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(54) **TEMPLATE-FIXED PEPTIDOMIMETICS AS MEDICAMENTS AGAINST HIV AND CANCER**

MATRIZENFIXIERTE PEPTIDMIMETIKA ALS MEDIKAMENTE GEGEN HIV UND KREBS

PEPTIDOMIMETIQUES FIXES SUR MATRICE, UTILISES COMME MEDICAMENTS CONTRE LE VIH ET LE CANCER

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Description

[0001] The present invention provides template-fixed β-hairpin peptidomimetics incorporating two template-fixed chains of 4 and 6 or 5 and 7 α-amino acid residues which, depending on their positions in the chains, are Gly or Pro, or of certain types, as defined herein below. These template-fixed β-hairpin mimetics have antagonizing CXCR4-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 antagonizing CXCR4 activity on the one hand, and hemolysis on red blood cells and cytotoxicity on the other.

[0002] To date the available therapies for the treatment of HIV infections have been leading to a remarkable improvement in symptoms and recovery from disease in infected people. Although the highly active anti retroviral therapy (HAART-therapy) which involves a combination of reverse transcriptase/protease inhibitor has dramatically improved the clinical treatment of individuals with AIDS or HIV infection, there have still remained several serious problems including multi drug resistance, significant adverse effects and high costs. Particularly desired are anti HIV agents that block the HIV infection at an early stage of the infection, such as the viral entry.

[0003] It has recently been recognized that for efficient entry into target cell, human immunodeficiency viruses require the chemokine receptors CCR5 and CXCR4 as well as the primary receptor CD4 (N. Levy, Engl. J. Med., 335, 29, 1528-1530). Accordingly, an agent which could block the CXCR4 chemokine receptors should prevent infections in healthy individuals and slow or halt viral progression in infected patients (Science, 1997, 275, 1261-1264).

[0004] Among the different types of CXCR4 inhibitors (M. Schwarz, T. N.C. Wells, A.E.I. Proudfoot, Receptors and Channels. 2001, 7, 417-428), one emerging class is based on naturally occurring cationic peptide analogues derived from Polyphemusin II which have an antiparallel β-sheet structure, and a β-hairpin that is maintained by two disulfide bridges (H. Nakashima, M. Masuda, T. Murakami, Y. Koyanagi, A. Matsumoto, N. Fujii, N. Yamamoto, Antimicrobial Agents and Chemoth. 1992, 36, 1249-1255; H. Tamamura, M. Kuroda, M. Masuda, A. Otaka, S. Funakoshi, H. Nakashima, N. Yamamoto, M. Waki, A. Matsumotu, J.M. Lancelin, D. Kohda, S. Tate, F. Inagaki, N. Fujii, Biochim. Biophys. Acta 1993, 209, 1163; WO 95/10534 A1).

[0005] Synthesis of structural analogs and structural studies by nuclear magnetic resonance (NMR) spectroscopy have shown that the cationic peptides adopt well defined β-hairpins conformations, due to the constraining effect of the single or two disulfide bridges (H. Tamamura, M. Sugioka, Y. Odagaki, A. Omagari, Y. Kahn, S. Oishi, H. Nakashima, N. Yamamoto, S.C. Peiper, N. Hamanaka, A. Otaka, N. Fujii, Bioorg. Med. Chem. Lett. 2001, 359-362).These results show that the β-hairpin structure plays an important role in antagonizing CXCR4-activity.
Additional structural studies have also indicated that the antagonizing activity can also be influenced by modulating amphiphilic structure and the pharmacophore (H. Tamamura, A. Omagari, K. Hiramatsu, K. Gotoh, T. Kanamoto, Y. Xu, E. Kodama, M. Matsuoka, T. Hattori, N. Yamamoto, H. Nakashima, A. Otaka, N. Fujii, Bioorg. Med Chem. Lett. 2001, 11. 1897-1902; H. Tamamura, A. Omagari, K. Hiramatsu, S. Oishi, H. Habashita, T. Kanamoto, K. Gotoh, N. Yamamoto, H. Nakashima, A. Otaka N. Fujii, Bioorg. Med.Chem. 2002, 10, 1417-1426; H. Tamamura, K. Hiramatsu, K. Miyamoto, A. Omagari, S. Oishi, H. Nakashima, N. Yamamoto, Y. Kuroda, T. Nakagawa, A. Otaki, N. Fujii, Bioorg. Med. Chem. Letters 2002, 12, 923-928).

[0006] A key issue in the design of CXCR4 antagonizing peptides is selectivity. The Polyphemusin II derived analogs exert still a cytotoxicity despite improvements (K. Matsuzaki, M. Fukui, N. Fujii, K. Miyajima, Biochim. Biophys. Acta 1991, 259, 1070; A. Otaka, H. Tamamura, Y. Terakawa, M. Masuda, T. Koide, T. Murakami, H. Nakashima, K. Matsuzaki, K. Miyajima, T. Ibuka, M. Waki, A. Matsumoto, N. Yamamoto, N. Fujii Bio/. Pharm. Bull. 1994, 17, 1669 and references cited above.

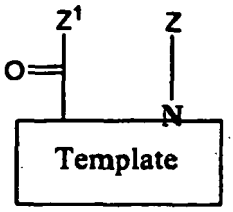
[0007] This cytotoxic activity essentially obviates use in vivo, and represents a serious disadvantage in clinical applications. Before intravenous use can be considered, the general toxicity, protein-binding activity in blood serum, as well as protease stability become serious issues which must be adequately addressed.

[0008] In addition it has recently been discovered, that the CXCR4-receptor is involved in chemotactic activity of cancer cells, such as breast cancer metastasis or ovarian cancer (A. Muller, B. Homey, H. Soto, N. Ge, D. Catron, M.E. Buchanan, T. Mc Clanahan, E. Murphey, W. Yuan, S.N. Wagner, J. Luis Barrera, A. Mohar, E. Verastegui, A. Zlotnik, Nature 2001, 50, 410, J. M. Hall, K. S. Korach, Molecular Endocrinology, 2003, 1-47;), Non-Hodgin's Lymphoma (F. Bertolini, C. DellÀgnola, P. Manusco, C. Rabascio, A. Burlini, S. Monestiroli, A. Gobbi, G. Pruneri, G. Martinelli, Cancer Research 2002, 62, 3106-3112), or lung cancer (T. Kijima, G. Maulik, P. C. Ma, E. V. Tibaldi, R:E. Turner, B. Rollins, M. Sattler, B.E. Johnson, R. Salgia, Cancer Research 2002, 62, 6304-6311) or in inflammatory diseases e.g. such as rheumatoid arthritis, asthma, or multiple sclerose (K.R. Shadidi et al, Scandinavian Journal of Immunolgy, 2003, 57, 192-198, J. A. Gonzalo J. Immunol. 2000, 165, 499-508, S. Hatse et al, FEBS Letters 2002 527, 255-262 and cited references). Blocking the chemotactic activity with a CXCR4 inhibitor should stop the migration of cancer cells. The mediation of recruitment of immunecells to sites of inflammation should be stopped by a CXCR4 inhibitor. Particularly desired are agents for treatment of cancer or agents for treatment of inflammatory disorders.

[0009] In the compounds described below, a new strategy is introduced to stabilize beta -hairpin conformations in bridged-backbone peptide mimetic exhibiting high CXCR4 antagonizing activity and anticancer activity and anti inflammatory 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. 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 CXCR4 antagonizing 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).

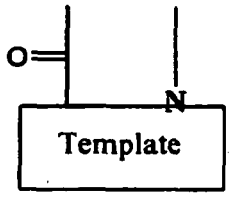
[0010] These methods allow the synthesis and screening of large hairpin mimetic libraries, which in turn considerably facilitates structure-activity studies, and hence the discovery of new molecules with highly potent CXCR4 antagonizing activity or anti cancer activity or anti inflammatory activity and low hemolytic activity to human red blood blood cells. β-Hairpin peptidomimetics obtained by the approach described here are useful as Anti-HIV agents and anticancer agents and anti-inflammatory agents.

[0011] The β-hairpin peptidomimetics of the present invention are compounds of the general formula 1. Compounds of the general formula



(I)

wherein



is a group of one of the formulae

^{D}Pro-^{L}Pro and ^{L}Pro-^{D}Pro

R^{20}	is H; alkyl; alkenyl; or aryl-lower alkyl;
R^{32}	is H; lower alkyl; or aryl-lower alkyl;
R^{33}	is H; alkyl, alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$; $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOR^{64}$; $-(CH_2)_o(CHR^{61})_s$-$CONR^{58}R^{59}$, $-(CH_2)_o(CHR^{61}),PO(OR^{60})_2$; $-(CH_2)_o(CHR^{61})_s\ SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
R^{34}	isH; lower alkyl; aryl, or aryl-lower alkyl;
R^{33} and R^{34}	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^{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^{50}	is H; lower alkyl; or aryl-lower alkyl;
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 $-(CH_2)_p(CHR^{61})_sNR^{34}R^{63}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{75}R^{82}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{78}R^{32}$;

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 $-CONR^{58}R^{59}$;

[0012] Z and Z^1 are chains of n and, respectively, n' α-amino acid residues whereby either n is 4 and n' is 6 or n is 5 and n' is 7, the positions of said amino acid residues in said chain Z being counted starting from the N-terminal amino acid and the positions of said amino acid residues in said chain Z^1 being counted starting from the C-terminal amino acid, whereby these amino acid residues are, depending on their position in the chains, Gly, or Pro, 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: $-NR^{20}-CH(CO-)-(CH_2)_{4-7}-CH(CO-)-NR^{20}-$;
$-NR^{20}-CH(CO-)-(CH_2)_pSS(CH_2)_p-CH(CO-)-NR^{20}-$;
$-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CO(CH_2)_p-CH(CO-)-NR^{20}-$;
$-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CONR^{20}(CH_2)_p-CH(CO-)-NR^{20}-$; and

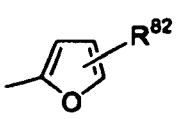
I: $-NR^{86}CH_2CO-$;

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

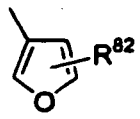
R^{73} is $-(CH_2)_oR^{77}$; $-(CH_2)_rO(CH_2)_oR^{77}$; $-(CH_2)_rS(CH_2)_oR^{77}$; or $-(CH_2)_rNR^{20}(CH_2)_oR^{77}$;

R^{74} is $-(CH_2)_pNR^{78}R^{79}$; $-(CH_2)_pNR^{77}R^{80}$; $-(CH_2)_pC(=NR^{80}NR^{78}R^{79}$; $-(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pNR^{80}C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_pN=(NR^{78}R^{80})NR^{79}R^{80}$;$-(CH_2)_pC_6H_4NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{77}R^{80}$;
$-(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_pC_6H_4N=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_rO(CH_2)_mNR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_mNR^{77}R^{80}$;
$-(CH_2)_rO(CH_2)_pC(=NR^{80}NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_rO(CH_2)_pC_6H_4CNR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC_6H_4C(=NOR^{50}NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mNR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_mNR^{77}R^{80}$;$-(CH_2)_rS(CH_2)_pC(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_mONR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$;
$-(CH_2)_rS(CH_2)_pC_6H_4CNR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$;

	$-(CH_2)_rS(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4NR^{80}C(=NR^{80}NR^{78}R^{79}$; $-(CH_2)_pNR^{80}COR^{64}$; $-(CH_2)_pNR^{80}COR^{77}$; $-(CH_2)_pNR^{80}CONR^{78}R^{79}$; 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^{77}	is R^{87}; or a heteroaryl group of one of the formulae



H1



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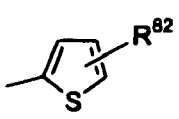

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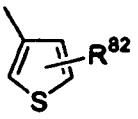

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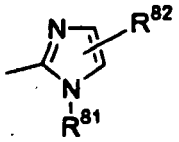

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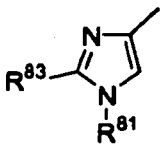

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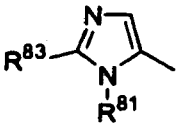

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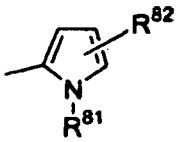

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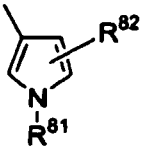

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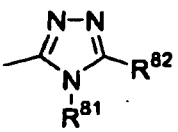

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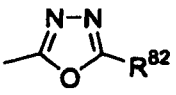

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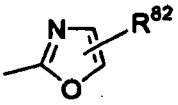

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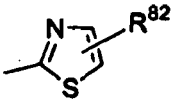

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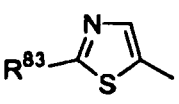

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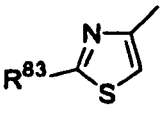

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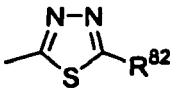

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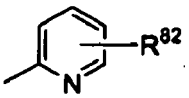

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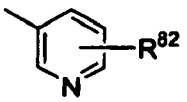

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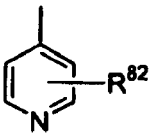

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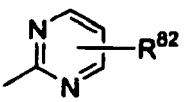

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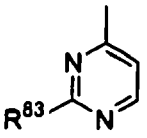

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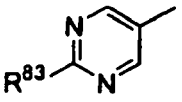

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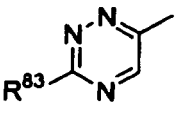

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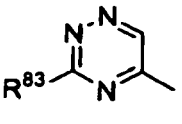

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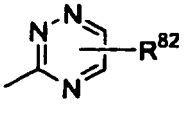

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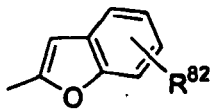

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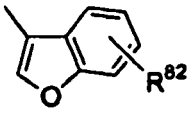

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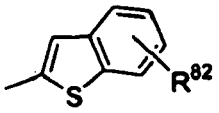

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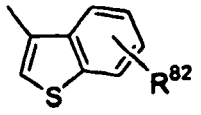

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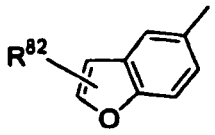

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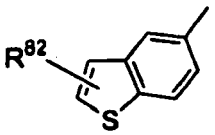

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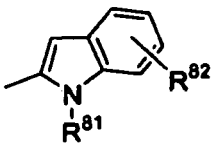

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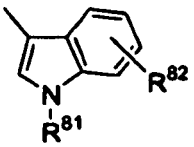

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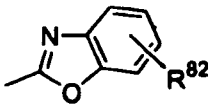

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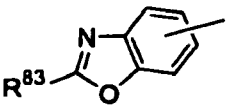

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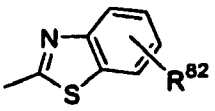

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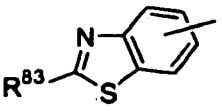

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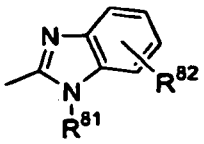

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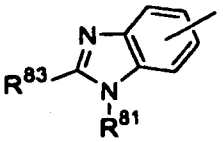

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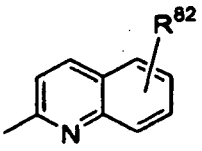

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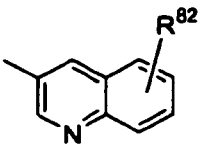

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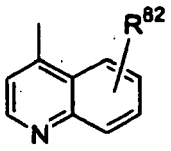

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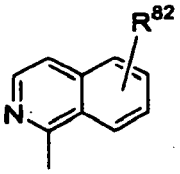

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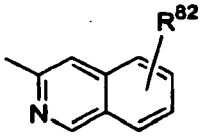

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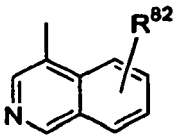

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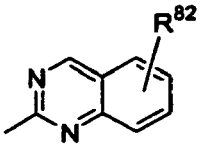

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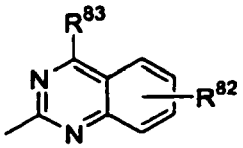

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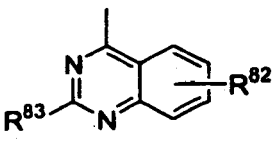

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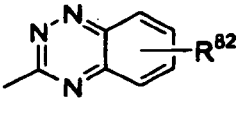

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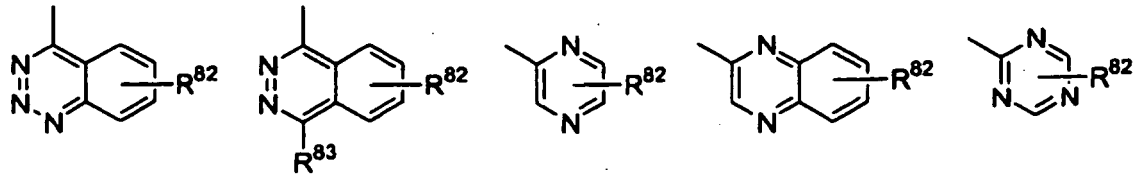

H50 H51 H52 H53 H54

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 $-(CH_2)_pCONR^{78}R^{79}$; $-(CH_2)_pNR^{80}CONR^{78}R^{79}$; $-(CH_2)_pC_6H_4CONR^{78}R^{79}$; or $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;
R^{85}	is lower alkyl; or lower alkenyl;
R^{86}	is R^{74}; $-[(CH_2)_u-X]_t(CH_2)_vNR^{78}R^{79}$; $-[(CH_2)_u-X]_t-(CH_2)_v-C(=NR^{80})NR^{78}R^{79}$; X is -O-, $-NR^{20}-$, -S-, -OCOO-, u is 1-3, t is 1-6, v is 1-3;
R^{87}	is is phenyl, p-hydrxyphenyl, 2-naphthyl, 1-naphthyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, 3-fluorophenyl, 2-fluorophenyl, p-benzyloxyphenyl, p-biphenyl or p-benzoylphenyl.

with the proviso that in said chains Z and Z^1 of n and, respectively, n' α-amino acid residues

- if n is 4 and n' is 6, the amino acid residues in positions 1 to 4 of Z and in positions 1' to 6' of Z^1 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;
  - P3: of type F, or the residue is Pro;
  - P4: of type E;

  - P1': of type C or of type D or of type E or of type F, or the residue is Gly;
  - P2': of type D or of type C;
  - P3': of type F or the residue is Pro;
  - P4': of type D or of type C;
  - P5': of type E, or of type F or the residue is Pro; and
  - P6': of type E or of type F, or the residue is Pro; or

  - P3 and P3', taken together, can form a group of type H;

  and

- if n is 5 and n' is 7, the amino acid residues in positions 1 to 5 of Z and in positions 1' to 7' of Z^1 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;
  - P3: of type F, or the residue is Pro;
  - P4: of type F;
  - P5: of type E

  - P1': of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2': of type F;

- P3': of type D or the residue is Pro;
- P4': of type E or of type F;
- P5': of type D, or the residue is Pro;
- P6': of type E or of type F, or the residue is Pro; and
- P7': of type E or of type I, or the residue is Gly; or

- P2 and P2' and/or P4 and P4', taken together, can form a group of type H;

at P7' also D-isomers being possible,

and pharmaceutically acceptable salts thereof.

