Isocitrate Lyase of *Paracoccidioides brasiliensis*: Effects of Cofactor on Dynamical Stability and Virtual Screening of Natural Products

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The enzyme isocitrate lyase (ICL) catalyzes the cleavage of isocitrate into glyoxylate and succinate. ICL and the entire glyoxylate cycle are known to be involved in virulence and pathogenicity of human pathogenic bacteria and fungi. The absence of this enzyme in mammals makes it an interesting target for design of specific inhibitors, with more selectivity and fewer side effects. In this work, we aim the ICL of the dimorphic fungus *Paracoccidioides brasiliensis* (*Pb*ICL) for *in silico* searching and designing of new antifungal compounds. Magnesium ion have been seen required for full activity of *Pb*ICL and have been proposed to be involved on stabilization of the substrate during enzymatic catalysis in ICL superfamily. A homology model for *Pb*ICL was built with I-TASSER server based on ICL structure of *Aspergillus nidulans* (PDB 1DQU) and its magnesium-binding site was modeled based on the ICL structure of *Magnaporthe oryzae* (PDB 5E9F). The effects of the ion cofactor in the structural stability were evaluated through 100 ns of molecular dynamics simulation (MD) using ff99SB-IDLN on GROMACS package. After cluster analysis, two ICL conformations from MD were selected for *in silico* virtual screening: one representative structure of the MD trajectory (cutoff 0.3 nm) and another applying the isocitrate binding as a positive control among the cluster structures (cutoff 0.15 nm). Virtual screening using AutoDock Vina were performed with 89399 natural products from ZINC database aiming at the cavity of the cofactor bind site. For each ICL conformation, 20 best ligands were selected taking into account criteria of affinity, efficiency and Tanimoto index. The same procedure of molecular dynamics and virtual screening was done for the enzyme in the absence of the magnesium ion. Overall structural dynamics, accessible surface area of the magnesium-binding site and topological profiles of the best ligand compounds were compared in the presence and absence of the cofactor.
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