MULTIVALENT SIALIC ACID DERIVATIVES AS POTENT SIALIDASES INHIBITORS AND THERAPEUTIC PERSPECTIVE AGAINST INTESTINAL INFLAMMATION

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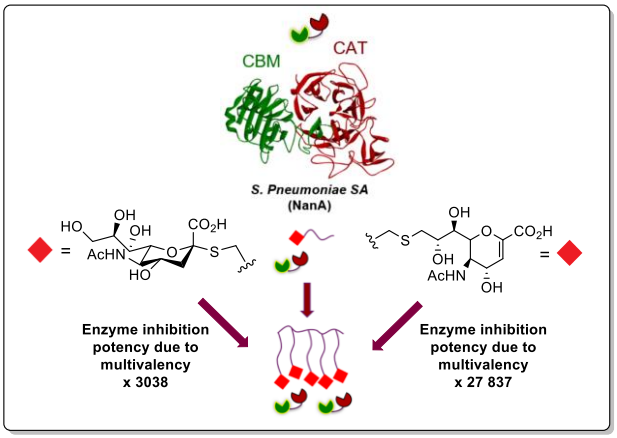

Bacterial sialidases are enzymes produced by certain viruses, parasites and bacteria. Excessive activity of these glycosidases can lead to proliferation of *Enterobacteriaceae* such as AIEC (*Adherent & Invasive Escherichia Coli*), responsible for inflammation of the intestinal wall.[1] Sialidases can have a single catalytic site (CAT) used to cleave sialosides present on intestinal wall mucins, while others can have a lectin site (CBM for Carbohydrate-Binding Module) in addition to this catalytic site. The CBM increases the catalytic efficiency of the enzyme by targeting the sialidases on the polymeric substrates through sugar-lectin interactions. Sialidases of both types represent potential therapeutic targets, and this project was dedicated to the design of selective and potent multivalent inhibitors of these enzymes. In recent years, several inhibitors have been developed with the same goal but unfortunately have not shown sufficient selectivity and efficacy. For this new generation of inhibitors, we are interested in the synthesis of non-hydrolysable multivalent inhibitors based on thiosialoside[2] and DANA (2,3-dehydro-3-deoxy-*N*-acetylneuraminic acid) ligands grafted by click chemistry on poly-azide scaffolds. To study the dual targeting of the enzyme sites and to validate the concept of multivalency, sialidases from *Vibrio cholerae* (VcSA), *Trypanosoma cruzi* (TcTS), *Bacteroides thetaiotaomicron* (BtSA) and *Streptococcus pneumoniae* (NanA) were produced with and without CBM. Promising results were first obtained on multivalent thiosialoside and DANA compounds which showed a much higher inhibition of the enzymatic activity compared to the monovalent references at equimolar ligand ratios. Polymeric DANA showed unprecedented Inhibitory values reaching the nano- to pico-molar range, and are therefore promising antivirulent factors of pathogens expressing sialidases [3].

References

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