Design And Synthesis Of New Anti-Tuberculosis Drugs Acting By Inhibition Of Mycobacterial Chorismate Mutase

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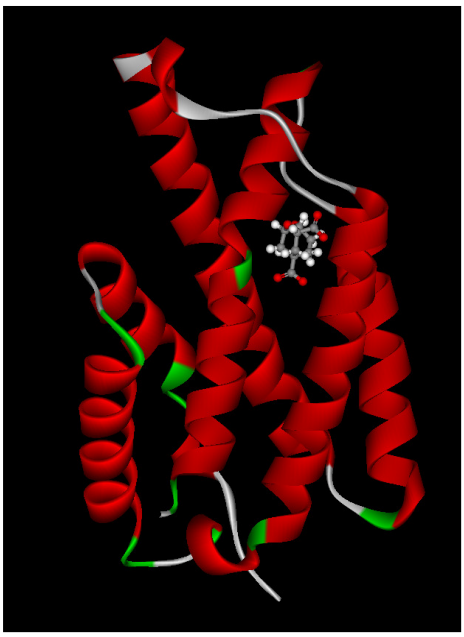
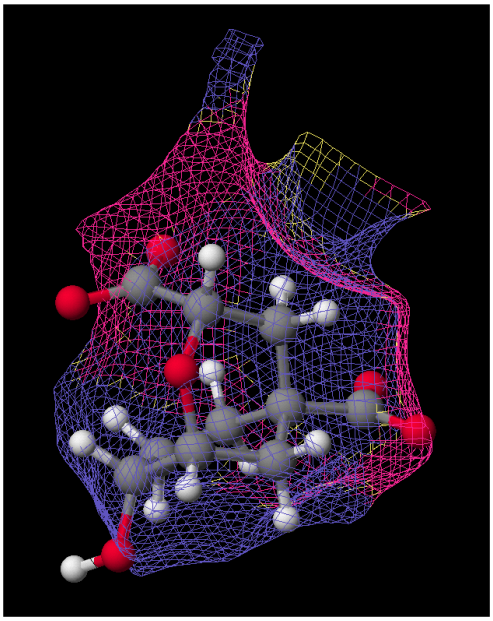


The enzyme chorismate mutase lies at a branch point in the shikimic acid pathway. It catalyzes the Claisen rearrangement of chorismate to prephenate, which is the first step in the synthesis of tyrosine and phenylalanine. This pathway is found in plants, bacteria and fungi but not in humans and as such is an ideal candidate for antimicrobial drug design. We have prepared a series of *in silico* models of the mycobacterial enzyme. These were derived from a published X-ray crystal structure (Okvist *et al*, *J. Mol. Biol.*, 2006, 35, 1483-1499) and elaborated by means of extensive molecular dynamics studies on docked protein-ligand complexes with known inhibitors of the enzyme. This allowed us to design a generation of synthetic targets for potential inhibitors of the enzyme. Their synthesis is ongoing.

This project will concentrate on computer-aided design of potential inhibitors of the enzyme followed by their synthesis.



Starting with our existing models, the scope of the enzyme active site will be further explored by means of molecular dynamics simulations in explicit water using the programme AMBER 9. Additional starting points for these simulations will be generated by investigation of the normal-modes of vibration of the protein. The target is to obtain protein models that give good docked conformations for inhibitors of the enzyme but which also discriminate against inactive compounds. When improved protein models have been obtained these will be used to design the next generation of potential inhibitors. These will be synthesised and put forward for biological evaluation.