Amino acid-based dendrimers as soft nanomaterials for biorelevant application

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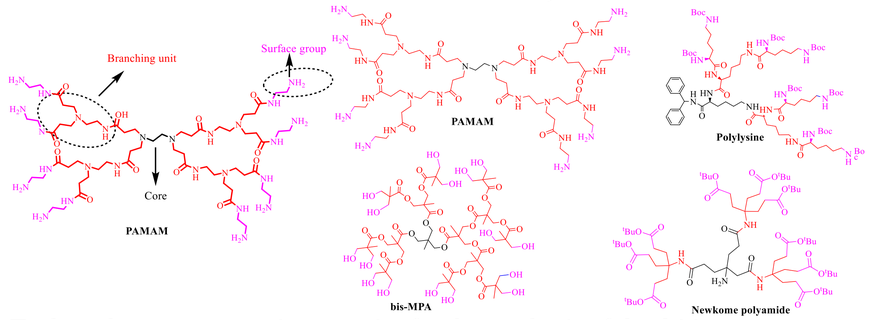
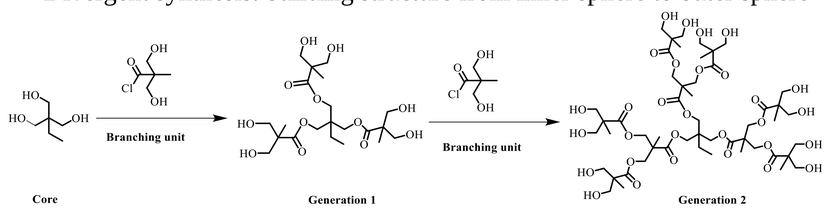
Introduction

Dendrimers are tree-like branched structures that are unimolecular in nature and are synthesized in a sequential manner. The first structure that can be interpreted as a dendrimer was first reported in the published paper by Fritz Vogtle and coworkers and the process was referred to as cascade synthesis. Below are the structures of some of the most widely studied dendrimers.

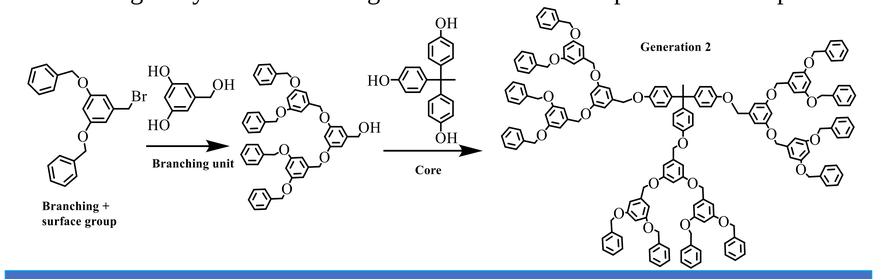


To date, there are two main strategies for the synthesis of dendritic macromolecules.

- Divergent synthesis: building structure from inner sphere to outer sphere

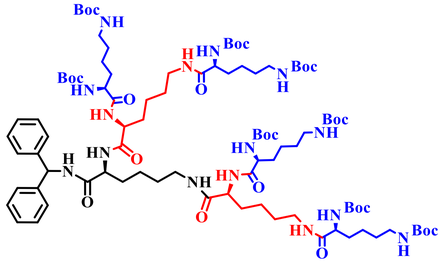


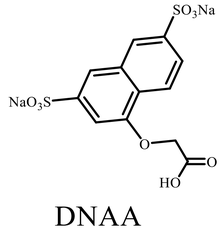
- Convergent synthesis: building structure from outer sphere to inner sphere



Polylysine dendrimers

Polylysine dendrimers are macromolecules entirely based on amino acid *L*-lysine and are among the most biocompatible dendrimers as their degradation product is thought to be a nontoxic essential amino acid *L*-Lysine. Of particular interest is the use of polylysine dendrimers as HIV inhibitors. It has been reported that DNAA terminated dendrimers inhibit HIV and HSV-2. However, due to issues with the synthesis, the molecules higher than G4 have never been tested.

