Abstract:
Templates-fixed β-hairpin peptidomimetics of the general formulae (I), wherein Z is a chain of 11 α-amino acid residues which, depending on their positions in the chain (counted starting from the N-terminal amino acid) are Gly, or Pro, or Pro(4NHCOphe), or of certain types which, as the remaining symbols in the above formula, are defined in the description and the claims, and salts thereof, have the property to inhibit proteases, in particular serine proteases, especially Cathepsin G or Elastase or Tryptase. These β-hairpin peptidomimetics can be manufactured by processes which are based on a mixed solid- and solution phase synthetic strategy.
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Template-fixed beta-hairpin peptidomimetics with protease inhibitory activity

Abstract: Templates-fixed beta-hairpin peptidomimetics of the general formula (I), wherein Z is a chain of 11 ε-amino acid residues which, depending on their positions in the chain (counted starting from the N-terminal amino acid) are Gly, or Pro, or Pro(4NHCOPh), or of certain types which, as the remaining symbols in the above formula, are defined in the description and the claims, and salts thereof, have the property to inhibit proteases, in particular serine proteases, especially Cathepsin G or Elastase or Trypsin. These beta-hairpin peptidomimetics can be manufactured by processes which are based on a mixed solid- and solution phase synthetic strategy.
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 trypstatase. 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.


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.

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, *Expert 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, *Bioorg. & 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 (Kᵢ<0.1nM), cathepsin G (Kᵢ~0.15nM), elastase (Kᵢ~105µM), chymotrypsin (Kᵢ~7.4µM) and thrombin (Kᵢ~136nM).

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

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

![Diagram of formula (I)](image)

wherein

![Diagram of template and formulae](image)

is a group of one of the formulae

- (a1)
- (a2)
- (a3)
wherein

\[
\text{A}
\]

5 is Gly or the residue of an L-α-amino acid with B being a residue of formula \(NR^2\text{R}^3\text{CH(R}^3\text{)}\) or the enantiomer of one of the groups A1 to A69 as defined hereinafter;

\[
\text{A}
\]
R¹ is H; lower alkyl; or aryl-lower alkyl;

R² is H; alkyl; alkenyl; -(CH₂)ₘ(CHR⁶¹)ₙORₕ; -(CH₂)ₘ(CHR⁶¹)ₙSRₕ;
-(CH₂)ₘ(CHR⁶¹)ₙNR³ₜR³ₜ; -(CH₂)ₘ(CHR⁶¹)ₙCOORₜₜ;
-(CH₂)ₘ(CHR⁶¹)ₙNR²₀CONR³ₜRₜ; -(CH₂)ₘ(CHR⁶¹)ₙCOORₘₜ; 5
-(CH₂)ₘ(CHR⁶¹)ₙCONR₈ₘₜ; -(CH₂)ₘ(CHR⁶¹)ₙPO(ORₜₜ)₂;
-(CH₂)ₘ(CHR⁶¹)ₙSO₂Rₘₜ; or -(CH₂)ₘ(CHR⁶¹)ₙC₆H₄Rₘₜ;

R³ is H; alkyl; alkenyl; -(CH₂)ₘ(CHR⁶¹)ₙORₕ; -(CH₂)ₘ(CHR⁶¹)ₙSRₕ;
-(CH₂)ₘ(CHR⁶¹)ₙNR³ₜRₜ; -(CH₂)ₘ(CHR⁶¹)ₙCOORₜₜ; 10
-(CH₂)ₘ(CHR⁶¹)ₙNR²₀CONR³ₜRₜ; -(CH₂)ₘ(CHR⁶¹)ₙCOORₕₜ; -(CH₂)ₘ(CHR⁶¹)ₙSO₂Rₕₜ; or -(CH₂)ₘ(CHR⁶¹)ₙC₆H₄Rₜ;
R^4 is H; alkyl; alkenyl; -(CH₂)m(CHR^61)₉OR₅₅; -(CH₂)m(CHR^61)₉SR₅₆; -(CH₂)m(CHR^61)₉NR₃₃R₃₄; -(CH₂)m(CHR^61)₉OCONR₃₃R₇₅; -(CH₂)m(CHR^61)₉NR₂₀CONR₃₃R₈₂; -(CH₂)m(CHR^61)₉COOR₅₇; -(CH₂)m(CHR^61)₉CONR₅₸R₅₉; 
5 -(CH₂)m(CHR^61)₉PO(OR₆₀)₂; -(CH₂)m(CHR^61)₉SO₂R₆₂; or -(CH₂)m(CHR^61)₉C₆H₄R₈;
R^5 is alkyl; alkenyl; -(CH₂)m(CHR^61)₉OR₅₅; -(CH₂)m(CHR^61)₉SR₅₆; -(CH₂)m(CHR^61)₉NR₃₃R₃₄; -(CH₂)m(CHR^61)₉OCONR₃₃R₇₅; -(CH₂)m(CHR^61)₉NR₂₀CONR₃₃R₈₂; 
10 -(CH₂)m(CHR^61)₉COOR₅₇; -(CH₂)m(CHR^61)₉CONR₅₸R₅₉; -(CH₂)m(CHR^61)₉PO(OR₆₀)₂; -(CH₂)m(CHR^61)₉SO₂R₆₂; or -(CH₂)m(CHR^61)₉C₆H₄R₈;
R^6 is H; alkyl; alkenyl; -(CH₂)m(CHR^61)₉OR₅₅; -(CH₂)m(CHR^61)₉SR₅₆; -(CH₂)m(CHR^61)₉NR₃₃R₃₄; 
15 -(CH₂)m(CHR^61)₉OCONR₃₃R₇₅; -(CH₂)m(CHR^61)₉NR₂₀CONR₃₃R₈₂; -(CH₂)m(CHR^61)₉COOR₅₇; -(CH₂)m(CHR^61)₉CONR₅₸R₅₉; -(CH₂)m(CHR^61)₉PO(OR₆₀)₂; -(CH₂)m(CHR^61)₉SO₂R₆₂; or -(CH₂)m(CHR^61)₉C₆H₄R₈;
R^7 is alkyl; alkenyl; -(CH₂)m(CHR^61)₉OR₅₅; -(CH₂)m(CHR^61)₉NR₃₃R₃₄; 
20 -(CH₂)m(CHR^61)₉OCONR₃₃R₇₅; -(CH₂)m(CHR^61)₉NR₂₀CONR₃₃R₈₂; -(CH₂)m(CHR^61)₉COOR₅₇; -(CH₂)m(CHR^61)₉CONR₅₸R₅₉; -(CH₂)m(CHR^61)₉PO(OR₆₀)₂; -(CH₂)m(CHR^61)₉SO₂R₆₂; or -(CH₂)m(CHR^61)₉C₆H₄R₈;
R^8 is H; Cl; F; CF₃; NO₂; lower alkyl; lower alkenyl; aryl; aryl-lower alkyl; 
25 -(CH₂)m(CHR^61)₉OR₅₅; -(CH₂)m(CHR^61)₉SR₅₆; -(CH₂)m(CHR^61)₉NR₃₃R₃₄; -(CH₂)m(CHR^61)₉OCONR₃₃R₇₅; -(CH₂)m(CHR^61)₉NR₂₀CONR₃₃R₈₂; -(CH₂)m(CHR^61)₉COOR₅₇; -(CH₂)m(CHR^61)₉CONR₅₸R₅₉; -(CH₂)m(CHR^61)₉PO(OR₆₀)₂; -(CH₂)m(CHR^61)₉SO₂R₆₂; or -(CH₂)m(CHR^61)₉COR₆₄;
R^9 is alkyl; alkenyl; -(CH₂)m(CHR^61)₉OR₅₅; -(CH₂)m(CHR^61)₉SR₅₆; -(CH₂)m(CHR^61)₉NR₃₃R₃₄; 
30 -(CH₂)m(CHR^61)₉OCONR₃₃R₇₅; -(CH₂)m(CHR^61)₉NR₂₀CONR₃₃R₈₂; -(CH₂)m(CHR^61)₉COOR₅₇; -(CH₂)m(CHR^61)₉CONR₅₸R₅₉; -(CH₂)m(CHR^61)₉PO(OR₆₀)₂; -(CH₂)m(CHR^61)₉SO₂R₆₂; or -(CH₂)m(CHR^61)₉C₆H₄R₈;
35 -(CH₂)m(CHR^61)₉SO₂R₆₂; or -(CH₂)m(CHR^61)₉C₆H₄R₈;
$R^{10}$ is alkyl; alkenyl; -(CH$_2$)$_n$(CHR$^{61}$)$_a$OR$^{55}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$SR$^{56}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$NR$^{33}$R$^{34}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$OCONR$^{33}$R$^{75}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$NR$^{30}$CONR$^{33}$R$^{82}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$COOR$^{57}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$CONR$^{58}$R$^{59}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$PO(OR$^{50}$)$_2$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$SO$_2$R$^{62}$; or -(CH$_2$)$_n$(CHR$^{61}$)$_a$C$_6$H$_5$R$^8$.

$R^{11}$ is H; alkyl; alkenyl; -(CH$_2$)$_m$(CHR$^{61}$)$_b$OR$^{55}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$NR$^{33}$R$^{34}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$OCONR$^{33}$R$^{75}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$NR$^{20}$CONR$^{33}$R$^{82}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$COOR$^{57}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$CONR$^{58}$R$^{59}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$PO(OR$^{50}$)$_2$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$SO$_2$R$^{62}$; or -(CH$_2$)$_m$(CHR$^{61}$)$_b$C$_6$H$_5$R$^8$.

$R^{12}$ is H; alkyl; alkenyl; -(CH$_2$)$_m$(CHR$^{61}$)$_b$OR$^{55}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$SR$^{56}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$NR$^{33}$R$^{34}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$OCONR$^{33}$R$^{75}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$NR$^{20}$CONR$^{33}$R$^{82}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$COOR$^{57}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$CONR$^{58}$R$^{59}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$PO(OR$^{50}$)$_2$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$SO$_2$R$^{62}$; or -(CH$_2$)$_m$(CHR$^{61}$)$_b$C$_6$H$_5$R$^8$.

$R^{13}$ is alkyl; alkenyl; -(CH$_2$)$_n$(CHR$^{61}$)$_a$OR$^{55}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$SR$^{56}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$NR$^{33}$R$^{34}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$OCONR$^{33}$R$^{75}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$NR$^{20}$CONR$^{33}$R$^{82}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$COOR$^{57}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$CONR$^{58}$R$^{59}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$PO(OR$^{50}$)$_2$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$SO$_2$R$^{62}$; or -(CH$_2$)$_n$(CHR$^{61}$)$_a$C$_6$H$_5$R$^8$.

$R^{14}$ is H; alkyl; alkenyl; -(CH$_2$)$_m$(CHR$^{61}$)$_b$OR$^{55}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$NR$^{33}$R$^{34}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$OCONR$^{33}$R$^{75}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$NR$^{20}$CONR$^{33}$R$^{82}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$COOR$^{57}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$CONR$^{58}$R$^{59}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$PO(OR$^{50}$)$_2$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$SO$_2$R$^{62}$; or -(CH$_2$)$_m$(CHR$^{61}$)$_b$C$_6$H$_5$R$^8$.

$R^{15}$ is alkyl; alkenyl; -(CH$_2$)$_m$(CHR$^{61}$)$_b$OR$^{55}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$SR$^{56}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$NR$^{33}$R$^{34}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$OCONR$^{33}$R$^{75}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$NR$^{20}$CONR$^{33}$R$^{82}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$COOR$^{57}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$CONR$^{58}$R$^{59}$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$PO(OR$^{50}$)$_2$; -(CH$_2$)$_m$(CHR$^{61}$)$_b$SO$_2$R$^{62}$; or -(CH$_2$)$_m$(CHR$^{61}$)$_b$C$_6$H$_5$R$^8$.

$R^{16}$ is alkyl; alkenyl; -(CH$_2$)$_n$(CHR$^{61}$)$_a$OR$^{55}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$SR$^{56}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$NR$^{33}$R$^{34}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$OCONR$^{33}$R$^{75}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$NR$^{20}$CONR$^{33}$R$^{82}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$COOR$^{57}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$CONR$^{58}$R$^{59}$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$PO(OR$^{50}$)$_2$; -(CH$_2$)$_n$(CHR$^{61}$)$_a$SO$_2$R$^{62}$; or -(CH$_2$)$_n$(CHR$^{61}$)$_a$C$_6$H$_5$R$^8$. 

(R=CH$_2$)}
-{(CH₂)ₙ(CHR¹)ₙOCONR²⁻R₅₇⁻; -(CH₂)ₙ(CHR¹)ₙNR²⁰⁻CONR³⁻R₈²⁻; 
-(CH₂)ₙ(CHR¹)ₙCOOR⁻⁶⁴⁻; -(CH₂)ₙ(CHR¹)ₙCONR⁻⁵⁸⁻R₉⁻; 
-(CH₂)ₙ(CHR¹)ₙPO(OR⁻⁶⁻)₂⁻; 
-(CH₂)ₙ(CHR¹)ₙSO₂R⁻⁶⁻; or -(CH₂)ₙ(CHR¹)ₙC₆H₅R⁻⁸⁻; 
R¹ is alkyl; alkenyl; -(CH₂)ₙ(CHR¹)ₙOR⁻⁵⁵⁻; -(CH₂)ₙ(CHR¹)ₙSR⁻⁵⁶⁻; 
-(CH₂)ₙ(CHR¹)ₙNR⁻³⁻R₃⁴⁻; 
-(CH₂)ₙ(CHR¹)ₙOCONR⁻³⁻R₅⁻; -(CH₂)ₙ(CHR¹)ₙNR²⁰⁻CONR⁻³⁻R₈²⁻; 
-(CH₂)ₙ(CHR¹)ₙCOOR⁻⁵⁷⁻; -(CH₂)ₙ(CHR¹)ₙCONR⁻⁵⁸⁻R₉⁻; 
-(CH₂)ₙ(CHR¹)ₙPO(OR⁻⁶⁻)₂⁻; 
-(CH₂)ₙ(CHR¹)ₙSO₂R⁻⁶⁻; or -(CH₂)ₙ(CHR¹)ₙC₆H₅R⁻⁸⁻; 
R¹ is alkyl; alkenyl; -(CH₂)ₙ(CHR¹)ₙOR⁻⁵⁵⁻; -(CH₂)ₙ(CHR¹)ₙSR⁻⁵⁶⁻; 
-(CH₂)ₙ(CHR¹)ₙNR⁻³⁻R₃⁴⁻; 
-(CH₂)ₙ(CHR¹)ₙOCONR⁻³⁻R₅⁻; -(CH₂)ₙ(CHR¹)ₙNR²⁰⁻CONR⁻³⁻R₈²⁻; 
-(CH₂)ₙ(CHR¹)ₙCOOR⁻⁵⁷⁻; -(CH₂)ₙ(CHR¹)ₙCONR⁻⁵⁸⁻R₉⁻; 
R¹ is lower alkyl; -(CH₂)ₙ(CHR¹)ₙOR⁻⁵⁵⁻; -(CH₂)ₙ(CHR¹)ₙSR⁻⁵⁶⁻; 
-(CH₂)ₙ(CHR¹)ₙNR⁻³⁻R₃⁴⁻; 
-(CH₂)ₙ(CHR¹)ₙOCONR⁻³⁻R₅⁻; -(CH₂)ₙ(CHR¹)ₙNR²⁰⁻CONR⁻³⁻R₈²⁻; 
-(CH₂)ₙ(CHR¹)ₙCOOR⁻⁵⁷⁻; -(CH₂)ₙ(CHR¹)ₙCONR⁻⁵⁸⁻R₉⁻; 
-(CH₂)ₙ(CHR¹)ₙPO(OR⁻⁶⁻)₂⁻; 
-(CH₂)ₙ(CHR¹)ₙSO₂R⁻⁶⁻; or -(CH₂)ₙ(CHR¹)ₙC₆H₅R⁻⁸⁻; or 
R¹ and R¹ taken together can form: -(CH₂)₂₋₀⁻; -(CH₂)₂₋₀O(CH₂)₂₋; -(CH₂)₂₋₀S(CH₂)₂₋; or 
-(CH₂)₂₋₀NR⁻⁵⁷⁻(CH₂)₂₋;
\[-(\text{CH}_2)_n(\text{CHR}^6)_i\text{COOR}^{57}; -(\text{CH}_2)_n(\text{CHR}^6)_i\text{CONR}^{58}\ R^{59}; -\]
\[\text{(CH}_2)_n(\text{CHR}^6)_i\text{PO(OR)}^{60}\_2;\]
\[-(\text{CH}_2)_n(\text{CHR}^6)_i\text{SO}_2\ R^{62}; \text{or } -(\text{CH}_2)_n(\text{CHR}^6)_i\text{C}_8\text{H}_4\ R^8;\]

$R^{23}$ is alkyl; alkenyl; -(CH$_2$)$_m$(CHR$^6$)$_i$OR$^{55}$; -(CH$_2$)$_m$(CHR$^6$)$_i$SR$^{56}$; -(CH$_2$)$_m$(CHR$^6$)$_i$NR$^{33}\ R^{34}$; -(CH$_2$)$_m$(CHR$^6$)$_i$OCONR$^{33}\ R^{75}$; -(CH$_2$)$_m$(CHR$^6$)$_i$NR$^{20}\ \text{CONR}^{33}\ R^{82}$; -(CH$_2$)$_m$(CHR$^6$)$_i$COOR$^{57}$; -(CH$_2$)$_m$(CHR$^6$)$_i$CONR$^{58}\ R^{59}$; -(CH$_2$)$_m$(CHR$^6$)$_i$PO(OR$^{60}$)$_2$; -(CH$_2$)$_m$(CHR$^6$)$_i$SO$^{62}$; or -(CH$_2$)$_m$(CHR$^6$)$_i$C$_8$H$_4$R$^8$;}

$R^{25}$ is H; alkyl; alkenyl; -(CH$_2$)$_m$(CHR$^6$)$_i$OR$^{55}$; -(CH$_2$)$_m$(CHR$^6$)$_i$SR$^{56}$; -(CH$_2$)$_m$(CHR$^6$)$_i$NR$^{33}\ R^{34}$; -(CH$_2$)$_m$(CHR$^6$)$_i$OCONR$^{33}\ R^{75}$; -(CH$_2$)$_m$(CHR$^6$)$_i$NR$^{20}\ \text{CONR}^{33}\ R^{82}$; -(CH$_2$)$_m$(CHR$^6$)$_i$COOR$^{57}$; -(CH$_2$)$_m$(CHR$^6$)$_i$CONR$^{58}\ R^{59}$; -(CH$_2$)$_m$(CHR$^6$)$_i$PO(OR$^{60}$)$_2$; -(CH$_2$)$_m$(CHR$^6$)$_i$SO$^{62}$; or -(CH$_2$)$_m$(CHR$^6$)$_i$C$_8$H$_4$R$^8$;}

$R^{26}$ is H; alkyl; alkenyl; -(CH$_2$)$_m$(CHR$^6$)$_i$OR$^{55}$; -(CH$_2$)$_m$(CHR$^6$)$_i$SR$^{56}$; -(CH$_2$)$_m$(CHR$^6$)$_i$NR$^{33}\ R^{34}$; -(CH$_2$)$_m$(CHR$^6$)$_i$OCONR$^{33}\ R^{75}$; -(CH$_2$)$_m$(CHR$^6$)$_i$NR$^{20}\ \text{CONR}^{33}\ R^{82}$; -(CH$_2$)$_m$(CHR$^6$)$_i$COOR$^{57}$; -(CH$_2$)$_m$(CHR$^6$)$_i$CONR$^{58}\ R^{59}$; -(CH$_2$)$_m$(CHR$^6$)$_i$PO(OR$^{60}$)$_2$; -(CH$_2$)$_m$(CHR$^6$)$_i$SO$^{62}$; or -(CH$_2$)$_m$(CHR$^6$)$_i$C$_8$H$_4$R$^8$; or

$R^{25}$ and $R^{26}$ taken together can form: -(CH$_2$)$_{2.9}$; -(CH$_2$)$_n$O(CH$_2$)$_r$; -(CH$_2$)$_n$S(CH$_2$)$_r$; or -(CH$_2$)$_n$NR$^{33}$; -(CH$_2$)$_n$;}

$R^{27}$ is H; alkyl; alkenyl; -(CH$_2$)$_m$(CHR$^6$)$_i$OR$^{55}$; -(CH$_2$)$_m$(CHR$^6$)$_i$SR$^{56}$; -(CH$_2$)$_m$(CHR$^6$)$_i$NR$^{33}\ R^{34}$; -(CH$_2$)$_m$(CHR$^6$)$_i$COOR$^{57}$; -(CH$_2$)$_m$(CHR$^6$)$_i$CONR$^{58}\ R^{59}$; -(CH$_2$)$_m$(CHR$^6$)$_i$OCONR$^{33}\ R^{72}$; -(CH$_2$)$_m$(CHR$^6$)$_i$NR$^{20}\ \text{CONR}^{33}\ R^{82}$; -(CH$_2$)$_m$(CHR$^6$)$_i$PO(OR$^{60}$)$_2$; -(CH$_2$)$_m$(CHR$^6$)$_i$SO$^{62}$; or -(CH$_2$)$_m$(CHR$^6$)$_i$C$_8$H$_4$R$^8$;}

$R^{28}$ is alkyl; alkenyl; -(CH$_2$)$_m$(CHR$^6$)$_i$OR$^{55}$; -(CH$_2$)$_m$(CHR$^6$)$_i$SR$^{56}$; -(CH$_2$)$_m$(CHR$^6$)$_i$NR$^{33}\ R^{34}$;
\[ -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{OCONR}^{33}\text{R}^{75}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{NR}^{20}\text{CONR}^{33}\text{R}^{82};\]
\[ -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{COOR}^{57}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{CONR}^{58}\text{R}^{59}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{PO(OR}^{60})_2;\]
\[ -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{SO}_2\text{R}^{62}; \text{or } -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{C}_6\text{H}_4\text{R}^{8};\]

5 \( R^{29} \) is alkyl; alkenyl; \(-\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{OR}^{55}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{SR}^{56}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{NR}^{33}\text{R}^{34};\)
\[ -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{OCONR}^{33}\text{R}^{75}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{NR}^{20}\text{CONR}^{33}\text{R}^{82};\]
\[ -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{COOR}^{57}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{CONR}^{58}\text{R}^{59}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{PO(OR}^{60})_2;\]

10 \( R^{30} \) is \( H; \) alkyl; alkenyl; or aryl-lower alkyl; \( R^{31} \) is \( H; \) alkyl; alkenyl; \(-\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{OR}^{55}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{NR}^{33}\text{R}^{34};\)
\[ -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{OCONR}^{33}\text{R}^{75}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{NR}^{20}\text{CONR}^{33}\text{R}^{82};\]
\[ -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{COOR}^{57}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{CONR}^{58}\text{R}^{59}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{PO(OR}^{60})_2;\]

15 \( R^{32} \) is \( H; \) lower alkyl; or aryl-lower alkyl; \( R^{33} \) is \( H; \) alkyl, alkenyl; \(-\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{OR}^{55}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{NR}^{33}\text{R}^{34};\)
\[ -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{OCONR}^{33}\text{R}^{75}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{NR}^{20}\text{CONR}^{33}\text{R}^{82};\]
\[ -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{COOR}^{57}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{CONR}^{58}\text{R}^{59}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{PO(OR}^{60})_2;\]

20 \( R^{34} \) is \( H; \) lower alkyl; alkyl; or aryl-lower alkyl; \( R^{33} \) and \( R^{34} \) taken together can form: \(-\text{(CH}_2\text{)}_2\text{So}^{57}; -\text{(CH}_2\text{)}_2\text{O(CH}_2\text{)}_2^{57}; -\text{(CH}_2\text{)}_2\text{S(CH}_2\text{)}_2^{57}; \) or
\[ -\text{(CH}_2\text{)}_n\text{NR}^{33}^{77}\text{(CH}_2\text{)}_2^{57};\]

25 \( R^{35} \) is \( H; \) alkyl, alkenyl; \(-\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{OR}^{55}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{NR}^{33}\text{R}^{34};\)
\[ -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{OCONR}^{33}\text{R}^{75}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{NR}^{20}\text{CONR}^{33}\text{R}^{82};\]
\[ -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{COOR}^{57}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{CONR}^{58}\text{R}^{59}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{PO(OR}^{60})_2;\]

30 \( R^{36} \) is \( H; \) alkyl, alkenyl; \(-\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{OR}^{55}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{NR}^{33}\text{R}^{34};\)
\[ -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{OCONR}^{33}\text{R}^{75}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{NR}^{20}\text{CONR}^{33}\text{R}^{82};\]
\[ -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{COOR}^{57}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{CONR}^{58}\text{R}^{59}; -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{PO(OR}^{60})_2;\]

35 \( -\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{SO}_2\text{R}^{62}; \) or \(-\text{(CH}_2\text{)}_n\text{(CHR}^{61})_m\text{C}_6\text{H}_4\text{R}^{8};\)
16

R^{37} \text{ is } H; F; Br; Cl; NO_{2}; CF_{3}; \text{ lower alkyl; } -(CH_{2})_{p}(CHR^{61})_{q}OR^{55}; -(CH_{2})_{p}(CHR^{61})_{q}NR^{33}R^{34}; -(CH_{2})_{p}(CHR^{61})_{q}OCONR^{33}R^{75}; -(CH_{2})_{p}(CHR^{61})_{q}NR^{20}CONR^{33}R^{82}; -(CH_{2})_{p}(CHR^{61})_{q}COOR^{57}; -(CH_{2})_{p}(CHR^{61})_{q}CONR^{58}R^{59}; -(CH_{2})_{p}(CHR^{61})_{q}PO(OR^{60})_{2}; -(CH_{2})_{p}(CHR^{61})_{q}SO_{2}R^{62}; \text{ or } -(CH_{2})_{p}(CHR^{61})_{q}C_{6}H_{4}R^{8};

R^{38} \text{ is } H; F; Br; Cl; NO_{2}; CF_{3}; \text{ alkyl; alkaryl; } -(CH_{2})_{p}(CHR^{61})_{q}OR^{55}; -(CH_{2})_{p}(CHR^{61})_{q}NR^{33}R^{34}; -(CH_{2})_{p}(CHR^{61})_{q}OCONR^{33}R^{75}; -(CH_{2})_{p}(CHR^{61})_{q}NR^{20}CONR^{33}R^{82}; -(CH_{2})_{p}(CHR^{61})_{q}COOR^{57}; -(CH_{2})_{p}(CHR^{61})_{q}CONR^{58}R^{59}; -(CH_{2})_{p}(CHR^{61})_{q}PO(OR^{60})_{2}; -(CH_{2})_{p}(CHR^{61})_{q}SO_{2}R^{62}; \text{ or } -(CH_{2})_{p}(CHR^{61})_{q}C_{6}H_{4}R^{8};

R^{39} \text{ is } H; \text{ alkyl; alkaryl; or aryl-lower alkyl;}

R^{40} \text{ is } H; \text{ alkyl; alkaryl; or aryl-lower alkyl;}

15

R^{41} \text{ is } H; F; Br; Cl; NO_{2}; CF_{3}; \text{ alkyl; alkaryl; } -(CH_{2})_{p}(CHR^{61})_{q}OR^{55}; -(CH_{2})_{p}(CHR^{61})_{q}NR^{33}R^{34}; -(CH_{2})_{p}(CHR^{61})_{q}OCONR^{33}R^{75}; -(CH_{2})_{p}(CHR^{61})_{q}NR^{20}CONR^{33}R^{82}; -(CH_{2})_{p}(CHR^{61})_{q}COOR^{57}; -(CH_{2})_{p}(CHR^{61})_{q}CONR^{58}R^{59}; -(CH_{2})_{p}(CHR^{61})_{q}PO(OR^{60})_{2}; -(CH_{2})_{p}(CHR^{61})_{q}SO_{2}R^{62}; \text{ or } -(CH_{2})_{p}(CHR^{61})_{q}C_{6}H_{4}R^{8};

R^{42} \text{ is } H; F; Br; Cl; NO_{2}; CF_{3}; \text{ alkyl; alkaryl; } -(CH_{2})_{p}(CHR^{61})_{q}OR^{55}; -(CH_{2})_{p}(CHR^{61})_{q}NR^{33}R^{34}; -(CH_{2})_{p}(CHR^{61})_{q}OCONR^{33}R^{75}; -(CH_{2})_{p}(CHR^{61})_{q}NR^{20}CONR^{33}R^{82}; -(CH_{2})_{p}(CHR^{61})_{q}COOR^{57}; -(CH_{2})_{p}(CHR^{61})_{q}CONR^{58}R^{59}; -(CH_{2})_{p}(CHR^{61})_{q}PO(OR^{60})_{2}; -(CH_{2})_{p}(CHR^{61})_{q}SO_{2}R^{62}; \text{ or } -(CH_{2})_{p}(CHR^{61})_{q}C_{6}H_{4}R^{8};

R^{43} \text{ is } H; \text{ alkyl; alkaryl; } -(CH_{2})_{p}(CHR^{61})_{q}OR^{55}; -(CH_{2})_{p}(CHR^{61})_{q}NR^{33}R^{34}; -(CH_{2})_{p}(CHR^{61})_{q}OCONR^{33}R^{75}; -(CH_{2})_{p}(CHR^{61})_{q}NR^{20}CONR^{33}R^{82}; -(CH_{2})_{p}(CHR^{61})_{q}COOR^{57}; -(CH_{2})_{p}(CHR^{61})_{q}CONR^{58}R^{59}; -(CH_{2})_{p}(CHR^{61})_{q}PO(OR^{60})_{2}; -(CH_{2})_{p}(CHR^{61})_{q}SO_{2}R^{62}; \text{ or } -(CH_{2})_{p}(CHR^{61})_{q}C_{6}H_{4}R^{8};

R^{44} \text{ is } \text{ alkyl; alkaryl; } -(CH_{2})_{p}(CHR^{61})_{q}OR^{55}; -(CH_{2})_{p}(CHR^{61})_{q}SR^{26}; -(CH_{2})_{p}(CHR^{61})_{q}NR^{33}R^{34}; -(CH_{2})_{p}(CHR^{61})_{q}OCONR^{33}R^{75}; -(CH_{2})_{p}(CHR^{61})_{q}NR^{20}CONR^{33}R^{82};
-$(\text{CH}_2)_n(\text{CHR}^{61})_n\text{COOR}^{57}; -$(\text{CH}_2)_m(\text{CHR}^{61})_m\text{CONR}^{58}R^{59}; -$

$(\text{CH}_2)_n(\text{CHR}^{61})_n\text{PO}$(OR$^{60}$)$_2$;

-$(\text{CH}_2)_n(\text{CHR}^{61})_n\text{SO}_2R^{62}$; or -$(\text{CH}_2)_n(\text{CHR}^{61})_n\text{C}_6\text{H}_5R^{8}$;

R$^{51}$ is H; alkyl; alkenyl; -$(\text{CH}_2)_n(\text{CHR}^{61})_n\text{OR}^{55}$; -$(\text{CH}_2)_m(\text{CHR}^{61})_m\text{SR}^{56}$;

R$^{52}$ is H; alkyl; alkenyl; -$(\text{CH}_2)_m(\text{CHR}^{61})_m\text{OR}^{55}$; -$(\text{CH}_2)_m(\text{CHR}^{61})_m\text{SR}^{56}$;

R$^{53}$ is H; alkyl; alkenyl; -$(\text{CH}_2)_m(\text{CHR}^{61})_m\text{OR}^{55}$; -$(\text{CH}_2)_m(\text{CHR}^{61})_m\text{SR}^{56}$;

R$^{54}$ is H; alkyl; alkenyl; -$(\text{CH}_2)_m(\text{CHR}^{61})_m\text{OR}^{55}$; -$(\text{CH}_2)_m(\text{CHR}^{61})_m\text{NR}^{33}R^{34}$;

R$^{55}$ is H; lower alkyl; lower alkenyl; or aryl-lower alkyl;
-\((\text{CH}_2)_m(\text{CHR}^{61})_n\text{NR}^{34}\text{R}^{63}\); 
-\((\text{CH}_2)_m(\text{CHR}^{61})_n\text{OCO}\text{NR}^{75}\text{R}^{82}\); 
-\((\text{CH}_2)_n(\text{CHR}^{61})_m\text{NR}^{20}\text{CONR}^{78}\text{R}^{82}\); 
-\((\text{CH}_2)_n(\text{CHR}^{61})_m\text{COR}^{64}\); 
-\((\text{CH}_2)_m(\text{CHR}^{61})_n\text{COOR}^{57}\); or 
-\((\text{CH}_2)_m(\text{CHR}^{61})_n\text{CONR}^{58}\text{R}^{59}\);

5 \text{R}^{56} \text{is} \ H; \text{lower alkyl}; \text{lower alkenyl}; \text{aryl-lower alkyl}; -\((\text{CH}_2)_m(\text{CHR}^{61})_n\text{OR}^{57}\); 
-\((\text{CH}_2)_m(\text{CHR}^{61})_n\text{NR}^{34}\text{R}^{63}\); 
-\((\text{CH}_2)_n(\text{CHR}^{61})_m\text{OCO}\text{NR}^{75}\text{R}^{82}\); 
-\((\text{CH}_2)_n(\text{CHR}^{61})_m\text{NR}^{20}\text{CONR}^{78}\text{R}^{82}\); 
-\((\text{CH}_2)_n(\text{CHR}^{61})_m\text{COR}^{64}\); or 
-\((\text{CH}_2)_m(\text{CHR}^{61})_n\text{CONR}^{58}\text{R}^{59}\);

\text{R}^{57} \text{is} \ H; \text{lower alkyl}; \text{lower alkenyl}; \text{aryl lower alkyl}; or \text{heteroaryl lower alkyl};

10 \text{R}^{58} \text{is} \ H; \text{lower alkyl}; \text{lower alkenyl}; \text{aryl}; \text{heteroaryl}; \text{aryl-lower alkyl}; or \text{heteroaryl-lower alkyl}; 
\text{R}^{59} \text{is} \ H; \text{lower alkyl}; \text{lower alkenyl}; \text{aryl}; \text{heteroaryl}; \text{aryl-lower alkyl}; or \text{heteroaryl-lower alkyl}; or 
\text{R}^{58} \text{and} \text{R}^{59} \text{taken together can form:} -\((\text{CH}_2)_2\text{O}\text{CH}(\text{CH}_2)_2\); 
-\((\text{CH}_2)_2\text{S}(\text{CH}(\text{CH}_2)_2)\); or 
-\((\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2\); 

\text{R}^{60} \text{is} \ H; \text{lower alkyl}; \text{lower alkenyl}; \text{aryl}; or \text{aryl-lower alkyl};

\text{R}^{61} \text{is} \ \text{alkyl}; \text{alkenyl}; \text{aryl}; \text{heteroaryl}; \text{aryl-lower alkyl}; \text{heteroaryl-lower alkyl}; 
-\((\text{CH}_2)_m\text{OR}^{55}\); 
-\((\text{CH}_2)_m\text{NR}^{34}\text{R}^{44}\); 
-\((\text{CH}_2)_m\text{OCO}\text{NR}^{75}\text{R}^{82}\); 
-\((\text{CH}_2)_m\text{NR}^{20}\text{CONR}^{78}\text{R}^{82}\);

20 \((\text{CH}_2)_m\text{COOR}^{57}\); 
-\((\text{CH}_2)_n\text{NR}^{38}\text{R}^{59}\); or \((\text{CH}_2)_n\text{PO}(\text{COR}^{65})_2\); 
\text{R}^{62} \text{is} \ \text{lower alkyl}; \text{lower alkenyl}; \text{aryl}, \text{heteroaryl}; or \text{aryl-lower alkyl};

\text{R}^{63} \text{is} \ H; \text{lower alkyl}; \text{lower alkenyl}; \text{aryl}, \text{heteroaryl}; \text{aryl-lower alkyl}; \text{heteroaryl-lower alkyl};

25 \text{COR}^{64}; \text{COOR}^{57}; \text{CONR}^{38}\text{R}^{59}; \text{SO}_{2}\text{R}^{62}; \text{or} -\text{PO}(\text{OR}^{65})_2; 
\text{R}^{64} \text{and} \text{R}^{65} \text{taken together can form:} -\((\text{CH}_2)_2\text{O}\text{O}(\text{CH}_2)_2\); 
-\((\text{CH}_2)_2\text{S}(\text{CH}(\text{CH}_2)_2)\); or 
-\((\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2\); 

\text{R}^{64} \text{is} \ H; \text{lower alkyl}; \text{lower alkenyl}; \text{aryl}; \text{heteroaryl}; \text{aryl-lower alkyl}; \text{heteroaryl-lower alkyl};

30 \((\text{CH}_2)_p(\text{CHR}^{61})_n\text{OR}^{65}\); 
\((\text{CH}_2)_p(\text{CHR}^{61})_n\text{SR}^{66}\); \text{or} \((\text{CH}_2)_p(\text{CHR}^{61})_n\text{NR}^{34}\text{R}^{63}\); 
\((\text{CH}_2)_p(\text{CHR}^{61})_n\text{OCO}\text{NR}^{75}\text{R}^{82}\); 
\((\text{CH}_2)_p(\text{CHR}^{61})_n\text{NR}^{20}\text{CONR}^{78}\text{R}^{82}\); 
\text{R}^{65} \text{is} \ H; \text{lower alkyl}; \text{lower alkenyl}; \text{aryl}, \text{aryl-lower alkyl}; \text{heteroaryl-lower alkyl}; \text{COR}^{57}; 
\text{COOR}^{57}; \text{or} -\text{CONR}^{38}\text{R}^{59};
R^{56} is H; lower alkyl; lower alkenyl; aryl; aryl-lower alkyl; heteroaryl-lower alkyl; or
-CONR^{58}R^{59};
m is 2-4; o is 0-4; p is 1-4; q is 0-2; r is 1 or 2; s is 0 or 1;

5 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 are, depending on their position in the chains, Gly, Pro, Pro(4NHCOPhe) or of
formula -A-CO-, or of formula -B-CO-, or of one of the types

10 C: -NR^{20}CH(R^{72})CO-;
D: -NR^{20}CH(R^{72})CO-;
E: -NR^{20}CH(R^{74})CO-;
F: -NR^{20}CH(R^{74})CO-; and
H: -NR^{20}-CH(CO-)-(CH_{2})_{4}CH(CO-)-NR^{20} -;
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}O\text{R}^{75}; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}S\text{R}^{75};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}NR^{33}R^{34}; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}O\text{CONR}^{33}R^{35};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}NR^{20}CONR^{20}(CH}_{2})_{p}(\text{CHR}-CO-)-NR^{20} -;

15 \text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}OR^{75}; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}SR^{75};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}NR^{33}R^{34}; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}O\text{CONR}^{33}R^{35};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}NR^{20}CONR^{20}(CH}_{2})_{p}(\text{CHR})_{p}(\text{CHR}-CO-)-NR^{20} -;

20 \text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}OR^{75}; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}SR^{75};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}NR^{33}R^{34}; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}O\text{CONR}^{33}R^{35};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}NR^{20}CONR^{20}(CH}_{2})_{p}(\text{CHR})_{p}(\text{CHR}-CO-)-NR^{20} -;

R^{71} is \text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}OR^{75}; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}SR^{75};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}NR^{33}R^{34}; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}O\text{CONR}^{33}R^{35};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}NR^{20}CONR^{20}(CH}_{2})_{p}(\text{CHR})_{p}(\text{CHR}-CO-)-NR^{20} -;

