BETA-HAIRPIN PEPTIDOMIMETICS

The present invention provides β-hairpin peptidomimetics having Gram-negative antimicrobial activity and being embraced by the general disclosures of, but not specifically disclosed in, WO02/070547 A1 and WO2004/018503 A1.

The β-hairpin peptidomimetics of the invention are compounds of the general formula (**I**), cyclo[P^1-P^2-P^3-P^4-P^5-P^6-P^7-P^8-P^9-P^{10}-P^{11}-P^{12}-T^1-T^2], and pharmaceutically acceptable salts thereof, with P^1 to P^{12}, T^1 and T^2 being elements as described herein below.

In addition, the present invention provides an efficient synthetic process by which these compounds can, if desired, be made in parallel library-format. Moreover, the β-hairpin peptidomimetics of the invention show improved efficacy, reduced hemolysis of red blood cells and reduced or no cytotoxicity.

A major cause of death worldwide and a leading cause of mortality in developed countries are infectious diseases. They result from the presence of pathogenic microbial agents including pathogenic viruses and pathogenic bacteria. The problem of bacterial resistance to established antibiotics has stimulated intense interest in developing novel antimicrobial agents with new modes of action (D. Obrecht, J.A. Robinson, F. Bernadini, C. Bisang, S.J. DeMarco, K. Moehle, F.O. Gombert, *Curr. Med. Chem.* **2009**, *16*, 42-65; H. Breithaupt, *Nat. Biotechnol.* **1999**, *17*, 1165-1169).

A growing unmet medical need is represented by Gram-negative bacteria causing 60% of nosocomial pneumonias (R. Frechette, *Ann. Rep. Med. Chem*., Elsevier, **2007**, 349-64). Extended spectrum beta lactamase (ESBL)-producing Gram-negative bacteria have also compromised the utility of many front-line beta-lactam drugs (S.J. Projan, P.A. Bradford, *Curr. Opin. Microbiol.*, **2007**, *10*, 441). The lack of suitable new compounds is forcing clinicians to use previously discarded antibiotics like colistin, despite well-known toxicity problems (M.E. Falagas, S.K. Kasiakou, *Crit. Care*, **2006**, *10*, R 27).

Therefore, novel approaches are needed to treat *inter alia* resistant strains of *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Escherichia coli* (H.W. Boucher, G.H. Talbot, J.S. Bradley, J.E. Edwards Jr, D. Gilbert, L.B. Rice, M. Scheld, B. Spellberg, J. Bartlett, IDSA Report on Development Pipeline, CID **2009**, *48*, 1).

One emerging class of antibiotics is based on naturally occurring cationic peptides (T. Ganz, R.I. Lehrer, *Mol. Medicine Today* **1999**, *5*, 292-297; R.M. Epand, H.J. Vogel, *Biochim. Biophys. Acta* **1999**, *1462*, 11-28). These include disulfide-bridged β-hairpin and β-sheet peptides (such as the protegrins [V.N. Kokryakov, S.S.L. Harwig, E.A. Panyutich, A.A. Shevchenko, G.M. Aleshina, O.V. Shamova, H.A. Korneva, R.I. Lehrer, *FEBS Lett.* **1993**, *327*, 231-236], tachyplesins [T. Nakamura, H. Furunaka, T. Miyata, F. Tokunaga, T. Muta, S. Iwanaga, M. Niwa, T. Takao, Y. Shimonishi, *J. Biol. Chem.* **1988**, *263*, 16709-16713], and the defensins [R.I. Lehrer, A.K. Lichtenstein, T. Ganz, *Annu. Rev. Immunol.* **1993**, *11*, 105-128], amphipathic α-helical peptides (e.g. cecropins, dermaseptins, magainins, and mellitins [A. Tossi, L. Sandri, A. Giangaspero, *Biopolymers* **2000**, *55*, 4-30]), as well as other linear and loop-structured peptides. Although the mechanisms of action of antimicrobial cationic peptides are not yet fully understood, their primary site of interaction is the microbial cell membrane (H.W. Huang, *Biochemistry* **2000**, *39*, 8347-8352). Upon exposure to these agents, the cell membrane undergoes permeabilization, which is followed by rapid cell death. However, more complex mechanisms of action, for example, involving receptor-mediated signaling, cannot presently be ruled out (M. Wu, E. Maier, R. Benz, R.E. Hancock, *Biochemistry* **1999**, *38*, 7235-7242).

In the compounds described below, a strategy is introduced to stabilize β-hairpin conformations in backbone-cyclic cationic peptide mimetics exhibiting broad spectrum Gram-negative antimicrobial activity. This involves transplanting the hairpin sequence onto a template, whose function is to restrain the peptide loop backbone into a hairpin geometry.

Template-bound hairpin mimetic peptides have been described in the literature (D. Obrecht, M. Altorfer, J.A. Robinson, *Adv. Med. Chem.* **1999**, *4*, 1-68; J.A. Robinson, *Syn. Lett.* **2000**, *4*, 429-441) and the ability to generate β-hairpin peptidomimetics using combinatorial and parallel synthesis methods has now been established (L. Jiang, K. Moehle, B. Dhanapal, D. Obrecht, J.A. Robinson, *Helv. Chim. Acta*. **2000**, *83*, 3097-3112). Antibacterial template–fixed peptidomimetics and methods for their synthesis have been described in international patent applications WO02/070547 A1, WO2004/018503 A1, WO2007/079605 A2 and WO2012/016595 A1 but these molecules do not show broad spectrum Gram-negative antimicrobial activity having high potency against *Klebsiella pneumoniae* and/or *Acinetobacter baumannii* and/or *Escherichia coli*.

The present invention relates to novel β-hairpin peptidomimetics of formula (I),

$$\text{cyclo}[P^1\text{-}P^2\text{-}P^3\text{-}P^4\text{-}P^5\text{-}P^6\text{-}P^7\text{-}P^8\text{-}P^9\text{-}P^{10}\text{-}P^{11}\text{-}P^{12}\text{-}T^1\text{-}T^2] \quad (I)$$

wherein the single elements T or P are connected in either direction from the carbonyl (C=O) point of attachment to the nitrogen (N) of the next element and wherein

T^1 is a naturally or non-naturally occurring D α-amino acid containing an optionally substituted side-chain which forms a five-membered heterocycle, or a bicyclic system comprising the α-carbon and the α-amino atom;

T^2 is a naturally or non-naturally occurring L α-amino acid containing an optionally substituted side-chain which forms a five- or six-membered heterocycle, or a bicyclic system comprising the α-carbon and the α-amino atom;

P^1, P^3 and P^{10} are independently

a naturally or non-naturally occurring aliphatic or aromatic L α-amino acid containing in total 1 to 25 carbon- and/or heteroatoms in a single side-chain;

P^2 and P^8 are independently

a naturally or non-naturally occurring aromatic L α-amino acid containing in total 1 to 25 carbon- and/or heteroatoms in a single side-chain;

P^4 and P^9 are independently

a naturally or non-naturally occurring basic L α-amino acid containing in total 1 to 25 carbon- and/or heteroatoms in a single side-chain comprising at least one amino function; or

a naturally or non-naturally occurring alcoholic L α-amino acid containing in total 1 to 25 carbon- and/or heteroatoms in a single side-chain;

P^5 and P^7 are independently

a naturally or non-naturally occurring basic L α-amino acid containing in total 1 to 25 carbon- and/or heteroatoms in a single side-chain comprising at least one amino function;

P^6 is a naturally or non-naturally occurring basic L or D α-amino acid or cyclic α,α-disubstituted α-amino acid containing in total 1 to 25 carbon- and/or heteroatoms in a single side-chain comprising at least one amino function;

P^{11} is a naturally or non-naturally occurring aliphatic or aromatic L α-amino acid containing in total 1 to 25 carbon- and/or heteroatoms in a single side-chain; or

a naturally or non-naturally occurring L α-amino acid containing in total 1 to 25 carbon- and/or heteroatoms in a single side-chain comprising at least one urea function, amide function, ester function, sulfone function or ether function; or

a naturally or non-naturally occurring alcoholic L α-amino acid containing in total 1 to 25 carbon- and/or heteroatoms in a single side-chain;

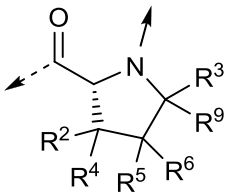
P^{12} is a naturally or non-naturally occurring aliphatic containing in total 1 to 25 carbon- and/or heteroatoms in a single side-chain; or

a naturally or non-naturally occurring alcoholic L α-amino acid containing in total 1 to 25 carbon- and/or heteroatoms in a single side-chain;

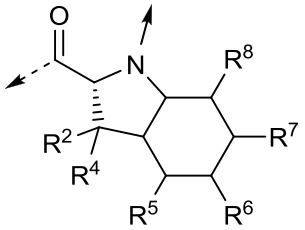
or a tautomer or rotamer thereof, or a salt, or a hydrate or solvate thereof.

A particular embodiment of the present invention relates to compounds according to general formula (I), wherein

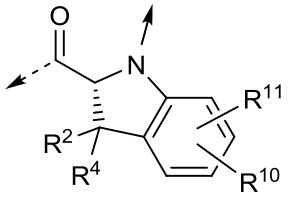
T^1 is an D α-amino acid residue of one of the formulae



AA1^D

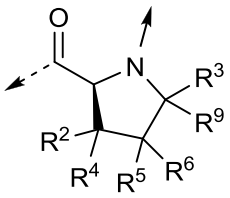


AA2^D

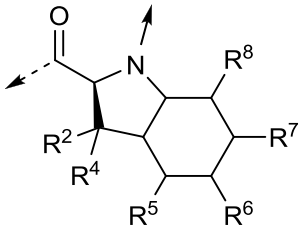


AA3^D

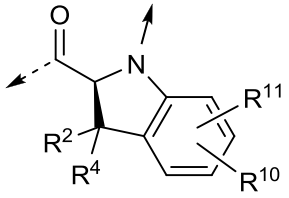
T^2 is an L α-amino acid residue of one of the formulae



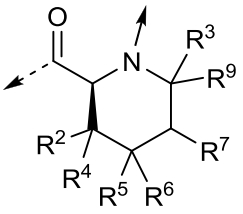
AA1



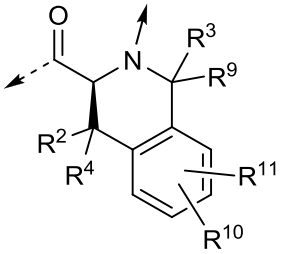
AA2



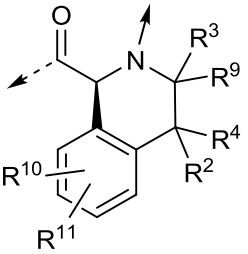
AA3



AA4

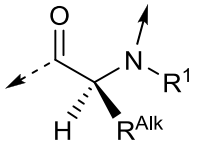


AA5

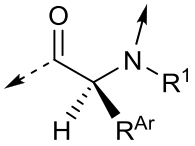


AA6

P^1, P^3 and P^{10} are independently an L α-amino acid residue of one of the formulae

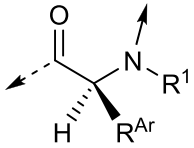


AA7



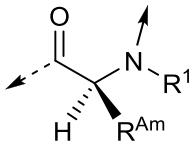
AA8

P^2 and P^8 are independently an L α-amino acid residue of formula

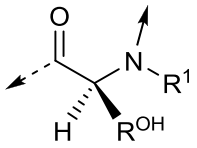


AA8

P^4 and P^9 are independently an L α-amino acid residue of one of the formulae

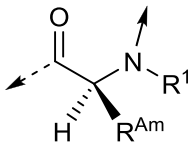


AA10



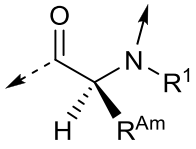
AA11

P^5 and P^7 are independently an L α-amino acid residue of formula

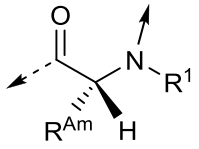


AA10

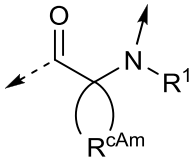
P^6 is an L or D α-amino acid residue of one of the formulae



AA10

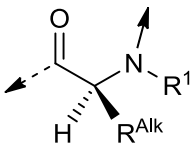


$AA10^D$

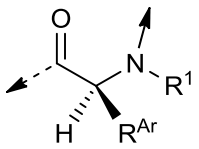


$AA10^C$

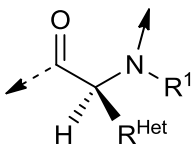
P^{11} is an L α-amino acid residue of one of the formulae



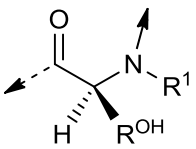
AA7



AA8

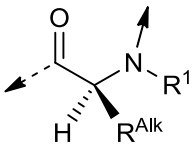


AA9

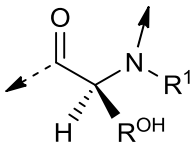


AA11

P^{12} is an L α-amino acid residue of one of the formulae



AA7



AA11

R^{Alk} is, with the proviso of containing less than 26 carbon- and/or heteroatoms,

$C_{1\text{-}12}$-alkyl; $C_{2\text{-}12}$-alkenyl; cycloalkyl; cycloalkyl-$C_{1\text{-}6}$-alkyl; or $C_{1\text{-}6}$-alkoxy-$C_{1\text{-}6}$-alkyl;

R^{Ar} is, with the proviso of containing less than 26 carbon- and/or heteroatoms,

$-(CR^1R^4)_nR^{19}$; $-(CH_2)_nO(CH_2)_mR^{19}$; $-(CH_2)_nS(CH_2)_mR^{19}$; or $-(CH_2)_nNR^{14}(CH_2)_mR^{19}$;

R^{Am} is, with the proviso of containing less than 26 carbon- and/or heteroatoms,

heterocycloalkyl; heterocycloalkyl-C_{1-6}-alkyl;

