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Molecular modelling of carbapenems with L,D-transpeptidase 5 from Mycobacterium tuberculosis

The failure to control tuberculosis (TB) is due to the emergence of Mycobacterium tuberculosis (Mtb) strains that multiply drug resistant toward the front line antimycobacterial drugs [1,2]. Peptidoglycan is the exoskeleton of bacterial cells and is required for their survival and growth. Among the L,d-transpeptidases (LdtMt1 to LdtMt5), any Mtb strain that lacks a functional copy of LdtMt5, displays aberrant growth phenotype and is more susceptible to killing by cell wall perturbing agents including carbapenems which are considered the last resort antibiotics to treat resistant bacterial infections in humans [3]. In this study, we used molecular dynamics (MD) Quantum Mechanical (QM) Quantum Mechanical (QM) simulations to probe the molecular interactions of LdtMt5 with carbapenems. LdtMt5 complexes with three carbapenems, ertapenem (ERT), imipenem (IMI) and meropenem (MERO) were simulated. The binding free energies of these complexes were calculated from the MD trajectories using the MM/GBSA approach, the theoretical results revealed higher ΔGbind for ERT—LdtMt5 and IMI—LdtMt5 than MERO—LdtMt5. To further understand the catalytic reaction mechanism of LdtMt5 with the selected carbapenems, the possible reaction pathway (thermodynamics and kinetics) was investigated using a two-layered ONIOM [B3LYP/6-31+g(d,p): Amber] model. The high free energies of activation (ΔG) for imipenem and meropenem, explain the reason behind inefficient binding of these carbapenems to LdtMt5. In comparison with LdtMt2 (experimental [4] and computational [5] results), it is clear that the corresponding interactions of these drugs are much weaker with LdtMt5. The inhibitor—enzyme pre-complex computational model for transpeptidases correctly reflects experimental observations[3]. This is the first computational project focussing on the elucidation of the interactions between carbapenems and LdtMt5. These results provide a better understanding of how the antibacterial agents function and will potentially contribute towards the discovery of more potent LdtMt5 inhibitors.
Literature

Presenter Biography

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