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(54) Title: β -HAIRPIN PEPTIDOMIMETICS

(57) Abstract: β -Hairpin peptidomimetics of the general formula Cyclo (-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-), enantiomers and pharmaceutically acceptable salts thereof, with Xaa¹ - Xaa¹⁴ being amino acid residues of certain types which are defined in the description and the claims, have anti-infective activity, e.g. to selectively inhibit the growth of or to kill microorganisms such as *Bacillus subtilis* and/or *Shigella boydii*. They can be used as medicaments to treat or prevent infections or as disinfectants for foodstuffs, cosmetics, medicaments or other nutrient-containing materials. These peptidomimetics can be manufactured by a process which is based on a mixed solid- and solution phase synthetic strategy.



β -Hairpin peptidomimetics

The present invention provides β -hairpin peptidomimetics having selective anti-infective activity.

5

The β -hairpin peptidomimetics of the invention are Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-), and pharmaceutically acceptable salts thereof, with Xaa¹ to Xaa¹⁴ being as described herein below.

10

In addition, the present invention provides an efficient synthetic process by which these compounds can, if desired, be made in parallel library-format. These β -hairpin peptidomimetics show a significantly enhanced ratio between
15 anti-infective activity on the one hand, and reduced hemolysis of red blood cells and reduced or no cytotoxicity on the other.

A major cause of death worldwide and a leading cause of
20 mortality in developed countries are infectious diseases. They result from the presence of pathogenic microbial agents including pathogenic viruses and pathogenic bacteria. The growing problem of bacterial resistance to established antibiotics has stimulated intense interest in developing
25 novel antimicrobial agents with new modes of action (D. Obrecht, J.A. Robinson, F. Bernadini, C. Bisang, S.J. DeMarco, K. Moehle, F.O. Gombert, *Curr. Med. Chem.* **2009**, *16*, 42-65; H. Breithaupt, *Nat. Biotechnol.* **1999**, *17*, 1165-1169). One emerging class of antibiotics is based on naturally
30 occurring cationic peptides (T. Ganz, R.I. Lehrer, *Mol. Medicine Today* **1999**, *5*, 292-297; R.M. Epand, H.J. Vogel, *Biochim. Biophys. Acta* **1999**, *1462*, 11-28). These include disulfide-bridged β -hairpin and β -sheet peptides (such as the *protegrins* [V.N. Kokryakov, S.S.L. Harwig, E.A.
35 Panyutich, A.A. Shevchenko, G.M. Aleshina, O.V. Shamova,

H.A. Korneva, R.I. Lehrer, *FEBS Lett.* **1993**, 327, 231-236],
tachyplesins [T. Nakamura, H. Furunaka, T. Miyata, F.
Tokunaga, T. Muta, S. Iwanaga, M. Niwa, T. Takao, Y.
Shimonishi, *J. Biol. Chem.* **1988**, 263, 16709-16713], and the
5 *defensins* [R.I. Lehrer, A.K. Lichtenstein, T. Ganz, *Annu.*
Rev. Immunol. **1993**, 11, 105-128], amphipathic α -helical
peptides (e.g. *cecropins*, *dermaseptins*, *magainins*, and
mellitins [A. Tossi, L. Sandri, A. Giangaspero, *Biopolymers*
2000, 55, 4-30]), as well as other linear and loop-
10 structured peptides. Although the mechanisms of action of
antimicrobial cationic peptides are not yet fully
understood, their primary site of interaction is the
microbial cell membrane (H.W. Huang, *Biochemistry* **2000**, 39,
8347-8352). Upon exposure to these agents, the cell membrane
15 undergoes permeabilization, which is followed by rapid cell
death. However, more complex mechanisms of action, for
example, involving receptor-mediated signaling, cannot
presently be ruled out (M. Wu, E. Maier, R. Benz, R.E.
Hancock, *Biochemistry* **1999**, 38, 7235-7242).

20

Unlike most antibiotics, antiviral agents do not destroy the
target viruses but they are able to inhibit the development
of viral pathogens at different stages of their replication
cycle, for example, by preventing the entry of the viruses
25 to the target cells or by blocking essential steps during
the viral synthesis within the target cells. Common diseases
caused by viruses are, for example, influenza, avian
influenza, swine influenza, severe acute respiratory
syndrome (SARS), or acquired immune deficiency syndrome
30 (AIDS). Encephalitis, meningitis, pharyngitis parotitis,
gingivostomatitis, hepatitis, myelitis, gastroenteritis,
pancreatitis, certain skin infections or cardiovascular
diseases as well as pneumonia or sexually transmitted
diseases can be caused by viral infections.

35

In the compounds described below, a new strategy is introduced to stabilize β -hairpin conformations in backbone-cyclic cationic peptide mimetics exhibiting selective anti-infective activity. This involves transplanting the hairpin
5 sequence onto a template, whose function is to restrain the peptide loop backbone into a hairpin geometry.

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 the ability to generate β -hairpin peptidomimetics using combinatorial and parallel synthesis methods has now been established (L. Jiang, K. Moehle, B. Dhanapal, D. Obrecht, J.A. Robinson, *Helv. Chim. Acta.* **2000**,
15 83, 3097-3112). Antibacterial template-fixed peptidomimetics and methods for their synthesis have been described in International Patent applications WO02/070547 A1, WO2004/018503 A1 and WO2007/079605 A2 but these molecules do not show high potency and selectivity against *Bacillus*
20 *subtilis* and/or *Shigella boydii*.

The β -hairpin peptidomimetics of the present invention are compounds of the general formula Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-), wherein
25 the amino acid residues Xaa¹ to Xaa¹⁴ are:

- Xaa¹: amino acid residue of type C, or of type D,
as described herein below;
- Xaa²: amino acid residue of type E,
30 as described herein below;
- Xaa³: amino acid residue of type C, or of type F,
as described herein below;
- Xaa⁴: amino acid residue of type C, or of type E,
as described herein below;

- Xaa⁵: amino acid residue of type C,
as described herein below;
- Xaa⁶: amino acid residue of type E, as described herein
below; or the D-isomer of an amino acid residue
5 of type E, as described herein below;
- Xaa⁷: amino acid residue of type F,
as described herein below, or Gly;
- Xaa⁸: amino acid residue of type E,
as described herein below;
- 10 - Xaa⁹: amino acid residue of type E,
as described herein below;
- Xaa¹⁰: amino acid residue of type C, or of type F,
as described herein below;
- Xaa¹¹: amino acid residue of type E, or of type F,
15 as described herein below;
- Xaa¹²: amino acid residue of type C, or of type E,
or of type F, as described herein below;
- Xaa¹³: amino acid residue of formula -A-CO-,
as described herein below;
- 20 - Xaa¹⁴: amino acid residue of formula -B-CO-,
as described herein below;

with the proviso that if

Xaa⁹ is an amino acid residue of type E,
as described herein below,

25 then Xaa⁹ is Dab; and/or if

Xaa¹² is an amino acid residue of type F,
as described herein below,

then Xaa¹² is Gln; and/or

at least two of the amino acid residues of
30 Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-
Xaa¹²-Xaa¹³-Xaa¹⁴-) are non-canonical amino acid residues,
as described herein below;

or

compounds of the general formula Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-), wherein the amino acid residues Xaa¹ to Xaa¹⁴ are:

- 5 - Xaa¹: amino acid residue of type D,
as described herein below;
- Xaa²: amino acid residue of type E,
as described herein below;
- Xaa³: amino acid residue of type C, or of type F,
10 as described herein below;
- Xaa⁴: amino acid residue of type E,
as described herein below;
- Xaa⁵: amino acid residue of type C,
as described herein below;
- 15 - Xaa⁶: amino acid residue of type E, or the D-isomer of
an amino acid residue of type E,
as described herein below;
- Xaa⁷: amino acid residue of type C, or of type D,
or of type E, or of type F,
20 as described herein below, or Gly;
- Xaa⁸: amino acid residue of type F,
as described herein below;
- Xaa⁹: amino acid residue of type E,
as described herein below;
- 25 - Xaa¹⁰: amino acid residue of type C, or of type D,
or of type F, as described herein below;
- Xaa¹¹: amino acid residue of type E, or or type F,
as described herein below;
- Xaa¹²: amino acid residue of type C or of type E,
30 as described herein below;
- Xaa¹³: amino acid residue of formula -A-CO-,
as described herein below;
- Xaa¹⁴: amino acid residue of formula -B-CO-,
as described herein below;
- 35 with the proviso that if
Xaa⁷ is an amino acid residue of type F,

as described herein below,
then Xaa⁷ is Gln or Thr; and/or if
Xaa¹⁰ is an amino acid residue of type F,
as described herein below,

5 then Xaa¹⁰ is Ser; and/or
at least one of the amino acid residues of
Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-
Xaa¹²-Xaa¹³-Xaa¹⁴-) is a non-canonical amino acid residue,
as described herein below;

10

or

compounds of the general formula Cyclo(-Xaa¹-Xaa²-Xaa³-
Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-),

15 wherein the amino acid residues Xaa¹ to Xaa¹⁴ are:

- Xaa¹: amino acid residue of type D,
as described herein below;
- Xaa²: amino acid residue of type E,
20 as described herein below;
- Xaa³: amino acid residue of type C,
as described herein below;
- Xaa⁴: amino acid residue of type E,
as described herein below;
- 25 - Xaa⁵: amino acid residue of type C,
as described herein below;
- Xaa⁶: amino acid residue of type E, as described herein
below, or the D-isomer of an amino acid residue
of type E, as described herein below;
- 30 - Xaa⁷: amino acid residue of type F,
as described herein below;
- Xaa⁸: amino acid residue of type D,
as described herein below;
- Xaa⁹: amino acid residue of type E,
35 as described herein below;

- Xaa¹⁰: amino acid residue of type F,
as described herein below;
- Xaa¹¹: amino acid residue of type E,
as described herein below;
- 5 - Xaa¹²: amino acid residue of type E,
as described herein below;
- Xaa¹³: amino acid residue of formula -A-CO-,
as described herein below;
- Xaa¹⁴: amino acid residue of formula -B-CO-,
10 as described herein below;

or

compounds of the general formula Cyclo(-Xaa¹-Xaa²-Xaa³-
15 Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-),
wherein the amino acid residues Xaa¹ to Xaa¹⁴ are:

- Xaa¹: amino acid residue of type D,
as described herein below;
- 20 - Xaa²: amino acid residue of type E,
as described herein below;
- Xaa³: amino acid residue of type E,
as described herein below;
- Xaa⁴: amino acid residue of type E,
25 as described herein below;
- Xaa⁵: amino acid residue of type C,
as described herein below, or Gly;
- Xaa⁶: amino acid residue of type E, or of type F,
as described herein below, or the D-isomer of an
30 amino acid residue of type E, as described herein
below, or -B-CO-, as described herein below or
Gly;
- Xaa⁷: amino acid residue of type E, as described herein
below, or the D-isomer of an amino acid residue
35 of type E, as described herein below, or Gly;

- Xaa⁸: amino acid residue of type F,
as described herein below, or Gly;
 - Xaa⁹: amino acid residue of type E,
as described herein below;
 - 5 - Xaa¹⁰: amino acid residue of type F,
as described herein below;
 - Xaa¹¹: amino acid residue of type E,
as described herein below;
 - Xaa¹²: amino acid residue of type E,
10 as described herein below;
 - Xaa¹³: amino acid residue of formula -A-CO-,
as described herein below;
 - Xaa¹⁴: amino acid residue of formula -B-CO-,
as described herein below;
- 15 with the proviso that at least one of the amino acid residues of Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-) is a non-canonical amino acid residue, as described herein below;

20 or

compounds of the general formula Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-),
wherein the amino acid residues Xaa¹ to Xaa¹⁴ are:

- 25
- Xaa¹: amino acid residue of type E,
as described herein below;
 - Xaa²: amino acid residue of type E,
as described herein below;
 - 30 - Xaa³: amino acid residue of type C, or of type F,
as described herein below;
 - Xaa⁴: amino acid residue of type E,
as described herein below;
 - Xaa⁵: amino acid residue of type C, or of type F,
35 as described herein below;

- Xaa⁶: amino acid residue of type E, as described herein below, or the D-isomer of an amino acid residue of type E, as described herein below;
 - Xaa⁷: Gly;
 - 5 - Xaa⁸: amino acid residue of type E, or of type F, as described herein below;
 - Xaa⁹: amino acid residue of type E, as described herein below;
 - Xaa¹⁰: amino acid residue of type C, or of type F, as described herein below;
 - 10 - Xaa¹¹: amino acid residue of type E, as described herein below;
 - Xaa¹²: amino acid residue of type E, as described herein below;
 - 15 - Xaa¹³: amino acid residue of formula -A-CO-, as described herein below;
 - Xaa¹⁴: amino acid residue of formula -B-CO-, as described herein below;
- with the proviso that at least two of the amino acid residues of Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-) are non-canonical amino acid residues;

or

- 25 compounds of the general formula Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-), wherein the amino acid residues Xaa¹ to Xaa¹⁴ are:
- Xaa¹: amino acid residue of type E, as described herein below;
 - 30 - Xaa²: amino acid residue of type C, or of type F, as described herein below;
 - Xaa³: amino acid residue of type E, as described herein below;
 - 35 - Xaa⁴: amino acid residue of type E, as described herein below;

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- Xaa⁵: amino acid residue of type C,
as described herein below;
 - Xaa⁶: amino acid residue of type E,
as described herein below;
 - 5 - Xaa⁷: Gly;
 - Xaa⁸: amino acid residue of type F,
as described herein below;
 - Xaa⁹: amino acid residue of type E,
as described herein below;
 - 10 - Xaa¹⁰: amino acid residue of type E, or of type F,
as described herein below;
 - Xaa¹¹: amino acid residue of type E, or of type F,
as described herein below;
 - Xaa¹²: amino acid residue of type E,
15 as described herein below;
 - Xaa¹³: amino acid residue of formula -A-CO-,
as described herein below;
 - Xaa¹⁴: amino acid residue of formula -B-CO-,
as described herein below;
 - 20 - the amino acid residues Xaa² and Xaa¹¹, taken together,
can form an amino acid residue of type H,
as described herein below;
- with the proviso that at least one of the amino acid
residues of Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-
25 Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-) are non-canonical amino
acid residues;

or

- 30 compounds of the general formula Cyclo(-Xaa¹-Xaa²-Xaa³-
Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-),
wherein the amino acid residues Xaa¹ to Xaa¹⁴ are:
- Xaa¹: amino acid residue of type, E or of type F,
35 as described herein below;

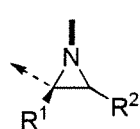
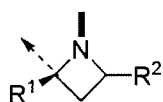
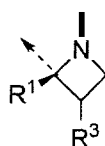
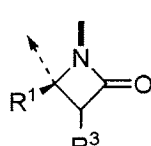
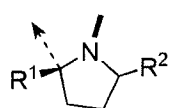
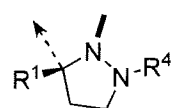
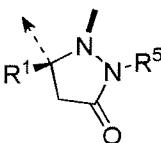
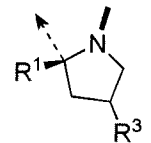
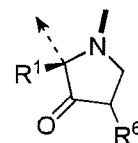
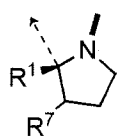
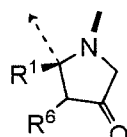
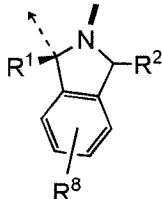
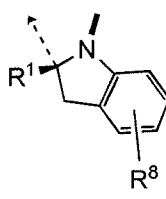
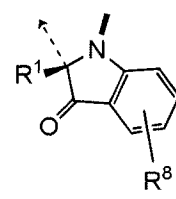
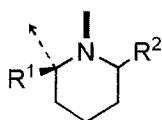
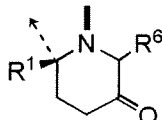
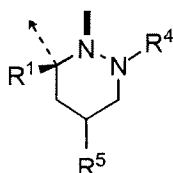
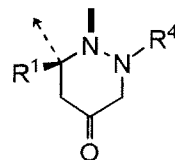
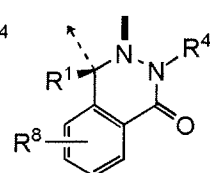
- Xaa²: amino acid residue of type C, or of type D, or of type E, or of type F, as described herein below;
- Xaa³: amino acid residue of type E, as described herein below, or the D-isomer of an amino acid residue of type E, as described herein below, or Gly;
- Xaa⁴: amino acid residue of type C, or of type D, or of type E, or of type F, as described herein below;
- Xaa⁵: amino acid residue of type E, as described herein below;
- Xaa⁶: amino acid residue of type E, or of type F, as described herein below, or Gly;
- Xaa⁷: amino acid residue of type D, or of type E, or of type F, as described herein below, or Gly;
- Xaa⁸: amino acid residue of type E, as described herein below;
- Xaa⁹: amino acid residue of type D, or of type E, as described herein below;
- Xaa¹⁰: amino acid residue of type C, or of type D, or of type E, or of type F, as described herein below;
- Xaa¹¹: amino acid residue of type D, or of type E, or of type F, as described herein below, or Gly;
- Xaa¹²: amino acid residue of type C, or of type D, or of type E, or of type F, as described herein below;
- Xaa¹³: amino acid residue of formula -A-CO-, as described herein below;
- Xaa¹⁴: amino acid residue of formula -B-CO-, as described herein below;
- the amino acid residues Xaa² and Xaa¹¹, taken together, can form an amino acid residue of type H, as described herein below;

with the proviso that at least two of the amino acid residues of Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-) are non-canonical amino acid residues;

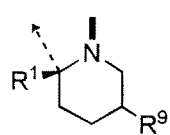
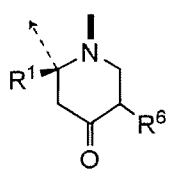
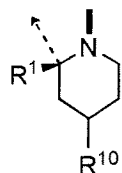
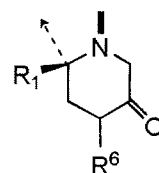
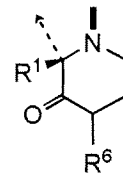
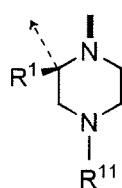
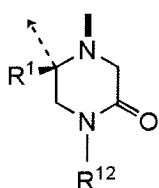
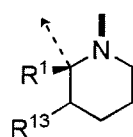
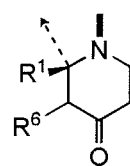
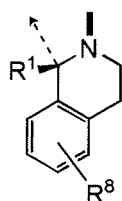
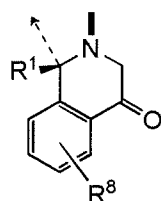
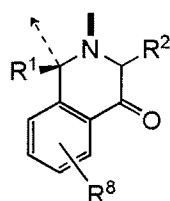
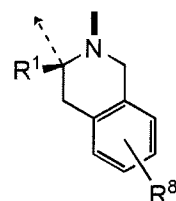
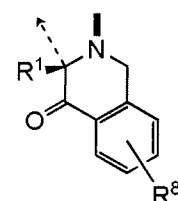
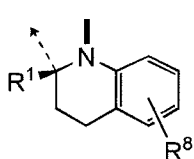
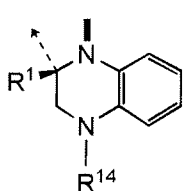
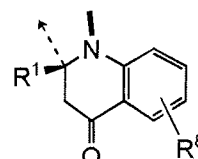
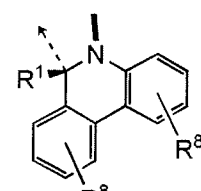
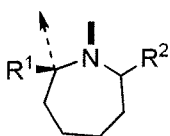
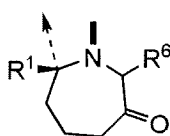
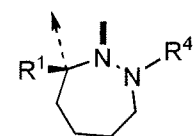
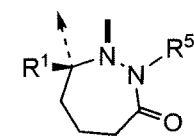
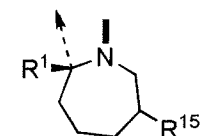
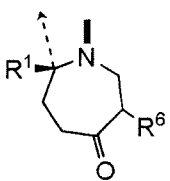
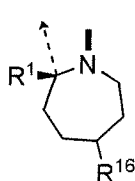
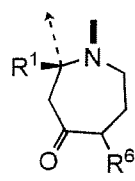
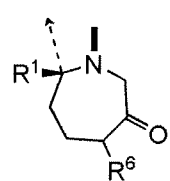
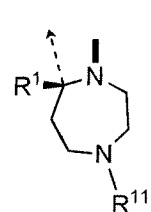
-B-CO- is Gly, NMeGly or the residue of an L- α -amino acid with B being a residue of formula $-\text{NR}^{20}\text{CH}(\text{R}^{71})-$, or $-\text{NR}^{20}\text{CH}(\text{R}^{72})-$, or $-\text{NR}^{20}\text{CH}(\text{R}^{73})-$, or $-\text{NR}^{20}\text{CH}(\text{R}^{74})-$, or $-\text{NR}^{20}\text{CH}(\text{R}^{84})-$, or the enantiomer of one of the groups **A1** to **A69** as

5 defined hereinafter;

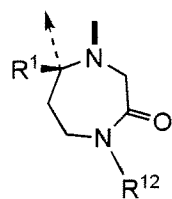
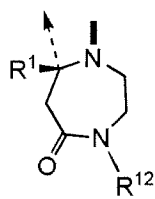
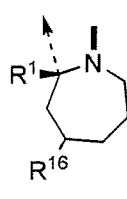
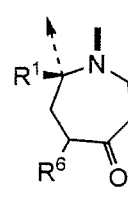
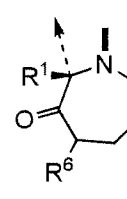
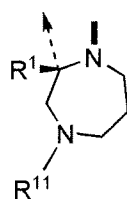
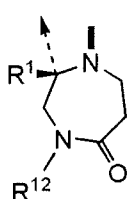
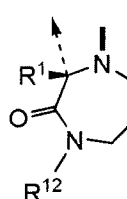
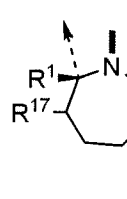
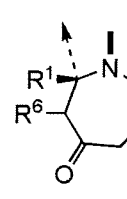
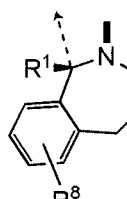
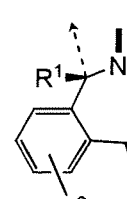
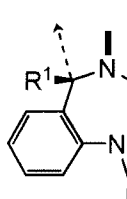
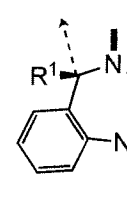
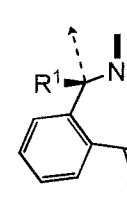
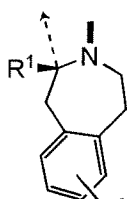
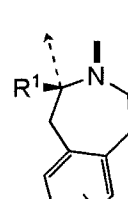
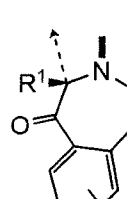
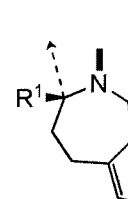
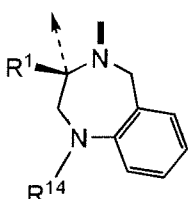
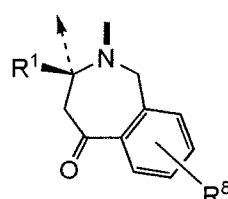
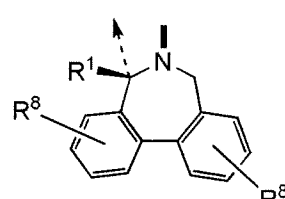
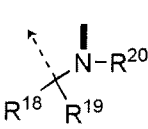
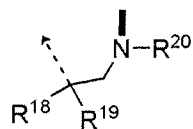
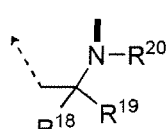
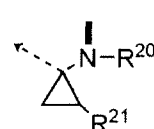
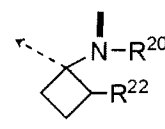
A of -A-CO- is a group of one of the formulae

