TEMPLATE-FIXED PEPTIDOMIMETICS WITH ANTIMICROBIAL ACTIVITY

The present invention provides template-fixed β-hairpin peptidomimetics incorporating template-fixed chains of 8 to 16 α-amino acid residues which, depending on their positions in the chains, are Gly or Pro, or of certain types, as defined hereinbelow. These template-fixed β-hairpin mimetics have broad spectrum antimicrobial and anticancer activity. 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 improved efficacy, bioavailability, half-life and most importantly a significantly enhanced ratio between antibacterial and anticancer activity on the one hand, and hemolysis of red blood cells on the other.

The growing problem of microbial resistance to established antibiotics has stimulated intense interest in developing novel antimicrobial agents with new modes of action (H. Breithaupt, *Nat. Biotechnol.* **1999**, *17*, 1165-1169). One emerging class of antibiotics is based on naturally 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.. M.; 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, Y. *J. Biol. Chem.* **1988**, *263*, 16709-16713], and the *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-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 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).

The antimicrobial activities of many of these cationic peptides usually correlate with their preferred secondary structures, observed either in aqueous solution or in membrane-like environments (N. Sitaram, R. Nagaraj, *Biochim. Biophys. Acta* **1999**, *1462*, 29-54). Structural studies by nuclear magnetic resonance (NMR) spectroscopy have shown that cationic peptides such as protegrin 1 (A. Aumelas, M. Mangoni, C. Roumestand, L. Chiche, E. Despaux, G. Grassy, B. Calas, A. Chavanieu, A. *Eur. J. Biochem.* **1996**, *237*, 575-583; R. L. Fahrner, T. Dieckmann, S. S. L. Harwig, R. I. Lehrer, D. Eisenberg, J. Feigon, J. *Chem. Biol.* **1996**, *3*, 543-550) and tachyplesin I (K. Kawano, T. Yoneya, T. Miyata, K. Yoshikawa, F. Tokunaga, Y. Terada, S. J. Iwanaga, S. *J. Biol. Chem.* **1990**, *265*, 15365-15367) adopt well defined β-hairpin conformations, due to the constraining effect of two disulfide bridges. In protegrin analogues lacking one or both of these disulfide bonds, the stability of the ß-hairpin conformation is diminished, and the antimicrobial activity is reduced (J. Chen, T. J. Falla, H. J. Liu, M. A. Hurst, C. A. Fujii, D. A. Mosca, J. R. EmbreeD. J. Loury, P. A. Radel, C. C. Chang, L. Gu, J. C. Fiddes, *Biopolymers* **2000**, *55*, 88-98; S. L. Harwig, A. Waring, H. J. Yang, Y. Cho, L. Tan, R. I. Lehrer, R. J. *Eur. J. Biochem.* **1996**, *240*, 352-357; M. E. Mangoni, A. Aumelas, P. Charnet, C. Roumestand, L. Chiche, E. Despaux, G. Grassy, B. Calas, A. Chavanieu, *FEBS Lett.* **1996**, *383*, 93-98; H. Tamamura, T. Murakami, S. Noriuchi, K. Sugihara, A. Otaka, W. Takada, T. Ibuka, M. Waki, N. Tamamoto, N. Fujii, *Chem. Pharm. Bull.* **1995**, *43*, 853-858). Similar observations have been made in analogues of tachyplesin I (H. Tamamura, R. Ikoma, M. Niwa, S. Funakoshi, T. Murakami, N. Fujii, *Chem. Pharm. Bull.* **1993**, *41*, 978-980) and in hairpin-loop mimetics of rabbit defensin NP-2 (S. Thennarasu, R. Nagaraj, *Biochem. Biophys. Res. Comm.* **1999**, *254*, 281-283). These results show that the β-hairpin structure plays an important role in the antimicrobial activity and stability of these protegrin-like peptides. In the case of the cationic peptides preferring α-helical structures, the amphililic structure of the helix appears to play a key role in determining antimicrobial activity (A. Tossi, L. Sandri, A. Giangaspero, A. *Biopolymers* **2000**, *55*, 4-30). Gramicidin S is a backbone-cyclic peptide with a well defined β-hairpin structure (S. E. Hull, R. Karlsson, P. Main, M. M. Woolfson, E. J. Dodson, *Nature* **1978**, *275*, 206-275) that displays potent antimicrobial activity against gram-positive and gram-negative bacteria (L. H. Kondejewski, S. W. Farmer, D. S. Wishart, R. E. Hancock, R. S. Hodges, *Int. J. Peptide Prot. Res.* **1996**, *47*, 460-466). The high hemolytic activity of *gramicidin S* has, however, hindered its widespread use as an antibiotic. Recent structural studies by NMR have indicated that the high hemolytic activity apparently correlates with the highly amphipathic nature of this cyclic β-hairpin-like molecule, but that it is possible to dissociate antimicrobial and hemolytic activities by modulating the conformation and amphiphilicity (L. H. Kondejewski, M. Jelokhani-Niaraki, S. W. Farmer, B. Lix, M. Kay, B. D. Sykes, R. E. Hancock, R. S. Hodges,

J. Biol. Chem. **1999**, *274*, 13181-13192; C. McInnesL. H. Kondejewski, R. S. Hodges, B. D. Sykes, *J. Biol. Chem.* **2000**, *275*, 14287-14294).

A new cyclic antimicrobial peptide RTD-1 was reported recently from primate leukocytes (Y.-Q. Tang, J. Yuan, G. Ösapay, K. Ösapay, D. Tran, C. J. Miller, A. J. Oellette, M. E. Selsted, *Science* **1999**, *286*, 498-502. This peptide contains three disulfide bridges, which act to constrain the cyclic peptide backbone into a hairpin geometry. Cleavage of the three disulfide bonds leads to a significant loss of antimicrobial activity. Analogues of protegrins (J. P. Tam, C. Wu, J.-L. Yang, *Eur. J. Biochem.* **2000**, *267*, 3289-3300) and tachyplesins (J.-P. Tam, Y.-A. Lu, J.-L. Yang, *Biochemistry* **2000**, 39, 7159-7169; N. Sitaram, R. Nagaraij, *Biochem. Biophys. Res. Comm.* **2000**, *267*, 783-790) containing a cyclic peptide backbone, as well as multiple disulfide bridges to enforce a amphiphilic hairpin structure, have also been reported. In these cases, removal of all the cystine constraints does not always lead to a large loss of antimicrobial activity, but does modulate the membranolytic selectivity (J. P. Tam, C. Wu, J.-L. Yang, *Eur. J. Biochem.* **2000**, *267*, 3289-3300).

A key issue in the design of new cationic antimicrobial peptides is selectivity. The naturally occurring protegrins and tachyplesins exert a significant hemolytic activity against human red blood cells. This is also the case for protegrin analogues such as IB367 (J. Chen, T. J. Falla, H. J. Liu, M. A. Hurst, C. A. Fujii, D. A. Mosca, J. R. Embree, D. J. Loury, P. A. Radel, C. C. Chang, L. Gu, J. C. Fiddes, *Biopolymers* **2000**, *55*, 88-98; C. Chang, L. Gu, J. Chen, *US-Pat: 5,916,872*, **1999**). This high hemolytic activity essentially obviates its use in vivo, and represents a serious disadvantage in clinical applications. Also, the antibiotic activity of analogues often decreases significantly with increasing salt concentration, such that under in vivo conditions (ca. 100-150 mM NaCl) the antimicrobial activity may be severely reduced. Before intravenous use can be considered, the general toxicity, protein-binding activity in blood serum, as well as protease stability become serious issues which must be adequately addressed.

Protegrin 1 exhibits potent and similar activity against gram-positive and gram-negative bacteria as well as fungi in both low- and high-salt assays. This broad antimicrobial activity combined with a rapid mode of action, and their ability to kill bacteria resistant to other classes of antibiotics, make them attractive targets for development of clinically useful antibiotics. The activity against gram-positive bacteria is typically higher than against gram-negative bacteria. However, protegrin 1 also exhibits a high hemolytic activity against human red blood cells, and hence a low selectivity towards microbial cells. Oriented CD experiments (W. T. Heller, A. J. Waring, R. I. Lehrer, H. W. Huang, *Biochemistry* **1998**, *37*, 17331-17338) indicate that protegrin 1 may exist in two different states as it interacts with membranes, and

these states are strongly influenced by lipid composition. Studies of cyclic protegrin analogues (J.-P. Tam, C. Wu, J.-L. Yang, *Eur. J. Biochem.* **2000**, *267*, 3289-3300) have revealed, that an increase in the conformational rigidity, resulting from backbone cyclization and multiple disulfide bridges, may confer membranolytic selectivity that dissociates antimicrobial activity from hemolytic activity, at least in the series of compounds studied. *Protegrin I* is an 18 residues linear peptide, with an amidated carboxyl terminus and two disulfide bridges. *Tachyplesin I* contains 17 residues, also has an amidated carboxyl terminus and contains two disulfide bridges. Recently described backbone-cyclic protegrin and tachyplesin analogues typically contain 18 residues and up to three disulfide bridges (J. P. Tam, C. Wu, J.-L. Yang, *Eur. J. Biochem.* **2000**, *267*, 3289-3300; J. P. Tam, Y.-A. Lu, J.-L. Yang, *Biochemistry* **2000**, 39, 7159-7169; N. Sitaram, R. Nagaraij, *Biochem. Biophys. Res. Comm.* **2000**, *267*, 783-790).

Cathelicidin , a 37-residue linear helical-type cationic peptide, and analogues are currently under investigation as inhaled therapeutic agents for *cystic fibrosis(CF) lung disease* (L. Saiman, S. Tabibi, T. D. Starner, P. San Gabriel, P. L. Winokur, H. P. Jia, P. B. McGray, Jr., B. F. Tack, *Antimicrob. Agents and Chemother.* **2001**, *45*, 2838-2844; R. E. W. Hancock, R. Lehrer, *Trends Biotechnol.* **1998**, *16*, 82-88). Over 80% of CF patients become chronically infected with *pseudomonas aeruginosa* (C. A. Demko, P. J. Biard, P. B. Davies, *J. Clin. Epidemiol.***1995**, *48*, 1041-1049; E. M. Kerem, R. Gold, H. Levinson, *J. Pediatr.* **1990**, *116*, 714-719).

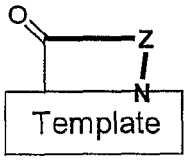
In addition, there is evidence from the literature that some cationic peptides exibit interesting anticancer activity. *Cerecropin B*, a 35-residue α-helical cationic peptide isolated from the hemolymph of the giant silk moth, and shorter analogues derived from *Cerecropin B* have been investigated as potential anticancer compounds (A. J. Moore, D. A. Devine, M. C. Bibby, *Peptide Research* **1994**, *7*, 265-269).

In the compounds described below, a new strategy is introduced to stabilize β-hairpin conformations in backbone-cyclic cationic peptide mimetic exhibiting antimicrobial and anticancer activity. This involves transplanting the cationic and hydrophobic hairpin sequence onto a template, whose function is to restrain the peptide loop backbone into a hairpin geometry. The rigidity of the hairpin may be further influenced by introducing a disulfide bridge. The template moiety may also act as an attachment point for other organic groups, that may modulate the antimicrobial and/or membranolytic targeting selectivity of the molecule, and be useful for producing dimeric species, where the templates in each monomer unit are linked through a short spacer or linker. 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), but such molecules have not previously

been evaluated for development of antimicrobial peptides. However, the ability to generate β-hairpin peptidomimetics using combinatorial and parallel synthesis methods has now been established (L. Jiang, K. Moehle, B. Dhanapal, D. Obrecht, J. A. Robinson, *Helv. Chim. Acta.* **2000**, *83*, 3097-3112).

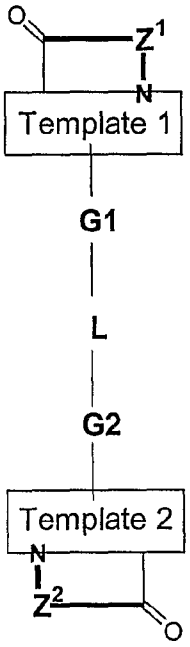
These methods allow the synthesis and screening of large hairpin mimetic libraries, which in turn considerably facilitates structure-activity studies, and hence the discovery of new molecules with potent antimicrobial and anticancer activity and low hemolytic activity to human red blood cells. Furthermore, the present strategy allows to synthesize β-hairpin peptidomimetics with novel selectivities towards different types of pathogens, e.g. towards various multi-drug resistant *pseudomonas* strains. β-Hairpin peptidomimetics obtained by the approach described here can be used amongst other applications, e.g. as broad spectrum antibiotics, as therapeutics for *cystic fibrosis* lung disease and anticancer agents.

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



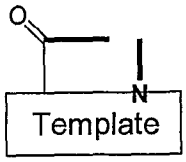
(Ia)

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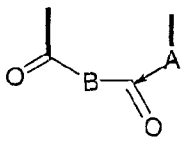


(Ib)

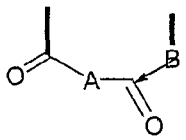
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is a group of one of the formulae

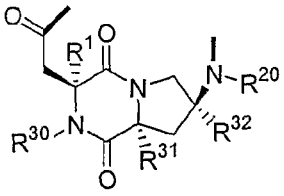


(a1)

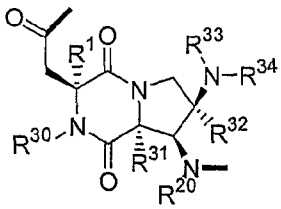


(a2)

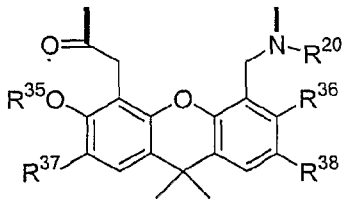
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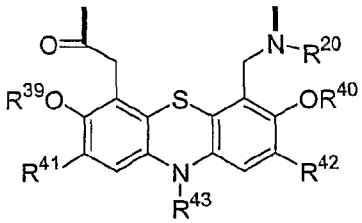
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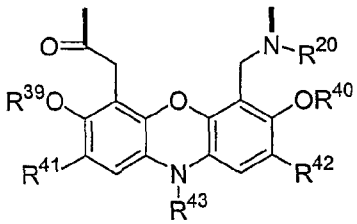
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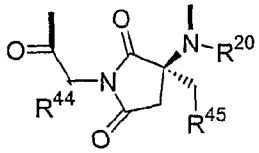
c1)



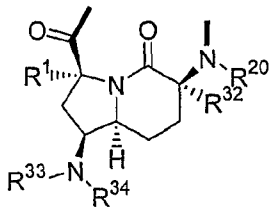
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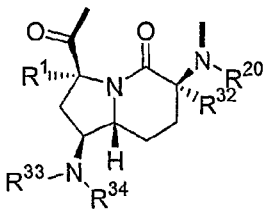
(c3)



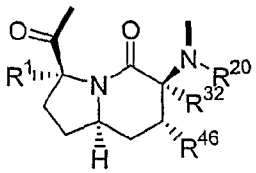
(d)



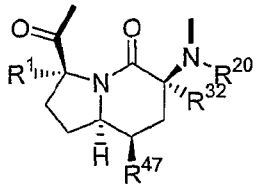
(e1)



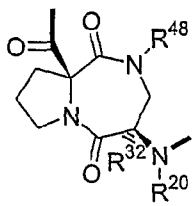
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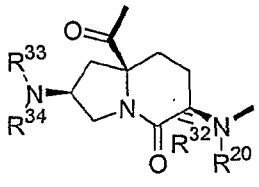
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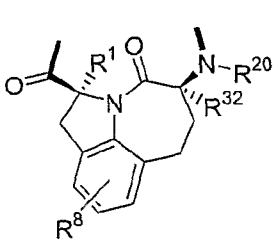
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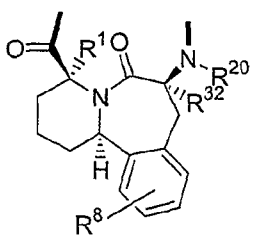
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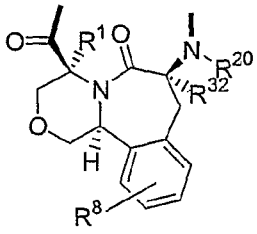
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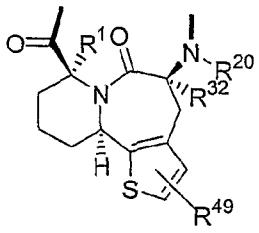
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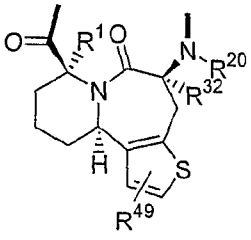
(i1)



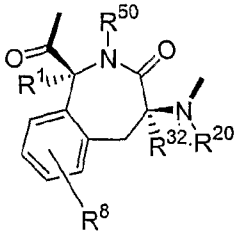
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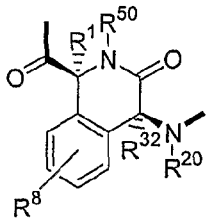
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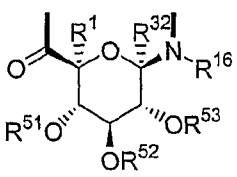
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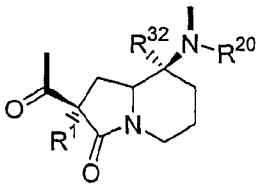
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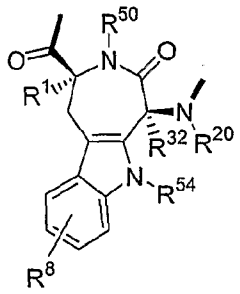
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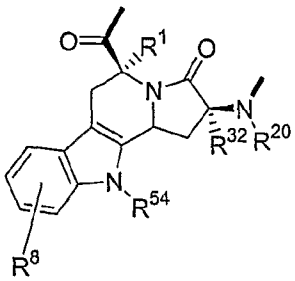
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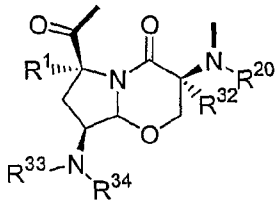


(n)



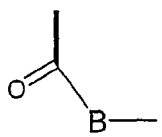
(o)

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(p)

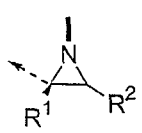
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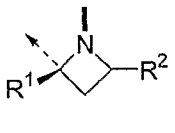
is the residue of an L-α-amino acid with B being a residue of formula -$NR^{20}CH(R^{71})$- or the enantiomer of one of the groups **A1** to **A69** as defined hereinafter;



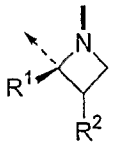
is a group of one of the formulae



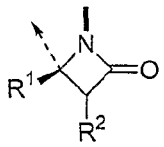
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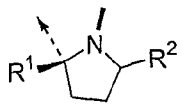
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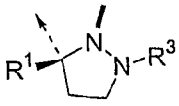
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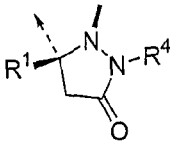
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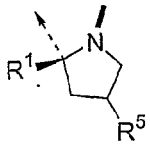
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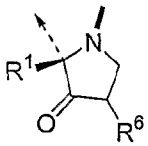
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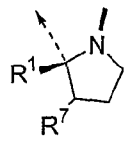
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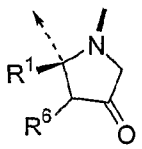
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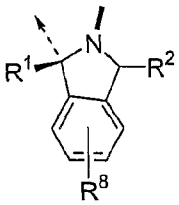
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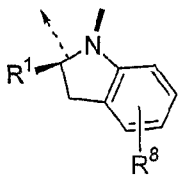
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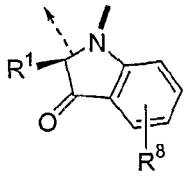
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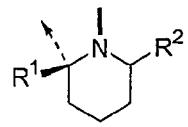
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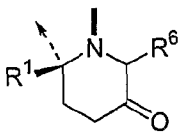
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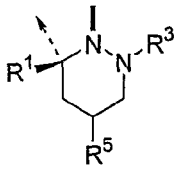
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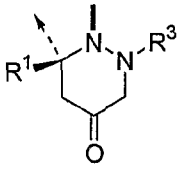
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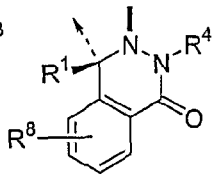
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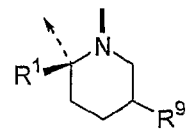
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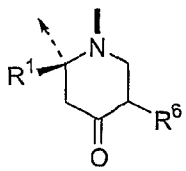
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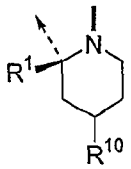
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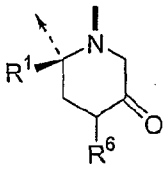
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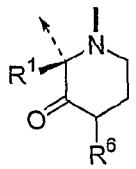
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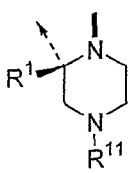
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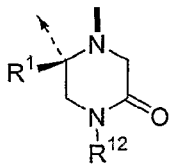
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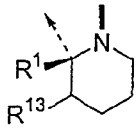
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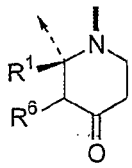
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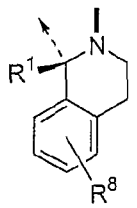
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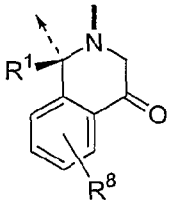
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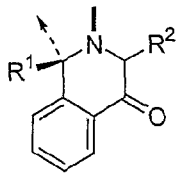
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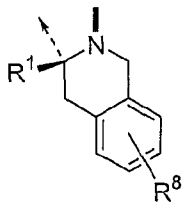
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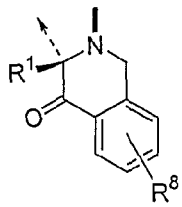
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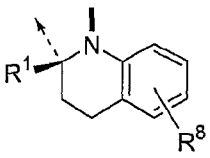
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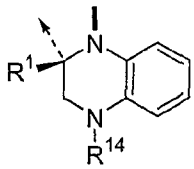
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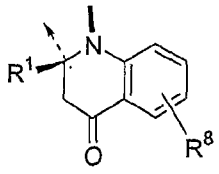
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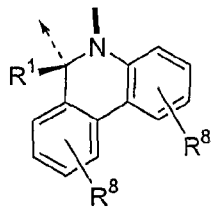
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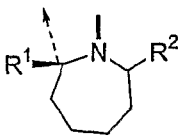
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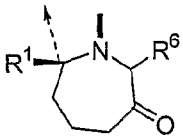
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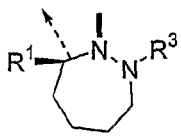
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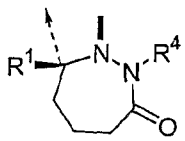
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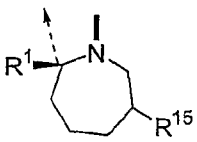
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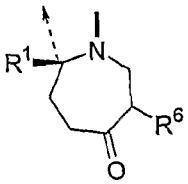
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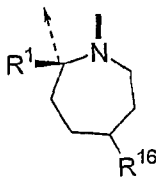
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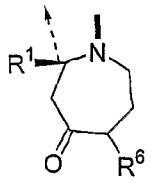
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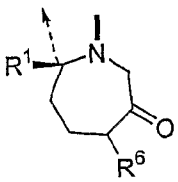
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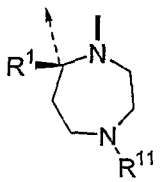
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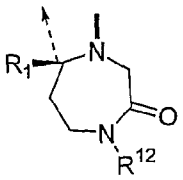
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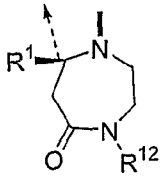
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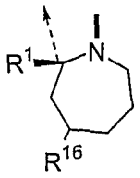
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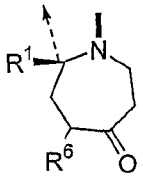
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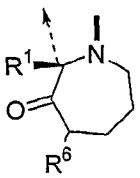
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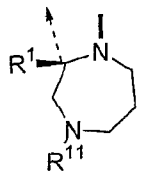
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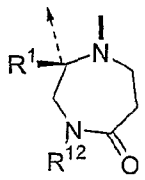
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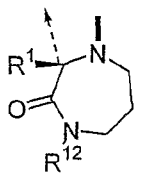
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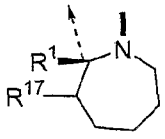
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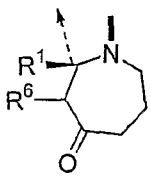
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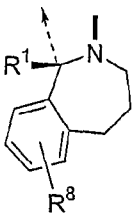
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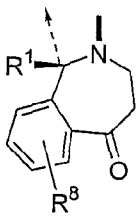
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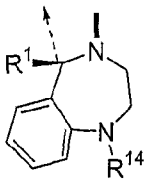
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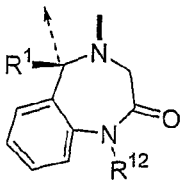
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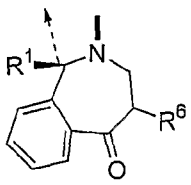
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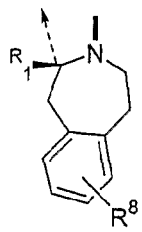
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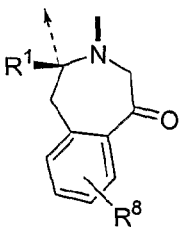
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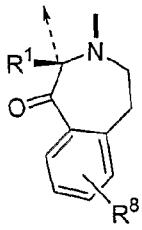
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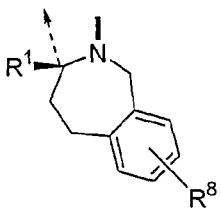
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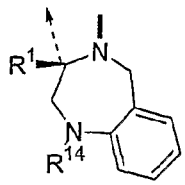
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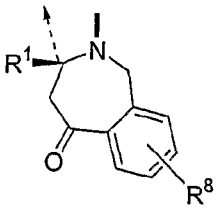
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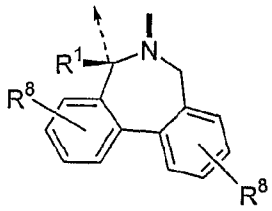
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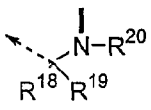
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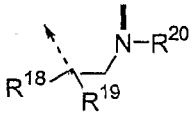
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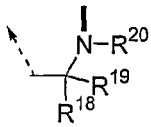
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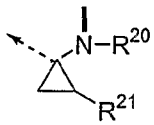
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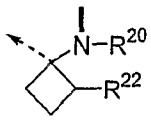
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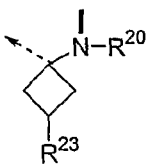
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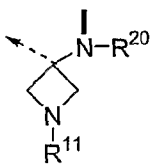
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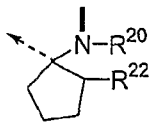
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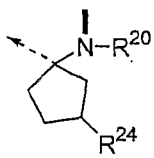
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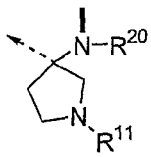
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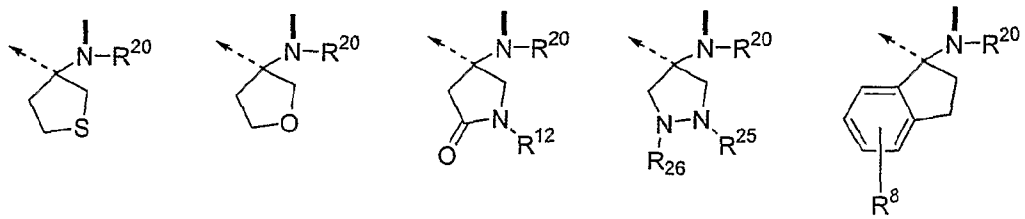
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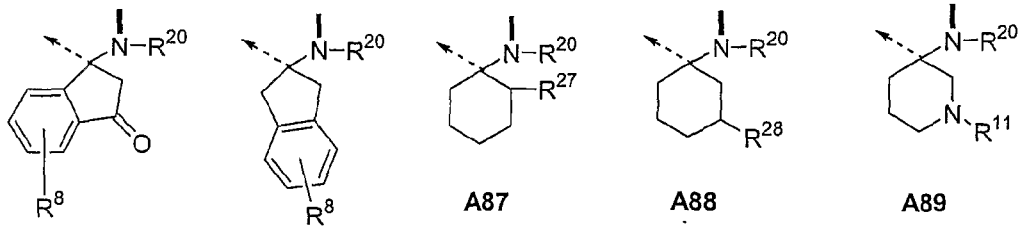
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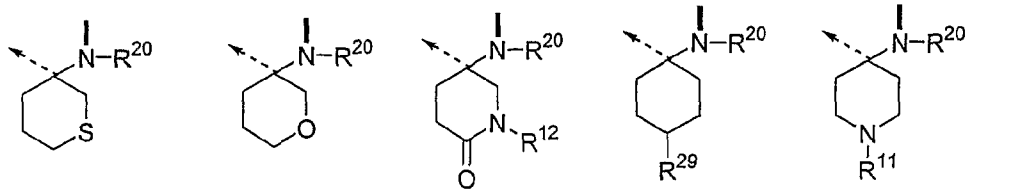
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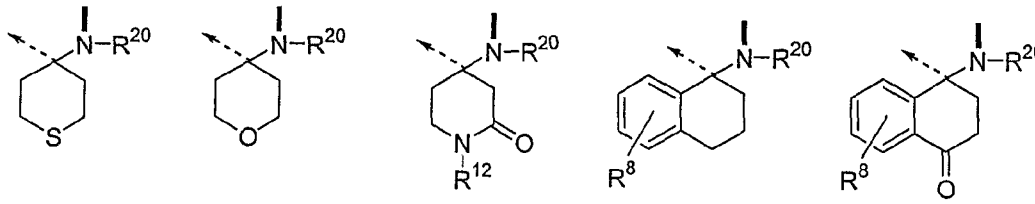
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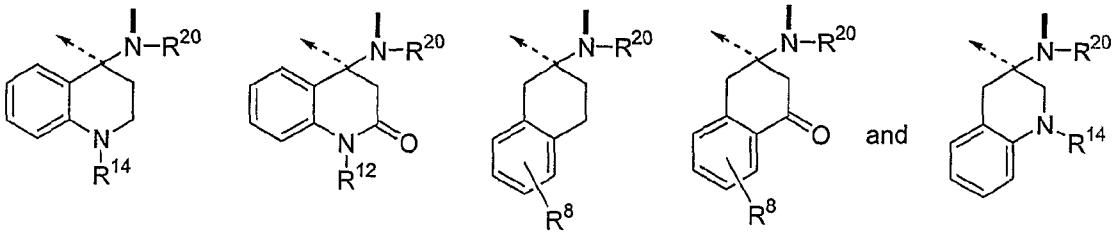
A85 A86 A87 A88 A89



A90 A91 A92 A93 A94



A95 A96 A97 A98 A99



A100 A101 A102 A103 and A104

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

R^2 is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$; $-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

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

$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^4 is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_p(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^5 is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^6 is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
$-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^7 is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_r(CHR^{61})_sCOOR^{57}$; $-(CH_2)_r(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_r(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_r(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_r(CHR^{61})_s\ C_6H_4R^8$;

R^8 is H; Cl; F; CF_3; NO_2; lower alkyl; lower alkenyl; aryl; aryl-lower alkyl;
$-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})NR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sCOR^{64}$;

R^9 is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{10} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
$-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{11} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s\ C_6H_4R^8$;

R^{12} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_r(CHR^{61})_sCOOR^{57}$;
$-(CH_2)_r(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_r(CHR^{61})_sPO(OR^{60})_2$; $-(CH_2)_r(CHR^{61})_s\ SO_2R^{62}$; or
$-(CH_2)_r(CHR^{61})_sC_6H_4R^8$;

R^{13} is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sSR^{56}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_q(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;

R^{14} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;.
$-(CH_2)_q(CHR^{61})_sSOR^{62}$; or $-(CH_2)_q(CHR^{61})_s\ C_6H_4R^8$;

R^{15} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{16} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{17} is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sSR^{56}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_q(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;

R^{18} is alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sSR^{56}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_p(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{19} is lower alkyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sSR^{56}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_p(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$; or

R^{18} and R^{19} taken together can form: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or

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

R^{20} is H; alkyl; alkenyl; or aryl-lower alkyl;

R^{21} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
$-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{22} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
$-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{23} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{24} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{25} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{26} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$; or

R^{25} and R^{26} taken together can form: $-(CH_2)_{2\text{-}6}-$; $-(CH_2)_rO(CH_2)_r-$; $-(CH_2)_rS(CH_2)_r-$; or
$-(CH_2)_rNR^{57}(CH_2)_r-$;

R^{27} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
$-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;

$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{28} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_s-OR^{55}$; $-(CH_2)_o(CHR^{61})_s SR^{56}$; $-(CH_2)_o(CHR^{61})_s NR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_s COOR^{57}$; $-(CH_2)_o(CHR^{61})_s CONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_s PO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;

R^{29} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{30} is H; alkyl; alkenyl; or aryl-lower alkyl;

R^{31} is H; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;

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

R^{33} is H; alkyl, alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOR^{64}$; $-(CH_2)_o(CHR^{61})_s-CONR^{58}R^{59}$, $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

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

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^{35} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_s C_6H_4R^8$;

R^{36} is H, alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;

R^{37} is H; F; Br; Cl; NO_2; CF_3; lower alkyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;

R^{38} is H; F; Br; Cl; NO_2; CF_3; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;
$-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{39} is H; alkyl; alkenyl; or aryl-lower alkyl;

R^{40} is H; alkyl; alkenyl; or aryl-lower alkyl;

R^{41} is H; F; Br; Cl; NO_2; CF_3; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;
$-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s\ C_6H_4R^8$;

R^{42} is H; F; Br; Cl; NO_2; CF_3; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;
$-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s\ C_6H_4R^8$;

R^{43} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s\ C_6H_4R^8$;

R^{44} is alkyl; alkenyl; $-(CH_2)_r(CHR^{61})_sOR^{55}$; $-(CH_2)_r(CHR^{61})_sSR^{56}$; $-(CH_2)_r(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_r(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_r(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_r(CHR^{61})_sCOOR^{57}$; $-(CH_2)_r(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_r(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_r(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_r(CHR^{61})_sC_6H_4R^8$;

R^{45} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; -
$(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_s(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_s(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_s(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_s(CHR^{61})_sC_6H_4R^8$;

R^{46} is H; alkyl; alkenyl; or $-(CH_2)_o(CHR^{61})_pC_6H_4R^8$;

R^{47} is H; alkyl; alkenyl; or $-(CH_2)_o(CHR^{61})_sOR^{55}$;

R^{48} is H; lower alkyl; lower alkenyl; or aryl-lower alkyl;

R^{49} is H; alkyl; alkenyl; $-(CHR^{61})_sCOOR^{57}$; $(CHR^{61})_sCONR^{58}R^{59}$; $(CHR^{61})_sPO(OR^{60})_2$;
$-(CHR^{61})_sSOR^{62}$; or $-(CHR^{61})_sC_6H_4R^8$;

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

R^{51} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;

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

$-(CH_2)_p(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;

R^{52} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;

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

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

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

$-(CH_2)_p(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;

R^{53} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;

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

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

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

$-(CH_2)_p(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;

R^{54} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;

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

$-(CH_2)_o(CHR^{61})COOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; or $-(CH_2)_o(CHR^{61})_s\ C_6H_4R^8$;

R^{55} is H; lower alkyl; lower alkenyl; 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}; $-(CH_2)_o(CHR^{61})COOR^{57}$;

or

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

R^{56} is H; lower alkyl; lower alkenyl; 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}; or

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

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

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

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

R^{58} and R^{59} taken together can form: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or

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

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

R^{61} is alkyl; alkenyl; aryl; heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl; $-(CH_2)_mOR^{55}$;

$-(CH_2)_mNR^{33}R^{34}$; $-(CH_2)_mOCONR^{75}R^{82}$; $-(CH_2)_mNR^{20}CONR^{78}R^{82}$; $-(CH_2)_oCOOR^{37}$;

$-(CH_2)_oNR^{58}R^{59}$; or $-(CH_2)_oPO(COR^{60})_2$;

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

R^{63} is H; lower alkyl; lower alkenyl; aryl, heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl;
$-COR^{64}$; $-COOR^{57}$; $-CONR^{58}R^{59}$; $-SO_2R^{62}$; or $-PO(OR^{60})_2$;

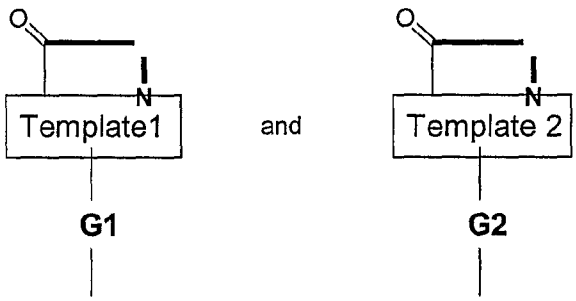
$R^{34}$and R^{63} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;

R^{64} is H; lower alkyl; lower alkenyl; aryl; heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl;
$-(CH_2)_p(CHR^{61})_sOR^{65}$; $-(CH_2)_p(CHR^{61})_sSR^{66}$; or $-(CH_2)_p(CHR^{61})_sNR^{34}R^{63}$;
$-(CH_2)_P(CHR^{61})_sOCONR^{75}R^{82}$; $-(CH_2)_P(CHR^{61})_sNR^{20}CONR^{78}R^{82}$;

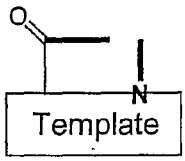
R^{65} is H; lower alkyl; lower alkenyl; aryl, aryl-lower alkyl; heteroaryl-lower alkyl; $-COR^{57}$; $-COOR^{57}$; or $-CONR^{58}R^{59}$;

R^{66} is H; lower alkyl; lower alkenyl; aryl; aryl-lower alkyl; heteroaryl-lower alkyl; or $-CONR^{58}R^{59}$;

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



independently have any of the significances defined above for



except **(a1)** or **(a2)** with B being $-NR^{20}CH(R^{71})-$ and with A being **A80, A81, A90, A91, A95** or **A96**, and except **(f)** and **(m)**, but wherein

R^2 is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^3 is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^4 is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_p(CHR^{61})_sCO-$;

R^5 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or

$-(CH_2)_o(CHR^{61})_sCO-$;

R^6 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^7 is $-(CH_2)_q(CHR^{61})_sO-$; $-(CH_2)_q(CHR^{61})_sNR^{34}-$; or $-(CH_2)_r(CHR^{61})_sCO-$;

R^8 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^9 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{10} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{11} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{12} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_r(CHR^{61})_sCO-$;

R^{13} is $-(CH_2)_q(CHR^{61})_sO-$; $-(CH_2)_q(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sNR^{34}-$; or $-(CH_2)_q(CHR^{61})_sCO-$;

R^{14} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_q(CHR^{61})_sCO-$;

R^{15} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{16} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{17} is $-(CH_2)_q(CHR^{61})_sO-$; $-(CH_2)_q(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sNR^{34}-$; or $-(CH_2)_q(CHR^{61})_sCO-$;

R^{18} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_p(CHR^{61})_sCO-$;

R^{19} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_p(CHR^{61})_sCO-$;

R^{21} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{22} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{23} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{24} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{25} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{26} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{27} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{28} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{29} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{31} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{33} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{37} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{38} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{41} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{42} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{43} is $-(CH_2)_m(CHR^{61})_sO$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{45} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_s(CHR^{61})_sCO-$;

R^{47} is $-(CH_2)_o(CHR^{61})_sO-$;

R^{49} is $-(CHR^{61})_sO-$; $-(CHR^{61})_sS-$; $-(CHR^{61})_sNR^{34}-$; or $-(CHR^{61})_sCO-$;

R^{51} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{52} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{53} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{54} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{55} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{56} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{64} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; or $-(CH_2)_p(CHR^{61})_sNR^{34}-$;

m, o, p, q, r and s being as defined above;

with the proviso that if more than one of the substituents R^2 to R^{19}, R^{21} to R^{29}, R^{31}, R^{33}, R^{37}, R^{38}, R^{41} to R^{43}, R^{45}, R^{47}, R^{49}, R^{51} to R^{56} and R^{64} is present, only one of these has one of the significances just mentioned whilst the other(s) has/have any of the significance(s) mentioned earlier;

L is a direct bond or one of the linkers

L1: $-(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_o-$;

L2: $-CO(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oCO-$;

L3: $-CONR^{34}(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oNR^{34}CO-$;

L4: $-O(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oO-$;

L5: $-S(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oS-$;

L6: $-NR^{34}(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oNR^{34}-$;

L7: $-(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}-$;

L8: $-CO(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}CO-$;

L9: $-CONR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}CO-$;

L10: $-O(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}O-$;

L11: $-S(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}S-$;

L12: $-NR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}-$;

L13: $-CO(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oNR^{34}-$;

L14: $-CO(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}-$;

L15 $-NR^{34}(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oCO-$; and

L16 $-NR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}CO-$;

m, o, p, q, r and s being as defined above; X being O; S; NR^{34}; $-NR^{32}CONR^{34}-$; or -OCOO-;

and Y being $-C_6R^{67}R^{68}R^{69}R^{70}-$;

R^{67} being H; Cl; Br; F; NO_2; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl;

R^{68} being H; Cl; Br; F; NO_2; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl;

R^{69} being H; Cl; Br; F; NO_2; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl; and

R^{70} being H; Cl; Br; F; NO_2; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl;

with the proviso that at least two of R^{67}, R^{68}, R^{69} and R^{70} are H; and

with the further proviso that

$-(CH_2)_m(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_o(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_p(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_q(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_m(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;

$-(CH_2)_o(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;

$-(CH_2)_p(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;

$-(CH_2)_q(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;

$-(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or form a disulfide bond with

$-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;

$-(CH_2)_m(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_o(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_p(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_q(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_o(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

$-(CH_2)_p(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

$-(CH_2)_q(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

$-(CH_2)_r(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

$-(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

$-(CH_2)_m(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_p(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_q(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_m(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_p(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_q(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_m(CHR^{61})_sNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_p(CHR^{61})_sNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_q(CHR^{61})_sNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CHR^{61})_sNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sX-$,$-(CH_2)_o(CHR^{61})_sX-$,$-(CH_2)_p(CHR^{61})_sX-$, $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

$-(CH_2)_p(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sX-$,$-(CH_2)_o(CHR^{61})_sX-$,$-(CH_2)_p(CHR^{61})_sX-$, $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

$-(CH_2)_q(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sX-$, $-(CH_2)_o(CHR^{61})_sX-$, $-(CH_2)_p(CHR^{61})_sX-$, $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

$-(CH_2)_r(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sX-$, $-(CH_2)_o(CHR^{61})_sX-$, $-(CH_2)_p(CHR^{61})_sX-$, $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

$-(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with $-(CH_2)_m(CHR^{61})_sX-$; $-(CH_2)_o(CHR^{61})_sX-$; $-(CH_2)_p(CHR^{61})_sX-$; $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

Z, Z^1 and Z^2 independently are chains of n α-amino acid residues, n being an integer from 8 to 16, the positions of said amino acid residues in said chains being counted starting from the N-terminal amino acid, whereby these amino acid residues are, depending on their position in the chains, Gly, or Pro, or of formula **-A-**CO-, or of formula **-B-**CO-, or of one of the types

C: $-NR^{20}CH(R^{72})CO-$;

D: $-NR^{20}CH(R^{73})CO-$;

E: $-NR^{20}CH(R^{74})CO-$;

F: $-NR^{20}CH(R^{84})CO-$; and

H: $-NR^{20}-CH(CO-)-(CH_2)_{4-7}-CH(CO-)-NR^{20}-$;

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

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

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

R^{71} is H; lower alkyl; lower alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{75}$; $-(CH_2)_p(CHR^{61})_sSR^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{75}$; $-(CH_2)_pCONR^{58}R^{59}$; $-(CH_2)_pPO(OR^{62})_2$; $-(CH_2)_pSO_2R^{62}$; or $-(CH_2)_o-C_6R^{67}R^{68}R^{69}R^{70}R^{76}$;

R^{72} is H; lower alkyl; lower alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{85}$; or $-(CH_2)_p(CHR^{61})_sSR^{85}$;

R^{73} is $-(CH_2)_oR^{77}$; $-(CH_2)_rO(CH_2)_oR^{77}$; $-(CH_2)_rS(CH_2)_oR^{77}$; or $-(CH_2)_rNR^{20}(CH_2)_oR^{77}$;

R^{74} is $-(CH_2)_pNR^{78}R^{79}$; $-(CH_2)_pNR^{77}R^{80}$; $-(CH_2)_pC(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;

$-(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pNR^{80}C(=NR^{80})NR^{78}R^{79}$;

$-(CH_2)_pN=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_pC_6H_4NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{77}R^{80}$;

$-(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;

$-(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$;

$-(CH_2)_pC_6H_4N=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_rO(CH_2)_mNR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_mNR^{77}R^{80}$;

$-(CH_2)_rO(CH_2)_pC(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_rO(CH_2)_pC_6H_4CNR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mNR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_mNR^{77}R^{80}$;$-(CH_2)_rS(CH_2)_pC(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$;
$-(CH_2)_rS(CH_2)_pC_6H_4CNR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pNR^{80}COR^{64}$; $-(CH_2)_pNR^{80}COR^{77}$;
$-(CH_2)_pNR^{80}CONR^{78}R^{79}$; or $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;

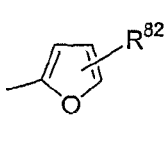
R^{75} is lower alkyl; lower alkenyl; or aryl-lower alkyl;

R^{33} and R^{75} taken together can form: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-;

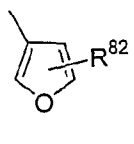
R^{75} and R^{82} taken together can form: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-;

R^{76} is H; lower alkyl; lower alkenyl; aryl-lower alkyl; $-(CH_2)_oOR^{72}$; $-(CH_2)_oSR^{72}$;
$-(CH_2)_oNR^{33}R^{34}$; $-(CH_2)_oOCONR^{33}R^{75}$; $-(CH_2)_oNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_oCOOR^{75}$; $-(CH_2)_oCONR^{58}R^{59}$; $-(CH_2)_oPO(OR^{60})_2$; $-(CH_2)_pSO_2R^{62}$; or
$-(CH_2)_oCOR^{64}$;

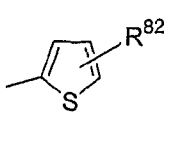
R^{77} is $-C_6R^{67}R^{68}R^{69}R^{70}R^{76}$; or a heteroaryl group of one of the formulae



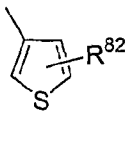
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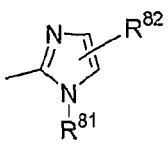
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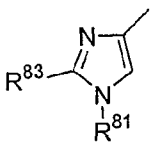
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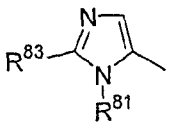
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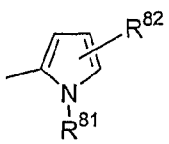
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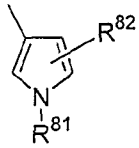
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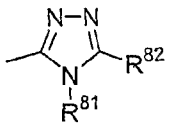
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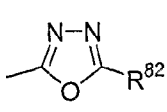
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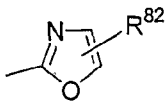
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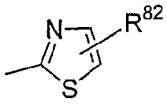
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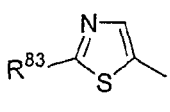
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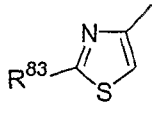
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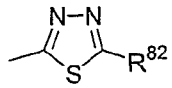
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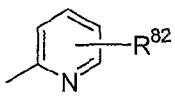
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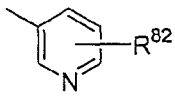
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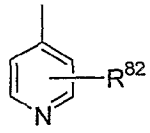
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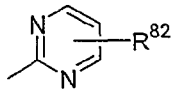
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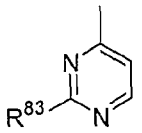
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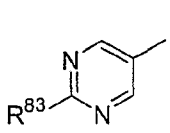
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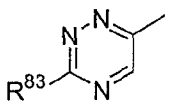
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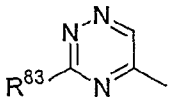
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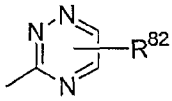
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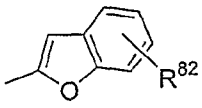
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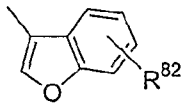
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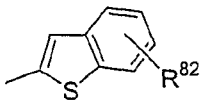
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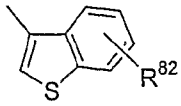
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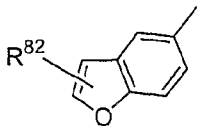
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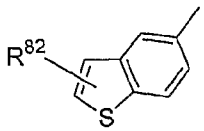
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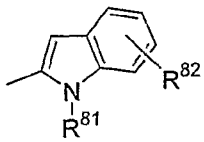
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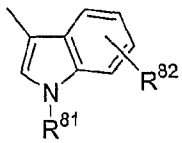
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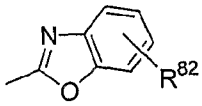
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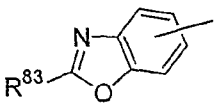
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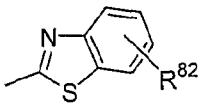
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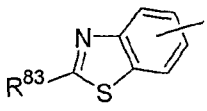
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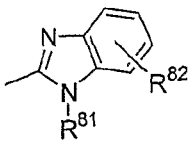
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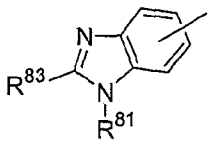
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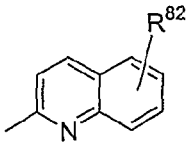
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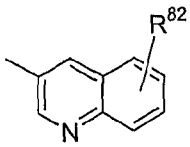
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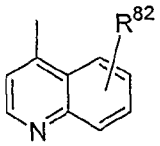
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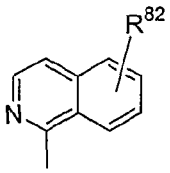
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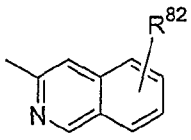
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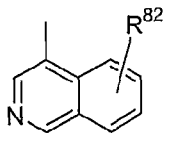
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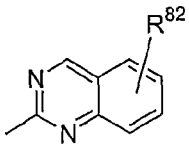
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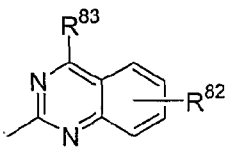
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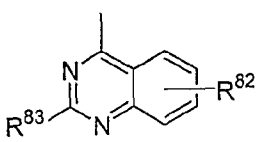
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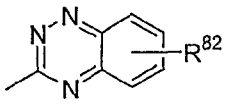
H46



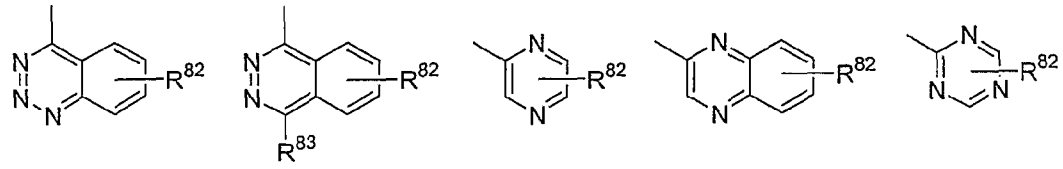
H47



H48



H49



H50 H51 H52 H53 H54

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

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

R^{79} is H; lower alkyl; 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;

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

R^{82} is H; lower alkyl; aryl; heteroaryl; or aryl-lower alkyl;

R^{33} and R^{82} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;

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

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

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

with the proviso that in said chain(s) of n α-amino acid residues Z, Z^1 and Z^2

- if n is 8, the amino acid residues in positions 1 to 8 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type D or of type F;
  - P3: of type E or of type C, or the residue is Pro;
  - P4: of type E or of formula -**A**-CO-;
  - P5: of type E or of formula -**B**-CO-, or the residue is Gly;
  - P6: of type D, or the residue is Pro;
  - P7: of type or of type C or of type D; and
  - P8: of type C or of type D or of type E or of type F, or the residue is Pro; or

  P2 and P7, taken together, can form a group of type H; and at P4 and P5 also D-isomers being possible;

- if n is 9, the amino acid residues in positions 1 to 9 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type D or of type F;
  - P3: of type C or of type D or of type E, or the residue is Pro;
  - P4: of type E or of type D, or the residue is Pro;
  - P5: of type E, or the residue is Gly or Pro;
  - P6: of type D or of type E, or the residue is Gly or Pro;
  - P7: of type E or of type D or of type C, or the residue is Pro;
  - P8: of type E or of type D; and
  - P9: of type C or of type D or of type E or of type F, or the residue is Pro; or
  - P2 and P8, taken together, can form a group of type H; and at P4, P5 and P6 also D-isomers being possible;

- if n is 10, the amino acid residues in positions 1 to 10 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type D, or the residue is Pro;
  - P3: of type C or of type E;
  - P4: of type E or of type D or of type F, or the residue is Pro;
  - P5: of type E or of type F or of formula **-A**-CO-, or the residue is Gly;
  - P6: of type E or of formula **-B**-CO-, or the residue is Gly;
  - P7: of type D or of type E, or the residue is Gly or Pro;
  - P8: of type D or of type E;
  - P9: of type E or of type D or of type C, or the residue is Pro; and
  - P10: of type C or of type D or of type E or of type F; or
  - P3 and P8, taken together, can form a group of type H; and at P5 and P6 also D-isomers being possible;

- if n is 11, the amino acid residues in positions 1 to 11 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type C or of type D;
  - P3: of type D or of type E, or the residue is Pro;
  - P4: of type E or of type C or of type F;
  - P5: of type E or of type F, or the residue is Gly or Pro;

- P6: of type E or of type F, or the residue is Gly or Pro;
- P7: of type E or of type F, or the residue is Gly or P ro;
- P8: of type D or of type E or of type F;
- P9: of type D or of type E, or the residue is Pro;
- P10: of type E or of type C or of type D; and
- P11: of type C or of type D or of type E or of type F, or the residue is Pro; or
- P4 and P8 and/or P2 and P10, taken together, can form a group of type H; and at P5, P6 and P7 also D-isomers being possible;

- if n is 12, the amino acid residues in positions 1 to 12 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type D;
  - P3: of type C or of type D, or the residue is Pro;
  - P4: of type E or of type F or of type D;
  - P5: of type E or of type D or of type C, or the residue is Gly or Pro;
  - P6: of type E or of type F or of formula -**A**-CO-, or the residue is Gly;
  - P7: of type E or of type F or of formula -**B**-CO-;
  - P8: of type D or of type C, or the residue is Pro;
  - P9: of type E or of type D or of type F;
  - P10: of type D or of type C, or the residue is Pro;
  - P11: of type E or of type D; and
  - P12: of type C or of type D or of type E or of type F, or the residue is Pro; or
  - P4 and P9 and/or P2 and P11, taken together, can form a group of type H; and at P6 and P7 also D-isomers being possible;

- if n is 13, the amino acid residues in positions 1 to 13 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type F or of type D;
  - P3: of type C or of type D or of type E, or the residue is Pro;
  - P4: of type E of type C or of type F;
  - P5: of type E or of type D, or the residue is Gly or Pro;
  - P6: of type E or of type F, or the residue is Gly or Pro;
  - P7: of type E or of type F, or the residue is Pro;
  - P8: of type D or of type E or of type F, or the residue is Pro;

- P9: of type D or of type E, or the residue is Pro;
- P10: of type E or of type C or of type F;
- P11: of type C or of type E, or the residue is Pro;
- P12: of type E or of type D or of type C; and
- P13: of type C or of type D or of type E or of type F, or the residue is Pro; or P4 and P10 and/or P2 and P12, taken together, can form a group of type H; and at P6, P7 and P8 also D-isomers being possible;

- if n is 14, the amino acid residues in positions 1 to 14 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type C or of type D, or the residue is Pro;
  - P3: of type C or of type D or of type E;
  - P4: of type D or of type C or of type E, or the residue is Pro;
  - P5: of type E or of type D;
  - P6: of type E or of type F, or the residue is Gly or Pro;
  - P7: of type E or of type F or of formula -**A**-CO-, or the residue is Gly;
  - P8: of type E or of type F or of formula -**B**-CO-, or the residue is Gly;
  - P9: of type D or of type E, or the residue is Pro;
  - P10: of type C or of type D or of type E;
  - P11: of type E or of type D or of type F, or the residue is Pro;
  - P12: of type D or of type E;
  - P13: of type E or of type C or of type D, or the residue is Pro; and
  - P14: of type C or of type D or of type E or of type F, or the residue is Pro; or
  - P5 and P10 and/or P3 and P12, taken together, can form a group of type H; and at P7 and P8 also D-isomers being possible;

- if n is 15, the amino acid residues in positions 1 to 15 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type F or of type D;
  - P3: of type C or of type D or of type E, or the residue is Pro;
  - P4: of type E or of type D or of type F;
  - P5: of type C or of type D or of type E, or the residue is Pro;
  - P6: of type E or of type D or of type F;
  - P7: of type C or of type E, or the residue is Pro;

P8: of type E or of type F, or the residue is Gly or Pro;
P9: of type E or of type F, or the residue is Gly or Pro;
P10: of type E or of type D;
P11: of type C or of type D or of type E, or the residue is Pro;
P12: of type E or of type C or of type F;
P13: of type D or of type E, or the residue is Pro;
P14: of type E or of type C or of type D; and
P15: of type C or of type D or of type E or of type F, or the residue is Pro; or

P6 and P10 and/or P4 and P12 and/or P2 and P14, taken together, can form a group of type H; and at P7, P8 and P9 also D-isomers being possible; and

- if n is 16, the amino acid residues in positions 1 to 16 are:
  - P1: of type D, or of type E or of type C or of type F, or the residue is Pro;
  - P2: of type E or of type F or of type D;
  - P3: of type C or of type D or of type E, or the residue is Pro;
  - P4: of type E or of type D or of type F;
  - P5: of type D or of type C or of type E, or the residue is Pro;
  - P6: of type E or of type D;
  - P7: of type E or of type F, or the residue is Gly or Pro;
  - P8: of type E or of type F or of formula -**A**-CO-,or the residue is Gly;
  - P9: of type E or of formula -**B**-CO-, or the residue is Gly;
  - P10: of type D or of type E, or the residue is Pro;
  - P11: of type E or of type C or of type D;
  - P12: of type D or of type C or of type E, or the residue is Pro;
  - P13: of type E or of type C or of type F;
  - P14: of type C or of type D or of type E, or the residue is Pro;
  - P15: of type E or of type C or of type D; and
  - P16: of type C or of type D or of type E or of type F, or the residue is Pro; or
  - P6 and P11 and/or P4 and P13 and/or P2 and P15, taken together, can form a group of type H; and at P8 and P9 also D-isomers being possible;

and pharmaceutically acceptable salts thereof.

