INVITED LECTURE

Development of New Antibiotics by Targeting Essential Enzymes in Bacteria: Structure-Based Design and Simulation Studies

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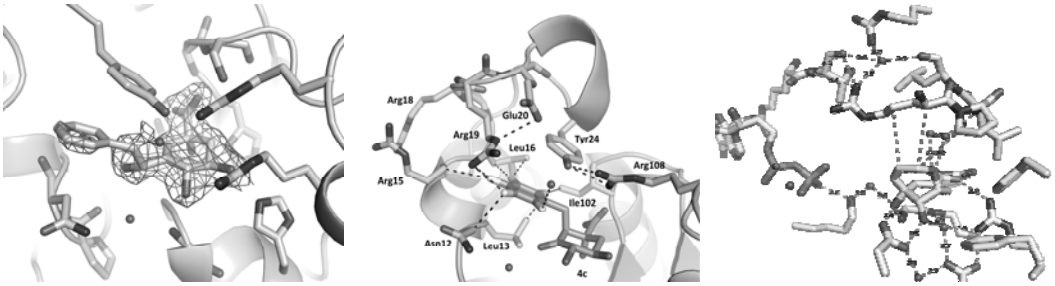
Infectious diseases are the second cuase of death worldwide. To its prevalence has undoubledly contributed the increasing development and spread of resistance to current antibiotics. To change this trend, the discovery of novel drugs and therapies to treat antibiotic-resistant infections and, particularly of drugs with new mechanisms of action is needed. In our research group we are studing 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. In particular, we have 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 important 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.[1-3] 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 recent progress in the project will be presented.



References

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