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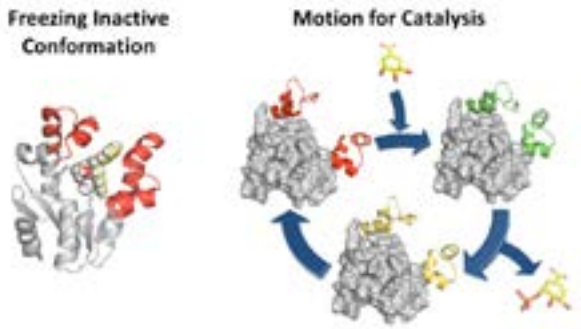
Disabling essential enzyme motion for catalysis: An efficient approach for shikimate kinase inhibition

Concepción González-Bello
University of Santiago de Compostela, Spain

Although antibiotics are one of the most successful drugs in clinic that have saved millions of lives, many of them are nowadays ineffective in treating infections caused by resistant bacteria. It is therefore urgent to search for new antibacterial agents and approaches to face this huge challenge. Considering that most current antibiotics that are highly successful in human clinical use, targeted at only four main key processes and resistance to these antibiotics is widespread and well known, 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. Our group is studying the possible development of new antibiotics by the selective and effective inhibition of an essential enzyme in bacteria that does not have any counterpart in human cells, shikimate kinase (SK, aroK gene). In particular, we are focused on SK from *M. tuberculosis* and *H. pylori*, two important pathogenic bacteria. Based on the essential enzyme motion for catalysis and product release studied by molecular dynamics simulation studies, potent reversible competitive inhibitors of the enzyme were developed. Compounds that stabilize the closed conformation for catalysis or the open conformation for product release were developed. An ester prodrug approach was used for achieving good *in vitro* activities against *H. pylori*. Our results also show that the less exploited motion-based design approach, not only is an alternative strategy for the development of competitive inhibitors, but could also be a way to achieve selectivity against a particular enzyme among its homologous ones. By using this approach, (1) the presence in the selected pocket of residues with markedly different properties would not be required, and (2) the effects of changes on residues to avoid the inhibition (resistance) should have a less pronounced effect.



Biography

Concepción González-Bello has obtained her PhD from the University of Santiago de Compostela (USC, Spain) in 1994. She did two Pre-doctoral stays at the University of Gent (Belgium) with professor vandewalle and at the Scripps Research Institute (USA) with professor Nicolaou. After a Post-doctoral stay at the University of Cambridge (UK) with professor 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 the author of about 80 papers and several book chapters 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.

concepcion.gonzalez.bello@usc.es

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