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

(a) coupling an appropriately functionalized solid support with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position $^{n}/_{2}$, $^{n}/_{2}+1$ or $^{n}/_{2}-1$ if n is an even number and, respectively, in position $^{n}/_{2}+^{1}/_{2}$ or $^{n}/_{2}-^{1}/_{2}$ if n is an odd number, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

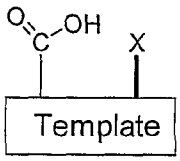
(b) removing the N-protecting group from the product thus obtained;

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

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

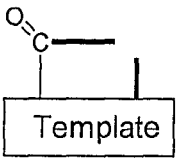
(e) repeating, if necessary, steps (c) and (d) until the N-terminal amino acid residue has been introduced;

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

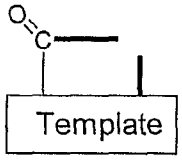


II

wherein



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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(q) if, desired

(qa) forming one or several interstrand linkage(s) between side-chains of appropriate amino acid residues at opposite positions of the β-strand region; and/or

(qb) connecting two building blocks of the type of formula Ia via a bridge

-G1 - L - G2-;

(r) 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

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

The peptidomimetics of the present invention can also be enantiomers of the compounds of formulae Ia and Ib. These enantiomers can be prepared by a modification of the above process in which enantiomers of all chiral starting materials are used.

As used in this description, the term "alkyl", taken alone or in combinations, designates saturated, straight-chain or branched hydrocarbon radicals having up to 24, preferably up to 12, carbon atoms. Similarly, the term "alkenyl" designates straight chain or branched hydrocarbon radicals having up to 24, preferably up to 12, carbon atoms and containing at least one or, depending on the chain length, up to four olefinic double bonds. The term "lower" designates radicals and compounds having up to 6 carbon atoms. Thus, for example, the term "lower alkyl" designates saturated, straight-chain or branched hydrocarbon radicals having up to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.-butyl, isobutyl, tert.-butyl and the like. The term "aryl" designates aromatic carbocyclic hydrocarbon radicals containing one or two six-membered rings, such as phenyl or naphthyl, which may be substituted by up to three substituents such as Br, Cl, F, CF_3, NO_2, lower alkyl or lower alkenyl. The term "heteroaryl" designates aromatic heterocyclic radicals containing one or two five- and/or six-membered rings, at least one of them containing up to three heteroatoms selected from the group consisting of O, S and N and said ring(s) being optionally substituted; representative examples of such optionally substituted heteroaryl radicals are indicated hereinabove in connection with the definition of R^{77}.

The structural element -**A**-CO- designates amino acid building blocks which in combination with the structural element -**B**-CO- form templates **(a1)** and **(a2)**. Templates **(a)** through **(p)** constitute building blocks which have an N-terminus and a C-terminus oriented in space in such a way that the distance between those two groups may lie between 4.0-5.5A. A peptide chain **Z**, $\mathbf{Z^1}$ or $\mathbf{Z^2}$ is linked to the C-terminus and the N-terminus of the templates **(a)** through **(p)** via the corresponding N- and C-termini so that the template and the chain form a cyclic structure such as that depicted in formula **Ia**. In a case as here where the distance between the N- and C- termini of the template lies between 4.0-5.5A the template will induce the H-bond network necessary for the formation of a β-hairpin conformation in the peptide chain **Z**, $\mathbf{Z^1}$ or $\mathbf{Z^2}$. Thus template and peptide chain form a *β-hairpin mimetic*. The β-hairpin mimetics can also be coupled through groups G1 and G2 and a linker unit L to form the dimeric constructs of formula **Ib**.

The β-hairpin conformation is highly relevant for the antibiotic and anticancer activities of the β-hairpin mimetics of the present invention. The β-hairpin stabilizing conformational properties of the templates **(a)** through **(p)** play a key role not only for antibiotic and anticancer activity but also for the synthesis process defined hereinabove, as incorporation of

the templates near the middle of the linear protected peptide precursors enhance significantly cyclization yields.

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

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

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

- *R^2*: H; lower alkyl; lower alkenyl; $(CH_2)_mOR^{55}$ (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; R^{33} and R^{34} taken together form: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-; R^{57}: H; or lower alkyl); $(CH_2)_mOCONR^{33}R^{75}$ (where R^{33}: H; or lower alkyl; or lower alkenyl; R^{75}: lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57}: H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; 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: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-

; 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^3*: 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; 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); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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; 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^4*: 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; 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); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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^5:* 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); -$(CH_2)_oOCONR^{33}R^{75}$ (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 -$(CH_2)_2NR^{57}(CH_2)_2$-; R^{57}: where H; or lower alkyl); $(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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}: alkyl; alkenyl; aryl; and aryl-lower alkyl; heteroaryl-lower alkyl); -$(CH_2)_oCOOR^{57}$ (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^6*: 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); -$(CH_2)_oOCONR^{33}R^{75}$ (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); -$(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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^7: 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; 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); $(CH_2)_qNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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).

- R^8: 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); $-(CH_2)_oNR^{33}R^{34}$ (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); $-(CH_2)_oOCONR^{33}R^{75}$ (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); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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^9: 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); $-(CH_2)_oOCONR^{33}R^{75}$ (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); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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^{10}*: 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); $-(CH_2)_oOCONR^{33}R^{75}$ (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); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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; 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^{11}*: 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; 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); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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; 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}*: 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; 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); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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}*: 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; 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); $-(CH_2)_qNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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); $-(CH_2)_rCOO^{57}$ (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); $-(CH_2)_rPO(OR^{60})_2$ (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).

- *R^{14}*: 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; 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); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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); $-(CH_2)_oCOOR^{57}$ (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); $-(CH_2)_qC_6H_4R^8$ (where R^8: H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).

- *R^{15}*: 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); $-(CH_2)_oOCONR^{33}R^{75}$ (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); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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}COlower alkyl (R^{20}=H; or lower alkyl); $-(CH_2)_oCOOR^{57}$ (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; lower alkyl; or R^{58}

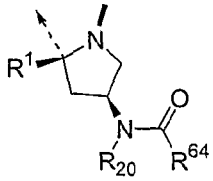
and R^{59} taken together form: -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57}: H; or lower alkyl); -$(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); -$(CH_2)_oSO_2R^{62}$ (where R^{62}: lower alkyl; or lower alkenyl); or -$(CH_2)_qC_6H_4R^8$ (where R^8: H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).

- *R^{16}*: 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); -$(CH_2)_oOCONR^{33}R^{75}$ (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); -$(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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}*: 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; 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); -$(CH_2)_qNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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; 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 -$(CH_2)_qC_5H_4R^8$ (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**. Most 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-chained 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. Venkatachalam, *Biopolymers*, **1968**, *6*, 1425-1434; W. Kabsch, C Sander, *Biopolymers* **1983**, *22*, 2577). Such building blocks or templates 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 Strategies for Efficient Lead Finding", *Adv. Med Chem.* **1999**, Vol.*4*, 1-68; P. Balaram, "Non-standard amino acids in peptide design and protein engineering", *Curr. Opin. Struct. Biol.* **1992**, *2*, 845-851; M. Crisma, G. Valle, C. Toniolo, S. Prasad, R. B. Rao, P. Balaram, "β-turn conformations in crystal structures of model peptides containing α,α- disubstituted amino acids", *Biopolymers* **1995**, *35*, 1-9; V. J. Hruby, F. Al-Obeidi, W. Kazmierski, *Biochem. J.* **1990**, *268*, 249-262).

It has been shown that both enantiomers of building blocks -**A70**-CO- to **A104**-CO- in combination with a building block -**B**-CO- of L-configuration can efficiently stabilize and induce β-hairpin conformations (D. Obrecht, M. Altorfer, J. A. Robinson, "Novel Peptide

Mimetic Building Blocks and Strategies for Efficient Lead Finding", *Adv. Med Chem.* **1999**, Vol.*4*, 1-68; D. Obrecht, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* **1992**, *75*, 1666-1696; D. Obrecht, U. Bohdal, J. Daly, C. Lehmann, P. Schönholzer, K. Müller, *Tetrahedron* **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).

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

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}*: lower alkyl.
- *R^{19}*: 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: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; 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; or lower alkyl; or lower alkenyl; R^{75}: lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57}: H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; 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: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; 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); $-(CH_2)_pSO_2R^{62}$ (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}*: 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); $-(CH_2)_oOCONR^{33}R^{75}$ (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); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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; 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^{22}*: 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); $-(CH_2)_oOCONR^{33}R^{75}$ (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); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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; 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; lower alkyl; lower alkenyl; or lower alkoxy).

- *R^{23}*: 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); $-(CH_2)_oOCONR^{33}R^{75}$ (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); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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}COlower alkyl (R^{20}=H; or lower alkyl); $-(CH_2)_oCOOR^{57}$ (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; 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^{24}: 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); $-(CH_2)_oOCONR^{33}R^{75}$ (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); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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}COlower alkyl (R^{20}=H ; or lower alkyl); $-(CH_2)_oCOOR^{57}$ (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; 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^{25}: 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); $-(CH_2)_mOCONR^{33}R^{75}$ (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); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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; 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}*: 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); $-(CH_2)_mOCONR^{33}R^{75}$ (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); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; 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; 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).

- Alternatively, *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}*: 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); $-(CH_2)_oOCONR^{33}R^{75}$ (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); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; 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;

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^{28}*: 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); $-(CH_2)_oOCONR^{33}R^{75}$ (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); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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; 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^{29}*: 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); $-(CH_2)_oOCONR^{33}R^{75}$ (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); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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 favored are NR^{20}COlower-alkyl (R^{20}=H; or lower alkyl); $-(CH_2)_oCOOR^{57}$ (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; 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).

For templates **(b)** to **(p)**, such as **(b1)** and **(c1)**, the preferred values for the various symbols are the following:

- *R^8*: 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); -$(CH_2)_oNR^{33}R^{34}$ (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); -$(CH_2)_oOCONR^{33}R^{75}$ (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); -$(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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^{20}*: H; or lower alkyl.
- *R^{30}*: H, methyl.
- *R^{31}*: H; lower alkyl; lower alkenyl; -$(CH_2)_pOR^{55}$ (where R^{55}: 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; 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); -$(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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); -$(CH_2)_oCOOR^{57}$ (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; 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 -$(CH_2)_rC_6H_4R^8$ (where R^8: H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy); most preferred is -$CH_2CONR^{58}R^{59}$ (R^{58}: H; or lower alkyl; R^{59}: lower alkyl; or lower alkenyl).

- *R^{32}*: H, methyl.
- *R^{33}*: lower alkyl; lower alkenyl; -$(CH_2)_mOR^{55}$ (where R^{55}: lower alkyl; or lower alkenyl); -$(CH_2)_mNR^{34}R^{63}$ (where R^{34}: lower alkyl; or lower alkenyl; R^{63}: H; or lower alkyl; or R^{34} and R^{63} taken together form: -$(CH_2)_{2\text{-}6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57}: H; or lower alkyl) ; $(CH_2)_mOCONR^{75}R^{82}$(where R^{75}: lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{75} and R^{82} taken together form: -$(CH_2)_{2\text{-}6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57}: H; or lower alkyl); -$(CH_2)_mNR^{20}CONR^{78}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{78}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{78} and R^{82} taken together form: -$(CH_2)_{2\text{-}6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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; lower alkyl; or R^{58} and R^{59} taken together form: -$(CH_2)_{2\text{-}6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57}: H; or lower alkyl).
- *R^{34}*: H; or lower alkyl.
- *R^{35}*: 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: -$(CH_2)_{2\text{-}6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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; or lower alkyl; or lower alkenyl; R^{75}: lower alkyl; or R^{33} and R^{75} taken together form: -$(CH_2)_{2\text{-}6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57}: H; or lower alkyl); -$(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -$(CH_2)_{2\text{-}6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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; lower alkyl; or R^{58} and R^{59} taken together form: -$(CH_2)_{2\text{-}6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57}: H; or lower alkyl).
- *R^{36}*: lower alkyl; lower alkenyl; or aryl-lower alkyl.
- *R^{37}*: H; lower alkyl; lower alkenyl; -$(CH_2)_pOR^{55}$ (where R^{55}: 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; 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); -$(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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); -$(CH_2)_oCOOR^{57}$ (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; 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 alky; 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^{38}*: H; lower alkyl; lower alkenyl; -$(CH_2)_pOR^{55}$ (where R^{55}: 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; or lower alkyl; or lower alkenyl; R^{75}: lower alkyl; or R^{33} and R^{78} 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); -$(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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); -$(CH_2)_oCOOR^{57}$ (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; 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^{39}*: H; lower alkyl; lower alkenyl; -$(CH_2)_mOR^{55}$ (where R^{55}: lower alkyl; or lower alkenyl); -$(CH_2)_mN(R^{20})COR^{64}$ (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; 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).

- *R^{40}*: lower alkyl; lower alkenyl; or aryl-lower alkyl.

- R^{41}: H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55}: 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; 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); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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); $-(CH_2)_oCOOR^{57}$ (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; lower alky; 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^{42}: H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55}: 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; 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); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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); $-(CH_2)_oCOOR^{57}$ (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; 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^{43}: 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; 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); -$(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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; 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^{44}*: 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; or lower alkyl; or lower alkenyl; R^{75}: lower alkyl; or R^{33} and R^{78} 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); -$(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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; 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); or -$(CH_2)_oC_6H_4R^8$ (where R^8: H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).

- *R^{45}*: 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); -$(CH_2)_sOCONR^{33}R^{75}$ (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); -$(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; 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; 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); or $-(CH_2)_sC_6H_4R^8$ (where R^8: H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).

- *R^{46}*: H; lower alkyl; lower alkenyl; $-(CH_2)_sOR^{55}$ (where R^{55}: lower alkyl; or lower alkenyl); $-(CH_2)_sSR^{56}$ (where R^{56}: lower alkyl; or lower alkenyl); $-(CH_2)_sNR^{33}R^{34}$ (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); $-(CH_2)_sOCONR^{33}R^{75}$ (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); $-(CH_2)_sNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57}: H; or lower alkyl); $-(CH_2)_sN(R^{20})COR^{64}$ (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; 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); or $-(CH_2)_sC_6H_4R^8$ (where R^8: H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).
- *R^{47}*: H; or OR^{55} (where R^{55}: lower alkyl; or lower alkenyl).
- *R^{48}*: H; or lower alkyl.
- *R^{49}*: H;lower alkyl; $-(CH_2)_oCOOR^{57}$ (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; 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); or $(CH_2)_sC_6H_4R^8$ (where R^8: H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).
- *R^{50}*: H; methyl.
- *R^{51}*: 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); $(CH_2)_mOCONR^{33}R^{75}$ (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); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; 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); $-(CH_2)_pCOOR^{57}$ (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; 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); or $-(CH_2)_rC_6H_4R^8$ (where R^8: H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).

- *R^{52}*: 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); $-(CH_2)_mOCONR^{33}R^{75}$ (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); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-; 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); $-(CH_2)_pCOOR^{57}$ (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; 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); or $-(CH_2)_rC_6H_4R^8$ (where R^8: H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).

- *R^{53}*: 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); $-(CH_2)_mOCONR^{33}R^{75}$ (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); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20}: H; or lower lower alkyl; R^{33}: H; or lower alkyl; or lower alkenyl; R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; 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); $-(CH_2)_pCOOR^{57}$ (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; 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); or $-(CH_2)_rC_6H_4R^8$ (where R^8: H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).

- *R^{54}*: lower alkyl; lower alkenyl; or aryl-lower alkyl.

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**.

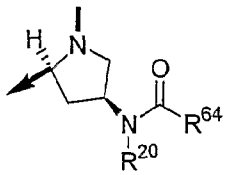
The building block -B-CO- within template **(a1)** and **(a2)** designates an L-amino acid residue. Preferred values for **B** are: $-NR^{20}CH(R^{71})-$ and enantiomers of groups **A5** with R^2 being H, **A8**, **A22**, **A25**, **A38** with R^2 being H, **A42**, **A47**, and **A50**. Most preferred are

Ala	L-Alanine
Arg	L-Arginine
Asn	L-Asparagine
Cys	L-Cysteine
Gln	L-Glutamine
Gly	Glycine
His	L-Histidine
Ile	L-Isoleucine
Leu	L-Leucine
Lys	L-Lysine
Met	L-Methionine
Phe	L-Phenylalanine
Pro	L-Proline
Ser	L-Serine
Thr	L-Threonine
Trp	L-Tryptophan
Tyr	L-Tyrosine
Val	L-Valine
Cit	L-Citrulline
Orn	L-Ornithine
tBuA	L-t-Butylalanine
Sar	Sarcosine
t-BuG	L-tert.-Butylglycine
4AmPhe	L-para-Aminophenylalanine
3AmPhe	L-meta-Aminophenylalanine
2AmPhe	L-ortho-Aminophenylalanine
Phe(mC(NH_2)=NH)	L-meta-Amidinophenylalanine
Phe(pC(NH_2)=NH)	L-para-Amidinophenylalanine
Phe(mNHC (NH_2)=NH)	L-meta-Guanidinophenylalanine
Phe(pNHC (NH_2)=NH)	L-para-Guanidinophenylalanine

Phg	L-Phenylglycine
Cha	L-Cyclohexylalanine
C_4al	L-3-Cyclobutylalanine
C_5al	L-3-Cyclopentylalanine
Nle	L-Norleucine
2-Nal	L-2-Naphthylalanine
1-Nal	L-1-Naphthylalanine
4Cl-Phe	L-4-Chlorophenylalanine
3Cl-Phe	L-3-Chlorophenylalanine
2Cl-Phe	L-2-Chlorophenylalanine
3,4Cl_2-Phe	L-3,4-Dichlorophenylalanine
4F-Phe	L-4-Fluorophenylalanine
3F-Phe	L-3-Fluorophenylalanine
2F-Phe	L-2-Fluorophenylalanine
Tic	L-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
Thi	L-β-2-Thienylalanine
Tza	L-2-Thiazolylalanine
Mso	L-Methionine sulfoxide
AcLys	L-N-Acetyllysine
Dpr	L-2,3-Diaminopropionic acid
A_2Bu	L-2,4-Diaminobutyric acid
Dbu	(S)-2,3-Diaminobutyric acid
Abu	γ-Aminobutyric acid (GABA)
Aha	ε-Aminohexanoic acid
Aib	α-Aminoisobutyric acid
Y(Bzl)	L-O-Benzyltyrosine
Bip	L-Biphenylalanine
S(Bzl)	L-O-Benzylserine
T(Bzl)	L-O-Benzylthreonine
hCha	L-Homo-cyclohexylalanine
hCys	L-Homo-cysteine
hSer	L-Homo-serine
hArg	L-Homo-arginine
hPhe	L-Homo-phenylalanine
Bpa	L-4-Benzoylphenylalanine
Pip	L-Pipecolic acid

OctG	L-Octylglycine
MePhe	L-N-Methylphenylalanine
MeNle	L-N-Methylnorleucine
MeAla	L-N-Methylalanine
MeIle	L-N-Methylisoleucine
MeVal	L-N-Methvaline
MeLeu	L-N-Methylleucine

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



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''-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**); cyclohexylmethyl (**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**); and n-nonyl (**A8''-40**).

The peptidic chains **Z**, $\mathbf{Z^1}$ and $\mathbf{Z^2}$ of the β-hairpin mimetics described herein are generally defined in terms of amino acid residues belonging to one of the following groups:

- **Group C** $-NR^{20}CH(R^{72})CO-$; "hydrophobic: small to medium-sized"
- **Group D** $-NR^{20}CH(R^{73})CO-$; "hydrophobic: large aromatic or heteroaromatic"
- **Group E** $-NR^{20}CH(R^{74})CO-$; "polar-cationic", "acylamino" and "urea-derived"
- **Group F** $-NR^{20}CH(R^{84})CO-$; "polar-non-charged"
- **Group H** $-NR^{20}-CH(CO-)-(CH_2)_{4-7}-CH(CO-)-NR^{20}-$;
  $-NR^{20}-CH(CO-)-(CH_2)_pSS(CH_2)_p-CH(CO-)-NR^{20}-$;
  $-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CO(CH_2)_p-CH(CO-)-NR^{20}-$; and
  $-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CONR^{20}(CH_2)_p-CH(CO-)-NR^{20}-$;
  "interstrand linkage"

Furthermore, the amino acid residues in chains **Z**, $\mathbf{Z^1}$ and $\mathbf{Z^2}$ can also be of formula **-A-CO-** or of formula **-B-CO-** wherein **A** and **B** are as defined above. Finally, Gly can also be an amino

acid residue in chains **Z**, $\mathbf{Z^1}$ and $\mathbf{Z^2}$, and Pro can be an amino acid residue in chains **Z**, $\mathbf{Z^1}$ and $\mathbf{Z^2}$, too, with the exception of positions where interstrand linkages (**H**) are possible.

Group C comprises amino acid residues with small to medium-sized *hydrophobic* side chain groups according to the 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) primary and secondary amides, primary and secondary amines and the corresponding protonated salts thereof, thiols, alcohols, phosphonates, phosphates, ureas or thioureas. However, they may contain hydrogen bond acceptor groups such as ethers, thioethers, esters, tertiary amides, alkyl- or aryl phosphonates and phosphates or tertiary amines. Genetically encoded small-to-medium-sized amino acids include alanine, isoleucine, leucine, methionine and valine.

Group D comprises amino acid residues with *aromatic* and *heteroaromatic* side chain groups according to the general definition for substituent R^{73}. An aromatic amino acid residue refers to a hydrophobic amino acid having a side chain containing at least one ring having a conjugated 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, tetriary amides, alkyl- or aryl phosphonates -and phosphates or tertiary amines. Genetically encoded aromatic amino acids include phenylalanine and tyrosine.

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

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

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

Group H comprises side chains of preferably (L)-amino acids at opposite positions of the β-strand region that can form an interstrand linkage. The most widely known linkage is the disulfide bridge formed by cysteines and homo-cysteines positioned at opposite positions of the β-strand. Various methods are known to form disulfide linkages including those described by: J. P. Tam et al. *Synthesis* **1979**, 955-957; Stewart et al. , *Solid Phase Peptide Synthesis*, 2d Ed., Pierce Chemical Company, III., **1984**; Ahmed et al. J. Biol. Chem. 1975, 250, 8477-8482 ; and Pennington et al., *Peptides*, pages 164-166, Giralt and Andreu, Eds., ESCOM Leiden, The Netherlands, **1990**. Most advantageously, for the scope of the present invention, disulfide linkages can be prepared as described hereinafter in the pertinent Examples (**procedure 3**), using acetamidomethyl (Acm)- protective groups for cysteine. A well established interstrand linkage consists in linking ornithines and lysines, respectively, with glutamic and aspartic acid residues located at opposite β-strand positions by means of an amide bond formation. Preferred protective groups for the side chain amino-groups of ornithine and lysine are allyloxycarbonyl (Alloc) and allylesters for aspartic and glutamic acid as described hereinafter in the pertinent Examples (**procedure 4**). Finally, interstrand linkages can also be established by linking the amino groups of lysine and ornithine located at opposite β-strand positions with reagents such as N,N-carbonylimidazole to form cyclic ureas.

As mentioned earlier, positions for interstrand linkages are the following:

- If **n=8**: Positions **P2** and **P7** taken together;
- if **n=9**: Positions **P2** and **P8** taken together;
- if **n=10**:Positions **P3** and **P8** taken together;
- if **n=11**:Positions **P4** and **P8**; and/or **P2** and **P10** taken together;
- if **n=12**:Positions **P4** and **P9**; and/or **P2** and **P11** taken together;

if **n=13**:Positions **P4** and **P10**; and/or Positions **P2** and **P12** taken together;

- if **n=14**:Positions **P5** and **P10**; and/or **P3** and **P12** taken together; and

if **n=15**:Positions **P6** and **P10**; and/or **P4** and **P12**; and/or **P2** and **P14**.

- if **n=16**:Positions **P6** and **P11**; and/or **P4** and **P13**; and/or **P2** and **P15** taken together.

Such interstrand linkages are known to stabilize the β-hairpin conformations and thus constitute an important structural element for the design of β-hairpin mimetics.

Most preferred amino acid residues chains **Z**, $\mathbf{Z^1}$ and $\mathbf{Z^2}$ are those derived from natural α-amino acids. Hereinafter follows a list of amino acids which, or the residues of which, are suitable for the purposes of the present invention, the abbreviations corresponding to generally adopted usual practice:

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

Trp	L-Tryptophan	W
Tyr	L-Tyrosine	Y
Val	L-Valine	V

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

Cit	L-Citrulline
Orn	L-Ornithine
tBuA	L-t-Butylalanine
Sar	Sarcosine
Pen	L-Penicillamine
t-BuG	L-tert.-Butylglycine
4AmPhe	L-para-Aminophenylalanine
3AmPhe	L-meta-Aminophenylalanine
2AmPhe	L-ortho-Aminophenylalanine
Phe(mC(NH_2)=NH)	L-meta-Amidinophenylalanine
Phe(pC(NH_2)=NH)	L-para-Amidinophenylalanine
Phe(mNHC (NH_2)=NH)	L-meta-Guanidinophenylalanine
Phe(pNHC (NH_2)=NH)	L-para-Guanidinophenylalanine
Phg	L-Phenylglycine
Cha	L-Cyclohexylalanine
C_4al	L-3-Cyclobutylalanine
C_5al	L-3-Cyclopentylalanine
Nle	L-Norleucine
2-Nal	L-2-Naphthylalanine
1-Nal	L-1-Naphthylalanine
4Cl-Phe	L-4-Chlorophenylalanine
3Cl-Phe	L-3-Chlorophenylalanine
2Cl-Phe	L-2-Chlorophenylalanine
3,4Cl_2-Phe	L-3,4-Dichlorophenylalanine
4F-Phe	L-4-Fluorophenylalanine
3F-Phe	L-3-Fluorophenylalanine
2F-Phe	L-2-Fluorophenylalanine
Tic	1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
Thi	L-β–2-Thienylalanine
Tza	L-2-Thiazolylalanine

Mso	L-Methionine sulfoxide
AcLys	N-Acetyllysine
Dpr	2,3-Diaminopropionic acid
A_2Bu	2,4-Diaminobutyric acid
Dbu	(S)-2,3-Diaminobutyric acid
Abu	γ-Aminobutyric acid (GABA)
Aha	ε-Aminohexanoic acid
Aib	α–Aminoisobutyric acid
Y(Bzl)	L-O-Benzyltyrosine
Bip	L-(4-phenyl)phenylalanine
S(Bzl)	L-O-Benzylserine
T(Bzl)	L-O-Benzylthreonine
hCha	L-Homo-cyclohexylalanine
hCys	L-Homo-cysteine
hSer	L-Homo-serine
hArg	L-Homo-arginine
hPhe	L-Homo-phenylalanine
Bpa	L-4-Benzoylphenylalanine
4-AmPyrr1	(2S,4S)-4-Amino-pyrrolidine-L-carboxylic acid
4-AmPyrr2	(2S,4R)-4-Amino-pyrrolidine-L-carboxylic acid
4-PhePyrr1	(2S,5R)-4-Phenyl-pyrrolidine-L-carboxylic acid
4-PhePyrr2	(2S,5S)-4-Phenyl-pyrrolidine-L-carboxylic acid
5-PhePyrr1	(2S,5R)-5-Phenyl-pyrrolidine-L-carboxylic acid
5-PhePyrr2	(2S,5S)-5-Phenyl-pyrrolidine-L-carboxylic acid
Pro(4-OH)1	(4S)-L-Hydroxyproline
Pro(4-OH)2	(4R)-L-Hydroxyproline
Pip	L-Pipecolic acid
^{D}Pip	D-Pipecolic acid
OctG	L-Octylglycine
MePhe	L-N-Methylphenylalanine
MeNle	L-N-Methylnorleucine
MeAla	L-N-Methylalanine
MeIle	L-N-Methylisoleucine
MeVal	L-N-Methylvaline
MeLeu	L-N-Methylleucine

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

Ala	L-Alanine
Ile	L-Isoleucine
Leu	L-Leucine
Met	L-Methionine
Val	L-Valine
tBuA	L-t-Butylalanine
t-BuG	L-tert.-Butylglycine
Cha	L-Cyclohexylalanine
C_4al	L-3-Cyclobutylalanine
C_5al	L-3-Cyclopentylalanine
Nle	L-Norleucine
hCha	L-Homo-cyclohexylalanine
OctG	L-Octylglycine
MePhe	L-N-Methylphenylalanine
MeNle	L-N-Methylnorleucine
MeAla	L-N-Methylalanine
MeIle	L-N-Methylisoleucine
MeVal	L-N-Methylvaline
MeLeu	L-N-Methylleucine

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

His	L-Histidine
Phe	L-Phenylalanine
Trp	L-Tryptophan
Tyr	L-Tyrosine
Phg	L-Phenylglycine
2-Nal	L-2-Naphthylalanine
1-Nal	L-1-Naphthylalanine
4Cl-Phe	L-4-Chlorophenylalanine
3Cl-Phe	L-3-Chlorophenylalanine
2Cl-Phe	L-2-Chlorophenylalanine
3,4Cl_2-Phe	L-3,4-Dichlorophenylalanine
4F-Phe	L-4-Fluorophenylalanine
3F-Phe	L-3-Fluorophenylalanine
2F-Phe	L-2-Fluorophenylalanine
Thi	L-β-2-Thienylalanine

Tza	L-2-Thiazolylalanine
Y(Bzl)	L-O-Benzyltyrosine
Bip	L-Biphenylalanine
S(Bzl)	L-O-Benzylserine
T(Bzl)	L-O-Benzylthreonine
hPhe	L-Homo-phenylalanine
Bpa	L-4-Benzoylphenylalanine

Particularly preferred residues for **group E** are

Arg	L-Arginine
Lys	L-Lysine
Orn	L-Ornithine
Dpr	L-2,3-Diaminopropionic acid
A_2Bu	L-2,4-Diaminobutyric acid
Dbu	(S)-2,3-Diaminobutyric acid
Phe(pNH_2)	L-para-Aminophenylalanine
Phe(mNH_2)	L-meta-Aminophenylalanine
Phe(oNH_2)	L-ortho-Aminophenylalanine
hArg	L-Homo-arginine
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
Cit	L-Citrulline

Particularly preferred residues for **group F** are

Asn	L-Asparagine
Cys	L-Cysteine
Glu	L-Glutamine
Ser	L-Serine
Thr	L-Threonine
Cit	L-Citrulline
Pen	L-Penicillamine
AcLys	L-N^{ε}-Acetyllysine
hCys	L-Homo-cysteine
hSer	L-Homo-serine

In the dimeric structures **Ib** the preferred substituents forming groups G1 and G2 are the following, with the proviso that R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; and R^{61} is H:

R^2: $-(CH_2)_mO-$; $-(CH_2)_mNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^5: $-(CH_2)_oO-$; $-(CH_2)_oNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^6: $-(CH_2)_oO-$; $-(CH_2)_oNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^8: $-(CH_2)_oO-$; $-(CH_2)_oNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^9: $-(CH_2)_oO-$; $-(CH_2)_oNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{10}: $-(CH_2)_oO-$; $-(CH_2)_oNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{11}: $-(CH_2)_mO-$; $-(CH_2)_mNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{14}: $-(CH_2)_mO-$; $-(CH_2)_mNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{15}: $-(CH_2)_mO-$; $-(CH_2)_mNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{16}: $-(CH_2)_mO-$; $-(CH_2)_mNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{18}: $-(CH_2)_pO-$; $-(CH_2)_pNR^{33}R^{34}-$; $-(CH_2)_pCO-$

R^{19}: $-(CH_2)_pO-$; $-(CH_2)_pNR^{33}R^{34}-$; $-(CH_2)_pCO-$

R^{21}: $-(CH_2)_oO-$; $-(CH_2)_oNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{23}: $-(CH_2)_oO-$; $-(CH_2)_oNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{24}: $-(CH_2)_oO-$; $-(CH_2)_oNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{25}: $-(CH_2)_mO-$; $-(CH_2)_mNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{26}: $-(CH_2)_mO-$; $-(CH_2)_mNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{28}: $-(CH_2)_oO-$; $-(CH_2)_oNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{29}: $-(CH_2)_oO-$; $-(CH_2)_oNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{31}: $-(CH_2)_pO-$; $-(CH_2)_pNR^{33}R^{34}-$; $-(CH_2)_pCO-$

R^{37}: $-(CH_2)_pO-$; $-(CH_2)_pNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{38}: $-(CH_2)_pO-$; $-(CH_2)_pNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{41}: $-(CH_2)_pO-$; $-(CH_2)_pNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{42}: $-(CH_2)_pO-$; $-(CH_2)_pNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{45}: $-(CH_2)_oO-$; $-(CH_2)_oNR^{33}R^{34}-$; $-(CH_2)_sCO-$

R^{47}: $-(CH_2)_oO-$

R^{49}: $-(CH_2)_sO-$; $-(CH_2)_sCO-$

R^{51}: $-(CH_2)_mO-$; $-(CH_2)_mNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{52}: $-(CH_2)_mO-$; $-(CH_2)_mNR^{33}R^{34}-$; $-(CH_2)_oCO-$

R^{53}: $-(CH_2)_mO-$; $-(CH_2)_mNR^{33}R^{34}-$; $-(CH_2)_oCO-$

and with the further provisos that the preferred linker molecules **L** are as defined below, that R^{34} is H; or lower alkyl; X is O; S; NR^{34}; $-NR^{34}CONR^{34}$; or -OCOO-; and Y is $C_6R^{67}R^{68}R^{69}R^{70}$:

L1: $-(CH_2)_p\,[X(CH_2)_p]_o-$

L2: $-CO(CH_2)_p\,[X(CH_2)_p]_oCO-$

L3: $-CONR^{34}(CH_2)_p\,[X(CH_2)_p]_oNR^{34}CO-$

L4: $-O(CH_2)_p\,[X(CH_2)_p]_oO-$

L6: $-NR^{34}(CH_2)_p\,[X(CH_2)_p]_oNR^{34}-$

L7: $-(CH_2)_oY(CH_2)_o-$

L8: $-CO(CH_2)_oY(CH_2)_oCO-$

L9: $-CONR^{34}(CH_2)_oY(CH_2)_oNR^{34}CO-$

L10: $-O(CH_2)_oY(CH_2)_oO-$

L11: $-S(CH_2)_oY(CH_2)_oS-$

L12: $-NR^{34}(CH_2)_oY(CH_2)_oNR^{34}-$

L13: $-CO(CH_2)_p\,[X(CH_2)_p]_oNR^{34}-$

L14: $-CO(CH_2)_oY(CH_2)_oNR^{34}-$

L15 $-NR^{34}(CH_2)_p\,[X(CH_2)_p]_oCO-$

L16 $-NR^{34}(CH_2)_oY(CH_2)_oCO-$

with the proviso that

$-(CH_2)_mO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_oO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_pO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_mNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_oNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_pNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_oCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

$-(CH_2)_pCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

$-(CH_2)_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

$-(CH_2)_mO-$ can be combined with linker L13 or L14 and the resulting combination with $-(CH_2)_oCO-$; $-(CH_2)_pCO-$; or $-(CH_2)_sCO-$;

$-(CH_2)_oO-$ can be combined with linker L13 or L14 and the resulting combination with $-(CH_2)_oCO-$; $-(CH_2)_pCO-$; or $-(CH_2)_sCO-$;

$-(CH_2)_pO-$ can be combined with linker L13 or L14 and the resulting combination with $-(CH_2)_oCO-$; $-(CH_2)_pCO-$; or $-(CH_2)_sCO-$;

$-(CH_2)_sO-$ can be combined with linker L13 or L14 and the resulting combination with $-(CH_2)_oCO-$; $-(CH_2)_pCO-$; or $-(CH_2)_sCO-$;

$-(CH_2)_mNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with $-(CH_2)_oCO-$; $-(CH_2)_pCO-$; or $-(CH_2)_sCO-$;

$-(CH_2)_oNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_oCO-$; $-(CH_2)_pCO-$; or $-(CH_2)_sCO-$;

$-(CH_2)_pNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with $-(CH_2)_oCO-$; $-(CH_2)_pCO-$; or $-(CH_2)_sCO-$;

$-(CH_2)_oCO-$ can be combined with linker L15 or L16 and the resulting combination with $-(CH_2)_mX-$; $-(CH_2)_oX-$; $-(CH_2)_pX-$; or $-(CH_2)_qX-$;

$-(CH_2)_pCO-$ can be combined with linker L15 or L16 and the resulting combination with $-(CH_2)_mX-$; $-(CH_2)_oX-$; $-(CH_2)_pX-$; or $-(CH_2)_qX-$;

$-(CH_2)_sCO-$ can be combined with linker L15 or L16 and the resulting combination with $-(CH_2)_mX-$; $-(CH_2)_oX-$;$-(CH_2)_pX-$; or $-(CH_2)_qX-$.

Generally, the peptidic chain **Z**, $\mathbf{Z^1}$ or $\mathbf{Z^2}$ within the β-hairpin mimetics of the invention comprises 8-16 amino acid residues (n = 8-16). The positions P^1 to P^n of each amino acid residue in the chain **Z**, $\mathbf{Z^1}$ or $\mathbf{Z^2}$ are unequivocally defined as follows: P^1 represents the first amino acid in the chain **Z**, $\mathbf{Z^1}$ or $\mathbf{Z^2}$ that is coupled with its N-terminus to the C-terminus of the templates **(b)-(p)** or of group **-B-**CO- in template **(a1)**, or of group **-A-**CO- in template **a2**, and P^n represents the last amino acid in the chain **Z**, $\mathbf{Z^1}$ or $\mathbf{Z^2}$ that is coupled with its C-terminus to the N-terminus of the templates **(b)-(p)** or of group **-A-**CO- in template **(a1)** or of group **–B-**CO- in template **(a2)**. Each of the positions P^1 to P^n will preferably contain an amino acid residue belonging to one or two of above types C to F, as follows:

- If **n is 8**, the amino acid residues in position 1 – 8 are preferably:
  - P1: of type **C** or of type D; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type **E**;
  - P4: of type **E** or of formula **-A1-A69-**CO-;
  - P5: of type **E** or of formula **-B-**CO-;
  - P6: of type **D**;
  - P7: of type **E**; or of type **D** and
  - P8: of type **C** or of type D; or of type **E**;
  - at P4 and P5 also D-isomers being possible;
- if **n is 9**, the amino acid residues in position 1 – 9 are preferably:
  - P1: of type **C** or of type D; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type **C**;
  - P4: of type **E**, or the residue is Pro;
  - P5: of type **E**, or the residue is Pro;
  - P6: of type **D** or of type E, or the residue is Pro;
  - P7: of type **E** or of type D;

- P8: of type **E**; or of type **D** and
- P9: of type **C** or of type D; or of type **E**;
- at P4, P5 and P6 also D-isomers being possible;

- if **n is 10**, the amino acid residues in position 1 – 10 are preferably:
  - P1: of type **C** or of type D; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type **C**;
  - P4: of type **E** or of type D;
  - P5: of type **E** or of formula **-A1-A69**-CO-;
  - P6: of type **E** or of formula **-B**-CO-;
  - P7: of type **D** or of type E;
  - P8: of type **D**;
  - P9: of type **E**; or of type **D** and
  - P10: of type **C** or of type D; or of type **E**;
  - at P5 and P6 also D-isomers being possible;
- if **n is 11**, the amino acid residues in position 1 – 11 are preferably:
  - P1: of type **C** or of type D; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type **D**;
  - P4: of type **E** or of type C;
  - P5: of type **E**, or the residue is Pro;
  - P6: of type **E**, or the residue is Pro;
  - P7: of type **E**, or the residue is Pro;
  - P8: of type **D** or of type E;
  - P9: of type **D**;
  - P10: of type **E**; or of type **D** and
  - P11: of type **C** or of type D; or of type **E**;
  - at P5, P6 and P7 also D-isomers being possible;
- if **n is 12**, the amino acid residues in position 1 – 12 are preferably:
  - P1: of type **C** or of type **E**; or of type D; or of type F;
  - P2: of type **E**; or of type **D**;
  - P3: of type **C** or of type D;
  - P4: of type **E**;
  - P5: of type **E**; or of type C;
  - P6: of type **E** or of type F or of formula **-A1-A69**-CO-;
  - P7: of type **E** or of formula **-B**-CO-;
  - P8: of type **D**;

- P9: of type **E** or of ype D;
- P10: of type **D**;
- P11: of type **E**; or of type **D** and
- P12: of type **C** or of type **E**; or of type D; or of type F;
- at P6 and P7 also D-isomers being possible;

- if **n is 13**, the amino acid residues in position 1 – 13 are preferably:
  - P1: of type **C** or of type D; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type **C** or of type D;
  - P4: of type **E** or of type C;
  - P5: of type **E** or of type D;
  - P6: of type **E** or of type F, or the residue is Pro;
  - P7: of type **E**, or the residue is Pro;
  - P8: of type **D**, or the residue is Pro;
  - P9: of type **D**;
  - P10: of type **E** or of type C;
  - P11: of type **C** or of type D;
  - P12: of type **E**; or of type **D** and
  - P13: of type **C** or of type D; or of type **E**;
  - at P6, P7 and P8 also D-isomers being possible;
- if **n is 14**, the amino acid residues in position 1 – 14 are preferably:
  - P1: of type **C** or of type D; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type **C** or of type D;
  - P4: of type **D**;
  - P5: of type **E**;
  - P6: of type **E**;
  - P7: of type **E** or of type F or of formula **-A1-A69**-CO-;
  - P8: of type **E** or of formula **-B**-CO-;
  - P9: of type **D**;
  - P10: of type **C**;
  - P11: of type **E** or of type D;
  - P12: of type **D** or of type C;
  - P13: of type **E**; or of type **D** and
  - P14: of type **C** or of type D; or of type **E**;
  - at P7 and P8 also D-isomers being possible;
- if **n is 15**, the amino acid residues in position 1 – 15 are preferably:

- P1: of type **C** and of type D; or of type **E**;
- P2: of type **E**; or of type **D**;
- P3: of type **C** and of type D;
- P4: of type **E** or of type C;
- P5: of type **C**;
- P6: of type **E** or of type D;
- P7: of type **C**, or the residue is Pro;
- P8: of type **E** or of type F, or the residue is Pro;
- P9: of type **E** or of type F, or the residue is Pro;
- P10: of type **E**;
- P11: of type **C**;
- P12: of type **E** or of type C;
- P13: of type **D** or of type C;
- P14: of type **E**; or of type **D** and
- P15: of type C and of type D; or of type **E**;
- at P7, P8 and P9 also D-isomers being possible; and

- if **n is 16**, the amino acid residues in position 1 – 16 are preferably:
  - P1: of type **D**; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type C or of type D;
  - P4: of type **E** or of type D;
  - P5: of type **D**;
  - P6: of type **E**;
  - P7: of type **E** or of type F;
  - P8: of type **E** or of type F or of formula **-A1-A69-**CO-;
  - P9: of type **E** or of formula **-B-**CO-;
  - P10: of type **D**;
  - P11: of type **E**;
  - P12: of type **D**;
  - P13: of type **E** or of type C;
  - P14: of type **C** or of type D;
  - P15: of type **E**; or of type **D** and
  - P16: of type **C** or of type D; or of type **E**;
  - at P8 and P9 also D-isomers being possible.

If **n is 12**, the amino acid residues in position 1 – 12 are most preferably:

- P1: Leu; Arg; Lys; Tyr; Trp; Val; Gln; or 4-AmPhe;

- P2: Arg; Trp; or Gln;
- P3: Leu; Val; Ile; or Phe;
- P4: Lys; Arg; Gln; or Orn;
- P5: Lys; or Arg;
- P6: Arg; Y(Bzl); or ^{D}Y(Bzl);
- P7: Arg;
- P8: Trp; Bip; 1-Nal; Y(Bzl); or Val;
- P9: Lys; Arg; Orn; Tyr; Trp; or Gln;
- P10: Tyr; T(Bzl); or Y(Bzl);
- P11: Arg; or Tyr; and
- P12: Val; Arg; 1-Nal; or 4-AmPhe.

Particularly preferred β-peptidomimetics of the invention include those described in Examples **106, 137, 161, 197, 206, 222, 230, 250, 256, 267, 277, 281, 283, 284, 285, 286, 289, 294, 295, 296, 297,** and **298.**

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

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

The solid support is functionalized by means of a linker, i.e. a bifunctional spacer molecule which contains on one end an anchoring group for attachment to the solid support and on the other end a selectively cleavable functional group used for the subsequent chemical transformations and cleavage procedures. For the purposes of the present invention the linker must be designed to eventually release the carboxyl group under mild acidic conditions which do not affect protecting groups present on any functional group in the side-chains of the

various amino acids. Linkers which are suitable for the purposes of the present invention form acid-labile esters with the carboxyl group of the amino acids, usually acid-labile benzyl, benzhydryl and trityl esters; examples of linker structures of this kind include 2-methoxy-4-hydroxymethylphenoxy (Sasrin^R linker), 4-(2,4-dimethoxyphenyl-hydroxymethyl)-phenoxy (Rink linker), 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid (HMPB linker), trityl and 2-chlorotrityl.

Preferably, the support is derived from polystyrene crosslinked with, most preferably 1-5%, divinylbenzene and functionalized by means of the 2-chlorotrityl linker.

When carried out as a parallel array synthesis the process of the invention can be advantageously carried out as described hereinbelow but it will be immediately apparent to those skilled in the art how this procedure will have to be modified in case it is desired to synthesize one single compound of the above formula Ia or Ib.

A number of reaction vessels (normally 24 to 192, typically 96) equal to the total number of compounds to be synthesized by the parallel method are loaded with 25 to 1000 mg, preferably 100 mg, of the appropriate functionalized solid support, 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), trifluoroethanol (TFE), isopropylalcohol and the like. Solvent mixtures containing as at least one component a polar solvent (e. g. 20% TFE/DCM, 35% THF/NMP) are beneficial for ensuring high reactivity and solvation of the resin-bound peptide chains (Fields, G. B., Fields, C. G., *J. Am. Chem. Soc.* **1991**, *113*, 4202-4207).

With the development of various linkers that release the C-terminal carboxylic acid group under mild acidic conditions, not affecting acid-labile groups protecting functional groups in the side chain(s), considerable progresses have been made in the synthesis of protected peptide fragments. The 2-methoxy-4-hydroxybenzylalcohol-derived linker (Sasrin^R linker, Mergler et al., *Tetrahedron Lett.* **1988**, 29 4005-4008) is cleavable with diluted trifluoroacetic acid (0.5-1% TFA in DCM) and is stable to Fmoc deprotection conditions during the peptide synthesis, Boc/tBu-based additional protecting groups being compatible with this protection scheme. Other linkers which are suitable for the process of the invention include the super acid labile 4-(2,4-dimethoxyphenyl-hydroxymethyl)-phenoxy linker (Rink linker, Rink, H.

Tetrahedron Lett. **1987**, *28*, 3787-3790), where the removal of the peptide requires 10% acetic acid in DCM or 0.2% trifluoroacetic acid in DCM; the 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid-derived linker (HMPB-linker, Flörsheimer & Riniker, *Peptides* **1991**,1990 131) which is also cleaved with 1%TFA/DCM in order to yield a peptide fragment containing all acid labile side- chain protective groups; and, in addition, the 2-chlorotritylchloride linker (Barlos et al., *Tetrahedron Lett.* **1989**, *30*, 3943-3946), which allows the peptide detachment using a mixture of glacial acetic acid/trifluoroethanol/DCM (1:2:7) for 30 min.

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

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

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

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

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

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

Pmc	2,2,5,7,8-pentamethylchroman-6-sulfonyl

Ts	tosyl (i. e. p-toluenesulfonyl)
Cbz	benzyloxycarbonyl
Pbf	pentamethyldihydrobenzofuran-5-sulfonyl

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

tBu	tert.-butyl
Bn	benzyl
Trt	trityl

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

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

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

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

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

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

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

1) The reaction wells are filled with solvent (preferably 5 ml), the reaction tubes, in combination with the holder block and manifold, are immersed and agitated for 5 to 300

minutes, preferably 15 minutes, and drained by gravity followed by gas pressure applied through the manifold inlet (while closing the outlet) to expel the solvent;

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

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

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

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

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

5 times as above with 3 to 5 ml of an appropriate solvent to extract (wash out) as much of the detached product as possible. The product solutions thus obtained are combined, taking care to avoid cross-mixing. The individual solutions/extracts are then manipulated as needed to isolate the final compounds. Typical manipulations include, but are not limited to, evaporation, concentration, liquid/liquid extraction, acidification, basification, neutralization or additional reactions in solution.

The solutions containing fully protected linear peptide derivatives which have been cleaved off from the solid support and neutralized with a base, are evaporated. Cyclization is then effected in solution using solvents such as DCM, DMF, dioxane, THF and the like. Various coupling reagents which were mentioned earlier can be used for the cyclization. The duration of the cyclization is about 6-48 hours, preferably about 24 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.

Before removing the protecting groups from the fully protected cyclic peptide, it is possible, if desired, to form an interstrand linkage between side-chains of appropriate amino acid residues at opposite positions of the β-strand region; and/or to connect two building blocks of the type of formula Ia via a bridge **-G1 - L - G2-** to give a dimeric structure of the type of formula Ib.

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 cysteines and homocysteines at opposite positions of the β-strand, or glutamic and aspartic acid residues linking ornithines and, respectively, lysines 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.

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For building up a bridge **-G1 - L - G2-** to give a dimeric structure, methods well known in the art can be used, too. Thus, for example, a fully side-chain protected β-hairpin peptidomimetic carrying a group G1 or G2 containing an appropriately protected alcohol group (e.g. as tert.-butyldiphenylsilyl protected), thiol group (e.g. as acetamidomethyl protected) or amino group (NR^{34}; e.g. as allyloxycarbonyl protected) can selectively be deprotected employing methods well known by the skilled in the art and reacted with suitably activated linker (**L**) precursors; e.g:

- for L1 the corresponding building block is $Br(Cl,I)(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oOH$: the resulting alcohol can be transformed into the corresponding bromide (chloride or iodide) by methods well known to those skilled in the art (e.g. $P(Ph)_3$, CBr_4) and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing an alcohol, thiol or amine group. The dimeric fully side-chain protected molecule can be fully deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- for L2 the corresponding building block is $ClOC(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oCOOAllyl$: the resulting ester can be transformed into the corresponding acid by methods well known in the art and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing an alcohol, thiol or amine group. The dimeric fully side-chain protected molecule can be fully deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- For L3 the corresponding building block is $O=C=N(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oNR^{34}Alloc$: the resulting Alloc-protected amine can be deprotected and transformed into the corresponding isocyanate by methods familiar to those skilled in the art (e.g. triphosgene) and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing an alcohol, thiol or amine group. The dimeric fully side-chain protected molecule can be fully deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- For L7 the corresponding building block is $Br(Cl,I)(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}OH$: the resulting alcohol can be transformed into the corresponding bromide (chloride or iodide) by methods well known in the art (e.g. $P(Ph)_3$, CBr_4) and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing an alcohol, thiol or amine group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- For L8 the corresponding building block is $ClOC(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}COOAllyl$: the resulting ester can be transformed into the corresponding acid by methods well known to those skilled in the art and combined with a second β-hairpin mimetic carrying a group

G1 or G2 containing an alcohol, thiol or amine group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.

- For L9 the corresponding building block is $O=C=N(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}Alloc$: the resulting Alloc-protected amine can be deprotected and transformed into the corresponding isocyanate by methods well known in the art (e.g. triphosgene) and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing an alcohol, thiol or amine group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- For L13 the corresponding building block is $ClOC(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oNR^{34}Alloc$: the resulting Alloc-protected amine can be deprotected by methods readily available to those skilled in the art and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- For L14 the corresponding building block is $ClOC(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}Alloc$: the resulting Alloc-protected amine can be deprotected by conventional methods and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.

Alternatively, a fully side-chain protected β-hairpin peptidomimetic carrying a group G1 or G2 containing an appropriately protected thiol group (e.g. as acetamidomethyl protected) can selectively be deprotected employing methods well known to those skilled in the art and reacted with a second β-hairpin peptidomimetic carrying a group G1 or G2 containing a thiol group forming a disulfide bond by oxidation (air or iodine). The dimeric molecule can subsequently be fully deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.

Finally, a fully side-chain protected β-hairpin peptidomimetic carrying a group G1 or G2 containing an appropriately protected carboxylic acid group (e.g. allyl ester), can selectively be deprotected employing methods well known in the art and reacted with a suitably activated linker (L) precursor; e.g:

- For L4 the corresponding building block is $HO(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oOAlloc$: the resulting Alloc-protected alcohol can be deprotected by methods well known to those skilled in the art and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- For L5 the corresponding building block is $HS(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oSAlloc$: the resulting Alloc-protected thiol can be deprotected by methods well known in the art and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- For L6 the corresponding building block is $HNR^{34}(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oNR^{34}Alloc$: the resulting Alloc-protected amine can be deprotected by methods familiar to those skilled in the art and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- For L10 the corresponding building block is $HO(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}OAlloc$: the resulting Alloc-protected alcohol can be deprotected by methods well known to those skilled in the art and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- For L11 the corresponding building block is $HS(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}SAlloc$: the resulting Alloc-protected thiol can be deprotected by methods well known in the art and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- For L12 the corresponding building block is $HNR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}Alloc$: the resulting Alloc-protected amine can be deprotected by methods well known to those skilled in the art and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.

- For L15 the corresponding building block is $HNR^{34}(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oCOOAllyl$: the resulting Allylester can be deprotected by conventional methods and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing an alcohol group, a thiol group or an amino (NR^{34}) group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- For L16 the corresponding building block is $HNR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}COOAllyl$: the resulting Allylester can be deprotected by methods well known to those skilled in the art and combined with a second β-hairpin mimetic carrying a group G1 or G2 containing an alcohol group, a thiol group or an amino (NR^{34}) group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.

Finally, the fully protected peptide derivative of type Ia or Ib is treated with 95% TFA, 2.5% H_2O, 2.5% TIS or another combination of scavengers for effecting the cleavage of protecting groups. The cleavage reaction time is commonly 30 minutes to 12 hours, preferably about 2 hours. Thereafter most of the TFA is evaporated and the product is precipitated with ether/hexane (1:1) or other solvents which are suitable therefor. After careful removal of the solvent, the cyclic peptide derivative obtained as end-product can be isolated. Depending on its purity, this peptide derivative can be used directly for biological assays, or it has to be further purified, for example by preparative HPLC.

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

The starting materials used in the process of the invention, pre-starting materials therefor, and the preparation of these starting and pre-starting materials will now be discussed in detail.

Building blocks of type **A** can be synthesized according to the literature methods described below. The corresponding amino acids have been described either as unprotected or as Boc- or Fmoc-protected racemates, (D)- or (L)-isomers. It will be appreciated that unprotected amino acid building blocks can be easily transformed into the corresponding Fmoc-protected amino acid building blocks required for the present invention by standard protecting group manipulations. Reviews describing general methods for the synthesis of α-amino acids include: R. Duthaler, *Tetrahedron (Report)* **1994**, *349*, 1540-1650; R. M. Williams, "Synthesis of optically active α-amino acids", *Tetrahedron Organic Chemistry Series*, Vol.7, J. E. Baldwin, P. D. Magnus (Eds.), Pergamon Press., Oxford **1989**. An especially useful method for the synthesis of optically active α-amino acids relevant for this invention includes kinetic resolution using hydrolytic enzymes (M. A. Verhovskaya, I. A. Yamskov, *Russian Chem. Rev.* **1991**, *60*, 1163-1179; R. M. Williams, "Synthesis of optically active α-amino acids", *Tetrahedron Organic Chemistry Series*, Vol.7, J. E. Baldwin, P. D. Magnus (Eds.), Pergamon Press., Oxford **1989**, Chapter 7, p.257-279). Hydrolytic enzymes involve hydrolysis of amides and nitriles by aminopeptidases or nitrilases, cleavage of N-acyl groups by acylases, and ester hydrolysis by lipases or proteases. It is well documented that certain enzymes will lead specifically to pure (L)-enantiomers whereas others yield the corresponding (D)-enantiomers (e.g. : R. Duthaler, *Tetrahedron Report* **1994**, *349*, 1540-1650; R. M. Williams, "Synthesis of optically active α-amino acids", *Tetrahedron Organic Chemistry Series*, Vol.7, J. E. Baldwin, P. D. Magnus (Eds.), Pergamon Press., Oxford **1989**).

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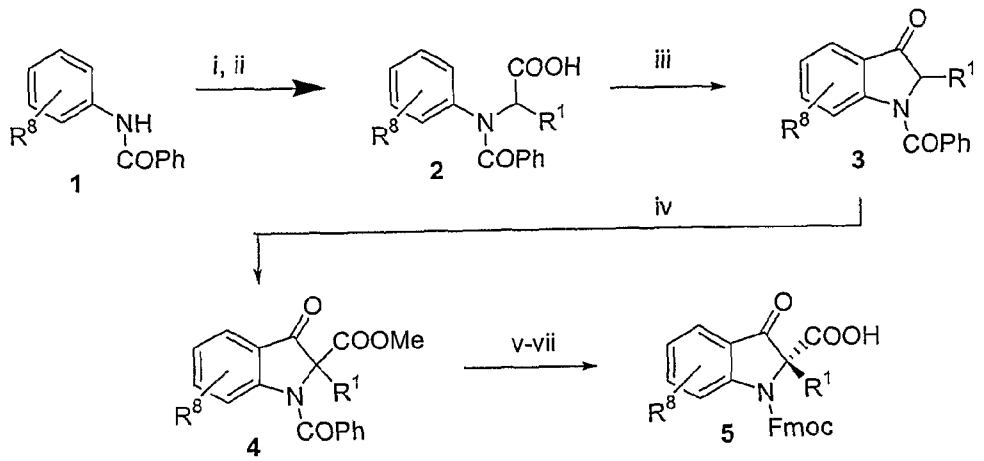
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A14: Amino acids of type **A14** can be made according to *Scheme 1*.

Scheme 1



i: NaH, $BrCH(R^1)COOMe$, DMF; ii: $LiOHx1H_2O$, MeOH, H_2O; iii: polyphosphoric acid(PPA); iv: NaH, ClCOOMe, THF; v: enzymatic resolution (e.g.lipase); vi: NaOH, MeOH, H_2O, heat; vii: FmocOSu, Na_2CO_3aq., dioxane

A15: See D. S. Perlow, J. M. Erb, N. P. Gould, R. D. Tung, R. M. Freidinger, *J. Org. Chem.* **1992**, *57*, 4394-4400; D. Y. Jackson, C. Quan, D. R. Artis, T. Rawson, B. Blackburn, *J. Med. Chem.* **1997**, *40*, 3359-3368 (R^1= H; R^2= H); H. H. Wasserman, K. Rodrigues, K. Kucharczyk, *Tetrahedron Lett.* **1989**, *30*, 6077-6080 (R^1= H; R^2= COOH).