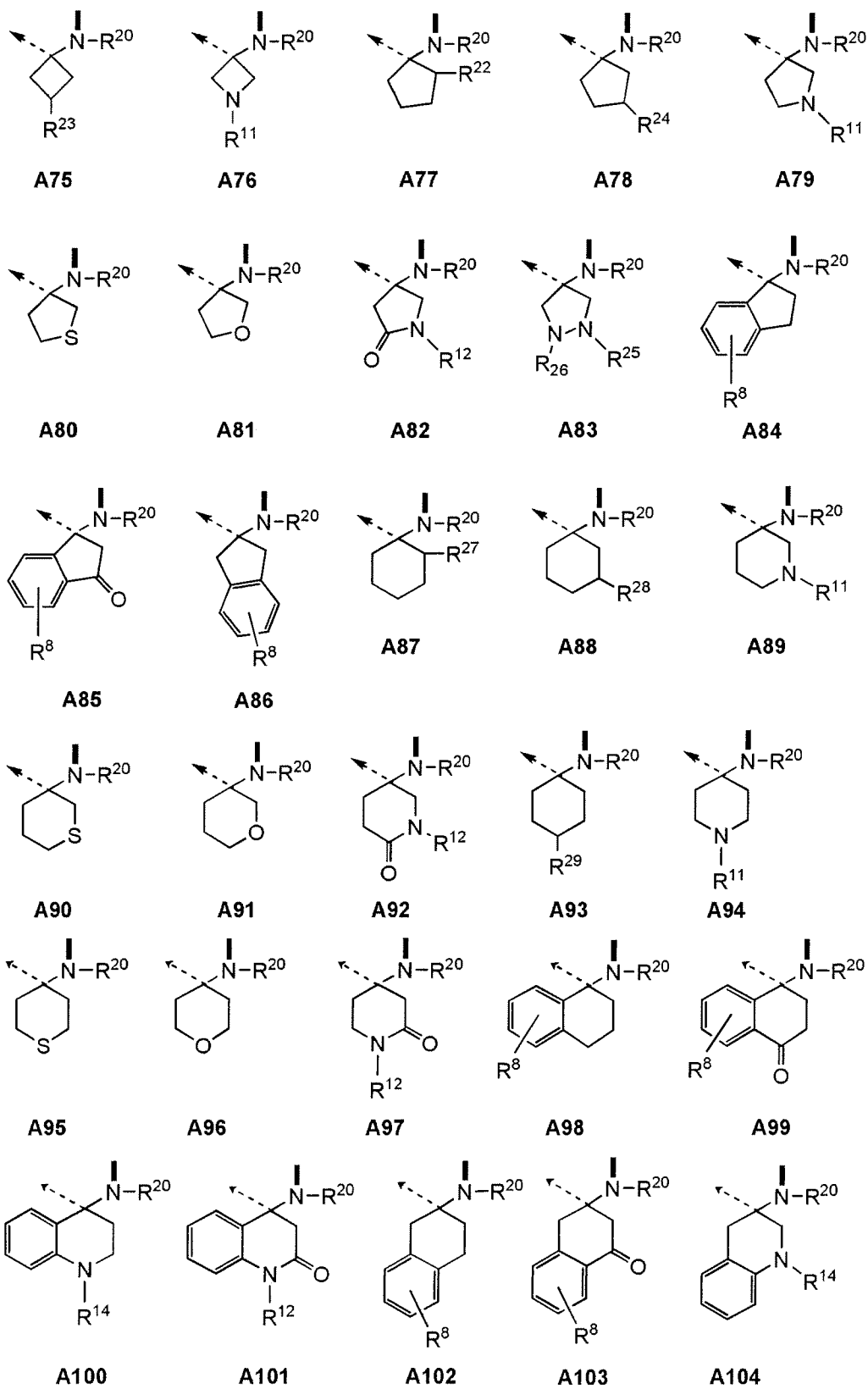
**A1****A2****A3****A4****A5****A6****A7****A8****A9****A10****A11****A12****A13****A14****A15****A16****A17****A18****A19**

13

**A20****A21****A22****A23****A24****A25****A26****A27****A28****A29****A30****A31****A32****A33****A34****A35****A36****A37****A38****A39****A40****A41****A42****A43****A44****A45****A46****A47**

14

**A48****A49****A50****A51****A52****A53****A54****A55****A56****A57****A58****A59****A60****A61****A62****A63****A64****A65****A66****A67****A68****A69****A70****A71****A72****A73****A74**



- R^1 is H; lower alkyl; lower cycloalkyl; lower alkyl-aryl or aryl-lower alkyl;
- R^2 is H; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;
 $-(CH_2)_p(CHR^{61})_sSR^{56}$;
 5 $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$;
 $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sR^{77}$;
- R^3 is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 10 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
- 15 R^4 is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
 20 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
- R^5 is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$;
 $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
 25 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
- R^6 is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$;
 $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 30 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
- R^7 is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 35 $-(CH_2)_r(CHR^{61})_sCOOR^{57}$; $-(CH_2)_r(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_r(CHR^{61})_sPO(OR^{60})_2$;

- $-(CH_2)_r(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_r(CHR^{61})_sC_6H_4R^8$;
 R^8 is H; Cl; F; CF_3 ; NO_2 ; lower alkyl; lower cycloalkyl;
 lower alkenyl; aryl; lower alkyl-aryl; aryl-lower
 alkyl; $-(CH_2)_o(CHR^{61})_sR^{77}$
- 5 $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 10 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sCOR^{64}$;
 R^9 is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 15 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{10} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 20 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{11} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
 25 $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{12} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$;
 30 $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_r(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_r(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_r(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_r(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_r(CHR^{61})_sC_6H_4R^8$;
 35 R^{13} is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sSR^{56}$;
 $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;

- $-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_q(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;
- 5 R^{14} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$; .
- 10 $-(CH_2)_q(CHR^{61})_sSOR^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;
 R^{15} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
15 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{16} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
20 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{17} is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sSR^{56}$;
 $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
25 $-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_q(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;
 R^{18} is alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sSR^{56}$;
30 $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;
35 R^{19} is lower alkyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sSR^{56}$;
 $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;

- $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$; or
5 R^{18} and R^{19} taken together can form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;
 R^{20} is H; alkyl; lower cycloalkyl; alkenyl; lower alkyl-aryl;
or aryl-lower alkyl;
 R^{21} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$;
10 $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
15 R^{22} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$;
 $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
20 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{23} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
25 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{24} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
30 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{25} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$;
 $-(CH_2)_m(CHR^{61})_sSR^{56}$;
35 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;

- $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{26} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$;
 $-(CH_2)_m(CHR^{61})_sSR^{56}$;
5 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$; or
 R^{25} and R^{26} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_rO(CH_2)_r$;
10 $-(CH_2)_rS(CH_2)_r-$; or $-(CH_2)_rNR^{57}(CH_2)_r-$;
 R^{27} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$;
 $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$;
15 $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{28} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_s-OR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
20 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{29} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
25 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{33} is H; alkyl, alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$;
30 $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$;
 $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOR^{64}$; $-(CH_2)_o(CHR^{61})_s-CONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
35 R^{34} is H; lower alkyl; lower cycloalkyl; lower alkyl-aryl;
aryl or aryl-lower alkyl; or

- R^{33} and R^{34} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;
- R^{50} is H; lower alkyl; lower cycloalkyl; lower alkyl-aryl; or
 aryl-lower alkyl;
- 5 R^{55} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; aryl-lower alkyl;
 $-(CH_2)_m(CHR^{61})_sOR^{57}$;
 $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$; $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$; $-(CH_2)_o(CHR^{61})_s-COR^{64}$;
- 10 $-(CH_2)_o(CHR^{61})COOR^{57}$; or
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
- R^{56} is H; lower alkyl; lower alkenyl; lower alkyl-aryl;
 aryl-lower alkyl;
 $-(CH_2)_m(CHR^{61})_sOR^{57}$;
- 15 $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$; $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$; $-(CH_2)_o(CHR^{61})_s-COR^{64}$; or
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
- R^{57} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; aryl-lower alkyl;
- 20 lower alkyl-heteroaryl; or heteroaryl-lower alkyl;
- R^{58} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; aryl-lower alkyl;
 lower alkyl-heteroaryl; or heteroaryl-lower alkyl;
- R^{59} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
- 25 lower alkyl-aryl; aryl-lower alkyl;
 lower alkyl-heteroaryl; or heteroaryl-lower alkyl; or
- R^{58} and R^{59} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$;
- 30 R^{60} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; aryl; or aryl-lower alkyl;
- R^{61} is alkyl; alkenyl; lower cycloalkyl; lower alkyl-aryl;
 lower alkyl-heteroaryl; aryl; heteroaryl;
 aryl-lower alkyl; heteroaryl-lower alkyl; $-(CH_2)_pOR^{55}$;
- 35 $-(CH_2)_pNR^{33}R^{34}$; $-(CH_2)_pOCONR^{75}R^{82}$; $-(CH_2)_pNR^{20}CONR^{78}R^{82}$;
 $-(CH_2)_oCOOR^{37}$; or $-(CH_2)_oPO(OR^{60})_2$;

- R^{62} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; lower alkyl-heteroaryl; aryl;
 heteroaryl; aryl-lower alkyl; or
 heteroaryl-lower alkyl;
- 5 R^{63} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; lower alkyl-heteroaryl; aryl;
 heteroaryl; aryl-lower alkyl; or
 heteroaryl-lower alkyl;
 $-\text{COR}^{64}$; $-\text{COOR}^{57}$; $-\text{CONR}^{58}\text{R}^{59}$; $-\text{SO}_2\text{R}^{62}$; or $-\text{PO}(\text{OR}^{60})_2$; or
- 10 R^{34} and R^{63} taken together can form: $-(\text{CH}_2)_{2-6}-$; $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$;
 $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2-$; or $-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2-$;
 R^{64} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; lower alkyl-heteroaryl; aryl;
 heteroaryl; aryl-lower alkyl; or
- 15 heteroaryl-lower alkyl;
 $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{OR}^{65}$; $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{SR}^{66}$;
 $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{NR}^{34}\text{R}^{63}$;
 $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{OCONR}^{75}\text{R}^{82}$; or $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{NR}^{20}\text{CONR}^{78}\text{R}^{82}$;
 R^{65} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
- 20 lower alkyl-aryl; lower alkyl-heteroaryl; aryl;
 heteroaryl; aryl-lower alkyl; or
 heteroaryl-lower alkyl; $-\text{COR}^{57}$;
 $-\text{COOR}^{57}$; or $-\text{CONR}^{58}\text{R}^{59}$;
 R^{66} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
- 25 lower alkyl-aryl; lower alkyl-heteroaryl; aryl;
 heteroaryl; aryl-lower alkyl; or
 heteroaryl-lower alkyl; or $-\text{CONR}^{58}\text{R}^{59}$;
 R^{67} is H; Cl; Br; F; NO_2 ; $-\text{NR}^{34}\text{COR}^{57}$; $-\text{CF}_3$; CN; $-\text{OCF}_3$; $-\text{OCHF}_2$;
 $-\text{OR}^{57}$; $-\text{SR}^{62}$; lower alkyl; or
- 30 lower alkenyl;
 R^{68} is H; Cl; Br; F; NO_2 ; $-\text{NR}^{34}\text{COR}^{57}$; $-\text{CF}_3$; CN; $-\text{OCF}_3$; $-\text{OCHF}_2$;
 $-\text{OR}^{57}$; $-\text{SR}^{62}$; lower alkyl; or
 lower alkenyl;
- R^{69} is H; Cl; Br; F; NO_2 ; $-\text{NR}^{34}\text{COR}^{57}$; $-\text{CF}_3$; CN; $-\text{OCF}_3$; $-\text{OCHF}_2$;
 35 $-\text{OR}^{57}$; $-\text{SR}^{62}$; lower alkyl; or
 lower alkenyl;

R^{70} is H; Cl; Br; F; NO_2 ; $-\text{NR}^{34}\text{COR}^{57}$; $-\text{CF}_3$; CN; $-\text{OCF}_3$; $-\text{OCHF}_2$;
 $-\text{OR}^{57}$; $-\text{SR}^{62}$; lower alkyl; or
 lower alkenyl;

R^{71} is lower alkyl; lower alkenyl; $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{OR}^{75}$;

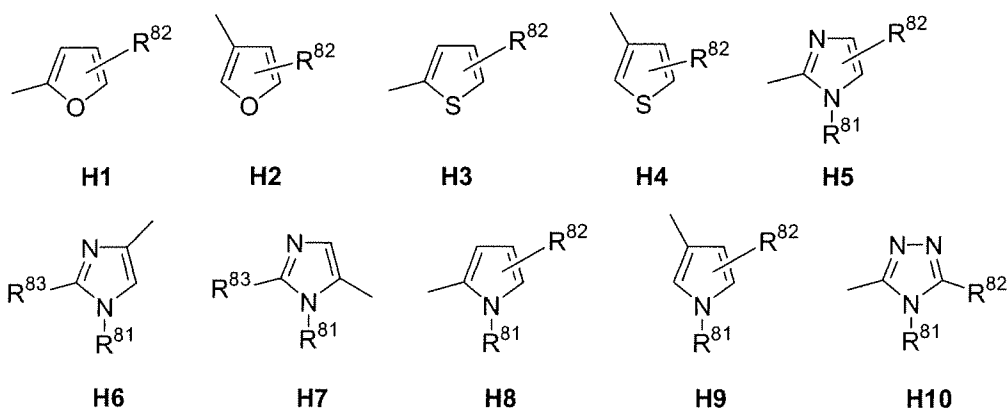
- 5 $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{SR}^{75}$;
 $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{NR}^{33}\text{R}^{34}$; $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{OCONR}^{33}\text{R}^{75}$;
 $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{NR}^{20}\text{CONR}^{33}\text{R}^{82}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{COOR}^{75}$; $-(\text{CH}_2)_p\text{CONR}^{58}\text{R}^{59}$; $-(\text{CH}_2)_p\text{PO}(\text{OR}^{62})_2$;
 $-(\text{CH}_2)_p\text{SO}_2\text{R}^{62}$; or
 10 $-(\text{CH}_2)_o-\text{C}_6\text{R}^{67}\text{R}^{68}\text{R}^{69}\text{R}^{70}\text{R}^{76}$;

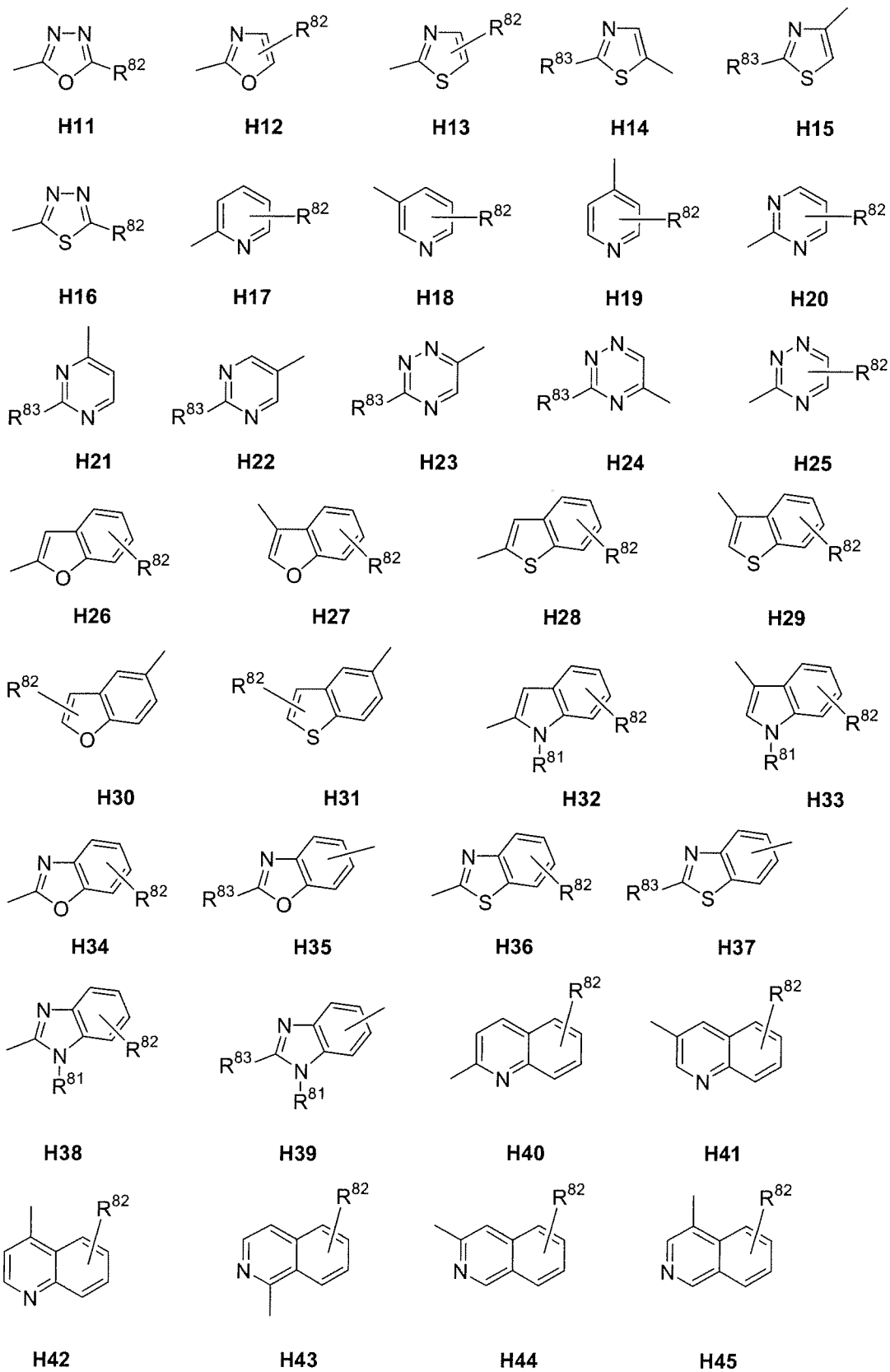
R^{72} is alkyl; alkenyl; lower cycloalkyl; $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{OR}^{85}$; or
 $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{SR}^{85}$;

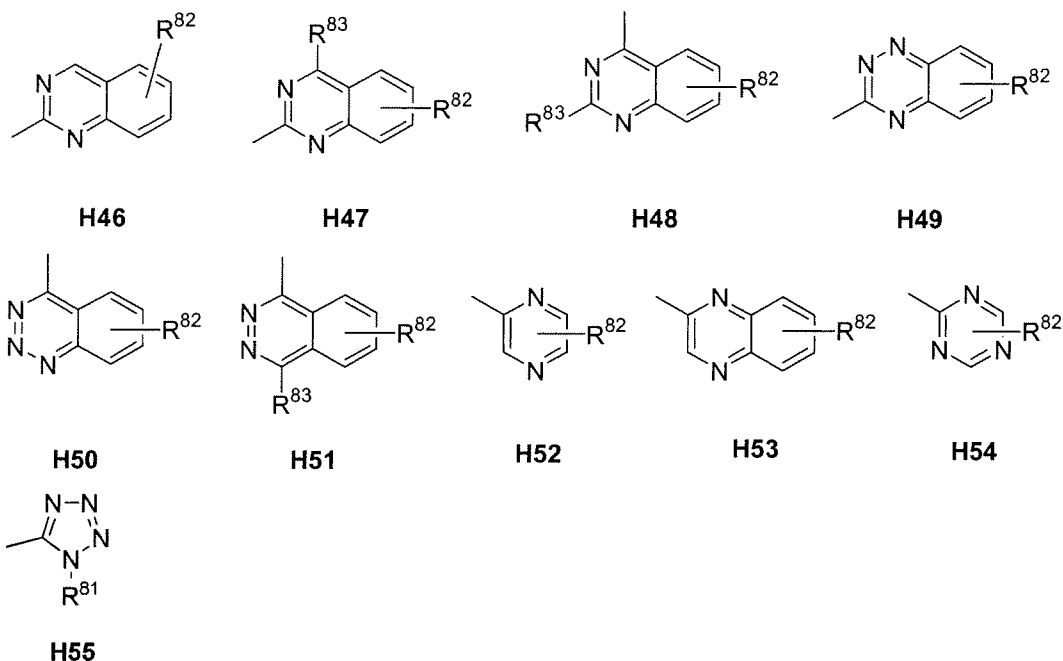
R^{73} is $-(\text{CH}_2)_o\text{R}^{77}$; $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_o\text{R}^{77}$; $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_o\text{R}^{77}$; or
 $-(\text{CH}_2)_r\text{NR}^{20}(\text{CH}_2)_o\text{R}^{77}$;

- 15 R^{74} is $-(\text{CH}_2)_p\text{NR}^{78}\text{R}^{79}$; $-(\text{CH}_2)_p\text{NR}^{77}\text{R}^{80}$; $-(\text{CH}_2)_p\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_p\text{C}(=\text{NOR}^{50})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_p\text{C}(=\text{NNR}^{78}\text{R}^{79})\text{NR}^{78}\text{R}^{79}$; $-(\text{CH}_2)_p\text{NR}^{80}\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_p\text{N}=\text{C}(\text{NR}^{78}\text{R}^{80})\text{NR}^{79}\text{R}^{80}$; $-(\text{CH}_2)_p\text{C}_6\text{H}_4\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_p\text{C}_6\text{H}_4\text{NR}^{77}\text{R}^{80}$;
 20 $-(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$; $-(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NOR}^{50})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NNR}^{78}\text{R}^{79})\text{NR}^{78}\text{R}^{79}$; $-(\text{CH}_2)_p\text{C}_6\text{H}_4\text{NR}^{80}\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_p\text{C}_6\text{H}_4\text{N}=\text{C}(\text{NR}^{78}\text{R}^{80})\text{NR}^{79}\text{R}^{80}$; $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_m\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_m\text{NR}^{77}\text{R}^{80}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$; $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}(=\text{NOR}^{50})\text{NR}^{78}\text{R}^{79}$;
 25 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}(=\text{NNR}^{78}\text{R}^{79})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_m\text{NR}^{80}\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_m\text{N}=\text{C}(\text{NR}^{78}\text{R}^{80})\text{NR}^{79}\text{R}^{80}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{CNR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$;
 30 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NOR}^{50})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NNR}^{78}\text{R}^{79})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{NR}^{80}\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$; $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_m\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_m\text{NR}^{77}\text{R}^{80}$; $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}(=\text{NOR}^{50})\text{NR}^{78}\text{R}^{79}$;
 35 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}(=\text{NNR}^{78}\text{R}^{79})\text{NR}^{78}\text{R}^{79}$;

- $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_m\text{NR}^{80}\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79};$
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_m\text{N}=\text{C}(\text{NR}^{78}\text{R}^{80})\text{NR}^{79}\text{R}^{80};$
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{CNR}^{78}\text{R}^{79}; -(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79};$
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NOR}^{50})\text{NR}^{78}\text{R}^{79};$
5 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NNR}^{78}\text{R}^{79})\text{NR}^{78}\text{R}^{79};$
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{NR}^{80}\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}; -(\text{CH}_2)_p\text{NR}^{80}\text{COR}^{64};$
 $-(\text{CH}_2)_p\text{NR}^{80}\text{COR}^{77};$
 $-(\text{CH}_2)_p\text{NR}^{80}\text{CONR}^{78}\text{R}^{79}; \text{ or } -(\text{CH}_2)_p\text{C}_6\text{H}_4\text{NR}^{80}\text{CONR}^{78}\text{R}^{79};$
 R^{75} is lower alkyl; lower alkenyl; lower cycloalkyl;
10 lower-alkyl-aryl; or aryl-lower alkyl; or
 R^{33} and R^{75} taken together can form: $-(\text{CH}_2)_{2-6}-$; $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$;
 $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2-$; or $-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2-$; or
 R^{75} and R^{82} taken together can form: $-(\text{CH}_2)_{2-6}-$; $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$;
 $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2-$; or
15 $-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2-$;
 R^{76} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
lower-alkyl-aryl; aryl-lower alkyl;
 $-(\text{CH}_2)_o\text{OR}^{72}; -(\text{CH}_2)_o\text{SR}^{72};$
 $-(\text{CH}_2)_o\text{NR}^{33}\text{R}^{34}; -(\text{CH}_2)_o\text{CONR}^{33}\text{R}^{75}; -(\text{CH}_2)_o\text{NR}^{20}\text{CONR}^{33}\text{R}^{81};$
20 $-(\text{CH}_2)_o\text{COOR}^{75}; -(\text{CH}_2)_o\text{CONR}^{58}\text{R}^{59}; -(\text{CH}_2)_o\text{PO}(\text{OR}^{60})_2;$
 $-(\text{CH}_2)_p\text{SO}_2\text{R}^{62}; \text{ or }$
 $-(\text{CH}_2)_o\text{COR}^{64};$
 R^{77} is $-\text{C}_6\text{R}^{67}\text{R}^{68}\text{R}^{69}\text{R}^{70}\text{R}^{76}$ with the proviso that at least two of R^{67} ,
 R^{68} , R^{69} and R^{70} are H; or a heteroaryl group of one of the
25 formulae







R^{78} is H; lower alkyl; lower cycloalkyl; lower alkyl-aryl;
aryl; or aryl-lower alkyl; or

R^{78} and R^{82} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;

5 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;

R^{79} is H; lower alkyl; lower alkyl-aryl; aryl; or
aryl-lower alkyl; or

R^{78} and R^{79} , taken together, can be $-(CH_2)_{2-7}-$; $-(CH_2)_2O(CH_2)_2-$;
or $-(CH_2)_2NR^{57}(CH_2)_2-$;

10 R^{80} is H; or lower alkyl;

R^{81} is H; lower alkyl; lower cycloalkyl; lower alkyl-aryl; or
aryl-lower alkyl; or

R^{33} and R^{81} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;

15 R^{82} is H; $-CF_3$; $-OCF_3$; $-OCHF_2$; lower alkyl; aryl; heteroaryl;
or aryl-lower alkyl;

R^{83} is H; lower alkyl; aryl; or $-NR^{78}R^{79}$;

R^{84} is $-(CH_2)_p(CHR^{61})_sOH$; $-(CH_2)_pCOOR^{80}$; $-(CH_2)_p(CHR^{61})_sSH$;
 $-(CH_2)_pCONR^{78}R^{79}$; $-(CH_2)_pNR^{80}CONR^{78}R^{79}$; $-(CH_2)_pC_6H_4CONR^{78}R^{79}$;
20 or $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;

R^{85} is lower alkyl; or lower alkenyl;

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R^{86} is R^{74} ; $-(CH_2)_oR^{77}$; $-(CH_2)_o-CHR^{33}R^{75}$; R^{84} ;
 $-[(CH_2)_u-X']_t-(CH_2)_vNR^{78}R^{79}$;
 $-[(CH_2)_u-X']_t-(CH_2)_v-C(=NR^{80})NR^{78}R^{79}$;
 $-[(CH_2)_u-X']_t-(CH_2)_vOR^{78}$; $-[(CH_2)_u-X']_t-(CH_2)_v-CONR^{78}R^{79}$;
5 $-[(CH_2)_u-X']_t-(CH_2)_v-NR^{80}CONR^{78}R^{79}$; $-[(CH_2)_u-X']_t-(CH_2)_vSR^{78}$
 where X' is $-O-$, $-NR^{20}-$, $-S-$; or $-OCOO-$, u is 1-3, t is
 1-6, and v is 1-3;

m is 2-4; o is 0-4; p is 1-4; q is 0-2; r is 1 or 2; s is 0
 10 or 1;

the amino acid residue of type C is a residue of formula
 $-NR^{20}CH(R^{72})CO-$;

the amino acid residue of type D is a residue of formula
 15 $-NR^{20}CH(R^{73})CO-$;

the amino acid residue of type E is a residue of the formula
 $-NR^{20}CH(R^{74})CO-$;

the amino acid residue of type F is a residue of the formula
 $-NR^{20}CH(R^{84})CO-$;

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the amino acid residue of type H is a residue of the one of
 the formulae $-NR^{20}-CH(CO-)-alkylene-CH(CO-)-NR^{20}-$;

$-NR^{20}-CH(CO-)-alkenylene-CH(CO-)-NR^{20}-$;

$-NR^{20}-CH(CO-)-alkynylene-CH(CO-)-NR^{20}-$;

25 $-NR^{20}-CH(CO-)-(CH_2)_pSS(CH_2)_p-CH(CO-)-NR^{20}-$;

$-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CO(CH_2)_p-CH(CO-)-NR^{20}-$; and

$-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CONR^{20}(CH_2)_p-CH(CO-)-NR^{20}-$;

non-canonical amino acid residues designate those amino acid
 30 residues being neither glycine nor the L- or D-isomers of
 alanine, arginine, aspartic acid, asparagine, cysteine,
 glutamic acid, glutamine, histidine, isoleucine, leucine,
 lysine, methionine, phenylalanine, proline, serine,
 threonine, tryptophan, tyrosine and valine;

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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 corresponds to Xaa^n , wherein n is 14, 13, 12, 7, 6 or 5, 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 corresponds to Xaa^{n-1} , 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 obtained in step (c);
- (e) effecting steps substantially corresponding to steps (c) and (d) using appropriately N-protected derivatives of amino acids which in the desired end-product are in positions n-2 to 1, any functional group(s) which may be present in said N-protected amino acid derivatives being likewise appropriately protected;
- (f) if n is not 14, further effecting steps substantially corresponding to steps (c) and (d) using appropriately N-protected derivatives of amino acids which in the desired end-product are in positions 14 to n + 1, any functional group(s) which may be present in said N-protected amino acid derivatives being likewise appropriately protected;
- (g) forming an interstrand linkage between side-chains of appropriate amino acid residues at P2 and P11; or alternatively, forming the aforesaid linkage subsequent to step (j), as described herein below;

- (h) detaching the product thus obtained from the solid support;
- (i) cyclizing the product cleaved from the solid support;
- (j) 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
- (k) 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 or into a different, pharmaceutically acceptable, salt.

