Supplementary Material

Molecular insight on the non-covalent interactions between carbapenems and L, D-Transpeptidase 2 from *Mycobacterium tuberculosis:* ONIOM study

Thandokuhle Ntombela, [a] Zeynab Fakhar, [b] Collins U. Ibeji, [a] Thavendran Govender, [a] Glenn E. M. Maguire, [a, c] Gyanu Lamichhane, [d] Hendrik G. Kruger[a*] and Bahareh Honarparvar[a*]

The supplementary material for the investigated carbapenem—Ldt_{Mt2} complexes.

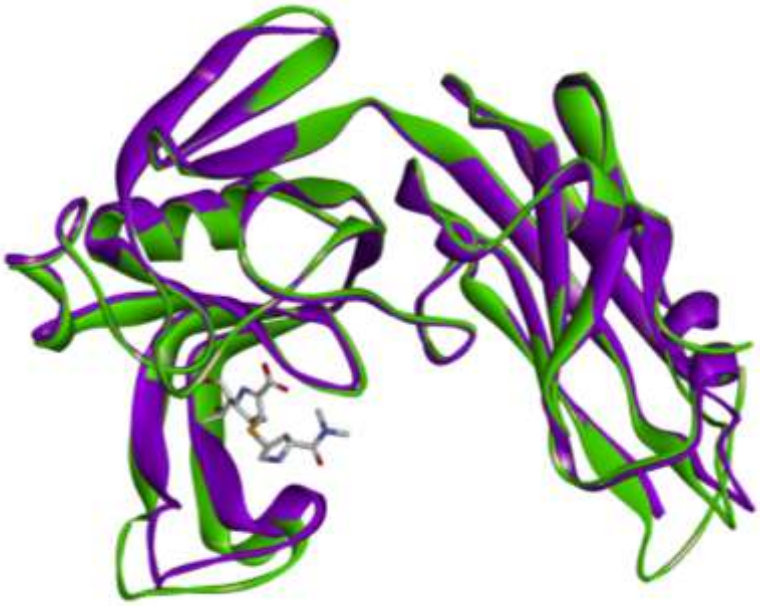

Figure 1S. The superimposed 3D structures of 3TUR (Ldt_{Mt2} in complex with peptidoglycan fragment as natural substrate) in purple and 3VYP (meropenem—Ldt_{Mt2} adduct) in green for the selected carbapenem—Ldt_{Mt2} complexes.