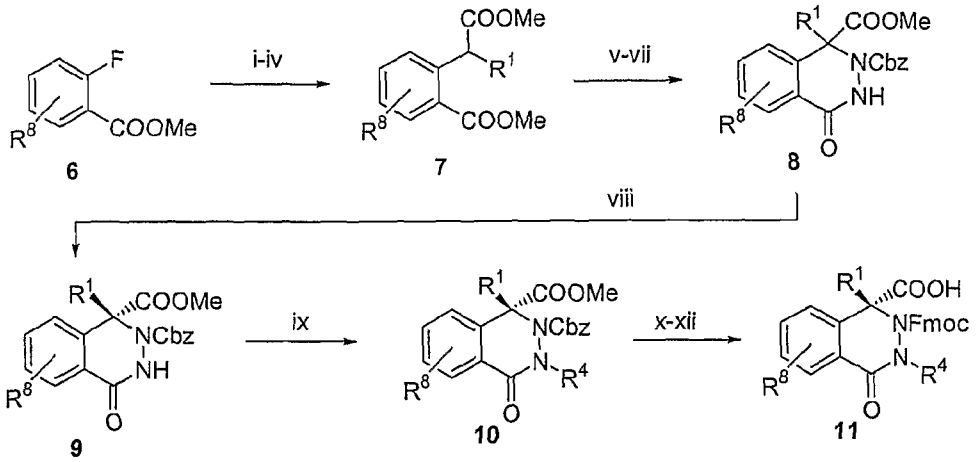
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1996, *52*, 1047-1068 ; M. H. Chen, O. P. Goel, J.-W. Hyun, J. Magano, J. R. Rubin, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1587-1592 (R^1= R^5= H; R^3= COOtBu); R. Baenteli, I. Brun, P. Hall, R. Metternich, *Tetrahedron Lett.* **1999**, *40*, 2109-2112 (R^1= R^5= H; R^3= COR); K. J. Hale, N. Jogiya, S. Manaviazar, *Tetrahedron* **1998**, *39*, 7163-7166 (R^1= H; R^3= COOBn; R^5= OBn); T. Kamenecka, S. J. Danishewsky, *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2995-2998(R^1= H; R^3= $COO(CH_2)_2SiMe_3$; R^5= $OSiMe_2tBu$.

A19: See Beilstein, Registry Number 648833 (R^1=R^4=R^8=H). Compounds of this type can be prepared according to *Scheme 2*.

Scheme 2.



i: NaH, $CH_2(COOMe)_2$, DMSO; ii: NaH, R^1-X, DMSO; iii: NaOHaq., MeOH, 75°; iv: DBU, MeI, DMF; v: LDA, BocN=NBoc; vi: TFA, CH_2Cl_2; vii: CbzCl, Na_2CO_3aq., dioxane; viii: enzymatic resolution (e.g. lipase); then DBU, MeI, DMF; ix: NaH, R^4-X, THF; x: Pd/C, H_2, EtOH; xi: LiOHx1H_2O, MeOH, H_2O; xii: FmocOSu,Na_2CO_3aq., dioxane

A20: See D. Hagiwara, H. Miyake, N. Igari, M. Karino, Y. Maeda, *J. Med. Chem.* **1994**, *37*, 2090-2099 (R^1= H; R^9= OH); Y. Arakawa, M. Yasuda, M. Ohnishi, S. Yoshifuji, *Chem. Pharm. Bull.* **1997**, *45*, 255-259 (R^1= H; R^9= COOH); P. J. Murray, I. D. Starkey, *Tetrahedron Lett.* **1996**, *37*, 1875-1878 (R^1= H; R^9= $(CH_2)_2NHCOCH_2Ph$); K. Clinch, A. Vasella, R. Schauer, *Tetrahedron Lett.* **1987**, *28*, 6425-6428 (R^1= H; R^9= NHAc).

A21: See A. Golubev, N. Sewald, K. Burger, *Tetrahedron Lett.* **1995**, *36*, 2037-2040; F. Machetti, F. M. Cordero, F. DeSario, A. Guarna, A. Brandi, *Tetrahedron Lett.* **1996**, *37*, 4205-4208; P. L. Ornstein, D. D. Schoepp, M. B. Arnold, J. D. Leander, D. Lodge, *J. Med. Chem.* **1991**, *34*, 90-97 ; R^1=R^6=H); P. D. Leeson, B. J. Williams, R. Baker, T. Ludduwahetty, K. W. Moore, M. Rowley, *J. Chem. Soc. Chem. Commun.* **1990**, 1578-1580; D. I. C. Scopes, N. F. Hayes, D. E. Bays, D. Belton, J. Brain, *J. Med. Chem.* **1992**, *35*, 490-501; H. Kessler, M. Kuehn, T. Löschner, *Liebigs Ann. Chem.* **1986**, 1-20 (R^1=R^6=H); C. Herdeis, W. Engel, *Arch. Pharm.* **1992**, *7*, 419-424 (R^1=R^6=Bn); C. Herdeis, W. Engel, *Arch. Pharm.* **1992**, 411-418 (R^1=COOMe; R^6=H); C. Herdeis, W. Engel, *Arch. Pharm.* **1992**, 419-424 (R^1=COOMe; R^6=Bn).

A22: See P. D. Leeson, B. J. Williams, R. Baker, T. Ladduwahetty, K. W. Moore, M. Rowley, *J. Chem. Soc. Chem. Comm.* **1990**, 1578-1580 (R^1= H; R^{10}= NHOBn).

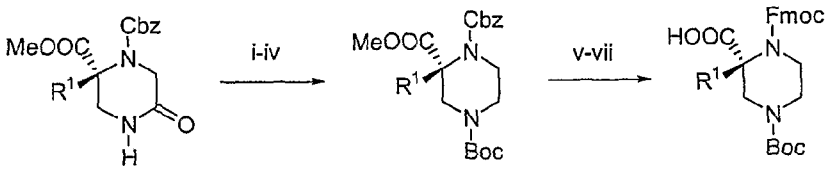
A23: See Beyerman, Boekee, *Recl. Trav. Chim. Pays-Bas* **1959**, *78*, 648-653; D. R. Adams, P. D . Bailey, I. D. Collier, J. D. Heffernan, S. Stokes *J. Chem. Soc. Chem. Commun.* **1996**, 349-350; J. E. Baldwin, R. M. Adlington, C. Godfrey, D. W. Collins, J. G. Vaughan, *J. Chem. Soc. Chem. Comm.* **1993**, 1434-1435 (R^1=R^6=H); C. Herdeis, W. Engel, *Arch. Pharm.* **1993**, 297-302 (R^1=COOMe; R^6=H).

A24: See Plieninger, Leonhäuser, *Chem. Ber.* **1959**, *92*, 1579-1584; D. W. Knight, N. Lewis, A. C. Share, D. Haigh, *J. Chem. Soc. Perkin Trans.1* **1998**, *22*, 3673-3684; J. Drummond, G. Johnson, D. G. Nickell, D. F. Ortwine, R. F. Bruns, B. Welbaum, *J. Med. Chem.* **1989**, *32*, 2116-2128; M. P. Moyer, P. L. Feldman, H. Rapoport, *J. Org. Chem.* **1985**, *50*, 5223-5230 (R^1=R^6=H); McElvain, Laughton, *J. Am. Chem. Soc.* **1951**, *73*, 448-451 (R^1=H; R^6=Ph); McElvain, Laughton, *J. Am. Chem. Soc.* **1951**, *73*, 448-451 (R^1=Ph; R^6=H);

A25: See L.-Y. Hu, T. R. Ryder, S. S. Nikam, E. Millerman, B. G. Szoke, M. F. Rafferty, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1121-1126; W. C. Lumma, R. D. Hartman, W. S. Saari, E. L. Engelhardt, V. J. Lotti, C. A. Stone, *J. Med. Chem.* **1981**, *24*, 93-101; N. Hosten, M. J. O. Antenuis, *Bull. Soc. Chim. Belg.* **1988**, *97*, 48-50; C. F. Bigge, S. J. Hays, P. M. Novak, J. T. Drummond, G. Johnson, T. P. Bobovski, *Tetrahedron Lett.* **1989**, *30*, 5193-5191; B. Aebischer, P. Frey, H.-P. Haerter, P. L. Herrling, W. Müller, *Helv. Chim. Acta* **1989**, *72*, 1043-1051; W. J. Hoeckstra, B. E. Maryanoff, B. P. Damiano, P. Andrade-Gordon, J. H. Cohen, M. J. Constanzo, B. J. Haertlein, L. R. Hecker, B. L. Hulshizer, J. A. Kauffman, P. Keane, *J. Med. Chem.* **1999**, *42*, 5254-5265 (R^1=H; R^{11}=H) ; B. D. Dorsey, R. B. Levin, S. L. McDaniel, J. P. Vacca, J. P. Guare, *J. Med. Chem.* **1994**, *37*, 3443-3451; M. Cheng, B. De, S. Pikul, N. G. Almstaed, M. G. Natchus, M. V. Anastasio, S. J. McPhail, C. J. Snider, Y. O. Taiwo, L. Chen, C. M. Dunaway, *J. Med. Chem.* **2000**, *43*, 369-380; R. Kuwano, Y. Ito, *J. Org. Chem.* **1999**, *64*, 1232-1237 (R^1=H; R^{11}=COOtBu); J. Kitchin, R. C. Bethell, N. Cammack, S. Dolan, D. N. Evans, *J. Med. Chem.* **1994**, *37*, 3707-3716 (R^1=H; R^{11}=COOPh); C. F. Bigge, S. J. Hays, P. M. Novak, J. T. Drummond, G. Johnson, T. P. Bobovski, *J. Med. Chem.* **1990**, *33*, 2916-2924 (R^1=H;R^{11}=COOtBu; $(CH_2)_3COOEt$; $(CH_2)_3PO(Me)OH$; $CH_2PO(OH)_2$; $(CH_2)_2PO(OEt)_2$; $(CH_2)_2PO(OH)_2$).

Compounds of type **A25** can also be prepared according to *Scheme 3:*

Scheme 3



12 13 14

i: Lawesson reagent, toluene, 80°; ii: DBU, MeI, DMF; iii: $NaBH_4$ or $NaCNBH_3$, MeOH; iv: Boc_2O, THF; v: $LiOHx1H_2O$, MeOH, H_2O; vi: Pd/C, H_2, EtOH; vii: FmocOSu, Na_2CO_3aq., dioxane

A26: See Koegel, *J. Biol. Chem.* **1953**, *201*, 547 (R^1=R^{12}=H).

A27: See G. Makara, G. R. Marshall, *Tetrahedron Lett.* **1997**, *38*, 5069-5072; R. N. Patel, A. Banerjee, R. L. Hanson, D. B. Brzozowski, L. W. Parker, L. J. Szarka, *Tetrahedron: Asymmetry* **1999**, *10*, 31-36 (R^1=H; R^{13}=OH, OtBu); J. E. Johanson, B. D. Christie, H. Rapoport, *J. Org. Chem.* **1981**, *46*, 4914-4920; N. Moss, J.-S. Duceppe, J.-M- Ferland, J. Gauthier, *J. Med. Chem.* **1996**, *39*, 2178-2187 (R^1= H ; R^{13}= CONHMe); G. M. Makara, G. R. Marshall, *Tetrahedron Lett.* **1997**, *38*, 5069-5072 (R^1=H; R^{13}= $SCH_2(4\text{-}MeO)C_6H_4$).

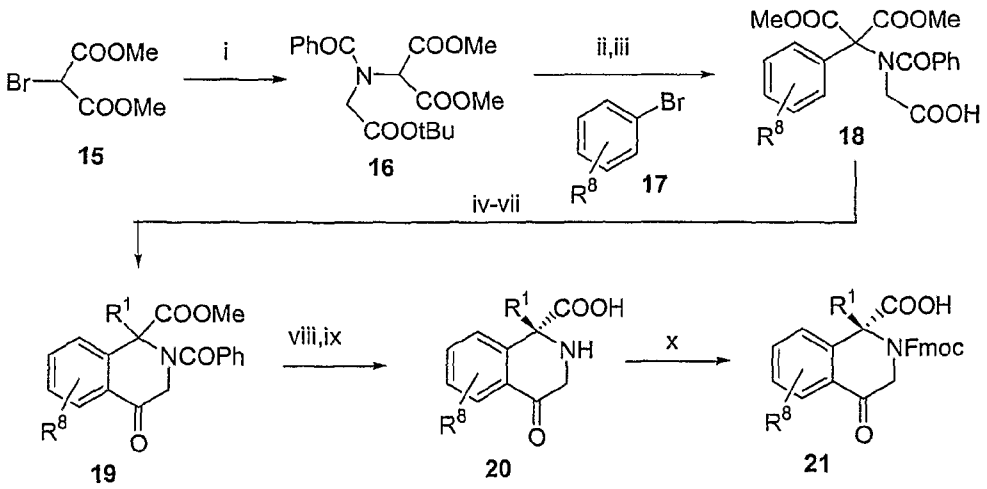
A28: See A. Golubev, N. Sewald, K. Burger, *Tetrahedron Lett.* **1995**, *36*, 2037-2040; P. L. Ornstein, D. D. Schoepp, M. B. Arnold, J. D. Leander, D. Lodge, *J. Med. Chem.* **1991**, *34*, 90-97 (R^1=R^6=H); P. D. Leeson, B. J. Williams, R. Baker, T. Ladduwahetty, K. W. Moore, M. Rowley, *J. Chem. Soc. Chem. Commun.* **1990**, *22*, 1578-1580; C. Herdeis, W. Engel, *Arch. Pharm.* **1991**, *324*, 670 (R^1=H ; R^6=Me); C. Herdeis, W. Engel, *Arch. Pharm.* **1991**, *324*, 670 (R^1=COOMe; R^6=H, Me).

A29: See Kawase, Masami, Chem. *Pharm. Bull.* **1997**, *45*, 1248-1253; I. G. C. Coutts, J. A. Hadfield, P. R. Huddleston, *J. Chem. Res. Miniprint*, **1987**, *9*, 2472-2500; I. G. C. Coutts, J. A. Hadfield, P. R. Huddleston, *J. Chem. Res. Miniprint*, **1987**, *9*, 2472-2500; V. J. Hrubi, W. L. Cody, A. M. Castrucci, M. E. Hadley, *Collect. Czech. Chem. Commun.* **1988**, *53*, 2549-2573; R. T. Shuman, R. B. Rothenberger, C. S. Campbell, G. F. Smith, D. S. Gifford-Moore, P. D. Gesellchen, *J. Med. Chem.* **1993**, *36*, 314-319; M. Kawase, Y. Okada, H. Miyamae, *Heterocycles*, **1998**, *48*, 285-294 (R^1=R^8=H); Kawase, Masami, Chem. *Pharm. Bull.* **1997**, *45*, 1248-1253 (R^1=H; R^8=6,7-(MeO_2); D. F. Ortwine, T. C. Malone, C. F. Bigge, J. T. Drummond, C. Humblet, *J. Med. Chem.* **1992**, *35*, 1345-1370 (R^1=H; R^8=7-$CH_2PO(OEt)_2$); E. J. Corey, D. Y. Gin, *Tetrahedron Lett.* **1996**, *37*, 7163-7166 (R^1= $CH_2SCOOtBu$); P. Dostert,

M. Varasi, A. DellaTorre, C. Monti, V. Rizzo, Eur. *J. Med. Chim. Ther.* **1992**, *27*, 57-59 (R^1=Me; R^8=6,7-$(OH)_2$); Z. Czarnocki, D. Suh, D. B. McLean, P. G. Hultin,W. A. Szarek, *Can. J. Chem.* **1992**, *70*, 1555-1561; B. Schönenberger, A. Brossi, *Helv. Chim. Acta* **1986**, *69*, 1486-1497 (R^1=Me; R^8=6-OH; 7-MeO); Hahn, Stiel, *Chem. Ber.* **1936**, *69*, 2627; M. Chrzanowska, B. Schönenberger, A. Brossi, J. L. Flippen-Anderson, *Helv. Chim. Acta* **1987**, *70*, 1721-1731; T. Hudlicky, *J. Org. Chem.* **1981**, *46*, 1738-1741 (R^1=Bn; R^8=6,7-$(OH)_2$); A. I. Meyers, M. A. Gonzalez, V. Struzka, A. Akahane, J. Guiles, J. S. Warmus, *Tetrahedron Lett.* **1991**, *32*, 5501-5504 (R^1=CH_2(3,4-methylenedioxy)C_6H_3; R^8=6,7-$(OMe)_2$).

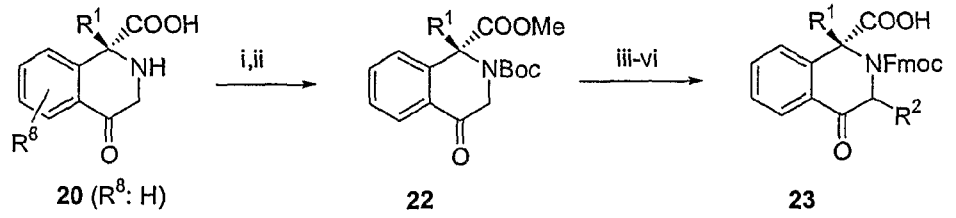
A30 and **A31** can be prepared according to *Schemes 4* and *5*.

Scheme 4



i: NaH, tert.-butyl N-benzoyl glycinate, DMF; ii: NaH, Pd(0), toluene; iii: TFA, CH_2Cl_2; iv: polyphosphoric acid; v: NaOHaq.,MeOH, 75°; then HClaq.; vi: DBU, MeI, DMF; vii: lithium hexamethyldisilazide,THF, chloro trimethylsilane, -78°; then R^1-X; viii: enzymatic resolution(e.g. lipase); then isolation as methylester: DBU, MeI, DMF; ix: NaOHaq., MeOH, heat; x: FmocOSu, Na_2CO_3aq., dioxane

Scheme 5



i: Boc_2O, Na_2CO_3aq., dioxane; ii: DBU, MeI, DMF; iii: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R^2-X; iv: $LiOHx1H_2O$, MeOH, H_2O; v:TFA, CH_2Cl_2; vi: FmocOSu, Na_2CO_3aq., dioxane

A32 can be prepared according to P. W. Schiller, G. Weltrowska, T. M.-D. Nguyen, C. Lemieux, N. Nga, *J. Med. Chem.* **1991**, *34*, 3125-3132; V. S. Goodfellow, M. V. Marathe, K. G. Kuhlman, T. D. Fitzpatrick, D. Cuadrato, *J. Med. Chem.* **1996**, *39*, 1472-1484; G. Caliendo, F. Fiorino, P. Grieco, E. Perissutti, S. DeLuca, A. Guiliano, G. Santelli, D. Califano, B. Severino, V. Santagada, *Farmacao*, **1999**, *54*, 785-790; V. S. Goodfellow, M. V. Marathe, K. G. Kuhlman, T. D. Fitzpatrick, D. Cuadro, *J. Med. Chem.* **1996**, *39*, 1472-1484

(R^1= R^8= H); D. Tourwe, E. Mannekens, N. T. Trang, P. Verheyden, H. Jaspers, *J. Med. Chem.* **1998**, *41*, 5167-5176; A.-K. Szardenings, M. Gordeev, D. V. Patel, *Tetrahedron Lett.* **1996**, *37*, 3635-3638; W. Wiczk, K. Stachowiak, P. Skurski, L. Lankiewicz, A. Michniewicz, A. Roy, *J. Am. Chem. Soc.* **1996**, *118*, 8300-8307; K. Verschuren, G. Toth, D. Tourwe, M. Lebl., G. van Binst, V. Hrubi, *Synthesis* **1992**, 458-460 (R^1= H; R^8= 6-OH); P. L. Ornstein, M. B. Arnold, N. K. Augenstein, J. W. Paschal, *J. Org. Chem.* **1991**, *56*, 4388-4392 (R^1= H; R^8= 6-MeO); D. Ma, Z. Ma, A. P. Kozikowski, S. Pshenichkin, J. T. Wroblenski, *Bioorg. Med. Lett.* **1998**, *8*, 2447-2450 (R^1= H; R^8= 6-COOH); U. Schöllkopf, R. Hinrichs, R. Lonsky, *Angew. Chem.* **1987**, *99*, 137-138 (R^1= Me; R^8=H); B. O. Kammermeier, U. Lerch, C. Sommer, *Synthesis* **1992**, 1157-1160 (R^1= COOMe; R^8=H); T. Gees, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **1993**, *76*, 2640-2653 (R^1= Me; R^8=6,7-(MeO_2).

A33: See Hinton, Mann, *J. Chem. Soc.* **1959**, 599-608.

A34: See G. P. Zecchini, M. P. Paradisi, *J. Heterocycl. Chem.* **1979**, *16*, 1589-1597; S. Cerrini, *J. Chem. Soc. Perkin Trans.1*, **1979**, 1013-1019; P. L. Ornstein, J. W. Paschal, P. D. Gesellchen, *J. Org. Chem.* **1990**, *55*, 738-741; G. M. Ksander, A. M. Yan, C. G. Diefenbacher, J. L. Stanton, *J. Med. Chem.* **1985**, *28*, 1606-1611; J. A. Robl, D. S. Karanewsky, M. M. Asaad, *Tetrahedron Lett.* **1995**, *36*, 1593-1596; S. Katayama, N. Ae, R. Nagata, *Tetrahedron: Asymmetry* **1998**, *9*, 4295-4300 (R^1=R^8=H); K. Hino, Y. Nagai, H. Uno, *Chem. Pharm. Bull.* **1988**, *36*, 2386-2400 (R^1=Me; R^8=H).

A35: See Beilstein Registry Numbers: 530775, 883013 (R^1=R^8=H).

A36: See R. W. Carling, P. D. Leeson, A. M. Moseley, R. Baker, A. C. Foster, *J. Med. Chem.* **1992**, *35*, 1942-1953; S. Kano, T. Ebata, S. Shibuya, *J. Chem. Soc. Perkin Trans.1*, **1980**, 2105-2111 (R^1=R^8=H); R. W. Carling, P. D. Leeson, A. M. Moseley, R. Baker, A. C. Foster, *J. Med. Chem.* **1992**, *35*, 1942-1953 (R^1=H; R^8=5-Cl; 7-Cl).

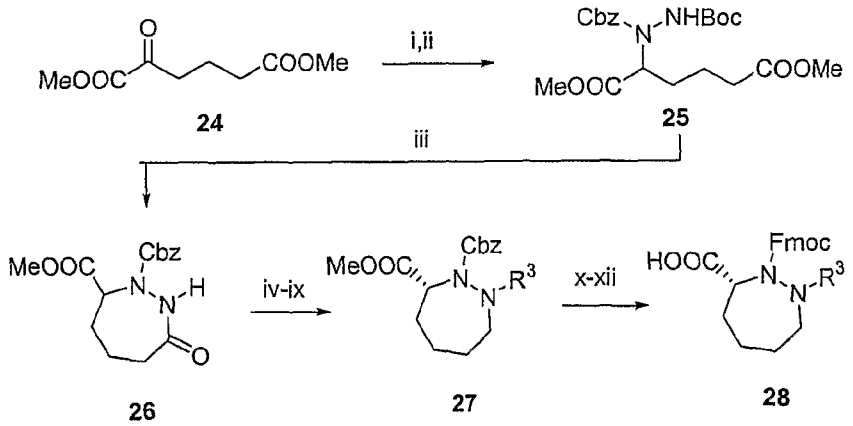
A37: See Nagarajan, *Indian J. Chem.* **1973**, *11*, 112 (R^1=CH_2COOMe; R^8=H).

A38: See R. Pauly, N. A. Sasaki, P. Potire, *Tetrahedron Lett.* **1994**, *35*, 237-240; J. Podlech, D. Seebach, *Liebigs Ann. Org. Bioorg. Chem.* **1995**, *7*, 1217-1228; K. C. Nicolaou, G.-Q. Shi, K. Namoto, F. Bernal, *J. Chem. Soc. Chem. Commun.* **1998**, 1757-1758 (R^1= H; R^2= H).

A39: See Beilstein, Registry Number 782885.

A40: See F. P. J. C. Rutjes, N. M. Terhuis, H. Hiemstra, N. W. Speckamp, *Tetrahedron* **1993**, *49*, 8605-8628 (R^1= H; R^3= Bn); compounds of this type can be prepared according to *Scheme 6*.

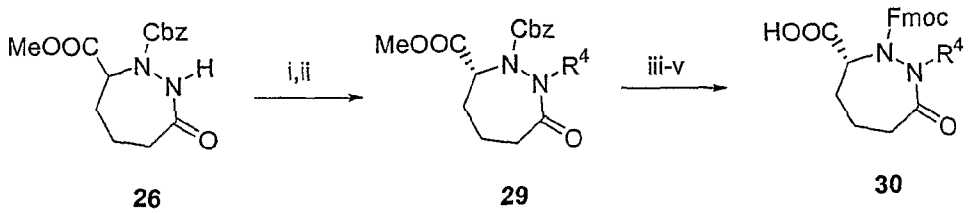
Scheme 6



i: $BocNHNH_2$, $NaCNBH_3$, MeOH, AcOH; ii: CbzCl, Et_3N, CH_2Cl_2; iii: TFA, CH_2Cl_2; then pyridine, DMAP, heat; iv: resolution (e.g. lipase); v: DBU, MeI, DMF; vi: Lawesson reagent, toluene, 75°; vii: DBU, MeI, DMF; viii: $NaBH_4$ or $NaCNBH_3$, MeOH; ix: R^3 introduced by reductive amination, alkylation or acylation; x: $LiOHx1H_2O$, MeOH, H_2O; xi: Pd/C, H_2, EtOH; xii: FmocOSu, Na_2CO_3aq., dioxane

A41: Compounds of this type can be prepared according to *Scheme 7*.

Scheme 7

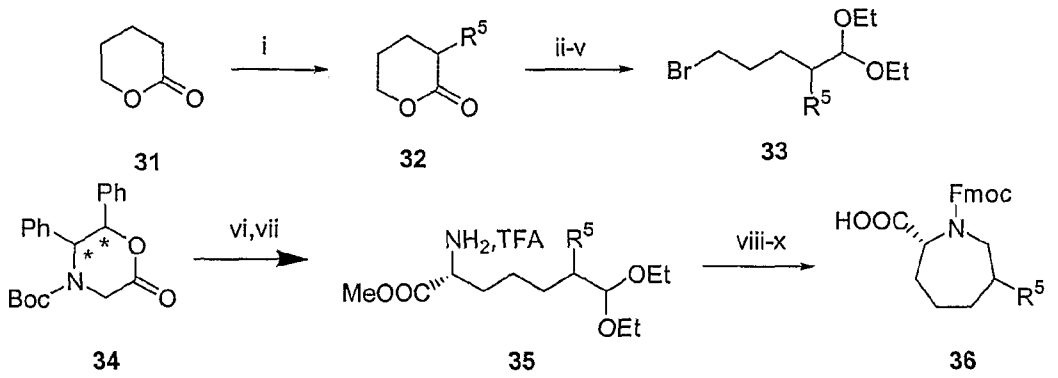


26 **29** **30**

i: resolution (e.g. lipase); then isolation as methylester: DBU, MeI, DMF;
ii: NaH, R^4-X, THF; iii: LiOHx1H_2O, MeOH, H_2O; iv: Pd/C, H_2, EtOH;
v: FmocOSu, Na_2CO_3aq., dioxane

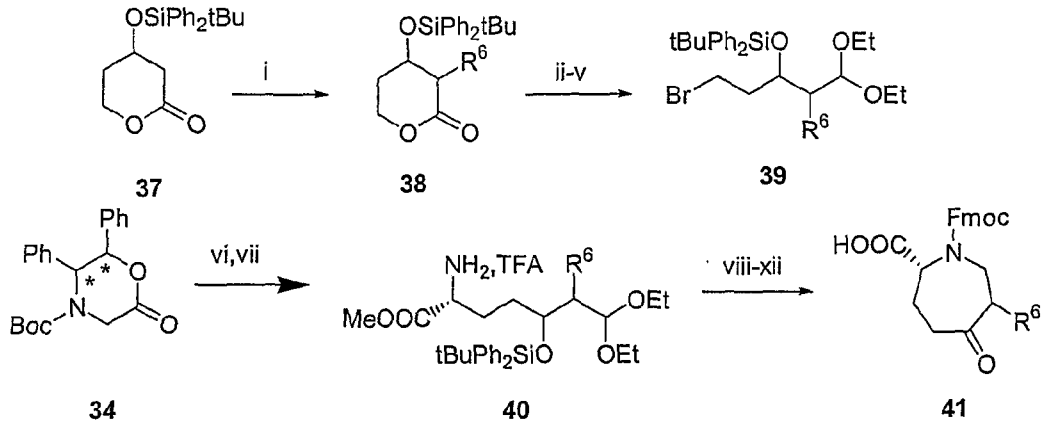
A42 to **A46**: Compounds of this type can be prepared according to *Scheme, 8* to *12*. Key intermediate **34** and α-amino acid synthesis involving this building block include: R. M. Williams, M.-N. Im, *Tetrahedron Lett.* **1988**, *29*, 6079-6082; R. M. Williams, M.-N. Im, *J. Am. Chem. Soc.***1991**, *113*, 9276-9286; J. F. Dellaria, B. D. Santarsiero, *Tetrahedron Lett.* **1988**, *29*, 6079-6082; J. F. Dellaria, B. D. Santarsiero, *J. Org. Chem.* **1989**, *54*, 3916-3926; J. E. Baldwin, V. Lee, C. J. Schofield, *Synlett* **1992**, 249-251; J. E. Baldwin, V. Lee, C. J. Schofield, *Heterocycles* **1992**, *34*, 903-906.

Scheme 8



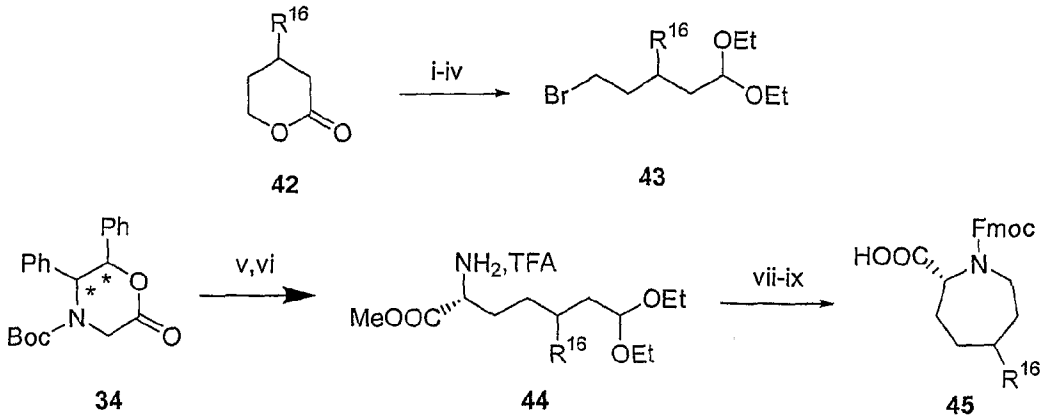
i: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R^5-X; ii: HBr; iii: DBU, MeI, DMF; iv: DIBAL-H, THF; v: EtOH, pyridinium p-toluenesulfonate, mol.sieves 4A; vi: lithium hexamethyldisilazide, THF, -78°, **33**; vii: Pd/C, H_2, EtOH; then DBU, MeI, DMF; then TFA, CH_2Cl_2; viii: HClaq., THF; then $Na(OAc)_3BH$, AcOH, dichloroethane; ix: $LiOHx1H_2O$, MeOH, H_2O; x: FmocOSu, Na_2CO_3aq., dioxane

Scheme 9



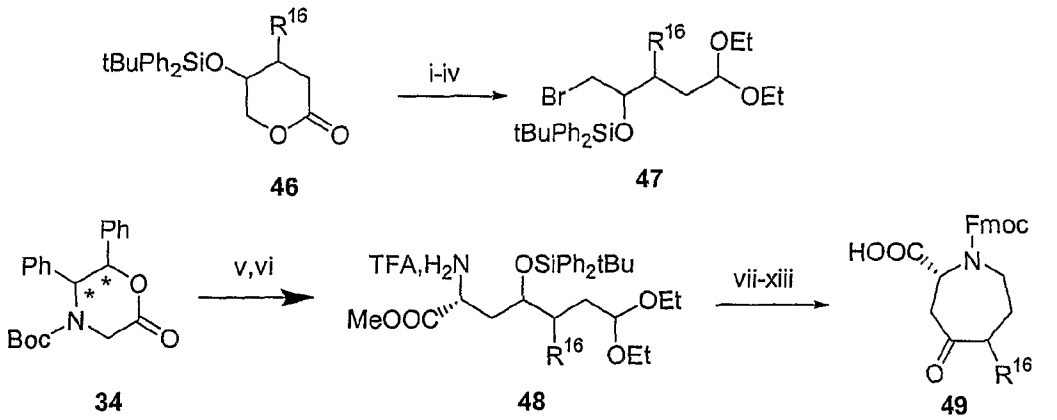
i: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R^6-X; ii: HBr; iii: DBU, MeI, DMF; iv: DIBAL-H, THF; v: EtOH, pyridinium p-toluenesulfonate, mol.sieves 4A; vi: lithium hexamethyldisilazide, THF, -78°, **39**; vii: Pd/C, H_2, EtOH; then DBU, MeI, DMF; then TFA, CH_2Cl_2; viii: HClaq., THF; then $Na(OAc)_3BH$, AcOH, dichloroethane; viii: Boc_2O, Et_3N, CH_2Cl_2; ix: $Bu_4NFx10H_2O$, THF; ix: pyridinium chlorochromate; x: $LiOHx1H_2O$, MeOH, H_2O; xi: TFA, CH_2Cl_2; xii: FmocOSu, Na_2CO_3aq., dioxane

Scheme 10



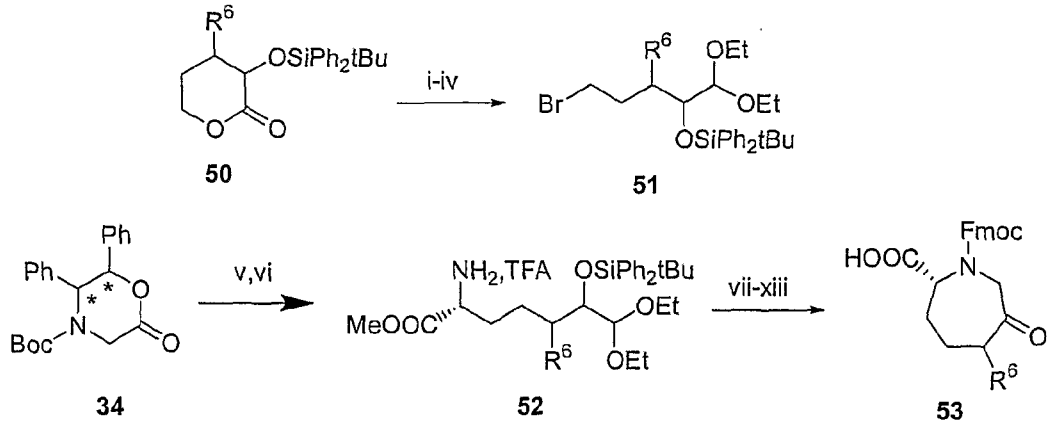
i: HBr; ii: DBU, MeI, DMF; iii: DIBAL-H, THF; iv: EtOH, pyridinium p-toluenesulfonate, mol. sieves 4A; v: lithium hexamethyldisilazide, THF, -78°, **43**; vi: Pd/C, H_2, EtOH; then DBU, MeI, DMF; then TFA, CH_2Cl_2; vii: HClaq., THF; then $Na(OAc)_3BH$, AcOH, dichloroethane; viii: $LiOHx1H_2O$, MeOH, H_2O; ix: FmocOSu, Na_2CO_3aq., dioxane

Scheme 11



i: HBr; ii: DBU, MeI, DMF; iii: DIBAL-H, THF; iv: EtOH, pyridinium p-toluenesulfonate, mol. sieves 4A; v: lithium hexamethyldisilazide, THF, -78°, **47**; vi: Pd/C, H_2, EtOH; then DBU,MeI, DMF; then TFA, CH_2Cl_2; vii: HClaq., THF; then $Na(OAc)_3BH$, AcOH, dichloroethane; viii Boc_2O, Et_3N, CH_2Cl_2; ix: $Bu_4NFx10H_2O$, THF; x: pyridinium chlorochromate; xi: $LiOHx1H_2O$, MeOH, H_2O; xii: TFA, CH_2Cl_2; xiii: FmocOSu, Na_2CO_3aq., dioxane

Scheme 12



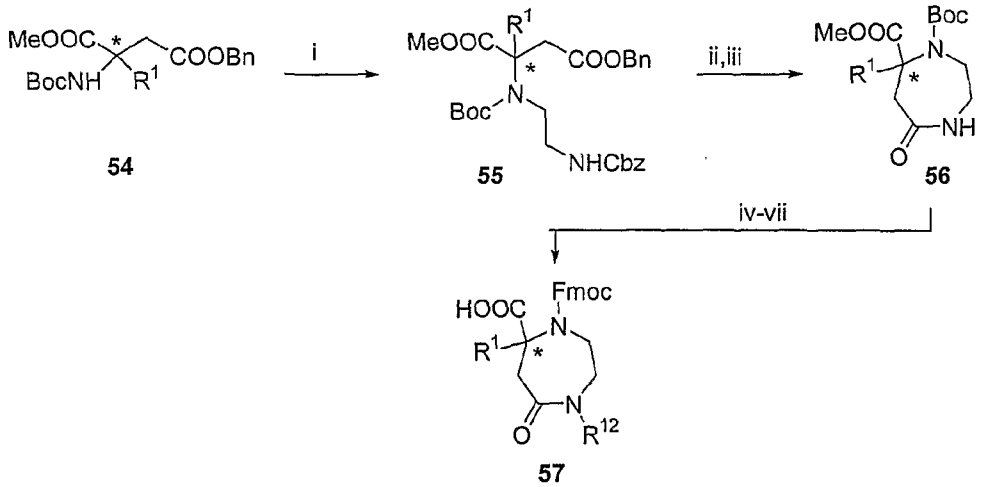
i: HBr; ii: DBU, MeI, DMF; iii: DIBAL-H, THF; iv: EtOH, pyridinium p-toluenesulfonate, mol. sieves 4A; v: lithium hexamethyldisilazide, THF, -78°, **51**; vi: Pd/C, H_2, EtOH; then DBU, MeI, DMF; then TFA, CH_2Cl_2; vii: HClaq., THF; then $Na(OAc)_3BH$, AcOH, dichloroethane; viii: Boc_2O, Et_3N, CH_2Cl_2; ix: $Bu_4NFx10H_2O$, THF; x: pyridinium chlorochromate; xi: $LiOHx1H_2O$, MeOH, H_2O; xii: TFA, CH_2Cl_2; xiii: FmocOSu, Na_2CO_3aq., dioxane

A47: See P. Barraclough, R. D. Farrant, D. Kettle, S. Smith, *J. Chem. Res. Miniprint* **1991**, *11*, 2876-2884 (R^1=R^{11}=H, Bn, $(CH_2)_2PO(OEt)_2$).

A48: See A. Nouvet, M. Binard, F. Lamaty, J. Martinez, R. Lazaro, *Tetrahedron* **1999**, *55*, 4685-4698 (R^1=R^{12}=H).

A49: See M. Y. Kolleganov, I. G. Kolleganova, M. D. Mitrofanova, L. I. Martynenko, P. P. Nazarov, V. I. Spitsyn, *Bull. Acad. Sci. USSR Div. Chem. Sci (Engl. Trans.)* **1983**, *32*, 1293-1299; *Izv. Akad. Nauk SSSR Ser. Khim.* **1983**, *6*, 1293-1299 ; V. P. Vasilev, T. D. Orlova, S. F. Ledenkov, *J. Gen. Chem. USSR* (Engl. Trans. **1989**, *59*, 1629-1634; *Zh. Obshch. Khim.* 1989, *59*, 1828-1833 (R^1=H; R^{12}= $CH(COOH)CH_2COOH$). Compounds of type **A49** can also be prepared according to *Scheme 13*.

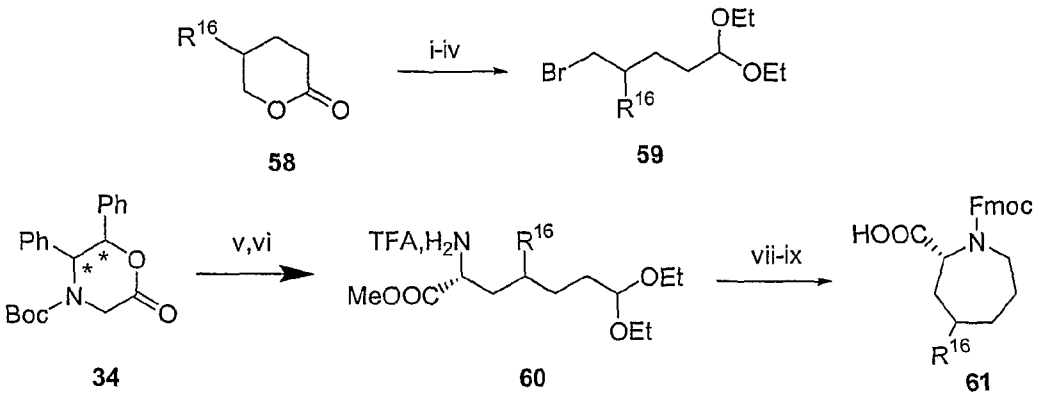
Scheme 13



i: NaH, $CbzNH(CH_2)_2Br$, THF; ii: Pd/C, H_2, EtOH; iii: EDCI, CH_2Cl_2, diisopropylethylamin; iv: NaH, R^{12}-X, THF; v: $LiOHx1H_2O$, MeOH, H_2O; vi: TFA, CH_2Cl_2; vii: FmocOSu, Na_2CO_3aq., dioxane

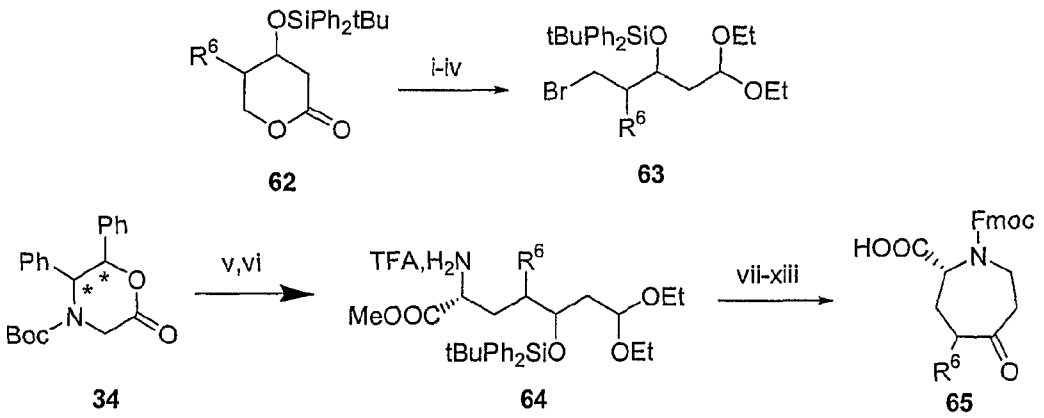
A50 and **A51**: Compounds of these types can be prepared according to *Schemes 14* and *15*.

Scheme 14



i: HBr; ii: DBU, MeI, DMF; *iii*: DIBAL-H, THF; *iv*: EtOH, pyridinium p-toluenesulfonate, mol. sieves 4A; v: lithium hexamethyldisilazide, THF, -78°, **59**; vi: Pd/C, H_2, EtOH; then DBU, MeI, DMF; then TFA, CH_2Cl_2; vii: HClaq., THF; then $Na(OAc)_3BH$, AcOH, dichloroethane; viii: $LiOHx1H_2O$, MeOH, H_2O; ix: FmocOSu, Na_2CO_3aq., dioxane

Scheme 15

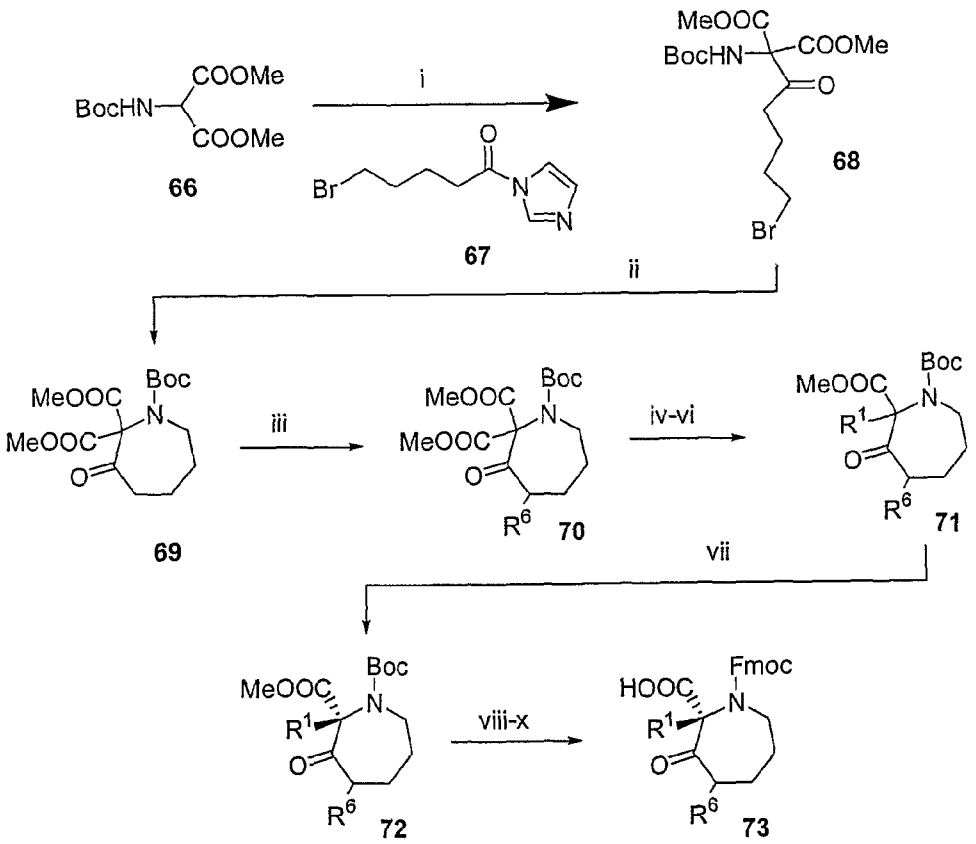


i: HBr; ii: DBU, MeI, DMF; iii: DIBAH, THF; iv: EtOH, pyridinium p-toluenesulfonate, mol. sieves 4A; v: lithium hexamethyldisilazide, THF, -78°, **63** vi: Pd/C, H_2, EtOH; then DBU, MeI, DMF; then TFA, CH_2Cl_2; vii: HClaq., THF; then $Na(OAc)_3BH$, AcOH, dichloroethane; viii: Boc_2O, Et_3N, CH_2Cl_2; ix: $Bu_4NFx10H_2O$, THF; x: pyridinium chlorochromate; xi: $LiOHx1H_2O$, MeOH, H_2O; xii: TFA, CH_2Cl_2; xiii: FmocOSu, Na_2CO_3aq., dioxane

A53: See P. Barraclough, R. D. Farrant, D. Kettle, S. Smith, *J. Chem. Res. Miniprint* **1991**, *11*, 2876-2884(R^1=R^{11}=H ; R^1=H ; R^{11}= Bn, $(CH_2)_3PO(OH)_2$); $(CH_2)_3PO(Et)_2$); J. I. Levin, J. F. DiJoseph, L. M. Killar; A. Sung, T. Walter, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2657-2662 (R^1=H; R^{11}= $4CF_3OC_6H_4CO$).

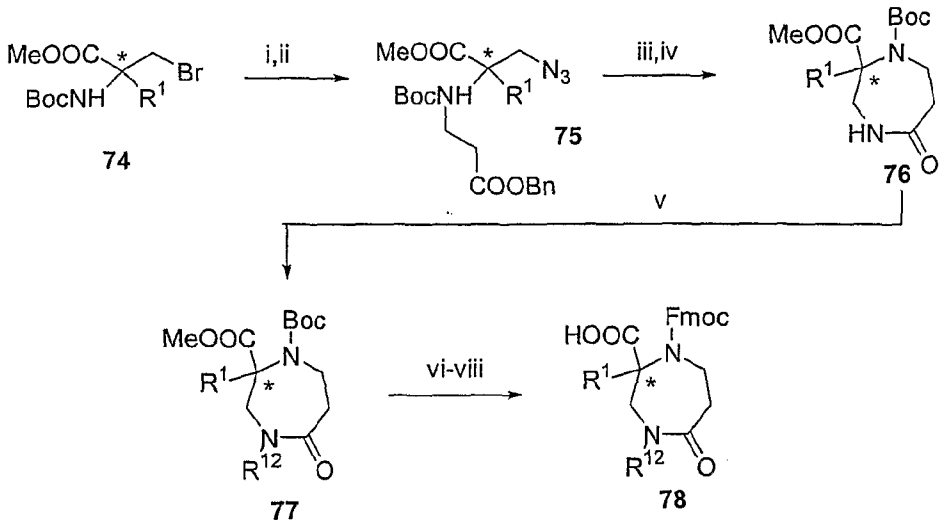
A 52 and A54: Compounds of this type can be prepared according to *Schemes 16* and *17*.

Scheme 16



i: iBuMgCl,THF; ii: NaH, THF; iii: lithium hexamethyldisilazide, THF, chlorotrimetylsilane, -78°; then R^6-X; iv: NaOHaq., MeOH, 75°; then HClaq.; v: DBU, MeI, DMF; vi: lithium hexamethyl-disilazide , THF, chlorotrimetylsilane, -78°; then R^1-X; vii: resolution (e.g. lipase); then DBU, MeI, DMF; viii: LiOHx1H_2O, MeOH, H_2O; ix: TFA, CH_2Cl_2; x: FmocOSu, Na_2CO_3aq., dioxane

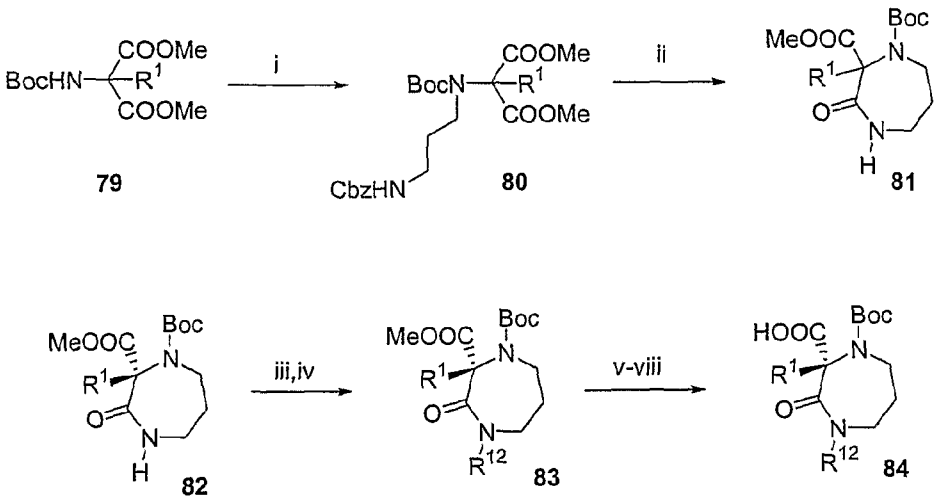
Scheme 17



i:NaN_3, DMSO; ii: NaH, THF, CH_2=CHCOOBn; iii: Pd/C, H_2, EtOH; iv: EDCI, CH_2Cl_2, diisopropylethylamine; v: NaH, R^{12}-X, THF; vi: LiOHx1H_2O, MeOH, H_2O; vii: TFA, CH_2Cl_2; viii: FmocOSu, Na_2CO_3aq., dioxane

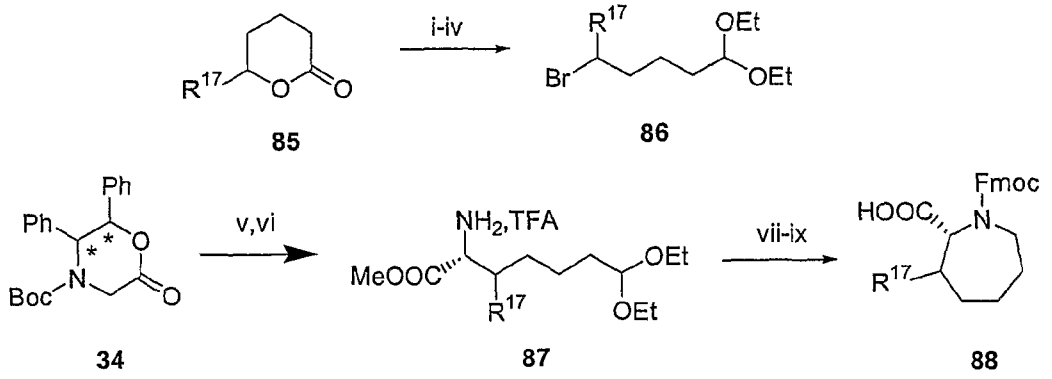
A55 and **A56**: Compounds of this type can be prepared according to *Schemes 18* and *19*.

Scheme 18



i:NaH, THF, $CbzNH(CH_2)_3Br$; ii: Pd/C, H_2, EtOH; then toluene, heat; iii: resolution (e.g. lipase); iv: DBU, MeI, DMF; v: NaH, R^{12}-X, THF; vi: $LiOHx1H_2O$, MeOH, H_2O; vii: TFA, CH_2Cl_2; viii: FmocOSu, Na_2CO_3aq., dioxane

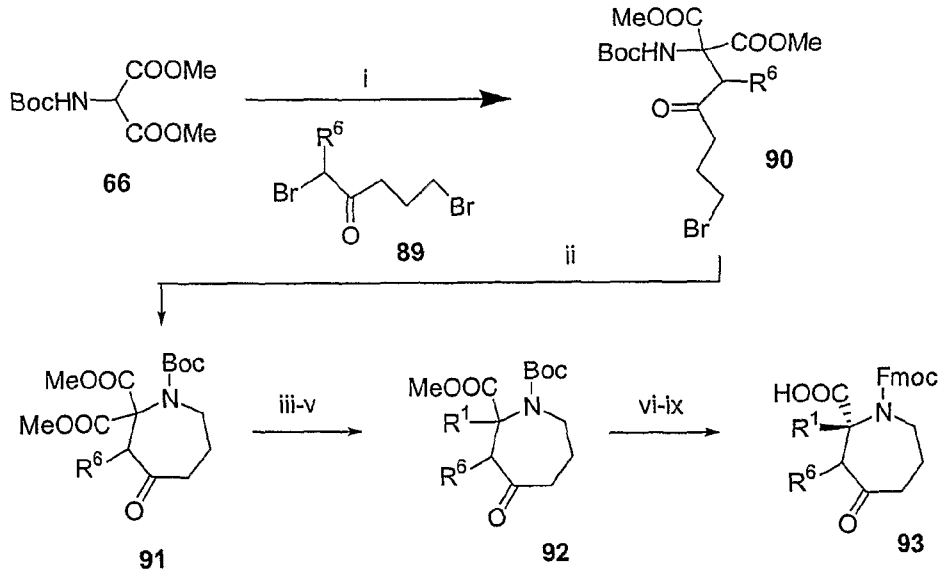
Scheme 19



i: HBr; ii: DBU, MeI, DMF; iii: DIBAL-H, THF; iv: EtOH, pyridinium p-toluenesulfonate, mol. sieves 4A; v: lithium hexamethyldisilazide, THF, -78°, **86**; vi: Pd/C, H_2, EtOH; then DBU, MeI, DMF; then TFA, CH_2Cl_2; vii: HClaq., THF; then $Na(OAc)_3BH$, AcOH, dichloroethane; viii: $LiOHx1H_2O$, MeOH, H_2O; ix: FmocOSu, Na_2CO_3aq., dioxane

A57: Compounds of this type can be prepared according to *Scheme 20*.

Scheme 20

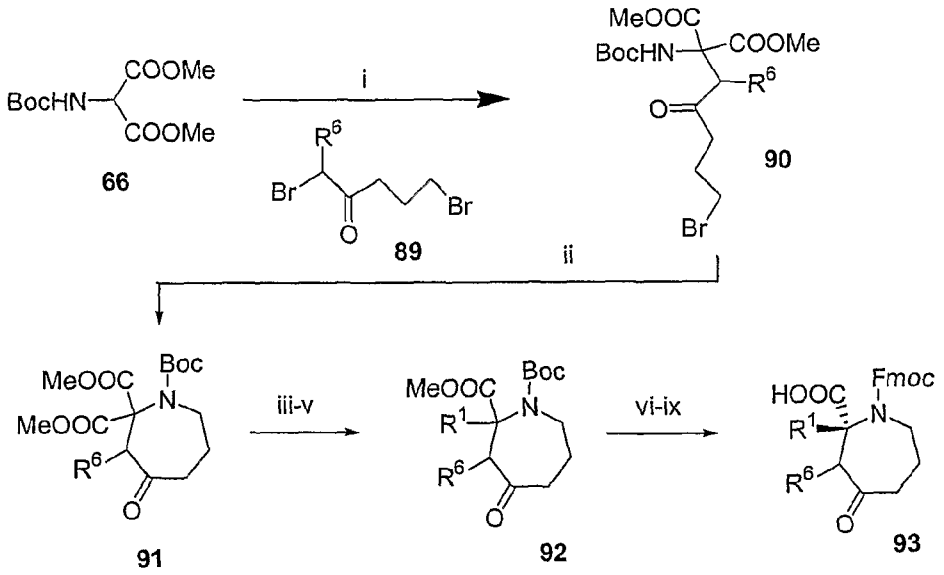


i: NaOMe, MeOH; ii: NaH, THF; iii: NaOHaq., MeOH, 75°; then HClaq.; iv: DBU, MeI, DMF; v: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R^1-X; vi: resolution (e.g. lipase); then isolation of methylester: DBU, MeI, DMF; vii: LiOHx1H_2O, MeOH, H_2O; viii:TFA, CH_2Cl_2; ix: FmocOSu, Na_2CO_3aq., dioxane

A58: See C.-H. Lee, H. Kohn, *J. Org. Chem.* **1990**, *55*, 6098-6104 (R^1=R^8=H).

A59: can be prepared according to *Scheme 21*.

