INVITED LECTURE

Glycosidase Inhibitors and Effectors as Therapeutic Tools

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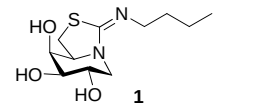
Glycosyl hydrolases play important roles in biological proccesses that result in the maintenance of life, including the degradation of polysaccharides, the lysosomal catabolism of glycoconjugates and the biosytnthesis of the oligosaccharide units in glycoproteins and glycolipids. Consequently, compounds that interfer with their function bear many prospects in medicine and biotechnology. Selectivity is a key issue for those channels. sp^2-Iminosugars, a family of glycomimetics characterized by the presence of an endocyclic pseudoamide-type nitrogen atom have shown much promise in this respect. Notably, several representatives exhibited potent glycosidase inhibitory activity and higher enzyme selectivity as compared with the parent iminosugars. At subinhibitory concentrations, some of these compounds acted as effectors of misfolded mutant enzymes involved in lysosomal storage disorders, showing high promise as pharmacological chaperones. In vitro and in vivo data support their potential for the treatment of Gaucher, GM_1 gangliosidosis (e.g. **1**)[1] and Fabry diseases. Moreover, sp^2-iminosugars pseudoglycosides (e.g. **2**) have been shown to interfere with glycoprotein biosynthesis in cancer cells, selectively promoting cell cycle arrest and apoptosis.[2] The possibility to modulate the biological activity of these compounds by multivalent presentation (e.g. **3**) will be also discussed.[3]



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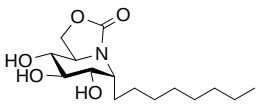

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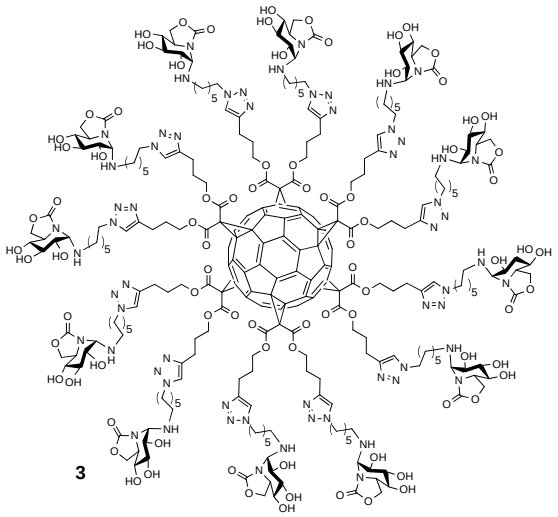

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References

[1] Takai, K.; Higaki, K.; Aguilar-Moncayo, M.; Mena-Barragán, T.; Hirano, Y.; Yura, K.; Yu, L.; Ninomiya, H.; García-Moreno, M. I.; Sakakibara, Y.; Ohno, K.; Nanba, E.; Ortiz Mellet, C.; García Fernández, J.M.; Suzuki, Y. *Mol. Ther.* **2013**, *21*, 526.

[2] Allan, G.; Ouadid-Ahidouch, H.; Sánchez-Fernández, E.; Rízquez-Cuadro, R.; García Fernández, J. M.; Ortiz Mellet, C.; Ahidouch. A. *PLOS ONE*. **2013**, *8* e76411.

[3] Rízquez-Cuadro, R.; García Fernández, J. M.; Nierengarten, J.-F.; Ortiz Mellet, C. *Chem. Eur. J.* **2013**, *19*, 16791.