Selective conformational inhibitors for glycosidases using cyclic sulfates and sulfamidates

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Selective inhibition of glycosidases by small molecule inhibitors has proven to be an essential tool to study glycosidases, their mechanisms and their role in complex biochemical pathways and on a larger scale, diseases. These enzymes can usually be divided into two groups based on their reaction mechanism. These mechanisms go through various conformational itineraries to navigate through any problems that might arise from any steric or electronic features. Mimicry of these conformational itineraries has been used to develop inhibitors for various glycosidases including GH47-α-mannosidases. This group of enzymes is essential for the maturation and quality control of glycoproteins in the secretory pathway. Previously, *cis*-cyclic sulfates electrophiles have shown to be covalent nanomolar inhibitors for α-glucosidases by mimicking there $^4C_1$Michaelis conformation (Figure 1).[1] A similar strategy has been applied to develop *cis*-cyclic sulfamidates which by introducing a nitrogen atom at the pseudo-anomeric position were able to function as selective competitive inhibitors for α-galactosidase and glucosidase.[2,3] In this study we describe the development of *trans*-cyclic sulfates and sulfamidates, which by virtue of their *trans*-stereochemistry switch to a $^1C_4$ chair conformation. Since GH47-α-Mannosidases follow a unusual $^3S_1$ (Michaelis complex) $^3H_4$ (transition state) $^1C_4$ (product) conformational itinerary, we capitalized on the $^1C_4$ trans-cyclic sulfates and sulfamidates to develop new selective inhibitors for GH47-α-Mannosidases through a bump and hole strategy (Figure 1).[4]

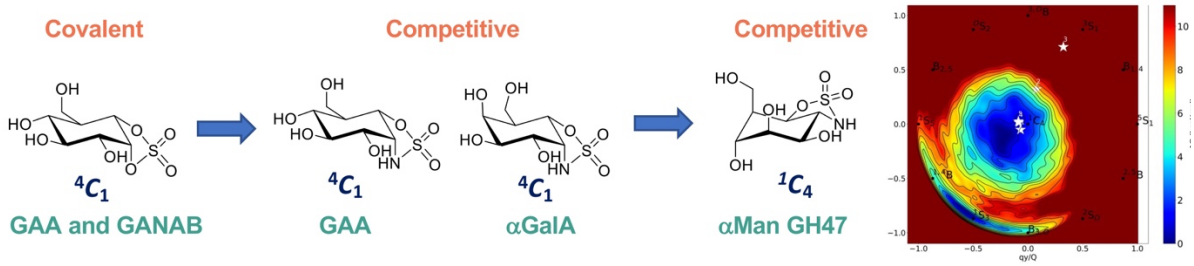

Figure 1. Cyclosulfate and cyclosulfamidate-based cyclitols as selective glycosidase inhibitors.

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