$-(CR^1R^{13})_qNR^{15}R^{16}$; $-(CH_2)_qC(=NR^{13})NR^{15}R^{16}$; $-(CH_2)_qC(=NOR^{17})NR^{15}R^{16}$;

$-(CH_2)_qC(=NNR^{15}R^{16})NR^{17}R^{18}$; $-(CR^1R^{13})_qNR^2C(=NR^{17})NR^{15}R^{16}$;

$-(CR^1R^{13})_qN=C(NR^{15}R^{16})NR^{17}R^{18}$; $-(CH_2)_nO(CH_2)_mNR^{15}R^{16}$;

$-(CH_2)_nO(CH_2)_mC(=NR^{17})NR^{15}R^{16}$; $-(CH_2)_nO(CH_2)_mC(=NOR^{17})NR^{15}R^{16}$;

$-(CH_2)_nO(CH_2)_mC(=NNR^{15}R^{16})NR^{17}R^{18}$; $-(CH_2)_nO(CH_2)_mNR^1C(=NR^{17})NR^{15}R^{16}$;

$-(CH_2)_nO(CH_2)_mN=C(NR^{15}R^{16})NR^{17}R^{18}$; $-(CH_2)_nS(CH_2)_mNR^{15}R^{16}$;

$-(CH_2)_nS(CH_2)_mC(=NR^{17})NR^{15}R^{16}$; $-(CH_2)_nS(CH_2)_mC(=NOR^{17})NR^{15}R^{16}$;

$-(CH_2)_nS(CH_2)_mC(=NNR^{15}R^{16})NR^{17}R^{18}$; $-(CH_2)_nS(CH_2)_mNR^1C(=NR^{17})NR^{15}R^{16}$; or

$-(CH_2)_nS(CH_2)_mN=C(NR^{15}R^{16})NR^{17}R^{18}$;

R^{cAm} is, $-(CH_2)_nNR^{15}(CH_2)_m-$;

R^{Het} is, with the proviso of containing less than 26 carbon- and/or heteroatoms,

$-(CR^1R^{13})_qOR^{14}$; $-(CR^1R^{13})_qSR^{15}$; $-(CR^1R^{13})_qSO_2R^{15}$; $-(CR^1R^{13})_qSO_2NR^1R^{14}$;

$-(CR^1R^{13})_qSO_2NR^{15}R^{16}$; $-(CR^1R^{13})_qNR^{14}SO_2R^{15}$; $-(CR^1R^{13})_qNR^{14}SO_2NR^{15}R^{16}$;

$-(CH_2)_nO(CH_2)_mOR^{14}$; $-(CH_2)_nO(CH_2)_mSR^{15}$; $-(CR^1R^{13})_qCOOR^{15}$;

$-(CR^1R^{13})_qCONR^{15}R^{16}$; or $-(CR^1R^{13})_qNR^2CONR^{15}R^{16}$;

R^{OH} is, with the proviso of containing less than 26 carbon- and/or heteroatoms,

$-(CR^1R^{13})_qOH$; $-(CR^1R^{13})_qSH$; $-(CH_2)_nO(CH_2)_mOH$; $-(CH_2)_nS(CH_2)_mOH$;

$-(CH_2)_nNR^1(CH_2)_mOH$; hydroxy-C_{1-8}-alkyl; hydroxy-C_{2-8}-alkenyl; hydroxy-cycloalkyl; or hydroxy-heterocycloalkyl;

R^1, R^2 and R^3 are independently

H; CF_3; C_{1-8}-alkyl; C_{2-8}-alkenyl; or aryl-C_{1-6}-alkyl;

R^4, R^5, R^6, R^7 and R^8 are independently

H; F; CF_3; C_{1-8}-alkyl; C_{2-8}-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C_{1-6}-alkyl; heteroaryl-C_{1-6}-alkyl; $-(CHR^{13})_oOR^{15}$; $-O(CO)R^{15}$; $-(CHR^{13})_oSR^{15}$; $-(CHR^{13})_oNR^{15}R^{16}$; $-(CHR^{13})_oOCONR^{15}R^{16}$; $-(CHR^{13})_oNR^1CONR^{15}R^{16}$; $-(CHR^{13})_oNR^1COR^{15}$; $-(CHR^{13})_oCOOR^{15}$; $-(CHR^{13})_oCONR^{15}R^{16}$; $-(CHR^{13})_oPO(OR^1)_2$; $-(CHR^{13})_oSO_2R^{15}$; $-(CHR^{13})_oNR^1SO_2R^{15}$; $-(CHR^{13})_oSO_2NR^{15}R^{16}$; $-(CR^1R^{13})_oR^{23}$; or $-(CHR^1)_nO(CHR^2)_mR^{23}$; or

R^4 and R^2; or R^5 and R^6 taken together can form:

=O; $=NR^1$; $=NOR^1$; $=NOCF_3$; or $-(CHR^1)_p-$;

R^4 and R^5; R^6 and R^7; R^7 and R^8; or R^6 and R^9 taken together can form:

$-(CHR^1)_p-$; $-(CH_2)_nO(CH_2)_m-$; $-(CH_2)_nS(CH_2)_m-$; or $-(CH_2)_nNR^1(CH_2)_m-$;

R^9 is H; F; CF_3; C_{1-8}-alkyl; C_{2-8}-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C_{1-6}-alkyl; heteroaryl-C_{1-6}-alkyl; $-(CHR^{13})_rOR^{15}$; $-O(CO)R^{15}$; $-(CHR^{13})_rSR^{15}$; $-(CHR^{10})_rNR^{15}R^{16}$; $-(CHR^{13})_rOCONR^{15}R^{16}$; $-(CHR^{13})_rNR^1CONR^{15}R^{16}$; $-(CHR^{13})_rNR^1COR^{15}$; $-(CHR^{13})_oCOOR^{15}$; $-(CHR^{13})_oCONR^{15}R^{16}$; $-(CHR^{13})_rPO(OR^1)_2$; $-(CHR^{13})_rSO_2R^{15}$; $-(CHR^{13})_rNR^1SO_2R^{15}$; $-(CHR^{13})_rSO_2NR^{15}R^{16}$; $-(CR^1R^{13})_oR^{23}$; or $-(CHR^1)_rO(CHR^1)_oR^{23}$;

R^{10}, R^{11} and R^{12} are independently

H; F; Cl; Br; I; CF_3; OCF_3; $OCHF_2$; CN; NO_2; C_{1-8}-alkyl; C_{2-8}-alkenyl; aryl; heteroaryl; aryl-C_{1-6}-alkyl; heteroaryl-C_{1-6}-alkyl; $-(CHR^{13})_oOR^{15}$; $-O(CO)R^{15}$; $-(CHR^{13})_oSR^{15}$; $-(CHR^{13})_oNR^{15}R^{16}$; $-(CHR^{13})_oOCONR^{15}R^{16}$; $-(CHR^{13})_oNR^1CONR^{15}R^{16}$; $-(CHR^{13})_oNR^1COR^{15}$; $-(CHR^{13})_oCOOR^{15}$; $-(CHR^{13})_oCONR^{15}R^{16}$; $-(CHR^{13})_oPO(OR^1)_2$; $-(CHR^{13})_oSO_2R^{15}$; $-(CHR^{13})_oNR^1SO_2R^{15}$; $-(CHR^{13})_oSO_2NR^{15}R^{16}$; or $-(CR^1R^{13})_oR^{23}$;

R^{13} is H; F; CF_3; C_{1-8}-alkyl; C_{2-8}-alkenyl; cycloalkyl; heterocycloalkyl; cycloalkyl-C_{1-6}-alkyl; heterocycloalkyl-C_{1-6}-alkyl; aryl; heteroaryl; aryl-C_{1-6}-alkyl; heteroaryl-C_{1-6}-alkyl; $-(CHR^1)_oOR^{15}$; $-OCOR^1$; $-(CHR^1)_oNR^{15}R^{16}$; $-COOR^{15}$; $-CONR^{15}R^{16}$; $-SO_2R^{15}$; or $-SO_2NR^{15}R^{16}$;

R^{14} is H; CF_3; C_{1-8}-alkyl; C_{2-8}-alkenyl; cycloalkyl; heterocycloalkyl; cycloalkyl-C_{1-6}-alkyl; heterocycloalkyl-C_{1-6}-alkyl; aryl; heteroaryl; aryl-C_{1-6}-alkyl; heteroaryl-C_{1-6}-alkyl; cycloalkyl-aryl; heterocycloalkyl-aryl; cycloalkyl-heteroaryl; heterocycloalkyl-heteroaryl; aryl-cycloalkyl; aryl-heterocycloalkyl; heteroaryl-cycloalkyl; heteroaryl-heterocycloalkyl; $-(CHR^1)_oOR^{15}$; $-(CHR^1)_oSR^{15}$; $-(CHR^1)_oNR^{15}R^{16}$; $-(CHR^1)_oCOOR^{15}$; $-(CHR^1)_oCONR^{15}R^{16}$; or $-(CHR^1)_oSO_2R^{15}$;

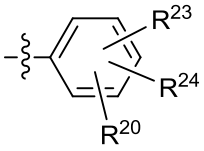
R^{15}, R^{16}, R^{17} and R^{18} are independently

H; C_{1-8}-alkyl; C_{2-8}-alkenyl; C_{1-6}-alkoxy; cycloalkyl; heterocycloalkyl;

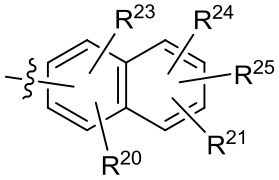
cycloalkyl-C_{1-6}-alkyl; heterocycloalkyl-C_{1-6}-alkyl; aryl; heteroaryl; aryl-C_{1-6}-alkyl; heteroaryl-C_{1-6}-alkyl; cycloalkyl-aryl; heterocycloalkyl-aryl; cycloalkyl-heteroaryl; heterocycloalkyl-heteroaryl; aryl-cycloalkyl; aryl-heterocycloalkyl; heteroaryl-cycloalkyl; or heteroaryl-heterocycloalkyl; or

the structural elements -$NR^{15}R^{16}$ and -$NR^{17}R^{18}$ can independently form: heterocycloalkyl; aryl-heterocycloalkyl; or heteroaryl-heterocycloalkyl;

R^{19} is an aryl group of one of the formulae

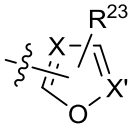


AR1

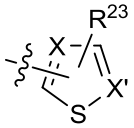


AR2

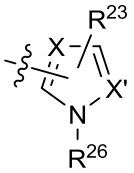
or a group of one of the formulae



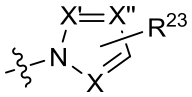
H1



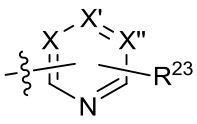
H2



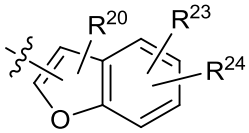
H3



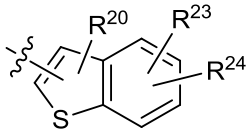
H4



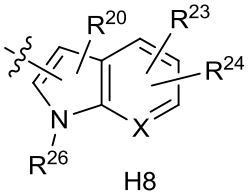
H5



H6



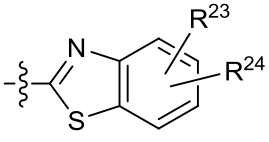
H7



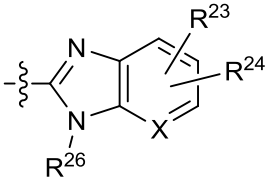
H8



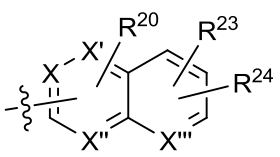
H9



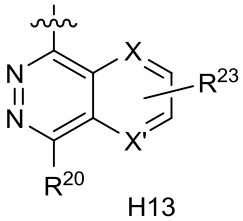
H10



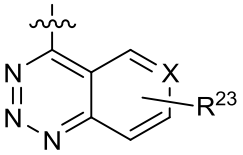
H10



H12



H13



H14

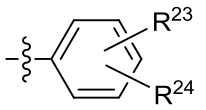
X, X', X'' and X''' are independently

-CR^{20}; or N;

R^{20} and R^{21} are independently

H; F; Cl; Br; I; OH; NH_2; NO_2; CN; CF_3; $OCHF_2$; OCF_3; C_{1-8}-alkyl; C_{2-8}-alkenyl; aryl; heteroaryl; aryl-C_{1-6}-alkyl; heteroaryl-C_{1-6}-alkyl; -$(CH_2)_oR^{22}$; -$(CH_2)_oOR^{15}$; -$O(CO)R^{15}$; -$O(CH_2)_oR^{22}$; -$(CH_2)_oSR^{15}$; -$(CH_2)_oNR^{15}R^{16}$; -$(CH_2)_oOCONR^{15}R^{16}$; -$(CH_2)_oNR^1CONR^{15}R^{16}$; -$(CH_2)_oNR^1COR^{15}$; -$(CH_2)_oCOOR^{15}$; -$(CH_2)_oCONR^{15}R^{16}$; -$(CH_2)_oPO(OR^1)_2$; -$(CH_2)_oSO_2R^{14}$; or -$(CH_2)_oCOR^{15}$;

R^{22} is an aryl group of the formula



AR3

R^{23}, R^{24} and R^{25} are independently

H; F; Cl; Br; I; OH; NH_2; NO_2; CN; CF_3; $OCHF_2$; OCF_3; C_{1-8}-alkyl; C_{2-8}-alkenyl; -$(CH_2)_oOR^{15}$; -$O(CO)R^{15}$; -$(CH_2)_oNR^1R^{15}$; -$(CH_2)_oCOOR^{15}$; -$(CH_2)_oCONR^1R^{15}$;

R^{26} is H; Ac; C_{1-8}-alkyl; or aryl-C_{1-6}-alkyl;

n and m are independently an integer of 0-5 with the proviso that $n+m \leq 6$;

o is 0-4; p is 2-6; q is 1-6; and r is 1-3;

or a pharmaceutically acceptable salt thereof.

Each single group "R^x" with the same index-number x for x = 1 – 26 is independently selected on each occurrence in a specific formula and, therefore, they can be the same or different.