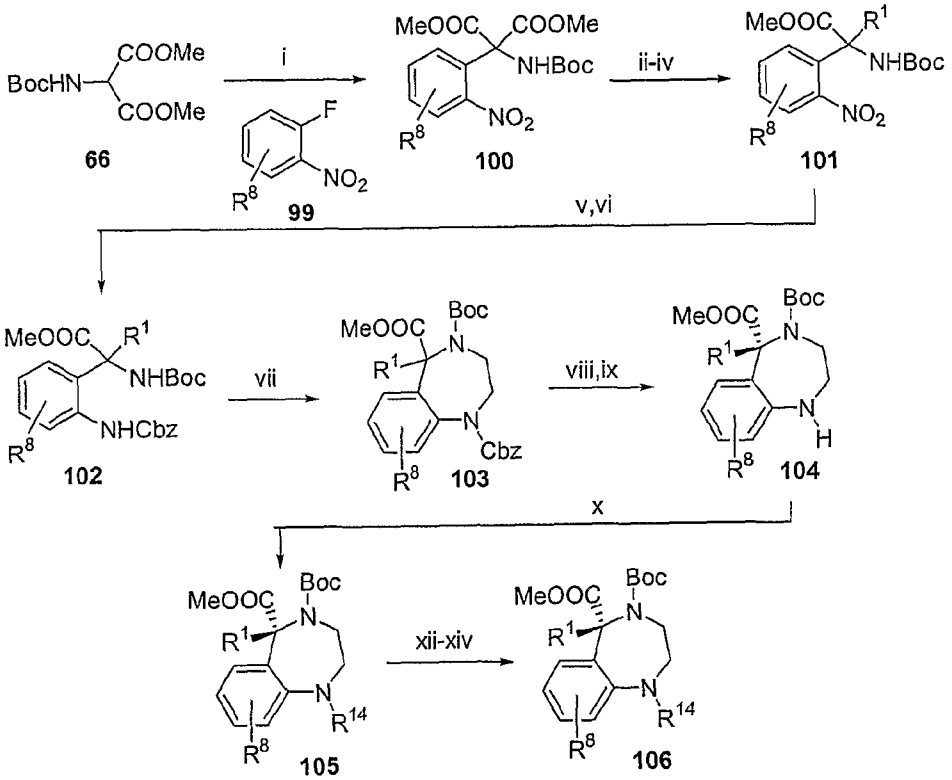
Scheme 21



i: NaOMe, MeOH; ii: NaH, THF; iii: NaOHaq., MeOH, 75°; then HClaq.; iv: DBU, MeI, DMF; v: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R^1-X; vi: resolution (e.g. lipase); then isolation of methylester: DBU, MeI, DMF; vii: LiOHx1H_2O, MeOH, H_2O; viii:TFA, CH_2Cl_2; ix: FmocOSu, Na_2CO_3aq., dioxane

A60: Compounds of this type can be prepared according to *Scheme 22*.

Scheme 22

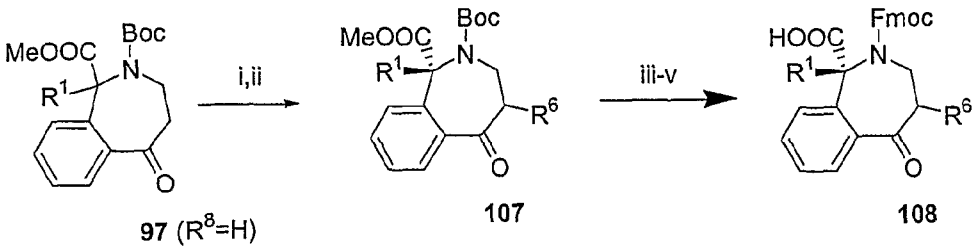


i: NaH, DMSO; ii: NaOHaq., MeOH, 75°; then HClaq.; iii: DBU, MeI, DMF; iv: NaOMe (2.2equiv.), R^1-X; v: Raney-Ni, H_2, EtOH; vi: CbzCl, Et_3N, CH_2Cl_2; vii: NaH, $Br(CH_2)_2Br$, THF; viii: resolution (e.g. lipase); then DBU, MeI, DMF; ix: Pd/C, H_2, EtOH; x: NaH, R^{14}-X, THF; xi: LiOHx1H_2O, MeOH, H_2O; xii: TFA, CH_2Cl_2; xiii: FmocOSu, Na_2CO_3aq., dioxane

A61: See D. R. Armour, K. M. Morriss, M. S. Congreve, A. B. Hawcock, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2037-2042 (R^1=R^{12}=H).

A62: Compounds of this type can be prepared according to *Scheme 23*.

Scheme 23

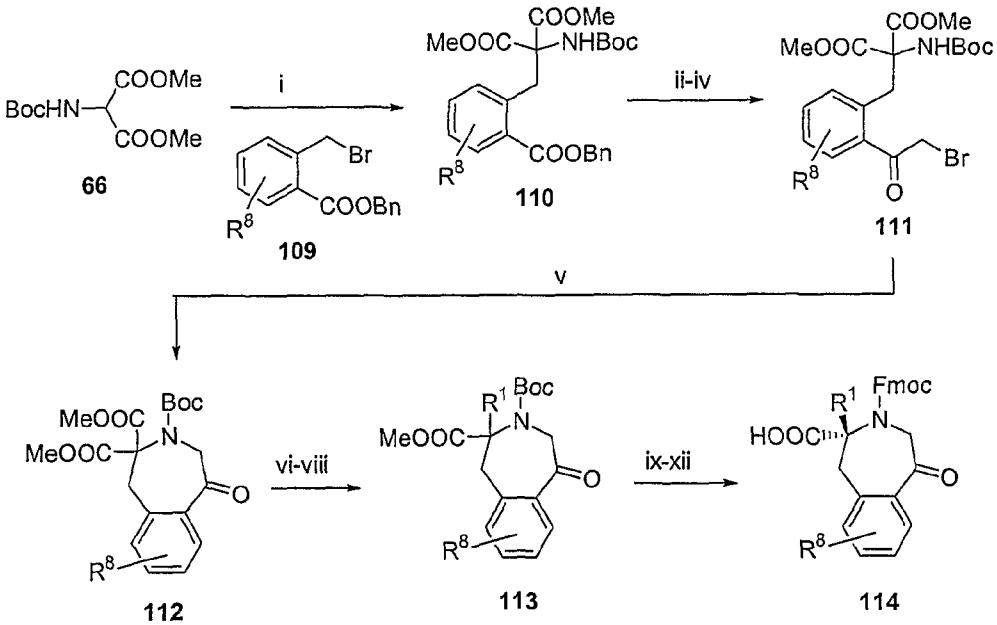


i: resolution (e.g. lipase); then DBU, MeI, DMF; ii: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R^6-X; iii: LiOHx1H_2O, MeOH, H_2O; iv: TFA, CH_2Cl_2; v: FmocOSu, Na_2CO_3aq., dioxane

A63: See S. E. Gibson, N. Guillo, R. J. Middleton, A. Thuilliez, M. J. Tozer, *J. Chem. Soc. Perkin Trans.1*, **1997**, *4*, 447-456; S. E. Gibson, N. Guillo, S. B. Kalindjan, M. J. Tozer, *Bioorg. Med. Chem. Lett,*. **1997**, *7*, 1289-1292 (R^1=H; R^8= H); Beilstein Registry Number: 459155 (R^1=H; R^8= 4,5-MeO_2).

A64: Compounds of this type can be prepared according to *Scheme 24*.

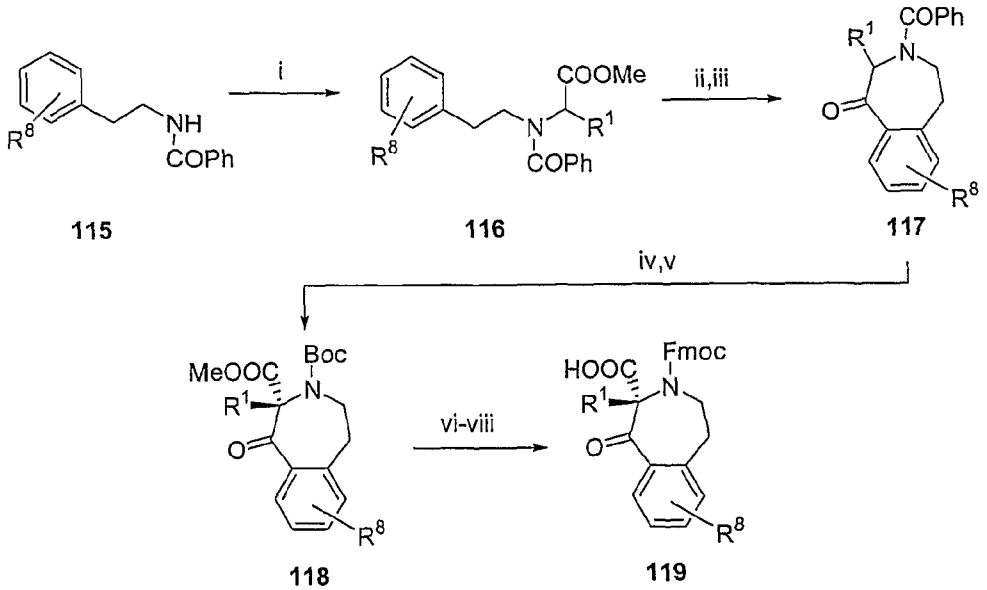
Scheme 24



i: NaH, DMSO; ii: Pd/C, H_2, EtOH; iii: iBuOCOCl, diisopropylethylamine, CH_2Cl_2; then diazomethane; iv: HBr, CH_2Cl_2; v: NaH, THF; vi: NaOHaq., MeOH, 75°; then HClaq.; vii: DBU, MeI, DMF; viii: lithium diisopropylamide, THF, chlorotrimethylsilane, -78°; then R^1-X; ix: resolution (e.g. lipase); then isolation of methylester: DBU, MeI, DMF; x: LiOHx1H_2O, MeOH, H_2O; xi: TFA, CH_2Cl_2; xii: FmocOSu, Na_2CO_3aq., dioxane

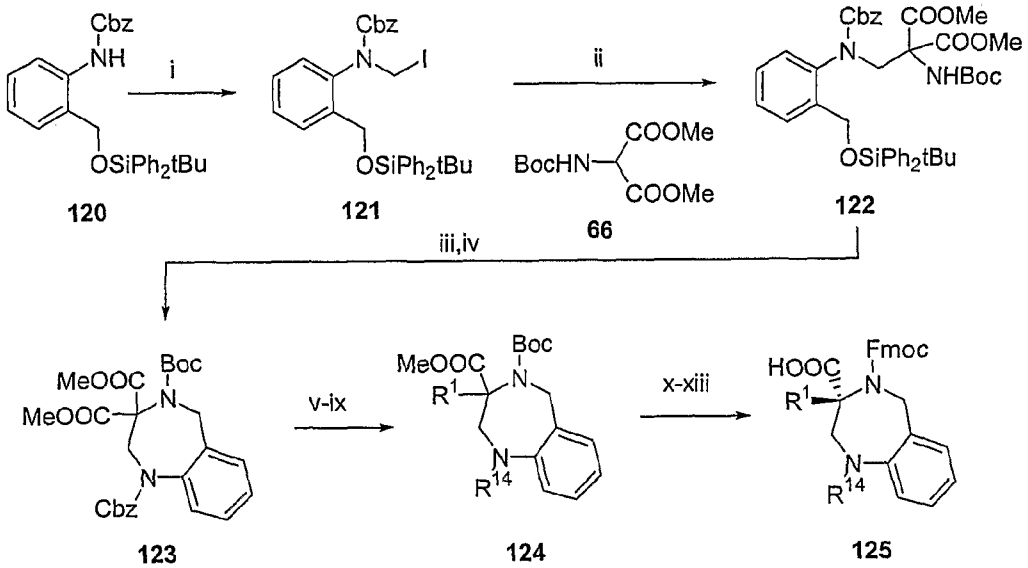
A65 and **A 67**: Compounds of these types can be prepared according to *Schemes 25* and *26*.

Scheme 25



i: NaH, DMSO, $BrCH(R^1)COOMe$; ii: $LiOHx1H_2O$, MeOH, H_2O; iii: polyphosphoric acid; iv: NaH, ClCOOMe, THF; v: resolution (e.g. lipase); then isolation as methylester: DBU, MeI, DMF; vi: $LiOHx1H_2O$, MeOH, H_2O; vii: TFA, CH_2Cl_2; viii: FmocOSu, Na_2CO_3aq., dioxane

Scheme 26



i: NaH, THF, CH_2I_2; ii: NaH, DMSO; iii: $Bu_4NFx10H_2O$, THF; iv: methanesulfonylchloride, Et_3N, CH_2Cl_2; then NaH, THF; v: NaOHaq., MeOH, 75°; then HClaq.; vi: DBU, MeI, DMF; vii: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R^1-X; viii: Pd/C, H_2, EtOH; ix: NaH, THF, R^{14}-X; x: resolution (e.g. lipase); then isolation of methylester: DBU, MeI, DMF; xi: $LiOHx1H_2O$, MeOH, H_2O; xii: TFA, CH_2Cl_2; xiii: FmocOSu, Na_2CO_3aq., dioxane

A66: See G. L. Grunewald, L. H. Dahanukar, *J. Heterocycl. Chem.* **1994**, *31*, 1609-1618 (R^1=H ; R^8=H, 8-NO_2 ; C(1)=O).

A68: See Griesbeck , H. Mauder, I. Müller, *Chem. Ber.* **1992**, *11*, 2467-2476; (R^1=R^8=H; C(1)=O).

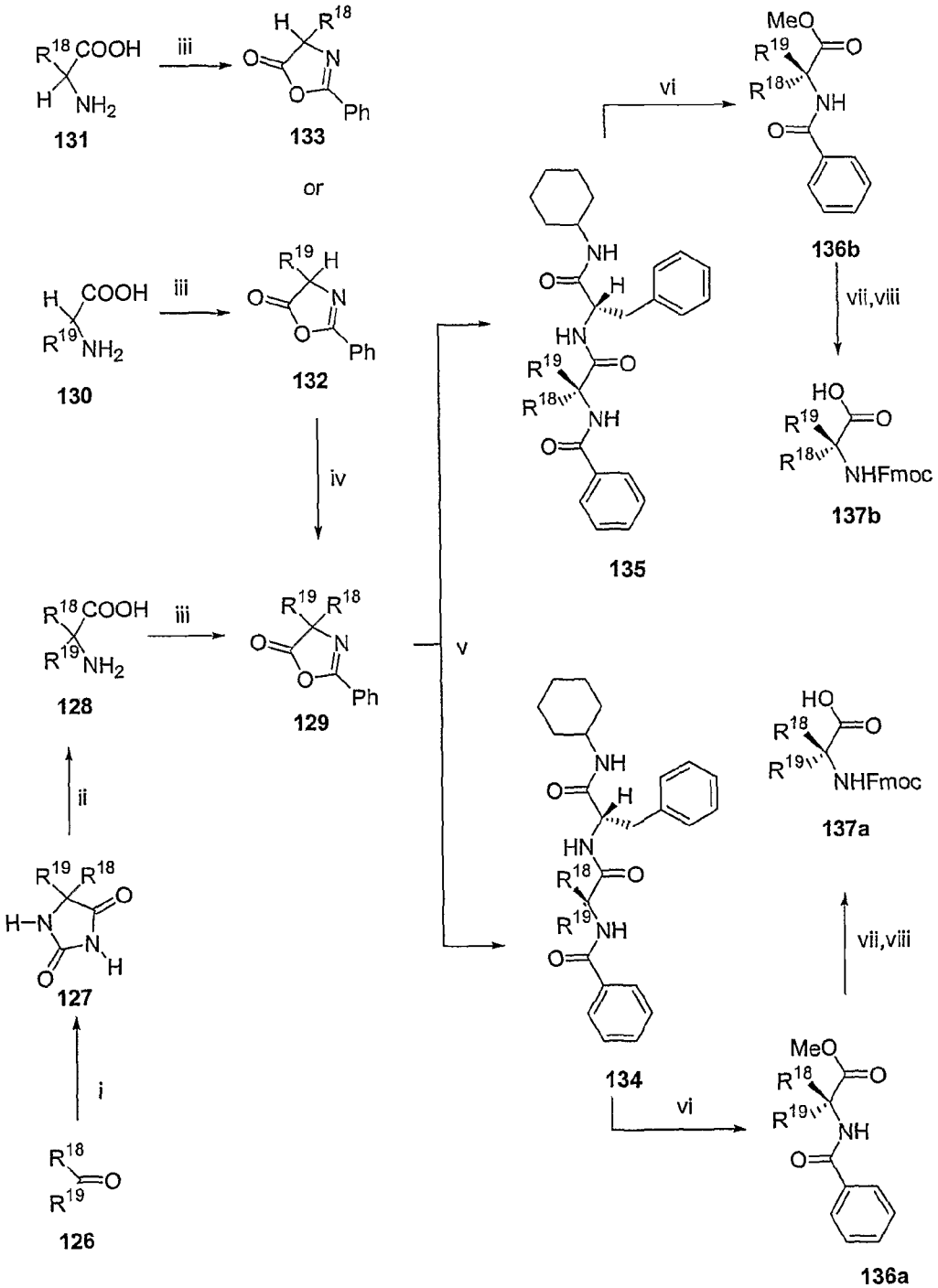
A69: R. Kreher, W. Gerhardt, *Liebigs Ann. Chem.* **1981**, 240-247 (R^1=R^8=H).

As explained above, building blocks **A70** belong to the class of open-chain α-substituted α-amino acids, **A71** and **A72** to the class of the the corresponding β-amino acid analogues and **A73-A104** to the class of the cyclic analogues of **A70**.

Building blocks of types **A70** and **A73-A104** have been synthesized by several different general methods: by [2+2] cycloaddition of ketenes with imines (I. Ojima, H. J. C. Chen, X. Quin, *Tetrahedron Lett.* **1988**, *44*, 5307-5318); by asymmetric aldol reaction (Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashikazi, T. Hayashi, *Tetrahedron Lett.* **1988**, *29*, 235-238; by the oxazolidinone method (J. S. Amato, L. M. Weinstock, S. Karady, US 4508921 A; M. Gander-Coquoz, D. Seebach, *Helv. Chim. Acta* **1988**, *71*, 224-236; A. K. Beck, D. Seebach, *Chimia* **1988**, *42*, 142-144; D. Seebach, J. D. Aebi, M. Gander-Coquoz, R. Naef, *Helv. Chim. Acta* **1987**, *70*, 1194-1216; D. Seebach, A. Fadel, *Helv. Chim. Acta* **1995**, *68*, 1243-1250; J. D. Aebi, D. Seebach, *Helv. Chim. Acta* **1985**, *68*, 1507-1518; A. Fadel, J. Salaun, *Tetrahedron Lett.* **1987**, *28*, 2243-2246); by Schmidt- rearrangement of α,α-disubstituted α-ketoesters (G. I. Georg, X. Guan, J. Kant, *Tetrahedron Lett.* **1988**, *29*, 403-406); asymmetric synthesis via chiral Ni(II)- derived Schiff-bases (Y. N. Belokon, V. I. Bakhmutov, N. I. Chernoglazova, K. A. Kochetov, S. V. Vitt, N. S. Garbalinskaya, V. M. Belikov, *J. Chem. Soc. Perkin Trans. 1*, **1988**, 305-312; M. Kolb, J. Barth, *Liebigs Ann. Chem.* **1983**, 1668-1688); by the bis-lactim ether synthesis (U. Schöllkopf, R. Hinrichs, R. Lonsky, *Angew. Chem.* **1987**, *99*, 137-138); by microbial resolution (K. Sakashita, I. Watanabe, JP 62/253397 A2) and by the hydantoin method combined with resolution of the racemic amino acids with chiral auxilliaries derived from L-phenylalanine amides (D. Obrecht, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* **1992**, *75*, 1666-1696; D. Obrecht, U. Bohdal, J. Daly, C. Lehmann, P. Schönholzer, K. Müller, *Tetrahedron* **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; D. Obrecht, M. Altorfer, C. Lehmann, P. Schönholzer, K. Müller, *J. Org. Chem.* **1996**, *61*,

4080-4086; D. Obrecht, C. Abrecht, M. Altorfer, U. Bohdal, A. Grieder, P. Pfyffer, K. Müller, *Helv. Chim. Acta* **1996**, *79*, 1315-1337). The latter method has been especially useful in preparing both enantiomers of building blocks of type **A70** (see Scheme 27) and **A73-A104** (see *Scheme 28*) in pure form.

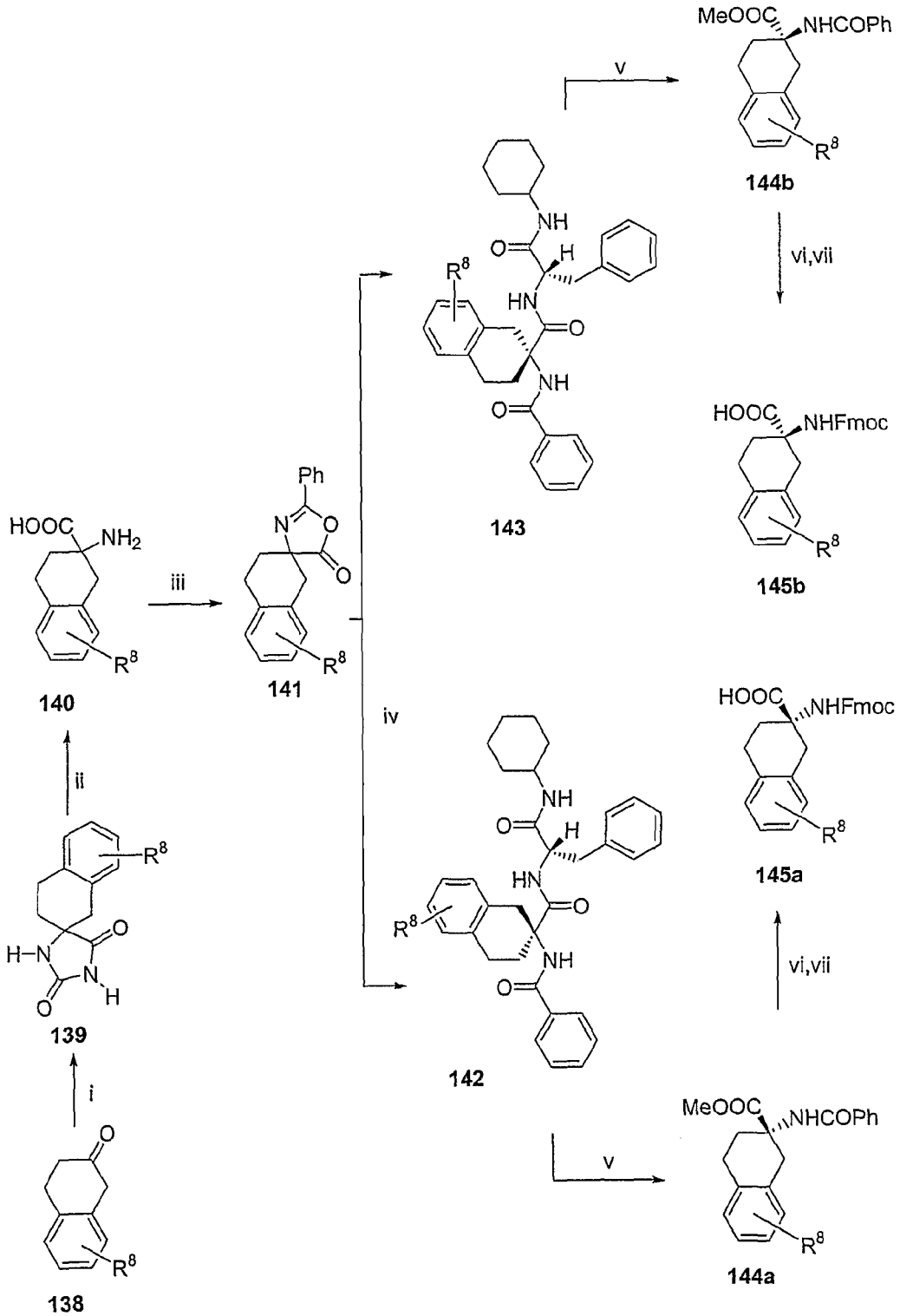
Scheme 27



i: KCN, $(NH_4)_2CO_3$, $EtOH/H_2O$; ii: $Ba(OH)_2$, H_2O; iii: aq.NaOH, PhCOCl, dioxane; then DCC, CH_2Cl_2; iv: NaH, DMF, R^{18}-X or R^{19}-X; v: L-phenylalanine cyclohexylamide, N-methylpyrrolidone, 70°; vi: CH_3SO_3H, MeOH, 80°; vii: 6N HClaq., dioxane, 100°; viii: Me_3SiCl, DIEA, CH_2Cl_2; then FmocCl

The method depicted in *Scheme 27* consists in treatment of the appropriate ketones **126** with KCN, $(NH_4)_2CO_3$ in a mixture of ethanol/water (E. Ware, *J. Chem. Res.* **1950**, *46*, 403; L. H. Goodson, I. L. Honigberg, J. J. Lehmann, W. H. Burton, *J. Org. Chem.* **1960**, *25*, 1920; S. N. Rastogi, J. S. Bindra, N. Anand, *Ind. J. Chem.* **1971**, 1175) to yield the corresponding hydantoins **127**, which were hydrolyzed with $Ba(OH)_2$ in water at 120-140° (R. Sarges, R. C. Schur, J. L. Belletire, M. J. Paterson, *J Med. Chem.* **1988**, *31*, 230) to give **128** in high yields. Schotten-Baumann acylation (Houben-Weyl, 'Methoden der Organischen Chemie', Volume XI/2, Stickstoff-Verbindungen II und III', Georg Tieme Verlag, Stuttgart, pp 339) followed by cyclization with N,N'-dicyclohexyl carbodiimide gave azlactones **129** (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, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* **1992**, *75*, 1666-1696). Alternatively, azlactones **129** could also be prepared starting from amino acids **130** and **131**, Schotten-Baumann acylation and cyclization with N,N'-dicyclohexyl carbodiimide to azlactones **132** and **133** and alkylation to yield **129** (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, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* **1992**, *75*, 1666-1696)(see *Scheme 1*). Treatment of **129** with L-phenylalanine cyclohexylamide (D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* **1995**, *78*, 563-580) gave diastereomeric peptides **134** and **135**, which could be conveniently separated by flash-chromatography or crystallisation. Treatment of **134** and **135** with methanesulphonic acid in methanol at 80° gave esters **136a** and **136b** which were converted into the corresponding Fmoc-protected final building blocks **137a** and **137b**.

Scheme 28

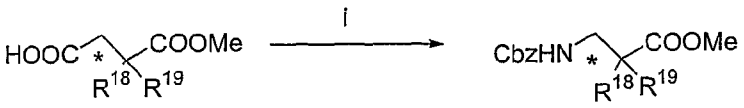


i: KCN, $(NH_4)_2CO_3$, EtOH/H_2O; ii: $Ba(OH)_2$, H_2O; iii: aq.NaOH, PhCOCl, dioxane; then DCC, CH_2Cl_2; iv: L-phenylalanine cyclohexylamide, N-methylpyrrolidone, 70°; v: CH_3SO_3H, MeOH, 80°; vi: 6N HClaq., dioxane, 100°; vii: Me_3SiCl, DIEA, CH_2Cl_2; the FmocCl

According to the general method described in *Scheme 28* (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, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* **1992**, *75*, 1666-1696) **A73-A104** can be prepared starting from the corresponding ketones **138**, hydantoin formation (**139**) (E. Ware, *J. Chem. Res.* **1950**, *46*, 403; L. H. Goodson, I. L. Honigberg, J. J. Lehmann, W. H. Burton, *J. Org. Chem.* **1960**, *25*, 1920; S. N. Rastogi, J. S. Bindra, N. Anand, *Ind. J. Chem.* **1971**, 1175; D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* **1995**, *78*, 563-580) and saponification ($Ba(OH)_2$) to yield the racemic amino acids **140**, which upon Schotten-Baumann-acylation and cyclization with N,N'-dicyclohexylcarbodiimide gave azlactones **141**. Reaction with L-phenylalanine cyclohexylamide (D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* **1995**, *78*, 563-580) gave the diastereomeric peptides **142** and **143**, which were separated by flash-chromatography or crystallization. Treatment of **142** and **143** with methanesulphonic acid in methanol at 80° gave esters **144a** and **144b** which were converted into the corresponding suitably protected amino acid precursors **145a** and **145b**, ready for peptide synthesis.

A71: Amino acid building blocks of this type (see formula **147**) can be conveniently prepared from the corresponding disubstituted succinates **146** by *Curtius*-rearrangement as shown in *Scheme 29*.

Scheme 29



146 **147**

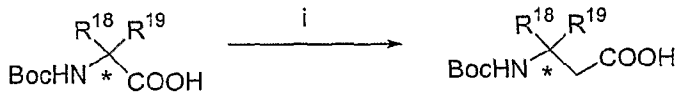
i: diphenylphosphoryl azide, toluene, 80°; then benzyl alcohol

A71: See D. Seebach, S. Abele, T. Sifferlen, M. Haenggi, S. Gruner, P. Seiler, *Helv. Chim. Acta* **1998**, *81*, 2218-2243 (R^{18} and R^{19} form: $-(CH_2)_2-$; $-(CH_2)_3-$; $-(CH_2)_4-$; $-(CH_2)_5-$; R^{20}=H); L. Ducrie, S. Reinelt, P. Seiler, F. Diederich, D. R. Bolin, R. M. Campbell, G. L. Olson, *Helv. Chim. Acta* **1999**, *82*, 2432-2447; C. N. C. Drey, R. J. Ridge, *J. Chem. Soc. Perkin Trans.1*, **1981**, 2468-2471; U. P. Dhokte, V. V. Khau, D. R. Hutchinson, M. J. Martinelli, *Tetrahedron Lett.* **1998**, *39*, 8771-8774 (R^{18}=R^{19}= Me; R^{20}=H); D. L. Varie, D. A. Hay, S. L. Andis, T. H. Corbett, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 369-374 (R^{18}=R^{19}= Et); Testa, *J. Org. Chem.*

1959, *24*, 1928-1936 (R^{18}= Et; R^{19}= Ph); M. Haddad, C. Wakselman, *J. Fluorine Chem.* **1995**, *73*, 57-60 (R^{18}= Me; R^{19}= CF_3; R^{20}=H); T. Shono, K. Tsubata, N. Okinaga, *J. Org. Chem.* **1984**, *49*, 1056-1059 (R^{18}=R^{19}=R^{20}=Me); K. Ikeda, Y. Terao, M. Sekiya, *Chem. Pharm. Bull.* **1981**, *29*, 1747-1749 (R^{18} and R^{19} form: -$(CH_2)_5$-; R^{20}=Me).

Amino acid building blocks of type **A72** can be conveniently prepared by *Arndt-Eistert* C1-homologation of compounds of type **A70** according to *Scheme 30*.

Scheme 30



148 **149**

i: iBuOCOCl, diisopropylethylamine, CH_2Cl_2; then diazomethane, hν or Cu(I)

A72: See Y. V. Zeifman, *J. Gen. Chem. USSR* (Engl.Trans.) **1967**, *37*, 2355-2363 (R^{18}=R^{19}=CF_3); W. R. Schoen, J. M. Pisano, K. Pendergast, M. J. Wyvratt, M. H. Fisher, *J. Med. Chem.* **1994**, *37*, 897-906; S. Thaisrivongs, D. T. Pals, D. W. DuCharme, S. Turner, G. L. DeGraaf, *J. Med. Chem.* **1991**, *34*, 655-642; T. K. Hansen, H. Thoegersen, B. S. Hansen, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2951-2954; R. J. DeVita, R. Bochis, A. J. Frontier, A. Kotliar, M. H. Fisher, *J. Med. Chem.* 1998, 41, 1716-1728; D. Seebach, P. E. Ciceri, M. Overhand, B. Jaun, D. Rigo, *Helv. Chim. Acta* **1996**, *79*, 2043-2066; R. P. Nargund, K. H. Barakat, K. Cheng, W. Chan, B. R. Butler, A. A. Patchett, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1265-1270 (R^{18}=R^{19}=Me); E. Altmann, K. Nebel, M. Mutter, *Helv. Chim. Acta* **1991**, *74*, 800-806 (R^{18}=Me; R^{19}=COOMe).

A73: Compounds of this type can be prepared according to C. Mapelli, G. Tarocy, F. Schwitzer, C. H. Stammer, *J. Org. Chem.* **1989**, *54*, 145-149 (R^{21}= 4-OHC_6H_4); F. Elrod, E. M. Holt, C. Mapelli, C. H. Stammer, *J. Chem. Soc. Chem. Commun.* **1988**, 252-253 (R^{21}= CH_2COOMe); R. E. Mitchell, M. C. Pirrung, G. M. McGeehan, *Phytochemistry* **1987**, *26*, 2695 (R^{21}= CH_2OH), J. Bland, A. Batolussi, C. H. Stammer, *J. Org. Chem.* **1988**, *53*, 992-995 (R^{21}= CH_2NH_2). Additional derivatives of **A73** have been described by T. Wakamiya, Y. Oda, H. Fujita, T. Shiba, *Tetrahedron Lett.* **1986**, *27*, 2143-2134; U. Schöllkopf, B. Hupfeld, R. Gull, *Angew. Chem.* **1986**, *98*, 755-756; J. E. Baldwin, R. M. Adlington, B. J. Rawlings, *Tetrahedron Lett.* **1985**, *26*, 481-484; D. Kalvin, K. Ramalinggam, R. Woodard, *Synth. Comm.* **1985**, *15*, 267-272 and L. M. Izquierdo, I. Arenal, M. Bernabe, E. Alvarez, *Tetrahedron Lett.* **1985**, *41*, 215-220.

A74: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding cyclobutanones.

A75 and **A76**: Compounds of this type can be prepared using the following methods: P. Hughes, J. Clardy, *J. Org. Chem.* **1988**, *53*, 4793-4796; E. A. Bell, M. Y. Qureshi, R. J. Pryce, D. H. Janzen, P. Lemke, J. Clardy, *J. Am. Chem. Soc.* **1980**, *102*, 1409; Y. Gaoni, *Tetrahedron Lett.* **1988**, *29*, 1591-1594; R. D. Allan, J. R. Haurahan, T. W. Hambley, G. A. R. Johnston, K. N. Mewett, A. D. Mitrovic, *J. Med. Chem.* **1990**, *33*, 2905-2915 (R^{23}= COOH); G. W. Fleet, J. A. Seijas, M. Vasquez Tato, *Tetrahedron* **1988**, *44*, 2077-2080 (R^{23}= CH_2OH).

A77: Compounds of this type can be prepared according to J. H. Burckhalter, G. Schmied, *J. Pharm. Sci.* **1966**, *55*, 443-445 (R^{23}= aryl).

A78: Compounds of this type can be prepared according to J. C. Watkins, P. Kroosgard-Larsen, T. Honoré, *TIPS* **1990**, *11*, 25-33; F. Trigalo, D. Brisson, R. Azerad, *Tetrahedron Lett.* **1988**, *29*, 6109 (R^{24}= COOH).

A79: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding pyrrolidine-3-ones.

A80-A82: Compounds of this type can be prepared according to D. M. Walker, E. W. Logusch, *Tetrahedron Lett.* **1989**, *30*, 1181-1184; Y. Morimoto, K. Achiwa, *Chem. Pharm. Bull.* **1989**, *35*, 3845-3849; J. Yoshimura, S. Kondo, M. Ihara, H. Hashimoto, *Carbohydrate Res.* **1982**, *99*, 129-142.

A83: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding pyrazoline-4-ones.

A84: Compounds of this type can be prepared according to R. M. Pinder, B. H. Butcher, D. H. Buxton, D. J. Howells, *J. Med. Chem.* **1971**, *14*, 892-893; D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* **1995**, *78*, 563-580.

A85: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding indane-1,3-diones.

A86: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding indane-2-ones.

A87: Compounds of this type and analogues thereof can be prepared according to C. Cativiela, M. D. Diaz de Villegas, A. Avenoza, J. M. Peregrina, *Tetrahedron* **1993**, *47*, 10987-10996; C. Cativiela, P. Lopez, J. A. Mayoral, *Tetrahedron Assymmetry* **1990**, *1*, 379; C. Cativiela, J. A. Mayoral, A. Avenoza, M. Gonzalez, M. A. Rey, *Synthesis* **1990**, 1114.

A87 and **A88**: Compounds of this type can be prepared according to L. Munday, *J. Chem. Soc.* **1961**, 4372; J. Ansell, D. Morgan, H. C. Price, *Tetrahedron Lett.* **1978**, *47*, 4615-4616.

A89: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding piperidine-3-ones.

A90: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding tetrahydrothiapyran-3-ones.

A91: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding tetrahydropyran-3-ones.

A92: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding piperidine-2,5-diones.

A93: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding cyclohexanones.

A94: Compounds of this type can be prepared according to *J. Org. Chem.* **1990**, *55*, 4208.

A95: Compounds of this type can be prepared according to N. J. Lewis, R. L. Inloes, J. Hes, R. H. Matthews, G. Milo, *J. Med. Chem.* **1978**, *21*, 1070-1073.

A96: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding tetrahydropyran-4-ones.

A97: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding piperidine-2,4-diones.

A98: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding 1-tetralones (D. Obrecht, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* **1992**, *75*, 1666-1696).

A99: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding tetraline-1,4-dione mono-diethylacetals.

A100: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding tetrahydroquinolin-4-ones.

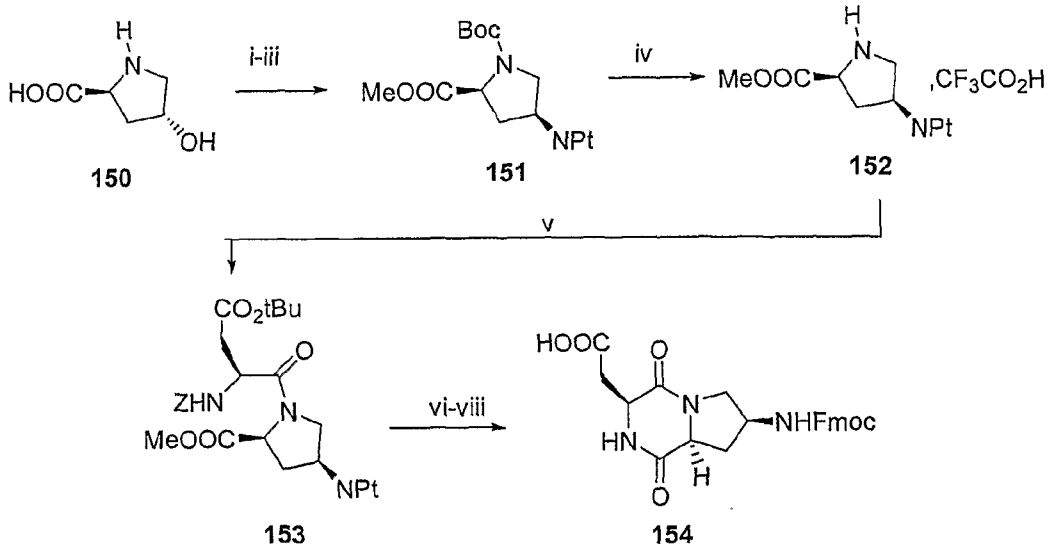
A101: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding tetrahydroquinoline-2,4-diones.

A102: Compounds of this type can be prepared according to K. Ishizumi, N. Ohashi, N. Tanno, *J. Org. Chem.* **1987**, *52*, 4477-4485; 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, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* **1992**, *75*, 1666-1696; D. R. Haines, R. W. Fuller, S. Ahmad, D. T. Vistica, V. E. Marquez, *J. Med. Chem.* **1987**, *30*, 542-547; T. Decks, P. A. Crooks, R. D. Waigh, *J. Pharm. Sci* **1984**, *73*, 457-460; I. A. Blair, L. N. Mander, *Austr. J. Chem.* **1979**, *32*, 1055-1065.

Overviews dealing with building blocks of types **(b)-(p)** are: S. Hanessian, G. McNaughton-Smith, H.-G. Lombart, W. D. Lubell, *Tetrahedron* **1997**, *38*, 12789-12854; D. Obrecht, M. Altorfer, J. A. Robinson, "Novel Peptide Mimetic Building Blocks and Strategies for Efficient Lead Finding", *Adv. Med. Chem.* **1999**, Vol.*4*, 1-68

Templates of type **(b1)** can be prepared according to *Schemes 31* and *32*.

Scheme 31



i: Treatment of **150** with a dehydrating reagent such as thionylchloride in methanol at an elevated temperature, conveniently at reflux.

ii: Introduction of Boc, e.g. using di-tert.-butyl dicarbonate and triethylamine in a suitable solvent such as dichloromethane; any other suitable N-protecting group (not shown in Reaction Scheme 31) can be introduced in an analogous manner.

iii: Reaction of formed product with phthalimide, diethyl diazodicarboxylate and triphenylphoshine under standard Mitsunobu conditions (Mitsunobu, O.; Wada, M.; Sano, T. J. *J. Am. Chem. Soc.* **1972**, *94*, 672) to conveniently yield **151**.

iv: Treatment of **151** with trifluoracetic acid in dichloromethane.

v: **152** is coupled under standard peptide coupling conditions with Cbz-Asp(tBu)OH in DMF with reagents such as HBTU and 1-hydroxybenztriazole (HOBt) with a base such as diisopropylethylamine to yield **153**.

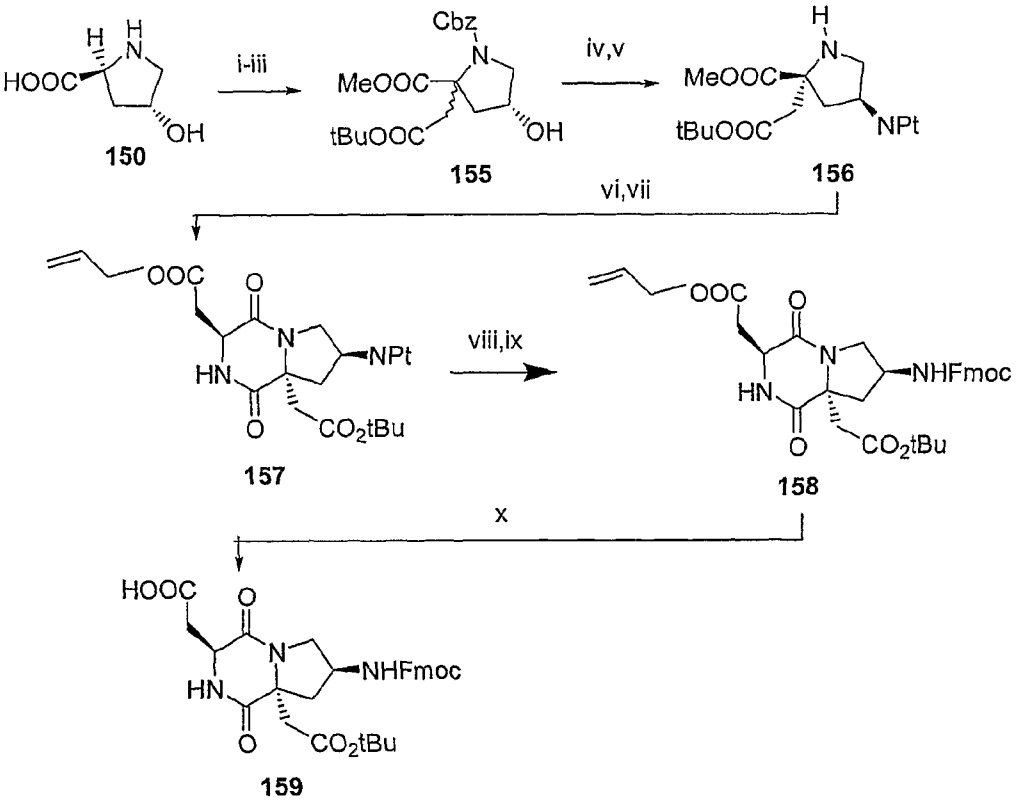
vi: Removal of the Cbz-group, conveniently by hydrogenation using H_2 and a catalyst such as Palladium on charcoal, in solvents such as ethanol, DMF and ethyl acetate.

vii: The phthalimide group is cleaved off from the resulting product, conveniently by treatment with hydrazine in a suitable solvent such as ethanol at an elevated temperature, suitably at about 80° C and cleavage of the formed product with trifluoracetic acid in CH_2Cl_2.

viii: The formed amino acid is conveniently protected with reagents such as 9-fluorenylmethoxcarbonyl chloride or 9-fluorenylmethoxcarbonyl succinimide using a

base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield **154** as described by Bisang, C.; Weber, C.; Robinson, J. A. *Helv. Chim. Acta* **1996**, *79*, 1825-1842.

Scheme 32



i: Treatment of **150** with a dehydrating reagent such as thionyl chloride in a suitable solvent such as methanol at an elevated temperature, conveniently at reflux.

ii: The resulting amino acid ester is N-protected under standard conditions for introducing the Cbz-group, e.g. using benzyloxycarbonyl chloride and triethylamine in a suitable solvent such as dichloromethane.

iii: The Cbz-protected amino acid methyl ester is treated with trimethylsilylchloride and a base such as triethylamine in a solvent such as tetrahydrofuran, cooled, conveniently to about –78° C, followed by reaction with a strong base such as lithium diisopropylamide or lithium hexamethyldisilylazide and tert.-butyl bromoacetate yielding **155** as a mixture of diastereomers as described by Bisang, C.; Jiang, L.; Freund, E.; Emery, F.; Bauch, C.; Matile, H,; Pluschke, G.; Robinson, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 7439-7449; Emery, F.; Bisang, C.; Favre, M.; Jiang, L.; Robinson, J. A. *J. Chem. Soc. Chem. Commun.* **1996**, 2155-2156.

iv: Reaction of **155** with phthalimide, diethyl diazodicarboxylate and triphenylphosphine under standard Mitsunobu conditions (Mitsunobu, O.; Wada, M.; Sano, T. J. *J. Am. Chem. Soc.* **1972**, *94*, 672).

v: The resulting product is hydrogenated using H_2 and a suitable catalyst such as palladium on charcoal in a solvent such as ethyl acetate, DMF or ethanol; subsequently separation of diastereomers takes place and yields **156**.

vi: **156** is coupled with Fmoc-Asp(allyl)OH under standard peptide coupling conditions using reagents such as HATU, HOAt and a base such as diisopropylethylamine in a suitable solvent such as DMF.

vii: Cyclization, conveniently with DBU in DMF to yield **157**.

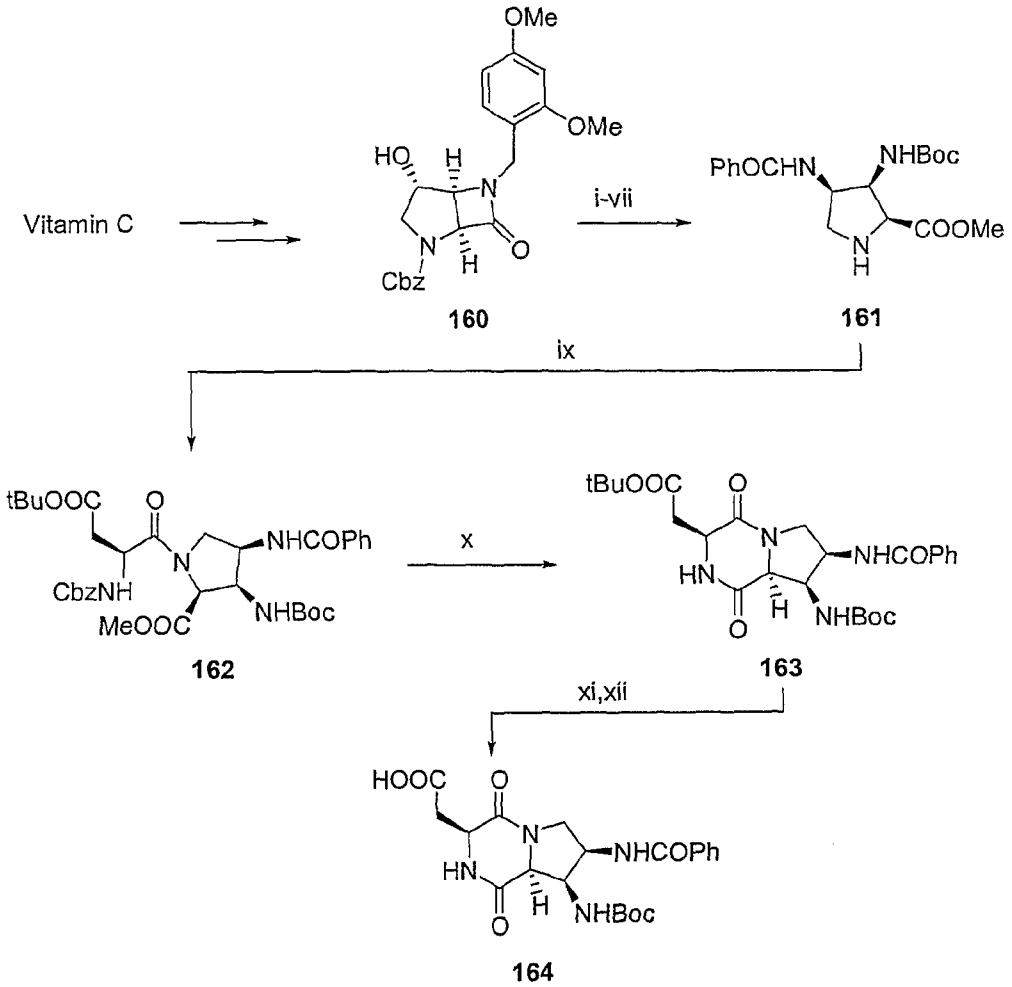
viii: The phthalimide group is cleaved off from resulting product, conveniently by hydrazinolysis, e.g. treatment with methylhydrazine in a suitable solvent such as DMF.

ix: The formed product is conveniently protected with reagents such as 9-fluorenylmethoxcarbonyl chloride or 9-fluorenylmethoxcarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield **158**.

x: Standard removal of an allyl ester group using e.g. palladium(0) as catalyst gives **159**.

Templates of type **(b2)** can be prepared according to *Scheme 33*.

Scheme 33



i: **160** (obtainable from Vitamin C as described by Hubschwerlen, C. (*Synthesis* **1986**, 962) is treated with phthalimide, diethyl diazodicarboxylate and triphenylphoshine under standard Mitsunobu conditions (Mitsunobu, O.; Wada, M.; Sano, T. J. *J. Am. Chem. Soc.* **1972**, *94*, 672).

ii: The phthalimide group is cleaved off from the product, conveniently by hydrazinolysis, e.g. by treatment with methylhydrazine in a suitable solvent such as DMF.

iii: The amino group is protected by treatment with a benzoylating reagent such as benzoic acid anhydride or benzoylchloride and a base such as triethylamine or 4-dimethylaminopyridine in a suitable solvent such as dichloromethane or DMF.

iv: Removal of the 2,4-dimethoxybenzyl group, e.g. with $K_2S_2O_8$ and Na_2HPO_4 in aqueous acetonitrile at an elevated temperature, e.g. at about 80° C.

v: Introduction of a tert.-butoxycarbonyl group using e.g. di-tert.-butyloxycarbonyl dicarbonate, triethylamine and a catalytic amount of 4-dimethylaminopyridine in a suitable solvent such as dichloromethane.

vi: Reaction with aqueous sodium carbonate in tetrahydrofuran followed by acidification.

vii: Esterification of the carboxylic acid group, conveniently with diazomethane in a suitable solvent such as diethylether yielding **161**.

viii Removal of the Cbz-group, conveniently by hydrogenation with H_2 in the presence of a catalyst such as palladium on charcoal in a solvent such as DMF to yield **161** as described by Pfeifer, M.; Robinson, J. A. *J. Chem. Soc. Chem. Commun.* **1998**, 1977.

ix: **161** is coupled under standard peptide coupling conditions with Cbz-Asp(tBu)OH in DMF with reagents such as HBTU and 1-hydroxybenztriazole with a base such as diisopropylethylamine to yield **162** as described by Pfeifer, M.; Robinson, J. A. *J. Chem. Soc. Chem. Commun.* **1998**, 1977.

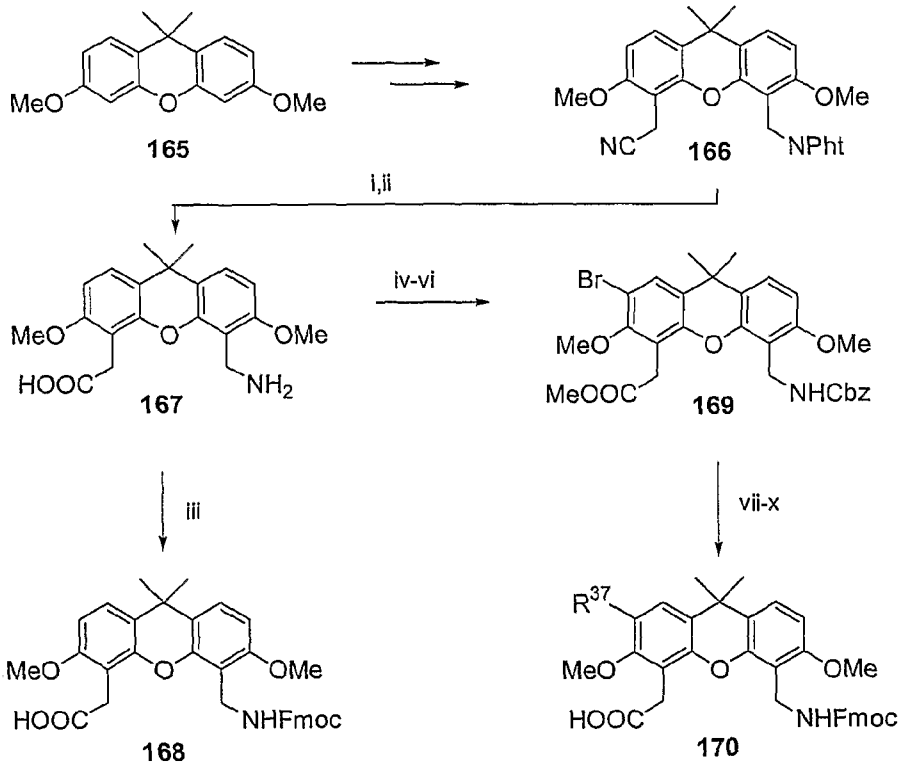
x: Removal of the Cbz-group, e.g. by hydrogenation using H_2 and a catalyst such as palladium on charcoal under standard conditions, yields **163** as described by Pfeifer, M.; Robinson, J. A. *J. Chem. Soc. Chem. Commun.* **1998**, 1977.

xi: Cleavage of the tert.-butyl ester and tert.-butyloxycarbonyl groups, conveniently using trifluoracetic acid in dichloromethane or 4N hydrochloric acid in dioxane.

xii: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxcarbonyl chloride or 9-fluorenylmethoxcarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield **164** as described by Pfeifer, M.; Robinson, J. A. *J. Chem. Soc. Chem. Commun.* **1998**, 1977.

Templates of type (**c1**) can be prepared according to *Schemes 34* to *37*.

Scheme 34



i: **166** can be synthesized from **165** according to P. Waldmeier, "Solid-supported synthesis of highly substituted xanthene-derived templates for the synthesis of β-turn stabilized cyclic peptide libraries", PhD-thesis, University of Zurich, **1996**. For cleaving the phthalimide group **166** is conveniently submitted to hydrazinolysis, e.g. by treatment with hydrazine hydrate in a suitable solvent such as ethanol at an elevated temperature, e.g. at about 80° C.

ii: The intermediate aminonitrile is saponified, conveniently under basic conditions, e.g. with aqueous sodium hydroxide in a suitable solvent such as ethanol at an elevated temperature, conveniently under reflux, to yield **167**.

iii: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxcarbonyl chloride or 9-fluorenylmethoxcarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield **168** as described by P. Waldmeier, "Solid-supported synthesis of highly substituted

xanthene-derived templates for the synthesis of β-turn stabilized cyclic peptide libraries", PhD-thesis, University of Zurich, **1996**.

iv: Regioselective bromination of **167** is performed preferably with bromine in acetic acid and dichloromethane. In a similar fashion $R^{37} = NO_2$ can be introduced by treatment with HNO_3 in acetic acid and $R^{37} = CH_2$-NPht by treatment with hydroxymethyl phthalimide in H_2SO_4.

v: The amino group is conveniently Cbz-protected with reagents such as benzyloxycarbonyl chloride or succinimide in a suitable solvent such as dioxane in presence of a base such as aqueous sodium hydroxide.

vi: The carboxylic acid group is esterified, preferably with DBU and methyl iodide in DMF to yield **169**.

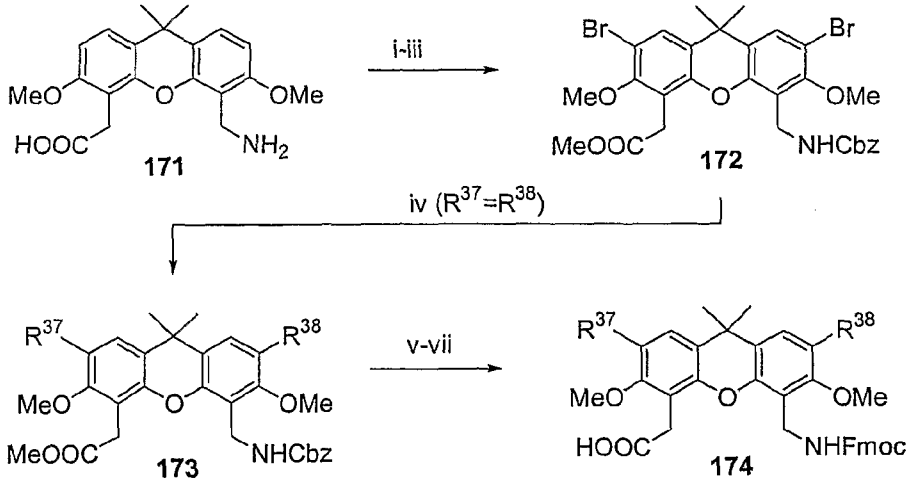
vii: Introduction of lower alkyl, substituted lower alkyl and aryl substituents (R^{37}), conveniently by palladium(0)- catalyzed Stille- (Stille, J.K. *Angew. Chem.***1986**, *68*, 504) and Suzuki- couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201). Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{37}.

viii: Removal of the Cbz-group, e.g. by hydrogenation using H_2 and a catalyst such as palladium on charcoal in a suitable solvent such as ethanol, DMF and ethyl acetate.

ix: Hydrolysis of the ester group, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, preferably at about 100° C.

x: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxcarbonyl chloride or 9-fluorenylmethoxcarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield **170**.

Scheme 35



i: Double ortho- bromination of **171** is performed preferably with excess bromine in acetic acid and dichloromethane. In a similar fashion $R^{37} = R^{38} = NO_2$ can be introduced by treatment with HNO_3 in acetic acid and $R^{37} = R^{38} = CH_2$-NPht by treatment with hydroxymethyl phthalimide in H_2SO_4.

ii: The amino group is protected, conveniently Cbz-protected, with reagents such as benzyloxycarbonyl chloride or succinimide in a suitable solvent such as dioxane in the presence of a base such as aqueous sodium hydroxide.

iii: The carboxylic acid group is esterified, preferably with DBU and methyl iodide in DMF to yield **172**.