[0013] In accordance with the present invention these β-hairpin peptidomimetics can be prepared by a process which comprises

A process for the manufacture of compounds according to any one of claims 1-11 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 4 of Z if n is 4 or in position 5 of Z if n is 5, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
(b) removing the N-protecting group from the product thus obtained;
(c) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in Z of the desired end-product is one position nearer the N-terminal amino acid residue, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
(d) removing the N-protecting group from the product thus obtained;
(e) repeating steps (c) and (d) until the N-terminal amino acid residue of Z has been introduced;
(f) coupling the product thus obtained

(fa) with an appropriately N-protected derivative of ^{D}Pro or ^{L}Pro;
(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 ^{L}Pro and, respectively, ^{D}Pro;

(g) removing the N-protecting group from the product obtained in step (fc);
(h) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position 1 of Z^1, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
(i) removing the N-protecting group from the product thus obtained;
(j) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position farther away from position 1 of Z^1, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
(k) removing the N-protecting group from the product thus obtained;
(l) repeating steps (j) and (k) until all amino acid residues of Z^1 have been introduced;
(m) if desired, selectively deprotecting one or several protected functional group(s) present in the molecule and appropriately substituting the reactive group(s) thus liberated;
(n) if desired, forming one or two interstrand linkage(s) between side-chains of appropriate amino acid residues at opposite positions of the β-strand region;
(o) detaching the product thus obtained from the solid support and 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
(p) 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.

[0014] Introducing an amino acid residue of type I can, alternatively, be effected by coupling with a leaving group-containing acetylating agent, such as bromo, chloro or iodo acetic acid, followed by nucleophilic displacement with an amine of the formula H_2NR^{86} which, if necessary, is appropriately protected.

[0015] The peptidomimetics of the present invention can also be enantiomers of the compounds of formula I. These enantiomers can be prepared by a modification of the above process in which enantiomers of all chiral starting materials are used.

[0016] 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}.

[0017] The template 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** is linked to the C-terminus of the template via the N-terminus, and the corresponding N-terminus of the template is linked to the C-terminus of Z^1 to form a β-hairpin structure such as that depicted in formula **I.** In a case as here where the distance between the N-and C- termini of the template lies between 4.0-5.5A the template will induce the H-bond network necessary for the formation of a β-hairpin conformation within the peptide chain **Z** and **Z^1**. Thus template and peptide chains form a β-hairpin mimetic. The β-hairpin conformation is highly relevant for the CXCR4 antagonizing activity of the β-hairpin mimetics of the present invention.

[0018] The peptidic chains Z and Z^1 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" 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"
- Group I $-NR^{86}CH_2CO-$; "polar-cationic"

[0019] Furthermore, Gly can also be an amino acid residue in chains Z and Z^1, and Pro can be an amino acid residue in chains Z and Z^1, too, with the exception of positions where interstrand linkages **(H)** are possible.

[0020] **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.

[0021] **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.

[0022] 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.

[0023] **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.

[0024] **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.

[0025] **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 homocysteines positioned at opposite positions of the β-strand. Various methods are known to form disulfide linkages including those described by: J. P. Tam et al. Synthesis 1979, 955-957; Stewart et al., Solid Phase Peptide Synthesis, 2d Ed., Pierce Chemical Company, III., 1984**;** Ahmed et al. J. Biol. Chem. 1975, 250, 8477-8482 ; and Pennington et al., Peptides, pages 164-166, Giralt and Andreu, Eds., ESCOM Leiden, The Netherlands, 1990**.** Most advantageously, for the scope of the present invention, disulfide linkages can be prepared using acetamidomethyl (Acm)- protective groups for cysteine. A well established interstrand linkage consists in linking ornithines and lysines, respectively, with glutamic and aspartic acid residues located at opposite β-stand positions by means of an amide bond formation. Preferred protective groups for the side chain amino-groups of ornithine and lysine are allyloxycarbonyl (Alloc) and allylesters for aspartic and glutamic acid. Finally, interstrand linkages can also be established by linking the amino groups of lysine and ornithine located at opposite β-strand positions with reagents such as N,N-carbonylimidazole to form cyclic ureas.

[0026] **Group I** comprises glycine having the amino group substituted by chains containing polar-cationic residues according to the general definition for substituent R^{86}. Polar-cationic refers to a basic side chain which is protonated at physiological pH.

[0027] As mentioned earlier, positions for interstrand linkages are the following:

If n is 4 and n' is 6	Postitions P3 and P3' taken together
If n is 5 and n' is 7	Postitions P2 and P2' and/or P4 and P4', taken together

[0028] 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.

[0029] Most preferred amino acid residues in chains Z and Z^1 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
He	L-Isoleucine	I
Leu	L-Leucine	L
Lys	L-Lysine	K
Met	L-Methionine	M
Phe	L-Phenylalanine	F
Pro	L-Proline	P

(continued)

three letter code		one letter code
^{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

[0030] 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

(continued)

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-PhePyrrl	(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	(25,5S)-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
W(6-Cl)	L-6-Cl-Tryptophan
(EA)G	N-(2-Aminoethyl)glycine
(PrA)G	N-(3-Amino-n-propyl)glycine
(BA)G	N-(4-Amino-n-butyl)glycine
(PeA)G	N-(5-Amino-n-pentyl)glycine
(EGU)G	N-(2-Guanidinoethyl)glycine
(PrGU)G	N-(3-Guanidino-n-propyl)glycine
(BGU)G	N-(4-Guanidino-n-butyl)glycine
(PeGU)G	N-(5-Guanidino-n-pentyl)glycine
$(PEG_3\text{-}NH_2)G$	$N\text{-}[(CH_2)_3O\text{-}(CH_2\text{-}CH_2O)_2\text{-}(CH_2)_3\text{-}NH_2]$glycine

[0031] 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

(continued)

MePhe	L-N-Methylphenylalanine
MeNle	L-N-Methylnorleucine
MeAla	L-N-Methylalanine
MeIle	L-N-Methylisoleucine
MeVal	L-N-Methylvaline
MeLeu	L-N-Methylleucine

[0032] Particularly preferred residues for group D are:

His	L-Histidine
Phe	L-Phenylalanine
Trp	L-Tryptophan
Tyr	L-Tyrosine
Phg	L-Phenylglycine
2-Nal	L-2-Naphthylalanine
1-Nal	L-1-Naphthylalanine
4Cl-Phe	L-4-Chlorophenylalanine
3Cl-Phe	L-3-Chlorophenylalanine
2Cl-Phe	L-2-Chlorophenylalanine
$3,4Cl_2$-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
W(6-Cl)	L-6-Cl-Tryptophan

[0033] Particularly preferred residues for group E are

Arg	L-Arginine
Lys	L-Lysine
Om	L-Ornithine
Dpr	L-2,3-Diaminopropionic acid
A_2Bu	L-2,4-Diaminobutyric acid
Dbu	(S)-2,3-Diaminobutyric acid
$F(pNH_2)$	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

[0034] Particularly preferred residues for group F are

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

[0035] Particularly preferred residues for group I are

(EA)G	N-(2-Aminoethyl)glycine
(PrA)G	N-(3-Amino-n-propyl)glycine
(BA)G	N-(4-Amino-n-butyl)glycine
(PeA)G	N-(5-Amino-n-pentyl)glycine
(EGU)G	N-(2-Guanidinoethyl)glycine
(PrGU)G	N-(3-Guanidino-n-propyl)glycine
(BGU)G	N-(4-Guanidino-n-butyl)glycine
(PeGU)G	N-(5-Guanidino-n-pentyl)glycine
(PEG_3-NH_2)G	N-[$(CH_2)_3O$-$(CH_2$-$CH_2O)_2$-$(CH_2)_3$-NH_2]glycine

[0036] As mentioned earlier, the peptidic chains Z and Z^1 within the β-hairpin mimetics of the invention comprise 4 and, respectively, 6 residues or 5 and, respectively, 7 residues. The positions P^1 to P^n and $P^{1'}$ to $P^{n'}$ of each amino acid residue in the chain Z and, respectively, $\mathbf{Z^1}$ are unequivocally defined as follows: $\mathbf{P^1}$ represents the first amino acid in the chain **Z** that is coupled with its C-terminus to the N-terminus of the template and P^n represents the last amino acid in the chain **Z**; $P^{1'}$ represents the first amino acid in the chain $\mathbf{Z^1}$ that is coupled with its N-terminus to the C-terminus of the template and $P^{n'}$ represents the last amino acid in the chain $\mathbf{Z^1}$.

[0037] Each of the positions P^1 to P^n or $P^{1'}$ to $P^{n'}$ will preferably contain an amino acid residue belonging to one or two or three of the above types C, D, E, F I, or being Pro or Gly, as follows:

If n is 4 and n' is 6, the amino acid residues in positions 1 to 4 of Z and the amino acid residues in positions 1' to 6' of Z^1 are preferably:

- P1: of type D or of type E or of type F, or the residue is Pro;
- P2: of type E or of type F;
- P3: of type F, or the residue is Pro;
- P4: of type E;

- P1': of type E or of type F, or the residue is Gly;
- P2': of type D;
- P3': of type F or the residue is Pro;
- P4': of type D;
- P5': of type E, or of type F or the residue is Pro; and
- P6': of type E or of type F, or the residue is Pro; or
- P3 and P3', taken together, can form a group of type H.

If n is 5 and n' is 7, the amino acid residues in positions 1 to 5 of Z and the amino acid residues in positions 1' to 7' of Z^1 are preferably:

- P1: of type D or of type E or of type F, or the residue is Pro;
- P2: of type E or of type F;
- P3: of type F, or the residue is Pro;

- P4: of type F;
- P5: of type E

- P1': of type D or of type E or of type F, or the residue is Pro;
- P2': of type F;
- P3': of type D or the residue is Pro;
- P4': of type F;
- P5': of type D, or the residue is Pro;
- P6': of type E or of type F, or the residue is Pro; and
- P7': of type E or of type I, or the residue is Gly; or
- P2 and P2' and/or P4 and P4', taken together, can form a group of type H;

at P7' also D-isomers being possible.

If n is 4 and n' is 6, the amino acid residues in positions 1 to 4 of Z and the amino acid residues in positions 1' to 6' of Z^1 are most preferably:

- P1: Tyr, Arg;
- P2: Cit, Arg;
- P3: Cys;
- P4: Arg-NH_2;
- P1': Lys, Arg;
- P2': Tyr;
- P3': Cys;
- P4': 2-Nal;
- P5': Arg; and
- P6': Arg.

Cys at pos P3 and P3' form a disulfide bridge

If n is 5 and n' is 7, the amino acid residues in positions 1 to 5 of Z and the amino acid residues in positions 1' to 7'of Z^1 are most preferably:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg; Arg-NH_2;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': 2-Nal, Trp, F(pNH_2), W(6-Cl);
- P6': Arg; and
- P7': ^{D}Arg, Arg, Ac-Arg, iPr-Arg, (EA)G, (PrA)G, (BA)G, (EGU)G, (PrGU)G, (BGU)G.

Cys at pos 4 and pos 4' form a disulfide bridge

[0038] Particularly preferred β-peptidomimetics of the invention include those described in Examples 3, 4, 6, 8, 11, and 16.

[0039] 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), and the templates play thereby key roles.

[0040] 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**).**

[0041] The solid support is functionalized by means of a linker, i.e. a bifunctional spacer molecule which contains on

one end an anchoring group for attachment to the solid support and on the other end a selectively cleavable functional group used for the subsequent chemical transformations and cleavage procedures. For the purposes of the present invention two types of linkers are used:

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

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

[0042] 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 these procedures will have to be modified in case it is desired to synthesize one single compound of the above formula I

[0043] 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.

[0044] 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).

[0045] Both the Rink linker that releases the C-terminal carboxylic amide group under acidic conditions and the 2-chlorotrityl linker that releases the C-terminal carboxylic acid group under acidic conditions, are stable to Fmoc deprotection conditions during the peptide synthesis.

[0046] The simultaneous release of the side chain protecting groups of the peptide fragment and the release of the peptide from the resin type 1 and type 2 is performed with 95% TFA and dichloromethane and scavencers such as phenol or triisopropylsilane (Bernatowicz, S.B. et al, Tetrahedron Lett., 1989, 30, 4645-4648).

[0047] 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

(continued)

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.

[0048] The 9-fluorenylmethoxycarbonyl- (Fmoc)-protected amino acid derivatives are preferably used as the building blocks for the construction of the template-fixed β-hairpin loop mimetics of formula I. For the deprotection, i. e. cleaving off of the Fmoc group, 20% piperidine in DMF or 2% DBU/2% piperidine in DMF can be used.

[0049] N-substituted glycine derivatives (type I) used as building blocks for the construction of certain compounds of formula I are derived from 9-fluorenylmedioxycarbonyl- (Fmoc)-protected amino acid derivatives or alternatively built up in two steps from leaving group-containing glycine precursors, such as bromo, chloro or iodo acetic acid, and suitable primary amine building blocks NH_2-R^{86}. The first synthesis step consists of the attachment of the leaving group-containing acetylating agent, such as bromo acetic acid, to the resin bound intermediate through formation of the amide bond. The second reaction step - the nucleophilic displacement - is accomplished using the primary amine building blocks, wherein the residues are, if necessary, suitably protected with groups as described above for side chains of amino acids.

[0050] 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.

[0051] 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.

[0052] 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).

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] Before detaching the peptide from the resin and removing the protecting groups from the fully protected peptide, it is also possible, if desired, to cyclize the linear peptide by forming an interstrand linkage between side-chains of appropriate amino acid residues at opposite positions of the β-strand region.

[0058] 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 omithines 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. For the formation of disulfide bridges preferably a solution of 10 equivalents of iodine solution in DMF is applied for 1.5 h. The procedure is repeated for another 3h after with a fresh solution after filtering of the iodine solution.

[0059] Detachment and complete deprotection of the fully protected 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.

[0060] Alternatively the detachment and complete deprotection of the fully protected peptide from the solid support is achieved manually in glass vessels.

[0061] The fully protected peptide derivative of type I 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 3.5 hours. The resin is filtered and the cleavage solution containing the peptide is evaporated. The product is dissolved in an acid and water and extracted with isopropyl ether or other solvents which are suitable therefor. After collecting the aqueous layer and optionally oxidizing bridges of type H (Cysteine) by passing air through the aqueous layer and 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.

[0062] 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 I or into a different, pharmaceutically acceptable, salt. Any of these operations can be carried out by methods well known in the art.

[0063] The starting materials of formula H_2NR^{86} are known or can be prepared by methods which are well known in the art.

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

[0064] The β-hairpin peptidomimetics may be administered per se or may be applied as an appropriate formulations together with carriers, diluents or excipients well known in the art.

[0065] When used to treat or prevent HIV infections or cancer the β-hairpin peptidomimetics can be administered singly, as mixtures of several β-hairpin peptidomimetics, in combination with other anti-HIV agents, or antimicrobial agents or anti cancer agents, or in combination with other pharmaceutically active agents. The β-hairpin peptidomimetics can be administered per se or as pharmaceutical compositions.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation as known in the art.

[0071] 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.

[0072] 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.

[0073] For buccal administration, the composition may take the form of tablets, lozenges, etc. formulated as usual.

[0074] 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.

[0075] 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.

[0076] In addition to the formulations described previously, the β-hairpin peptidomimetics of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (e.g. subcutaneously or intramuscularly) or by intramuscular injection. For the manufacture of such depot preparations the β-hairpin peptidomimetics of the invention may be formulated with suitable polymeric or hydrophobic materials (e.g. as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble salts.

[0077] 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.

[0078] As the β-hairpin pepdidomimetics of the invention may contain charged residues, they may be included in any of the above-described formulations as such or as pharmaceutically acceptable salts. Pharmaceutically acceptable salts tend to be more soluble in aqueous and other protic solvents than are the corresponding free base forms.

[0079] 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.

[0080] For topical administration to treat or prevent 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.

[0081] For systemic administration, a therapeutically effective dose can be estimated initially from in vitro assays. For example, a dose can be formulated in animal models to achieve a circulating β-hairpin peptidomimetic concentration range that includes the IC_{50} as determined in the cell culture (i.e. the concentration of a test compound that is lethal to 50% of a cell culture). Such information can be used to more accurately determine useful doses in humans.

[0082] 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.

