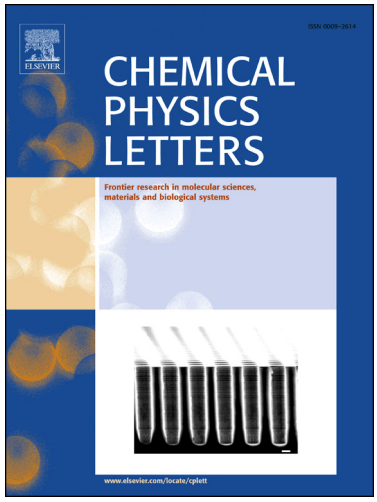

Research paper

Fast pulling of ligand approach for the design of β-secretase 1 inhibitors

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Fast pulling of ligand approach for the design of β-secretase 1 inhibitors

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Abstract

The fast pulling of ligand (FPL) method, which evaluates the relative ligand-protein binding affinity with low CPU usage and high accuracy, was applied for the first time to determine the affinity of β-secretase 1 (BACE1) and its inhibitors using steered-molecular dynamics simulations. The total non-bonded interaction energy difference ΔE_{total} is a highly appropriate criterion to predict the relative BACE1-inhibitor binding affinity with strong correlation to experimental data ($R = 0.92$) and small deviation ($\delta E_{total} = 7\%$). The van der Waals interaction and electrostatic interaction contribute 56% and 44% to the total non-bonded interaction energy between BACE1 and its inhibitors.

Keywords: Fast pulling of ligand approach; β-secretase 1; SMD; relative binding affinity; interaction energy; pulling work;

1. Introduction

The neurogenesis in elder person with Alzheimer's disease (AD) is slowly damaged by β-Amyloid (Aβ) oligomers according to the amyloid cascade hypothesis [1]. In amyloidegenic process, the amyloid precursor protein (APP), a transmembrane protein inserted into the surface of neuron cell, is cleaved by β-secretases 1 (BACE1) and γ-secretases to form Aβ peptides [2]. Subsequently, self-assembly of Aβ peptides results in oligomers, which further aggregate to form fibrils inside the AD patient brain [3]. Numerous studies were thus performed to design the inhibitor for Aβ peptide aggregation [4-7]. However, efficient inhibitors have not been found due to the lack of detailed information on the solvated Aβ oligomers, including their three

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