Enantiomers of the compounds defined herein before form also part of the present invention. These enantiomers can be prepared by a modification of the above process wherein enantiomers of all chiral starting materials are utilized.

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", taken alone or in combinations, 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 "alkylene" designates a divalent "alkyl", e.g. $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, having 4 to 24, preferably 4 to 12, carbon atoms. Similarly, the term "alkenylene" designates a divalent "alkenyl", e.g. $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-$, having 4 to 24, preferably 4 to 12, carbon atoms and containing at least one or, depending on the chain length, up to four olefinic double bonds. Likewise, the term "alkynylene" designates a divalent straight chain or branched hydrocarbon radical, having 4 to 24, preferably 4 to 12, carbon atoms and containing at least one or, depending on the chain length,

up to four carbon-carbon triple 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. Similarly, the term "lower cycloalkyl" designates saturated cyclic hydrocarbon radicals having up to 6 carbon atoms, such as cyclopentyl, cyclohexyl 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 R⁷⁷.

The β -hairpin conformation of Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-) is highly relevant for the anti-infective activity of the β -hairpin peptidomimetics of the present invention and also for the synthesis process defined hereinabove, as incorporation of the residues Xaa⁶, Xaa⁷ and Xaa¹³ near the beginning or near the middle of the linear protected peptide precursors enhances cyclization yields significantly.

Building blocks **A1-A69** of the structural element **-A-CO-** 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 can be combined with a building block **-B-CO-** of (L)-configuration. Thus, for example, ^DPro-^LPro constitutes the prototype of such a combination.

- 5 It will be appreciated that building blocks **-A1-CO-** to **-A69-CO-** in which **A** has (D)-configuration, are carrying a group R¹ at the β-position to the N-terminus.

The preferred values for R¹ are H and lower alkyl with the most preferred values for R¹ being H and methyl. It will be
 10 recognized by those skilled in the art, that **A1-A69** are shown in (D)-configuration which, for R¹ being H and methyl, corresponds to the (R)-configuration. Depending on the priority of other values for R¹ according to the Cahn, Ingold and Prelog rules, this configuration may also have to be
 15 expressed as (S).

In addition to R¹ building blocks **-A1-CO-** to **-A69-CO-** can carry an additional substituent designated as R² to R¹⁷. This additional substituent can be H, and if it is other than H, it is preferably a *small to medium-sized aliphatic or*
 20 *aromatic* group. Examples of preferred values for R¹ to R¹⁷ are:

- R¹ is hydrogen or lower alkyl;

- R² is H; lower alkyl; lower alkenyl;

- (CH₂)_pOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);

25 - (CH₂)_pSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);

- (CH₂)_pNR³³R³⁴ (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-;

30 - (CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);

- (CH₂)_pOCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ taken together form: -(CH₂)₂₋₆-; -(CH₂)₂O(CH₂)₂-;

35 - (CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);

- (CH₂)_pNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³:

- H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 5 $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 10 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : H; lower alkyl; or lower alkenyl);
- 15 $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl);
- $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy); or
- 20 $-(CH_2)_qCHN_4R^8$.
- R^3 is H; lower alkyl; lower alkenyl;
- $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 25 $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 30 $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
- 35

- $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$
 (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} :
 lower alkyl; or lower alkenyl);
 5 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower
 alkenyl);
 $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower
 alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59}
 taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 10 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 lower alkyl);
 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower
 alkenyl);
 $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower
 15 alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl;
 lower alkenyl; or lower alkoxy).
 - R^4 is H; lower alkyl; lower alkenyl;
 $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
 20 $-(CH_2)_mSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
 $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower
 alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken
 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 25 lower alkyl);
 $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower
 alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken
 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 30 lower alkyl);
 $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} :
 H; lower alkyl; or lower alkenyl; R^{81} : H; or lower
 alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$
 35 (where R^{57} : H; or lower alkyl);
 $-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} :

- lower alkyl; or lower alkenyl);
- $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
- $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- 15 - R^5 is lower alkyl; lower alkenyl;
- $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_mSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : alkyl; alkenyl; aryl; aryl-lower alkyl; or heteroaryl-lower alkyl);
- 35 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower

- alkenyl);
- (CH₂)_oCONR⁵⁸R⁵⁹ (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-;
- 5 -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_oPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl);
- 10 -(CH₂)_oSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or
- (CH₂)_qC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
- R⁶ is H; lower alkyl; lower alkenyl;
- (CH₂)_oOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
- 15 -(CH₂)_oSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
- (CH₂)_oNR³³R³⁴ (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-;
- 20 -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_oOCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ taken together form: -(CH₂)₂₋₆-; -(CH₂)₂O(CH₂)₂-;
- 25 -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_oNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³: H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower alkyl; or R³³ and R⁸¹ taken together form: -(CH₂)₂₋₆-;
- 30 -(CH₂)₂O(CH₂)₂-; -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_oN(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl);
- (CH₂)_oCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl);
- 35 -(CH₂)_oCONR⁵⁸R⁵⁹ (where R⁵⁸: lower alkyl; or lower alkenyl; and R⁵⁹: H; or lower alkyl; or R⁵⁸ and R⁵⁹

- taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
lower alkyl);
 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower
5 alkenyl);
 $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower
alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl;
lower alkenyl; or lower alkoxy).
- 10 - R^7 is lower alkyl; lower alkenyl;
 $-(CH_2)_qOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
 $-(CH_2)_qSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
 $-(CH_2)_qNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower
alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken
15 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
lower alkyl);
 $-(CH_2)_qOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower
alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken
20 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
lower alkyl);
 $-(CH_2)_qNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} :
H; lower alkyl; or lower alkenyl; R^{81} : H; or lower
25 alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$
(where R^{57} : H; or lower alkyl);
 $-(CH_2)_qN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} :
lower alkyl; or lower alkenyl);
30 $-(CH_2)_rCOOR^{57}$ (where R^{57} : lower alkyl; or lower
alkenyl);
 $-(CH_2)_qCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower
alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59}
taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
35 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
lower alkyl);

- $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
 $-(CH_2)_rSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
 5 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
 - R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl;
 $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
 10 $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form:
 $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 15 $-(CH_2)_oCONR^{33}R^{75}$ (where R^{33} : H; ~~or~~ lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form:
 $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 20 $-(CH_2)_oNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form:
 $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 25 $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form:
 $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 30 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
 35 $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower

- alkenyl); or
- $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^9 is lower alkyl; lower alkenyl;
- 5 $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
- 10 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_oCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
- 15 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
- 20 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- 25 $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
- $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 30 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
- 35 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).

- R¹⁰ is lower alkyl; lower alkenyl;
 -(CH₂)_oOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
 -(CH₂)_oSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
 -(CH₂)_oNR³³R³⁴ (where R³³: lower alkyl; or lower
 5 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)_oOCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower
 10 alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ 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)_oNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³:
 15 H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower
 alkyl; or R³³ and R⁸¹ 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)_oN(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴:
 20 lower alkyl; or lower alkenyl);
 -(CH₂)_oCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower
 alkenyl);
 -(CH₂)_oCONR⁵⁸R⁵⁹ (where R⁵⁸: lower alkyl; or lower
 alkenyl; and R⁵⁹: H; or lower alkyl; or R⁵⁸ and R⁵⁹
 25 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)_oPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower
 alkenyl);
 30 -(CH₂)_oSO₂R⁶² (where R⁶²: lower alkyl; or lower
 alkenyl); or
 -(CH₂)_qC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl;
 lower alkenyl; or lower alkoxy).
 - R¹¹ is H; lower alkyl; lower alkenyl;
 35 -(CH₂)_mOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
 -(CH₂)_mSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);

- $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
- $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- $-R^{12}$ is H; lower alkyl; lower alkenyl;
- $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_mSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;

- $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
5 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
10 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
15 $-(CH_2)_rCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
 $-(CH_2)_rCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
20 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
25 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{13} is lower alkyl; lower alkenyl;
 $-(CH_2)_qOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
30 $-(CH_2)_qSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
 $-(CH_2)_qNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
35 $-(CH_2)_qOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower

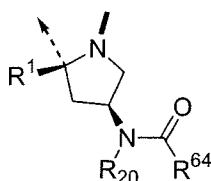
- alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 5 $-(CH_2)_qNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 10 $-(CH_2)_qN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- $-(CH_2)_rCOO^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- $-(CH_2)_qCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 15 $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- 20 $-(CH_2)_rSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
- $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- 25 - R^{14} is H; lower alkyl; lower alkenyl;
- $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_mSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 30 $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 35 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);

- lower alkyl);
- 5 $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} : H; lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- 10 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 15 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl);
- 20 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{15} is lower alkyl; lower alkenyl;
- $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- 25 $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 30 $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 35 $-(CH_2)_oNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower

- alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$
 (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} :
 5 lower alkyl; or lower alkenyl); particularly favoured
 being $-NR^{20}CO$ -lower alkyl (where R^{20} : H; or lower
 alkyl);
 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower
 alkenyl);
 10 $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower
 alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59}
 taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 lower alkyl);
 15 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower
 alkenyl);
 $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower
 alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl;
 20 lower alkenyl; or lower alkoxy).
 - R^{16} is lower alkyl; lower alkenyl;
 $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower
 25 alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken
 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 lower alkyl);
 $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower
 30 alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken
 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 lower alkyl);
 $-(CH_2)_oNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} :
 35 H; lower alkyl; or lower alkenyl; R^{81} : H; or lower
 alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;

- $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$
 (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} :
 lower alkyl; or lower alkenyl);
 5 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower
 alkenyl);
 $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower
 alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59}
 taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 10 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 lower alkyl);
 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower
 alkenyl);
 $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower
 15 alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl;
 lower alkenyl; or lower alkoxy).
 - R^{17} is lower alkyl; lower alkenyl;
 $-(CH_2)_qOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
 20 $-(CH_2)_qSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
 $-(CH_2)_qNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower
 alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken
 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 25 lower alkyl);
 $-(CH_2)_qOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower
 alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken
 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 30 lower alkyl);
 $-(CH_2)_qNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} :
 H; lower alkyl; or lower alkenyl; R^{81} : H; or lower
 alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$
 35 (where R^{57} : H; or lower alkyl);
 $-(CH_2)_qN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} :

- lower alkyl; or lower alkenyl);
 $-(CH_2)_rCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
 $-(CH_2)_qCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
 $-(CH_2)_rSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- Among the building blocks **A1** to **A69** the following are preferred: **A5** with R^2 being H, **A8**, **A22**, **A25**, **A38** with R^2 being H, **A42**, **A47**, and **A50**. Also, and particularly, preferred are building blocks of type **A8'**:

**A8'**

- wherein R^{20} is H or lower alkyl; and R^{64} is alkyl; alkenyl; aryl; aryl-lower alkyl; or heteroaryl-lower alkyl; especially those wherein R^{64} is n-hexyl (**A8'-1**); n-heptyl (**A8'-2**); 4-(phenyl)benzyl (**A8'-3**); diphenylmethyl (**A8'-4**); 3-amino-propyl (**A8'-5**); 5-amino-pentyl (**A8'-6**); methyl (**A8'-7**); ethyl (**A8'-8**); isopropyl (**A8'-9**); isobutyl (**A8'-10**); n-propyl (**A8'-11**); cyclohexyl (**A8'-12**); cyclohexylmethyl (**A8'-13**); n-butyl (**A8'-14**); phenyl (**A8'-15**); benzyl (**A8'-16**); (3-indolyl)methyl (**A8'-17**);

2-(3-indolyl)ethyl (**A8'-18**); (4-phenyl)phenyl (**A8'-19**); and n-nonyl (**A8'-20**).

Building block **A70** belongs to the class of open-chain
5 α -substituted α -amino acids, building blocks **A71** and **A72** to
the corresponding β -amino acid analogues and building blocks
A73-A104 to the cyclic analogues of **A70**. Such amino acid
derivatives have been shown to constrain small peptides in
well defined reverse turn or U-shaped conformations (C.M.
10 Venkatachalam, *Biopolymers* **1968**, 6, 1425-1434; W. Kabsch, C.
Sander, *Biopolymers* **1983**, 22, 2577). Such building blocks
are ideally suited for the stabilization of β -hairpin
conformations in peptide loops (D. Obrecht, M. Altorfer,
J.A. Robinson, "Novel Peptide Mimetic Building Blocks and
15 Strategies for Efficient Lead Finding", *Adv. Med. Chem.* **1999**,
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25 It has been shown that both enantiomers of building blocks
-**A70**-CO- to **A104**-CO- in combination with a building block
-**B**-CO- being an α -amino acid with L-configuration can
efficiently stabilize and induce β -hairpin conformations (D.
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35 **1995**, 51, 10883-10900; D. Obrecht, C. Lehmann, C. Ruffieux,

P. Schönholzer, K. Müller, *Helv. Chim. Acta* **1995**, 78, 1567-1587; D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* **1995**, 78, 563-580; D. Obrecht, H. Karajiannis, C. Lehmann, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* **1995**, 78, 703-714).

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

$-R^{18}$ is lower alkyl.

$-R^{19}$ is lower alkyl; lower alkenyl;

$-(CH_2)_pOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);

$-(CH_2)_pSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);

$-(CH_2)_pNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);

$-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);

$-(CH_2)_pNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);

$-(CH_2)_pN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);

$-(CH_2)_pCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);

$-(CH_2)_pCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;

- $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
 5 $-(CH_2)_pSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
 $-(CH_2)_oC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
 $-R^{21}$ is H; lower alkyl; lower alkenyl;
 10 $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 15 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 20 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
 25 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
 30 $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 35 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower

alkenyl);
 $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower
 alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl;
 5 lower alkenyl; or lower alkoxy).
 $-R^{22}$ is lower alkyl; lower alkenyl;
 $-(CH_2)_6OR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
 $-(CH_2)_6SR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
 $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower
 10 alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken
 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 lower alkyl);
 $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower
 15 alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken
 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 lower alkyl);
 $-(CH_2)_6NR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} :
 20 H; lower alkyl; or lower alkenyl; R^{81} : H; or lower
 alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$
 (where R^{57} : H; or lower alkyl);
 $-(CH_2)_6N(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} :
 25 lower alkyl; or lower alkenyl);
 $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower
 alkenyl);
 $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower
 alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59}
 30 taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 lower alkyl);
 $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower
 alkenyl);
 35 $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower
 alkenyl); or

- $-(CH_2)_q C_6H_4R^8$ (where R^8 : H; F; Cl; CF; lower alkyl; lower alkenyl; or lower alkoxy).
- $-R^{23}$ is H; lower alkyl; lower alkenyl;
- $-(CH_2)_o OR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_o SR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- $-(CH_2)_o NR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_o OCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_o NR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_o N(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); particularly favoured are $NR^{20}CO$ -lower alkyl (where R^{20} : H; or lower alkyl);
- $-(CH_2)_o COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- $-(CH_2)_o CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_o PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- $-(CH_2)_o SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
- $-(CH_2)_q C_6H_4R^8$ (where R^8 : H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

- R²⁴ is lower alkyl; lower alkenyl;
- (CH₂)_oOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
- (CH₂)_oSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
- (CH₂)_oNR³³R³⁴ (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)_oOCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ 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)_oNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³: H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower alkyl; or R³³ and R⁸¹ 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)_oN(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl); particularly favoured are NR²⁰CO-lower alkyl (where R²⁰: H; or lower alkyl);
- (CH₂)_oCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl);
- (CH₂)_oCONR⁵⁸R⁵⁹ (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)_oPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl);
- (CH₂)_oSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or
- (CH₂)_qC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
- R²⁵ is H; lower alkyl; lower alkenyl;
- (CH₂)_mOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);

- $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
- $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- $-R^{26}$ is H; lower alkyl; lower alkenyl;
- $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or

- lower alkyl);
- (CH₂)_mCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ taken together form: -(CH₂)₂₋₆-; -(CH₂)₂O(CH₂)₂-;
- 5 -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_mNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³: H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower alkyl; or R³³ and R⁸¹ taken together form: -(CH₂)₂₋₆-;
- 10 -(CH₂)₂O(CH₂)₂-; -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_mN(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl);
- (CH₂)_oCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl);
- 15 -(CH₂)_oCONR⁵⁸R⁵⁹ (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);
- 20 -(CH₂)_oPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl);
- (CH₂)_oSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or
- 25 -(CH₂)_qC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy)-; or, alternatively,
- R²⁵ and R²⁶ taken together can be
- (CH₂)₂₋₆-; -(CH₂)₂O(CH₂)₂-; -(CH₂)₂S(CH₂)₂-; or
- (CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl).
- 30 -R²⁷ is H; lower alkyl; lower alkenyl;
- (CH₂)_oOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
- (CH₂)_oSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
- (CH₂)_oNR³³R³⁴ (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-;
- 35 -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or

- lower alkyl);
- (CH₂)_oCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ taken together form: -(CH₂)₂₋₆-; -(CH₂)₂O(CH₂)₂-;
- 5 -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_oNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³: H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower alkyl; or R³³ and R⁸¹ taken together form: -(CH₂)₂₋₆-;
- 10 -(CH₂)₂O(CH₂)₂-; -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_oN(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl);
- (CH₂)_oCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl);
- 15 -(CH₂)_oCONR⁵⁸R⁵⁹ (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);
- 20 -(CH₂)_oPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl);
- (CH₂)_oSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or
- 25 -(CH₂)_qC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
- R²⁸ is lower alkyl; lower alkenyl;
- (CH₂)_oOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
- (CH₂)_oSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
- 30 -(CH₂)_oNR³³R³⁴ (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);
- 35 -(CH₂)_oCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ taken

together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
lower alkyl);
 $-(CH_2)_6NR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} :
5 H; lower alkyl; or lower alkenyl; R^{81} : H; or lower
alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$
(where R^{57} : H; or lower alkyl);
 $-(CH_2)_6N(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} :
10 lower alkyl; or lower alkenyl);
 $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower
alkenyl);
 $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower
alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59}
15 taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
lower alkyl);
 $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower
alkenyl);
20 $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower
alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl;
lower alkenyl; or lower alkoxy).
 $-R^{29}$ is lower alkyl; lower alkenyl;
25 $-(CH_2)_6OR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
 $-(CH_2)_6SR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
 $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower
alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken
together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
30 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
lower alkyl);
 $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower
alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken
together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
35 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
lower alkyl);

- $-(CH_2)_6NR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_6N(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); particularly favored are $NR^{20}CO$ -lower-alkyl (where R^{20} : H; or lower alkyl);
 $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
 $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
 $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).

Among the building blocks **A70** to **A104** the following are preferred: **A74** with R^{22} being H, **A75**, **A76**, **A77** with R^{22} being H, **A78** and **A79**.

- The building block **-B-CO-** designates an L-amino acid residue. Preferred values for **B** are: $-NR^{20}CH(R^{71})-$, or $-NR^{20}CH(R^{72})-$ or, $-NR^{20}CH(R^{73})-$, or $-NR^{20}CH(R^{74})-$, or $-NR^{20}CH(R^{84})-$, or enantiomers of groups **A5** with R^2 being H, **A8**, **A22**, **A25**, **A38** with R^2 being H, **A42**, **A47**, and **A50**. Most preferred building blocks **-B-CO-** are

Ala	L-Alanine
Arg	L-Arginine
Asn	L-Asparagine
Asp	L-Aspartic acid

	Cys	L-Cysteine
	Gln	L-Glutamine
	Glu	L-Glutamic acid
	Gly	Glycine
5	His	L-Histidine
	Ile	L-Isoleucine
	Leu	L-Leucine
	Lys	L-Lysine
	Met	L-Methionine
10	Phe	L-Phenylalanine
	Pro	L-Proline
	Ser	L-Serine
	Thr	L-Threonine
	Trp	L-Tryptophan
15	Tyr	L-Tyrosine
	Val	L-Valine
	Cit	L-Citrulline
	Orn	L-Ornithine
	tBuA	L-t-Butylalanine
20	Sar	Sarcosine
	t-BuG	L-tert.-Butylglycine
	4AmPhe	L-para-Aminophenylalanine
	3AmPhe	L-meta-Aminophenylalanine
	2AmPhe	L-ortho-Aminophenylalanine
25	Phe (mC (NH ₂) =NH)	L-meta-Amidinophenylalanine
	Phe (pC (NH ₂) =NH)	L-para-Amidinophenylalanine
	Phe (mNHC (NH ₂) =NH)	L-meta-Guanidinophenylalanine
	Phe (pNHC (NH ₂) =NH)	L-para-Guanidinophenylalanine
	Phg	L-Phenylglycine
30	Cha	L-Cyclohexylalanine
	C ₄ al	L-3-Cyclobutylalanine
	C ₅ al	L-3-Cyclopentylalanine
	Nle	L-Norleucine
	2-Nal	L-2-Naphthylalanine
35	1-Nal	L-1-Naphthylalanine
	4Cl-Phe	L-4-Chlorophenylalanine

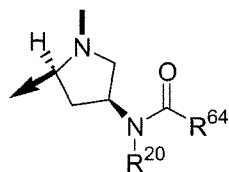
	3Cl-Phe	L-3-Chlorophenylalanine
	2Cl-Phe	L-2-Chlorophenylalanine
	3,4Cl ₂ -Phe	L-3,4-Dichlorophenylalanine
	4F-Phe	L-4-Fluorophenylalanine
5	3F-Phe	L-3-Fluorophenylalanine
	2F-Phe	L-2-Fluorophenylalanine
	Tic	L-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
	Thi	L-β-2-Thienylalanine
10	Tza	L-2-Thiazolylalanine
	Mso	L-Methionine sulfoxide
	AcLys	L-N-Acetyllysine
	Dpr	L-2,3-Diaminopropionic acid
	Dab	L-2,4-Diaminobutyric acid
15	Dbu	(2S, 3S)-2,3-Diaminobutyric acid
	Abu	γ-Aminobutyric acid (GABA)
	Aha	ε-Aminohexanoic acid
	Aib	α-Aminoisobutyric acid
	Y(Bzl)	L-O-Benzyltyrosine
20	Bip	L-Biphenylalanine
	S(Bzl)	L-O-Benzylserine
	T(Bzl)	L-O-Benzylthreonine
	hCha	L-Homo-cyclohexylalanine
	hCys	L-Homo-cysteine
25	hSer	L-Homo-serine
	hArg	L-Homo-arginine
	hPhe	L-Homo-phenylalanine
	Bpa	L-4-Benzoylphenylalanine
	Pip	L-Pipecolic acid
30	MePhe	L-N-Methylphenylalanine
	MeNle	L-N-Methylnorleucine
	MeAla	L-N-Methylalanine
	MeIle	L-N-Methylisoleucine
	MeVal	L-N-Methvaline
35	MeLeu	L-N-Methyllleucine

60

4Hyp1	(4S)-L-Hydroxyproline
4Hyp2	(4R)-L-Hydroxyproline
4Mp1	(4S)-L-Mercaptoproline
4Mp2	(4R)-L-Mercaptoproline

5

In addition, the most preferred values for **B** also include groups of type **A8''** of (L)-configuration:



10

A8''

wherein R²⁰ is H or lower alkyl and R⁶⁴ is alkyl; alkenyl; $-(\text{CH}_2)_u\text{-X}-\text{CH}_3$ (where X is -O-, -NR²⁰-, or -S-; u = 1-3, and t = 1-6), aryl; aryl-lower alkyl; or heteroaryl-lower alkyl; especially those wherein R⁶⁴ 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**); cyclohexyl-methyl (**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**); CH₃-OCH₂CH₂-OCH₂- (**A8''-41**) and CH₃-(OCH₂CH₂)₂-OCH₂- (**A8''-42**).

