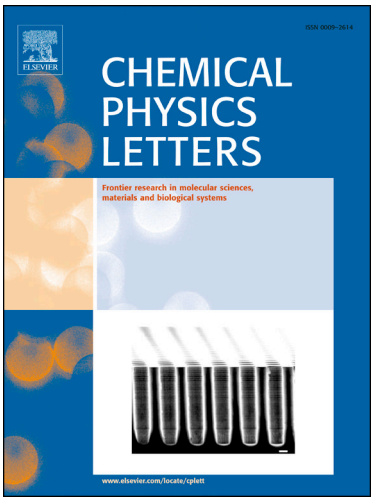

Research paper

Influence of various force fields in estimating the binding affinity of acetylcholinesterase inhibitors using fast pulling of ligand scheme

Nguyen Minh Tam, Khanh B. Vu, Van V. Vu, Son Tung Ngo

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Influence of various force fields in estimating the binding affinity of acetylcholinesterase inhibitors using fast pulling of ligand scheme

Nguyen Minh Tam[ab,*], Khanh B. Vu[c], Van V. Vu[c], and Son Tung Ngo[ab,*]

[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]*NTT Hi-Tech Institute, Nguyen Tat Thanh University, Ho Chi Minh City, Vietnam*

Abstract

Acetylcholinesterase (AChE) is considered as one of the most favored drug targets for Alzheimer's disease. The effects of different force fields (FFs) on ranking affinity of acetylcholinesterase inhibitors were obtained using the fast pulling of ligand (FPL) method in steered-molecular dynamics (SMD) simulations. GROMOS, AMBER, CHARMM, and OPLS-AA FFs were investigated in this work. The pulling work derived with GROMOS FF has the strongest correlation and smallest error compared with experimental binding affinity. Moreover, the CPU consumption in the calculations using GROMOS FF is the lowest, which could allow us to rank affinity of a large number of AChE ligands.

Keywords: FPL; Acetylcholinesterase; AMBER; CHARMM; OPLS; GROMOS.

1. Introduction

Alzheimer's disease (AD) currently affects more than 40 million people worldwide and eventually damage the brain to the point of causing a slow death [1]. As a result, several billions of US dollars have been paid for the treatment and health care services, and the amount rapidly increases due to the increase in the advanced AD patients. Numerous assumptions including amyloid and cholinergic hypotheses, which were emerged as the most acceptable scenarios, have been proposed to describe the mechanisms of AD [2]. In spite of the amyloid cascade hypothesis being assisted by several experimental and genetic evidences [3], inhibitor efforts being screened [4,5], and Aβ oligomeric structures being investigated [6,7], recent clinical trials of drug candidates aiming Aβ peptides have not yet been successful [8-10].

* Corresponding author. Tel.: + 84 – 28 – 37 755 035; fax: + 84 – 28 – 37 755 055.
E-mail address: nguyenminhtam@tdt.edu.vn; ngosontung@tdt.edu.vn