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Multivalent sugars and glycomimetics as enzyme stabilizers for lysosomal storage diseases

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Lysosomal Storage Diseases (LSDs) are rare inherited metabolic disorders caused by lysosomal enzymes deficiency and/or misfolding, leading to undegraded substrates accumulation, cellular dysfunction and progressive multisystem damage[1]. β-Glucocerebrosidase (GCase) is a glycosidase that hydrolyzes glucosylceramide and glucosylsphingosine and is related with the most common LSD, Gaucher disease (GD). *N*-Acetylgalactosamine-6-sulfatase (GALNS) removes sulfate groups in keratan sulfate and chondroitin 6-sulfate and is related to the lysosomal storage disease Morquio A.

The use of mimetics of natural substrates that can behave as pharmacological chaperones (PCs), *i.e.* molecules able to bind and stabilize misfolded proteins allowing them to recover their native folding and thus their biological activity, is a key step to develop new therapies for LSDs[2]. Recent findings have demonstrated that the multivalent presentation of iminosugar glycomimetics can significantly improve the stabilization of misfolded GCase[3] and GALNS[4].

In this context, a series of novel multivalent systems incorporating sugar (galactosides) and iminosugar glycomimetic ligands (blue moieties, Figure 1) have been synthesized. Control over spatial presentation was achieved by tuning the core scaffold (red moiety, Figure 1) and the valency of the ligands. Preliminary evaluation of the multivalent architectures as GCase enhancers in human cell extracts from GD patients and as GALNS stabilizers on human recombinant enzymes showed promising results.

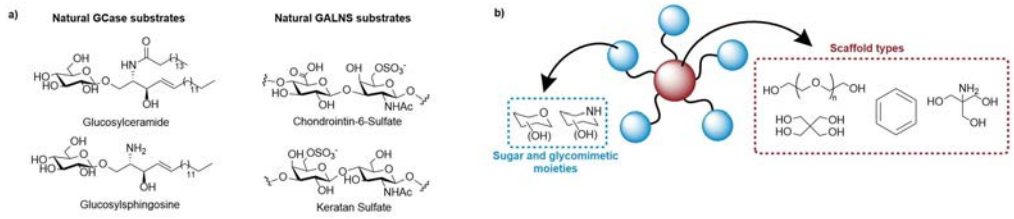

Figure 1: a) Natural GCase and GALNS substrates; b) multivalent sugars and glycomimetics (blue spheres) conjugated to a central molecular scaffold (red sphere).

References:

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