Homology modeling of Chorismate synthase from \textit{Clamydia trachomatis}:
Molecular docking and molecular dynamics simulations.

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INTRODUCTION: Trachoma is a highly infectious eye disease caused by \textit{Chlamydia trachomatis}, a Gram negative bacterium. The transmission occurs by direct or indirect contact and the infected people worldwide are at serious risk of blindness. There is no specific treatment against trachoma and the current therapy is based on different kinds of antibiotics, which may induce \textit{C. trachomatis} and/or other opportunistic organisms to acquire resistance. These facts justify the research for new kinds of treatment. Therefore, the aim of this work was to solve the structure of the enzyme Chorismate synthase (E.C. 4.2.3.5) from \textit{C. trachomatis} (\textit{CtCS}) as a target for drug discovery. MATERIAL AND METHODS: The monomeric protein sequence was aligned with \textit{Hpylori} CS and \textit{Spneumoniae} CS as templates bonded to FMN (cofactor) and EPSP (substrate) by Modeler software. The best of 2200 output models was submitted to 90,000 steps of energy minimization. Virtual screening for purchasable ligands was performed at Zinc database considering 90% similarity from known CS inhibitors. Docking protocol was validated by redocking procedures using Autodock and Molegro programs. RESULTS AND DISCUSSION: Stereochemical evaluation shows that model is better than template. Superimposition of final model over templates shows important replacements at the inhibitor’s binding site which allow selective drug design. EPSP redocking (rmsd < 0.4 Å) in \textit{CtCS} shows $\Delta G_{\text{binding}}$ of -8.7 Kcal/mol, lower than \textit{S. pneumoniae} (-8.3 Kcal/mol) indicating that the affinity of \textit{CtCS} by ligand is higher than template. The 10ns NPT molecular dynamics simulation shows that nine residues presented a contact frequency with EPSP greater than 75%, delimiting the active site. CONCLUSIONS: The results show important new considerations for the selective design of \textit{CtCS} inhibitors suggesting that enzymes from shikimate pathway may be interesting and unexplored drug targets for the treatment of trachoma.

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