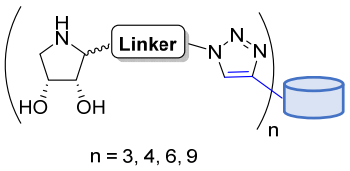
INHIBITION OF LYSOSOMAL GLYCOSIDASES BY MULTIMERIC PRESENTATIONS OF PYRROLIDINE-BASED IMINOSUGARS

Macarena Martínez-Bailén[a], Ana T. Carmona[a], Camilla Matassini[b], Francesca Cardona[b], Atsushi Kato[c], Inmaculada Robina[a], Antonio J. Moreno-Vargas[a]

[a] Department of Organic Chemistry, Faculty of Chemistry, University of Seville, 41012-Seville, Spain
[b] Dipartimento di Chimica "Ugo Schiff", Università degli Studi di Firenze, 50019 Sesto Fiorentino (FI), Italy
[c] Department of Hospital Pharmacy, University of Toyama, Toyama 930-0194, Japan

Multivalency is a phenomenon broadly studied in the field of carbohydrate-protein interactions [1]. Recently, this concept has been applied in the field of glycosidase inhibition as a promising alternative to prepare potent inhibitors for the treatment of diseases involving enzymatic hydrolysis of glycosidic bonds in carbohydrates [2].

The aim of the present work was to study if the multimeric presentation of pyrrolidine-triazole inhitopes onto several platforms influences the inhibition properties towards human lysosomal β-glucocerebrosidase and α-galactosidase A, enzymes involved in Gaucher and Fabry diseases. For the synthesis of the multivalent compounds we have used the Cu(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC) between several alkynyl functionalized scaffolds and three pairs of epimeric pyrrolidine derived azides.



n = 3, 4, 6, 9

Some of the compounds showed relevant inhibition towards α-galactosidase A and constitute the first examples of a remarkable multivalent effect in the inhibition of this enzyme.

[1] Pieters, R. J. *Org. Biomol. Chem.*, **2009**, *7*, 2013–2025.

[2] For reviews, see: (a) Gouin, S. G. *Chem. Eur. J.* **2014**, *20*, 11616-11628. (b) Zelli, R.; Longevial, J.-F.; Dumy, P.; Marra, A. *New J. Chem.* **2015**, *30*, 5050-5074.