[0083] Dosage amount for applications as anti-HN agents may be adjusted individually to provide plasma levels of the β-hairpin peptidomimetics of the invention which are sufficient to maintain the therapeutic effect. Therapeutically effective serum levels may be achieved by administering multiple doses each day.

[0084] 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.

[0085] 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.

[0086] The anti-HIV therapy may be repeated intermittently while infections are detectable or even when they are not detectable. The therapy may be provided alone or in combination with other drugs, such as for example other anti-HIV agents or anti cancer agents, or anti inflammatory agents or other antimicrobial agents.

[0087] Normally, a therapeutically effective dose of the β-hairpin peptidomimetics described herein will provide therapeutic benefit without causing substantial toxicity.

[0088] 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.l, p.1).

[0089] 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;
DIC: diisopropylcarbodiimide;
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 to the resin

[0090] The synthesis was carried out using a ACT 90 synthesizer (Advanced Chemtec)

A) Preparation of preloaded Rink amide resin:

[0091] 11 g 1% DVB- Aminomethyl-PS (loading 1.14 mmol/g) from Rapp Polymer GmbH, Germany (H1020, no. 100/0002) was allowed to swell in CH_2Cl_2 (100 ml) for 12 h, the solvent was filtered off and the resin was suspended in DMF (100 ml) for 30 min. After filtering off DMF, a solution of 1.2 eq p-{(R,S)-α-[1-(9H-Fluoren-9-yl)-methoxyformamido]-2,4-dimethoxybenzyl}-phenoxyacetic acid (Fmoc Rink linker, Novabiochem, Switzerland), 1.2 eq HOBT and 1.2 eq. DIC in 50 ml DMF was given to the resin and shaken at 25°C for 12h. The solution was filtered of and the resin was washed with DMF (3x) and CH_2Cl_2 (3x). The resin was dried under vacuum for 12 hours.
The Fmoc-group was removed by treatment with a solution of 40% piperidine in DMF (191 ml) for 45 min at 25°C, the resin was washed DMF (1x), and the treatment was repeated. The resin was washed with DMF (1 x) and CH_2Cl_2 (1x) and dried under vacuum for 12 hours. Loading was typically 0.7-0.85 mMol/g.

[0092] 1.0 g of Rink amide resin (0.85 mMol/g, 0.85 mmol) was filled into a dried flask. The resin was suspended in CH_2Cl_2 (50 ml) and allowed to swell at room temperature under constant stirring for 60 min, the solvent was filtered off and the resin was suspended in DMF (50 ml) for 5 hours. After filtering off the solvent, the resin was treated with 5eq of the first suitably protected amino acid residue (see below), 5eq HOBT, and 5eq DIC in DMF (40 ml), the mixture was shaken at 25°C for 12 hours. The resin then was washed in the following order with CH_2Cl_2 (1x), DMF (1x), CH_2Cl_2 (1x) and dried under vacuum for 5 hours.

[0093] Loading was typically 0.4-0.55 mMol/g.

[0094] The following preloaded resin was prepared: Fmoc-Arg(Pbf)-NH-Rink amide resin.

B) Preparation of preloaded chlorotrityl resin

[0095] 0.5 g of 2-chlorotritylchloride resin (Barlos et al. Tetrahedron Lett. 1989, 30, 3943-3946) (0.83 mMol/g, 0.415 mmol) was filled into a dried flask. The resin was suspended in CH_2Cl_2 (2.5 ml) and allowed to swell at room temperature under constant stirring for 30 min. The resin was treated with 0.415 mMol (1eq) of the first suitably protected amino acid residue (see below) and 284 μl (4eq) of diisopropylethylamine (DIEA) in CH_2Cl_2 (2.5 ml), the mixture was shaken at 25°C for 4 hours. The resin colour changed to purple and the solution remained yellowish. The resin was shaken (CH_2Cl_2 /MeOH/DIEA : 17/2/1), 30 ml for 30 min; then washed in the following order with CH_2Cl_2 (1x), DMF (1x), CH_2Cl_2 (1x), MeOH (lx), CH_2Cl_2(1x), MeOH (1x), CH_2Cl_2 (2x), Et_2O (2x) and dried under vacuum for 6 hours.
Loading was typically 0.6-0.7 mMol/g.

[0096] The following preloaded resin was prepared: Fmoc-Arg(Pbf)O-chlorotritylresin.

Synthesis of the fully protected peptide fragment

[0097] 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	20 % piperidine/DMF	1 x 5 min.
4	DMF, wash	5 x 2 min.
5	5 equiv. Fmoc amino acid/DMF/NMP 2/1	
	+ 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.		

Formation of disulfide bridge (interstrand linkage)

[0098] 0.05 mmol of peptide-carrying resin was swelled in 3 mL of dry DCM for 1 h and after filtering off the DCM, with dry DMF (3 mL) for overnight. Then 10 equivalents of iodine solution in DMF (6 mL) was added to the reactor and stirred for 1.5 h. The resin was filtered and the fresh solution of iodine (10 equivalents) in DMF (6 mL) was added and stirred for another 3 h. The resin was filtered and washed thoroughly several times with DMF and DCM.

Cleavage and deprotection of the fully protected peptide fragment

[0099] Cleavage from the resin and full deprotection of the peptide were done by 7.5 mL of the cleavage mixture TFA: TIS:H_2O (95:2.5:2.5) for 3.5 h. The resin was filtered and the cleaved peptide was collected in a tube and evaporated to dryness under vaccum. The crude peptide was dissolved in 20% AcOH in water (7 mL) and extracted with isopropyl ether (4 mL) for three times. The aqueous layer was collected and evaporated to dryness. For final oxidation of the cysteine (for formation of disulfide bridge), air was passed through the diluted solution of crude peptide in H_2O (6 mL) for 12 h.

Purification of the end-product:

[0100] The water phase was dried under vacuum and then the product purified by preparative reverse phase HPLC.
[0101] The products were analysed by ESI-MS and after lyophilisation the products were obtained as a white powder. The analytical data comprising HPLC retention times and ESI-MS are shown in table 1 and table 2.
[0102] Analytical HPLC retention times (RT, in minutes) were determined using a VYDAC 218MS5215 column with the following solvents A (H_2O + 0.02% TFA) and B (CH_3CN) and the gradient: 0 min: 92%A, 8%B; 8 min: 62%A 38%B; 9-12 min: 0% A, 100%B.
[0103] **Examples 1** and **2** (n = 4, n' = 6) are shown in *table 1*. The peptides were synthesized starting with the amino acid Arg which was grafted to the resin. Starting resin was Fmoc-Arg(Pbf)-Rink-amide resin, which was prepared as described above. The linear peptides were synthesized on solid support according to procedure described above in the following sequence: Resin-P4-P3-P2-P1-^{L}Pro-^{D}Pro-P1'-P2'-P3'-P4'-P5'-P6; disulfide bridge formation, cleavage from the resin, deprotection and purification were effected as indicated.
HPLC-retention times (minutes) were determined using the *gradient* described above.
[0104] **Example 3 and 6-15** (n = 5, n' = 7) are shown in *table* 2. The peptides were synthesized starting with the amino acid Arg which was grafted to the resin. Starting resin was Fmoc-Arg(Pbf)-Rink-amide resin, which was prepared as described above. The linear peptides were synthesized on solid support according to procedure described above in the following sequence: Resin-P5-P4-P3-P2-P1-^{L}Pro-^{D}Pro-P1'-P2'-P3'-P4'-P5'-P6'-P7'; disulfide bridge formation, cleavage from the resin, deprotection and purification were effected as indicated. HPLC-retention times (minutes) were determined using the *gradient* described above:

Ex. 3 (4.27), **Ex. 6** (4.13), **Ex.** 7 (3.68), **Ex. 8** (2.28), **Ex. 9** (4.13), **Ex. 10** (5.96), **Ex. 11** (5.76), **Ex. 12** (5.82), **Ex. 13** (5.90), **Ex. 14** (5.90), **Ex. 15** (5.84).

[0105] **Example 4** (n = 5, n' = 7) is shown in *table* 2. The peptide was synthesized starting with the amino acid Arg

which was grafted to the resin. Starting resin was Fmoc-Arg(Pbf)-Rink-amide resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-P5-P4-P3-P2-P1-^{L}Pro-^{D}Pro-P1'-P2'-P3-P4'-P5'-P6'-P7', and the disulfide bridge was formed. The resin was then swelled in dry DCM for 0.5 hrs. DCM was filtered off and 5 mL of dry DCM was added to the resin. 0.5 mL (2.92 mmol) of DIPEA and 0.125 mL (1.32 mmol) of acetic anhydride were added to the resin and stirred for 4 hrs. The resin was filtered and washed thoroughly with DCM, DMF, DCM, MeOH, Et_2O and dried in vaccum. The peptide was cleaved from the resin, deprotected and purified as indicated.

HPLC-retention time was determined using the *gradient* described above: 4.33 minutes.

[0106] Example 5 (n = 5, n' = 7) is shown in *table 2*. The peptide was synthesized starting with the amino acid Arg which was grafted to the resin. Starting resin was Fmoc-Arg(Pbf)-Rink-amide resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-P5-P4-P3-P2-P1-^{L}pro-^{D}pro-P1'-P2'-P3'-P4'-P5'-P6'-P7' and the disulfide bridge was formed. 2.5 mL of dry THF and 200 μL of acetone was added to the reactor followed by addition of 2.5 mL of 50:50 (H_2O: Acetic acid) and stirred for 4 hrs. The solution of $NaCNBH_3$ (120 mg, 1.90 mmol) in THF (2 mL) was added to the reactor and stirred for 4 hrs. Then the solvent was filtered and washed with DCM, DMF, DCM, MeOH, Et_2O and dried in vaccum. The peptide was cleaved from the resin, deprotected and purified as indicated.

HPLC-retention times was determined using the *gradient* described above: 4.37 minutes.

[0107] Example 16 (n = 5, n'= 7) is shown in *table* 2. The peptide was synthesized starting with the amino acid Arg which was grafted to the resin. Starting resin was Fmoc-Arg(Pbf)-chlorctrityl resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-P5-P4-P3-P2-P1- ^{L}Pro- ^{D}pro -P1'-P2'-P3'-P4'-P5'-P6'-P7'; disulfide bridge formation, cleavage from the resin, deprotection and purification were effected as indicated.

HPLC-retention time was determined using the *gradient* described above: 4.35 minutes.

[0108] Example 17 (n = 5, n' = 7) is shown in *table 2*. The peptide was synthesized starting with the amino acid Arg which was grafted to the resin. Starting resin was Fmoc-Arg(Pbf)-Rink-amide resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-P5-P4-P3-P2-P1-^{D}Pro-^{L}Pro-P1'-P2'-P3'-P4'-P5'-P6'-P7'; disulfide bridge formation, cleavage from the resin, deprotection and purification were effected as indicated.

HPLC-retention time was determined using the *gradient* described above: 4.13, 4.40* minutes.

* The MS is showing the correct mass.

[0109] Example 18 (n = 5, n' = 7) is shown in *table* 2. The peptide was synthesized starting with the amino acid Arg which was grafted to the resin. Starting resin was Fmoc-Arg(Pbf)-Rink-amide resin, which was prepared as described above. The linear peptide was synthesized on solid support according to procedure described above in the following sequence: Resin-P5-P4-P3-P2-P1-^{L}Pro-^{L}Pro-P1'-P2'-P3'-P4'-P5'-P6'-P7'; disulfide bridge formation, cleavage from the resin, deprotection and purification were effected as indicated.

HPLC-retention time was determined using the *gradient* described above: 4.08 minutes.

Table 1: Examples 1-6, n = 4, n'= 6

Example	Sequ.ID	P6'	P5'	P4'	P3'	P2'	P1'	Template	P1	P2	P3	P4	RT	Purity%[a)]	[M+ H]/2
1	SEQ ID NO 4	Arg	Arg	2-Nal	Cys	Tyr	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cys	Arg-NH_2	4.62	100	845.9
2	SEQ ID NO:5	Arg	Arg	2-Nal	Cys	Tyr	Arg	^{D}Pro^{L}Pro	Tyr	Arg	Cys	Arg-NH_2	4.83	98	860.0

a) %-purility of compounds after prep. HPLC.
cysteines at position P3' and P3 are linked by a disulfide bridge

Table 2: Examples 7-25, n = 6, n'= 7

Example	Sequ.ID	P7'	P6'	P5'	P4'	P3'	P2'	P1'	Template	P1	P2	P3	P4	P5	Purity%[a)]	[M+H]/2
3	SEQ ID NO:7	H-Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	88	1003.6
4	SEQ ID NO:8	AcArg[b]	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	100	1023.8
5	SEQ ID NO 9	iPrArg[c]	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	95	1025.1
6	SEQ ID NO:10	H-^{D}Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	98	1003.6
7	SEQ ID NO:11	H-Arg	Arg	Trp	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	100	997.4
8	SEQ ID NO:12	H-Arg	Arg	F(pNH_2)	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	100	985.3
9	SEQ ID NO:13	H-Arg	Arg	W(6-Cl)	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	100	1015.3
10	SEQ ID NO 14	H-(EA)G	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	84	1010.3
11	SEQ ID NO 15	H-(PrA)G	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	100	982.0
12	SEQ ID NO:16	H-(BA)G	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	89	989
13	SEQ ID NO:17	H-(EGU)G	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	96	1003.0
14	SEQ ID NO:18	H-(PrGU)G	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	99	1009.9
15	SEQ ID NO:19	H-(BGU)G	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	86	989.0
16	SEQ ID NO:20	H-Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-OH	100	1004.2
17	SEQ ID NO:23	H-Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{L}Pro^{D}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	100	1002.9
18	SEQ ID NO:24	H-Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{L}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2	100	1002.9

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

b) Ac: Acetyl

c) iPr: Isopropyl

cysteines at position P4' and P4 are linked by a disulfide bridge

2. Biological methods

2.1. Preparation of the peptides.

[0110] Lyophilized peptides were weighed on a Microbalance (Mettler MT5) and dissolved in sterile water to a final concentration of 1 mM unless stated otherwise. Stock solutions were kept at + 4°C, light protected.

2.2. Ca^{2+}- assay: CXCR4-antagonizing activity of the peptides.

[0111] 3-4 Mio CXCR4 transfected pre-B cells [see references 1,2 and 3, below] per measurement were resuspended in 200 μl MSB (20 mM 4-(2-Hyddroxyethyl)-piperazin-1-ethansulfonic acid (HEPES), 136 mM NaCl, 4.8 mM KCl and 1 mM $CaCl_2$) containing 5 mM D-Glucose and were loaded with 0.75 μl of 1 mM Fura-2-acetoxymethylester for 17 minutes at 37°C. The cells were washed free from Fura-2-AM with a platelet centrifuge and resuspended in 800 μl MSB containing 5 mM D-Glucose. The peptides to be administered were diluted to a 100 fold end concentration in MSB/0.2 % PPL, and 8 μl were injected. $[Ca^{2+}]_i$-dependent fluorescence change in response to single or sequential stimulation with the peptide was recorded with a fluorimeter at an excitation wavelength of 340 nM and an end emission wavelength of 510 nM [see ref. 4, below]. Measurements were done under continuous stirring at 37°C. The signal intension was calibrated with 3 mM $CaCl_2$/I mM Ionomycin (maximal fura-2-acetoxymethylester saturation) and 10 μM $MnCl_2$ (minimal Fura-2-acetoxymethylester saturation) and $[Ca^{2+}]_i$-changes are presented in % fura-2-acetoxymethylester saturation. The rate of $[Ca^{2+}]_i$-changes was calculated on the basis of the initial $[Ca^{2+}]_i$-changes and plotted in dependence of chemokine concentration to obtain a sigmoidal curve and to determine the IC_{50} values.
MSB: 20 mM HEPES, 136 mM NaCl, 4.8 mM KCl, 1 mM $CaCl_2$●$2H_2O$, pH 7.4; Osmolarity: 310 mOsm adjusted with NaOH or HCl, adjusted with dH2O or PBS.
MSB plus: 5 mM D-glucose in MSB (50 mg/50mL).
Fura 2-acetoxymethylester: 1 mM stock solution in dimethylsulfoxide.

2.3. FIGS-Assay™

[0112] The assay was performed according to ref. 5, below. Stock dilutions of the peptides (10 mM) were prepared by dissolving in 10 mM Tris-HCl at room temperature. Stock solutions were kept at + 4°C, light protected. Working dilutions were prepared extemporaneously by serial dilution in Phosphate Buffered Saline (PBS) and added in a final volume of 10μL directly to the cell cultures. After 48 hours of co-cultivation the cultures were rinsed with PBS and then exposed to glutaraldehyde/ formaldehyde (0.2 % / 2 %) in PBS for five minutes. For photometric quantification the fixed cultures were subsequently incubated with ortho-nitrophenyl-galactopyranoside (ONPG) as a β-galactosidase substrate, which was enzymatically converted into the chromophore ortho-nitrophenol (ONP). The read out is directly obtained by measuring optical density of wells at 405 nm in an iEMS 96well-plate reader.

