Amphawan Maitarad 2009: Quantum Chemical Calculations on Particular Interaction Energy of HIV-1 RT Inhibitors (68nv, T4 and T5) Bound in Various Types of HIV-1 RT Enzymes. Master of Science (Chemistry), Major Field: Chemistry, Department of Chemistry. Thesis Advisor: Miss Patchreenart Suparpakorn, Ph.D. 79 pages.

Mutations of the HIV-1 Reverse Transcriptase protein (HIV-1 RT) are an increasing problem in the treatment of HIV and considerable effort has been expended in both industry and academic to tackle this problem. In effort to minimize the loss in potency of nevirapine derivatives to HIV-1 RT mutants has led to the synthesis of 2-chloro-8-arylthiomethyl dipyridodiazepinone derivatives which show very interesting biological activities at known mutants.

Therefore, the aim of this computationally based study is to investigate the role of the key residues in the HIV-1 RT allosteric binding pocket and to understand their roles in inhibitor binding. Theoretical protein-ligand complexes for HIV-1 RT proteins (wild-type (WT), K103N and Y181C) and three NNRTIs were generated using: GOLD docking (model A) and GOLD docking with AMBER minimization (model B). The pairwise interaction energies between the inhibitors and individual residues within 4 Å were calculated at B3LYP/6-31G(d,p) and MP2/6-31G(d,p) levels of theory and energies were also corrected with basis set super position error.

In addition, the principal components analysis (PCA) was used to study the relationship between the theoretical parameters obtained from the 3 different inhibitors at 3 distinct protein variants, because of the large number of variables generated and the significant cross correlation in the dataset. An analysis of the loading and score plots derived PCA model were discussed. The obtained results can be summarized as following: (a) the impact of the different starting models. The results found that the AMBER force field minimizations (model B) can decrease more replusive interaction energy in binding site of Gold docking (model A) and it can remain important attractive interaction in binding site. Moreover, (b) analysis of structural and energetic parameters of model B and (c) the relationship between the quantum energies and $IC_{50}$ differences found that the results from calculations agreed well with their experimental activities.

/ /

Student's signature Thesis Advisor's signature