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Computational Molecular Modeling of Alzheimer's Drug Derivatives

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Computational Molecular Modeling of Alzheimer's Drug Derivatives

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Department of Chemistry, Kenyon College, Summer Science 2008
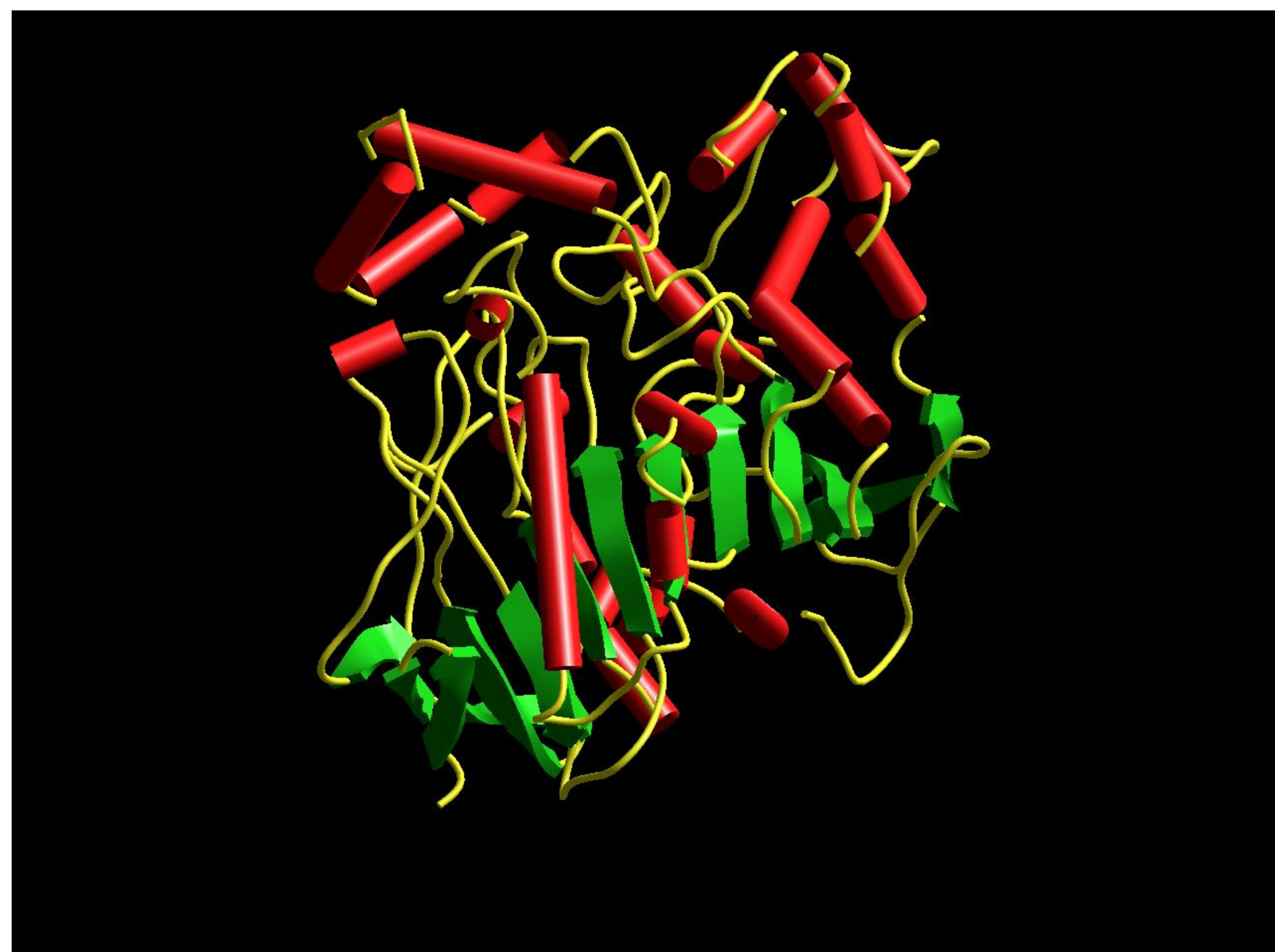
Aricept and Acetylcholinesterase

