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Pharmacophore mapping-based virtual screening followed by molecular docking studies in search of potential acetylcholinesterase inhibitors as anti-Alzheimer's agents

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ABSTRACT

Alzheimer's disease (AD) is turning out to be one of the lethal diseases in older people. Acetylcholinesterase (AChE) is a crucial target in designing of drugs against AD. The present *in silico* study was carried out to explore natural compounds as potential AChE inhibitors. Virtual screening, via drug-like ADMET filter, best pharmacophore model and molecular docking analyses, has been utilized to identify putative novel AChE inhibitors. The InterBioScreen's Natural Compound (NC) database was first filtered by applying drug-like ADMET properties and then with the pharmacophore-based virtual screening followed by molecular docking analyses. Based on docking score, interaction patterns and calculated activity, the final hits were selected and these consist of coumarin and non-coumarin classes of compounds. Few hits were found to have been already reported for their AChE inhibitory activity in different literatures confirming reliability of our pharmacophore model. The remaining hits are suggested to be potential AChE inhibitors for AD.

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1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia affecting older people. It is allied with a number of factors including extensive failure of cholinergic neurons in various parts of the brain, that gradually destroys thinking skills, memory and, finally even the capability to perform basic activities of daily living (ADLs) (Birks, 2006; ADEAR, 2013). The early diagnosis and the treatment of AD is now an emerging research field, though there is no cure for the disease with the existing anti-Alzheimer drugs and only symptomatic treatment is possible. At present, the disability weight (DW) of this disease in people older than 60 years is greater than other lethal diseases like cardiovascular diseases, stroke, cancer, and musculoskeletal disorders (Minati et al., 2009). According to the World Alzheimer Report, Alzheimer's Disease International estimated that there were 35.6 million people living with dementia worldwide in 2010, with a possible increase to 65.7 million by 2030 and 115.4 million by 2050 (Wimo and Prince, 2010). AD was first documented more than a century ago, but research into its root causes, symptoms, risk factors and treatment has achieved momentum only in the past few decades. Even though research has revealed a number of biological targets against AD such as acetylcholinesterase (AChE), N-methyl-D-aspartate (NMDA) receptor, glycogen synthase kinase 3β (GSK3β), cyclin-dependent kinase 5 (CDK5), β secretase, etc. but the specific drug molecules against these targets showing a complete cure of the disease remain unknown (Minati et al., 2009; Association, 2009).

According to cholinergic hypothesis, AD is caused by a decline in the level of the neurotransmitter acetylcholine (ACh), and thus to raise the level of ACh, a key enzyme in the breakdown of the ACh *i.e.* AChE can be targeted (Babic, 1999). Acetylcholinesterase, (AChE; E.C. 3.1.1.7) which is among the most efficient enzymes with a turnover number of $>10^4$ s^{-1}, is one of the potential targets, which has led to some palliative drugs approved for the treatment of AD (Kryger et al., 2000; Martinez and Castro, 2006). The most prominent and known neuropathological characteristics found in AD patients are the presence of amyloid beta (Aβ) plaques and neurofibrillary tangles in the brain (Mattson, 2004). It is found that AChE present in the cholinergic terminals accelerates this Aβ aggregation (Inestrosa et al., 1996). More recent studies suggest that the AChE–Aβ complex boost the Aβ dependent deregulation of intracellular Ca^{2+} plus mitochondrial dysfunction in hippocampal neurons, which causes more deterioration than Aβ alone (Margarita et al., 2010). The FDA approved acetyl cholinesterase inhibitors (AChEIs) namely tacrine, donepezil, galantamine and rivastigmine are based on the same findings of decreased levels of cholinergic markers in the brain of AD patients. Other drugs which are acting on different targets have been assessed for treating AD, but memantine (N-methyl-D-aspartate antagonist) is the

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best known and widely approved among these drugs. However, all these approved drugs are useful in only mild to moderate restoring in memory and cognitive function, but unable to stop the progressive neurodegeneration (Minati et al., 2009; Tariot and Federoff, 2003; Scarpini et al., 2003).

3D-structures of AChE enzyme co-crystallized with diverse ligands such as tacrine (Harel et al., 1993), galantamine (Greenblatt et al., 1999), donepezil (Kryger et al., 1999), and huperzine (Raves et al., 1997) have provided crucial information related to structural elements and the motifs vital for its catalytic mechanism. Human AChE (hAChE) consists of three major sites: catalytic triad – an active site (A-site), a peripheral anionic site (PAS) and a long narrow hydrophobic gorge, which connects the A-site and the PAS. The catalytic triad consists of Ser203 (a catalytically reactive residue), His447, and Glu334, all are positioned in the A-site. The PAS that holds the positive quaternary amine of ACh encloses several aromatic residues Tyr72, Asp74, Trp86, Tyr124, Trp286, and Tyr341. Its function is to guide the orientation of charged part of the substrate in the active site and also offers a putative binding site for allosteric inhibitors. There are 14 aromatic residues (Tyr72, Trp86, Phe123, Tyr124, Tyr133, Trp236, Trp286, Phe295, Phe297, Tyr337, Tyr 341, Phe338, Trp439, and Tyr449) that line the hydrophobic gorge. These 14 residues are well conserved across different species, and Trp86 is highly vital for ACh binding since mutation in it results in 3000 fold decrease in reactivity. The aromatic gorge in the active site is about 20 Å deep and penetrates half way the hAChE (Harel et al., 1993; Axelsen et al., 1994; Sussman et al., 1991; Guo et al., 2010). The interaction between the hAChE enzyme and known potent inhibitors such as donepezil or tacrine, is characterized by π–cation interactions between the conserved aromatic residues (especially Trp86) and the protonated atoms of these inhibitors. Also, π–π stacking interaction between the above mentioned aromatic residues and the aromatic groups present in the inhibitors, and the ionic interactions between the anionic Asp74 and the protonated atoms of the inhibitors play vital function in receptor–ligand binding. Most of the ligands are placed at the base of the hydrophobic gorge, while larger ligands like donepezil extend up to the opening of the gorge (Lu et al., 2011). Notably, ligands which bind to both A-site and PAS are known as dual binding site inhibitors.