As used in this description, the term “alkyl”, taken alone or in combinations (i.e. as part of another group, such as “aryl-C_{1-6}-alkyl”) designates saturated, straight-chain or branched hydrocarbon radicals and may be optionally substituted. The term “C_{x-y}-alkyl” (x and y each being an integer) refers to an alkyl group as defined before containing x to y carbon atoms. For example a C_{1-6}-alkyl group contains one to six carbon atoms. Representative examples of alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *n*-hexyl and the like.

The term “alkenyl”, taken alone or in combinations, designates straight chain or branched hydrocarbon radicals containing at least one or, depending on the chain length, up to four olefinic double bonds. Such alkenyl moieties are optionally substituted and can independently exist as *E* or *Z* configurations per double bond, which are all part of the invention. The term “C_{x-y}-alkenyl” (x and y each being an integer) refers to an alkenyl group as defined before containing x to y carbon atoms.

The term “cycloalkyl”, taken alone or in combinations, refers to a saturated or partially unsaturated alicyclic moiety having from three to ten carbon atoms and may be optionally substituted. Examples of this moiety include, but are not limited to, cyclohexyl, norbornyl, decalinyl and the like.

The term “heterocycloalkyl”, taken alone or in combinations, describes a saturated or partially unsaturated mono- or bicyclic moiety having from three to nine ring carbon atoms and one or more ring heteroatoms selected from nitrogen, oxygen or sulphur. This term includes, for example, morpholino, piperazino, azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, octahydro-1*H*-indolyl, 1,7-diazaspiro[4.4]nonanyl and the like. Said heterocycloalkyl ring(s) might be optionally substituted.

The term “aryl”, taken alone or in combinations, designates aromatic carbocyclic hydrocarbon radicals containing one or two six-membered rings, such as phenyl or naphthyl, which may be optionally substituted by up to three substituents such as Br,

Cl, F, CF_3, OH, OCF_3, $OCHF_2$, NH_2, $N(CH_3)_2$, NO_2, CN, C_{1-6}-alkyl, C_{2-6}-alkenyl, phenyl or phenoxy.

The term "heteroaryl", taken alone or in combinations, 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 whereby the heteroaryl radicals or tautomeric forms thereof may be attached via any suitable atom. Said heteroaryl ring(s) are optionally substituted, e.g. as indicated above for "aryl".

The term "aryl-C_{x-y}-alkyl", as used herein, refers to an C_{x-y}-alkyl group as defined above, substituted by an aryl group, as defined above. Representative examples of aryl-C_{x-y}-alkyl moieties include, but are not limited to, benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and the like.

The term "heteroaryl-C_{x-y}-alkyl", as used herein, refers to an C_{x-y}-alkyl group as defined above, substituted by a heteroaryl group, as defined above. Examples of heteroaryl-C_{x-y}-alkyl groups include pyridin-3-ylmethyl, (1*H*-pyrrol-2-yl)ethyl and the like.

The term "aryl-cycloalkyl", as used herein, refers to a cycloalkyl group as defined above, substituted or annelated by an aryl group, as defined above. Examples of aryl-cycloalkyl moieties include, but are not limited to, phenylcyclopentyl, 2,3-dihydro-1*H*-indenyl, 1,2,3,4-tetrahydronaphthalenyl and the like.

The term "aryl-heterocycloalkyl", as used herein, refers to a heterocycloalkyl group as defined above, substituted or annelated by an aryl group, as defined above. Examples of aryl-heterocycloalkyl moieties include, but are not limited to, indolinyl, 1,2,3,4-tetrahydroquinolinyl and the like.

The term “heteroaryl-cycloalkyl”, as used herein, refers to a cycloalkyl group as defined above, substituted or annelated by a heteroaryl group, as defined above. Examples of heteroaryl-cycloalkyl moieties include, but are not limited to, 5,6,7,8-tetrahydro-quinolinyl and the like.

The term “heteroaryl-heterocycloalkyl”, as used herein, refers to a heterocycloalkyl group as defined above, substituted or annelated by a heteroaryl group, as defined above. Examples of heteroaryl-heterocycloalkyl moieties include, but are not limited to, 4-(thiazol-2-yl)piperazinyl, 5,6,7,8-tetrahydro-1,6-naphthyridinyl and the like.

The terms “cycloalkyl-aryl”, “heterocycloalkyl-aryl”, “cycloalkyl-heteroaryl”, and “heterocycloalkyl-heteroaryl”, as used herein, are defined analogously to the terms “aryl-cycloalkyl”, “aryl-heterocycloalkyl”, “heteroaryl-cycloalkyl” and “heteroaryl-heterocycloalkyl”, as defined above, but connected in the opposite direction, e.g. instead of 4-(thiazol-2-yl)piperazinyl the term refers to 2-(piperazin-1-yl)thiazolyl and the like.

The terms “hydroxy”, “alkoxy“ and “aryloxy“, taken alone or in combinations, refer to the groups of -OH, -O-alkyl and -O-aryl respectively, wherein an alkyl group or an aryl group is as defined above. The term “C_{x-y}-alkoxy” (x and y each being an integer) refers to an -O-alkyl group as defined before containing x to y carbon atoms attached to an oxygen atom. Representative examples of alkoxy groups include methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy and the like. Examples of aryloxy include e.g. phenoxy. For avoidance of doubt e.g. the term “hydroxy-C_{1-8}-alkyl” represents, among others, groups like e.g. hydroxymethyl, 1-hydroxypropyl, 2-hydroxypropyl or 3-hydroxy-2,3-dimethylbutyl.

The term “optionally substituted” is in general intended to mean that a group, such as, but not limited to C_{x-y}-alkyl, C_{x-y}-alkenyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, C_{x-y}-alkoxy and aryloxy may be substituted with one or more substituents

independently selected from amino (-NH_2), dimethylamino, nitro (-NO_2), halogen (F, Cl, Br, I), CF_3, cyano (-CN), hydroxy, methoxy, ethoxy, phenyloxy, benzyloxy, acetoxy, oxo (=O), carboxy, carboxamido, methyl, ethyl, phenyl, benzyl, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate.

In the context of this invention the term “naturally or non-naturally occurring α-amino acid” typically comprises any natural α-amino acid, such as the proteogenic amino acids (examples listed below), their natural or semi-synthetic derivatives as well as α-amino acids of purely synthetic origin. This term includes as well α-amino acids which are optionally substituted at the α-nitrogen of the amino acid such as, but not limited to, acetylation or alkylation, e.g. methylation, or benzylation.

The term “aliphatic α-amino acid” refers to α-amino acids with an aliphatic side-chain, such as, but not limited to, alanine, valine, leucine, isoleucine, *n*-octylglycine etc.

The term “aromatic α-amino acid” refer to α-amino acids with a side-chain comprising an aromatic or heteroaromatic group, such as, but not limited to, phenylalanine, tryptophan, histidine, *O*-methyl-tyrosine, 4-trifluormethyl-phenylalanine, 3,4-dichloro-homophenylalanine etc.

The term “basic α-amino acid” refers to α-amino acids with a side-chain comprising at least one amino group, such as, but not limited to, lysine, ornithine etc. and further substituted derivatives thereof. The aforesaid amino group can be substituted by amidino groups to form α-amino acids, such as, but not limited to, arginine, homoarginine etc. and further substituted derivatives thereof, or by diamino methylidine groups.

The term “alcoholic α-amino acid” refers to α-amino acids with a side-chain comprising an alcoholic or thioalcoholic group, i.e. a hydroxy or sulfhydryl function, such as, but not limited to, serine, threonine etc.

For the avoidance of doubt the term “single side-chain” in the context of an α-amino acid refers to a structure where the α-carbon of the amino acid is covalently connected to the (in-chain) groups of the carbonyl (C=O) and nitrogen (N) as well as to one hydrogen (H) and one variable side-chain, e.g. as defined above. A “single side-chain” may include as well a heterocyclic structure comprising the α-amino atom, such as but not limited to, proline, pipecolic acid etc.

For the avoidance of doubt the term “heteroatom” refers to any atom that is not carbon or hydrogen.

The descriptors L respectively D refer to the stereochemistry at the α-position of an α-amino acid and are used according the Fischer-Rosanoff convention of the IUPAC.
The peptidomimetics of the present invention can also be diastereomers (e.g. epimers) of compounds of formula **(I)** if no specific stereochemistry of the chiral center is determined in the description. These stereoisomers can be prepared by a modification of the process described below in which the appropriate isomers (e.g. epimers/ enantiomers) of chiral starting materials are used. In case of ambiguous stereochemistry in the above description each single epimer is part of the present invention as well as a mixture of both.

A further embodiment of the present invention may also include compounds, which are identical to the compounds of formula **(I)**, except that one or more atoms are replaced by an atom having an atomic mass number or mass different from the atomic mass number or mass usually found in nature, e.g. compounds enriched in ^{2}H (D), ^{3}H, ^{11}C, ^{14}C, ^{127}I etc. These isotopic analogs and their pharmaceutical salts and formulations are considered useful agents in the therapy and/or diagnostic, for example, but not limited to, where a fine-tuning of *in vivo* half-life time could lead to an optimized dosage regimen.

A further particular embodiment of the invention relates to derivatives of general formula **(I)**, wherein specifically

T^1 is the D α-amino acid residue $AA1^D$; and

T^2 is the L α-amino acid residue AA1;

or a pharmaceutically acceptable salt thereof.

An alternative particular embodiment of the invention relates to derivatives of general formula **(I)**, wherein specifically

P^{11} is an L α-amino acid residue of one of the formulae

AA7; AA9; or AA11;

or a pharmaceutically acceptable salt thereof.

Another alternative particular embodiment of the invention relates to derivatives of general formula **(I)**, wherein specifically

P^4 is the L α-amino acid residue AA10;

P^6 is an α-amino acid residue of one of the formulae

$AA10^D$; or $AA10^C$; and

P^{10} is the L α-amino acid residue AA7;

or a pharmaceutically acceptable salt thereof.

In a further particular embodiment of the invention the elements of general formula **(I)** are defined as follows

T^1 is ^{D}Pro; ^{D}Pro((3*R*)OH); ^{D}Pro((3*S*)OH); ^{D}Pro((4*R*)OH); ^{D}Pro((4*S*)OH); ^{D}Pic; or ^{D}Tic;

T^2 is Pro; Pro((4*R*)NH_2); Pro((4*S*)NH_2); Pro((4*R*)OH); Pro((4*S*)OH); Pro((3*R*)OH); Pro((3*S*)OH); Pro((4*S*)OBn); Pic; Oic; Tic; or Tic(7OH);

P^1, P^3 and P^{10} are independently

Ala; Abu; Ala(CF_3); Leu; Nle; Ile; Val; Nva; Cha;Chg; *t*BuGly; OctGly; Phe; Trp; Tyr; Tyr(Me); or Tza;

P^2 and P^8 are independently

His; Phe; Trp; Tyr; Tyr(Me); or Tza;

P^4 and P^9 are independently

Ser; Hse; Thr; Dab; Dab(*i*Pr); Dap; Lys; Orn; or Orn(*i*Pr);

P^5 and P^7 are independently

Dab; Dab(2PyrMe); Dap; Lys; Orn; or Orn(*i*Pr);

P^6 is Dab; Dap; ^{D}Dab; ^{D}Dap; or Pip;

P^{11} is Ala; Abu; Ala(CF_3); Leu; Nle; Ile; Val; Nva; Cha; Chg; *t*BuGly; OctGly; Alb; Ser; Hse; Asn; Thr; or Tyr; and

P^{12} is Ala; Leu; Ile; Val; Nva; Ser; Hse; Thr; or *allo*Thr;

or a pharmaceutically acceptable salt thereof.

In another further particular embodiment of the invention the elements of general formula **(I)** are defined as follows

T^1 is ^{D}Pro; ^{D}Pro((3*R*)OH); ^{D}Pro((3*S*)OH); ^{D}Pro((4*R*)OH); ^{D}Pro((4*S*)OH); ^{D}Pic; or ^{D}Tic;

T^2 is Pro; Pro((4*R*)NH_2); Pro((4*S*)NH_2); Pro((4*R*)OH); Pro((4*S*)OH); Pro((3*R*)OH); Pro((3*S*)OH); Pro((4*S*)OBn); Pic; Oic; Tic; or Tic(7OH);

P^1, P^3 and P^{10} are independently

Ala; Abu; Ala(CF_3); Leu; Nle; Ile; Val; Nva; Cha; Chg; *t*BuGly; OctGly; Phe; Trp; Tyr; Tyr(Me); or Tza;

P^2 and P^8 are independently

His; Phe; Trp; Tyr; Tyr(Me); or Tza;

P^4 and P^9 are independently

Ser; Hse; Thr; Dab; Dab(*i*Pr); Dap; Lys; Orn; or Orn(*i*Pr);

P^5 and P^7 are independently

Dab; Dab(2PyrMe); Dap; Lys; Orn; or Orn(*i*Pr);

P^6 is Dab; Dap; ^{D}Dab; ^{D}Dap or Pip;

P^{11} is Ala; Abu; Ala(CF_3); Leu; Nle; Ile; Val; Nva; Cha; Chg; *t*BuGly; OctGly; Alb; Ser; Hse; Asn; or Thr; and

P^{12} is Ala; Leu; Ile; Val; Nva; Ser; Hse; Thr; or *allo*Thr;

or a pharmaceutically acceptable salt thereof.

In another further particular embodiment of the invention the elements of general formula **(I)** are defined as follows

T^1 is ^{D}Pro;

T^2 is Pro; or Pro((3*S*)OH);

P^1 is Leu; Ile; Val; Nva; or Trp;

P^2 is His; Trp; or Tyr;

P^3 is Leu; Cha; *t*BuGly; Trp; Tyr; or Tyr(Me);

P^4 is Dab;

P^5 is Orn; or Lys;

P^6 is Dab; ^{D}Dab; or Pip;

P^7 is Dab;

P^8 is Trp;

P^9 is Hse; or Dab;

P^{10} is *t*BuGly; Ile; Val; Nva; Cha; Chg; or Trp;

P^{11} is Ala; Val; Alb; Ser; Asn; or Tyr; and

P^{12} is Val; Ser; or *allo*Thr;

or a pharmaceutically acceptable salt thereof.