R^{72} is H, lower alkyl; lower alkenyl; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}OR^{85}; -(CH}_{2})_{p}(\text{CHR}^{61})_{q}SR^{85};
R^{73} is -(CR^{80}R^{87})_{p}R^{77}; -(CH}_{2})_{p}O(CH}_{2})_{p}R^{77}; -(CH}_{2})_{p}S(CH}_{2})_{p}R^{77}; -(CH}_{2})_{p}NR^{20}(CH}_{2})_{p}R^{77};
R^{74} is -(CH}_{2})_{p}NR^{78}R^{79}; -(CH}_{2})_{p}NR^{78}R^{80}; -(CH}_{2})_{p}C(=\text{NR}^{80})NR^{78}R^{79}; -(CH}_{2})_{p}C(=\text{NOR}^{50})NR^{78}R^{79};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}NR^{78}R^{79}; -(CH}_{2})_{p}NR^{80}C(=\text{NR}^{80})NR^{78}R^{79};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}NR^{78}R^{79}; -(CH}_{2})_{p}NR^{80}C(=\text{NOR}^{50})NR^{78}R^{79};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}NR^{78}R^{79}; -(CH}_{2})_{p}C_{6}H_{4}NR^{78}R^{79}; -(CH}_{2})_{p}C_{6}H_{4}NR^{78}R^{79};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}NR^{78}R^{79}; -(CH}_{2})_{p}C_{6}H_{4}CR^{78}R^{79}; -(CH}_{2})_{p}C_{6}H_{4}CR^{78}R^{79};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}NR^{78}R^{79}; -(CH}_{2})_{p}C_{6}H_{4}NR^{78}R^{79}; -(CH}_{2})_{p}C_{6}H_{4}NR^{78}R^{79};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}NR^{78}R^{79}; -(CH}_{2})_{p}C_{6}H_{4}CR^{78}R^{79}; -(CH}_{2})_{p}C_{6}H_{4}CR^{78}R^{79};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}NR^{78}R^{79}; -(CH}_{2})_{p}C_{6}H_{4}NR^{78}R^{79}; -(CH}_{2})_{p}C_{6}H_{4}NR^{78}R^{79};
-\text{lower alkyl; lower alkenyl; -(CH}_{2})_{p}NR^{78}R^{79}; -(CH}_{2})_{p}C_{6}H_{4}CR^{78}R^{79}; -(CH}_{2})_{p}C_{6}H_{4}CR^{78}R^{79};
-\((CH_2)_nO(CH_2)_mC_6H_4C(=NR^{80})NR^{78}\)R^{79}; -(CH_2)_nO(CH_2)_mC_6H_4C(=NOR^{80})NR^{78}\)R^{79};

-\(\text{[other structures]}\)

R^{75} is lower alkyl; lower alkenyl; or aryl-lower alkyl;

R^{33} and R^{75} taken together can form: -(CH_2)_2-C-; -(CH_2)_2O(CH_2)_2--; -(CH_2)_2S(CH_2)_2--; or 

-\(\text{[other structures]}\)

R^{75} and R^{82} taken together can form: -(CH_2)_2-C-; -(CH_2)_2O(CH_2)_2--; -(CH_2)_2S(CH_2)_2--; or 

-\(\text{[other structures]}\)

R^{76} is H; lower alkyl; lower alkenyl; aryl-lower alkyl; -(CH_2)_nOR^{72}; -(CH_2)_nSR^{72}; 

-\(\text{[other structures]}\)

R^{77} is -C_6H_5R^{67}R^{69}\)R^{70}R^{76}; or a heteroaryl group of one of the formulae

\(\text{[diagrams]}\)
R^{82} is H; lower alkyl; aryl; or aryl-lower alkyl;
R^{78} and R^{82} taken together can form: -(CH_2)_2-; -(CH_2)_2O(CH_2)_2--; -(CH_2)_2S(CH_2)_2--; or -(CH_2)_2NR^{57}(CH_2)_2--; 

5  
R^{79} is H; lower alkyl; aryl; or aryl-lower alkyl; or 
R^{78} and R^{79}, taken together, can be -(CH_2)_2--; -(CH_2)_2O(CH_2)_2--; or -(CH_2)_2NR^{57}(CH_2)_2--; 
R^{80} is H; or lower alkyl;  
R^{81} is H; lower alkyl; or aryl-lower alkyl;  
R^{82} is H; lower alkyl; aryl; heteroaryl; or aryl-lower alkyl; 

10  
R^{83} and R^{82} taken together can form: -(CH_2)_2-; -(CH_2)_2O(CH_2)_2--; -(CH_2)_2S(CH_2)_2--; or -(CH_2)_2NR^{57}(CH_2)_2--; 
R^{83} is H; lower alkyl; aryl; or -NR^{78}R^{79};  
R^{84} is -(CH_2)_m(CHR^{61})_sOH; -(CR^{86}R^{87})_pOR^{60}; -(CR^{86}R^{87})_pCOOR^{60}; -(CH_2)_m(CHR^{61})_sSH; -(CR^{86}R^{87})_pSR^{60}; -(CH_2)_pCONR^{78}R^{79}; -(CH_2)_pNR^{80}CONR^{78}R^{79}; - 

15  
(CH_2)_pC_6H_4CONR^{78}R^{79}; -(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}; -(CR^{86}R^{87})_pPO(OR^{60})_2--; -(CR^{86}R^{87})_pSO_2R^{60}; -(CR^{86}R^{87})_pSOR^{60}; -(CH_2)_m(CHR^{61})_sOPO(OR^{60})_2--; or -(CH_2)_m(CHR^{61})_sOSO_2R^{60}; 
R^{85} is lower alkyl; or lower alkenyl;  
R^{86} is H; lower alkyl, where H is maybe substituted by halogen; or halogen;  

20  
R^{87} is H; lower alkyl, where H is maybe substituted by halogen; or halogen; 
with the proviso that in said chain of 11 α-amino acid residues Z
- if n is 11, the amino acid residues in positions 1 to 11 are:
  - P1: of type C or of type D or of type E or of type F;
  - P2: of type C or of type D or of type E, or of type F;
  - P3: of type C, of type F, or the residue is Gly;
  - P4: of type C, or of type D, or of type F, or of type E, or the residue is Gly or Pro;
  - P5: of type E, or of type C, or of type F, or the residue is Gly or Pro;
  - P6: of type D, or of type F, or of type E or of type C, or the residue is Gly or Pro;
  - P7: of type C, or of type E, or of type F, or of formula –A-CO–, or the residue is Gly or Pro;
  - P8: of type D, or of type C, or of type F, or of formula –A-CO–, or the residue is Gly or Pro or Pro(4NHCOPhenyl); 
  - P9: of type C, or of type D, or of type E, or of type F;
  - P10: of type D, or of type C, or of type F, or of type E; and
  - P11: of type C, or of type D, or of type E, or of type F; or
  - P2 and P10, taken together, can form a group of type H; and with the further proviso that if the template is Pro-Pro, the amino acid residues in positions P1 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
- P7: Pro
- P8: Pro
- P9: Ile
- P10: Cys, linked with Cys in position P10 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

\[ \text{Template} \]

\[ \text{II} \]

15 wherein

\[ \text{Template} \]

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

\[ \text{Template} \]

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

\[ \text{HOOC-B-H III} \]

or

\[ \text{HOOC-A-H IV} \]
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; and, respectively, if

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is to be group (a3), above,

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

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 O     X
onas
 Template
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```
 O
 Template
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wherein

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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

\[ \text{HOOC-B-H} \quad \text{III} \quad \text{or} \quad \text{HOOC-A-H} \quad \text{IV} \]

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; and, respectively, if

is to be group (a3), above,

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

As used in this description, the term "alkyl", taken alone or in combinations, designates saturated, straight-chain or branched hydrocarbon radicals having up to 24, preferably up to 12, carbon atoms. Similarly, the term "alkenyl" designates straight chain or branched hydrocarbon radicals having up to 24, preferably up to 12, carbon atoms and containing at least one or, depending on the chain length, up to four olefinic double bonds. The term "lower" designates radicals and compounds having up to 6 carbon atoms. Thus, for example, the term "lower alkyl" designates saturated, straight-chain or branched hydrocarbon radicals having up to 6 carbon atoms, such as methyl, ethyl, n-propyl,
isopropyl, n-butyl, sec.-butyl, isobutyl, tert.-butyl and the like. The term "aryl" designates aromatic carbocyclic hydrocarbon radicals containing one or two six-membered rings, such as phenyl or naphthyl, which may be substituted by up to three substituents such as Br, Cl, F, CF₃, NO₂, lower alkyl or lower alkenyl. The term "heteroaryl" designates aromatic heterocyclic radicals containing one or two five- and/or six-membered rings, at least one of them containing up to three heteroatoms selected from the group consisting of O, S and N and said ring(s) being optionally substituted; representative examples of such optionally substituted heteroaryl radicals are indicated hereinabove in connection with the definition of R^7.

The structural element -A-CO- designates amino acid building blocks which in combination with the structural element -B-CO- form templates (a1) and (a2). The structural element -B-CO- forms in combination with another structural element -B-CO- template (a3). The template (a3) is less preferred in formula I. Templates (a) through (p) 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 4.0-5.5 Å. The peptide chain Z is linked to the C-terminus and the N-terminus of the templates (a) through (p) 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 4.0-5.5 Å 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 (a) through (p) 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.

Building blocks A1-A69 belong to a class of amino acids wherein the N-terminus is a secondary amine forming part of a ring. Among the genetically encoded amino acids only proline falls into this class. The configuration of building block A1 through A69 is (D), and they are combined with a building block -B-CO- of (L)-configuration. Preferred
combinations for templates (a1) are $^\text{D}A1\text{-CO}-^\text{L}B\text{-CO}$- to $^\text{D}A69\text{-CO}-^\text{L}B\text{-CO}$-. Thus, for example, $^\text{D}\text{Pro}$-$^\text{L}\text{Pro}$ constitutes the prototype of templates (a1). Less preferred, but possible are combinations $^\text{L}A1\text{-CO}-^\text{D}B\text{-CO}$- to $^\text{L}A69\text{-CO}-^\text{D}B\text{-CO}$- forming templates (a2). Thus, for example, $^\text{L}\text{Pro}$-$^\text{D}\text{Pro}$ constitutes the prototype of template (a2).

It will be appreciated that building blocks -A1-CO- to -A69-CO- in which A has (D)-configuration, are carrying a group R$^1$ at the α-position to the N-terminus. The preferred values for R$^1$ are H and lower alkyl with the most preferred values for R$^1$ being H and methyl. It will be recognized by those skilled in the art, that A1-A69 are shown in (D)-configuration which, for R$^1$ being H and methyl, corresponds to the (R)-configuration. Depending on the priority of other values for R$^1$ according to the Cahn, Ingold and Prelog-rules, this configuration may also have to be expressed as (S).

In addition to R$^1$ building blocks -A1-CO- to -A69-CO- can carry an additional substituent designated as R$^2$ to R$^{17}$. This additional substituent can be H, and if it is other than H, it is preferably a small to medium-sized aliphatic or aromatic group. Examples of preferred values for R$^2$ to R$^{17}$ are:

- $R^2$: H; lower alkyl; lower alkenyl; (CH$_2$)$_m$OR$^{35}$ (where R$^{35}$: lower alkyl; or lower alkenyl); (CH$_2$)$_n$SR$^{56}$ (where R$^{56}$: lower alkyl; or lower alkenyl); (CH$_2$)$_m$NR$^{33}$R$^{34}$ (where R$^{33}$: lower alkyl; or lower alkenyl; R$^{34}$: H; or lower alkyl; R$^{33}$ and R$^{34}$ taken together:

- (CH$_2$)$_2$O(CHR$^2$)$_2$; -(CH$_2$)$_2$S(CHR$^2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CHR$^2$)$_2$-; R$^{57}$: H; or lower alkyl); (CH$_2$)$_m$OCONR$^{33}$R$^{75}$ (where R$^{33}$: H; or lower alkyl; or lower alkenyl; R$^{75}$: lower alkyl; or R$^{33}$ and R$^{75}$ taken together: -(CH$_2$)$_2$O(CHR$^2$)$_2$-; -(CH$_2$)$_2$S(CHR$^2$)$_2$-; or 

- (CH$_2$)$_2$NR$^{57}$(CHR$^2$)$_2$-; where R$^{57}$: H; or lower alkyl); -(CH$_2$)$_m$NR$^{30}$CONR$^{33}$R$^{82}$ (where R$^{30}$: H; or lower lower alkyl; R$^{33}$: H; or lower alkyl; or lower alkenyl; R$^{82}$: H; or lower alkyl; or R$^{33}$ and R$^{82}$ taken together: -(CH$_2$)$_2$O(CHR$^2$)$_2$-; -(CH$_2$)$_2$S(CHR$^2$)$_2$-; or 

- (CH$_2$)$_2$NR$^{57}$(CHR$^2$)$_2$-; where R$^{57}$: H; or lower alkyl); -(CH$_2$)$_m$N(RO$^{30}$)COR$^{64}$ (where: R$^{30}$: H; or lower alkyl; R$^{64}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_n$COOR$^{75}$ (where R$^{75}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_m$CONR$^{38}$R$^{59}$ (where R$^{38}$: lower alkyl; or lower alkenyl; and R$^{59}$: H; or lower alkyl; or R$^{59}$ and R$^{59}$ taken together form: -(CH$_2$)$_2$O(CHR$^2$)$_2$-; 

-(CH$_2$)$_2$S(CHR$^2$)$_2$-; or -(CH$_2$)$_2$NR$^{57}$(CHR$^2$)$_2$-; where R$^{57}$: H; or lower alkyl); -
(CH₂)₃PO(OR)₆ (where R = lower alkyl; or lower alkenyl); - (CH₂)₅SO₂R (where R = lower alkyl; or lower alkenyl); or - (CH₂)₅C₆H₅R (where R = H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

- R₁: H; lower alkyl; lower alkenyl; - (CH₂)₅OR (where R = lower alkyl; or lower alkenyl); - (CH₂)₅SR (where R = lower alkyl; or lower alkenyl); - (CH₂)₅NR₂ (where R = lower alkyl; or lower alkenyl; or lower alkoxy).
(CH$_2$)$_2$O(CH$_2$)$_2$;
-(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; where R$_{57}$: H; or lower alkyl); -(CH$_2$)$_2$PO(OR$_{60}$)$_2$ (where R$_{60}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$SO$_2$R$_{62}$ (where R$_{62}$: lower alkyl; or lower alkenyl); or -(CH$_2$)$_3$C$_6$H$_5$R$_8$ (where R$_8$: H; F; Cl; CF$_3$; lower alkyl; lower alkenyl; or lower alkoxy).

- R$^1$: lower alkyl; lower alkenyl; -(CH$_2$)$_3$OR$_{55}$ (where R$_{55}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$SR$_{56}$ (where R$_{56}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$NR$_{53}$R$_{34}$ (where R$_{33}$: lower alkyl; or lower alkenyl; R$_{34}$: H; or lower alkyl; or R$_{33}$ and R$_{34}$ taken together form: -(CH$_2$)$_3$O(CH$_2$)$_2$; -(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; R$_{57}$: where H; or lower alkyl); (CH$_2$)$_3$NR$_{35}$CONR$_{33}$R$_{32}$ (where R$_{33}$: H; or lower alkyl; or lower alkenyl; R$_{32}$: H; or lower alkyl; or R$_{33}$ and R$_{32}$ taken together form: -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; where R$_{57}$: H; or lower alkyl); -(CH$_2$)$_3$OCONR$_{33}$R$_{25}$ (where R$_{25}$: H; or lower alkyl; or lower alkenyl; R$_{33}$: lower alkyl; or lower alkenyl; or R$_{33}$ and R$_{25}$ taken together form: -(CH$_2$)$_3$O(CH$_2$)$_2$; -(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; where R$_{57}$: H; or lower alkyl); (CH$_2$)$_3$NR$_{55}$CONR$_{33}$R$_{32}$ (where R$_{32}$: H; or lower alkyl; or lower alkenyl; R$_{33}$: lower alkyl; or lower alkenyl; R$_{33}$ and R$_{32}$ taken together form: -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; where R$_{57}$: H; or lower alkyl); -(CH$_2$)$_3$COOR$_{57}$ (where R$_{57}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$CONR$_{35}$R$_{59}$ (where R$_{59}$: H; or lower alkyl; or lower alkenyl; R$_{35}$: lower alkyl; or lower alkenyl; or R$_{59}$ and R$_{35}$ taken together form: -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; where R$_{57}$: H; or lower alkyl); -(CH$_2$)$_3$PO(OR$_{60}$)$_2$ (where R$_{60}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$SO$_2$R$_{62}$ (where R$_{62}$: lower alkyl; or lower alkenyl); or -(CH$_2$)$_3$C$_6$H$_5$R$_8$ (where R$_8$: H; F; Cl; CF$_3$; lower alkyl; lower alkenyl; or lower alkoxy).

- R$_6$: H; lower alkyl; lower alkenyl; -(CH$_2$)$_3$OR$_{55}$ (where R$_{55}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$SR$_{56}$ (where R$_{56}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$NR$_{53}$R$_{34}$ (where R$_{33}$: lower alkyl; or lower alkenyl; R$_{34}$: H; or lower alkyl; or R$_{33}$ and R$_{34}$ taken together form: -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; where R$_{57}$: H; or lower alkyl); -(CH$_2$)$_3$OCONR$_{33}$R$_{25}$ (where R$_{25}$: H; or lower alkyl; or lower alkenyl; R$_{33}$: lower alkyl; or lower alkenyl; R$_{33}$ and R$_{25}$ taken together form: -(CH$_2$)$_3$O(CH$_2$)$_2$; -(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; where R$_{57}$: H; or lower alkyl); -(CH$_2$)$_3$NR$_{55}$CONR$_{33}$R$_{32}$ (where R$_{32}$: H; or lower alkyl; or lower alkenyl; R$_{33}$: lower alkyl; or lower alkenyl; R$_{33}$ and R$_{32}$ taken together form: -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; where R$_{57}$: H; or lower alkyl); -(CH$_2$)$_3$COOR$_{57}$ (where R$_{57}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$CONR$_{35}$R$_{59}$ (where R$_{59}$: H; or lower alkyl; or lower alkenyl; R$_{35}$: lower alkyl; or lower alkenyl; or R$_{59}$ and R$_{35}$ taken together form: -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; where R$_{57}$: H; or lower alkyl); -(CH$_2$)$_3$PO(OR$_{60}$)$_2$ (where R$_{60}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$SO$_2$R$_{62}$ (where R$_{62}$: lower alkyl; or lower alkenyl); or -(CH$_2$)$_3$C$_6$H$_5$R$_8$ (where R$_8$: H; F; Cl; CF$_3$; lower alkyl; lower alkenyl; or lower alkoxy).

- R$_{35}$: lower alkyl; lower alkenyl; -(CH$_2$)$_3$OR$_{55}$ (where R$_{55}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$SR$_{56}$ (where R$_{56}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$NR$_{53}$R$_{34}$ (where R$_{33}$: lower alkyl; or lower alkenyl; R$_{34}$: H; or lower alkyl; or R$_{33}$ and R$_{34}$ taken together form: -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; where R$_{57}$: H; or lower alkyl); -(CH$_2$)$_3$OCONR$_{33}$R$_{25}$ (where R$_{25}$: H; or lower alkyl; or lower alkenyl; R$_{33}$: lower alkyl; or lower alkenyl; R$_{33}$ and R$_{25}$ taken together form: -(CH$_2$)$_3$O(CH$_2$)$_2$; -(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; where R$_{57}$: H; or lower alkyl); -(CH$_2$)$_3$NR$_{55}$CONR$_{33}$R$_{32}$ (where R$_{32}$: H; or lower alkyl; or lower alkenyl; R$_{33}$: lower alkyl; or lower alkenyl; R$_{33}$ and R$_{32}$ taken together form: -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; where R$_{57}$: H; or lower alkyl); -(CH$_2$)$_3$COOR$_{57}$ (where R$_{57}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$CONR$_{35}$R$_{59}$ (where R$_{59}$: H; or lower alkyl; or lower alkenyl; R$_{35}$: lower alkyl; or lower alkenyl; or R$_{59}$ and R$_{35}$ taken together form: -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_3$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$_{57}$(CH$_2$)$_2$; where R$_{57}$: H; or lower alkyl); -(CH$_2$)$_3$PO(OR$_{60}$)$_2$ (where R$_{60}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$SO$_2$R$_{62}$ (where R$_{62}$: lower alkyl; or lower alkenyl); or -(CH$_2$)$_3$C$_6$H$_5$R$_8$ (where R$_8$: H; F; Cl; CF$_3$; lower alkyl; lower alkenyl; or lower alkoxy).
$-(\text{CH}_2)_n\text{NR}^{57}(\text{CH}_2)_2; \text{ where } R^{57}: \text{H; or lower alkyl}; -(\text{CH}_2)_n\text{N}(\text{R}^{20})\text{COR}^{64} \text{ (where: } R^{20}: \text{H; or lower alkyl; } R^{64}: \text{lower alkyl; or lower alkenyl}); -(\text{CH}_2)_n\text{COOR}^{57} \text{ (where } R^{57}: \text{lower alkyl; or lower alkenyl); -(CH}_2)_n\text{CONR}^{58}R^{59} \text{ (where } R^{58}: \text{lower alkyl; or lower alkenyl; and } R^{59}: \text{H; or lower alkyl; or } R^{20} \text{ and } R^{59} \text{ taken together form: } -(\text{CH}_2)_2\text{O}^{65}; -$

$-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2; \text{ where } R^{57}: \text{H; or lower alkyl}); -(\text{CH}_2)_n\text{PO}(\text{OR}^{60})_2 \text{ (where } R^{60}: \text{lower alkyl; or lower alkenyl); -(CH}_2)_n\text{SO}_2R^{62} \text{ (where } R^{62}: \text{lower alkyl; or lower alkenyl; or } -(\text{CH}_2)_n\text{C}_8\text{H}_8R^{8} \text{ (where } R^{8}: \text{H; F; Cl; CF}_3; \text{ lower alkyl; lower alkenyl; or lower alkoxy).}$

$- R^{6}: \text{lower alkyl; lower alkenyl; -(CH}_2)_n\text{OR}^{55} \text{ (where } R^{55}: \text{lower alkyl; or lower alkenyl); -(CH}_2)_n\text{SR}^{56} \text{ (where } R^{56}: \text{lower alkyl; or lower alkenyl); -(CH}_2)_n\text{NR}^{33}R^{34} \text{ (where } R^{33}: \text{lower alkyl; or lower alkenyl; } R^{34}: \text{H; or lower alkyl; or } R^{33} \text{ and } R^{34} \text{ taken together form: } -(\text{CH}_2)_2\text{O}^{65}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_2; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2; \text{ where } R^{57}: \text{H; or lower alkyl); -(\text{CH}_2)_n\text{OCONR}^{33}R^{35} \text{ (where } R^{33}: \text{H; or lower alkyl; or lower alkenyl; } R^{35}: \text{lower alkyl; or } R^{33} \text{ and } R^{35} \text{ taken together form: } -(\text{CH}_2)_2\text{O}^{65}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_2; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2; \text{ where } R^{57}: \text{H; or lower alkyl); -(\text{CH}_2)_n\text{NR}^{20}\text{CONR}^{33}R^{82} \text{ (where } R^{20}: \text{H; or lower lower alkyl; } R^{33}: \text{H; or lower alkyl; or lower alkenyl; or } R^{82}: \text{H; or lower alkyl; or } R^{33} \text{ and } R^{82} \text{ taken together form: } -(\text{CH}_2)_2\text{O}^{65}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_2; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2; \text{ where } R^{57}: \text{H; or lower alkyl); -(\text{CH}_2)_n\text{NR}^{33}R^{34} \text{ (where } R^{33}: \text{lower alkyl; or lower alkenyl; } R^{34}: \text{H; or lower alkyl; or } R^{33} \text{ and } R^{34} \text{ taken together form: } -(\text{CH}_2)_2\text{O}^{65}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_2; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2; \text{ where } R^{57}: \text{H; or lower alkyl); -(\text{CH}_2)_n\text{OCONR}^{33}R^{35} \text{ (where } R^{33}: \text{lower alkyl; or lower alkenyl; and } R^{35}: \text{H; or lower alkyl; or } R^{33} \text{ and } R^{35} \text{ taken together form: } -(\text{CH}_2)_2\text{O}^{65}; -$

$R^{8}: \text{H; F; Cl; CF}_3; \text{ lower alkyl; lower alkenyl; -(CH}_2)_n\text{OR}^{55} \text{ (where } R^{55}: \text{lower alkyl; or lower alkenyl); -(CH}_2)_n\text{SR}^{56} \text{ (where } R^{56}: \text{lower alkyl; or lower alkenyl); -(CH}_2)_n\text{NR}^{33}R^{34} \text{ (where } R^{33}: \text{lower alkyl; or lower alkenyl; } R^{34}: \text{H; or lower alkyl; or } R^{33} \text{ and } R^{34} \text{ taken together form: } -(\text{CH}_2)_2\text{O}^{65}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_2; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2; \text{ where } R^{57}: \text{H; or lower alkyl); -(\text{CH}_2)_n\text{OCONR}^{33}R^{35} \text{ (where } R^{33}: \text{H; or lower alkyl; or lower alkenyl; and } R^{35}: \text{lower alkyl; or lower alkenyl; } R^{20}: \text{lower alkyl; or } R^{33} \text{ and } R^{20} \text{ taken together form: } -(\text{CH}_2)_2\text{O}^{65}; -$
(CH₂)₂4; - (CH₂)₂O(CH₂)₂; - (CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl; - (CH₂)₆NR²⁰CONR³³R⁸₂ (where R²⁰: H; or lower lower alkyl; R³³: H; or lower alkyl; or lower alkenyl; R⁸₂: H; or lower alkyl; or R³³ and R⁸₂ taken together form: -(CH₂)₂-6; - (CH₂)₂O(CH₂)₂; - (CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl; - (CH₂)₆N(R⁵⁰)COR⁴⁴ (where: R⁵⁰: H; or lower alkyl; R⁴⁴: lower alkyl; or lower alkenyl); - (CH₂)₆COOR⁴⁷ (where R⁴⁷: lower alkyl; or lower alkenyl); -(CH₂)₆CONR⁵⁸R⁵⁹ (where R⁵⁸: lower alkyl; or lower alkenyl; and R⁵⁹: H; or lower alkyl; or R⁵⁸ and R⁵⁹ taken together form: - (CH₂)₂-6; - (CH₂)₂O(CH₂)₂; - (CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); - (CH₂)₆PO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl); - (CH₂)₆SO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or -(CH₂)₄C₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkyox). - R⁶: lower alkyl; lower alkenyl; -(CH₂)₆OR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl); -(CH₂)₆SR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl); -(CH₂)₆SR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl); -(CH₂)₆NR³³R³⁴ (where R³³: lower alkyl; or lower alkenyl; R³⁴: H; or lower alkyl; or R³³ and R³⁴ taken together form: - (CH₂)₂-6; - (CH₂)₂O(CH₂)₂; - (CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl; -(CH₂)₆NR²⁰CONR³³R⁸₂ (where R²⁰: H; or lower lower alkyl; R³³: H; or lower alkyl; or lower alkenyl; R⁸₂: H; or lower alkyl; or R³³ and R⁸₂ taken together form: -(CH₂)₂-6; - (CH₂)₂O(CH₂)₂; - (CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl; -(CH₂)₆NR²⁰CONR³³R⁸₂ (where R²⁰: H; or lower lower alkyl; R³³: H; or lower alkyl; or lower alkenyl; R⁸₂: H; or lower alkyl; or R³³ and R⁸₂ taken together form: -(CH₂)₂-6; - (CH₂)₂O(CH₂)₂; - (CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl; - (CH₂)₆PO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl); -(CH₂)₆SO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or -(CH₂)₄C₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkyox). - R¹⁰: lower alkyl; lower alkenyl; -(CH₂)₆OR⁵⁵ (where R⁵⁵: lower alkyl; or lower
alkenyl); -(CH₂)₆SR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl); -(CH₂)₆NR³³R⁴⁴ (where R³³: lower alkyl; or lower alkenyl; R⁴⁴: H; or lower alkyl; or R³³ and R⁴⁴ taken together form: -(CH₂)₂-z; -(CH₂)₂O(CH₂)₂-z; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); -(CH₂)₆OCOR⁵⁷ (where R⁵⁷: H; or lower alkyl; or lower alkenyl; R⁷: lower alkyl; or R³³ and R⁷ taken together form: -(CH₂)₂-z; -(CH₂)₂O(CH₂)₂-z; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); -(CH₂)₆OR⁵⁷ (where R⁵⁷: H; or lower alkyl); -(CH₂)₆NR²⁰CONR³³R⁸² (where R²⁰: H; or lower alkyl; R³³: H; or lower alkyl; or lower alkenyl; R⁸²: H; or lower alkyl; or R³³ and R⁸² taken together form: -(CH₂)₂-z; -(CH₂)₂O(CH₂)₂-z; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); -(CH₂)₆NR²⁰COOR⁶⁴(where: R²⁰: H; or lower alkyl; or lower alkenyl; -(CH₂)₆COOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl); -(CH₂)₆CONR³³R⁵⁹ (where R³³: lower alkyl; or lower alkenyl; and R⁵⁹: H; lower alkyl; or R⁵⁸ and R⁵⁹ taken together form: -(CH₂)₂-z; -(CH₂)₂O(CH₂)₂-z; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); -(CH₂)₆PO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl); -(CH₂)₆SO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or -(CH₂)₆C₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

- R⁶⁷: H; lower alkyl; lower alkenyl; -(CH₂)₆OR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl); -(CH₂)₆SR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl); -(CH₂)₆NR³³R⁴⁴ (where R³³: lower alkyl; or lower alkenyl; R⁴⁴: H; or lower alkyl; or R³³ and R⁴⁴ taken together form: -(CH₂)₂-z; -(CH₂)₂O(CH₂)₂-z; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); -(CH₂)₆OCOR⁵⁷ (where R⁵⁷: H; or lower alkyl; or lower alkenyl; -(CH₂)₆COOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl); -(CH₂)₆CONR³³R⁵⁹ (where R³³: lower alkyl; or lower alkenyl; and R⁵⁹: H; lower alkyl; or R⁵⁸ and R⁵⁹ taken together form: -(CH₂)₂-z; -(CH₂)₂O(CH₂)₂-z; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); -(CH₂)₆COOR⁶⁴(where: R²⁰: H; or lower alkyl; or lower alkenyl; -(CH₂)₆COOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl); -(CH₂)₆CONR³³R⁵⁹ (where R³³: lower alkyl; or lower alkenyl; and R⁵⁹: H; lower alkyl; or R⁵⁸ and R⁵⁹ taken together form: -(CH₂)₂-z; -(CH₂)₂O(CH₂)₂-z; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); -(CH₂)₆PO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl); -(CH₂)₆SO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or -(CH₂)₆C₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
lower alkenyl; or lower alkoxy).

- $R^{12}$: $H$; lower alkyI; lower alkenyl; -(CH$_2$)$_m$OR$^{55}$ (where R$^{55}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_m$SR$^{56}$ (where R$^{56}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_m$NR$^{33}$R$^{34}$ (where R$^{33}$: lower alkyl; or lower alkenyl; R$^{34}$: $H$; or lower alkyl; or R$^{33}$ and R$^{34}$ taken together form: -(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_{2-}$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: $H$; or lower alkyl); -(CH$_2$)$_m$OCONR$^{33}$R$^{75}$ (where R$^{33}$: $H$; or lower alkyl; or lower alkenyl; R$^{75}$: lower alkyl; or R$^{33}$ and R$^{75}$ taken together form: -(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: $H$; or lower alkyl); -(CH$_2$)$_m$NR$^{20}$CONR$^{33}$R$^{42}$ (where R$^{20}$: $H$; or lower alkyl; R$^{33}$: $H$; or lower alkyl; or lower alkenyl; R$^{42}$: $H$; or lower alkyl; or R$^{33}$ and R$^{42}$ taken together form: -(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: $H$; or lower alkyl); -(CH$_2$)$_m$N(R$^{20}$)COR$^{64}$ (where: R$^{20}$: $H$; or lower alkyl; R$^{64}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_2$COOR$^{57}$ (where R$^{57}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_2$CONR$^{38}$R$^{59}$ (where R$^{38}$: lower alkyl; or lower alkenyl; and R$^{59}$: $H$; or lower alkyl; or R$^{38}$ and R$^{59}$ taken together form: -(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: $H$; or lower alkyl); -(CH$_2$)$_m$PO(OR$^{60}$)$_2$ (where R$^{60}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_m$SO$_2$R$^{62}$ (where R$^{62}$: lower alkyl; or lower alkenyl); or -(CH$_2$)$_m$C$_6$H$_4$R$^8$ (where R$^8$: $H$; F; Cl; CF$_3$; lower alkyl; lower alkenyl; or lower alkoxy).

- $R^{13}$: lower alkyl; lower alkenyl; -(CH$_2$)$_n$OR$^{55}$ (where R$^{55}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_n$SR$^{56}$ (where R$^{56}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_n$NR$^{33}$R$^{34}$ (where R$^{33}$: lower alkyl; or lower alkenyl; R$^{34}$: $H$; or lower alkyl; or R$^{33}$ and R$^{34}$ taken together form: -(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: $H$; or lower alkyl); -(CH$_2$)$_n$OCONR$^{33}$R$^{75}$ (where R$^{33}$: $H$; or lower alkyl; or lower alkenyl; R$^{75}$: lower alkyl; or R$^{33}$ and R$^{75}$ taken together form: -(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: $H$; or lower alkyl); -(CH$_2$)$_n$N(R$^{20}$)COR$^{64}$ (where: R$^{20}$: $H$; or lower alkyl; R$^{64}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_n$COOR$^{57}$ (where R$^{57}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_n$CONR$^{38}$R$^{59}$ (where R$^{38}$: lower alkyl; or lower alkenyl; and R$^{59}$: $H$; or lower alkyl; or R$^{38}$ and R$^{59}$ taken together form: -(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: $H$; or lower alkyl); -(CH$_2$)$_n$NR$^{20}$CONR$^{33}$R$^{42}$ (where R$^{20}$: $H$; or lower alkyl; R$^{33}$: $H$; or lower alkyl; or lower alkenyl; R$^{42}$: $H$; or lower alkyl; or R$^{33}$ and R$^{42}$ taken together form: -(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: $H$; or lower alkyl); -(CH$_2$)$_n$PO(OR$^{60}$)$_2$ (where R$^{60}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_n$SO$_2$R$^{62}$ (where R$^{62}$: lower alkyl; or lower alkenyl); or -(CH$_2$)$_n$C$_6$H$_4$R$^8$ (where R$^8$: $H$; F; Cl; CF$_3$; lower alkyl; lower alkenyl; or lower alkoxy).
(CH₂)₂S(CH₃)₂--; or -(CH₂)₂NR₅(CH₂)₁--; where R₅: H; or lower alkyl; -(CH₂)₂PO(OR₆)₂ (where R₆: lower alkyl; or lower alkenyl); -(CH₂)₂SO₂R₆ (where R₆: lower alkyl; or lower alkenyl); 
- (CH₂)₉C₆H₄R₇ (where R₇: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

R₄: H; lower alkyl; lower alkenyl; -(CH₂)₉OR₅ (where R₅: lower alkyl; or lower alkenyl); -(CH₂)₉SR₆ (where R₆: lower alkyl; or lower alkenyl); -(CH₂)₉NR₅R₇ (where R₅, R₇: H; or lower alkyl; or lower alkenyl; R₃: H; or lower alkyl; or R₃ and R₄ taken together form: -(CH₂)₂₆--; -(CH₂)₉O(CH₂)₁--; -(CH₂)₉S(CH₂)₁--; or -(CH₂)₉NR₅(CH₂)₂--; where R₅: H; or lower alkyl); -(CH₂)₉OCO NR₅R₇ (where R₅: H; or lower alkyl; or lower alkenyl; or lower alkoxy).

R₃ and R₄ taken together form: -(CH₂)₂₆--; -(CH₂)₉O(CH₂)₁--; -(CH₂)₉S(CH₂)₁--; or -(CH₂)₉NR₅(CH₂)₂--; where R₅: H; or lower alkyl; or lower alkenyl).

R₄ and R₅: H; lower alkyl; lower alkenyl; -(CH₂)₉O(CH₂)₁--; -(CH₂)₉S(CH₂)₁--; or -(CH₂)₉NR₅(CH₂)₂--; where R₅: H; or lower alkyl; or lower alkenyl; or lower alkoxy.

R₅: lower alkyl; or R₃ and R₅ taken together form: -(CH₂)₂₆--; -(CH₂)₉O(CH₂)₁--; -(CH₂)₉S(CH₂)₁--; or -(CH₂)₉NR₅(CH₂)₂--; where R₅: H; or lower alkyl; or lower alkenyl; or lower alkoxy).

R₄ and R₅ taken together form: -(CH₂)₂₆--; -(CH₂)₉O(CH₂)₁--; -(CH₂)₉S(CH₂)₁--; or -(CH₂)₉NR₅(CH₂)₂--; where R₅: H; or lower alkyl; or lower alkenyl; or lower alkoxy.

R₃: lower alkyl; or lower alkenyl; -(CH₂)₉OR₅ (where R₅: lower alkyl; or lower alkenyl); -(CH₂)₉SR₆ (where R₆: lower alkyl; or lower alkenyl); -(CH₂)₉NR₅R₇ (where R₅: H; or lower alkyl; or lower alkenyl; R₃: H; or lower alkyl; or R₃ and R₄ taken together form: -(CH₂)₂₆--; -(CH₂)₉O(CH₂)₁--; -(CH₂)₉S(CH₂)₁--; or -(CH₂)₉NR₅(CH₂)₂--; where R₅: H; or lower alkyl; or lower alkenyl; or lower alkoxy).

R₃ and R₅ taken together form: -(CH₂)₂₆--; -(CH₂)₉O(CH₂)₁--; -(CH₂)₉S(CH₂)₁--; or -(CH₂)₉NR₅(CH₂)₂--; where R₅: H; or lower alkyl; or lower alkenyl; or lower alkoxy.

R₃: lower alkyl; or lower alkenyl; -(CH₂)₉OR₅ (where R₅: lower alkyl; or lower alkenyl); -(CH₂)₉SR₆ (where R₆: lower alkyl; or lower alkenyl); -(CH₂)₉NR₅R₇ (where R₅: H; or lower alkyl; or lower alkenyl; R₃: H; or lower alkyl; or R₃ and R₄ taken together form: -(CH₂)₂₆--; -(CH₂)₉O(CH₂)₁--; -(CH₂)₉S(CH₂)₁--; or -(CH₂)₉NR₅(CH₂)₂--; where R₅: H; or lower alkyl; or lower alkenyl; or lower alkoxy).

R₃ and R₅ taken together form: -(CH₂)₂₆--; -(CH₂)₉O(CH₂)₁--; -(CH₂)₉S(CH₂)₁--; or -(CH₂)₉NR₅(CH₂)₂--; where R₅: H; or lower alkyl; or lower alkenyl; or lower alkoxy.

R₃: lower alkyl; or lower alkenyl; -(CH₂)₉OR₅ (where R₅: lower alkyl; or lower alkenyl); -(CH₂)₉SR₆ (where R₆: lower alkyl; or lower alkenyl); -(CH₂)₉NR₅R₇ (where R₅: H; or lower alkyl; or lower alkenyl; R₃: H; or lower alkyl; or R₃ and R₄ taken together form: -(CH₂)₂₆--; -(CH₂)₉O(CH₂)₁--; -(CH₂)₉S(CH₂)₁--; or -(CH₂)₉NR₅(CH₂)₂--; where R₅: H; or lower alkyl; or lower alkenyl; or lower alkoxy).
NR^{20}CO\text{lower alkyl} (R^{26}=H; or lower alkyl); -(CH_2)_nCOOR^{57} (where R^{57}: lower alkyl; or lower alkenyl);
-(CH_2)_nCONR^{58}R^{59} (where R^{58}: lower alkyl, or lower alkenyl; and R^{59}: H; lower alkyl; or R^{58} and R^{59} taken together form: -(CH_2)_2=O; -(CH_2)_2O(CH_2)_2; -(CH_2)_2S(CH_2)_2; or -(CH_2)_2NR^{57}(CH_2)_2; where R^{57}: H; or lower alkyl); -(CH_2)_nPO(OR^{60})_2 (where R^{60}: lower alkyl; or lower alkenyl); -(CH_2)_nSO_2R^{62} (where R^{62}: lower alkyl; or lower alkenyl); or -(CH_2)_nC_6H_4R^{8} (where R^{8}: H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).