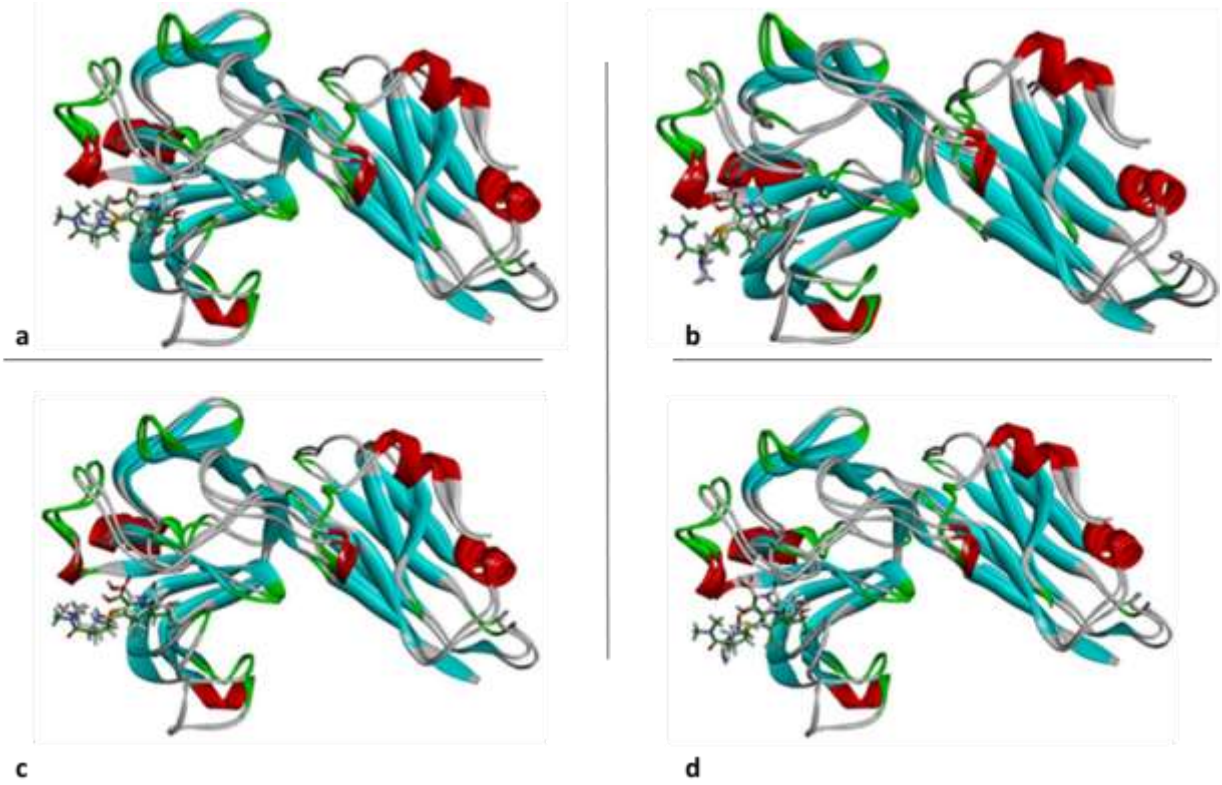

Figure 2S. The 3D structures of 3TUR superimposed with carbapenem—Ldt_{Mt2} complexes. (a) Bia—Ldt_{Mt2} (b) Imi—Ldt_{Mt2} (c) Mero—Ldt_{Mt2} (d) Tebi—Ldt_{Mt2}

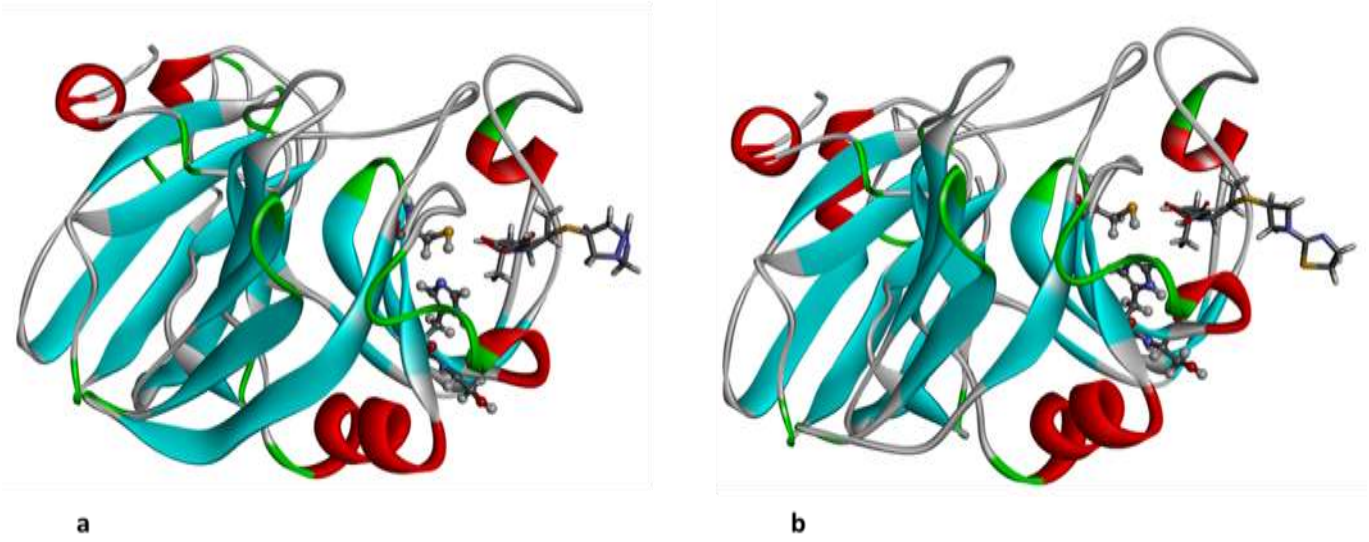

Figure 3S. 3D-structures of carbapenem—Ldt_{Mt2} complexes showing poses obtained after frequency calculations. (**A**) Bia—Ldt_{Mt2} (**B**) Tebi—Ldt_{Mt2}

Table 1S: The ONIOM binding interaction energies of carbapenem—Ldt_{Mt2} complexes evaluated using (B3LYP/6-31+G (d): AMBER). Note: catalytic residues [His336 (187), Ser337 (188), His352 (203), Cys354 (205) and Asn356 (207)] are considered at high level.

