	68.7	0	0	5.5	3.5	5	nd	nd
138	43856	19	12.2	77.1	4.6	17.1	12.6	14.4	0	nd	nd
139	nd	18	nd	nd	nd	nd	nd	nd	nd	nd	nd

Table 3 continued

Ex	Cathepsin G IC50 (nmol)	Elastase IC50 (nmol)	Trypsin at 100 μM %	Chymo-trypsin at 100 μM %	Chymase at 100 μM %	Thrombin at 100 μM %	FXa at 100 μM %	Urokinase at 100 μM %	Tryptase at 100 μM %	Cyto-toxicity LC_{50}/ GI_{50} *Hela cells*	Hemo-lysis at 100 μM %
140	20195	18	10.8	79.6	0	20.6	13.3	10.4	4.2	nd	nd
141	63.4 at 100 μM %	18	0	72.9	0	0	15.3	nd	44.5	56	nd
142	nd	16	nd	nd	nd	nd	nd	nd	nd	nd	nd
143	28 at 100 μM %	15	12	91	0	12	0	8	18	nd	nd
144	21175	7.5	7.5	80.6	0	3.6	0	6.2	0	nd	nd
145	nd	14	nd	nd	nd	nd	nd	nd	nd	nd	nd
146	1 at 100 μM %	12	3	87	0	11	1	0	22	nd	nd
147	nd	11	nd	nd	nd	nd	nd	nd	nd	nd	nd
148	52 at 100 μM %	11	9	91	7	32	8	12	30	nd	nd
149	nd	11	nd	nd	nd	nd	nd	nd	nd	nd	nd
150	nd	10	nd	nd	nd	nd	nd	nd	nd	nd	nd
151	nd	10	nd	nd	nd	nd	nd	nd	nd	nd	nd
152	nd	9	nd	nd	nd	nd	nd	nd	nd	nd	nd
153	56 at 100 μM %	8.5	8	84	0	16	11	16	9	nd	nd
154	27 at 100 μM %	8.3	0	4	0	7	0	1	15	nd	nd
155	52 at 100 μM %	8.2	18	83	3	19	9	12	30	nd	nd
156	46 at 100 μM %	7.5	0	5	0	17	0	7	15	nd	nd
157	nd	7	nd	nd	nd	nd	nd	nd	nd	nd	nd
158	55 at 100 μM %	7.1	8	93	0	2	1	10	13	nd	nd
159	nd	7	nd	nd	nd	nd	nd	nd	nd	nd	nd
160	55 at 100 μM %	6	3	94	2	23	1	14	30	nd	nd
161	nd	6	nd	nd	nd	nd	nd	nd	nd	nd	nd
162	nd	12.5	nd	nd	nd	nd	nd	nd	nd	nd	nd
163	nd	24	nd	nd	nd	nd	nd	nd	nd	nd	nd

Table 3 continued

Ex	Cathe-psin G IC50 (nmol)	Elastase IC50 (nmol)	Trypsin at 100 μM %	Chymo-trypsin at 100 μM %	Chymase at 100 μM %	Thrombin at 100 μM %	FXa at 100 μM %	Urokinase at 100 μM %	Tryptase at 100 μM %	Cyto-toxicity LC_{50}/ GI_{50} *Hela cells*	Hemo-lysis at 100 μM %
164	nd	24	nd	nd	nd	nd	nd	nd	nd	nd	nd
165	nd	22	nd	nd	nd	nd	nd	nd	nd	nd	nd
166	nd	18	nd	nd	nd	nd	nd	nd	nd	nd	nd
167	35134	18	19	60.2	6.4	0	19.6	11.1	0.2	nd	nd
168	11155	18	12.8	72.9	1.2	0	5.6	5.7	4.6	nd	nd
169	20295	18	10.8	79.6	0	20.6	13.3	10.4	4.2	nd	nd
170	nd	16	nd	nd	nd	nd	nd	nd	nd	nd	nd
171	nd	13	nd	nd	nd	nd	nd	nd	nd	nd	nd
172	nd	13	nd	nd	nd	nd	nd	nd	nd	nd	nd
173	nd	12	nd	nd	nd	nd	nd	nd	nd	nd	nd
174	56 at 100 μM %	12	7	85	0	11	3	1	10	nd	nd
175	nd	12	nd	nd	nd	nd	nd	nd	nd	nd	nd
176	69 at 100 μM %	10.3	7	55	2	15	1	8	17	nd	nd
177	54 at 100 μM %	7	5	86	3	17	7	12	15	nd	nd
178	nd	6	nd	nd	nd	nd	nd	nd	nd	nd	nd
179	nd	50	>100000 , IC50 (nmol)	76.0	nd	nd	nd	nd	0	nd	nd