R^{66}: lower alkyl; lower alkenyl; -(CH_2)_nOR^{55} (where R^{55}: lower alkyl; or lower alkenyl); -(CH_2)_nSR^{56} (where R^{56}: lower alkyl; or lower alkenyl); -(CH_2)_nNR^{53}R^{34} (where R^{33}: lower alkyl; or lower alkenyl; R^{34}: H; or lower alkyl; or R^{33} and R^{34} taken together form:
-(CH_2)_2=O; -(CH_2)_2O(CH_2)_2; -(CH_2)_2S(CH_2)_2; or -(CH_2)_2NR^{57}(CH_2)_2; where R^{57}: H; or lower alkyl); -(CH_2)_nOCONR^{53}R^{75} (where R^{53}: H; or lower alkyl; or lower alkenyl; R^{75}: lower alkyl; or R^{33} and R^{75} taken together form: -(CH_2)_2=O; -(CH_2)_2O(CH_2)_2; or -(CH_2)_2S(CH_2)_2; or -(CH_2)_2NR^{57}(CH_2)_2; where R^{57}: H; or lower alkyl); -(CH_2)_nNRR^{62} (where R^{62}: H; or lower alkyl; or R^{33} and R^{62} taken together form: -(CH_2)_2=O; -(CH_2)_2O(CH_2)_2; -(CH_2)_2S(CH_2)_2; or -(CH_2)_2NR^{57}(CH_2)_2; where R^{57}: H; or lower alkyl); -(CH_2)_nNR^{57}(CH_2)_2; where R^{57}: H; or lower alkyl); -(CH_2)_nOR^{60} (where R^{60}: lower alkyl; or lower alkenyl); -(CH_2)_nSO_2R^{62} (where R^{62}: lower alkyl; or lower alkenyl); or -(CH_2)_nC_6H_4R^{8} (where R^{8}: H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).

R^{77}: lower alkyl; lower alkenyl; -(CH_2)_nOR^{55} (where R^{55}: lower alkyl; or lower alkenyl); -(CH_2)_nSR^{56} (where R^{56}: lower alkyl; or lower alkenyl); -(CH_2)_nNR^{53}R^{34} (where R^{33}: lower alkyl; or lower alkenyl; R^{34}: H; or lower alkyl; or R^{33} and R^{34} taken together form:
-(CH_2)_2=O; -(CH_2)_2O(CH_2)_2; -(CH_2)_2S(CH_2)_2; or -(CH_2)_2NR^{57}(CH_2)_2; where R^{57}: H; or lower alkyl); -(CH_2)_nOCONR^{53}R^{75} (where R^{53}: H; or lower alkyl; or lower alkenyl; R^{75}: lower alkyl; or R^{33} and R^{75} taken together form: -(CH_2)_2=O; -(CH_2)_2O(CH_2)_2; or -(CH_2)_2S(CH_2)_2; or
-(CH₂)₂NR⁵⁷(CH₂)₂--; where R⁵⁷: H; or lower alkyl; -(CH₂)₂NR⁻⁵⁸(CONR⁻³³⁻⁵⁸⁻⁸² (where R⁻²⁰: H; or lower lower alkyl; R⁻³³: H; or lower alkyl; or lower alkenyl; R⁻⁸²: H; or lower alkyl; or R⁻³³ and R⁻⁸² taken together form: -(CH₂)₂⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻˓


Thus, for the purposes of the present invention templates \((a1)\) can also consist of \(-\text{A70-CO-}\) to \(\text{A104-CO-}\) where building block \(\text{A70}\) to \(\text{A104}\) is of either (D)- or (L)-configuration, in combination with a building block \(-\text{B-CO-}\) of (L)-configuration.

Preferred values for \(R^{20}\) in \(\text{A70}\) to \(\text{A104}\) are H or lower alkyl with methyl being most preferred. Preferred values for \(R^{18}, R^{19}\) and \(R^{21}\) to \(R^{29}\) in building blocks \(\text{A70}\) to \(\text{A104}\) are the following:

- \(R^{18}\): lower alkyl.
- \(R^{19}\): lower alkyl; lower alkenyl; \(-(\text{CH}_2)_p OR^{55}\) (where \(R^{55}\): lower alkyl; or lower alkenyl); \(-(\text{CH}_2)_p SR^{56}\) (where \(R^{56}\): lower alkyl; or lower alkenyl); \(-(\text{CH}_2)_p NR^{33}R^{34}\) (where \(R^{33}\): lower alkyl; or lower alkenyl; \(R^{34}\): H; or lower alkyl; or \(R^{33}\) and \(R^{34}\) taken together

form:
-(CH₂)₂₆⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR₇⁻(CH₂)₂⁻; where R₇⁻: H; or lower alkyl; -(CH₂)₇pOCONR₃²⁵R₇⁵ (where R₃³: H; or lower alkyl; or lower alkenyl; R₇⁵: lower alkyl; or R₃³ and R₇⁵ taken together form: -(CH₂)₂₆⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; (CH₂)₂; or

- (CH₂)₂NR₇⁻(CH₂)₂⁻; where R₇⁻: H; or lower alkyl; -(CH₂)₇pNR²⁰CONR₃¹⁵R₆² (where R²⁰: H; or lower lower alkyl; R₃¹: H; or lower alkyl; or lower alkenyl; R₆²: H; or lower alkyl; or R₃¹ and R₆² taken together form: -(CH₂)₂₆⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR₇⁻(CH₂)₂⁻; where R₇⁻: H; or lower alkyl; -(CH₂)₇pN(R²⁵)COR₆⁴ (where: R²⁵: H; or lower alkyl; or R₆⁴: lower alkyl; or lower alkenyl); -(CH₂)₂pCOOR₅⁷ (where R₅⁷: lower alkyl; or lower alkenyl); -(CH₂)₂pCONR₅⁸R₅⁹ (where R₅⁸: lower alkyl; or lower alkenyl; and R₅⁹: H; or lower alkyl; or R₅⁸ and R₅⁹ taken together form: -(CH₂)₂₆⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or (CH₂)₂pPO(O₆⁰)₂ (where R₆⁰: lower alkyl; or lower alkenyl); -(CH₂)₂pSO₂R₆² (where R₆²: lower alkyl; or lower alkenyl); or -(CH₂)₂C₆H₄R₅ (where R₅: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

= R²¹: H; lower alkyl; lower alkenyl; -(CH₂)₇pOR₅⁵ (where R₅⁵: lower alkyl; or lower alkenyl); -(CH₂)₇pSR₅⁶ (where R₅⁶: lower alkyl; or lower alkenyl); -(CH₂)₇pNR₃²⁵R₃⁴ (where R₃³: lower alkyl; or lower alkenyl; R₃⁴: H; or lower alkyl; or R₃³ and R₃⁴ taken together form:

-(CH₂)₂₆⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR₇⁻(CH₂)₂⁻; where R₇⁻: H; or lower alkyl; -(CH₂)₂OCH₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂OCH₂⁻; -(CH₂)₂S(CH₂)₂⁻; where R₇⁻: H; or lower alkyl; -(CH₂)₂NR₇⁻(CH₂)₂⁻; where R₇⁻: H; or lower alkyl; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR₇⁻(CH₂)₂⁻; where R₇⁻: H; or lower alkyl; -(CH₂)₂pN(R²⁵)COR₆⁴ (where: R²⁵: H; or lower alkyl; or R₆⁴: lower alkyl; or lower alkenyl); -(CH₂)₂pCOOR₅⁷ (where R₅⁷: lower alkyl; or lower alkenyl); -(CH₂)₂pCONR₅⁸R₅⁹ (where R₅⁸: lower alkyl; or lower alkenyl; and R₅⁹: H; or lower alkyl; or R₅⁸ and R₅⁹ taken together form: -(CH₂)₂₆⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or (CH₂)₂pPO(O₆⁰)₂ (where R₆⁰: lower alkyl; or lower alkenyl); -(CH₂)₂pSO₂R₆² (where R₆²: lower alkyl; or lower alkenyl); or -(CH₂)₂C₆H₄R₅ (where R₅: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
- $R^{22}$: lower alkyl; lower alkenyl; -(CH$_2$)$_n$OR$^{55}$ (where R$^{55}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_n$SR$^{56}$ (where R$^{56}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_n$NR$^{33}$R$^{24}$ (where R$^{33}$: lower alkyl; or lower alkenyl; R$^{34}$: H; or lower alkyl; or R$^{33}$ and R$^{34}$ taken together form:

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- (CH$_2$)$_{2,6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: H; or lower alkyl); -(CH$_2$)$_2$OCONR$^{33}$R$^{75}$ (where R$^{33}$: H; or lower alkyl; or lower alkenyl; R$^{75}$: lower alkyl; or R$^{33}$ and R$^{75}$ taken together form: -(CH$_2$)$_{2,6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: H; or lower alkyl); -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: H; or lower alkyl; or lower alkenyl; -(CH$_2$)$_2$NR$^{20}$CONR$^{33}$R$^{82}$ (where R$^{20}$: H; or lower alkyl; or lower alkenyl; R$^{33}$: H; or lower alkyl; or lower alkenyl; R$^{82}$: H; or lower alkyl; or R$^{33}$ and R$^{82}$ taken together form: -(CH$_2$)$_{2,6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: H; or lower alkyl); -(CH$_2$)$_2$N(R$^{20}$)COR$^{64}$ (where: R$^{20}$: H; or lower alkyl; R$^{64}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_2$COOR$^{57}$ (where R$^{57}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_2$CONR$^{58}$R$^{59}$ (where R$^{58}$: lower alkyl; or lower alkenyl; and R$^{59}$: H; lower alkyl; or R$^{58}$ and R$^{59}$ taken together form: -(CH$_2$)$_{2,6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: H; or lower alkyl); -(CH$_2$)$_2$CONR$^{58}$R$^{59}$ (where R$^{58}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_2$OR$^{55}$ (where R$^{55}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_2$S$^{56}$ (where R$^{56}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_2$NR$^{33}$R$^{34}$ (where R$^{33}$: lower alkyl; or lower alkenyl; R$^{34}$: H; or lower alkyl; or R$^{33}$ and R$^{34}$ taken together form:

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- (CH$_2$)$_{2,6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: H; or lower alkyl); -(CH$_2$)$_2$OCONR$^{33}$R$^{75}$ (where R$^{33}$: H; or lower alkyl; or lower alkenyl; R$^{75}$: lower alkyl; or R$^{33}$ and R$^{75}$ taken together form: -(CH$_2$)$_{2,6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: H; or lower alkyl); -(CH$_2$)$_2$COOR$^{57}$ (where R$^{57}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_2$CONR$^{58}$R$^{59}$ (where R$^{58}$: lower alkyl; or lower alkenyl; and R$^{59}$: H; lower alkyl; or R$^{58}$ and R$^{59}$ taken together form: -(CH$_2$)$_{2,6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: H; or lower alkyl); -(CH$_2$)$_2$NR$^{20}$CONR$^{33}$R$^{82}$ (where R$^{20}$: H; or lower alkyl; or lower alkenyl; R$^{33}$: H; or lower alkyl; or lower alkenyl; R$^{82}$: H; or lower alkyl; or R$^{33}$ and R$^{82}$ taken together form: -(CH$_2$)$_{2,6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: H; or lower alkyl); -(CH$_2$)$_2$NR$^{20}$CONR$^{33}$R$^{82}$ (where R$^{20}$: H; or lower alkyl; or lower alkenyl; R$^{33}$: H; or lower alkyl; or lower alkenyl; R$^{82}$: H; or lower alkyl; or R$^{33}$ and R$^{82}$ taken together form: -(CH$_2$)$_{2,6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: H; or lower alkyl); -(CH$_2$)$_2$N(R$^{20}$)COR$^{64}$ (where: R$^{20}$: H; or lower alkyl; R$^{64}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_2$COOR$^{57}$ (where R$^{57}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_2$CONR$^{58}$R$^{59}$ (where R$^{58}$: lower alkyl; or lower alkenyl; and R$^{59}$: H; lower alkyl; or
R^{38} and R^{39} taken together form: -\((\text{CH}_2)_{2}O\((\text{CH}_2)_{2}\)=; -\((\text{CH}_2)_{2}S\((\text{CH}_2)_{2}\)=; or
-\((\text{CH}_2)_{2}NR^{57}(\text{CH}_2)_{2}\)=; where R^{57}: H; or lower alkyl; -\((\text{CH}_2)_{2}PO(\text{OR}^{60})_{2}\)= (where R^{60}: lower alkyl; or lower alkenyl); -\((\text{CH}_2)_{2}SO_{2}R^{62}\) (where R^{62}: lower alkyl; or lower alkenyl); or
-\((\text{CH}_2)_{2}C_{6}H_{4}R^{8}\) (where R^{8}: H; F; Cl; CF_{3}; lower alkyl; lower alkenyl; or lower alkoxy);

- R^{54}: lower alkyl; lower alkenyl; -\((\text{CH}_2)_{2}OR^{55}\) (where R^{55}: lower alkyl; or lower alkenyl); -\((\text{CH}_2)_{2}SR^{56}\) (where R^{56}: lower alkyl; or lower alkenyl); -\((\text{CH}_2)_{2}NR^{33}R^{24}\) (where R^{33}: lower alkyl; or lower alkenyl; R^{24}: H; or lower alkyl; or R^{33} and R^{24} taken together form:
-\((\text{CH}_2)_{2}O\((\text{CH}_2)_{2}\)=; -\((\text{CH}_2)_{2}S\((\text{CH}_2)_{2}\)=; or
-\((\text{CH}_2)_{2}NR^{57}(\text{CH}_2)_{2}\)=; where R^{57}: H; or lower alkyl; -\((\text{CH}_2)_{2}OCONR^{33}R^{75}\) (where R^{33}: H; or lower alkyl; or lower alkenyl; R^{75}: lower alkyl; or R^{33} and R^{75} taken together form: -\((\text{CH}_2)_{2}O\((\text{CH}_2)_{2}\)=; -\((\text{CH}_2)_{2}S\((\text{CH}_2)_{2}\)=; or
-\((\text{CH}_2)_{2}NR^{57}(\text{CH}_2)_{2}\)=; where R^{57}: H; or lower alkyl; -\((\text{CH}_2)_{2}NR^{20}CONR^{33}R^{82}\) (where R^{20}: H; or lower alkyl; R^{33}: H; or lower alkenyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -\((\text{CH}_2)_{2}O\((\text{CH}_2)_{2}\)=; -\((\text{CH}_2)_{2}O\((\text{CH}_2)_{2}\)=; -\((\text{CH}_2)_{2}S\((\text{CH}_2)_{2}\)=; or
-\((\text{CH}_2)_{2}NR^{57}(\text{CH}_2)_{2}\)=; where R^{57}: H; or lower alkyl; -\((\text{CH}_2)_{2}NR^{20}CO\((\text{CH}_2)_{2}\)=; or lower alkyl; -\((\text{CH}_2)_{2}COOR^{57}\) (where R^{57}: lower alkyl; or lower alkenyl); -\((\text{CH}_2)_{2}CONR^{58}R^{59}\) (where R^{58}: lower alkyl, or lower alkenyl; and R^{59}: H; lower alkyl; or R^{58} and R^{59} taken together form: -\((\text{CH}_2)_{2}O\((\text{CH}_2)_{2}\)=; -\((\text{CH}_2)_{2}S\((\text{CH}_2)_{2}\)=; or
-\((\text{CH}_2)_{2}NR^{57}(\text{CH}_2)_{2}\)=; where R^{57}: H; or lower alkyl; -\((\text{CH}_2)_{2}PO(\text{OR}^{50})_{2}\) (where R^{50}: lower alkyl; or lower alkenyl; -\((\text{CH}_2)_{2}SO_{2}R^{62}\) (where R^{62}: lower alkyl; or lower alkenyl); or
-\((\text{CH}_2)_{2}C_{6}H_{4}R^{8}\) (where R^{8}: H; F; Cl; CF_{3}; lower alkyl; lower alkenyl; or lower alkoxy);

- R^{25}: lower alkyl; lower alkenyl; -\((\text{CH}_2)_{2}OR^{55}\) (where R^{55}: lower alkyl; or lower alkenyl); -\((\text{CH}_2)_{2}NR^{33}R^{24}\) (where R^{33}: lower alkyl; or lower alkenyl; R^{24}: H; or lower alkyl; or R^{33} and R^{24} taken together form: -\((\text{CH}_2)_{2}O\((\text{CH}_2)_{2}\)=; -\((\text{CH}_2)_{2}S\((\text{CH}_2)_{2}\)=; or
-\((\text{CH}_2)_{2}NR^{57}(\text{CH}_2)_{2}\)=; where R^{57}: H; or lower alkyl; -\((\text{CH}_2)_{2}OCONR^{33}R^{75}\) (where R^{33}: H; or lower alkyl; or lower alkenyl; R^{75}: lower alkyl; or R^{33} and R^{75} taken together form: -\((\text{CH}_2)_{2}O\((\text{CH}_2)_{2}\)=; -\((\text{CH}_2)_{2}S\((\text{CH}_2)_{2}\)=; or
-\((\text{CH}_2)_{2}NR^{57}(\text{CH}_2)_{2}\)=; where R^{57}: H; or lower alkyl; -\((\text{CH}_2)_{2}NR^{20}CONR^{33}R^{82}\) (where R^{20}: H; or lower alkyl; R^{33}: H; or lower alkenyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -\((\text{CH}_2)_{2}O\((\text{CH}_2)_{2}\)=; -\((\text{CH}_2)_{2}S\((\text{CH}_2)_{2}\)=; or
-\((\text{CH}_2)_{2}NR^{57}(\text{CH}_2)_{2}\)=; where R^{57}: H; or lower alkyl;
alkyl;  
-(CH₂)ₙN(R²⁰)COR⁶⁴ (where: R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl);  
-(CH₂)ₙCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl); -(CH₂)ₙCNR⁵⁸R⁵⁹ (where R⁵⁸: lower alkyl; or lower alkenyl; and R⁵⁹: H; lower alkyl; or R⁵⁸ and R⁵⁹ taken together form: -
-(CH₂)₂₋₄₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷: H; or lower alkyl; -(CH₂)ₙPO(OR⁶⁰) (where R⁶⁰: lower alkyl; or lower alkenyl); -
(CH₂)ₙSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or -(CH₂)ₙC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

R²⁶: H; lower alkyl; lower alkenyl; -(CH₂)ₙOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl); -(CH₂)ₙNR²⁴R⁴⁴ (where R²⁴: lower alkyl; or lower alkenyl; R⁴⁴: H; or lower alkyl; or R²⁴ and R⁴⁴ taken together form: -(CH₂)₂₋₄₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; or
-(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷: H; or lower alkyl); -(CH₂)ₙOCONR⁵⁵R²¹ (where R⁵⁵: H; or lower alkyl; or lower alkenyl; R²¹: lower alkyl; or lower alkenyl; or lower alkoxy).

R⁷⁵: lower alkyl; or R⁵⁵ and R⁷⁵ taken together form: -(CH₂)₂₋₄₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷: H; or lower alkyl; -(CH₂)ₙNR²⁰CONR⁵⁵R⁸² (where R²⁰: H; or lower alkyl; R⁸²: H; or lower alkyl; or lower alkenyl; R⁵⁵: lower alkyl; or lower alkenyl; or lower alkoxy).

R⁸²: H; or lower alkyl; or R⁵⁵ and R⁸² taken together form: -(CH₂)₂₋₄₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷: H; or lower alkyl; -(CH₂)ₙN(R²⁰)COR⁶⁴(where: R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl); -(CH₂)ₙCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl); -(CH₂)ₙCNR⁵⁸R⁵⁹ (where R⁵⁸: lower alkyl; or lower alkenyl; and R⁵⁹: H; lower alkyl; or R⁵⁸ and R⁵⁹ taken together form:
-(CH₂)₂₋₄₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷: H; or lower alkyl); -(CH₂)ₙPO(OR⁶⁰) (where R⁶⁰: lower alkyl; or lower alkenyl); -
(CH₂)ₙSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or -(CH₂)ₙC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

Alternatively, R²⁵ and R²⁶ taken together can be -(CH₂)₂₋₄₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷: H; or lower alkyl).

R⁷⁷: H; lower alkyl; lower alkenyl; -(CH₂)ₙOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl); -(CH₂)ₙS⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl); -(CH₂)ₙNR³⁵R³⁴ (where R³⁵: lower alkyl; or lower alkenyl; R³⁴: H; or lower alkyl; or R³⁵ and R³⁴ taken together
form:

\(-\text{(CH}_2\text{)}_2\text{-}^6\); \(-\text{(CH}_2\text{)}_2\text{O(}\text{CH}_2\text{)}_2\); \(-\text{(CH}_2\text{)}_2\text{S(}\text{CH}_2\text{)}_2\); or \(-\text{(CH}_2\text{)}_2\text{NR}^{57}\text{(}\text{CH}_2\text{)}_2\); where \(R^{57}\): H; or lower alkyl); \(-\text{(CH}_2\text{)}_2\text{OCONR}^{33}\text{R}^{75}\) (where \(R^{33}\): H; or lower alkyl; or lower alkenyl; \(R^{75}\): lower alkyl; or \(R^{33}\) and \(R^{75}\) taken together form: \(-\text{(CH}_2\text{)}_{2-6}; \text{-}\text{(CH}_2\text{)}_2\text{O(}\text{CH}_2\text{)}_2\); -

\(-\text{(CH}_2\text{)}_2\text{S(}\text{CH}_2\text{)}_2\); or

\(-\text{(CH}_2\text{)}_2\text{NR}^{57}\text{(}\text{CH}_2\text{)}_2\); where \(R^{57}\): H; or lower alkyl); \(-\text{(CH}_2\text{)}_2\text{NR}^{20}\text{CONR}^{33}\text{R}^{82}\) (where \(R^{20}\); H; or lower lower alkyl; \(R^{33}\): H; or lower alkyl; or lower alkenyl; \(R^{82}\): H; or lower alkyl; or \(R^{33}\) and \(R^{82}\) taken together form: \(-\text{(CH}_2\text{)}_{2-6}; \text{-}\text{(CH}_2\text{)}_2\text{O(}\text{CH}_2\text{)}_2\); -\(\text{(CH}_2\text{)}_2\text{S(}\text{CH}_2\text{)}_2\); or

\(-\text{(CH}_2\text{)}_2\text{NR}^{57}\text{(}\text{CH}_2\text{)}_2\); where \(R^{57}\): H; or lower alkyl); \(-\text{(CH}_2\text{)}_2\text{N(}R^{20}\text{)}\text{COR}^{64}\) (where: \(R^{20}\): H; or lower alkyl; \(R^{64}\): lower alkyl; or lower alkenyl); \(-\text{(CH}_2\text{)}_2\text{COOR}^{37}\) (where \(R^{37}\): lower alkyl; or lower alkenyl); \(-\text{(CH}_2\text{)}_2\text{CONR}^{58}\text{R}^{59}\) (where \(R^{58}\): lower alkyl; or lower alkenyl; and \(R^{59}\): H; lower alkyl; or \(R^{58}\) and \(R^{59}\) taken together form: \(-\text{(CH}_2\text{)}_{2-6}; \text{-}\text{(CH}_2\text{)}_2\text{O(}\text{CH}_2\text{)}_2\); -\(\text{(CH}_2\text{)}_2\text{S(}\text{CH}_2\text{)}_2\); or \(-\text{(CH}_2\text{)}_2\text{NR}^{57}\text{(}\text{CH}_2\text{)}_2\); where \(R^{57}\): H; or lower alkyl); \(-\text{(CH}_2\text{)}_2\text{S(}\text{CH}_2\text{)}_2\); or

\(-\text{(CH}_2\text{)}_2\text{NR}^{57}\text{(}\text{CH}_2\text{)}_2\); where \(R^{57}\): H; or lower alkyl); \(-\text{(CH}_2\text{)}_2\text{NR}^{20}\text{CONR}^{33}\text{R}^{82}\) (where \(R^{20}\); H; or lower lower alkyl; \(R^{33}\): H; or lower alkyl; or lower alkenyl; \(R^{82}\): H; or lower alkyl; or \(R^{33}\) and \(R^{82}\) taken together form: \(-\text{(CH}_2\text{)}_{2-6}; \text{-}\text{(CH}_2\text{)}_2\text{O(}\text{CH}_2\text{)}_2\); -\(\text{(CH}_2\text{)}_2\text{S(}\text{CH}_2\text{)}_2\); or

\(-\text{(CH}_2\text{)}_2\text{NR}^{57}\text{(}\text{CH}_2\text{)}_2\); where \(R^{57}\): H; or lower alkyl); \(-\text{(CH}_2\text{)}_2\text{N(}R^{20}\text{)}\text{COR}^{64}\) (where: \(R^{20}\): H; or lower alkyl; \(R^{64}\): lower alkyl; or lower alkenyl); \(-\text{(CH}_2\text{)}_2\text{COOR}^{37}\) (where \(R^{37}\): lower alkyl; or lower alkenyl); or \(-\text{(CH}_2\text{)}_2\text{O}_4\text{H}_4\text{R}^{8}\) (where \(R^{8}\): H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

\(-\text{R}^{20}\): lower alkyl; lower alkenyl; \(-\text{(CH}_2\text{)}_2\text{OR}^{55}\) (where \(R^{55}\): lower alkyl; or lower alkenyl); \(-\text{(CH}_2\text{)}_2\text{SR}^{59}\) (where \(R^{56}\): lower alkyl; or lower alkenyl); \(-\text{(CH}_2\text{)}_2\text{NR}^{33}\text{R}^{14}\) (where \(R^{33}\): lower alkyl; or lower alkenyl; \(R^{14}\): H; or lower alkyl; or \(R^{33}\) and \(R^{14}\) taken together form

\(-\text{(CH}_2\text{)}_{2-6}; \text{-}\text{(CH}_2\text{)}_2\text{O(}\text{CH}_2\text{)}_2\); -\(\text{(CH}_2\text{)}_2\text{S(}\text{CH}_2\text{)}_2\); or

\(-\text{(CH}_2\text{)}_2\text{NR}^{57}\text{(}\text{CH}_2\text{)}_2\); where \(R^{57}\): H; or lower alkyl); \(-\text{(CH}_2\text{)}_2\text{NR}^{20}\text{CONR}^{33}\text{R}^{82}\) (where \(R^{20}\); H; or lower lower alkyl; \(R^{33}\): H; or lower alkyl; or lower alkenyl; \(R^{82}\): H; or lower alkyl; or \(R^{33}\) and \(R^{82}\) taken together form: \(-\text{(CH}_2\text{)}_{2-6}; \text{-}\text{(CH}_2\text{)}_2\text{O(}\text{CH}_2\text{)}_2\); -\(\text{(CH}_2\text{)}_2\text{S(}\text{CH}_2\text{)}_2\); or

\(-\text{(CH}_2\text{)}_2\text{NR}^{57}\text{(}\text{CH}_2\text{)}_2\); where \(R^{57}\): H; or lower alkyl); \(-\text{(CH}_2\text{)}_2\text{N(}R^{20}\text{)}\text{COR}^{64}\) (where: \(R^{20}\): H; or lower alkyl; \(R^{64}\): lower alkyl; or lower alkenyl); \(-\text{(CH}_2\text{)}_2\text{COOR}^{37}\) (where \(R^{37}\): lower alkyl; or lower alkenyl); or \(-\text{(CH}_2\text{)}_2\text{O}_4\text{H}_4\text{R}^{8}\) (where \(R^{8}\): H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
\[-R^{29}: \text{lower alkyl}; \text{lower alkenyl}; -(\text{CH}_2)_3\text{OR}^{55} \text{ (where } R^{55}: \text{lower alkyl}; \text{or lower alkenyl}); -(\text{CH}_2)_3\text{SR}^{56} \text{ (where } R^{56}: \text{lower alkyl}; \text{or lower alkenyl}); -(\text{CH}_2)_3\text{NR}^{33}R^{34} \text{ (where } R^{33}: \text{lower alkyl}; \text{or lower alkenyl}; R^{34}: H; \text{or lower alkyl}; \text{or } R^{33} \text{ and } R^{34} \text{ taken together form: }
\]
\[-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_2; \text{or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2; \text{ where } R^{57}: H; \text{or lower alkyl}); -(\text{CH}_2)_2\text{OCONR}^{33}R^{75} \text{ (where } R^{33}: H; \text{or lower alkyl}; \text{or lower alkenyl}; R^{75}: \text{lower alkyl}; \text{or } R^{33} \text{ and } R^{75} \text{ taken together form: } -(\text{CH}_2)_2\text{O}^{65}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_2; \text{ or }
\]
\[-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2; \text{ where } R^{57}: H; \text{or lower alkyl}); -(\text{CH}_2)_3\text{NR}^{20}\text{CONR}^{33}R^{82} \text{ (where } R^{20}: H; \text{or lower alkyl); } R^{23}: H; \text{or lower alkyl}; \text{or lower alkenyl}; R^{82}: H; \text{or lower alkyl}; \text{or } R^{33} \text{ and } R^{82} \text{ taken together form: } -(\text{CH}_2)_2\text{O}^{65}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_2; \text{ or }
\]
\[-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2; \text{ where } R^{57}: H; \text{or lower alkyl}); -(\text{CH}_2)_3\text{N}(\text{R}^{20})\text{COR}^{64}(\text{where } R^{20}: H; \text{or lower alkyl); } R^{84}: \text{lower alkyl; or lower alkenyl); particularly favored are }
\]
\[-\text{NR}^{20}\text{CO} \text{lower-alkyl} (R^{20}=\text{H; or lower alkyl); } -(\text{CH}_2)_3\text{COOR}^{57} \text{ (where } R^{57}: \text{lower alkyl; or lower alkenyl); }
\]
\[-(\text{CH}_2)_2\text{CONR}^{58}R^{59} \text{ (where } R^{58}: \text{lower alkyl, or lower alkenyl; and } R^{59}: H; \text{lower alkyl; or } R^{58} \text{ and } R^{59} \text{ taken together form: } -(\text{CH}_2)_2\text{O}^{65}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_2; \text{ or }
\]
\[-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2; \text{ where } R^{57}: H; \text{or lower alkyl); -(\text{CH}_2)_3\text{PO}^{60} \text{ (where } R^{60}: \text{lower alkyl; or lower alkenyl); } -(\text{CH}_2)_3\text{SO}^{62} \text{ (where } R^{62}: \text{lower alkyl; or lower alkenyl); or }
\]
\[-(\text{CH}_2)_3\text{CH}_2R^{8} \text{ (where } R^{8}: \text{H; F; Cl; CF}_3; \text{lower alkyl; lower alkenyl; or lower alkoxy).}
\]

The preferred value for } R^{23}, R^{24} \text{ and } R^{29} \text{ is } -\text{NR}^{20}-\text{CO} \text{-lower alkyl where } R^{20} \text{ is } H \text{ or lower alkyl.}

For templates (b) to (p), such as (b1) and (l), the preferred values for the various symbols are the following:

\[-R^{1}: H; \text{or lower Alkyl; }
\]
\[-R^{5}: H; F; Cl; CF_3; \text{lower alkyl; lower alkenyl; -(CH}_2)_3\text{OR}^{55} \text{ (where } R^{55}: \text{lower alkyl; or lower alkenyl); -(CH}_2)_3\text{SR}^{56} \text{ (where } R^{56}: \text{lower alkyl; or lower alkenyl); }
\]
\[-(\text{CH}_2)_3\text{NR}^{33}R^{34} \text{ (where } R^{33}: \text{lower alkyl; or lower alkenyl; R}^{34}: H; \text{or lower alkyl; or } R^{33} \text{ and } R^{34} \text{ taken together form: } -(\text{CH}_2)_2\text{O}^{65}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_2; \text{ or }
\]
\[-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2; \text{ where } R^{57}: H; \text{or lower alkyl); -(\text{CH}_2)_3\text{OCONR}^{33}R^{75} \text{ (where } R^{33}: H; \text{or lower alkyl; or lower alkenyl; R}^{75}: \text{lower alkyl; or } R^{33} \text{ and } R^{75} \text{ taken together form: } -(\text{CH}_2)_2\text{O}^{65}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_2; \text{ or }
\]
\[-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2; \text{ where } R^{57}: H; \text{or lower alkyl).} \]
-(CH₂)ₙNR²⁰CONR³³R²⁸ (where R²⁰: H; or lower lower alkyl; R³³: H; or lower alkyl; or lower alkenyl; R²⁸: H; or lower alkyl; or R³³ and R²⁸ taken together form: -(CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷: H; or lower alkyl);
- \( R^{32} \): H, methyl.

- \( R^{31} \): lower alkyl; lower alkenyl; -(CH\(_2\)_\(_m\)OR\(^{55}\) (where \( R^{55} \): lower alkyl; or lower alkenyl); -(CH\(_2\)_\(_m\)NR\(^{34}\)R\(^{63}\) (where \( R^{34} \): lower alkyl; or lower alkenyl; \( R^{63} \): H; or lower alkyl; or \( R^{34} \) and \( R^{63} \) taken together form: -(CH\(_2\))\(_{2-6}\); -(CH\(_2\))\(_2\)O(CH\(_2\))\(_2\); -(CH\(_2\))\(_2\)S(CH\(_2\))\(_2\); or -(CH\(_2\))\(_2\)S(CH\(_2\))\(_2\); or

  or

  -(CH\(_2\))\(_m\)NR\(^{34}\)(CH\(_2\))\(_2\); where \( R^{57} \): H; or lower alkyl) ; (CH\(_2\))\(_m\)OCONR\(^{75}\)R\(^{82}\)(where \( R^{75} \): lower alkyl; or lower alkenyl; \( R^{82} \): H; or lower alkyl; or \( R^{75} \) and \( R^{82} \) taken together form: -(CH\(_2\))\(_{2-6}\); -(CH\(_2\))\(_2\)O(CH\(_2\))\(_2\); -(CH\(_2\))\(_2\)S(CH\(_2\))\(_2\); or -(CH\(_2\))\(_2\)NR\(^{34}\)(CH\(_2\))\(_2\); where \( R^{57} \): H; or lower alkyl);

- -(CH\(_2\))\(_m\)NR\(^{30}\)CONR\(^{78}\)R\(^{82}\) (where \( R^{20} \): H; or lower lower alkyl; \( R^{78} \): H; or lower alkyl; or lower alkenyl; \( R^{82} \): H; or lower alkyl; or \( R^{78} \) and \( R^{82} \) taken together form: -(CH\(_2\))\(_{2-6}\); -(CH\(_2\))\(_2\)O(CH\(_2\))\(_2\); -(CH\(_2\))\(_2\)S(CH\(_2\))\(_2\); or -(CH\(_2\))\(_2\)NR\(^{34}\)(CH\(_2\))\(_2\); where \( R^{57} \): H; or lower alkyl);

- -(CH\(_2\))\(_m\)N(R\(^{20}\))COR\(^{64}\) (where: \( R^{20} \): H; or lower alkyl; \( R^{64} \): lower alkyl; or lower alkenyl);

- -(CH\(_2\))\(_m\)COOR\(^{57}\) (where \( R^{57} \): lower alkyl; or lower alkenyl); -(CH\(_2\))\(_m\)CONR\(^{59}\)R\(^{39}\) (where \( R^{58} \): lower alkyl; or lower alkenyl; and \( R^{59} \): H; lower alkyl; or \( R^{58} \) and \( R^{59} \) taken together form:

  -(CH\(_2\))\(_{2-6}\); -(CH\(_2\))\(_2\)O(CH\(_2\))\(_2\); -(CH\(_2\))\(_2\)S(CH\(_2\))\(_2\); or -(CH\(_2\))\(_2\)NR\(^{34}\)(CH\(_2\))\(_2\); where \( R^{57} \): H; or lower alkyl).

- \( R^{44} \): H; or lower alkyl.

- \( R^{35} \): H; lower alkyl; lower alkenyl; -(CH\(_2\))\(_m\)OR\(^{55}\) (where \( R^{55} \): lower alkyl; or lower alkenyl); -(CH\(_2\))\(_m\)NR\(^{34}\)R\(^{63}\) (where \( R^{34} \): lower alkyl; or lower alkenyl; \( R^{63} \): H; or lower alkyl; or \( R^{34} \) and \( R^{63} \) taken together form: -(CH\(_2\))\(_{2-6}\); -(CH\(_2\))\(_2\)O(CH\(_2\))\(_2\); -(CH\(_2\))\(_2\)S(CH\(_2\))\(_2\); or

  or

  -(CH\(_2\))\(_2\)NR\(^{34}\)(CH\(_2\))\(_2\); where \( R^{57} \): H; or lower alkyl); -(CH\(_2\))\(_m\)OCONR\(^{33}\)R\(^{75}\) (where \( R^{35} \): H; or lower alkyl; or lower alkenyl; \( R^{75} \): lower alkyl; or \( R^{35} \) and \( R^{75} \) taken together form: -(CH\(_2\))\(_{2-6}\);

  -(CH\(_2\))\(_2\)O(CH\(_2\))\(_2\); -(CH\(_2\))\(_2\)S(CH\(_2\))\(_2\); or -(CH\(_2\))\(_2\)NR\(^{34}\)(CH\(_2\))\(_2\); where \( R^{57} \): H; or lower alkyl);

- -(CH\(_2\))\(_m\)NR\(^{20}\)CONR\(^{33}\)R\(^{82}\) (where \( R^{20} \): H; or lower lower alkyl; \( R^{33} \): H; or lower alkyl; or lower alkenyl; \( R^{82} \): H; or lower alkyl; or \( R^{33} \) and \( R^{82} \) taken together form: -(CH\(_2\))\(_{2-6}\);

  -(CH\(_2\))\(_2\)O(CH\(_2\))\(_2\); -(CH\(_2\))\(_2\)S(CH\(_2\))\(_2\); or -(CH\(_2\))\(_2\)NR\(^{34}\)(CH\(_2\))\(_2\); where \( R^{57} \): H; or lower alkyl);

- -(CH\(_2\))\(_m\)N(R\(^{20}\))COR\(^{64}\) (where: \( R^{20} \): H; or lower alkyl; \( R^{64} \): lower alkyl; or lower alkenyl);

- -(CH\(_2\))\(_m\)COOR\(^{57}\) (where \( R^{57} \): lower alkyl; or lower alkenyl); -(CH\(_2\))\(_m\)CONR\(^{58}\)R\(^{59}\) (where
R^{58}: lower alkyl; or lower alkenyl; and R^{59}: H; lower alkyl; or R^{58} and R^{59} taken together form:

- \((\text{CH}_2)_n\)-; \(-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\); \(-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\); or \(-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2\); where R^{57}: H; or lower alkyl).

- R^{56}: lower alkyl; lower alkenyl; or aryl-lower alkyl.

- \(R^{57}: \text{H; lower alkyl; lower alkenyl; -(CH}_2)_n\text{OR}^{55}\) (where R^{55}: lower alkyl; or lower alkenyl); -(CH)_2NR^{33}R^{34} (where R^{33}: lower alkyl; or lower alkenyl; R^{34}: H; or lower alkyl; or R^{33} and R^{34} taken together form: -(CH)_2O(CH}_2)_2; -(CH)_2O(CH}_2)_2; -(CH)_2S(CH}_2)_2; or -(CH)_2NR^{57}(CH}_2)_2; where R^{57}: H; or lower alkyl);

- (CH)_2NR^{33}CONR^{33}R^{82} (where R^{20}: H; or lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -(CH)_2O(CH}_2)_2; -(CH)_2O(CH}_2)_2; -(CH)_2S(CH}_2)_2; or -(CH)_2NR^{57}(CH}_2)_2; where R^{57}: H; or lower alkyl);

- (CH)_2NR^{33}CONR^{33}R^{82} (where R^{20}: H; or lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -(CH)_2O(CH}_2)_2; -(CH)_2O(CH}_2)_2; -(CH)_2S(CH}_2)_2; or -(CH)_2NR^{57}(CH}_2)_2; where R^{57}: H; or lower alkyl);

- (CH)_2R^{64}COR^{64} (where: R^{20}: H; or lower alkyl; R^{64}: lower alkyl; or lower alkenyl); -(CH)_2COOR^{27} (where R^{57}: lower alkyl; or lower alkenyl); -(CH)_2CONR^{38}R^{39} (where R^{58}: lower alkyl; or lower alkenyl; and R^{59}: H; lower alkyl; or R^{58} and R^{59} taken together form:

- -(CH)_2O(CH}_2)_2; -(CH)_2O(CH}_2)_2; -(CH)_2S(CH}_2)_2; or -(CH)_2NR^{57}(CH}_2)_2; where R^{57}: H; or lower alkyl); -(CH)_2PO(OR^{60})_2 (where R^{60}: lower alkyl; or lower alkenyl); -(CH)_2SO_R^{62} (where R^{58}: lower alkyl; or lower alkenyl); or -(CH)_2CO_H; (where R^{8}: H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).