In drug discovery, the chemoinformatics techniques such as virtual screening, pharmacophore modeling, quantitative structure-activity relationship (QSAR), data mining, etc. are of great significance, being considerably precise as well as saving time and cost. For designing new scaffolds rationally, one can develop ligand-based predictive models to extract information regarding distinctive structural features required for ligand–receptor interaction. One of the several ways is to develop a 3D-pharmacophore model and utilize it in the virtual screening of available databases, which seems to be more significant and time-saving (Sun, 2008). Pharmacophore modeling-based virtual screening methods are highly useful to screen huge databases more rapidly and by their propensity to extract diverse leads in terms of structure. The database can be initially screened for drug-like molecules by applying different rational filters such as the Lipinski's Rule of five, (Lipinski, 2000) and drug-like ADME properties (Ghose et al., 1999). Subsequently it can be further subjected to molecular docking interaction based screening. Docking technique usually utilize an energy-based scoring function to acquire the most favorable ligand orientation and conformation, required for binding in the active site. As seen in various reported studies, pharmacophore modeling-based virtual screening has been found to be a successful method, especially when combined with docking analyses (Saxena et al., 2010; Sakkiah et al., 2011).

In the present study, natural compounds from InterBioScreen's Natural Compound (NC) database (InterBioScreen's NC database, 2012) were filtered by applying the drug-like ADMET properties, which includes Lipinski's rule of five (Lipinski, 2000). Subsequently, a qualitative pharmacophore model was developed based on 404 hAChE inhibitors which were obtained from the literature (Yan and Wang, 2012) and was successfully employed in the further screening of the database compounds. The lead compounds were selected based on their best fit values and then subjected to docking analyses to refine the list of retrieved hits. This study has led to the set of hits as possible candidates for the designing of potential hAChE inhibitors. Most of the clinically available anti-Alzheimer agents are acetylcholinesterase inhibitors, suggesting the obvious importance of this category of compounds for development of novel agents. We have explored here, using *in silico* tools, natural compounds as AChE inhibitors with specificity (dual binding inhibition) for their possible use in Alzheimer's disease.

2. Materials and methods

2.1. Data set

3D-QSAR pharmacophore modeling compares activity values with the spatial arrangement of varied structural features in a group of active compounds. In this study, 404 AChE inhibitors were obtained from the literature (Yan and Wang, 2012) comprising of diverse series of compounds. These compounds employed similar experimental procedures and conditions (Ellman's method) for calculating biological activity. For development of pharmacophore models, the bioactivities of all the compounds were expressed as IC_{50} values (nM). Among them, 85 compounds were randomly selected as the training set compounds with bioactivity values ranging from 0.950 nM to 11,587.77 nM and the remaining 319 molecules were selected as the test set (all the structures can be found in the SDF file format in Supplementary data). A normality distribution plot of the pIC_{50} values of the compounds is shown in Fig. S1 in Supplementary materials.

The 2D structures of all training set compounds were imported into Discovery Studio (DS) version 2.1 (Discovery Studio, 2012) and then converted into the 3D structures. As molecules can alter their conformation to bind to a receptor site, thus each molecule in the training set is represented by a set of energetically favorable conformations. DS uses a poling algorithm (Smellie et al., 1995) which ensures conformational diversity. For each compound, a maximum of 100 conformers were generated using the "BEST" conformational search method based on the CHARMm force field, (Brooks et al., 2004) with an energy threshold of 20 kcal/mol, and all other parameters were kept default.

2.2. Pharmacophore modeling

HypoGen (Li et al., 2000) algorithm was employed to develop top scoring 3D-QSAR pharmacophore models using DS version 2.1. In this algorithm, the biological activities of the training set compounds are employed to build top 10 hypotheses that are common among the actives but not among the inactives. It builds the simplest hypotheses which gives the best correlation among calculated activities and experimental activities. The pharmacophores are built in three phases – a constructive, a substractive and an optimization phase (Li et al., 2000). In the constructive phase, active compounds are identified. All pharmacophoric features (maximum five) among the two most active compounds are extracted and stored. The pharmacophore that fits a minimum subset of features of the remaining active compounds are kept. A compound is considered active, if its activity value satisfies the following condition: $MA \times Unc_{MA} - \left(\frac{A}{Unc_A}\right) > 0.0$, where MA is the activity of the most active compound, Unc is the uncertainty of the compounds, and A is the activity of the compound in question.

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