Table 3 continued

Ex	Cathe-psin G IC50 (nmol)	Elastase IC50 (nmol)	Trypsin IC50 (nmol)	Chymo-trypsin at 100 μM %	Chymase at 100 μM %	Thrombin at 100 μM %	FXa at 100 μM %	Urokinase at 100 μM %	**Tryptase** IC50 (nmol)	Cyto-toxicity LC_{50}/ GI_{50} *Hela cells*	Hemo-lysis at 100 μM %
180	120	nd	60	nd	nd	nd	nd	nd	<100	nd	nd
181	127	nd	113	nd	nd	nd	nd	nd	40	nd	nd
182	111	nd	59	nd	nd	nd	nd	nd	39	nd	nd
183	243	nd	146	nd	nd	nd	nd	nd	25	nd	nd
184	221	nd	48	nd	nd	nd	nd	nd	27	nd	nd
185	514	nd	126	nd	nd	nd	nd	nd	14	nd	nd
186	337	nd	99	nd	nd	nd	nd	nd	15	nd	nd
187	158	nd	39	nd	nd	nd	nd	nd	<100	nd	nd
188	105	nd	34	nd	nd	nd	nd	nd	<100	nd	nd
189	164	nd	39	nd	nd	nd	nd	nd	<100	nd	nd
190	1500	nd	172	nd	nd	nd	nd	nd	<100	nd	nd
191	400	nd	66	nd	nd	nd	nd	nd	21	nd	nd
192	650	nd	72	nd	nd	nd	nd	nd	16	nd	nd
193	431	nd	35	nd	nd	nd	nd	nd	6	nd	nd
194	1570	nd	431	nd	nd	nd	nd	nd	9	nd	nd
195	4000	nd	108	nd	nd	nd	nd	nd	12	nd	nd
196	2165	nd	70	nd	nd	nd	nd	nd	52	nd	nd

Nd: not determined

The results of the experiment described in 2.5 above are indicated in Table 4 herein below.

Table 4

Ex.	Stability human Plasma $t_{1/2}$ (min)	Stability rat Plasma $t_{1/2}$ (min)
22	300	300
23	300	300
75	300	300
121	300	300
158	300	300

The results of the experiment described in 2.6 (PK), above, are indicated in Table 5 herein below.

Table 5

Administration route	**Intravenous**	**Oral**
Dose (mg/kg)	5	50
Dose $_{norm}$ (mg/kg)	5	5
AUC $_{0-t}$ (ng·h/ml)	6044	782
AUC $_{0-\infty}$ (ng·h/ml)	6047	813
AUC $_{0-\infty\ norm}$ (ng·h/ml)	6047	81
$\mathbf{T}_{max\ observed}$ (hours)	10752	464
$\mathbf{T}_{max\ norm}$ (hours)	10752	46
$\mathbf{C}_{max\ norm}$ (ng/ml)	0.08	0.25
β (hours^{-1})		
Terminal $t_{1/2}$ (hours)	0.5	0.87
Vd (ml/kg)	547	1008
% absorbed (F) (percentage of normalized $AUC_{0-\infty}$ po. against normalized $AUC_{0-\infty}$ i.v.)	100%	1.3%

The large inter-individual variation in plasma concentration of **Ex. 75** was most pronounced after single oral administration (lor i.v.: %C.V = 6 - 68%, except for one value at the lowest measurable concentration 173%; for p.o. %C.V.: 113 - 173%).

Intravenous administration

After intravenous administration of **Ex. 75** at a dose level of 5 mg/kg body weight, **Ex. 75** followed intravenous kinetic characteristics. After PK analysis, **Ex 75** showed an extrapolated $C_{initial}$ of 14069 ng/ml and a C_{max} observed of 10762 ng/ml at 5 min (0.083 hour). Plasma levels rapidly decreased to 5774 and 3455 ng/ml at 15 min and 30 min, respectively. From 1 to 2 hours plasma levels decreased with a terminal $t_{1/2}$ of 0.46 hours to 18 ng/ml at 4 hours. The AUC_{0-t} and AUC_0-infinite amounted to 6044 and 6047 ng x

h/ml, respectively; the initial distribution volume amounted to 355 ml/kg. The apparent distribution volume was 547 ml/kg.

