# PHARMACOLOGICAL CHAPERONES BY DESIGN

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**Abstract.** One of the most successful approaches in the synthesis of inhibitors of the glycosidases is the substitution of the endocyclic oxygen in monosaccharides by a nitrogen atom to get iminosugars. Given that many diseases have their origin in the malfunctioning of these enzymes, this glycomimetics bear strong potential as drug candidates. At their protonated state, iminosugars are supposed to mimic the glycosyloxacarbenium cation, a common intermediate in the enzymatic glycoside hydrolysis of both α- and β-glycosides. Similarly to this species, most of iminosugars lack an anomeric substituent at the pseudoanomeric carbon and behave as broad range glycosidase inhibitors: they show configurational selectivity but not anomeric selectivity nor selectivity among isoenzymes. Fifteen years ago we conceived that the substitution of the $sp^3$ endocyclic nitrogen atom in classical iminosugars by a $sp^2$ pseudoamide-type nitrogen should result in a very efficient overlapping of the orbital hosting the N-lone-pair with the antibonding σ* orbital of the contiguous C—O bond, increasing the anomeric effect. This orbital interaction leads to a very high stabilization of axially oriented pseudoanomeric substituents, resulting in compounds with configurational and conformational integrity even in polar solvents. We called this new type of glycomimetics $sp^2$-iminosugars.[1] Most interestingly, their synthesis is compatible with molecular diversity-oriented approaches, allowing structural modifications at the heterocyclic core, the hydroxylation profile and the nature and location of exocyclic substituents with a relatively low synthetic cost. Very selective glycosidase ligands became thus accessible. By taken advantage of the information obtained from X-ray data of $sp^2$-iminosugar:glycosidase complexes, compounds capable of inducing the correct folding of lysosomal storage disorders (LSDs)-associated glycosidase mutants (pharmacological champerones) have been designed. Different strategies for the preparation of these pharmacological chaperones for the treatment of Gaucher disease, $GM_1$ gangliosidosis[2] and Fabry disease will be presented.

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