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Determination of ligand position in aspartic proteases by correlating tanimoto coefficient and binding affinity with root mean square deviation

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ABSTRACT

The objective of this study was to develop and validate of Structure-Based Virtual Screening (SBVS) protocol which was used to select the best pose of inhibitor-aspartic protease complex interaction in the active sites of HIV-1 protease, plasmepsin I, II, and IV. Retrospective validation was performed on enhanced dataset of ligands and decoys (DUD-E) for HIV-1 protease. The crystal structures 1XL2, 3QS1, 1SME, and 1LS5 were obtained from Protein Data Bank. The protocol was then challenged to re-dock the ligands to its origin places in the active sites by correlating *Tanimoto coefficient* (Tc) and binding affinity (Ei) with Root Mean Square Deviation (RMSD). Enrichment factor at 1% false positives ($EF_{1\%}$) values for Tc and Ei were 18.26 and 9.03, respectively, while the Area Under Curve (AUC) values for Tc and Ei were 76.84 and 60.95. The SBVS protocol was valid and showed better virtual screening qualities in ligand identification for HIV-1 protease compared to the original protocol accompanying the release of DUD-E and showed its ability to reproduce the co-crystal pose in the HIV-1 protease, plasmepsin I, II, and IV to its origin places in the active sites.

INTRODUCTION

Aspartic proteases are a family member of protease enzymes that use two highly conserved aspartic acid residues in the active site for catalytic cleavage of their peptide substrates. The generally accepted mechanism of action is acid-base mechanism involving coordination of a water molecule between the two highly conserved aspartate residues. Both of these aspartic acid residues respectively act as proton donors and acceptors, as well as the catalytic hydrolysis of peptide bonds in proteins. The first aspartic acid residue responsible for the initial activation of a water molecule, producing carbon nucleophile then attacks the amide substrate. Tetrahedral intermediate generated would then accept a proton from the second aspartic acid residues and forming products (Davies, 1990). Perhaps the most extensively studies as drug discovery targets are HIV-1 protease for anti-HIV, and plasmepsins for the treatment of malaria. A bioinformatic analysis has demonstrated that *P. falciparum* plasmepsin II, which is similar to the secretory aspartic protease 2 of *Candida albicans* (the first nonretroviral microorganism proven to be susceptible to plasmepsins), is one of the eukaryotic proteases that most resemble the HIV-1 protease (Cassone *et al.,* 2002). Critical information on this similarity comes from a search that was conducted in the National Center for Biotechnology Information (NCBI) database with the Vector Alignment Search Tool (VAST), of structural neighbors of the HIV-1 protease. This search revealed a highly significant (P = .00003, by VAST) structural similarity between the HIV-1 protease and plasmepsin II, as well as between the HIV-1 protease and plasmepsin IV, another member of the aspartic protease family of *P. falciparum* (Tacconelli *et al.,* 2004). Computational studies in drug discovery for anti-HIV and antimalarial have been carried out using aspartic proteases as targets. The one popular method is by Structure-Based Virtual Screening (SBVS) or molecular docking. AutoDock Vina is one of the molecular docking programs. This program is a popular freeware that has been proven could increase the speed and accuracy of docking process (Trott and Olson, 2010), which results are ligand poses and binding affinity (Ei) of each pose as the docking score. SBVS originally only calculates docking score, a simple form of actual binding between ligand and its target. Recently, a novel method defined as interaction fingerprint (IFP), is used as alternative method to visualize the actual binding between ligand and its target. While docking score indicates the affinity of ligand-protein interaction, IFP shows the

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