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Binding of Beta-site Amyloid Precursor Protein Cleaving Enzyme 1 (BACE1) Inhibitor Aminoquinoline (68K) for Possible Treatment of Alzheimer's Disease

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3d molecular designs

Nova Southeastern University Honors Protein Modeling

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Modeling binding of the BACE1 inhibitor aminoquinoline (68K) for the possible treatment of Alzheimer's Disease (AD)

PDB: 5I3Y and Primary Citation (for the pdb):

Jordan, J. B., Whittington, D. A., Bartberger, M. D., Sickmier, E. A., Chen, K., Cheng, Y., & Judd, T. (2016). Fragment-linking approach using 19F NMR spectroscopy to obtain highly potent and selective inhibitors of β-secretase. *Journal of Medicinal Chemistry*, *59*(8), 3732–3749. https://doi.org/10.1021/acs.jmedchem.5b01917

Alzheimer's Disease (AD) is a neurodegenerative disease that leads to loss of neural connections and eventually cell death. It affects more than 24 million people world-wide. Alzheimer's Disease is primarily characterized by amyloid plaques within the brain, which are deposits of amyloid-β peptides. Because excess amyloid-β levels have been linked to the start of neurotoxicity within neural tissue, much Alzheimer's research has been focused on limiting amyloid-β production through either targeting the amyloid cascade to halt the excessive production of amyloid-β peptides or developing inhibitors for the enzymes needed within the amyloid cascade. This model presents an inhibitor of amyloid-β peptide production.

Amyloid-β peptides consist of amyloid processing protein, or APP. The processing of APP into amyloid-β peptides is a multi-step process involving a sequential cleavage of β-secretase followed by gamma-secretase. The primary candidate for inhibition has been β-site APP cleaving enzyme 1 (BACE1), a type I transmembrane aspartyl protease (501 aa long). Among a more than 10 categories of inhibitors, pdb 5I3Y, which shows BACE 1 interacting with inhibitor 68K (aminoquinoline), has resulted in the lowest IC50 and experimental Kd values. This ligand binds with the BACE1 protein through multiple sets of interactions as well as stronger interactions in comparison to other ligands studied in the paper. Inhibitor 68K has strong interactions with 32 amino acid residues in BACE1, some of which are intertwined with one another. For example, BACE 1's residues Val69, Pro70, and Tyr71 are known collectively as "the flap". "The flap" is a β-hairpin loop structure that is positioned directly over BACE1's catalytic dyad, which is a group of amino acids within the active site of the enzyme. "The flap" is also responsible for regulating a given substrate or inhibitor access to a given enzyme's catalytic dyad (Asp 32 and Asp 228). Researchers found the inhibitor 68K to have interactions with the flap which maximize the strength of the interaction with BACE1 residues, thus minimizing the distance between the inhibitor's various functional groups and their specific polarities.

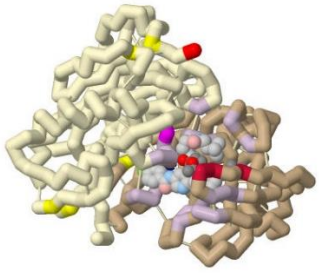
The main challenge with the vast number of therapies involving the development or application of BACE1 inhibitors has to do with the blood-brain barrier (BBB). Many molecules are either unable to cross the BBB in sufficient quantities or are unable to effectively target BACE1 upon crossing the BBB. The inhibitor,68K, also has difficulty crossing the BBB. Additionally, the active site for BACE1 is relatively large making its inhibition difficult. BACE also shares sequence homology with other aspartyl proteases (BACE2, pepsin, renin, cathepsin

D, and Cathepsin E) and as such an inhibitor must be specific to BACE1, so as not to inhibit these other enzymes.

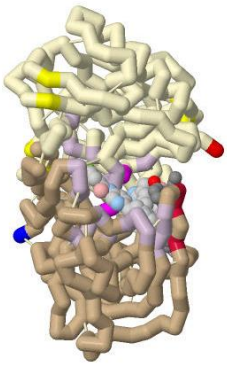
There are currently 16 structural types of potent and selective BACE1 inhibitors (Coimbra et al., 2018). As a member of the aminoquinoline group (68K ligand) is a promising candidate for "the miracle drug" that research teams involved in AD therapeutics have been dedicating their lives towards developing. However, none of these drugs have emerged as successful through clinical trials to date (https://pubmed.ncbi.nlm.nih.gov/31347728/). This protein model shows the ligand interacting with BACE1.

Specific Model Details

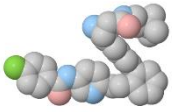
Beta-site APP Cleaving Enzyme 1 (BACE1) was modeled along with the aminoquinoline inhibitor (68K). The inhibitor is shown in light cpk colors and is able to be detached with magnets. For the BACE1 enzyme: N (blue) and C (red terminus) are marked. The enzyme is a lobed shaped protein with the lobes extending into the extracellular space. The short, alpha helical transmembrane domain was not crystalized in this pdb. The N terminal domain is colored tan and the C terminal domain is colored pale yellow (lemonchiffon). The catalytic dyad (Asp 32 and Asp 228) is colored magenta with sidechains in cpk coloring. Note that the negatively charged Asp interact with the positively charged nitrogens of the inhibitor (ligand). The hydrophobic flap in BACE1 (Val 69, Tyr71, and Thr72) is colored crimson with sidechains in cpk coloring. The flap helps to keep the ligand in place. BACE1 also has 6 cysteine residues that form 3 intramolecular disulfide bonds important to maintaining its structure. These 6 cysteines are shown in yellow. Twenty-six additional amino acids (gly11, gln12, gly13, leu30, gly34, ser35, gly74, lys75, trp76, asp106, lys107, phe108, ile110, trp115, ile118, ile126, arg128, tyr198, ile226, ser229, gly230, thr231, thr231, ala335, arg307, glu339) were highlighted in light purple (thistle) as they are known to interact with the ligand.



Model view A:
highlighting the ligand binding



Model view B:
highlighting catalytic aspartates (magenta)



Model view C:
Spacefill model of the BACE1 inhibitor 68K in light cpk coloring (gray is carbon, blue is nitrogen, pink is oxygen, green is fluorine)

Additional References

Coimbra, J. R., Marques, D. F., Baptista, S. J., Pereira, C. M., Moreira, P. I., Dinis, T. C., Santos, A. E., & Salvador, J. A. (2018). Highlights in BACE1 inhibitors for Alzheimer's disease treatment. *Frontiers in Chemistry*, *6*. https://doi.org/10.3389/fchem.2018.00178

Hamed, M. Prediction of Drug Potencies of BACE1 Inhibitors: A Molecular Dynamics Simulation and MM_GB(PB)SA Scoring. Preprints 2020, 2020110292 (doi: 10.20944/preprints202011.0292.v1).