- R^{38}: H; lower alkyl; lower alkenyl; -(CH)_2OR^{55} (where R^{55}: lower alkyl; or lower alkenyl); -(CH)_2NR^{33}R^{34} (where R^{33}: lower alkyl; or lower alkenyl; R^{34}: H; or lower alkyl; or R^{33} and R^{34} taken together form: -(CH)_2O(CH}_2)_2; -(CH)_2O(CH}_2)_2; -(CH)_2S(CH}_2)_2; or -(CH)_2NR^{57}(CH}_2)_2; where R^{57}: H; or lower alkyl);

- (CH)_2CONR^{38}R^{39} (where R^{20}: H; or lower lower alkyl; R^{38}: H; or lower alkyl; or lower alkenyl; R^{38}: H; or lower alkyl; or R^{33} and R^{38} taken together form: -(CH)_2O(CH}_2)_2; -(CH)_2O(CH}_2)_2; -(CH)_2S(CH}_2)_2; or -(CH)_2NR^{57}(CH}_2)_2; where R^{57}: H; or lower alkyl);

- (CH)_2CONR^{38}R^{39} (where R^{20}: H; or lower lower alkyl; R^{38}: H; or lower alkyl; or lower alkenyl; R^{38}: H; or lower alkyl; or R^{33} and R^{38} taken together form: -(CH)_2O(CH}_2)_2;
(CH₂)₂O(CH₂)₂⁻; (CH₂)₂S(CH₂)₂⁻; or (CH₂)₂NR₅⁷(CH₂)₂⁻; where R₅⁷: H; or lower alkyl;

-(CH₂)₂N(R²⁰)COR₆⁴ (where: R²⁰: H; or lower alkyl; R₆⁴: lower alkyl; or lower alkenyl);

-(CH₂)₂COOR₅⁷ (where R₅⁷: lower alkyl; or lower alkenyl); -(CH₂)₂CONR₈⁸R₉⁰ (where R₈⁸: lower alkyl; or lower alkenyl); and R₉⁰: H; lower alkyl; or R₈⁸ and R₉⁰ taken together form:

-(CH₂)₂⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR₅⁷(CH₂)₂⁻; where R₅⁷: H; or lower alkyl; -(CH₂)₂PO(OCH₆₆)₂ (where R₆₆: lower alkyl; or lower alkenyl);

-(CH₂)₂SO₂R₆² (where R₆²: lower alkyl; or lower alkenyl); or -(CH₂)₃C₆H₄R₈ (where R₈: H; F; Cl; CF₃; lower alkyl; or lower alkenyl; or lower alkoxy).

-R₉⁰: lower alkyl; or lower alkenyl; -(CH₂)ₙOR₅⁵ (where R₅⁵: lower alkyl; or lower alkenyl); -(CH₂)ₙN(R²⁰)COR₆⁴ (where: R²⁰: H; or lower alkyl; R₆⁴: lower alkyl; or lower alkenyl); -(CH₂)ₙCOOR₅⁷ (where R₅⁷: lower alkyl; or lower alkenyl); -(CH₂)ₙCONR₈⁸R₉⁰ (where R₈⁸: lower alkyl; or lower alkenyl); and R₉⁰: H; lower alkyl; or R₈⁸ and R₉⁰ taken together form: -(CH₂)₂⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR₅⁷(CH₂)₂⁻; where R₅⁷: H; or lower alkyl).

-R₆²: lower alkyl; or lower alkenyl; or aryl-lower alkyl.

-R₆⁴: H; or lower alkyl; lower alkenyl; -(CH₂)ₙOR₅⁵ (where R₅⁵: lower alkyl; or lower alkenyl); -(CH₂)ₙNR₃₃R₃₄ (where R₃₃: lower alkyl; or lower alkenyl; R₃₄: H; or lower alkyl; or R₃₃ and R₃₄ taken together form: -(CH₂)₂⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR₅⁷(CH₂)₂⁻; where R₅⁷: H; or lower alkyl);

-(CH₂)ₙNR₅⁷(CH₂)₂⁻; where R₅⁷: H; or lower alkyl); -(CH₂)ₙOCOCONR₃₃R₇⁵ (where R₃₃: H; or lower alkyl; or lower alkenyl; R₇⁵: lower alkyl; or R₃₃ and R₇⁵ taken together form: -(CH₂)₂⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR₅⁷(CH₂)₂⁻; where R₅⁷: H; or lower alkyl);

-(CH₂)ₙCOOR₆⁴ (where: R²⁰: H; or lower alkyl; R₆⁴: lower alkyl; or lower alkenyl); -(CH₂)ₙCOO⁻ (where R₅⁷: lower alkyl; or lower alkenyl); -(CH₂)ₙCONR₈⁸R₉⁰ (where R₈⁸: lower alkyl; or lower alkenyl; and R₉⁰: H; lower alkyl; or R₈⁸ and R₉⁰ taken together form: -(CH₂)₂⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR₅⁷(CH₂)₂⁻; where R₅⁷: H; or lower alkyl);
lower alkyl; -(CH₂)₆PO(OR⁻)₂ (where R⁻: lower alkyl; or lower alkenyl); -(CH₂)₆SO₂R⁻ (where R⁻: lower alkyl; or lower alkenyl); or -(CH₂)₆C₆H₄R⁻ (where R⁻: H; F; Cl; CF₃; lower alkyl; or lower alkoxy).

- R⁻²⁻; H; lower alkyl; lower alkenyl; -(CH₂)₆OR⁻⁵⁻ (where R⁻⁵⁻: lower alkyl; or lower alkenyl); -(CH₂)₆NR⁻³⁻⁻⁵⁻ (where R⁻³⁻⁻⁵⁻: lower alkyl; or lower alkenyl); -(CH₂)₆NR⁻³⁻⁻⁴⁻ (where R⁻³⁻⁻⁴⁻: lower alkyl; or lower alkenyl); and R⁻³⁻⁻⁴⁻ took together form: -(CH₂)₂₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋_-
-(CH₂)₂NR²⁷(CH₂)₂⁻; where R²⁷: H; or lower alkyl; -(CH₂)ₙN(R²⁰⁰)COR⁶⁴ (where: R²⁰⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl); -(CH₂)ₙCOOR²⁷ (where R²⁷: lower alkyl; or lower alkenyl); -(CH₂)ₙCONR⁸₆R⁵⁹ (where R⁵⁹: lower alkyl; or lower alkenyl); and R⁸₆: H; lower alkyl; or R⁵⁹ and R⁸₆ taken together form: -(CH₂)₂₆₋⁻; -(CH₂)₂O(CH₂)₂⁻;

-(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR²⁷(CH₂)₂⁻; where R²⁷: H; or lower alkyl); -(CH₂)ₙPO(OH)⁶⁰₂⁻ (where R⁶⁰: lower alkyl; or lower alkenyl); -(CH₂)ₙSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or -(CH₂)ₙC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

- R⁴⁺: lower alkyl; lower alkenyl; -(CH₂)ₙOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl); -(CH₂)ₙSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl); -(CH₂)ₙNR³³R³⁴ (where R³³: lower alkyl; or lower alkenyl; R³⁴: H; or lower alkyl; or R³³ and R³⁴ taken together form: -(CH₂)₂₆₋⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR²⁷(CH₂)₂⁻; where R²⁷: H; or lower alkyl); -(CH₂)ₙNR²⁰⁰CONR³³R⁸₂ (where R²⁰⁰: H; or lower alkyl; R³³: H; or lower alkyl; or lower alkenyl; R⁸₂: H; or lower alkyl; or R³³ and R⁸₂ taken together form: -(CH₂)₂₆₋⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR²⁷(CH₂)₂⁻; where R²⁷: H; or lower alkyl); -(CH₂)ₙN(R²⁰⁰)COR⁶⁴ (where: R²⁰⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl); -(CH₂)ₙCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl); -(CH₂)ₙCONR⁵⁹R⁸₅ (where R⁵⁹: lower alkyl; or lower alkenyl; and R⁵⁹: H; lower alkyl; or R⁸₅ and R⁵⁹ taken together form: -(CH₂)₂₆₋⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR²⁷(CH₂)₂⁻; where R²⁷: H; or lower alkyl); or -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR²⁷(CH₂)₂⁻; where R²⁷: H; or lower alkyl); -(CH₂)ₙNR²⁰⁰CONR³³R⁸₂ (where R²⁰⁰: H; or lower alkyl; or lower alkenyl; and R⁵⁹: H; lower alkyl; or lower alkenyl; or R⁸₂ and R⁵⁹ taken together form: -(CH₂)₂₆₋⁻; -(CH₂)₂O(CH₂)₂⁻; -(CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR²⁷(CH₂)₂⁻; where R²⁷: H; or lower alkyl); or -(CH₂)ₙNR²⁵(CH₂)₂⁻; where R²⁵: H; or lower alkyl).
or $R^{53}$ and $R^{82}$ taken together form: -(CH$_2$)$_3$-; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where $R^{57}$: H; or lower alkyl); -(CH$_2$)$_3$N(R$^{20}$)COR$^{64}$ (where: $R^{20}$: H; or lower alkyl; $R^{64}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$COOR$^{57}$ (where $R^{57}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$CONR$^{58}$$^{59}$ (where $R^{58}$: lower alkyl; or lower alkenyl; and $R^{59}$: H; lower alkyl); or $R^{58}$ and $R^{59}$ taken together form: -(CH$_2$)$_3$-; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where $R^{57}$: H; or lower alkyl) or -(CH$_2$)$_3$C$_6$H$_4$R$^8$ (where $R^8$: H; F; Cl; CF$_3$; lower alkyl; lower alkenyl; or lower alkoxy).

- $R^{66}$: H; lower alkyl; lower alkenyl; -(CH$_2$)$_3$OR$^{55}$ (where $R^{55}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$SR$^{56}$ (where $R^{56}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$NR$^{55}$$^{56}$ (where $R^{55}$: lower alkyl; or lower alkenyl; and $R^{56}$: lower alkyl; or lower alkenyl; or lower alkoxy).

and $R^{33}$: lower alkyl; or lower alkenyl; $R^{34}$: H; or lower alkyl; or $R^{33}$ and $R^{34}$ taken together form:

-(CH$_2$)$_3$-; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where $R^{57}$: H; or lower alkyl); -(CH$_2$)$_3$OCONR$^{53}$$^{54}$ (where $R^{53}$: H; or lower alkyl; or lower alkenyl; and $R^{54}$: lower alkyl; or lower alkenyl; or lower alkoxy).

- $(CH_2)_3S(CH_2)_2$; or

-(CH$_2$)$_3$NR$^{57}$(CH$_2$)$_2$; where $R^{57}$: H; or lower alkyl); -(CH$_2$)$_3$NR$^{20}$CONR$^{33}$$^{52}$ (where $R^{20}$: H; or lower alkyl; or lower alkenyl; and $R^{33}$: H; or lower alkyl; or lower alkenyl; or lower alkoxy).

or $R^{33}$ and $R^{82}$ taken together form: -(CH$_2$)$_3$-; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_3$OCONR$^{53}$$^{54}$ (where $R^{53}$: H; or lower alkyl; or lower alkenyl; and $R^{54}$: lower alkyl; or lower alkenyl; or lower alkoxy).

-(CH$_2$)$_3$C$_6$H$_4$R$^8$ (where $R^8$: H; F; Cl; CF$_3$; lower alkyl; lower alkenyl; or lower alkoxy).

- $R^{77}$: H; or OR$^{55}$ (where $R^{55}$: lower alkyl; or lower alkenyl).

- $R^{66}$: H; or lower alkyl.

- $R^{69}$: H; lower alkyl; -(CH$_2$)$_3$COOR$^{57}$ (where $R^{57}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_3$CONR$^{58}$$^{59}$ (where $R^{58}$: lower alkyl; or lower alkenyl; and $R^{59}$: H; lower alkyl; or $R^{58}$ and $R^{59}$ taken together form: -(CH$_2$)$_3$-; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_3$NR$^{57}$(CH$_2$)$_2$; where $R^{57}$: H; or lower alkyl) or -(CH$_2$)$_3$C$_6$H$_4$R$^8$ (where $R^8$: H; F; Cl; CF$_3$; lower alkyl; lower alkenyl; or lower alkoxy).

- $R^{50}$: H; methyl.

- $R^{71}$: H; lower alkyl; lower alkenyl; -(CH$_2$)$_m$OR$^{55}$ (where $R^{55}$: lower alkyl; or lower alkenyl); -(CH$_2$)$_m$NR$^{33}$$^{34}$ (where $R^{33}$: lower alkyl; or lower alkenyl; and $R^{34}$: H; or lower alkyl; or $R^{33}$ and $R^{34}$ taken together form: -(CH$_2$)$_3$-; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$;
or

\[(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-}; \text{ where } R^{57}: \text{H} \text{ or lower alkyl}; (\text{CH}_2)_{\text{nOCONR}^{33}R^{75}} \text{ (where } R^{33}: \text{H}; \text{ or lower alkyl); or lower alkenyl; } R^{75}: \text{lower alkyl}; \text{ or } R^{33} \text{ and } R^{75} \text{ taken together form: } -(\text{CH}_2)_2\text{R}^{6};\]

\[5 -(\text{CH}_2)_2\text{O}(\text{CH}_2)_{2-}; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_{2-}; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-}; \text{ where } R^{57}: \text{H} \text{ or lower alkyl);}\]

\[-(\text{CH}_2)_{\text{nNR}^{26}\text{CONR}^{33}R^{82} \text{ (where } R^{20}: \text{H} \text{ or lower lower alkyl); } R^{33}: \text{H}; \text{ or lower alkyl; or lower alkenyl; } R^{82}: \text{H}; \text{ or lower alkyl; or } R^{33} \text{ and } R^{82} \text{ taken together form: } -(\text{CH}_2)_2\text{R}^{6};\]

\[-(\text{CH}_2)_2\text{O}(\text{CH}_2)_{2-}; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_{2-}; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-}; \text{ where } R^{57}: \text{H} \text{ or lower alkyl);}\]

\[-(\text{CH}_2)_{\text{mN}(R^{20})\text{COR}^{64} \text{ (where: } R^{20}: \text{H} \text{ or lower alkyl); } R^{64}: \text{ lower alkyl; or lower alkenyl); -(CH}_2)_{\text{pCOOR}^{57} \text{ (where } R^{57}: \text{lower alkyl; or lower alkenyl); -(CH}_2)_{\text{pCONR}^{38}R^{59} \text{ (where } R^{58}: \text{ lower alkyl; or lower alkenyl; and } R^{59}: \text{H}; \text{ lower alkyl; or } R^{58} \text{ and } R^{59} \text{ taken together form:}\]

\[10 -(\text{CH}_2)_2\text{R}^{6}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_{2-}; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_{2-}; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-}; \text{ where } R^{57}: \text{H} \text{ or lower alkyl);}\]

\[-(\text{CH}_2)_2\text{O}(\text{CH}_2)_{2-}; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_{2-}; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-}; \text{ where } R^{57}: \text{H} \text{ or lower alkoxy).}\]

\[- \quad R^{52}: \text{H}; \text{ lower alkyl; lower alkenyl; } -(\text{CH}_2)_{\text{mOR}^{55} \text{ (where } R^{55}: \text{ lower alkyl; or lower alkenyl); -(CH}_2)_{\text{mNR}^{33}R^{34} \text{ (where } R^{33}: \text{lower alkyl; or lower alkenyl; } R^{34}: \text{H}; \text{ or lower alkyl; or } R^{33} \text{ and } R^{34} \text{ taken together form: } -(\text{CH}_2)_2\text{R}^{6};\]

\[20 -(\text{CH}_2)_2\text{O}(\text{CH}_2)_{2-}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_{2-}; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_{2-}; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-}; \text{ where } R^{57}: \text{H}; \text{ or lower alkyl); -(CH}_2)_{\text{mOCONR}^{33}R^{75} \text{ (where } R^{33}: \text{H}; \text{ or lower alkyl; or lower alkenyl; } R^{75}: \text{lower alkyl; or } R^{33} \text{ and } R^{75} \text{ taken together form: } -(\text{CH}_2)_2\text{R}^{6};\]

\[-(\text{CH}_2)_2\text{O}(\text{CH}_2)_{2-}; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_{2-}; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-}; \text{ where } R^{57}: \text{H}; \text{ or lower alkyl);}\]

\[-(\text{CH}_2)_2\text{O}(\text{CH}_2)_{2-}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_{2-}; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_{2-}; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-}; \text{ where } R^{57}: \text{H}; \text{ or lower alkyl);}\]

\[-(\text{CH}_2)_{\text{nNR}^{20}\text{CONR}^{33}R^{82} \text{ (where } R^{20}: \text{H}; \text{ or lower lower alkyl); } R^{33}: \text{H}; \text{ or lower alkyl; or lower alkenyl; } R^{82}: \text{H}; \text{ or lower alkyl; or } R^{33} \text{ and } R^{82} \text{ taken together form: } -(\text{CH}_2)_2\text{R}^{6};\]

\[-(\text{CH}_2)_2\text{O}(\text{CH}_2)_{2-}; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_{2-}; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-}; \text{ where } R^{57}: \text{H}; \text{ or lower alkyl);}\]

\[-(\text{CH}_2)_{\text{mN}(R^{20})\text{COR}^{64} \text{ (where: } R^{20}: \text{H}; \text{ or lower alkyl; } R^{64}: \text{ lower alkyl; or lower alkenyl); -(CH}_2)_{\text{pCOOR}^{57} \text{ (where } R^{57}: \text{lower alkyl; or lower alkenyl); -(CH}_2)_{\text{pCONR}^{38}R^{59} \text{ (where } R^{58}: \text{ lower alkyl; or lower alkenyl; and } R^{59}: \text{H}; \text{ lower alkyl; or } R^{58} \text{ and } R^{59} \text{ taken together form:}\]

\[30 -(\text{CH}_2)_2\text{R}^{6}; -(\text{CH}_2)_2\text{O}(\text{CH}_2)_{2-}; -(\text{CH}_2)_2\text{S}(\text{CH}_2)_{2-}; \text{ or } -(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-}; \text{ where } R^{57}: \text{H}; \text{ or
lower alkyl), or -(CH₂)ₐC₆H₄Rₖ (where Rₖ: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

- R₃⁵: H; lower alkyl; lower alkenyl; -(CH₂)ₐOR₃⁵ (where R₃⁵: lower alkyl; or lower alkenyl); -(CH₂)ₐNR₃⁵R₃⁶ (where R₃⁵: lower alkyl; or lower alkenyl; R₃⁶: H; or lower alkyl; or R₃³ and R₃⁴ taken together form: -(CH₂)ₐ-O-(CH₂)₂O(CH₂)₂--; (CH₂)₂S(CH₂)₂--; or -(CH₂)₂NR₃⁵(CH₂)₂--; where R₃⁵: H; or lower alkyl); -(CH₂)ₐO(CH₂)₂--; -(CH₂)₂O(CH₂)₂--; (CH₂)₂S(CH₂)₂--; or -(CH₂)₂NR₃⁵(CH₂)₂--; where R₃⁵: H; or lower alkyl); -(CH₂)ₐNR₃⁵R₃⁶COR₃⁶ (where R₃⁶: H; or lower alkyl; or lower alkenyl; R₃₆: H; or lower alkyl; or lower alkenyl; R₃₆: H; or lower alkyl; or R₃₃ and R₃₄ taken together form: -(CH₂)₂-O--; -(CH₂)₂O(CH₂)₂--; (CH₂)₂S(CH₂)₂--; or -(CH₂)₂NR₃⁵(CH₂)₂--; where R₃⁵: H; or lower alkyl); -(CH₂)ₐN-(CH₂)₂COR₃⁶ (where: R₃⁶: H; or lower alkyl; R₆: lower alkyl; or lower alkenyl); -(CH₂)ₐCOOR₃⁶ (where: R₃⁶: lower alkyl; or lower alkenyl); -(CH₂)ₐCONR₃⁶R₃⁷ (where R₃⁶: lower alkyl; or lower alkenyl; and R₃⁷: H; lower alkyl; or R₃₈ and R₃₉ taken together form: -(CH₂)₂-O--; -(CH₂)₂O(CH₂)₂--; (CH₂)₂S(CH₂)₂--; or -(CH₂)₂NR₃⁵(CH₂)₂--; where R₃⁵: H; or lower alkyl); -(CH₂)ₐC₆H₄Rₖ (where Rₖ: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

- R₄₄: lower alkyl; lower alkenyl; or aryl-lower alkyl.

Most preferably R¹ is H; R²₀ is H; R₃⁰ is H; R₃¹ is carboxymethyl; or lower alkoxy carbonylmethyl; R₃² is H; R₃₅ is methyl; R₃₆ is methoxy; R₃⁷ is H and R₃₈ is H.

Among the building blocks A₇₀ to A₁₄ the following are preferred: A₇₄ with R₂² being H, A₇₅, A₇₆, A₇₇ with R₂² being H, A₇₈ and A₇₉.

The building block -B-COO- within templates (a₁), (a₂) and (a₃) designates an L-amino acid residue. Preferred values for B are: -NR₃⁸CH(R₇¹)- and enantiomers of groups A₅ with R² being H, A₈, A₂₂, A₂₅, A₃₈ with R² being H, A₄₂, A₄₇, and A₅₀. Most preferred are

- Ala: L-Alanine
- Arg: L-Arginine
<p>| | | |</p>
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<td>Phe(pC(NH$_2$)=NH)</td>
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<td>Phe(mNHC(NH$_2$)=NH)</td>
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<tr>
<td>Phe(pNHC(NH$_2$)=NH)</td>
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<tr>
<td>2-Nal</td>
<td>L-2-Naphthylalanine</td>
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</table>
1-Nal   L-1-Naphthylalanine
4Cl-Phe L-4-Chlorophenylalanine
3Cl-Phe L-3-Chlorophenylalanine
2Cl-Phe L-2-Chlorophenylalanine

3,4Cl₂-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-Thiazollylalanine
Mso     L-Methionine sulfoxide
AcLys   L-N-Acetylysine

Dpr     L-2,3-Diaminopropionic acid
A₂Bu    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-Pipeolic acid
OctG    L-Octylglycine
MePhe   L-N-Methylphenylalanine
MeNle   L-N-Methylnorleucine

MeAla   L-N-Methylalanine
In addition, the most preferred values for B also include groups of type A8" of (L)-configuration:

![Chemical Structure](image)

wherein R^{20} is H or lower alkyl and R^{64} is alkyl; alkenyl; -[(CH\_2)_n-X]_m-CH\_3 (where X is -O-, -NR^{20}, or -S-, u is 1-3 and t is 1-6), aryl; aryl-lower alkyl; or heteroaryl-lower alkyl; especially those wherein R^{64} is n-hexyl (A8"^21); n-heptyl (A8"^22); 4-(phenyl)benzyl (A8"^23); diphenylmethyl (A8"^24); 3-amino-propyl (A8"^25); 5-amino-pentyl (A8"^26); methyl (A8"^27); ethyl (A8"^28); isopropyl (A8"^29); isobutyl (A8"^30); n-propyl (A8"^31); cyclohexyl (A8"^32); cyclohexymethyl (A8"^33); n-butyl (A8"^34); phenyl (A8"^35); benzyl (A8"^36); (3-indolyl) methyl (A8"^37); 2-(3-indolyl)ethyl (A8"^38); (4-phenyl)phenyl (A8"^39); n-nonyl (A8"^40); CH\_2-OCH\_2CH\_2-OCH\_2 (A8"^41) and CH\_2(OCH\_2CH\_2)_2-OCH\_2 (A8"^42).

The peptidic chain Z of the \(\beta\)-hairpin mimetics described herein is generally defined in terms of amino acid residues belonging to one of the following groups:

- Group C \(-NR^{20}CH(R^{72})CO_2-\) "hydrophobic: small to medium-sized"
- Group D \(-NR^{20}CH(R^{73})CO_2-\) "hydrophobic: large aromatic or heteroaromatic"
- Group E \(-NR^{20}CH(R^{74})CO_2-\) "polar-cationic" and "urea-derived"
- Group F \(-NR^{20}CH(R^{84})CO_2-\) "polar-non-charged or anionic"
- Group H \(-NR^{20}CH(CO-)-(CH\_2)_n-CH(CO-)NR^{20}elia; \-NR^{20}CH(CO-)-(CH\_2)_nSS(CH\_2)_n-CH(CO-)NR^{20}elia; \-NR^{20}CH(CO-)-(CH\_2)_nNR^{20}CO(CH\_2)_n-CH(CO-)NR^{20}; and \-NR^{20}CH(CO-)-(CH\_2)_nNR^{20}CONR^{20}(CH\_2)_n-CH(CO-)NR^{20}elia; "interstrand linkage"
Furthermore, the amino acid residues in chain Z can also be of formula -A-CO- or of formula -B-CO- wherein A and B are as defined above. Finally, Gly can also be an amino acid residue in chain Z, and Pro and Pro(4-NHCO-Phe) can be amino acid residues in chain Z, too, with the exception of positions where an interstrand linkage (H) is possible.

Group C comprises amino acid residues with small to medium-sized hydrophobic side chain groups according to the general definition for substituent R\textsuperscript{72}. A hydrophobic residue refers to an amino acid side chain that is uncharged at physiological pH and that is repelled by aqueous solution. Furthermore these side chains generally do not contain hydrogen bond donor groups, such as (but not limited to) primary and secondary amides, primary and secondary amines and the corresponding protonated salts thereof, thiols, alcohols, phosphonates, phosphates, ureas or thioureas. However, they may contain hydrogen bond acceptor groups such as ethers, thioethers, esters, tertiary amides, alkyl- or aryl phosphonates and phosphates, or tertiary amines. Genetically encoded small-to-medium-sized amino acids include alanine, isoleucine, leucine, methionine and valine.

Group D comprises amino acid residues with aromatic and heteroaromatic side chain groups according to the general definition for substituent R\textsuperscript{73}. An aromatic amino acid residue refers to a hydrophobic amino acid having a side chain containing at least one ring having a conjugated \pi-electron system (aromatic group). In addition they may contain hydrogen bond donor groups such as (but not limited to) primary and secondary amides, primary and secondary amines and the corresponding protonated salts thereof, thiols, alcohols, phosphonates, phosphates, ureas or thioureas, and hydrogen bond acceptor groups such as (but not limited to) ethers, thioethers, esters, tertiary amides, alkyl- or aryl phosphonates and phosphates, or tertiary amines. Genetically encoded aromatic amino acids include phenylalanine and tyrosine.

A heteroaromatic amino acid residue refers to a hydrophobic amino acid having a side chain containing at least one ring having a conjugated \pi-system incorporating at least one heteroatom such as (but not limited to) O, S and N according to the general definition for substituent R\textsuperscript{77}. In addition such residues may contain hydrogen bond donor groups such as (but not limited to) primary and secondary amides, primary and secondary amines and the corresponding protonated salts thereof, thiols, alcohols, phosphonates, phosphates, ureas or thioureas, and hydrogen bond acceptor groups such as (but not limited to) ethers, thioethers, esters, tertiary amides, alkyl- or aryl phosphonates and phosphates, or tertiary
amines. Genetically encoded heteroaromatic amino acids include tryptophan and histidine.

**Group E** comprises amino acids containing side chains with polar-cationic, acylamino- and urea-derived residues according to the general definition for substituent R^{74}. Polar-cationic refers to a basic side chain which is protonated at physiological pH. Genetically encoded polar-cationic amino acids include arginine, lysine and histidine. Citrulline is an example for an urea derived amino acid residue.

**Group F** comprises amino acids containing side chains with polar-non-charged or anionic residues according to the general definition for substituent R^{84}. A polar-non-charged or anionic residue refers to a hydrophilic side chain that is uncharged and, respectively anionic at physiological pH (carboxylic acids being included), but that is not repelled by aqueous solutions. Such side chains typically contain hydrogen bond donor groups such as (but not limited to) primary and secondary amides, carboxylic acids and esters, primary and secondary amines, thiols, alcohols, phosphonates, phosphates, ureas or thioureas. These groups can form hydrogen bond networks with water molecules. In addition they may also contain hydrogen bond acceptor groups such as (but not limited to) ethers, thioethers, esters, tertiary amides, carboxylic acids and carboxylates, alkyl- or aryl phosphonates and phosphates, or tertiary amines. Genetically encoded polar-non-charged amino acids include asparagine, cysteine, glutamine, serine and threonine, but also aspartic acid and glutamic acid.

**Group H** comprises side chains of preferably (L)-amino acids at opposite positions of the β-strand region that 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 Penninger 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. A well established interstrand linkage consists in linking ornithines and lysines, respectively, with glutamic and aspartic acid residues located at opposite β-strand positions by means of an amide bond formation. Preferred
protective groups for the side chain amino-groups of ornithine and lysine are allyloxycarbonyl (Alloc) and allylesters for aspartic and glutamic acid. Finally, interstrand linkages can also be established by linking the amino groups of lysine and ornithine located at opposite β-strand positions with reagents such as N,N-carbonylimidazole to form cyclic ureas.

As mentioned earlier, positions for an interstrand linkage are positions P2 and 10, 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:

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<th>one letter code</th>
<th>three letter code</th>
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<td>L-Serine</td>
<td>Ser</td>
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</tbody>
</table>
Thr | L-Threonine | T  
Trp | L-Tryptophan | W  
Tyr | L-Tyrosine | Y  
Val | L-Valine | V  

5

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

Cit | L-Citrulline  
Orn | L-Ornithine  
10 tBuA | L-t-Butylalanine  
Sar | Sarcosine  
Pen | L-Penicillamine  
t-BuG | L-tert.-Butylglycine  
4AmPhe | L-para-Aminophenylalanine  

15 3AmPhe | L-meta-Aminophenylalanine  
2AmPhe | L-ortho-Aminophenylalanine  
Phe(mC(NH$_2$)=NH) | L-meta-Aminophenylalanine  
Phe(pC(NH$_2$)=NH) | L-para-Aminophenylalanine  
Phe(mNHC(NH$_2$)=NH) | L-meta-Guanidinophenylalanine  

20 Phe(pNHC(NH$_2$)=NH) | L-para-Guanidinophenylalanine  
Phg | L-Phenylglycine  
Cha | L-Cyclohexylalanine  
C$_4$al | L-3-Cyclobutylalanine  
C$_5$al | L-3-Cyclopentylalanine  

25 Nle | L-Norleucine  
2-Nal | L-2-Naphthylalanine  
1-Nal | L-1-Naphthylalanine  

4Cl-Phe | L-4-Chlorophenylalanine  
3Cl-Phe | L-3-Chlorophenylalanine  

30 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  

35 Tic | 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
Thi L-β-2-Thi(en)alanine
Tza L-2-Thiazolylalanine
Mso L-Methionine sulfoxide
AcLys N-Acetyllysine

5
Dpr 2,3-Diaminopropionic acid
A$_2$Bu 2,4-Diaminobutyric acid
Dbu (S)-2,3-Diaminobutyric acid
Abu γ-Aminobutyric acid (GABA)
Aha ε-Aminohexanoic acid

10
Aib α-Aminoisobutyric acid
Y(Bzl) L-O-Benzyltyrosine
Bip L-(4-phenyl)phenylalanine
S(Bzl) L-O-Benzylserine
T(Bzl) L-O-Benzylthreonine

15
hCha L-Homo-cyclohexylalanine
hCys L-Homo-cysteine
hSer L-Homo-serine
hArg L-Homo-arginine
hPhe L-Homo-phenylalanine

20
Bpa L-4-Benzoylphenylalanine
4-AmPyrr1 (2S,4S)-4-Amino-pyrrolidine-L-carboxylic acid
4-AmPyrr2 (2S,4R)-4-Amino-pyrrolidine-L-carboxylic acid
4-PhePyrr1 (2S,5R)-4-Phenyl-pyrrolidine-L-carboxylic acid
4-PhePyrr2 (2S,5S)-4-Phenyl-pyrrolidine-L-carboxylic acid

25
5-PhePyrr1 (2S,5R)-5-Phenyl-pyrrolidine-L-carboxylic acid
5-PhePyrr2 (2S,5S)-5-Phenyl-pyrrolidine-L-carboxylic acid
Pro(4-OH)$_1$ (4S)-L-Hydroxyproline
Pro(4-OH)$_2$ (4R)-L-Hydroxyproline
Pip L-Pipeolic acid

30
$^p$Pip D-Pipeolic acid
OctG L-Octylglycine
NGly N-Methylglycine
MePhe L-N-Methylphenylalanine
MeNle L-N-Methylnorleucine

35
MeAla L-N-Methylalanine
64

MeIle  L-N-Methylisoleucine
MeVal  L-N-Methylvaline
MeLeu  L-N-Methylleucine
DimK  L-(N',N'-Dimethyl)-lysine

5  Lpzp  L-Piperazinic acid
Dpzp  D-Piperazinic acid
Isorn  L-(N', N'-diisobutyryl)-ornithine
PipAla  L-2-(4'-piperidinyl)-alanine
PirrAla  L-2-(3'-pyrrolidinyl)-alanine

10  Ampc  4-Amino-piperidine-4-carboxylic acid
NMeR  L-N-Methylarginine
NMeK  L-N-Methyllysine
NMePhe  L-N-Methylphenylalanine

IPegK  L-2-Amino-6-{2-[2-(2-methoxy-ethoxy)ethoxy]acetylamo}no-hexanoic acid

15

S PegK  L-2-Amino-6-[2-(2-methoxy-ethoxy)acetylamin]o-hexanoic acid

Dab  L-2,4-Diamino-butyrlic acid

IPegDab  L-2-Amino-4{2-[2-(2-methoxy-ethoxy)-ethoxy]acetylamin}o-butyrlic acid

20

S PegDab  L-2-Amino-4[2-(2-methoxy-ethoxy)-acetylamin]o-butyrlic acid

4-PyrAla  L-2-(4'-Pyridinyl)-alanine

OrnPyr  L-2-Amino-5-{[2’ carbonylpyrazine]amino}pentanoic acid

25

BnG  N-Benzylglycine

AlloT  Allo-Threonin

Pro(4NHCO Phe)  (2S)-4-benzamido-pyrrolidine-2-carboxylic acid

30

Aoc  2-(S)-Amino-octanoic acid

Particularly preferred residues for group C are:

35

Ala  L-Alanine
Ile  L-Isoleucine
Leu  L-Leucine

Met  L-Methionine
Val  L-Valine

5
tBuA  L-t-Butylalanine
t-BuG  L-tert.-Butylglycine
Cha  L-Cyclohexylalanine

C₄al  L-3-Cyclobutylalanine
C₅al  L-3-Cyclopentylalanine
Nle  L-Norleucine
hCha  L-Homo-cyclohexylalanine
OctG  L-Octylglycine

10
MePhe  L-N-Methylphenylalanine
MeNle  L-N-Methylnorleucine
MeAla  L-N-Methylalanine
MeLe  L-N-Methylisoleucine
MeVal  L-N-Methylvaline

15
MeLeu  L-N-Methylleucine
Aoc  2-(S)-Aminooccanoic acid

Particularly preferred residues for group D are:

His  L-Histidine

Phe  L-Phenylalanine
Trp  L-Tryptophan
Tyr  L-Tyrosine
Phg  L-Phenylglycine
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

3,4Cl₂-Phe  L-3,4-Dichlorophenylalanine

4F-Phe  L-4-Fluorophenylalanine
3F-Phe  L-3-Fluorophenylalanine
2F-Phe  L-2-Fluorophenylalanine

Thi  L-β-2-Thienylalanine
Tza  L-2-Thiazolylalanine

35
Y(Bzl)  L-O-Benzyltyrosine
Bip  L-Biphenylalanine
S(Bzl)  L-O-Benzylserine
T(Bzl)  L-O-Benzylthreonine
hPhe  L-Homo-phenylalanine
5  Bpa  L-4-Benzoylphenylalanine
PirrAla  L-2-(3'-pyrrolidinyl)-alanine
NMMePhe  L-N-Methylphenylalanine
4-PyrAla  L-2-(4'-Pyridyl)-alanine

10  Particularly preferred residues for group E are

    Arg  L-Arginine
    Lys  L-Lysine
    Orn  L-Ornithine
15  Dpr  L-2,3-Diaminopropionic acid
    A2Bu  L-2,4-Diaminobutyric acid
    Dbu  \(\text{(S)-2,3-Diaminobutyric acid}\)
    Phe(pNH2)  L-para-Aminophenylalanine
    Phe(mNH2)  L-meta-Aminophenylalanine
20  Phe(oNH2)  L-ortho-Aminophenylalanine
    hArg  L-Homo-arginine
    Phe(mC(NH2)=NH)  L-meta-Aminophenylalanine
    Phe(pC(NH2)=NH)  L-para-Aminophenylalanine
    Phe(mNHC(NH2)=NH)  L-meta-Guanidinophenylalanine
25  Phe(pNHC(NH2)=NH)  L-para-Guanidinophenylalanine
    DimK  L-(N',N'-Dimethyl)-lysine
    Isorn  L-(N',N'-diisobutyl)-ornithine
    NMMeR  L-N-Methylarginine
    NMMeK  L-N-Methyllysine
30  IPegK  L-2-Amino-6-{2-[2-(methoxy-ethoxy)ethoxy]acetylamino}-hexanoic acid
    SPegK  L-2-Amino-6-{2-[2(methoxy-ethoxy)-acetylamino]-hexanoic acid
    Dab  L-2,4-Diamino-buteric acid
35  IPegDab  L-2-Amino-4{2-[2-(methoxy-ethoxy)-ethoxy]-
acetylamino)-butyric acid

SPEGDAB  L-2-Amino-4-[2-(2-methoxy-ethoxy)-acetylamino] butyric acid

ORNPYR  L-2-Amino-5-[2'-carbonylpyrazine]amino-

pentanoic

PipAla  L-2-(4'-piperidinyl)-alanine

Particularly preferred residues for group F are

<table>
<thead>
<tr>
<th>10</th>
<th>Asn</th>
<th>L-Asparagine</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Asp</td>
<td>L-Aspartic acid</td>
</tr>
<tr>
<td>10</td>
<td>Cys</td>
<td>L-Cysteine</td>
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<tr>
<td>10</td>
<td>Gln</td>
<td>L-Glutamine</td>
</tr>
<tr>
<td>10</td>
<td>Glu</td>
<td>L-Glutamic acid</td>
</tr>
<tr>
<td>15</td>
<td>Ser</td>
<td>L-Serine</td>
</tr>
<tr>
<td>15</td>
<td>Thr</td>
<td>L-Threonine</td>
</tr>
<tr>
<td>15</td>
<td>AlloThr</td>
<td>Allo Threonine</td>
</tr>
<tr>
<td>15</td>
<td>Cit</td>
<td>L-Citrulline</td>
</tr>
<tr>
<td>15</td>
<td>Pen</td>
<td>L-Penicillamine</td>
</tr>
<tr>
<td>20</td>
<td>AcLys</td>
<td>L-N(^{\circ})-Acetylylsine</td>
</tr>
<tr>
<td>20</td>
<td>hCys</td>
<td>L-Homo-cysteine</td>
</tr>
<tr>
<td>20</td>
<td>hSer</td>
<td>L-Homo-serine</td>
</tr>
</tbody>
</table>

25 Generally, the peptidic chain Z within the \(\beta\)-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 the templates (b)-(p), or of group -B-CO- in template (a1), or of group -A-CO- in template (a2), or of the group -B-CO- forming the C-terminus of template (a3); and P11 represents the last amino acid in the chain Z that is coupled with its C-terminus to the N-terminus of the templates (b)-(p), or of group -A-CO- in template (a1), or of group -B-CO- in template (a2), or of the group -B-CO- forming the N-terminus of template (a3). Each of the positions P1 to P11 will preferably contain an amino acid residue belonging to one of the above types C, D, E, F,
H, or of formula -A-CO- or of formula -B-CO-, or being Gly, Pro or Pro(4NHCOPhe) as follows:

In general the α-amino acid residues in positions 1 to 11 of the chain Z are preferably:

- P1: of type C, or of type D, or of type E, or of type F;
- P2: of type E, or of type F, or of type C;
- P3: or of type C, of type F or the residue is Gly;
- P4: of type C, or of type E, or of type F, or the residue is Gly or Pro;
- P5: of type E, or of type F, or the residue is Gly or Pro;
- P6: of type C, or of type D, or of type F, or the residue is Gly or Pro;
- P7: of type F or of formula -A-CO- or the residue is Gly or Pro;
- P8: of type D, or of type C, or of formula -A-CO- or the residue is Gly or Pro or Pro(4NHCOPhe);
- P9: of type C, or of type D, or of type E, or of type F;
- P10: of type F, or of type C, or type E;
- P11: of type E, or of type F, or of type C or of type D; or
- P2 and P10, taken together, form a group of type H;

with the proviso that if template is $^{D}$Pro-$^{L}$Pro the amino acid residues in positions

P1 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
- P7: Pro
- P8: Pro
- P9: Ile
- P10: Cys, linked with Cys in position P10 by a disulfide bridge; and
- P11: Phe.

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, 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.