In another further particular embodiment of the invention the elements of general formula **(I)** are defined as follows

T^1 is ^{D}Pro;

T^2 is Pro; or Pro((3*S*)OH);

P^1 is Leu; Ile; Val; Nva; or Trp;

P^2 is His; Trp; or Tyr;

P^3 is Leu; Cha; *t*BuGly; Trp; Tyr; or Tyr(Me);

P^4 is Dab;

P^5 is Orn; or Lys;

P^6 is Dab; ^{D}Dab; or Pip;

P^7 is Dab;

P^8 is Trp;

P^9 is Hse; or Dab;

P^{10} is *t*BuGly; Ile; Val; Nva; Cha; Chg; or Trp;

P^{11} is Ala; Val; Alb; Ser; or Asn; and

P^{12} is Val; Ser; or *allo*Thr;

or a pharmaceutically acceptable salt thereof.

In another further particular embodiment of the invention the elements of general formula **(I)** are defined as follows

T^1 is ^{D}Pro;

T^2 is Pro; or Pro((3*S*)OH);

P^1 is Leu; Val; Nva; or Trp;

P^2 is His; or Trp;

P^3 is Leu; Cha; *t*BuGly; Tyr; or Tyr(Me);

P^4 is Dab;

P^5 is Orn; or Lys;

P^6 is ^{D}Dab; or Pip;

P^7 is Dab;

P^8 is Trp;

P^9 is Hse; or Dab;

P^{10} is *t*BuGly; Val; Nva; Cha; or Chg;

P^{11} is Ala; Val; Alb; or Ser; and

P^{12} is Val; Ser; or *allo*Thr;

or a pharmaceutically acceptable salt thereof.

In another further particular embodiment of the invention the elements of general formula **(I)** are defined as follows

T^1 is ^{D}Pro;

T^2 is Pro; Pro((4*S*)OH); Pro((3*R*)OH); or Pro((3*S*)OH);

P^1 is Ala; Leu; Ile; Val; Nva; Phe; Trp; or Tyr;

P^2 is His; Phe; Trp; or Tyr;

P^3 is Ala; Leu; Ile; Val; Nva; Cha; Chg; *t*BuGly; Phe; Trp; Tyr; or Tyr(Me);

P^4 and P^7 are Dab;

P^5 is Lys; Orn; or Orn(*i*Pr);

P^6 is Dab; Dap; ^{D}Dab; ^{D}Dap or Pip;

P^8 is Phe; Trp; Tyr; or Tyr(Me);

P^9 is Ser; Hse; Dab; or Dap;

P^{10} is Ala; Leu; Ile; Val; Nva; Cha; Chg; or *t*BuGly;

P^{11} is Ala; Leu; Ile; Val; Nva; Alb; Ser; Hse; or Thr; and

P^{12} is Ala; Leu; Ile; Val; Nva; Ser; Hse; Thr; or *allo*Thr;

or a pharmaceutically acceptable salt thereof.

In another further particular embodiment of the invention the elements of general formula **(I)** are defined as follows

T^1 is ^{D}Pro;

T^2 is Pro; or Pro((3*S*)OH);

P^1 is Leu; Ile; Val; Nva; or Trp;

P^2 is His; Trp; or Tyr;

P^3 is Leu; Cha; *t*BuGly; Trp; Tyr; or Tyr(Me);

P^4 and P^7 are Dab;

P^5 is Orn; or Lys;

P^6 is ^{D}Dab; or Pip;

P^8 is Trp;

P^9 is Hse; or Dab;

P^{10} is *t*BuGly; Ile; Val; Nva; Cha; or Chg;

P^{11} is Ala; Val; Alb; Ser; Asn; or Tyr; and

P^{12} is Val; Ser; or *allo*Thr;

or a pharmaceutically acceptable salt thereof.

In another further particular embodiment of the invention the elements of general formula **(I)** are defined as follows

T^1 is ^{D}Pro;

T^2 is Pro; or Pro((3*S*)OH);

P^1 is Leu; Ile; Val; Nva; or Trp;

P^2 is His; Trp; or Tyr;

P^3 is Leu; Cha; *t*BuGly; Trp; Tyr; or Tyr(Me);

P^4 and P^7 are Dab;

P^5 is Orn; or Lys;

P^6 is ^{D}Dab; or Pip;

P^8 is Trp;

P^9 is Hse; or Dab;

P^{10} is *t*BuGly; Ile; Val; Nva; Cha; or Chg;

P^{11} is Ala; Val; Alb; Ser; or Asn; and

P^{12} is Val; Ser; or *allo*Thr;

or a pharmaceutically acceptable salt thereof.

In another further particular embodiment of the invention the elements of general formula **(I)** are defined as follows

T^1 is ^{D}Pro;

T^2 is Pro; or Pro((3*S*)OH);

P^1 is Leu; Val; Nva; or Trp;

P^2 is His; or Trp;

P^3 is Leu; Cha; Chg; *t*BuGly; Tyr; or Tyr(Me);

P^4 and P^7 are Dab;

P^5 is Lys; or Orn;

P^6 is ^{D}Dab; or Pip;

P^8 is Trp;

P^9 is Hse; or Dab;

P^{10} is Val; Nva; Cha; Chg; or *t*BuGly;

P^{11} is Ala; Val; Alb; or Ser; and

P^{12} is Val; Ser; or *allo*Thr;

or a pharmaceutically acceptable salt thereof.

Hereinafter follows a list of abbreviations, corresponding to generally adopted usual practice, of amino acids which, or the residues of which, are suitable for the purposes of the present invention and referred to in this document.

In spite of this specific determination of amino acids, it is noted that, for a person skilled in the art, it is obvious that derivatives of these amino acids, resembling alike structural and physico-chemical properties, lead to functional analogs with similar biological activity, and therefore still form part of the gist of this invention.

Ala	L-Alanine
Arg	L-Arginine
Asn	L-Asparagine
Asp	L-Aspartic acid
Cit	L-Citrulline
Cys	L-Cysteine
Gln	L-Glutamine
Glu	L-Glutamic acid
Gly	Glycine
His	L-Histidine
Ile	L-Isoleucine
Leu	L-Leucine
Lys	L-Lysine
Met	L-Methionine
Orn	L-Ornithine
Phe	L-Phenylalanine
Pro	L-Proline
Ser	L-Serine
Thr	L-Threonine

Trp	L-Tryptophan
Tyr	L-Tyrosine
Val	L-Valine
Abu	(*S*)-2-aminobutanoic acid
Agp	(*S*)-2-amino-3-guanidinopropanoic acid
Ala(*t*Bu)	(*S*)-2-amino-4,4-dimethylpentanoic acid
Ala(4butoxyPhUr)	(*S*)-2-amino-3-(3-(4-butoxyphenyl)ureido)propanoic acid
Ala(*c*Hex)	(*S*)-2-amino-3-cyclohexylpropanoic acid
Ala(*c*Pr)	(*S*)-2-amino-3-cyclopropylpropanoic acid
Ala(*i*PrUr)	(*S*)-2-amino-3-(3-isopropylureido)propanoic acid
Ala(2ClPhUr)	(*S*)-2-amino-3-(3-(2-chlorophenyl)ureido)propanoic acid
Ala(4ClPhUr)	(*S*)-2-amino-3-(3-(4-chlorophenyl)ureido)propanoic acid
Ala(2Furyl)	(*S*)-2-amino-3-(furan-2-yl)propanoic acid
Ala(3Furyl)	(*S*)-2-amino-3-(furan-3-yl)propanoic acid
Ala(1Im)	(*S*)-2-amino-3-(1H-imidazol-1-yl)propanoic acid
Ala(2Im)	(*S*)-2-amino-3-(1H-imidazol-2-yl)propanoic acid
Ala(Ppz)	(*S*)-2-amino-3-(piperazin-1-yl)propanoic acid
Ala(*c*Pr)	(*S*)-2-amino-3-cyclopropylpropanoic acid
Ala(Pyrazinyl)	(*S*)-2-amino-3-(pyrazin-2-yl)propanoic acid
Ala(1Pyrazolyl)	(*S*)-2-amino-3-(1H-pyrazol-1-yl)propanoic acid
Ala(3Pyrazolyl)	(*S*)-2-amino-3-(1H-pyrazol-3-yl)propanoic acid
Ala(2Pyrimidin)	(*S*)-2-amino-3-(pyrimidin-2-yl)propanoic acid
Ala(4Pyrimidin)	(*S*)-2-amino-3-(pyrimidin-4-yl)propanoic acid
Ala(5Pyrimidin)	(*S*)-2-amino-3-(pyrimidin-5-yl)propanoic acid
Ala(3PyrMeUr)	(*S*)-2-amino-3-(3-(pyridin-3-ylmethyl)ureido)propanoic acid
Ala(2Quin)	(*S*)-2-amino-3-(quinolin-2-yl)propanoic acid
Ala(3Quin)	(*S*)-2-amino-3-(quinolin-3-yl)propanoic acid
Ala(4Quin)	(*S*)-2-amino-3-(quinolin-4-yl)propanoic acid
Alb	(*S*)-2-amino-3-ureidopropanoic acid

*t*BuGly	(*S*)-2-amino-3,3-dimethylbutanoic acid
Bbta	(*S*)-2-amino-3-(1-benzothiophen-3-yl)propanoic acid
Bip	(*S*)-2-amino-3-(4-biphenylyl)propanoic acid
Cha	(*S*)-2-amino-3-cyclohexylpropanoic acid
Chg	(*S*)-2-amino-2-cyclohexylacetic acid
Dab	(*S*)-2,4-diaminobutanoic acid
Dab(Ac)	(*S*)-4-acetamido-2-aminobutanoic acid
Dab(*c*Pr)	(*S*)-2-amino-4-(cyclopropylamino)butanoic acid
Dab(*i*Pr)	(*S*)-2-amino-4-(isopropylamino)butanoic acid
Dab(2PyrMe)	(*S*)-2-amino-4-(pyridin-2-ylmethylamino)butanoic acid
Dap	(*S*)-2,3-diaminopropanoic acid
Dap(Ac)	(*S*)-3-acetamido-2-aminopropanoic acid
Dap(AcThr)	(*S*)-3-((2*S*,3*R*)-2-acetamido-3-hydroxybutanamido)-2-aminopropanoic acid
Dap(*c*Pr)	(*S*)-2-amino-3-(cyclopropylamino)propanoic acid
Dap(*i*Pr)	(*S*)-2-amino-3-(isopropylamino)propanoic acid
Dap($MeSO_2$)	(*S*)-2-amino-3-(methylsulfonamido)propanoic acid
Dap(2,3-OHpropionyl)	(2*S*)-2-amino-3-(2,3-dihydroxypropanamido)propanoic acid
Dap(Thr)	(*S*)-2-amino-3-((2S,3R)-2-amino-3-hydroxybutanamido)-propanoic acid
Gly(*c*Pr)	(*S*)-2-amino-2-cyclopropylacetic acid
hAla(1Im)	(*S*)-2-amino-3-(1H-imidazol-1-yl)-butanoic acid
hAla(2Im)	(*S*)-2-amino-3-(1H-imidazol-2-yl)-butanoic acid
hArg	(*S*)-2-amino-6-guanidinohexanoic acid
hCha	(*S*)-2-amino-4-cyclohexylbutanoic acid
hCys	(*S*)-2-amino-4-mercaptobutanoic acid
hHis	(*S*)-2-amino-4-(1*H*-imidazol-5-yl)butanoic acid
hLeu	(*S*)-2-amino-5-methylhexanoic acid
hLys	(*S*)-2,7-diaminoheptanoic acid
h2Pal	(*S*)-2-amino-4-(pyridin-2-yl)-butanoic acid

h3Pal	(*S*)-2-amino-4-(pyridine-3-yl)-butanoic acid
h4Pal	(*S*)-2-amino-4-(pyridine-4-yl)-butanoic acid
hSer	(*S*)-2-amino-4-hydroxybutanoic acid
hTrp	(*S*)-2-amino-4-(1*H*-indol-3-yl)butanoic acid
hTyr	(*S*)-2-amino-4-(4-hydroxyphenyl)butanoic acid
His(Me)	(*S*)-2-amino-3-(1-methyl-1*H*-imidazol-5-yl)propanoic acid
His(Bn)	(*S*)-2-amino-3-(1-benzyl-1*H*-imidazol-5-yl)propanoic acid
Hse	(*S*)-2-amino-4-hydroxybutanoic acid
Lys(Bz)	(*S*)-2-amino-6-benzamidohexanoic acid
Lys(Me)	(*S*)-2-amino-6-(methylamino)hexanoic acid
Lys(Nic)	(*S*)-2-amino-6-(nicotinamido)hexanoic acid
Met(O_2)	(*S*)-2-amino-4-(methylsulfonyl)butanoic acid
1Nal	(*S*)-2-amino-3-naphthalen-1-ylpropanoic acid
2Nal	(*S*)-2-amino-3-naphthalen-2-ylpropanoic acid
Nle	(*S*)-2-amino-hexanoic acid
Nle(6OBn)	(*S*)-2-amino-6-(benzyloxy)hexanoic acid
Nva	(*S*)-2-aminopentanoic acid
OctG	(*S*)-2-aminodecanoic acid
Oic	(2*S*,3a*S*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid
Orn(Ac)	(*S*)-5-acetamido-2-aminopentanoic acid
Orn(*c*Pr)	(*S*)-2-amino-5-(cyclopropylamino)pentanoic acid
Orn(*i*Pr)	(*S*)-2-amino-5-(isopropylamino)pentanoic acid
2Pal	(*S*)-2-amino-3-(pyridine-2-yl) propionic acid
3Pal	(*S*)-2-amino-3-(pyridine-3-yl)propionic acid
4Pal	(*S*)-2-amino-3-(pyridine-4-yl)propionic acid
Phe(2Cl)	(*S*)-2-amino-3-(2-chlorophenyl)propanoic acid
Phe(3Cl)	(*S*)-2-amino-3-(3-chlorophenyl)propanoic acid
Phe(4Cl)	(*S*)-2-amino-3-(4-chlorophenyl)propanoic acid
Phe(3,4Cl_2)	(*S*)-2-amino-3-(3,4-dichlorophenyl)propanoic acid
Phe(2F)	(*S*)-2-amino-3-(2-fluorophenyl)propanoic acid

