Phornphimon Maitarad 2008: Molecular Modelling and Quantum Chemical Calculations Study on Antifolate Antimalarial Inhibitors. Doctor of Philosophy (Chemistry), Major Field: Chemistry, Department of Chemistry. Thesis Advisor: Associate Professor Supa Hannongbua, Dr.rer.nat. 125 pages.

The goal of the research is the demonstrating the cause of the antifolate drugs resistance which came from the changing of Ser108 to Asn108 using the CoMFA and quantum chemical calculations studies. Over all obtained results can be used to guide the new designed potent antifolate inhibitors for specific mutant enzyme.

Comparative molecular field analysis (CoMFA) was performed on twenty-three pyrimethamine (Pyr) derivatives actived against quadruple mutant type (Asn51Ile, Cys59Arg, Ser108Asn, Ile164Leu) *plasmodium falciparum* dihydrofolate reductase (*Pf*DHFR). The best model (r^2_{cv} = 0.702, S_{press} = 0.608, r^2_{nv} = 0.980, s = 0.156, and $r^2_{test\ set}$ = 0.698) with combined three types of probe atoms, C_{sp3} (+1), O_{sp3} (-1) and H (+1), can be used to explain steric and electrostatic structural requirements for Pyr compounds. In addition, the CoMFA method was also performed on twenty-five cycloguanil (Cyc) derivatives of both wild type (r^2_{cv} = 0.727 and r^2 = 0.985) and quadruple muatnt (r^2_{cv} = 0.786 and r^2 = 0.979) *Pf*DHFR models. These two models can be determined the different structural requirements for the potency of inhibiting between the wild type and the quadruple mutant *Pf*DHFRs. Deeply in molecular details, an understanding of particular interaction energy between antifolate inhibitors and surrounding residues in the binding pocket was performed by using MP2/6-31G(d,p) accurate quantum chemical calculations. The obtained results clearly demonstrate that Asn108 is the caused of Pyr and Cyc resistances. Furthermore, we investigated the different binding energy between the potent WR99210 inhibitor and the poor inhibitors represented by Pyr and Cyc, active against the quadruple mutant type of *Pf*DHFR. The AMBER molecular dynamics simulations are well bimolecular force fields for constructing and optimizing the complexes of three antifolates and the mutant *Pf*DHFR. Consequently, the binding energies of all complexes were extrapolated using the ONIOM3 (B3LYP/6-31G(d,p):PM3:UFF) calculations. The WR99210/*Pf*DHFR gave highest total binding energy. Basically, the loss of ligand/enzyme binding is the key point to clear that any mutations lead to unstable of ligand in the binding pocket. The obtained molecular dynamics minimizations and ONIOM3 binding energy extrapolations indicate that the mutated residue Asn108 is the main cause of the less potency K_i for Pyr and Cyc drugs which dued to the loss of high binding energy for small region (antifolate inhibitor + Asp54 + Asn108 + Leu164). Hence, this appearance accorded to experimental biological activity.

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