Krystian Pyta et al., Med Chem (Los Angeles) 2017, 7:8(Suppl)
DOI: 10.4172/2161-0444-C1-034

Cascade approach to modification of lactone macrolide antibiotics

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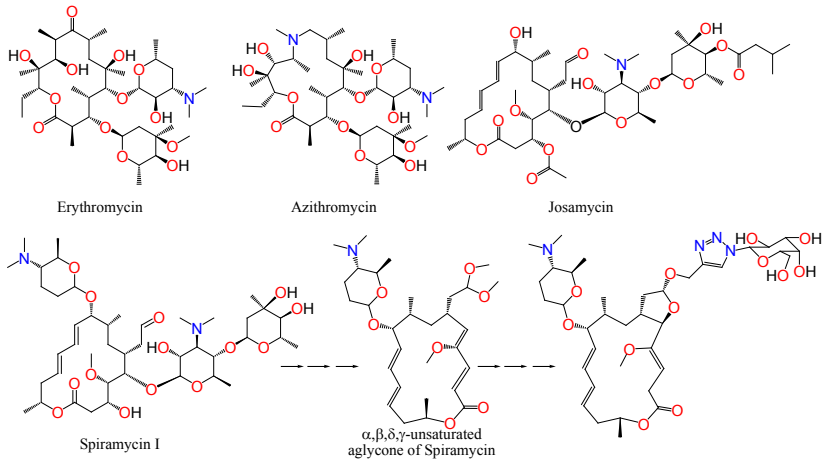
Macrolide antibiotics are produced by various *Streptomyces strains* and belong to large group of natural products. Macrolides can be classified by size of the macrolide ring[1] as for e.g. lactone macrolides 14-membered erythromycins, 15-membered azithromycins, and 16-membered spiramycins, or leucomycins (Fig 1). The macrolide lactone antibiotics' mechanism of action is based on the inhibition of bacterial protein biosynthesis at different stages by reversible binding to the bacterial 50s subunit at the ribosome[2]. In our laboratory we work on new modifications of lactone macrolide antibiotics, of an improved binding profile to biological target and of increased antibacterial potency. Our modifications are performed using cascade and click approaches to enable better matching between antibiotic and target protein. For example, using of NaH on protected Spiramycin led to obtain the stereospecific product, α,β,γ,δ – unsaturated aglycone of Spiramycin, in three cascade reactions: intramolecular transesterification and double E1cB elimination (Fig 1).[3,4] In the next stage aldehyde group of the product was deprotected and a entirely new series bicyclic type derivatives of aglycone of Spiramycin were synyhesised via intramolecular regio- and stereospecific subsequent 1,2-addition to aldehyde group followed by 1,6-conjugate addition (Fig 1).3,4 To restore disaccharide moiety a new bicyclic type compound was used as a reagent in 1,3-dipolar Huisgen cycloaddition with azides containing sugar moiety in their structure (Fig 1).3,4 We try to apply this approach to modification of another group of natural macrolide antibiotics like 14-membered lactone erythromycins to obtain efficient alternatives to the currently used antibiotics in clinical therapy.



Biography

Krystian Pyta has completed his PhD at the age of 28 years from Faculty of Chemistry of Adam mickiewicz University in Poznan. He has published more than 30 papers in reputed journals.

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