2.4. Cytotoxicity assay

[0113] The cytotoxicity of the peptides to HELA cells (Acc57) and COS-7 cells (CRL-1651) was determined using the MTT reduction assay [see ref. 6 and 7, below]. Briefly the method was as follows: HELA cells and COS-7 cells were seeded at $7.0 \cdot 10^3$ and, respectively, $4.5 \cdot 10^3$ cells per well and grown in 96-well microtiter plates for 24 hours at 37°C at 5% CO_2. At this point, time zero (Tz) was determined by MTT reduction (see below).The supernatant of the remaining wells was discarded and fresh medium and the peptides in serial dilutions of 12.5, 25 and 50 μM were pipeted into the wells. Each peptide concentration was assayed in triplicate. Incubation of the cells was continued for 48 hours at 37°C at 5% CO_2. Wells were then washed once with PBS and subsequently 100 μl MTT reagent (0.5 mg/mL in medium RPMI1640 and, respectively, DMEM) was added to the wells. This was incubated at 37°C for 2 hours and subsequently the medium was aspirated and 100 μl isopropanol was added to each well. The absorbance at 595 nm of the solubilized product was measured (OD_{595}peptide). For each concentration averages were calculated from triplicates. The percentage of growth was calculated as follows: (OD_{595}peptide-OD_{595}Tz-OD_{595}Empty well) / (OD_{595}Tz-OD_{595}Empty well) x 100% and was plotted for each peptide concentration.
The LC 50 values (Lethal Concentration, defined as the concentration that kills 50% of the cells) were determined for each peptide by using the trend line function of EXCEL (Microsoft Office 2000) for the concentrations (50, 25, 12.5 and 0 μM), the corresponding growth percentages and the value -50, (=TREND(C50:C0,%50:%0,-50))

2.5. Cell culture

[0114] 'CCR5' cells were cultured in DMEM medium with 4500 mg/mL glucose, 10 % fetal bovine serum (FBS),

supplemented with 50 U/ml Penicillin and 50 μg/mL Streptomycin (Pen/Strept.). Hut/4-3 cells were maintained in RPMI medium, 10% FBS, supplemented with Pen/Strept. and 10 mM HEPES. HELA cells and CCRF-CEM cells were maintained in RPMI1640 plus 5% FBS, Pen/Strept and 2 mM L-Glutamine. Cos-7 cells were grown in DMEM medium with 4500 mg/mL glucose supplemented with 10% FCS, Pen/Strept. and 2 mM L-Glutamine. All cell lines were grown at 37°C at 5% CO_2. Cell media, media supplements, PBS-buffer, HEPES, Pen/Strept., L-Glutamine and sera were purchased from Gibco (Pailsey, UK). All fine chemicals came from Merck (Darmstadt, Germany).

2.6. Hemolysis

[0115] The peptides were tested for their hemolytic activity against human red blood cells (hRBC). Fresh hRBC were washed three times with phosphate buffered saline (PBS) by centrifugation for 10 min at 2000 x g. Peptides at a concentration of 100 μM were incubated with 20% v/v hRBC for 1 hour at 37°C. The final erythrocyte concentration was approximately $0.9x10^9$ cells per mL. A value of 0% resp. 100% cell lysis was determined by incubation of the hRBC in the presence of PBS alone and respectively 0.1% Triton X-100 in H_2O. The samples were centrifuged 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% lyses value ($OD_{540}H_20$) gave an OD_{540} of approximately 1.3-1.8. Percent hemolysis was calculated as follows: (OD_{540}peptide/$OD_{540}H_20$) x 100%.

2.7. Chemotactic Assay (Cell migration assay)

[0116] The chemotactic response of CCRF-CEM cells to a gradient of stromal cell-derived factor 1α (SDF-1) was measured using disposable assay plates from Neuroprobe (5 μ pore size) (Gaithersburg, MD), according to the manufacturer's directions and references therein [especially ref. 8, below]. Briefly, one 175 cm^2 flask was washed once with Dubecco's phosphate buffered saline (DPBS), and trypsinized for 10 minutes or until cells had lifted. The trypsin was neutralized by the addition of fresh medium containing serum and the cells were pelleted, washed once in DPBS, and resuspended at 1-0.5 X 10^7 cells/ml in RPMI + 0.5% bovine serum albumin (BSA). 45μl of cell suspension were mixed with 5 μl of 10-fold concentrated PEM peptide diluted in the same assay medium. 35 μl of this mixture were applied to the top of the assay filter. The cells were allowed to migrate (at 37°) into the bottom chamber of the assay plate containing 1 nM SDF-1. After 4 hours, the filter was removed and MTT was added to the migrated cells to a final concentration of 0.5 mg/ml, and incubated for a further 4 hours. After labeling with MTT, all medium was removed and 100 μl of isopropanol + 10 mM HCl were added to the cells. The optical absorbance at 595 nm (ABS_{595}) was read using a Tecan Genios plate reader with Magellan software. The number of cells migrated was determined by comparing ABS_{595} values against a standard curve generated with a known number of cells in the assay plate and were plotted against SDF-I concentration to obtain a sigmoidal curve and to determine the IC_{50} values. The values for IC50 were determined using the Trendline function in Microsoft Excel by fitting a logarithmic curve to the averaged datapoints.

2.7. Results

[0117] The results of the experiments described above are indicated in Table 3 hereinbelow.

Ex	IC_{50} (nM) Ca^{2+} assay	FIGS™		Cytotoxicity LC_{50}	Hemolysis at 100 μM	IC_{50} (μM) Cell migration assay
		% inhibition at 200 nM	St.dev. at 200 nM			
1	848.3	26.0	5.6	> 300	0.3	n.d.
2	131.5	16.4	3.5	67	0.7	n.d.
3	n.d.	n.d.	n.d.	56	0.3	0.55
4	13.9	90.6	3.4	226	0.1	5.0
6	21.5	82.0	9.4	118	0.6	0.55
8	13.9	71.3	7.0	226	0.1	5.0

(continued)

Ex	IC_{50} (nM) Ca^{2+} assay	FIGS™		Cytotoxicity LC_{50}	Hemolysis at 100 μM	IC_{50} (μM) Cell migration assay
		% inhibition at 200 nM	St.dev. at 200 nM			
11 12	n.d.	n.d.	n.d.	n.d.	n.d.	0.57
	n.d.	n.d.	n.d.	n.d.	n.d.	1.04
14	n.d.	n.d.	n.d.	n.d.	n.d.	0.65
15	n.d.	n.d.	n.d.	n.d.	n.d.	0.85
16	15.5	At 300 nM: 100	n.d.	138	0.2	n.d.
24	100	17.1	8.9	67	1.1	n.d
n.d.: not determined						

References

[0118]

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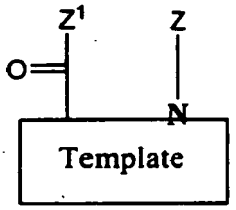
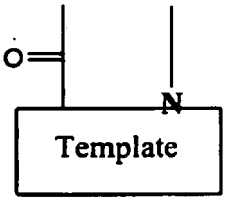
Claims

1. Compounds of the general formula



(I)

wherein



is a group of one of the formulae

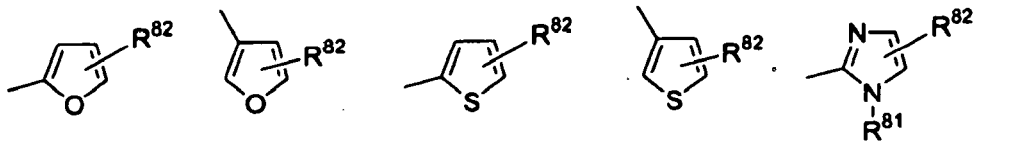
^{D}Pro-^{L}Pro and ^{L}Pro-^{D}Pro

R^{20} isH; alkyl; alkenyl; or aryl-lower alkyl;
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} isH; lower alkyl; aryl, or aryl-lower alkyl;
R^{33} and R^{34} 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^{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^{50} is H; lower alkyl; or aryl-lower alkyl;
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: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-; $-(CH_2)_2S(CH_2)_2$-; or $-(CH_2)_2NR^{57}(CH_2)_2$-;
R^{64} is H; lower alkyl; lower alkenyl; aryl; heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl;
$-(CH_2)_pCHR^{61})_sOR^{65}$; $-(CH_2)_p(CHR^{61})_sSR^{66}$; 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
$-CONR^{58}R^{59}$;

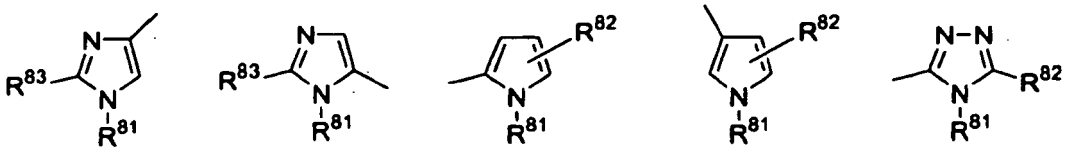
Z and Z^1 are chains of n and, respectively, n' α-amino acid residues whereby either n is 4 and n' is 6 or n is 5 and n' is 7, the positions of said amino acid residues in said chain Z being counted starting from the N-terminal amino acid and the positions of said amino acid residues in said chain Z^1 being counted starting from the C-terminal amino

acid, whereby these amino acid residues are, depending on their position in the chains, Gly, or Pro, or of one of the types

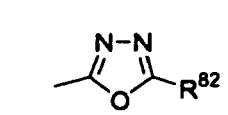
C: -$NR^{20}CH(R^{72})CO$-;
D: -$NR^{20}CH(R^{73})CO$-;
E: -$NR^{20}CH(R^{74})CO$-;
F: -$NR^{20}CH(R^{84})CO$-; and
H: -NR^{20}-CH(CO-)-$(CH_2)_{4\text{-}7}$-CH(CO-)-NR^{20}-;
-NR^{20}-CH(CO-)-$(CH_2)_pSS(CH_2)_p$-CH(CO-)-NR^{20}-;
-NR^{20}-CH(CO-)-(-$(CH_2)_pNR^{20}CO(CH_2)_p$-CH(CO-)-$NR^{20}$-;
-NR^{20}-CH(CO-)-(-$(CH_2)_pNR^{20}CONR^{20}(CH_2)_p$-CH(CO-)-$NR^{20}$-; and
I: -$NR^{86}CH_2CO$-;
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 -$(CH_2)_pNR^{78}R^{79}$; -$(CH_2)_pNR^{77}R^{80}$; -$(CH_2)_pC(=NR^{80})NR^{78}R^{79}$; -$(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;
-$(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; -$(CH_2)_pNR^{80}C(=NR^{80})NR^{78}R^{79}$;
-$(CH_2)_pN=C(NR^{78}R^{80})NR^{79}R^{80}$-$(CH_2)_pC_6H_4NR^{78}R^{79}$; -$(CH_2)_pC_6H_4NR^{77}R^{80}$;
-$(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; -$(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;
-$(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$; -$(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$;
-$(CH_2)_pC_6H_4N=C(NR^{79}R^{80})NR^{78}R^{80}$; -$(CH_2)_rO(CH_2)_mNR^{78}R^{79}$; -$(CH_2)_rO(CH_2)_mNR^{77}R^{80}$;
-$(CH_2)_rO(CH_2)_pC(=NR^{80})NR^{78}R^{79}$; -$(CH_2)_rO(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;
-$(CH_2)_rO(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; -$(CH_2)_rO(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$;
-$(CH_2)_rO(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$; -$(CH_2)_rO(CH_2)_pC_6H_4CNR^{78}R^{79}$;
-$(CH_2)_rO(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; -$(CH_2)_r(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;
-$(CH_2)_rO(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
-$(CH_2)_rO(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; -$(CH_2)_rS(CH_2)_mNR^{78}R^{79}$;
-$(CH_2)_rS(CH_2)_mNR^{77}R^{80}$;-$(CH_2)_rS(CH_2)_pC(=NR^{80})NR^{78}R^{79}$;
-$(CH_2)_rS(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$; -$(CH_2)_rS(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$;
-$(CH_2)_rS(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$; -$(CH_2)_rS(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$;
-$(CH_2)_rS(CH_2)_pC_6H_4CNF^{78}R^{79}$; -$(CH_2)_rS(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$;
-$(CH_2)_rS(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$; -$(CH_2)_rS(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
-$(CH_2)_rS(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; -$(CH_2)_pNR^{80}COR^{64}$; -$(CH_2)_pNR^{80}COR^{77}$;
-$(CH_2)_pNR^{80}CONR^{78}R^{79}$; 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^{77} is R^{87}; or a heteroaryl group of one of the formulae



H1 H2 H3 H4 H5



H6 H7 H8 H9 H10



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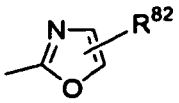

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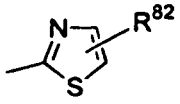

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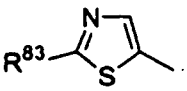

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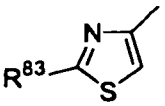

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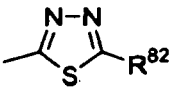

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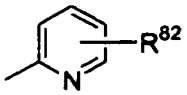

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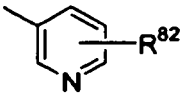

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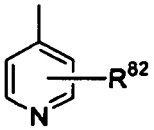

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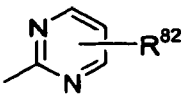

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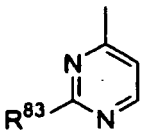

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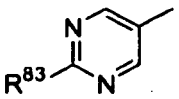

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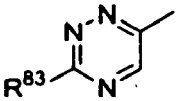

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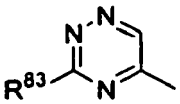

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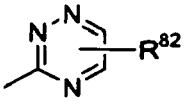

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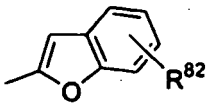

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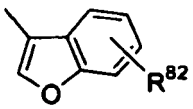

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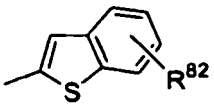

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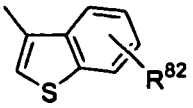

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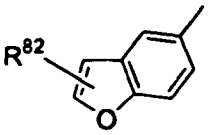

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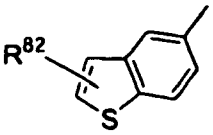

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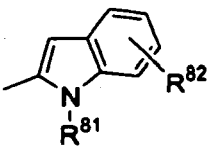

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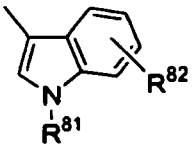

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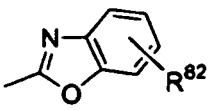

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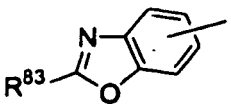

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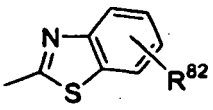

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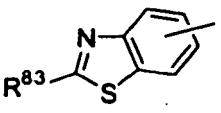

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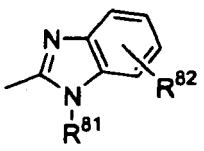

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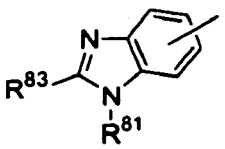

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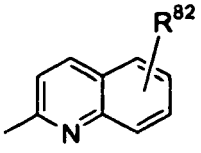

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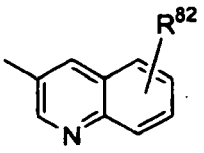

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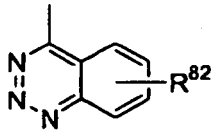

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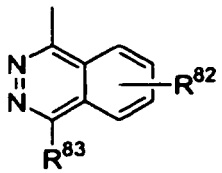

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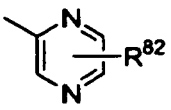

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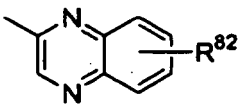

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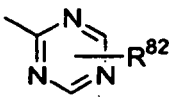

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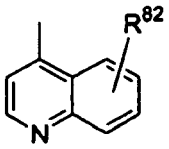

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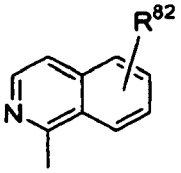

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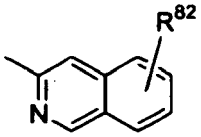

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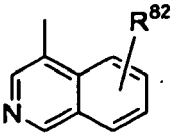

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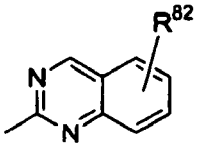

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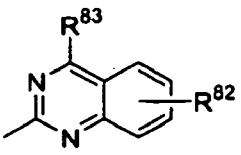

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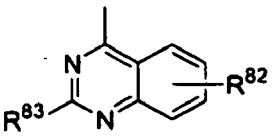
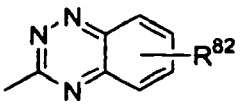


H48



H49

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 $-(CH_2)_pCONR^{78}R^{79}$; $-(CH_2)_pNR^{80}CONR^{78}R^{79}$; $-(CH_2)_pC_6H_4CONR^{78}R^{79}$; or $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;
R^{85} is lower alkyl; or lower alkenyl;
R^{86} is R^{74}; $-[(CH_2)_u-X]_t-(CH_2)_vNR^{78}R^{79}$; $-[(CH_2)_u-X]_t-(CH_2)_v-C(=NR^{80})NR^{78}R^{79}$; X is -O-, $-NR^{20}-$, -S-, -OCOO-, u is 1-3, t is 1-6, v is 1-3;
R^{87} is is phenyl, p-hydrxyphenyl, 2-naphthyl, 1-naphthyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, 3-fluorophenyl, 2-fluorophenyl, p-benzyloxyphenyl, p-biphenyl or p-benzoylphenyl.

with the proviso that in said chains Z and Z^1 of n and, respectively, n' α-amino acid residues

- if n is 4 and n' is 6, the amino acid residues in positions 1 to 4 of Z and in positions 1' to 6' of Z^1 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;
  - P3: of type F, or the residue is Pro;
  - P4: of type E;
  - P1': of type C or of type D or of type E or of type F, or the residue is Gly;
  - P2': of type D or of type C;
  - P3': of type F or the residue is Pro;
  - P4': of type D or of type C;
  - P5': of type E, or of type F or the residue is Pro; and
  - P6': of type E or of type F, or the residue is Pro; or
  - P3 and P3', taken together, can form a group of type H;

and

- if n is 5 and n' is 7, the amino acid residues in positions 1 to 5 of Z and in positions 1' to 7' of Z^1 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;
  - P3: of type F, or the residue is Pro;
  - P4: of type F;
  - P5: of type E
  - P 1': of type C or of type D or of type E or of type F, or the residue is Pro;
  - P2': of type F;
  - P3': of type D or the residue is Pro;
  - P4': of type E or of type F;
  - P5': of type D, or the residue is Pro;
  - P6': of type E or of type F, or the residue is Pro; and
  - P7': of type E or of type I, or the residue is Gly; or
  - P2 and P2' and/or P4 and P4', taken together, can form a group of type H;

at P7' also D-isomers being possible,

and pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1 wherein n is 4, n' is 6 and the α-amino acid residues in positions 1 to 4 of the chain Z and 1'-6' in chain Z^1 are:

- P1: of type D or of type E or of type F, or the residue is Pro;
- P2: of type E or of type F;
- P3: of type F, or the residue is Pro;
- P4: of type E;
- P1': of type E or of type F, or the residue is Gly;
- P2': of type D;
- P3': of type F or the residue is Pro;
- P4': of type D;
- P5': of type E, or of type F or the residue is Pro; and
- P6': of type E or of type F, or the residue is Pro; or
- P3 and P3', taken together, can form a group of type H

3. Compounds according to claim 2 wherein n is 5, n' is 7 and the α-amino acid residues in positions 1 to 5 of the chain Z and 1'-7' in chain Z^1 are:

- P1: of type D or of type E or of type F, or the residue is Pro;
- P2: of type E or of type F;
- P3: of type F, or the residue is Pro;

- P4: of type F;
- P5: of type E
- P1': of type D or of type E or of type F, or the residue is Pro;
- P2': of type F;
- P3': of type D or the residue is Pro;
- P4': of type F;
- P5': of type D, or the residue is Pro;
- P6': of type E or of type F, or the residue is Pro; and
- P7': of type E or of type I, or the residue is Gly; or
- P2 and P2' and/or P4 and P4', taken together, can form a group of type H;

at P7' also D-isomers being possible.