For inhibitors of Cathepsin G the α-amino acid residues in positions 1 to 11 of the chain Z are preferably:
P1: of type C, or of type D, or of type E;
P2: of type F, or of type C;
P3: of type F;
P4: of type C, or of type E;
P5: of type E, or of type F;
P6: of type F;
P7: of type F, or of formula -A-CO-, or the residue is Gly or Pro;
P8: of type C, or of formula -A-CO-, or the residue is Gly or Pro or
Pro(4NHCOPhe);
P9: of type C, or of type D, or of type F;
P10: of type F, or of type C, or type E;
P11: of type E, or of type D, or of type F; or
P2 and P10, taken together, form a group of type H.

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, Arg, Trp, 2Cl-Phe, Arg, 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 of the chain Z are preferably
P1: of type C, or of type D;
P2: of type F;
P3: of type F or of type C;
P4: of type C or of type F;
P5: of type F;
P6: of type C;
P7: of formula –A-CO– or the residue is Gly or Pro;
P8: of formula –A-CO or the residue is Gly or Pro or Pro(4NHCOPhe);
P9: of type D, or of type F or of type C;
P10: of type F, or of type C, or type E;
P11: of type E, or of type F, or of type D; or
P2 and P10, taken together, form a group of type H.

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, 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.

10 For inhibitors of Tryptase the α-amino acid residues in positions 1 to 11 of the chain Z are preferably:
- P1: of type C, or of type D, or of type E;
- P2: of type F;
- P3: of type F;
- P4: of type E;
- P5: of type F;
- P6: of type C, or of type D;
- P7: of type F, or of formula -A-CO-, or the residue is Gly or Pro;
- P8: of type C, or of formula -A-CO-, or the residue is Gly or Pro;
- P9: of type C, or of type E, or of type F;
- P10: of type F;
- P11: of type E, or of type D; or
- P2 and P10, taken together, form a group of type H;
with the proviso that if the template is D-Pro L-Pro, the amino acid residues in positions P1 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
- P7: Pro
- P8: Pro
- P9: Ile
- P10 Cys, linked with Cys in position P10 by a disulfide bridge; and
For inhibitors of Tryptase the \(\alpha\)-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 \(\beta\)-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, 121, 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 \(\beta\)-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\textsuperscript{8}); and polyacrylamide resins (see also Obrecht, D.; Villalgordo, J.-M, "Solid- Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight..."

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-methylbenzydylamine PS resin (Rink amide MBHA PS Resin), and 4-[((2,4-dimethoxyphenyl)Fmoc-aminomethyl)phenoxyacetamido] aminomethyl] benzhydylamine 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\textsuperscript{R} linker), 4-(2,4-dimethoxyphenyl-hydroxymethyl)-phenoxy (Rink linker), 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid (HMPB linker), trityl and 2-chlorotryptyl. Preferably, the support is derived from polystyrene crosslinked with, most preferably 1-5%, divinylbenzene and functionalized by means of the 2-chlorotryptyl 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® 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 & Rink, 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 benzylxycarbonyl
- Boc tert.-butyloxycarbonyl
- Fmoc 9-fluorenylmethoxycarbonyl

5
- Alloc allyloxycarbonyl
- Teoc trimethylsilylthoxycarbonyl
- Tcc trichloroethoxycarbonyl
- Nps o-nitrophenylsulfonyl;
- Trt triphenylmethoxy 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

15
- Tse trimethylsilylethyl
- Tce trichloroethyl;

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

25
- Pmc 2,2,5,7,8-pentamethylchroman-6-sulfonyl
- Ts tosyl (i.e. p-toluenesulfonyl)
- Cbz benzylxycarbonyl
- Pbf pentamethyldihydrobenzofuran-5-sulfonyl

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

30
- tBu tert.-butyl
- Bn benzyl
- Trt trityl

35
and for the mercapto group (as is present e.g. in the side-chain of cysteine)

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acm</td>
<td>acetamidomethyl</td>
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<tr>
<td>tBu</td>
<td>tert.-butyl</td>
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<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Trt</td>
<td>trityl</td>
</tr>
<tr>
<td>Mtr</td>
<td>4-methoxytrityl</td>
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</tbody>
</table>

The 9-fluorenylethoxycarbonyl- (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 benzo triazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP, Castro et al., Tetrahedron Lett. 1975, 14, 1219-1222; Synthesis, 1976, 751-752), or benzo triazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (Py-BOP, Coste et al., Tetrahedron Lett. 1990, 31, 205-208), or 2-(1H-benzo triazol-1-yl)-1,1,3,3-tetram ethyluronium tetrafluoroborate (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 diphen ox yphosphoryl azide (DPPA) or O-(7-aza-benzo triazol-1-yl)-N,N,N',N'-tetram ethyluronium tetrafluoroborate (TATU) or O-(7-aza-benzo triazol-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 CH₂Cl₂, 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. For the formation of pegylated amino acids such as IPegK, or SPegK, preferably a solution of 5 equivalents of HATU (N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide) in dry DMF and a solution of 10 equivalents of DIPEA (Diisopropyl ethylamine) in dry DMF and 5 equivalents of 2-[2-(2-methoxyethoxy)ethoxy] acetic acid (IPeg) and, respectively, 2-(2-methoxyethoxy)acetic acid (sPeg), is applied to the liberated amino group of the appropriate amino acid side chain for 3 h. The procedure is thereafter repeated for another 3h with a fresh solution of reagents after filtering and washing the resin.
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 made regarding groups of the type H 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 CH₂Cl₂/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 NaHCO₃ 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$_2$O, 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 pulmonary 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, atherosclerosis, psoriasis, 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 auxiliaries 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, trichlorofluoromethane, 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 pepididimetics 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 peptidodimetics 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 peptidodimetics 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-tetramethyluronium hexafluorophosphate
  (Knorr et al. Tetrahedron Lett. 1989, 30, 1927-1930);
HOBt: 1-hydroxybenzotriazole;
DIEA: diisopropylethylamine;
HOAT: 7-aza-1-hydroxybenzotriazole;
Examples

1. Peptide synthesis

5  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 CH₂Cl₂ (2.5 ml) and allowed to swell at room temperature under constant stirring for 30 min. The resin was treated with 0.415 mMol (1 eq) of the first suitably protected amino acid residue (see below) and 284 µl (4 eq) of diisopropylethylamine (DIEA) in CH₂Cl₂ (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 (CH₂Cl₂ : MeOH : DIEA : 17/2/1), 30 ml for 30 min; then washed in the following order with CH₂Cl₂ (1x), DMF (1x), CH₂Cl₂ (1x), MeOH (1x), CH₂Cl₂ (1x), MeOH (1x), CH₂Cl₂ (2x), Et₂O (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,

20  Fmoc-Asp(OtBu)-2-chlorotritylresin, Fmoc-Pro(SRPhe)-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:
<table>
<thead>
<tr>
<th>Step</th>
<th>Reagent</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂, wash and swell (manual)</td>
<td>3 x 1 min.</td>
</tr>
<tr>
<td>2</td>
<td>DMF, wash and swell</td>
<td>1 x 5 min.</td>
</tr>
<tr>
<td>3</td>
<td>40% piperidine/DMF</td>
<td>1 x 5 min.</td>
</tr>
<tr>
<td>4</td>
<td>DMF, wash</td>
<td>5 x 2 min.</td>
</tr>
<tr>
<td>5</td>
<td>5 equiv. Fmoc amino acid/DMF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ 5 eq. HBTU</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ 5 eq. HOBt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ 5 eq. DIEA</td>
<td>1 x 120 min.</td>
</tr>
<tr>
<td>6</td>
<td>DMF, wash</td>
<td>4 x 2 min.</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂, wash (at the end of the synthesis)</td>
<td>3 x 2 min.</td>
</tr>
</tbody>
</table>

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

15 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.

20 **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 CH₂Cl₂ (v/v) for 3 minutes, filtered and the filtrate was neutralized with 1ml (1.17 mMol, 3 eq.) of 20% DIEA in CH₂Cl₂ (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 CH₂Cl₂ and
extracted with 10% acetonitrile in water (4.5 ml) three times. The CH₂Cl₂ 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 (H₂O + 0.1% TFA) and B (CH₃CN + 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 CH₂Cl₂ (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 CH₂Cl₂ (v/v) for 3 minutes and filtered, and the filtrate was neutralized with 1ml (1.17 mMol, 3eq.) of 20% DIEA in CH₂Cl₂ (v/v). This procedure
was repeated twice to ensure completion of the cleavage. The resin was washed with 2ml of CH₂Cl₂. The CH₂Cl₂ 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 CH₂Cl₂ and extracted with 10% acetonitrile in water (4.5 ml) three times. The CH₂Cl₂ layer was evaporated to dryness. To deprotect the peptide fully, 3 ml of cleavage cocktail TFA:H₂O (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-\(^{13} \text{Pro}-\text{P11}-\text{P10}-\text{P9}-\text{P8}-\text{P7}-\text{P6}-\text{P5}-\text{P4}-\text{P3}-\text{P2}-\text{P1}. \) 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 performed as indicated in procedure A. The deprotection was performed using the following procedure:

To deprotect the peptide fully, 5 ml of cleavage cocktail TFA:H₂O:Phenol:Thioanisole:Ethanedithiol (82.5:5:5:5:2.5) were added, and the mixture was kept for 5 h at room temperature. The peptide was precipitated by addition of cold diethylether (10 ml). 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.
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-DAsp(OtBu)-P1-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)-DPro-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)\textsuperscript{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.\textsuperscript{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-\textsuperscript{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.\textsuperscript{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-\textsuperscript{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.\textsuperscript{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-\textsuperscript{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:

5 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(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-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-DThr(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-DIle-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-DPro-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-5\textsuperscript{D}Ser(OrBu)-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-15\textsuperscript{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-25\textsuperscript{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(OrBu)-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)-DPhe-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. 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-DPro-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)-DPro-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-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)-\textsuperscript{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)-\textsuperscript{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 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-\textsuperscript{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-\textsuperscript{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:

5 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)-P1-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:

15 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)-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:

25 Ex. 171 (15.40), 176 (13.67).
<table>
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<th>Example</th>
<th>Sequ.ID</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
<th>P7</th>
<th>P8</th>
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<th>P10</th>
<th>P11</th>
<th>Template</th>
<th>Purity%a</th>
<th>[M+ H]</th>
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</table>
| 1       | SEQ ID NO: 1 | Phe    | Cys    | Thr    | Lys    | Ser    | Glu    | Pro    | Pro    | Pro    | Ile    | Cys    | Thr
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1385.7 |
| 2       | SEQ ID NO: 2 | Phe    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Ile    | Cys    | Asp
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 93       | 1399.5 |
| 3       | SEQ ID NO: 3 | Phe    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Ile    | Cys    | Asn
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1398.5 |
| 4       | SEQ ID NO: 4 | Phe    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Ile    | Cys    | Ser
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1371.1 |
| 5       | SEQ ID NO: 5 | Phe    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Ile    | Cys    | Tyr
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1447.5 |
| 6       | SEQ ID NO: 6 | Tyr    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Ile    | Cys    | Thr
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1401.7 |
| 7       | SEQ ID NO: 7 | Arg    | Glu    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Ile    | Arg    | Phe
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1521.2 |
| 8       | SEQ ID NO: 8 | Arg    | Nle    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Ile    | Nle    | Phe
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 92       | 1462.4 |
| 9       | SEQ ID NO: 9 | 4AmPheCys | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Pro    | Ile    | Cys    | Ser
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 93       | 1386.9 |
| 10      | SEQ ID NO: 10 | Nle   | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Ile    | Cys    | Ser
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1337.8 |
| 11      | SEQ ID NO: 11 | Chg   | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Ile    | Cys    | Ser
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1363.8 |
| 12      | SEQ ID NO: 12 | Chg   | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Ile    | Cys    | Arg
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1432.7 |
| 13      | SEQ ID NO: 13 | 2Cl-PheCys | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Pro    | Ile    | Cys    | Arg
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1474.5 |
| 14      | SEQ ID NO: 14 | Ile    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Ala    | Ile    | Cys
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 93       | 1380.5 |
| 15      | SEQ ID NO: 15 | Phe    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Nle    | Cys    | Ser
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1371.8 |
| 16      | SEQ ID NO: 16 | Phe    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Pro    | Cys    | Ser
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1411.6 |
| 17      | SEQ ID NO: 17 | Ile    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Pro    | Cys    | Arg
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| 18      | SEQ ID NO: 18 | Ile    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Pro    | Tyr    | Cys
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| 19      | SEQ ID NO: 19 | Ile    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Pro    | Nle    | Cys
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1476.6 |
| 20      | SEQ ID NO: 20 | Ile    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Pro    | Cys    | Arg
|         |         |        |        |        |        |        |        |        |        |        |        |        | DPro²Pro                  | 95       | 1446.5 |
| 21      | SEQ ID NO: 21 | Ile    | Cys    | Thr    | Lys    | Ser    | Glu    | Pro    | Pro    | Pro    | Pro    | Cys    | Ser
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| 22      | SEQ ID NO: 22 | Phe    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Pro    | Ile    | Cys
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| 23      | SEQ ID NO: 23 | Phe    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Pro    | Ile    | Cys
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| 24      | SEQ ID NO: 24 | Phe    | Cys    | Thr    | Lys    | Ser    | AlloThr| Asp    | Pro    | Pro    | Pro    | Ile    | Cys
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| 25      | SEQ ID NO: 25 | Phe    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Pro    | Ile    | Cys
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| 26      | SEQ ID NO: 26 | Tyr    | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Pro    | Ile    | Cys
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| 27      | SEQ ID NO: 27 | hPhe   | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Pro    | Ile    | Cys
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| 28      | SEQ ID NO: 28 | hPhe   | Cys    | Thr    | Lys    | Ser    | Asp    | Pro    | Pro    | Pro    | Pro    | Ile    | Cys
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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 CaCl₂, 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.

25 \( K_m/K_i \) 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).
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<td>N-Met-Ala-Pro-Val-p-nitroanilide /Sigma</td>
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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% CO2. 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% CO2. 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 (OD595peptide). For each concentration averages were calculated from triplicates. The percentage of growth was calculated as follows: (OD595peptide-OD595Tz-OD595Empty well) / (OD595Tz-OD595Empty 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:%60,-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(C50:C0,%50,%60,50)).
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 0.9x10⁹ 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 H₂O. 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 (OD₅₄₀H₂O) gave an OD₅₄₀ of approximately 1.3-1.8. Percent hemolysis was calculated as follows: (OD₅₄₀peptide/OD₅₄₀H₂O) 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 follows: 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 Tₐ/T₀). 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 occurred 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% NH₃ in water. Samples were then diluted with 400 μl of 1% NH₃ in water and loaded. The plate was washed with 1 ml of methanol/1% NH₃ 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→∞) was estimated as Ct/b (b: elimination rate constant). AUC(0→t) is the sum of AUC(0→t) and AUC(t→∞).

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 (r²), which should be at least above 0.85 and most optimally above 0.96. In case of i.v. administration the initial concentration at t₀ 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→∞) 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.
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Table 3 continued

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<th>Elastase IC50 (nmol)</th>
<th>Trypsin at 100 μM %</th>
<th>Chymotrypsin at 100 μM %</th>
<th>Chymase at 100 μM %</th>
<th>Thrombin at 100 μM %</th>
<th>FXα at 100 μM %</th>
<th>Urokinase at 100 μM %</th>
<th>Tryptase IC50 (nmol)</th>
<th>Cytoxicity LC50/EC50 Hela cells</th>
<th>Hemolysis at 100 μM %</th>
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Nd: not determined
The results of the experiment described in 2.5 above are indicated in Table 4 herein below.

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Stability human Plasma t_{1/2} (min)</th>
<th>Stability rat Plasma t_{1/2} (min)</th>
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<td>22</td>
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<td>23</td>
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The results of the experiment described in 2.6 (PK), above, are indicated in Table 5 herein below.

<table>
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<th>Administration route</th>
<th>Intravenous</th>
<th>Oral</th>
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</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>5</td>
<td>50</td>
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<tr>
<td>Dose norm (mg/kg)</td>
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</tr>
<tr>
<td>AUC 0→t (ng·h/ml)</td>
<td>6044</td>
<td>782</td>
</tr>
<tr>
<td>AUC 0→∞ (ng·h/ml)</td>
<td>6047</td>
<td>813</td>
</tr>
<tr>
<td>AUC 0→∞ norm (ng·h/ml)</td>
<td>6047</td>
<td>81</td>
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<tr>
<td>T_{max observed} (hours)</td>
<td>10752</td>
<td>464</td>
</tr>
<tr>
<td>T_{max norm} (hours)</td>
<td>10752</td>
<td>46</td>
</tr>
<tr>
<td>C_{max norm} (ng/ml)</td>
<td>0.08</td>
<td>0.25</td>
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<tr>
<td>β (hours⁻¹)</td>
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<tr>
<td>Terminal t_{1/2} (hours)</td>
<td>0.5</td>
<td>0.87</td>
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<tr>
<td>Vd (ml/kg)</td>
<td>547</td>
<td>1008</td>
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<tr>
<td>% absorbed (F) (percentage of normalized AUC_{0→∞} po. against normalized AUC_{0→∞} i.v.)</td>
<td>100%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

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

After 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 $C_{\text{max}}$ 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$_{0-4}$ and AUC$_{\infty}$
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$_{\infty}$ 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 $C_{\text{max}}$ 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

   GraFit, Erithacus Software Ltd., Staines, U.K.
CLAIMS

1. Compounds of the general formula

\begin{align*}
\text{Template} \\
Z \text{N} \\
\text{Template}
\end{align*}

is a group of one of the formulae

\begin{align*}
\text{Template} \\
\text{Template}
\end{align*}

(a1) (a2) (a3)

(b1) (b2) (c1)
is Gly or the residue of an L-α-amino acid with B being a residue of formula $\text{NR}^{20}\text{CH(R}^{71})$- or the enantiomer of one of the groups A1 to A69 as defined hereinafter;
R\(^1\) is H; lower alkyl; or aryl-lower alkyl;

R\(^2\) is H; alkyl; alkenyl; -(CH\(_2\))\(_m\)(CHR\(^{61}\))OR\(^{55}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))SR\(^{56}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))NR\(^{33}\)R\(^{34}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))OCONR\(^{33}\)R\(^{75}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))NR\(^{20}\)CONR\(^{25}\)R\(^{32}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))COOR\(^{57}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))CONR\(^{58}\)R\(^{59}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))PO(OR\(^{60}\))\(_2\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))SO\(_2\)R\(^{62}\); or -(CH\(_2\))\(_m\)(CHR\(^{61}\))C\(_6\)H\(_4\)R\(^{8}\);

R\(^3\) is H; alkyl; alkenyl; -(CH\(_2\))\(_m\)(CHR\(^{61}\))OR\(^{55}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))SR\(^{56}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))NR\(^{33}\)R\(^{34}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))OCONR\(^{33}\)R\(^{75}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))NR\(^{20}\)CONR\(^{25}\)R\(^{32}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))COOR\(^{57}\);
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-(CH\(_2\))\(_m\)(CHR\(^{61}\))SO\(_2\)R\(^{62}\); or -(CH\(_2\))\(_m\)(CHR\(^{61}\))C\(_6\)H\(_4\)R\(^{8}\);

R\(^4\) is H; alkyl; alkenyl; -(CH\(_2\))\(_m\)(CHR\(^{61}\))OR\(^{55}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))SR\(^{56}\);
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-(CH\(_2\))\(_m\)(CHR\(^{61}\))SO\(_2\)R\(^{62}\); or -(CH\(_2\))\(_m\)(CHR\(^{61}\))C\(_6\)H\(_4\)R\(^{8}\);
R\(^5\) is alkyl; alkenyl; -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)OR\(^{35}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)SR\(^{36}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)NR\(^{33}\)R\(^{34}\);
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-(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)SO\(_2\)R\(^{62}\); or -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)C\(_6\)H\(_4\)R\(^{8}\);
R\(^6\) is H; alkyl; alkenyl; -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)OR\(^{55}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)SR\(^{56}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)NR\(^{33}\)R\(^{34}\);
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-(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)SO\(_2\)R\(^{62}\); or -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)C\(_6\)H\(_4\)R\(^{8}\);
R\(^7\) is alkyl; alkenyl; -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)OR\(^{55}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)NR\(^{33}\)R\(^{34}\);
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-(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)SO\(_2\)R\(^{62}\); or -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)COR\(^{64}\);
R\(^8\) is H; Cl; F; CF\(_3\); NO\(_2\); lower alkyl; lower alkenyl; aryl; aryl-lower alkyl;
-(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)OR\(^{55}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)SR\(^{56}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)NR\(^{33}\)R\(^{34}\);
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-(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)SO\(_2\)R\(^{62}\); or -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)COR\(^{64}\);
R\(^9\) is alkyl; alkenyl; -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)OR\(^{55}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)SR\(^{56}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)NR\(^{33}\)R\(^{34}\);
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-(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)SO\(_2\)R\(^{62}\); or -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)C\(_6\)H\(_4\)R\(^{8}\);
R\(^10\) is alkyl; alkenyl; -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)OR\(^{55}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)SR\(^{56}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)NR\(^{33}\)R\(^{34}\);
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-(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)COOR\(^{57}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)CONR\(^{58}\)R\(^{59}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)PO(OR\(^{60}\))\(_2\);
-(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)SO\(_2\)R\(^{62}\); or -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)C\(_6\)H\(_4\)R\(^{8}\);
R\(^11\) is H; alkyl; alkenyl; -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)OR\(^{55}\); -(CH\(_2\))\(_m\)(CHR\(^6\))\(_n\)NR\(^{33}\)R\(^{34}\);
(-CH₂)m(CHR₆¹)OCONR³³R⁷⁵, -(-CH₂)m(CHR₆¹)₂NR²⁰CONR³³R⁸²,
(-CH₂)m(CHR₆¹)₂COOR⁵⁷, -(CH₂)m(CHR₆¹)₃CONR⁵⁸R⁵⁹,
-(CH₂)m(CHR₆¹)₃PO(OR⁶⁰)₂;
-(CH₂)n(CHR₆¹)₂SO₂R⁶², or -(CH₂)n(CHR₆¹)₃C₆H₄R⁸;

5 R¹² is H; alkyl; alkenyl; -(CH₂)m(CHR₆¹)OR⁵⁵; -(CH₂)m(CHR₆¹)₂SR⁵⁶;
-(CH₂)m(CHR₆¹)₂NR³³R⁷⁴;
-(CH₂)n(CHR₆¹)₂OCONR³³R⁷⁵, -(CH₂)n(CHR₆¹)₂NR²⁰CONR³³R⁸²;
-(CH₂)n(CHR₆¹)₂COOR⁵⁷, -(CH₂)n(CHR₆¹)₃CONR⁵⁸R⁵⁹;
-(CH₂)n(CHR₆¹)₂PO(OR⁶⁰)₂;

10 R¹³ is alkyl; alkenyl; -(CH₂)n(CHR₆¹)₃OR⁵⁵; -(CH₂)n(CHR₆¹)₃SR⁵⁶;
-(CH₂)n(CHR₆¹)₂NR³³R⁷⁴;
-(CH₂)n(CHR₆¹)₂OCONR³³R⁷⁵, -(CH₂)n(CHR₆¹)₂NR²⁰CONR³³R⁸²;
-(CH₂)n(CHR₆¹)₂COOR⁵⁷, -(CH₂)n(CHR₆¹)₃CONR⁵⁸R⁵⁹;
-(CH₂)n(CHR₆¹)₂PO(OR⁶⁰)₂;

15 -(CH₂)n(CHR₆¹)₂SO₂R⁶², or -(CH₂)n(CHR₆¹)₃C₆H₄R⁸;

R¹⁴ is H; alkyl; alkenyl; -(CH₂)m(CHR₆¹)OR⁵⁵; -(CH₂)m(CHR₆¹)₂NR³³R⁷⁴;
-(CH₂)m(CHR₆¹)₂OCONR³³R⁷⁵, -(CH₂)m(CHR₆¹)₂NR²⁰CONR³³R⁸²;
-(CH₂)n(CHR₆¹)₂COOR⁵⁷, -(CH₂)n(CHR₆¹)₃CONR⁵⁸R⁵⁹;
-(CH₂)n(CHR₆¹)₂PO(OR⁶⁰)₂;

20 -(CH₂)n(CHR₆¹)₂SR⁵⁶, or -(CH₂)n(CHR₆¹)₃C₆H₄R⁸;

R¹⁵ is alkyl; alkenyl; -(CH₂)n(CHR₆¹)₃OR⁵⁵; -(CH₂)n(CHR₆¹)₃SR⁵⁶;
-(CH₂)n(CHR₆¹)₂NR³³R⁷⁴;
-(CH₂)n(CHR₆¹)₂OCONR³³R⁷⁵, -(CH₂)n(CHR₆¹)₂NR²⁰CONR³³R⁸²;
-(CH₂)n(CHR₆¹)₂COOR⁵⁷, -(CH₂)n(CHR₆¹)₃CONR⁵⁸R⁵⁹;

25 -(CH₂)n(CHR₆¹)₂PO(OR⁶⁰)₂;
-(CH₂)n(CHR₆¹)₂SO₂R⁶², or -(CH₂)n(CHR₆¹)₃C₆H₄R⁸;

R¹⁶ is alkyl; alkenyl; -(CH₂)n(CHR₆¹)₃OR⁵⁵; -(CH₂)n(CHR₆¹)₃SR⁵⁶;
-(CH₂)n(CHR₆¹)₂NR³³R⁷⁴;
-(CH₂)n(CHR₆¹)₂OCONR³³R⁷⁵, -(CH₂)n(CHR₆¹)₂NR²⁰CONR³³R⁸²;

30 -(CH₂)n(CHR₆¹)₂COOR⁵⁷, -(CH₂)n(CHR₆¹)₃CONR⁵⁸R⁵⁹;
-(CH₂)n(CHR₆¹)₂PO(OR⁶⁰)₂;
-(CH₂)n(CHR₆¹)₂SO₂R⁶², or -(CH₂)n(CHR₆¹)₃C₆H₄R⁸;

R¹⁷ is alkyl; alkenyl; -(CH₂)n(CHR₆¹)₃OR⁵⁵; -(CH₂)n(CHR₆¹)₃SR⁵⁶;
-(CH₂)n(CHR₆¹)₂NR³³R⁷⁴;

35 -(CH₂)n(CHR₆¹)₂OCONR³³R⁷⁵, -(CH₂)n(CHR₆¹)₂NR²⁰CONR³³R⁸²,
135
-(CH₂)₄(CHR¹⁶)₄COOR⁵⁷; -(CH₂)₄(CHR¹⁶)₄CONR⁵⁸R⁵⁹; -(CH₂)₄(CHR¹⁶)₄PO(OR⁶₀)₂;
-(CH₂)₄(CHR¹⁶)₄SO₂R⁶²; or -(CH₂)₄(CHR¹⁶)₄C₆H₄R⁸;
R¹⁸ is alkyl; alkenyl; -(CH₂)₄(CHR¹⁶)₄OR⁵⁵; -(CH₂)₄(CHR¹⁶)₄SR⁵⁶;
5
(CH₂)₄(CHR¹⁶)₄NR³⁵R³⁴;
-(CH₂)₄(CHR¹⁶)₄OCOCONR³⁵R⁷⁵; -(CH₂)₄(CHR¹⁶)₄NR²⁰CONR³³R⁸²;
-(CH₂)₄(CHR¹⁶)₄COOR⁵⁷; -(CH₂)₄(CHR¹⁶)₄CONR⁵⁸R⁵⁹;
(CH₂)₄(CHR¹⁶)₄PO(OR⁶₀)₂;
-(CH₂)₄(CHR¹⁶)₄SO₂R⁶²; or -(CH₂)₄(CHR¹⁶)₄C₆H₄R⁸;
10 R¹⁹ is lower alkyl; -(CH₂)₄(CHR¹⁶)₄OR⁵⁵; -(CH₂)₄(CHR¹⁶)₄SR⁵⁶;
(CH₂)₄(CHR¹⁶)₄NR³⁵R³⁴;
-(CH₂)₄(CHR¹⁶)₄OCOCONR³⁵R⁷⁵; -(CH₂)₄(CHR¹⁶)₄NR²⁰CONR³³R⁸²;
-(CH₂)₄(CHR¹⁶)₄COOR⁵⁷; -(CH₂)₄(CHR¹⁶)₄CONR⁵⁸R⁵⁹;
(CH₂)₄(CHR¹⁶)₄PO(OR⁶₀)₂;
-(CH₂)₄(CHR¹⁶)₄SO₂R⁶²; or -(CH₂)₄(CHR¹⁶)₄C₆H₄R⁸; or
R¹⁸ and R¹⁹ taken together can form: -(CH₂)₂₉-; -(CH₂)₂₉O(CH₂)₂₉; -(CH₂)₂₉S(CH₂)₂₉; or
-(CH₂)₂₉NR³⁵(CH₂)₂₉;
R²⁰ is H; alkyl; alkenyl; or aryl-lower alkyl;
R²¹ is H; alkyl; alkenyl; -(CH₂)₄(CHR¹⁶)₄OR⁵⁵; -(CH₂)₄(CHR¹⁶)₄SR⁵⁶;
20
(CH₂)₄(CHR¹⁶)₄NR³⁵R³⁴;
-(CH₂)₄(CHR¹⁶)₄OCOCONR³⁵R⁷⁵; -(CH₂)₄(CHR¹⁶)₄NR²⁰CONR³³R⁸²;
-(CH₂)₄(CHR¹⁶)₄COOR⁵⁷; -(CH₂)₄(CHR¹⁶)₄CONR⁵⁸R⁵⁹;
(CH₂)₄(CHR¹⁶)₄PO(OR⁶₀)₂;
-(CH₂)₄(CHR¹⁶)₄SO₂R⁶²; or -(CH₂)₄(CHR¹⁶)₄C₆H₄R⁸;
25 R²² is H; alkyl; alkenyl; -(CH₂)₄(CHR¹⁶)₄OR⁵⁵; -(CH₂)₄(CHR¹⁶)₄SR⁵⁶;
(CH₂)₄(CHR¹⁶)₄NR³⁵R³⁴;
-(CH₂)₄(CHR¹⁶)₄OCOCONR³⁵R⁷⁵; -(CH₂)₄(CHR¹⁶)₄NR²⁰CONR³³R⁸²;
-(CH₂)₄(CHR¹⁶)₄COOR⁵⁷; -(CH₂)₄(CHR¹⁶)₄CONR⁵⁸R⁵⁹;
(CH₂)₄(CHR¹⁶)₄PO(OR⁶₀)₂;
-(CH₂)₄(CHR¹⁶)₄SO₂R⁶²; or -(CH₂)₄(CHR¹⁶)₄C₆H₄R⁸;
R²³ is alkyl; alkenyl; -(CH₂)₄(CHR¹⁶)₄OR⁵⁵; -(CH₂)₄(CHR¹⁶)₄SR⁵⁶;
30
(CH₂)₄(CHR¹⁶)₄NR³⁵R³⁴;
-(CH₂)₄(CHR¹⁶)₄OCOCONR³⁵R⁷⁵; -(CH₂)₄(CHR¹⁶)₄NR²⁰CONR³³R⁸²;
-(CH₂)₄(CHR¹⁶)₄COOR⁵⁷; -(CH₂)₄(CHR¹⁶)₄CONR⁵⁸R⁵⁹;
(CH₂)₄(CHR¹⁶)₄PO(OR⁶₀)₂;
-(CH₂)₄(CHR¹⁶)₄SO₂R⁶²; or -(CH₂)₄(CHR¹⁶)₄C₆H₄R⁸;
35
R²⁴ is alkyl; alkenyl; -(CH₂)ₐ(CHR¹⁺)ₐOR⁺; -(CH₂)ₐ(CHR¹⁺)ₐSR⁺; -(CH₂)ₐ(CHR¹⁺)ₐNR³₊R⁴⁺;
- (CH₂)ₐ(CHR¹⁺)ₐOCONR²⁺R⁵⁺; -(CH₂)ₐ(CHR¹⁺)ₐNR²⁺CONR³⁺R⁸⁺;
- (CH₂)ₐ(CHR¹⁺)ₐCOOR⁺; -(CH₂)ₐ(CHR¹⁺)ₐCONR⁵⁺R⁹⁺; -(CH₂)ₐ(CHR¹⁺)ₐPO(OR⁶⁺)₂⁺;
- (CH₂)ₐ(CHR¹⁺)ₐSO₂R⁺; or -(CH₂)ₐ(CHR¹⁺)ₐC₆H₄R⁺;
R²⁵ is H; alkyl; alkenyl; -(CH₂)ₐ(CHR¹⁺)ₐOR⁺; -(CH₂)ₐ(CHR¹⁺)ₐSR⁺; -(CH₂)ₐ(CHR¹⁺)ₐNR³⁺R⁴⁺;
- (CH₂)ₐ(CHR¹⁺)ₐOCONR²⁺R⁵⁺; -(CH₂)ₐ(CHR¹⁺)ₐCONR³⁺R⁸⁺; -(CH₂)ₐ(CHR¹⁺)ₐCOOR⁺;
- (CH₂)ₐ(CHR¹⁺)ₐCONR⁵⁺R⁹⁺; -(CH₂)ₐ(CHR¹⁺)ₐPO(OR⁶⁺)₂⁺;
- (CH₂)ₐ(CHR¹⁺)ₐSO₂R⁺; or -(CH₂)ₐ(CHR¹⁺)ₐC₆H₄R⁺; or
R²⁶ is H; alkyl; alkenyl; -(CH₂)ₐ(CHR¹⁺)ₐOR⁺; -(CH₂)ₐ(CHR¹⁺)ₐSR⁺; -(CH₂)ₐ(CHR¹⁺)ₐNR³⁺R⁴⁺;
- (CH₂)ₐ(CHR¹⁺)ₐOCONR²⁺R⁵⁺; -(CH₂)ₐ(CHR¹⁺)ₐCONR³⁺R⁸⁺; -(CH₂)ₐ(CHR¹⁺)ₐCOOR⁺;
- (CH₂)ₐ(CHR¹⁺)ₐCONR⁵⁺R⁹⁺; -(CH₂)ₐ(CHR¹⁺)ₐPO(OR⁶⁺)₂⁺;
- (CH₂)ₐ(CHR¹⁺)ₐSO₂R⁺; or -(CH₂)ₐ(CHR¹⁺)ₐC₆H₄R⁺; or
R²³ and R²⁶ taken together can form: -(CH₂)₂₋₆₋; -(CH₂)₂O(CH₂)ₓ₋₁₋; -(CH₂)ₓS(CH₂)ₓ₋₁₋; or
- (CH₂)ₐNR⁵⁺(CH₂)ₓ₋₁₋;
R²⁷ is H; alkyl; alkenyl; -(CH₂)ₐ(CHR¹⁺)ₐOR⁺; -(CH₂)ₐ(CHR¹⁺)ₐSR⁺; -(CH₂)ₐ(CHR¹⁺)ₐNR³⁺R⁴⁺;
- (CH₂)ₐ(CHR¹⁺)ₐOCONR²⁺R⁵⁺; -(CH₂)ₐ(CHR¹⁺)ₐCONR³⁺R⁸⁺; -(CH₂)ₐ(CHR¹⁺)ₐCOOR⁺;
- (CH₂)ₐ(CHR¹⁺)ₐCONR⁵⁺R⁹⁺; -(CH₂)ₐ(CHR¹⁺)ₐPO(OR⁶⁺)₂⁺;
- (CH₂)ₐ(CHR¹⁺)ₐSO₂R⁺; or -(CH₂)ₐ(CHR¹⁺)ₐC₆H₄R⁺; or
R²⁸ is alkyl; alkenyl; -(CH₂)ₐ(CHR¹⁺)ₐOR⁺; -(CH₂)ₐ(CHR¹⁺)ₐSR⁺; -(CH₂)ₐ(CHR¹⁺)ₐNR³⁺R⁴⁺;
- (CH₂)ₐ(CHR¹⁺)ₐOCONR²⁺R⁵⁺; -(CH₂)ₐ(CHR¹⁺)ₐCONR³⁺R⁸⁺; -(CH₂)ₐ(CHR¹⁺)ₐCOOR⁺;
- (CH₂)ₐ(CHR¹⁺)ₐCONR⁵⁺R⁹⁺; -(CH₂)ₐ(CHR¹⁺)ₐPO(OR⁶⁺)₂⁺;
- (CH₂)ₐ(CHR¹⁺)ₐSO₂R⁺; or -(CH₂)ₐ(CHR¹⁺)ₐC₆H₄R⁺; or
R²⁹ is alkyl; alkenyl; -(CH₂)ₐ(CHR¹⁺)ₐOR⁺; -(CH₂)ₐ(CHR¹⁺)ₐSR⁺; -(CH₂)ₐ(CHR¹⁺)ₐNR³⁺R⁴⁺;
- (CH₂)ₐ(CHR¹⁺)ₐOCONR²⁺R⁵⁺; -(CH₂)ₐ(CHR¹⁺)ₐCONR³⁺R⁸⁺; -(CH₂)ₐ(CHR¹⁺)ₐCOOR⁺;
- (CH₂)ₐ(CHR¹⁺)ₐCONR⁵⁺R⁹⁺; -(CH₂)ₐ(CHR¹⁺)ₐPO(OR⁶⁺)₂⁺;
- (CH₂)ₐ(CHR¹⁺)ₐSO₂R⁺; or -(CH₂)ₐ(CHR¹⁺)ₐC₆H₄R⁺; or
R$^{30}$ is H; alkyl; alkenyl; or aryl-lower alkyl;

R$^{31}$ is H; alkyl; alkenyl; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$O$^{R55}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$NR$^{33}$R$^{34}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$OCONR$^{33}$R$^{75}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$NR$^{20}$CONR$^{33}$R$^{82}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$COOR$^{57}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$CONR$^{38}$R$^{59}$;

5
(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$PO(OR$^{60}$)$_{p}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$SO$_{2}$R$^{62}$; or -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$C$_{6}$H$_{4}$R$^{5}$;  

R$^{32}$ is H; lower alkyl; or aryl-lower alkyl;

R$^{33}$ is H; alkyl, alkenyl; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$O$^{R55}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$NR$^{34}$R$^{63}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$OCONR$^{33}$R$^{75}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$NR$^{20}$CONR$^{33}$R$^{82}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$COOR$^{57}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$CONR$^{38}$R$^{59}$;

10
(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$PO(OR$^{60}$)$_{m}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$SO$_{2}$R$^{62}$; or -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$C$_{6}$H$_{4}$R$^{5}$;  

R$^{34}$ is H; lower alkyl; aryl, or aryl-lower alkyl;

R$^{35}$ and R$^{34}$ taken together can form: -(CH$_{2}$)$_{2}$O(-(CH$_{2}$)$_{2}$-; -(CH$_{2}$)$_{2}$S(-(CH$_{2}$)$_{2}$-; or 

15
-(CH$_{2}$)$_{2}$NR$^{57}$(-(CH$_{2}$)$_{2}$-;

R$^{35}$ is H; alkyl; alkenyl; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$O$^{R55}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$NR$^{34}$R$^{63}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$OCONR$^{33}$R$^{75}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$NR$^{20}$CONR$^{33}$R$^{82}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$COOR$^{57}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$CONR$^{38}$R$^{59}$;

20
(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$PO(OR$^{60}$)$_{m}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$SO$_{2}$R$^{62}$; or -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$C$_{6}$H$_{4}$R$^{5}$;  

R$^{36}$ is H, alkyl; alkenyl; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$O$^{R55}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$NR$^{34}$R$^{63}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$OCONR$^{33}$R$^{75}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$NR$^{20}$CONR$^{33}$R$^{82}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$COOR$^{57}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$CONR$^{38}$R$^{59}$;

25
(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$PO(OR$^{60}$)$_{m}$; -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$SO$_{2}$R$^{62}$; or -(CH$_{2}$)$_{m}$(CHR$^{61}$)$_{n}$C$_{6}$H$_{4}$R$^{5}$;  

R$^{37}$ is H; F; Br; Cl; NO$_{2}$; CF$_{3}$; lower alkyl; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$O$^{R55}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$NR$^{34}$R$^{34}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$OCONR$^{33}$R$^{75}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$NR$^{20}$CONR$^{33}$R$^{82}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$COOR$^{57}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$CONR$^{38}$R$^{59}$;

30
(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$PO(OR$^{60}$)$_{p}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$SO$_{2}$R$^{62}$; or -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$C$_{6}$H$_{4}$R$^{5}$;  

