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Computer Modeling of Drug-Protein Interactions Between Derivatives of Aricept® and Human Acetylcholinesterase

Josh Zhang

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Abstract

Aricept, a drug used in reducing symptoms of Alzheimer’s disease (AD), was docked into Human Acetylcholinesterase. Chemical structure of Aricept was modified with methyl, hydroxyl, amine, chloro, and carbonyl groups to test for relative stability between the drug and the protein. Calculations were performed in Hyperchem Professional 7.5 using MM+ force field mode. Out of 29 trials run, 14 trials showed improved stability over Aricept, and 6 trials showed improvements of ΔG greater than 2 kcal/mol.

Introduction

Alzheimer’s disease (AD) is a progressive, neurodegenerative disease characterized in the brain by abnormal clumps (amyloid plaques) and tangled bundles of fibers (neurofibrillary tangles) composed of misplaced proteins (1). It is estimated that nearly five million individuals in the United States alone are affected by this brain disorder that gradually destroys a person’s memory and ability to learn, reason, make judgments, communicate and carry out daily activities (2).

Current research for AD cures has focused on inhibiting Human Acetylcholinesterase (AChE), an enzyme that catalyzes the hydrolysis of acetylcholine into choline and acetic acid. This enzyme functions at the base of a 20Å deep active site gorge. Thus, with AChE inhibited, more acetylcholine will be produced and made available to the brain. Acetylcholine is a critical neurotransmitter used in forming and keeping memories. It is believed that by increasing acetylcholine levels these drugs slow down the progress of dementia caused by AD. Aricept is a reversible inhibitor of AChE, known chemically as (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-phenylmethyl]-4-piperidinyl]methyl]-1H-inden-1-one hydrochloride. Aricept is commonly referred to in the pharmacological literature as E2020.

Aricept, also known as Donepezil, has an empirical formula of C24H29NO3HCl and a molecular weight of 415.96, and has the following structure:

\[ \text{Aricept bound to active site of Human Acetylcholinesterase} \]

H\text{CO}_3

H\text{CO}_3

Aricept is a white crystalline powder and is freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in acetonitrile and practically insoluble in ethyl acetate and in n-hexane (3).

Methods

The structure of human acetylcholinesterase complexed with fasciculin was obtained from the NIH Protein Database. Since no pdb (protein database) files for human AchE complexed with Aricept® existed in the database, fasciculin was removed from the human AchE and Aricept® was inserted into its active site. Data obtained by previous research (Becca Palacios, Summer 2002) was analyzed, and 29 promising structures of the 230 modifications performed by Palacios was examined for conformational stability. Aricept® was modified by adding or deleting various methyl, amine, hydroxyl, chloro, and carbonyl groups.

Results

Aricept® was successfully and stably docked into the active site of human AChE. The protein-drug binding energy determined by Hyperchem was -5418.418 kcal/mol. Of the 29 modification trials ran for Aricept®, 14 trials had greater binding stability than Aricept®, and 6 compounds (A-F) showed an increased stability of 2 kcal/mol or more. Table 1 shows a summary of these more stable compounds.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>ΔG (kcal/mol)</th>
<th>Estimated K_i (M)</th>
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</thead>
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<td>A</td>
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<td>F</td>
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<td>-2.889</td>
<td>0.02550</td>
</tr>
</tbody>
</table>

Table 1. Structure, relative binding energy, and predicted binding constant K_i of the six most stable analogs of Aricept®

Discussion and Future Studies

This data shows that analogs of Aricept® show potential for increased binding stability for human acetylcholinesterase, and thus become a valuable instrument in finding cures for Alzheimer’s. These more stable modifications, particularly the compounds that exhibi

References

(1) ApoE, Amyloid, and Alzheimer’s Disease
John Hardy
(2) Defect in Alzheimer’s is on Chromosome 21
Deborah M. Barnes
(3) ARICEPT®(Donepezil Hydrochloride Tablets)

Acknowledgements

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