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# The catalytic role of explicit water molecule in the binding of carbapenems against L, D-transpeptidase2 from Mycobacterium tuberculosis: ONIOM study

L, D transpeptidase (LdtMt2) is an essential enzyme in Mycobacterium tuberculosis (M. tuberculosis) that generate crucial peptide cross-linkages (3⟶3) during the biosynthesis of cell wall structure. Therefore, this enzyme has been considered as the suitable therapeutic target towards elimination of drug-resistant M. tuberculosis. The β-lactam sub-class of antibiotics, carbapenems, exhibited inhibitory activities against LdtMt2. Also, the role of explicit water molecule is presumed to have significant contribution in the binding free energies of protein-ligand complexes.

Herein, a hybrid two-layered ONIOM model (B3LYP/6-31+ G(d)): Amber) was employed to investigate the molecular and electronic properties of the presence of a bridging water molecule in the carbapenem—LdtMt2 complex binding interface. The carbapenems (biapenem, imipenem, meropenem and tebipenem), water molecule and the active site residues [His336 (187), Ser337 (188), His352 (203), Cys354 (205) and Asn356 (207)] of LdtMt2 were modelled at QM (B3LYP/6-31+G(d)) level of theory and the remaining part of the enzyme was evaluated at MM level of theory (AMBER force field). The computational resources used to conduct the study were provided by CHPC under subject name: HEAL0839 workspace (Lustre file system) on Lengau Cluster. Two programs were used to execute the jobs: Gaussian09/D01 and Amber. 24-cores, 1 node and 96:00 hours wall time were used.

The obtained theoretical binding free energies (⊠G) reveal the significant role of the presence of a water molecule in the binding interface of carbapenem—LdtMt2 complex. The water molecule facilitated the binding landscape of LdtMt2 and recognition of carbapenems thus the order of the Gibb's free energies follows that observed experimentally. The enthalpy (⊠H) and entropy (⊠S) contributed significantly in the binding free energies of carbapenem—water—LdtMt2 complexes. Furthermore, AIM and NBO analysis authenticated the importance of bridging water in mediating hydrogen bond interactions which contributed to the stability and improved binding affinities of carbapenems. Our results highlight the importance of the catalytic water molecule in the carbapenem—LdtMt2 binding interfaces which could be useful, applied and extended for rational drug design of novel therapeutic anti-TB drugs with improved efficacies.

**Keywords**: Mycobacterium tuberculosis (M. tuberculosis); Carbapenems, L, D-Transpeptidase 2 (LdtMt2); Our own N-layered Integrated molecular orbital and molecular mechanics (ONIOM); Atoms in molecules (AIM); Natural bond orbital (NBO)

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