R$^{38}$ is H; F; Br; Cl; NO$_{2}$; CF$_{3}$; alkyl; alkenyl; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$O$^{R55}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$NR$^{34}$R$^{34}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$OCONR$^{33}$R$^{75}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$NR$^{20}$CONR$^{33}$R$^{82}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$COOR$^{57}$; -(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$CONR$^{38}$R$^{59}$;

35
(CH$_{2}$)$_{p}$(CHR$^{61}$)$_{q}$PO(OR$^{60}$)$_{p}$;
- (CH₂)ₙ(CHR₆¹)ₙSO₂R₆²; or -(CH₂)ₙ(CHR₆¹)ₙC₆H₄R₈;

R₃⁹ is H; alkyl; alkenyl; or aryl-lower alkyl;

R₄⁰ is H; alkyl; alkenyl; or aryl-lower alkyl;

R₄¹ is H; F; Br; Cl; NO₂; CF₃; alkyl; alkenyl; -(CH₂)ₙ(CHR₆¹)ₙOR₅⁵; -

5 (CH₂)ₙ(CHR₆¹)ₙNR₃₃R₃⁴;

-(CH₂)ₙ(CHR₆¹)ₙOCONR₃₃R₇₅; -(CH₂)ₙ(CHR₆¹)ₙNR₂⁰CONR₃₃R₈₂;

-(CH₂)ₙ(CHR₆¹)ₙCOOR₅⁷; -(CH₂)ₙ(CHR₆¹)ₙCONR₅₈R₅⁹;

-(CH₂)ₙ(CHR₆¹)ₙPO(OR₆⁰)₂;

-(CH₂)ₙ(CHR₆¹)ₙSO₂R₆²; or -(CH₂)ₙ(CHR₆¹)ₙC₆H₄R₈;

R₄² is H; F; Br; Cl; NO₂; CF₃; alkyl; alkenyl; -(CH₂)ₙ(CHR₆¹)ₙOR₅⁵; -

10 (CH₂)ₙ(CHR₆¹)ₙNR₃₃R₃⁴;

-(CH₂)ₙ(CHR₆¹)ₙOCONR₃₃R₇₅; -(CH₂)ₙ(CHR₆¹)ₙNR₂⁰CONR₃₃R₈₂;

-(CH₂)ₙ(CHR₆¹)ₙCOOR₅⁷; -(CH₂)ₙ(CHR₆¹)ₙCONR₅₈R₅⁹;

-(CH₂)ₙ(CHR₆¹)ₙPO(OR₆⁰)₂;

-(CH₂)ₙ(CHR₆¹)ₙSO₂R₆²; or -(CH₂)ₙ(CHR₆¹)ₙC₆H₄R₈;

R₄³ is H; alkyl; alkenyl; -(CH₂)ₙ(CHR₆¹)ₙOR₅⁵; -(CH₂)ₙ(CHR₆¹)ₙNR₃₃R₃⁴;

-(CH₂)ₙ(CHR₆¹)ₙOCONR₃₃R₇₅; -(CH₂)ₙ(CHR₆¹)ₙNR₂⁰CONR₃₃R₈₂;

-(CH₂)ₙ(CHR₆¹)ₙCOOR₅⁷; -(CH₂)ₙ(CHR₆¹)ₙCONR₅₈R₅⁹;

-(CH₂)ₙ(CHR₆¹)ₙPO(OR₆⁰)₂;

-(CH₂)ₙ(CHR₆¹)ₙSO₂R₆²; or -(CH₂)ₙ(CHR₆¹)ₙC₆H₄R₈;

R₄⁴ is alkyl; alkenyl; -(CH₂)ₙ(CHR₆¹)ₙOR₅⁵; -(CH₂)ₙ(CHR₆¹)ₙSR₅⁶; -

20 (CH₂)ₙ(CHR₆¹)ₙNR₃₃R₃⁴;

-(CH₂)ₙ(CHR₆¹)ₙOCONR₃₃R₇₅; -(CH₂)ₙ(CHR₆¹)ₙNR₂⁰CONR₃₃R₈₂;

-(CH₂)ₙ(CHR₆¹)ₙCOOR₅⁷; -(CH₂)ₙ(CHR₆¹)ₙCONR₅₈R₅⁹;

-(CH₂)ₙ(CHR₆¹)ₙPO(OR₆⁰)₂;

-(CH₂)ₙ(CHR₆¹)ₙSO₂R₆²; or -(CH₂)ₙ(CHR₆¹)ₙC₆H₄R₈;

R₄⁵ is H; alkyl; alkenyl; -(CH₂)ₙ(CHR₆¹)ₙOR₅⁵; -(CH₂)ₙ(CHR₆¹)ₙSR₅⁶; -

25 (CH₂)ₙ(CHR₆¹)ₙNR₃₃R₃⁴;

-(CH₂)ₙ(CHR₆¹)ₙOCONR₃₃R₇₅; -(CH₂)ₙ(CHR₆¹)ₙNR₂⁰CONR₃₃R₈₂;

-(CH₂)ₙ(CHR₆¹)ₙCOOR₅⁷; -(CH₂)ₙ(CHR₆¹)ₙCONR₅₈R₅⁹;

-(CH₂)ₙ(CHR₆¹)ₙPO(OR₆⁰)₂;

-(CH₂)ₙ(CHR₆¹)ₙSO₂R₆²; or -(CH₂)ₙ(CHR₆¹)ₙC₆H₄R₈;

R₄⁶ is H; alkyl; alkenyl; or -(CH₂)ₙ(CHR₆¹)ₙC₆H₄R₈;

R₄⁷ is H; alkyl; alkenyl; or -(CH₂)ₙ(CHR₆¹)ₙOR₅⁵;

35 R₄⁸ is H; lower alkyl; lower alkenyl; or aryl-lower alkyl;

R₄⁹ is H; alkyl; alkenyl; -(CHR₆¹)ₙCOOR₅⁷; (CHR₆¹)ₙCONR₅₈R₅⁹; (CHR₆¹)ₙPO(OR₆⁰)₂;
(CHR\(^{61}\))\(_m\)SOR\(^{62}\); or -(CHR\(^{61}\))\(_n\)C\(_6\)H\(_{12}\)R\(^{8}\);

R\(^{50}\) is 
H; lower alkyl; or aryl-lower alkyl;

R\(^{51}\) is 
H; alkyl; alkenyl: -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)OR\(^{55}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)SR\(^{56}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)NR\(^{33}\)R\(^{34}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)OCO\(_2\)R\(^{75}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)NR\(^{20}\)CONR\(^{33}\)R\(^{82}\); -(CH\(_2\))\(_n\)(CHR\(^{61}\))\(_n\)COOR\(^{57}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)CONR\(^{58}\)R\(^{59}\); -(CH\(_2\))\(_n\)(CHR\(^{61}\))\(_n\)PO(OR\(^{60}\))\(_2\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)SO\(_2\)R\(^{62}\); or -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)C\(_6\)H\(_{12}\)R\(^{8}\);

R\(^{52}\) is 
H; alkyl; alkenyl: -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)OR\(^{55}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)SR\(^{56}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)NR\(^{33}\)R\(^{34}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)OCO\(_2\)R\(^{75}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)NR\(^{20}\)CONR\(^{33}\)R\(^{82}\); -(CH\(_2\))\(_n\)(CHR\(^{61}\))\(_n\)COOR\(^{57}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)CONR\(^{58}\)R\(^{59}\); -(CH\(_2\))\(_n\)(CHR\(^{61}\))\(_n\)PO(OR\(^{60}\))\(_2\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)SO\(_2\)R\(^{62}\); or -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)C\(_6\)H\(_{12}\)R\(^{8}\);

R\(^{53}\) is 
H; alkyl; alkenyl: -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)OR\(^{55}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)SR\(^{56}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)NR\(^{33}\)R\(^{34}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)OCO\(_2\)R\(^{75}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)NR\(^{20}\)CONR\(^{33}\)R\(^{82}\); -(CH\(_2\))\(_n\)(CHR\(^{61}\))\(_n\)COOR\(^{57}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)CONR\(^{58}\)R\(^{59}\); -(CH\(_2\))\(_n\)(CHR\(^{61}\))\(_n\)PO(OR\(^{60}\))\(_2\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)SO\(_2\)R\(^{62}\); or -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)C\(_6\)H\(_{12}\)R\(^{8}\);

R\(^{54}\) is 
H; alkyl; alkenyl: -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)OR\(^{55}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)NR\(^{33}\)R\(^{34}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)OCO\(_2\)R\(^{75}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)NR\(^{20}\)CONR\(^{33}\)R\(^{82}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)COOR\(^{57}\); -(CH\(_2\))\(_n\)(CHR\(^{61}\))\(_n\)CONR\(^{58}\)R\(^{59}\); or -(CH\(_2\))\(_n\)(CHR\(^{61}\))\(_n\)C\(_6\)H\(_{12}\)R\(^{8}\);

R\(^{55}\) is 
H; lower alkyl; lower alkenyl; aryl-lower alkyl; -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)OR\(^{57}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)NR\(^{34}\)R\(^{63}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)OCO\(_2\)R\(^{75}\)R\(^{82}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)NR\(^{20}\)CONR\(^{34}\)R\(^{82}\); -(CH\(_2\))\(_n\)(CHR\(^{61}\))\(_n\)COR\(^{64}\);

R\(^{56}\) is 
H; lower alkyl; lower alkenyl; aryl-lower alkyl; -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)OR\(^{57}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)NR\(^{34}\)R\(^{63}\); -(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)OCO\(_2\)R\(^{75}\)R\(^{82}\);
-(CH\(_2\))\(_m\)(CHR\(^{61}\))\(_n\)NR\(^{20}\)CONR\(^{34}\)R\(^{82}\); -(CH\(_2\))\(_n\)(CHR\(^{61}\))\(_n\)COR\(^{64}\);

R\(^{57}\) is 
H; lower alkyl; lower alkenyl; aryl lower alkyl; or heteroaryl lower alkyl;

R\(^{58}\) is 
H; lower alkyl; lower alkenyl; aryl; heteroaryl; aryl-lower alkyl; or heteroaryl-lower alkyl;

R\(^{59}\) is 
H; lower alkyl; lower alkenyl; aryl; heteroaryl; aryl-lower alkyl; or heteroaryl-lower alkyl; or

R\(^{58}\) and R\(^{59}\) taken together can form: -(CH\(_2\))\(_{2-6}\)-; -(CH\(_2\))\(_2\)O(CH\(_2\))\(_2\)-; -(CH\(_2\))\(_2\)S(CH\(_2\))\(_2\)-; or
R^{60} is H; lower alkyl; lower alkenyl; aryl; or aryl-lower alkyl;
R^{61} is alkyl; alkenyl; aryl; heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl; -
(CH\_2\_m)\_mOR^{55};

\(-\text{(CH}_2\text{)}\_m\text{NR}^{33}\text{R}^{34}; -\text{(CH}_2\text{)}\_m\text{OCONR}^{35}\text{R}^{82}; -\text{(CH}_2\text{)}\_m\text{NR}^{26}\text{CONR}^{78}\text{R}^{82}; -\text{(CH}_2\text{)}\_m\text{COOR}^{37};
\)
\(-\text{(CH}_2\text{)}\_n\text{NR}^{58}\text{R}^{59}; \text{or -(CH}_2\text{)}\_n\text{POCOR}^{60};\)

R^{62} is lower alkyl; lower alkenyl; aryl; heteroaryl; or aryl-lower alkyl;
R^{63} is H; lower alkyl; lower alkenyl; aryl; heteroaryl; or aryl-lower alkyl; heteroaryl-lower alkyl;

-COR^{64}; -COOR^{57}; -CONR^{58}\text{R}^{59}; -\text{SO}_2\text{R}^{62}; \text{or -(PO)R}^{60};\)

R^{64} and R^{65} taken together can form: -\text{(CH}_2\text{)}\_2\text{O}; -\text{(CH}_2\text{)}\_2\text{O(CH}_2\text{)}\_2; -\text{(CH}_2\text{)}\_2\text{S(CH}_2\text{)}\_2; or
\(-\text{(CH}_2\text{)}\_2\text{NR}^{57}\text{(CH}_2\text{)}\_2;\)

R^{65} is H; lower alkyl; lower alkenyl; aryl; heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl;

-\text{(CH}_2\text{)}\_p\text{CHR}^{61}\text{OR}^{45}; -\text{(CH}_2\text{)}\_p\text{CHR}^{61}\text{SR}^{66}; \text{or -(CH}_2\text{)}\_p\text{CHR}^{61}\text{NR}^{34}\text{R}^{63};
\(-\text{(CH}_2\text{)}\_p\text{CHR}^{61}\text{OCONR}^{37}\text{R}^{82}; -\text{(CH}_2\text{)}\_p\text{CHR}^{61}\text{NR}^{26}\text{CONR}^{78}\text{R}^{82};\)

R^{65} is H; lower alkyl; lower alkenyl; aryl; aryl-lower alkyl; heteroaryl-lower alkyl; -
-COR^{57};

\(-\text{COOR}^{57}; \text{or -(CONR}^{58}\text{R}^{59};\)

R^{66} is H; lower alkyl; lower alkenyl; aryl; aryl-lower alkyl; heteroaryl-lower alkyl; or
-CONR^{58}\text{R}^{59};
m is 2-4; o is 0-4; p is 1-4; q is 0-2; r is 1 or 2; s is 0 or 1;

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 are, depending on their position in the chains, Gly, Pro, Pro(4NHCOPh), or of formula -A-CO-, or of formula -B-CO-, or of one of the types

30 C: -NR^{20}\text{CH(R}^{73}\text{)CO-};
D: -NR^{26}\text{CH(R}^{73}\text{)CO-};
E: -NR^{20}\text{CH(}^{70}\text{)CO-};
F: -NR^{20}\text{CH(R}^{84}\text{)CO-}; and
H: -NR^{20}\text{-CH(CO-)-(CH}_2\text{)}\_4\text{-CH(CO-)-NR}^{20};

\(-\text{NR}^{20}\text{-CH(CO-)-(CH}_2\text{)}\_p\text{SS(CH}_2\text{)}\_p\text{-CH(CO-)-NR}^{20};
\(-\text{NR}^{20}\text{-CH(CO-)-(CH}_2\text{)}\_p\text{NR}^{20}\text{CO(CH}_2\text{)}\_p\text{-CH(CO-)-NR}^{20}; \text{and}\)
141
-NR²⁻⁻CH(CO)-{(CH₂)₃-NR⁵⁻⁻CONR⁶⁻⁻(CH₂)₄-CH(CO)-}-NR²⁻⁻;

R⁷¹ is lower alkyl; lower alkenyl; -(CH₂)₂(CHR⁶⁻⁻)₃OR⁷⁻⁻; -(CH₂)₂(CHR⁶⁻⁻)₃SR⁷⁻⁻;
-(CH₂)₄(CHR⁶⁻⁻)₃N₃R⁷⁻⁻; -(CH₂)₄(CHR⁶⁻⁻)₃OCONR⁷⁻⁻; -(CH₂)₄(CHR⁶⁻⁻)₃NR²⁻⁻CONR³⁻⁻R⁵⁻⁻;
-(CH₂)₄(CHR⁶⁻⁻)₃COOR⁷⁻⁻; -(CH₂)₄CONR⁵⁻⁻R⁷⁻⁻; -(CH₂)₄PO(OR⁶⁻⁻); -(CH₂)₄SO₂R⁶⁻⁻; or
-(CH₂)₂-S-C₆R⁷⁻⁻R⁸⁻⁻R⁹⁻⁻R⁷₀⁻⁻R⁷₁⁻⁻;

5
R⁷² is H, lower alkyl; lower alkenyl; -(CH₂)₂(CHR⁶⁻⁻)₃OR⁸⁻⁻; or -(CH₂)₂(CHR⁶⁻⁻)₃SR⁸⁻⁻;
R⁷³ is -(CR⁶⁻⁻R⁷⁻⁻)₃R⁷⁻⁻; -(CH₂)₂O(CH₂)₃R⁷⁻⁻; -(CH₂)₂S(CH₂)₃R⁷⁻⁻; or -(CH₂)₂NR²⁻⁻(CH₂)₂R⁷⁻⁻;
R⁷⁴ is -(CH₂)₂NR³⁻⁻R⁷⁻⁻; -(CH₂)₂NR⁴⁻⁻R⁷⁻⁻; -(CH₂)₂C(=-NR⁶⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -
(CH₂)₂C(=-NOR⁵⁻⁻)NR⁷⁻⁻R⁷⁻⁻;

10
-(CH₂)₂C(=-NNR⁷⁻⁻R⁹⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -(CH₂)₂NR⁸⁻⁻C(=-NR⁶⁻⁻)NR⁷⁻⁻R⁷⁻⁻;
-(CH₂)₄N=C(NR⁷⁻⁻R⁸⁻⁻)NR⁷⁻⁻R⁸⁻⁻; -(CH₂)₂C₆H₄NR⁷⁻⁻R⁸⁻⁻; -(CH₂)₂C₆H₄N²⁻⁻R⁸⁻⁻;
-(CH₂)₂C₆H₄C(=-NOR⁶⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -(CH₂)₂C₆H₄C(=-NOR⁵⁻⁻)NR⁷⁻⁻R⁷⁻⁻;
-(CH₂)₂C₆H₄C(=-NNR⁷⁻⁻R⁸⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -(CH₂)₂C₆H₄NR⁸⁻⁻C(=-NR⁶⁻⁻)NR⁷⁻⁻R⁷⁻⁻;

15
-(CH₂)₂O(CH₂)₃N²⁻⁻R⁷⁻⁻R⁸⁻⁻; -(CH₂)₂O(CH₂)₃NR⁷⁻⁻R⁷⁻⁻;
-(CH₂)₂O(CH₂)₃C(=-NR⁶⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -(CH₂)₂O(CH₂)₃C(=-NOR⁵⁻⁻)NR⁷⁻⁻R⁷⁻⁻;
-(CH₂)₂O(CH₂)₃C(=-NNR⁷⁻⁻R⁹⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -(CH₂)₂O(CH₂)₃C(=-NOR⁵⁻⁻)NR⁷⁻⁻R⁷⁻⁻;

20
-(CH₂)₂O(CH₂)₃C₆H₄C(=-NOR⁶⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -(CH₂)₂O(CH₂)₃C₆H₄C(=-NOR⁵⁻⁻)NR⁷⁻⁻R⁷⁻⁻;
-(CH₂)₂O(CH₂)₃C₆H₄C(=-NNR⁷⁻⁻R⁹⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -(CH₂)₂O(CH₂)₃C₆H₄C(=-NOR⁵⁻⁻)NR⁷⁻⁻R⁷⁻⁻;
-(CH₂)₂O(CH₂)₃C₆H₄C(=-NNR⁷⁻⁻R⁹⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -(CH₂)₂O(CH₂)₃C₆H₄C(=-NOR⁵⁻⁻)NR⁷⁻⁻R⁷⁻⁻;

25
-(CH₂)₂O(CH₂)₃C₆H₄C(=-NNR⁷⁻⁻R⁹⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -(CH₂)₂O(CH₂)₃C₆H₄C(=-NOR⁵⁻⁻)NR⁷⁻⁻R⁷⁻⁻;
-(CH₂)₂O(CH₂)₃C₆H₄CN⁻⁻R⁷⁻⁻R⁷⁻⁻; -(CH₂)₂O(CH₂)₃C₆H₄C(=-NR⁶⁻⁻)NR⁷⁻⁻R⁷⁻⁻;
-(CH₂)₂O(CH₂)₃C₆H₄C(=-NOR⁵⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -(CH₂)₂O(CH₂)₃C₆H₄C(=-NNR⁷⁻⁻R⁹⁻⁻)NR⁷⁻⁻R⁷⁻⁻;

30
-(CH₂)₂O(CH₂)₃C₆H₄C(=-NOR⁵⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -(CH₂)₂O(CH₂)₃C₆H₄C(=-NOR⁵⁻⁻)NR⁷⁻⁻R⁷⁻⁻;
-(CH₂)₂O(CH₂)₃C₆H₄C(=-NNR⁷⁻⁻R⁹⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -(CH₂)₂O(CH₂)₃C₆H₄C(=-NOR⁵⁻⁻)NR⁷⁻⁻R⁷⁻⁻;
-(CH₂)₂O(CH₂)₃C₆H₄C(=-NNR⁷⁻⁻R⁹⁻⁻)NR⁷⁻⁻R⁷⁻⁻; -(CH₂)₂O(CH₂)₃C₆H₄C(=-NOR⁵⁻⁻)NR⁷⁻⁻R⁷⁻⁻;

35
R⁷⁵ and R⁷⁵ taken together can form: -(CH₂)₂-e⁻; -(CH₂)₂O(CH₂)₂-e⁻; -(CH₂)₂S(CH₂)₂-e⁻; or
-(CH₂)₂-NR⁷⁻⁻(CH₂)₂-e⁻;
R\textsuperscript{75} and R\textsuperscript{82} taken together can form: -(CH\textsubscript{2})\textsubscript{3-6}; -(CH\textsubscript{2})\textsubscript{2}O(CH\textsubscript{2})\textsubscript{2}; -(CH\textsubscript{2})\textsubscript{2}S(CH\textsubscript{2})\textsubscript{2}; or -(CH\textsubscript{2})\textsubscript{2}NR\textsuperscript{77}(CH\textsubscript{2})\textsubscript{2};

R\textsuperscript{78} is H; lower alkyl; lower alkenyl; aryl-lower alkyl; -(CH\textsubscript{2})\textsubscript{6}OR\textsuperscript{72}; -(CH\textsubscript{2})\textsubscript{6}SR\textsuperscript{72}; -(CH\textsubscript{2})\textsubscript{6}NR\textsuperscript{73}R\textsuperscript{34}; -(CH\textsubscript{2})\textsubscript{6}OCONR\textsuperscript{73}R\textsuperscript{75}; -(CH\textsubscript{2})\textsubscript{6}NR\textsuperscript{76}CONR\textsuperscript{73}R\textsuperscript{82};

-(CH\textsubscript{2})\textsubscript{6}COOR\textsuperscript{75}; -(CH\textsubscript{2})\textsubscript{6}CON(R\textsuperscript{58}R\textsuperscript{59}; -(CH\textsubscript{2})\textsubscript{6}PO(OR\textsuperscript{60})\textsubscript{2}; -(CH\textsubscript{2})\textsubscript{6}SO\textsubscript{2}R\textsuperscript{62}; or -(CH\textsubscript{2})\textsubscript{6}COR\textsuperscript{64};

R\textsuperscript{77} is -C\textsubscript{6}H\textsubscript{5}R\textsuperscript{67}R\textsuperscript{68}R\textsuperscript{69}R\textsuperscript{70}R\textsuperscript{76}; or a heteroaryl group of one of the formulae

\begin{align*}
\text{H1} & \quad \text{H2} & \quad \text{H3} & \quad \text{H4} & \quad \text{H5} \\
\text{H6} & \quad \text{H7} & \quad \text{H8} & \quad \text{H9} & \quad \text{H10} \\
\text{H11} & \quad \text{H12} & \quad \text{H13} & \quad \text{H14} & \quad \text{H15} \\
\text{H16} & \quad \text{H17} & \quad \text{H18} & \quad \text{H19} & \quad \text{H20} \\
\text{H21} & \quad \text{H22} & \quad \text{H23} & \quad \text{H24} & \quad \text{H25} \\
\text{H26} & \quad \text{H27} & \quad \text{H28} & \quad \text{H29} \\
\end{align*}
$R^{78}$ is H; lower alkyl; aryl; or aryl-lower alkyl;

$R^{78}$ and $R^{82}$ taken together can form: \((-\text{CH}_2)_{2-6}\); \((-\text{CH}_2)\text{O(\text{CH}_2)}_2\); \((-\text{CH}_2)\text{S(\text{CH}_2)}_2\); or
- \((\text{CH}_2)_2\text{NR}^7\text{(CH}_2)_2\text{)}^{-};
R^75 \text{ is } H; \text{ lower alkyl; aryl; or aryl-lower alkyl; or}
R^78 \text{ and } R^79, \text{ taken together, can be } -\text{(CH}_2)_2\text{Z-}; -\text{(CH}_2)_2\text{O(CH}_2)_2\text{Z-}; \text{ or } -\text{(CH}_2)_2\text{NR}^7\text{(CH}_2)_2\text{Z-};
R^80 \text{ is } H; \text{ or lower alkyl;}
\text{ 5} \ R^81 \text{ is } H; \text{ lower alkyl; or aryl-lower alkyl;}
R^82 \text{ is } H; \text{ lower alkyl; or heteroaryl; or aryl-lower alkyl;}
R^83 \text{ and } R^84 \text{ taken together can form: } -\text{(CH}_2)_2\text{Z-6-}; -\text{(CH}_2)_2\text{O(CH}_2)_2\text{Z-}; -\text{(CH}_2)_2\text{S(CH}_2)_2\text{Z-; or}
-\text{(CH}_2)_2\text{NR}^7\text{(CH}_2)_2\text{Z-};
R^85 \text{ is } H; \text{ lower alkyl; or lower alkenyl;}
\text{ 10} \ R^86 \text{ is } H; \text{ lower alkyl, where } H \text{ is maybe substituted by halogen; or halogen;}
R^87 \text{ is } H; \text{ lower alkyl, where } H \text{ is maybe substituted by halogen; or halogen;}

\text{with the proviso that in said chain of } 11 \alpha\text{-amino acid residues } Z

\text{20} \ \text{the amino acid residues in positions 1 to 11 are:}
- P1: of type C, or of type D, or of type E, or of type F;
- P2: of type C, or of Type D, or of type E, or of type F;
- P3: or of type C, of type F, or the residue is Gly;
- P4: of type C, or of type D, or of type F, or of type E, or the residue is Gly or Pro;
- P5: of type E, or of type C, or of type F, or the residue is Gly or Pro;
- P6: of type E, or of type C, or of type E, or of type C, or the residue is Gly or Pro;
- P7: of type C, or of type E, or of type F or of formula } -\text{A-CO}-, \text{ or the residue is Gly or Pro;}
- P8: of type D, or of type C, or of type F, or of formula } -\text{A-CO}-, \text{ or the residue is Gly or Pro or Pro(4NHCOPhe)};
- P9: of type C, or of type D, or of type E, or of type F;
- P10: of type D, or of type C, or of type F, or of type E; and
- P11: of type C, or of type D, or of type E, or of type F; or
- P2 and P10, taken together, can form a group of type H; and with the further proviso that if the template is $^{D}$Pro$^{L}$Pro the amino acid residues in positions P1 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
- P7: Pro
- P8: Pro
- P9: Ile
- P10: Cys, linked with Cys in position P10 by a disulfide bridge; and
- P11: Phe;

and pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1 or 2 wherein

\[
\begin{array}{c}
\text{Template} \\
\end{array}
\]

is a group of formula (a1) or (a2) or (a3).

3. Compounds according to claim 2 wherein A is a group of one of the formulae A1 to A69;

25 R$^{1}$ is hydrogen or lower alkyl;
R$^{2}$ is H, lower alkyl; lower alkenyl; -(CH$_{2}$)$_{n}$OR$^{55}$ (where R$^{55}$ is lower alkyl; or lower alkenyl); -(CH$_{2}$)$_{n}$SR$^{56}$ (where R$^{56}$ is lower alkyl; or lower alkenyl); -(CH$_{2}$)$_{n}$NR$^{53}$R$^{54}$ (where R$^{53}$ is lower alkyl; or lower alkenyl; R$^{54}$ is H; or lower alkyl; or R$^{53}$ and R$^{54}$ taken together are -(CH$_{2}$)$_{2}$-; -(CH$_{2}$)$_{2}$O(CH$_{2}$)$_{2}$-;
- (CH$_{2}$)$_{2}$S(CH$_{2}$)$_{2}$-; or -(CH$_{2}$)$_{2}$NR$^{57}$(CH$_{2}$)$_{2}$-; where R$^{57}$ is H; or lower alkyl); - (CH$_{2}$)$_{n}$OCONR$^{53}$R$^{75}$ (where R$^{33}$ is H; lower alkyl; or lower alkenyl; R$^{75}$ is lower alkyl; or R$^{33}$ and R$^{75}$ taken together are -(CH$_{2}$)$_{2}$-; -(CH$_{2}$)$_{2}$O(CH$_{2}$)$_{2}$-; -(CH$_{2}$)$_{2}$S(CH$_{2}$)$_{2}$-; or -(CH$_{2}$)$_{2}$NR$^{57}$(CH$_{2}$)$_{2}$-; where R$^{57}$ is H; or}
lower alkyl); -\((\text{CH}_2)\text{nNR}^{35}\text{CONR}^{33}\text{R}^{82}\) (where \(\text{R}^{20}\) is H; or lower alkyl; \(\text{R}^{33}\) is H; or lower alkyl; or lower alkenyl; \(\text{R}^{82}\) is H; or lower alkyl; or \(\text{R}^{33}\) and \(\text{R}^{82}\) taken together are \(-\text{CH}_2\text{O(CH}_2\text{)}\text{z}\)-; \(-\text{CH}_2\text{S(CH}_2\text{)}\text{z}\)-; 5
\(-\text{CH}_2\text{S(CH}_2\text{)}\text{z}\)-; or \(-\text{CH}_2\text{pNR}^{57}\text{(CH}_2\text{)}\text{z}\)-; where \(\text{R}^{57}\) is H; or lower alkyl); -\((\text{CH}_2)\text{pN(OR}^{20}\text{)}\text{COR}^{64}\) (where: \(\text{R}^{20}\) is H; or lower alkyl; \(\text{R}^{64}\) is lower alkyl; or lower alkenyl); \((\text{CH}_2)\text{pCOOR}^{57}\) (where \(\text{R}^{57}\) is lower alkyl; or lower alkenyl); \((\text{CH}_2)\text{pCONR}^{58}\text{R}^{59}\) (where \(\text{R}^{58}\) is lower alkyl; or lower alkenyl; and \(\text{R}^{59}\) is H; or lower alkyl; or \(\text{R}^{58}\) and \(\text{R}^{59}\) taken together are \(-\text{CH}_2\text{O(CH}_2\text{)}\text{z}\)-; \(-\text{CH}_2\text{S(CH}_2\text{)}\text{z}\)-; or \(-\text{CH}_2\text{pNR}^{57}\text{(CH}_2\text{)}\text{z}\)-; where \(\text{R}^{57}\) is H; or lower alkyl; \(\text{R}^{3}\) is H; or lower alkenyl; \(-\text{CH}_2\text{pOR}^{55}\) (where \(\text{R}^{55}\) is lower alkyl; or lower alkyl); -\((\text{CH}_2)\text{pSR}^{56}\) (where \(\text{R}^{56}\) is lower alkyl; or lower alkenyl); \((\text{CH}_2)\text{pNR}^{33}\text{R}^{34}\) (where \(\text{R}^{33}\) is lower alkyl; or lower alkenyl; \(\text{R}^{34}\) is H; or lower alkyl; or \(\text{R}^{33}\) and \(\text{R}^{34}\) taken together are \(-\text{CH}_2\text{O(CH}_2\text{)}\text{z}\)-; \(-\text{CH}_2\text{S(CH}_2\text{)}\text{z}\)-; \(-\text{CH}_2\text{pNR}^{57}\text{(CH}_2\text{)}\text{z}\)-; where \(\text{R}^{57}\) is H; or lower alkyl; \(\text{R}^{3}\) is H; or lower alkenyl; \(-\text{CH}_2\text{pOR}^{55}\) (where \(\text{R}^{55}\) is lower alkyl; or lower alkyl); \(-\text{CH}_2\text{pOCONR}^{53}\text{R}^{75}\) (where \(\text{R}^{75}\) is H; or lower alkyl; or lower alkenyl; \(\text{R}^{75}\) is lower alkyl; or \(\text{R}^{33}\) and \(\text{R}^{75}\) taken together are \(-\text{CH}_2\text{O(CH}_2\text{)}\text{z}\)-; \(-\text{CH}_2\text{S(CH}_2\text{)}\text{z}\)-; \(-\text{CH}_2\text{pNR}^{57}\text{(CH}_2\text{)}\text{z}\)-; where \(\text{R}^{57}\) is H; or lower alkyl; \((\text{CH}_2)\text{pNR}^{20}\text{CONR}^{33}\text{R}^{82}\) (where \(\text{R}^{20}\) is H; or lower alkyl; \(\text{R}^{58}\) is lower alkyl; or lower alkenyl; \(\text{R}^{33}\) is H; or lower alkyl; \(\text{R}^{33}\) and \(\text{R}^{82}\) taken together are \(-\text{CH}_2\text{O(CH}_2\text{)}\text{z}\)-; \(-\text{CH}_2\text{S(CH}_2\text{)}\text{z}\)-; \(-\text{CH}_2\text{pNR}^{57}\text{(CH}_2\text{)}\text{z}\)-; where \(\text{R}^{57}\) is H; or lower alkyl; \(-\text{CH}_2\text{pO(OR}^{60}\text{)}\text{z}\)-; \(-\text{CH}_2\text{pSO}_2\text{R}^{62}\) (where \(\text{R}^{62}\) is lower alkyl; or lower alkenyl); \(-\text{CH}_2\text{pCOOR}^{57}\) (where \(\text{R}^{57}\) is lower alkyl; or lower alkenyl); \(-\text{CH}_2\text{pCONR}^{58}\text{R}^{59}\) (where \(\text{R}^{58}\) is lower alkyl; or lower alkenyl; and \(\text{R}^{59}\) is H; or lower alkyl; or \(\text{R}^{58}\) and \(\text{R}^{59}\) taken together are \(-\text{CH}_2\text{O(CH}_2\text{)}\text{z}\)-; \(-\text{CH}_2\text{S(CH}_2\text{)}\text{z}\)-; or \(-\text{CH}_2\text{pNR}^{57}\text{(CH}_2\text{)}\text{z}\)-; where \(\text{R}^{57}\) is H; or lower alkyl; or lower alkenyl); \(-\text{CH}_2\text{pO(OR}^{60}\text{)}\text{z}\)-; \(-\text{CH}_2\text{pSO}_2\text{R}^{62}\) (where \(\text{R}^{62}\)
is lower alkyl; or lower alkenyl; or -(CH₂)₅C₆H₄R⁸ (where R⁸ is H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

R⁴ is H; lower alkyl; lower alkenyl; -(CH₂)₅OR⁵⁵ (where R⁵⁵ is lower alkyl; or lower alkenyl);

5  -(CH₂)₅SR⁵⁶ (where R⁵⁶ is lower alkyl; or lower alkenyl); -(CH₂)₅NR³⁵R³⁴ (where R³³ is lower alkyl; or lower alkenyl; R³⁴ is H; or lower alkyl; or R³³ and R³⁴ taken together are -(CH₂)₂₋₆₋;

 -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷ is H; or lower alkyl);

10  -(CH₂)₅OCONR³⁵R⁷⁵ (where R³³ is H; or lower alkyl; or lower alkenyl; R⁷⁵ is lower alkyl; or R³³ and R⁷⁵ taken together are -(CH₂)₂₋₆₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷ is H; or lower alkyl); -(CH₂)₅NR²⁰CONR³⁵R⁸² (where R²⁰ is H; or lower alkyl; R³³ is H; or lower alkyl; or lower alkenyl; R⁸² is H; or lower alkyl; or R³³ and R⁸² taken together are -(CH₂)₂₋₆₋;

15  -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷ is H; or lower alkyl);

 -(CH₂)₅N(R²⁰)COR⁵⁶ (where: R²⁰ is H; or lower alkyl; R⁵⁶ is lower alkyl; or lower alkenyl);

 -(CH₂)₅COOR⁵⁷ (where R⁵⁷ is lower alkyl; or lower alkenyl); -(CH₂)₅CONR²⁸R⁵⁹ (where R²⁰ is H; or lower alkyl; and R⁵⁹ is H; or lower alkyl; or R²⁰ and R⁵⁹ taken together are -(CH₂)₂₋₆₋;

 -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷ is H; or lower alkyl);

 -(CH₂)₅PO(OR⁶₀)₂ (where R⁶₀ is lower alkyl; or lower alkenyl); -(CH₂)₅SO₂R⁶² (where R⁶² is lower alkyl; or lower alkenyl); or -(CH₂)₅C₆H₄R⁸ (where R⁸ is H; F; C½; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

 R⁵ is lower alkyl; lower alkenyl; -(CH₂)₅OR⁵⁵ (where R⁵⁵ is lower alkyl; or lower alkenyl);

 -(CH₂)₅SR⁵⁶ (where R⁵⁶ is lower alkyl; or lower alkenyl); (CH₂)₅NR³⁵R³⁴ (where R³³ is lower alkyl; or lower alkenyl; R³⁴ is H; or lower alkyl; or R³³ and R³⁴ taken together are -(CH₂)₂₋₆₋; -(CH₂)₂O(CH₂)₂₋;

 -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷ is H; or lower alkyl); -(CH₂)₅OCONR³⁵R⁷⁵ (where R³³ is H; or lower alkyl; or lower alkenyl; R⁷⁵ is lower alkyl; or R³³ and R⁷⁵ taken together are -(CH₂)₂₋₆₋; or -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷ is H; or lower alkyl); -(CH₂)₅NR²⁰CONR³⁵R⁸² (where R²⁰ is H; or lower lower alkyl; R³³ is H; or
lower alkyl; or lower alkenyl; R^32 is H; or lower alkyl; or R^33 and R^32 taken together are -
(CH_2)_2O(CH_2)_2; -
(CH_2)_2S(CH_2)_2; or -
(CH_2)_2NR^37(CH_2)_2; where R^37 is H; or lower alkyl); -
(CH_2)_2N(R^20)COR^64 (where: R^20 is H; or lower alkyl; R^64 is alkyl; aryl; aryl-
lower alkyl; or heteroaryl-lower alkyl); -
(CH_2)_2COOR^57 (where R^57 is lower alkyl; or lower alkenyl); -
(CH_2)_2CONR^58R^59 (where R^58 is lower alkyl; or lower alkenyl; and R^59 is
H; or lower alkyl; or R^58 and R^59 taken together are -
(CH_2)_2O(CH_2)_2; -
(CH_2)_2S(CH_2)_2; or -
(CH_2)_2NR^57(CH_2)_2; where R^57 is H; or lower alkyl)

- 
(CH_2)_2PO(OR^60)_2 (where R^60 is lower alkyl; or lower alkenyl); -
(CH_2)_2SO_2R^62 (where R^62 is lower alkyl; or lower alkenyl); or -
(CH_2)_2C_6H_5R^8 (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy):
R^8 is H; lower alkyl; lower alkenyl; -
(CH_2)_2OR^55 (where R^55 is lower alkyl; or lower alkenyl):

- 
(CH_2)_2SR^56 (where R^56 is lower alkyl; or lower alkenyl); -
(CH_2)_2NR^33R^34 (where R^33 is
lower alkyl; or lower alkenyl; R^34 is H; or lower alkyl; or R^33 and R^34 taken together are -
(CH_2)_2O(CH_2)_2; -
(CH_2)_2S(CH_2)_2; or -
(CH_2)_2NR^37(CH_2)_2; where R^37 is H; or lower alkyl)

- 
(CH_2)_2OCONR^35R^36 (where R^35 is H; or lower alkyl; or lower alkenyl; R^36 is H; or lower alkyl; or R^35 and R^36 taken together are -
(CH_2)_2O(CH_2)_2; -
(CH_2)_2S(CH_2)_2; or -
(CH_2)_2NR^57(CH_2)_2; where R^57 is H; or lower alkyl)

- 
(CH_2)_2N(R^20)COR^64 (where R^20 is H; or lower alkyl; R^64 is lower alkyl; or lower alkenyl):

- 
(CH_2)_2COOR^57 (where R^57 is lower alkyl; or lower alkenyl); -
(CH_2)_2CONR^58R^59 (where R^58 is lower alkyl; or lower alkenyl; and R^59 is H; or lower alkyl; or R^58 and R^59 taken together are -
(CH_2)_2O(CH_2)_2; -
(CH_2)_2S(CH_2)_2; or -
(CH_2)_2NR^57(CH_2)_2; where R^57 is H; or lower alkyl)

- 
(CH_2)_2PO(OR^60)_2 (where R^60 is lower alkyl; or lower alkenyl); -
(CH_2)_2SO_2R^62 (where R^62 is lower alkyl; or lower alkenyl); or -
(CH_2)_2C_6H_5R^8 (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy):
R^8 is lower alkyl; lower alkenyl; -
(CH_2)_2OR^55 (where R^55 is lower alkyl; or lower alkenyl)