25

Besides the structural element -B-CO- the β -hairpin peptidomimetics of the present invention can comprise the structural element -A-CO- and amino acid residues belonging to one of the following groups:

- 30 - Group C -NR²⁰CH(R⁷²)CO-; "hydrophobic: small to medium-sized"
- Group D -NR²⁰CH(R⁷³)CO-; "hydrophobic: large aromatic or heteroaromatic"

- Group E $-\text{NR}^{20}\text{CH}(\text{R}^{74})\text{CO}-$; "polar-cationic" and "urea-derived"
- Group F $-\text{NR}^{20}\text{CH}(\text{R}^{84})\text{CO}-$; "polar-non-charged or anionic"
- 5 - Group H $-\text{NR}^{20}-\text{CH}(\text{CO})-\text{alkylene}-\text{CH}(\text{CO})-\text{NR}^{20}-$;
 $-\text{NR}^{20}-\text{CH}(\text{CO})-\text{alkenylene}-\text{CH}(\text{CO})-\text{NR}^{20}-$;
 $-\text{NR}^{20}-\text{CH}(\text{CO})-\text{alkynylene}-\text{CH}(\text{CO})-\text{NR}^{20}-$;
 $-\text{NR}^{20}-\text{CH}(\text{CO})-(\text{CH}_2)_p\text{SS}(\text{CH}_2)_p-\text{CH}(\text{CO})-\text{NR}^{20}-$;
 $-\text{NR}^{20}-\text{CH}(\text{CO})-(\text{CH}_2)_p\text{NR}^{20}\text{CO}(\text{CH}_2)_p-\text{CH}(\text{CO})-\text{NR}^{20}-$;
10 $-\text{NR}^{20}-\text{CH}(\text{CO})-(\text{CH}_2)_p\text{NR}^{20}\text{CONR}^{20}(\text{CH}_2)_p-\text{CH}(\text{CO})-\text{NR}^{20}-$;
"interstrand linkage"

Group C comprises amino acid residues with small to medium-sized *hydrophobic* side chain groups according to the
15 general definition for substituent R^{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)
20 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
25 aryl phosphonates and phosphates or tertiary amines. Genetically encoded small-to-medium-sized hydrophobic amino acids include alanine, isoleucine, leucine, methionine and valine.

30 **Group D** comprises amino acid residues with *aromatic* and *heteroaromatic* side chain groups according to the general definition for substituent R^{73} . An aromatic amino acid residue refers to a hydrophobic amino acid having a side chain containing at least one ring having a conjugated
35 π -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.
- 10 A heteroaromatic amino acid residue refers to a hydrophobic amino acid having a side chain containing at least one ring having a conjugated π -system incorporating at least one heteroatom such as (but not limited to) O, S and N according to the general definition for substituent R⁷⁷. In addition
- 15 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
- 20 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.
- 25 **Group E** comprises amino acids containing side chains with *polar-cationic*, acylamino- and urea-derived residues according to the general definition for substituent R⁷⁴. Polar-cationic refers to a basic side chain which is protonated at physiological pH. Genetically encoded
- 30 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
- 35 *polar-non-charged or anionic* residues according to the general definition for substituent R⁸⁴. 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
5 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
10 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
15 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
20 an interstrand linkage. Various methods are known to form interstrand 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, Rockford, III, **1984**; Ahmed et al. *J. Biol. Chem.* **1975**, 250,
25 8477-8482; and Pennington et al., *Peptides*, pages 164-166, Giralt and Andreu, Eds., ESCOM Leiden, The Netherlands, **1990**; C.E. Schafmeister et al., *J. Am. Chem. Soc.* **2000**, 122, 5891. The most widely known linkage is the disulfide bridge formed by cysteines and homo-cysteines positioned at
30 opposite positions of the β -strand. Preferably, for the scope of the present invention, disulfide linkages can be prepared using acetamidomethyl (Acm)- or trityl (Trt)-protective groups for cysteine. Another well established interstrand linkage consists in linking ornithines and
35 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-carboxylimidazole to form cyclic ureas.

As mentioned earlier, Xaa² and Xaa¹¹ of Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-) are amino acid residues which, taken together, can form an interstrand linkage. Such an interstrand linkage is 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 Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-), 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:

25	three letter code	one letter code	
	Ala	L-Alanine	A
	Arg	L-Arginine	R
	^D Arg	D-Arginine	^D R
30	Asn	L-Asparagine	N
	Asp	L-Aspartic acid	D
	Cys	L-Cysteine	C
	Glu	L-Glutamic acid	E
	Gln	L-Glutamine	Q
35	Gly	Glycine	G

65

	His	L-Histidine	H
	Ile	L-Isoleucine	I
	Leu	L-Leucine	L
	Lys	L-Lysine	K
5	^D Lys	D-Lysine	^D K
	Met	L-Methionine	M
	Phe	L-Phenylalanine	F
	Pro	L-Proline	P
	^D Pro	D-Proline	^D P
10	Ser	L-Serine	S
	Thr	L-Threonine	T
	Trp	L-Tryptophan	W
	Tyr	L-Tyrosine	Y
	Val	L-Valine	V

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

	Cit	L-Citrulline
20	^D Cit	D-Citrulline
	Orn	L-Ornithine
	^D Orn	D-Ornithine
	tBuA	L-t-Butylalanine
	Pen	L-Penicillamine
25	tBuG	L-tert.-Butylglycine
	^D tBuG	D-tert.-Butylglycine
	4AmPhe	L-para-Aminophenylalanine
	^D 4AmPhe	D-para-Aminophenylalanine
	3AmPhe	L-meta-Aminophenylalanine
30	^D 3AmPhe	D-meta-Aminophenylalanine
	2AmPhe	L-ortho-Aminophenylalanine
	^D 2AmPhe	D-ortho-Aminophenylalanine
	Phe (mC (NH ₂) =NH)	L-meta-Amidinophenylalanine
	^D Phe (mC (NH ₂) =NH)	D-meta-Amidinophenylalanine
35	Phe (pC (NH ₂) =NH)	L-para-Amidinophenylalanine
	^D Phe (pC (NH ₂) =NH)	D-para-Amidinophenylalanine

	Phe (mNHC (NH ₂)=NH)	L-meta-Guanidinophenylalanine
	^D Phe (mNHC (NH ₂)=NH)	D-meta-Guanidinophenylalanine
	Phe (pNHC (NH ₂)=NH)	L-para-Guanidinophenylalanine
	^D Phe (pNHC (NH ₂)=NH)	D-para-Guanidinophenylalanine
5	Agp	(2S)-2-Amino-3-guanidino-propionic acid
	Agb	(2S)-2-Amino-4-guanidino-butanoic acid
	2Pal	(2S)-2-Amino-3-(pyridine-2'-yl)-propionic acid
	4Pal	(2S)-2-Amino-3-(pyridine-4'-yl)-propionic acid
	Phg	L-Phenylglycine
10	C ₃ al	L-3-Cyclopropylalanine
	C ₄ al	L-3-Cyclobutylalanine
	C ₅ al	L-3-Cyclopentylalanine
	Cha	L-Cyclohexylalanine
	C ₃ g	L-Cyclopropylglycine
15	C ₄ g	L-Cyclobutylglycine
	C ₅ g	L-Cyclopentylglycine
	Nle	L-Norleucine
	2-Nal	L-2-Naphthylalanine
	1-Nal	L-1-Naphthylalanine
20	4ClPhe	L-4-Chlorophenylalanine
	3ClPhe	L-3-Chlorophenylalanine
	2ClPhe	L-2-Chlorophenylalanine
	3,4Cl ₂ Phe	L-3,4-Dichlorophenylalanine
	4FPhe	L-4-Fluorophenylalanine
25	3FPhe	L-3-Fluorophenylalanine
	2FPhe	L-2-Fluorophenylalanine
	Thi	L-β-2-Thienylalanine
	Tza	L-2-Thiazolylalanine
	Mso	L-Methionine sulfoxide
30	AcLys	N-Acetyllysine
	^D AcLys	N-Acetyl-D-lysine
	Dpr	2,3-Diaminopropionic acid
	^D Dpr	D-2,3-Diaminopropionic acid
	Dab	2,4-Diaminobutyric acid
35	^D Dab	(2R)-2,4-Diaminobutyric acid
	Dbu	(2S)-2,3-Diamino-butyric acid

	^D Dbu	(2R)-2,3-Diamino-butyric acid
	Abu	γ-Aminobutyric acid (GABA)
	Aha	ε-Aminohexanoic acid
	Aib	α-Aminoisobutyric acid
5	Cyp	1-Aminocyclopentane carboxylic acid
	Y(Bzl)	L-O-Benzyltyrosine
	H(Bzl)	(3S)-2-Amino-3-(1'-benzylimidazole-4'-yl)- propionic acid
	Bip	L-(4-phenyl)phenylalanine
10	S(Bzl)	L-O-Benzylserine
	T(Bzl)	L-O-Benzylthreonine
	alloT	(2S, 3S)-2-Amino-3-hydroxy-butyric acid
	Leu3OH	(2S, 3R)-2-Amino-3-hydroxy-4-methyl-pentanoic acid
15	hAla	L-Homo-alanine
	hArg	L-Homo-arginine
	^D hArg	D-Homo-arginine
	hCys	L-Homo-cysteine
	hGlu	L-Homo-glutamic acid
20	hGln	L-Homo-glutamine
	hHis	L-Homo-histidine
	hIle	L-Homo-isoleucine
	hLeu	L-Homo-leucine
	hNle	L-Homo-norleucine
25	hLys	L-Homo-lysine
	^D hLys	D-Homo-lysine
	hMet	L-Homo-methionine
	hPhe	L-Homo-phenylalanine
	hSer	L-Homo-serine
30	hThr	L-Homo-threonine
	hTrp	L-Homo-tryptophan
	hTyr	L-Homo-tyrosine
	hVal	L-Homo-valine
	hCha	L-Homo-cyclohexylalanine
35	Bpa	L-4-Benzoylphenylalanine

	Tic	(3S)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
	^D Tic	(3R)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
5	Tiq	(1S)-1,2,3,4-Tetrahydroisoquinoline-1-carboxylic acid
	^D Tiq	(1R)-1,2,3,4-Tetrahydroisoquinoline-1-carboxylic acid
	4AmPyrr1	(2S, 4S)-4-Amino-pyrrolidine-2-carboxylic acid
10	^D 4AmPyrr1	(2R, 4S)-4-Amino-pyrrolidine-2-carboxylic acid
	4AmPyrr2	(2S, 4R)-4-Amino-pyrrolidine-2-carboxylic acid
	^D 4AmPyrr2	(2R, 4R)-4-Amino-pyrrolidine-2-carboxylic acid
	4PhePyrr1	(2S, 4R)-4-Phenyl-pyrrolidine-2-carboxylic acid
15	^D 4PhePyrr1	(2R, 4R)-4-Phenyl-pyrrolidine-2-carboxylic acid
	4PhePyrr2	(2S, 4S)-4-Phenyl-pyrrolidine-2-carboxylic acid
20	^D 4PhePyrr2	(2R, 4S)-4-Phenyl-pyrrolidine-2-carboxylic acid
	5PhePyrr1	(2S, 5R)-5-Phenyl-pyrrolidine-2-carboxylic acid
	^D 5PhePyrr1	(2R, 5R)-5-Phenyl-pyrrolidine-2-carboxylic acid
25	5PhePyrr2	(2S, 5S)-5-Phenyl-pyrrolidine-2-carboxylic acid
	^D 5PhePyrr2	(2R, 5S)-5-Phenyl-pyrrolidine-2-carboxylic acid
	4Hyp1	(4S)-L-Hydroxyproline
30	^D 4Hyp1	(4S)-D-Hydroxyproline
	4Hyp2	(4R)-L-Hydroxyproline
	^D 4Hyp2	(4R)-D-Hydroxyproline
	4Mp1	(4S)-L-Mercaptoproline
	^D 4Mp1	(4S)-D-Mercaptoproline
35	4Mp2	(4R)-L-Mercaptoproline
	^D 4Mp2	(4R)-D-Mercaptoproline

	Pip	L-Pipecolic acid
	^D Pip	D-Pipecolic acid
	NMeAla	L-N-Methylalanine
	NMeVal	L-N-Methylvaline
5	NMeIle	L-N-Methylisoleucine
	NMeLeu	L-N-Methylleucine
	NMeNle	L-N-Methylnorleucine
	NMeMet	L-N-Methylmethionine
	NMeTyr	L-N-Methyltyrosine
10	NMeHis	L-N-Methylhistidine
	NMePhe	L-N-Methylphenylalanine
	NMeTrp	L-N-Methyltryptophane
	NMeSer	L-N-Methylserine
	NMeAsp	L-N-Methylaspartic acid
15	NMeGlu	L-N-Methylglutamic acid
	NMeLys	L-N-Methyllysine
	NMe ^D Lys	D-N-Methyllysine
	NMeArg	L-N-Methylarginine
	NMe ^D Arg	D-N-Methylarginine
20	NMeDab	L-N-Methyl-2,4-diamino butyric acid
	NMe ^D Dab	D-N-Methyl-2,4-diamino butyric acid
	NMeCys	L-N-Methylcysteine
	NMeAsn	L-N-Methylasparagine
	NMeGln	L-N-Methylglutamine
25	NMeThr	L-N-Methylthreonine

In a preferred embodiment of the present invention, Xaa¹³ is ^DPro, ^DCha, NMe^DIle, ^DTyr, ^DHis, ^DHis(Bzl), ^D4Pal, NMe^DTyr, NMe^DLys, (ABu)G, ^DIle, NMe^DAla, ^DLys, or ^DDab; Xaa¹⁴ is ^LPro; 30 the aforesaid ^DPro moiety and/or the aforesaid ^LPro moiety being optionally substituted as shown in formulae A8' and, respectively, A8'', as defined above.

Particularly preferred residues for **group C** are:

35	Ala	L-Alanine
	Ile	L-Isoleucine

	Leu	L-Leucine
	Met	L-Methionine
	Val	L-Valine
	tBuA	L-t-Butylalanine
5	tBuG	L-tert.-Butylglycine
	C ₃ al	L-3-Cycloproylalanine
	C ₄ al	L-3-Cyclobutylalanine
	C ₅ al	L-3-Cyclopentylalanine
	Cha	L-Cyclohexylalanine
10	C ₃ g	L-Cycloproylglycine
	C ₄ g	L-Cyclobutylglycine
	C ₅ g	L-Cyclopentylglycine
	Nle	L-Norleucine
	hAla	L-Homo-alanine
15	hIle	L-Homo-isoleucine
	hLeu	L-Homo-leucine
	hMet	L-Homo-methionine
	hVal	L-Homo-valine
	hCha	L-Homo-cyclohexylalanine
20	NMeAla	L-N-Methylalanine
	NMeVal	L-N-Methylvaline
	NMeIle	L-N-Methylisoleucine
	NMeLeu	L-N-Methyllleucine
	NMeNle	L-N-Methylnorleucine
25	NMeNle	L-N-Methylnorleucine
	NMeMet	L-N-Methylmethionine

Particularly preferred residues for **group D** are:

	His	L-Histidine
30	Phe	L-Phenylalanine
	Trp	L-Tryptophan
	Tyr	L-Tyrosine
	2Pal	(2S)-2-Amino-3-(pyridine-2'-yl)-propionic acid
	4Pal	(2S)-2-Amino-3-(pyridine-4'-yl)-propionic acid
35	Phg	L-Phenylglycine
	2Nal	L-2-Naphthylalanine

	1-Nal	L-1-Naphthylalanine
	4ClPhe	L-4-Chlorophenylalanine
	3ClPhe	L-3-Chlorophenylalanine
	2ClPhe	L-2-Chlorophenylalanine
5	3,4Cl ₂ Phe	L-3,4-Dichlorophenylalanine
	4FPhe	L-4-Fluorophenylalanine
	3FPhe	L-3-Fluorophenylalanine
	2FPhe	L-2-Fluorophenylalanine
	Thi	L-β-2-Thienylalanine
10	Tza	L-2-Thiazolylalanine
	Y(Bzl)	L-O-Benzyltyrosine
	H(Bzl)	(3S)-2-Amino-3-(1'-benzylimidazole-4'-yl)- propionic acid
	Bip	L-(4-phenyl)phenylalanine
15	S(Bzl)	L-O-Benzylserine
	T(Bzl)	L-O-Benzylthreonine
	hPhe	L-Homo-phenylalanine
	hTrp	L-Homo-tryptophan
	hTyr	L-Homo-tyrosine
20	hHis	L-Homo-histidine
	Bpa	L-4-Benzoylphenylalanine
	NMePhe	L-N-Methylphenylalanine
	NMeTyr	L-N-Methyltyrosine
	NMeHis	L-N-Methylhistidine
25	NMeTrp	L-N-Methyltryptophane

Particularly preferred residues for **group E** are

	Arg	L-Arginine
	^D Arg	D-Arginine
30	Lys	L-Lysine
	^D Lys	D-Lysine
	Orn	L-Ornithine
	^D Orn	D-Ornithine
	Dpr	L-2,3-Diaminopropionic acid
35	^D Dpr	D-2,3-Diaminopropionic acid
	Dab	L-2,4-Diaminobutyric acid

	^D Dab	(2R)-2,4-Diaminobutyric acid
	Dbu	(2S, 3S)-2,3-Diaminobutyric acid
	^D Dbu	(2R)-2,3-Diamino-butyric acid
	Cit	L-Citrulline
5	^D Cit	D-Citrulline
	4AmPhe	L-para-Aminophenylalanine
	^D 4AmPhe	D-para-Aminophenylalanine
	3AmPhe	L-meta-Aminophenylalanine
	^D 3AmPhe	D-meta-Aminophenylalanine
10	2AmPhe	L-ortho-Aminophenylalanine
	^D 2AmPhe	D-ortho-Aminophenylalanine
	Phe (mC (NH ₂) =NH)	L-meta-Amidinophenylalanine
	^D Phe (mC (NH ₂) =NH)	D-meta-Amidinophenylalanine
	Phe (pC (NH ₂) =NH)	L-para-Amidinophenylalanine
15	^D Phe (pC (NH ₂) =NH)	D-para-Amidinophenylalanine
	Phe (mNHC (NH ₂) =NH)	L-meta-Guanidinophenylalanine
	^D Phe (mNHC (NH ₂) =NH)	D-meta-Guanidinophenylalanine
	Phe (pNHC (NH ₂) =NH)	L-para-Guanidinophenylalanine
	^D Phe (pNHC (NH ₂) =NH)	D-para-Guanidinophenylalanine
20	Agp	(2S)-2-Amino-3-guanidino-propionic acid
	Agb	(2S)-2-Amino-4-guanidino-butanoic acid
	hArg	L-Homo-arginine
	^D hArg	D-Homo-arginine
	hLys	L-Homo-lysine
25	^D hLys	D-Homo-lysine
	NMeLys	L-N-Methyllysine
	NMe ^D Lys	D-N-Methyllysine
	NMeArg	L-N-Methylarginine
	NMe ^D Arg	D-N-Methylarginine
30	NMeDab	L-N-Methyl-2,4-diamino butyric acid
	NMe ^D Dab	D-N-Methyl-2,4-diamino butyric acid

Particularly preferred residues for **group F** are

	Asn	L-Asparagine
35	Asp	L-Aspartic acid
	Cys	L-Cysteine

	Gln	L-Glutamine
	Glu	L-Glutamic acid
	Ser	L-Serine
	Thr	L-Threonine
5	Pen	L-Penicillamine
	AcLys	L-N'-Acetyllysine
	alloT	(2S, 3S)-2-Amino-3-hydroxy-butyric acid
	Leu3OH	(2S, 3R)-2-Amino-3-hydroxy-4-methyl-pentanoic acid
10	hCys	L-Homo-cysteine
	hSer	L-Homo-serine
	hGlu	L-Homo-glutamic acid
	hGln	L-Homo-glutamine
	hThr	L-Homo-threonine
15	NMeSer	L-N-Methylserine
	NMeAsp	L-N-Methylaspartic acid
	NMeGlu	L-N-Methylglutamic acid
	NMeCys	L-N-Methylcysteine
	NMeAsn	L-N-Methylasparagine
20	NMeGln	L-N-Methylglutamine
	NMeThr	L-N-Methylthreonine

In a preferred embodiment of the invention the amino acid residues in Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-) are:

- Xaa¹: Trp;
- Xaa²: Arg, Dab or Orn;
- Xaa³: Ile;
- Xaa⁴: Arg, Dab or Orn;
- 30 - Xaa⁵: Ile;
- Xaa⁶: ^DArg, Dab, ^DDab, Orn;
- Xaa⁷: Asn, Gln, Thr, Leu or Tyr;
- Xaa⁸: Lys, Gln, Trp or His;
- Xaa⁹: Arg or Dab;
- 35 - Xaa¹⁰: Asn, Leu, Cha, Tyr or Trp;
- Xaa¹¹: Arg or Gln;

- Xaa¹²: Arg, Dab, Ala or Gln;
- Xaa¹³: DPro;
- Xaa¹⁴: LPro;

5 Particularly preferred β -peptidomimetics of the invention include those described in Examples 2, 5, 16, and 17.

The process of the invention can advantageously be carried out as parallel array synthesis to yield libraries of β -hairpin peptidomimetics of the invention. Such parallel syntheses allow one to obtain arrays of numerous (normally
5 12 to 192, typically 96) compounds as described above in moderate to 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) and site of cyclization play
10 thereby key roles.

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

20

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
25 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
30 acid conditions (H. Rink, *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
35 resin, 4-(((2,4-dimethoxyphenyl)Fmoc-aminomethyl)phenoxyacetamido) aminomethyl] -4-methyl-benzydrylamine PS resin

(Rink amide MBHA PS Resin), and 4-((((2,4-dimethoxyphenyl)Fmoc-aminomethyl)phenoxyacetamido) aminomethyl] benzhydrylamine PS-resin (Rink amide BHA PS resin). Preferably, the support is derived from polystyrene crosslinked with, most preferably 1-5%, divinylbenzene and functionalized by means of the 4-((((2,4-dimethoxyphenyl)Fmoc-aminomethyl)phenoxyacetamido) linker.

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

When carried out as parallel array synthesis the process 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 invention.

A number of reaction vessels (normally 12 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 60 mg, of the appropriate functionalized solid support, preferably 1 to 3% cross-linked polystyrene or 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),
5 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 (G.B. Fields, C.G. Fields, *J. Am.*
10 *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
15 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 (SasrinTM linker, Mergler et al., *Tetrahedron Lett.* **1988**, 29 4005-4008) is cleavable with diluted
20 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 process of the invention include the super
25 acid labile 4-(2,4-dimethoxyphenyl-hydroxymethyl)-phenoxy linker (Rink linker, H. Rink, *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
30 linker (HMPB-linker, Flörsheimer & Riniker, **1991**, *Peptides* 1990: Proceedings of the Twenty-First European Peptide Symposium, 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
35 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,
5 respectively, for their residues are, for example,

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

10	Cbz	benzyloxycarbonyl
	Boc	tert.-butoxycarbonyl
	Fmoc	9-fluorenylmethoxycarbonyl
	Alloc	allyloxycarbonyl
	Teoc	trimethylsilylethoxycarbonyl
15	Tcc	trichloroethoxycarbonyl
	Nps	o-nitrophenylsulfonyl;
	Trt	triphenylmethyl or trityl

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

	tBu	tert.-butyl
	Bn	benzyl
25	Me	methyl
	Ph	phenyl
	Pac	phenacyl
		allyl
	Tse	trimethylsilylethyl
30	Tce	trichloroethyl;

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

35	Pmc	2,2,5,7,8-pentamethylchroman-6-sulfonyl
	Ts	tosyl (i. e. p-toluenesulfonyl)

Cbz benzyloxycarbonyl
Pbf pentamethyldihydrobenzofuran-5-sulfonyl

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

 tBu tert.-butyl
 Bn benzyl
 Trt trityl
10 Alloc allyloxycarbonyl

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

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

20

The 9-fluorenylmethoxycarbonyl- (Fmoc) -protected amino acid derivatives are preferably used as the building blocks for the construction of the β -hairpin loop mimetics of the invention. For the deprotection, i. e. cleaving off of the
25 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
30 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
35 reasonable time. The preferred workstations (without, however, being limited thereto) are Labsource's Combi-chem

station, Protein Technologies' Symphony and MultiSyn Tech's-Syro synthesizer, the latter additionally equipped with a transfer unit and a reservoir box during the process of detachment of the fully protected linear peptide from the solid support. All synthesizers are able to provide a controlled environment, for example, reactions can be accomplished at temperatures different from room temperature as well as under inert gas atmosphere, if desired.

