Redesigning PAMAMs: Antimicrobial Inverse-Polyamidoamine (i-PAMAM) Dendrimers

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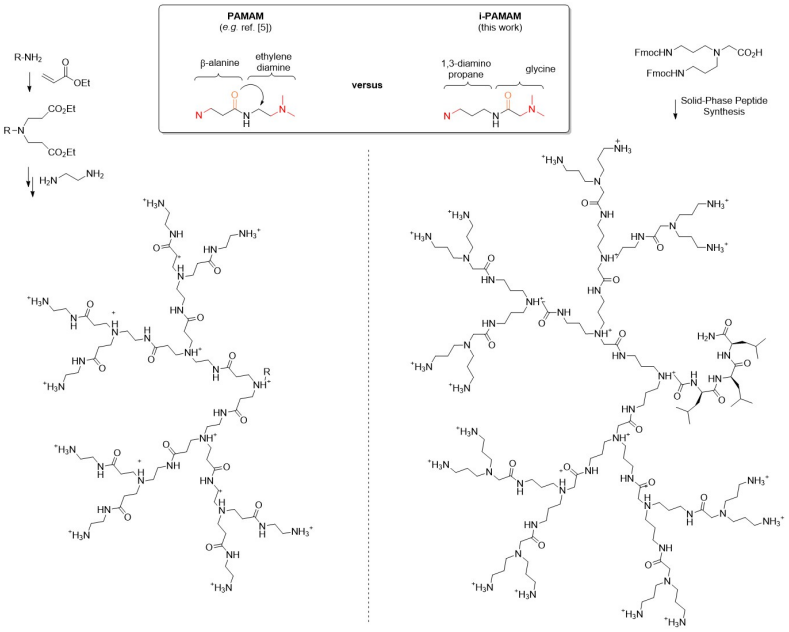
Polyamidoamine (PAMAM) dendrimers have shown various interesting properties ranging from technology to medicine.[1-5] However, PAMAM dendrimers suffer from an intrinsic instability due to the presence of the β-alaninyl-amidoethylamine branch in their structure, which easily undergoes retro-*Michael* reaction.[6] For this reason, we redesigned the branches of PAMAM dendrimers by moving the carbonyl group of β-alanine across the amide bond. This modification transforms the ethylene diamine unit into glycine and the β-alanine into 1,3-diaminopropane, removing the possibility of a retro-*Michael* reaction, and resulting in inverse PAMAM (i-PAMAM) dendrimers. Contrary to the preparation of PAMAMs in solution and the difficulties encountered during their purification, our strategy gave us access to solid-phase peptide synthesis at high temperature by iterative coupling and deprotection of the commercially available *N,N*-bis(N′-Fmoc-3-aminopropyl)glycine. Good purity was reached after preparative reverse phase HPLC and no degradation of our i-PAMAMs could be detected over time. To demonstrate this new class of dendrimers, we synthesised potent so far non-membrane disruptive antimicrobial dendrimers with activities against both *Gram*-negative and *Gram*-positive bacteria.[7]



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