β-Lactones and β-lactams: Design and synthesis of novel antimycobacterial compounds

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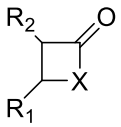
β-Lactones are potent serine hydrolase inhibitors which are important for the survival and proliferation of bacteria and mycobacteria, including Mycobacterium tuberculosis (*M.tb.*) that causes tuberculosis. Tuberculosis was the leading cause of death from a single infectious agent prior to the Covid-19 pandemic [1]. The most important β-lactone in the market is Xenical® or tetrahydrolipstatin that inhibits the activity of human digestive lipases and is prescribed against obesity.

Our group works on the design, synthesis and antimycobacterial study of β-lactones bearing an aliphatic carbon atom chain, saturated or unsaturated, at the α-position and a small propyl chain at the β-position [2]. In this work, we present novel β-lactones that bear a fluorine atom for the improvement of the activity and the pharmacokinetic properties, along with synthetic routes to their synthesis. Also, we present β-lactones that bear a terminal alkyne at the α-position that may be used as chemical probes for the identification of the target enzymes in mycobacteria. The synthesis of β-lactams based on the structure of the most promising β-lactones is also disclosed. Finally, a synthetic methodology for the synthesis of the most active β-lactones in optically pure form is discussed.



The chemical structure of α,β-disubstituted β-lactones (X=O) and β-lactams (X=NH).

This research work was supported by the Special Account for Research Grants of the National and Kapodistrian University of Athens (SARG/NKUA) and the Centre National de la Recherche Scientifique (CNRS), Aix Marseille University.

1. World Health Organization. Global Tuberculosis Report (Geneva, 2022).
2. P. Santucci, C. Dedaki, A. Athanasoulis, L. Gallorini, A. Munoz, S. Canaan, J.-F. Cavalier, V. Magrioti, ChemMedChem 14 (2019) 349-358.