Synthesis of novel iminosugars containing an aziridine moiety, evaluation as inhibitors and as selective probes for α-glucosidases

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Keywords : Iminosugar synthesis – Glycosidase inhibition – Mechanism – SPR-based enzyme probes

Context

Iminosugars are a promising class of molecules with therapeutic applications in the treatment of diabetes and lysosomal disorders.[1] Miglitol and miglustat are examples of drugs already marketed for such applications, and other iminosugars are currently considered clinically as antivirals. Their mechanism of action involves inhibition or activation of glycosidases, which are biological catalysts for oligosaccharide hydrolysis. Such enzymes are essential for the digestion process and for the maturation of functional glycoproteins. However, as these enzymes are ubiquitous, the current bottleneck to the development of iminosugars as drugs is the prevalence of side effects, due to a lack of selectivity in enzyme inhibition. Indeed, it is often difficult to inhibit a specific enzyme without affecting those involved in normal cell functions. In the last few years, our team has been involved in the development of novel synthetic methods to prepare iminosugars from nitrones.[2] This has recently allowed us to identify a new class of iminosugars which are **potent glycosidase inhibitors** (nanomolar K_i) endowed with **exceptionnal selectivity towards α-glucosidases**.[3]

Objectives of the PhD project

- to **synthesize new congeners** with enhanced activity and selectivity based on structure-activity relationships, and containing an aziridine moiety as a potential warhead for covalent binding to the target enzymes
- to **evaluate their bioactivity** in collaboration with international partners
- to study their immobilization on gold surfaces to **implement an innovative biosensor** based on Surface Plasmon Resonance (SPR) thanks to the ability of these iminosugars to bind tightly and selectively to specific glycosidases.

The PhD student will be involved in the development of new synthetic methods to access original iminosugar scaffolds to complement those already existing. Carbohydrate-derived nitrones will be used as key intermediates to prepare iminosugars exhibiting adequate configuration and conformation to interact selectively with α-glucosidases. In particular, we will aim at preparing aziridinyl-iminosugars equipped with a functional anchor. The latter will allow their grafting on gold surfaces for SPR studies, and conception of the first iminosugar-based biosensors, for detection and quantification of glycosidases in biological samples. The development of biosensors will be conducted in partnership with the Symmes/Creab laboratory, at CEA Grenoble (Dr. A. Spinelli-Bouchet).

The main activity of the PhD student will be organic synthesis, with a possibility to participate in enzyme inhibition studies in our international partners' groups and to implement SPRi biosensors with his/her iminosugar biochips.

Candidate profile: Master student with good records (top 30%), previous experience in multi-step organic synthesis and interest in bio-analytical methods; dedicated, curious and with good communication skills.

Application: before April 5, 2018. Please send your CV, motivation letter, and names of 2 references by e-mail to: Dr. Sandrine PY, Sandrine.Py@univ-grenoble-alpes.fr

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[2] See for examples : a) Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459. b) Gilles, P.; Py, S. *Org. Lett.* **2012**, *14*, 1042. c) Tangara, S.; Aupic, C.; Kanazawa, A.; Poisson, J.-F.; Py, S. *Org. Lett.,* **2017**, *19*, 4842.

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