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REGULAR ARTICLE

Free Energy Profiles of Binding Processes of HIV-1 Protease-2AH/4AH by Potential of Mean Force Simulations

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Abstract: Inhibitors targeting HIV-1 protease are quite efficient in HIV/AIDS therapy. In this paper, we employed potential of mean force (PMF) simulations to obtain the free energy profiles of HIV-1 Protease-2AH and HIV-1 Protease-4AH binding processes, and some dynamic details of the binding processes are presented. The binding free energies of HIV-1 Protease-2AH and HIV-1 Protease-4AH are -31.2kcal/mol and -30.9kcal/mol, respectively. These two values are very close, qualitively consistent with experimental results.

AMS subject classifications: 92C40, 82C99, 97R30

Keywords: HIV/AIDS, HIV-1 protease, PMF simulations, binding free energy

Introduction

HIV/AIDS, has deprived the life or life quality of millions of people worldwide, since the beginning of the global pandemic of it in the early 1980s [1-4]. Thanks to the development of multiple therapeutic agents targeting HIV-1 reverse transcriptase (RT), protease (PR), integrase(IN), and so on, which is critical to some step of the HIV-1 life cycle, HIV-1 infection has been transformed from an inevitably fatal disease into a manageable chronic ailment [1].

HIV-1 protease is essential for HIV-1 replication because in the maturation step of HIV-1

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life cycle, HIV-1 protease must be employed to process Gag and Gag-Pol gene product into some series of structural proteins(p17, p24, p7, p6, p2, p1) and functional proteins(PR, RT, IN). Therefore, inhibitors targeting HIV-1 protease are quite efficient for therapy of HIV/AIDS.

HIV-1 protease is homodimer of two 99 amino acid subunits (**Figure1**). Asp25-Thr26-Gly27, catalytic triad from one monomer, together with Asp25'-Thr26'-Gly27', catalytic triad from another monomer, form the catalytic active site of the enzyme. The active site was covered by two flexible glycine-rich β flaps. When a substrate is binding the HIV-1 protease, the β flaps tranform from an open-state to a closed-state. If an inhibitor entered the active site, the HIV-1 protease will lose its activity now that the enzyme couldn't accept any substrate any more.

Up to now, 9 inhibitors for HIV-1 protease have been approved by the FDA, including saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, tipranavir and darunavir [1-5] . In 2006, Anders Hallberg reported a class of HIV-1 protease inhibitors which were structurally related to both atazanavir and indinavir. 2AH and 4AH (**Figure 2**) are two of them [5]. As shown in **Figure 2**, 2AH and 4AH are almost the same except that a nitrogen atom is at the ortho and meta position of pyridine, respectively [5-6].

Always there are many studies, experimental or computational, concerning the binding process of HIV-1 protease-inhibitors, however, the major works only focus on calculating the binding free energy, through experimental K_i or MMPB (GB)SA method, etc. By contrast, studies regard the dynamic details of the binding process is relatively rare. In this study, we employed PMF (potential of mean force) simulations to obtain the free energy profiles of HIV-1 Protease-2AH and HIV-1 Protease-4AH binding processes, hoping to discover some dynamic details of the binding processes.

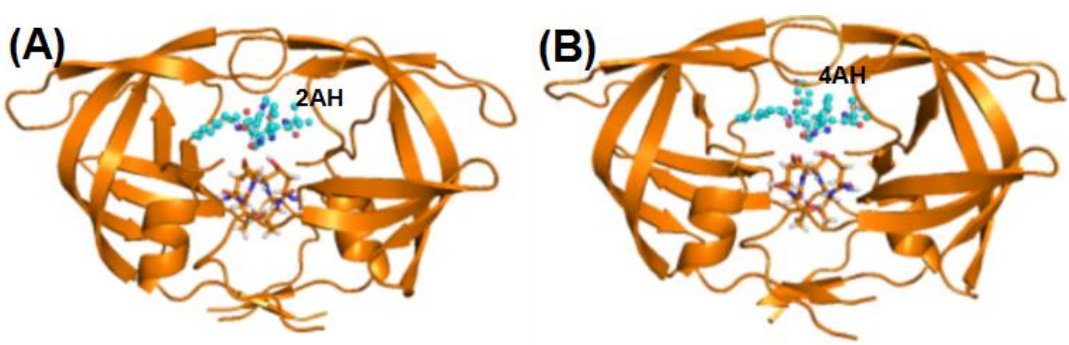

Figure 1: MD-simulated HIV-1 Protease-2AH/4AH binding structures. The enzyme is shown as golden ribbons, and 2AH/4AH is in ball-and-stick style. The two symmetric Asp25-Thr26-Gly27 catalytic triads of HIV-1 Protease are shown in stick style and colored by atom types. (**A**) HIV-1 Protease-2AH; (**B**) HIV-1 Protease-4AH.