Complexes	**ΔG**	**ΔH**	**ΔS**	**ΔS_{trans}**	**ΔS_{rot}**	**ΔS_{vib}**
	kcal mol^{-1}	**kcal mol^{-1}**	**cal mol^{-1} K^{-1}**	**cal mol^{-1} K^{-1}**	**cal mol^{-1} K^{-1}**	**cal mol^{-1} K^{-1}**
Tebi—Ldt_{Mt2}	-35.9	-52.7	-56.4	-43.7	-36.3	23.5
Imi—Ldt_{Mt2}	-30.4	-46.5	-54.1	-43.0	-34.8	23.7
Bia—Ldt_{Mt2}	-25.0	-42.8	-59.8	-43.4	-35.5	19.2
Mero—Ldt_{Mt2}	-24.3	-48.7	-54.4	-43.7	-36.0	25.3

Gibb's free energy (**ΔG**), Enthalpy change (**ΔH**), Entropy change **(ΔS**), S translational (**ΔS_{trans}**), S rotational (**ΔS_{rot}**), S vibrational **(ΔS_{vib}**). (ONIOM calculations were carried out at default temperature of 298.15 K)

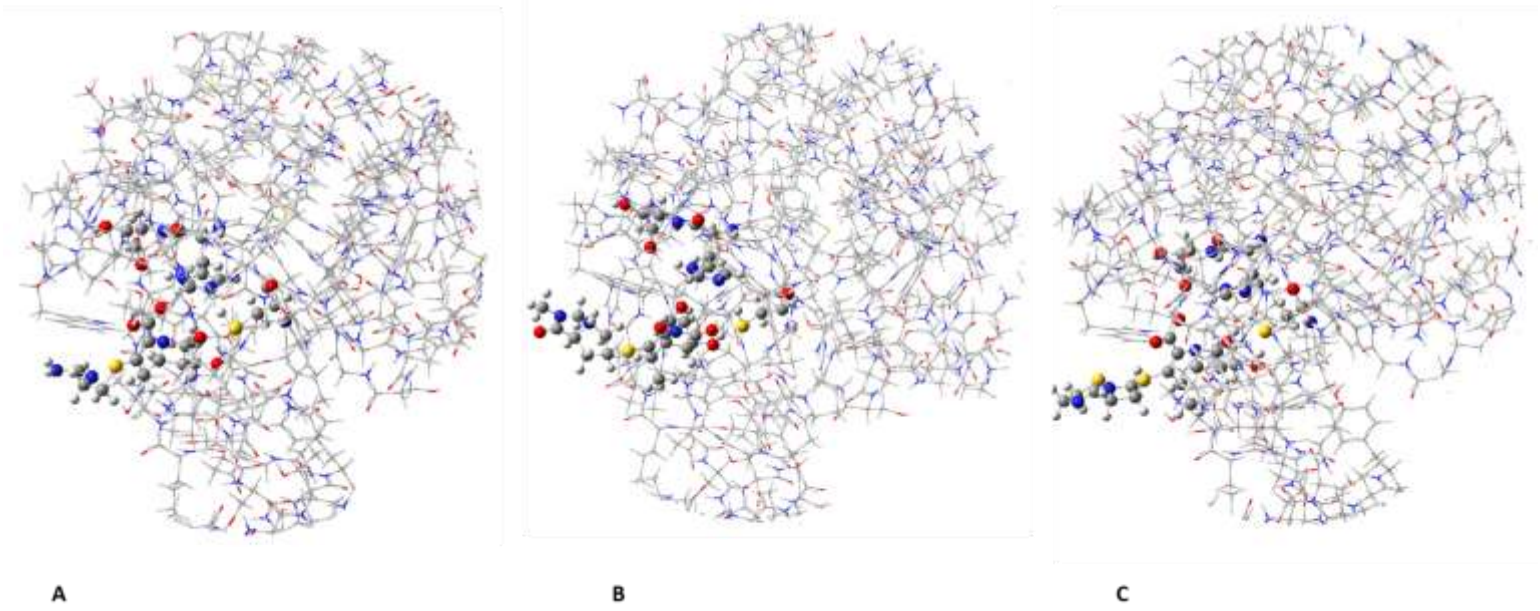

Figure 4S A two-layered QM:MM ONIOM (B3LYP/6-31+G (d): AMBER) model of (**A**)Imi—Ldt_{Mt2}, (**B**) Mero—Ldt_{Mt2} and (**C**)Tebi—Ldt_{Mt2} complexes. Active site residues His336 (187), Ser337 (188) and Cys354 (205) were also treated at the same QM level.