4. Compounds according to claim 2 wherein the α-amino acid residues in positions 1 to 4 of the chain Z and the α-amino acid residues in positions 1' to 6' chain Z^1 are:

- P1: Tyr, or Arg;
- P2: Cit, or Arg;
- P3: Cys;
- P4: Arg-NH_2;
- P1': Lys, or Arg;
- P2': Tyr;
- P3': Cys;
- P4': 2-Nal;
- P5': Arg; and
- P6': Arg.
- Cys at pos P3 and P3' form a disulfide bridge

5. Compounds according to claim 3 wherein the α-amino acid residues in positions 1 to 5 of the chain Z and the α-amino acid residues in positions 1' to 7' chain Z^1 are:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg, or Arg-NH_2;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': 2-Nal, Trp, F(pNH_2), or W(6-Cl);
- P6': Arg; and
- P7': ^{D}Arg, Arg, Ac-Arg, iPr-Arg, (EA)G, (PrA)G, (BA)G, (EGU)G,
- (PrGU)G, or (BGU)G.
- Cys at pos P4 and P4' form a disulfide bridge

6. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro, n is 5, n' is 7 and the amino acid residues in positions 1 to 5 of the chain Z and the amino acid residues in positions 1' to 7' chain Z^1 are:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg-NH_2;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;

- P5': 2-Nal;
- P6': Arg; and
- P7': Arg.

Cys at position P4' and P4 form a disulfide bridge

7. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro, n is 5, n' is 7 and the amino acid residues in positions 1 to 5 of the chain Z and the amino acid residues in positions 1' to 7' chain Z^1 are:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg-NH_2;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': 2-Nal;
- P6': Arg; and
- P7': Ac-Arg.

Cys at position P4' and P4 form a disulfide bridge

8. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro, n is 5, n' is 7 and the amino acid residues in positions 1 to 5 of the chain Z and the amino acid residues in positions 1' to 7' chain Z^1 are:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg-NH_2;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': 2-Nal
- P6': Arg; and
- P7': ^{D}Arg.

Cys at position P4' and P4 form a disulfide bridge

9. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro, n is 5, n' is 7 and the amino acid residues in positions 1 to 5 of the chain Z and the amino acid residues in positions 1' to 7' chain Z^1 are:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg-NH_2;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': Phe(pNH_2);
- P6': Arg; and
- P7': Arg.

Cys at position P4' and P4 form a disulfide bridge

10. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro, n is 5, n' is 7 and the amino acid residues in positions 1 to 5 of the chain Z and the amino acid residues in positions 1' to 7' chain Z^1 are:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg-NH_2;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': 2-Nal;
- P6': Arg; and
- P7': (PrA)G.

Cys at position P4' and P4 form a disulfide bridge

11. A compound of formula I according to claim 1 wherein the template is ^{D}Pro-^{L}Pro, n is 5, n' is 7 and the amino acid residues in positions 1 to 5 of the chain Z and the amino acid residues in positions 1' to 7' chain Z^1 are:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': 2-Nal;
- P6': Arg; and

P7': Arg.
Cys at position P4' and P4 form a disulfide bridge

12. Enantiomers of the compounds of formulae I as defined in claim 1.

13. Compounds according to any one of claims 1 to 12 for use as therapeutically active substances.

14. Compounds according the claims 13 for use as CXCR4 antagonists.

15. A pharmaceutical composition containing a compound according to any one of claims 1 to 12 and a pharmaceutically inert carrier.

16. Compositions according to claim 15 in a form suitable for oral, topical, transdermal, injection, buccal, transmucosal, pulmonary or inhalation administration.

17. Compositions according to claim 15 or 16 in form of tablets, dragees, capsules, solutions, liquids, gels, plaster, creams, ointments, syrup, slurries, suspensions, spray, nebuliser or suppositories.

18. The use of compounds according to any one of claims 1 to 12 for the manufacture of a medicament for treating or preventing of HIV infections, or for treatment of cancer or for treatment of inflammatory disorders.

19. A process for the manufacture of compounds according to any one of claims 1-11 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 4 of Z if n is 4 or in position 5 of Z if n is 5, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
(b) removing the N-protecting group from the product thus obtained;
(c) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in Z of the desired end-product is one position nearer the N-terminal amino acid residue, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
(d) removing the N-protecting group from the product thus obtained;
(e) repeating steps (c) and (d) until the N-terminal amino acid residue of Z has been introduced;
(f) coupling the product thus obtained

(fa) with an appropriately N-protected derivative of ^{D}Pro or ^{L}Pro;
(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 ^{L}Pro and, respectively, ^{D}Pro;

(g) removing the N-protecting group from the product obtained in step (fc) ;
(h) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position 1 of Z^1, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
(i) removing the N-protecting group from the product thus obtained;
(j) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position farther away from position 1 of Z^1, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
(k) removing the N-protecting group from the product thus obtained;
(l) repeating steps (j) and (k) until all amino acid residues of Z^1 have been introduced;
(m) if desired, selectively deprotecting one or several protected functional group(s) present in the molecule and appropriately substituting the reactive group(s) thus liberated;
(n) if desired, forming one or two interstrand linkage(s) between side-chains of appropriate amino acid residues at opposite positions of the β-strand region;
(o) detaching the product thus obtained from the solid support and 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
(p) 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.

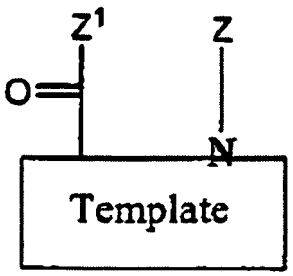
20. A process according to claim 19 but wherein an amino acid residue of type I is introduced by coupling with a leaving group-containing acetylating agent, followed by nucleophilic displacement with an amine of the formula H_2NR^{86} which, if necessary, is appropriately protected.

21. A process according to claim 20 wherein said leaving group-containing acetylating agent is bromo, chloro or iodo acetic acid.

22. A modification of the process according to any one of claims 19 to 21 for the manufacture of compounds according to claim 12 in which enantiomers of all chiral starting materials are used.

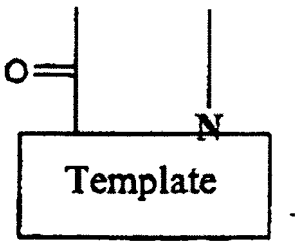
Patentansprüche

1. Verbindungen der allgemeinen Formel



(I)

worin



eine Gruppe bedeutet der Formel ^{D}Pro-^{L}Pro und ^{L}Pro-^{D}Pro

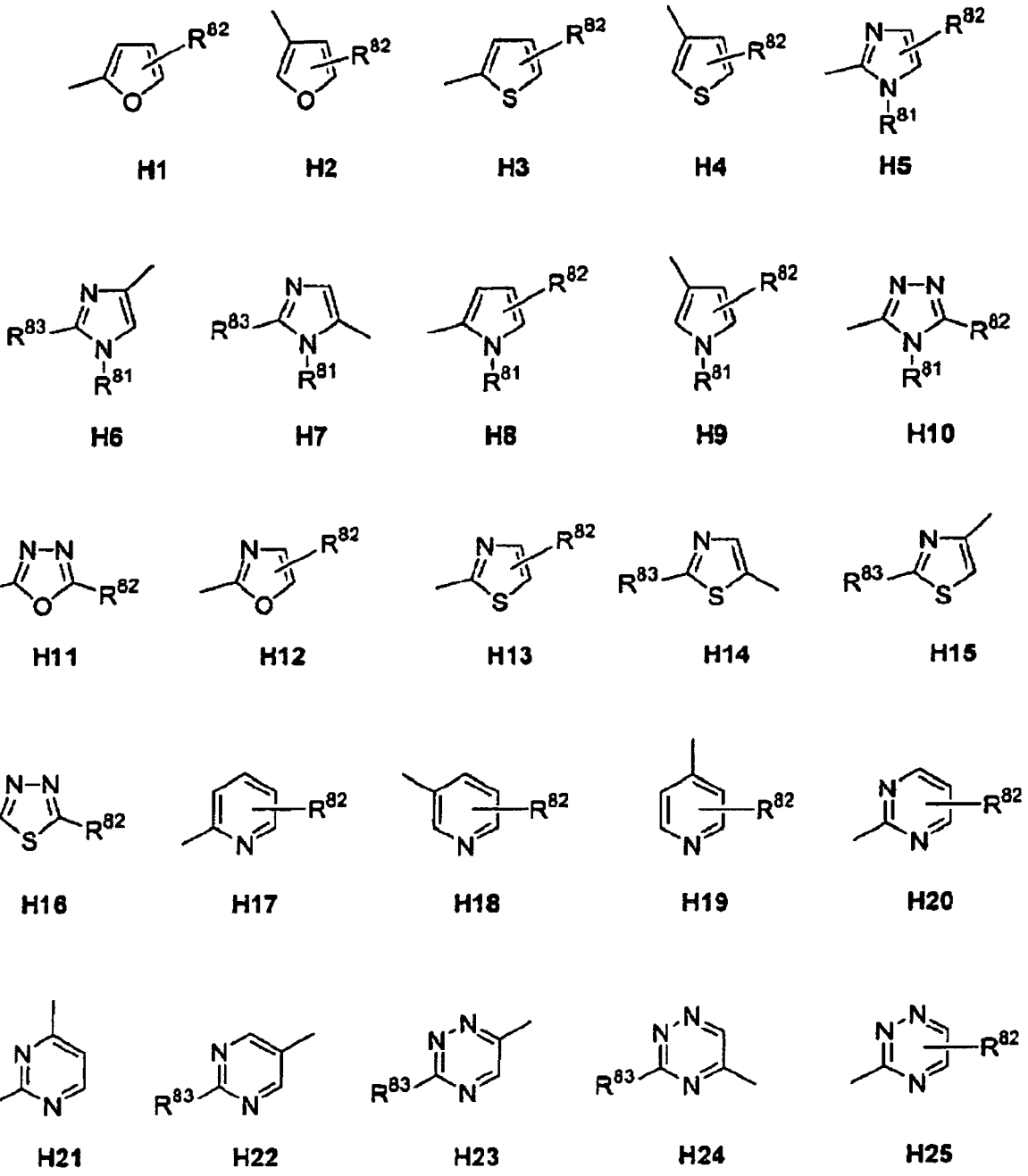
R^{20} bedeutet H; Alkyl; Alkenyl; oder Aryl - niedriges Alkyl;
R^{32} bedeutet H; niedriges Alkyl; oder Aryl - niedriges Alkyl;
R^{33} bedeutet H; Alkyl, Alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOR^{64}$; $-(CH_2)_o(CHR^{61})_s$-$CONR^{58}R^{59}$,
$-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$; $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; oder
$-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
R^{34} bedeutet H; niedriges Alkyl; Aryl, oder Aryl - niedriges Alkyl;
R^{33} und R^{34} können gemeinsam formen: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$-;
$-(CH_2)_2S(CH_2)_2$-; oder $-(CH_2)_2NR^{57}(CH_2)_2$-;
R^{37} bedeutet H; F; Br; Cl; NO_2; CF_3; niedriges Alkyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;
$-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; oder $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
R^{50} bedeutet H; niedriges Alkyl; oder Aryl - niedriges Alkyl;
R^{55} bedeutet H; niedriges Alkyl; niedriges Alkenyl; Aryl - niedriges Alkyl;
$-(CH_2)_m(CHR^{61})_sOR^{57}$; $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$;
$-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$;
$-(CH_2)_o(CHR^{61})_sCOR^{64}$; $-(CH_2)_o(CHR^{61})COOR^{57}$;
oder $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
R^{56} bedeutet H; niedriges Alkyl; niedriges Alkenyl; Aryl - niedriges 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}; oder $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
R^{57} bedeutet H; niedriges Alkyl; niedriges Alkenyl; Aryl niedriges Alkyl; oder Heteroaryl niedriges Alkyl;
R^{58} bedeutet H; niedriges Alkyl; niedriges Alkenyl; Aryl; Heteroaryl; Aryl - niedriges Alkyl; oder Heteroaryl - niedriges Alkyl;
R^{59} bedeutet H; niedriges Alkyl; niedriges Alkenyl; Aryl; Heteroaryl; Aryl - niedriges Alkyl; oder Heteroaryl - niedriges Alkyl; oder

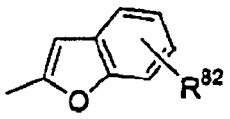
R^{58} und R^{59} können gemeinsam formen: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; oder $-(CH_2)_2NR^{57}(CH_2)_2-$;
R^{60} bedeutet H; niedriges Alkyl; niedriges Alkenyl; Aryl; oder Aryl - niedriges Alkyl;
R^{61} bedeutet Alkyl; Alkenyl; Aryl; Heteroaryl; Aryl-niedriges Alkyl; Heteroaryl - niedriges Alkyl; $-(CH_2)_mOR^{55}$; $-(CH_2)_mNR^{33}R^{34}$; $-(CH_2)_mOCONR^{75}R^{82}$; $-(CH_2)_mNR^{20}CONR^{78}R^{82}$;
$-(CH_2)_oCOOR^{37}$; $-(CH_2)_oNR^{58}R^{59}$; oder $-(CH_2)_oPO(COR^{60})_2$;
R^{62} bedeutet niedriges Alkyl; niedriges Alkenyl; Aryl, Heteroaryl; oder Aryl - niedriges Alkyl;
R^{63} bedeutet H; niedriges Alkyl; niedriges Alkenyl; Aryl, Heteroaryl; Aryl - niedriges Alkyl; Heteroaryl - niedriges Alkyl;
$-COR^{64}$; $-COOR^{57}$; $-CONR^{58}R^{59}$; $-SO_2R^{62}$; oder $-PO(OR^{60})_2$;
R^{34} und R^{63} können gemeinsam formen: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; oder $-(CH_2)_2NR^{57}(CH_2)_2-$;
R^{64} bedeutet H; niedriges Alkyl; niedriges Alkenyl; Aryl; Heteroaryl; Aryl - niedriges Alkyl; Heteroaryl - niedriges Alkyl; $-(CH_2)_p(CHR^{61})_sOR^{65}$; $-(CH_2)_p(CHR^{61})_sSR^{66}$; oder $-(CH_2)_p(CHR^{61})_sNR^{34}R^{63}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{75}R^{82}$, $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{78}R^{82}$;
R^{65} bedeutet H; niedriges Alkyl; niedriges Alkenyl; Aryl, Aryl - niedriges Alkyl; Heteroaryl niedriges Alkyl; $-COR^{57}$; $-COOR^{57}$; oder $-CONR^{58}R^{59}$;
R^{66} bedeutet H; niedriges Alkyl; niedriges Alkenyl; Aryl; Aryl - niedriges Alkyl; Heteroaryl - niedriges Alkyl; oder $-CONR^{58}R^{59}$;

Z und Z^1 sind Ketten von n resp. n' α-Aminosäureresten, wobei entweder n = 4 und n' = 6 sind oder n = 5 und n' = 7 sind, wobei die Positionen der besagten Aminosäurereste in der Kette Z von der N-terminalen Aminosäure an gezählt werden, und die Positionen der besagten Aminosäurereste in der Kette Z^1 von der C-terminalen Aminosäure an gezählt werden, wobei diese Aminosäurereste, je nach der Position in den Ketten, Gly oder Pro sind oder ein Rest vom Typ

