VIET NAM NATIONAL UNIVERSITY HCMC
UNIVERSITY OF TECHNOLOGY

THE SOCIALIST REPUBLIC OF VIETNAM

INFORMATION OF DOCTORAL DISSERTATION

PhD student: **NGUYEN QUOC THAI**

Title: **STUDY ON THE THERAPEUTIC POSSIBILITIES OF ALZHEIMER'S DISEASE OF POTENTIAL COMPOUNDS BASED ON COMPUTER SIMULATION**

Major: **Engineering Physics - Computational Physics**

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1. Abstract

Alzheimer's disease (AD) is one of the most common forms of dementia. Clinically it is defined as a progressive decline in memory, speech and other cognitive functions. AD is the sixth-leading cause of death in the United States and total payments for patients with AD and other dementia were estimated at $226 billion in 2015 posing a huge burden to the society.

The cause of AD has not been disclosed yet. In general, potential causes can be divided into three major categories as follows: cellular, genetic, and molecular imbalances. In particular, the amyloid hypothesis belongs to the type of molecular imbalance, which is the most studied. The amyloid hypothesis admits that the AD etiology is associated with self-assembly of amyloid beta (Aβ) peptides inside the brain. The Aβ peptides are produced by proteolytic cleavage of the amyloid precursor protein (APP) by β-secretase and γ-secretase. The most abundant forms of Aβ peptides are $A\beta_{1-40}$ and $A\beta_{1-42}$ which have 40 and 42 amino acids, respectively. In addition, in terms of gene imbalance, there are many genes that are dangerous, and were shown to level up AD risk. For example, the Apolipoprotein E (ApoE) gene, which is expressed by nuclear receptor proteins, are peroxisome proliferator activated receptors (PPAR: alpha, beta/delta, gamma) and liver X receptor (LXR: alpha, beta). Among them PPARγ is appreciated to have ability to modulate inflammation response in animal model of AD. PPARγ agonist can reduce not only Aβ plaque burden, but also inflammation. Meanwhile, LXRα agonist also reduced Aβ formation in a mouse model

of AD. Thus PPARγ and LXRα are considered as a research direction, and have emerged as therapeutic targets for the treatment of AD.

Combining Lipinski's rule with the docking and steered molecular dynamics simulations and using the PubChem data base of about 1.4 million compounds (2014), we have obtained DNA dyes Hoechst 34580 and Hoechst 33342 as top-leads for AD. The binding properties of these ligands to Aβ fibrils, peroxisome proliferator-activated receptor γ, retinoic X receptor α-secretases, β-secretases and γ-secretases were thoroughly studied by *in silico* and *in vitro* experiments. By all-atom molecular dynamics (MD) simulations, we obtained the binding free energy of Hoechst 34580, Hoechst 33342, CID 16040294 and CID 9998128 to targets of AD. The obtained results agree very well with the experimentally measured values of the IC50 inhibition constant. Especially, CID 9998128 can inhibit multiple targets of AD. Both *in vitro* and *in silico* experiments showed that Hoechst 34580, Hoechst 33342, CID 16040294 and CID 9998128 are good candidates for treating AD.

Recently Cramer *et al* (Science, 2012, 335, 1503-1506) have reported that bexarotene shows astonishing efficacy in mice models of AD reducing Aβ plaques by about 50% within just 72 hours. Following this study, many groups around the world tried to evaluate the ability of bexarotene to treat AD, by using *in vivo* and *in silico* experiments, but the results of different groups sometimes contradict each other. In order to probe the interaction of bexarotene with Aβ fibrils, we have performed *in vitro* experiment using the Thioflavin T fluorescence assay and atomic force microscopy technique (AFM). Combining the docking and molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) method, we have shown that bexarotene is weakly bound to Aβ fibrils, which is consistent with our *in vitro* results on its impotency in clearance of fibrils. Thus, our study has revealed the molecular mechanisms underlying the effects of bexarotene on the Aβ fibril growth and stability.

2. The main scientific contributions

- In terms of methodology, we propose to incorporate SMD (steered molecular dynamics) simulation into a multistep scheme for virtual screening of drug candidates from large databases. This new scheme improves the accuracy and efficiency of calculations, since the SMD method is fast, but at the same time it provides high accuracy.

- By simulation method combined with experiment, screened CID 16040294, Hoechst 34580, Hoechst 33342 and CID 9998128 are potential drugs to treat AD. Especially CID 9998128 can inhibit multi-receptor.

- Unraveling the mechanism of bexarotene interaction with Aβ fibrils, it was demonstrated that bexarotene is not capable to clear fibrils due to its low binding affinity, while the prolongation of the lag phase is associated with the reduction of β-sheet content in monomer state.

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