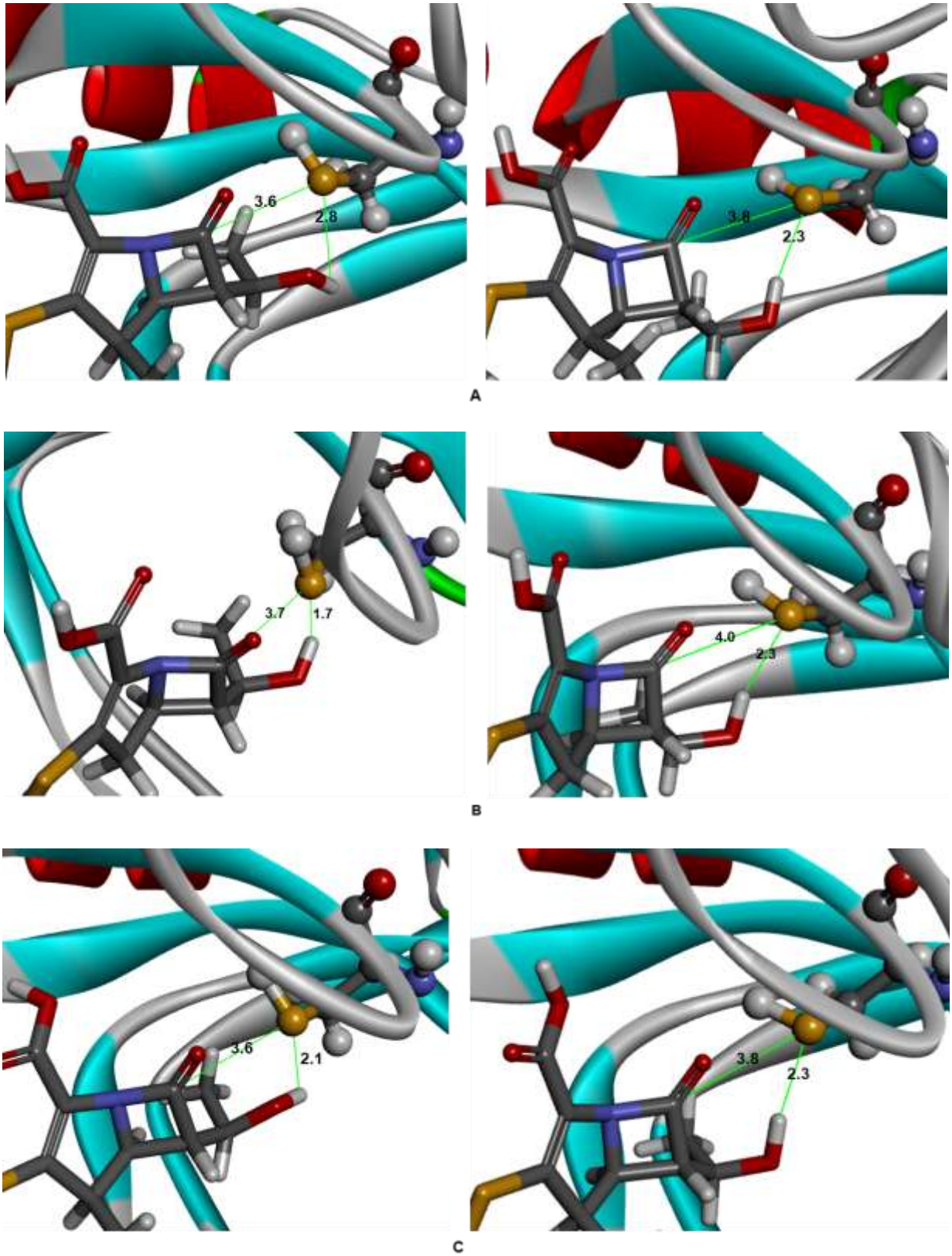

Figure 5S: Schematic representation of hydrogen bond and intermolecular interactions and their respective distances in angstrom (Å) before and after optimization. **A.** Bia—Ldt_{Mt2} **B**. Imi—Ldt_{Mt2} and **C**. Tebi—Ldt_{Mt2}