Figure 1) Secondary structure of acetylcholinesterase

As many as 3.8 million patients have already used Aricept to slow down the progression of Alzheimer's disease (AD), but Aricept is not a cure for AD. Aricept belongs to a group of drugs called N-benzylpiperidine-based acetylcholinesterase (AChE) inhibitors.[2] Aricept works by inhibiting the enzyme acetylcholinesterase, which basically means that the drug delays the breakdown of the neurotransmitter acetylcholine. This in turn increases the concentration of acetylcholine in synapses, which improves nerve cells' communication and the Alzheimer's patients' ability to maintain their memory for years longer than they would be able to without Aricept.[3]

Introduction:

Currently, over 5 million Americans suffer from the degenerative brain disease known as Alzheimer's disease (AD). Alzheimer's disease slowly destroys brain cells, which causes memory loss, behavioral changes, and eventually death. Alzheimer's disease currently ranks as the 7th leading cause of death in the United States. Worst of all, it has no cure. Drugs like Aricept work to treat the symptoms of Alzheimer's disease, but no drug currently on the market is able to stop the progression of Alzheimer's disease completely.[1]

Everyone has trouble remembering things as they get older, but the severe memory loss associated with Alzheimer's disease is completely different. Researchers believe that plaque buildup within the brain and the formation of neurofibrillary tangles cause some of this memory loss. Plaques may disrupt the ability of nerve cells to communicate effectively. An enzyme called beta-secretase cleaves amyloid precursor protein (APP) into smaller fragments called beta-amyloid fibrils (Aß fibrils), which stick together to form the plaques. Plaques form between the nerve cells while tangles, which are made of tau protein, form within the dying cells.

In late stages of the disease, the brain noticeably shrinks due to the large amount of neuronal death. This shrinkage occurs due to a decrease in the size of the cortex, which controls our ability to think, plan, and remember. The hippocampus, which allows humans to make new memories, also becomes significantly smaller in late stage Alzheimer's disease patients. Also, the water-filled ventricles, which are basically dead space in the brain because they contain no neurons, grow considerably.[1]
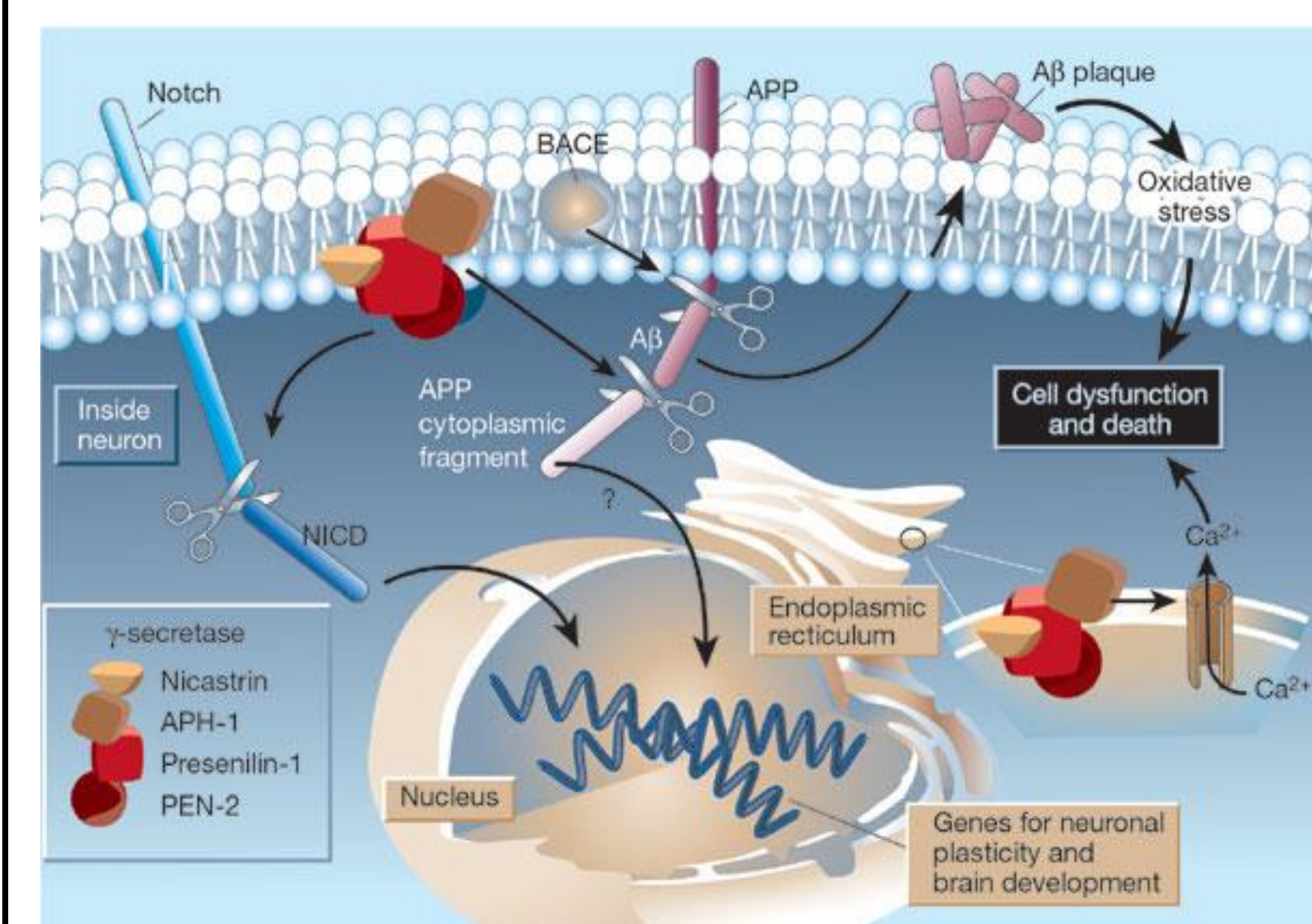
Research Goal:

The goal of this project was to use the computational molecular modeling software, Hyperchem Professional, to make derivatives of known inhibitors and calculate the delta Gibbs free energies in an attempt to find derivatives that bind more strongly to their respective enzymes.

Figure 2) Shows how beta and gamma secretase work to cleave APP. The portion of APP cleaved by gamma-secretase is called the cytoplasmic fragment, and the portion cleaved by beta-secretase is what forms the Aß plaques.

Image from: http://employees.csbsju.edu/hjakubowski/classes/ch331/catalysis/alzheimcleavagenat.jpg
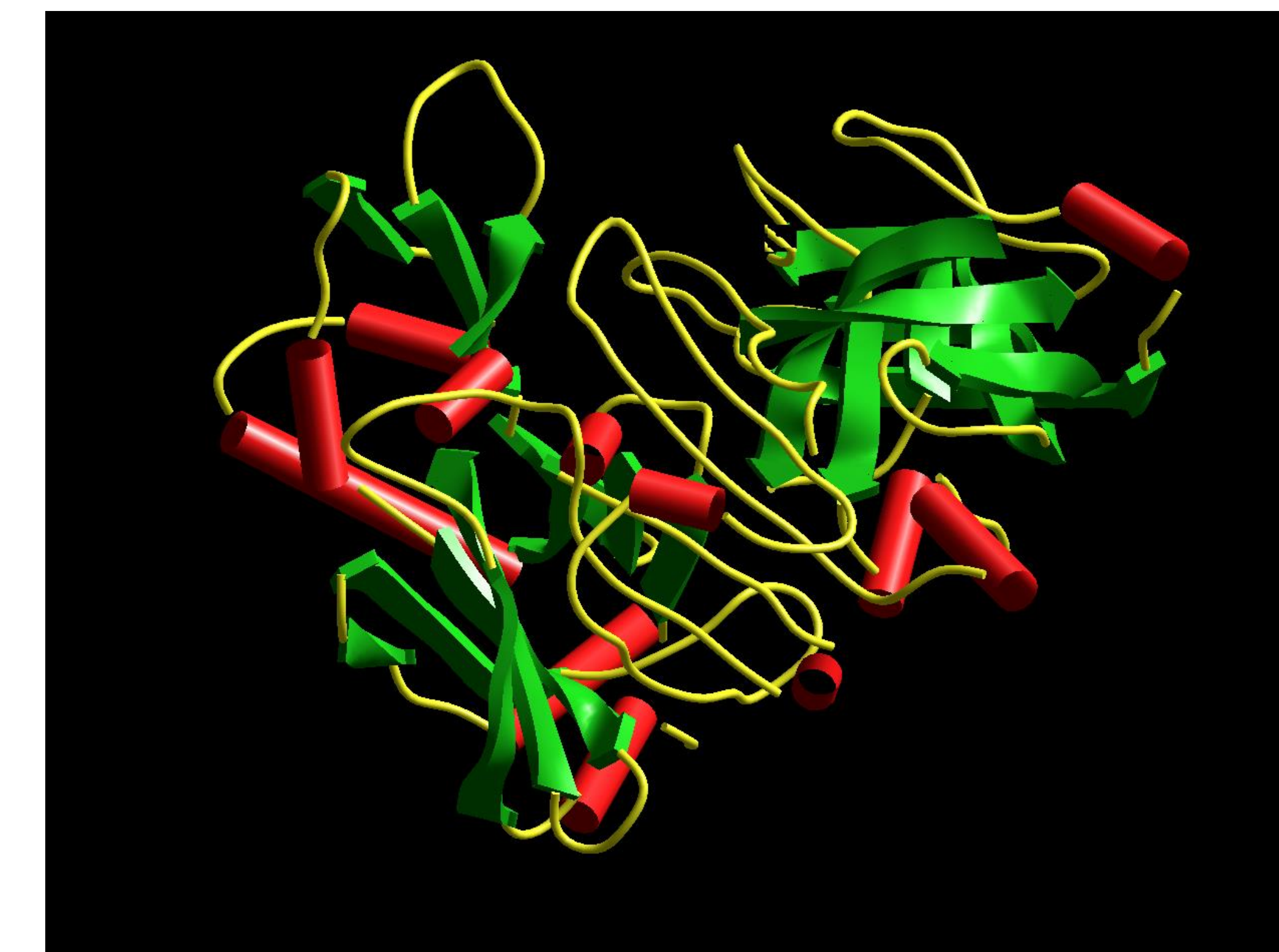
Beta-Secretase

Figure 3) Secondary structure of beta-secretase

Beta-secretase (BACE) is of interest to researchers because of its potential to slow down the actual progression of Alzheimer's disease. Basically, researchers hope to interrupt the plaque formation pathway, which BACE is an integral part of. If a selective inhibitor for BACE can be found, plaque formation could be slowed down or even stopped, which could potentially slow down the progression of the disease instead of just treat the symptoms like Aricept does.

Since no well-known drugs on the market inhibit BACE, two inhibitors, Inhibitor 2 (I2) and Inhibitor 3 (I3), found by Arun k. Ghosh and his colleagues were used as the starting points for making derivatives.[4]

Aricept Results

Derivative of Aricept	Delta G (kcal/mol)	Aricept Delta G – Derivative Delta G
Aricept	-1309.487427	0
	-1391.434204	-81.946777
	-1415.123169	-105.635742
	-1415.591187	-106.10376
	-1420.28833	-110.800903
	-1424.322388	-114.834961

The table above shows the 5 best Aricept derivatives tried (out of 26). The best delta G values were found for derivatives that contained multiple halogens, especially iodine and bromine. Methyl, ethyl, and hydroxyl groups were also tried but did not have as good delta G values as the derivatives with halogens.

Naming:

Early on in the project, a naming system was developed for organizing the many Hyperchem files, and to prevent calculations from being repeated multiple times. First, Aricept and the starting inhibitors in the BACE project were numbered (see below).