Phe(3F)	(*S*)-2-amino-3-(3-fluorophenyl)propanoic acid
Phe(4F)	(*S*)-2-amino-3-(4-fluorophenyl)propanoic acid
Phe(3,4F_2)	(*S*)-2-amino-3-(3,4-difluorophenyl)propanoic acid
Phe(3CN)	(*S*)-2-amino-3-(3-cyanophenyl)propanoic acid
Phe(4CN)	(*S*)-2-amino-3-(4-cyanophenyl)propanoic acid
Phe(2CF_3)	(*S*)-2-amino-3-(2-(trifluoromethyl)phenyl)propanoic acid
Phe(3CF_3)	(*S*)-2-amino-3-(3-(trifluoromethyl)phenyl)propanoic acid
Phe(4CF_3)	(*S*)-2-amino-3-(4-(trifluoromethyl)phenyl)propanoic acid
Phe(3,4(CF_3)$_2$)	(*S*)-2-amino-3-(3,4-bis(trifluoromethyl)phenyl)propanoic acid
Phe(4COOMe)	(*S*)-2-amino-3-(4-(methoxycarbonyl)phenyl)propanoic acid
Phg	(*S*)-2-amino-2-phenylacetic acid
Pic	(*S*)-piperidine-2-carboxylic acid
Pip	4-aminopiperidine-4-carboxylic acid
Pro((4*R*)NH_2)	(2*S*,4*R*)-4-aminopyrrolidine-2-carboxylic acid
Pro((4*S*)NH_2)	(2*S*,4*S*)-4-aminopyrrolidine-2-carboxylic acid
Pro((3*R*)OH)	(2*S*,3*R*)-3-hydroxypyrrolidine-2-carboxylic acid
Pro((3*S*)OH)	(2*S*,3*S*)-3-hydroxypyrrolidine-2-carboxylic acid
Pro((4*R*)OH)	(2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid
Pro((4*S*)OH)	(2*S*,4*S*)-4-hydroxypyrrolidine-2-carboxylic acid
Pro((4*R*)OBn)	(2*S*,4*R*)-4-(benzyloxy)pyrrolidine-2-carboxylic acid
Pro((4*S*)OBn)	(2*S*,4*S*)-4-(benzyloxy)pyrrolidine-2-carboxylic acid
Ser(Bn)	(*S*)-2-amino-3-(benzyloxy)propanoic acid
Ser(Me)	(*S*)-2-amino-3-methoxy-propanoic acid
Thi	(*S*)-2-amino-3-(thiophen-2-yl)propanoic acid
*allo*Thr	(2*S*,3*S*)-2-amino-3-hydroxybutanoic acid
Thr(Bn)	(2*S*,3*R*)-2-amino-3-(benzyloxy)butanoic acid
Thr(Me)	(2*S*,3*R*)-2-amino-3-(methyloxy)butanoic acid
Thz	(*R*)-thiazolidine-4-carboxylic acid
Thz(5,5Me_2)	(*R*)-2,2-dimethylthiazolidine-4-carboxylic acid
Tic	(*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid

Tic(7OH)	(*S*)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
Trp(7Aza)	(*S*)-2-amino-3-(1*H*-pyrrolo[2,3-b]pyridin-3-yl)propanoic acid
Trp(5Br)	(*S*)-2-amino-3-(5-bromo-1*H*-indol-3-yl)propanoic acid
Trp(6Br)	(*S*)-2-amino-3-(6-bromo-1*H*-indol-3-yl)propanoic acid
Trp(6CF_3)	(*S*)-2-amino-3-(6-(trifluoromethyl)-1*H*-indol-3-yl)propanoic acid
Trp(5Cl)	(*S*)-2-amino-3-(5-chloro-1*H*-indol-3-yl)propanoic acid
Trp(6Cl)	(*S*)-2-amino-3-(6-chloro-1*H*-indol-3-yl)propanoic acid
Trp(5,6Cl)	(*S*)-2-amino-3-(5,6-dichloro-1*H*-indol-3-yl)propanoic acid
Trp(5OH)	(*S*)-2-amino-3-(5-hydroxy-1*H*-indol-3-yl)propanoic acid
Tyr(Bn)	(*S*)-2-amino-3-(4-(benzyloxy)phenyl)propanoic acid
Tyr(Me)	(*S*)-2-amino-3-(4-methoxyphenyl)propanoic acid
Tyr(Ph)	(*S*)-2-amino-3-(4-phenoxyphenyl)propanoic acid
Tyr(4OHPh)	(*S*)-2-amino-3-[4-(4-hydroxyphenoxy)phenyl]propanoic acid
Tza	(*S*)-2-amino-3-(thiazol-4-yl)propanoic acid

The abbreviation of D-isomers, e.g. ^{D}Lys corresponds to the epimer at the 2-position of the appropriate amino acid described above. Same applies for the generic descriptions of the amino acids, e.g. AA1 which has AA1^{D} as the corresponding α-epimer.

In preferred embodiment of the invention the β-hairpin peptidomimetics of general formula **(I)** are selected from the group consisting of:

cyclo(-Trp-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Hse-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-His-Cha-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Nva-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-His-Cha-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Val-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Cha-Dab-Orn-Pip-Dab-Trp-Dab-*t*BuGly-Alb-Ser-^{D}Pro-Pro-);

cyclo(-Val-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Nva-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-His-Cha-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Chg-Alb-Ser-^{D}Pro-Pro-);

cyclo(-Trp-Trp-Cha-Dab-Lys-^{D}Dab-Dab-Trp-Dab-Chg-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-Trp-Cha-Dab-Lys-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-Trp-*t*BuGly-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Cha-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-Trp-Leu-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Val-Ala-Val-^{D}Pro-Pro-);

cyclo(-Trp-His-Cha-Dab-Orn-Pip-Dab-Trp-Dab-*t*BuGly-Ser-Ser-^{D}Pro-Pro((3*S*)OH)-) ;

cyclo(-Trp-Trp-Cha-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ser-Ser-^{D}Pro-Pro((3*S*)OH)-) ;

cyclo(-Trp-His-Tyr(Me)-Dab-Orn-^{D}Dab-Dab-Trp-Hse-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Cha-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-*allo*Thr-^{D}Pro-Pro-);

or a pharmaceutically acceptable salt thereof.

In another preferred embodiment of the invention the β-hairpin peptidomimetics of general formula **(I)** are selected from the group consisting of:

cyclo(-Trp-His-Tyr-Dab-Orn-Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-His-Cha-Dab-Orn-Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Ile-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Ile-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Ile-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Tyr-Dab-Orn-Dab-Dab-Trp-Dab-Chg-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Chg-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Trp-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Tyr-Dab-Lys-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-Trp-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Cha-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-Trp-Trp-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-Trp-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Trp-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ser-Ser-^{D}Pro-Pro-);

cyclo(-Leu-Trp-Tyr-Dab-Lys-^{D}Dab-Dab-Trp-Dab-Cha-Ser-Ser-^{D}Pro-Pro-);

cyclo(-Leu-Trp-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Cha-Ser-Ser-^{D}Pro-Pro-);

cyclo(-Leu-Tyr-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Asn-Ser-^{D}Pro-Pro-);

cyclo(-Leu-Trp-*t*BuGly-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Chg-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Ile-Trp-*t*BuGly-Dab-Lys-^{D}Dab-Dab-Trp-Dab-Cha-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-Trp-*t*BuGly-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Chg-Ser-Ser-^{D}Pro-Pro-);

cyclo(-Leu-Trp-Cha-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ser-Ser-^{D}Pro-Pro-);

or a pharmaceutically acceptable salt thereof.

In another preferred embodiment of the invention the β-hairpin peptidomimetic of general formula **(I)** is:

cyclo(-Leu-Tyr-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-tBuGly-Tyr-Ser-^{D}Pro-Pro-);

or a pharmaceutically acceptable salt thereof.

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

a) coupling an appropriately functionalized solid support with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position T^1 or T^2 or P^1 to P^{12} as defined above; any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

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

(c) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is in the position of the next element (T or P), following counterclockwise or clockwise the sequence according to general formula (I) in –COOH to –NH2 orientation; 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 all amino acid residues have been introduced;

(f) if desired, selectively deprotecting one or several protected functional group(s) present in the molecule and chemically transforming the reactive group(s) thus liberated;

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

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

(i) 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;

(j) if desired, implementing additional chemical transformations of one or more reactive group(s) present in the molecule; and

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

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

The process of the invention can advantageously be carried out as parallel array synthesis to yield libraries of β-hairpin peptidomimetics of the invention. Such parallel syntheses allow one to obtain arrays of numerous (normally 12 to 192, typically 96) compounds as described above in moderate to high yields and defined purities, minimizing the formation of dimeric and polymeric by-products. The proper choice of the functionalized solid-support (i.e. solid support plus linker molecule) and site of cyclization play thereby key roles.

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

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

Type 1 linkers are designed to release the amide group under acidic conditions (H. Rink, *Tetrahedron Lett*. **1987**, *28*, 3783-3790). Linkers of this kind form amides of the carboxyl group of the amino acids; examples of resins functionalized by such linker structures include 4-[(((2,4-dimethoxyphenyl)Fmoc-aminomethyl) phenoxyacetamido) aminomethyl] PS resin, 4-[(((2,4-dimethoxyphenyl) Fmoc-aminomethyl)phenoxy-acetamido) aminomethyl]-4-methyl-benzydrylamine PS resin (Rink amide MBHA PS Resin), and 4-[(((2,4-dimethoxy-phenyl) 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-dimethoxy-phenyl) 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™ linker), 4-(2,4-dimethoxyphenyl-hydroxymethyl)-phenoxy (Rink linker), 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid (HMPB linker), trityl and 2-chlorotrityl. Preferably, the support is derived from polystyrene crosslinked with, most preferably 1-5%, divinylbenzene and functionalized by means of the 2-chlorotrityl linker.

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

A number of reaction vessels (normally 12 to 192, typically 96) equal to the total number of compounds to be synthesized by the parallel method are loaded with 25 to 1000 mg, preferably 60 mg, of the appropriate functionalized solid support, preferably 1 to 5% cross-linked polystyrene or Tentagel resin.

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

With the development of various linkers that release the C-terminal carboxylic acid group under mild acidic conditions, not affecting acid-labile groups protecting functional groups in the side chain(s), considerable progresses have been made in the synthesis of protected peptide fragments. The 2-methoxy-4-hydroxybenzylalcohol-derived linker (Sasrin™ linker, Mergler et al., *Tetrahedron Lett*. **1988**, 29 4005-4008) is cleavable with diluted trifluoroacetic acid (0.5-1% TFA in DCM) and is stable to Fmoc deprotection conditions during the peptide synthesis, Boc/tBu-based additional protecting groups being compatible with this protection scheme. Other linkers which are suitable for the process of the invention include the super acid labile 4-(2,4-dimethoxyphenyl-hydroxymethyl)-phenoxy linker (Rink linker, H. Rink, *Tetrahedron Lett.* **1987**, *28*, 3787-3790), where the removal of the peptide requires 10% acetic acid in DCM or 0.2% trifluoroacetic acid in DCM; the 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid-derived linker (HMPB-linker, Flörsheimer & Riniker, **1991**, Peptides 1990: Proceedings of the Twenty-First European Peptide Symposium, 131) which is also cleaved with 1% TFA/DCM in order to yield a peptide fragment containing all acid labile side-chain protective groups; and, in addition, the 2-chlorotritylchloride linker (Barlos et al., *Tetrahedron Lett.* **1989**, *30*, 3943-3946), which allows the peptide detachment using a mixture of glacial acetic acid/trifluoroethanol/DCM (1:2:7) for 30 min.

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

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

Cbz	benzyloxycarbonyl
Boc	tert.-butyloxycarbonyl
Fmoc	9-fluorenylmethoxycarbonyl
Alloc	allyloxycarbonyl
Teoc	trimethylsilylethoxycarbonyl

Tcc	trichloroethoxycarbonyl
Nps	o-nitrophenylsulfonyl;
Trt	triphenylmethyl or trityl

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

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

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

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

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

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

The 9-fluorenylmethoxycarbonyl- (Fmoc) -protected amino acid derivatives are preferably used as the building blocks for the construction of the β-hairpin loop mimetics of the invention. For the deprotection, i.e. cleaving off of the Fmoc group, 20% piperidine in DMF or 2% DBU/2% piperidine in DMF can be used as well as 25% hexafluoroisopropanol in CH_2Cl_2.

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 preferred workstations (without, however, being limited thereto) are Labsource's Combi-chem station, Protein Technologies' Symphony and MultiSyn Tech's-Syro synthesizer, the latter additionally equipped with a transfer unit and a reservoir box during the process of detachment of the fully protected linear peptide from the solid support. All synthesizers are able to provide a controlled environment, for example, reactions can be accomplished at temperatures different from room temperature as well as under inert gas atmosphere, if desired.