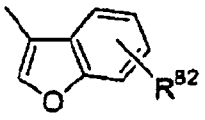
C: $-NR^{20}CH(R^{72})CO-$;
D: $-NR^{20}CH(R^{73})CO-$;
E: $-NR^{20}CH(R^{74})CO-$;
F: $-NR^{20}CH(R^{84})CO-$; und
H: $-NR^{20}-CH(CO-)-(CH_2)_{4-7}-CH(CO-)-NR^{20}-$;
$-NR^{20}-CH(CO-)-(CH_2)_pSS(CH_2)_p-CH(CO-)-NR^{20}-$;
$-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CO(CH_2)_p-CH(CO-)-NR^{20}-$;
$-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CONR^{20}(CH_2)_p-CH(CO-)-NR^{20}-$; und
I: $-NR^{86}CH_2CO-$;
R^{72} bedeutet H, niedriges Alkyl; niedriges Alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{85}$; oder $-(CH_2)_p(CHR^{61})_sSR^{85}$;
R^{73} bedeutet $-(CH_2)_oR^{77}$; $-(CH_2)_rO(CH_2)_oR^{77}$; $-(CH_2)_rS(CH_2)_oR^{77}$; oder $-(CH_2)_rNR^{20}(CH_2)_oR^{77}$;
R^{74} bedeutet $-(CH_2)_pNR^{78}R^{79}$; $-(CH_2)_pNR^{77}R^{80}$; $-(CH_2)_pC(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pNR^{80}C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_pN=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_pC_6H_4NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{77}R^{80}$;
$-(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_pC_6H_4N=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_rO(CH_2)_mNR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_mNR^{77}R^{80}$;
$-(CH_2)_rO(CH_2)_pC(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_rO(CH_2)_pC_6H_4CNR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mNR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_mNR^{77}R^{80}$; $-(CH_2)_rS(CH_2)_pC(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$;
$-(CH_2)_rS(CH_2)_pC_6H_4CNR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pNR^{80}COR^{64}$;
$-(CH_2)_pNR^{80}COR^{77}$; $-(CH_2)_pNR^{80}CONR^{78}R^{79}$; oder $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;

R^{75} bedeutet niedriges Alkyl; niedriges Alkenyl; oder Aryl - niedriges Alkyl;
R^{33} und R^{75} können gemeinsam formen: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; oder $-(CH_2)_2NR^{57}(CH_2)_2-$;
R^{75} und R^{82} können gemeinsam formen: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; oder $-(CH_2)_2NR^{57}(CH_2)_2-$;
R^{77} bedeutet R^{87}; oder eine der Heteroarylgruppen der folgenden Formeln





H26



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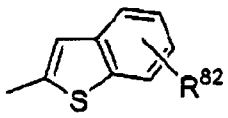
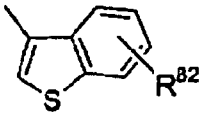


H28



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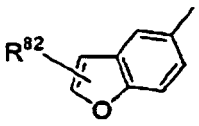
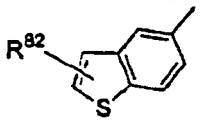


H30



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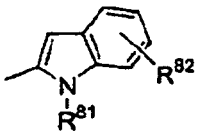
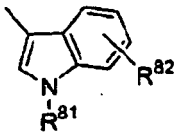
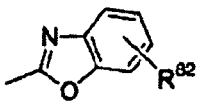


H32



H33



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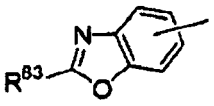

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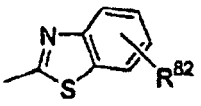
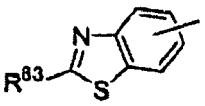
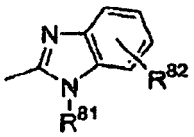


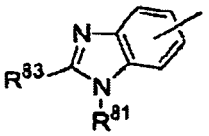
H36



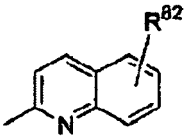
H37



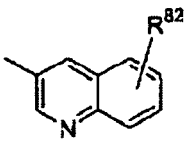
H38



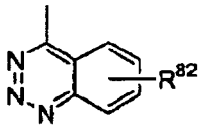
H39



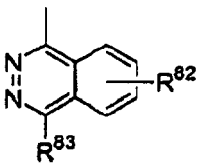
H40



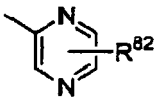
H41



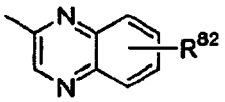
H50



H51



H52



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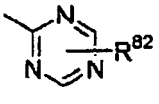
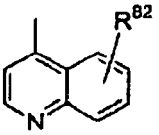
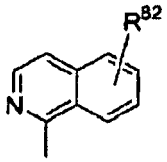


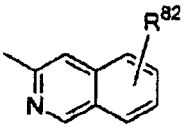
H54



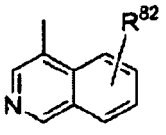
H42



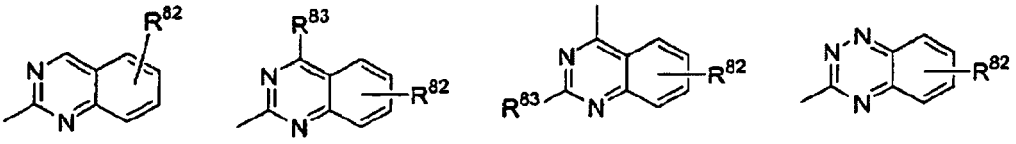
H43



H44



H45



H46 H47 H48 H49

R^{78} bedeutet H; niedriges Alkyl; Aryl; oder Aryl - niedriges Alkyl;
R^{78} und R^{82} können gemeinsam formen: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; oder $-(CH_2)_2NR^{57}(CH_2)_2-$;
R^{79} bedeutet H; niedriges Alkyl; Aryl; oder Aryl - niedriges Alkyl; oder
R^{78} und R^{79} können gemeinsam formen $-(CH_2)_{2-7}-$; $-(CH_2)_2O(CH_2)_2-$; oder $-(CH_2)_2NR^{57}(CH_2)_2-$;
R^{80} bedeutet H; oder niedriges Alkyl;
R^{81} bedeutet H; niedriges Alkyl; oder Aryl - niedriges Alkyl;
R^{82} bedeutet H; niedriges Alkyl; Aryl; Heteroaryl; oder Aryl - niedriges Alkyl;
R^{33} und R^{82} können gemeinsam formen: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; oder $-(CH_2)_2NR^{57}(CH_2)_2-$;
R^{83} bedeutet H; niedriges Alkyl; Aryl; oder $-NR^{78}R^{79}$;
R^{84} bedeutet $-(CH_2)_pCONR^{78}R^{79}$; $-(CH_2)_pNR^{80}CONR^{78}R^{79}$; $-(CH_2)_pC_6H_4CONR^{78}R^{79}$ oder $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;
R^{85} bedeutet niedriges Alkyl; oder niedriges Alkenyl;
R^{86} bedeutet R^{74}; $-[(CH_2)_u-X]_t-(CH_2)_vNR^{78}R^{79}$; $-[(CH_2)_u-X]_t-(CH_2)_v-C(=NR^{80})NR^{78}R^{79}$; X ist -O-, $-NR^{20}-$, -S-, -OCOO-, u ist 1 - 3, t ist 1 - 6, v ist 1 - 3;
R^{87} bedeutet Phenyl, p-Hydrxyphenyl, 2-Naphthyl, 1-Naphthyl, 4-Chlorophenyl, 3-Chlorophenyl, 2-Chlorophenyl, 3,4-Dichlorophenyl, 4-Fluorophenyl, 3-Fluorophenyl, 2-Fluorophenyl, p-Benzyloxyphenyl, p-Biphenyl oder p-Benzoylphenyl.

mit der Bedingung, dass in den Ketten Z und Z^1 der n resp. n' α-Aminosäurereste

- wenn n = 4 und n' = 6 sind, dann sind die Aminosäurereste in den Positionen 1 bis 4 von Z und in den Positionen 1' bis 6' von Z^1:

  - P1: vom Typ C oder vom Typ D oder vom Typ E oder vom Typ F, oder der Rest ist Pro;
  - P2: vom Typ E oder vom Typ F;
  - P3: vom Typ F, oder der Rest ist Pro;
  - P4: vom Typ E;
  - P1': vom Typ C oder vom Typ D oder vom Typ E oder vom Typ F, oder der Rest ist Gly;
  - P2': vom Typ D oder vom Typ C;
  - P3': vom Typ F oder der Rest ist Pro;
  - P4': vom Typ D oder vom Typ C;
  - P5': vom Typ E oder vom Typ F oder der Rest ist Pro; und
  - P6': vom Typ E oder vom Typ F, oder der Rest ist Pro; oder
  - P3 und P3' können gemeinsam eine Gruppe vom Typ H bilden;

und

- wenn n = 5 und n' = 7 sind, dann sind die Aminosäurereste in den Positionen 1 bis 5 von Z und in den Positionen 1' bis 7' von Z^1:

  - P1: vom Typ C oder vom Typ D oder vom Typ E oder vom Typ F, oder der Rest ist Pro;
  - P2: vom Typ E oder vom Typ F;
  - P3: vom Typ F, oder der Rest ist Pro;
  - P4: vom Typ F;
  - P5: vom Typ E
  - P1': vom Typ C oder vom Typ D oder vom Typ E oder vom Typ F, oder der Rest ist Pro;
  - P2': vom Typ F;

- P3': vom Typ D oder der Rest ist Pro;
- P4': vom Typ E oder vom Typ F;
- P5': vom Typ D oder der Rest ist Pro;
- P6': vom Typ E oder vom Typ F, oder der Rest ist Pro; und
- P7': vom Typ E oder vom Typ I, oder der Rest ist Gly; oder
- P2 und P2' und/oder P4 und P4' können gemeinsam eine Gruppe vom Typ H bilden;

in P7' sind auch D-Isomere möglich,

und deren pharmazeutisch akzeptable Salze.

2. Verbindungen nach Anspruch 1, in welchen n = 4, n' = 6 ist und die α-Aminosäurereste in den Positionen 1 bis 4 der Kette Z und in den Positionen 1' bis 6' der Kette Z^1 bedeuten:

- P1: vom Typ D oder vom Typ E oder vom Typ F, oder der Rest ist Pro;
- P2: vom Typ E oder vom Typ F;
- P3: vom Typ F, oder der Rest ist Pro;
- P4: vom Typ E;
- P1': vom Typ E oder vom Typ F, oder der Rest ist Gly;
- P2': vom Typ D;
- P3': vom Typ F oder der Rest ist Pro;
- P4': vom Typ D;
- P5': vom Typ E oder vom Typ F oder der Rest ist Pro; und
- P6': vom Typ E oder vom Typ F, oder der Rest ist Pro; oder
- P3 und P3' können gemeinsam eine Gruppe vom Typ H bilden.

3. Verbindungen nach Anspruch 2, in welchen n = 5, n' = 7 ist und die α-Aminosäurereste in den Positionen 1 bis 5 der Kette Z und in den Positionen 1' bis 7' der Kette Z^1 bedeuten:

- P1: vom Typ D oder vom Typ E oder vom Typ F, oder der Rest ist Pro;
- P2: vom Typ E oder vom Typ F;
- P3: vom Typ F, oder der Rest ist Pro;
- P4: vom Typ F;
- P5: vom Typ E
- P1': vom Typ D oder vom Typ E oder vom Typ F, oder der Rest ist Pro;
- P2': vom Typ F;
- P3': vom Typ D oder der Rest ist Pro;
- P4': vom Typ F;
- P5': vom Typ D oder der Rest ist Pro;
- P6': vom Typ E oder vom Typ F, oder der Rest ist Pro; und
- P7': vom Typ E oder vom Typ I, oder der Rest ist Gly; oder
- P2 und P2' und/oder P4 und P4' können gemeinsam eine Gruppe vom Typ H bilden;

in P7' sind auch D-Isomere möglich.

4. Verbindungen nach Anspruch 2, in welchen die α-Aminosäurereste in den Positionen 1 bis 4 der Kette Z und die α-Aminosäurereste in den Positionen 1' bis 6' der Kette Z^1 bedeuten:

- P1: Tyr oder Arg;
- P2: Cit oder Arg;
- P3: Cys;
- P4: Arg - NH_2;
- P1': Lys oder Arg;
- P2': Tyr;
- P3': Cys;
- P4': 2-Nal;
- P5': Arg; und
- P6': Arg.

- Cys in den Positionen P3 und P3' bildet eine Disulfidbrücke.

5. Verbindungen nach Anspruch 3, in welchen die α-Aminosäurereste in den Positionen 1 bis 5 der Kette Z und die α-Aminosäurereste in den Positionen 1' bis 7' der Kette Z^1 bedeuten:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg oder Arg - NH_2;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': 2-Nal, Trp, F(pNH_2) oder W(6-Cl);
- P6': Arg; und
- P7': ^{D}Arg, Arg, Ac-Arg, iPr-Arg, (EA)G, (PrA)G, (BA)G, (EGU)G, (PrGU)G, oder (BGU)G.
- Cys in den Positionen P4 und P4' bildet eine Disulfidbrücke.

6. Verbindung der Formel I nach Anspruch 1, in welcher die Template (Grundstruktur) ^{D}Pro - ^{L}Pro ist, n ist 5, n' ist 7 und die Aminosäurereste in den Positionen 1 bis 5 der Kette Z und die Aminosäurereste in den Positionen 1' bis 7' der Kette Z^1 bedeuten:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg - NH_2;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': 2-Nal;
- P6': Arg; und
- P7': Arg.

Cys in den Positionen P4' und P4 bildet eine Disulfidbrücke.

7. Verbindung der Formel I nach Anspruch 1, in welcher die Template ^{D}Pro - ^{L}Pro ist, n ist 5, n' ist 7 und die Aminosäurereste in den Positionen 1 bis 5 der Kette Z und die Aminosäurereste in den Positionen 1' bis 7' der Kette Z^1 bedeuten:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg - NH_2;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': 2-Nal;
- P6': Arg; und
- P7': Ac - Arg.

Cys in den Positionen P4' und P4 bildet eine Disulfidbrücke.

8. Verbindung der Formel I nach Anspruch 1, in welcher die Template ^{D}Pro - ^{L}Pro ist, n ist 5, n' ist 7 und die Amino-

säurereste in den Positionen 1 bis 5 der Kette Z und die Aminosäurereste in den Positionen 1' bis 7' der Kette Z^1 bedeuten:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg - NH_2;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': 2-Nal;
- P6': Arg; und
- P7': ^{D}Arg.

Cys in den Positionen P4' und P4 bildet eine Disulfidbrücke.

9. Verbindung der Formel I nach Anspruch 1, in welcher die Template ^{D}Pro - ^{L}Pro ist, n ist 5, n' ist 7 und die Aminosäurereste in den Positionen 1 bis 5 der Kette Z und die Aminosäurereste in den Positionen 1' bis 7' der Kette Z^1 bedeuten:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg - NH_2;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': Phe(pNH_2);
- P6': Arg; und
- P7': Arg.

Cys in den Positionen P4' und P4 bildet eine Disulfidbrücke.

10. Verbindung der Formel I nach Anspruch 1, in welcher die Template ^{D}Pro - ^{L}Pro ist, n ist 5, n' ist 7 und die Aminosäurereste in den Positionen 1 bis 5 der Kette Z und die Aminosäurereste in den Positionen 1' bis 7' der Kette Z^1 bedeuten:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg - NH_2;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': 2-Nal;
- P6': Arg; und
- P7': (PrA)G.

Cys in den Positionen P4' und P4 bildet eine Disulfidbrücke.

11. Verbindung der Formel I nach Anspruch 1, in welcher die Template ^{D}Pro - ^{L}Pro ist, n ist 5, n' ist 7 und die Aminosäurereste in den Positionen 1 bis 5 der Kette Z und die Aminosäurereste in den Positionen 1' bis 7' der Kette Z^1

bedeuten:

- P1: Tyr;
- P2: Arg;
- P3: Cit;
- P4: Cys;
- P5: Arg;
- P1': Lys;
- P2': Cit;
- P3': Tyr;
- P4': Cys;
- P5': 2-Nal;
- P6': Arg; und
- P7': Arg.

Cys in den Positionen P4' und P4 bildet eine Disulfidbrücke.

12. Enantiomere der Verbindungen der Formel I gemäß der Definition nach Anspruch 1.

13. Verbindungen nach einem der Ansprüche 1 bis 12 für die Verwendung als therapeutisch aktive Wirkstoffe.

14. Verbindungen nach Anspruch 13 für die Verwendung als CXCR4 Antagonisten.

15. Pharmazeutische Zusammensetzung, welche eine Verbindung nach einem der Ansprüche 1 bis 12 und einen pharmazeutisch inerten Träger enthält.

16. Zusammensetzungen nach Anspruch 15 in einer Form, welche für die orale, topische, transdermale Verabreichung, für die Injektion, für die bukkale, transmukosale, pulmonale Verabreichung oder für die Inhalation geeignet ist.

17. Zusammensetzungen nach Anspruch 15 oder 16 in Form von Tabletten, Dragees, Kapseln, Lösungen, Flüssigkeiten, Gels, Pflaster, Cremen, Salben, Sirup, Emulsionen, Suspensionen, Spray, Zerstäuber oder Zäpfchen.

18. Verwendung der Verbindungen nach einem der Ansprüche 1 bis 12 für die Herstellung eines Medikaments zur Behandlung oder zur Vorbeugung von HIV Infektionen oder zur Krebsbehandlung oder zur Behandlung von Entzündungskrankheiten.