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, respectively, diisopropylurea is insoluble and, respectively, soluble in the solvents generally used. In a variation of the carbodiimide method 1-hydroxybenzotriazole (HOBt, König & Geiger, *Chem. Ber.* **1970**, 103, 788-798) is included as an additive to the coupling mixture. HOBt prevents dehydration, suppresses racemization of the activated amino acids and acts as a catalyst to improve the sluggish coupling reactions. Certain phosphonium reagents have been used as direct coupling reagents, such as benzotriazol-1-yl-oxy-tris-(dimethyl-amino)-phosphonium hexafluorophosphate (BOP, Castro et al., *Tetrahedron Lett.* **1975**, 14, 1219-1222; *Synthesis* **1976**, 751-752), or benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (Py-BOP, Coste et al., *Tetrahedron Lett.* **1990**, 31, 205-208), or 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium 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

diphenoxyphosphoryl azide (DPPA) or O-(7-aza-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TATU) or O-(7-aza-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU)/7-aza-1-hydroxy benzotriazole (HOAt, Carpino et al., *Tetrahedron Lett.* **1994**, 35, 2279-2281) or -(6-Chloro-1H-benzotriazol-1-yl)-N,N,N',N'-1,1,3,3-tetramethyluronium tetrafluoroborate (TCTU), or hexafluorophosphate (HCTU, Marder, Shivo and Albericio: HCTU and TCTU: New Coupling Reagents: Development and Industrial Applications, Poster Presentation, Gordon Conference February 2002) have also been used as coupling reagents as well as 1,1,3,3-Bis(tetramethylene)chlorouronium hexafluorophosphate (PyClU) especially for coupling N-methylated amino acids (J. Coste, E. Frérot, P. Jouin, B. Castro, *Tetrahedron Lett.* **1991**, 32, 1967).

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 or 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 vessel 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 vessels are filled with solvent (preferably 5 mL), agitated for 5 to 300 minutes, preferably 15 minutes, and drained to expel the solvent;

2) The reaction vessels are filled with solvent (preferably 5 mL) and drained 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 tubes 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, an interstrand linkage between Xaa² and Xaa¹¹ of -Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴- can be formed.

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 a disulfide bridge 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% NaHCO₃ to pH 5-6 for 4h, or in water after adjusting to pH 8 with ammonium hydroxide solution by stirring for 24h, or in a solution of NMP and tri-n-butylphosphine (preferably 50 eq.).

Alternatively, the formation of the disulfide bridge between Xaa² and Xaa¹¹ of -Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴- can be carried out subsequent to the work-up method 2), as described herein below, by stirring the crude fully deprotected and cyclized peptide for 24h in water containing DMSO up to 15% by volume, buffered with 5% NaHCO₃ to pH 5-6, or buffered with ammonium acetate to pH 7-8, or adjusted with ammonium hydroxide to pH 8. Following evaporation to dryness Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-), disulfide bond between Cys² and Cys¹¹ is obtained as end-product.

20

Detachment of the fully protected linear peptide from the solid support is achieved by exposing the loaded resin with a solution of the reagent used for cleavage (preferably 3 to 5 mL). Temperature control, agitation, and reaction monitoring are implemented as described above. Via a transfer-unit the reaction vessels are connected with a reservoir box containing reservoir tubes to efficiently collect the cleaved product solutions. The resins remaining in the reaction vessels are 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 products 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,

35

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% H₂O, 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.

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

After full deprotection one of the following methods can be used for further work-up:

1) 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 peptide, Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-), is obtained as final product;

- 5 2) The deprotection mixture is concentrated under vacuum. Following precipitation of the fully deprotected peptide in diethylether at preferably 0 °C the solid is washed up to about 10 times, preferably 3 times, dried, and the the fully deprotected peptide, Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-) is obtained as final
10 product, if a disulfide bond between Xaa² and Xaa¹¹ has been formed on solid support as described herein above.

As mentioned earlier, it is thereafter possible, if desired,
15 to convert the fully deprotected product of Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-), thus obtained into a pharmaceutically acceptable salt or to convert a pharmaceutically acceptable, or unacceptable, salt thus obtained into the corresponding
20 free compound of Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-), or into a different, pharmaceutically acceptable, salt. Any of these operations can be carried out by methods well known in the art.

25 The β -hairpin peptidomimetics of the invention can be used in a wide range of applications in order to inhibit the growth of or to kill microorganisms. In particular they can be used to selectively inhibit the growth of or to kill
30 microorganisms such as *Bacillus subtilis* and/or *Shigella boydii* and/or to inhibit the development of viral pathogens as, for example, human immunodeficiency viruses (HIV).

They can be used for example as disinfectants or as
35 preservatives for materials such as foodstuffs, cosmetics, medicaments and other nutrient-containing materials.

The β -hairpin peptidomimetics of the invention can also be used to treat or prevent diseases related to microbial infection in plants and animals.

- 5 For use as disinfectants or preservatives the β -hairpin peptidomimetics can be added to the desired material singly, as mixtures of several β -hairpin peptidomimetics or in combination with other anti-infective agents. The β -hairpin peptidomimetics may be administered per se or may be applied
10 as an appropriate formulation together with carriers, diluents or excipients well known in the art.

- When used to treat or prevent infections or diseases related to such infections, particularly infections related to
15 respiratory diseases such as cystic fibrosis, emphysema, asthma or pneumonia; infections related to skin or soft tissue diseases such as surgical wounds, traumatic wounds, burn wounds or herpes, smallpox, rubella or measles; infections related to gastrointestinal diseases such as
20 epidemic diarrhea, necrotizing enterocolitis, typhlitis or gastroenteritis or pancreatitis; infections related to eye diseases such as keratitis and endophthalmitis; infections related to ear diseases such as otitis; infections related to CNS diseases such as brain abscess and meningitis or
25 encephalitis; infections related to bone diseases such as osteochondritis and osteomyelitis; infections related to cardiovascular diseases such as endocarditis and pericarditis; or infections related to gastrourinal diseases such as epididymitis, prostatitis and urethritis; infections
30 related to liver diseases such as hepatitis; infections related to sexually transmitted diseases such as AIDS; infections related to diseases such as common cold, influenza, parotitis or gingivostomatitis; the β -hairpin peptidomimetics can be administered singly, as mixtures of
35 several β -hairpin peptidomimetics, in combination with other antimicrobial or antibiotic agents, or anti cancer agents,

or antiviral (e. g. anti-HIV) agents, or in combination with other pharmaceutically active agents. The β -hairpin peptidomimetics can be administered per se or as pharmaceutical compositions.

5

The β -hairpin peptidomimetics of the invention can be used in a wide range of applications in order to prevent HIV infections in healthy individuals and slow or halt viral progression in infected patients.

10

The β -hairpin peptidomimetics of the invention may be administered per se or may be applied as an appropriate formulation together with carriers, diluents or excipients well known in the art.

15

Pharmaceutical compositions comprising β -hairpin peptidomimetics of the invention may be manufactured by means of conventional mixing, dissolving, granulating, coated tablet-making, levigating, emulsifying, 20 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 25 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 30 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 35 administration by injection, e.g. subcutaneous, intravenous,

intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal, oral or pulmonary administration.

5 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
10 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.

15

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

20 For oral administration, the compounds can be readily formulated by combining the active β -hairpin peptidomimetics of the invention with pharmaceutically acceptable carriers well known in the art. Such carriers enable the β -hairpin peptidomimetics of the invention to be formulated as
25 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, such as lactose, sucrose, mannitol
30 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,
35 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.

5

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.

10

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

15 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
20 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
25 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
30 suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described above, the β -hairpin peptidomimetics of the invention may also be formulated as depot preparations. Such long acting
35 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
5 (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
10 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 (e.g. for
15 coated stents). 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
20 biological stability of the therapeutic agent, additional strategies for protein stabilization may be employed.

As the β -hairpin peptidomimetics of the invention may contain charged residues, they may be included in any of the
25 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.

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

For example, for use as a disinfectant or preservative, an antimicrobially effective amount of a β -hairpin peptidomimetic of the invention, or a composition thereof, is applied or added to the material to be disinfected or preserved. By antimicrobially effective amount is meant an amount of a β -hairpin peptidomimetic of the invention, or a composition thereof, that inhibits the growth of, or is lethal to, a target microbe population. While the antimicrobially effective amount will depend on a particular application, for use as disinfectants or preservatives the β -hairpin peptidomimetics of the invention, or compositions thereof, are usually added or applied to the material to be disinfected or preserved in relatively low amounts. Typically, the β -hairpin peptidomimetics of the invention comprise less than about 5% by weight of a disinfectant solution or material to be preserved, preferably less than 1% by weight and more preferably less than 0.1% by weight. An ordinary skilled expert will be able to determine antimicrobially effective amounts of particular β -hairpin peptidomimetics of the invention for particular applications without undue experimentation using, for example, the results of the in vitro assays provided in the examples.

For use to treat or prevent microbial infections or diseases related to such infections, the β -hairpin peptidomimetics of the invention, or compositions thereof, are administered or applied in a therapeutically effective amount. By therapeutically effective amount is meant an amount effective in ameliorating the symptoms of, or in ameliorating, treating or preventing microbial infections or diseases related thereto. Determination of a therapeutically effective amount is well within the capacities of those skilled in the art, especially in view of the detailed disclosure provided herein.

As in the case of disinfectants and preservatives, for topical administration to treat or prevent bacterial infections and/or viral infections a therapeutically effective dose can be determined using, for example, the results of the in vitro assays provided in the examples. The treatment may be applied while the infection is visible, or even when it is not visible. An ordinary skilled expert will be able to determine therapeutically effective amounts to treat topical infections without undue experimentation.

10

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 (i.e. the concentration of a test compound that is lethal to 50% of a 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 anti-infective agents may be adjusted individually to provide plasma levels of the β -hairpin peptidomimetics of the invention which are sufficient to maintain the therapeutic effect. Therapeutically effective serum levels may be achieved by administering multiple doses each day.

In cases of local administration or selective uptake, the effective local concentration of the β -hairpin peptidomimetics of the invention may not be related to plasma concentration. One having the ordinary skill in the

art will be able to optimize therapeutically effective local dosages without undue experimentation.

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

The anti-infective therapy may be repeated intermittently while infections are detectable or even when they are not detectable. The therapy may be provided alone or in combination with other drugs, such as for example other anti-HIV agents or anti-cancer agents, or other antimicrobial agents.

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

20

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 LD₅₀ (the dose lethal to 50% of the population) or the LD₁₀₀ (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).

5

The present invention may also include compounds, which are identical to the compounds of the general formula
Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-
Xaa¹²-Xaa¹³-Xaa¹⁴-), except that one or more atoms are

10 replaced by an atom having an atomic mass number or mass different from the atomic mass number or mass usually found in nature, e.g. compounds enriched in ²H (D), ³H, ¹¹C, ¹⁴C, ¹²⁷I etc. These isotopic analogs and their pharmaceutical salts and formulations are considered useful agents in the
15 therapy and/or diagnostic, for example, but not limited to, where a fine-tuning of in vivo half-life time could lead to an optimized dosage regimen.

The following Examples illustrate the present invention but
20 are not to be construed as limiting its scope in any way.

Examples

1. Peptide Synthesis

5 *Coupling of the first protected amino acid residue to the resin*

1 g (1.4 mMol) 2-chlorotritylchloride resin (1.4 mMol/g; Barlos et al. *Tetrahedron Lett.* **1989**, 30, 3943-3946) was
10 filled into a dried flask. The resin was suspended in CH₂Cl₂ (5 mL) and allowed to swell at room temperature under constant shaking for 30 min. A solution of 0.98 mMol (0.7 eq) of the first suitably protected amino acid residue (see below) in CH₂Cl₂ (5 mL) mixed with 960 µl (4 eq) of
15 diisopropylethylamine (DIEA) was added. After shaking the reaction mixture for 4 hours at 25 °C, the resin was filtered off and washed successively with CH₂Cl₂ (1x), DMF (1x) and CH₂Cl₂ (1x). A solution of CH₂Cl₂/MeOH/DIEA (17/2/1, 10 mL) was added to the resin and the suspension was shaken
20 for 30 min. After filtration the resin was 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.

25 Loading was typically 0.6-0.7 mMol/g.

Fmoc-Pro-O-chlorotrityl resin was prepared as a preloaded resin and used in the synthesis.

30 The synthesis was carried out employing a Syro-peptide synthesizer (MultiSynTech) using 24-96 reaction vessels. In each vessel 0.04 mMol of the above resin was placed and the resin was swollen in CH₂Cl₂ and DMF for 15 min, respectively. The following reaction cycles were programmed and carried
35 out:

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	Step	Reagent	Time
	1	DMF, wash	2x1 min
	2	20% piperidine/DMF	1x5 min, 1x15 min
5	3	DMF, wash	5x1 min
	4a	5 eq Fmoc amino acid/DMF	
		+5 eq HCTU/DMF, 10 eq DIEA/DMF	1x60 min
	5	DMF, wash	3x1 min

10 Step 4a was repeated once.

Unless indicated otherwise, the final coupling of an amino acid was followed by a Fmoc deprotection by applying steps 1-3 of the above described reaction cycle.

15

Cyclization and work up of backbone cyclized peptides

Cleavage of the fully protected peptide fragment

20

After completion of the synthesis, the resin (0.04 mMol) was suspended in 1 mL (0.13 mMol, 3.4 eq) of 1% TFA in CH₂Cl₂ (v/v) for 3 minutes, filtered, and the filtrate was neutralized with 1 mL (0.58 mMol, 14.6 eq) of 10% DIEA in CH₂Cl₂ (v/v). This procedure was repeated three times to ensure completion of the cleavage. The filtrate was evaporated to dryness and a sample of the product was fully deprotected by using a cleavage mixture containing 95% trifluoroacetic acid (TFA), 2.5% water and 2.5% triisopropylsilane (TIS) to be analyzed by reverse phase-HPLC (C₁₈ column) and ESI-MS to monitor the efficiency of the linear peptide synthesis.

35

Cyclization of the linear peptide

The fully protected linear peptide (0.04 mMol) was dissolved in DMF (4 μ Mol/mL). Then 30.4 mg (0.08 mMol, 2 eq) of HATU, 10.9 mg (0.08 mMol, 2 eq) of HOAt and 28 μ l (0.16 mMol, 4 eq) DIEA were added, and the mixture was vortexed at 25°C for 16 hours and subsequently concentrated under high vacuum. The residue was partitioned between CH₂Cl₂ and H₂O/CH₃CN (90/10: v/v). The CH₂Cl₂ phase was evaporated to yield the fully protected cyclic peptide.

Full deprotection of the cyclic peptide

The cyclic peptide obtained was dissolved in 3 mL of the cleavage mixture containing 82.5% trifluoroacetic acid (TFA), 5% water, 5% thioanisole, 5% phenol and 2.5% ethanedithiols (EDT). The mixture was allowed to stand at 25 °C for 2.5 hours and thereafter concentrated under vacuum. After precipitation of the cyclic fully deprotected peptide in diethylether (Et₂O) at 0 °C the solid was washed twice with Et₂O and dried.

Analytical method 1:

Analytical HPLC retention times (RT, in minutes) were determined using a GeminiNX C18 3 μ m column with the following solvents A (H₂O + 0.1% TFA) and B (CH₃CN + 0.09% TFA) and the gradient: 0-0.1 min: 97 % A, 3 % B; 2.7 min: 3 % A, 97 % B; 2.71-3 min: 3 % A, 97 % B; 3.05 min: 97 % A, 3 % B; 3.06-3.3 min: 97 % A, 3 % B.

30

Analytical method 2:

Analytical HPLC retention times (RT, in minutes) were determined using a Xbridge C18 2.5 μ m column with the following solvents A (H₂O + 0.1% TFA) and B (CH₃CN + 0.09% TFA) and the gradient: 0-0.05 min: 97 % A, 3 % B; 3.0 min:

35

3 % A, 97 % B; 3.01-3.6 min: 3 % A, 97 % B; 3.6 min: 97 % A,
3 % B; 3.61-4.3 min: 97 % A, 3 % B.

Examples 1-18 as shown in *Table 1* were synthesized starting
5 with the amino acid Pro (Xaa¹⁴), which was grafted to the
resin. Starting resin was Fmoc-Pro-O-chlorotrityl resin,
which was prepared as described above. The linear peptide
was synthesized on solid support according to the procedure
described above in the following sequence: Resin-Pro¹⁴-Xaa¹³-
10 Xaa¹²-Xaa¹¹-Xaa¹⁰-Xaa⁹-Xaa⁸-Xaa⁷-Xaa⁶-Xaa⁵-Xaa⁴-Xaa³-Xaa²-Xaa¹-.
Following a final Fmoc deprotection as described above, the
peptide was cleaved from the resin, cyclized, deprotected
and purified as indicated above.
The HPLC-retention times (minutes, see *Table 2*) for **Ex. 1, 2**
15 and **4-16** were determined using the analytical method 1, as
described above, whereas the HPLC-retention times (minutes,
see *Table 2*) for **Ex. 3, 17** and **18** were determined using the
analytical method 2, as described above.

Table 1: Examples (Ex.)

Ex.	Seq ID	Xaa ¹	Xaa ²	Xaa ³	Xaa ⁴	Xaa ⁵	Xaa ⁶	Xaa ⁷	Xaa ⁸	Xaa ⁹	Xaa ¹⁰	Xaa ¹¹	Xaa ¹²	Xaa ¹³	Xaa ¹⁴
1.	Seq ID No:1	Trp	Arg	Ile	Arg	Ile	^D Arg	Asn	Lys	Dab	Leu	Arg	Arg	^D Pro	Pro
2.	Seq ID No:2	Trp	Arg	Ile	Arg	Ile	^D Arg	Asn	Lys	Arg	Leu	Arg	Gln	^D Pro	Pro
3.	Seq ID No:3	Trp	Arg	Ile	Arg	Ile	^D Arg	Asn	Lys	Arg	Asn	Arg	Ala	^D Pro	Pro
4.	Seq ID No:4	Trp	Arg	Ile	Arg	Ile	^D Arg	Asn	Gln	Arg	Cha	Gln	Ala	^D Pro	Pro
5.	Seq ID No:5	Trp	Dab	Ile	Arg	Ile	^D Arg	Asn	Gln	Arg	Leu	Gln	Ala	^D Pro	Pro
6.	Seq ID No:6	Trp	Orn	Ile	Arg	Ile	^D Arg	Asn	Gln	Arg	Leu	Gln	Ala	^D Pro	Pro
7.	Seq ID No:7	Trp	Arg	Ile	Dab	Ile	^D Arg	Asn	Gln	Arg	Leu	Gln	Ala	^D Pro	Pro
8.	Seq ID No:8	Trp	Arg	Ile	Orn	Ile	^D Arg	Asn	Gln	Arg	Leu	Gln	Ala	^D Pro	Pro
9.	Seq ID No:9	Trp	Arg	Ile	Arg	Ile	Orn	Asn	Gln	Arg	Leu	Gln	Ala	^D Pro	Pro
10.	Seq ID No:10	Trp	Arg	Ile	Arg	Ile	Dab	Asn	Gln	Arg	Leu	Gln	Ala	^D Pro	Pro
11.	Seq ID No:11	Trp	Arg	Ile	Arg	Ile	^D Arg	Gln	Gln	Arg	Leu	Gln	Ala	^D Pro	Pro
12.	Seq ID No:12	Trp	Arg	Ile	Arg	Ile	^D Arg	Thr	Gln	Arg	Leu	Gln	Ala	^D Pro	Pro
13.	Seq ID No:13	Trp	Arg	Ile	Arg	Ile	^D Arg	Leu	Gln	Arg	Leu	Gln	Ala	^D Pro	Pro
14.	Seq ID No:14	Trp	Arg	Ile	Arg	Ile	^D Arg	Tyr	Gln	Arg	Leu	Gln	Ala	^D Pro	Pro
15.	Seq ID No:15	Trp	Arg	Ile	Arg	Ile	^D Arg	Asn	Gln	Arg	Tyr	Gln	Ala	^D Pro	Pro
16.	Seq ID No:16	Trp	Arg	Ile	Arg	Ile	^D Arg	Asn	Gln	Arg	Trp	Gln	Ala	^D Pro	Pro
17.	Seq ID No:17	Trp	Arg	Ile	Arg	Ile	^D Dab	Asn	Trp	Dab	Asn	Arg	Dab	^D Pro	Pro
18.	Seq ID No:18	Trp	Arg	Ile	Arg	Ile	^D Arg	Asn	His	Arg	Asn	Arg	Arg	^D Pro	Pro

100

Table 2:

Ex.	Purity [%] ^{a)}	(M+3H)/3	RT [min]
1	94	615.2	1.38
2	90	624.5	1.44
3	95	605.8	1.86
4	92	609.5	1.76
5	97	577.5	1.68
6	97	582.1	1.69
7	97	577.4	1.69
8	97	582.1	1.69
9	95	582.1	1.68
10	92	577.5	1.67
11	97	600.8	1.69
12	94	591.8	1.69
13	97	595.8	1.71
14	97	612.5	1.7
15	94	612.7	1.66
16	94	620.5	1.70
17	95	597.5	1.79
18	94	637.2	1.71

a) %-purity of compounds after prep. HPLC.

2. Biological methods

2.1. Preparation of the peptides

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

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2.2. Antimicrobial activity of the peptides

The selective antimicrobial activities of the peptides were determined in 96-well plates (Greiner, polypropylene) by the
15 standard NCCLS broth microdilution method (National Committee for Clinical Laboratory Standards **1993**. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 3rd ed. Approved standard M7-A6. National Committee for Clinical laboratory standards, Wayne,
20 PA) with slight modifications. Inocula of the microorganisms were diluted into Mueller-Hinton II (MH, cation adjusted) broth + 0.02% BSA and compared with a 0.5 McFarland standard to give appr. 10⁶ colony forming units (CFU)/mL. Aliquots (50 µl) of inoculate were added to 50 µl of MH broth + 0.02%
25 BSA containing the peptide in serial two-fold dilutions. The following microorganisms were used to determine antibiotic selectivity of the peptides: *Bacillus subtilis* DSM 10 and *Shigella boydii* DSM 7532. Antimicrobial activities of the peptides were expressed as the minimal inhibitory
30 concentration (MIC) in µg/mL at which no visible growth was observed after 18-20 hours of incubation at 37 °C.

35

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 (T. Mossman, *J. Immunol. Meth.* **1983**, 65, 55-63; M.V. Berridge, A.S. Tan, *Arch. Biochem. Biophys.* **1993**, 303, 474-482). Briefly, the method was as follows: 4000 HELA cells/well and 3400 COS-7 cells/well were seeded and grown in 96-well microtiter plates for 24 h at 37 °C at 5% CO₂. Thereafter, time zero (Tz) was determined by MTT reduction (see below). The supernatant of the remaining wells was discarded, and fresh medium and compounds in serial dilutions (12.5, 25 and 50 µg/mL, triplicates) were pipetted into the wells. After incubation of the cells for 48 h at 37 °C at 5% CO₂ the supernatant was discarded again and 100 µL MTT reagent (0.5 mg/mL in RPMI1640 and DMEM, respectively)/well was added. Following incubation at 37 °C for 2-4 h the media were aspirated and the cells were spiked (100 µL isopropanol/well). The absorbance of the solubilized formazan was measured at 595 nm (OD₅₉₅peptide). For each concentration averages were calculated from triplicates. The percentage of growth was calculated as follows: $(OD_{595}peptide - OD_{595}Tz - OD_{595}Empty\ well) / (OD_{595}Tz - OD_{595}Empty\ well) \times 100\%$. The GI₅₀ (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:%₀, 50)).

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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) and centrifuged for 10 min at 2000 x g. Compounds (100 µg/mL)

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were incubated with 20% hRBC (v/v) for 1 h at 37 °C and shaking at 300 rpm. The final erythrocyte concentration was approximately 0.9×10^9 cells/mL. A value of 0% and 100% cell lyses, respectively, was determined by incubation of hRBC in the presence of PBS containing 0.001% acetic acid and 2.5% Triton X-100 in H₂O, respectively. The samples were centrifuged, the supernatants were 8-fold diluted in PBS buffer and the optical densities (OD) were measured at 540 nm. The 100% lyses value (OD_{540H₂O}) gave an OD₅₄₀ of approximately 0.5-1.0.

Percent hemolysis was calculated as follows:
(OD_{540peptide}/OD_{540H₂O}) x100%.

The results of the experiments described in 2.2 - 2.4 are indicated in Table 3 herein below.