Amide bond formation requires the activation of the α-carboxyl group for the acylation step. When this activation is being carried out by means of the commonly used carbodiimides such as dicyclohexylcarbodiimide (DCC, Sheehan & Hess, *J. Am. Chem. Soc*. **1955,** *77*, 1067-1068) or diisopropylcarbodiimide (DIC, Sarantakis et al *Biochem. Biophys. Res. Commun.* **1976**, *73*, 336-342), the resulting dicyclohexylurea and, respectively, diisopropylurea is insoluble and, respectively, soluble in the solvents generally used. In a variation of the carbodiimide method 1-hydroxy benzotriazole (HOBt, König & Geiger, *Chem. Ber.* **1970**, *103*, 788-798) is included as an additive to the coupling mixture. HOBt prevents dehydration, suppresses racemization of the activated amino acids and acts as a catalyst to improve the sluggish coupling reactions. Certain phosphonium reagents have been used as direct coupling reagents, such as

benzotriazol-1-yl-oxy-tris-(dimethyl-amino)-phosphonium hexafluorophosphate (BOP, Castro et al., *Tetrahedron Lett.* **1975**, *14,* 1219-1222; *Synthesis* **1976**, 751-752), or benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexaflurophoshate (Py-BOP, Coste et al., *Tetrahedron Lett*. **1990**, *31*, 205-208), or 2-(1H-benzotriazol-1-yl-)1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), or hexafluorophosphate (HBTU, Knorr et al., *Tetrahedron Lett.* **1989**, *30*, 1927-1930); these phosphonium reagents are also suitable for in situ formation of HOBt esters with the protected amino acid derivatives. More recently diphenoxyphosphoryl azide (DPPA) or O-(7-aza-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoro borate (TATU) or O-(7-aza-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexa fluorophosphate (HATU)/7-aza-1-hydroxybenzotriazole (HOAt, Carpino et al., *Tetrahedron Lett.* **1994***, 35*, 2279-2281) or -(6-Chloro-1H-benzotriazol-1-yl-)- N,N,N',N'-1,1,3,3-tetramethyl uronium tetrafluoroborate (TCTU), or hexafluoro phosphate (HCTU, Marder, Shivo and Albericio: HCTU and TCTU: New Coupling Reagents: Development and Industrial Applications, Poster Presentation, Gordon Conference February 2002) have also been used as coupling reagents as well as 1,1,3,3-bis(tetramethylene)chlorouronium hexafluorophosphate (PyClU) especially for coupling of N-methylated amino acids (J. Coste, E. Frérot, P. Jouin, B. Castro, *Tetrahedron Lett.* **1991**, *32*, 1967) or pentafluorophenyl diphenyl-phosphinate (S. Chen, J. Xu, *Tetrahedron Lett.* **1991**, *32*, 6711).

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

The resin-bound intermediate within each reaction vessel is washed free of excess of retained reagents, of solvents, and of by-products by repetitive exposure to pure solvent(s).

Washing procedures are repeated up to about 30 times (preferably about 5 times), monitoring the efficiency of reagent, solvent, and by-product removal by methods such as TLC, GC, LC-MS or inspection of the washings.

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

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

After detachment of the fully protected linear peptide from the solid support the individual solutions/extracts are then manipulated as needed to isolate the final compounds. Typical manipulations include, but are not limited to, evaporation,

concentration, liquid/liquid extraction, acidification, basification, neutralization or additional reactions in solution.

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

Finally, the fully protected peptide derivative is treated with 95% TFA, 2.5% H_2O, 2.5% TIS, or 87.5% TFA, 2.5% DODT, 5% thioanisol, 5% H_2O or another combination of scavengers for effecting the cleavage of protecting groups. The cleavage reaction time is commonly 30 minutes to 12 hours, preferably about 2.5 hours. The volatiles are evaporated to dryness and the crude peptide is dissolved in 20% AcOH in water and extracted with isopropyl ether or other solvents which are suitable therefore. The aqueous layer is collected and evaporated to dryness, and the fully deprotected cyclic peptide is obtained. Alternatively the deprotected cyclic peptide can be precipitated and washed using cold Et_2O.

For some compounds of the present invention according general formula **(I)** additional synthetic steps are required. These transformations can be applied either on a partially deprotected cyclic or linear peptide, attached or already released from the solid support or on the final deprotected molecule.

Depending on its purity, the final product as obtained above can be used directly for biological assays, or has to be further purified, for example by preparative HPLC.

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

In general the building blocks for the peptidomimetics of the present invention can be synthesized according to the literature methods, which are known to a person skilled in the art or are commercially available. All other corresponding amino acids have been described either as unprotected or as Boc- or Fmoc-protected racemates, (D)- or (L)-isomers. It will be appreciated that unprotected amino acid building blocks can be easily transformed into the corresponding Fmoc-protected amino acid building blocks required for the present invention by standard protecting group manipulations. Reviews describing general methods for the synthesis of α-amino acids include: R. Duthaler, *Tetrahedron (Report)* **1994**, *349*, 1540-1650; R.M. Williams, "Synthesis of optically active α-amino acids", *Tetrahedron Organic Chemistry Series*, Vol.7, J.E. Baldwin, P.D. Magnus (Eds.), Pergamon Press., Oxford 1**989**. An especially useful method for the synthesis of optically active α-amino acids relevant for this invention includes kinetic resolution using hydrolytic enzymes (M.A. Verhovskaya, I.A. Yamskov, *Russian Chem. Rev.* **1991**, *60*, 1163-1179; R.M. Williams, "Synthesis of optically active α-amino acids", *Tetrahedron Organic Chemistry Series*, Vol.7, J.E. Baldwin, P.D. Magnus (Eds.), Pergamon Press., Oxford **1989**, Chapter 7, p.257-279). Kinetic resolution using hydrolytic enzymes involves hydrolysis of amides and nitriles by aminopeptidases or nitrilases, cleavage of N-acyl groups by acylases, and ester hydrolysis by lipases or proteases. It is well documented that certain enzymes will lead specifically to pure (L)-enantiomers whereas others yield the corresponding (D)-enantiomers (e.g.: R. Duthaler, *Tetrahedron Report* **1994**, *349*, 1540-1650; R.M. Williams, "Synthesis of

optically active α-amino acids", *Tetrahedron Organic Chemistry Series*, Vol.7, J.E. Baldwin, P.D. Magnus (Eds.), Pergamon Press., Oxford **1989**).

The β-hairpin peptidomimetics of the invention can be used in a wide range of applications in order to inhibit the growth of or to kill microorganisms leading to the desired therapeutic effect in man or, due to their similar etiology, in other mammals. In particular they can be used to inhibit the growth of or to kill Gram-negative bacteria such as *Klebsiella pneumoniae* and/or *Acinetobacter baumannii* and/or *Escherichia coli*.

They can be used for example as disinfectants or as preservatives for materials such as foodstuffs, cosmetics, medicaments and other nutrient-containing materials. The β-hairpin peptidomimetics of the invention can also be used to treat or prevent diseases related to microbial infection in plants and animals.

For use as disinfectants or preservatives the β-hairpin peptidomimetics can be added to the desired material singly, as mixtures of several β-hairpin peptidomimetics or in combination with other antimicrobial agents.

The β-hairpin peptidomimetics of the invention can be used to treat or prevent infections or diseases related to such infections, particularly nosocomial infections caused by Gram-negative bacteria related to diseases such as ventilator-associated pneumonia (VAP), hospital-acquired pneumonia (HAP), healthcare-associated pneumonia (HCAP); catheter-related and non-catheter-related infections such as urinary tract infections (UTIs) or bloodstream infections (BSIs); infections related to respiratory diseases such as cystic fibrosis, emphysema, asthma or pneumonia; infections related to skin or soft tissue diseases such as surgical wounds, traumatic wounds or burn; infections related to gastrointestinal diseases such as epidemic diarrhea, necrotizing enterocolitis, typhlitis, gastroenteritis or pancreatitis; infections related to eye diseases such as keratitis and endophthalmitis; infections related to ear diseases such as otitis; infections related to CNS diseases such as brain abscess and

meningitis or encephalitis; infections related to bone diseases such as osteochondritis and osteomyelitis; infections related to cardiovascular diseases such as endocartitis and pericarditis; or infections related to genitourinary diseases such as epididymitis, prostatitis and urethritis. They can be administered singly, as mixtures of several β-hairpin peptidomimetics, in combination with other antimicrobial or antibiotic agents, or anti cancer agents, or antiviral (e.g. anti-HIV) agents, or in combination with other pharmaceutically active agents. The β-hairpin peptidomimetics can be administered per se or as pharmaceutical compositions.

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

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

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

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

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

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

For oral administration, the 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 by a patient to be treated. For oral formulations such as, for example, powders, capsules and tablets, suitable excipients include fillers such as sugars, such as lactose, sucrose, mannitol and sorbitol; cellulose preparations such as maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP); granulating agents; and binding agents. If desired, desintegrating agents may be added, such as cross-linked polyvinylpyrrolidones, agar, or alginic acid or a salt thereof, such as sodium alginate. If desired, solid dosage forms may be sugar-coated or enteric-coated using standard techniques.

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

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

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

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

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

In addition, other pharmaceutical delivery systems may be employed such as liposomes and emulsions well known in the art. Certain organic solvents such as dimethylsulfoxide may also be employed. Additionally, the β-hairpin peptidomimetics of the invention may be delivered using a sustained-release system, such as semipermeable matrices of solid polymers containing the therapeutic agent (e.g. for coated stents). Various sustained-release materials have been established and are well

known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic agent, additional strategies for protein stabilization may be employed.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Abbreviations:

Ac	Acetyl;
BSA	Bovine serum albumin;
Boc	*tert*-Butyloxycarbonyl;
DCHA	Dicyclohexylamine;
DEAD	Diethyl azodicarboxylate;
DIPEA	Diisopropylethylamine;
DMEM	Dulbecco's Modified Eagle's Medium;
DODT	3,6-dioxa-1,8-octanedithiol;
FCS	Fetal Calf Serum;
Fmoc	Fluorenylmethyloxycarbonyl;
HATU	O-(7-Aza-benzotriazole-1-yl)-N,N,N’,N’-tetramethyluronoium hexafluorophosphate;
HBSS	Hank's Buffered Salt Solution;
HBTU	O-(Benzotriazol-1-yl)-N,N,N’,N’-tetramethyluronium hexafluorophosphate;
HCTU	O-(6-Chlorobenzotriazol-1-yl)-N,N,N’,N’-tetramethyluronium hexafluorophosphate;
Hepes	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid;
HOAt	1-Hydroxy-7-azabenzotriazole;
IMDM	Iscove's Modified Dulbecco's Media;
PyBop®	(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate;
TIS	Triisopropylsilane;
TPP	Triphenylphosphine;
RPMI	Roswell Park Memorial Institute medium;
rt	Room temperature.

Examples

1. Peptide synthesis

1.1 General synthetic procedures

A general method for the synthesis of the peptidomimetics of the present invention is exemplified in the following. This is to demonstrate the principal concept and does not limit or restrict the present invention in any way. A person skilled in the art is easily able to modify these procedures, especially, but not limited to, choosing a different starting position within the ring system, to still achieve the preparation of the claimed cyclic peptidomimetic compounds of the present invention.

Coupling of the first protected amino acid residue to the resin

In a dried flask, 2-chlorotritylchloride resin (polystyrene, 1% crosslinked; loading: 1.4 mmol/g) was swollen in dry CH_2Cl_2 for 30 min (7 ml CH_2Cl_2 per g resin). A solution of 0.8 eq of the Fmoc-protected amino acid and 6 eq of DIPEA in dry CH_2Cl_2/DMF (4/1) (10 ml per g resin) was added. After shaking for 2-4 h at rt the resin was filtered off and washed successively with CH_2Cl_2, DMF, CH_2Cl_2, DMF and CH_2Cl_2. Then a solution of dry CH_2Cl_2/MeOH/DIPEA (17:2:1) was added (10 ml per g resin). After shaking for 3 x 30 min the resin was filtered off in a pre-weighed sinter funnel and washed successively with CH_2Cl_2, DMF, CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2 (2x) and Et_2O (2x). The resin was dried under high vacuum overnight. The final mass of resin was calculated before the qualitative control.

The following preloaded resins were prepared: Fmoc-Dab(Boc)-2-chlorotrityl resin, Fmoc-Pro-2-chlorotrityl resin, Fmoc-^{D}Pro-2-chlorotrityl resin, Fmoc-*allo*Thr-2-chlorotrityl resin, and Fmoc-Tyr(Me)-2-chlorotrityl resin.

Synthesis of the fully protected peptide fragment

The synthesis was carried out on a Syro-peptide synthesizer (MultiSynTech GmbH) using 24 to 96 reaction vessels. In each vessel were placed approximately 80 mg of the above resin (weight of the resin before loading). The following reaction cycles were programmed and carried out:

Step	Reagent	Time
1	CH_2Cl_2, wash and swell (manual)	1 x 3 min
2	DMF, wash and swell	2 x 30 min
3	20 % piperidine/DMF	1 x 5 min and 1 x 15 min
4	DMF, wash	5 x 1 min
5	3.5 eq. Fmoc amino acid/DMF	
	+ 3.5 eq. PyBOP	
	+ 7 eq. DIPEA	1 x 60 min
6	3.5 eq. Fmoc amino acid/DMF	
	+ 3.5 eq. HATU or PyBOP or HCTU	
	+ 7 eq. DIPEA	1 x 60 min
7	DMF, wash	5 x 1 min
8	20 % piperidine/DMF	1 x 5 min and 1 x 15 min
9	DMF, wash	5 x 1 min
10	CH_2Cl_2, wash (at the end of the synthesis)	3 x 1 min

Steps **5** to **9** are repeated to add each amino-acid residue.

After the synthesis of the fully protected peptide fragment had been terminated, the cleavage, cyclization and work up procedures, as described herein below, were used for the preparation of the final compounds.

Cleavage, backbone cyclization and deprotection

After assembly of the linear peptide, the resin was suspended in 1 ml of 1% TFA in CH_2Cl_2 (*v/v*; 0.14 mmol) for 3 minutes and filtered, and the filtrate was neutralized with 1 ml of 20% DIPEA in CH_2Cl_2 (*v/v*; 1.15 mmol). This procedure was repeated four times to ensure completion of the cleavage. The resin was washed three times with 1 ml of CH_2Cl_2. The CH_2Cl_2 layers containing product were evaporated to dryness.

The fully protected linear peptide was solubilised in 8 ml of dry DMF. Then 2 eq. of HATU and 2. eq. of HOAt in dry DMF (1-2 ml) and 4 eq. of DIPEA in dry DMF (1-2 ml) were added to the peptide, followed by stirring for ca. 16 h. The volatiles were removed by evaporation. The crude cyclic peptide was dissolved in 7 ml of CH_2Cl_2 and washed three times with 4.5 ml 10% acetonitrile in water (*v/v*). The CH_2Cl_2 layer was then evaporated to dryness.

