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Development of new antibiotics by targeting essential enzymes in bacteria: structure-based design and simulation studies

Concepción González-Bello
Universidad de Santiago de Compostela, Spain

Abstract

The possible development of new antibiotics whose mode of action is based on the selective and effective inhibition of an essential route in bacteria that does not have any counterpart in human cells, the shikimic acid pathway, will be discussed. In particular, the talk will be focused in the inhibition of the third and the fifth enzyme of this pathway, type II dehydroquinase and shikimate kinase. Both enzymes are essential in certain pathogenic microorganisms, such as *Mycobacterium tuberculosis* and *Helicobacter pylori*, which are responsible for tuberculosis and stomach cancer, respectively. The key interactions of the substrate and product binding and the enzyme movements that are essential for catalytic turnover of both enzymes have been investigated by structural and computational studies. Based on the mode of action of the enzyme, molecular modeling, dynamic simulations and structural studies and by creating favorable interactions with key residues in the enzymatic mechanism several potent inhibitors were designed and identified. Some of them are analogues of the natural substrate, and the others are mimics of the enzyme reaction intermediate. The crystal structures of enzyme/inhibitors complexes reveal an important change in the conformation and flexibility of the loop that closes over substrate binding. Our results on this project will be presented.

Biography

Concepción González-Bello has obtained her PhD at the University of Santiago de Compostela(USC, Spain) in 1994. She did two predoctoral stays in the University of Gent (Belgium) with Prof. Vandewalle and in the Scripps Research Institute (USA) with Prof. Nicolaou. After three years postdoctoral stay in the University of Cambridge (UK) with Prof. Chris Abell, she joined USC as an Assistant Professor, was promoted to Associate Professor in 2003 and obtained the Spanish habilitation to full Professor in 2011. She is a member of the ChemMedChem International Advisory Board and has published about 50 papers in reputed journals.