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Interaction analyse of human serum albumin-clomiphene/warfarin complexes by molecular dynamics simulations in aqueous solution

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Factors of positive allosteric effects between clomiphene (CLM) and warfarin (WAR) on binding to human serum albumin (HSA) were examined by using molecular dynamics (MD) simulations method in aqueous solution. The absolute binding free energy of CLM to HSA with/without WAR was estimated by MM/PBSA method. As a result, the calculated binding free energy of CLM in HSA-CLM complex (-8.0kcal/mol) was in reasonable agreement with experiment (-8.8kcal/mol). Furthermore, the binding free energy of CLM in HSA-WAR-CLM complex was smaller than that in HSA-CLM complex, and hence binding affinity of CLM in HSA-WAR-CLM complex is stronger than in HSA-CLM complex. This corresponds with the report of Sengupte and Hage. Components of interaction energy were calculated about HSA-CLM and HSA-WAR-CLM complexes by the ANAL module of AMBER. From the analyses of the component of calculated binding free energies and the molecular mechanics energies between each residue of HSA and ligands, it was suggested that Glu450 and Asp451 played an important part for binding of CLM via electrostatic interaction and that the van der Waals interaction between CLM and WAR were dominant factor for the allosteric effects.