**Table 3: Minimal inhibitory concentrations (MIC) in
Mueller- Hinton broth, cytotoxicity and hemolysis**

Ex.	Bactillus subtilis DSM 10 MIC [µg/mL]	Shigella boydii DSM 7532 MIC [µg/mL]	Cytotoxicity		Hemolysis at 100 µg/mL [%]
			Hela Cells GI ₅₀ [µg/mL]	Cos-7 Cells GI ₅₀ [µg/mL]	
1	4	8	> 50	> 50	0.0
2	2	4	> 50	> 50	0.0
3	4	16	> 50	> 50	0.1
4	4	> 16	> 50	> 50	0.8
5	2	16	> 50	> 50	0.0
6	4	> 16	> 50	> 50	0.0
7	4	> 16	> 50	> 50	0.0
8	2	16	> 50	> 50	0.0
9	2	> 16	> 50	> 50	0.0
10	4	> 16	> 50	> 50	0.4
11	4	> 16	> 50	> 50	0.0
12	4	> 16	> 50	> 50	0.7
13	4	16	> 50	> 50	0.0
14	4	16	> 50	> 50	0.0
15	4	16	> 50	> 50	0.0
16	2	16	> 50	> 50	0.5
17	2	4	38	44	0.2
18	16	4	39	> 50	0.3

CLAIMS

1. Compounds of the general formula

Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴- Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-
5 Xaa¹²-Xaa¹³-Xaa¹⁴-), wherein the amino acid residues Xaa¹ to
Xaa¹⁴ are:

- Xaa¹: amino acid residue of type C, or of type D,
as described herein below;
- 10 - Xaa²: amino acid residue of type E,
as described herein below;
- Xaa³: amino acid residue of type C, or of type F,
as described herein below;
- Xaa⁴: amino acid residue of type C, or of type E,
15 as described herein below;
- Xaa⁵: amino acid residue of type C,
as described herein below;
- Xaa⁶: amino acid residue of type E, as described herein
below; or the D-isomer of an amino acid residue
20 of type E, as described herein below;
- Xaa⁷: amino acid residue of type F,
as described herein below, or Gly;
- Xaa⁸: amino acid residue of type E,
as described herein below;
- 25 - Xaa⁹: amino acid residue of type E,
as described herein below;
- Xaa¹⁰: amino acid residue of type C, or of type F,
as described herein below;
- Xaa¹¹: amino acid residue of type E, or of type F,
30 as described herein below;
- Xaa¹²: amino acid residue of type C, or of type E,
or of type F, as described herein below;
- Xaa¹³: amino acid residue of formula -A-CO-,
as described herein below;
- 35 - Xaa¹⁴: amino acid residue of formula -B-CO-,
as described herein below;

with the proviso that if

Xaa⁹ is an amino acid residue of type E,
as described herein below,

then Xaa⁹ is Dab; and/or if

5 Xaa¹² is an amino acid residue of type F,
as described herein below,

then Xaa¹² is Gln; and/or

at least two of the amino acid residues of
Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-

10 Xaa¹²-Xaa¹³-Xaa¹⁴-) are non-canonical amino acid residues,
as described herein below;

or

15 compounds of the general formula Cyclo(-Xaa¹-Xaa²-Xaa³-
Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-),
wherein the amino acid residues Xaa¹ to Xaa¹⁴ are:

- Xaa¹: amino acid residue of type D,
20 as described herein below;
- Xaa²: amino acid residue of type E,
as described herein below;
- Xaa³: amino acid residue of type C, or of type F,
as described herein below;
- 25 - Xaa⁴: amino acid residue of type E,
as described herein below;
- Xaa⁵: amino acid residue of type C,
as described herein below;
- Xaa⁶: amino acid residue of type E, or the D-isomer of
30 an amino acid residue of type E,
as described herein below;
- Xaa⁷: amino acid residue of type C, or of type D,
or of type E, or of type F,
as described herein below, or Gly;
- 35 - Xaa⁸: amino acid residue of type F,
as described herein below;

- Xaa⁹: amino acid residue of type E,
as described herein below;
- Xaa¹⁰: amino acid residue of type C, or of type D,
or of type F, as described herein below;
- 5 - Xaa¹¹: amino acid residue of type E, or or type F,
as described herein below;
- Xaa¹²: amino acid residue of type C or of type E,
as described herein below;
- Xaa¹³: amino acid residue of formula -A-CO-,
10 as described herein below;
- Xaa¹⁴: amino acid residue of formula -B-CO-,
as described herein below;

with the proviso that if

- 15 Xaa⁷ is an amino acid residue of type F,
as described herein below,

then Xaa⁷ is Gln or Thr; and/or if

- Xaa¹⁰ is an amino acid residue of type F,
as described herein below,

then Xaa¹⁰ is Ser; and/or

- 20 at least one of the amino acid residues of
Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-
Xaa¹²-Xaa¹³-Xaa¹⁴-) is a non-canonical amino acid residue,
as described herein below;

25 or

compounds of the general formula Cyclo(-Xaa¹-Xaa²-Xaa³-
Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-),
wherein the amino acid residues Xaa¹ to Xaa¹⁴ are:

30

- Xaa¹: amino acid residue of type D,
as described herein below;
- Xaa²: amino acid residue of type E,
as described herein below;
- 35 - Xaa³: amino acid residue of type C,
as described herein below;

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- Xaa⁴: amino acid residue of type E,
as described herein below;
- Xaa⁵: amino acid residue of type C,
as described herein below;
- 5 - Xaa⁶: amino acid residue of type E, as described herein
below, or the D-isomer of an amino acid residue
of type E, as described herein below;
- Xaa⁷: amino acid residue of type F,
as described herein below;
- 10 - Xaa⁸: amino acid residue of type D,
as described herein below;
- Xaa⁹: amino acid residue of type E,
as described herein below;
- Xaa¹⁰: amino acid residue of type F,
as described herein below;
- 15 - Xaa¹¹: amino acid residue of type E,
as described herein below;
- Xaa¹²: amino acid residue of type E,
as described herein below;
- 20 - Xaa¹³: amino acid residue of formula -A-CO-,
as described herein below;
- Xaa¹⁴: amino acid residue of formula -B-CO-,
as described herein below;

25 or

compounds of the general formula Cyclo(-Xaa¹-Xaa²-Xaa³-
Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-),
wherein the amino acid residues Xaa¹ to Xaa¹⁴ are:

30

- Xaa¹: amino acid residue of type D,
as described herein below;
- Xaa²: amino acid residue of type E,
as described herein below;
- 35 - Xaa³: amino acid residue of type E,
as described herein below;

- Xaa⁴: amino acid residue of type E,
as described herein below;
- Xaa⁵: amino acid residue of type C,
as described herein below, or Gly;
- 5 - Xaa⁶: amino acid residue of type E, or of type F,
as described herein below, or the D-isomer of an
amino acid residue of type E, as described herein
below, or -B-CO-, as described herein below or
Gly;
- 10 - Xaa⁷: amino acid residue of type E, as described herein
below, or the D-isomer of an amino acid residue
of type E, as described herein below, or Gly;
- Xaa⁸: amino acid residue of type F,
as described herein below, or Gly;
- 15 - Xaa⁹: amino acid residue of type E,
as described herein below;
- Xaa¹⁰: amino acid residue of type F,
as described herein below;
- Xaa¹¹: amino acid residue of type E,
20 as described herein below;
- Xaa¹²: amino acid residue of type E,
as described herein below;
- Xaa¹³: amino acid residue of formula -A-CO-,
as described herein below;
- 25 - Xaa¹⁴: amino acid residue of formula -B-CO-,
as described herein below;

with the proviso that at least one of the amino acid
residues of Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-
Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-) is a non-canonical amino
30 acid residue, as described herein below;

or

compounds of the general formula Cyclo(-Xaa¹-Xaa²-Xaa³-
35 Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-),
wherein the amino acid residues Xaa¹ to Xaa¹⁴ are:

- Xaa¹: amino acid residue of type E,
as described herein below;
 - Xaa²: amino acid residue of type E,
as described herein below;
 - Xaa³: amino acid residue of type C, or of type F,
as described herein below;
 - Xaa⁴: amino acid residue of type E,
as described herein below;
 - Xaa⁵: amino acid residue of type C, or of type F,
as described herein below;
 - Xaa⁶: amino acid residue of type E, as described herein
below, or the D-isomer of an amino acid residue
of type E, as described herein below;
 - Xaa⁷: Gly;
 - Xaa⁸: amino acid residue of type E, or of type F,
as described herein below;
 - Xaa⁹: amino acid residue of type E,
as described herein below;
 - Xaa¹⁰: amino acid residue of type C, or of type F,
as described herein below;
 - Xaa¹¹: amino acid residue of type E,
as described herein below;
 - Xaa¹²: amino acid residue of type E,
as described herein below;
 - Xaa¹³: amino acid residue of formula -A-CO-,
as described herein below;
 - Xaa¹⁴: amino acid residue of formula -B-CO-,
as described herein below;
- with the proviso that at least two of the amino acid
residues of Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-
Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-) are non-canonical amino
acid residues;

or

compounds of the general formula $\text{Cyclo}(-\text{Xaa}^1-\text{Xaa}^2-\text{Xaa}^3-\text{Xaa}^4-\text{Xaa}^5-\text{Xaa}^6-\text{Xaa}^7-\text{Xaa}^8-\text{Xaa}^9-\text{Xaa}^{10}-\text{Xaa}^{11}-\text{Xaa}^{12}-\text{Xaa}^{13}-\text{Xaa}^{14}-)$, wherein the amino acid residues Xaa^1 to Xaa^{14} are:

- 5 - Xaa^1 : amino acid residue of type E,
 as described herein below;
- Xaa^2 : amino acid residue of type C, or of type F,
 as described herein below;
- Xaa^3 : amino acid residue of type E,
10 as described herein below;
- Xaa^4 : amino acid residue of type E,
 as described herein below;
- Xaa^5 : amino acid residue of type C,
 as described herein below;
- 15 - Xaa^6 : amino acid residue of type E,
 as described herein below;
- Xaa^7 : Gly;
- Xaa^8 : amino acid residue of type F,
 as described herein below;
- 20 - Xaa^9 : amino acid residue of type E,
 as described herein below;
- Xaa^{10} : amino acid residue of type E, or of type F,
 as described herein below;
- Xaa^{11} : amino acid residue of type E, or of type F,
25 as described herein below;
- Xaa^{12} : amino acid residue of type E,
 as described herein below;
- Xaa^{13} : amino acid residue of formula $-\text{A}-\text{CO}-$,
 as described herein below;
- 30 - Xaa^{14} : amino acid residue of formula $-\text{B}-\text{CO}-$,
 as described herein below;
- the amino acid residues Xaa^2 and Xaa^{11} , taken together,
 can form an amino acid residue of type H,
 as described herein below;
- 35 with the proviso that at least one of the amino acid
 residues of $\text{Cyclo}(-\text{Xaa}^1-\text{Xaa}^2-\text{Xaa}^3-\text{Xaa}^4-\text{Xaa}^5-\text{Xaa}^6-\text{Xaa}^7-\text{Xaa}^8-$

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Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-) are non-canonical amino acid residues;

or

5

compounds of the general formula Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-), wherein the amino acid residues Xaa¹ to Xaa¹⁴ are:

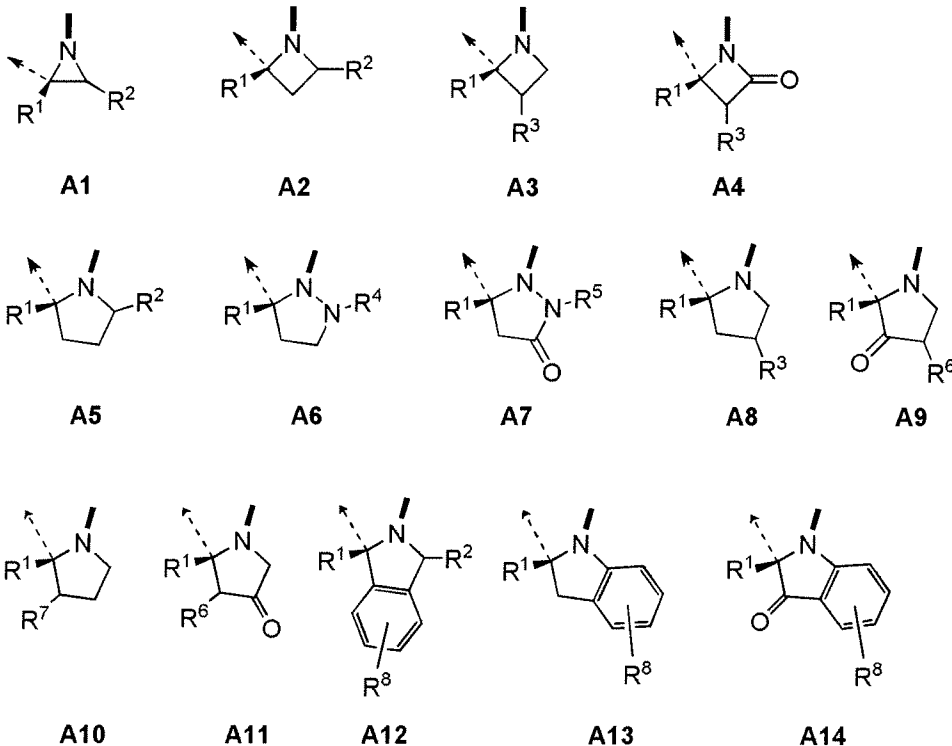
- 10 - Xaa¹: amino acid residue of type, E or of type F, as described herein below;
- Xaa²: amino acid residue of type C, or of type D, or of type E, or of type F, as described herein below;
- Xaa³: amino acid residue of type E, as described herein
15 below, or the D-isomer of an amino acid residue of type E, as described herein below, or Gly;
- Xaa⁴: amino acid residue of type C, or of type D, or of type E, or of type F, as described herein below;
- Xaa⁵: amino acid residue of type E,
20 as described herein below;
- Xaa⁶: amino acid residue of type E, or of type F, as described herein below, or Gly;
- Xaa⁷: amino acid residue of type D, or of type E, or of type F, as described herein below, or Gly;
- 25 - Xaa⁸: amino acid residue of type E, as described herein below;
- Xaa⁹: amino acid residue of type D, or of type E, as described herein below;
- Xaa¹⁰: amino acid residue of type C, or of type D, or of
30 type E, or of type F, as described herein below;
- Xaa¹¹: amino acid residue of type D, or of type E, or of type F, as described herein below, or Gly;
- Xaa¹²: amino acid residue of type C, or of type D, or of type E, or of type F, as described herein below;
- 35 - Xaa¹³: amino acid residue of formula -A-CO-, as described herein below;

- Xaa¹⁴: amino acid residue of formula -B-CO-,
as described herein below;
- the amino acid residues Xaa² and Xaa¹¹, taken together,
can form an amino acid residue of type H,
as described herein below;

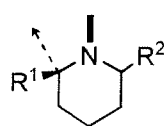
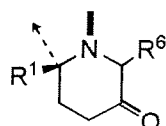
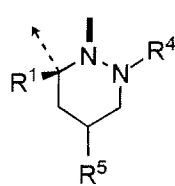
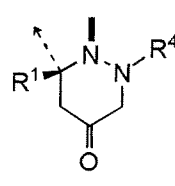
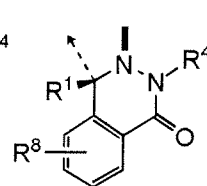
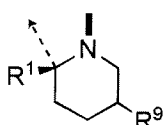
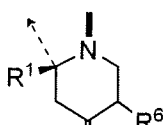
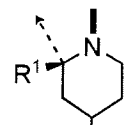
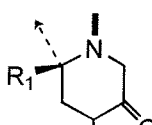
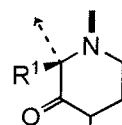
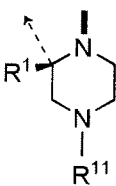
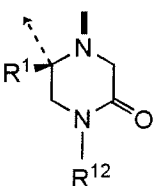
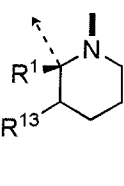
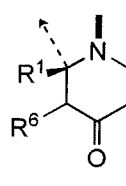
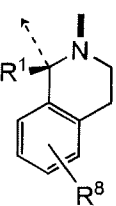
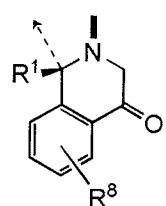
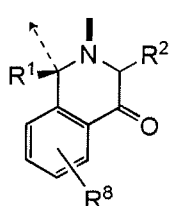
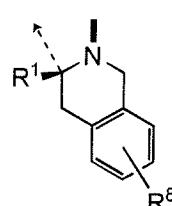
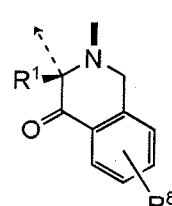
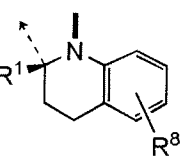
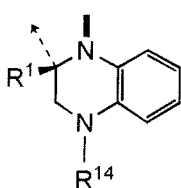
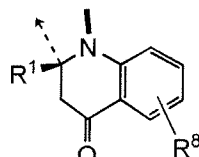
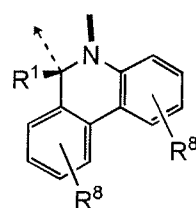
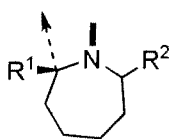
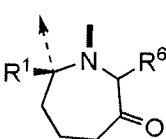
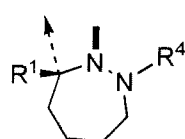
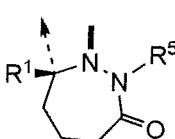
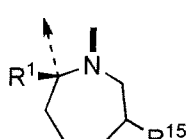
with the proviso that at least two of the amino acid residues of Cyclo(-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Xaa¹²-Xaa¹³-Xaa¹⁴-) are non-canonical amino acid residues;

-B-CO- is Gly, NMeGly or the residue of an L- α -amino acid with B being a residue of formula -NR²⁰CH(R⁷¹)-, or -NR²⁰CH(R⁷²)-, or -NR²⁰CH(R⁷³)-, or -NR²⁰CH(R⁷⁴)-, or -NR²⁰CH(R⁸⁴)-, or the enantiomer of one of the groups **A1** to **A69** as defined hereinafter;

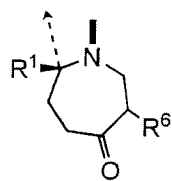
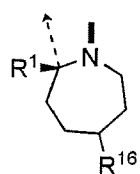
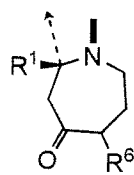
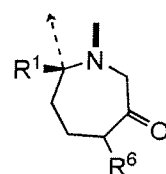
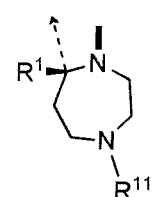
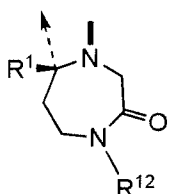
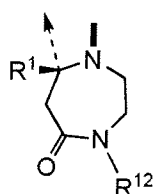
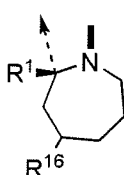
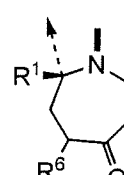
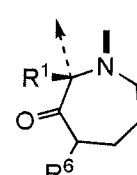
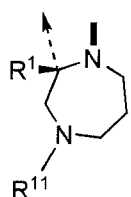
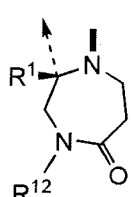
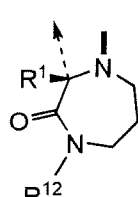
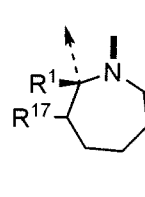
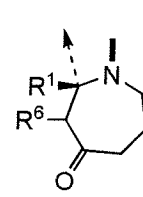
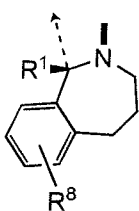
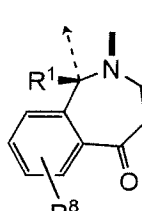
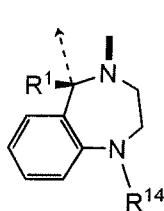
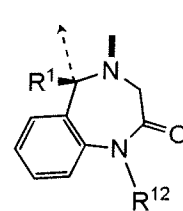
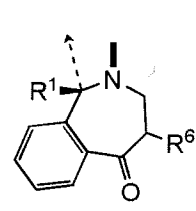
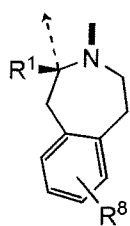
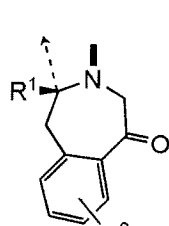
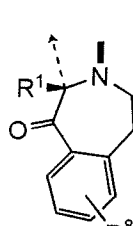
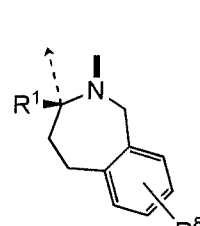
A of -A-CO- is a group of one of the formulae

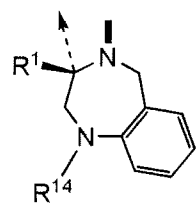
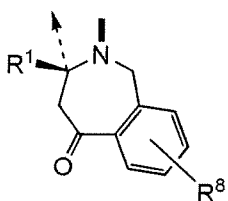
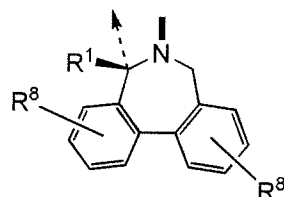
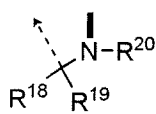
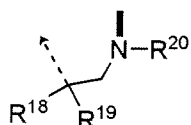
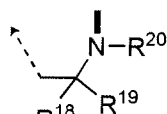
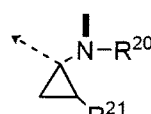
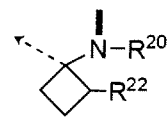
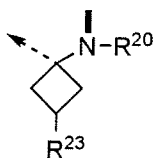
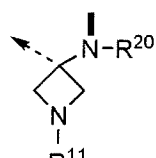
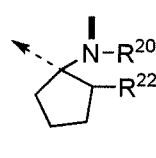
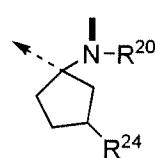
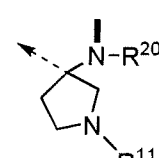
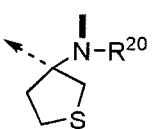
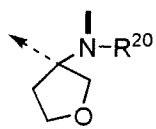
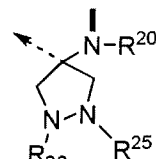
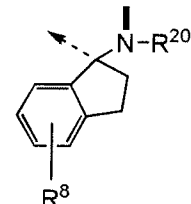
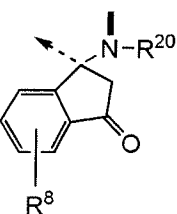
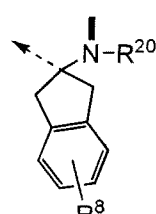
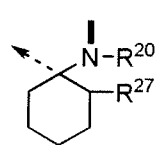
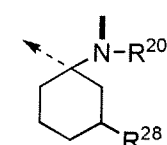
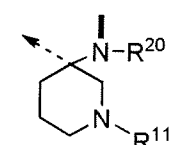
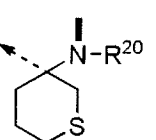
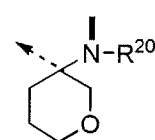
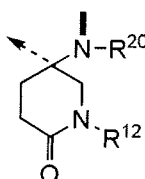
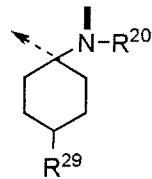
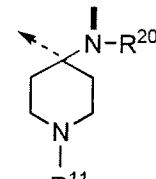


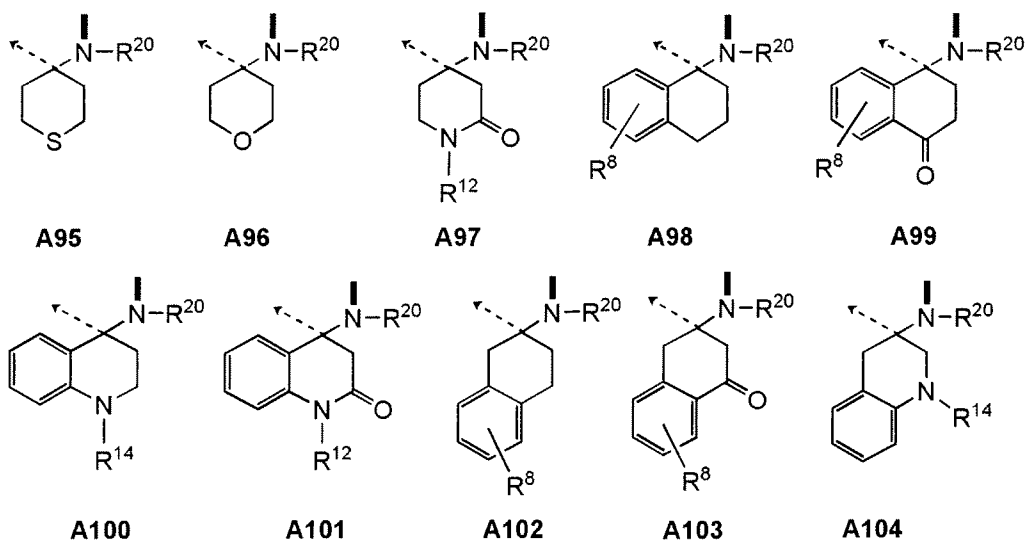
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**A15****A16****A17****A18****A19****A20****A21****A22****A23****A24****A25****A26****A27****A28****A29****A30****A31****A32****A33****A34****A35****A36****A37****A38****A39****A40****A41****A42**

115

**A43****A44****A45****A46****A47****A48****A49****A50****A51****A52****A53****A54****A55****A56****A57****A58****A59****A60****A61****A62****A63****A64****A65****A66**

**A67****A68****A69****A70****A71****A72****A73****A74****A75****A76****A77****A78****A79****A80****A81****A82****A83****A84****A85****A86****A87****A88****A89****A90****A91****A92****A93****A94**



R^1 is H; lower alkyl; lower cycloalkyl; lower alkyl-aryl or aryl-lower alkyl;

R^2 is H; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;

5 $-(CH_2)_p(CHR^{61})_sSR^{56}$;

$-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$;

$-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;

$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;

$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sR^{77}$;

10 R^3 is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;

$-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;

$-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;

15 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^4 is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;

$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

$-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$;

20 $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;

$-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^5 is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$;

$-(CH_2)_m(CHR^{61})_sSR^{56}$;

$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;

- $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^6 is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$;
5 $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
10 R^7 is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_r(CHR^{61})_sCOOR^{57}$; $-(CH_2)_r(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_r(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_r(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_r(CHR^{61})_sC_6H_4R^8$;
15 R^8 is H; Cl; F; CF_3 ; NO_2 ; lower alkyl; lower cycloalkyl;
lower alkenyl; aryl; lower alkyl-aryl; aryl-lower
alkyl; $-(CH_2)_o(CHR^{61})_sR^{77}$
 $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
20 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sCOR^{64}$;
 R^9 is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
25 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
30 R^{10} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
35 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

- R^{11} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
5 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
- R^{12} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$;
 $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
10 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_r(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_r(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_r(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_r(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_r(CHR^{61})_sC_6H_4R^8$;
- R^{13} is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sSR^{56}$;
 $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
15 $-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_q(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;
- R^{14} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$;
20 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_q(CHR^{61})_sSOR^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;
- 25 R^{15} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
30 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
- R^{16} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
35 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