- 
(CH_2)_2SR^56 (where R^56 is lower alkyl; or lower alkenyl); -
(CH_2)_2NR^33R^34 (where R^33 is lower alkyl; or lower alkenyl; R^34 is H; or lower alkyl; or R^33 and R^34 taken together are -
(CH₂)₂S(CH₂)₂⁻; - (CH₂)₂O(CH₂)₂⁻; 
- (CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR⁻(CH₂)₂⁻; where R⁻ is H; or lower alkyl); - 
(CH₂)₂OCONR⁻R⁻(CH₂)₂⁻; (where R⁻ is H; or lower alkyl; or lower alkenyl; R⁻ is lower alkyl; 
or R⁻ and R⁻ taken together are 
5 - (CH₂)₂2; - (CH₂)₂O(CH₂)₂⁻; - (CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR⁻(CH₂)₂⁻; where R⁻ is H; or 
lower alkyl); - (CH₂)₂QR⁻CONR⁻R⁻(CH₂)₂⁻; (where R⁻ is H; or lower alkyl; R⁻ is H; or lower 
alkyl; or lower alkenyl; R⁻ is H; or lower alkyl; or R⁻ and R⁻ taken together are - (CH₂)₂. 
5-; - (CH₂)₂O(CH₂)₂⁻; - (CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR⁻(CH₂)₂⁻; where R⁻ is H; or lower 
alkyl); - (CH₂)₂N(R⁻COR⁻(where: R⁻ is H; or lower alkyl; R⁻ is lower alkyl; or lower 
alkenyl); - (CH₂)₂COOR⁻ (where R⁻ is lower alkyl; or lower alkenyl); - 
(CH₂)₂CONR⁻R⁻(where: R⁻ is lower alkyl; or lower alkenyl; and R⁻ is H; or lower alkyl; or R⁻ and R⁻ taken together are 
10 - (CH₂)₂2; - (CH₂)₂O(CH₂)₂⁻; - (CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR⁻(CH₂)₂⁻; where R⁻ is H; or lower 
alkyl); - (CH₂)₂OR⁻(where: R⁻ is H; or lower alkyl; or lower alkenyl); - 
(CH₂)₂CONR⁻R⁻(where: R⁻ is lower alkyl; or lower alkenyl; and R⁻ is H; or lower alkyl; or R⁻ and R⁻ taken together are 
15 - (CH₂)₂2; - (CH₂)₂O(CH₂)₂⁻; - (CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR⁻(CH₂)₂⁻; where R⁻ is H; or lower 
alkyl); - (CH₂)₂OR⁻(where: R⁻ is H; or lower alkyl; or lower alkenyl); - 
(CH₂)₂CONR⁻R⁻(where: R⁻ is lower alkyl; or lower alkenyl; and R⁻ is H; or lower alkyl; or R⁻ and R⁻ taken together are 
20 (CH₂)₂2; - (CH₂)₂O(CH₂)₂⁻; - (CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR⁻(CH₂)₂⁻; where R⁻ is H; or lower 
alkyl); - (CH₂)₂CONR⁻R⁻(where: R⁻ is H; or lower alkyl; or lower alkenyl; R⁻ is lower alkyl; 
or R⁻ and R⁻ taken together are - (CH₂)₂2; - (CH₂)₂O(CH₂)₂⁻; - (CH₂)₂S(CH₂)₂⁻; or - 
25 (CH₂)₂NR⁻(CH₂)₂⁻; where R⁻ is H; or lower alkyl); - (CH₂)₂OR⁻(where: R⁻ is H; or lower alkyl; or lower alkenyl; R⁻ is H; or lower alkyl; or lower alkenyl; R⁻ is H; or lower alkyl; or R⁻ and R⁻ taken together are - (CH₂)₂2; - 
20 (CH₂)₂O(CH₂)₂⁻; - (CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR⁻(CH₂)₂⁻; where R⁻ is H; or lower 
alkyl); - (CH₂)₂OR⁻(where: R⁻ is H; or lower alkyl; or lower alkenyl); - 
(CH₂)₂CONR⁻R⁻(where: R⁻ is lower alkyl; or lower alkenyl); - (CH₂)₂CONR⁻R⁻(where: R⁻ is lower alkyl; or lower alkenyl); - 
30 (CH₂)₂OR⁻(where: R⁻ is H; or lower alkyl; R⁻ is lower alkyl; or lower alkenyl); - (CH₂)₂COOR⁻(where: R⁻ is lower alkyl; or lower alkenyl); - (CH₂)₂CONR⁻R⁻(where: R⁻ is lower alkyl; or lower alkenyl); - (CH₂)₂CONR⁻R⁻(where: R⁻ is lower alkyl; or lower alkenyl; and R⁻ is H; or lower alkyl; or R⁻ and R⁻ taken together are - (CH₂)₂2; - 
35 (CH₂)₂O(CH₂)₂⁻; - (CH₂)₂S(CH₂)₂⁻; or -(CH₂)₂NR⁻(CH₂)₂⁻; where R⁻ is H; or lower 
alkyl);
150
-(CH$_2$)$_n$PO(OR$^{60}$)$_2$ (where R$^{60}$ is lower alkyl; or lower alkenyl); -(CH$_2$)$_n$SO$_2$R$^{62}$ (where R$^{62}$ is lower alkyl; or lower alkenyl); or -(CH$_2$)$_n$C$_8$H$_8$R$^{8}$ (where R$^{8}$ is H; F; Cl; CF$_3$; lower alkyl; lower alkenyl; or lower alkoxy);
R$^9$ is lower alkyl; lower alkenyl; -(CH$_2$)$_n$OR$^{55}$ (where R$^{55}$ is lower alkyl; or lower alkylen); -(CH$_2$)$_n$SR$^{56}$ (where R$^{56}$ is lower alkyl; or lower alkenyl); -(CH$_2$)$_n$NR$^{33}$R$^{34}$ (where R$^{33}$ is lower alkyl; or lower alkenyl; R$^{34}$ is H; or lower alkyl; or R$^{33}$ and R$^{34}$ taken together are -
(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$ is H; or lower alkyl); -
(CH$_2$)$_n$OCONR$^{33}$R$^{75}$ (where R$^{33}$ is H; or lower alkyl; or lower alkenyl; R$^{75}$ is lower alkyl; or R$^{33}$ and R$^{75}$ taken together are
(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$ is H; or lower alkyl); -
(CH$_2$)$_n$N(R$^{20}$)COR$^{64}$ (where R$^{20}$ is H; or lower alkyl; R$^{64}$ is lower alkyl; or lower alkenyl); -(CH$_2$)$_n$COOR$^{57}$ (where R$^{57}$ is lower alkyl; or lower alkenyl); -(CH$_2$)$_n$CONR$^{38}$R$^{59}$ (where R$^{38}$ is lower alkyl; or lower alkenyl; and R$^{59}$ is H; or lower alkyl; or R$^{38}$ and R$^{59}$ taken together are
(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$ is H; or lower alkyl); -(CH$_2$)$_n$PO(OR$^{60}$)$_2$ (where R$^{60}$ is lower alkyl; or lower alkenyl); -(CH$_2$)$_n$SO$_2$R$^{62}$ (where R$^{62}$ is lower alkyl; or lower alkenyl); or -(CH$_2$)$_n$C$_8$H$_8$R$^{8}$ (where R$^{8}$ is H; F; Cl; CF$_3$; lower alkyl; lower alkenyl; or lower alkoxy);
25
R$^{10}$ is lower alkyl; lower alkenyl; -(CH$_2$)$_n$OR$^{55}$ (where R$^{55}$ is lower alkyl; or lower alkylen); -(CH$_2$)$_n$SR$^{56}$ (where R$^{56}$ is lower alkyl; or lower alkenyl); -(CH$_2$)$_n$NR$^{33}$R$^{34}$ (where R$^{33}$ is lower alkyl; or lower alkenyl; R$^{34}$ is H; or lower alkyl; or R$^{33}$ and R$^{34}$ taken together are -
(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$ is H; or lower alkyl); -
(CH$_2$)$_n$OCONR$^{33}$R$^{75}$ (where R$^{33}$ is H; or lower alkyl; or lower alkenyl; R$^{75}$ is lower alkyl; or R$^{33}$ and R$^{75}$ taken together are
(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$; -(CH$_2$)$_2$S(CH$_2$)$_2$; or -(CH$_2$)$_2$NR$^{57}$(CH$_2$)$_2$; where R$^{57}$: H is or lower alkyl); -(CH$_2$)$_n$NR$^{20}$CONR$^{38}$R$^{59}$ (where R$^{20}$ is H; or lower lower alkyl; R$^{33}$ is H; or lower alkyl; or lower alkenyl; R$^{82}$ is H; or lower alkyl; or R$^{33}$ and R$^{82}$ taken together are -
(CH$_2$)$_{2-6}$; -(CH$_2$)$_2$O(CH$_2$)$_2$;
- (CH₂)₃S(CH₂)₂--; or -(CH₂)₂NR³⁷(CH₂)₂--; where R³⁷ is H; or lower alkyl; - (CH₂)₃N(R²⁵)COR⁶⁴ (where R²⁵ is H; or lower alkyl; R⁶⁴ is lower alkyl; or lower alkenyl); -(CH₂)₂COOR⁵⁷ (where R⁵⁷ is lower alkyl; or lower alkenyl); -(CH₂)₂CONR³⁸R⁵⁹ (where R³⁸ is lower alkyl; or lower alkenyl; and R⁵⁹ is H; lower alkyl; or R³⁸ and R⁵⁹ taken together are

- (CH₂)₂O(CH₂)₂--; -(CH₂)₂S(CH₂)₂--; or -(CH₂)₂NR³⁷(CH₂)₂--; where R³⁷ is H; or lower alkyl; -(CH₂)₂PO(OR⁶⁰)₂ (where R⁶⁰ is lower alkyl; or lower alkenyl); -(CH₂)₂SO₂R⁶² (where R⁶² is lower alkyl; or lower alkenyl); or -(CH₂)₂C₆H₄R⁸ (where R⁸ is H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy);

R¹¹ is H; lower alkyl; lower alkenyl; -(CH₂)ₘOR⁵⁵ (where R⁵⁵ is lower alkyl; or lower alkenyl);

-(CH₂)ₘSR⁶⁶ (where R⁶⁶ is lower alkyl; or lower alkenyl); -(CH₂)ₘNR³⁵R⁴⁹ (where R³⁵ is lower alkyl; or lower alkenyl; R⁴⁹ is H; or lower alkyl; or R³⁵ and R⁴⁹ taken together are

-(CH₂)₂O(CH₂)₂--; -(CH₂)₂S(CH₂)₂--; or -(CH₂)₂NR³⁷(CH₂)₂--; where R³⁷ is H; or lower alkyl;

-(CH₂)ₘOCONR³⁶R⁷⁰ (where R³⁶ is H; or lower alkyl; or lower alkenyl; R⁷⁰ is lower alkyl; or lower alkenyl; or R³⁶ and R⁷⁰ taken together are

-(CH₂)₂O(CH₂)₂--; -(CH₂)₂S(CH₂)₂--; or -(CH₂)₂NR³⁷(CH₂)₂--; where R³⁷ is H; or lower alkyl;

-(CH₂)ₘN(R²⁰)COR⁶⁴ (where R²⁰ is H; or lower alkyl; R⁶⁴ is lower alkyl; or lower alkenyl);

-(CH₂)ₙCOOR³⁷ (where R³⁷ is lower alkyl; or lower alkenyl); -(CH₂)ₙCONR³⁸R⁵⁹ (where R³⁸ is lower alkyl; or lower alkenyl; and R⁵⁹ is H; lower alkyl; or R³⁸ and R⁵⁹ taken together are

-(CH₂)₂O(CH₂)₂--; -(CH₂)₂S(CH₂)₂--; or -(CH₂)₂NR³⁷(CH₂)₂--; where R³⁷ is H; or lower alkyl;

-(CH₂)ₙPO(OR⁶⁰)₂ (where R⁶⁰ is lower alkyl; or lower alkenyl); -(CH₂)ₙSO₂R⁶² (where R⁶² is lower alkyl; or lower alkenyl); or -(CH₂)ₙC₆H₄R⁸ (where R⁸ is H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy);

R¹² is H; lower alkyl; lower alkenyl; -(CH₂)ₘOR⁵⁵ (where R⁵⁵ is lower alkyl; or lower alkenyl);

-(CH₂)ₘSR⁶⁶ (where R⁶⁶ is lower alkyl; or lower alkenyl); -(CH₂)ₘNR³⁵R⁴⁹ (where R³⁵ is lower alkyl; or lower alkenyl); and R⁴⁹ is H; lower alkyl; or R³⁵ and R⁴⁹ taken together are

-(CH₂)₂O(CH₂)₂--; -(CH₂)₂S(CH₂)₂--; or -(CH₂)₂NR³⁷(CH₂)₂--; where R³⁷ is H; or lower alkyl;
lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -
(CH_2)_2-; -(CH_2)_2O(CH_2)_2-; -(CH_2)_2S(CH_2)_2-; or -(CH_2)_2NR^{57}(CH_2)_2-; where R^{57} is H; or lower
alkyl);

5
-(CH_2)_mOCONR^{35}R^{75} (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl;
or R^{33} and R^{75} taken together are -
(CH_2)_2-; -(CH_2)_2O(CH_2)_2-; -(CH_2)_2S(CH_2)_2-; or -(CH_2)_2NR^{57}(CH_2)_2-; where R^{57} is H; or lower
alkyl); -(CH_2)_nNR^{20}CONR^{35}R^{82} (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower
alkenyl; or R^{33} and R^{82} taken together are -
(CH_2)_2-; -(CH_2)_2O(CH_2)_2-; -(CH_2)_2S(CH_2)_2-; or -(CH_2)_2NR^{57}(CH_2)_2-; where R^{57} is H; or lower
alkyl);

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-(CH_2)_mN(R^{20})COR^{64} (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower
alkenyl);
-(CH_2)_mCOOR^{57} (where R^{57} is lower alkyl; or lower alkenyl); -(CH_2)_mCONR^{58}R^{59} (where
R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken

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together are -
(CH_2)_2-; -(CH_2)_2O(CH_2)_2-; -(CH_2)_2S(CH_2)_2-; or -(CH_2)_2NR^{57}(CH_2)_2-; where R^{57} is H; or lower
alkyl);
-(CH_2)_mPO(OR^{60})_2 (where R^{60} is lower alkyl; or lower alkenyl); -(CH_2)_nSO_2R^{62} (where R^{62}
is lower alkyl; or lower alkenyl); or -(CH_2)_nC_6H_4R^{6} (where R^{4} is H; F; Cl; CF_3; lower
alkyl; or lower alkenyl; or lower alkoxy):
R^{13} is lower alkyl; lower alkenyl; -(CH_2)_nOR^{55} (where R^{55} is lower alkyl; or lower
alkenyl);
-(CH_2)_nSR^{56} (where R^{56} is lower alkyl; or lower alkenyl); -(CH_2)_nNR^{32}R^{34} (where R^{32} is
lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -
(CH_2)_2-; -(CH_2)_2O(CH_2)_2-; -(CH_2)_2S(CH_2)_2-; or -(CH_2)_2NR^{57}(CH_2)_2-; where R^{57} is H; or lower
alkyl); -(CH_2)_nOCONR^{31}R^{73} (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl;
or R^{33} and R^{75} taken together are -
(CH_2)_2-; -(CH_2)_2O(CH_2)_2-; -(CH_2)_2S(CH_2)_2-; or -(CH_2)_2NR^{57}(CH_2)_2-; where R^{57} is H; or lower
alkyl); -(CH_2)_nNR^{20}CONR^{35}R^{82} (where R^{20} is H; or lower alkyl; R^{33} is H; or lower
alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are -
(CH_2)_2-; -(CH_2)_2O(CH_2)_2-; -(CH_2)_2S(CH_2)_2-; or -(CH_2)_2NR^{57}(CH_2)_2-; where R^{57} is H; or lower
alkyl); -(CH_2)_nN(R^{2b})COR^{64} (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower
alkenyl); -(CH_2)_nCOOR^{57} (where R^{57} is lower alkyl; or lower alkenyl); -
(CH₂)₄CONR²⁵R⁵⁹ (where R²⁵ is lower alkyl; or lower alkenyl; and R⁵⁹ is H; or lower alkyl; or R²⁵ and R⁵⁹ taken together are - (CH₂)₂₋₆₋; - (CH₂)₂O(CH₃)₂₋; - (CH₂)₂S(CH₂)₂₋; or - (CH₂)₂NR²⁷(CH₂)₂₋; where R²⁷ is H; or lower alkyl); - (CH₂)₂PO(OR²⁰)₂ (where R²⁰ is lower alkyl; or lower alkenyl); - (CH₂)₂SO₂R⁶² (where R⁶² is lower alkyl; or lower alkenyl); or - (CH₂)₄C₆H₄R⁸ (where R⁸ is H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy); R¹⁴ is H; lower alkyl; lower alkenyl; - (CH₂)ₗOR⁵⁵ (where R⁵⁵ is lower alkyl; or lower alkenyl); - (CH₂)ₗSR²⁶ (where R²⁶ is lower alkyl; or lower alkenyl); - (CH₂)ₗNR³⁳R⁴⁴ (where R³³ is lower alkyl; or lower alkenyl; R³⁴ is H; or lower alkyl; or R³³ and R³⁴ taken together are - (CH₂)₂₋₆₋; - (CH₂)₂O(CH₂)₂₋; - (CH₂)₂S(CH₂)₂₋; or - (CH₂)₂NR²⁷(CH₂)₂₋; where R²⁷ is H; or lower alkyl); - (CH₂)ₗOCONR³⁵R⁷⁵ (where R³⁵ is H; or lower alkyl; or lower alkenyl; R⁷⁵ is lower alkyl; or R³³ and R⁷⁵ taken together are - (CH₂)₂₋₆₋; - (CH₂)₂O(CH₂)₂₋; - (CH₂)₂S(CH₂)₂₋; or - (CH₂)₂NR²⁷(CH₂)₂₋; where R²⁷ is H; or lower alkyl); - (CH₂)ₗN(R²⁰)COR⁶⁴ (where: R²⁰ is H; lower alkyl; R⁶⁴ is lower alkyl; or lower alkenyl); - (CH₂)ₗCOOR⁵⁷ (where R⁵⁷ is lower alkyl; or lower alkenyl); - (CH₂)ₗCONR²⁵R⁵⁹ (where R²⁵ is lower alkyl; or lower alkenyl; and R⁵⁹ is H; or lower alkyl; or R²⁵ and R⁵⁹ taken together are - (CH₂)₂₋₆₋; - (CH₂)₂O(CH₂)₂₋; - (CH₂)₂S(CH₂)₂₋; or - (CH₂)₂NR²⁷(CH₂)₂₋; where R²⁷ is H; or lower alkyl); - (CH₂)ₗPO(OR²⁰)₂ (where R²⁰ is lower alkyl; or lower alkenyl); - (CH₂)ₗSO₂R⁶² (where R⁶² is lower alkyl; or lower alkenyl); or - (CH₂)₄C₆H₄R⁸ (where R⁸ is H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy); R¹⁵ is lower alkyl; lower alkenyl; - (CH₂)ₗOR⁵⁵ (where R⁵⁵ is lower alkyl; or lower alkenyl); - (CH₂)ₗSR²⁶ (where R²⁶ is lower alkyl; or lower alkenyl); - (CH₂)ₗNR³³R⁴⁴ (where R³³ is lower alkyl; or lower alkenyl; R⁴⁴ is H; or lower alkyl; or R³³ and R⁴⁴ taken together are - (CH₂)₂₋₆₋; - (CH₂)₂O(CH₂)₂₋; - (CH₂)₂S(CH₂)₂₋; or - (CH₂)₂NR²⁷(CH₂)₂₋; where R²⁷ is H; or lower alkyl); - (CH₂)ₗOCONR³⁵R⁷⁵ (where R³⁵ is H; or lower alkyl; or lower alkenyl; R⁷⁵ is lower alkyl; or lower alkenyl; or lower alkoxy);
or $R^{33}$ and $R^{75}$ taken together are 
- $(CH_2)_2$O$(CH_2)_2$; - $(CH_2)_2O$(CH$_2$)$_2$; - $(CH_2)_2S$(CH$_2$)$_2$; or - $(CH_2)_2NR^{57}$(CH$_2$)$_2$; where $R^{57}$ is H; or lower alkyl; - $(CH_2)_2NR^{20}CONR^{68}$ (where $R^{38}$ is H; or lower lower alkyl; $R^{35}$ is H; or lower alkyl; or lower alkenyl; $R^{82}$ is H; or lower alkyl; or $R^{33}$ and $R^{82}$ taken together are -
- $(CH_2)_2$O$(CH_2)_2$; - $(CH_2)_2S$(CH$_2$)$_2$; - $(CH_2)_2NR^{57}$(CH$_2$)$_2$; where $R^{57}$ is H; or lower alkyl; - $(CH_2)_3N$(R$^{20}$)COR$^{54}$ (where $R^{20}$ is H; or lower alkyl; $R^{64}$ is lower alkyl; or lower alkenyl); -NR$^{20}$COlower alkyl (R$^{20}$=H; or lower alkyl); being particularly favoured; -
- $(CH_2)_3COOR^{57}$ (where $R^{57}$ is lower alkyl; or lower alkenyl); -$(CH_2)_3CONR^{58}$R$^{59}$ (where $R^{58}$ is lower alkyl, or lower alkenyl; and $R^{59}$ is H; lower alkyl; or $R^{58}$ and $R^{59}$ taken together are - $(CH_2)_2$O$(CH_2)_2$; - $(CH_2)_2S$(CH$_2$)$_2$; or - $(CH_2)_2NR^{57}$(CH$_2$)$_2$; where $R^{57}$ is H; or lower alkyl; - $(CH_2)_3PO(OR^{60})_2$ (where $R^{60}$ is lower alkyl; or lower alkenyl); -$(CH_2)_2SO$_2$R^{62}$ (where $R^{62}$ is lower alkyl; or lower alkenyl); or $(CH_2)_4C_6H_4R^8$ (where $R^8$ is H; F; Cl; CF$_3$; lower alkyl; lower alkenyl; or lower alkoxy); $R^{16}$ is lower alkyl; lower alkenyl; -$(CH_2)_3OR^{55}$ (where $R^{55}$ is lower alkyl; or lower alkenyl); -$(CH_2)_3SR^{55}$ (where $R^{56}$ is lower alkyl; or lower alkenyl); -$(CH_2)_3NR^{23}R^{34}$ (where $R^{33}$ is lower alkyl; or lower alkenyl; $R^{34}$ is H; or lower alkyl; or $R^{33}$ and $R^{34}$ taken together are -
- $(CH_2)_2$O$(CH_2)_2$; - $(CH_2)_2S$(CH$_2$)$_2$; or - $(CH_2)_2NR^{57}$(CH$_2$)$_2$; where $R^{57}$ is H; or lower alkyl; - $(CH_2)_3NR^{20}CONR^{13}$R$^{82}$ (where $R^{20}$ is H; or lower lower alkyl; $R^{33}$ is H; or lower alkyl; or lower alkenyl; $R^{82}$ is H; or lower alkyl; or $R^{33}$ and $R^{82}$ taken together are -
- $(CH_2)_2$O$(CH_2)_2$; - $(CH_2)_2S$(CH$_2$)$_2$; or - $(CH_2)_2NR^{57}$(CH$_2$)$_2$; where $R^{57}$ is H; or lower alkyl; - $(CH_2)_3N$(R$^{20}$)COR$^{54}$ (where $R^{20}$ is H; or lower alkyl; $R^{64}$ is lower alkyl; or lower alkenyl); -$(CH_2)_3COOR^{57}$ (where $R^{57}$ is lower alkyl; or lower alkenyl); -$(CH_2)_3CONR^{58}$R$^{59}$ (where $R^{58}$ is lower alkyl; or lower alkenyl; and $R^{59}$ is H; lower alkyl; or $R^{58}$ and $R^{59}$ taken together are - $(CH_2)_2$O$(CH_2)_2$; - $(CH_2)_2S$(CH$_2$)$_2$; or - $(CH_2)_2NR^{57}$(CH$_2$)$_2$; where $R^{57}$ is H; or lower alkyl; - $(CH_2)_3PO(OR^{60})_2$ (where $R^{60}$ is lower alkyl; or lower alkenyl); -$(CH_2)_2SO$_2$R^{62}$ (where $R^{62}$ is lower alkyl; or lower alkenyl); or $(CH_2)_4C_6H_4R^8$ (where $R^8$ is H; F; Cl; CF$_3$; lower alkyl; lower alkenyl; or lower alkoxy); and
R^{17} is lower alkyl; lower alkenyl; -(CH_{2})_{n}OR^{55} (where R^{55} is lower alkyl; or lower alkenyl);
-(CH_{2})_{n}SR^{56} (where R^{56} is lower alkyl; or lower alkenyl); -(CH_{2})_{n}NR^{33}R^{34} (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -(CH_{2})_{n-o}; -(CH_{2})_{2}O(CH_{2})_{2};
-(CH_{2})_{2}S(CH_{2})_{2}; or -(CH_{2})_{2}NR^{57}(CH_{2})_{2}; where R^{57} is H; or lower alkyl); -(CH_{2})_{2}OCONR^{33}R^{75} (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are -(CH_{2})_{n-o}; -(CH_{2})_{2}O(CH_{2})_{2}; -(CH_{2})_{2}S(CH_{2})_{2}; or -(CH_{2})_{2}NR^{57}(CH_{2})_{2}; where R^{57} is H; or lower alkyl); -(CH_{2})_{2}NR^{20}CONR^{33}R^{82} (where R^{20} is H; or lower alkyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are -(CH_{2})_{2-o}; -(CH_{2})_{2}O(CH_{2})_{2}; -(CH_{2})_{2}S(CH_{2})_{2}; or -(CH_{2})_{2}NR^{57}(CH_{2})_{2}; where R^{57} is H; or lower alkyl); -(CH_{2})_{2}N(R^{20})COR^{64} (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); -(CH_{2})_{2}COOR^{57} (where R^{57} is lower alkyl; or lower alkenyl); -(CH_{2})_{2}CONR^{58}R^{59} (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are -(CH_{2})_{2-o}; -(CH_{2})_{2}O(CH_{2})_{2}; -(CH_{2})_{2}S(CH_{2})_{2}; or -(CH_{2})_{2}NR^{37}(CH_{2})_{2}; where R^{57} is H; or lower alkyl); -(CH_{2})_{2}PO(OR^{60})_{2} (where R^{60} is lower alkyl; or lower alkenyl);
-(CH_{2})_{2}SO_{2}R^{62} (where R^{62} is lower alkyl; or lower alkenyl); or -(CH_{2})_{n}C_{6}H_{5}R^{8} (where R^{8} is H; F; Cl; CF_{3}; lower alkyl; lower alkenyl; or lower alkoxy).

4. Compounds according to claim 3 wherein A is a group of one of the formulae A5 (with R^{3} being H); A8; A22; A25; A38 (with R^{3} being H); A42; and A50.

5. Compounds according to claim 4 wherein A is a group of formula

\[ R^{1'} \]
\[ \text{A8'} \]

wherein R^{20} is H or lower alkyl; and R^{64} is alkyl; alkenyl; -[(CH_{2})_{n}-X]_{t}-CH_{3}, wherein X is -O-, -NR^{20}- or -S-, u is 1-3 and t is 1-6; aryl; aryl-lower alkyl; or heteroaryl-lower alkyl.

6. Compounds according to claim 5 wherein R^{64} is n-hexyl; n-heptyl; 4-(phenyl)benzyl; diphenylmethyl; 3-amino-propyl; 5-amino-pentyl; methyl; ethyl;
isopropyl; isobutyl; n-propyl; cyclohexyl; cyclohexylmethyl; n-butyl; phenyl; benzyl; (3-indolylmethyl); 2-(3-indolyl)ethyl; (4-phenyl)phenyl; n-nonyl; CH₃-OCH₂CH₂-OCH₂- or CH₃-(OCH₂CH₂)₂-OCH₂-.

7. Compounds according to claim 2 wherein A is a group of one of the formulae A70 to A104;
R²⁰ is H; or lower alkyl;
R¹⁸ is lower alkyl;
R¹⁹ is lower alkyl; lower alkenyl; -(CH₂)₂OR⁵⁵ (where R⁵⁵ is lower alkyl; or lower alkenyl);
(Ch₂)₂SR⁵⁶ (where R⁵⁶ is lower alkyl; or lower alkenyl); -(CH₂)₂NR³⁵R³⁴ (where R³³ is lower alkyl; or lower alkenyl; R³⁴ is H; or lower alkyl; or R³³ and R³⁴ taken together are -)
-(Ch₂)₂O(CH₂)₂-;
-(Ch₂)₂S(CH₂)₂-; or -(Ch₂)₂NR⁵⁷(CH₂)₂-; where R⁵⁷ is H; or lower alkyl;
(Ch₂)₂OCONR³⁵R⁷⁵ (where R³³ is H; or lower alkyl; or lower alkenyl; R⁷⁵ is lower alkyl; or R³³ and R⁷⁵ taken together are
(Ch₂)₂O(CH₂)₂-;
-(Ch₂)₂O(CH₂)₂-; or -(Ch₂)₂S(CH₂)₂; where R⁵⁷ is H; or lower alkyl);
(Ch₂)ₙN(R²⁰)COR⁶⁴ (where: R²⁰ is H; or lower alkyl; R⁶⁴ is lower alkyl; or lower alkenyl); (Ch₂)ₙCOOR⁷⁵ (where: R⁷⁵ is lower alkyl; or lower alkenyl); (Ch₂)ₙCONR⁵⁸R⁵⁹ (where R⁵⁸ is lower alkyl; or lower alkenyl; and R⁵⁹ is H; or lower alkyl; or R⁵⁸ and R⁵⁹ taken together are -(Ch₂)₂O(CH₂)₂-; -(Ch₂)₂O(CH₂)₂-; or -(Ch₂)₂S(CH₂)₂; or -(Ch₂)₂NR⁵⁷(CH₂)₂-; where R⁵⁷ is H; or lower alkyl); -(Ch₂)ₙPO(OR⁶⁶)₂ (where: R⁶⁶ is lower alkyl; or lower alkenyl); -(Ch₂)ₙSO₂R⁶⁶ (where: R⁶⁶ is lower alkyl; or lower alkenyl); or (Ch₂)ₙC₆H₄R⁸ (where: R⁸ is H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy);
R²¹ is H; lower alkyl; lower alkenyl; -(Ch₂)ₙOR⁵⁵ (where: R⁵⁵ is lower alkyl; or lower alkenyl);
(Ch₂)ₙSR⁵⁶ (where R⁵⁶ is lower alkyl; or lower alkenyl); -(Ch₂)ₙNR³⁵R³⁴ (where R³³ is lower alkyl; or lower alkenyl; R³⁴ is H; or lower alkyl; or R³³ and R³⁴ taken together are -(Ch₂)₂O(CH₂)₂-;
-(Ch₂)₂O(CH₂)₂-; or -(Ch₂)₂S(CH₂)₂; or -(Ch₂)₂NR⁵⁷(CH₂)₂-; where R⁵⁷ is H; or lower alkyl);
(Ch₂)ₙOCONR³⁵R⁷⁵ (where R³³ is H; or lower alkyl; or lower alkenyl; R⁷⁵ is lower alkyl; or R³³ and R⁷⁵ taken together are.
-(CH₂)₂, -(CH₂)₂O(CH₂)₂, -(CH₂)₂S(CH₂)₂, or -(CH₂)₂NRᵣ⁻¹(CH₂)₂, where Rᵣ⁻¹ is H; or lower alkyl; -(CH₂)ₙNR⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻�
(-CH₂)₇SR₅⁶ (where R₅⁶ is lower alkyl; or lower alkenyl); -(CH₂)₇NR₃₃R₃⁴ (where R₃₃ is lower alkyl; or lower alkenyl; R₃⁴ is H; or lower alkyl; or R₃₃ and R₃⁴ taken together are -(CH₂)₂₋₅₋; -(CH₂)₆O(CH₂)₂₋;
-(CH₂)₇S(CH₂)₂₋; or -(CH₂)₇NR₅⁷(CH₂)₂₋; where R₅⁷ is H; or lower alkyl); -(CH₂)₇OCOR₃₃R₇⁵ (where R₃₃ is H; or lower alkyl; or lower alkenyl; R₇⁵ is lower alkyl; or R₃₃ and R₇⁵ taken together are -(CH₂)₂₋₅₋; -(CH₂)₆O(CH₂)₂₋;
-(CH₂)₇S(CH₂)₂₋; or -(CH₂)₇NR₅⁷(CH₂)₂₋; where R₅⁷ is H; or lower alkyl); -(CH₂)₇NR₂₀CONR₃₃R₈² (where R₂₀ is H; or lower alkyl; R₃₃ is H; or lower alkyl; or lower alkenyl; R₈² is H; or lower alkyl; or R₃₃ and R₈² taken together are -(CH₂)₂₋₅₋;
-(CH₂)₆O(CH₂)₂₋; -(CH₂)₇S(CH₂)₂₋; or -(CH₂)₇NR₅⁷(CH₂)₂₋; where R₅⁷ is H; or lower alkyl); -(CH₂)₇N(R₂⁰)COR₆⁴ (where: R₂⁰ is H; or lower alkyl; R₆⁴ is lower alkyl; or lower alkenyl); -NR₂⁰CO(lower alkyl (R₂⁰=H; or lower alkyl) being particularly favoured; -(CH₂)₇COOR₅⁷ (where R₅⁷ is lower alkyl; or lower alkenyl); -(CH₂)₇CONR₃₈R₅⁹ (where R₃₈ is lower alkyl, or lower alkenyl; and R₅⁹ is H; lower alkyl; or R₃₈ and R₅⁹ taken together are -(CH₂)₂₋₅₋; -(CH₂)₆O(CH₂)₂₋;
-(CH₂)₇S(CH₂)₂₋; or -(CH₂)₇NR₅⁷(CH₂)₂₋; where R₅⁷ is H; or lower alkyl); -(CH₂)₇PO(OR₆⁰)₂ (where R₆⁰ is lower alkyl; or lower alkenyl); -(CH₂)₇SO₂R₆² (where R₆² is lower alkyl; or lower alkenyl); or -(CH₂)₇C₆H₄R₈ (where R₈ is H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy);
R₄₄ is lower alkyl; lower alkenyl; -(CH₂)₆OR₅⁵ (where R₅₅ is lower alkyl; or lower alkenyl);
-(CH₂)₇SR₅⁶ (where R₅⁶ is lower alkyl; or lower alkenyl); -(CH₂)₇NR₃₃R₃⁴ (where R₃₃ is lower alkyl; or lower alkenyl; R₃⁴ is H; or lower alkyl; or R₃₃ and R₃⁴ taken together are -(CH₂)₂₋₅₋; -(CH₂)₆O(CH₂)₂₋;
-(CH₂)₇S(CH₂)₂₋; or -(CH₂)₇NR₅⁷(CH₂)₂₋; where R₅⁷ is H; or lower alkyl); -(CH₂)₇OCOR₃₃R₇⁵ (where R₃₃ is H; or lower alkyl; or lower alkenyl; R₇⁵ is lower alkyl; or R₃₃ and R₇⁵ taken together are -(CH₂)₂₋₅₋; -(CH₂)₆O(CH₂)₂₋;
-(CH₂)₇S(CH₂)₂₋; or -(CH₂)₇NR₅⁷(CH₂)₂₋; where R₅⁷ is H; or lower alkyl); -(CH₂)₇NR₂₀CONR₃₃R₈² (where R₂₀ is H; or lower lower alkyl; R₃₃ is H; or lower alkyl; or lower alkenyl; R₈² is H; or lower alkyl; or R₃₃ and R₈² taken together are -(CH₂)₂₋₅₋; -(CH₂)₆O(CH₂)₂₋;
-(CH₂)₇S(CH₂)₂₋; or -(CH₂)₇NR₅⁷(CH₂)₂₋; where R₅⁷ is H; or lower alkyl); -(CH₂)₇N(R₂⁰)COR₆⁴ (where: R₂⁰ is H; or lower alkyl; R₆⁴ is lower alkyl; or lower alkenyl); -NR₂⁰CO(lower alkyl (R₂⁰=H; or lower alkyl) being particularly favoured; -(CH₂)₇COOR₅⁷ (where R₅⁷ is lower alkyl; or lower alkenyl); -(CH₂)₇CONR₃₈R₅⁹ (where R₃₈ is lower alkyl, or lower alkenyl; and R₅⁹ is H; lower alkyl; or R₃₈ and R₅⁹ taken
together are -(CH₂)₂₋₆₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR²⁷(CH₂)₂₋; where R²⁷ is H; or lower alkyl); -(CH₂)₃PO(OR⁶⁰)₂ (where R⁶⁰ is lower alkyl; or lower alkenyl); -(CH₂)₃SO₂R⁶² (where R⁶² is lower alkyl; or lower alkenyl); or -(CH₂)₈C₆H₄R⁸ (where R⁸ is H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy);

R²⁵ is H; lower alkyl; lower alkenyl; -(CH₂)₈OR⁵⁵ (where R⁵⁵ is lower alkyl; or lower alkenyl);

-(CH₂)₈NR⁳³R⁴⁴ (where R³³ is lower alkyl; or lower alkenyl; R⁴⁴ is H; or lower alkyl; or R³³ and R⁴⁴ taken together are -(CH₂)₂₋₆₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷ is H; or lower alkyl); -(CH₂)₈OCONR²³R⁷⁵ (where R²³ is H; or lower alkyl; or lower alkenyl; R⁷⁵ is lower alkyl; or lower alkenyl; R³³ and R⁷⁵ taken together are -(CH₂)₂₋₆₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷ is H; or lower alkyl); -(CH₂)₈N(OR²⁰)COR⁶⁴ (where; R²⁰ is H; or lower alkyl; R⁶⁴ is lower alkyl; or lower alkenyl); -(CH₂)₈COOR⁵⁷ (where R⁵⁷ is lower alkyl; or lower alkenyl); -(CH₂)₈CONR⁵⁸R⁵⁹ (where R⁵⁸ is lower alkyl; or lower alkenyl; and R⁵⁹ is H; lower alkyl; or R⁵⁸ and R⁵⁹ taken together are -(CH₂)₂₋₆₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷ is H; or lower alkyl);

-(CH₂)₈PO(OR⁶⁰)₂ (where R⁶⁰ is lower alkyl; or lower alkenyl); -(CH₂)₈SO₂R⁶² (where R⁶² is lower alkyl; or lower alkenyl); or -(CH₂)₈C₆H₄R⁸ (where R⁸ is H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy);

R⁶⁵ is H; lower alkyl; lower alkenyl; -(CH₂)₈OR⁵⁵ (where R⁵⁵ is lower alkyl; or lower alkenyl);

-(CH₂)₈NR³³R⁴⁴ (where R³³ is lower alkyl; or lower alkenyl; R⁴⁴ is H; or lower alkyl; or R³³ and R⁴⁴ taken together are -(CH₂)₂₋₆₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷ is H; or lower alkyl); -(CH₂)₈OCONR³³R⁷⁵ (where R³³ is H; or lower alkyl; or lower alkenyl; R⁷⁵ is lower alkyl; or lower alkenyl; R³³ and R⁷⁵ taken together are -(CH₂)₂₋₆₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷ is H; or lower alkyl); -(CH₂)₈N(OR²⁰)COR⁶⁴ (where; R²⁰ is H; or lower alkyl; R⁶⁴ is lower alkyl; or lower alkenyl); -(CH₂)₈COOR⁵⁷ (where R⁵⁷ is lower alkyl; or lower alkenyl); -(CH₂)₈CONR⁵⁸R⁵⁹ (where R⁵⁸ is lower alkyl; or lower alkenyl; and R⁵⁹ is H; lower alkyl; or R⁵⁸ and R⁵⁹ taken together are -(CH₂)₂₋₆₋; -(CH₂)₂O(CH₂)₂₋; -(CH₂)₂S(CH₂)₂₋; or -(CH₂)₂NR⁵⁷(CH₂)₂₋; where R⁵⁷ is H; or lower alkyl);
alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are -(CH_{2})_{2}O:-
- (CH_{2})_{2}O(CH_{2})_{2}; -(CH_{2})_{2}S(CH_{2})_{2}; or -(CH_{2})_{2}N=NR^{57}(CH_{2})_{2}; where R^{57} is H; or lower alkyl;
- (CH_{2})_{2}PO(OR^{60})_{2} (where R^{60} is lower alkyl; or lower alkenyl); -(CH_{2})_{2}SO_{2}R^{62} (where R^{62}
is lower alkyl; or lower alkenyl); or -(CH_{2})_{6}C_{6}H_{5}R^{8} (where R^{8} is H; F; Cl; CF_{3}; lower alkyl; lower alkenyl; or lower alkoxy); or, alternatively, R^{25} and R^{26} taken together are -(CH_{2})_{2}O:-
- (CH_{2})_{2}O(CH_{2})_{2};
- (CH_{2})_{2}S(CH_{2})_{2}; or -(CH_{2})_{2}NR^{54}(CH_{2})_{2};
R^{27} is H; lower alkyl; lower alkenyl; -(CH_{2})_{6}OR^{55} (where R^{55} is lower alkyl; or lower alkenyl);
- (CH_{2})_{6}SR^{56} (where R^{56} is lower alkyl; or lower alkenyl); -(CH_{2})_{6}NR^{35}R^{34} (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -(CH_{2})_{2}O:-
- (CH_{2})_{2}O(CH_{2})_{2};
- (CH_{2})_{2}S(CH_{2})_{2}; or -(CH_{2})_{2}NR^{57}(CH_{2})_{2}; where R^{57} is H; or lower alkyl); -(CH_{2})_{6}CONR^{35}R^{75} (where R^{75} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are -(CH_{2})_{2}O:-
- (CH_{2})_{2}O(CH_{2})_{2};
- (CH_{2})_{2}S(CH_{2})_{2}; or -(CH_{2})_{2}NR^{57}(CH_{2})_{2}; where R^{57} is H; or lower alkyl); 
(Ch_{2})_{6}N(R^{20})COR^{64} (where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
- (CH_{2})_{6}COOR^{57} (where R^{57} is lower alkyl; or lower alkenyl); -(CH_{2})_{6}CONR^{35}R^{59} (where R^{59} is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are -(CH_{2})_{2}O:-
- (CH_{2})_{2}O(CH_{2})_{2};
- (CH_{2})_{2}S(CH_{2})_{2}; or -(CH_{2})_{2}NR^{57}(CH_{2})_{2}; where R^{57} is H; or lower alkyl); -(CH_{2})_{6}PO(OR^{60})_{2} (where R^{60} is lower alkyl; or lower alkenyl); -(CH_{2})_{6}SO_{2}R^{62} (where R^{62} is lower alkyl; or lower alkenyl); or -(CH_{2})_{6}C_{6}H_{5}R^{8} (where R^{8} is H; F; Cl; CF_{3}; lower alkyl; lower alkenyl; or lower alkoxy);
R^{28} is lower alkyl; lower alkenyl; -(CH_{2})_{6}OR^{55} (where R^{55} is lower alkyl; or lower alkenyl);
- (CH_{2})_{6}SR^{56} (where R^{56} is lower alkyl; or lower alkenyl); -(CH_{2})_{6}NR^{35}R^{34} (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -(CH_{2})_{2}O:-
- (CH_{2})_{2}O(CH_{2})_{2};
- (CH_{2})_{2}S(CH_{2})_{2}; or -(CH_{2})_{2}NR^{57}(CH_{2})_{2}; where R^{57} is H; or lower alkyl); 
(Ch_{2})_{6}CONR^{35}R^{75} (where R^{75} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are
or R^3 and R^25 taken together are
-\((\text{CH}_2)_2\text{O}(\text{CH}_2)_2\); -\((\text{CH}_2)_2\text{S}(\text{CH}_2)_2\); or -\((\text{CH}_2)_2\text{NR}^7(\text{CH}_2)_2\); where R^7 is H; or lower alkyl; -\((\text{CH}_2)_2\text{NR}^20\text{CONR}^3\text{R}^8\) (where \(\text{R}^20\) is H; or lower alkyl; \(\text{R}^3\) is H; or lower alkyl; or lower alkenyl; \(\text{R}^8\) is H; or lower alkyl; or \(\text{R}^3\) and \(\text{R}^8\) taken together are -\((\text{CH}_2)_2\).