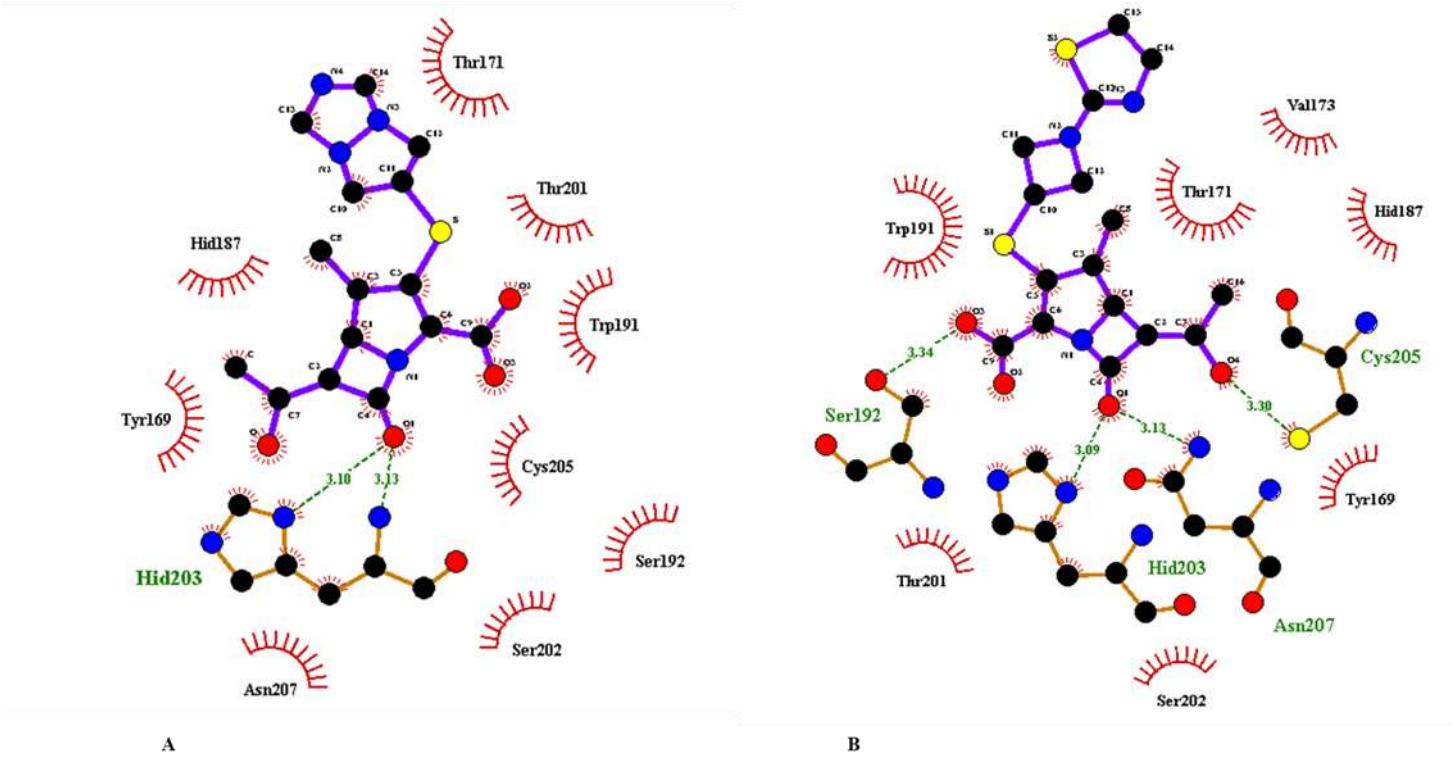

Figure 6S. A 2-D schematic representation of hydrogen bond and hydrophobic interactions between catalytic amino acid residues and the carbapenems. **A.** Bia—Ldt_{Mt2} and **B.** Tebi—Ldt_{Mt2}. Hydrogen bonds are denoted with dashed line and hydrophobic interactions are shown as arcs. Both the figures were made using LigPLOT program.