- R^{17} is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sSR^{56}$;
 $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$;
5 $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_q(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;
 R^{18} is alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sSR^{56}$;
 $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
10 $-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;
 R^{19} is lower alkyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sSR^{56}$;
 $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
15 $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$; or
 R^{18} and R^{19} taken together can form: $-(CH_2)_{2-6}-$;
20 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;
 R^{20} is H; alkyl; lower cycloalkyl; alkenyl; lower alkyl-aryl;
or aryl-lower alkyl;
 R^{21} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$;
 $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
25 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{22} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$;
30 $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
35 R^{23} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;

- $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{OCONR}^{33}\text{R}^{75}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{NR}^{20}\text{CONR}^{33}\text{R}^{82}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{COOR}^{57}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{CONR}^{58}\text{R}^{59}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{PO}(\text{OR}^{60})_2$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{SO}_2\text{R}^{62}$; or $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{C}_6\text{H}_4\text{R}^8$;
5 R^{24} is alkyl; alkenyl; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{OR}^{55}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{SR}^{56}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{NR}^{33}\text{R}^{34}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{OCONR}^{33}\text{R}^{75}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{NR}^{20}\text{CONR}^{33}\text{R}^{82}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{COOR}^{57}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{CONR}^{58}\text{R}^{59}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{PO}(\text{OR}^{60})_2$;
10 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{SO}_2\text{R}^{62}$; or $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{C}_6\text{H}_4\text{R}^8$;
 R^{25} is H; alkyl; alkenyl; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{OR}^{55}$;
 $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{SR}^{56}$;
 $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{NR}^{33}\text{R}^{34}$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{OCONR}^{33}\text{R}^{75}$;
 $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{NR}^{20}\text{CONR}^{33}\text{R}^{82}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{COOR}^{57}$;
15 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{CONR}^{58}\text{R}^{59}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{PO}(\text{OR}^{60})_2$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{SO}_2\text{R}^{62}$; or $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{C}_6\text{H}_4\text{R}^8$;
 R^{26} is H; alkyl; alkenyl; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{OR}^{55}$;
 $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{SR}^{56}$;
 $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{NR}^{33}\text{R}^{34}$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{OCONR}^{33}\text{R}^{75}$;
20 $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{NR}^{20}\text{CONR}^{33}\text{R}^{82}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{COOR}^{57}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{CONR}^{58}\text{R}^{59}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{PO}(\text{OR}^{60})_2$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{SO}_2\text{R}^{62}$; or $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{C}_6\text{H}_4\text{R}^8$; or
 R^{25} and R^{26} taken together can form: $-(\text{CH}_2)_{2-6}-$; $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_r$;
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_r-$; or $-(\text{CH}_2)_r\text{NR}^{57}(\text{CH}_2)_r-$;
25 R^{27} is H; alkyl; alkenyl; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{OR}^{55}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{SR}^{56}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{NR}^{33}\text{R}^{34}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{COOR}^{57}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{CONR}^{58}\text{R}^{59}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{OCONR}^{33}\text{R}^{75}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{NR}^{20}\text{CONR}^{33}\text{R}^{82}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{PO}(\text{OR}^{60})_2$;
30 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{SO}_2\text{R}^{62}$; or $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{C}_6\text{H}_4\text{R}^8$;
 R^{28} is alkyl; alkenyl; $-(\text{CH}_2)_o(\text{CHR}^{61})_s-\text{OR}^{55}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{SR}^{56}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{NR}^{33}\text{R}^{34}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{OCONR}^{33}\text{R}^{75}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{NR}^{20}\text{CONR}^{33}\text{R}^{82}$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{COOR}^{57}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{CONR}^{58}\text{R}^{59}$;
35 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{PO}(\text{OR}^{60})_2$;
 $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{SO}_2\text{R}^{62}$; or $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{C}_6\text{H}_4\text{R}^8$;

- R^{29} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
5 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{33} is H; alkyl, alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$;
 $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$;
 $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$;
10 $-(CH_2)_o(CHR^{61})_sCOR^{64}$; $-(CH_2)_o(CHR^{61})_s-CONR^{58}R^{59}$;
 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{34} is H; lower alkyl; lower cycloalkyl; lower alkyl-aryl;
aryl or aryl-lower alkyl; or
15 R^{33} and R^{34} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;
 R^{50} is H; lower alkyl; lower cycloalkyl; lower alkyl-aryl; or
aryl-lower alkyl;
 R^{55} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
20 lower alkyl-aryl; aryl-lower alkyl;
 $-(CH_2)_m(CHR^{61})_sOR^{57}$;
 $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$; $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$; $-(CH_2)_o(CHR^{61})_s-COR^{64}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; or
25 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 R^{56} is H; lower alkyl; lower alkenyl; lower alkyl-aryl;
aryl-lower alkyl;
 $-(CH_2)_m(CHR^{61})_sOR^{57}$;
 $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$; $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$;
30 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$; $-(CH_2)_o(CHR^{61})_s-COR^{64}$; or
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 R^{57} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
lower alkyl-aryl; aryl-lower alkyl;
lower alkyl-heteroaryl; or heteroaryl-lower alkyl;

- R^{58} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; aryl-lower alkyl;
 lower alkyl-heteroaryl; or heteroaryl-lower alkyl;
- R^{59} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; aryl-lower alkyl;
 lower alkyl-heteroaryl; or heteroaryl-lower alkyl; or
- R^{58} and R^{59} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$;
- R^{60} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; aryl; or aryl-lower alkyl;
- R^{61} is alkyl; alkenyl; lower cycloalkyl; lower alkyl-aryl;
 lower alkyl-heteroaryl; aryl; heteroaryl;
 aryl-lower alkyl; heteroaryl-lower alkyl; $-(CH_2)_pOR^{55}$;
 $-(CH_2)_pNR^{33}R^{34}$; $-(CH_2)_pOCONR^{75}R^{82}$; $-(CH_2)_pNR^{20}CONR^{78}R^{82}$;
 $-(CH_2)_oCOOR^{37}$; or $-(CH_2)_oPO(OR^{60})_2$;
- R^{62} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; lower alkyl-heteroaryl; aryl;
 heteroaryl; aryl-lower alkyl; or
- heteroaryl-lower alkyl;
- R^{63} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; lower alkyl-heteroaryl; aryl;
 heteroaryl; aryl-lower alkyl; or
- heteroaryl-lower alkyl;
- $-\text{COR}^{64}$; $-\text{COOR}^{57}$; $-\text{CONR}^{58}R^{59}$; $-\text{SO}_2R^{62}$; or $-\text{PO}(OR^{60})_2$; or
- R^{34} and R^{63} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;
- R^{64} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; lower alkyl-heteroaryl; aryl;
 heteroaryl; aryl-lower alkyl; or
- heteroaryl-lower alkyl;
- $-(CH_2)_p(\text{CHR}^{61})_sOR^{65}$; $-(CH_2)_p(\text{CHR}^{61})_sSR^{66}$;
 $-(CH_2)_p(\text{CHR}^{61})_sNR^{34}R^{63}$;
 $-(CH_2)_p(\text{CHR}^{61})_sOCONR^{75}R^{82}$; or $-(CH_2)_p(\text{CHR}^{61})_sNR^{20}CONR^{78}R^{82}$;
- R^{65} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
 lower alkyl-aryl; lower alkyl-heteroaryl; aryl;

- heteroaryl; aryl-lower alkyl; or
heteroaryl-lower alkyl; -COR⁵⁷;
-COOR⁵⁷; or -CONR⁵⁸R⁵⁹;
- R⁶⁶ is H; lower alkyl; lower alkenyl; lower cycloalkyl;
5 lower alkyl-aryl; lower alkyl-heteroaryl; aryl;
heteroaryl; aryl-lower alkyl; or
heteroaryl-lower alkyl; or -CONR⁵⁸R⁵⁹;
- R⁶⁷ is H; Cl; Br; F; NO₂; -NR³⁴COR⁵⁷; -CF₃; CN; -OCF₃; -OCHF₂;
-OR⁵⁷; -SR⁶²; lower alkyl; or
10 lower alkenyl;
- R⁶⁸ is H; Cl; Br; F; NO₂; -NR³⁴COR⁵⁷; -CF₃; CN; -OCF₃; -OCHF₂;
-OR⁵⁷; -SR⁶²; lower alkyl; or
lower alkenyl;
- R⁶⁹ is H; Cl; Br; F; NO₂; -NR³⁴COR⁵⁷; -CF₃; CN; -OCF₃; -OCHF₂;
15 -OR⁵⁷; -SR⁶²; lower alkyl; or
lower alkenyl;
- R⁷⁰ is H; Cl; Br; F; NO₂; -NR³⁴COR⁵⁷; -CF₃; CN; -OCF₃; -OCHF₂;
-OR⁵⁷; -SR⁶²; lower alkyl; or
lower alkenyl;
- 20 R⁷¹ is lower alkyl; lower alkenyl; -(CH₂)_p(CHR⁶¹)_sOR⁷⁵;
-(CH₂)_p(CHR⁶¹)_sSR⁷⁵;
-(CH₂)_p(CHR⁶¹)_sNR³³R³⁴; -(CH₂)_p(CHR⁶¹)_sOCONR³³R⁷⁵;
-(CH₂)_p(CHR⁶¹)_sNR²⁰CONR³³R⁸²;
-(CH₂)_o(CHR⁶¹)_sCOOR⁷⁵; -(CH₂)_pCONR⁵⁸R⁵⁹; -(CH₂)_pPO(OR⁶²)₂;
25 -(CH₂)_pSO₂R⁶²; or
-(CH₂)_o-C₆R⁶⁷R⁶⁸R⁶⁹R⁷⁰R⁷⁶;
- R⁷² is alkyl; alkenyl; lower cycloalkyl; -(CH₂)_p(CHR⁶¹)_sOR⁸⁵; or
-(CH₂)_p(CHR⁶¹)_sSR⁸⁵;
- R⁷³ is -(CH₂)_oR⁷⁷; -(CH₂)_rO(CH₂)_oR⁷⁷; -(CH₂)_rS(CH₂)_oR⁷⁷; or
30 -(CH₂)_rNR²⁰(CH₂)_oR⁷⁷;
- R⁷⁴ is -(CH₂)_pNR⁷⁸R⁷⁹; -(CH₂)_pNR⁷⁷R⁸⁰; -(CH₂)_pC(=NR⁸⁰)NR⁷⁸R⁷⁹;
-(CH₂)_pC(=NOR⁵⁰)NR⁷⁸R⁷⁹;
-(CH₂)_pC(=NNR⁷⁸R⁷⁹)NR⁷⁸R⁷⁹; -(CH₂)_pNR⁸⁰C(=NR⁸⁰)NR⁷⁸R⁷⁹;
-(CH₂)_pN=C(NR⁷⁸R⁸⁰)NR⁷⁹R⁸⁰; -(CH₂)_pC₆H₄NR⁷⁸R⁷⁹;
35 -(CH₂)_pC₆H₄NR⁷⁷R⁸⁰;
-(CH₂)_pC₆H₄C(=NR⁸⁰)NR⁷⁸R⁷⁹; -(CH₂)_pC₆H₄C(=NOR⁵⁰)NR⁷⁸R⁷⁹;

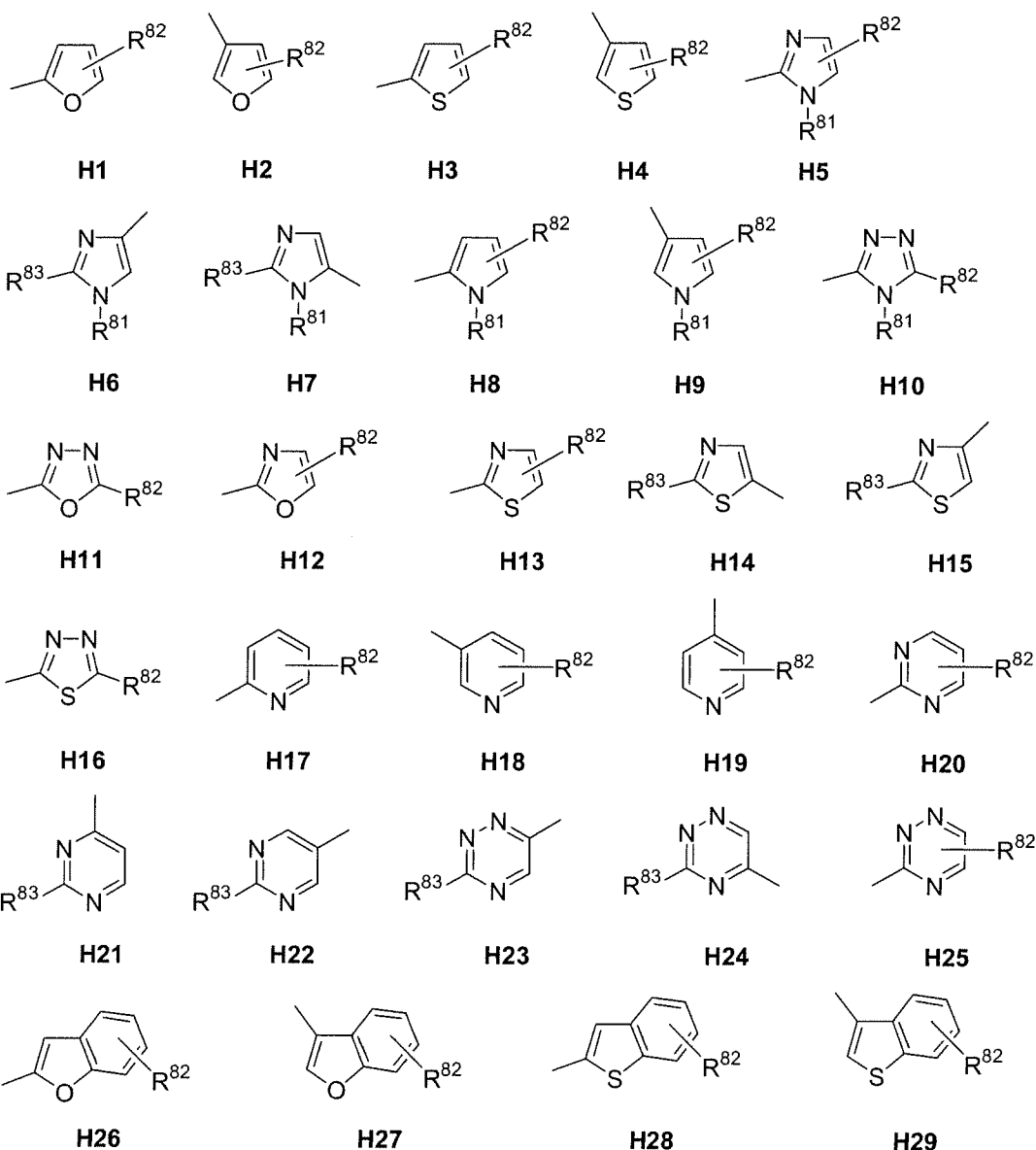
- $-(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NNR}^{78}\text{R}^{79})\text{NR}^{78}\text{R}^{79}$; $-(\text{CH}_2)_p\text{C}_6\text{H}_4\text{NR}^{80}\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_p\text{C}_6\text{H}_4\text{N}=\text{C}(\text{NR}^{78}\text{R}^{80})\text{NR}^{79}\text{R}^{80}$; $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_m\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_m\text{NR}^{77}\text{R}^{80}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$; $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}(=\text{NOR}^{50})\text{NR}^{78}\text{R}^{79}$;
5 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}(=\text{NNR}^{78}\text{R}^{79})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_m\text{NR}^{80}\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_m\text{N}=\text{C}(\text{NR}^{78}\text{R}^{80})\text{NR}^{79}\text{R}^{80}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{CNR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$;
10 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NOR}^{50})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NNR}^{78}\text{R}^{79})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{NR}^{80}\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$; $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_m\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_m\text{NR}^{77}\text{R}^{80}$; $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}(=\text{NOR}^{50})\text{NR}^{78}\text{R}^{79}$;
15 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}(=\text{NNR}^{78}\text{R}^{79})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_m\text{NR}^{80}\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_m\text{N}=\text{C}(\text{NR}^{78}\text{R}^{80})\text{NR}^{79}\text{R}^{80}$;
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{CNR}^{78}\text{R}^{79}$; $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NOR}^{50})\text{NR}^{78}\text{R}^{79}$;
20 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{C}(=\text{NNR}^{78}\text{R}^{79})\text{NR}^{78}\text{R}^{79}$;
 $-(\text{CH}_2)_r\text{S}(\text{CH}_2)_p\text{C}_6\text{H}_4\text{NR}^{80}\text{C}(=\text{NR}^{80})\text{NR}^{78}\text{R}^{79}$; $-(\text{CH}_2)_p\text{NR}^{80}\text{COR}^{64}$;
 $-(\text{CH}_2)_p\text{NR}^{80}\text{COR}^{77}$;
 $-(\text{CH}_2)_p\text{NR}^{80}\text{CONR}^{78}\text{R}^{79}$; or $-(\text{CH}_2)_p\text{C}_6\text{H}_4\text{NR}^{80}\text{CONR}^{78}\text{R}^{79}$;
 R^{75} is lower alkyl; lower alkenyl; lower cycloalkyl;
25 lower-alkyl-aryl; or aryl-lower alkyl; or
 R^{33} and R^{75} taken together can form: $-(\text{CH}_2)_{2-6}-$; $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$;
 $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2-$; or $-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2-$; or
 R^{75} and R^{82} taken together can form: $-(\text{CH}_2)_{2-6}-$; $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$;
 $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2-$; or
30 $-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2-$;
 R^{76} is H; lower alkyl; lower alkenyl; lower cycloalkyl;
lower-alkyl-aryl; aryl-lower alkyl;
 $-(\text{CH}_2)_o\text{OR}^{72}$; $-(\text{CH}_2)_o\text{SR}^{72}$;
 $-(\text{CH}_2)_o\text{NR}^{33}\text{R}^{34}$; $-(\text{CH}_2)_o\text{OCONR}^{33}\text{R}^{75}$; $-(\text{CH}_2)_o\text{NR}^{20}\text{CONR}^{33}\text{R}^{81}$;

$-(\text{CH}_2)_o\text{COOR}^{75}$; $-(\text{CH}_2)_o\text{CONR}^{58}\text{R}^{59}$; $-(\text{CH}_2)_o\text{PO}(\text{OR}^{60})_2$;

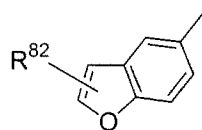
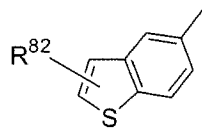
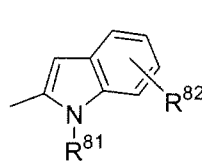
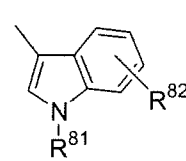
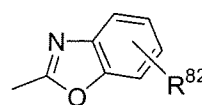
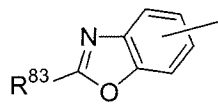
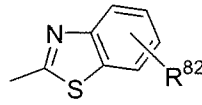
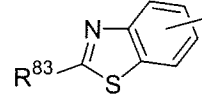
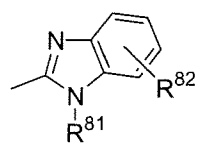
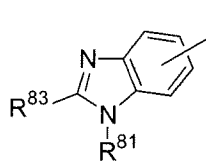
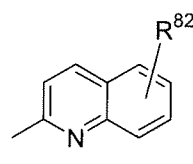
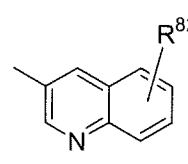
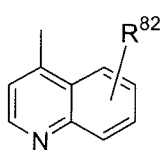
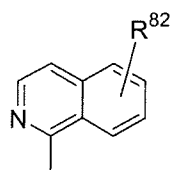
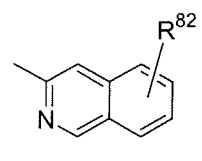
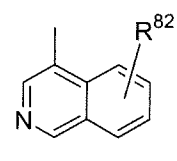
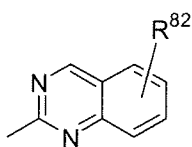
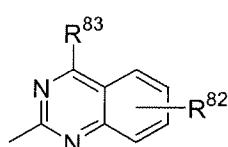
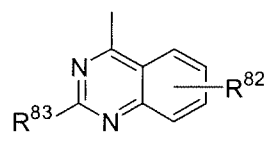
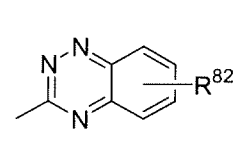
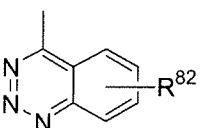
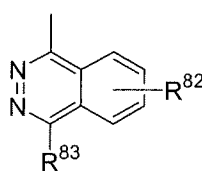
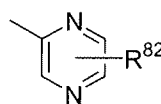
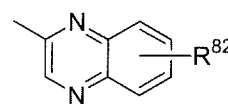
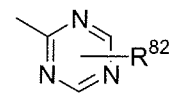
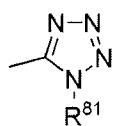
$-(\text{CH}_2)_p\text{SO}_2\text{R}^{62}$; or

$-(\text{CH}_2)_o\text{COR}^{64}$;

R^{77} is $-\text{C}_6\text{R}^{67}\text{R}^{68}\text{R}^{69}\text{R}^{70}\text{R}^{76}$ with the proviso that at least two of R^{67} ,
 5 R^{68} , R^{69} and R^{70} are H; or a heteroaryl group of one of the formulae



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**H30****H31****H32****H33****H34****H35****H36****H37****H38****H39****H40****H41****H42****H43****H44****H45****H46****H47****H48****H49****H50****H51****H52****H53****H54****H55**

- R^{78} is H; lower alkyl; lower cycloalkyl; lower alkyl-aryl;
aryl; or aryl-lower alkyl; or
 R^{78} and R^{82} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;
- 5 R^{79} is H; lower alkyl; lower alkyl-aryl; aryl; or
aryl-lower alkyl; or
 R^{78} and R^{79} , taken together, can be $-(CH_2)_{2-7}-$; $-(CH_2)_2O(CH_2)_2-$;
or $-(CH_2)_2NR^{57}(CH_2)_2-$;
- R^{80} is H; or lower alkyl;
- 10 R^{81} is H; lower alkyl; lower cycloalkyl; lower alkyl-aryl; or
aryl-lower alkyl; or
 R^{33} and R^{81} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;
- R^{82} is H; $-CF_3$; $-OCF_3$; $-OCHF_2$; lower alkyl; aryl; heteroaryl;
15 or aryl-lower alkyl;
- R^{83} is H; lower alkyl; aryl; or $-NR^{78}R^{79}$;
- R^{84} is $-(CH_2)_p(CHR^{61})_sOH$; $-(CH_2)_pCOOR^{80}$; $-(CH_2)_p(CHR^{61})_sSH$;
 $-(CH_2)_pCONR^{78}R^{79}$; $-(CH_2)_pNR^{80}CONR^{78}R^{79}$; $-(CH_2)_pC_6H_4CONR^{78}R^{79}$;
or $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;
- 20 R^{85} is lower alkyl; or lower alkenyl;
- R^{86} is R^{74} ; $-(CH_2)_oR^{77}$; $-(CH_2)_o-CHR^{33}R^{75}$; R^{84} ;
 $-(CH_2)_u-X']_t-(CH_2)_vNR^{78}R^{79}$;
 $-(CH_2)_u-X']_t-(CH_2)_v-C(=NR^{80})NR^{78}R^{79}$;
 $-(CH_2)_u-X']_t-(CH_2)_vOR^{78}$; $-(CH_2)_u-X']_t-(CH_2)_v-CONR^{78}R^{79}$;
25 $-(CH_2)_u-X']_t-(CH_2)_v-NR^{80}CONR^{78}R^{79}$; $-(CH_2)_u-X']_t-(CH_2)_vSR^{78}$
where X' is $-O-$, $-NR^{20}-$, $-S-$; or $-OCOO-$, u is 1-3, t is
1-6, and v is 1-3;

- m is 2-4; o is 0-4; p is 1-4; q is 0-2; r is 1 or 2; s is 0
30 or 1;

the amino acid residue of type C is a residue of formula
 $-NR^{20}CH(R^{72})CO-$;

- the amino acid residue of type D is a residue of formula
35 $-NR^{20}CH(R^{73})CO-$;

the amino acid residue of type E is a residue of the formula

$-\text{NR}^{20}\text{CH}(\text{R}^{74})\text{CO}-$;

the amino acid residue of type F is a residue of the formula

$-\text{NR}^{20}\text{CH}(\text{R}^{84})\text{CO}-$;

- 5 the amino acid residue of type H is a residue of the one of the formulae $-\text{NR}^{20}-\text{CH}(\text{CO}-)-\text{alkylene}-\text{CH}(\text{CO}-)-\text{NR}^{20}-$;
 $-\text{NR}^{20}-\text{CH}(\text{CO}-)-\text{alkenylene}-\text{CH}(\text{CO}-)-\text{NR}^{20}-$;
 $-\text{NR}^{20}-\text{CH}(\text{CO}-)-\text{alkynylene}-\text{CH}(\text{CO}-)-\text{NR}^{20}-$;
 $-\text{NR}^{20}-\text{CH}(\text{CO}-)-(\text{CH}_2)_p\text{SS}(\text{CH}_2)_p-\text{CH}(\text{CO}-)-\text{NR}^{20}-$;
 10 $-\text{NR}^{20}-\text{CH}(\text{CO}-)-(-(\text{CH}_2)_p\text{NR}^{20}\text{CO}(\text{CH}_2)_p-\text{CH}(\text{CO}-)-\text{NR}^{20}-$; and
 $-\text{NR}^{20}-\text{CH}(\text{CO}-)-(-(\text{CH}_2)_p\text{NR}^{20}\text{CONR}^{20}(\text{CH}_2)_p-\text{CH}(\text{CO}-)-\text{NR}^{20}-$;

non-canonical amino acid residues designate those amino acid residues being neither glycine nor the L- or D-isomers of

