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Targeting the motion of shikimate kinase-Opportunities for antibiotic drug development

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The increasing development and spread of resistance to current antibiotics have turned ordinary bacterial infections into illnesses that cannot be controlled. Infections from resistant bacteria are now too common and some pathogens have even become resistant to multiple types of antibiotics. Therefore, it is urgent to search for new antibacterial agents and approaches to face the challenge of multidrug resistance. The disruption of the growth cycle by preventing the synthesis and assembly of key components of bacterial processes is the most widely used strategy to combat bacterial infections. Most current antibiotics that are highly successful in human clinical use, surprisingly targeted at only four main key processes and resistance to these antibiotics is widespread and well known. Therefore, the search for unexplored bacterial functions appears to be a good option for the development of novel antimicrobial agents with a new mechanism of action. For this purpose, our research group is studying the possible development of new antibiotics whose mode of action is based on the selective and effective inhibition of an essential enzyme in bacteria that does not have any counterpart in human cells, shikimate kinase (SK). This enzyme is essential in relevant pathogenic bacteria such as *Mycobacterium tuberculosis*, *Helicobacter pylori* and *Pseudomonas aeruginosa*. The starting point for our inhibitors design was the study of: (a) the substrate binding requirements, (b) the phosphoryl-transfer mechanism and (c) the essential enzyme motions for product release. Here we report results from NMR, biochemical, structural and Molecular Dynamics simulation studies that help understand the catalytic mechanism, the binding requirements and the essential enzyme motions for product release of the SK enzyme. Based on these results, potent reversible competitive inhibitors of the enzyme were developed. An ester pro-drug approach was used for achieving good *in vitro* activities against *H. pylori*. Our recent 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 Pre-doctoral stays in the University of Gent (Belgium) with Prof. Vandewalle and in the Scripps Research Institute (USA) with Prof. Nicolaou. After a Post-doctoral stay in University of Cambridge (UK) with Prof. 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 joined the Center for Research in Biological Chemistry and Molecular Materials (CIQUS) as a Group Leader in 2011. She is author of more than 70 papers and several book chapters. She is a member of the ChemMedChem International Advisory Board and an Academic Editor of PLOS ONE. Her main research interest is to develop updated therapies targeting infectious diseases, in particular, drugs with new mechanisms of action to combat the growth of antibiotic-resistant bacteria.

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