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Multivalent iminosugars as enhancers of the lysosomal enzyme GCase activity

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Iminosugars are sugars mimetics characterized by the presence of a nitrogen atom in place of the endocyclic oxygen atom of carbohydrates and are well known to inhibit carbohydrate-processing enzymes. Recently, their role as pharmacological chaperones (PCs) for the treatment of Lysosomal Storage Disorders (LSDs) has been disclosed. PCs are molecules able to bind and stabilize misfolded enzymes involved in these diseases resulting in enzyme activity's enhancement. No PCs has been yet identified for Gaucher Disease, which is caused by a misfolding of the lysosomal enzyme β-glucocerebrosidase (GCase) [1].

Recent studies showed that *N*-alkylated 3,4,5-trihydroxypiperidines (red moiety **1** in Figure 1) are promising PCs for GCase [1], and even more promising are the results obtained with a trivalent derivative of **1** [2]. The efficacy of multivalency in modulating GCase activity, prompted us to multimerize suitable derivatized moiety **1** bearing a thiol-ending linker onto gold nanoparticles (AuNPs) as a scaffold.

In parallel, since the *C2*-alkylated 3,4,5-trihydroxypiperidine (green moiety **2** in Figure 1) behaves as a better GCase PC compared to the *N*-alkylated analogue [3], a synthetic strategy was started to obtain multivalent systems (both dendrimers and AuNPs) based on **2**. *In vitro* biological assays are ongoing to test the ability of these new nanosystems to act as PCs for GCase.

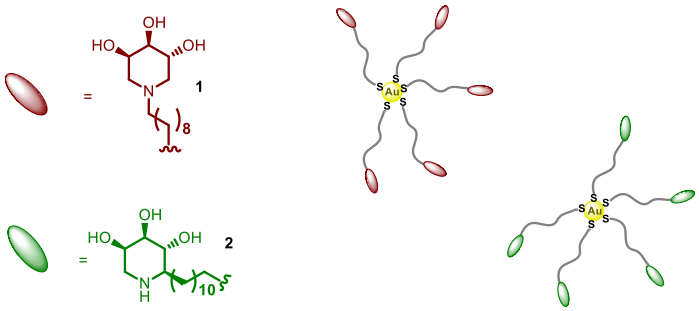

Figure 1: Schematic representation of AuNPs, one of the topics of this project

[1] M. Martìnez-Bailén et al., *Pharmaceuticals* **2022**, *15*, 823 and references cited therein.
[2] C. Vanni et al., *ChemBioChem* **2022**, 23, e202200077.
[3] F. Clemente et al., *Bioorg. Chem.* **2020**, *98*, 103740.