Efficient mannosylated calixarene-dendrimer ligands for uropathogenic *E. coli* FimH adhesin

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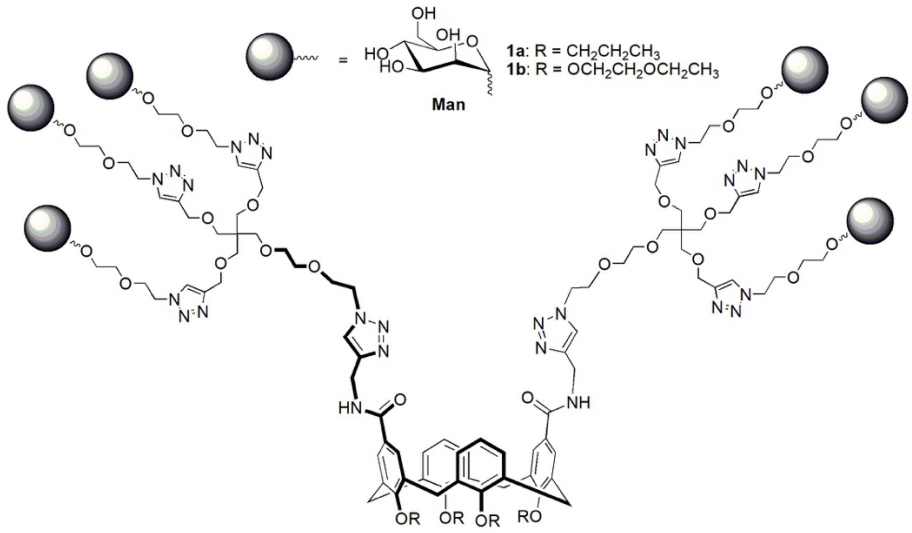
Uropathogenic *E. coli* (upEc) is an antibiotic resistant bacterium included in the priority list of WHO for which it is urgent to define innovative treatments [1]. It is one of the main responsible for urinary tract infections [2] and its ability of colonizing gut, bladder and kidney largely depends on adhesins [3]. Extracellular fibers, in particular type 1 pili, exploit these proteins to trigger the infection starting with a cell adhesion process [4]. Type 1 pili use FimH adhesin [5] that interacts with mannoside units of bladder epithelium glycoproteins. The inhibition of this recognition process can represent a therapeutic approach to prevent the upEc invasion. Calixarenes demonstrated to be versatile scaffolds for the preparation of polyglycosylated ligands that, thanks to multivalent effects, show high efficiency and selectivity in the interaction with different types of lectins [6]. In this work we designed calixarene-based dendrimers displaying multiple copies of α-mannoside and investigated their ability to interact with upEc and to inhibit its adhesion activity. Molecular Modelling studies shed light on the arrangement in the space of the ligand saccharide units, STD NMR experiments demonstrated the interaction and established the binding epitope map for the ligands while yeast agglutination assays evidenced the inhibition against upEc unequivocally due to the recognition between mannosides and FimH adhesin. Remarkably, the calixarene-based ligands showed potency significantly higher than simple dendrimers equipped with the same or a higher number of epitope units.



The studied multivalent mannosylated calixarene-dendrimer ligands.

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