- 15 alanine, arginine, aspartic acid, asparagine, cysteine, glutamic acid, glutamine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine;

- 20 and pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1 wherein A is a group of one of the formulae A1-A69;

- R^1 is hydrogen or lower alkyl;

- 25 - R^2 is H; lower alkyl; lower alkenyl;

$-(\text{CH}_2)_p\text{OR}^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);

$-(\text{CH}_2)_p\text{SR}^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);

$-(\text{CH}_2)_p\text{NR}^{33}\text{R}^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken

- 30 together form: $-(\text{CH}_2)_{2-6}-$; $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$;

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

$-(\text{CH}_2)_p\text{OCONR}^{33}\text{R}^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken

- 35 together form: $-(\text{CH}_2)_{2-6}-$; $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$;
 $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2-$; or $-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2-$ (where R^{57} : H; or

- lower alkyl);
- 5 $-(CH_2)_pNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- 10 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 15 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : H; lower alkyl; or lower alkenyl);
- $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl);
- 20 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy); or
- $-(CH_2)_qCHN_4R^8$.
- R^3 is H; lower alkyl; lower alkenyl;
- $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- 25 $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 30 $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 35 $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} :

- H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower alkyl; or R³³ and R⁸¹ 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);
- 5 -(CH₂)₆N(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl);
- (CH₂)₆COOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl);
- 10 -(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);
- 15 -(CH₂)₆SO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or
- (CH₂)₄C₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
- 20 - R⁴ is H; lower alkyl; lower alkenyl;
- (CH₂)_mOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
- (CH₂)_mSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
- (CH₂)_mNR³³R³⁴ (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-;
- 25 -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_mOCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ taken together form: -(CH₂)₂₋₆-; -(CH₂)₂O(CH₂)₂-;
- 30 -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_mNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³: H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower alkyl; or R³³ and R⁸¹ taken together form: -(CH₂)₂₋₆-;
- 35 -(CH₂)₂O(CH₂)₂-; -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂-

- (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- 5 $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 10 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
- 15 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^5 is lower alkyl; lower alkenyl;
- $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_mSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- 20 $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 25 $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 30 $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 35 $-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : alkyl; alkenyl; aryl; aryl-lower alkyl; or

- heteroaryl-lower alkyl);
- (CH₂)_oCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl);
- (CH₂)_oCONR⁵⁸R⁵⁹ (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)_oPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl);
- (CH₂)_oSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or
- (CH₂)_qC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
- 15 - R⁶ is H; lower alkyl; lower alkenyl;
- (CH₂)_oOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
- (CH₂)_oSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
- (CH₂)_oNR³³R³⁴ (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);
- 20 -(CH₂)_oCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ 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);
- 25 -(CH₂)_oNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³: H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower alkyl; or R³³ and R⁸¹ 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);
- 30 -(CH₂)_oN(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl);
- 35 -(CH₂)_oCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl);

- $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
- $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- $-R^7$ is lower alkyl; lower alkenyl;
- $-(CH_2)_qOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_qSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- $-(CH_2)_qNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_qOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_qNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_qN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- $-(CH_2)_rCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- $-(CH_2)_qCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;

- (CH₂)₂S(CH₂)₂-; or - (CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_rPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl);
- 5 - (CH₂)_rSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or
- (CH₂)_qC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
- R⁸ is H; F; Cl; CF₃; lower alkyl; lower alkenyl;
- 10 - (CH₂)_oOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
- (CH₂)_oSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
- (CH₂)_oNR³³R³⁴ (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-;
- 15 - (CH₂)₂S(CH₂)₂-; or - (CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_oOCONR³³R⁷⁵ (where R³³: H; ~~or~~ lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ taken together form: - (CH₂)₂₋₆-; - (CH₂)₂O(CH₂)₂-;
- 20 - (CH₂)₂S(CH₂)₂-; or - (CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_oNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³: H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower alkyl; or R³³ and R⁸¹ taken together form: - (CH₂)₂₋₆-;
- 25 - (CH₂)₂O(CH₂)₂-; - (CH₂)₂S(CH₂)₂-; or - (CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_oN(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl);
- (CH₂)_oCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl);
- 30 - (CH₂)_oCONR⁵⁸R⁵⁹ (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);
- 35 - (CH₂)_oPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower

- alkenyl);
- (CH₂)_oSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or
- (CH₂)_qC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
- 5 - R⁹ is lower alkyl; lower alkenyl;
- (CH₂)_oOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
- (CH₂)_oSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
- (CH₂)_oNR³³R³⁴ (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);
- 10 - (CH₂)_oOCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ 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);
- 15 - (CH₂)_mNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³: H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower alkyl; or R³³ and R⁸¹ 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);
- 20 - (CH₂)_oN(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl);
- 25 - (CH₂)_oCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl);
- (CH₂)_oCONR⁵⁸R⁵⁹ (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);
- 30 - (CH₂)_oPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl);
- 35 - (CH₂)_oSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or

- (CH₂)_qC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
- R¹⁰ is lower alkyl; lower alkenyl;
- (CH₂)_oOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
- 5 - (CH₂)_oSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
- (CH₂)_oNR³³R³⁴ (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);
- 10 - (CH₂)_oOCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ 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);
- 15 - (CH₂)_oNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³: H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower alkyl; or R³³ and R⁸¹ 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);
- 20 - (CH₂)_oN(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl);
- (CH₂)_oCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl);
- 25 - (CH₂)_oCONR⁵⁸R⁵⁹ (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);
- 30 - (CH₂)_oPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl);
- (CH₂)_oSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or
- (CH₂)_qC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
- 35

- R¹¹ is H; lower alkyl; lower alkenyl;
- (CH₂)_mOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
- (CH₂)_mSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
- (CH₂)_mNR³³R³⁴ (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)_mCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ 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)_mNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³: H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower alkyl; or R³³ and R⁸¹ 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)_mN(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl);
- (CH₂)_oCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl);
- (CH₂)_oCONR⁵⁸R⁵⁹ (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)_oPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl);
- (CH₂)_oSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or
- (CH₂)_qC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
- R¹² is H; lower alkyl; lower alkenyl;
- (CH₂)_mOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
- (CH₂)_mSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);

- $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- $-(CH_2)_rCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- $-(CH_2)_rCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
- $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- $-R^{13}$ is lower alkyl; lower alkenyl;
- $-(CH_2)_qOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_qSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- $-(CH_2)_qNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;

- $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_qOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
5 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_qNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
10 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_qN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
15 $-(CH_2)_rCOO^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
 $-(CH_2)_qCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
20 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
 $-(CH_2)_rSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
25 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{14} is H; lower alkyl; lower alkenyl;
 $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
30 $-(CH_2)_mSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
 $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
35 $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower

- alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 5 $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 10 $-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} : H; lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 15 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- 20 $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl);
 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- 25 $-R^{15}$ is lower alkyl; lower alkenyl;
 $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 30 $-(CH_2)_oCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 35 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);

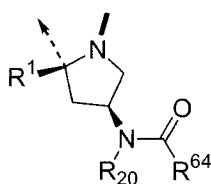
- lower alkyl);
- 5 $-(CH_2)_oNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 10 $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); particularly favoured being $-NR^{20}CO$ -lower alkyl (where R^{20} : H; or lower alkyl);
- $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- 15 $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- 20 $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
- $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{16} is lower alkyl; lower alkenyl;
- 25 $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
- 30 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
- 35 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);

- $-(CH_2)_oNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
- $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- $-R^{17}$ is lower alkyl; lower alkenyl;
- $-(CH_2)_qOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_qSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- $-(CH_2)_qNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_qOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_qNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;

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- $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$
 (where R^{57} : H; or lower alkyl);
 $-(CH_2)_qN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} :
 lower alkyl; or lower alkenyl);
 5 $-(CH_2)_rCOOR^{57}$ (where R^{57} : lower alkyl; or lower
 alkenyl);
 $-(CH_2)_qCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower
 alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59}
 taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 10 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 lower alkyl);
 $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower
 alkenyl);
 $-(CH_2)_rSO_2R^{62}$ (where R^{62} : lower alkyl; or lower
 15 alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl;
 lower alkenyl; or lower alkoxy).

3. Compounds according to claim 1 or 2 wherein A is a group
 20 of formula

**A8'**

wherein R^{20} is H or lower alkyl; and R^{64} is alkyl; alkenyl;
 25 aryl; aryl-lower alkyl; or heteroaryl-lower alkyl;
 especially those wherein R^{64} is n-hexyl (**A8'-1**); n-heptyl
 (**A8'-2**); 4-(phenyl)benzyl (**A8'-3**); diphenylmethyl (**A8'-4**);
 3-amino-propyl (**A8'-5**); 5-amino-pentyl (**A8'-6**); methyl
 (**A8'-7**); ethyl (**A8'-8**); isopropyl (**A8'-9**); isobutyl
 30 (**A8'-10**); n-propyl (**A8'-11**); cyclohexyl (**A8'-12**);
 cyclohexylmethyl (**A8'-13**); n-butyl (**A8'-14**); phenyl

(A8'-15); benzyl (A8'-16); (3-indolyl)methyl (A8'-17);
2-(3-indolyl)ethyl (A8'-18); (4-phenyl)phenyl (A8'-19); and
n-nonyl (A8'-20).

- 5 4. Compounds according to claim 1 wherein A is a group of
one of the formulae A70 to A104;
-R¹⁸ is lower alkyl.
-R¹⁹ is lower alkyl; lower alkenyl;
- (CH₂)_pOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
10 - (CH₂)_pSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
- (CH₂)_pNR³³R³⁴ (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
15 lower alkyl);
- (CH₂)_pOCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower
alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ taken
together form: - (CH₂)₂₋₆-; - (CH₂)₂O (CH₂)₂-;
- (CH₂)₂S (CH₂)₂-; or - (CH₂)₂NR⁵⁷ (CH₂)₂- (where R⁵⁷: H; or
20 lower alkyl);
- (CH₂)_pNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³:
H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower
alkyl; or R³³ and R⁸¹ taken together form: - (CH₂)₂₋₆-;
- (CH₂)₂O (CH₂)₂-; - (CH₂)₂S (CH₂)₂-; or - (CH₂)₂NR⁵⁷ (CH₂)₂-
25 (where R⁵⁷: H; or lower alkyl);
- (CH₂)_pN(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴:
lower alkyl; or lower alkenyl);
- (CH₂)_pCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower
alkenyl);
30 - (CH₂)_pCONR⁵⁸R⁵⁹ (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);
35 - (CH₂)_oPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower
alkenyl);

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- $-(CH_2)_pSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
 $-(CH_2)_oC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- 5 $-R^{21}$ is H; lower alkyl; lower alkenyl;
 $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken
- 10 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken
- 15 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower
- 20 alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- 25 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 30 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower
- 35 alkenyl); or

- $-(CH_2)_q C_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- $-R^{22}$ is lower alkyl; lower alkenyl;
- $-(CH_2)_o OR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_o SR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- $-(CH_2)_o NR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_o OCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_o NR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_o N(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- $-(CH_2)_o COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- $-(CH_2)_o CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- $-(CH_2)_o PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- $-(CH_2)_o SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
- $-(CH_2)_q C_6H_4R^8$ (where R^8 : H; F; Cl; CF; lower alkyl; lower alkenyl; or lower alkoxy).

- R²³ is H; lower alkyl; lower alkenyl;
 -(CH₂)_oOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
 -(CH₂)_oSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
 -(CH₂)_oNR³³R³⁴ (where R³³: lower alkyl; or lower
 5 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)_oOCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower
 10 alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ 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)_oNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³:
 15 H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower
 alkyl; or R³³ and R⁸¹ 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)_oN(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴:
 20 lower alkyl; or lower alkenyl); particularly favoured
 are NR²⁰CO-lower alkyl (where R²⁰: H; or lower alkyl);
 -(CH₂)_oCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower
 alkenyl);
 -(CH₂)_oCONR⁵⁸R⁵⁹ (where R⁵⁸: lower alkyl, or lower
 25 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)_oPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower
 30 alkenyl);
 -(CH₂)_oSO₂R⁶² (where R⁶²: lower alkyl; or lower
 alkenyl); or
 -(CH₂)_qC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl;
 lower alkenyl; or lower alkoxy).
 35 -R²⁴ is lower alkyl; lower alkenyl;
 -(CH₂)_oOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);

- $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
5 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
10 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
15 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); particularly favoured are $NR^{20}CO$ -lower alkyl (where R^{20} : H; or lower alkyl);
20 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
25 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
30 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
 $-R^{25}$ is H; lower alkyl; lower alkenyl;
 $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
35 $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken

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together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 lower alkyl);
 $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower
 5 alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken
 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 lower alkyl);
 $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} :
 10 H; lower alkyl; or lower alkenyl; R^{81} : H; or lower
 alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$
 (where R^{57} : H; or lower alkyl);
 $-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} :
 15 lower alkyl; or lower alkenyl);
 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower
 alkenyl);
 $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower
 alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59}
 20 taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 lower alkyl);
 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower
 alkenyl);
 25 $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower
 alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl;
 lower alkenyl; or lower alkoxy).
 $-R^{26}$ is H; lower alkyl; lower alkenyl;
 30 $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
 $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower
 alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken
 together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 35 lower alkyl);
 $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower

- alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 5 $-(CH_2)_mNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 10 $-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 15 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy); or, alternatively,
- 20 $-R^{25}$ and R^{26} taken together can be $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl).
- $-R^{27}$ is H; lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- 30 $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 35 $-(CH_2)_oCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower

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- alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 5 $-(CH_2)_oNR^{20}CONR^{33}R^{81}$ (where R^{20} : H; or lower alkyl; R^{33} : H; lower alkyl; or lower alkenyl; R^{81} : H; or lower alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 10 $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 15 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl);
- 20 $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
- $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- 25 $-R^{28}$ is lower alkyl; lower alkenyl;
- $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl);
- $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 30 $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} : H; lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or lower alkyl);
- 35 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or

- lower alkyl);
- (CH₂)_oNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³: H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower alkyl; or R³³ and R⁸¹ taken together form: -(CH₂)₂₋₆-;
- 5 -(CH₂)₂O(CH₂)₂-; -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂- (where R⁵⁷: H; or lower alkyl);
- (CH₂)_oN(R²⁰)COR⁶⁴ (where R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl);
- (CH₂)_oCOOR⁵⁷ (where R⁵⁷: lower alkyl; or lower
- 10 alkenyl);
- (CH₂)_oCONR⁵⁸R⁵⁹ (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
- 15 lower alkyl);
- (CH₂)_oPO(OR⁶⁰)₂ (where R⁶⁰: lower alkyl; or lower alkenyl);
- (CH₂)_oSO₂R⁶² (where R⁶²: lower alkyl; or lower alkenyl); or
- 20 -(CH₂)_qC₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
- R²⁹ is lower alkyl; lower alkenyl;
- (CH₂)_oOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl);
- (CH₂)_oSR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl);
- 25 -(CH₂)_oNR³³R³⁴ (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);
- 30 -(CH₂)_oOCONR³³R⁷⁵ (where R³³: H; lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ 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);
- 35 -(CH₂)_oNR²⁰CONR³³R⁸¹ (where R²⁰: H; or lower alkyl; R³³: H; lower alkyl; or lower alkenyl; R⁸¹: H; or lower

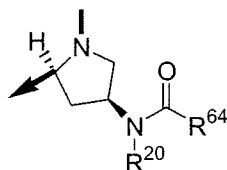
alkyl; or R^{33} and R^{81} taken together form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$
 (where R^{57} : H; or lower alkyl);
 $-(CH_2)_6N(R^{20})COR^{64}$ (where R^{20} : H; or lower alkyl; R^{64} :
 5 lower alkyl; or lower alkenyl); particularly favored
 are $NR^{20}CO$ -lower-alkyl (where R^{20} : H; or lower alkyl);
 $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower
 alkenyl);
 $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower
 10 alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59}
 taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$ (where R^{57} : H; or
 lower alkyl);
 $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower
 15 alkenyl);
 $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower
 alkenyl); or
 $-(CH_2)_6C_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl;
 lower alkenyl; or lower alkoxy).

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5. Compounds according to any one of claims 1 to 4 wherein
 B is a group of formula $-NR^{20}CH(R^{71})-$, or $-NR^{20}CH(R^{72})-$, or
 $-NR^{20}CH(R^{73})-$, or $-NR^{20}CH(R^{74})-$, or $-NR^{20}CH(R^{84})-$, or an
 enantiomer of one of the groups A5 (with R^2 being H); A8;
 25 A22; A25; A38 (with R^2 being H); A42; A47 and A50.

6. Compounds according to claim 5 wherein B-CO is Ala; Arg;
 Asn; Asp; Cys; Gln; Glu; Gly; His; Ile; Leu; Lys; Met; Phe;
 Pro; Ser; Thr; Trp; Tyr; Val; Cit; Orn; tBuA; Sar; t-BuG;
 30 4AmPhe; 3AmPhe; 2AmPhe; Phe(mC(NH₂)=NH); Phe(pC(NH₂)=NH);
 Phe(mNHC(NH₂)=NH); Phe(pNHC(NH₂)=NH); Phg; Cha; C₄al; C₅al;
 Nle; 2-Nal; 1-Nal; 4Cl-Phe; 3Cl-Phe; 2Cl-Phe; 3,4Cl₂Phe;
 4F-Phe; 3F-Phe; 2F-Phe; Tic; Thi; Tza; Mso; AcLys; Dpr; A₂Bu;
 Dbu; Abu; Aha; Aib; Y(Bzl); Bip; S(Bzl); T(Bzl); hCha; hCys;
 35 hSer, hArg; hPhe; Bpa; Pip; MePhe; MeNle; MeAla; MeIle;
 MeVal; MeLeu; 4Hyp1; 4Hyp2; 4Mp1; 4Mp2.

7. Compounds according to any one of the claim 1 to 4 wherein B is a group, having (L)-configuration, of formula



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A8''

wherein R^{20} is H or lower alkyl and R^{64} is alkyl; alkenyl; $-(CH_2)_u-X]_t-CH_3$ (where X is -O-, $-NR^{20}-$, or -S-; $u = 1-3$, and $t = 1-6$), 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**); cyclohexyl-methyl (**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**); $CH_3-OCH_2CH_2-OCH_2-$ (**A8'''-41**) and $CH_3-(OCH_2CH_2)_2-OCH_2-$ (**A8'''-42**).

8. Compounds according to claim 1 wherein Xaa^{13} is DPro , DCha , NMe^DIle , DTyr , DHis , $^DHis(Bzl)$, D4Pal , NMe^DTyr , NMe^DLys , $(ABu)G$, DIle , NMe^DAla , DLys , or DDab ; Xaa^{14} is LPro ; the aforesaid DPro moiety and/or the aforesaid LPro moiety being optionally substituted as shown in formulae A8' and, respectively, A8'', as defined in claim 3 and, respectively, in claim 7.

9. Compounds according to claim 1 wherein the amino acid residues in $Cyclo(-Xaa^1-Xaa^2-Xaa^3-Xaa^4-Xaa^5-Xaa^6-Xaa^7-Xaa^8-Xaa^9-Xaa^{10}-Xaa^{11}-Xaa^{12}-Xaa^{13}-Xaa^{14}-)$ are:

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- Xaa¹: Trp;
- Xaa²: Arg, Dab or Orn;
- Xaa³: Ile;
- Xaa⁴: Arg, Dab or Orn;
- 5 - Xaa⁵: Ile;
- Xaa⁶: ^DArg, Dab, ^DDab, Orn;
- Xaa⁷: Asn, Gln, Thr, Leu or Tyr;
- Xaa⁸: Lys, Gln, Trp or His;
- Xaa⁹: Arg or Dab;
- 10 - Xaa¹⁰: Asn, Leu, Cha, Tyr or Trp;
- Xaa¹¹: Arg or Gln;
- Xaa¹²: Arg, Dab, Ala or Gln;
- Xaa¹³: DPro;
- Xaa¹⁴: LPro;

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10. A compound according to claim 1 wherein the amino acid residues are:

- Xaa¹: Trp;
- Xaa²: Arg;
- 20 - Xaa³: Ile;
- Xaa⁴: Arg;
- Xaa⁵: Ile;
- Xaa⁶: ^DArg;
- Xaa⁷: Asn;
- 25 - Xaa⁸: Lys;
- Xaa⁹: Arg;
- Xaa¹⁰: Leu;
- Xaa¹¹: Arg;
- Xaa¹²: Gln;
- 30 - Xaa¹³: ^DPro;
- Xaa¹⁴: ^LPro;

or wherein the amino acid residues are:

- Xaa¹: Trp;
- Xaa²: Dab;
- 35 - Xaa³: Ile;
- Xaa⁴: Arg;

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5 - Xaa⁵: Ile;
 - Xaa⁶: ^DArg;
 - Xaa⁷: Asn;
 - Xaa⁸: Gln;
 - Xaa⁹: Arg;
 - Xaa¹⁰: Leu;
 - Xaa¹¹: Gln;
 - Xaa¹²: Ala;
 - Xaa¹³: ^DPro;
10 - Xaa¹⁴: ^LPro;

or wherein the amino acid residues are:

 - Xaa¹: Trp;
 - Xaa²: Arg;
 - Xaa³: Ile;
15 - Xaa⁴: Arg;
 - Xaa⁵: Ile;
 - Xaa⁶: ^DArg;
 - Xaa⁷: Asn;
 - Xaa⁸: Gln;
20 - Xaa⁹: Arg;
 - Xaa¹⁰: Trp;
 - Xaa¹¹: Gln;
 - Xaa¹²: Ala;
 - Xaa¹³: ^DPro;
25 - Xaa¹⁴: ^LPro;

or wherein the amino acid residues are:

 - Xaa¹: Trp;
 - Xaa²: Arg;
 - Xaa³: Ile;
30 - Xaa⁴: Arg;
 - Xaa⁵: Ile;
 - Xaa⁶: ^DDab;
 - Xaa⁷: Asn;
 - Xaa⁸: Trp;
35 - Xaa⁹: Dab;
 - Xaa¹⁰: Asn;

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- Xaa¹¹: Arg;
- Xaa¹²: Dab;
- Xaa¹³: ^DPro;
- Xaa¹⁴: ^LPro;

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11. Enantiomers of the compounds as defined in claim 1.

12. Compounds according to any one of claims 1 to 11 for use as therapeutically active substances, particularly as
10 substances having selective anti-infective activity, especially as substances having selective antibacterial activity against *Bacillus subtilis* and/or *Shigella boydii*.

13. A pharmaceutical composition containing a compound
15 according to any one of claims 1 to 11 and a pharmaceutically inert carrier, particularly in a form suitable for oral, topical, transdermal, injection, buccal, transmucosal, pulmonary or inhalation administration such as tablets, dragees, capsules, solutions, liquids, gels,
20 plaster, creams, ointments, syrup, slurries, suspensions, spray, nebuliser or suppositories.

14. The use of compounds according to any one of claims 1 to 11 for the manufacture of a medicament, particularly
25 intended to be used for preventing or treating infections or diseases related to such infections, particularly infections related to respiratory diseases or skin or soft tissue diseases or gastrointestinal diseases or eye diseases or ear diseases or CNS diseases or bone diseases or cardiovascular
30 diseases or gastrourinal diseases, liver diseases, sexually transmitted diseases or diseases such as common cold, influenza, parotitis or gingivostomatitis, or as a disinfectants or preservatives for foodstuffs, cosmetics, medicaments and other nutrient-containing materials.

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15. A process for the manufacture of compounds according to any one of claims 1-10 which process comprises

- 5 (a) coupling an appropriately functionalized solid support with an appropriately N-protected derivative of that amino acid which in the desired end-product corresponds to Xaa^n , wherein n is 14, 13, 12, 7, 6 or 5, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
- 10 (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 corresponds to Xaa^{n-1} ,
15 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 obtained in step (c);
- 20 (e) effecting steps substantially corresponding to steps (c) and (d) using appropriately N-protected derivatives of amino acids which in the desired end-product are in positions n-2 to 1, any functional group(s) which may be present in said N-protected amino acid derivatives
25 being likewise appropriately protected;
- (f) if n is not 14, further effecting steps substantially corresponding to steps (c) and (d) using appropriately N-protected derivatives of amino acids which in the desired end-product are in positions 14 to n + 1, any
30 functional group(s) which may be present in said N-protected amino acid derivatives being likewise appropriately protected;
- (g) forming an interstrand linkage between side-chains of appropriate amino acid residues at P2 and P11; or
35 alternatively, forming the aforesaid linkage subsequent to step (j), as described herein below;

- (h) detaching the product thus obtained from the solid support;
- (i) cyclizing the product cleaved from the solid support;
- (j) 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
- (k) 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 or into a different, pharmaceutically acceptable, salt.

16. A modification of the processes according to claim 15 for the manufacture of compounds according to claim 14 in which enantiomers of all chiral starting materials are used.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/061445

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K14/435

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ROBINSON J A ET AL: "Properties and structure-activity studies of cyclic beta-hairpin peptidomimetics based on the cationic antimicrobial peptide protegrin I", BIOORGANIC & MEDICINAL CHEMISTRY, PERGAMON, GB, vol. 13, no. 6, 15 March 2005 (2005-03-15) , pages 2055-2064, XP004759006, ISSN: 0968-0896, DOI: DOI:10.1016/J.BMC.2005.01.009 page 2055 ----- -/--	1-16



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

14 December 2010

Date of mailing of the international search report

22/12/2010

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/061445

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 2007/079597 A1 (POLYPHOR LTD [CH]; UNIV ZUERICH [CH]; ROBINSON JOHN ANTHONY [CH]; SRIN) 19 July 2007 (2007-07-19) claims 1-41 -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/061445

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