Oral administration

Alter oral administration of **Ex 75** at a dose level of 50 mg /kg body weight, plasma levels of **Ex. 75** followed oral kinetic characteristics. After PK analysis, **Ex. 75** showed an observed C_{max} of 464 ng/ml at 0.25 hour (15 min). From 0.25 hours, plasma levels decreased with a terminal $t_{1/2}$ of 0.87 hours to 24 ng/ml at 4 hours. The AUC_{0-t} and $AUC_{0-infinite}$ amounted to 782 and 813 ng x h/ml. respectively. Taking into account the absorption of 1.3%, the apparent distribution volume was 1008 ml/kg.

Oral versus intravenous administration

Due to the different dose levels between the oral group *versus* the i.v. group, values were compared after dose normalisation.

Compared to the normalized $AUC_{0-infinite}$ value after i.v. administration of **Ex. 75** (100%: 6047 ng-h/ml), the percentage of **Ex. 75** absorbed (F) after oral administration amounted to 1.3% (81 ng x h/ml) at an about 234 times lower normalised C_{max} value after oral administration (46 *versus* 10762 ng/ml; Table 3). The apparent distribution volume after oral administration was about 1.8 fold higher than after i.v. administration (1008 versus 547 ml/kg).

References

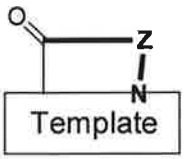
1. Barrtt, A.J. Methods in Enzymology **1981**, *80*, 561-565; Leatherbarrow, R. J. **1992**, *GraFit*, Erithacus Software Ltd., Staines, U.K.

2. Mossman T. *J.Immunol.Meth.* **1983**, *65*:55-63

3. Berridge MV, Tan AS. *Arch.Biochem.Biophys.* **1993**, *303*:474-482

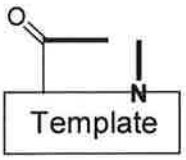
CLAIMS

1. Compounds of the general formula

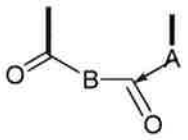


(I)

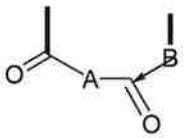
wherein



is a group of one of the formulae

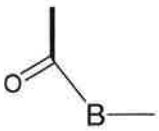


(a1)



(a2)

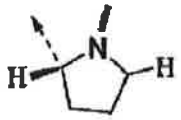
wherein



is Ala; Arg; Asn; Cys; Gln; Gly; His; Ile; Leu; Lys; Met; Phe; Pro; Pro(5RPhe), Ser; Thr; Trp; Tyr; Val; Cit; Orn; tBuA; Sar; t-BuG; 4AmPhe; 3AmPhe; 2AmPhe; Phe(mC(NH_2)=NH); Phe(pC(NH_2)=NH); Phe(mNHC(NH_2)=NH); Phe(pNHC(NH_2)=NH); Phg; Cha; C_4al; C_5al; Nle; 2-Nal; 1-Nal; 4Cl-Phe; 3Cl-Phe; 2Cl-Phe; 3,4Cl_2Phe; 4F-Phe; 3F-Phe; 2F-Phe; Tic; Thi; Tza; Mso; AcLys; Dpr; A_2Bu; Dbu; Abu; Aha; Aib; Y(Bzl); Bip; S(Bzl); T(Bzl); hCha; hCys; hSer;



is a group of the formula



A5

Z is a chain of 11 α-amino acid residues, the positions of said amino acid residues in said chain being counted starting from the N-terminal amino acid, whereby these amino acid residues in positions 1 to 11 of the chain Z are:

- P1: Nle, Ile, Aoc, hLeu, Chg, OctG, hPhe, 4AmPhe, Phe, Tyr, 2Cl-Phe, Trp, 1-Nal, Leu, Cha or Arg;
- P2: Cys, Glu, Nle, Thr, or Gln ;
- P3: Thr, Ala or Abu;
- P4: Lys, Nle, Ala, Abu, or Thr;
- P5: Ser, AlloThr or Dpr;
- P6: Ile, c5al, Leu, Nle, Aoc, OctG, Cha, hLeu, hPhe, Chg, t-BuA, Glu, or Asp;
- P7: Pro;
- P8: Pro, Ala, or Pro(4NHCOPhe);
- P9: Tyr, Phe, Ile, Nle, Cha, Gln, Arg, Lys, His, Thr, or Ala;
- P10: Cys, Arg, Nle, Gln, Lys, Met, Thr, or Ser;
- P11: Tyr, Gln, Arg, Ser, Nle, 2-Nal, 2Cl-Phe, Cha, Phg, Tyr, Phe, Asp Asn, or Thr; and
- Cys, if present at P2 and P10, may form a disulfide bridge.

with the proviso that if the template is ^{D}Pro^{L}Pro the amino acid residues in positions P1 to P6 and P8 to P11 are other than

- P1: Arg
- P2: Cys, linked with Cys in position P10 by a disulfide bridge

- P3: Thr
- P4 Lys
- P5 Ser
- P6 Ile
- P8 Pro
- P9 Ile
- P10 Cys, linked with Cys in position P2 by a disulfide bridge; and
- P11 Phe;

and pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1 wherein the α-amino acid residues in positions 1 to 11 are:

- P1: Phe, hPhe, 4AmPhe, Nle, Chg, Ile, Tyr, Arg, Trp, 2Cl-Phe, 1-Nal, or Cha;
- P2: Cys, Glu, or Nle;
- P3: Thr;
- P4: Lys, or Nle;
- P5: Ser, AlloThr, or Dpr;
- P6: Asp, or Glu;
- P7: Pro;
- P8: Pro;
- P9: Ile, Nle, Cha, Gln, Tyr, or Ala;
- P10: Cys, Arg, or Nle;
- P11: Thr, Asp, Ser, Tyr, Phe, Asn, or Arg; and
- Cys, if present at P2 and P10, may form a disulfide bridge.

3. Compounds according to claim 1 wherein the α-amino acid residues in positions 1 to 11 are:

- P1: Ile, Nle, Aoc, hLeu, Chg, OctG, or hPhe;
- P2: Cys, Glu, Thr, or Gln;
- P3: Thr, Ala, or Abu;
- P4: Ala, Thr, or Abu;
- P5: Ser;
- P6: OctG, Ile, Cha, Leu, C5al, Nle, Aoc, Chg, tBuA, or hLeu;
- P7: Pro;

- P8: Pro, or Pro(4NHCOPhe);
- P9: Gln, Tyr, Ile, or Phe;
- P10: Cys, Lys, Gln, Thr, Met, or Arg;
- P11: Tyr, Ser, Arg, Gln, Nle, 2-Nal, 2Cl-Phe, Phe, Cha, or Phg; and
- Cys, if present at P2 and P10, may form a disulfide bridge.

4. Compounds according to claim 1 wherein the α-amino acid residues in positions 1 to 11 of the chain Z are:

- P1: Cha, Tyr , or Trp
- P2: Cys
- P3: Thr
- P4: Lys
- P5: Ser
- P6: Leu
- P7: Pro
- P8: Pro
- P9: Lys
- P10: Cys
- P11: Arg; and

the Cys residues present at P2 and P10 may form a disulfide bridge.

5. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: Phe;
- P2: Cys;
- P3: Thr;
- P4: Lys;
- P5: Ser;
- P6: Asp;
- P7: Pro;
- P8: Pro;
- P9: Ile;
- P10: Cys;
- P11: Tyr;

Cys at P2 and P10 forming a disulfide bridge.

6. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: Ile;
- P2: Cys;
- P3: Thr;
- P4: Lys;
- P5: Ser;
- P6: Asp;
- P7: Pro;
- P8: Pro;
- P9: Nle;
- P10: Cys;
- P11: Arg;

Cys at P2 and P10 forming a disulfide bridge.

7. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: Ile;
- P2: Cys;
- P3: Thr;
- P4: Lys;
- P5: Ser;
- P6: Asp;
- P7: Pro;
- P8: Pro;
- P9: Cha;
- P10: Cys;
- P11: Arg;

Cys at P2 and P10 forming a disulfide bridge.

8. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: Ile;
- P2: Cys;
- P3: Thr;

- P4: Nle;
- P5: Ser;
- P6: Asp;
- P7: Pro;
- P8: Pro;
- P9: Ile;
- P10: Cys;
- P11: Arg

Cys at P2 and P10 forming a disulfide bridge.

9. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: Phe;
- P2: Cys;
- P3: Thr;
- P4: Nle;
- P5: Ser;
- P6: Asp;
- P7: Pro;
- P8: Pro;
- P9: Ile;
- P10: Cys;
- P11: Tyr;

Cys at P2 and P10 forming a disulfide bridge.

10. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: Chg;
- P2: Cys;
- P3: Thr;
- P4: Lys;
- P5: Ser;
- P6: Asp;
- P7: Pro;
- P8: Pro;
- P9: Ile;

- P10: Cys;
- P11: Tyr;

Cys at P2 and P10 forming a disulfide bridge.

11. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: Arg;
- P2: Cys;
- P3: Thr;
- P4: Lys;
- P5: Ser;
- P6: Asp;
- P7: Pro;
- P8: Pro;
- P9: Ile;
- P10: Cys;
- P11: Phe;

Cys at P2 and P10 forming a disulfide bridge.

12. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: Nle;
- P2: Cys;
- P3: Thr;
- P4: Ala;
- P5: Ser;
- P6: Ile;
- P7: Pro;
- P8: Pro;
- P9: Gln;
- P10: Cys;
- P11: Gln;

Cys at P2 and P10 forming a disulfide bridge.

13. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: hPhe;
- P2: Cys;
- P3: Thr;
- P4: Ala;
- P5: Ser;
- P6: OctG;
- P7: Pro;
- P8: Pro;
- P9: Gln;
- P10: Cys;
- P11: Gln

Cys at P2 and P10 forming a disulfide bridge.

14. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: OctG;
- P2: Gln;
- P3: Thr;
- P4: Ala;
- P5: Ser;
- P6: Ile;
- P7: Pro;
- P8: Pro;
- P9: Gln;
- P10: Thr;
- P11: Tyr.

15. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: hPhe;
- P2: Cys;
- P3: Thr;
- P4: Ala;

- P5: Ser;
- P6: Cha;
- P7: Pro;
- P8: Pro;
- P9: Gln;
- P10: Cys;
- P11: Phe;

Cys at P2 and P10 forming a disulfide bridge.

16. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: OctG;
- P2: Glu;
- P3: Thr;
- P4: Ala;
- P5: Ser;
- P6: Ile;
- P7: Pro;
- P8: Pro;
- P9: Gln;
- P10: Lys;
- P11: Tyr.

17. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: OctG;
- P2: Cys;
- P3: Thr;
- P4: Ala;
- P5: Ser;
- P6: Cha;
- P7: Pro;
- P8: Pro;
- P9: Gln;
- P10: Cys;

- P11: Phe;

Cys at P2 and P10 forming a disulfide bridge.

18. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: hPhe;
- P2: Cys;
- P3: Thr;
- P4: Ala;
- P5: Ser;
- P6: Cha;
- P7: Pro;
- P8: Pro;
- P9: Gln;
- P10: Cys;
- P11: Gln;

Cys at P2 and P10 forming a disulfide bridge.

19. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: OctG;
- P2: Cys;
- P3: Thr;
- P4: Ala;
- P5: Ser;
- P6: Cha;
- P7: Pro;
- P8: Pro(4NHCOPhe);
- P9: Gln;
- P10: Cys;
- P11: Gln;

Cys at P2 and P10 forming a disulfide bridge.

20. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: hPhe;
- P2: Cys;
- P3: Thr;
- P4: Ala;
- P5: Ser;
- P6: OctG;
- P7: Pro;
- P8: Pro;
- P9: Gln;
- P10: Cys;
- P11: Tyr;

Cys at P2 and P10 forming a disulfide bridge.

21. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: Chg;
- P2: Cys;
- P3: Thr;
- P4: Lys;
- P5: Ser;
- P6: Asp;
- P7: Pro;
- P8: Pro;
- P9: Ile;
- P10: Cys;
- P11: Thr;

Cys at P2 and P10 forming a disulfide bridge.

22. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: Chg;
- P2: Cys;
- P3: Thr;
- P4: Lys;
- P5: Ser;

- P6: Asp;
- P7: Pro;
- P8: Pro;
- P9: Ile;
- P10: Cys;
- P11: Asp;

Cys at P2 and P10 forming a disulfide bridge.

23. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: OctG;
- P2: Cys;
- P3: Thr;
- P4: Ala;
- P5: Ser;
- P6: Cha;
- P7: Pro;
- P8: Pro;
- P9: Gln;
- P10: Cys;
- P11: Gln;

Cys at P2 and P10 forming a disulfide bridge.

24. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: OctG;
- P2: Cys;
- P3: Thr;
- P4: Ala;
- P5: Ser;
- P6: OctG;
- P7: Pro;
- P8: Pro;
- P9: Gln;
- P10: Cys;

- P11: Gln;

Cys at P2 and P10 forming a disulfide bridge.

25. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: Cha;
- P2: Cys;
- P3: Thr;
- P4: Lys;
- P5: Ser;
- P6: Leu;
- P7: Pro;
- P8: Pro;
- P9: Lys;
- P10: Cys;
- P11: Arg;

Cys at P2 and P10 forming a disulfide bridge.

26. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: Tyr;
- P2: Cys;
- P3: Thr;
- P4: Lys;
- P5: Ser;
- P6: Leu;
- P7: Pro;
- P8: Pro;
- P9: Lys;
- P10: Cys;
- P11: Arg;

Cys at P2 and P10 forming a disulfide bridge.

27. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro and the amino acid residues in position 1 – 11 are:

- P1: Trp;
- P2: Cys;
- P3: Thr;
- P4: Lys;
- P5: Ser;
- P6: Leu;
- P7: Pro;
- P8: Pro;
- P9: Lys;
- P10: Cys;
- P11: Arg;

Cys at P2 and P10 forming a disulfide bridge.

28. Enantiomers of the compounds of formula I as defined in claim 1.

29. Compounds according to any one of claims 1 to 28 for use as therapeutically active substances.

30. Compounds according to claim 29 having selective protease inhibitory activity in particular against Cathepsin G or Elastase or Tryptase and/or anticancer activity and/or anti inflammatory activity and/or anti infective activity and/or anticardiovascular activity and/or antiimmunological activity and/or antineurodegenerative activity.

31. A pharmaceutical composition containing a compound according to any one of claims 1 to 28 and a pharmaceutically inert carrier.

32. A composition according to claim 31, characterized in that it is present in a form suitable for oral, buccal, rectal, vaginal, topical, transdermal, transmucosal, pulmonary, injection, inhalation or implantation administration.

33. A composition according to claim 31 or 32, characterized in that it is present in the form of a tablet, a degree, a capsule, a lozenge, a pill, a powder, a liquid, a solution, a syrup, an elixir, a slurry, a suspension, an emulsion, a gel, a cream, an ointment, a plaster, a spray, a nebulizer, an inhaler, an insufflator, a suppository, a sustained-release system, a long acting formulation, a depot preparation or a lipsome.

34. The use of a compound as defined in any one of claims 1 to 28 of the formula I, in free form or in pharmaceutically acceptable salt form, for the manufacture of a medicament for use in the treatment or prevention of a disease selected from the group of diseases, consisting of an inflammatory disease, a pulmonary disease, an infection, an immunological disease, a cardiovascular disease, a neurodegenerative disease and a cancer.

35. The use according to claim 34, characteried in that the disease is selected from the group of diseases, consisting of pulmonary emphysema, rheumatoid arthritis, osteoarthritis, atherosclerosis, psoriasis, cystic fibrosis, multiple sclerosis, adult respiratory distress syndrome, pancreatitis, asthma, allergic rhinitis, an inflammatory dermatosis, post-angioplasty restenosis, cardiac hypertrophy, heart failure and a cancer.