\(\text{R}^5\); -\((\text{CH}_2)_2\text{O}(\text{CH}_2)_2\); -\((\text{CH}_2)_2\text{S}(\text{CH}_2)_2\); or -\((\text{CH}_2)_2\text{NR}^7(\text{CH}_2)_2\); where R^7 is H; or lower alkyl; -\((\text{CH}_2)_2\text{NR}^20\text{COR}^6\) (where \(\text{R}^20\) is H; or lower alkyl; \(\text{R}^6\) is lower alkyl; or lower alkenyl); -\((\text{CH}_2)_2\text{COOR}^5\) (where \(\text{R}^5\) is lower alkyl; or lower alkenyl; and \(\text{R}^8\) is H; lower alkenyl; or \(\text{R}^8\) and \(\text{R}^5\) taken together are -\((\text{CH}_2)_2\).

10 \((\text{CH}_2)_2\text{NR}^7(\text{CH}_2)_2\); where R^7 is H; or lower alkyl); -\((\text{CH}_2)_2\text{PO(OR}^6\text{)}_2\) (where \(\text{R}^6\) is lower alkyl; or lower alkenyl); -\((\text{CH}_2)_2\text{SO}_2\text{R}^8\) (where \(\text{R}^8\) is lower alkyl; or lower alkenyl); or -\((\text{CH}_2)_2\text{C}_4\text{H}_9\text{R}^8\) (where \(\text{R}^8\) is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy); and \(\text{R}^8\) is lower alkyl; lower alkenyl; -\((\text{CH}_2)_2\text{OR}^5\) (where \(\text{R}^5\) is lower alkyl; or lower alkenyl);

\((\text{CH}_2)_2\text{SR}^6\) (where \(\text{R}^6\) is lower alkyl; or lower alkenyl); -\((\text{CH}_2)_2\text{NR}^3\text{R}^4\) (where \(\text{R}^3\) is lower alkyl; or lower alkenyl; \(\text{R}^4\) is H; or lower alkyl; or \(\text{R}^3\) and \(\text{R}^4\) taken together are -\((\text{CH}_2)_2\).

\((\text{CH}_2)_2\text{O}(\text{CH}_2)_2\); -\((\text{CH}_2)_2\text{S}(\text{CH}_2)_2\); or -\((\text{CH}_2)_2\text{NR}^7(\text{CH}_2)_2\); where R^7 is H; or lower alkyl; -\((\text{CH}_2)_2\text{NR}^20\text{CONR}^3\text{R}^8\) (where \(\text{R}^20\) is H; or lower alkyl; \(\text{R}^3\) is H; or lower alkyl; or lower alkenyl; \(\text{R}^8\) is H; or lower alkyl; or \(\text{R}^3\) and \(\text{R}^8\) taken together are -\((\text{CH}_2)_2\).

20 \((\text{CH}_2)_2\text{OCONR}^3\text{R}^7\) (where \(\text{R}^3\) is H; or lower alkyl; or lower alkenyl; \(\text{R}^7\) is lower alkyl; or lower alkenyl; or \(\text{R}^3\) and \(\text{R}^7\) taken together are -\((\text{CH}_2)_2\).

\((\text{CH}_2)_2\text{O}(\text{CH}_2)_2\); -\((\text{CH}_2)_2\text{S}(\text{CH}_2)_2\); or -\((\text{CH}_2)_2\text{NR}^7(\text{CH}_2)_2\); where R^7 is H; or lower alkyl; -\((\text{CH}_2)_2\text{NR}^20\text{CONR}^3\text{R}^8\) (where \(\text{R}^20\) is H; or lower alkyl; \(\text{R}^3\) is H; or lower alkyl; or lower alkenyl; \(\text{R}^8\) is H; or lower alkyl; or \(\text{R}^3\) and \(\text{R}^8\) taken together are -\((\text{CH}_2)_2\).

25 \((\text{CH}_2)_2\text{O}(\text{CH}_2)_2\); -\((\text{CH}_2)_2\text{S}(\text{CH}_2)_2\); or -\((\text{CH}_2)_2\text{NR}^7(\text{CH}_2)_2\); where R^7 is H; or lower alkyl; -\((\text{CH}_2)_2\text{NR}^20\text{COR}^6\) (where \(\text{R}^20\) is H; or lower alkyl; \(\text{R}^6\) is lower alkyl; or lower alkenyl; -\(\text{NR}^20\text{CO}-\text{lower-alkyl (R}^20=\text{H; or lower alkyl) being particularly favoured; -\((\text{CH}_2)_2\text{COOR}^7\) (where \(\text{R}^7\) is lower alkyl; or lower alkenyl);

\((\text{CH}_2)_2\text{CONR}^8\text{R}^9\) (where \(\text{R}^8\) is lower alkyl, or lower alkenyl; and \(\text{R}^9\) is H; lower alkyl; or \(\text{R}^8\) and \(\text{R}^9\) taken together are -\((\text{CH}_2)_2\).

30 \((\text{CH}_2)_2\text{O}(\text{CH}_2)_2\); -\((\text{CH}_2)_2\text{S}(\text{CH}_2)_2\); or -\((\text{CH}_2)_2\text{NR}^7(\text{CH}_2)_2\); where R^7 is H; or lower alkyl; -\((\text{CH}_2)_2\text{PO(OR}^6\text{)}_2\) (where \(\text{R}^6\) is lower alkyl; or lower alkenyl);

\((\text{CH}_2)_2\text{SO}_2\text{R}^8\) (where \(\text{R}^8\) is lower alkyl; or lower alkenyl); or -\((\text{CH}_2)_2\text{C}_4\text{H}_9\text{R}^8\) (where \(\text{R}^8\) is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).
8. Compounds according to claim 7 wherein \( R^{22}, R^{24} \) and \( R^{20} \) are -NR\(^{20}\)-CO-lower alkyl where \( R^{20} \) is H or lower alkyl.

9. Compounds according to claim 7 or 8 wherein \( A \) is a group of one of the formulae
      \( \text{A74 (with } R^{22} \text{ being H); A75; A76; A77 (with } R^{22} \text{ being H); A78; and A79.} \)

10. Compounds according to any one of claims 2 to 9 wherein \( B \) is a group of formula
      -NR\(^{20}\)CH(\(R^{21}\))- or an enantiomer of one of the groups A5 (with \( R^{2} \) being H); A8; A22;
      A25; A38 (with \( R^{2} \) being H); A42; A47; and A50.

11. Compounds according to claim 10 wherein \( B \)-CO 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\(_{20}\); C\(_{30}\); Nle; 2-Nal; 1-Nal; 4Cl-Phe; 3Cl-Phe; 2Cl-Phe; 3,4Cl\(_2\)-Phe; 4F-Phe; 3F-Phe; 2F-Phe; Tic; Thi; Tza; Mso; AcLys; Dpr; A\(_2\)Bu; Dbu; Abu; Aha; Aib; Y(Bzl); Bip; S(Bzl); T(Bzl); hCha; hCys; hSer, hArg; hPhe; Bpa; Pip; OctG; MePhe; MeNle; Meala; Melle; MeVal; or MeLeu.

12. Compounds according to claim 10 wherein \( B \) is a group, having (L)-configuration, of formula

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\( R^{20} = \text{H; or lower alkyl; and } R^{64} = \text{alkyl; alkenyl; } [(\text{CH})_2\_X]_t\_CH_3, \text{ wherein } X \) is

-\( -O\_2\_ \),
-\( -NR^{20} \) - or -S-, \( u \) is 1-3 and \( t \) is 1-6; aryl; aryl-lower alkyl; or heteroaryl-lower alkyl.

13. Compounds according to claim 12 wherein \( R^{64} \) is n-hexyl; n-heptyl; 4-

(phenyl)benzyl; diphenylmethyl, 3-amino-propyl; 5-amino-pentyl; methyl; ethyl;
isopropyl; isobutyl; n-propyl; cyclohexyl; cyclohexylmethyl; n-buty1; phenyl; benzyl; (3-
indolyl)methyl; 2-(3-indolyl)ethyl; (4-phenyl)phenyl; n-nonyl; CH\(_3\)-OCH\(_2\)CH\(_2\)-OCH\(_2\)- or
CH\(_2\)-(OCH\(_2\)CH\(_2\))\(_2\)-OCH\(_2\)._
Compounds according to claim 1 wherein

\[
\begin{array}{c}
\text{Template}\\
\end{array}
\]

is a group of formula (b1) or (l);

5 \( R^1 \) is H; or lower alkyl;
\( R^{20} \) is H; or lower alkyl;
\( R^{20} \) is H; or methyl;
\( R^{31} \) is H; lower alkyl; lower alkenyl; \(- \text{CH}_2 \text{OR}^{55} \) (where \( R^{55} \) is lower alkyl; or lower alkenyl);

10 \(- \text{CH}_2 \text{pNR}^{33} \text{R}^{34} \) (where \( R^{33} \) is lower alkyl; or lower alkenyl; \( R^{34} \) is H; or lower alkyl; or \( R^{33} \) and \( R^{34} \) taken together are \(- \text{CH}_2 \text{O} \text{CH}_2 \text{CH}_2 \); \(- \text{CH}_2 \text{S} \text{CH}_2 \text{CH}_2 \); or \(- \text{CH}_2 \text{N} \text{R}^{57} \text{CH}_2 \text{CH}_2 \); where \( R^{57} \) is H; or lower alkyl); \(- \text{CH}_2 \text{pOCONR}^{33} \text{R}^{75} \) (where \( R^{33} \) is H; or lower alkyl; or lower alkenyl; \( R^{75} \) is lower alkyl; or \( R^{33} \) and \( R^{75} \) taken together are \(- \text{CH}_2 \text{O} \text{CH}_2 \text{CH}_2 \); \(- \text{CH}_2 \text{S} \text{CH}_2 \text{CH}_2 \); or

15 \(- \text{CH}_2 \text{pNR}^{57} \text{CH}_2 \text{CH}_2 \); where \( R^{57} \) is H; or lower alkyl); \(- \text{CH}_2 \text{pNR}^{20} \text{CONR}^{33} \text{R}^{82} \) (where \( R^{20} \) is H; or lower alkyl; \( R^{33} \) is H; or lower alkyl; or lower alkenyl; \( R^{82} \) is H; or lower alkyl; or \( R^{33} \) and \( R^{82} \) taken together are \(- \text{CH}_2 \text{O} \text{CH}_2 \text{CH}_2 \); \(- \text{CH}_2 \text{S} \text{CH}_2 \text{CH}_2 \); or \(- \text{CH}_2 \text{NR}^{57} \text{CH}_2 \text{CH}_2 \); where \( R^{57} \) is H; or lower alkyl); \(- \text{CH}_2 \text{pN} \text{R}^{20} \text{COR}^{64} \) (where: \( R^{20} \) is H; or lower alkyl; or lower alkenyl); \(- \text{CH}_2 \text{pCOOR}^{57} \) (where \( R^{57} \) is H; or lower alkyl; or lower alkenyl); \(- \text{CH}_2 \text{pCONR}^{58} \text{R}^{59} \) (where \( R^{58} \) is lower alkyl; or lower alkenyl; and \( R^{59} \) is H; lower alkyl; or \( R^{58} \) and \( R^{59} \) taken together are \(- \text{CH}_2 \text{O} \text{CH}_2 \text{CH}_2 \); \(- \text{CH}_2 \text{S} \text{CH}_2 \text{CH}_2 \); or \(- \text{CH}_2 \text{NR}^{57} \text{CH}_2 \text{CH}_2 \); where \( R^{57} \) is H; or lower alkyl); \(- \text{CH}_2 \text{pPO} \text{OR}^{60} \text{R}^{60} \) (where \( R^{60} \) is lower alkyl; or lower alkenyl); \(- \text{CH}_2 \text{pSO} \text{OR}^{62} \) (where \( R^{62} \) is lower alkyl; or lower alkenyl); or \(- \text{CH}_2 \text{C}_2 \text{H}_4 \text{R}^{8} \) (where \( R^{8} \) is H; F; Cl; CF\(_3\); lower alkyl; lower alkenyl; or lower alkoxy); most preferably \(- \text{CH}_2 \text{CONR}^{58} \text{R}^{59} \) (where \( R^{58} \) is H; or lower alkyl; and \( R^{59} \) is lower alkyl; or lower alkenyl);

20 \( R^{32} \) is H; or methyl;
\( R^{33} \) is lower alkyl; lower alkenyl; \(- \text{CH}_2 \text{mOR}^{55} \) (where \( R^{55} \) is lower alkyl; or lower alkenyl);

25 \(- \text{CH}_2 \text{mNR}^{34} \text{R}^{63} \) (where \( R^{34} \) is lower alkyl; or lower alkenyl; \( R^{63} \) is H; or lower alkyl; or \( R^{34} \) and \( R^{63} \) taken together are \(- \text{CH}_2 \text{O} \text{CH}_2 \text{CH}_2 \); \(- \text{CH}_2 \text{S} \text{CH}_2 \text{CH}_2 \); or -
(CH$_2$)$_m$R$^5$ (CH$_2$)$_n$; where R$^5$ is H; or lower alkyl; (CH$_2$)$_m$OCONR$^7$(CH$_2$)$_n$ (where R$^7$ is lower alkyl; or lower alkenyl; R$^8$ is H; or lower alkyl; or R$^7$ and R$^8$ taken together are -
(CH$_2$)$_n$-; -(CH$_2$)$_3$O(CH$_2$)$_n$; -(CH$_2$)$_3$S(CH$_2$)$_n$; or -
(CH$_2$)$_3$NR$^7$(CH$_2$)$_n$ where R$^7$ is H; or lower alkyl); -(CH$_2$)$_m$NR$^8$(CH$_2$)$_n$CONR$^8$ (where R$^8$ is H; or lower alkyl; R$^9$ is H; or lower alkyl; or R$^8$ and R$^9$ taken together are -
(CH$_2$)$_n$-; -(CH$_2$)$_3$O(CH$_2$)$_n$; -(CH$_2$)$_3$S(CH$_2$)$_n$; or -
(CH$_2$)$_3$NR$^7$(CH$_2$)$_n$; where R$^7$ is H; or lower alkyl; -(CH$_2$)$_m$N(R$^{20}$)COR$^6$ (where R$^{20}$ is H; or lower alkyl; R$^{21}$ is H; or lower alkyl); -(CH$_2$)$_n$COOR$^5$ (where R$^5$ is lower alkyl; or lower alkenyl); -(CH$_2$)$_m$CONR$^{58}$R$^{59}$ (where R$^{58}$ is lower alkyl; or lower alkenyl; and R$^{59}$ is H; lower alkyl; or R$^{58}$ and R$^{59}$ taken together are -
(CH$_2$)$_n$-; -(CH$_2$)$_3$O(CH$_2$)$_n$; -(CH$_2$)$_3$S(CH$_2$)$_n$; or -
(CH$_2$)$_3$NR$^7$(CH$_2$)$_n$; where R$^7$ is H; or lower alkyl); R$^{33}$ is H; or lower alkyl; or R$^{33}$ and R$^{34}$ taken together are -
(CH$_2$)$_n$-; -(CH$_2$)$_3$O(CH$_2$)$_n$; -(CH$_2$)$_3$S(CH$_2$)$_n$; or -
(CH$_2$)$_3$NR$^7$(CH$_2$)$_n$; where R$^7$ is H; or lower alkyl); -(CH$_2$)$_m$CONR$^{53}$R$^{54}$ (where R$^{53}$ is H; or lower alkyl; or lower alkenyl; R$^{54}$ is H; or lower alkyl; or R$^{53}$ and R$^{54}$ taken together are -
(CH$_2$)$_n$-; -(CH$_2$)$_3$O(CH$_2$)$_n$; -(CH$_2$)$_3$S(CH$_2$)$_n$; or -
(CH$_2$)$_3$NR$^7$(CH$_2$)$_n$; where R$^7$ is H; or lower alkyl); -(CH$_2$)$_m$N(R$^{20}$)COR$^6$ (where R$^{20}$ is H; or lower alkyl; R$^{21}$ is H; or lower alkyl); -(CH$_2$)$_n$COOR$^5$ (where R$^5$ is lower alkyl; or lower alkenyl; and R$^{58}$ is H; lower alkyl; or R$^{58}$ and R$^{59}$ taken together are -
(CH$_2$)$_n$-; -(CH$_2$)$_3$O(CH$_2$)$_n$; -(CH$_2$)$_3$S(CH$_2$)$_n$; or -
(CH$_2$)$_3$NR$^7$(CH$_2$)$_n$; where R$^7$ is H; or lower alkyl); R$^{33}$ is H; or lower alkyl; or R$^{33}$ and R$^{34}$ taken together are -
(CH$_2$)$_n$-; -(CH$_2$)$_3$O(CH$_2$)$_n$; -(CH$_2$)$_3$S(CH$_2$)$_n$; or -
(CH$_2$)$_3$NR$^7$(CH$_2$)$_n$; where R$^7$ is H; or lower alkyl); -(CH$_2$)$_m$NR$^{20}$CONR$^{32}$R$^{33}$ (where R$^{20}$ is H; or lower alkyl; R$^{33}$ is H; or lower alkyl; or R$^{32}$ is H; or lower alkyl; or R$^{33}$ and R$^{34}$ taken together are -
(CH$_2$)$_n$-; -(CH$_2$)$_3$O(CH$_2$)$_n$; -(CH$_2$)$_3$S(CH$_2$)$_n$; or -
(CH$_2$)$_3$NR$^7$(CH$_2$)$_n$; where R$^7$ is H; or lower alkyl); -(CH$_2$)$_m$N(R$^{20}$)COR$^6$ (where R$^{20}$ is H; or lower alkyl; R$^{21}$ is H; or lower alkyl); -(CH$_2$)$_n$COOR$^5$ (where R$^5$ is lower alkyl; or lower alkenyl; and R$^{58}$ is H; lower alkyl; or R$^{58}$ and R$^{59}$ taken together are -
(CH$_2$)$_n$-; -(CH$_2$)$_3$O(CH$_2$)$_n$; -(CH$_2$)$_3$S(CH$_2$)$_n$; or -
(CH$_2$)$_3$NR$^7$(CH$_2$)$_n$; where R$^7$ is H; or lower alkyl); R$^{36}$ is lower alkyl; lower alkenyl; or aryl-lower alkyl; R$^{37}$ is H; lower alkyl; lower alkenyl; -(CH$_2$)$_n$OR$^{55}$ (where R$^{55}$ is lower alkyl; or lower alkenyl); -(CH$_2$)$_n$NR$^{33}$R$^{34}$ (where R$^{33}$ is lower alkyl; or lower alkenyl; R$^{34}$ is H; or lower alkyl; or R$^{33}$ and R$^{34}$ taken together are -
(CH$_2$)$_n$-; -(CH$_2$)$_3$O(CH$_2$)$_n$; -(CH$_2$)$_3$S(CH$_2$)$_n$; or -
(CH$_2$)$_3$NR$^7$(CH$_2$)$_n$; where R$^7$ is H; or lower alkyl); -(CH$_2$)$_m$OCONR$^{33}$R$^{35}$ (where R$^{33}$ is H; or lower alkyl; or lower alkenyl; R$^{35}$ is lower alkyl; or R$^{33}$ and R$^{35}$ taken together are -
(CH$_2$)$_n$-; -(CH$_2$)$_3$O(CH$_2$)$_n$; -(CH$_2$)$_3$S(CH$_2$)$_n$; or -
(CH$_2$)$_3$NR$^7$(CH$_2$)$_n$; where R$^7$ is H; or lower alkyl); -(CH$_2$)$_m$CONR$^{35}$R$^{36}$ (where R$^{35}$ is lower alkyl; or lower alkenyl; and R$^{36}$ is H; lower alkyl; or R$^{35}$ and R$^{36}$ taken together are -
(CH$_2$)$_n$-; -(CH$_2$)$_3$O(CH$_2$)$_n$; -(CH$_2$)$_3$S(CH$_2$)$_n$; or -
- \((\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-5}\); where \(R^{57}\) is \(H\); or lower alkyl; \(-\text{(CH}_2)_n\text{NR}^{20}\text{CONR}^{53}\text{R}^{82}\) (where \(R^{20}\) is \(H\); or lower alkyl; \(R^{33}\) is \(H\); or lower alkyl; or lower alkenyl; \(R^{82}\) is \(H\); or lower alkyl; or \(R^{33}\) and \(R^{82}\) taken together are \(-\text{(CH}_2)_{2-6}\); \(-\text{(CH}_2)_2\text{O(}\text{CH}_2)_{2-3}\); \(-\text{(CH}_2)_2\text{S(}\text{CH}_2)_{2-3}\); or \(-\text{(CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-3}\); where \(R^{57}\) is \(H\); or lower alkyl; \(R^{44}\) is lower alkyl; or lower alkenyl); \(-\text{(CH}_2)_n\text{COOR}^{57}\) (where \(R^{57}\) is lower alkyl; or lower alkenyl); \(-\text{(CH}_2)_n\text{CONR}^{38}\text{R}^{59}\) (where \(R^{38}\) is lower alkyl, or lower alkenyl; and \(R^{59}\) is \(H\); lower alkyl; or \(R^{58}\) and \(R^{59}\) taken together are \(-\text{(CH}_2)_{2-6}\); \(-\text{(CH}_2)_2\text{O}(\text{CH}_2)_{2-3}\); \(-\text{(CH}_2)_2\text{S(}\text{CH}_2)_{2-3}\); or \(-\text{(CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-3}\); where \(R^{57}\) is \(H\); or lower alkyl); 

\(-\text{(CH}_2)_n\text{PO(OR}^{60})_{2}\) (where \(R^{60}\) is lower alkyl; or lower alkenyl); \(-\text{(CH}_2)_n\text{SO}_2\text{R}^{62}\) (where \(R^{62}\) is lower alkyl; or lower alkenyl); \(-\text{(CH}_2)_{6}\text{C}_6\text{H}_5\text{R}^{8}\) (where \(R^{8}\) is \(H\); \(F\); \(Cl\); \(CF_3\); lower alkyl; lower alkenyl; or lower alkoxy); and \(R^{38}\) is \(H\); lower alkyl; lower alkenyl; \(-\text{(CH}_2)_n\text{OR}^{55}\) (where \(R^{55}\) is lower alkyl; or lower alkenyl); 

\(-\text{(CH}_2)_n\text{NR}^{33}\text{R}^{34}\) (where \(R^{33}\) is lower alkyl; or lower alkenyl; \(R^{34}\) is \(H\); or lower alkyl; or \(R^{33}\) and \(R^{34}\) taken together are \(-\text{(CH}_2)_{2-6}\); \(-\text{(CH}_2)_2\text{O(}\text{CH}_2)_{2-3}\); \(-\text{(CH}_2)_2\text{S(}\text{CH}_2)_{2-3}\); or \(-\text{(CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-3}\); where \(R^{57}\) is \(H\); or lower alkyl; \(R^{75}\) is lower alkyl; or \(R^{33}\) and \(R^{75}\) taken together are \(-\text{(CH}_2)_{2-6}\); \(-\text{(CH}_2)_2\text{O(}\text{CH}_2)_{2-3}\); \(-\text{(CH}_2)_2\text{S(}\text{CH}_2)_{2-3}\); or \(-\text{(CH}_2)_2\text{PO(OR}^{60})_{2}\) (where \(R^{60}\) is lower alkyl; or lower alkenyl); \(-\text{(CH}_2)_n\text{NR}^{20}\text{CONR}^{33}\text{R}^{82}\) (where \(R^{20}\) is \(H\); or lower alkyl; \(R^{33}\) is \(H\); or lower alkyl; \(R^{82}\) is \(H\); or lower alkyl; or \(R^{33}\) and \(R^{82}\) taken together are \(-\text{(CH}_2)_{2-6}\); \(-\text{(CH}_2)_2\text{O(}\text{CH}_2)_{2-3}\); \(-\text{(CH}_2)_2\text{S(}\text{CH}_2)_{2-3}\); or \(-\text{(CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-3}\); where \(R^{57}\) is \(H\); or lower alkyl; \(R^{44}\) is lower alkyl; or lower alkenyl); \(-\text{(CH}_2)_n\text{CONR}^{58}\text{R}^{59}\) (where \(R^{58}\) is lower alkyl, or lower alkenyl; and \(R^{59}\) is \(H\); lower alkyl; or \(R^{58}\) and \(R^{59}\) taken together are \(-\text{(CH}_2)_{2-6}\); \(-\text{(CH}_2)_2\text{O(}\text{CH}_2)_{2-3}\); \(-\text{(CH}_2)_2\text{S(}\text{CH}_2)_{2-3}\); or \(-\text{(CH}_2)_2\text{NR}^{57}(\text{CH}_2)_{2-3}\); where \(R^{57}\) is \(H\); or lower alkyl; \(-\text{(CH}_2)_n\text{PO(OR}^{50})_{2}\) (where \(R^{60}\) is lower alkyl; or lower alkenyl); \(-\text{(CH}_2)_n\text{SO}_2\text{R}^{62}\) (where \(R^{62}\) is lower alkyl; or lower alkenyl); \(-\text{(CH}_2)_{6}\text{C}_6\text{H}_5\text{R}^{8}\) (where \(R^{8}\) is \(H\); \(F\); \(Cl\); \(CF_3\); lower alkyl; lower alkenyl; or lower alkoxy).

15. Compounds according to claim 14 wherein \(R^1\) is \(H\); \(R^{20}\) is \(H\); \(R^{30}\) is \(H\); \(R^{31}\) is carboxymethyl; or lower alkoxy carbonylmethyl; \(R^{32}\) is \(H\); \(R^{35}\) is methyl; \(R^{36}\) is methoxy; 

\(R^{37}\) is \(H\) and \(R^{38}\) is \(H\).
16. Compounds according to any one of claims 1 to 15 wherein the α-amino acid residues in positions 1 to 11 in the chain Z are:

- P1: of type C, or of type D, or of type E, or of type F;
- P2: of type E, or of type F, or of type C;
- P3: or of type C, of type F or the residue is Gly;
- P4: of type C, or of type E, or of type F, or the residue is Gly or Pro;
- P5: of type E, or of type F, or the residue is Gly or Pro;
- P6: of type C, or of type D, or of type F, or the residue is Gly or Pro;
- P7: of type F or of formula -A-CO or the residue is Gly or Pro;
- P8: of type D, or of type C, or of formula -A-CO or the residue is Gly or Pro or Pro(4NHCOPhe);
- P9: of type C, or of type D, or of type E, or of type F;
- P10: of type F, or of type C, or type E;
- P11: of type E, or of type F, or of type C or of type D; or
- P2 and P10, taken together, form a group of type H;

with the proviso that if template is $^3$Pro-$^1$Pro the amino acid residues in positions P1 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
- P7: Pro
- P8: Pro
- P9: Ile
- P10: Cys, linked with Cys in position P10 by a disulfide bridge; and
- P11: Phe.

17. Compounds according to claim 16 wherein the α-amino acid residues in positions 1 to 11 of the chain Z 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;
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- 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, Gin, 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.

18. Compounds according to any one of claims 1 to 15 wherein the \( \alpha \)-amino acid residues in positions 1 to 11 in the chain Z are:

15
- P1: of type C, or of type D, or of type E;
- P2: of type F, or of type C;
- P3: of type F;
- P4: of type C, or of type E;
- P5: of type E, or of type F;
- P6: of type F;
- P7: of type F, or of formula \(-A-CO_2\), or the residue is Gly or Pro;
- P8: of type C, or of formula \(-A-CO_2\), or the residue is Gly or Pro or Pro(4NHCOPhe);
- P9: of type C, or of type D, or of type F;

20
- P10: of type F, or of type C, or type E;
- P11: of type E, or of type D, or of type F; or
- P2 and P10, taken together, form a group of type H;

19. Compounds according to claim 18 wherein the \( \alpha \)-amino acid residues in

30
positions 1 to 11 are:

- P1: Phe, hPhe, 4AmPhe, Nle, Chg, Ile, Tyr, Arg, Trp, 2Cl-Phe, Arg, 1-
  Nal, or Cha;
- P2: Cys, Glu, or Nle;
- P3: Thr;
- P4: Lys, or Nle;
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- 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.

5

20. Compounds according to any one of claims 1 to 15 wherein the α-amino acid residues in positions 1 to 11 in the chain Z are:
- P1: of type C, or of type D;
- P2: of type F;
- P3: of type F or of type C;
- P4: of type C or of type F;
- P5: of type F;
- P6: of type C;
- P7: of formula A-CO₂, or the residue is Gly or Pro;
- P8: of formula -A-CO₂, or the residue is Gly or Pro or
  Pro(4NHCOPhē);
- P9: of type D, or of type F or of type C;
- P10: of type F, or of type C, or type E;
- P11: of type E, or of type F, or of type D; or
- P2 and P10, taken together, form a group of type H.

25

21. Compounds according to claim 20 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(4NHCOPhē);
- P9: Gln, Tyr, ILē, or Phe;
22. Compounds according to any one of claims 1 to 15 wherein the \(\alpha\)-amino acid residues in positions 1 to 11 in the chain Z are:

- P1: of type C, or of type D, or of type E;
- P2: of type F;
- P3: of type F;
- P4: of type E;
- P5: of type F;
- P6: of type C or of type D;
- P7: of type F or of formula -A-CO-, or the residue is Gly or Pro;
- P8: of type C, or of formula -A-CO-, or the residue is Gly or Pro;
- P9: of type C, or of type E, or of type F;
- P10: of type F;
- P11: of type E, or of type D; or

P2 and P10, taken together, form a group of type H; with the proviso that if the template is DPro-LPro, the amino acid residues in positions P1 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
- P7: Pro
- P8: Pro
- P9: Ile
- P10: Cys, linked with Cys in position P10 by a disulfide bridge; and
- P11: Phe.

23. Compounds according to claim 22 wherein the \(\alpha\)-amino acid residues in positions 1 to 11 of the chain Z are:

- P1: Cha, Tyr, or Trp
- P2: Cys
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:

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

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

25  - P11: Tyr;

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:

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

35  - P6: Asp;
    - P7: Pro;
5 Cys at P2 and P10 forming a disulfide bridge.

26. A compound of formula I according to claim 1 wherein the template is $^\text{D}\text{Pro}^{-1}\text{Pro}$ 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.

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

- P1: Phe;
- P2: Cys;
- P3: Thr;
- P4: Nle;
- P5: Ser;
- P6: Asp;
- P7: Pro;

Cys at P2 and P10 forming a disulfide bridge.

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

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

Cys at P2 and P10 forming a disulfide bridge.

30. A compound of formula I according to claim 1 wherein the template is \(^{D}\text{Pro}^{L}\text{Pro}\) 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;

5  - P9: Ile;
   - P10: Cys;
   - P11: Phe;
   Cys at P2 and P10 forming a disulfide bridge.

10  31. A compound of formula I according to claim 1 wherein the template is \(^{3}\text{Pro-}^{1}\text{Pro}\) and the amino acid residues in position 1 – 11 are:
   - P1: Nle;
   - P2: Cys;
   - P3: Thr;

15  - P4: Ala;
   - P5: Ser;
   - P6: Ile;
   - P7: Pro;
   - P8: Pro;

20  - P9: Gln;
   - P10: Cys;
   - P11: Gln;
   Cys at P2 and P10 forming a disulfide bridge.

25  32. A compound of formula I according to claim 1 wherein the template is \(^{3}\text{Pro-}^{1}\text{Pro}\) and the amino acid residues in position 1 – 11 are:
   - P1: Nle;
   - P2: Cys;
   - P3: Thr;

30  - P4: Ala;
   - P5: Ser;
   - P6: Ile;
   - P7: Pro;
   - P8: Pro;

35  - P9: Gln;
   - P10: Cys;
- P11: Tyr;
Cys at P2 and P10 forming a disulfide bridge.

33. 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.

34. 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.

35. 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;

5
- P7: Pro;
- P8: Pro;
- P9: Gln;
- P10: Cys;
- P11: Phe;

10 Cys at P2 and P10 forming a disulfide bridge.

36. A compound of formula I according to claim 1 wherein the template is \( \text{Pro}^1 \text{Pro} \) and the amino acid residues in position 1 – 11 are:

- P1: OctG;
- P2: Glu;
- P3: Thr;
- P4: Ala;
- P5: Ser;
- P6: Ile;

15 - P7: Pro;
- P8: Pro;
- P9: Gln;
- P10: Lys;
- P11: Tyr.

20

37. A compound of formula I according to claim 1 wherein the template is \( \text{Pro}^1 \text{Pro} \) and the amino acid residues in position 1 – 11 are:

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

30 - P4: Ala;
- P5: Ser;
- P6: Cha;
- P7: Pro;

35 - P8: Pro;
- P9: Gln;
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- P10: Cys;
- P11: Phe;
Cys at P2 and P10 forming a disulfide bridge.

5 38. 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.

20 39. 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(4NHCOPh); 
- P9: Gln;
- P10: Cys;
- P11: Gln;
Cys at P2 and P10 forming a disulfide bridge.

35 40. 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;

5 - P5: Ser;
- P6: OctG;
- P7: Pro;
- P8: Pro;
- P9: Gln;

10 - P10: Cys;
- P11: Tyr;

Cys at P2 and P10 forming a disulfide bridge.

41. A compound of formula I according to claim 1 wherein the template is \(^5\text{Pro}^-1\text{Pro}\) and the amino acid residues in position 1 – 11 are:
- P1: Chg;
- P2: Cys;
- P3: Thr;
- P4: Lys;

20 - P5: Ser;
- P6: Asp;
- P7: Pro;
- P8: Pro;
- P9: Ile;

25 - P10: Cys;
- P11: Thr;

Cys at P2 and P10 forming a disulfide bridge.

42. A compound of formula I according to claim 1 wherein the template is \(^5\text{Pro}^-1\text{Pro}\) and the amino acid residues in position 1 – 11 are:
- P1: Chg;
- P2: Cys;
- P3: Thr;
- P4: Lys;

35 - P5: Ser;
- P6: Asp;
43. A compound of formula I according to claim 1 wherein the template is $^{\beta}$Pro-$^{\beta}$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.

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

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

Cys at P2 and P10 forming a disulfide bridge.
45. 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.

46. 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.

47. 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.

48. A compound of formula I according to claim 1 wherein the template is Pro-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.

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

50. Compounds according to any one of claims 1 to 49 for use as therapeutically active substances.

51. Compounds according to claim 50 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.
52. A pharmaceutical composition containing a compound according to any one of claims 1 to 49 and a pharmaceutically inert carrier.

53. Compositions according to claim 52 in a form suitable for oral, topical, transdermal, buccal, transmucosal or pulmonary administration or for administration by injection or inhalation.

54. Compositions according to claim 52 or 53 in form of tablets, dragees, capsules, solutions, liquids, gels, plaster, creams, ointments, syrup, slurries, suspensions, spray, nebuliser or suppositories.

55. The use of compounds according to any one of claims 1 to 49 for the manufacture of a medicament for use as an inhibitor of protease enzymes.

56. The use according to claim 55 wherein said protease inhibiting medicament is intended to be used for preventing infections in healthy individuals or for slowing infections in infected patients; or where cancer is mediated or resulting from; or where an immunological diseases are mediated or resulting from protease activity or where inflammation is mediated or resulting from protease activity; or where immunological reaction is mediated or resulting from protease activity.

57. The use of compounds according to any one of claims 18, 19 and 24-30 for the manufacture of a medicament for use as an inhibitor of Cathepsin G.

58. The use of compounds according to any one of claims 20, 21 and 31-42 for the manufacture of a medicament for use as an inhibitor of Elastase.

59. The use of compounds according to any one of claims 22, 23 and 43-45 for the manufacture of a medicament for use as an inhibitor of Tryptase.

60. A process for the manufacture of compounds according to any one of claims 1-48 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

\[
\begin{array}{c}
\text{Template} \\
\end{array}
\]

wherein

\[
\begin{array}{c}
\text{Template} \\
\end{array}
\]

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

\[
\begin{array}{c}
\text{Template} \\
\end{array}
\]

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

\[
\text{HOOC-B-H} \quad \text{III} \quad \text{or} \quad \text{HOOC-A-H} \quad \text{IV}
\]

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; and, respectively, if

\[ \text{Template} \]

is to be group (a3) 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 above general formula III, 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 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) 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.

61. A process for the manufacture of compounds according to any one of claims 1-48 which process comprises

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

\[
\begin{array}{c}
\text{Template} \\
\end{array}
\]

wherein

\[
\begin{array}{c}
\text{Template} \\
\end{array}
\]

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

\[
\begin{array}{c}
\text{Template} \\
\end{array}
\]

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; and, respectively, if

```
  O==
     N
```

is to be group (a3) 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 above general formula III, 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 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'), (a'c') 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.

62. A modification of the processes according to claim 60 or 61 for the manufacture
of compounds according to claim 49 in which enantiomers of all chiral starting materials
are used.
Template