Computational Insights into Potential Marine Natural Products as Selective Inhibitors of *Mycobacterium tuberculosis* InhA: A Structure-Based Virtual Screening Study

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Abstract

Several factors are associated with the emergence of drug resistance mechanisms, such as impermeable cell walls, gene mutations, and drug efflux systems. Consequently, bacteria acquire resistance, leading to a decrease in drug efficacy. A new and innovative strategy is required to combat drug resistance in tuberculosis (TB) effectively. Therefore, targeting the mycolic acid biosynthesis pathway, which is involved in synthesising mycolic acids (MAs), essential structural components responsible for mycobacterial pathogenicity, has garnered interest in TB research and the concept of drug resistance. In this context, InhA, which plays a crucial role in the fatty acid synthase-II (FAS-II) system of the MA biosynthetic pathway, was selected as a druggable target for screening investigation. To identify potential lead molecules against InhA, diverse marine natural products (MNPs) were collected from the comprehensive marine natural products database (CMNPD). Virtual screening studies aided in selecting potential lead molecules that best fit within the substrate-binding pocket (SBP) of InhA, forming crucial hydrogen bond interaction with the catalytic residue **Tyr158**. Three MNPs, CMNPD30814, CMNPD1702, and CMNPD27355, were chosen as prospective alternative molecules due to their favorable pharmacokinetic properties and lack of toxicity according to ProTox-II predictions. Additionally, improved reactivity of the MNPs was observed in the results of density functional theory (DFT) studies. Furthermore, comparative molecular dynamics simulation (MDS), principal component (PC)-based free energy landscape (FEL) analysis, and molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) were employed to show enhanced structural stability, increased H-bond potential, and high binding affinity toward the target InhA. Moreover, the hot spot residues that contributed to the high binding energy profile and anchored the stability of the complexes were revealed with their individual interaction energy. The computational insights from this study provide potential avenues to combat TB through the multifaceted mode of action of these marine lead molecules, which can be further explored in future experimental investigations.

Keywords: Drug-resistant TB; Marine natural products; Molecular dynamics simulation; Principal component analysis; Free energy landscape mapping

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