peptides and peptide-like molecules has been identified which have a net positive charge and a lipophilic group or groups. While for the first generation of these molecules a pore-forming mode of action was assumed and they typically incorporated ten or more amino acids, it has more recently been shown that much smaller molecules can retain therapeutically relevant levels of activity and selectivity (Strøm M.B. et al,, J. Med. Chem. 2003, 46, 1567-1570).

Nevertheless, the sometimes conflicting objectives of therapeutic activity, selectivity, toxicity, *in vivo* and *in vitro* stability, cost of production and ease of delivery means there is a constant need to develop new drug candidates within this general class of molecule.

Summary

In one aspect, the present invention refers to a peptide, peptidomimetic or amino acid derivative having a net positive
charge of at least +2 at pH 7.0 and incorporating a disubstituted β amino acid, each of the substituting groups in the β amino acid, which may be the same or different, comprises at least 7 non-hydrogen atoms, is lipophilic and has at least one cyclic group, one or more cyclic groups within a substituting group may be linked or fused to one or more cyclic groups within the other substituting group and where cyclic groups are fused in this way the combined total number of non-hydrogen atoms for the two substituting groups is at least 12, and wherein said peptide, peptidomimetic or amino acid derivative is 1 to 4 amino acids or equivalent subunits in length, for use as a cytolytic therapeutic agent.

In another aspect, the present invention refers to a peptide, peptidomimetic or amino acid derivative as defined in the present invention for use as an antimicrobial agent.

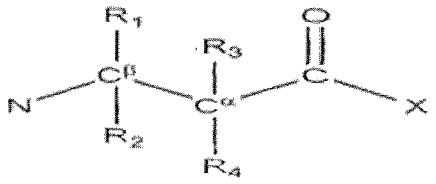
In another aspect, the present invention refers to a peptide, peptidomimetic or amino acid derivative as defined the present invention for use as an antitumoural agent.

In another aspect, the present invention refers to an ex *vivo* use of a peptide, peptidomimetic or amino acid derivative as defined in the present invention as a cytolytic agent.

In another aspect, the present invention refers to use of a peptide, peptidomimetic or amino acid derivative as defined in the present invention in the manufacture of a medicament for treating a microbial infection.

In another aspect, the present invention refers to use of a peptide, peptidomimetic or amino acid derivative as defined in the present invention in the manufacture of a medicament for treating tumour cells or preventing or reducing the growth, establishment spread, or metastasis of a tumour.

In another aspect, the present invention refers to a peptide, peptidomimetic or amino acid derivative having a net positive charge of at least +2 at pH 7.0 which incorporates a β amino acid shown as a group of formula I:



(I)

wherein any 2 from R_1, R_2, R_3 and R_4, are hydrogen atoms and 2 are substituting groups, which may be the same *or* different, comprise at least 7 non-hydrogen atoms, are lipophilic and include a cyclic group, said cyclic group not being attached directly to the α or β carbon atom but optionally being linked or fused to a cyclic group in the other substituting group, where cyclic groups are fused the combined total number of non-hydrogen atoms for the two substituting group is at least 12, and wherein X represents O, C, N or S, and wherein said peptide, peptidomimetic or amino acid derivative is 1 to 4 amino acids or equivalent subunits in length.

In another aspect, the present invention refers to a formulation comprising a peptide, peptidomimetic or amino acid derivative according to the present invention and a diluent, carrier or excipient.

In another aspect, the present invention refers to a peptide, peptidomimetic or amino acid derivative according to the present invention for use in therapy.

In another aspect, the present invention refers to a product comprising (a) a peptide, peptidomimetic or amino acid derivative as defined in the present invention and (b) a further antimicrobial agent as a combined preparation for separate, simultaneous or sequential use in the treatment of an antimicrobial infection.

In another aspect, the present invention refers to a product comprising (a) a peptide, peptidomimetic or amino acid derivative as defined in the present invention and (b) a further antitumoural agent as a combined preparation for separate, simultaneous or sequential use in the treatment of tumour cells.

Detail Description

The present inventors have found that by utilising a disubstituted β amino acid a new class of cytolytic molecule can be generated which has highly promising activity and other desirable characteristics, including a broad spectrum of antibacterial activity, for example activity against both Gram-positive and Gramnegative species. Preferably the molecules are suitable for oral delivery.

Thus, in one aspect, the present invention provides a peptide, peptidomimetic or (modified) amino acid having a net positive charge of at least +2 and incorporating a disubstituted β amino acid, each of the substituting groups in the β amino acid, which may be the same or different, comprises at least 7 non-hydrogen atoms, is lipophilic and has at least one cyclic group, one or more cyclic groups within a substituting group may be linked or fused to one or more cyclic groups within the other substituting group and where cyclic groups are fused in this way the combined total number of non-hydrogen atoms for the two

substituting groups is at least 12, for use as a cytolytic therapeutic agent. The 2 substituting groups on the β amino acid are preferably the same.

Without wishing to be bound by theory, it seems the inclusion of a disubstituted β amino acid increases stability of the molecule, and though the forced conformational charges improves the amphipathicity of the molecule, as well as causing a powerful disruptive effect on the membrane due to the repulsive interactions of the two lipophilic moieties in the disubstituted residue. This gives a cytolytic effect which can be cytotoxic.

The cytolytic activity may be an antimicrobial, preferably an antibacterial activity and/or an antitumoural activity and such medical uses constitute preferred embodiments of the present invention. Thus the present invention provides the peptides, peptidomimetics and modified amino acids as defined above (and described in more detail below) for use as cytolytic antimicrobial or antitumoural