

# SYNTHESIS AND ANTIFUNGAL ACTIVITY STUDY OF TRIMETHYL LOCK-MODIFIED GLUCOSAMINE-6-PHOSPHATE SYNTHASE INHIBITOR

Michał G. Nowak<sup>a</sup>, Dorota Martynow<sup>b</sup>, Andrzej S. Skwarecki<sup>b</sup> and Maria J. Milewska<sup>a</sup>

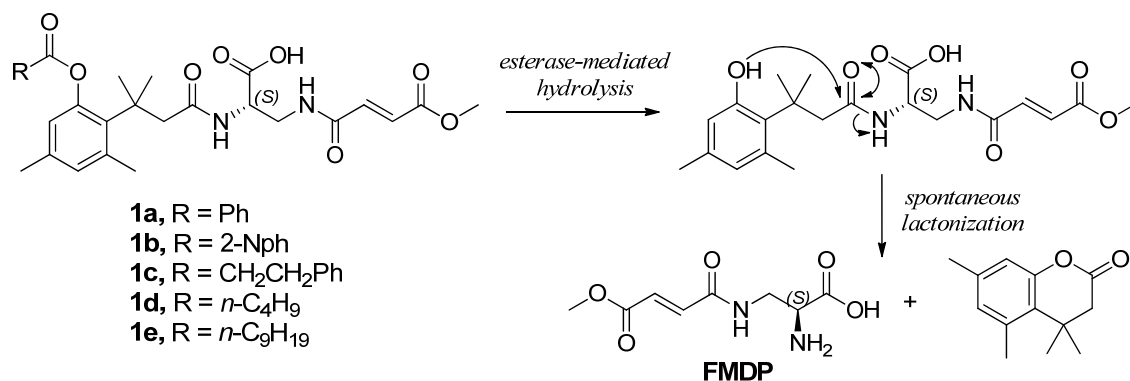
<sup>a</sup>Department of Organic Chemistry, Chemical Faculty, Gdansk University of Technology, 11/12 Narutowicza Str., 80-233 Gdansk, Poland

<sup>b</sup>Department of Pharmaceutical Technology and Biochemistry, Chemical Faculty, Gdansk University of Technology, 11/12 Narutowicza Str., 80-233 Gdansk, Poland

(*S*)-*N*<sup>3</sup>-(4-methoxyfumaroyl)-2,3-diaminopropionic acid (**FMDP**) is a potent glucosamine-6-phosphate synthase inhibitor that displays high affinity to the fungal enzyme [1]. Simultaneously, due to its highly hydrophilic character, it also exhibits poor biological activity against fungal cells, caused by highly reduced fungal cell membrane permeability.

The idea of ‘trimethyl lock’ (TML) systems is based on a rapid lactonization of *o*-hydroxydihydrocinnamic acid derivatives and are often used as a molecular triggers in conjugation chemistry for controlled drug release in a presence of various enzymes or other specific conditions [2].

Herein we propose chemical synthesis and biological activity evaluation of the series of compounds (**1a-e**) which can be described as esterase-sensitive FMDP-TML conjugates exhibiting increased lipophilic character in comparison to FMDP molecule. We expect that presented FMDP-TML conjugates (**1a-e**) should provide improved permeability of fungal cell membrane and allow to release FMDP molecule in native form inside pathogenic fungal cell.



[1] Milewski S. Glucosamine-6-phosphate synthase - The multi-facets enzyme. *Biochim Biophys Acta Protein Struct Mol Enzymol.* 2002;1597(2):173-192

[2] Okoh OA, Klahn P. Trimethyl Lock: A Multifunctional Molecular Tool for Drug Delivery, Cellular Imaging, and Stimuli-Responsive Materials. *ChemBioChem.* 2018;19(16):1668-1694.