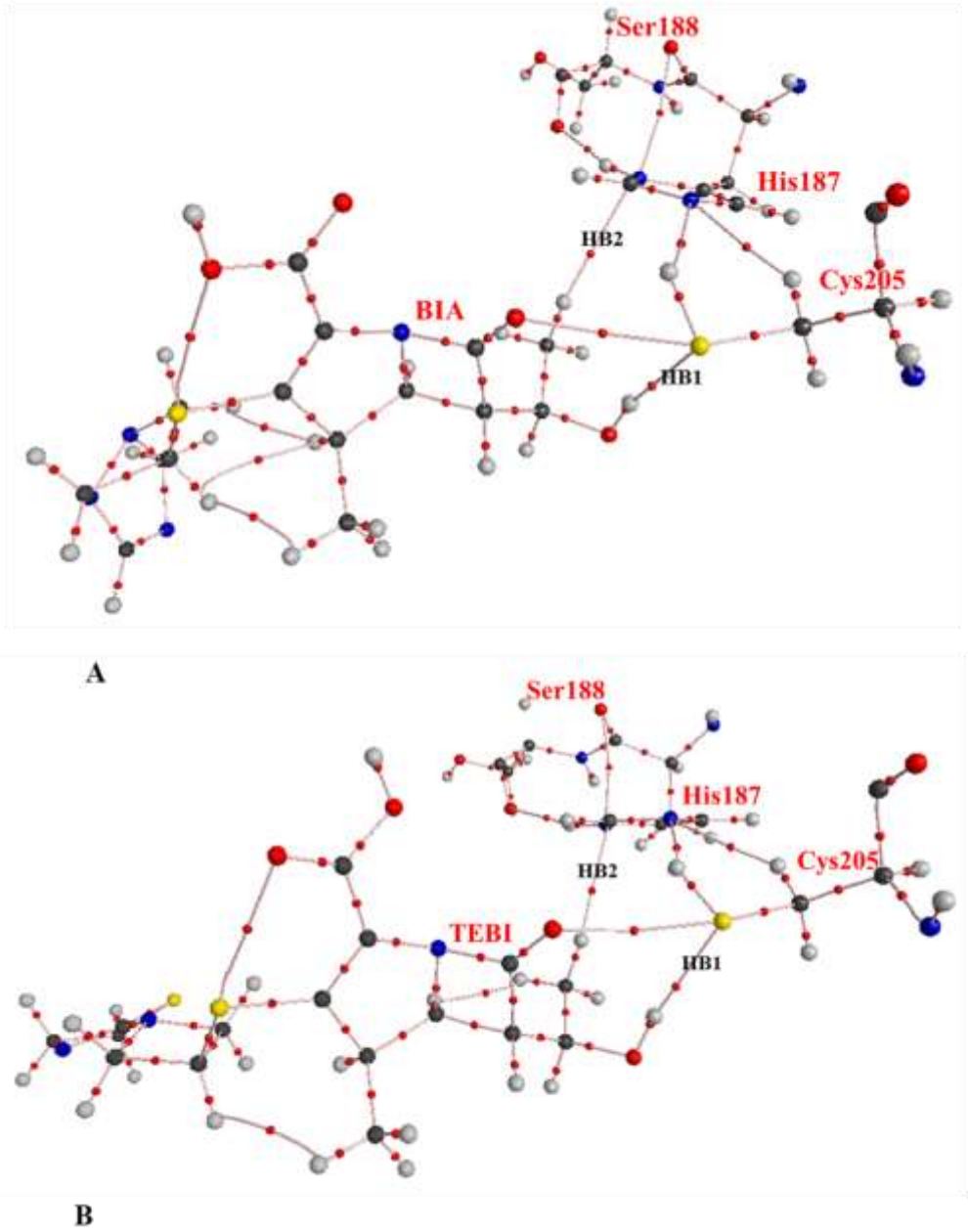

Figure 7S. Molecular graph of **A**. Bia—Ldt_{Mt2} and **B**. Tebi—Ldt_{Mt2} complexes generated using AIM2000 software. Small red spheres and lines correspond to the bond critical points (BCP) and the bond paths, respectively.