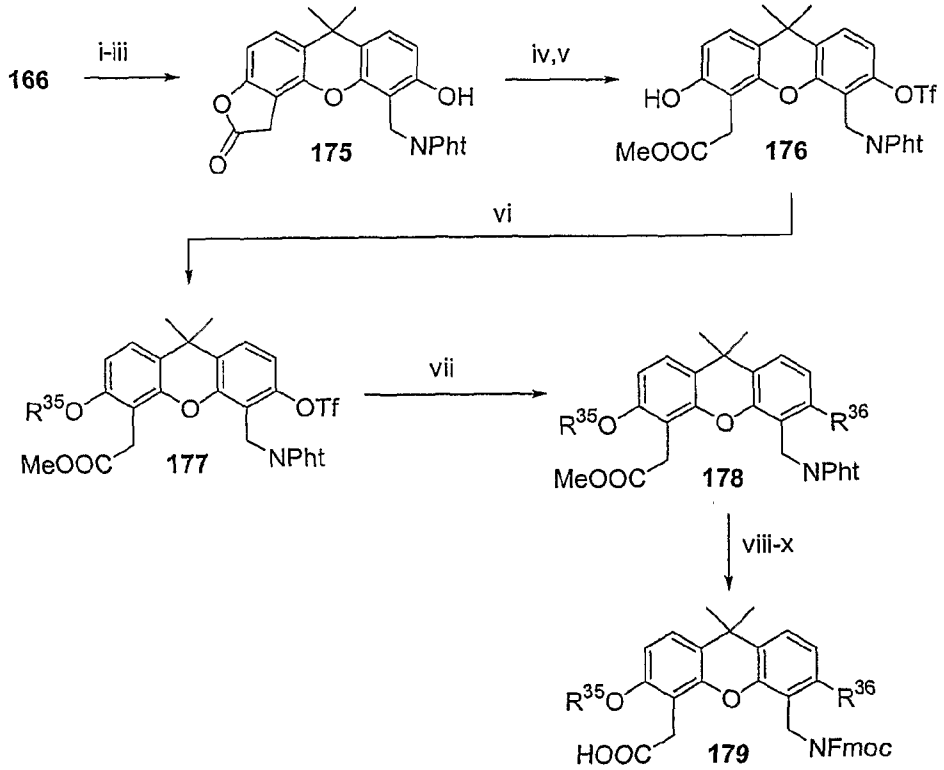
iv: Introduction of lower alkyl, substituted lower alkyl and aryl substituents ($R^{37} = R^{38}$), e.g. by palladium(0)- catalyzed Stille- (Stille, J.K. *Angew. Chem.***1986**, *68*, 504) and Suzuki- couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201). Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{37} and R^{38}.

v: Removal of the Cbz-group of **173**, e.g. by hydrogenation using H_2 and a catalyst such as palladium on charcoal in a suitable solvent such as ethanol, DMF or ethyl acetate.

vi: Hydrolysis of the ester group, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, conveniently at about 100° C.

vii: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxcarbonyl chloride or 9-fluorenylmethoxcarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield **174**.

Scheme 36



i: Cleavage of the methoxy groups of **166**, preferably by treatment with an excess of boron tribromide in a suitable solvent such as dichloromethane.

ii: Hydrolysis of the cyano group under acidic conditions, preferably with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, conveniently at about 100° C.

iii: The resulting acid is treated with a dehydrating agent such as thionyl chloride in a suitable solvent such as dioxane to yield **175**.

iv: Treatment of **175** with an appropriate triflating reagent, preferably trifluoromethanesulfonic acid anhydride in the presence of a base such as 2,6-di-tert.-butyl-pyridine in a suitable solvent such as dichloromethane.

v: Heating of the intermediate, conveniently in a suitable solvent such as methanol.

vi: Introduction of lower alkyl or aryl-lower alkyl (R^{35}) by alkylation to yield **177**. Any other functionalization known for phenol groups can be employed for introduction of substituents R^{35}.

vii: Introduction of lower alkyl or aryl (R^{36}), conveniently by palladium(0)- catalyzed Suzuki- coupling (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201) to

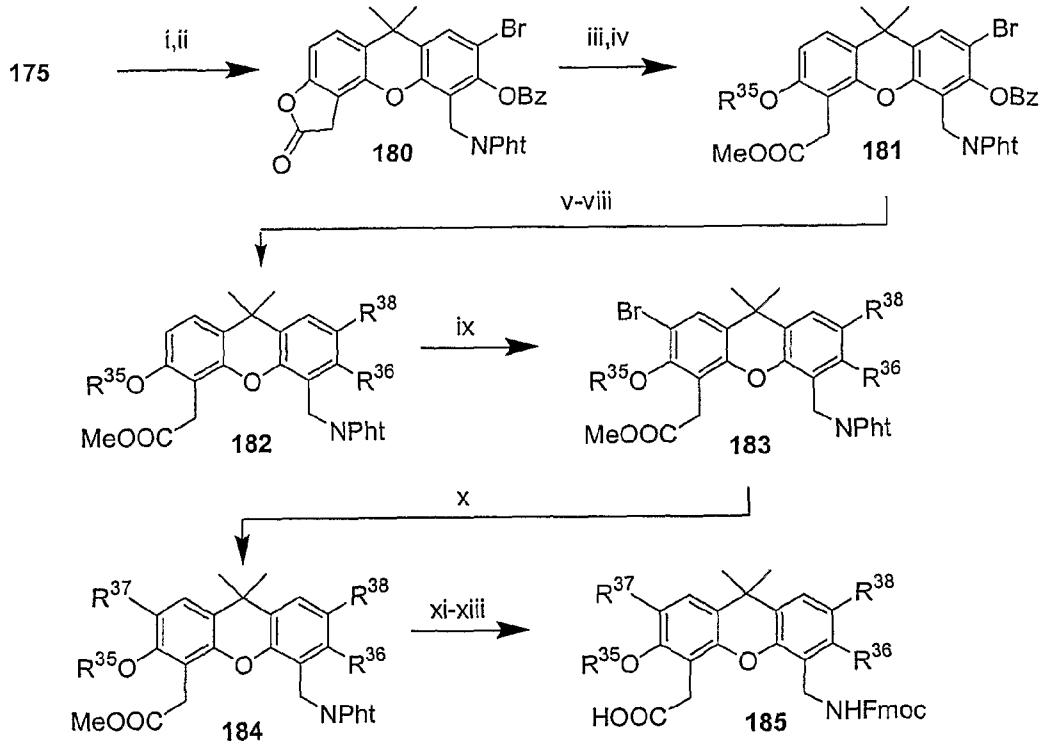
yield **178**. Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{36}.

viii: Hydrolysis of the ester group under acidic conditions, conveniently with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, e.g. at about 100° C.

ix: Cleavage of the phthalimido group, conveniently by hydrazinolysis, e.g. with hydrazine hydrate in a suitable solvent such as ethanol.

x: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxcarbonyl chloride or 9-fluorenylmethoxcarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield **179**.

Scheme 37



i: Bromination of **175** using reagents such as bromine in a mixture of acetic acid and dichloromethane at temperatures ranging from about 0° C to about room temperature.

ii: Benzoylation of the hydroxy group using an appropriate acylating agent such as benzoyl chloride or benzoic acid anhydride, a base such as pyridine or triethylamine and a suitable solvent such as dichloromethane to yield **180**.

iii: **180** is treated with methanol and a catalytic amount of an acidic catalyst such as camphor sulfonic acid under heating.

iv: Introduction of lower alkyl or aryl-lower alkyl (R^{35}) by alkylation using a base such as sodium hydride or potassium tert.-butoxide in a solvent such as tetrahydrofuran, dimethoxyethane or DMF gives **181**.

v: Lower alkyl, substituted lower alkyl and aryl substituents (R^{38}) are introduced, e.g. by palladium(0)- catalyzed Stille- (Stille, J.K. *Angew. Chem.***1986**, *68*, 504) and Suzuki-couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201). Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{38}.

vi: For cleaving the benzyloxy group the intermediate is conveniently heated with sodium cyanide adsorbed on aluminum oxide and methanol.

vii: Treatment with an appropriate triflating reagent, preferably trifluoromethanesulfonic acid anhydride, in the presence of a base such as 2,6-di-tert.-butyl-pyridine in a suitable solvent such as dichloromethane.

viii: Introduction of lower alkyl and aryl substituents (R^{36}), e.g. by palladium(0)- catalyzed Stille- (Stille, J.K. *Angew. Chem.***1986**, *68*, 504) and Suzuki- couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201) yields **182**. Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{36}.

ix: Bromination under standard conditions such as using bromine in acetic acid and dichloromethane at temperatures ranging from about 0° C to about room temperature.

x: Lower alkyl, substituted lower alkyl and aryl substituents (R^{37}) are introduced, e.g. by palladium(0)- catalyzed Stille- (Stille, J.K. *Angew. Chem.***1986**, *68*, 504) and Suzuki- couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201) to yield **184**. Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{37}.

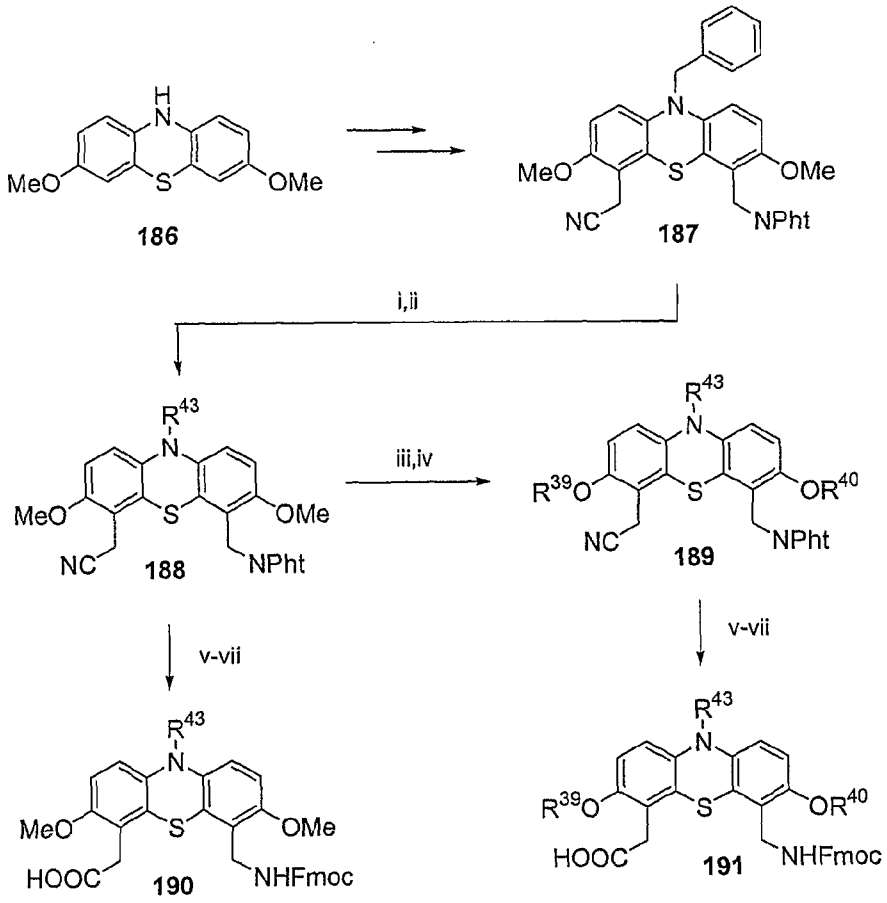
xi: The ester group is hydrolyzed under acidic conditions, conveniently with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, e.g. at about 100° C.

xii: The phthalimido group is cleaved, e.g. by hydrazinolysis, conveniently with hydrazine hydrate in a suitable solvent such as ethanol.

xiii: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxcarbonyl chloride or 9-fluorenylmethoxcarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield **185**.

Templates of type **(c2)** can be prepared as shown in *Schemes 38* and *39*.

Scheme 38



i: 3,7-Dimethoxyphenothiazine **186** is prepared and converted into **187** according to Müller, K.; Obrecht, D.; Knierzinger, A.; Spiegler, C.; Bannwarth, W.; Trzeciak, A.; Englert, G.; Labhardt, A.; Schönholzer, P. *Perspectives in Medicinal Chemistry*, Editor Testa, B.; Kyburz, E.; Fuhrer, W.; Giger, R., Weinheim, New York, Basel, Cambridge: Verlag Helvetica Chimica Acta, **1993**, 513-531; Bannwarth, W.; Gerber, F.; Grieder, A.; Knierzinger, A.; Müller, K.; Obrecht. D.; Trzeciak, A. *Can. Pat. Appl.* CA2101599(131 pages). The benzyl group is cleaved off from **187** conveniently by hydrogenation, e.g. with H_2 and a catalyst such as palladium on charcoal in a suitable solvent such as ethanol, DMF or ethyl acetate.

ii: Introduction of lower alkyl (R^{43}) by alkylation using an appropriate alkylating agent (R^{43}-X'; X'= OTf, Br, I) and strong bases such as sodium amide in liquid ammonia or sodium hydride in tetrahydrofuran, dioxan or DMF in the presence of a phase transfer catalyst such as TDA-I. In a similar manner substituted lower alkyl (R^{43}) can be

introduced; thus, for example $R^{43} = CH_2COOR^{55}$ and $CH_2CH_2COOR^{55}$ can be introduced by treatment with the appropriate 2-halo acetic and, respectively, 3-halo propionic acid derivatives. Any other functionalization known for diarylamines can be employed for introduction of substituents R^{43}.

iii: Cleavage of the methoxy groups of **188**, conveniently by treatment with an excess of boron tribromide in a suitable solvent such as dichloromethane at temperatures ranging from about –20° C to about room temperature.

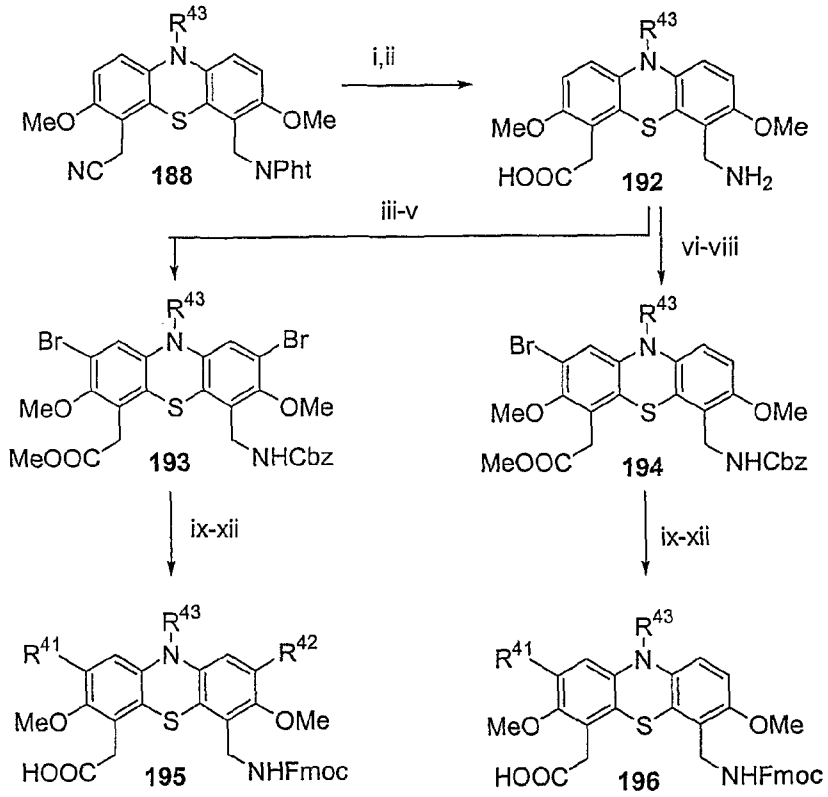
iv: For the introduction of lower alkyl, substituted lower alkyl or aryl-lower alkyl substituents (R^{39} and R^{40}) the intermediate bis-phenol derivative is conveniently reacted with a reagent of the formula R^{39}-and R^{40}-X' (X' = OTf, Br, I) in the presence of strong bases such as sodium hydride in tetrahydrofuran, dioxan or DMF in the presence of a phase transfer catalyst such as TDA-I. Any other functionalization known for phenol groups can be employed for introduction of substituents R^{39} and R^{40}.

v: The cyano group of **188** and, respectively, **189** is hydrolyzed, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, e.g. at about 100° C.

vi: The phthalimide group of the intermediate is cleaved, conveniently by hydrazinolysis, e.g. with hydrazine hydrate in a suitable solvent such as ethanol.

vii: The free amino group is conveniently protected with reagents such as 9-fluorenylmethoxcarbonyl chloride or 9-fluorenylmethoxcarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield **190** and, respectively, **191**.

Scheme 39



i: The cyano group of **188** is hydrolyzed, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, e.g. at about 100° C.

ii: The phthalimide group of the intermediate is cleaved, conveniently by hydrazinolysis, e.g. with hydrazine hydrate in a suitable solvent such as ethanol to yield **192**.

iii: Double ortho- bromination of **192** is performed preferably with excess bromine in acetic acid and dichloromethane. In a similar fashion $R^{41} = R^{42} = NO_2$ can be introduced by treatment with HNO_3 in acetic acid and $R^{41} = R^{42} = CH_2$-NPht by treatment with hydroxymethyl phthalimide in H_2SO_4. Any other functionalization by electrophilic aromatic substitution known can be employed for introduction of substituents R^{41} and R^{42}.

iv: The amino group is protected, conveniently Cbz-protected, with reagents such as benzyloxycarbonyl chloride or succinimide in a suitable solvent such as dioxane in the presence of a base such as aqueous sodium hydroxide.

v: The carboxylic acid group is esterified, preferably with DBU and methyl iodide in DMF to yield **193**.

vi: Regioselective bromination of **192** is performed preferably with bromine in acetic acid and dichloromethane. In a similar fashion $R^{41} = NO_2$ can be introduced by treatment with HNO_3 in acetic acid and $R^{41} = CH_2$-NPt by treatment with hydroxymethyl phthalimide in H_2SO_4. Any other functionalization by electrophilic aromatic substitution known can be employed for introduction of substituents R^{41}.

vii: The amino group is conveniently Cbz-protected with reagents such as benzyloxycarbonyl chloride or succinimide in a suitable solvent such as dioxane in presence of a base such as aqueous sodium hydroxide.

viii: The carboxylic acid group is esterified, preferably with DBU and methyl iodide in DMF to yield **194**.

ix: Introduction of lower alkyl, substituted lower alkyl and aryl substituents (R^{41})for **194** and (R^{41} and R^{42}) for **193**, conveniently by palladium(0)- catalyzed Stille- (Stille, J.K. *Angew. Chem.***1986**, *68*, 504) and Suzuki- couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201). Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{41} and R^{42}.

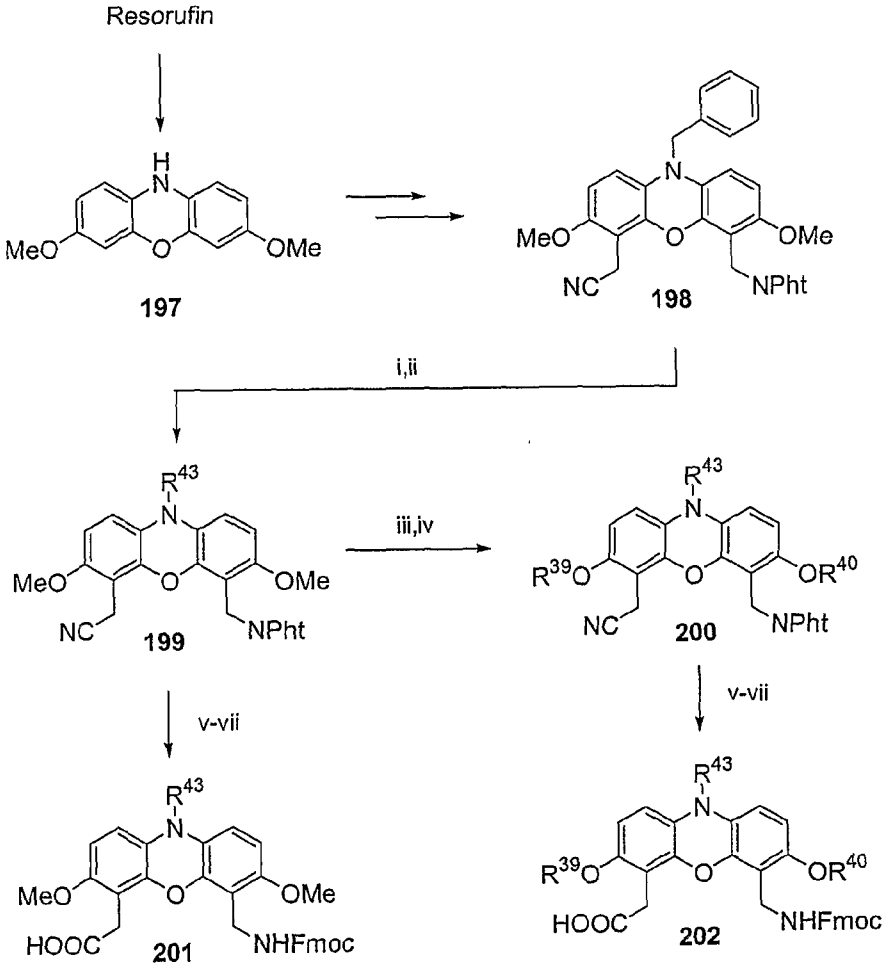
x: Removal of the Cbz-group, e.g. by hydrogenation using H_2 and a catalyst such as palladium on charcoal in a suitable solvent such as ethanol, DMF and ethyl acetate.

xi: Hydrolysis of the ester group, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, preferably at about 100° C.

xii: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxcarbonyl chloride or 9-fluorenylmethoxcarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield **195** and **196**.

Templates of type (c3) can be prepared as shown in *Schemes 40* and *41*.

Scheme 40



i: **197** can be prepared from commercial resorufin and coverted into **198** according to Müller, K.; Obrecht, D.; Knierzinger, A.; Spiegler, C.; Bannwarth, W.; Trzeciak, A.; Englert, G.; Labhardt, A.; Schönholzer, P. *Perspectives in Medicinal Chemistry*, Editor Testa, B.; Kyburz, E.; Fuhrer, W.; Giger, R., Weinheim, New York, Basel, Cambridge: Verlag Helvetica Chimica Acta, **1993**, 513-531; Bannwarth, W.; Gerber, F.; Grieder, A.; Knierzinger, A.; Müller, K.; Obrecht. D.; Trzeciak, A. *Can. Pat. Appl.* CA2101599(131 pages). For splitting off the benzyl group **198** is conveniently hydrogenated e.g. with H_2 and a catalyst such as palladium on charcoal in a suitable solvent such as ethanol, DMF or ethyl acetate.

ii: Introduction of lower alkyl (R^{43}) by alkylation with R^{43}-X' (X' = OTf, Br, I) using strong bases such as sodium amide in liquid ammonia or sodium hydride in tetrahydrofuran, dioxan or DMF in the presence of a phase transfer catalyst such as TDA-I to yield **199**. In a similar manner substituted lower alkyl (R^{43}) can be introduced; thus, for example, R^{43} = CH_2COOR^{55} and $CH_2CH_2COOR^{55}$ can be introduced by treatment with the appropriate 2-halo acetic and, respectively, 3-halo propionic acid derivatives. Any other functionalization of diarylamino groups known can be employed for introduction of substituents R^{43}.

iii: Cleavage of the methoxy groups of **199**, conveniently by treatment with excess boron tribromide in dichloromethane at temperatures ranging from about –20° to about room temperature.

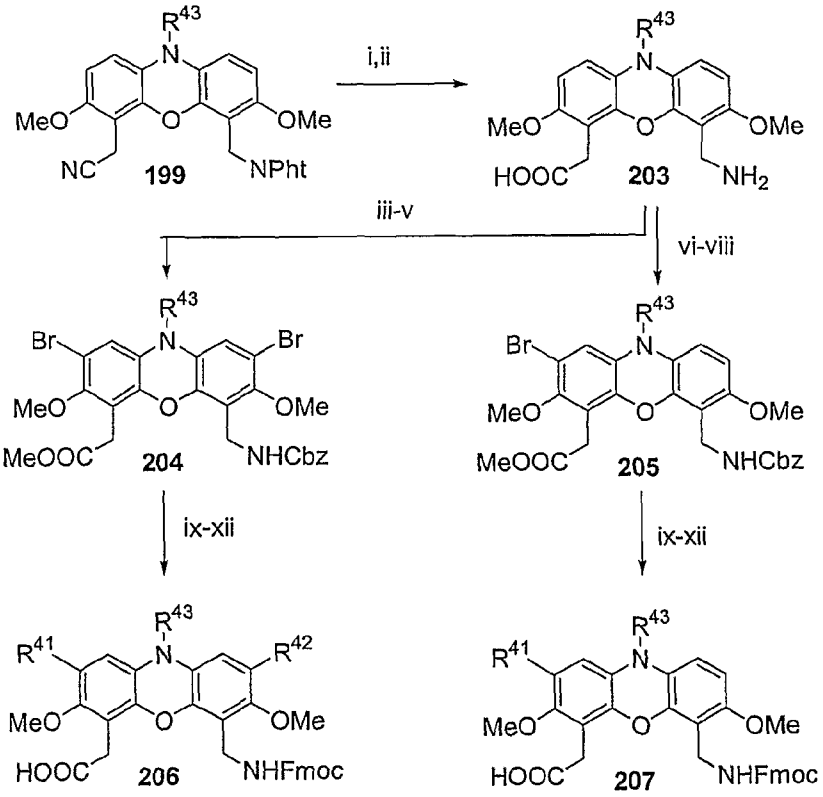
iv: The intermediate bis-phenol derivative is preferably reacted with R^{39} and R^{40}-X' (X'= OTf, Br, I) in the presence of strong bases such as sodium hydride in tetrahydrofuran, dioxan or DMF in the presence of a phase transfer catalyst such as TDA-I. Any other functionalization for phenol groups can be employed for introduction of substituents R^{39} and R^{40}.

v: The cyano group of **199** and, respectively, **200** is hydrolyzed under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, conveniently at about 100° C.

vi: The phthalimide group is cleaved, conveniently by hydrazinolysis, e.g. with hydrazine hydrate in suitable solvent such as ethanol.

vii: The free amino group is conveniently protected with reagents such as 9-fluorenylmethoxcarbonyl chloride or 9-fluorenylmethoxcarbonyl succinimide using a base such as sodium carbonate or triethylamine in suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield **201** and, respectively, **202**.

Scheme 41



i: The cyano group of **199** is hydrolyzed, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, e.g. at about 100° C.

ii: The phthalimide group of the intermediate is cleaved, conveniently by hydrazinolysis, e.g. with hydrazine hydrate in a suitable solvent such as ethanol to yield **203**.

iii: Double ortho- bromination of **203** is performed preferably with excess bromine in acetic acid and dichloromethane. In a similar fashion $R^{41} = R^{42} = NO_2$ can be introduced by treatment with HNO_3 in acetic acid and $R^{41} = R^{42} = CH_2$-NPht by treatment with hydroxymethyl phthalimide in H_2SO_4. Any other functionalization by electrophilic aromatic substitution can be employed for introduction of substituents R^{41} and R^{42}.

iv: The amino group is protected, conveniently Cbz-protected, with reagents such as benzyloxycarbonyl chloride or succinimide in a suitable solvent such as dioxane in the presence of a base such as aqueous sodium hydroxide.

v: The carboxylic acid group is esterified, preferably with DBU and methyl iodide in DMF to yield **204**.

vi: Regioselective bromination of **203** is performed preferably with bromine in acetic acid and dichloromethane. In a similar fashion $R^{41} = NO_2$ can be introduced by treatment with HNO_3 in acetic acid and R^{41}=CH_2-NPht by treatment with hydroxymethyl phthalimide in H_2SO_4.

vii: The amino group is conveniently Cbz-protected with reagents such as benzyloxycarbonyl chloride or succinimide in a suitable solvent such as dioxane in presence of a base such as aqueous sodium hydroxide.

viii: The carboxylic acid group is esterified, preferably with DBU and methyl iodide in DMF to yield **205**.

ix: Introduction of lower alkyl, substituted lower alkyl and aryl substituents (R^{41})for **205** and (R^{41} and R^{42}) for **204**, conveniently by palladium(0)- catalyzed Stille- (Stille, J.K. *Angew. Chem.*1986, *68*, 504) and Suzuki- couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201). Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{41} and R^{42}.

x: Removal of the Cbz-group, e.g. by hydrogenation using H_2 and a catalyst such as palladium on charcoal in a suitable solvent such as ethanol, DMF and ethyl acetate.

xi: Hydrolysis of the ester group, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, preferably at about 100° C.

xii: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxcarbonyl chloride or 9-fluorenylmethoxcarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield **206** and **207**.

Templates**(d)** can be prepared according to D. Obrecht, U. Bohdal, C. Lehmann, P. Schönholzer, K. Müller, *Tetrahedron* **1995**, *51*, 10883; D. Obrecht, C. Abrecht, M. Altorfer, U. Bohdal, A. Grieder, M. Kleber, P. Pfyffer, K. Müller, *Helv. Chim. Acta* **1996**, *79*, 1315-1337.

Templates **(e1)** and **(e2)**: See R. Mueller, L. Revesz, *Tetrahedron Lett.* **1994**, *35*, 4091; H.-G. Lubell, W. D. Lubell, *J. Org. Chem.* **1996**, *61*, 9437; L. Colombo, M. DiGiacomo, G. Papeo, O. Carugo, C. Scolastico, L. Manzoni, *Tetrahedron Lett.* **1994**, *35*, 4031.

Templates **(e3)**: See S. Hanessian, B. Ronan, A. Laoui, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1397.

Templates (**e4**): See S. Hanessian, G. McNaughton-Smith, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1567.

Templates (**f**): See T.P. Curran, P. M. McEnay, *Tetrahedron Lett.* **1995**, *36*, 191-194.

Templates (**g**): See D. Gramberg, C. Weber, R. Beeli, J. Inglis, C. Bruns, J. A. Robinson, *Helv. Chem. Acta* **1995**, *78*, 1588-1606; K. H. Kim, J. P. Dumas, J. P. Germanas, *J. Org. Chem.* **1996**, *61*, 3138-3144.

Templates (**h**): See S. de Lombart, L. Blanchard, L. B. Stamford, D. M. Sperbeck, M. D. Grim, T. M. Jenson, H. R. Rodriguez, *Tetrahedron Lett.* **1994**, *35*, 7513-7516.

Templates (**i1**): See J. A. Robl, D. S. Karanewski, M. M. Asaad, *Tetrahedron Lett.* **1995**, *5*, 773-758.

Templates (**i2**): See T. P. Burkholder, T.-B. Le, E. L. Giroux, G. A. Flynn, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 579.

Templates (**i3**) and (**i4**): See L. M. Simpkins, J. A. Robl, M. P. Cimarusti, D. E. Ryono, J. Stevenson, C.-Q. Sun, E. W. Petrillo, D. S. Karanewski, M. M. Asaad, J. E. Bird, T. R. Schaeffer, N. C. Trippodo, Abstracts of papers, 210th Am. Chem. Soc Meeting, Chicago, I11, MEDI 064 (**1995**).

Templates (**k**): See D. BenIshai, A. R. McMurray, *Tetrahedron* **1993**, *49*, 6399.

Templates (**l**): See E. G. von Roedern, H. Kessler, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 687-689.

Templates (**m**): See R. Gonzalez-Muniz, M. J. Dominguez, M. T. Garcia-Lopez, *Tetrahedron* **1992**, *48*, 5191-5198.

Templates (**n**): See F. Esser, A. Carpy, H. Briem, H. Köppen, K.-H. Pook, *Int. J. Pept. Res.* **1995**, *45*, 540-546.

Templates (**o**): See N. De la Figuera, I. Alkorta, T. Garcia-Lopez, R. Herranz, R. Gonzalez-Muniz, *Tetrahedron* **1995**, *51*, 7841.

Templates (**p**): See U. Slomcynska, D. K. Chalmers, F. Cornille, M. L. Smythe, D. D. Benson, K. D. Moeller, G. R. Marshall, *J. Org. Chem.* **1996**, *61*, 1198-1204.

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 and/or cancer cells.

They can be used for example as disinfectants or as preservatives for materials such as foodstuffs, cosmetics, medicaments and other nutrient-containing materials or for preventing surfaces from microbial colonization [J. M. Schierholz, C. Fleck, J. Beuth, G. Pulverer, *J. Antimicrob. Chemother.*, **2000**, 46, 45-50]. The β-hairpin peptidomimetics of the invention can also be used to treat or prevent diseases related to microbial infection in plants and animals.

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 antimicrobial agents. The β-hairpin peptidomimetics may be administered per se or may be applied as an appropriate formulation together with carriers, diluents or excipients well known in the art, expediently in a form suitable for oral, topical, transdermal, injection, buccal, transmucosal, pulmonary or inhalation administration, such as tablets, dragees, capsules, solutions, liquids, gels, plasters, creams, ointments, syrups, slurries, suspensions, sprays, nebulisers or suppositories.

When used to treat or prevent infections or diseases related to such infections or cancer, the β-hairpin peptidomimetics can be administered singly, as mixtures of several β-hairpin peptidomimetics, in combination with other antimicrobial, antibiotic or anicancer agents or in combination with other pharmaceutically active agents. The β-hairpin peptidomimetics can be administered per se or as pharmaceutical compositions.

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

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

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

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

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

For oral administration, the 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 tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions etc., for oral ingestion of 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 and sorbitol; cellulose preparations such as maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP); granulating agents; and binding agents. If desired, desintegrating agents may be added, such as cross-linked polyvinylpyrrolidones, agar, or alginic acid or a salt thereof, such as sodium alginate. If desired, solid dosage forms may be sugar-coated or enteric-coated using standard techniques.

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

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

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

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

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

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

As the β-hairpin pepdidomimetics of the invention may contain charged residues, they may be included in any of the above-described formulations as free bases or as pharmaceutically

acceptable salts. Pharmaceutically acceptable salts tend to be more soluble in aqueous and other protic solvents than are the corresponding free base forms.

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

For example, for use as a desinfectant 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 desinfected or preserved. By antimicrobially effective amount is meant an amount of a β-hairpin peptidomimetic of the invention or composition 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 desinfectants or preservatives the β-hairpin peptidomimetics of the invention, or compositions thereof, are usually added or applied to the material to be desinfected or preserved in relatively low amounts. Typically, the β-hairpin peptidomimetics of the invention comprise less than about 5% by weight of a desinfectant 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 pepdidomimetics of the invention for particular applications without undue experimentation using, for example, the in vitro assays provided in the examples.

For use to treat or prevent microbial infections or diseases related thereto and cancer, the β-hairpin pepidomimetics 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 ameliorate, treat or prevent 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 desinfectants and preservatives, for topical administration to treat or prevent bacterial, yeast, fungal or other infections a therapeutically effective dose can be determined using, for example, the in vitro assays provided in the examples. The treatment may be applied while the 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.

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), the MIC, as determined in cell culture (i.e. the concentration of a test compound that is lethal to 100% 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 skills in the art could readily optimize administration to humans based on animal data.

Dosage amount for applications as antimicrobial 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. Usual patient dosages for administration by injection range from about 0.1-5mg/kg/day, preferably from about 0.5 to 1 mg/kg/day. 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 skills 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 antimicrobial 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 antibiotics or other antimicrobial agents.

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

Hemolysis of red blood cells is often employed for assessment of toxicity of related compounds such as *protegrin* or *tachyplesin*. Values are given as %-lysis of red blood cells observed at a concentration of 100μg/ml. Typical values determined for cationic peptides such as *protegrin* and *tachyplesin* range between 30-40% with average MIC-values of 1-5 μg/ml over a wide range of pathogens. Normally, β-hairpin peptidomimetics of the invention will show hemolysis in a range of 0.5-10%, often in a range of 1-5%, at activity levels comparable to those mentioned above for *protegrin* and *tachyplesin*. Thus preferred compounds exhibit low MIC-values and low %-hemolysis of red blood cells observed at a concentration of 100μg/ml.

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

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

HBTU : 1-benzotriazol-1-yl-tetramethylurounium hexafluorophosphate
(Knorr et al. *Tetrahedron Lett.* **1989**, *30*, 1927-1930)
HOBt : 1-hydroxybenzotriazole
DIEA : diisopropylethylamine
HOAT: 7-aza-1-hydroxybenzotriazole
HATU: O-(7-aza-benzotriazole-1-yl)-N,N,N',N'-tetramethyluronoium hexafluorophosphate
Carpino et al. *Tetrahedron Lett.* **1994**, *35*, 2279-2281)

Examples

1. Peptide synthesis

Coupling of the first protected amino acid residue

0.5 g of 2-chlorotritylchloride resin (Barlos et al. *Tetrahedron Lett.* **1989**, *30*, 3943-3946) (0.83 mMol/g, 0.415 mmol) was filled into a dried flask. The resin was suspended in CH_2Cl_2 (2.5 ml) and allowed to swell at room temperature under constant stirring. The resin was treated with 0.415 mMol (1eq) of the first suitably protected amino acid residue (see below) and 284 µl (4eq) of diisopropylethylamine (DIEA) in CH_2Cl_2 (2.5 ml), the mixture was shaken at 25°C for 15 minutes, poured onto the pre-swollen resin and stirred at 25°C for 18 hours. The resin colour changed to purple and the solution remained yellowish. The resin was washed extensively (CH_2Cl_2 /MeOH/DIEA : 17/2/1; CH_2Cl_2, DMF; CH_2Cl_2; Et_2O, 3 times each) and dried under vacuum for 6 hours.
Loading was typically 0.6-0.7 mMol/g.
The following preloaded resins were prepared: Fmoc-GlyO-chlorotritylresin; Fmoc-Arg(Pbf)O-chlorotritylresin; Fmoc-Lys(Boc)O-chlorotritylresin.

1.1. Procedure 1

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

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

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

Cleavage of the fully protected peptide fragment

After completion of the synthesis, the resin was suspended in 1 ml (0.39 mMol) of 1% TFA in CH_2Cl_2 (*v/v*) for 3 minutes, filtered and the filtrate was neutralized with 1ml (1.17 mMol, 3eq.) of 20% DIEA in CH_2Cl_2 (*v/v*). This procedure was repeated twice to ensure completion of the cleavage. The filtrate was evaporated to dryness and the product was fully deprotected to be analyzed by reverse phase-HPLC (column C_{18}) to monitor the efficiency of the linear peptide synthesis.

Cyclization of the linear peptide

100 mg of the fully protected linear peptide were dissolved in DMF (9 ml, conc. 10 mg/ml). Then 41.8 mg (0.110 mMol, 3 eq.) of HATU, 14.9 mg (0.110 mMol, 3 eq) of HOAt and 1 ml (0.584 mMol) of 10% DIEA in DMF (*v/v*) were added and the mixture vortexed at 20°C for 16 hours and subsequently concentrated under high vacuum. The residue was partitioned

between CH_2Cl_2 and H_2O/CH_3CN (90/10: *v/v*). The CH_2Cl_2 phase was evaporated to yield the fully protected cyclic peptide.

Deprotection and purification of the cyclic peptide:

The cyclic peptide obtained was dissolved in 1 ml of the cleavage mixture containing 95% trifluoroacetic acid (TFA), 2.5% water and 2.5% triisopropylsilane (TIS). The mixture was left to stand at 20°C for 2.5 hours and then concentrated under vacuum. The residue was dissolved in a solution of H_2O/acetic acid (75/25: *v/v*) and the mixture extracted with di-isopropylether.

The water phase was dried under vacuum and then the product purified by preparative reverse phase HPLC.

After lyophilisation products were obtained as a white powder and analysed by ESI-MS. The analytical data comprising HPLC retension times and ESI-MS are shown in tables 1-7.

Analytical HPLC retension times (RT, in minutes) were determined using a VYDAC 218TP104 (length 25cm) column with *gradient A*: (10% CH_3CN + 0.1% TFA and 90% H_2O + 0.1% TFA to 98% CH_3CN + 0.1% TFA and 2% H_2O + 0.1% TFA in 20minutes) and with *gradient B*: (10% CH_3CN + 0.1% TFA and 90% H_2O + 0.1% TFA to 98% CH_3CN + 0.1% TFA and 2% H_2O + 0.1% TFA in 21minutes).

Examples ex.1-7 (n=8) are shown in *table 1*. The peptides were synthesized starting with the amino acid at position P4 which was coupled to the resin. Starting resins were Fmoc-Arg(Pbf)O-chlorotritylresin and Fmoc-Lys(Boc)O-chlorotritylresin, which were prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P5-P6-P7-P8-^{D}Pro-Pro-P1-P2-P3-P4-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retension times (minutes) were determined using *gradient A*.

Examples ex.8-31 (n=9) are shown in *table 2*. The peptides were synthesized starting with the amino acid at position P5 which was coupled to the resin. Starting resin was Fmoc-Arg(Pbf)O-chlorotritylresin, which was prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-P8-P9-^{D}Pro-Pro-P1-P2-P3-P4-P5-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retension times (minutes) were determined using *gradient A*.

Examples ex.32-58 (n=10) are shown in *table 3*. The peptides were synthesized starting with the amino acid at position P5 which was coupled to the resin. Starting resin was Fmoc-

Arg(Pbf)O-chlorotritylresin, which was prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-P8-P9-P10-^{D}Pro-Pro-P1-P2-P3-P4-P5-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retension times (minutes) were determined using *gradient A*.

Examples ex.59-70 (n=11) are shown in *table 4*. The peptides were synthesized starting with the amino acid at position P5 which was coupled to the resin. Starting resin was Fmoc-Arg(Pbf)O-chlorotritylresin, which was prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-P8-P9-P10-P11-^{D}Pro-Pro-P1-P2-P3-P4-P5-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retension times (minutes) were determined using *gradient A*.

Examples ex.71-84 (n=14) are shown in *table 5*. The peptides were synthesized starting with the amino acid at position P7 which was coupled to the resin. Starting resin was Fmoc-Arg(Pbf)O-chlorotritylresin, which was prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P8-P9-P10-P11-P12-P13-P14-^{D}Pro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retension times (minutes) were determined using *gradient A*.

Examples ex.85-95 (n=16) are shown in *table 6*. The peptides were synthesized starting with the amino acid at position P8 which was coupled to the resin. Starting resins were Fmoc-Arg(Pbf)O-chlorotritylresin and Fmoc-Lys(Boc)O-chlorotritylresin, which were prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P9-P10-P11-P12-P13-P13-P15-P16-^{D}Pro-Pro-P1-P2-P3-P4-P5-P6-P7-P8-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retension times (minutes) were determined using *gradient A*.

Examples ex.96-246, ex.276 (n=12) are shown in *table 7*. The peptides (exept **ex.177** and **ex.181**) were synthesized starting with the amino acid at position P6 which was grafted to the resin. Starting resins were Fmoc-Arg(Pbf)O-chlorotritylresin and Fmoc-Lys(Boc)O-chlorotritylresin, which were prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P7-P8-P9-P10-P11-P12-^{D}Pro-Pro-P1-P2-P3-P4-P5-P6-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retension times (minutes) were determined using *gradient A*.

Examples ex.177 to **ex.181** (n=12) are shown in *table 7*. The peptides were synthesized starting with the amino acid at position P7 which was coupled to the resin. Starting resin was

Fmoc-Arg(Pbf)O-chlorotritylresin, which were prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P8-P9-P10-P11-P12-^{D}Pro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retension times (minutes) were determined using *gradient A*.

Examples ex.247-277 (n=12) are shown in *table 7*. The peptides were synthesized starting with the amino acid at position P6 which was grafted to the resin. Starting resins were Fmoc-Arg(Pbf)O-chlorotritylresin and Fmoc-Lys(Boc)O-chlorotritylresin, which were prepared as described above. The linear peptides were synthesized on solid support according to ***procedure 1*** in the following sequence: P7-P8-P9-P10-P11-P12-^{D}Pro-*BB*-P1-P2-P3-P4-P5-P6-resin, cleaved, cyclized, deprotected and purified as indicated.
BB: Gly (ex.247); Arg(Pmc) (ex.248); Y(Bzl) (ex.249); Phe (ex.250); Trp (ex.251); Leu (ex.252); Ile (ex.253); Cha (ex.254); 2-Nal (ex.255); **219a** (ex.256); **219b** (ex.257); **219c** (ex.258); **219d** (ex.259); **219e** (ex.260); **219f** (ex.261); **219g** (ex.262); **219h** (ex.263); **219i** (ex.264); **219k** (ex.265); **219l** (ex.266); **219m**(ex.267); **219n** (ex.268); **219o** (ex.269); **219p** (ex.270); **219q** (ex.271); **219r** (ex.272); **219s** (ex.273); **219t** (ex.274); **219u** (ex.275).
Building blocks **219a-u** are described below.

Example ex.277 (n=12) is shown in *table 7*. The peptide was synthesized starting with the amino acid at position P6 which was grafted to the resin. Starting resin was Fmoc-Arg(Pbf)O-chlorotritylresin, which were prepared as described above. The linear peptide was synthesized on solid support according to **procedure 1** in the following sequence: P7-P8-P9-P10-P11-P12-(**c1-1**)-P1-P2-P3-P4-P5-P6-resin, cleaved, cyclized, deprotected and purified as indicated.
Building block (**c1-1**) is described below.

Examples ex.278-300 (n=12) are shown in *table 7*. The peptides were synthesized starting with the amino acid at position P6 which was grafted to the resin. Starting resins were Fmoc-Arg(Pbf)O-chlorotritylresin, Fmoc-Tyr(Bzl)O-chlorotrityl resin and Fmoc-^{D}Tyr(Bzl)O-chlorotrityl resin which were prepared as described above. The linear peptide was synthesized on solid support according to **procedure 1** in the following sequence: P7-P8-P9-P10-P11-P12-^{D}Pro-Pro-P1-P2-P3-P4-P5-P6-resin, cleaved, cyclized, deprotected and purified as indicated. Analytical HPLC-retention times (RT, in minutes) were determined using a VYDAC 218TP104 (length 25cm) column with *gradient B* (10% CH_3CN + 0.1% TFA and 90% H_2O + 0.1% TFA to 98% CH_3CN + 0.1% TFA and 2% H_2O + 0.1% TFA in 21minutes).

Retention times (minutes) were the following: **ex.278** (11.43); **ex.279** (11.64); **ex.280** (10.57); **ex.281** (10.04); **ex.282** (10.63); **ex.283** (10.00); **ex.284** (9.21).

Retention times (minutes) for examples **285-300** were determined with *gradient C*: VYDAC C_{18}- column (length 15cm) ; (8% CH_3CN + 0.1% TFA and 92% H_2O + 0.1% TFA to 62.8% CH_3CN + 0.1% TFA and 37.2% H_2O + 0.1% TFA in 8 minutes to 100% CH_3CN + 0.1% TFA in 9 minutes).

ex.285 (5.37; 5.57)*; **ex.286** (5.17); **ex.287** (5.0); **ex.288** (4.15;4.37)*; **ex.289** (4.47; 4.72)*; **ex.290** (3.45; 3.72)*; **ex.291** (3.65; 3.82)*; **ex.292** (4.27); **ex.293** (4.10); **ex.294** (3.83; 4.13)*; **ex.296** (4.38; 4.67)*; **ex.297** (4.10; 4.32)*; **ex.298** (4.12); **ex.299**(4.47); **ex.300**(5.03).

* double peaks which show both correct MS and chiral amino acid analysis. At 60° only one peak is observed.

Table 1: Examples **ex.1-7** (n=8)

a) %-purity of crude product. All compounds were purified by preparative HPLC-chromatography as indicated. Purities>90%.

Example	SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	Template	RT(')	%[a)]	MS
1.	SEQ ID NO:1	Tyr	Val	Arg	Arg	Arg	Phe	Leu	Val	$^{D}Pro^{L}Pro$	18.6	76	1284.6
2.	SEQ ID NO:2	Tyr	Val	Arg	Lys	Gly	Phe	Leu	Val	$^{D}Pro^{L}Pro$	18.8	86	1157.4
3.	SEQ ID NO:3	Trp	Val	Arg	Lys	Gly	Phe	Leu	Trp	$^{D}Pro^{L}Pro$	22.0	70	1263.8
4.	SEQ ID NO:4	Tyr	Val	Arg	Arg	Arg	Trp	Leu	Val	$^{D}Pro^{L}Pro$	19.1	35	1323.6
5.	SEQ ID NO:5	Tyr	Val	Tyr	Arg	Arg	Phe	Leu	Val	$^{D}Pro^{L}Pro$	20.7	81	1287.6
6.	SEQ ID NO:6	Lys	Val	Tyr	Arg	Arg	Phe	Leu	Val	$^{D}Pro^{L}Pro$	16.7	75	1256.6
7.	SEQ ID NO:7	Lys	Val	Tyr	Lys	Gly	Phe	Leu	Trp	$^{D}Pro^{L}Pro$	19.5	64	1216.5

Table 2: Examples **ex.8-29** (n=9)

a) %-purity of crude product. All compounds were purified by preparative HPLC-chromatography as indicated. Purities obtained >90%.

Example	SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	Template	RT(')	%[a)]	MS
8.	SEQ ID NO:8	Arg	Phe	Leu	Arg	Arg	Arg	Leu	Phe	Arg	$^{D}Pro^{L}Pro$	10.5	35	1495.9
9.	SEQ ID NO:9	Arg	Tyr	Leu	Arg	Arg	Arg	Leu	Tyr	Arg	$^{D}Pro^{L}Pro$	8.8	46	1527.9
10.	SEQ ID NO:10	Arg	Phe	Phe	Arg	Arg	Arg	Leu	Phe	Arg	$^{D}Pro^{L}Pro$	10.0	26	1529.9
11.	SEQ ID NO:11	Arg	Tyr	Tyr	Arg	Arg	Arg	Leu	Tyr	Arg	$^{D}Pro^{L}Pro$	8.0	90	1577.9
12.	SEQ ID NO:12	Leu	Phe	Phe	Arg	Arg	Arg	Leu	Phe	Arg	$^{D}Pro^{L}Pro$	10.2	52	1502.9
13.	SEQ ID NO:13	Leu	Tyr	Tyr	Arg	Arg	Arg	Leu	Tyr	Arg	$^{D}Pro^{L}Pro$	8.4	30	1550.9
14.	SEQ ID NO:14	Arg	Phe	Leu	Phe	Arg	Arg	Leu	Leu	Arg	$^{D}Pro^{L}Pro$	10.1	51	1468.9
15.	SEQ ID NO:15	Arg	Tyr	Leu	Tyr	Arg	Arg	Leu	Leu	Arg	$^{D}Pro^{L}Pro$	8.8	55	1500.9
16.	SEQ ID NO:16	Leu	Phe	Leu	Phe	Arg	Arg	Leu	Phe	Arg	$^{D}Pro^{L}Pro$	9.7	38	1459.9
17.	SEQ ID NO:17	Leu	Tyr	Leu	Tyr	Arg	Arg	Leu	Tyr	Arg	$^{D}Pro^{L}Pro$	11.8	67	1507.9
18.	SEQ ID NO:18	Arg	Phe	Leu	Phe	Arg	Arg	Leu	Phe	Leu	$^{D}Pro^{L}Pro$	10.3	57	1459.9
19.	SEQ ID NO:19	Arg	Tyr	Leu	Tyr	Arg	Arg	Leu	Tyr	Leu	$^{D}Pro^{L}Pro$	11.7	66	1507.9
20.	SEQ ID NO:20	Phe	Leu	Leu	Phe	Arg	Arg	Leu	Phe	Arg	$^{D}Pro^{L}Pro$	9.9	67	1459.9
21.	SEQ ID NO:21	Tyr	Leu	Leu	Tyr	Arg	Arg	Leu	Tyr	Arg	$^{D}Pro^{L}Pro$	11.9	57	1507.9
22.	SEQ ID NO:22	Arg	Leu	Leu	Phe	Arg	Arg	Leu	Phe	Phe	$^{D}Pro^{L}Pro$	10.1	68	1459.9
23.	SEQ ID NO:23	Arg	Leu	Leu	Tyr	Arg	Arg	Leu	Tyr	Tyr	$^{D}Pro^{L}Pro$	11.5	63	1507.9
24.	SEQ ID NO:24	Arg	Phe	Leu	Arg	Arg	Phe	Leu	Phe	Arg	$^{D}Pro^{L}Pro$	8.5	33	1502.9
25.	SEQ ID NO:25	Arg	Phe	Leu	Arg	Arg	Phe	Phe	Leu	Arg	$^{D}Pro^{L}Pro$	10.3	30	1502.9
26.	SEQ ID NO:26	Arg	Tyr	Leu	Arg	Arg	Tyr	Tyr	Leu	Arg	$^{D}Pro^{L}Pro$	12.6	65	1550.9
27.	SEQ ID NO:27	Leu	Tyr	Leu	Arg	Arg	Tyr	Leu	Tyr	Arg	$^{D}Pro^{L}Pro$	10.1	29	1491.8
28.	SEQ ID NO:28	Leu	Leu	Phe	Phe	Arg	Arg	Leu	Phe	Arg	$^{D}Pro^{L}Pro$	12.1	35	1443.8
29.	SEQ ID NO:29	Leu	Leu	Tyr	Tyr	Arg	Arg	Leu	Tyr	Arg	$^{D}Pro^{L}Pro$	10.3	33	1491.8
30.	SEQ ID NO:30	Arg	Leu	Phe	Phe	Arg	Arg	Leu	Phe	Leu	$^{D}Pro^{L}Pro$	12.1	35	1459.9
31.	SEQ ID NO:31	Arg	Leu	Tyr	Tyr	Arg	Arg	Leu	Tyr	Leu	$^{D}Pro^{L}Pro$	10.3	33	1507.8

Table 3: Examples **ex.32-58** (n=10)

a) %-purity of crude product. All compounds were purified by preparative HPLC-chromatography as indicated. Purities obtained >90%.

Example	Sequ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	Template	RT(')	%[a)]	MS
32.	SEQ ID NO:32	Arg	Phe	Leu	Phe	Arg	Arg	Arg	Leu	Phe	Arg	$^{D}Pro^{L}Pro$	10.2	37	1643.0
33.	SEQ ID NO:33	Arg	Tyr	Leu	Tyr	Arg	Arg	Arg	Leu	Tyr	Arg	$^{D}Pro^{L}Pro$	8.3	41	1691.0
34.	SEQ ID NO:34	Arg	Phe	Phe	Phe	Arg	Arg	Arg	Leu	Leu	Arg	$^{D}Pro^{L}Pro$	10.1	45	1643.0
35.	SEQ ID NO:35	Arg	Tyr	Tyr	Tyr	Arg	Arg	Arg	Leu	Leu	Arg	$^{D}Pro^{L}Pro$	8.87	70	1691.0
36.	SEQ ID NO:36	Arg	Leu	Phe	Phe	Arg	Arg	Arg	Leu	Phe	Arg	$^{D}Pro^{L}Pro$	10.4	56	1643.0
37.	SEQ ID NO:37	Leu	Tyr	Leu	Tyr	Arg	Arg	Arg	Leu	Tyr	Arg	$^{D}Pro^{L}Pro$	9.6	35	1648.0
38.	SEQ ID NO:38	Arg	Phe	Leu	Phe	Arg	Arg	Arg	Leu	Phe	Leu	$^{D}Pro^{L}Pro$	11.1	50	1600.0
39.	SEQ ID NO:39	Arg	Tyr	Leu	Tyr	Arg	Arg	Arg	Leu	Tyr	Leu	$^{D}Pro^{L}Pro$	9.81	41	1648.0
40.	SEQ ID NO:40	Leu	Leu	Phe	Phe	Arg	Arg	Arg	Leu	Phe	Arg	$^{D}Pro^{L}Pro$	11.8	58	1600.0
41.	SEQ ID NO:41	Arg	Leu	Phe	Phe	Arg	Arg	Arg	Leu	Phe	Leu	$^{D}Pro^{L}Pro$	11.6	54	1600.0
42.	SEQ ID NO:42	Leu	Tyr	Tyr	Tyr	Arg	Arg	Arg	Leu	Leu	Arg	$^{D}Pro^{L}Pro$	9.9	51	1648.0
43.	SEQ ID NO:43	Arg	Phe	Phe	Phe	Arg	Arg	Arg	Leu	Leu	Leu	$^{D}Pro^{L}Pro$	11.3	49	1600.0
44.	SEQ ID NO:44	Arg	Tyr	Tyr	Tyr	Arg	Arg	Arg	Leu	Leu	Leu	$^{D}Pro^{L}Pro$	9.9	63	1648.0
45.	SEQ ID NO:45	Arg	Leu	Leu	Phe	Arg	Gly	Arg	Phe	Phe	Arg	$^{D}Pro^{L}Pro$	10.6	78	1543.9
46.	SEQ ID NO:46	Arg	Leu	Leu	Tyr	Arg	Gly	Arg	Tyr	Tyr	Arg	$^{D}Pro^{L}Pro$	9.1	45	1591.9
47.	SEQ ID NO:47	Arg	Phe	Phe	Phe	Arg	Gly	Arg	Leu	Leu	Arg	$^{D}Pro^{L}Pro$	10.4	43	1543.9
48.	SEQ ID NO:48	Arg	Tyr	Tyr	Tyr	Arg	Gly	Arg	Leu	Leu	Arg	$^{D}Pro^{L}Pro$	8.8	48	1591.9
49.	SEQ ID NO:49	Leu	Phe	Leu	Phe	Arg	Gly	Arg	Leu	Phe	Arg	$^{D}Pro^{L}Pro$	12.4	65	1500.9
50.	SEQ ID NO:50	Leu	Tyr	Leu	Tyr	Arg	Gly	Arg	Leu	Tyr	Arg	$^{D}Pro^{L}Pro$	10.3	58	1548.9
51.	SEQ ID NO:51	Arg	Phe	Leu	Phe	Arg	Gly	Arg	Leu	Phe	Leu	$^{D}Pro^{L}Pro$	12.3	42	1500.9
52.	SEQ ID NO:52	Arg	Tyr	Leu	Tyr	Arg	Gly	Arg	Leu	Tyr	Leu	$^{D}Pro^{L}Pro$	10.6	20	1548.9
53.	SEQ ID NO:53	Leu	Arg	Phe	Phe	Arg	Leu	Arg	Leu	Phe	Arg	$^{D}Pro^{L}Pro$	11.9	51	1600.0
54.	SEQ ID NO:54	Leu	Arg	Tyr	Tyr	Arg	Leu	Arg	Leu	Tyr	Arg	$^{D}Pro^{L}Pro$	9.9	50	1648.0
55.	SEQ ID NO:55	Leu	Leu	Phe	Phe	Arg	Gly	Arg	Leu	Phe	Arg	$^{D}Pro^{L}Pro$	12.5	50	1500.9
56.	SEQ ID NO:56	Leu	Leu	Tyr	Tyr	Arg	Gly	Arg	Leu	Tyr	Arg	$^{D}Pro^{L}Pro$	10.1	38	1548.9
57.	SEQ ID NO:57	Arg	Phe	Leu	Phe	Arg	Gly	Arg	Phe	Arg	Leu	$^{D}Pro^{L}Pro$	11.3	57	1543.9
58.	SEQ ID NO:58	Arg	Tyr	Leu	Tyr	Arg	Gly	Arg	Tyr	Arg	Leu	$^{D}Pro^{L}Pro$	10.8	56	1591.9

Table 4: Examples **ex.59-70** (n=11)

a) %-purity of crude product. All compounds were purified by preparative HPLC-chromatography as indicated. Purities >90%.

