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Irreversible covalent modification of type I dehydroquinase: Structure-based design and simulation studies

A promising approach in the search of new antimicrobial or antivirulence agents to combat resistant bacteria is a detailed knowledge of the catalytic mechanism and the binding determinants of enzymes involved in biosynthetic pathways or processes that do not have mammalian homologues but they are essential for bacterial survival or relevant for virulence. That is the case of the shikimic acid pathway enzymes, through which chorismic acid is biosynthesized. This compound is the precursor in the synthesis of aromatic compounds, including the aromatic amino acids L-Phe, L-Tyr and L-Trp, folate cofactors, ubiquinone and vitamins E and K. Here we report results from structural, biochemical and computational studies conducted to improve our understanding of the third enzyme of the shikimic acid pathway, the type I dehydroquinase (DHQ1). This enzyme is a class I aldolase that catalyzes the syn elimination of water in 3-dehydroquinic acid by multi-step mechanism that involves the formation of a Schiff base. Several mimetics of the natural substrate were designed to study the substrate binding, the role of the conserved residues and the substrate-covering loop, as well as the irreversible inhibition of the enzyme. The first crystal structure of DHQ1 from *Salmonella typhimurium* covalently modified by a new irreversible inhibitor at 1.4 Å will be presented. This structure revealed that the modified ligand is surprisingly covalently attached to the essential Lys170 by the formation of a stable Schiff base and after several chemical modifications of the inhibitor.

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 a postdoctoral stay in the 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 is author of more than 50 papers and several book chapters. She is a member of the ChemMedChem International Advisory Board.

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