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QSAR and primary docking studies of *trans*-stilbene (TSB) series of imaging agents for β-amyloid plaques

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Abstract

In vivo imaging β-amyloid plaques can help to diagnose Alzheimer's disease (AD). Some *trans*-stilbene derivatives are hopeful as probes for in vivo evaluation of β-amyloid plaques. In order to explore the interaction mechanism, quantitative structure-activity relationship (QSAR) and molecular docking studies were performed on *trans*-stilbene (TSB) compounds. First, 22 TSB-based analogues were optimized using DFT method. Through QSAR analysis, highly predictive QSAR model was developed with r^2 value of 0.857. Based on the QSAR model, one possible binding site was proposed and validated by molecular docking studies. The Lamarckian Genetic Algorithm (LGA) was applied to deal with the ligand-protein interactions. A good correlation between the calculated binding energies and the experimental binding affinities suggests that the identified binding site is reliable. The QSAR model and the information of the ligand–protein interaction would be useful in developing new imaging agents for β-amyloid plaques.

Keywords: Stilbene; β-amyloid; QSAR; Docking

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and accounts for two thirds of all cases. It destroys brain cells and nerves, particularly those responsible for storing memories. Nowadays, it has been a major public health problem and caused heavy financial and emotional burden for both the society and family, As a result of aging society, AD will cause an increasingly financial and emotional cost on society in the next decades.

Currently, early appraisal of clinical symptoms for diagnosis of AD is often difficult and unreliable. It has been found that formation and accumulation of β-amyloid (Aβ) peptide in the brain are crucial factors in the development and progression of AD. The only definitive confirmation of AD is by postmortem histopathological examination of Aβ deposits in the brain.

In vivo neuroimaging of Aβ plaques would be a non-invasive method for early diagnosis of AD and development of treatment strategies. Detection of deposited Aβ with non-invasive techniques such as positron emission tomography (PET) and single photo emission computed tomography (SPECT) could enable the diagnosis of AD in its pre-symptomatic stages. To detect Aβ plaques with PET and/or with SPECT, it is necessary to develop probes with a high affinity for Aβ plaques. Many ligands with high affinity have been developed as imaging agents for Aβ plaques. Each of main compound classes, derived from Thioflavin-T (PIB [1–4], SB-13 [5–8]), Congo Red (BSB [9–11]), and aminonaphthalene (FDDNP [12–15]) are found to bind to mutually exclusive sites on the Aβ plaques [16–18]. But little information is known about the interaction between the ligands and Aβ plaques.

Developed by H. F. Kung et al. [19], *trans*-stilbene (TSB) derivatives are simple and relatively small molecules, which are hopeful as probes for in vivo evaluation of Aβ plaques containing $A\beta_{1\text{-}40}$ aggregates in the brain of AD. To the best of our knowledge, neither its quantitative structure–activity relationship (QSAR) model nor crystal structure of ligand–protein complex are available. Thus, we carried out a QSAR analysis and molecular docking to investigate their interaction mode. The results from this study should be useful in understanding the ligand–protein interaction and in designing new imaging agents for Aβ plaques.

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2. Computational methods

2.1. Molecular calculation

Twenty-two TSB-based ligands were employed in this study (Table 1). The initial structures of these compounds were built on the basis of *trans*-stilbene crystal structure [20] with the help of ChemOffice 6.0 [21]. A system conformational search for *trans*-stilbene molecules was performed using conformational search module in HyperChem [22]. The flexibility of all the torsion angles was considered. The local minimum-energy and the lowest-energy conformations of each molecule were obtained, followed by an energy minimization to a convergence of 0.1 kcal/mol using AM1 method and the conformation with lowest energy was fully optimized with DFT(B3LYP)/6-31G(d) method in GAUSSIAN 98 program package [23,24]. All of the geometric parameters of the stationary point have been located at B3LYP/6-31G(d) level and characterized by vibrational frequency. The electronic descriptors were obtained from the result of density functional calculation. Other descriptors such as molecular volume and partition coefficient (cLogP) were calculated using the QSAR module in HyperChem.