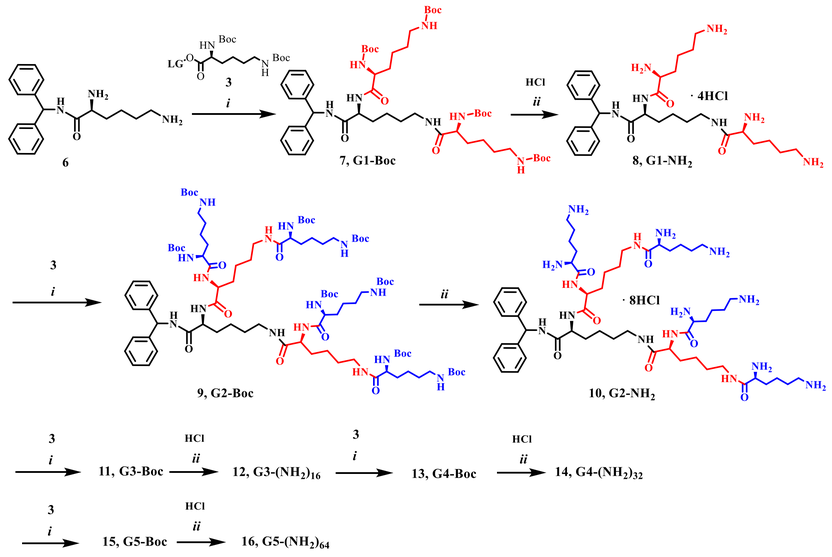




DNAA

Experimental Design

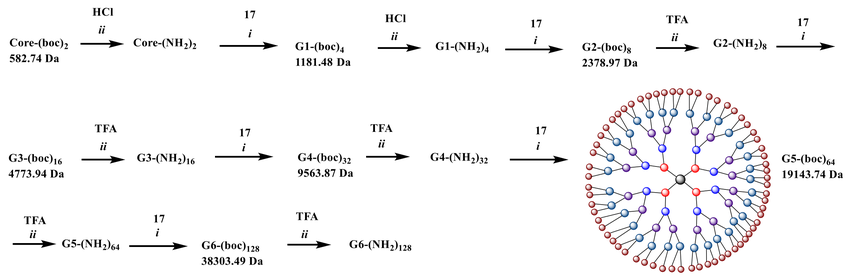
The current method for polylysine dendrimer synthesis is able to produce structure up to G5. However, due to the steric bias between α and ε amino group of *L*-lysine, structures of only up to generation 4 has been converted into functional molecules. Amino group at α position is significantly more shielded limiting the synthesis of high generation molecules.



Result

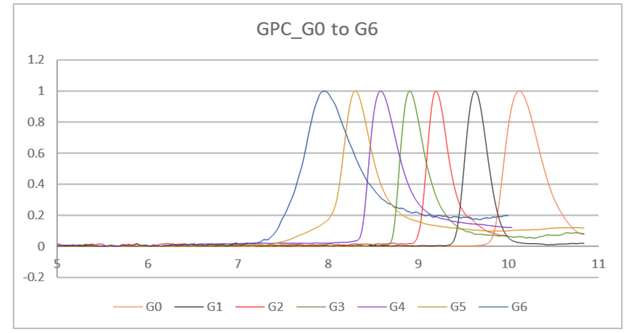
To overcome this limitation, this project was focused on the development of novel synthetic pathway by introducing another amino acid in the branching unit along with *L*-lysine to balance the steric environment of α and ε amino groups. The synthetic route consists of divergent growth method utilizing two repeating steps, (*i*) Growth (*ii*) Deprotection steps. During the growth step, branching unit is added to the core or deprotected dendrimer while the deprotection is achieved under acidic environment.

The synthesis started from linking two amino acid synthesis to afford the branching unit. The branching unit was activated with a proper leaving group such as 4-nitrophenol or N-hydroxysuccinimide for the dendrimer growth step. To afford the core unit, diphenylmethanamine was coupled with activated branching unit **17**. Higher generation products was then achieved by iterative steps mentioned above. To date, this approach has achieved the synthesis of generation 6. The synthesis of higher generations is ongoing.



Result

The identity and the purity of synthesized dendrimers were confirmed by a variety of analytical techniques. ^{1}H and ^{13}C NMR were used to confirm the reaction progress and the structure of the molecules, albeit providing a rather limited information in case of high generation molecules. Gel Permeation Chromatography (GPC) and Matrix Assisted Laser Desorption/Ionization-Time of Fly (MALDI-TOF) was employed to confirm the molecular weight and the purity of each molecule. As seen in figure below, a clear shift toward low retention times were detected in GPC traces indicating an increased size and hydrodynamic volume.



Conclusion and Future work

To conclude, this project provides an alternate method of synthesis of high generation *L*-lysine based dendrimers. The key highlights of this works are:

- No column chromatography is needed
- High generation are achieved (>G6).
- High reaction yields (70-90%)
- Flexible synthesis method allows multiple amino acid analogs to be synthesized
- In the future, we planned to establish the procedures for the surface groups modification, and to study the anti-HIV activity of thus prepared molecules.

Reference

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