New promising vectors for gene delivery by a step-wise functionalization of a polyester-based non toxic dendrimer with *N, N*-dimethylglicine, *N*-methylglicine, lysine and arginine

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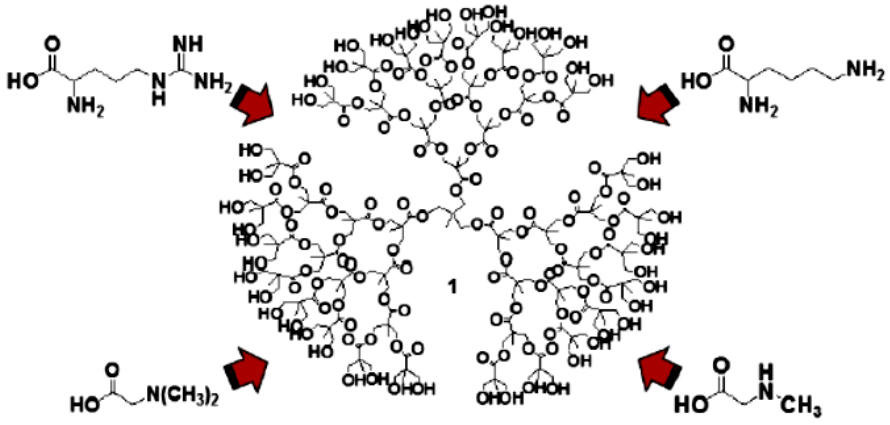
Polycationic dendrimers are able to electrostatically bind genetic material forming nanosized complexes (polyplexes). They result very appealing for applications as non-viral vectors to bring DNA or RNA within genetically defective cells for treating or solving several diseases including cancer. Commonly used cationic polymers (*b*PEI) or dendrimers (PAMAM), thanks to a good buffer capacity due to the several weakly basic amines in their structure, once in the cell, induce an osmotic swelling of endosomes that contain the polyplexes leading to content release (1). For this reason *b*PEI and PAMAM are endowed with high transfection efficiencies (2) but, if not chemically modified do not find real applications in gene therapy because of their cytotoxicity. It is also known that dendrimers containing arginine improve *si*RNA cellular uptake (3) and are equipped with higher efficiency of transfection and reduced toxicity (4, 5). In respect of this background in this communication we report the setting up of versatile protocols to introduce on the hydrolysable polyester-based fourth generation dendrimer (**1**) previously prepared, a mixture of *N, N*-dimethyl glycine, *N*-methylglicine, lysine, and arginine. The synergic presence of nitrogen atoms with different pKa and the arginine moiety should have promoted the cellular up-take and should have contributed to an optimal buffering capacity enhancing the endosomal escape and improving transfection activity.



The obtained products in the hydrochloride forms were subjected to volumetric titration to determine experimental molecular weight and to NMR analysis to confirm the structures. Potentiometric titration to calculate the buffer capacity (β) and then the average buffer capacity and the NMR characterization of all the intermediates were also performed.

References: 1. Behr, J. P. *Chimia* **1997**, *51*, 34-36. 2. Akinc, A.; Thomas, M.; Klibanov, A. M.; Langer, R. *J Gene Med.* **2005**, *7*, 657–663. 3. Liu, X.; Liu, C.; Zhou, J.; Chen, C.; Qu, F.; Rossi, J. J.; Rocchi, P.; Peng L. *Nanoscale* **2015**, *7*, 3867-3875. 4. Kim, T.; Bai, C. Z.; Nam, K.; Park, J. *J. Control. Release* **2009**, *136*, 132-139. 5. Peng, Q.; Zhu, J.; Yu, Y.; Hoffman, L.; Yang, X. *J. Biomater. Sci. Polym. Ed.* **2015**, *26*, 1163-1177.