Example	SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	Template	RT(')	%	MS
59.	SEQ ID NO:59	Arg	Leu	Phe	Leu	Arg	Arg	Arg	Phe	Phe	Arg	Leu	^{D}Pro^{L}Pro	11.1	75	1756.2
60.	SEQ ID NO:60	Arg	Leu	Tyr	Leu	Arg	Arg	Arg	Tyr	Tyr	Arg	Leu	^{D}Pro^{L}Pro	9.5	28	1804.2
61.	SEQ ID NO:61	Leu	Leu	Phe	Leu	Arg	Arg	Arg	Phe	Phe	Arg	Arg	^{D}Pro^{L}Pro	10.8	65	1756.2
62.	SEQ ID NO:62	Arg	Leu	Phe	Leu	Arg	Arg	Arg	Leu	Phe	Arg	Phe	^{D}Pro^{L}Pro	11.3	57	1756.2
63.	SEQ ID NO:63	Phe	Leu	Phe	Leu	Arg	Arg	Arg	Leu	Phe	Arg	Arg	^{D}Pro^{L}Pro	11.1	76	1756.2
64.	SEQ ID NO:64	Tyr	Leu	Tyr	Leu	Arg	Arg	Arg	Leu	Tyr	Arg	Arg	^{D}Pro^{L}Pro	9.5	70	1804.2
65.	SEQ ID NO:65	Arg	Arg	Phe	Leu	Arg	Gly	Arg	Phe	Phe	Leu	Arg	^{D}Pro^{L}Pro	9.8	36	1700.1
66.	SEQ ID NO:66	Leu	Leu	Tyr	Tyr	Arg	Arg	Leu	Tyr	Tyr	Arg	Arg	^{D}Pro^{L}Pro	9.9	47	1811.2
67.	SEQ ID NO:67	Leu	Tyr	Leu	Tyr	Arg	Arg	Tyr	Leu	Tyr	Arg	Arg	^{D}Pro^{L}Pro	9.9	47	1811.2
68.	SEQ ID NO:68	Arg	Arg	Phe	Phe	Arg	Arg	Leu	Phe	Phe	Leu	Leu	^{D}Pro^{L}Pro	12.4	46	1747.2
69.	SEQ ID NO:69	Arg	Leu	Tyr	Tyr	Arg	Arg	Leu	Tyr	Tyr	Arg	Leu	^{D}Pro^{L}Pro	9.9	51	1811.2
70.	SEQ ID NO:70	Arg	Leu	Phe	Phe	Arg	Gly	Arg	Phe	Phe	Arg	Leu	^{D}Pro^{L}Pro	10.5	26	1691.1

Table 5: Examples **ex.71-84** (n=14)

a) %-purity of crude product. All compounds were purified by preparative HPLC-chromatography. Purities>90%.

Example	SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	Template	RT(')	%	MS
71.	SEQ ID NO:71	Arg	Tyr	Leu	Leu	Tyr	Arg	Arg	Arg	Tyr	Leu	Leu	Tyr	Arg	Arg	$^{D}Pro^{L}Pro$	9.4	48	2236.7
72.	SEQ ID NO:72	Arg	Leu	Leu	Tyr	Tyr	Arg	Arg	Arg	Tyr	Leu	Leu	Tyr	Arg	Arg	$^{D}Pro^{L}Pro$	9.4	29	2236.7
73.	SEQ ID NO:73	Arg	Leu	Leu	Leu	Tyr	Arg	Arg	Arg	Tyr	Leu	Tyr	Tyr	Arg	Arg	$^{D}Pro^{L}Pro$	9.4	50	2236.7
74.	SEQ ID NO:74	Arg	Phe	Leu	Phe	Leu	Arg	Arg	Arg	Phe	Phe	Leu	Phe	Arg	Arg	$^{D}Pro^{L}Pro$	10.9	78	2206.7
75.	SEQ ID NO:75	Arg	Tyr	Leu	Tyr	Leu	Arg	Arg	Arg	Tyr	Tyr	Leu	Tyr	Arg	Arg	$^{D}Pro^{L}Pro$	9.1	51	2286.7
76.	SEQ ID NO:76	Arg	Phe	Leu	Phe	Leu	Arg	Arg	Arg	Phe	Leu	Phe	Leu	Arg	Arg	$^{D}Pro^{L}Pro$	10.6	79	2172.7
77.	SEQ ID NO:77	Arg	Tyr	Leu	Tyr	Leu	Arg	Arg	Arg	Tyr	Leu	Tyr	Leu	Arg	Arg	$^{D}Pro^{L}Pro$	9.1	53	2236.7
78.	SEQ ID NO:78	Arg	Arg	Leu	Leu	Phe	Arg	Arg	Arg	Phe	Leu	Leu	Phe	Phe	Arg	$^{D}Pro^{L}Pro$	11.0	42	2172.7
79.	SEQ ID NO:79	Arg	Arg	Leu	Leu	Tyr	Arg	Arg	Arg	Tyr	Leu	Leu	Tyr	Tyr	Arg	$^{D}Pro^{L}Pro$	9.4	91	2236.7
80.	SEQ ID NO:80	Arg	Arg	Leu	Tyr	Tyr	Arg	Arg	Arg	Tyr	Leu	Leu	Tyr	Tyr	Arg	$^{D}Pro^{L}Pro$	9.3	72	2286.7
81.	SEQ ID NO:81	Arg	Arg	Leu	Leu	Tyr	Arg	Arg	Arg	Tyr	Leu	Tyr	Tyr	Leu	Arg	$^{D}Pro^{L}Pro$	9.5	65	2236.7
82.	SEQ ID NO:82	Arg	Arg	Leu	Phe	Leu	Arg	Arg	Arg	Phe	Phe	Leu	Phe	Phe	Arg	$^{D}Pro^{L}Pro$	11.1	34	2206.7
83.	SEQ ID NO:83	Arg	Arg	Leu	Tyr	Leu	Arg	Arg	Arg	Tyr	Tyr	Leu	Tyr	Tyr	Arg	$^{D}Pro^{L}Pro$	9.3	89	2286.7
84.	SEQ ID NO:84	Arg	Arg	Leu	Tyr	Leu	Arg	Arg	Arg	Tyr	Leu	Tyr	Leu	Tyr	Arg	$^{D}Pro^{L}Pro$	9.3	47	2236.7

Table 6: Examples **ex.85-95** (n=16)

a) %-purity of crude product. All compounds were purified by preparative HPLC-chromatography. Purities>90%.

Example	Sequ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	Template	RT(')	%	MS
85.	SEQ ID NO:85	Lys	Arg	Leu	Lys	Tyr	Val	Arg	Arg	Arg	Trp	Leu	Val	Lys	Val	Leu	Arg	$^{D}Pro^{L}Pro$	13.7	70	2346.0
86.	SEQ ID NO:86	Lys	Arg	Leu	Lys	Tyr	Val	Arg	Arg	Gly	Trp	Leu	Val	Lys	Val	Leu	Arg	$^{D}Pro^{L}Pro$	13.9	38	2246.8
87.	SEQ ID NO:87	Lys	Arg	Leu	Lys	Tyr	Trp	Arg	Arg	Arg	Trp	Tyr	Val	Lys	Val	Leu	Arg	$^{D}Pro^{L}Pro$	13.6	34	2483.1
88.	SEQ ID NO:88	Lys	Arg	Leu	Tyr	Tyr	Trp	Arg	Arg	Arg	Trp	Tyr	Val	Phe	Val	Leu	Arg	$^{D}Pro^{L}Pro$	14.3	35	2537.1
89.	SEQ ID NO:89	Lys	Arg	Leu	Lys	Tyr	Trp	Arg	Arg	Gly	Trp	Tyr	Val	Lys	Val	Leu	Arg	$^{D}Pro^{L}Pro$	13.7	27	2383.9
90.	SEQ ID NO:90	Lys	Arg	Leu	Tyr	Tyr	Trp	Arg	Arg	Gly	Trp	Tyr	Val	Phe	Val	Leu	Arg	$^{D}Pro^{L}Pro$	14.6	39	2437.9
91.	SEQ ID NO:91	Lys	Arg	Leu	Tyr	Tyr	Trp	Arg	Arg	Arg	Trp	Lys	Val	Phe	Val	Leu	Arg	$^{D}Pro^{L}Pro$	13.9	22	2402.1
92.	SEQ ID NO:92	Lys	Arg	Leu	Lys	Tyr	Trp	Arg	Arg	Gly	Trp	Lys	Val	Lys	Val	Leu	Arg	$^{D}Pro^{L}Pro$	13.4	26	2348.9
93.	SEQ ID NO:93	Tyr	Lys	Leu	Arg	Leu	Lys	Tyr	Arg	Arg	Trp	Lys	Tyr	Arg	Val	Lys	Phe	$^{D}Pro^{L}Pro$	12.5	34	2402.1
94.	SEQ ID NO:94	Tyr	Lys	Leu	Gln	Leu	Lys	Trp	Arg	Arg	Phe	Lys	Tyr	Gln	Val	Lys	Phe	$^{D}Pro^{L}Pro$	12.1	21	2348.9
95.	SEQ ID NO:95	Tyr	Lys	Leu	Gln	Leu	Gln	Lys	Lys	Gly	Trp	Gln	Tyr	Gln	Val	Lys	Phe	$^{D}Pro^{L}Pro$	11.1	84	2383.9

Table 7: Examples **ex.96-128** (n=12);
a) %-purity of crude product. Purities of all compounds after prep. HPLC>90%.

Example	Sequ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template	RT(')	%	MS
96.	SEQ ID NO:96	Leu	Arg	Leu	Val	Tyr	Lys	Gly	Phe	Leu	Tyr	Arg	Val	^{D}Pro^{L}Pro	21.6	92	1703.1
97.	SEQ ID NO:97	Leu	Arg	Phe	Val	Tyr	Lys	Gly	Phe	Leu	Tyr	Arg	Val	^{D}Pro^{L}Pro	21.6	95	1737.1
98.	SEQ ID NO:98	Leu	Arg	Thr	Val	Tyr	Lys	Gly	Phe	Leu	Tyr	Arg	Val	^{D}Pro^{L}Pro	20.0	93	1691.1
99.	SEQ ID NO:99	Leu	Arg	Lys	Val	Arg	Lys	Gly	Arg	Leu	Tyr	Arg	Val	^{D}Pro^{L}Pro	15.7	99	1720.2
100.	SEQ ID NO:100	Leu	Arg	Lys	Trp	Tyr	Lys	Gly	Phe	Trp	Tyr	Arg	Val	^{D}Pro^{L}Pro	17.6	60	1878.3
101.	SEQ ID NO:101	Leu	Arg	Lys	Val	Tyr	Arg	Gly	Phe	Leu	Tyr	Arg	Val	^{D}Pro^{L}Pro	17.8	61	1845.3
102.	SEQ ID NO:102	Leu	Lys	Lys	Val	Tyr	Arg	Arg	Phe	Leu	Lys	Lys	Val	^{D}Pro^{L}Pro	15.9	59	1754.3
103.	SEQ ID NO:103	Leu	Arg	Leu	Lys	Tyr	Arg	Arg	Phe	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	20.5	36	1874.3
104.	SEQ ID NO:104	Leu	Arg	Leu	Glu	Tyr	Arg	Arg	Phe	Glu	Tyr	Arg	Val	^{D}Pro^{L}Pro	21.5	99	1876.2
105.	SEQ ID NO:105	Leu	Arg	Leu	Gln	Tyr	Arg	Arg	Phe	Gln	Tyr	Arg	Val	^{D}Pro^{L}Pro	21.5	58	1874.2
106.	SEQ ID NO:106	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	18.1	51	1879.7
107.	SEQ ID NO:107	Leu	Arg	Leu	Lys	Trp	Arg	Arg	Lys	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	20.2	28	1879.7
108.	SEQ ID NO:108	Leu	Arg	Trp	Lys	Tyr	Arg	Arg	Phe	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	20.9	40	1948.7
109.	SEQ ID NO:109	Lys	Val	Arg	Phe	Arg	Arg	Arg	Lys	Leu	Lys	Leu	Arg	^{D}Pro^{L}Pro	15.7	75	1833.7
110.	SEQ ID NO:110	Leu	Arg	Leu	Gln	Tyr	Arg	Arg	Trp	Gln	Tyr	Arg	Val	^{D}Pro^{L}Pro	21.9	30	1913.3
111.	SEQ ID NO:111	Leu	Arg	Leu	Gln	Trp	Arg	Arg	Phe	Gln	Tyr	Arg	Val	^{D}Pro^{L}Pro	22.6	75	1897.3
112.	SEQ ID NO:112	Leu	Arg	Leu	Gln	Lys	Arg	Arg	Trp	Gln	Tyr	Arg	Val	^{D}Pro^{L}Pro	18.9	49	1878.3
113.	SEQ ID NO:113	Leu	Arg	Leu	Gln	Trp	Arg	Arg	Lys	Gln	Tyr	Arg	Val	^{D}Pro^{L}Pro	21.2	75	1878.3
114.	SEQ ID NO:114	Phe	Arg	Leu	Gln	Tyr	Arg	Arg	Phe	Gln	Tyr	Arg	Val	^{D}Pro^{L}Pro	22.3	50	1908.3
115.	SEQ ID NO:115	Leu	Arg	Leu	Gln	Tyr	Arg	Arg	Phe	Gln	Tyr	Arg	Phe	^{D}Pro^{L}Pro	22.4	99	1908.3
116.	SEQ ID NO:116	Phe	Arg	Leu	Gln	Tyr	Arg	Arg	Phe	Gln	Tyr	Arg	Phe	^{D}Pro^{L}Pro	22.9	99	1956.3
117.	SEQ ID NO:117	Leu	Arg	Leu	Gln	Tyr	Arg	Arg	Phe	Gln	Trp	Arg	Val	^{D}Pro^{L}Pro	22.7	15	1897.3
118.	SEQ ID NO:118	Leu	Arg	Trp	Gln	Tyr	Arg	Arg	Phe	Gln	Tyr	Arg	Val	^{D}Pro^{L}Pro	21.9	21	1947.3
119.	SEQ ID NO:119	Gln	Val	Arg	Phe	Arg	Arg	Arg	Lys	Leu	Gln	Leu	Arg	^{D}Pro^{L}Pro	17.2	46	1831.3
120.	SEQ ID NO:120	Phe	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.5	52	1912.4
121.	SEQ ID NO:121	Cha	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.6	36	1918.4
122.	SEQ ID NO:122	hPhe	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	9.6	95	1926.4
123.	SEQ ID NO:123	2Nal	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	9.6	69	1962.4
124.	SEQ ID NO:124	1Nal	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	11.8	47	1962.4
125.	SEQ ID NO:125	Nle	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.3	63	1878.4
126.	SEQ ID NO:126	Leu	Arg	Phe	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.6	44	1912.4
127.	SEQ ID NO:127	Leu	Arg	Cha	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.8	41	1918.4
128.	SEQ ID NO:128	Leu	Arg	Y(bzl)	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	11.5	23	2018.5

Table 7 (continued): Examples **ex.129-161** (n=12)

Example	SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template	RT(')	%	MS
129.	SEQ ID NO:129	Leu	Arg	Trp	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.5	41	1951.4
130.	SEQ ID NO:130	Leu	Arg	hPhe	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.6	32	1926.4
131.	SEQ ID NO:131	Leu	Arg	2Nal	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	11.0	42	1962.4
132.	SEQ ID NO:132	Leu	Arg	1Nal	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.9	43	1962.4
133.	SEQ ID NO:133	Leu	Arg	Val	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.0	47	1864.3
134.	SEQ ID NO:134	Leu	Arg	Ile	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.3	34	1878.4
135.	SEQ ID NO:135	Leu	Arg	Nle	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.3	90	1878.4
136.	SEQ ID NO:136	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	9.9	48	1855.3
137.	SEQ ID NO:137	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Y(Bzl)	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	11.0	33	1945.4
138.	SEQ ID NO:138	Leu	Arg	Leu	Lys	Lys	Arg	Arg	hPhe	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.3	52	1853.3
139.	SEQ ID NO:139	Leu	Arg	Leu	Lys	Lys	Arg	Arg	2Nal	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.5	53	1889.4
140.	SEQ ID NO:140	Leu	Arg	Leu	Lys	Lys	Arg	Arg	1Nal	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.5	34	1889.4
141.	SEQ ID NO:141	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Val	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	9.9	49	1889.4
142.	SEQ ID NO:142	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Ile	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.0	32	1791.3
143.	SEQ ID NO:143	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Leu	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.1	46	1805.3
144.	SEQ ID NO:144	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Nle	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.1	43	1805.3
145.	SEQ ID NO:145	Leu	Arg	Leu	Lys	Lys	Arg	Arg	His	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	9.8	56	1829.3
146.	SEQ ID NO:146	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Phe	Arg	Val	^{D}Pro^{L}Pro	10.9	45	1862.3
147.	SEQ ID NO:147	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Y(Bzl)	Arg	Val	^{D}Pro^{L}Pro	11.4	15	1968.5
148.	SEQ ID NO:148	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Trp	Arg	Val	^{D}Pro^{L}Pro	10.8	56	1901.4
149.	SEQ ID NO:149	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	hPhe	Arg	Val	^{D}Pro^{L}Pro	11.3	32	1876.4
150.	SEQ ID NO:150	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	1Nal	Arg	Val	^{D}Pro^{L}Pro	11.6	24	1912.4
151.	SEQ ID NO:151	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Val	Arg	Val	^{D}Pro^{L}Pro	10.6	48	1814.3
152.	SEQ ID NO:152	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Ile	Arg	Val	^{D}Pro^{L}Pro	10.9	40	1828.3
153.	SEQ ID NO:153	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Leu	Arg	Val	^{D}Pro^{L}Pro	10.7	18	1828.3
154.	SEQ ID NO:154	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Nle	Arg	Val	^{D}Pro^{L}Pro	11.2	40	1828.3
155.	SEQ ID NO:155	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Phe	^{D}Pro^{L}Pro	10.6	35	1926.4
156.	SEQ ID NO:156	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Cha	^{D}Pro^{L}Pro	11.2	60	1932.5
157.	SEQ ID NO:157	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Y(Bzl)	^{D}Pro^{L}Pro	11.7	37	2032.5
158.	SEQ ID NO:158	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Trp	^{D}Pro^{L}Pro	10.4	69	1965.4
159.	SEQ ID NO:159	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	hPhe	^{D}Pro^{L}Pro	10.8	95	1940.4
160.	SEQ ID NO:160	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	2Nal	^{D}Pro^{L}Pro	11.2	30	1976.5
161.	SEQ ID NO:161	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	1Nal	^{D}Pro^{L}Pro	11.3	89	1976.5

Table 7 (continued): Examples **ex.162-194** (n=12)

Example		P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template	RT(')	%	MS
162.	SEQ ID NO:162	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Ile	$^{D}Pro^{L}Pro$	10.5	56	1892.4
163.	SEQ ID NO:163	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Nle	$^{D}Pro^{L}Pro$	10.5	91	1892.4
164.	SEQ ID NO:164	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	His	$^{D}Pro^{L}Pro$	8.6	88	1916.4
165.	SEQ ID NO:165	Leu	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.4	55	1908.4
166.	SEQ ID NO:166	Leu	Leu	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.6	88	1835.3
167.	SEQ ID NO:167	Leu	Thr	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.4	94	1823.3
168.	SEQ ID NO:168	Leu	Gln	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.4	55	1850.3
169.	SEQ ID NO:169	Leu	Arg	Leu	Leu	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.9	62	1863.3
170.	SEQ ID NO:170	Leu	Arg	Leu	Arg	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.3	45	1906.4
171.	SEQ ID NO:171	Leu	Arg	Leu	Thr	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.4	94	1851.3
172.	SEQ ID NO:172	Leu	Arg	Leu	Gln	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.3	76	1878.3
173.	SEQ ID NO:173	Leu	Arg	Leu	Lys	Leu	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	11.9	43	1863.3
174.	SEQ ID NO:174	Leu	Arg	Leu	Lys	His	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.5	53	1887.3
175.	SEQ ID NO:175	Leu	Arg	Leu	Lys	Arg	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.4	37	1906.4
176.	SEQ ID NO:176	Leu	Arg	Leu	Lys	Thr	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	11.4	45	1851.3
177.	SEQ ID NO:177	Leu	Arg	Leu	Lys	Lys	Leu	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.8	58	1835.3
178.	SEQ ID NO:178	Leu	Arg	Leu	Lys	Lys	His	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.2	46	1859.3
179.	SEQ ID NO:179	Leu	Arg	Leu	Lys	Lys	Lys	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.3	53	1850.3
180.	SEQ ID NO:180	Leu	Arg	Leu	Lys	Lys	Thr	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.4	82	1823.3
181.	SEQ ID NO:181	Leu	Arg	Leu	Lys	Lys	Gln	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.4	36	1850.3
182.	SEQ ID NO:182	Leu	Arg	Leu	Lys	Lys	Arg	Trp	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.8	70	1908.4
183.	SEQ ID NO:183	Leu	Arg	Leu	Lys	Lys	Arg	His	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.3	74	1859.3
184.	SEQ ID NO:184	Leu	Arg	Leu	Lys	Lys	Arg	Lys	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.2	50	1850.3
185.	SEQ ID NO:185	Bip	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	11.4	39	1988.5
186.	SEQ ID NO:186	4ClPhe	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	11.1	53	1946.8
187.	SEQ ID NO:187	AmPhe	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	8.6	83	1927.4
188.	SEQ ID NO:188	S(Bzl)	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.4	66	1942.4
189.	SEQ ID NO:189	T(Bzl)	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.8	51	1956.4
190.	SEQ ID NO:190	Orn	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	8.4	84	1879.3
191.	SEQ ID NO:191	Leu	Arg	Bip	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	11.3	39	1988.5
192.	SEQ ID NO:192	Leu	Arg	4ClPhe	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.9	50	1946.8
193.	SEQ ID NO:193	Leu	Arg	AmPhe	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	9.2	82	1927.4
194.	SEQ ID NO:194	Leu	Arg	S(Bzl)	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.7	80	1942.4

Table 7 (continued): Examples **ex.195-227** (n=12)

Example		P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template	RT(')	%	MS
195.	SEQ ID NO:195	Leu	Arg	T(Bzl)	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.7	37	1956.4
196.	SEQ ID NO:196	Leu	Arg	Orn	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	9.2	48	1879.3
197.	SEQ ID NO:197	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.8	57	1915.4
198.	SEQ ID NO:198	Leu	Arg	Leu	Lys	Lys	Arg	Arg	4ClPhe	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.4	49	1873.8
199.	SEQ ID NO:199	Leu	Arg	Leu	Lys	Lys	Arg	Arg	AmPhe	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	9.8	43	1854.3
200.	SEQ ID NO:200	Leu	Arg	Leu	Lys	Lys	Arg	Arg	S(Bzl)	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.3	48	1869.3
201.	SEQ ID NO:201	Leu	Arg	Leu	Lys	Lys	Arg	Arg	T(Bzl)	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.2	87	1883.4
202.	SEQ ID NO:202	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Orn	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	9.7	31	1806.3
203.	SEQ ID NO:203	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Bip	Arg	Val	$^{D}Pro^{L}Pro$	11.6	46	1938.5
204.	SEQ ID NO:204	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	4ClPhe	Arg	Val	$^{D}Pro^{L}Pro$	11.21	48	1896.8
205.	SEQ ID NO:205	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	S(Bzl)	Arg	Val	$^{D}Pro^{L}Pro$	11.5	32	1892.4
206.	SEQ ID NO:206	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	T(Bzl)	Arg	Val	$^{D}Pro^{L}Pro$	11.5	36	1906.4
207.	SEQ ID NO:207	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Orn	Arg	Val	$^{D}Pro^{L}Pro$	9.4	49	1829.3
208.	SEQ ID NO:208	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Bip	$^{D}Pro^{L}Pro$	11.7	37	2002.5
209.	SEQ ID NO:209	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	4ClPhe	$^{D}Pro^{L}Pro$	11.0	32	1960.8
210.	SEQ ID NO:210	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	AmPhe	$^{D}Pro^{L}Pro$	8.6	88	1941.4
211.	SEQ ID NO:211	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	T(Bzl)	$^{D}Pro^{L}Pro$	10.9	51	1970.5
212.	SEQ ID NO:212	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Orn	$^{D}Pro^{L}Pro$	8.3	75	1893.4
213.	SEQ ID NO:213	Leu	Orn	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.3	63	1836.3
214.	SEQ ID NO:214	Leu	Arg	Leu	Orn	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.4	44	1864.3
215.	SEQ ID NO:215	Leu	Arg	Leu	Lys	Orn	Arg	Arg	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.2	44	1864.3
216.	SEQ ID NO:216	Leu	Arg	Leu	Lys	Lys	Arg	Orn	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.2	44	1836.3
217.	SEQ ID NO:217	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Orn	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.3	40	1864.3
218.	SEQ ID NO:218	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Orn	Val	$^{D}Pro^{L}Pro$	10.2	92	1836.3
219.	SEQ ID NO:219	Leu	Arg	Leu	Lys	Lys	Arg	Gln	Trp	Lys	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.4	92	1850.3
220.	SEQ ID NO:220	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Tyr	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.5	88	1913.4
221.	SEQ ID NO:221	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	His	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.4	49	1887.3
222.	SEQ ID NO:222	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Arg	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.3	53	1906.4
223.	SEQ ID NO:223	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Thr	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.5	84	1851.3
224.	SEQ ID NO:224	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Gln	Tyr	Arg	Val	$^{D}Pro^{L}Pro$	10.5	52	1878.3
225.	SEQ ID NO:225	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Val	$^{D}Pro^{L}Pro$	10.6	54	1885.3
226.	SEQ ID NO:226	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Trp	Val	$^{D}Pro^{L}Pro$	10.9	47	1908.4
227.	SEQ ID NO:227	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Bip	Arg	Val	$^{D}Pro^{L}Pro$	12.3	50	1975.5

Table 7 (continued): Examples **ex.228-255** (n=12)

Example		P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template	RT(')	%	MS
228.	SEQ ID NO:228	Leu	Arg	Leu	Arg	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.9	46	1943.4
229.	SEQ ID NO:229	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Bip	Arg	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.9	41	1943.4
230.	SEQ ID NO:230	Leu	Trp	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	11.0	73	1945.4
231.	SEQ ID NO:231	Leu	Trp	Leu	Arg	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	11.0	71	1973.5
232.	SEQ ID NO:232	Leu	Trp	Leu	Lys	Lys	Arg	Arg	Bip	Arg	Tyr	Arg	Val	^{D}Pro^{L}Pro	11.0	71	1973.5
233.	SEQ ID NO:233	Leu	Trp	Leu	Arg	Lys	Arg	Arg	Bip	Lys	Bip	Arg	Val	^{D}Pro^{L}Pro	12.4	60	2033.6
234.	SEQ ID NO:234	Leu	Trp	Leu	Lys	Lys	Arg	Arg	Bip	Arg	Bip	Arg	Val	^{D}Pro^{L}Pro	12.4	85	2033.6
235.	SEQ ID NO:235	Leu	Trp	Leu	Arg	Lys	Arg	Arg	Bip	Arg	Bip	Arg	Bip	^{D}Pro^{L}Pro	11.6	50	2185.7
236.	SEQ ID NO:236	4ClPhe	Arg	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	10.7	39	1983.9
237.	SEQ ID NO:237	4ClPhe	Arg	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Bip	Arg	Val	^{D}Pro^{L}Pro	13.0	36	2043.9
238.	SEQ ID NO:238	4ClPhe	Arg	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Bip	^{D}Pro^{L}Pro	12.9	52	2108.0
239.	SEQ ID NO:239	4ClPhe	Arg	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Bip	Arg	Bip	^{D}Pro^{L}Pro	12.6	68	2168.1
240.	SEQ ID NO:240	4ClPhe	Arg	Leu	Arg	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	11.7	46	2011.9
241.	SEQ ID NO:241	4ClPhe	Arg	Leu	Lys	Lys	Arg	Arg	Bip	Arg	Tyr	Arg	Val	^{D}Pro^{L}Pro	11.7	41	2011.9
242.	SEQ ID NO:242	4ClPhe	Trp	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	11.8	48	2013.9
243.	SEQ ID NO:243	4ClPhe	Trp	Leu	Arg	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	11.9	38	2041.9
244.	SEQ ID NO:244	4ClPhe	Trp	Leu	Lys	Lys	Arg	Arg	Bip	Arg	Tyr	Arg	Val	^{D}Pro^{L}Pro	11.9	74	2041.9
245.	SEQ ID NO:245	4ClPhe	Trp	Leu	Arg	Lys	Arg	Arg	Bip	Lys	Bip	Arg	Val	^{D}Pro^{L}Pro	13.2	66	2102.0
246.	SEQ ID NO:246	4ClPhe	Trp	Leu	Lys	Lys	Arg	Arg	Bip	Arg	Bip	Arg	Val	^{D}Pro^{L}Pro	13.2	49	2102.0
247.	SEQ ID NO:247	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-Gly	9.5	58	1838.3
248.	SEQ ID NO:248	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-Arg	9.3	57	1937.4
249.	SEQ ID NO:249	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-Tyr	9.9	29	1944.4
250.	SEQ ID NO:250	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-Phe	10.7	34	1928.4
251.	SEQ ID NO:251	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-Trp	10.7	25	1967.5
252.	SEQ ID NO:252	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-Leu	10.5	21	1894.4
253.	SEQ ID NO:253	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-Ile	10.4	42	1894.4
254.	SEQ ID NO:254	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-Cha	11.2	36	1934.5
255.	SEQ ID NO:255	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-2Nal	11.4	27	1978.5

Table 7 (continued): Examples **ex.256-286** (n=12)

All products were purified by preparative HPLC-chromatography. Purities >90%.

Example	SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template	MS
256.	SEQ ID NO:256		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-1	1990.5
257.	SEQ ID NO:257		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-2	2018.3
258.	SEQ ID NO:258		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-3	2086.4
259.	SEQ ID NO:259		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-4	2086.4
260.	SEQ ID NO:260		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-5	1978.3
261.	SEQ ID NO:261		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-6	2023.3
262.	SEQ ID NO:262		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-7	1934.3
263.	SEQ ID NO:263		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-8	1948.2
264.	SEQ ID NO:264		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-9	1962.2
265.	SEQ ID NO:265		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-10	1976.3
266.	SEQ ID NO:266		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-11	1962.2
267.	SEQ ID NO:267		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-12	2002.3
268.	SEQ ID NO:268		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-13	2016.3
269.	SEQ ID NO:269		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-14	1976.3
270.	SEQ ID NO:270		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-15	1996.2
271.	SEQ ID NO:271		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-16	2011.4
272.	SEQ ID NO:272		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-17	2049.3
273.	SEQ ID NO:273		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-18	2063.4
274.	SEQ ID NO:274		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-19	2072.3
275.	SEQ ID NO:275		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro-A8'-20	2046.4
276.	SEQ ID NO:276		Leu	Arg	Leu	Lys	Lys	Gly	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	1779.2
277.	SEQ ID NO:277		Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	(c1)-1	2023.2
278.	SEQ ID NO:278		Leu	Tyr	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Val	^{D}Pro^{L}Pro	1892.3
279.	SEQ ID NO:279		Leu	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Val	^{D}Pro^{L}Pro	1915.4
280.	SEQ ID NO:280		Arg	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Trp	Val	^{D}Pro^{L}Pro	1981.4
281.	SEQ ID NO:281		Arg	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Val	^{D}Pro^{L}Pro	1958.4
282.	SEQ ID NO:282		Leu	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	1995.5
283.	SEQ ID NO:283		Leu	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	1972.4
284.	SEQ ID NO:284		Arg	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	2015.5
285.	SEQ ID NO:285		Leu	Arg	Leu	Lys	Lys	Y(Bzl)	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	1975.5
286.	SEQ ID NO:286		Leu	Arg	Leu	Lys	Lys	^{D}Y(Bzl)	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro	1975.5

Table 7 (continued): Examples **ex.287-300** (n=12)

All products were purified by preparative HPLC-chromatography. Purities >90%.

Example	SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template	MS
287.	SEQ ID NO:287	Bip	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	2082.6
288.	SEQ ID NO:288	Thr	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	1960.4
289.	SEQ ID NO:289	Arg	Bip	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	2052.5
290.	SEQ ID NO:290	Arg	Thr	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	1930.4
291.	SEQ ID NO:291	Arg	Trp	Thr	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	2003.4
292.	SEQ ID NO:292	Arg	Trp	Leu	Arg	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	2043.5
293.	SEQ ID NO:293	Arg	Trp	Leu	Gln	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	2015.4
294.	SEQ ID NO:294	Lys	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	1987.5
295.	SEQ ID NO:295	Tyr	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	2022.5
296.	SEQ ID NO:296	Trp	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	2045.5
297.	SEQ ID NO:297	Val	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	2082.4
298.	SEQ ID NO:298	Gln	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	1987.4
299.	SEQ ID NO:299	Cha	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	2012.5
300.	SEQ ID NO:300	Y(bzl)	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro	2112.6

1.2. Procedure 2

Examples **ex.256-275** were also synthesized using **procedure 2.**

The peptide synthesis was carried out by solid phase method using standard Fmoc chemistry on a peptide synthesizer-ABI 433A.

The first amino acid, Fmoc-Arg(Pbf)-OH (1.29g, 1.2 equiv.) was coupled to the 2-chlorotritylchloride resin (Barlos et al. *Tetrahedron Lett.* **1989**, *30*, 3943-3946) (2g, 0.83 mmol/g) in presence of DIEA (1.12mL, 4 equiv.) in CH_2Cl_2 (20 mL), with swirling for 3 hr at room temperature. The resin was then washed with 3 x CH_2Cl_2 /MeOH/DIEA(17:2:1), 3 x CH_2Cl_2, 2 x DMF, 2 x CH_2Cl_2, 2 x MeOH. Finally, the resin was dried under vacuum and the substitution level was measured by weight increase (~0.6 mmol/g)

The resin with the synthesized linear peptide, Fmoc-Arg(Pbf)-Trp(Boc)-Lys(Boc)-Tyr(tBu)-Arg(Pbf)-Val-^{D}Pro-**212**-Leu-Arg(Pbf)-Leu-Lys(Boc)-Lys(Boc)-Arg(Pbf)-resin, was preferably divided into equal parts and placed in different reaction vessels in order to carry out the acylation reaction in parallel format. The coupling and deprotection reactions in the following steps were monitored by Kaiser's test (Kaiser et al. *Anal. Biochemistry* **1970**, *43*, 595).

Removal of Alloc protecting group:

To the linear peptide resin (100 mg in each reaction vessel) was added $Pd(PPh_3)_4$ (15mg, 0.5 equiv.) under argon followed by dry CH_2Cl_2 (10 mL) and phenylsilane (17μL, 30 equiv.). The reaction mixture was left for 1 hour in the dark, filtered, and the resin was washed twice with CH_2Cl_2, DMF, and CH_2Cl_2.

Acylation of 4-amino-proline group

To the resin was added the corresponding acylating agent (usually a carboxyxlic acid ($R^{64'}COOH$, 3 equiv.), HBTU (22.3mg, 4 equiv.), HOBt (8mg, 4 equiv.) and DIEA (125μL, 6 equiv.) in DMF (2mL) for 1.5-2 hrs at room temperature. The resin was filtered, washed with 2 x DMF, 3 x CH_2Cl_2, 2 x DMF.

Deprotection of N^{α}-Fmoc group:

Deprotection of the Fmoc-group was achieved by treating the resin with 20% piperidine in DMF for 20 min. The resin was subsequently filtered and washed three times with DMF, and CH_2Cl_2 , and twice with DMF, and CH_2Cl_2.

Cleavage of peptide from the resin:

The linear side-chain protected peptide was cleaved from the resin using AcOH: TFE: CH_2Cl_2 (2:2:6, *v/v/v*) for 2 hrs at room temperature. The resin was filtered off and washed twice with a mixture of AcOH:TFE:DCM and once with CH_2Cl_2. The filtrate was subsequently diluted with hexane (14 times by vol.) and concentrated. Evaporation was repeated twice with hexane to remove traces of AcOH. The residue was dried under vacuum. Yield of the linear protected peptide was generally about 40-50 mg.

Cyclization of the linear protected peptide:

Cyclization was carried out in DMF at a concentration of 5 mg/mL using HATU (13.12 mg, 3 equiv.), HOAT (4.7 mg, 3 equiv.), DIEA (153µL, 6 equiv.). The reaction mixture was stirred for 16 hrs at room temperature and the completion of reaction was monitored by HPLC. After the evaporation of DMF, CH_3CN/H_2O (90/10, *v/v*) was added to the residue and extracted with DCM. The organic layer was washed once with water and evaporated to dryness. Dried under vacuum.

Cleavage of side chain protecting groups:

The final deprotection of the side-chain protecting groups was carried out by treating the peptide with TFA:triisopropylsilane:H_2O (95:2.5:2.5, *v/v/v*) at room temperature for 3 hrs. TFA was then evaporated and the residue triturated with cold ether.

Purification:

The crude peptides thus obtained were analyzed and purified by HPLC on a VYDAC C18 preparative column using 5-60% CH_3CN/H_2O+0.1%TFA in 30 min as gradient and a flow rate of 10ml/min. The purity of the final peptide was checked by analytical HPLC and by ESI-MS. Analytical data are shown in *table 7*.

1.3. Procedure 3

Procedure 3 describes the synthesis of peptides having disulfide β-strand linkages.

a) n=8: :The peptides are synthesized according to **procedure 1** starting with the amino acid at position P4, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P5-P6-**P7**-P8-^{D}Pro-Pro-P1-**P2**-P3-P4-resin, where at positions **P2** and **P7** Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and cyclized as described in **procedure 1**. The cyclized side chain protected β-hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1N, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure 1**.

b) n=9: :The peptides are synthesized according to **procedure 1** starting with the amino acid at position P5, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-**P8**-P9-^{D}Pro-Pro-P1-**P2**-P3-P4-P5-resin, where at positions **P2** and **P8** Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and cyclized as described in **procedure 1**. The cyclized side chain protected β-hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1N, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure 1**.

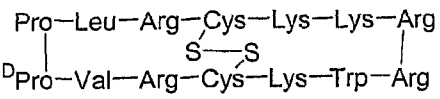
c) n=10: :The peptides are synthesized according to **procedure 1** starting with the amino acid at position P5, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-**P8**-P9-P10-^{D}Pro-Pro-P1-P2-**P3**-P4-P5-resin, where at positions **P3** and **P8** Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and cyclized as described in **procedure 1**. The cyclized side chain protected β-hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1N, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure 1**.

d) n=11: :The peptides are synthesized according to **procedure 1** starting with the amino acid at position P5, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-**P8**-P9-P10-P11-^{D}Pro-Pro-P1-P2-P3-**P4**-P5-resin, or P6-P7-P8-P9-**P10**-P11-^{D}Pro-Pro-P1-**P2**-P3-P4, or P5-P6-P7-**P8**-P9-**P10**-P11-^{D}Pro-Pro-P1-**P2**-P3-**P4**-P5-resin, where at positions **P2, P4, P8 and P10** Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and

cyclized as described in **procedure 1**. The cyclized side chain protected β-hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1N, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure 1**.

e) **n=12:** :The peptides are synthesized according to **procedure 1** starting with the amino acid at position P6, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P7-P8-**P9**-P10-P11-P12-^{D}Pro-Pro-P1-P2-P3-**P4**-P5-P6-resin, or P7-P8-P9-P10-**P11**-^{D}Pro-Pro-P1-**P2**-P3-P4-P5-P6-resin, or P7-P8-**P9**-P10-**P11**-^{D}Pro-Pro-P1-**P2**-P3-**P4**-P5-P6-resin, where at positions **P2, P4, P9** and **P11** Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and cyclized as described in **procedure 1**. The cyclized side chain protected β-hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1*N*, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure 1**.

Ex.301:



Following **procedure 3** NH_2Arg(Pbf)-Lys(Boc)-Lys(Boc)-Cys(Acm)-Arg(Pbf)-Leu-Pro-^{D}Pro-Val-Arg-Cys(Acm)-Lys(Boc)-Trp(Boc)-Arg(Pbf)- [SEQ ID NO:301], coupled to the resin, was synthesized on the resin, the linear side-chain protected peptide cleaved and cyclized, followed by disulfide formation, deprotection and preparative HPLC chromatography yielding the above product [SEQ ID NO:302] as a white amorphous powder. ESI-MS: 1806.2 ([M+H]+).

f) **n=14:** :The peptides are synthesized according to **procedure 1** starting with the amino acid at position P7, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P8-P9-**P10**-P11-P12-P13-P14-^{D}Pro-Pro-P1-P2-P3-P4-**P5**-P6-P7-resin, or P8-P9-P10-P11-**P12**-P13-P14-^{D}Pro-Pro-P1-P2-**P3**-P4-P5-P6-P7-resin, or P8-P9-**P10**-P11-**P12**-P14-^{D}Pro-Pro-P1-P2-**P3**-P4-**P5**-P6-P7-resin, where at positions **P3, P5, P10** and **P12** Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and cyclized as described in **procedure** 1. The

cyclized side chain protected β-hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1*N*, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure** 1.

g) n=16: :The peptides are synthesized according to **procedure 1** starting with the amino acid at position P8, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure** 1 in the following sequence: P9-P10-P11-P12-P13-P14-**P15**-P16-^{D}Pro-Pro-P1-**P2**-P3-P4-P5-P6-P7-P8-resin, or P9-P10-P11-P12-**P13**-P14-P15-P16-^{D}Pro-Pro-P1-P2-P3-**P4**-P5-P6-P7-P8-resin, or P9-P10-**P11**-P12-P13-P14-P15-P16-^{D}Pro-Pro-P1-P2-P3-P4-P5-**P6**-P7-P8-resin, or P9-P10-P11-P12-**P13**-P14-**P15**-P16-^{D}Pro-Pro-P1-**P2**-P3-**P4**-P5-P6-P7-P8-resin, or P9-P10-**P11**-P12-**P13**-P14-P15-P16-^{D}Pro-Pro-P1-P2-P3-**P4**-P5-**P6**-P7-P8-resin, or P9-P10-**P11**-P12-P13-P14-**P15**-P16-^{D}Pro-Pro-P1-**P2**-P3-P4-P5-**P6**-P7-P8-resin, or P9-P10-**P11**-P12-**P13**-P14-**P15**-P16-^{D}Pro-Pro-P1-**P2**-P3-**P4**-P5-**P6**-P7-P8-resin, where at positions **P2, P4, P6, P11, P13** and **P15** Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and cyclized as described in **procedure 1.** The cyclized side chain protected β-hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1*N*, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure 1.**

1.4. Procedure 4

Procedure 4 describes the synthesis of peptides having amide β-strand linkages.

a) n=8: :The peptides are synthesized according to **procedure 1** starting with the amino acid at position P4, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P5-P6-**P7**-P8-^{D}Pro-Pro-P1-**P2**-P3-P4-resin, where at position **P2** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH, and at position **P7** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at position **P2** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at position **P7** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in **procedure 2.** The amide linkage is subsequently performed as described for the cyclization according to **procedures 1** and **2**, the side chain protective groups are removed and the products are purified as described in **procedures 1** and **2.**

b) n=9: :The peptides are synthesized according to **procedure 1** starting with the amino acid at position P5, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-**P8**-P9-^{D}Pro-Pro-P1-**P2**-P3-P4-P5-resin, where at position **P2** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH, and at position **P8** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at position **P2** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at position **P8** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in **procedure 2**. The amide linkage is subsequently performed as described for the cyclization according to **procedures 1** and **2**, the side chain protective groups are removed and the products are purified as described in **procedures 1** and **2.**

c) n=10: :The peptides are synthesized according to **procedure 1** starting with the amino acid at position P5, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-**P8**-P9-P10-^{D}Pro-Pro-P1-P2-**P3**-P4-P5-resin, where at position **P3** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH, and at position **P8** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at position **P3** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at position **P8** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in **procedure 2**. The amide linkage is subsequently performed as described for the cyclization according to **procedures 1** and **2**, the side chain protective groups are removed and the products are purified as described in **procedures 1** and **2.**

d) n=11: : The peptides are synthesized according to **procedure 1** starting with the amino acid at position P5, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-**P8**-P9-P10-P11-^{D}Pro-Pro-P1-P2-P3-**P4**-P5-resin, or P6-P7-P8-P9-**P10**-P11-^{D}Pro-Pro-P1-**P2**-P3-P4-P5-resin, or P6-P7-**P8**-P9-**P10**-P11-^{D}Pro-Pro-P1-**P2**-P3-**P4**-P5-resin; where at positions **P2** and/or **P4** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH, and at positions **P8** and/or **P10** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at positions **P2** and/or **P4** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at positions **P8** and/or **P10** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in **procedure 2**. The amide linkage is subsequently performed as described for the cyclization according to **procedures 1**

and **2**, the side chain protective groups are removed and the products are purified as described in **procedures 1** and **2.**

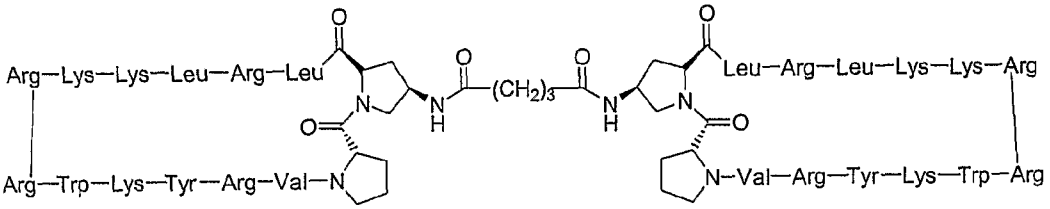
e) n=12: :The peptides are synthesized according to **procedure 1** starting with the amino acid at position P6, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P7-P8-**P9**-P10-P11-P12-^{D}Pro-Pro-P1-P2-P3-**P4**-P5-P6-resin, or P7-P8-P9-P10-**P11**-P12-^{D}Pro-Pro-P1-**P2**-P3-P4-P5-P6-resin, or P7-P8-**P9**-P10-**P11**-P12-^{D}Pro-Pro-P1-**P2**-P3-**P4**-P5-P6-resin; where at positions **P2** and/or **P4** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH, and at positions **P9** and/or **P11** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at positions **P2** and/or **P4** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at positions **P9** and/or **P11** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in **procedure 2.** The amide linkage is subsequently performed as described for the cyclization according to **procedures 1** and **2**, the side chain protective groups are removed and the products are purified as described in **procedures 1** and **2.**

f) n=14: :The peptides are synthesized according to **procedure 1** starting with the amino acid at position P7, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P8-P9-**P10**-P11-P12-P3-P14-^{D}Pro-Pro-P1-P2-P3-P4-**P5**-P6-P7-resin, or P8-P9-P10-P11-**P12**-P13-P14-^{D}Pro-Pro-P1-P2-**P3**-P4-P5-P6-P7-resin, or P8-P9-**P10**-P11-**P12**-R14-^{D}Pro-Pro-P1-P2-**P3**-P4-**P5**-P6-P7-resin; where at positions **P3** and/or **P5** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH, and at positions **P10** and/or **P12** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at positions **P3** and/or **P5** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at positions **P10** and/or **P12** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in **procedure 2.** The amide linkage was subsequently performed as described for the cyclization according to **procedures 1** and **2**, the side chain protective groups are removed and the products are purified as described in **procedures 1** and **2.**

g) n=16: :The peptides are synthesized according to **procedure 1** starting with the amino acid at position P7, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P8-P9-P10-P11-P12-P13-P14-**P15**-P16-^{D}Pro-Pro-P1-**P2**-P3-P4-P5-P6-P7-resin, or P8-P9-P10-P11-P12-**P13**-P14-P15-P16-^{D}Pro-Pro-P1-P2-P3-**P4**-P5-P6-P7-resin, or P9-P9-P10-**P11**-P12-P4-P5-P16-^{D}Pro-Pro-P1-P2-P3-P4-P5-**P6**-P7-resin, or P8-P9-P10-P11-P12-**P13**-P14-**P15**-P16-^{D}Pro-Pro-P1-**P2**-P3-**P4**-P5-P6-P7-

resin, or P8-P9-P10-**P11**-P12-**P13**-P14-P15-P16-^{D}Pro-Pro-P1-P2-P3-**P4**-P5-**P6**-P7-resin, or P8-P9-P10-**P11**-P12-P13-P14-**P15**-P16-^{D}Pro-Pro-P1-**P2**-P3-P4-P5-**P6**-P7-resin, or P8-P9-P10-**P11**-P12-**P13**-P14-**P15**-P16-^{D}Pro-Pro-P1-**P2**-P3-**P4**-P5-**P6**-P7-resin; where at positions **P2** and/or **P4** and/or **P6** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH, and at positions **P11**and/or **P13** and/or **P15** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at positions **P2** and/or **P4** and/or **P6** Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at positions **P11** and/or **P13** and/or **P15** Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in **procedure 2**. The amide linkage is subsequently performed as described for the cyclization according to **procedures 1** and **2**, the side chain protective groups are removed and the products are purified as described in **procedures 1** and **2.**

Ex.302:

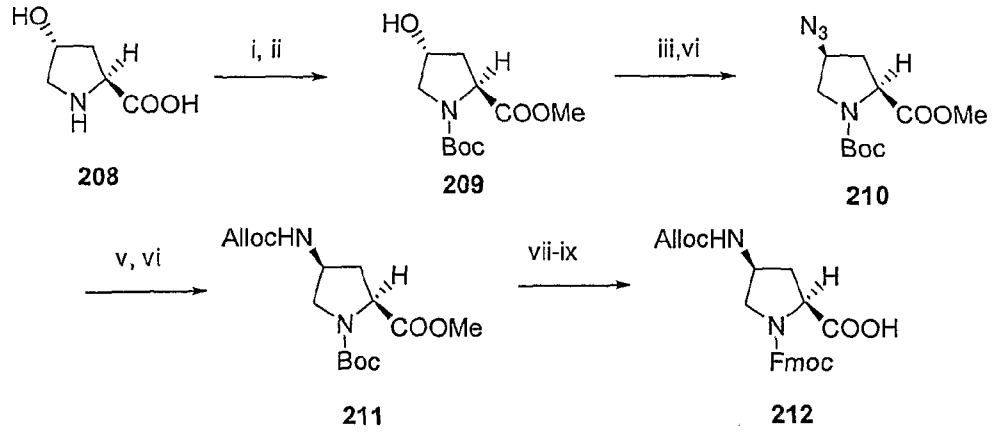


Following **procedure 2** NH_2Arg(Pbf)-Trp(Boc)-Lys(Boc)-Tyr(tBu)-Arg(Pbf)-DPro-**212**-Leu-Arg(Pbf)-Leu-Lys(Boc)-Lys(Boc)-Arg(Pbf)- [SEQ ID NO:303], coupled to the resin, was prepared, the linear peptide cleaved and cyclized. The Alloc-group was removed from building block **212** as described in **procedure 2**, half of the resulting amine reacted with excess glutaric anhydride in pyridine and DMAP and the solvents were removed. The resulting acid was coupled with the second half of the above mentioned amine in DMF and in the presence of TATU, HOAt and DIEA. The protective groups were removed as described in **procedure 2** and the product purified by preparative HPLC chromatography as described in **procedure 2** to yield the above product [SEQ ID NO:304] as a white amorphous powder. ESI-MS: 3882.3 ([M+H]$^{+}$).

2. Synthesis of templates

2.1. The synthesis of (2*S*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(*9H*-fluoren-9-yl)methoxycarbonyl] –proline (**212**) and (2*S*,4*R*)-4-[(Allyloxy)carbonylamino]-1-[(*9H*-fluoren-9-yl)methoxy-carbonyl]proline (**217**) are shown in *Schemes 42* and *43*.

Scheme 42



i: $SOCl_2$, MeOH; ii: Boc_2O, DMAP, Et_3N; iii: $pNO_2C_6H_4SO_2Cl$, Et_3N; iv: NaN_3, DMF; v: $SnCl_2$,dioxane/H_2O; vi: $ClCOOCH_2CH{=}CH_2$, aq.$NaHCO_3$, dioxane: vii: LiOH, MeOH, H_2O; viii: TFA, CH_2Cl_2; ix: Fmoc-OSu, DIEA

(2*S*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(*9H*-fluoren-9-yl)methoxycarbonyl]- proline (**212**)

i,ii: To a solution of (2*S*,4*R*)-4-hydroxyproline (30 g, 0.18 mol) in abs. methanol (300 ml) at 0 °C thionyl chloride (38 ml, 2.5 eq, 0.45 mol) was added dropwise. The solution was heated to reflux and stirred for 3 h under nitrogen. Then the solution was concentrated by rotary evaporation and the ester precipitated by adding diethylether. After filtration the white solid was washed with diethylether, then dried at HV: (2*S*,4*R*)-4-hydroxyproline-methylester·hydrochloride as a white solid (29.9 g, 90 %). %). TLC (CH_2Cl_2/MeOH/water 70:28:2): R_f 0.82. $[\alpha]_D^{20}$= -24.5 (c = 1.01, MeOH). IR (KBr): 3378*s* (br.), 2950*m*, 2863*w*, 1745*s*, 1700*s*, 1590*m*, 1450*s*, 1415*s*, 1360*s*, 1215*s*, 1185*s*, 1080*m*, 700*m*. ^{1}H-NMR (300MHz, MeOH-d_4) 4.66-4.55 (*m*, 2H, H-C(4), H-C(2)); 3.85 (*s*, 3H, H_3C-O); 3.45 (*dd*, J= 12.2, 3.8, 1H, H-C(5)); 3.37-3.25 (*m*, 1H, H-C(5)); 2.44-2.34 (*m*, 1H, H-C(3)), 2.27-2.12 (*m*, 1H, H-C(3)). ^{13}C-NMR (75MHz, MeOH-d_4): 170.8 (*s*, COOMe); 70.8 (*d*, C(4)); 59.6 (*d*, C(2)); 55.2 (*t*, C(5)); 54.2 (*q*, Me); 38.7 (*t*, C(3)). CI-MS (NH_3): 146.1 ([*M*-Cl]$^+$).

30 g (0.17 mmol) of the above intermediate was dissolved in CH_2Cl_2 (300 ml), cooled to 0 °C and triethylamine (45 ml, 1.5 eq, 0.25 mol) was added dropwise. Then di-tert.-butyldicarbonate (54.0 g, 1.5 eq, 0.25 mmol) in CH_2Cl_2 (15 ml) and 4-*N*,*N*-dimethylaminopyridine (2.50 g, 0.1 eq, 17 mmol) was added and the solution stirred at room temperature overnight. Then the solution was washed with 1N aq. citric acid solution, sat. aq.

$NaHCO_3$ solution, dried (Na_2SO_4), evaporated and the residue dried at high vaccum: (2*S*,4*R*)-4-Hydroxy-1-[(*tert*-butoxy)carbonyl]proline-methylester (**209**) as a white solid (39.6 g, 78 %). TLC (CH_2Cl_2/MeOH 9:1): R_f 0.55. $[\alpha]_D^{24}$ = -55.9 (c = 0.983, $CHCl_3$). IR (KBr): 3615*w*, 3440w (br.), 2980*m*, 2950m, 2880m, 1750*s*, 1705*s*, 1680*s*, 1480*m*, 1410*s*, 1370*s*, 1340*m*, 1200*s*, 1160*s*, 1130*m*, 1090*m*, 1055*w*, 960*w*, 915*w*, 895*w*, 855*m*, 715*m*. ^{1}H-NMR (300MHz, $CDCl_3$): 4.47-4.37 (*m*, 2H, H-C(4), H-C(2)); 3.73 (*s*, 3H, H_3C-O)); 3.62 (*dd*, J= 11.8, 4.1, 1H, H-C(5)); 3.54-3.44 (*m*, 1H, H-C(5)); 2.32-2.25 (*m*, 1H, H-C(3)); 2.10-2.03 (*m*, 1H, H-C(3)); 1.46+1.41 (2*s*, 9H, *t*Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.6 (*s*, COOMe); 154.3+153.9 (2*s*, COO*t*Bu); 80.3 (*s*, C-*t*Bu); 70.0+69.3 (2*d*, C(4)); 57.9+57.4 (2*d*, C(2)); 54.6 (*t*, C(5)); 51.9 (*q*, Me); 39.0+38.4 (2*t*, C(3)); 28.1+27.6 (2*q*, *t*Bu). CI-MS: 246.2 ([*M*+H]$^+$); 190.1 ([*M*-*t*Bu+H]$^+$); 146.1 ([*M*-BOC+H]$^+$).

iii,iv: 39 g (0.16 mol) of **209** was dissolved in CH_2Cl_2 (300 ml) followed by addition of 4-nitrobenzenesulfonyl chloride (46 g, 1.3 eq, 0.21 mol) and Et_3N (33 ml, 1.5 eq, 0.24 mol) at 0 °C. Then the solution was stirred overnight and brought gradually to room temperature, washed with 1N hydrochloric acid, sat. aq. $NaHCO_3$ solution and dried (Na_2SO_4). The solvents were evaporated and the crude product was purified by filtration on silica gel with (2:1) hexane/AcOEt. The product was crystallized from hexane/AcOEt: (2S,4*S*)-4-[(*p*-nitrobenzyl)sulfonyloxy]-1-[(*tert*-butoxy)carbonyl]proline methylester as white crystals (46.4 g, 65 %). TLC (hexane/AcOEt 1:1): R_f 0.78. M.p.: 93-95 °C. $[\alpha]_D^{20}$ = -32.3 ° (c = 0.907, $CHCl_3$). IR (KBr): 3110*w*, 3071*w*, 2971*w*, 1745*s*, 1696*s*, 1609*s*, 1532*s*, 1414s, 1365*s*, 1348*m*, 1289*m*, 1190*m*, 1173*m*, 1122*w*, 1097*w*, 1043*w*, 954*w*, 912*w*, 755*w*, 578*w*. ^{1}H-NMR (600MHz, $CDCl_3$): 8.42-8.34 (*m*, 2H, H-C(Nos)); 8.11-8.04 (*m*, 2H, H-C(Nos)); 5.14 (*s*, 1H, H-C(4)); 4.39-4.28 (*m*, 1H, H-C(2)); 3.70-3.56 (*m*, 5H, H_2-C(5), H_3C-O); 2.58-2.38 (*m*, 1H, H-C(3)); 2.25-2.11 (*m*, 1H, H-C(3)); 1.37+1.33 (2*s*, 9H, *t*Bu). ^{13}C-NMR (150 MHz, $CDCl_3$): 172.4+172.2 (2*s*, COOMe); 153.6+153.0 (2*s*, COO*t*Bu); 150.8+142.0 (2*s*, C(Nos)); 129.0+124.6 (2*d*, C(Nos)); 80.4 (*s*, C-*t*Bu); 80.8+79.9 (2*d*, C(4)); 57.1+56.9 (2*d*, C(2)); 52.2+51.7 (2*t*, C(5)); 52.3 (*q*, Me); 37.1+35.9 (2*t*, C(3)); 28.0 (*q*, *t*Bu). ESI-MS (MeOH + NaI): 453.0 ([*M*+Na]$^+$).