To fully deprotect the peptide, 7 ml of cleavage cocktail TFA/DODT/thioanisol/H_2O (87.5:2.5:5:5) were added, and the mixture was kept for 2.5-4 h at room temperature until the reaction was completed. The reaction mixture was evaporated close to dryness and the peptide precipitated with 7 ml of cold Et_2O. The precipitate was washed 3 times with 4 ml of cold Et_2O.

Purification procedure (preparative reverse phase LC-MS)

Compounds were purified by reverse phase chromatography using a Phenomenex Gemini NX-C18 column, 30 x 100 mm, 5 µm (Cat No. 00D-4435-U0-AX) or a Waters XBridge C18 OBD column, 30 x 100 mm, 5 µm (Cat No. 186002982).

Mobile phases used were:

A: 0.1% TFA in Water/Acetonitrile 95/5 v/v

B: 0.1 % TFA in Acetonitrile

Gradient slopes in the preparative runs were adapted each time based on analytical LC-MS analysis of the crude product. As an example, a typical run (purification of **Ex. 11**) was executed using the Phenomenex column with a flow rate of 35 ml/min running

a gradient from 0-1 min 0% B, at 1.1 min 25% B to a final of 8 min 45% B (retention time: 5.96 min in this case).

Detection: MS and UV @ 220 nm

Fractions collected were evaporated using a Genevac HT4 evaporator or a Büchi system.

Alternatively for larger amounts the following LC-purification system was used:

Column: Waters XBridge C18 OBD column, 50 x 250 mm, 10 µm (Cat No. 186003900)

Mobile phase A: 0.1% TFA in Water

Mobile phase B: Acetonitrile

Flow rate: 150 ml/min

Detection: UV @ 220 nm

After lyophilisation the products were obtained typically as white to off-white powders and analysed by HPLC-ESI-MS methods as described below. Analytical data after preparative HPLC purification are shown in *Table 1*.

1.2 Analytical Methods

Analytical method A:

Analytical HPLC retention times (RT, in minutes) were determined using an Ascentis Express C18 column, 50 x 2.1 mm, 2.7 µm, with the following solvents **A** (H_2O + 0.1% TFA) and **B** (CH_3CN + 0.085% TFA) and the gradient: 0-0.05 min: 97% A, 3% B; 3.3 min: 15% A, 85% B; 3.32 min: 3% A, 97% B; 3.32-3.55 min: 3% A, 97% B; 3.57-3.7 min: 97% A, 3% B. Flow rate = 1.6 ml/min at 55°C.

Analytical method B:

Analytical HPLC retention times (RT, in minutes) were determined using an Ascentis Express C18 column, 50 x 3.0 mm, 2.7 µm, with the following solvents **A** (H_2O + 0.1% TFA) and **B** (CH_3CN + 0.085% TFA) and the gradient: 0-0.05 min: 97% A, 3% B; 4.95 min:

3% A, 97% B; 4.95-5.35 min: 3% A, 97% B; 5.37-5.4 min: 97% A, 3% B. Flow rate = 1.3 ml/min at 55°C.

Analytical method C:

Analytical HPLC retention times (RT, in minutes) were determined using an Gemini NX C18 column, 50 x 2.0 mm, 3.0 µm, with the following solvents **A** (H_2O + 0.1% TFA) and **B** (CH_3CN + 0.085% TFA) and the gradient: 0-0.1 min: 97% A, 3% B; 2.7 min: 3% A, 97% B; 2.7-3.0 min: 3% A, 97% B; 3.05-3.3 min: 97% A, 3% B. Flow rate = 0.8 ml/min at 45°C.

1.3 Synthesis of peptide sequences

Examples 1 – 13, 18 – 38 are shown in *Table 1*.

The peptides were synthesized according the general method starting with the amino acid L-prolin, which was grafted to the resin (Fmoc-Pro-2-chlorotrityl resin). The linear peptides were synthesized on the solid support according to the procedure described above in the following sequence: Resin-Pro-T^1-P^{12}-P^{11}-P^{10}-P^9-P^8-P^7-P^6-P^5-P^4-P^3-P^2-P^1. The products were cleaved from the resin, cyclized, deprotected, and finally purified by preparative reverse phase LC-MS as described above.

After lyophilisation the products were obtained as white to off-white powders and characterised by HPLC-MS. For analytical data, see **Ex. 1 – 13**, **18 – 38** in *Table 1*.

Example 14 is shown in *Table 1*.

The peptide was synthesized according the general method starting with the amino acid D-proline, which was grafted to the resin (Fmoc-^{D}Pro-2-chlorotrityl resin). The linear peptide was synthesized on the solid support according to the procedure described above in the following sequence: Resin-^{D}Pro-Ser-Ser-*t*BuGly-Dab-Trp-Dab-Pip-Orn-Dab-Cha-His-Trp-Pro((3*S*)OH). The product was cleaved from the resin, cyclized, deprotected and finally purified by preparative reverse phase LC-MS as described above.

After lyophilisation the product was obtained as a white to off-white powder and characterised by HPLC-MS. For analytical data, see **Ex. 14** in *Table 1*.

Example 15 is shown in *Table 1*.

The peptide was synthesized according the general method starting with the amino acid (*S*)-2-amino-4-(*tert*-butoxycarbonylamino)butanoic acid, which was grafted to the resin (Fmoc-Dab(Boc)-2-chlorotrityl resin). The linear peptide was synthesized on the solid support according to the procedure described above in the following sequence: Resin-Dab-Cha-Trp-Trp-Pro((3*S*)OH)-^{D}Pro-Ser-Ser-*t*BuGly-Dab-Trp-Dab-^{D}Dab-Orn. The product was cleaved from the resin, cyclized, deprotected and finally purified by preparative reverse phase LC-MS as described above.

After lyophilisation the product was obtained as a white to off-white powder and characterised by HPLC-MS. For analytical data, see **Ex. 15** in *Table 1*.

Example 16 is shown in *Table 1*.

The peptide was synthesized according the general method starting with the amino acid (*S*)-2-amino-3-(4-methoxyphenyl)propanoic acid, which was grafted to the resin (Fmoc-Tyr(Me)-2-chlorotrityl resin). The linear peptide was synthesized on the solid support according to the procedure described above in the following sequence: Resin-Tyr(Me)-His-Trp-Pro-^{D}Pro-Ser-Ala-*t*BuGly-Hse-Trp-Dab-^{D}Dab-Orn-Dab. The product was cleaved from the resin, cyclized, deprotected and finally purified by preparative reverse phase LC-MS as described above.

After lyophilisation the product was obtained as a white to off-white powder and characterised by HPLC-MS. For analytical data, see **Ex. 16** in *Table 1*.

Example 17 is shown in *Table 1*.

The peptide was synthesized according the general method starting with the amino acid (2*S*,3*S*)-2-amino-3-hydroxybutanoic acid, which was grafted to the resin (Fmoc-*allo*Thr-2-chlorotrityl resin). The linear peptide was synthesized on the solid support according to the procedure described above in the following sequence: Resin-*allo*Thr-

Ala-*t*BuGly-Dab-Trp-Dab-^{D}Dab-Orn-Dab-Cha-His-Leu-^{D}Pro-Pro. The product was cleaved from the resin, cyclized, deprotected and finally purified by preparative reverse phase LC-MS as described above.

After lyophilisation the product was obtained as a white to off-white powder and characterised by HPLC-MS. For analytical data, see **Ex. 17** in *Table 1*.

1.4 Sequence data

Table 1: Examples (Ex.)

Ex.	P^1 a)	P^2 a)	P^3 a)	P^4 a)	P^5 a)	P^6 a)	P^7 a)	P^8 a)	P^9 a)	P^{10} a)	P^{11} a)	P^{12} a)	T^1 a)	T^2 a)	Analyt. Meth.	MS b)	RT [min]	Purity [%]
1	Trp	His	Tyr	Dab	Orn	^{D}Dab	Dab	Trp	Hse	*t*BuGly	Ala	Ser	^{D}Pro	Pro	B	827.3	1.81	87
2	Trp	His	Tyr	Dab	Orn	^{D}Dab	Dab	Trp	Dab	*t*BuGly	Ala	Ser	^{D}Pro	Pro	B	827.0	1.82	88
3	Trp	His	Cha	Dab	Orn	^{D}Dab	Dab	Trp	Dab	Nva	Ala	Ser	^{D}Pro	Pro	B	815.2	1.93	93
4	Trp	His	Cha	Dab	Orn	^{D}Dab	Dab	Trp	Dab	*t*BuGly	Val	Ser	^{D}Pro	Pro	A	558.0	1.33	82
5	Leu	His	Tyr	Dab	Orn	^{D}Dab	Dab	Trp	Dab	*t*BuGly	Ala	Ser	^{D}Pro	Pro	B	790.5	1.80	87
6	Leu	His	Cha	Dab	Orn	Pip	Dab	Trp	Dab	*t*BuGly	Alb	Ser	^{D}Pro	Pro	B	827.4	1.98	85
7	Val	His	Tyr	Dab	Orn	^{D}Dab	Dab	Trp	Dab	*t*BuGly	Ala	Ser	^{D}Pro	Pro	B	522.6	1.73	95
8	Nva	His	Tyr	Dab	Orn	^{D}Dab	Dab	Trp	Dab	*t*BuGly	Ala	Ser	^{D}Pro	Pro	B	783.5	1.72	89
9	Trp	His	Cha	Dab	Orn	^{D}Dab	Dab	Trp	Dab	Chg	Alb	Ser	^{D}Pro	Pro	A	576.4	1.33	68
10	Trp	Trp	Cha	Dab	Lys	^{D}Dab	Dab	Trp	Dab	Chg	Ala	Ser	^{D}Pro	Pro	C	578.1	1.60	94
11	Trp	Trp	Cha	Dab	Lys	^{D}Dab	Dab	Trp	Dab	*t*BuGly	Ala	Ser	^{D}Pro	Pro	C	569.4	1.57	99
12	Trp	Trp	*t*BuGly	Dab	Orn	^{D}Dab	Dab	Trp	Dab	Cha	Ala	Ser	^{D}Pro	Pro	C	847.0	1.57	92
13	Trp	Trp	Leu	Dab	Orn	^{D}Dab	Dab	Trp	Dab	Val	Ala	Val	^{D}Pro	Pro	A	550.6	1.53	88
14	Trp	His	Cha	Dab	Orn	Pip	Dab	Trp	Dab	*t*BuGly	Ser	Ser	^{D}Pro	Pro((3*S*)OH)	B	851.0	1.90	90
15	Trp	Trp	Cha	Dab	Orn	^{D}Dab	Dab	Trp	Dab	*t*BuGly	Ser	Ser	^{D}Pro	Pro((3*S*)OH)	C	575.5	1.51	98
16	Trp	His	Tyr(Me)	Dab	Orn	^{D}Dab	Dab	Trp	Hse	*t*BuGly	Ala	Ser	^{D}Pro	Pro	B	557.6	1.89	83
17	Leu	His	Cha	Dab	Orn	^{D}Dab	Dab	Trp	Dab	*t*BuGly	Ala	*allo*Thr	^{D}Pro	Pro	A	528.9	1.35	89
18	Trp	His	Tyr	Dab	Orn	Dab	Dab	Trp	Dab	*t*BuGly	Ala	Ser	^{D}Pro	Pro	A	827.4	1.14	90
19	Trp	His	Cha	Dab	Orn	Dab	Dab	Trp	Dab	*t*BuGly	Ala	Ser	^{D}Pro	Pro	A	822.4	1.29	82

Table 1: Examples (continued)

Ex.	P[1] a)	P[2] a)	P[3] a)	P[4] a)	P[5] a)	P[6] a)	P[7] a)	P[8] a)	P[9] a)	P[10] a)	P[11] a)	P[12] a)	T[1] a)	T[2] a)	Analyt. Meth.	MS b)	RT [min]	Purity [%]
20	Ile	His	Tyr	Dab	Orn	DDab	Dab	Trp	Dab	*t*BuGly	Ala	Ser	DPro	Pro	B	790.8	1.8	85
21	Ile	His	Tyr	Dab	Orn	DDab	Dab	Trp	Dab	Ile	Ala	Ser	DPro	Pro	B	790.7	1.79	92
22	Leu	His	Tyr	Dab	Orn	Dab	Dab	Trp	Dab	Chg	Ala	Ser	DPro	Pro	B	803.7	1.79	90
23	Leu	His	Tyr	Dab	Orn	DDab	Dab	Trp	Dab	Chg	Ala	Ser	DPro	Pro	A	803.8	1.23	91
24	Leu	His	Trp	Dab	Orn	DDab	Dab	Trp	Dab	*t*BuGly	Ala	Ser	DPro	Pro	A	802	1.25	89
25	Leu	His	Tyr	Dab	Lys	DDab	Dab	Trp	Dab	*t*BuGly	Ala	Ser	DPro	Pro	A	797.9	1.17	87
26	Leu	Trp	Tyr	Dab	Orn	DDab	Dab	Trp	Dab	Cha	Ala	Ser	DPro	Pro	A	835.3	1.33	95
27	Leu	Trp	Trp	Dab	Orn	DDab	Dab	Trp	Dab	*t*BuGly	Ala	Ser	DPro	Pro	A	826.7	1.31	94
28	Leu	Trp	Tyr	Dab	Orn	DDab	Dab	Trp	Dab	*t*BuGly	Ala	Ser	DPro	Pro	A	815.3	1.2	95
29	Leu	His	Tyr	Dab	Orn	DDab	Dab	Trp	Dab	Trp	Ala	Ser	DPro	Pro	A	827	1.15	87
30	Leu	His	Tyr	Dab	Orn	DDab	Dab	Trp	Dab	*t*BuGly	Ser	Ser	DPro	Pro	A	798.5	1.18	82
31	Leu	Trp	Tyr	Dab	Lys	DDab	Dab	Trp	Dab	Cha	Ser	Ser	DPro	Pro	A	850.2	1.3	94
32	Leu	Trp	Tyr	Dab	Orn	DDab	Dab	Trp	Dab	Cha	Ser	Ser	DPro	Pro	A	843.2	1.32	94
33	Leu	Tyr	Tyr	Dab	Orn	DDab	Dab	Trp	Dab	*t*BuGly	Asn	Ser	DPro	Pro	A	825.3	1.21	88
34	Leu	Trp	*t*BuGly	Dab	Orn	DDab	Dab	Trp	Dab	Chg	Ala	Ser	DPro	Pro	A	803.2	1.26	94
35	Ile	Trp	*t*BuGly	Dab	Lys	DDab	Dab	Trp	Dab	Cha	Ala	Ser	DPro	Pro	A	817.3	1.32	90
36	Leu	Trp	*t*BuGly	Dab	Orn	DDab	Dab	Trp	Dab	Chg	Ser	Ser	DPro	Pro	A	811.3	1.27	95
37	Leu	Trp	Cha	Dab	Orn	DDab	Dab	Trp	Dab	*t*BuGly	Ser	Ser	DPro	Pro	A	818.3	1.35	89
38	Leu	Tyr	Tyr	Dab	Orn	DDab	Dab	Trp	Dab	*t*BuGly	Tyr	Ser	DPro	Pro	A	849.8	1.26	87

a) Abbreviations of amino acid see listing above
b) MS: either $[M+2H]^{2+}$ or $[M+3H]^{3+}$.