Basically, if the hydrogen attached to carbon number 6 on Aricept were replaced with a bromine then the file would be called Aricept-6-Br
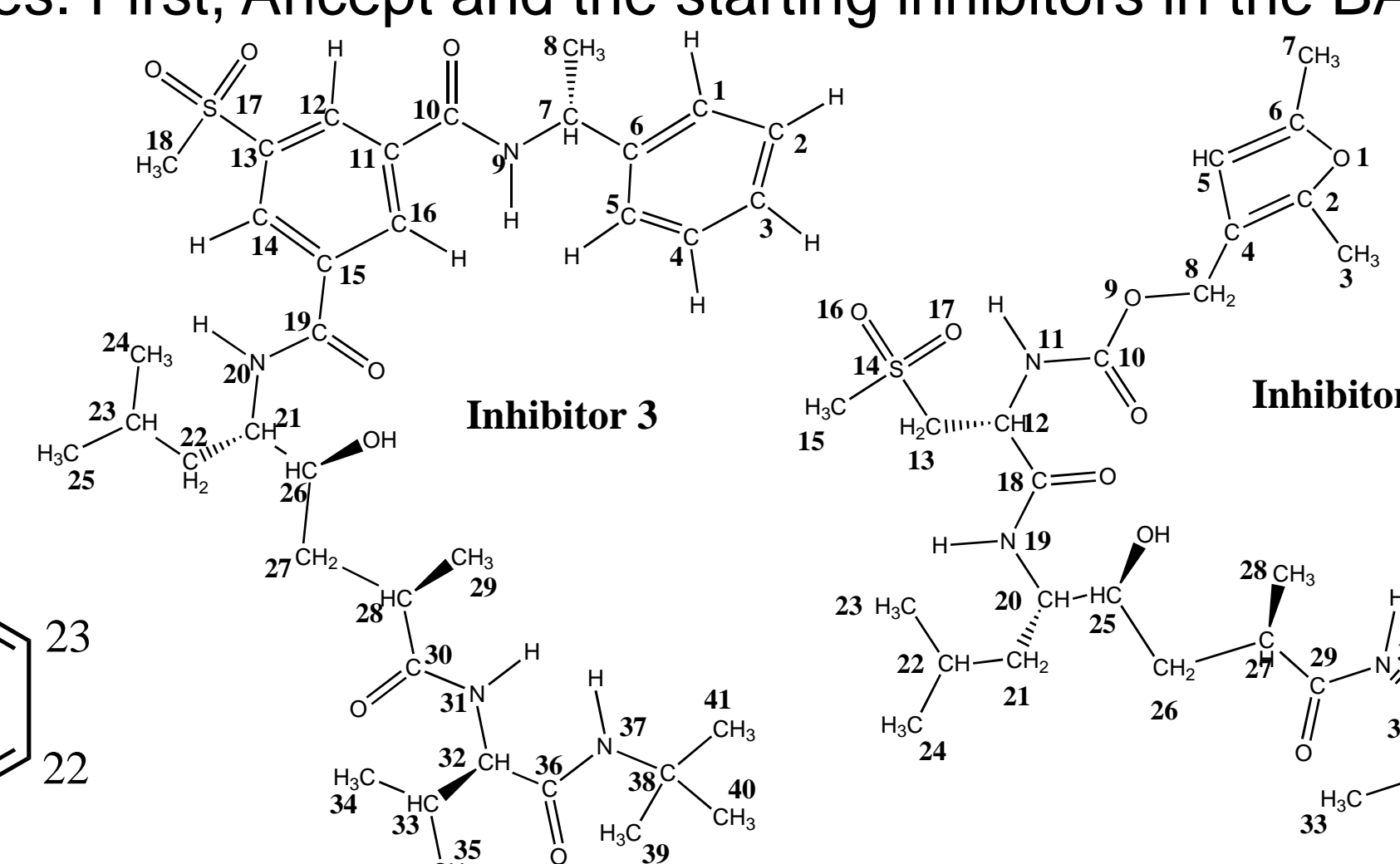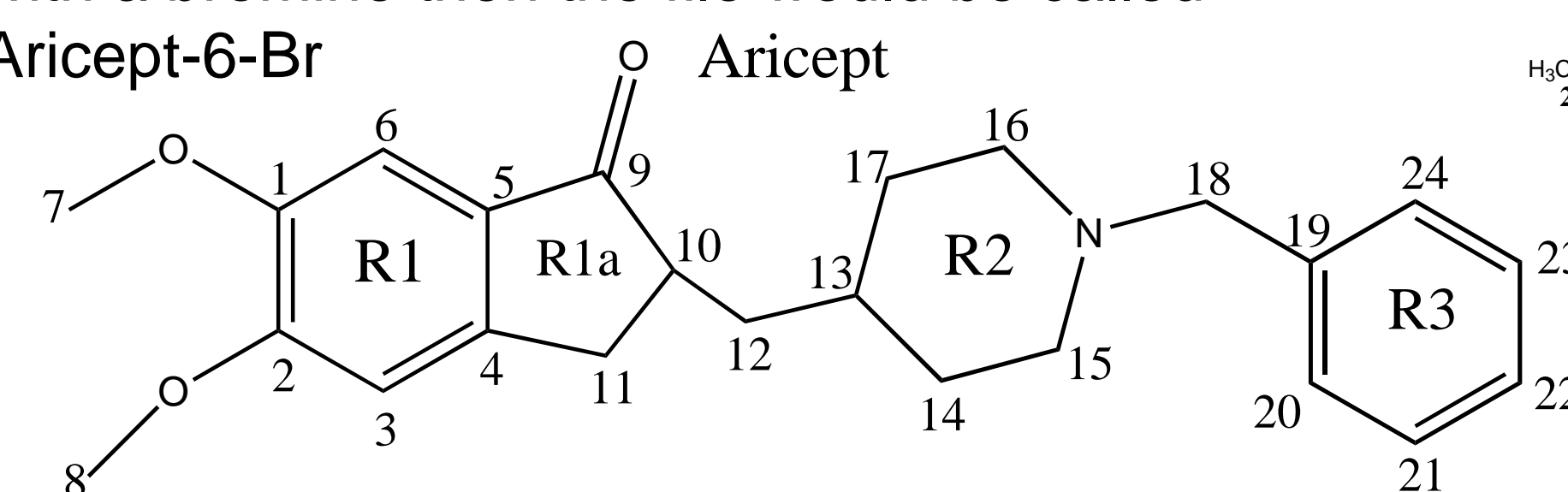
Works Cited:

