Analysis of Affinity and Selectivity of Novel Inhibitors of Polyketide Synthase 13 of Mycobacterium tuberculosis by Molecular Dynamics Simulation and Binding Free Energy Calculations

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Abstract

Polyketide Synthase 13 (Pks13) is an essential enzyme that forms mycolic acids, which are critical for viability and virulence of Mycobacterium tuberculosis. Pks13 performs the final assembly step of the mycolic acid synthesis, i.e., the Claisen-type condensation of a C26 a-alkyl branch and C40–60 meromycolate precursors. In the present study, we investigated the binding mode, the affinity, and selectivity of novel inhibitors, Tam5 and Tam6, against the Pks13 binding pocket by molecular dynamics simulation (MD) and binding free energy calculations. Our analyses showed that all Pks13-inhibitors systems reach the stabilization after 30 ns of MD, exhibiting for protein backbone an average RMSD value of 1.61 and 1.59 and the inhibitors also showed a high affinity to the residues of binding pocket exhibiting the following energies (?Gbind) -46.26 $\pm$ 0.07 kcal.mol-1 and -36.52 $\pm$ 0.05 kcal.mol-1, respectively. Ligand pairwise per-residue energy decomposition analysis showed that Ser1636, Tyr1637, Asn1640, Ala1667, Phe1670, and Tyr1674, exhibited the most energetic contribution for ligands stabilization in Pks13 binding pocket. These preliminary results will be useful to further in silico studies that aim to develop novel analog inhibitors with improved selectivity and affinity against Pks13 binding pocket.

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