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Synthesis, antibacterial and anticancer potency of new lactone and lactam macrolide derivatives

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Macrolide antibiotics are large group of natural products of attractive biological properties and produced by *Streptomyces* strains. Macrolides can be classified via inter-alia the type and the size of the macrolide ring[1] as for e.g. lactone macrolides 14-membered erythromycins, 15-membered azithromycins, and 16-membered spiramycins and leucomycins, or lactam 26-membered rifamycins as e.g. rifampicine. Macrolide antibiotics, especially lactone ones, can be divided also by the type of saccharide moiety attached at the aglycone.[2] Mechanism of action of macrolide lactone antibiotics' is based on the inhibition of bacterial protein biosynthesis at different stages by reversible binding at bacterial 50S subunit of ribosomes[3] whereas macrolide lactam antibiotics mechanism of action as rifamycins depends on inhibition of bacterial RNA polymerases[4]. Our modifications were performed using cascade and 'click' approaches in aim to construct novel semisynthetic antibiotics of well-balanced physico-chemical parameters (lipophilicity, water solubility) and of improved docking mode at the biological target. For example, modifications at aglycone ring *via* complete reconstruction of saccharides parts using regio- and diastereoselective cascade combination of intramolecular esterifications, tandem E1cB eliminations and subsequent 1,2-addition to carbonyl followed by 1,6-conjugate addition at α,β,γ,δ – unsaturated aglycone yielded novel lactone macrolides of enhanced antibacterial and anticancer activities.5,6 We use also analogous combined cascade and 'click' approaches to modification of other group of natural macrolide antibiotics like lactone erythromycins to obtain alternatives to the currently used antibiotics in clinical therapy. The project is financially supported by Polish National Science Centre (NCN), decision number **UMO-2015/19/B/ST5/00231**. (1) Bryskier, A et al. *Macrolides, chemistry, pharmacology and clinical uses*, Oxford, England, **1993**, 5-66; (2) Przybylski, P. *Curr. Org. Chem*. **2011**, 15, 328; (3) Katz, L.; Ashley, G. W. *Chem. Rev*. 2005, 105, 499; (4) Campbell E. A. et al. *Cell*, **2001**, 104901; (5) Domagalska et al. *ChemMedChem* **2016**, 1886; (6) Klich et al. J. Med. Chem., **2016**, *59*, 7963.

Biography

Piotr Przybylski, Chemistry Doctor's (Ph.D. - 2004) and Doctor Science (D. Sc.-2011) degrees at Adam Mickiewicz University in Poznan, now is an associate professor of organic chemistry, head of the research team at Faculty of Chemistry of Adam Mickiewicz University. He obtained "*Maxima Cum Laude*" award for best graduates of Faculty of Chemistry (2000) AMU Poznan, Stipend of President of Poznan city (2004), Award for Ph. D thesis of Prime Minister of Poland (2005), Award for Young Scientists (Warsaw 2005, 2006) and scholarship for research in West Pomeranian University of Technology of the Foundation for Polish Science (2007); postdoctoral researches in cooperation with Prof. F. Bartl from Charité – Universitätsmedizin, Institute Physik und Biophysik, Berlin and Humboldt Universität zu Berlin Lebenswissenschaftliche Fakultät Institut für Biologie, Berlin (2017, DAAD stipend), Germany. Currently Dr. Przybylski studies are focused on structure-activity relationships of natural products and their derivatives (macrolides, ionophore antibiotics and natural polyphenols) tautomerization, atropisomerization and proton transfer processes and the impact of these phenomenons on biological activity. Member of Ed. Board of Journal of Spectroscopy (since 2012) and Member of Committee of Chemical Sciences, Pol. Acad. Sci., Poznań Division (since 2011). He has published 106 papers in reputed journals.

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