[1]What is Alzheimer's? (2007, November 21). *Alzheimer's Disease*. Retrieved February 10, 2008, from Alzheimer's Association Web site: http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp

[2]Zhang, J., & Lutton, J., PhD. (2005, August/September). Computer Modeling of Drug-Protein Interactions Between Derivatives of Aricept and Human Acetylcholinesterase. In *Summer Science HHMI Posters*. Retrieved February 10, 2008, from http://biology.kenyon.edu/HHMI/posters_2005/ZhangJ.jpg

[3]Hill, C., PhD. (2008, February 5). All About Aricept. In *Alzheimer's Disease*. Retrieved February 10, 2008, from http://alzheimers.about.com/od/treatmentofalzheimers/p/aricept.htm

[4]Ghosh, A. K., Kumaragurubaran, N., Hong, L., Kulkarni, S., Xu, X., Miller, H. B. et al. (2008). Potent memapsin 2 (β-secretase) inhibitors: Design, synthesis, protein-ligand X-ray structure, and in vivo evaluation. *Bioorganic & Medicinal Chemistry Letters*, 18(3), 1031-1036.

Beta-Secretase Results

Derivative of Inhibitor 2	Delta G (kcal/mol)	Inhibitor 2 Delta G – Derivative Delta G
Inhibitor 2	-3929.077637	0
	-3961.534668	-32.457031
	-3961.859375	-32.781738
	-3961.81665	-32.739013
	-3961.85376	-32.776123
	-3961.859375	-32.781738
	-3966.460449	-37.382812

The table above contains the 6 derivatives of inhibitor 2 that had the best delta G values (out of 187). Like Aricept, the derivatives with multiple halogens were found to have the best delta G values, iodine especially. Also, changing the original ring on the left end of the molecule into a phenyl greatly improved the delta G value. Also, converting the hydroxyl group on carbon 25 into a carbonyl group is highly favorable.

Future Goals: I would like to reduce the size of the inhibitor without compromising the delta G. A smaller molecule would be able to pass the blood brain barrier more easily, which would make it a more effective drug.