19. Verfahren für die Herstellung von Verbindungen nach einem der Ansprüche 1 bis 11 umfassend

(a) Verbinden eines geeigneten funktionellen festen Trägers mit einem in geeigneter Weise N-geschützten Derivat von der Aminosäure, welche in dem gewünschten Endprodukt in der Position 4 von Z ist, wenn n = 4 ist oder in der Position 5 von Z wenn n = 5 ist, wobei jegliche funktionelle Gruppe, welche in dem besagten N-geschützten Aminosäurederivat anwesend sein kann, ebenfalls in geeigneter Weise geschützt ist;
(b) Entfernen der N-Schutzgruppe von dem derart erhaltenen Produkt;
(c) Verbinden des derart erhaltenen Produkts mit einem in geeigneter Weise N-geschützten Derivat von der Aminosäure, welche in Z des gewünschten Endprodukts eine Position näher zum N-terminalen Aminosäurerest ist, wobei jegliche funktionelle Gruppe, welche in dem besagten N-geschützten Aminosäurederivat anwesend sein kann, ebenfalls in geeigneter Weise geschützt ist;
(d) Entfernen der N-Schutzgruppe von dem derart erhaltenen Produkt;
(e) Wiederholen der Stufen (c) und (d) bis der N-terminale Aminosäurerest von Z eingeführt ist;
(f) Verbinden des derart erhaltenen Produkts

(fa) mit einem in geeigneter Weise N-geschützten Derivat von ^{D}Pro oder ^{L}Pro;
(fb) Entfernen der N-geschützten Gruppe von dem derart erhaltenen Produkt; und
(fc) Verbinden des derart erhaltenen Produkts mit einem in geeigneter Weise N-geschützten Derivat von ^{L}Pro resp. ^{D}Pro;

(g) Entfernen der N-Schutzgruppe von dem in der Stufe (fc) erhaltenen Produkt;
(h) Verbinden des derart erhaltenen Produkts mit einem in geeigneter Weise N-geschützten Derivat von der

Aminosäure, welche in dem gewünschten Endprodukt in der Position 1 von Z^1 ist, wobei jegliche funktionelle Gruppe, welche in dem besagten N-geschützten Aminosäurederivat anwesend sein kann, ebenfalls in geeigneter Weise geschützt ist;
(i) Entfernen der N-Schutzgruppe von dem derart erhaltenen Produkt;
(j) Verbinden des derart erhaltenen Produkts mit einem in geeigneter Weise N-geschützten Derivat von der Aminosäure, welche in dem gewünschten Endprodukt eine Position von Position 1 von Z^1 entfernt ist, wobei jegliche funktionelle Gruppe, welche in dem besagten N-geschützten Aminosäurederivat anwesend sein kann, ebenfalls in geeigneter Weise geschützt ist;
(k) Entfernen der N-Schutzgruppe von dem derart erhaltenen Produkt;
(l) Wiederholen der Stufen (j) und (k) bis alle Aminosäurereste von Z^1 eingeführt sind;
(m) falls gewünscht, selektives Entschützen einer funktionellen Gruppe oder mehrerer funktionellen Gruppen, welche in dem Molekül anwesend sind, und geeignetes Substituieren der derart freien Reaktionsgruppe(n);
(n) falls gewünscht, Bilden einer oder zwei zwischenstrangiger Bindungen zwischen den Seitenketten der geeigneten Aminosäurereste an gegenüberliegenden Positionen des β-Strang-Bereichs;
(o) Lösen des derart erhaltenen Produkts von dem festen Träger und Entfernen sämtlicher Schutzgruppen, welche an den funktionellen Gruppen aller Kettenglieder der Aminosäurereste anwesend sind, und falls gewünscht, sämtlicher Schutzgruppe(n), welche zusätzlich in dem Molekül anwesend sein kann; und
(p) falls gewünscht, Umsetzen des derart erhaltenen Produkts in ein pharmazeutisch akzeptables Salz oder Umsetzen eines derart erhaltenen pharmazeutisch akzeptablen oder nicht-akzeptablen Salzes in die entsprechende freie Verbindung der Formel I oder in ein anderes pharmazeutisch akzeptables Salz.

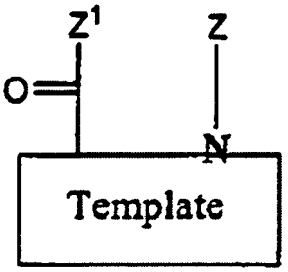
20. Verfahren nach Anspruch 19, worin jedoch ein Aminosäurerest des Typs I eingeführt wird durch Verbinden mit einem Acetylierungsmittel, welches eine Abgangsgruppe umfasst, gefolgt von einer nukleophilen Verschiebung mit einem Amin der Formel H_2NR^{86}, welches nötigenfalls in geeigneter Weise geschützt wird.

21. Verfahren nach Anspruch 20, wobei das Acetylierungsmittel, welches die Abgangsgruppe enthält, Bromo, Chloro oder Iodo Essigsäure ist.

22. Modifikation des Verfahrens nach einem der Ansprüche 19 bis 21 für die Herstellung der Verbindungen nach Anspruch 12, in welchen Enantiomere von allen chiralen Ausgangsmaterialien verwendet werden.

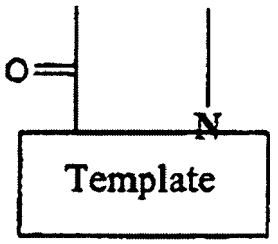
Revendications

1. Composés de la formule générale



(I)

dans laquelle



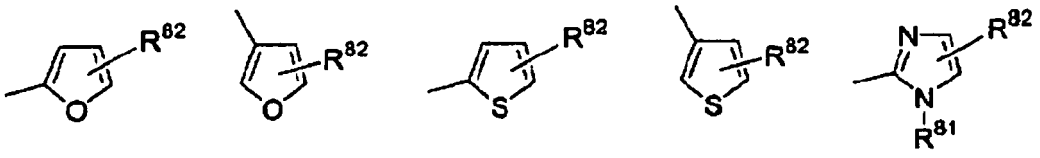
représente un groupe de la formule ^{D}Pro-^{L}Pro et ^{L}Pro-^{D}Pro

R^{20} représente H ; alkyle ; alcényle ; ou aryl-alkyle inférieur ;
R^{32} représente H ; alkyle inférieur ; ou aryl-alkyle inférieur ;
R^{33} représente H ; alkyle, alcényle ; $-(CH_2)_m(CHR^{61})_sOR^{55}$;
$-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$; $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOR^{64}$;
$-(CH_2)_o(CHR^{61})_s$-$CONR^{58}R^{59}$, $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; ou $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
R^{34} représente H ; alkyle inférieur ; aryle, ou aryl-alkyle inférieur ;
R^{33} et R^{34} ensemble peuvent former: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$- ;
$-(CH_2)_2S(CH_2)_2$- ; ou $-(CH_2)_2NR^{57}(CH_2)_2$- ;
R^{37} représente H ; F ; Br ; Cl ; NO_2 ; CF_3 ; alkyle inférieur ; $-(CH_2)_p(CHR^{61})_sOR^{55}$;
$-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$;
$-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; ou $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
R^{50} représente H ; alkyle inférieur ; ou aryl-alkyle inférieur ;
R^{55} représente H ; alkyle inférieur ; alcényle inférieur ; aryl-alkyle inférieur ;
$-(CH_2)_m(CHR^{61})_sOR^{57}$; $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$; $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$; $-(CH_2)_o(CHR^{61})_s$-COR^{64} ; $-(CH_2)_o(CHR^{61})COOR^{57}$;
ou
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
R^{56} représente H ; alkyle inférieur ; alcényle inférieur ; aryl-alkyle inférieur ;
$-(CH_2)_m(CHR^{61})_sOR^{57}$;
$-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$; $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$;
$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$; $-(CH_2)_o(CHR^{61})_s$-COR^{64} ; ou
$-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
R^{57} représente H ; alkyle inférieur ; alcényle inférieur ; aryle alkyle inférieur ; ou hétéroaryle alkyle inférieur ;
R^{58} représente H ; alkyle inférieur ; alcényle inférieur ; aryle ; hétéroaryle ; aryl-alkyle inférieur ; ou hétéroaryl-alkyle inférieur ;
R^{59} représente H ; alkyle inférieur ; alcényle inférieur ; aryle ; hétéroaryle ; aryl-alkyle inférieur ; ou hétéroaryl-alkyle inférieur ; ou
R^{58} et R^{59} ensemble peuvent former: $-(CH_2)_{2\text{-}6}$- ; $-(CH_2)_2O(CH_2)_2$- ; $-(CH_2)_2S(CH_2)_2$- ; ou $-(CH_2)_2NR^{57}(CH_2)_2$- ;
R^{60} représente H ; alkyle inférieur ; alcényle inférieur ; aryle ; ou aryl-alkyle inférieur ;
R^{61} représente alkyle ; alcényle ; aryle ; hétéroaryle ; aryl-alkyle inférieur ; hétéroaryl-alkyle inférieur ; $-(CH_2)_mOR^{55}$; $-(CH_2)_mNR^{33}R^{34}$; $-(CH_2)_mOCONR^{75}R^{82}$; $-(CH_2)_mNR^{20}CONR^{78}R^{82}$;
$-(CH_2)_oCOOR^{37}$; $-(CH_2)_oNR^{58}R^{59}$; ou $-(CH_2)_oPO(COR^{60})_2$;
R^{62} représente alkyle inférieur ; alcényle inférieur ; aryle, hétéroaryle ; ou aryl-alkyle inférieur ;
R^{63} représente H ; alkyle inférieur ; alcényle inférieur ; aryle, hétéroaryle ; aryl-alkyle inférieur ; hétéroaryl-alkyle inférieur ;
$-COR^{64}$; $-COOR^{57}$; $-CONR^{58}R^{59}$; $-SO_2R^{62}$; ou $-PO(OR^{60})_2$;
R^{34} et R^{63} ensemble peuvent former: $-(CH_2)_{2\text{-}6}$-; $-(CH_2)_2O(CH_2)_2$- ; $-(CH_2)_2S(CH_2)_2$- ; ou $-(CH_2)_2NR^{57}(CH_2)_2$- ;
R^{64} représente H ; alkyle inférieur ; alcényle inférieur ; aryle ; hétéroaryle ; aryl-alkyle inférieur ; hétéroaryl-alkyle inférieur ;
$-(CH_2)_p(CHR^{61})_sOR^{65}$; $-(CH_2)_p(CHR^{61})_sSR^{66}$; ou $-(CH_2)_p(CHR^{61})_sNR^{34}R^{63}$;
$-(CH_2)_p(CHR^{61})_sOCONR^{75}R^{82}$, $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{78}R^{82}$;

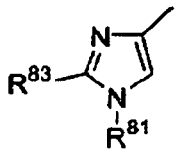
R^{65} représente H ; alkyle inférieur ; alcényle inférieur ; aryle, aryl-alkyle inférieur ; hétéroaryl-alkyle inférieur ; $-COR^{57}$; $-COOR^{57}$; ou $-CONR^{58}R^{59}$;
R^{66} représente H ; alkyle inférieur ; alcényle inférieur ; aryle ; aryl-alkyle inférieur ; hétéroaryl-alkyle inférieur ; ou $-CONR^{58}R^{59}$;

Z et Z^1 sont des chaînes de n, respectivement, n' résidus d'acides α-aminés où soit n est 4 et n' est 6 soit n est 5 et n' est 7, où les positions des dits résidus d'acides aminés dans la chaîne Z sont comptées à partir de l'acide aminé N-terminal et les positions des dits résidus d'acides aminés dans la chaîne Z^1 sont comptées à partir de l'acide aminé C-terminal, où ces résidus d'acides aminés sont, en fonction de leur position dans les chaînes, Gly ou Pro, ou un résidu du type

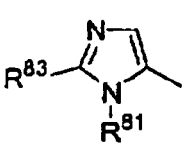
C: $-NR^{20}CH(R^{72})CO-$;
D: $-NR^{20}CH(R^{73})CO-$;
E: $-NR^{20}CH(R^{74})CO-$;
F: $-NR^{20}CH(R^{84})CO-$; et
H: $-NR^{20}-CH(CO-)-(CH_2)_{4-7}-CH(CO-)-NR^{20}-$;
$-NR^{20}-CH(CO-)-(CH_2)_pSS(CH_2)_p-CH(CO-)-NR^{20}-$;
$-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CO(CH_2)_{p-}CH(CO-)-NR^{20}-$;
$-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CONR^{20}(CH_2)_{p-}CH(CO-)-NR^{20}-$; et
I: $-NR^{86}CH_2CO-$;
R^{72} représente H, alkyle inférieur ; alcényle inférieur ; $-(CH_2)_p(CHR^{61})_sOR^{85}$; ou $-(CH_2)_p(CHR^{61})_sSR^{85}$;
R^{73} représente $-(CH_2)_oR^{77}$; $-(CH_2)_rO(CH_2)_oR^{77}$; $-(CH_2)_rS(CH_2)_oR^{77}$; ou $-(CH_2)_rNR^{20}(CH_2)_oR^{77}$;
R^{74} représente $-(CH_2)_pNR^{78}R^{79}$; $-(CH_2)_pNR^{77}R^{80}$; $-(CH_2)_pC(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pNR^{80}C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_pN=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_pC_6H_4NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{77}R^{80}$;
$-(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_pC_6H_4N=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_rO(CH_2)_mNR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_mNR^{77}R^{80}$;
$-(CH_2)_rO(CH_2)_pC(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_rO(CH_2)_pC_6H_4CNR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rO(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mNR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_mNR^{77}R^{80}$; $-(CH_2)_rS(CH_2)_pC(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$;
$-(CH_2)_rS(CH_2)_pC_6H_4CNR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
$-(CH_2)_rS(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pNR^{80}COR^{64}$;
$-(CH_2)_pNR^{80}COR^{77}$; $-(CH_2)_pNR^{80}CONR^{78}R^{79}$; ou $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;
R^{75} représente alkyle inférieur ; alcényle inférieur ; ou aryl-alkyle inférieur ;
R^{33} et R^{75} ensemble peuvent former: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; ou $-(CH_2)_2NR^{57}(CH_2)_2-$;
R^{75} et R^{82} ensemble peuvent former: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; ou $-(CH_2)_2NR^{57}(CH_2)_2-$;
R^{77} représente R^{87} ; ou un groupe hétéroaryle parmi ceux de la formule



H1 H2 H3 H4 H5



H6



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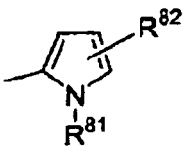
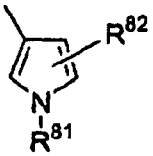
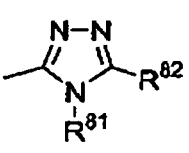


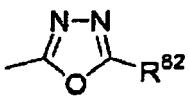
H8



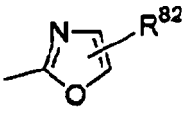
H9



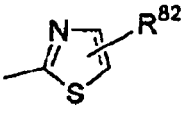
H10



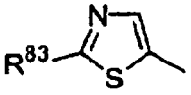
H11



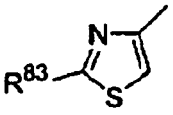
H12



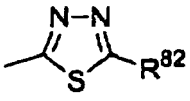
H13



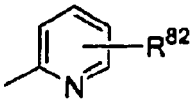
H14



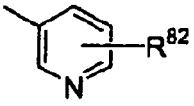
H15



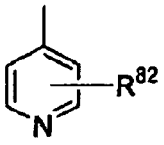
H16



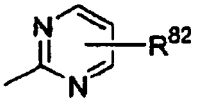
H17



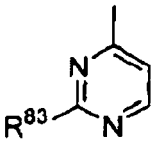
H18



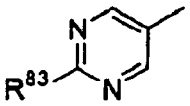
H19



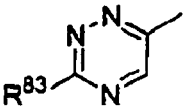
H20



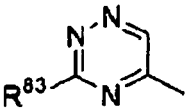
H21



H22



H23



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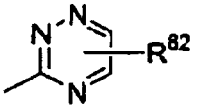

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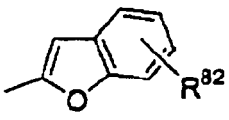

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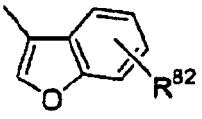

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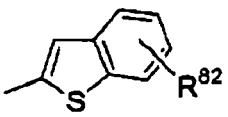

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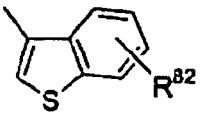

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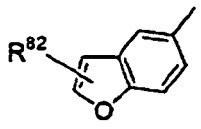
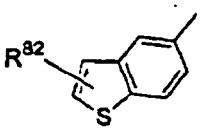
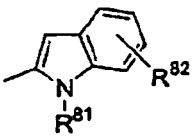


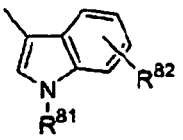
H30



H31



H32



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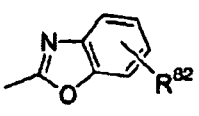
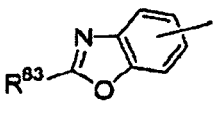
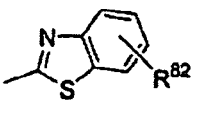


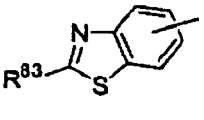
H34



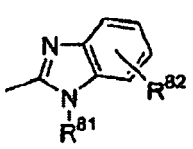
H35



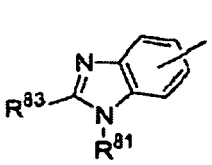
H36



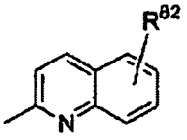
H37



H38



H39



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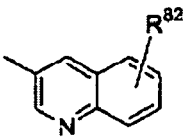

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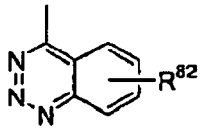
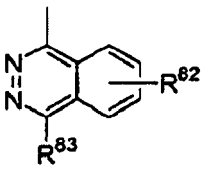
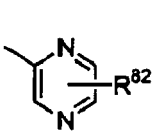