38 g (88 mmol) of the above intermediate was dissolved in DMF (450 ml) then heated to 40 °C when sodium azide (34 g, 6 eq, 0.53 mol) was added and the solution stirred overnight. DMF was evaporated and the solid suspended in diethylether. The suspension was washed with water and dried (Na_2SO_4). The solvent was evaporated and the product dried at high vacuum: (2S,4*S*)-4-Azido-1-[(*tert*-butoxy)carbonyl]proline methylester (**210**) yellow oil (21.1 g, 88 %). $[\alpha]_D^{20}$ = -36.9 (c = 0.965, $CHCl_3$). ^{1}H-NMR (600MHz, $CDCl_3$): 4.46-4.25 (2*m*, 1H, H-C(2)); 4.20-4.10 (*m*, 1H, H-C(4)); 3.80-3.65 (*m*, 4H, H-C(5), H_3C-O); 3.53-3.41 (*m*, 1H, H-C(5)); 2.54-2.39 (*m*, 1H, H-C(3)); 2.21-2.12 (*m*, 1H, H-C(3)); 1.47+1.41 (2*s*, 9H, *t*Bu). ^{13}C-

NMR (150 MHz, $CDCl_3$): 172.2+171.9 (2*s*, COOMe); 153.9+153.4 (2*s*, COO*t*Bu); 80.5 (*s*, C-*t*Bu); 59.2+58.2 (2*d*, C(4)); 57.7+57.3 (2*d*, C(2)); 52.4+52.2 (2*q*, Me); 51.2+50.7 (2*t*, C(5)); 36.0+35.0 (2*t*, C(3)); 28.3+28.2 (2*q*, *t*Bu). EI-MS (70ev): 270.1 ($[M]^+$); 227.1 ($[M\text{-}CO_2\text{+H}]^+$); 169.1 ($[M\text{-BOC+H}]^+$);.

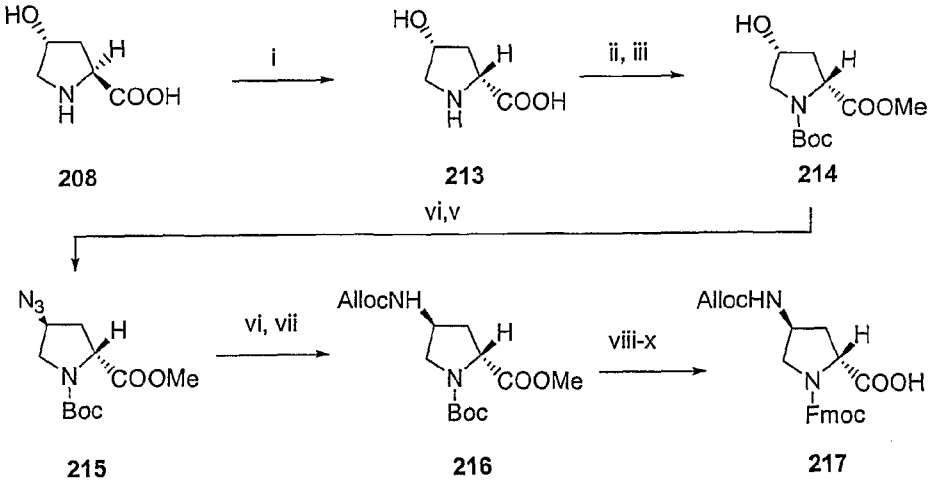
v, vi: 21.1 g (78 mmol) of the above intermediate was dissolved in a (3:1)-mixture of dioxane/water (500 ml) and $SnCl_2$ (59.2 g, 4 eq, 0.31 mol) was added at 0° and the solution stirred for 30 min. and gradualllly brought to room temperature and stirred for another 5h. After adjusting the pH to 8 with solid $NaHCO_3$, allyl chloroformate (41.5 ml, 5 eq, 0.39 mol) was added and the solution stirred at room temperature overnight. The reaction mixture was evaporated and extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), the solvent evaporated and the product was dried at high vacuum: (2*S*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(*tert*-butoxy)carbonyl]proline methylester (**211**) as a clear thick oil (22.3 g, 87 %). $[\alpha]_D^{20}$ = -30.2 ° (c = 1.25, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): 5.98-5.77 (*m*, 1H, H-C(β)(Alloc)); 5.32-5.12 (*m*, 2H, H_2-C(γ)(Alloc); 4.59-4.46 (*m*, 2H, H_2-C(α)(Alloc)); 4.40-4.16 (*m*, 2H, H-C(4), H-C(2)); 3.80-3.53 (*m*, 4H, H-C(5), H_3C-O); 3.53-3.31 (*m*, 1H, H-C(5)); 2.54-2.17 (*m*, 1H, H-C(3)); 1.98-1.84 (*m*, 1H, H-C(3)); 1.41+1.37 (2*s*, 9H, *t*Bu). ESI-MS (MeOH+ CH_2Cl_2): 351.2 ($[M\text{+Na}]^+$); 229.0 ($[M\text{-BOC+H}]^+$).

vii-ix : 22 g, 67 mmol) of **211** was dissolved in a (4:1)-mixture of methanol/water (100 ml) and LiOH (5 g, 2 eq, 134 mmol) was added at room temperature and the solution stirred for 3.5 h. The reaction mixture was evaporated and extracted with 1*N* hydrochloric acid (100 ml) and AcOEt. The solvent was removed and the resulting solid dissolved in 1:1 TFA/ CH_2Cl_2 (200ml) and stirred for 2 h. The solvents were evaporated and the product dried at high vacuum: (2S,4*S*)-4-[(Allyloxy)carbonylamino]proline as a clear oil (21 g, 96 %) ^{1}H-NMR (600MHz, MeOH-d_4): 5.98-5.85 (*m*, 1H, H-C(β)(Alloc)); 5.30 (*dd*, J=17.1, 1.5 Hz, 1H, H-C(γ)(Alloc)); 5.12 (*d*, J=10.7 Hz, 1H, H-C(γ)(Alloc)); 4.54 (*d*, J=4.4 Hz, 2H, H_2-C(α)(Alloc)); 4.44 (*t*, J=8.9 Hz, 1H, H-C(2)); 4.36-4.27 (*m*, 1H, H-C(4)); 3.58 (*dd*, J=12.2, 7.3 Hz, 1H, H-C(5)); 3.34-3.32 (*m*, 1H, H-C(5)); 2.73 (*ddd*, J=13.6, 8.7, 7.2 Hz, 1H, H-C(3)); 2.23-2.15 (*m*, 1H, H-C(3)). ^{13}C-NMR (150 MHz, MeOH-d_4): 171.3 (*s*, COOMe); 158.3 (*s*, COOAllyl); 134.1 (*d*, C(β)(Alloc)); 118.0 (*t*, C(γ)(Alloc)); 66.8 (*t*, C(α)(Alloc)); 59.7 (*d*, C(2)); 51.3 (*d*, C(4)); 51.1 (*t*, C(5)); 34.9 (*t*, C(3)). ESI-MS (DCM+MeOH): 237.0 ($[M\text{+Na}]^+$); 215.0 ($[M\text{+H}]^+$).

15 g (70 mmol) of the above intermediate and 9-fluorenylmethoxycarbonylsuccinimid (28 g, 1.2 eq, 84 mmol) were dissolved in DCM (700 ml) and DIEA (48 ml, 6 eq, 0.42 mol) was added and the solution stirred overnight at room temperature. The solvent was removed and the residue dissolved in AcOEt and washed with 1*N* hydrochloric acid and dried (Na_2SO_4). After evaporation, the crude product was purified by filtration on silica gel with a gradient of

(3:1) hexane/AcOEt to AcOEt. The solvent was evaporated and the residue crystallized from hexane at -20 °C. The product was dried at high vacuum: (2*S*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(*9H*-fluoren-9-yl)methoxycarbonyl]- proline (**212**) as a white solid (23.8 mg, 78 %) $[\alpha]_D^{20}$ = -27.0 (c = 1.1, $CHCl_3$). IR (KBr): 3321*w* (br.), 3066*w*, 2953*w*, 1707*s*, 1530*m*, 1451*s*, 1422*s*, 1354*m*, 1250*m*, 1205*m*, 1173*m*, 1118*m*, 1033*m*, 977*m*, 936*m*, 759*m*, 739*s*, 621*m*, 597*w*, 571*w*, 545*s*. ^{1}H-NMR (300MHz, MeOH-d_4): 7.88-7.78 (*m*, 2H, H-C(4')(Fmoc)); 7.71-7.61 (*m*, 2H, H-C(1')(Fmoc)); 7.49-7.29 (*m*, 4H, H-C(3')(Fmoc), H-C(2')(Fmoc)); 6.08-5.68 (*m*, 1H, H-C(β)(Alloc)); 5.41-5.17 (*m*, 2H, H_2-C(γ)(Alloc); 4.58 (*s*, 2H, H_2-C(α)(Alloc)); 4.74-4.17 (*m*, 5H, H_2-C(10')(Fmoc), H-C(9')(Fmoc), H-C(4), H-C(2)); 3.94-3.73 (*m*, 1H, H-C(5)); 3.41-3.26 (*m*, 1H, H-C(5)); 2.74-2.54 (*m*, 1H, H-C(3)); 2.12-1.92 (*m*, 1H, H-C(3)). ESI-MS (DCM+MeOH): 459.3 ([*M*+Na]$^+$); 437.3 ([*M*+H]$^+$).

Scheme 43



i: Ac_2O, AcOH; ii: $SOCl_2$, MeOH; iii: Boc_2O, DMAP, Et_3N; vi: $pNO_2C_6H_4SO_2Cl$, Et_3N; v: NaN_3, DMF; vi: $SnCl_2$,dioxane/H_2O; vii: $ClCOOCH_2CH{=}CH_2$, aq.$NaHCO_3$, dioxane: viii: LiOH, MeOH, H_2O; ix: TFA, CH_2Cl_2; x: Fmoc-OSu, DIEA

2.2. (2*R*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(*9H*-fluoren-9-yl)methoxycarbonyl]-proline (**217**)

i: A solution of acetic anhydride (1.02 kg, 5.3eq, 10 mol) in glacial acetic acid (3 l) was heated to 50 °C and (2*S*,4*R*)-4-hydroxyproline (**208**) (247 g, 1.88 mol) was added in one portion. The solution was refluxed for 5.5 h., cooled to room temperature and the solvent was removed under reduced pressure giving a thick oil. The oil was then dissolved in 2*N* hydrochloric acid (3.5 l) and heated to reflux for 4 h and treated with charcoal and filtered through Celite. As the solution was evaporated, white needles formed, which were filtered. The product was dried at high vacuum: (2*R*,4*R*)-4-hydroxyproline·hydrochloride (**213**) white cryst. needles (220.9 g, 70 %). M.p.: 117 °C. $[\alpha]_D^{20}$ = +19.3 ° (c = 1.04, water). IR (KBr): 3238*s* 3017*s*, 2569*m*, 1712*s*, 1584*m*, 1376*s*, 1332*m*, 1255*s*, 1204*m*, 1181*w*, 1091*w*, 1066*w*, 994*w*, 725*m*, 499*s*. ^{1}H-NMR (600MHz, MeOH-d_4): 9.64 (*s*, 1H, H-N); 8.89 (*s*, 1H, H-N); 4.55-4.53 (*m*, 1H, H-C(4)); 4.51 (*dd*, J= 10.4, 3.6 Hz, 1H, H-C(2)); 3.44-3.35 (*m*, 2H, H_2-C(5)); 2.54-2.48 (*m*, 1H, H-C(3)); 2.40-2.34 (*m*, 1H, H-C(3)). ^{13}C-NMR (150MHz, MeOH-d_4): 171.9 (*s*, COOH); 70.3 (*d*, C(4)); 59.6 (*d*, C(2)); 55.0 (*t*, C(5)); 38.5 (*t*, C(3)). EI-MS (NH_3): 132.1 ([*M*-Cl]$^+$). The filtrate was further concentrated to give an additional 59.5 g (19 %).

ii,iii: To a solution of **213** (30 g, 0.18 mol) in abs. methanol (550 ml) was added dropwise at 0 °C thionyl chloride (38 ml, 2.5 eq, 0.45 mol). The solution refluxed for 3 h under nitrogen

atmosphere. The solution was evaporated and the ester hydrochloride precipitated by adding diethylether. After filtration the white solid was washed with diethylether and dried at high vacuum: (2*R*,4*R*)-4-hydroxyproline methylester·hydrochloride white solid (29 g, 89 %). $[\alpha]_D^{20}$ = +8.6 ° (c = 0.873, MeOH). IR (KBr): 3388*s* (br.), 2980*s* (br.), 1730*s*, 1634*m*, 1586*s*, 1384*s*, 1248*s*, 1095*s*, 1064*s*, 1030*m*, 877*m*. ^{1}H-NMR (300MHz, MeOH-d_4): 4.59-4.44 (*m*, 2H, H-C(4), H-C(2)); 3.81 (*s*, 3H, H_3C-O); 3.37-3.31 (*m*, 2H, H_2-C(5)); 2.50-2.37 (*m*, 1H, H-C(3)), 2.37-2.27 (*m*, 1H, H-C(3)). ^{13}C-NMR (75MHz, MeOH-d_4): 170.9 (*s*, COOMe); 70.2 (*d*, C(4)); 59.8 (*d*, C(2)); 55.1 (*t*, C(5));)); 54.1 (*q*, C(Me)); 38.4 (*t*, C(3)). EI-MS (NH_3): 146.1 ([*M*-Cl]$^+$).

10 g (55 mmol) of the above intermediate was dissolved in CH_2Cl_2 (100 ml), cooled to 0 °C and triethylamine (15.2 ml, 2 eq, 0.11 mol) was added dropwise. Then di-tert.-butyldicarbonate (18.0 g, 1.5 eq, 83 mmol) in CH_2Cl_2 (10 ml) and 4-*N*,*N*-dimethylaminopyridine (0.67 g, 0.1 eq, 5 mmol) were added and the solution was stirred at RT overnight. The solution was washed with 1*M* aq. citric acid solution and sat. aqueous $NaHCO_3$ solution, dried (Na_2SO_4), the solvents evaporated and dried at high vaccum: (2*R*,4*R*)-4-hydroxy-1-[(*tert*-butoxy)-carbonyl]prolinemethylester (**214**) as a white solid (13 g, 97 %). $[\alpha]_D^{20}$ = +13.0 ° (c = 1.06, $CHCl_3$). IR (KBr): 3466*s* (br.), 2985*s*, 2930*m*, 1729*s*, 1679*s*, 1424s, 1283*m*, 1262*m*, 1122*s*, 1089*s*, 969*m*, 770*m*. ^{1}H-NMR (300MHz, $CDCl_3$): 4.43-4.26 (*m*, 2H, H-C(4), H-C(2)); 3.80+3.79 (2*s*, 3H, H_3C-O)); 3.76-3.47 (*m*, 2H, H_2-C(5)); 2.44-2.24 (*m*, 1H, H-C(3)); 2.16-2.03 (*m*, 1H, H-C(3)); 1.47+1.43 (2*s*, 9H, *t*Bu). ESI-MS: 268.1 ([*M*+Na]$^+$).

iv,v: **214** (12.2 g, 50 mmol) was dissolved in CH_2Cl_2 (130 ml), cooled to 0 °C and 4-nitrobenzenesulfonyl chloride (14.3 g, 1.3 eq, 65 mmol) and Et_3N (10.3 ml, 1.5 eq, 75 mmol) were added. The reaction mixture was stirred overnight and gradually brought to room temperature. The solution was washed with 1*N* hydrochloric acid and saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4), the solvents were evaporated and the crude product was purified by filtration on silica gel with (2:1)-mixture of hexane/AcOEt: 18 g (84 %). The product was then recrystallized from hexane/AcOEt: (2*R*,4*R*)-4-[(*p*-nitrobenzyl)sulfonyloxy]-1-[(*tert*-butoxy)carbonyl]proline-methylester as white crystals (13.7 g, 64 %). TLC (hexane/AcOEt 1:1): R_f 0.76. M.p.: 113-115 °C. $[\alpha]_D^{20}$ = +21.6 ° (c = 0.924, $CHCl_3$). IR (KBr): 3112*s* (br.), 2981*s*, 2955*s*, 2882*m*, 1755*s*, 1683*s*, 1532*s*, 1413*s*, 1375*s*, 1348*s*, 1192*s*, 928*s*, 911*s*, 759*m*, 745*s*, 610*s*. ^{1}H-NMR (600MHz, $CDCl_3$): 8.45-8.35 (*m*, 2H, H-C(Nos)); 8.15-8.06 (*m*, 2H, H-C(Nos)); 5.27-5.16 (*m*, 1H, H-C(4)); 4.53-4.32 (*m*, 1H, H-C(2)); 3.75-3.60 (*m*, 5H, H_2-C(5), H_3C-O); 2.59-2.35 (*m*, 2H, H_2-C(3)); 1.42+1.39 (2*s*, 9H, *t*Bu). ^{13}C-NMR (150 MHz, $CDCl_3$): 171.8 + 171.6 (*s*, COOMe); 153.8+153.4 (*s*, COO*t*Bu); 151.0+142.6 (*s*, C(Nos)); 129.2+124.7 (*d*, C(Nos)); 81.0 (*s*, C-*t*Bu); 80.8+79.7 (*d*, C(4));

57.4+57.1 (*d*, C(2)); 52.6+52.5+52.3+51.8 (*t*, C(5), *q*, Me); 37.2+36.3 (*t*, C(3)); 28.5+28.3 (*q*, *t*Bu). ESI-MS (DCM + MeOH + NaI): 453.2 ([*M*+Na]$^+$).

13 g (30 mmol) of the above intermediate was dissolved in DMF (200 ml), heated to 40 °C and sodium azide (14.3 g, 6 eq, 180 mmol) was added and the reaction mixture stirred overnight. The reaction mixture was evaporated and the residue suspended in diethylether. The suspension was filtered, the filtrate washed with water and the organic phase dried(Na_2SO_4). The solvent was evaporated and the product dried at high vacuum: (2*R*,4*S*)-4-azido-1-[(*tert*-butoxy)carbonyl]prolinemethylester (**215**) as a yellow oil (8.15 g, 99 %). $[\alpha]_D^{20}$ = +42.8 ° (c = 1.05, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): 4.58-4.37 (*m*, 1H, H-C(2)); 4.34-4.23 (*m*, 1H, H-C(4)); 3.92-3.51 (*m*, 5H, H_2-C(5), H_3C-O); 2.52-2.33 (*m*, 1H, H-C(3)); 2.33-2.20 (*m*, 1H, H-C(3)); 1.56+1.51 (2*s*, 9H, *t*Bu). CI-MS (NH_3): 288.2 ([*M*+NH_4]$^+$); 271.1 ([*M*+H]$^+$).

vi,vii: **215** (8 g, 30 mmol) was dissolved in a (3:1)-mixture of dioxane/water (400 ml), cooled to 0 °C and $SnCl_2$ (22.4 g, 4 eq, 120 mmol) was added and the reaction mixture stirred for 30 min. at 0°, gradually warmed to room temperature and stirred for another 5h. After adjusting the pH of the solution to 8 with solid $NaHCO_3$, allyl chloroformate (15.7 ml, 5 eq, 150 mmol) was added. The reaction mixture was stirred overnight at room temperature, evaporated and extracted with AcOEt and the organic phase washed with brine. After drying the organic phase (Na_2SO_4), the solvent was evaporated and the product dried at high vacuum: (2*R*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(*tert*-butoxy)carbonyl] proline-methylester as a clear thick oil (**216**) (8.7 g, 89 %). $[\alpha]_D^{20}$ = +41.9° (c = 0.928, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): 5.98-5.87 (*m*, 1H, H-C(β)(Alloc)); 5.34-5.02 (*m*, 2H, H_2-C(γ)(Alloc); 4.62-4.49 (*m*, 2H, H_2-C(α)(Alloc)); 4.41-4.23 (*m*, 2H, H-C(4), H-C(2)); 3.82-3.66 (*m*, 4H, H-C(5), H_3C-O); 3.43-3.20 (*m*, 1H, H-C(5)); 2.33-2.07 (*m*, 2H, H_2-C(3)); 1.43+1.39 (2*s*, 9H, *t*Bu). CI-MS (NH_3): 329.1 ([*M*+H]$^+$).

vii-x: **216** (8.4 g, 25 mmol) was dissolved in (4:1)-mixture of methanol/water (100 ml) at room temperature, LiOH (2.2 g, 2 eq, 50 mmol) added and the solution stirred overnight. Methanol was evaporated and the residue poured onto 1*N* hydrochloric acid (100 ml) and extracted with AcOEt. The solvent was removed and the residue dissolved in (1:1)-mixture of TFA/ CH_2Cl_2 (200ml) and stirred for 2h. The solvents were evaporated and the product dried at high vaccum: (2*R*,4*R*)-4-[(Allyloxy)carbonylamino]proline as a clear oil (5.2 g, 96 %) ^{1}H-NMR (300MHz, MeOH-d_4): 6.04-5.88 (*m*, 1H, H_2-C(β)(Alloc)); 5.38-5.19 (*m*, 2H, H_2-C(γ)(Alloc); 4.64-4.54 (*m*, 3H, H_2-C(α)(Alloc), H-C(4)); 4.39-4.22 (*m*, 1H, H-C(2)); 3.71-3.60 (*m*, 1H, H-C(5)); 3.45-3.32 (*m*, 1H, H-C(5)); 2.51-2.41 (*m*, 2H, H_2-C(3)). CI-MS (NH_3): 215.1 ([*M*+H]$^+$).

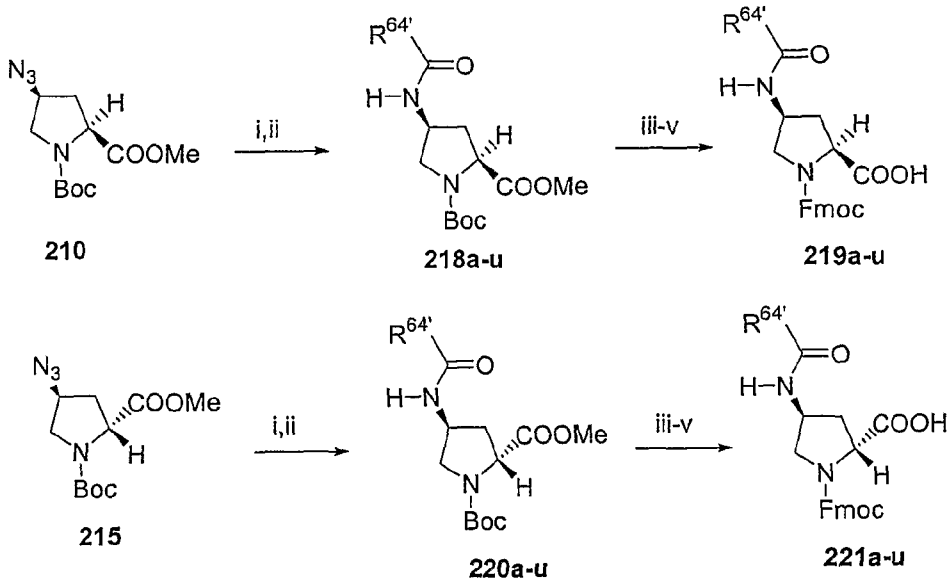
200 mg (0.86 mmol) of the above intermediate and 9-fluorenylmethoxycarbonylsuccinimide (440 mg, 1.5 eq, 1.3 mmol) were dissolved in CH_2Cl_2 (10 ml) and DIEA (466 µl, 4 eq, 3.44

mmol) was added, and the solution stirred overnight at room temperature. The solvent was removed and the residue dissolved in AcOEt, washed with 1*N* hydrochloric acid dried (Na_2SO_4). After evaporation, the crude product was purified by filtration over silica gel with first a gradient of (3:1) hexane/AcOEt to AcOEt. The solvent was coevaporated with CH_2Cl_2 and the product dried at high vacuum: (2*R*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(*9H*-fluoren-9-yl)methoxy-carbonyl]- proline (**217**) white solid (90 mg, 33 %) $[\alpha]_D^{20} = +29.3$ ° (c = 1.08, $CHCl_3$). IR (KBr): 3314*s* (br.), 3066*s* (br.), 2952*s* (br.), 1708*s* (br.), 1536*m*, 1424*s*, 1353*s*, 1126*m*, 1030*m*, 909*m*, 759*m*, 738*s*, 620*m*. ^{1}H-NMR (300MHz, $CDCl_3$): 8.74 (*s*, 1H, H-N); 7.79-7.66 (*m*, 2H, H-C(4')(fmoc)); 7.62-7.49 (*m*, 2H, H-C(1')(fmoc)); 7.44-7.22 (*m*, 4H, H-C(3')(fmoc), H-C(2')(fmoc)); 6.03-5.74 (*m*, 1H, H-C(β)(Alloc)); 5.41-5.07 (*m*, 2H, H_2-C(γ)(Alloc); 4.74-4.17 (*m*, 7H, H_2-C(10')(fmoc), H-C(9')(fmoc), H-C(4), H-C(2), H_2-C(α)(Alloc)); 3.91-3.76 (*m*, 1H, H-C(5)); 3.48-3.25 (*m*, 1H, H-C(5)); 2.45-2.08 (*m*, 2H, H_2-C(3)). ESI-MS (MeOH): 437.3 ([*M*+H]$^+$); ESI-MS (MeOH+Na): 459.1 ([*M*+Na]$^+$).

2.3. Starting from derivatives **210** and **215** the key precursors **219a-u** and **221a-u** can be prepared according to *Scheme 44*.

R^{64}: n-hexyl (**219a, 221a**); n-heptyl (**219b, 221b**); 4-(phenyl)benzyl (**219c, 221c**); diphenylmethyl (**219d, 221d**); 3-amino-propyl (**219e, 221e**); 5-amino-pentyl (**219f, 221f**); methyl (**219g, 221g**); ethyl (**219h, 221h**); isopropyl (**219I, 221i**); isobutyl (**219k, 221k**); n-propyl (**219l, 221l**); cyclohexyl (**219m, 221m**); cyclohexylmethyl (**219n, 221n**); n-butyl (**219o, 221o**); phenyl (**219p, 221p**); benzyl (**219q, 221q**); (3-indolyl)methyl (**219r, 221r**); 2-(3-indolyl)ethyl (**219s, 221s**); (4-phenyl)phenyl (**219t, 221t**); n-nonyl (**219u, 221u**).

Scheme 44



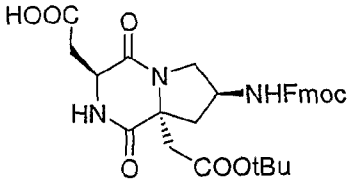
i: $SnCl_2$, dioxane/H_2O; ii: $R^{64}COCl$, diisopropylethylamine, CH_2Cl_2; iii: LiOHx1H_2O, MeOH, H_2O; iv: TFA, CH_2Cl_2; v: FmocOSu, Na_2CO_3 aq., dioxane

i, ii: Typical procedures:

To a solution of 78 mmol of azides **210** and **215** in a (3:1)-mixture of dioxane/water (500 ml) was added at 0 °C $SnCl_2$ (59.2 g, 4 eq, 0.31 mol) and the solution was stirred for 30 minutes. The reaction mixture was gradually warmed up to room temperature and stirred for another 5 hours. After adjusting the pH to 8 with solid $NaHCO_3$, the reaction mixture was extracted with CH_2Cl_2, the organic fraction dried ($MgSO_4$), evaporated and the residue dried under reduced pressure. The residue was dissolved in CH_2Cl_2 (300ml), cooled to 4° with an ice bath, followed by addition of DIEA (20.0ml, 117mmol) and a solution of the appropriate acid chloride $R^{64'}COCl$ (101.0mmol) in CH_2Cl_2 (50ml) at 4°C. The reaction mixture was stirred for 1 hour at 4° and for 18 hours at room temperature and extracted with HCl aq. (0.5*N*, 200ml) and CH_2Cl_2. The organic fraction was dried ($MgSO_4$), evaporated and the residue chromatographed on SiO_2 with gradients of ethylacetate/hexane yielding **218a-u** and **220a-u**, which were converted into the final products **219a-u** and **221a-u** as described for the conversion of **216** into **217**. The overall yields were 50-60%.

Templates (**b1**):

Synthesis of (2*S*,6*S*,8a*R*)-8a-{[(tert.-butyl)oxycarbonyl]methyl}perhydro-5,8-dioxo-{[(9H-fluoren-9-yl)methoxycarbonyl]amino}-pyrrolo[1,2-a]pyrazine-6-acetic acid (**222**):

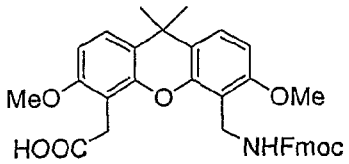


222

To a stirred solution of 250mg (0.414mmol) of allyl {(2*S*,6*S*,8a*R*)-8a-[(tert.-butyl)oxycarbonyl] methyl}perhydro-5,8-dioxo-{[(9H-fluoren-9-yl)methoxycarbonyl]amino} -pyrrolo[1,2-a]pyrazin-6-acetate in a degassed mixture of dichloromethane/methanol (9:1, 3ml) were added under argon 25mg (0.0216mmol) of tetrakis(triphenylphosphine)palladium, 0.05ml of acetic acid and 0.025ml of N-methylmorpholine. The reaction mixture was stirred for 48 hours at room temperature and poured onto water and dichloromethane. The organic phase was dried ($MgSO_4$), evaporated and the residue chromatographed on SiO_2 with dichloromethane/methanol (9:1) to yield 180mg (77%) of (2*S*,6*S*,8a*R*)-8a-{[(tert.-butyl)oxycarbonyl]methyl}perhydro-5,8-dioxo-{[(9H-fluoren-9-yl)-methoxycarbonyl]amino} -pyrrolo[1,2-a]pyrazine-6-acetic acid (**222**) as a white powder.

^{1}H-NMR(300MHz, DMSO-d_6): 8.30 (s, 1H); 7.88 (d, J= 7.2, 2H); 7.67 (d, J=7.4, 2H); 7.62 (br.s, 1H); 7.41 (t, J= 7.2, 2H); 7.33 (t, J=7.4, 2H); 4.35-4.2 (m, 5H); 3.55 (br.d, J= 6.3, 2H); 2.8-2.55 (m, 3H); 2.45-2.25 (m, 2H); 2.1-1.95 (m, 1H); 1.35 (s, 9H); MS(ESI): 586.1 $(M+Na)^+$, 564.1 $(M+H)^+$.

Templates (**c1**):



(c1-1)(168)

Experimental procedure described in W. Bannwarth, A. Knierzinger, K. Müller, D. Obrecht, A. Trzeciak, EP 0 592 791 A2, **1993**.

3. Biological methods

3.1. Preparation of the peptides.

Lyophilized peptides were weighed on a Microbalance (Mettler MT5) and dissolved in sterile water containing 0.01% acetic acid. Tachyplesin was purchased from *Bachem Ltd.* (Bubendorf Switzerland).

3.2. Antimicrobial activity of the peptides.

The antimicrobial activities of the peptides were determined by the standard NCCLS broth microdilution method (see ref 1, below) examined in sterile 96-wells plates (Nunclon polystyrene microtiter plates) in a total volume of 100 µl. Innocula of the microorganisms were prepared with 0.5 Mcfarland standard and then diluted into Mueller-Hinton (MH) broth to give appr. 10^6 colony forming units (CFU)/ml for bacteria or 5 x 10^3 CFU/ml for *Candida.* Aliquots (50 µl) of the innocula were added to 50 µl of MH broth containing the peptide in serial twofold dilutions. The microorganisms used were *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa (P. aeruginosa*) (ATCC 27853), *Staphylococcus aureus* (ATCC 29213 and ATCC 25923) and *Candida albicans*. A selected number of peptides were screened for activity against a larger panel of gram-negative strains. These strains were; *Escherichia coli* ATCC 43827 and clinical isolates of *Pseudomonas* (*P. aeruginosa* VO7 14482, *P. aeruginosa* 15288, *P. aeruginosa* V02 15328 and *P. aeruginosa* V09 16085) and *Acinetobacter (Acinetobacter* V04 19905/1, *Acinetobacter* V12 21143/1 and *Acinetobacter* V12 21193/1). Antimicrobial activities of the peptides were expressed as the minimal inhibitory concentration (MIC) in µg/ml at which no visible growth was observed after 18-20 hours of incubation of the microtiter plates at 37°C.

3.3. Antimicrobial activity of the peptides in 1% Salt

Salt sensitivity of the peptides was tested by the microtiter serial dilution assay as described above. Only MH broth was replaced by MH broth containing 1 % NaCl.

3.4. Antimicrobial activity of the peptides in Human serum

Serum binding of the peptides was tested by microtiter serial dilution assay as described above. Only MH broth was replaced by MH broth containing 90% human serum (BioWhittaker).

3.5. Hemolysis

The peptides were tested for their hemolytic activity against human red blood cells (hRBC). Fresh hRBC were washed three times with phosphate buffered saline (PBS) by centrifugation for 10 min at 2000 x *g*. Peptides at a concentration of 100 µg/ml were incubated with 20% v/v hRBC for 1 hour at 37°C. The final erythrocyte concentration was appr. 0.9 x 10^9 /ml. A value of 0% resp. 100% cell lysis was determined by incubation of the hRBC in the presence of PBS alone and resp. 0.1% Triton X-100 in H_2O. The samples were centrifuged and the supernatant was 20 fold diluted in PBS buffer and the optical density (OD) of the sample at 540 nM was measured. The 100% lysis value ($OD_{540}H_20$) gave an OD of approximately 1.6-2.0. Percent hemolysis was calculated as follows: (OD_{540}peptide/$OD_{540}H_20$) x100%.

3.6. Cytotoxicity assay

The cytotoxicity of the peptides to HELA cells (Acc57) and MCF-7 cells (Acc115) was determined using the MTT reduction assay (see ref 2and 3, below). Briefly the method is as follows; HELA cells and MCF-7 cells were grown in RPMI1640 plus 5% fetal calf serum in microtiter plates for 48 hours at 37°C at 5% CO_2. The total number of cells was finally 10^6 cells per well. The supernatant of the cell cultures was discarded and fresh RPMI1640 medium containing 5% fetal calf serum and the peptides in serial dilutions of 12.5, 25 and 50 µg/ml were pipeted into the wells. Each peptide concentration was assayed in triplicate. Incubation of the cells was continued for 20-24 hours at 37°C at 5% CO_2. Wells were then washed three times with fresh RPMI medium and finally 100 µl MTT reagent (0,5 mg/ml in RPMI1640) was added to each well. This was incubated at 37°C for 2 hours and subsequently the wells were washed once with PBS. 100 µl isopropanol was added to each well and the absorbance at 595 nm of the solubilized product was measured (OD_{595}peptide). The 100 percent growth value (OD_{595}Medium) was determined from wells containing HELA or MCF-7 cells with RPMI1640 plus 5% fetal calf serum but no peptides. The zero percent growth value (OD_{595}Empty well) was extracted from wells that did not contain HELA or MCF-7 cells. The percentage MTT reduction for a certain peptide concentration was calculated as follows: (OD_{595}peptide-OD_{595}Empty well) / (OD_{595}Medium-OD_{595}Empty well) x 100% and was plotted for each peptide concentration. The EC_{50} of a peptide is defined as the concentration at which 50% inhibition of MTT reduction was observed and was calculated for each peptide.

References

1. National Committee for Clinical Laboratory Standards. **1993**. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 3rd ed. Approved standard M7-A3. National Committee for Clinical laboratory standards, Villanova, Pa.

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

3. Berridge MV, Tan AS. *Archives of Biochemistry & Biophysics* **1993**, *303*, 474-482

3.7. Results

Table 8. Minimal inhibitory concentrations (MIC in µg/ml) and percentage hemolyses at a concentration of 100 µg/ml of peptide

Ex.	*Escherichia coli* ATCC 25922	*Pseudo-monas putida* ATCC 27853	*Staphylo-coccus aureus* ATCC 29213	*Staphylo-coccus aureus* ATCC 25923	*Candida albicans*	*Hemo-lyses hRBC*
11	25	100	100	100	100	0.2
36	25	25	25	50	25	0.5
40	25	50	25	50	25	1.2
59	4.7	50	25	50	25	3.0
63	6.2	50	12.5	25	12.5	3.0
71	12.5	100	12.5	12.5	50	1.2
87	6.2	6.2	9.4	9.4	12.5	3.7
101	12.5	50	>50	>50	50	0.2
103	9.4	25	25	25	12.5	18.3
105	6.2	9.4	12.5	6.2	6.2	31.0
106	12.5	6.2	25	12.5	12.5	1.4
107	25	6.2	12.5	9.4	12.5	10.4
109	50	25	50	50	12.5	3.2
112	25	50	25	25	25	2.6
113	50	100	100	100	100	9.2
119	50	25	>100	100	50	3.5
120	18.8	9.4	18.8	9.4	12.5	1.1
121	25	25	6.2	6.2	6.2	7.1
126	25	25	25	50	25	2.6
128	6.2	12.5	6.2	6.2	12.5	13.9
133	6.2	6.2	12.5	25	12.5	1.1
134	12.5	6.2	12.5	25	12.5	1.2
137	25	6.2	6.2	6.2	6.2	3.1
139	25	6.2	12.5	9.4	6.2	3.5
140	12.5	6.2	12.5	12.5	6.2	2.7
141	25	12.5	25	25	12.5	2.0
142	25	12.5	50	25	12.5	2.3

Ex.	*Escherichia coli* ATCC 25922	*Pseudo-monas putida* ATCC 27853	*Staphylo-coccus aureus* ATCC 29213	*Staphylo-coccus aureus* ATCC 25923	*Candida albicans*	*Hemo-lyses hRBC*
146	12.5	12.5	25	12.5	6.2	30.1
147	50	25	25	25	12.5	1.9
148	25	12.5	12.5	9.4	6.2	3.9
150	25	12.5	12.5	12.5	12.5	29.3
151	50	50	100	50	25	4.9
152	25	25	50	25	12.5	29.1
154	12.5	12.5	25	12.5	12.5	31.5
155	6.2	12.5	6.2	12.5	6.2	10.1
156	50	12.5	12.5	6.2	12.5	35.2
158	12.5	6.2	12.5	12.5	12.5	10.5
159	12.5	12.5	12.5	12.5	12.5	21.7
161	25	12.5	6.2	6.2	12.5	3.7
163	12.5	12.5	12.5	12.5	12.5	24.6
165	6.2	12.5	25	18	12.5	0.2
168	12.5	12.5	25	25	12.5	1.1
172	6.2	25	25	25	12.5	1.0
173	12.5	25	6.2	12.5	12.5	27.4
175	12.5	6.2	12.5	12.5	12.5	2.4
177	25	12.5	25	25	12.5	4.1
182	12.5	6.2	6.2	25	12.5	6.2
185	12.5	6.2	6.2	6.2	12.5	17.6
186	6.2	3.1	6.2	6.2	6.2	11.5
187	12.5	100	50	100	25	0.3
197	12.5	3.1	6.2	6.2	6.2	3.4
203	6.2	6.2	6.2	6.2	6.2	33.0
205	6.2	6.2	12.5	6.2	6.2	27.0
206	6.2	6.2	12.5	12.5	6.2	8.5
207	50	50	25	50	25	0.1
208	12.5	6.2	6.2	6.2	12.5	18.4
209	12.5	6.2	12.5	12.5	18.8	6.4
210	12.5	6.2	25	25	25	1.9
214	12.5	6.2	12.5	12.5	12.5	1.0
216	12.5	6.2	12.5	25	12.5	1.4
217	18.8	6.2	12.5	25	12.5	1.7
218	25	6.2	25	25	25	2.2
219	12.5	12.5	50	50	25	2.6
220	12.5	18.8	25	25	12.5	2.3
222	12.5	6.2	12.5	12.5	6.2	2.2
223	6.2	12.5	12.5	25	12.5	2.7
224	6.2	12.5	18.8	25	12.5	3.7
225	6.2	12.5	12.5	25	12.5	4.4
228	12.5	6.2	6.2	6.2	12.5	6.3
229	12.5	6.2	3.1	6.2	6.2	4.8

Ex.	*Escherichia coli* ATCC 25922	*Pseudo-monas putida* ATCC 27853	*Staphylo-coccus aureus* ATCC 29213	*Staphylo-coccus aureus* ATCC 25923	*Candida albicans*	*Hemo-lyses hRBC*
230	6.2	6.2	6.2	9.4	12.5	1.7
232	6.2	12.5	9.4	6.2	9.4	1.5
233	9.4	12.5	9.4	6.2	12.5	37
234	6.2	12.5	6.2	3.1	12.5	33.9
242	6.2	12.5	6.2	12.5	12.5	19.4
244	3.1	12.5	6.2	6.2	12.5	22.7
250	6.2	6.2	12.5	12.5	12.5	0.7
251	6.2	9.4	6.2	12.5	12.5	4.1
254	12.5	6.2	6.2	12.5	12.5	11.7
256	3.1	3.1	6.2	6.2	6.2	2.7
257	6.2	6.2	6.2	6.2	25	19.6
258	6.2	6.2	6.2	6.2	12.5	23.6
259	6.2	6.2	6.2	6.2	12.5	18.0
267	12.5	6.2	6.2	12.5	12.5	3.4
277	25	18.8	3.1	6.2	6.2	12.7
278	12.5	25	50	50	50	5.3
279	12.5	12.5	50	50	50	4.9
280	12.5	12.5	50	100	25	1.8
281	12.5	4.7	100	100	50	1.1
282	12.5	12.5	25	50	25	1.6
283	12.5	4.7	100	100	50	1.0
284	6.2	1.6	12.5	12.5	12.5	0.7
287	25	50	12.5	25	25	28.5
288	25	1.5	100	100	100	1.1
289	50	3.1	25	25	25	1.7
292	25	6.2	50	100	25	1.3
293	25	12.5	100	100	100	1.3
294	25	3.1	100	100	50	1.5
295	25	6.5	50	100	50	2.0
296	12.5	6.2	25	50	25	1.9
297	25	3.1	100	100	50	0.9
298	25	3.1	100	200	50	1.0
299	50	6.2	25	100	50	2.5
300	25	12.5	12.5	25	50	6.5
301	25	50.0	50.0	25	50.0	0.5
302	6.2	3.1	3.1	6.2	6.2	3.4

Table 9. Minimal inhibitory concentration (MIC in μg/ml) in Mueller-Hinton broth containing 1% NaCl

Ex.	*Escherichia coli* ATCC 25922	*Pseudomonas putida* ATCC 27853	*Staphylococcus aureus* ATCC 29213	*Staphylococcus aureus* ATCC 25923	*Candida albicans*
106	100	50	100	100	100
197	12.5	6.2	18.8	12.5	12.5
230	25	50	50	50	18.8
250	12.5	50	100	50	50
229	50	18.8	25	25	12.5
256	6.2	6.2	25	25	25

Several compounds which showed a preference towards Gram-negative bacteria were tested against several pseudomonas strains as shown in *Table 10*.

Table 10. Minimal inhibitory concentrations (MIC in μg/ml) against pseudomonas strains

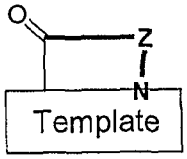
MIC (□g/ml)	ex.197	ex.284	ex.283	ex.288	ex.289	ex.292	ex.296	ex.297	ex.298
Escherichia coli ATCC 25922	12.5	6.2	25	25	25	25	12.5	25	25
Escherichia coli ATCC 43827	12.5	12.5	12.5	12.5	25	25	12.5	12.5	12.5
P. aeruginosa ATCC 278853	3.1	1.6	3.1	3.1	6.2	6.2	3.1	3.1	3.1
P. aeruginosa VO7 14482	12.5	3.1	4.7	3.1	6.2	12.5	12.5	4.7	3.1
P. aeruginosa 15288	12.5	3.1	25	6.2	6.2	12.5	12.5	6.2	4.7
P. aeruginosa V02 15328	12.5	3.1	6.2	3.1	6.2	12.5	12.5	6.2	3.1
P. aeruginosa V09 16085	9.4	1.6	3.1	6.2	6.2	6.2	6.2	3.1	3.1
Acinetobacter V04 19905/1	12.5	6.2	6.2	6.2	12.5	12.5	6.2	6.2	6.2
Acinetobacter V12 21143/1	12.5	3.1	6.2	6.2	6.2	6.2	6.2	6.2	9.4
Acinetobacter V12 21193/1	12.5	3.1	3.1	6.2	3.1	6.2	3.1	6.2	6.2

Table 11: Anticancer activity (EC_{50}-values) in µg/ml

Example ex.	Hela (µg/ml)	MCF (µg/ml)	Hemolysis hRBC
80	337	nd	nd
106	43	39	1.4
170	24	41	nd
197	20	23	3.4
229	13	25	4.8
230	23	32	1.7
285	11	11	4.2
286	nd	23	17.1

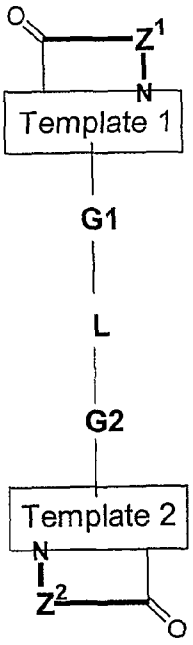
CLAIMS

1. Compounds of the general formulae



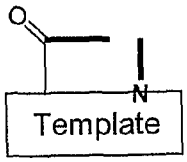
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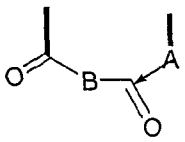


(Ib)

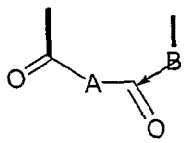
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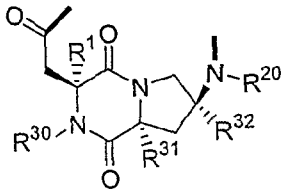


(a1)

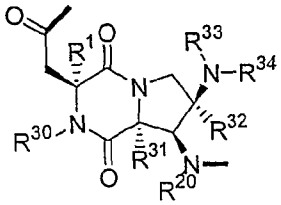


(a2)

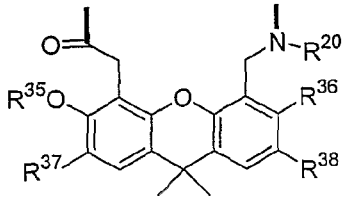
10 is a group of one of the formulae



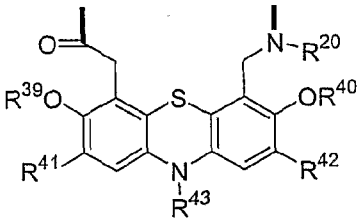
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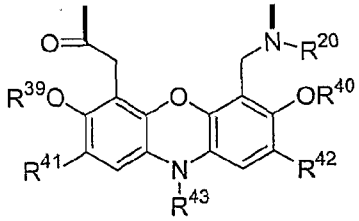
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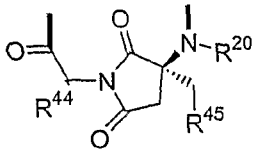
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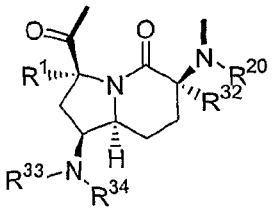
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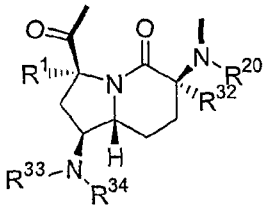
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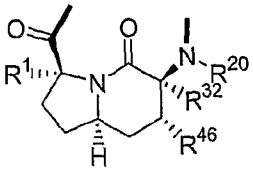
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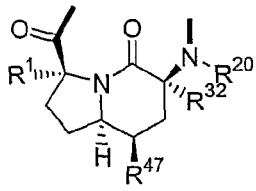
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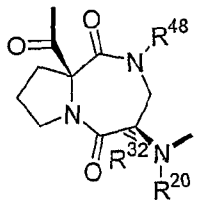
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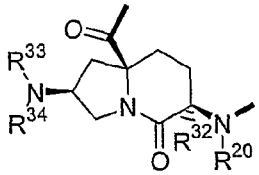
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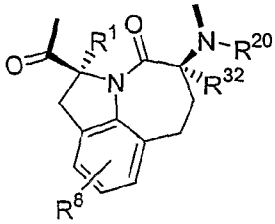
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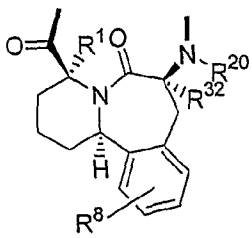
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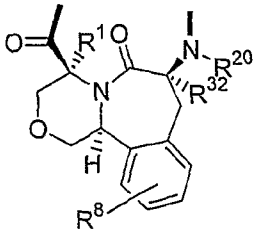
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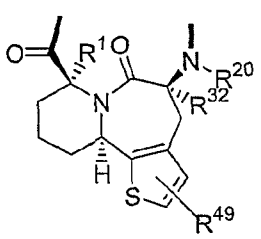
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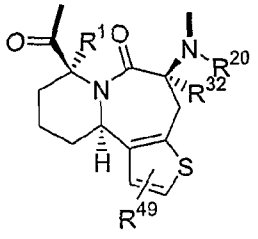
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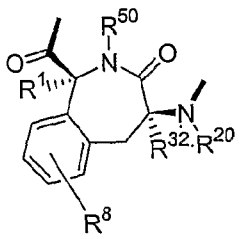
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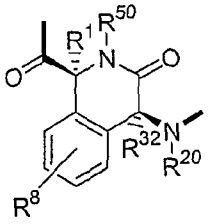
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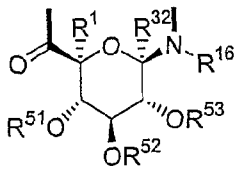
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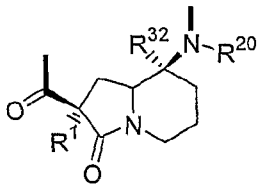
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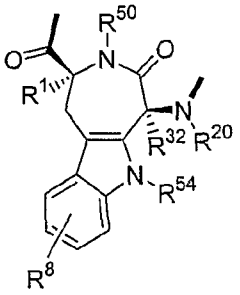
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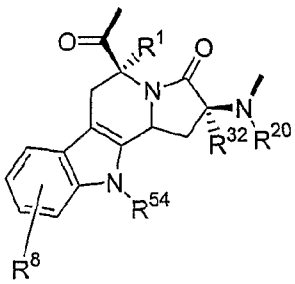
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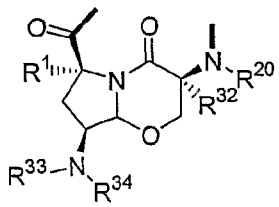


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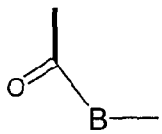


(o)

and



(p)

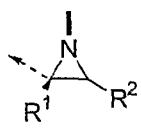


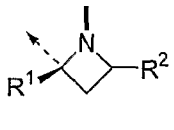
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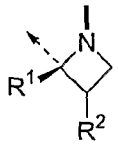
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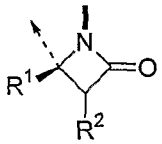


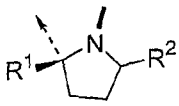
is a group of one of the formulae

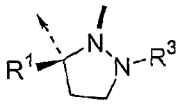

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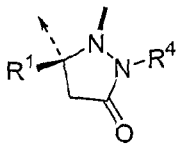

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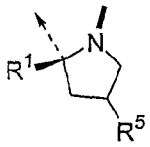

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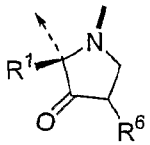

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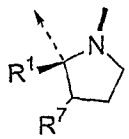

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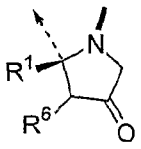

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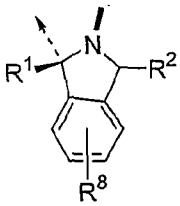

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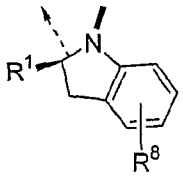

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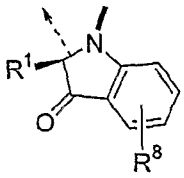

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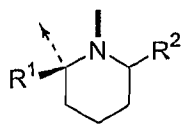

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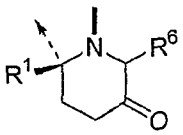

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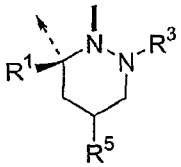

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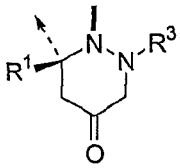

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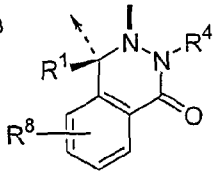

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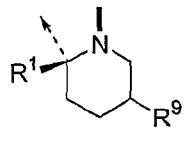

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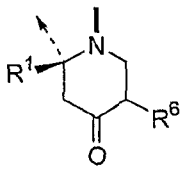

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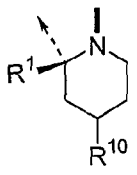

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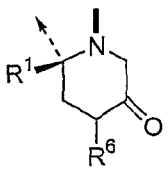

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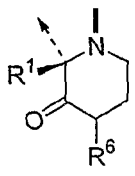

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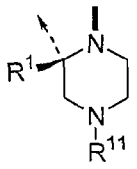

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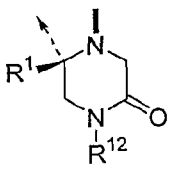

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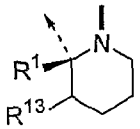

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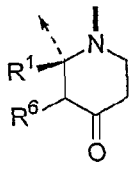
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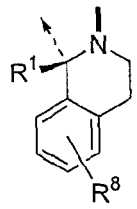
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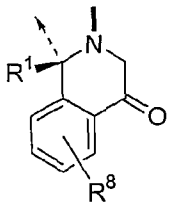
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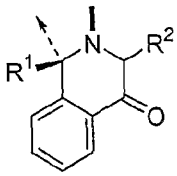
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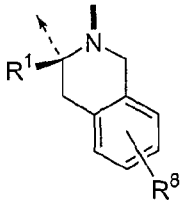
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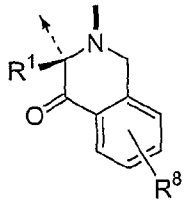
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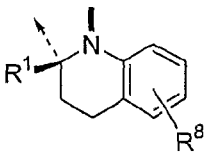
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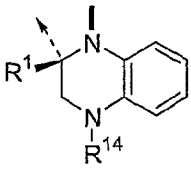
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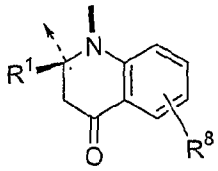
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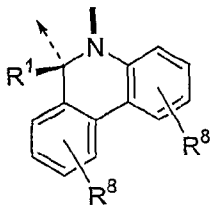
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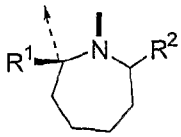
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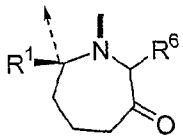
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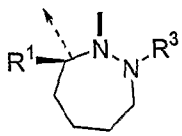
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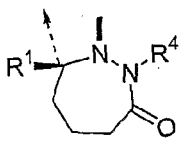
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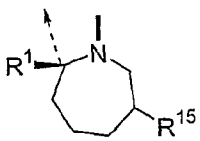
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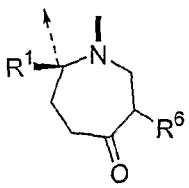
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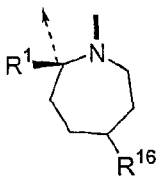
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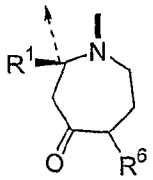
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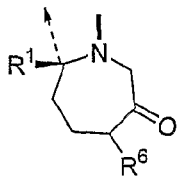
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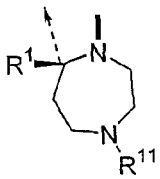
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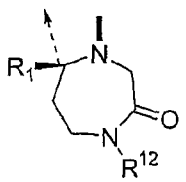
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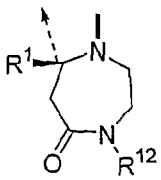
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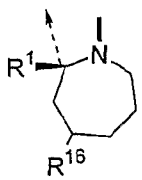
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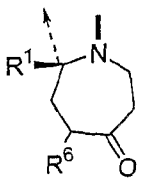
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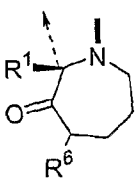
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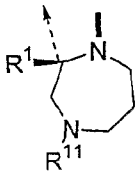
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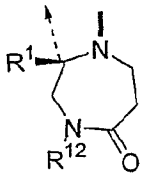
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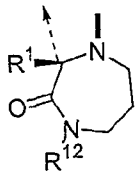
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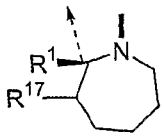
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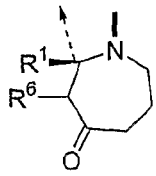
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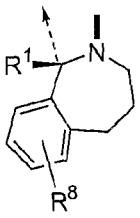
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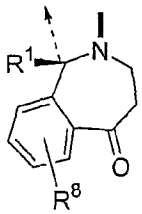
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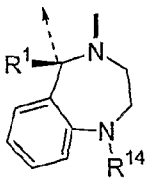
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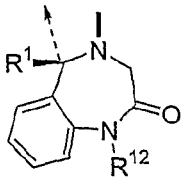
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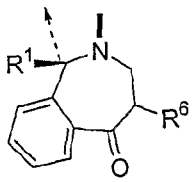
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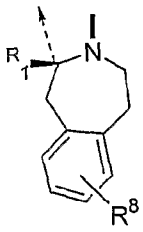
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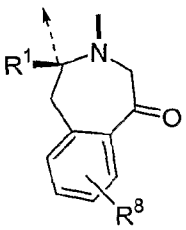
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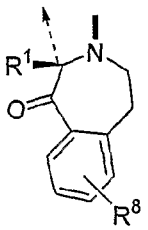
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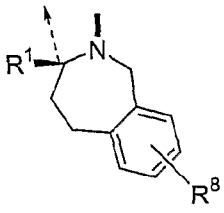
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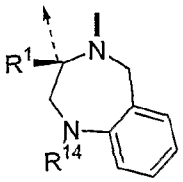
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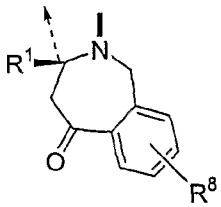
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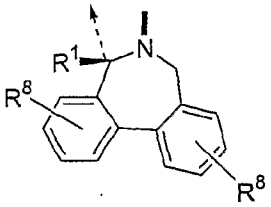
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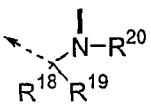
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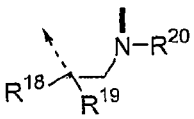
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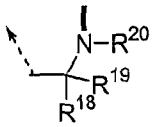
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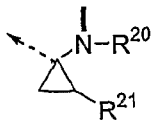
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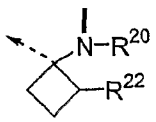
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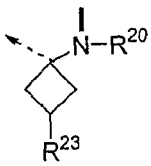
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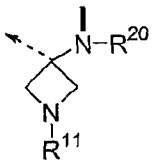
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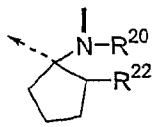
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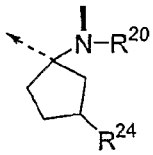
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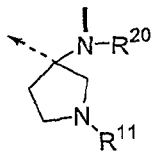
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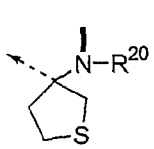
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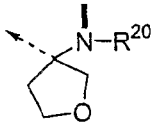
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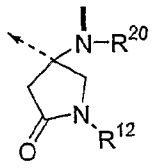
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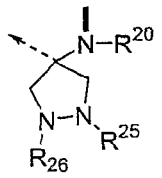
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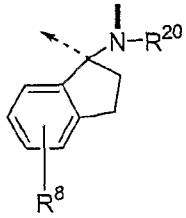
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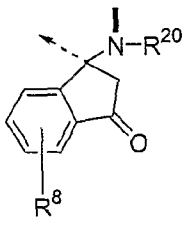
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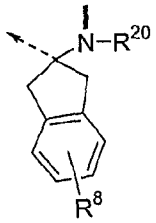
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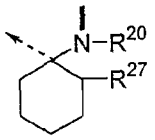
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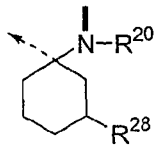
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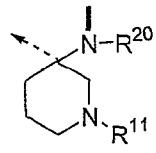
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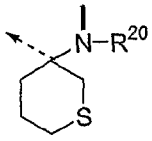
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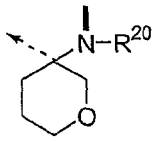
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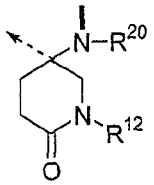
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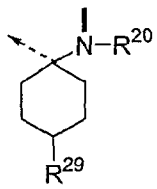
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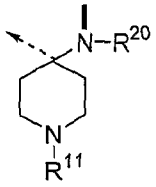
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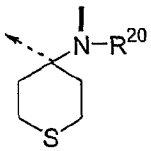
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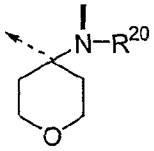
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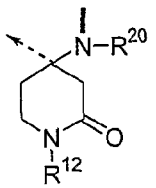
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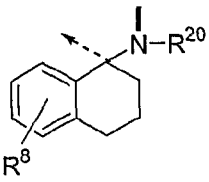
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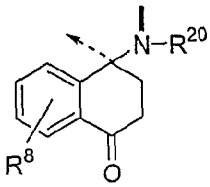
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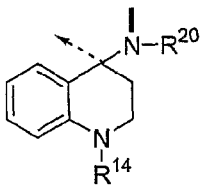
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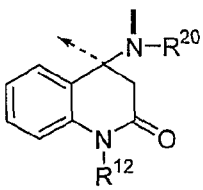
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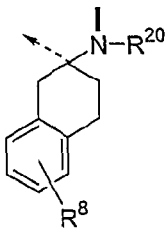
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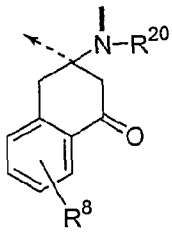
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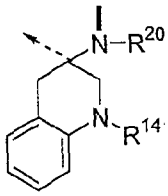