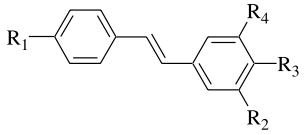
2.2. QSAR

QSAR studies were performed on the original data of the 22 compounds. The dependent variable was defined as the inverse log of the Ki value. The relationship between binding affinities, expressed as the pKi ($-\log$Ki), and a series of molecular descriptors was quantitatively studied by the means of partial least-squares analysis (PLS).

2.3. Molecular docking

Based on the result of QSAR, a possible binding site was proposed. Three ligands (No. 22, 21 and 20) with low binding affinities, three ligands (No. 16, 13 and 9) with mediate binding affinities and two ligands (No. 4 and 3) with high binding affinities were randomly selected in docking studies to validate this proposal. The $A\beta_{1\text{-}40}$ structure generated by A. T. Petkova et al. [25] was chosen as the macromolecule model. Of course, precise docking can only be done with accurate β-amyloid structure; however, some conclusions can be drawn with current β-amyloid structure. Since the whole amyloid fibril was composed of repeated β-strands, this fragment with five repeated strands involved in docking could contain the possible biding sites. Firstly, a systemic search for binding site was done using the whole protein molecule as the target. The result showed that the ligand entered a channel with much higher probability (data not shown). A hydrophobic channel was formed by PHE-19 and PHE-20 and residues of 31-36 along its long axis and the hydrophobicity of this area was detected using DRY probe in Grid program [26]. The advanced docking program AutoDock 3.0.5 [27] was used to automatically dock the ligands to β-amyloid

Table 1
The structure and in vitro binding affinities of the 22 TSB-based analogues



No	R_1	R_2	R_3	R_4	pKi^a	Ref.
1	$-N(CH_3)_2$	–Br	–OH	–H	8.70	[1][b]
2	$-N(CH_3)_2$	–H	–Br	$-NH_2$	8.55	ibid
3	$-N(CH_3)_2$	–H	–CH=C(OMe)-R4	–CH=CH-R_3	8.15	ibid
4	$-N(CH3)_2$	–H	–CH=CH-R_4	–CH=C(CH3)-R_3	8.14	ibid
5	$-N(CH_2CH_3)_2$	–H	–OH	–H	8.00	ibid
6	$-N(CH3)_2$	–H	–H	–Br	7.90	ibid
7	$-N(CH_3)2$	–H	–H	$-OCH_3$	7.87	ibid
8	$-N(CH_3)2$	–H	$-NHCH_3$	–H	7.82	ibid
9	$-N(CH_3)_2$	–H	$-N(CH_3)_2$	–H	7.73	ibid
10	$-NH_2$	–H	$-OCH_{2CH2F}$	–H	7.59	ibid
11	$-N(CH_3)_2$	–H	$-NH_2$	–H	7.58	–
12	$-N(CH_3)2$	–H	–H	$-NO_2$	7.56	[1][b]
13	$-N(CH_3)2$	–H	-CH=CH-R_4	–OCO-R_3	7.55	ibid
14	$-NHCH_2CH_2F$	–H	–OH	–H	7.52	ibid
15	$-N(CH_3)2$	–H	$-C_{6H5}$	–H	7.47	ibid
16	$-NH_2$	–H	$-OCH_3$	–H	7.44	ibid
17	$-NHCH_{2CH2F}$	–H	$-OCH_{2CH2F}$	–H	7.41	ibid
18	$-OCH_3$	–H	–H	–H	7.36	ibid
19	$-N(CH_3)_2$	–H	–H	–H	7.35	ibid
20	$-OCH_3$	-H	$-NO_2$	–H	7.33	ibid
21	$-ON_2$	$-CH_3$	–H	–H	6.82	–
22	–H	–H	–H	–H	6.24	[1][b]

[a] pKi = $-\log$Ki.
[b] [1] H.F. Kung, M.P. Kung, Z.P. Zhuang, Patent No. WO 2 003018070.