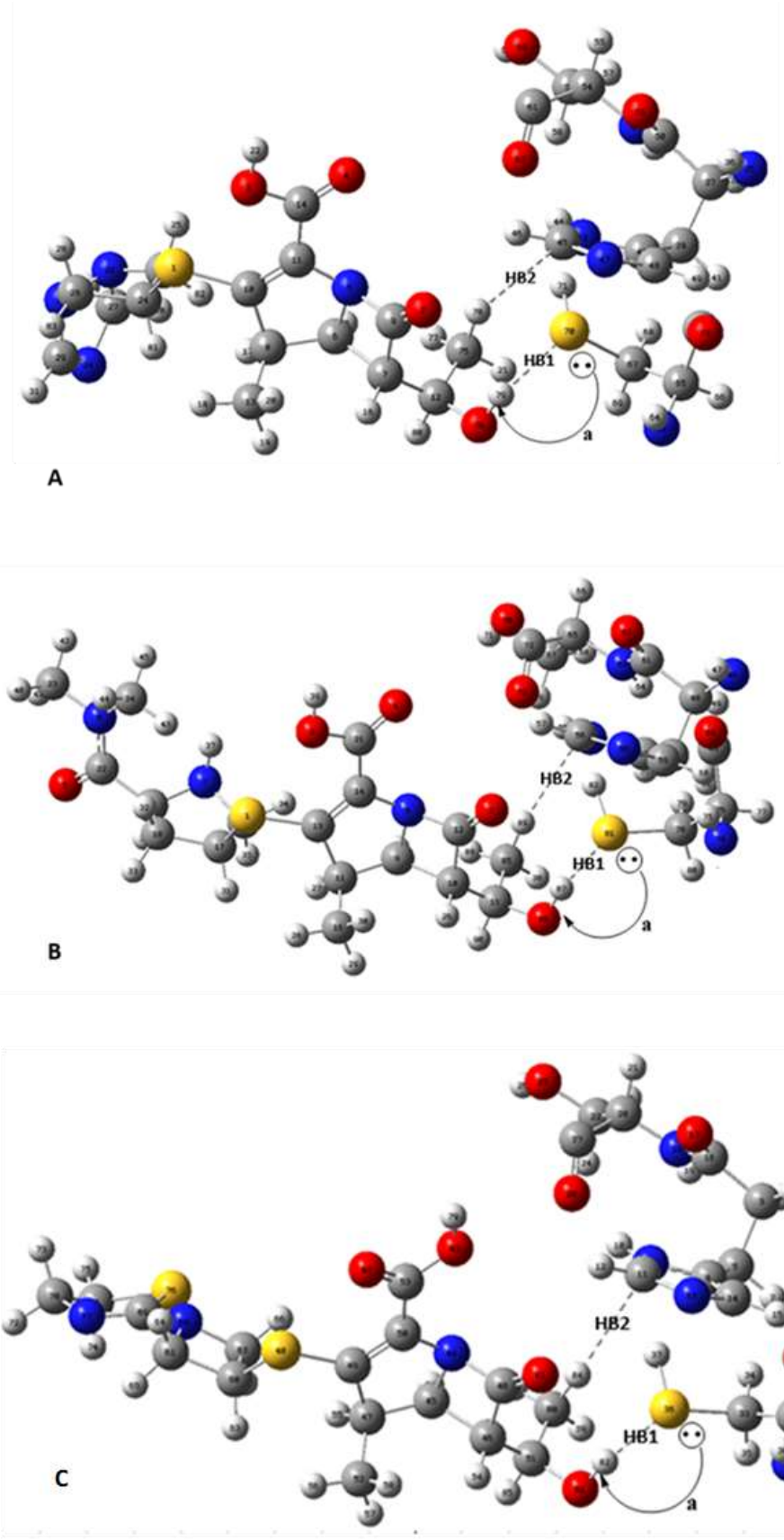

Figure 8S. Depiction of electrons transfer for carbapenem—Ldt_{Mt2} complexes derived by second-order perturbation theory of NBO analysis. The curved arrow (**a**) depict the direction of charge transfer from lone pair to antibonding (LP→ σ*): (**A**) Bia—Ldt_{Mt2} (**B**) Mero—Ldt_{Mt2} and (**C**) Tebi—Ldt_{Mt2} as listed in **Table 3.**