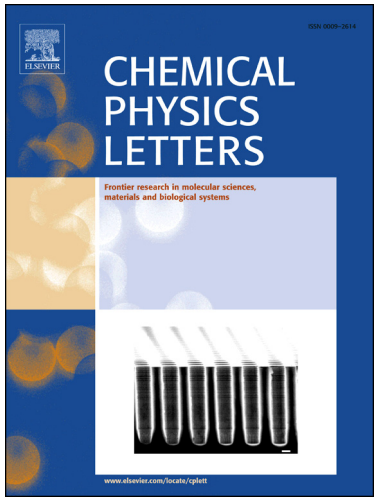

Research paper

Determination of the absolute binding free energies of HIV-1 protease inhibitors using non-equilibrium molecular dynamics simulations

Son Tung Ngo, Minh Tung Nguyen, Minh Tho Nguyen

PII: S0009-2614(17)30253-1
DOI: http://dx.doi.org/10.1016/j.cplett.2017.03.034
Reference: CPLETT 34634

To appear in: *Chemical Physics Letters*

Received Date: 9 January 2017
Revised Date: 9 March 2017
Accepted Date: 13 March 2017

Please cite this article as: S.T. Ngo, M.T. Nguyen, M.T. Nguyen, Determination of the absolute binding free energies of HIV-1 protease inhibitors using non-equilibrium molecular dynamics simulations, *Chemical Physics Letters* (2017), doi: http://dx.doi.org/10.1016/j.cplett.2017.03.034

Determination of the absolute binding free energies of HIV-1 protease inhibitors using non-equilibrium molecular dynamics simulations

Son Tung Ngo,[ab,]* Minh Tung Nguyen,[c] Minh Tho Nguyen[abd,*]

[a]*Computational Chemistry Research Group, Ton Duc Thang University, Ho Chi Minh City, Vietnam*

[b]*Faculty of Applied Sciences, Ton Duc Thang University, Ho Chi Minh City, Vietnam*

[c]*Binh Duong University, Thu Dau Mot City, Binh Duong Province, Vietnam*

[d]*Department of Chemistry, KU Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium.*

Abstract

The absolute binding free energy of an inhibitor to HIV-1 Protease (PR) was determined throughout evaluation of the non-bonded interaction energy difference between the two *bound* and *unbound* states of the inhibitor and surrounding molecules by the fast pulling of ligand (FPL) process using non-equilibrium molecular dynamics (NEMD) simulations. The calculated free energy difference terms help clarifying the nature of the binding. Theoretical binding affinities are in good correlation with experimental data, with $R = 0.89$. The paradigm used is able to rank two inhibitors having the maximum difference of ~1.5 kcal/mol in absolute binding free energies.

Keywords: Fast pulling of ligand approach; HIV-1 PR; NEMD simulations; absolute binding affinity; interaction energy; pulling work;

1. Introduction

The binding free energies between proteins and their inhibitors are of great interest in part due to their role in the understanding of biophysical problems [1]. Several methods were established to evaluate the protein-ligand binding affinity including the thermodynamic integration (TI) [2], free energy perturbation (FEP) [3],

* Corresponding author. Tel.: + 84 – 8 – 37 755 035; fax: + 84 – 8 – 37 755 055.
E-mail addresses: ngosontung@tdt.edu.vn (Son Tung Ngo); nguyenminhtho@tdt.edu.vn & minh.nguyen@kuleuven.be (Minh Tho Nguyen)