DESIGN AND SYNTHESIS OF INHIBITORS OF DC-SIGN MEDIATED INFECTIONS

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DC-SIGN (Dendritic Cell-Specific ICAM-3 Grabbing Nonintegrin) is a C-type (Calcium dependent) lectin, expressed as homotetramers (presenting four copies of a Carbohydrate Recognition Domain (CRD) at the C-terminus) on the surface of immature Dendritic Cells. [1]
Dendritic Cells (DCs) are one of the most important classes of Antigen Presenting Cells (APCs). They recognize many pathogens through several receptors such as DC-SIGN, MR, etc. After recognition, pathogens are internalized and DCs mature and migrate to lymph nodes.[2] Then, DCs relay the corresponding processing antigens as MHC complexes to naive T-cells, which differentiate allowing the appropriate immune response. Some of these pathogens, such as HIV, hijack this mechanism to infect the immune system cells: the pathogens are recognized by DCs but escape the processing pathway. Indeed, using DCs, HIV particles are finally transported, stabilised and presented in a fully native and infectious form to their target, the T-cells.
The main carbohydrate ligand recognized by DC-SIGN is the high mannose glycan $(Man)_9(GlcNAc)_2$, also known as Man_9, a branched oligosaccharide which is presented in multiple copies by several pathogen glycoproteins (gp120, GP1, …). Hence, a multivalent mannose display should be an adequate strategy to interact with this lectin with high affinity.
In vivo, mannosides are normally hydrolyzed by mannosidases: the use of a structural mimic in place of the natural sugar could avoid the easy degradation in a biological environment. The aim of this project is to design and prepare products that meet these requirements.

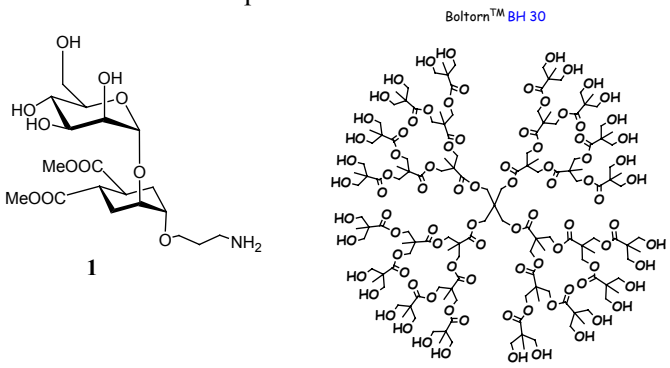

Figure 1: The monovalent mimic 1 and the Boltorn dendrimer BH 30.

So far, we have demonstrated, using NMR, that the monovalent mimic **1** shown in Figure 1 interacts with DC-SIGN. Also, this compound inhibits the DC-SIGN mediated infection in a pseudo-typed Ebola virus model.[3] Moreover, this molecule has been conjugated to a Boltorn-type dendrimer, leading to neo-glycoconjugates that inhibit the binding of DC-SIGN to gp120 (envelope protein of HIV).
In this communication we will report the synthesis of new monovalent inhibitors and the results of their binding assays by SPR. We will show also the synthesis of some multivalent compounds.

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[1] T. B. H. Geijtenbeek, , Y. van Kook, *et al.*, Cell **2000**, *100*, 575-585.
[2] Y. van Kooyk, T. B. H. Geijtenbeek, *Nat. Rev. Immunol.* **2003**, *3*, 697-709.
[3] José J. Reina, Sara Sattin, Donatella Invernizzi, Silvia Mari, Lorena Martínez-Prats, Georges Tabarani, Franck Fieschi, Rafael Delgado, Pedro M. Nieto, Javier Rojo, Anna Bernardi, *ChemMedChem* , **2007,** *2(7)*,1030-1036.