2. Biological methods

2.1. Preparation of the peptides

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

2.2. Antimicrobial activity of the peptides

The selective antimicrobial activities of the peptides were determined in 96-well plates (Greiner, polystyrene) by the standard NCCLS broth microdilution method (National Committee for Clinical Laboratory Standards **1993**. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 3rd ed. Approved standard M7-A6; National Committee for Clinical laboratory standards, Wayne, PA) with slight modifications. Inocula of the microorganisms were diluted into Mueller-Hinton II (MH, cation adjusted) broth + 0.02% BSA and compared with a 0.5 McFarland standard to give appr. 10^6 colony forming units (CFU)/ml. Aliquots (50 µl) of inoculate were added to 50 µl of MH broth + 0.02% BSA containing the peptide in serial two-fold dilutions. The following microorganisms were used to determine antibiotic selectivity of the peptides: *Escherichia coli* ATCC 25922*, Klebsiella pneumoniae* ATCC 13883 and *Acinetobacter baumannii* DSM 30008. Antimicrobial activities of the peptides were expressed as the minimal inhibitory concentration (MIC) in µg/ml at which no visible growth was observed after 18-20 hours of incubation at 35 °C.

2.3. Hemolysis

The peptides were tested for their hemolytic activity against human red blood cells (hRBC). Fresh hRBC were washed three times with phosphate buffered saline (PBS) and centrifuged for 10 min at 2000 x g. Compounds (100 µg/ml) were incubated with 20% hRBC (v/v) for 1 h at 37 °C and shaking at 300 rpm. The final erythrocyte concentration was approximately 0.9 x 10^9 cells/ml. A value of 0% and 100% cell lyses, respectively, was determined by incubation of hRBC in the presence of PBS containing 0.001% acetic acid and 2.5% Triton X-100 in H_2O, respectively. The samples were centrifuged, the supernatants were 8-fold diluted in PBS buffer and the optical densities (OD) were measured at 540 nm. The 100% lyses value ($OD_{540}H_2O$) gave an OD_{540} of approximately 0.5-1.0.

Percent hemolysis was calculated as follows: (OD_{540}peptide/$OD_{540}H_2O$) x100%.

The results of the experiments described in **2.2** – **2.3** are indicated in *Table 2* herein below.

Table 2: Minimal inhibitory concentrations (MIC) in Mueller- Hinton broth II and hemolysis

Ex.	*Escherichia coli* **ATCC 25922** MIC [µg/ml]	*Klebsiella pneumoniae* **ATCC 13883** MIC [µg/ml]	*Acinetobacter baumannii* **DSM 30008** MIC [µg/ml]	**Hemolysis** at 100 µg/ml [%]
1	0.5	1	2	1
2	0.25	1	1	1
3	0.5	1	2	3
4	0.5	1	2	5
5	0.5	2	2	0
6	0.5	1	1	3
7	0.5	1	1	1
8	1	4	2	1
9	1	0.5	1	n.d.
10	2	1	4	1
11	1	1	2	1
12	1	0.5	2	3
13	2	1	2	2
14	0.25	0.5	1	4
15	1	1	4	0
16	0.5	2	n.d.	1
17	1	2	4	5
18	2	2	2	0
19	2	1	2	0
20	2	1	2	0
21	1	2	2	1
22	2	2	4	0
23	2	2	4	3
24	2	1	4	1
25	2	2	2	0
26	1	1	2	1
27	2	1	4	0
28	2	2	4	1
29	2	2	4	0
30	1	1	2	1
31	1	1	2	1
32	1	0.5	2	3
33	1	1	2	5
34	2	2	4	1

Table 2, continuation

Ex.	*Escherichia coli* **ATCC 25922** MIC [µg/ml]	*Klebsiella pneumoniae* **ATCC 13883** MIC [µg/ml]	*Acinetobacter baumannii* **DSM 30008** MIC [µg/ml]	**Hemolysis** at 100 µg/ml [%]
35	1	1	4	1
36	2	1	4	1
37	2	2	4	1
38	2	2	2	0

n.d.: not determined

CLAIMS

1. A compound of the general formula **(I)**,

cyclo[P^1-P^2-P^3-P^4-P^5-P^6-P^7-P^8-P^9-P^{10}-P^{11}-P^{12}-T^1-T^2]

(I)

T^1 is ^{D}Pro;

T^2 is Pro; or Pro((3*S*)OH);

P^1 is Leu; Ile; Val; Nva; or Trp;

P^2 is His; Trp; or Tyr;

P^3 is Leu; Cha; *t*BuGly; Trp; Tyr; or Tyr(Me);

P^4 is Dab;

P^5 is Orn; or Lys;

P^6 is Dab; ^{D}Dab; or Pip;

P^7 is Dab;

P^8 is Trp;

P^9 is Hse; or Dab;

P^{10} is *t*BuGly; Ile; Val; Nva; Cha; Chg; or Trp;

P^{11} is Ala; Val; Alb; Ser; Asn; or Tyr; and

P^{12} is Val; Ser; or *allo*Thr;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein

T^1 is ^{D}Pro;

T^2 is Pro; or Pro((3*S*)OH);

P^1 is Leu; Ile; Val; Nva; or Trp;

P^2 is His; Trp; or Tyr;

P^3 is Leu; Cha; *t*BuGly; Trp; Tyr; or Tyr(Me);

P^4 is Dab;

P^5 is Orn; or Lys;

P^6 is Dab; ^{D}Dab; or Pip;

P^7 is Dab;

P^8 is Trp;

P^9 is Hse; or Dab;

P^{10} is *t*BuGly; Ile; Val; Nva; Cha; Chg; or Trp;

P^{11} is Ala; Val; Alb; Ser; or Asn; and

P^{12} is Val; Ser; or *allo*Thr;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claims 1 or 2 wherein

T^1 is ^{D}Pro;

T^2 is Pro; or Pro((3*S*)OH);

P^1 is Leu; Ile; Val; Nva; or Trp;

P^2 is His; Trp; or Tyr;

P^3 is Leu; Cha; *t*BuGly; Trp; Tyr; or Tyr(Me);

P^4 and P^7 are Dab;

P^5 is Orn; or Lys;

P^6 is ^{D}Dab; or Pip;

P^8 is Trp;

P^9 is Hse; or Dab;

P^{10} is *t*BuGly; Ile; Val; Nva; Cha; or Chg;

P^{11} is Ala; Val; Alb; Ser; Asn; or Tyr; and

P^{12} is Val; Ser; or *allo*Thr;

or a pharmaceutically acceptable salt thereof.

4. A compound according to any one of claims 1 to 3 which is selected from

cyclo(-Trp-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Hse-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-His-Cha-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Nva-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-His-Cha-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Val-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Cha-Dab-Orn-Pip-Dab-Trp-Dab-*t*BuGly-Alb-Ser-^{D}Pro-Pro-);

cyclo(-Val-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Nva-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-His-Cha-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Chg-Alb-Ser-^{D}Pro-Pro-);

cyclo(-Trp-Trp-Cha-Dab-Lys-^{D}Dab-Dab-Trp-Dab-Chg-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-Trp-Cha-Dab-Lys-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-Trp-*t*BuGly-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Cha-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-Trp-Leu-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Val-Ala-Val-^{D}Pro-Pro-);

cyclo(-Trp-His-Cha-Dab-Orn-Pip-Dab-Trp-Dab-*t*BuGly-Ser-Ser-^{D}Pro-Pro((3*S*)OH)-) ;

cyclo(-Trp-Trp-Cha-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ser-Ser-^{D}Pro-Pro((3*S*)OH)-) ;

cyclo(-Trp-His-Tyr(Me)-Dab-Orn-^{D}Dab-Dab-Trp-Hse-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Cha-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-*allo*Thr-^{D}Pro-Pro-);

or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 3 which is selected from

cyclo(-Trp-His-Tyr-Dab-Orn-Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Trp-His-Cha-Dab-Orn-Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Ile-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Ile-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Ile-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Tyr-Dab-Orn-Dab-Dab-Trp-Dab-Chg-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Chg-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Trp-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Tyr-Dab-Lys-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-Trp-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Cha-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-Trp-Trp-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-Trp-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Trp-Ala-Ser-^{D}Pro-Pro-);

cyclo(-Leu-His-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ser-Ser-^{D}Pro-Pro-);
cyclo(-Leu-Trp-Tyr-Dab-Lys-^{D}Dab-Dab-Trp-Dab-Cha-Ser-Ser-^{D}Pro-Pro-);
cyclo(-Leu-Trp-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Cha-Ser-Ser-^{D}Pro-Pro-);
cyclo(-Leu-Tyr-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Asn-Ser-^{D}Pro-Pro-);
cyclo(-Leu-Trp-*t*BuGly-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Chg-Ala-Ser-^{D}Pro-Pro-);
cyclo(-Ile-Trp-*t*BuGly-Dab-Lys-^{D}Dab-Dab-Trp-Dab-Cha-Ala-Ser-^{D}Pro-Pro-);
cyclo(-Leu-Trp-*t*BuGly-Dab-Orn-^{D}Dab-Dab-Trp-Dab-Chg-Ser-Ser-^{D}Pro-Pro-);
cyclo(-Leu-Trp-Cha-Dab-Orn-^{D}Dab-Dab-Trp-Dab-*t*BuGly-Ser-Ser-^{D}Pro-Pro-);

or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 1 or 3, 5 to 6, 8 or 10 which is

cyclo(-Leu-Tyr-Tyr-Dab-Orn-^{D}Dab-Dab-Trp-Dab-tBuGly-Tyr-Ser-^{D}Pro-Pro-);

or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition containing a compound or a mixture of compounds according to any one of claims 1 to 6 and at least one pharmaceutically inert carrier.

8. A pharmaceutical composition according to claim 7 in a form suitable for oral, topical, transdermal, injection, buccal, transmucosal, rectal, pulmonary or inhalation administration, especially in the form of tablets, dragees, capsules, solutions, liquids, gels, plaster, creams, ointments, syrup, slurries, suspensions, spray, nebulizer or suppositories.

9. A compound of formula **(I)** according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, for use as a medicament.

10. A compound according to any one of claims 1 to 6 for use as a pharmaceutically active substance having antibiotic activity.

11. A compound according to any one of claims 1 to 6, or a composition according claim 7 or 8, for the treatment or prevention of infections or diseases related to such infections; particularly infections related to respiratory diseases or skin or soft tissue diseases or gastrointestinal diseases or eye diseases or ear diseases or CNS diseases or bone diseases or cardiovascular diseases or genitourinary diseases, or nosocomial infections, or catheter-related and non-catheter-related infections, or urinary tract infections, or bloodstream infections; or as a disinfectants or preservatives for foodstuffs, cosmetics, medicaments and other nutrient-containing materials.

12. A process for the preparation of a compound according to any one of claims 1 to 6 which comprises

(a) coupling an appropriately functionalized solid support with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position T^1 or T^2 or P^1 to P^{12} as defined above; any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

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

(c) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is in the position of the next element (T or P), following counterclockwise or clockwise the sequence according to general formula **(I)** in –COOH to $–NH_2$ orientation; 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 all amino acid residues have been introduced;

(f) if desired, selectively deprotecting one or several protected functional group(s) present in the molecule and chemically transforming the reactive group(s) thus liberated;

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

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

(i) 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;

(j) if desired, implementing additional chemical transformations of one or more reactive group(s) present in the molecule; and

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

13. A compound according to any one of claims 1 to 6 for use in the treatment or prevention of infections or diseases related to such infections; particularly infections related to respiratory diseases or skin or soft tissue diseases or gastrointestinal diseases or eye diseases or ear diseases or CNS diseases or bone diseases or cardiovascular diseases or genitourinary diseases, or nosocomial infections, or catheter-related and non-catheter-related infections, or urinary tract infections, or bloodstream infections; or as a disinfectants or preservatives for foodstuffs, cosmetics, medicaments and other nutrient-containing materials.

14. A compound according to any one of claims 1 to 6 for use in the treatment of an infection, especially infections such as nosocomial infections, catheter-related and non-catheter-related infections, urinary tract infections, bloodstream infections, or a disease or disorder associated with an infection, especially diseases or disorders such as ventilator-associated pneumonia (VAP), hospital-acquired pneumonia (HAP), healthcare-associated pneumonia (HCAP), cystic fibrosis, emphysema, asthma, pneumonia, epidemic diarrhea, necrotizing enterocolitis, typhlitis, gastroenteritis, pancreatitis, keratitis, endophthalmitis, otitis, brain abscess, meningitis, encephalitis, osteochondritis, pericarditis, epididymitis, prostatitis, urethritis, surgical wounds, traumatic wounds, burns, comprising administering to a subject in need thereof a

pharmaceutically acceptable amount of a compound or pharmaceutical composition according to any one of claims 1 to 8.