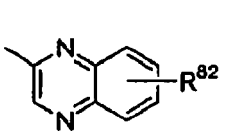
H50



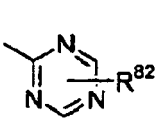
H51



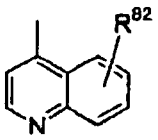
H52



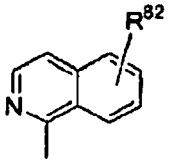
H53



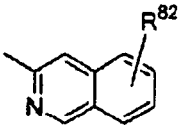
H54



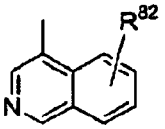
H42



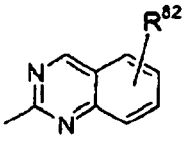
H43



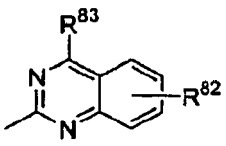
H44



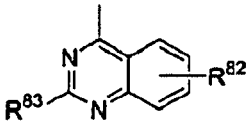
H45



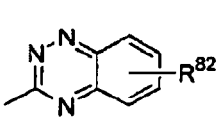
H46



H47



H48



H49

R^{78} représente H ; alkyle inférieur ; aryle ; ou aryl-alkyle inférieur ;
R^{78} et R^{82} ensemble peuvent former: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$ ou $-(CH_2)NR^{57}(CH_2)_2-$;
R^{79} représente H ; alkyle inférieur ; aryle ; ou aryl-alkyle inférieur ; ou
R^{78} et R^{79}, pris ensemble, peuvent être $-(CH_2)_{2-7}-$; $-(CH_2)_2O(CH_2)_2-$; ou $-(CH_2)_2NR^{57}(CH_2)_2-$;
R^{80} représente H ; ou alkyle inférieur ;
R^{81} représente H ; alkyle inférieur ; ou aryl-alkyle inférieur ;
R^{82} représente H ; alkyle inférieur ; aryle ; hétéroaryle ; ou aryl-alkyle inférieur ;
R^{33} et R^{82} ensemble peuvent former: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$ ou $-(CH_2)_2NR^{57}(CH_2)_2-$;
R^{83} représente H ; alkyle inférieur ; aryle ; ou $-NR^{78}R^{79}$;
R^{84} représente $-(CH_2)_pCONR^{78}R^{79}$; $-(CH_2)_pNR^{80}CONR^{78}R^{79}$; $-(CH_2)_pC_6H_4CONR^{78}R^{79}$ ou $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;
R^{85} représente alkyle inférieur ; ou alcényle inférieur ;
R^{86} représente R^{74} ; $-[(CH_2)_u-X]_t-(CH_2)_vNR^{78}R^{79}$; $-[(CH_2)_u-X]_t-(CH_2)_v-C(=NR^{80})NR^{78}R^{79}$; X est -O-, $-NR^{20}-$, -S-, -OCOO-, u est 1-3, t est 1-6, v est 1-3 ;
R^{87} représente phényle, p-hydrxyphényle, 2-naphthyle, 1-naphthyle, 4-chlorophényle, 3-chlorophényle, 2-chlorophényle, 3,4-dichlorophényle, 4-fluorophényle, 3-fluorophényle, 2-fluorophényle, p-benzyloxyphényle, p-biphényle ou p-benzoylphényle.

à condition que dans les chaînes Z et Z^1 de n, respectivement, n' résidus d'acides α-aminés

- si n est 4 et n' est 6, les résidus d'acides aminés dans les positions 1 à 4 de Z et dans les positions 1'à 6' de Z^1 sont:

- P1 : du type C ou du type D ou du type E ou du type F, ou le résidu est Pro ;
- P2 : du type E ou du type F ;
- P3 : du type F, ou le résidu est Pro ;
- P4 : du type E ;
- P1' : du type C ou du type D ou du type E ou du type F, ou le résidu est Gly ;
- P2' : du type D ou du type C ;
- P3' : du type F ou le résidu est Pro ;
- P4' : du type D ou du type C ;
- P5' : du type E ou du type F ou le résidu est Pro ; et
- P6' : du type E ou du type F, ou le résidu est Pro ; ou
- P3 et P3', pris ensemble, peuvent former un groupe du type H ;

et

- si n est 5 et n' est 7, les résidus d'acides aminés dans les positions 1 à 5 de Z et dans les positions 1' à 7' de Z^1 sont:

- P1 : du type C ou du type D ou du type E ou du type F, ou le résidu est Pro ;
- P2 : du type E ou du type F ;
- P3 : du type F, ou le résidu est Pro ;
- P4 : du type F ;
- P5 : du type E
- P1' : du type C ou du type D ou du type E ou du type F, ou le résidu est Pro ;
- P2' : du type F;
- P3' : du type D ou le résidu est Pro ;
- P4' : du type E ou du type F ;
- P5' : du type D ou le résidu est Pro ;
- P6' : du type E ou du type F, ou le résidu est Pro ; et
- P7' : du type E ou du type I, ou le résidu est Gly ; ou
- P2 et P2' et/ou P4 et P4', pris ensemble, peuvent former un groupe du type H ;

dans P7', des isomères D sont également possibles,

et leurs sels pharmaceutiquement acceptables.

2. Des composés selon la revendication 1 dans lesquels n est 4, n' est 6 et les résidus d'acides α-aminés dans les positions 1 à 4 de la chaîne Z et dans les positions 1' à 6' de la chaîne Z^1 sont:

- P1 : du type D ou du type E ou du type F, ou le résidu est Pro ;
- P2 : du type E ou du type F ;
- P3 : du type F, ou le résidu est Pro ;
- P4 : du type E ;
- P1' : du type E ou du type F, ou le résidu est Gly ;
- P2' : du type D ;
- P3' : du type F ou le résidu est Pro ;
- P4' : du type D ;
- P5' : du type E ou du type F ou le résidu est Pro ; et
- P6' : du type E ou du type F, ou le résidu est Pro ; ou
- P3 et P3', pris ensemble, peuvent former un groupe du type H.

3. Des composés selon la revendication 2 dans lesquels n est 5, n' est 7 et les résidus d'acides α-aminés dans les positions 1 à 5 de la chaîne Z et dans les positions 1' à 7' de la chaîne Z^1 sont:

- P1 : du type D ou du type E ou du type F, ou le résidu est Pro ;
- P2 : du type E ou du type F ;
- P3 : du type F, ou le résidu est Pro ;
- P4 : du type F ;

- P5 : du type E
- P1' : du type D ou du type E ou du type F, ou le résidu est Pro ;
- P2' : du type F;
- P3' : du type D ou le résidu est Pro ;
- P4' : du type F;
- P5' : du type D ou le résidu est Pro ;
- P6' : du type E ou du type F, ou le résidu est Pro ; et
- P7' : du type E ou du type 1, ou le résidu est Gly ; ou
- P2 et P2' et/ou P4 et P4', pris ensemble, peuvent former un groupe du type H ;

dans P7', des isomères D sont également possibles.

4. Des composés selon la revendication 2 dans lesquels les résidus d'acides α-aminés dans les positions 1 à 4 de la chaîne Z et les résidus d'acides α-aminés dans les positions 1' à 6' de la chaîne Z^1 sont:

- P1 : Tyr ou Arg ;
- P2 : Cit ou Arg ;
- P3 : Cys ;
- P4 : Arg - NH_2 ;
- P1' : Lys ou Arg ;
- P2' : Tyr ;
- P3' : Cys ;
- P4' : 2-Nal ;
- P5' : Arg ; et
- P6' : Arg.
- Cys à la position P3 et P3' forme un pont disulfure.

5. Des composés selon la revendication 3 dans lesquels les résidus d'acides α-aminés dans les positions 1 à 5 de la chaîne Z et les résidus d'acides α-aminés dans les positions 1' à 7' de la chaîne Z^1 sont:

- P1 : Tyr ;
- P2 : Arg ;
- P3 : Cit ;
- P4 : Cys ;
- P5 : Arg ou Arg - NH_2 ;
- P1' : Lys ;
- P2' : Cit ;
- P3' : Tyr;
- P4' : Cys ;
- P5' : 2-Nal, Trp, F(pNH_2) ou W(6-Cl) ;
- P6' : Arg ; et
- P7' : ^{D}Arg, Arg, Ac-Arg, iPr-Arg, (EA)G, (PrA)G, (BA)G, (EGU)G, (PrGU)G ou (BGU)G.
- Cys à la position P4 et P4' forme un pont disulfure.

6. Un composé de la formule I selon la revendication 1 dans lequel le template représente ^{D}Pro - ^{L}Pro, n est 5, n' est 7 et les résidus d'acides aminés dans les positions 1 à 5 de la chaîne Z et les résidus d'acides aminés dans les positions 1' à 7' de la chaîne Z^1 sont:

- P1 : Tyr ;
- P2 : Arg ;
- P3 : Cit ;
- P4 : Cys ;
- P5 : Arg - NH_2;
- P1' : Lys ;
- P2' : Cit ;
- P3' : Tyr ;
- P4' : Cys ;
- P5' : 2-Nal ;

- P6' : Arg ; et
- P7' : Arg.

Cys à la position P4' et P4 forme un pont disulfure.

7. Un composé de la formule I selon la revendication 1 dans lequel le template représente ^{D}Pro - ^{L}Pro, n est 5, n' est 7 et les résidus d'acides aminés dans les positions 1 à 5 de la chaîne Z et les résidus d'acides aminés dans les positions 1' à 7' de la chaîne Z^1 sont:

- P1 : Tyr ;
- P2 : Arg ;
- P3 : Cit ;
- P4 : Cys ;
- P5 : Arg - NH_2 ;
- P1' : Lys ;
- P2' : Cit ;
- P3' : Tyr;
- P4' : Cys ;
- P5' : 2-Nal ;
- P6' : Arg ; et
- P7' : Ac - Arg.

Cys à la position P4' et P4 forme un pont disulfure.

8. Un composé de la formule 1 selon la revendication 1 dans lequel le template représente ^{D}Pro - ^{L}Pro, n est 5, n' est 7 et les résidus d'acides aminés dans les positions 1 à 5 de la chaîne Z et les résidus d'acides aminés dans les positions 1' à 7' de la chaîne Z^1 sont:

- P1 : Tyr ;
- P2 : Arg ;
- P3 : Cit ;
- P4 : Cys ;
- P5 : Arg - NH_2;
- P1' : Lys ;
- P2' : Cit ;
- P3' : Tyr;
- P4' : Cys ;
- P5' : 2-Nal ;
- P6' : Arg ; et
- P7' : ^{D}Arg.

Cys à la position P4' et P4 forme un pont disulfure.

9. Un composé de la formule I selon la revendication 1 dans lequel le template représente ^{D}Pro - ^{L}Pro, n est 5, n' est 7 et les résidus d'acides aminés dans les positions 1 à 5 de la chaîne Z et les résidus d'acides aminés dans les positions 1' à 7' de la chaîne Z^1 sont:

- P1 : Tyr ;
- P2 : Arg ;
- P3 : Cit ;
- P4 : Cys ;
- P5 : Arg - NH_2 ;
- P1' : Lys ;
- P2' : Cit ;
- P3' : Tyr;
- P4' : Cys ;
- P5' : Phe(pNH_2) ;
- P6' : Arg ; et

- P7' : Arg.

Cys à la position P4' et P4 forme un pont disulfure.

10. Un composé de la formule 1 selon la revendication 1 dans lequel le template représente ^{D}Pro - ^{L}Pro, n est 5, n' est 7 et les résidus d'acides aminés dans les positions 1 à 5 de la chaîne Z et les résidus d'acides aminés dans les positions 1' à 7' de la chaîne Z^1 sont:

- P1 : Tyr ;
- P2 : Arg ;
- P3 : Cit ;
- P4 : Cys ;
- P5 : Arg - NH_2 ;
- P1' : Lys ;
- P2' : Cit ;
- P3' : Tyr;
- P4' : Cys ;
- P5' : 2-Nal ;
- P6' : Arg ; et
- P7' : (PrA)G.

Cys à la position P4' et P4 forme un pont disulfure.

11. Un composé de la formule I selon la revendication 1 dans lequel le template représente ^{D}Pro - ^{L}Pro, n est 5, n' est 7 et les résidus d'acides aminés dans les positions 1 à 5 de la chaîne Z et les résidus d'acides aminés dans les positions 1' à 7' de la chaîne Z^1 sont:

- P1 : Tyr ;
- P2 : Arg ;
- P3 : Cit ;
- P4 : Cys ;
- P5 : Arg ;
- P1' : Lys ;
- P2' : Cit ;
- P3' : Tyr;
- P4' : Cys ;
- P5' : 2-Nal ;
- P6' : Arg ; et
- P7' : Arg.

Cys à la position P4' et P4 forme un pont disulfure.

12. Des énantiomères des composés de la formule I selon la définition dans la revendication 1.

13. Des composés selon l'une quelconque des revendications 1 à 12 pour l'utilisation en tant que substances thérapeutiquement actives.

14. Des composés selon la revendication 13 pour l'utilisation en tant qu'antagonistes CXCR4.

15. Une composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 12 et un porteur pharmaceutiquement inerte.

16. Des compositions selon la revendication 15 sous une forme appropriée pour l'administration orale, topicale, transdermale, par injection, buccale, transmucosal, pulmonaire ou par inhalation.

17. Des compositions selon la revendication 15 ou 16 sous forme de tablettes, dragées, capsules, solutions, liquides, gels, sparadraps, crèmes, pommades, sirops, émulsions, suspensions, spray, vaporisateur ou suppositoires.

18. L'utilisation des composés selon l'une quelconque des revendications 1 à 12 pour la fabrication d'un médicament pour le traitement ou la prévention d'infections HIV ou pour le traitement du cancer ou pour le traitement de maladies inflammatoires.

19. Un procédé pour la fabrication de composés selon l'une quelconque des revendications 1 à 11 où ce procédé comprend

(a) coupler un support solide convenablement fonctionnalisé avec un dérivé convenablement N-protégé de cet acide aminé qui est dans le produit final souhaité à la position 4 de Z si n est 4 ou à la position 5 de Z si n est 5, tout groupe fonctionnel qui peut être présent dans le dit dérivé d'acide aminé N-protégé étant également protégé de manière appropriée ;
(b) éliminer le groupe protecteur de N du produit ainsi obtenu ;
(c) coupler le produit ainsi obtenu avec un dérivé convenablement N-protégé de cet acide aminé qui est dans Z du produit final souhaité une position plus proche du résidu d'acide aminé N-terminal, tout groupe fonctionnel qui peut être présent dans le dérivé d'acide aminé N-protégé étant également protégé de manière appropriée ;
(d) éliminer le groupe protecteur de N du produit ainsi obtenu ;
(e) répéter les étapes (c) et (d) jusqu'à ce que le résidu d'acide aminé N-terminal de Z ait été introduit ;
(f) coupler le produit ainsi obtenu

(fa) avec un dérivé convenablement N-protégé de ^{D}Pro ou ^{L}Pro ;
(fb) éliminer le groupe protecteur de N du produit ainsi obtenu ; et
(fc) coupler le produit ainsi obtenu avec un dérivé convenablement N-protégé de ^{L}Pro, respectivement, ^{D}Pro ;

(g) éliminer le groupe protecteur de N du produit obtenu dans l'étape (fc) ;
(h) coupler le produit ainsi obtenu avec un dérivé convenablement N-protégé de cet acide aminé qui est dans le produit final souhaité dans la position 1 de Z^1, tout groupe fonctionnel qui peut être présent dans le dérivé d'acide aminé N-protégé étant également protégé de manière appropriée ;
(i) éliminer le groupe protecteur de N du produit ainsi obtenu ;
(j) coupler le produit ainsi obtenu avec un dérivé convenablement N-protégé de cet acide aminé qui est dans le produit final souhaité une position plus loin que la position 1 de Z^1, tout groupe fonctionnel qui peut être présent dans le dérivé d'acide aminé N-protégé étant également protégé de manière appropriée ;
(k) éliminer le groupe protecteur de N du produit ainsi obtenu ;
(l) répéter les étapes (j) et (k) jusqu'à ce que tous les résidus d'acides aminés de Z^1 ait été introduits ;
(m) optionnellement, déprotection sélective d'un groupe fonctionnel protégé ou de quelques groupes fonctionnels protégés présents dans la molécule et substitution appropriée du groupe réactif ou des groupes réactifs ainsi libérés ;
(n) optionnellement, formation d'un ou de deux liaisons entre brins entre les chaînes latérales des résidus d'acides aminés appropriés aux positions opposées de la zone du brin β;
(o) détacher le produit ainsi obtenu du support solide et éliminer tous les groupes protecteurs sur les groupes fonctionnels de tout membre de la chaîne des résidus d'acides aminés et, optionnellement, le ou les groupes protecteurs qui peut additonnellement être présent dans la molécule ; et
(p) optionnellement, convertir le produit ainsi obtenu en un sel pharmaceutiquement acceptable ou convertir un sel pharmaceutiquement acceptable ou non-acceptable ainsi obtenu en le composé libre correspondant de la formule I ou en un autre sel différent, pharmaceutiquement acceptable.

20. Un procédé selon la revendication 19, mais où un résidu d'acide aminé du type I est introduit par couplage avec un agent acétylant contenant un groupe de départ, suivi par un déplacement nucléophilique avec une amine de la formule H_2NR^{86} qui est protégée de manière appropriée, si nécessaire.

21. Un procédé selon la revendication 20 où le dit agent acétylant contenant le groupe de départ est bromo, chloro ou iodo acide acétique.

22. Une modification du procédé selon l'une quelconque des revendications 19 à 21 pour la fabrication de composés selon la revendication 12 dans lesquels des énantiomères de toutes les matières de départ chirales sont utilisées.

REFERENCES CITED IN THE DESCRIPTION

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