A102



A103

and



A104

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

R^2 is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

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

$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^4 is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_p(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^5 is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^6 is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
$-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^7 is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_r(CHR^{61})_sCOOR^{57}$; $-(CH_2)_r(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_r(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_r(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_r(CHR^{61})_s\ C_6H_4R^8$;

R^8 is H; Cl; F; CF_3; NO_2; lower alkyl; lower alkenyl; aryl; aryl-lower alkyl;
$-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})NR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sCOR^{64}$;

R^9 is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{10} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
$-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{11} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s\ C_6H_4R^8$;

R^{12} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_r(CHR^{61})_sCOOR^{57}$; -
$(CH_2)_r(CHR^{61})_sCONR^{58}R^{59}$;
$-(CH_2)_r(CHR^{61})_sPO(OR^{60})_2$; $-(CH_2)_r(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_r(CHR^{61})_sC_6H_4R^8$;

R^{13} is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sSR^{56}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_q(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;

R^{14} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_q(CHR^{61})_sSOR^{62}$; or $-(CH_2)_q(CHR^{61})_s\ C_6H_4R^8$;

R^{15} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{16} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{17} is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sSR^{56}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_q(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;

R^{18} is alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sSR^{56}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_p(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{19} is lower alkyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sSR^{56}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_p(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$; or

R^{18} and R^{19} taken together can form: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or

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

R^{20} is H; alkyl; alkenyl; or aryl-lower alkyl;

R^{21} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
$-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{22} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
$-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{23} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{24} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{25} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{26} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
$-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$; $-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$; or

R^{25} and R^{26} taken together can form: $-(CH_2)_{2\text{-}6}-$; $-(CH_2)_rO(CH_2)_r-$; $-(CH_2)_rS(CH_2)_r-$; or
$-(CH_2)_rNR^{57}(CH_2)_r-$;

R^{27} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; -
$(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; -
$(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;

$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{28} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_s-OR^{55}$; $-(CH_2)_o(CHR^{61})_s SR^{56}$; $-(CH_2)_o(CHR^{61})_s NR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_s COOR^{57}$; $-(CH_2)_o(CHR^{61})_s CONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_s PO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;

R^{29} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{30} is H; alkyl; alkenyl; or aryl-lower alkyl;

R^{31} is H; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;

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

R^{33} is H; alkyl, alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOR^{64}$; $-(CH_2)_o(CHR^{61})_s-CONR^{58}R^{59}$, $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

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

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^{35} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_s C_6H_4R^8$;

R^{36} is H, alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_p(CHR^{51})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;

R^{37} is H; F; Br; Cl; NO_2; CF_3; lower alkyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;

R^{38} is H; F; Br; Cl; NO_2; CF_3; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;
$-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{39} is H; alkyl; alkenyl; or aryl-lower alkyl;

R^{40} is H; alkyl; alkenyl; or aryl-lower alkyl;

R^{41} is H; F; Br; Cl; NO_2; CF_3; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;
$-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;

R^{42} is H; F; Br; Cl; NO_2; CF_3; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;
$-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;

R^{43} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;

R^{44} is alkyl; alkenyl; $-(CH_2)_r(CHR^{61})_sOR^{55}$; $-(CH_2)_r(CHR^{61})_sSR^{56}$; $-(CH_2)_r(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_r(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_r(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_r(CHR^{61})_sCOOR^{57}$; $-(CH_2)_r(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_r(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_r(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_r(CHR^{61})_sC_6H_4R^8$;

R^{45} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
$-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_s(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_s(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_s(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_s(CHR^{61})_sC_6H_4R^8$;

R^{46} is H; alkyl; alkenyl; or $-(CH_2)_o(CHR^{61})_pC_6H_4R^8$;

R^{47} is H; alkyl; alkenyl; or $-(CH_2)_o(CHR^{61})_sOR^{55}$;

R^{48} is H; lower alkyl; lower alkenyl; or aryl-lower alkyl;

R^{49} is H; alkyl; alkenyl; $-(CHR^{61})_sCOOR^{57}$; $(CHR^{61})_sCONR^{58}R^{59}$; $(CHR^{61})_sPO(OR^{60})_2$;
$-(CHR^{61})_sSOR^{62}$; or $-(CHR^{61})_sC_6H_4R^8$;

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

R^{51} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;

$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_pPO(OR^{60})_2$;
$-(CH_2)_p(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;

R^{52} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_pPO(OR^{60})_2$;
$-(CH_2)_p(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;

R^{53} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_pPO(OR^{60})_2$;
$-(CH_2)_p(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;

R^{54} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_o(CHR^{61})COOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;

R^{55} is H; lower alkyl; lower alkenyl; 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}; $-(CH_2)_o(CHR^{61})COOR^{57}$;
or
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;

R^{56} is H; lower alkyl; lower alkenyl; 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}; or
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;

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

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

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

R^{58} and R^{59} taken together can form: $-(CH_2)_{2-6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or
$-(CH_2)_2NR^{57}(CH_2)_2$-;

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

R^{61} is alkyl; alkenyl; aryl; heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl; $-(CH_2)_mOR^{55}$;
$-(CH_2)_mNR^{33}R^{34}$; $-(CH_2)_mOCONR^{75}R^{82}$; $-(CH_2)_mNR^{20}CONR^{78}R^{82}$; $-(CH_2)_oCOOR^{37}$;
$-(CH_2)_oNR^{58}R^{59}$; or $-(CH_2)_oPO(COR^{60})_2$;

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

R^{63} is H; lower alkyl; lower alkenyl; aryl, heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl;
$-COR^{64}$; $-COOR^{57}$; $-CONR^{58}R^{59}$; $-SO_2R^{62}$; or $-PO(OR^{60})_2$;

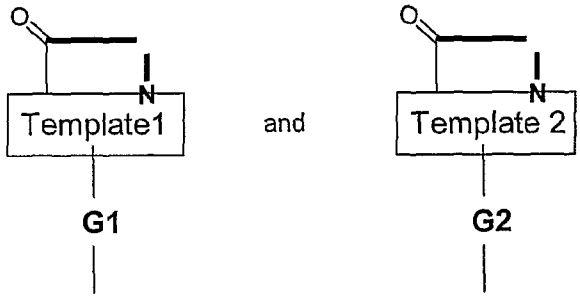
$R^{34}$and R^{63} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
$-(CH_2)_2NR^{57}(CH_2)_2-$;

R^{64} is H; lower alkyl; lower alkenyl; aryl; heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl;
$-(CH_2)_p(CHR^{61})_sOR^{65}$; $-(CH_2)_p(CHR^{61})_sSR^{66}$; or $-(CH_2)_p(CHR^{61})_sNR^{34}R^{63}$;
$-(CH_2)_P(CHR^{61})_sOCONR^{75}R^{82}$; $-(CH_2)_P(CHR^{61})_sNR^{20}CONR^{78}R^{82}$;

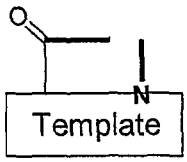
R^{65} is H; lower alkyl; lower alkenyl; aryl, aryl-lower alkyl; heteroaryl-lower alkyl; $-COR^{57}$;
$-COOR^{57}$; or $-CONR^{58}R^{59}$;

R^{66} is H; lower alkyl; lower alkenyl; aryl; aryl-lower alkyl; heteroaryl-lower alkyl; or
$-CONR^{58}R^{59}$;

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



independently have any of the significances defined above for



except **(a1)** and **(a2)** with B being $-NR^{20}CH(R^{71})-$ and with A being **A80, A81, A90, A91, A95** or **A96**, and except **(f)** and **(m)**, but wherein

R^2 is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or
$-(CH_2)_o(CHR^{61})_sCO-$;

R^3 is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or
$-(CH_2)_o(CHR^{61})_sCO-$;

R^4 is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or
$-(CH_2)_p(CHR^{61})_sCO-$;

R^5 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or

$-(CH_2)_o(CHR^{61})_sCO-$;

R^6 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^7 is $-(CH_2)_q(CHR^{61})_sO-$; $-(CH_2)_q(CHR^{61})_sNR^{34}-$; or $-(CH_2)_r(CHR^{61})_sCO-$;

R^8 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^9 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{10} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{11} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{12} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_r(CHR^{61})_sCO-$;

R^{13} is $-(CH_2)_q(CHR^{61})_sO-$; $-(CH_2)_q(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sNR^{34}-$; or $-(CH_2)_q(CHR^{61})_sCO-$;

R^{14} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_q(CHR^{61})_sCO-$;

R^{15} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{16} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{17} is $-(CH_2)_q(CHR^{61})_sO-$; $-(CH_2)_q(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sNR^{34}-$; or $-(CH_2)_q(CHR^{61})_sCO-$;

R^{18} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_p(CHR^{61})_sCO-$;

R^{19} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_p(CHR^{61})_sCO-$;

R^{21} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{22} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{23} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{24} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{25} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{26} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{27} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{28} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{29} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{31} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{33} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{37} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{38} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{41} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{42} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{43} is $-(CH_2)_m(CHR^{61})_sO$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{45} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_s(CHR^{61})_sCO-$;

R^{47} is $-(CH_2)_o(CHR^{61})_sO-$;

R^{49} is $-(CHR^{61})_sO-$; $-(CHR^{61})_sS-$; $-(CHR^{61})_sNR^{34}-$; or $-(CHR^{61})_sCO-$;

R^{51} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{52} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{53} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{54} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{55} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{56} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;

R^{64} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; or $-(CH_2)_p(CHR^{61})_sNR^{34}-$;

m, o, p, q, r and s being as defined above;

with the proviso that if more than one of the substituents R^2 to R^{19}, R^{21} to R^{29}, R^{31}, R^{33}, R^{37}, R^{38}, R^{41} to R^{43}, R^{45}, R^{47}, R^{49}, R^{51} to R^{56} and R^{64} is present, only one of these has one of the significances just mentioned whilst the other(s) has/have any of the significance(s) mentioned earlier;

L is a direct bond or one of the linkers

L1: $-(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_o-$;

L2: $-CO(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oCO-$;

L3: $-CONR^{34}(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oNR^{34}CO-$;

L4: $-O(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oO-$;

L5: $-S(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oS-$;

L6: $-NR^{34}(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oNR^{34}-$;

L7: $-(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}-$;

L8: $-CO(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}CO-$;

L9: $-CONR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}CO-$;

L10: $-O(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}O-$;

L11: $-S(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}S-$;

L12: $-NR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}-$;

L13: $-CO(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oNR^{34}-$;

L14: $-CO(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}-$;

L15 $-NR^{34}(CH_2)_pCHR^{61}[X(CH_2)pCHR^{61}]_oCO-$; and

L16 $-NR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}CO-$;

m, o, p, q, r and s being as defined above; X being O; S; NR^{34}; $-NR^{32}CONR^{34}-$; or -OCOO-;

and Y being $-C_6R^{67}R^{68}R^{69}R^{70}-$;

R^{67} being H; Cl; Br; F; NO_2; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl;

R^{68} being H; Cl; Br; F; NO_2; $-NR^{34}COR^{57}$; lower ; or lower alkenyl;

R^{69} being H; Cl; Br; F; NO_2; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl; and

R^{70} being H; Cl; Br; F; NO_2; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl;

with the proviso that at least two of R^{67}, R^{68}, R^{69} and R^{70} are H; and

with the further proviso that

$-(CH_2)_m(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_o(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_p(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_q(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_m(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;

$-(CH_2)_o(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;

$-(CH_2)_p(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;

$-(CH_2)_q(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;

$-(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;

$-(CH_2)_m(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_o(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_p(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_q(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

$-(CH_2)_o(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

$-(CH_2)_p(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

$-(CH_2)_q(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

$-(CH_2)_r(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

$-(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

$-(CH_2)_m(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_p(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_q(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_m(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_p(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_q(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_m(CHR^{61})_sNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_p(CHR^{61})_sNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_q(CHR^{61})_sNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CHR^{61})_sNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sX-$, $-(CH_2)_o(CHR^{61})_sX-$, $-(CH_2)_p(CHR^{61})_sX-$, $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

$-(CH_2)_p(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sX-$, $-(CH_2)_o(CHR^{61})_sX-$, $-(CH_2)_p(CHR^{61})_sX-$, $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

$-(CH_2)_q(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sX-$, $-(CH_2)_o(CHR^{61})_sX-$, $-(CH_2)_p(CHR^{61})_sX-$, $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

$-(CH_2)_r(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sX-$, $-(CH_2)_o(CHR^{61})_sX-$, $-(CH_2)_p(CHR^{61})_sX-$, $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

$-(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with $-(CH_2)_m(CHR^{61})_sX-$; $-(CH_2)_o(CHR^{61})_sX-$; $-(CH_2)_p(CHR^{61})_sX-$; $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX$;

Z, Z^1 and Z^2 independently are chains of n α-amino acid residues, n being an integer from 8 to 16, the positions of said amino acid residues in said chains being counted starting from the N-terminal amino acid, whereby these amino acid residues are, depending on their position in the chains, Gly, or Pro, or of formula **-A-**CO-, or of formula **-B-**CO-, or of one of the types

C: $-NR^{20}CH(R^{72})CO-$;

D: $-NR^{20}CH(R^{73})CO-$;

E: $-NR^{20}CH(R^{74})CO-$;

F: $-NR^{20}CH(R^{84})CO-$; and

H: $-NR^{20}-CH(CO-)-(CH_2)_{4-7}-CH(CO-)-NR^{20}-$;

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

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

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

R^{71} is H; lower alkyl; lower alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{75}$; $-(CH_2)_p(CHR^{61})_sSR^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{75}$; $-(CH_2)_pCONR^{58}R^{59}$; $-(CH_2)_pPO(OR^{62})_2$; $-(CH_2)_pSO_2R^{62}$; or $-(CH_2)_o-C_6R^{67}R^{68}R^{69}R^{70}R^{76}$;

R^{72} is H; lower alkyl; lower alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{85}$; or $-(CH_2)_p(CHR^{61})_sSR^{85}$;

R^{73} is $-(CH_2)_oR^{77}$; $-(CH_2)_rO(CH_2)_oR^{77}$; $-(CH_2)_rS(CH_2)_oR^{77}$; or $-(CH_2)_rNR^{20}(CH_2)_oR^{77}$;

R^{74} is $-(CH_2)_pNR^{78}R^{79}$; $-(CH_2)_pNR^{77}R^{80}$; $-(CH_2)_pC(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;

$-(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pNR^{80}C(=NR^{80})NR^{78}R^{79}$;

$-(CH_2)_pN=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_pC_6H_4NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{77}R^{80}$;

$-(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;

$-(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$;

$-(CH_2)_pC_6H_4N=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_rO(CH_2)_mNR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_mNR^{77}R^{80}$;

$-(CH_2)_rO(CH_2)_pC(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_rO(CH_2)_pC_6H_4CNR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mNR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_mNR^{77}R^{80}$;$-(CH_2)_rS(CH_2)_pC(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$;
$-(CH_2)_rS(CH_2)_pC_6H_4CNR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pNR^{80}COR^{64}$; $-(CH_2)_pNR^{80}COR^{77}$;
$-(CH_2)_pNR^{80}CONR^{78}R^{79}$; or $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;

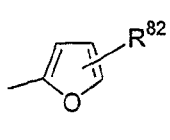
R^{75} is lower alkyl; lower alkenyl; or aryl-lower alkyl;

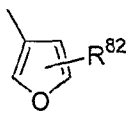
R^{33} and R^{75} taken together can form: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-;

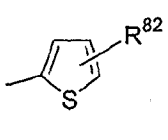
R^{75} and R^{82} taken together can form: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-;

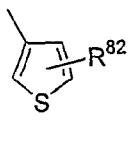
R^{76} is H; lower alkyl; lower alkenyl; aryl-lower alkyl; $-(CH_2)_oOR^{72}$; $-(CH_2)_oSR^{72}$;
$-(CH_2)_oNR^{33}R^{34}$; $-(CH_2)_oOCONR^{33}R^{75}$; $-(CH_2)_oNR^{20}CONR^{33}R^{82}$;
$-(CH_2)_oCOOR^{75}$; $-(CH_2)_oCONR^{58}R^{59}$; $-(CH_2)_oPO(OR^{60})_2$; $-(CH_2)_pSO_2R^{62}$; or
$-(CH_2)_oCOR^{64}$;

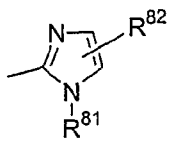
R^{77} is $-C_6R^{67}R^{68}R^{69}R^{70}R^{76}$; or a heteroaryl group of one of the formulae

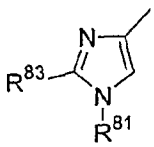

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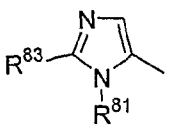

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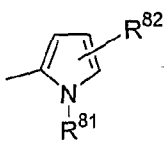

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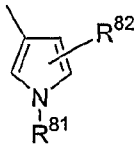

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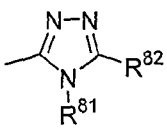

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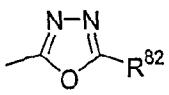

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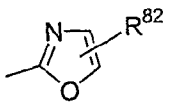

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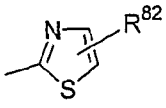

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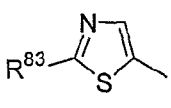

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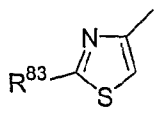

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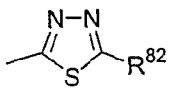

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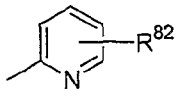

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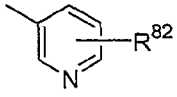

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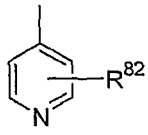
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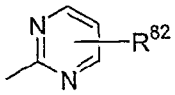
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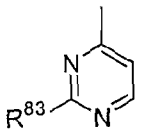
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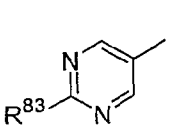
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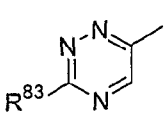
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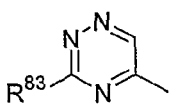
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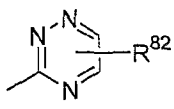
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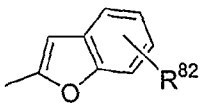
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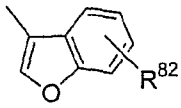
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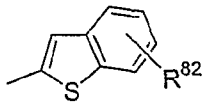
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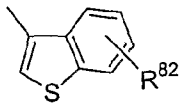
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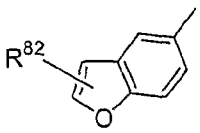
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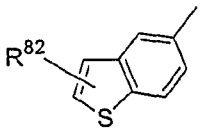
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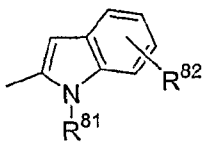
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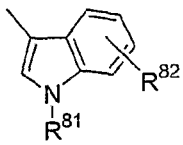
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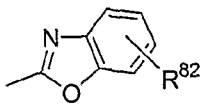
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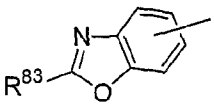
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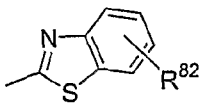
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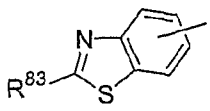
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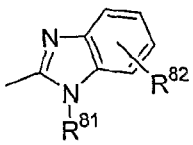
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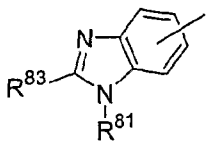
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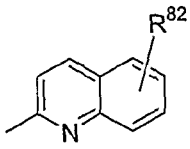
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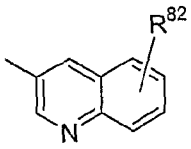
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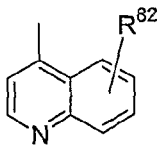
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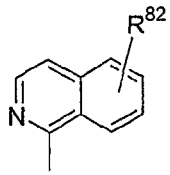
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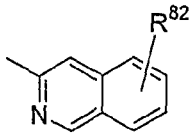
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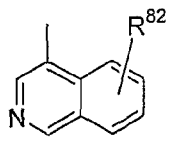
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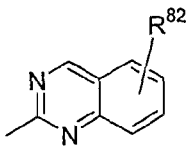
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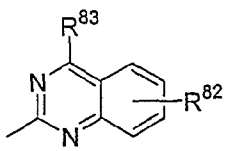
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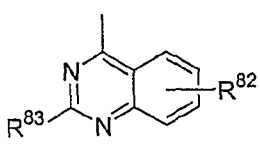
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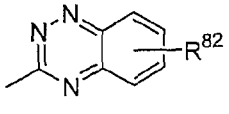
H46



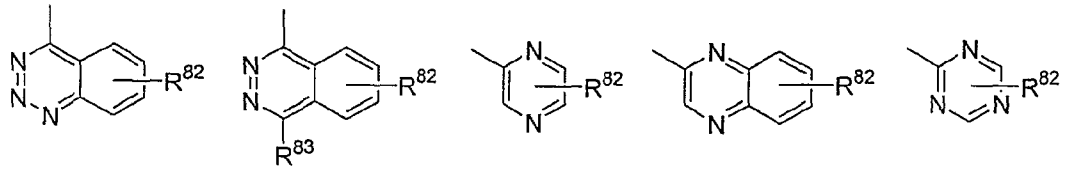
H47



H48



H49



H50 H51 H52 H53 H54

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

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

R^{79} is H; lower alkyl; 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;

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

R^{82} is H; lower alkyl; aryl; heteroaryl; or aryl-lower alkyl;

R^{33} and R^{82} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;

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

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

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

with the proviso that in said chain(s) of *n* α-amino acid residues Z, Z^1 and Z^2

- if n is 8, the amino acid residues in positions 1 to 8 are:
  - P1: of type C or or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type D or of type F;
  - P3: of type E or of type C, or the residue is Pro;
  - P4: of type E or of formula -**A**-CO-;
  - P5: of type E or of formula -**B**-CO-, or the residue is Gly;
  - P6: of type D, or the residue is Pro;
  - P7: of type or of type C or of type D or of type E; and
  - P8: of type C or of type D or of type E or of type F, or the residue is Pro; or

  P2 and P7, taken together, can form a group of type H; and at P4 and P5 also D-isomers being possible;

- if n is 9, the amino acid residues in positions 1 to 9 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type D or of type F;
  - P3: of type C or of type D or of type E, or the residue is Pro;
  - P4: of type E or of type D, or the residue is Pro;
  - P5: of type E, or the residue is Gly or Pro;
  - P6: of type D or of type E, or the residue is Gly or Pro;
  - P7: of type E or of type D or of type C, or the residue is Pro;
  - P8: of type E or of type D; and
  - P9: of type C or of type D or of type E or of type F, or the residue is Pro; or
  - P2 and P8, taken together, can form a group of type H; and at P4, P5 and P6 also D-isomers being possible;

- if n is 10, the amino acid residues in positions 1 to 10 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type D, or the residue is Pro;
  - P3: of type C or of type E;
  - P4: of type E or of type D or of type F, or the residue is Pro;
  - P5: of type E or of type F or of formula -**A**-CO-, or the residue is Gly;
  - P6: of type E or of formula -**B**-CO-, or the residue is Gly;
  - P7: of type D or of type E, or the residue is Gly or Pro;
  - P8: of type D or of type E;
  - P9: of type E or of type D or of type C, or the residue is Pro; and
  - P10: of type C or of type D or of type E or of type F; or
  - P3 and P8, taken together, can form a group of type H; and at P5 and P6 also D-isomers being possible;

- if n is 11, the amino acid residues in positions 1 to 11 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type C or of type D;
  - P3: of type D or of type E, or the residue is Pro;
  - P4: of type E or of type C or of type F;

- P5: of type E or of type F, or the residue is Gly or Pro;
- P6: of type E or of type F, or the residue is Gly or Pro;
- P7: of type E or of type F, or the residue is Gly or P ro;
- P8: of type D or of type E or of type F;
- P9: of type D or of type E, or the residue is Pro;
- P10: of type E or of type C or of type D; and
- P11: of type C or of type D or of type E or of type F, or the residue is Pro; or
- P4 and P8 and/or P2 and P10, taken together, can form a group of type H; and at P5, P6 and P7 also D-isomers being possible;

- if n is 12, the amino acid residues in positions 1 to 12 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type D;
  - P3: of type C or of type D, or the residue is Pro;
  - P4: of type E or of type F or of type D;
  - P5: of type E or of type D or of type C, or the residue is Gly or Pro;
  - P6: of type E or of type F or of formula -**A**-CO-, or the residue is Gly;
  - P7: of type E or of type F or of formula -**B**-CO-;
  - P8: of type D or of type C, or the residue is Pro;
  - P9: of type E or of type D or of type F;
  - P10: of type D or of type C, or the residue is Pro;
  - P11: of type E or of type D; and
  - P12: of type C or of type D or of type E or of type F, or the residue is Pro; or
  - P4 and P9 and/or P2 and P11, taken together, can form a group of type H; and at P6 and P7 also D-isomers being possible;

- if n is 13, the amino acid residues in positions 1 to 13 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type F or of type D;
  - P3: of type C or of type D or of type E, or the residue is Pro;
  - P4: of type E of type C or of type F;
  - P5: of type E or of type D, or the residue is Gly or Pro;
  - P6: of type E or of type F, or the residue is Gly or Pro;
  - P7: of type E or of type F, or the residue is Pro;

P8: of type D or of type E or of type F, or the residue is Pro;

P9: of type D or of type E, or the residue is Pro;

P10: of type E or of type C or of type F;

P11: of type C or of type E, or the residue is Pro;

P12: of type E or of type D or of type C; and

P13: of type C or of type D or of type E or of type F, or the residue is Pro; or

P4 and P10 and/or P2 and P12, taken together, can form a group of type H;

and at P6, P7 and P8 also D-isomers being possible;

- if n is 14, the amino acid residues in positions 1 to 14 are:
  - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2: of type E or of type C or of type D, or the residue is Pro;
  - P3: of type C or of type D or of type E;
  - P4: of type D or of type C or of type E, or the residue is Pro;
  - P5: of type E or of type D;
  - P6: of type E or of type F, or the residue is Gly or Pro;
  - P7: of type E or of type F or of formula -**A**-CO-, or the residue is Gly;
  - P8: of type E or of type F or of formula -**B**-CO-, or the residue is Gly;
  - P9: of type D or of type E, or the residue is Pro;
  - P10: of type C or of type D or of type E;
  - P11: of type E or of type D or of type F, or the residue is Pro;
  - P12: of type D or of type E;
  - P13: of type E or of type C or of type D, or the residue is Pro; and
  - P14: of type C or of type D or of type E or of type F, or the residue is Pro; or
  - P5 and P10 and/or P3 and P12, taken together, can form a group of type H;

  and at P7 and P8 also D-isomers being possible;

- if n is 15, the amino acid residues in positions 1 to 15 are:

  P1: of type C or of type D or of type E or of type F, or the residue is Pro;

  P2: of type E or of type F or of type D;

  P3: of type C or of type D or of type E, or the residue is Pro;

  P4: of type E or of type D or of type F;

  P5: of type C or of type D or of type E, or the residue is Pro;

  P6: of type E or of type D or of type F;

P7: of type C or of type E, or the residue is Pro;

P8: of type E or of type F, or the residue is Gly or Pro;

P9: of type E or of type F, or the residue is Gly or Pro;

P10: of type E or of type D;

P11: of type C or of type D or of type E, or the residue is Pro;

P12: of type E or of type C or of type F;

P13: of type D or of type E, or the residue is Pro;

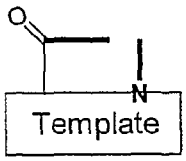
P14: of type E or of type C or of type D; and

P15: of type C or of type D or of type E or of type F, or the residue is Pro; or

P6 and P10 and/or P4 and P12 and/or P2 and P14, taken together, can form a group of type H; and at P7, P8 and P9 also D-isomers being possible; and

- if n is 16, the amino acid residues in positions 1 to 16 are:
  - P1: of type D, or of type E or of type C or of type F, or the residue is Pro;
  - P2: of type E or of type F or of type D;
  - P3: of type C or of type D or of type E, or the residue is Pro;
  - P4: of type E or of type D or of type F;
  - P5: of type D or of type C or of type E, or the residue is Pro;
  - P6: of type E or of type D;
  - P7: of type E or of type F, or the residue is Gly or Pro;
  - P8: of type E or of type F or of formula -**A**-CO-,or the residue is Gly;
  - P9: of type E or of formula -**B**-CO-, or the residue is Gly;
  - P10: of type D or of type E, or the residue is Pro;
  - P11: of type E or of type C or of type D;
  - P12: of type D or of type C or of type E, or the residue is Pro;
  - P13: of type E or of type C or of type F;
  - P14: of type C or of type D or of type E, or the residue is Pro;
  - P15: of type E or of type C or of type D; and
  - P16: of type C or of type D or of type E or of type F, or the residue is Pro; or
  - P6 and P11 and/or P4 and P13 and/or P2 and P15, taken together, can form a group of type H; and at P8 and P9 also D-isomers being possible;

and pharmaceutically acceptable salts thereof.



2. Compounds according to claim 1 wherein

is other than a group of formula (a2);

R^2 to R^{19}, R^{21} to R^{29}, R^{31}, R^{35} to R^{38}, R^{41} to R^{45}, R^{51} to R^{54} and R^{76} are other than $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$ or $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

R^{33}, R^{55}, R^{56}, R^{61} and R^{64} are other than $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$ or $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$;

R^{33} and R^{34}, or R^{34} and R^{63} are other than, taken together, $-CH_{2-6}$-; $-(CH_2)_2O(CH_2)_2$-, $-(CH_2)_2S(CH_2)_2$- or $-(CH_2)_2NR^{57}(CH_2)_2$-;

R^{57} in $-(CH_2)_2NR^{57}(CH_2)_2$- or $-(CH_2)_rNR^{57}(CH_2)_r$- is other than lower alkenyl or heteroaryl-lower alkyl;

R^{71} is H, lower alkyl, lower alkenyl, $-(CH_2)_p(CHR^{61})_sOR^{75}$, $-(CH_2)_p(CHR^{61})_sSR^{75}$, $-(CH_2)_pNR^xR^y$, $-(CH_2)_o(CHR^{61})_sCOOR^{75}$, $-(CH_2)_pCONR^xR^y$, $-(CH_2)_pPO(OR^{62})_2$, $-(CH_2)_pSO_2R^{62}$, or $-(CH_2)_o$-$C_6R^{67}R^{68}R^{69}R^{70}R^{76}$;

R^{74} is other than $-(CH_2)_pNR^{77}R^{80}$, $-(CH_2)_pC_6H_4NR^{77}R^{80}$, $-(CH_2)_pO(CH_2)_mNR^{77}R^{80}$, $-(CH_2)_pS(CH_2)_mNR^{77}R^{80}$, $-(CH_2)_pN=C(NR^{78}R^{80})NR^{79}R^{80}$, $-(CH_2)_pC_6H_4N=C(NR^{78}R^{80})NR^{79}R^{80}$, $-(CH_2)_pO(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$, $-(CH_2)_pS(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$, $-(CH_2)_pNR^{80}COR^{64}$, or $-(CH_2)_pNR^{80}COR^{77}$;

is other than H52, H53 and H54;

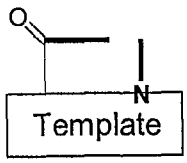
in Z, Z^1 or Z^2

- if n is 8, the amino acid residues in positions 1, 7 and 8 are:
  - P1: of type C or of type D or of type E, or the residue is Pro;
  - P7: of type C or of type D; and
  - P8: of type C or of type D or of type E, or the residue is Pro;
- if n is 9, the amino acid residues in positions 1 and 9 are:
  - P1: of type C or of type D or of type E, or the residue is Pro; and
  - P9: of type C or of type D or of type E, or the residue is Pro;
- if n is 10, the amino acid residues in positions 1 and 10 are:
  - P1: of type C or of type D or of type E, or the residue is Pro; and
  - P10: of type C or of type D or of type E;
- if n is 11, the amino acid residues in positions 1 and 11 are:

- P1: of type C or of type D or of type E, or the residue is Pro; and
- P11: of type C or of type D or of type E, or the residue is Pro;

- if n is 12, the amino acid residues in positions 1, 5 and 12 are:
  - P1: of type C or of type D or of type E, or the residue is Pro;
  - P5: of type E or of type D, or the residue is Gly or Pro; and
  - P12: of type C or of type D or of type E, or the residue is Pro;
- if n is 13, the amino acid residues in positions 1 and 13 are:
  - P1: of type C or of type D or of type E, or the residue is Pro; and
  - P13: of type C or of type D or of type E, or the residue is Pro;
- if n is 14, the amino acid residues in positions 1 and 14 are:
  - P1: of type C or of type D or of type E, or the residue is Pro; and
  - P14: of type C or of type D or of type E, or the residue is Pro;
- if n is 15, the amino acid residues in positions 1 and 15 are:
  - P1: of type C or of type D or of type E, or the residue is Pro; and
  - P15: of type C or of type D or of type E, or the residue is Pro;
- if n is 16, the amino acid residues in positions 1 and 16 are:
  - P1: of type D or of type E or of type C, or the residue is Pro; and
  - P16: of type C or of type D or of type E, or the residue is Pro.

3. Compounds according to claim 1 or 2 wherein



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

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

R^1 is hydrogen or lower alkyl;

R^2 is H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-CH_2)_mSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2\text{-}6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are

-$(CH_2)_{2\text{-}6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

-$(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are -$(CH_2)_{2\text{-}6}$-;

-$(CH_2)_2O(CH_2)_2$-;

-$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

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

$(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); -$(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are

-$(CH_2)_{2\text{-}6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or

-$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); -$(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or

-$(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy);

R^3 is H; lower alkyl; lower alkenyl; -$(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);

-$(CH_2)_mSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); -$(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -$(CH_2)_{2\text{-}6}$-;

-$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

-$(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are -$(CH_2)_{2\text{-}6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or

-$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are -$(CH_2)_{2\text{-}6}$-;

-$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

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

-$(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); -$(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are -$(CH_2)_{2\text{-}6}$-;

-$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

-$(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); -$(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or -$(CH_2)_qC_6H_4R^8$ (where R^8 is 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} is lower alkyl; or lower alkenyl);

-$(CH_2)_mSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); -$(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -$(CH_2)_{2\text{-}6}$-;

-$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

$-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$;
$-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$(where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$;
$-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57}: isH; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).

R^5 is lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are
$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
$-(CH_2)_oN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is alkyl; alkenyl; aryl; aryl-lower alkyl; or heteroaryl-lower alkyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
$-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy):

R^6 is H; lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$;

$-(CH_2)_2O(CH_2)_2-$;

$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

$-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;

$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

$-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or

$-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is 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} is lower alkyl; or lower alkenyl); $-(CH_2)_qSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_qNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$;

$-(CH_2)_2O(CH_2)_2-$;

$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_qOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_qNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

$-(CH_2)_qN(R^{20})COR^{64}$(where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_rCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_qCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or

$-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_rSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is 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} is lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken

together are -$(CH_2)_{2-6}$-;

-$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

-$(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are -$(CH_2)_{2-6}$-;

-$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

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

-$(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); -$(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are -$(CH_2)_{2-6}$-;

-$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

-$(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); -$(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or -$(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy);

R^9 is lower alkyl; lower alkenyl; -$(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); -$(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); -$(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -$(CH_2)_{2-6}$-;

-$(CH_2)_2O(CH_2)_2$-;

-$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

-$(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are

-$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-;

-$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

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

-$(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); -$(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or

-$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); -$(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or

-$(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy);

R^{10} is lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;

$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

$-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57}: H is or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;

$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

$-(CH_2)_oN(R^{20})COR^{64}$(where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or

$-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy);

R^{11} is H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);

$-(CH_2)_mSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$;

$-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

$-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together ar $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$;

$-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

$-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$;

$-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

$-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is

lower alkyl; or lower alkenyl); or -$(CH_2)_qC_6H_4R^8$ (where R^8 is 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} is lower alkyl; or lower alkenyl);

-$(CH_2)_mSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); -$(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -$(CH_2)_{2-6}$-;

-$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

-$(CH_2)_mOCONR^{33}R^{75}$ (where $R^{33}$is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are -$(CH_2)_{2-6}$-;

-$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

-$(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); -$(CH_2)_rCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); -$(CH_2)_rCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are -$(CH_2)_{2-6}$-;

-$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

-$(CH_2)_rPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); -$(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or -$(CH_2)_qC_6H_4R^8$ (where R^8 is 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} isis lower alkyl; or lower alkenyl); -$(CH_2)_qSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); -$(CH_2)_qNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -$(CH_2)_{2-6}$-;

-$(CH_2)_2O(CH_2)_2$-;

-$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

-$(CH_2)_qOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are

-$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_qNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-;

-$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

-$(CH_2)_qN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); -$(CH_2)_rCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); -$(CH_2)_qCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_rSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is 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} is lower alkyl; or lower alkenyl);

$-(CH_2)_mSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$;

$-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl is R^{82}: H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$;

$-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} is H; lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$;

$-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is 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} is lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;

$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;

$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

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

$-NR^{20}COlower\ alkyl$ (R^{20}=H; or lower alkyl); being particularly favoured; $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy);

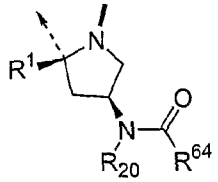
R^{16} is lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy); and

R^{17} is lower alkyl; lower alkenyl; $-(CH_2)_qOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_qSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_qNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); $-(CH_2)_qOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); $-(CH_2)_qNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

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

5. Compounds according to claim 3 or 4 wherein A is a group of one of the formulae A5 (with R^2 being H); A8; A22; A25; A38 (with R^2 being H); A42; and A50.

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



A8'

wherein R^{20} is H or lower alkyl; and R^{64} is alkyl; alkenyl; aryl; aryl-lower alkyl; or heteroaryl-lower alkyl.

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

8. Compounds according to claim 3 wherein A is a group of one of the formulae A70 to A104;

R^{20} is H; or lower alkyl;

R^{18} is lower alkyl;

R^{19} is lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_pSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;

$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

$-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is 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} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_pSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $(CH_2)_oC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy);

R^{21} is H; lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);

$-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;

$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl) ;

$-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

$-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$;

$-(CH_2)_2O(CH_2)_2-$;

$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

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

$-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or

$-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy);

R^{22} is lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);

$-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$;

$-(CH_2)_2O(CH_2)_2-$;

$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

$-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oN(R^{20})COR^{64}$(where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl);

$-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF; lower alkyl; lower alkenyl; or lower alkoxy);

R^{23} is H; lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);

$-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$;

$-(CH_2)_2O(CH_2)_2-$;

$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

$-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;

$-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

$-(CH_2)_oN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-NR^{20}$COlower alkyl (R^{20}=H; or lower alkyl) being particularly favoured; $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl);

$-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy);

R^{24} is lower alkyl; lower alkenyl; -$(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); -$(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); -$(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-;

-$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_oN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); -NR^{20}COlower alkyl (R^{20}=H ; or lower alkyl) being particularly favoured; -$(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); -$(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); -$(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or -$(CH_2)_qC_6H_4R^8$ (where R^8 is 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} is lower alkyl; or lower alkenyl); -$(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); -$(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); -$(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); -$(CH_2)_oSO_2R^{62}$ (where R^{62} is

lower alkyl; or lower alkenyl); or -$(CH_2)_qC_6H_4R^8$ (where R^8 is 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} is lower alkyl; or lower alkenyl);

-$(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); -$(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); -$(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); -$(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or -$(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy); or, alternatively, R^{25} and R^{26} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-;

-$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{34}(CH_2)_2$-;

R^{27} is H; lower alkyl; lower alkenyl; -$(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);

-$(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); -$(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-;

-$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

-$(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-;

-$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl);

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

$-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy);

R^{28} is lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oN(R^{20})COR^{64}$(where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy); and

R^{29} is lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oN(R^{20})COR^{64}$(where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);

-NR^{20}COlower-alkyl (R^{20}=H; or lower alkyl) being particularly favoured; -$(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl);
-$(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are -$(CH_2)_{2-6}$-; -$(CH_2)_2O(CH_2)_2$-; -$(CH_2)_2S(CH_2)_2$-; or -$(CH_2)_2NR^{57}(CH_2)_2$-; where R^{57} is H; or lower alkyl); -$(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl);
-$(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or -$(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).

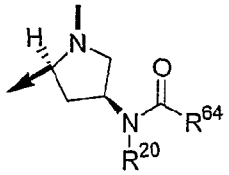
9. Compounds according to claim 8 wherein R^{23}, R^{24} and R^{29} are -NR^{20}-CO-lower alkyl where R^{20} is H; or lower alkyl.

10. Compounds according to claim 8 or 9 wherein A is a group of one of the formulae A74 (with R^{22} being H); a75; A76; A77 (with R^{22} being H); A78; and A79.

11. Compounds according to any one of claims 3 to 10 wherein B is a group of formula -$NR^{20}CH(R^{71})$- or an enantiomer of one of the groups A5 (with R^2 being H); A8; A22; A25; A38 (with R^2 being H); A42; A47; and A50.

12. Compounds according to claim 11 wherein B-CO is Ala; Arg; Asn; Cys; Gln; Gly; His; Ile; Leu; Lys; Met; Phe; Pro; Ser; Thr; Trp; Tyr; Val; Cit; Orn; tBuA; Sar; t-BuG; 4AmPhe; 3AmPhe; 2AmPhe; Phe(mC(NH_2)=NH; Phe(pC(NH_2)=NH; Phe(mNHC (NH_2)=NH; Phe(pNHC (NH_2)=NH; Phg; Cha; C_4al; C_5al; Nle; 2-Nal; 1-Nal; 4Cl-Phe; 3Cl-Phe; 2Cl-Phe; 3,4Cl_2Phe; 4F-Phe; 3F-Phe; 2F-Phe; Tic; Thi; Tza; Mso; AcLys; Dpr; A_2Bu; Dbu; Abu; Aha; Aib; Y(Bzl); Bip; S(Bzl); T(Bzl); hCha; hCys; hSer, hArg; hPhe; Bpa; Pip; OctG; MePhe; MeNle; MeAla; MeIle; MeVal; or MeLeu.

13. Compounds according to claim 11 or 12 wherein B is a group, having (L)-configuration, of formula

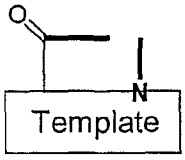


A8"

wherein R^{20} is H; or lower alkyl; and R^{64} is alkyl; alkenyl; aryl; aryl-lower alkyl; or heteroaryl-lower alkyl.

14. Compounds according to claim 13 wherein R^{64} is n-hexyl; n-heptyl; 4-(phenyl)benzyl; diphenylmethyl, 3-amino-propyl; 5-amino-pentyl; methyl; ethyl; isopropyl; isobutyl; n-propyl; cyclohexyl; cyclohexylmethyl; n-butyl; phenyl; benzyl; (3-indolyl)methyl; 2-(3-indolyl)ethyl; (4-phenyl)phenyl; or n-nonyl.

15. Compounds according to claim 1 or 2 wherein



is a group of formula (b1) or (1);

R^1 is H; or lower alkyl;

R^{20} is H; or lower alkyl;

R^{30} is H; or methyl;

R^{31} is H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);

$-(CH_2)_pNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_rC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy); most preferably $-CH_2CONR^{58}R^{59}$ (where R^{58} is H; or lower alkyl; and R^{59} is lower alkyl; or lower alkenyl);

R^{32} is H; or methyl;

R^{33} is lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{34}R^{63}$ (where R^{34} is lower alkyl; or lower alkenyl; R^{63} is H; or lower alkyl; or R^{34} and R^{63} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mOCONR^{75}R^{82}$ (where R^{75} is lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{75} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{78}R^{82}$ (where R^{20} is H; or lower alkyl; R^{78} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{78} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57}: H; or lower alkyl);

R^{34} is H; or lower alkyl;

R^{35}: isH; 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} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);

R^{36}: lower alkyl; lower alkenyl; or aryl-lower alkyl;

R^{37} is H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);

$-(CH_2)_pNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);- $(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}-$;

$-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
$-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
$-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
$-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alky; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy); and
R^{38} is H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
$-(CH_2)_pNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together sre $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
$-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
$-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
$-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3; lower alkyl; lower alkenyl; or lower alkoxy).

16. Compounds according to claim 15 wherein R^1 is H; R^{20} is H; R^{30} is H; R^{31} is carboxymethyl; or lower alkoxycarbonylmethyl; R^{32} is H; R^{35} is methyl; R^{36} is methoxy; R^{37} is H and R^{38} is H.

17. Compounds according to any one of claims 1 to 16 wherein in the chain(s) of α-amino acid residues Z, Z^1 and Z^2

- If **n is 8**, the amino acid residues in position 1 – 8 are:
  - P1: of type **C** or of type D; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type **E**;
  - P4: of type **E** or of formula -**A1-A69**-CO-;
  - P5: of type **E** or of formula -**B**-CO-;
  - P6: of type **D**;
  - P7: of type **E**; or of type **D** and
  - P8: of type **C** or of type D; or of type **E**;
  - at P4 and P5 also D-isomers being possible;
- if **n is 9**, the amino acid residues in position 1 – 9 are:
  - P1: of type **C** or of type D; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type **C**;
  - P4: of type **E**, or the residue is Pro;
  - P5: of type **E**, or the residue is Pro;
  - P6: of type **D** or of type E, or the residue is Pro;
  - P7: of type **E** or of type D;
  - P8: of type **E**; or of type **D** and
  - P9: of type **C** or of type D; or of type **E**;
  - at P4, P5 and P6 also D-isomers being possible;
- if **n is 10**, the amino acid residues in position 1 – 10 are:
  - P1: of type **C** or of type D; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type **C**;
  - P4: of type **E** or of type D;
  - P5: of type **E** or of formula -**A1-A69**-CO-;
  - P6: of type **E** or of formula -**B**-CO-;
  - P7: of type **D** or of type E;
  - P8: of type **D**;
  - P9: of type **E**; or of type **D** and
  - P10: of type **C** or of type D; or of type **E**;
  - at P5 and P6 also D-isomers being possible;
- if **n is 11**, the amino acid residues in position 1 – 11 are:
  - P1: of type **C** or of type D; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type **D**;

- P4: of type **E** or of type C;
- P5: of type **E**, or the residue is Pro;
- P6: of type **E**, or the residue is Pro;
- P7: of type **E**, or the residue is Pro;
- P8: of type **D** or of type E;
- P9: of type **D**;
- P10: of type **E**; or of type **D** and
- P11: of type **C** or of type D; or of type **E**;
- at P5, P6 and P7 also D-isomers being possible;

- if **n is 12**, the amino acid residues in position 1 – 12 are:
  - P1: of type **C** or of type **E**; or of type D; or of type F;
  - P2: of type **E**; or of type **D**;
  - P3: of type **C** or of type D;
  - P4: of type **E**;
  - P5: of type **E**; or of type C;
  - P6: of type **E** or of type F or of formula -**A1**-**A69**-CO-;
  - P7: of type **E** or of formula -**B**-CO-;
  - P8: of type **D**;
  - P9: of type **E** or of type D;
  - P10: of type **D**;
  - P11: of type **E**; or of type **D** and
  - P12: of type **C** or of type **E**; or of type D; or of type F;
  - at P6 and P7 also D-isomers being possible;
- if **n is 13**, the amino acid residues in position 1 – 13 are:
  - P1: of type **C** or of type D; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type **C** or of type D;
  - P4: of type **E** or of type C;
  - P5: of type **E** or of type D;
  - P6: of type **E** or of type F, or the residue is Pro;
  - P7: of type **E**, or the residue is Pro;
  - P8: of type **D**, or the residue is Pro;
  - P9: of type **D**;
  - P10: of type **E** or of type C;
  - P11: of type **C** or of type D;
  - P12: of type **E**; or of type **D** and
  - P13: of type **C** or of type D; or of type **E**;

- at P6, P7 and P8 also D-isomers being possible;

- if **n is 14**, the amino acid residues in position 1 – 14 are:
  - P1: of type **C** or of type D; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type **C** or of type D;
  - P4: of type **D**;
  - P5: of type **E**;
  - P6: of type **E**;
  - P7: of type **E** or of type F or of formula -**A1**-**A69**-CO-;
  - P8: of type **E** or of formula -**B**-CO-;
  - P9: of type **D**;
  - P10: of type **C**;
  - P11: of type **E** or of type D;
  - P12: of type **D** or of type C;
  - P13: of type **E**; or of type **D** and
  - P14: of type **C** or of type D; or of type **E**;
  - at P7 and P8 also D-isomers being possible;

- if **n is 15**, the amino acid residues in position 1 – 15 are:
  - P1: of type **C** and of type D; or of type **E**;
  - P2: of type **E**; or of type **D**;
  - P3: of type **C** and of type D;
  - P4: of type **E** or of type C;
  - P5: of type **C**;
  - P6: of type **E** or of type D;
  - P7: of type **C**, or the residue is Pro;
  - P8: of type **E** or of type F, or the residue is Pro;
  - P9: of type **E** or of type F, or the residue is Pro;
  - P10: of type **E**;
  - P11: of type **C**;
  - P12: of type **E** or of type C;
  - P13: of type **D** or of type C;
  - P14: of type **E**; or of type **D** and
  - P15: of type **C** and of type D; or of type **E**;
  - at P7, P8 and P9 also D-isomers being possible; and

- if **n is 16**, the amino acid residues in position 1 – 16 are:
  - P1: of type **D**; or of type **E**;
  - P2: of type **E**; or of type **D**;

- P3: of type **C** or of type D;
- P4: of type **E** or of type D;
- P5: of type **D**;
- P6: of type **E**;
- P7: of type **E** or of type F;
- P8: of type **E** or of type F or of formula -**A1-A69**-CO-;
- P9: of type **E** or of formula -**B**-CO-;
- P10: of type **D**;
- P11: of type **E**;
- P12: of type **D**;
- P13: of type **E** or of type C;
- P14: of type **C** or of type D;
- P15: of type **E**; or of type **D** and
- P16: of type **C** or of type D; or of type **E**;
- at P8 and P9 also D-isomers being possible.

18. Compounds according to claim 17 wherein n is 12 and the amino acid residues in position 1 – 12 are:

- P1: Leu; Arg; Lys; Tyr; Trp; Val; Gln;or 4-AmPhe;
- P2: Arg; Trp; or Gln;
- P3: Leu,; Val; Ile; or Phe;
- P4: Lys; Arg; Gln; or Orn;
- P5: Lys; or Arg;
- P6: Arg; Y(Bzl); or ^{D}Y(Bzl)
- P7: Arg;
- P8: Trp; Bip; 1-Nal; Y(Bzl); or Val;
- P9: Lys; Arg; Orn; Tyr; Trp; or Gln;
- P10: Tyr; T(Bzl); or Y(Bzl);
- P11: Arg; or Tyr; and
- P12: Val; Arg; 1-Nal; or 4-AmPhe.

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

- P1: Leu;
- P2: Arg;
- P3: Leu;
- P4: Lys;

- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

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

- P1: Leu;
- P2: Arg;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Y(Bzl);
- P9: Lys;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

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

- P1: Leu;
- P2: Arg;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Arg; and

- P12: 1-Nal.

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

- P1: Leu;
- P2: Arg;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Bip;
- P9: Lys;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

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

- P1: Leu;
- P2: Arg;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: T(Bzl);
- P11: Arg; and
- P12: Val.

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

- P1: Leu;
- P2: Arg;
- P3: Leu;

- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Arg;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

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

- P1: Leu;
- P2: Trp;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Bip;
- P9: Lys;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

26. A compound of formula Ia according to claim 1 wherein the template is ^{D}Pro-Phe; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Leu;
- P2: Arg;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;

- P11: Arg; and
- P12: Val.

27. A compound of formula Ia according to claim 1 wherein the template is ^{D}Pro-(2R,4S)-4-[n-hexylcarbonylamino]-^{L}Pro; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Leu;
- P2: Arg;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

28. A compound of formula Ia according to claim 1 wherein the template is ^{D}Pro-(2R,4S)-4-[cyclohexylcarbonylamino]-^{L}Pro; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Leu;
- P2: Arg;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

29. A compound according to claim 1 wherein the template is of formula (c1) wherein R^{20} is H; R^{35} is methyl; R^{36} is methoxy; R^{37} is H and R^{38} is H; n is 12; and the amino acid residues

in position

1 – 12 are:

- P1: Leu;
- P2: Arg;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

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

- P1: Arg;
- P2: Trp;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Tyr; and
- P12: Val.

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

- P1: Leu;
- P2: Trp;
- P3: Leu;
- P4: Lys;
- P5: Lys;

- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Tyr; and
- P12: Arg.

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

- P1: Arg;
- P2: Trp;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Tyr; and
- P12: Arg.

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

- P1: Leu;
- P2: Arg;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: ^{D}Y(Bzl);
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

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

- P1: Arg;
- P2: Bip;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Tyr; and
- P12: Arg.

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

- P1: Lys;
- P2: Trp;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Tyr; and
- P12: Arg.

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

- P1: Tyr;
- P2: Trp;
- P3: Leu;
- P4: Lys;

- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Tyr; and
- P12: Arg.

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

- P1: Trp;
- P2: Trp;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Tyr; and
- P12: Arg.

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

- P1: Val;
- P2: Trp;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Tyr; and

- P12: Arg.

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

- P1: Gln;
- P2: Trp;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Tyr; and
- P12: Arg.

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

- P1: Leu;
- P2: Arg;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Y(Bzl);
- P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

41. Enantiomers of the compounds of formulae Ia and Ib as defined in claim 1.

42. Compounds according to any one of claims 1 to 41 for use as therapeutically active substances.

43. A pharmaceutical composition containing a compound according to any one of claims 1 to 41 and a pharmaceutically inert carrier.

44. Compositions according to claim 43 in a form suitable for oral, topical, transdermal, injection, buccal, transmucosal, pulmonary or inhalation administration.

45. Compositions according to claim 43 or 44 in form of tablets, dragees, capsules, solutions, liquids, gels, plasters, creams, ointments, syrups, slurries, suspensions, sprays, nebulisers or suppositories.

46. The use of compounds according to any one of claims 1 to 41 for the manufacture of a medicament for treating or preventing infections or diseases related to such infections, said infections being in particular cystic fibrosis lung infections, or for the manufacture of a medicament useful against malignant cells for treatment of cancer.

47. The use of compounds according to any one of claims 1 to 41 as disinfectants or preservatives for foodstuffs, cosmetics, medicaments and other nutrient-containing materials.

48. The use of compounds according to claims 1-41 for preventing surfaces from microbial colonisation.

49. A process for the manufacture of compounds according to any one of claims 1 to 40 which process comprises

(a) coupling an appropriately functionalized solid support with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position $^{n}/_{2}$, $^{n}/_{2}+1$ or $^{n}/_{2}-1$ if n is an even number and, respectively, in position $^{n}/_{2}+^{1}/_{2}$ or $^{n}/_{2}-^{1}/_{2}$ if n is an odd number, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

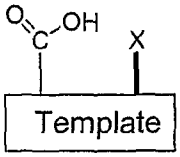
(b) removing the N-protecting group from the product thus obtained;

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

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

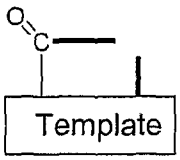
(e) repeating, if necessary, steps (c) and (d) until the N-terminal amino acid residue has been introduced;

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

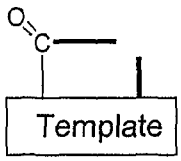


II

wherein



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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(q) if, desired

(qa) forming one or several interstrand linkage(s) between side-chains of appropriate amino acid residues at opposite positions of the β-strand region; and/or

(qb) connecting two building blocks of the type of formula Ia via a bridge

-G1 - L - G2-;

(r) 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

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

50. A modification of the process of claim 49 for the manufacture of compounds according to claim 41 in which enantiomers of all chiral starting materials are used.