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Hydrogen Bonding Interactions with the Binding of AriceptÂ® with Acetylcholinesterase

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Hydrogen Bonding Interactions in the Binding of Aricept® with the Enzyme Acetylcholinesterase

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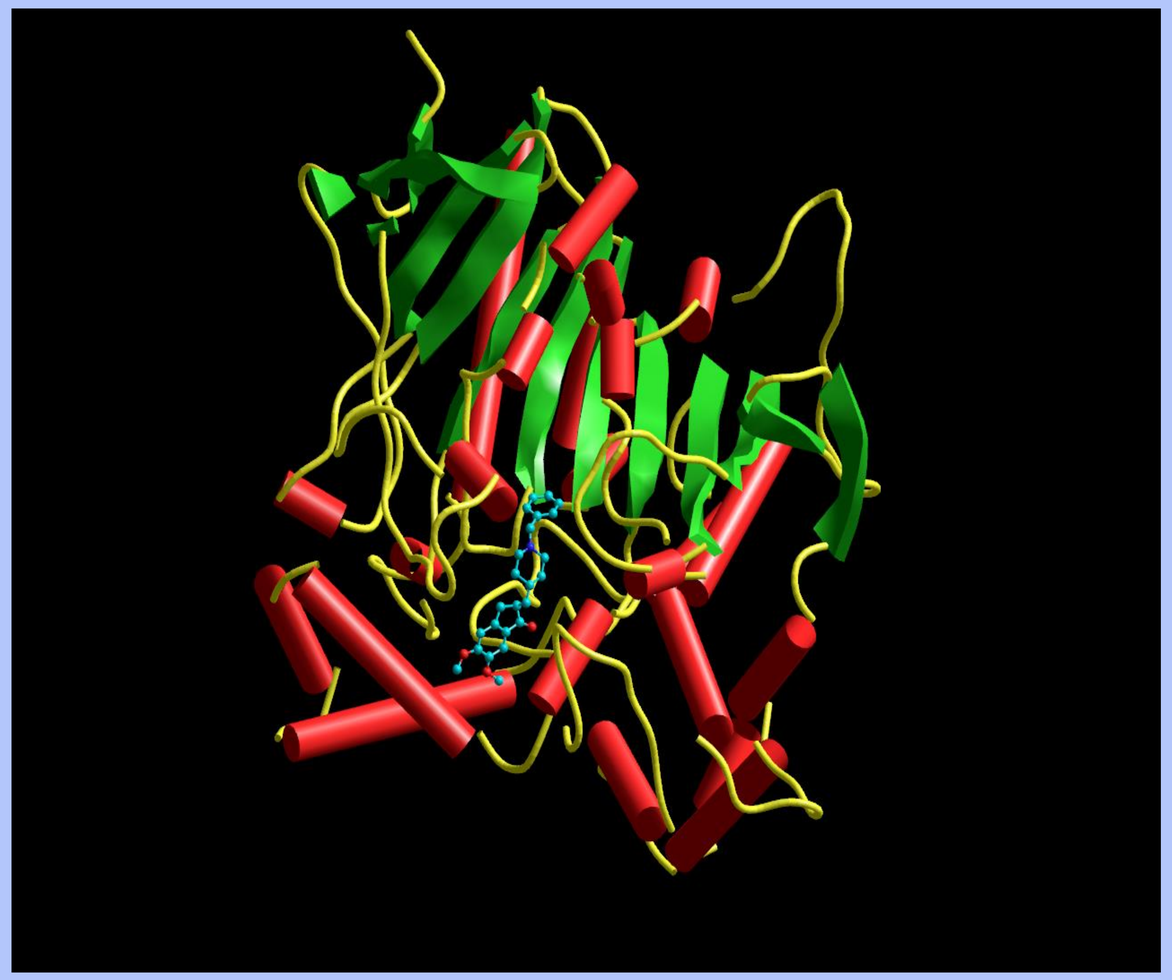
Abstract:
The anti-Alzheimer’s drug Aricept® was docked into a computer model of the enzyme acetylcholinesterase using the Amber force field mode of HyperChem 7.5 Professional. The importance of hydrogen bonding within the active site gorge was investigated by systematically mutating tyrosine and serine to phenylalanine and alanine, respectively. Two amino acids within the active site gorge, Tyr 130 and Ser 81, showed less favorable binding in the absence of the hydroxyl group.

Introduction:
Alzheimer’s is a progressive, degenerative disease of the brain that affects more than 5 million Americans. Alzheimer’s disease is marked by gradual and irreversible declines in cognitive functions, including memory, communication skills and the ability to learn new material. The cognitive impairments typically associated with this disease suggest dysfunction in the cholinergic system. Recent efforts in the treatment of Alzheimer’s have focused on the inhibition of acetylcholinesterase, the enzyme responsible for the hydrolysis of acetylcholine. The hydrolytic function of this enzyme occurs at the base of a 20 Å deep active site gorge. With the inhibition of the enzyme, higher levels of acetylcholine are available to the brain.



Methods:
The structure of *Torpedo californica* acetylcholinesterase complexed with Aricept® was obtained from the NIH Protein Data Base. Using the molecular modeling program HyperChem 7.5 Professional, docking studies of Aricept® with acetylcholinesterase were completed. The amino acid residues tyrosine and serine were systematically mutated to phenylalanine and alanine, respectively, in order to determine the relative importance of each hydroxyl group in the docking of Aricept® with acetylcholinesterase. After each mutation, the Amber force field was used to calculate the theoretical binding energy. By comparing these values to the value of the un-mutated enzyme, it was possible to infer which hydroxyl groups are particularly important in the stabilization of the acetylcholinesterase-Aricept® complex.

Results:
The active site gorge contains 5 tyrosine residues and 5 serine residues, as well as about 20 additional amino acids. Tyr 130 and Ser 81 were the only two residues that showed less favorable binding energies when mutated to phenylalanine and alanine, respectively.

Force Field	Energy	Cycles	Points	Time
Amber	-8471.793	1088	2362	20 hrs
Opls	-31795.8	4384	9913	22 hrs
MM+	-5072.19	937	2164	49 hrs
Bio CHARMM	-2264.4	1344	2831	21 hrs

Discussion:
When amino acids are mutated, the complex becomes either more stable (- ΔG) or less stable (+ ΔG). The differences in binding energies are caused by a combination of factors including hydrogen bond interactions and sterics. In the cases where more favorable binding occurs in the absence of a hydroxyl group, it is likely that the steric hindrance caused by the oxygen plays a larger role than do the attractive forces of the hydrogen bond interactions. Another possible explanation could be that the hydrogen bond forces are strong enough so as to prevent the amino acids from acquiring more stable conformations, ones that they are able to adapt in the absence of the constraints caused by hydrogen bonding.

Amino Acid Mutated	Mutated to:	ΔG	Cycles	Points
No mutation	N/A	0	1088	2362
Ser 200	Ala	-93.313	1087	2307
Ser 81	Ala	+181.501	822	1766
Ser 124	Ala	-126.788	989	2062
Ser 286	Ala	-156.55	954	1998
Ser 122	Ala	-181.046	1144	2378
Tyr 70	Phe	-49.578	955	2016
Tyr 442	Phe	-46.226	930	1966
Tyr 334	Phe	-92.526	944	2006
Tyr 121	Phe	-118.086	930	1964
Tyr 130	Phe	+24.42	1030	2177

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