36. A process for the manufacture of compounds according to any one of claims 1-27 which process comprises

(a) coupling an appropriately functionalized solid support with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position 5, 6 or 7, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

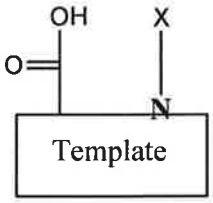
(b) removing the N-protecting group from the product thus obtained;

(c) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position nearer the N-terminal amino acid residue, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(d) removing the N-protecting group from the product thus obtained;

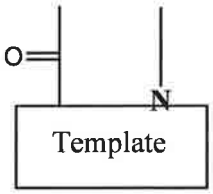
(e) repeating steps (c) and (d) until the N-terminal amino acid residue has been introduced;

(f) coupling the product thus obtained with a compound of the general formula

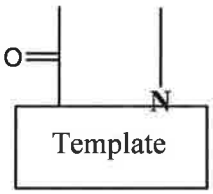


II

wherein



is as defined in claim 1 and X is an N-protecting group or, alternatively, if



is to be group (a1) or (a2) as defined in claim 1,

(fa) coupling the product obtained in step (e) with an appropriately N-protected derivative of an amino acid of the general formula

HOOC-B-H **III** or HOOC-A-H **IV**

wherein B and A are as defined in claim 1 , any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(fb) removing the N-protecting group from the product thus obtained; and

(fc) coupling the product thus obtained with an appropriately N-protected derivative of an amino acid of the above general formula IV and, respectively, III, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(g) removing the N-protecting group from the product obtained in step (f) or (fc);

(h) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position 11, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(i) removing the N-protecting group from the product thus obtained;

(j) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position farther away from position 11, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(k) removing the N-protecting group from the product thus obtained;

(l) repeating steps (j) and (k) until all amino acid residues have been introduced;

(m) if desired, selectively deprotecting one or several protected functional group(s) present in the molecule and appropriately substituting the reactive group(s) thus liberated;

(n) if desired, forming an interstrand linkage between side-chains of appropriate amino acid residues at positions 2 and 10;

(o) detaching the product thus obtained from the solid support;

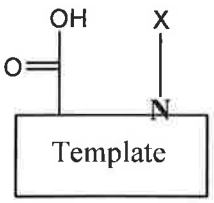
(p) cyclizing the product cleaved from the solid support;

(q) removing any protecting groups present on functional groups of any members of the chain of amino acid residues and, if desired, any protecting group(s) which may in addition be present in the molecule; and

(r) if desired, converting the product thus obtained into a pharmaceutically acceptable salt or converting a pharmaceutically acceptable, or unacceptable, salt thus obtained into the corresponding free compound of formula I or into a different, pharmaceutically acceptable, salt.

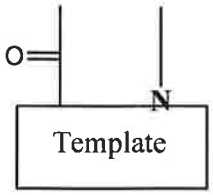
37. A process for the manufacture of compounds according to any one of claims 1-27 which process comprises

(a') coupling an appropriately functionalized solid support with a compound of the general formula

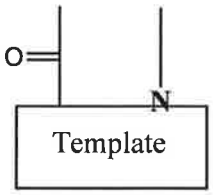


II

Wherein



is as defined in claim 1 and X is an N-protecting group or, alternatively, if



is to be group (a1) or (a2) as defined in claim 1,

(a'a) coupling said appropriately functionalized solid support with an appropriately N-protected derivative of an amino acid of the general formula

HOOC-B-H **III** or HOOC-A-H **IV**

wherein B and A are as defined in claim 1, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(a'b) removing the N-protecting group from the product thus obtained; and

(a'c) coupling the product thus obtained with an appropriately N-protected derivative of an amino acid of the above general formula IV and, respectively, III, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(b') removing the N-protecting group from the product obtained in step (a'), or (a'c);

(c') coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position 11, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(d') removing the N-protecting group from the product thus obtained;

(e') coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position farther away from position, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(f') removing the N-protecting group from the product thus obtained;

(g') repeating steps (e') and (f') until all amino acid residues have been introduced;

(h') if desired, selectively deprotecting one or several protected functional group(s) present in the molecule and appropriately substituting the reactive group(s) thus liberated;

(i') if desired forming an interstrand linkage between side-chains of appropriate amino acid residues at positions 2 and 10;

(j') detaching the product thus obtained from the solid support;

(k') cyclizing the product cleaved from the solid support;

(l') removing any protecting groups present on functional groups of any members of the chain of amino acid residues and, if desired, any protecting group(s) which may in addition be present in the molecule; and

(m') if desired, converting the product thus obtained into a pharmaceutically acceptable salt or converting a pharmaceutically acceptable, or unacceptable, salt thus obtained into the corresponding free compound of formula I or into a different, pharmaceutically acceptable, salt.

38. A modification of the processes according to claim 36 or 37 for the manufacture of compounds according to claim 28 in which enantiomers of all chiral starting materials are used.