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Dual targeting approach for Mycobacterium tuberculosis drug discovery: insights from DFT calculations and molecular dynamics simulations

Abstract
Drug resistant Tuberculosis (TB) infections are on the rise and anti-tuberculosis drugs that inhibit Mycobacterium tuberculosis (M. tuberculosis) through a new novel mechanism could be an important component of evolving TB therapy. Pantothenate Kinase (PanK) and CTP synthetase (PyrG) are both essential for de novo pyrimidine biosynthesis. Given the extensive knowledge base on de novo pyrimidine biosynthesis inhibition of M. tuberculosis growth and survival, these enzymes present an interesting opportunity for anti-mycobacterial drug discovery. A recent experimental study shows that CDD-823953 and GSK-735826A act as dual PanK and PyrG inhibitors, respectively. However, the molecular mechanisms of their selective inhibition remain elusive. Herein, Density functional theory (DFT) calculation was applied to unveil the molecular and reactivity properties of two lead compounds targeting these enzymes in a shot. Molecular dynamics simulations were then employed to investigate the inhibitory mechanism as well as selectivity impact of these potential inhibitors for their enzymes. Computational modeling of the ligands and the enzyme—ligand systems reveal that CDD-823953 and GSK-735826A lead compounds, can potentially inhibit both PanK and PyrG thereby creating a pathway via the use of double target approach in tuberculosis treatment.

Keywords: Tuberculosis, PanK, PyrG, Dual Targeting, DFT, and Molecular dynamics simulation

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