REPORT ON MOLECULAR DOCKING OF AMYLOID BETA (5HOX) AND DONEPEZIL

Introduction to Protein and Ligand

- **Protein**: Proteins are complex macromolecules essential for numerous biological processes. They serve various roles, including enzymatic catalysis, structural support, cellular signaling, and immune response. The amyloid beta protein (Aβ) is associated with Alzheimer's disease and forms plaques in the brain, disrupting neural function. Specifically, **5HOX** is the crystal structure of the amyloid beta fibrils, providing insights into the aggregation of Aβ peptides.

  PDB Link: **RCSB PDB - 5HOX: X-ray crystallographic structure of an A-beta 17_36 beta-hairpin. Synchrotron data set. (LVFFAEDCGSNKCAII(SAR)LMV).**

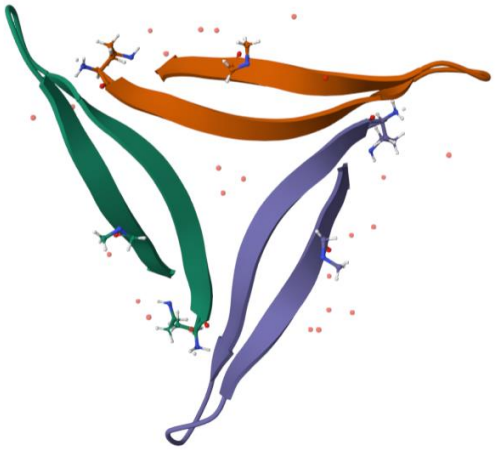

Fig: 3D Structure of the 5HOX protein

- **Ligand**: A ligand is a small molecule that binds to a specific site on a protein, potentially altering its function. Ligands are crucial in drug discovery, as they can modulate protein activity**.** Donepezil is a well-known cholinesterase inhibitor used to treat Alzheimer's disease. It enhances cholinergic function by preventing the breakdown of acetylcholine. While its primary action targets acetylcholinesterase, its potential to interact with amyloid beta structures has gained research interest.

- **Pubchem Link**: Donepezil | C24H29NO3 | CID 3152 - PubChem

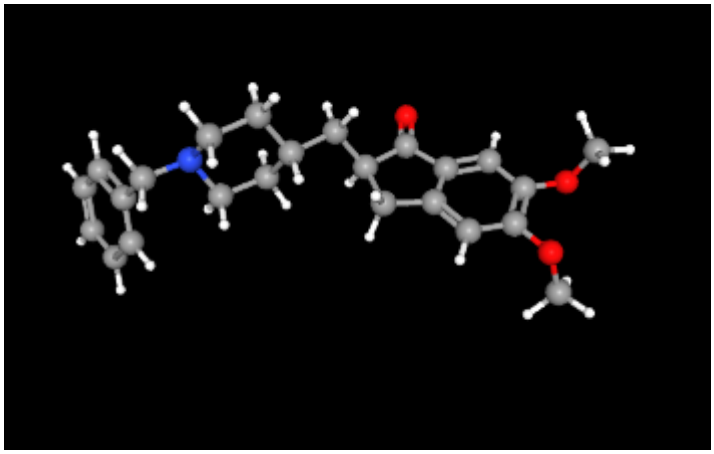

Fig: 3D Structure of Ligand Donepezil

Molecular Docking

Molecular docking is a computational technique used to predict the interaction between a protein and a ligand. It helps visualize how the ligand binds to the protein's active or binding site, providing insights into the binding affinity and interaction strength.

Amyloid Beta (5HOX) and Donepezil Interaction

1. **Protein Structure (5HOX)**:
    - **Description**: 5HOX is the resolved structure of amyloid beta fibrils derived from Alzheimer's disease. It offers insights into the arrangement of Aβ peptides into plaques, essential for understanding aggregation mechanisms.
    - **Key Features**:
        - Composed of β-sheet structures.
        - Contains hydrophobic regions critical for fibril formation.
    - **Significance**: Targeting amyloid beta can disrupt plaque formation, a key therapeutic strategy.
2. **Ligand Properties (Donepezil)**:
    - **Chemical Formula**: $C_{24}H_{29}NO_3$
    - **Mechanism of Action**: Inhibits acetylcholinesterase, increasing acetylcholine levels. Its interaction with amyloid beta fibrils could offer additional neuroprotective effects.

- **Therapeutic Goal**: Alleviate cognitive symptoms and possibly modulate amyloid beta aggregation.

Docking Process

1. **Preparation**:
   - Retrieve 3D structure of 5HOX from **RCSB Protein Data Bank**.
   - Obtain Donepezil's structure from chemical databases (e.g., PubChem).
   - Perform energy minimization to optimize the geometry of both structures.
2. **Tools and Methods**:
   - Use molecular docking software like **AutoDock** and **PyMOL**
   - Define the binding site using the active region identified in 5HOX.
3. **Docking Simulation**:
   - Simulate the interaction between 5HOX and Donepezil.
   - Analyze binding affinities, docking scores, and interaction residues.
4. **Key Observations**:
   - Donepezil interacts with hydrophobic grooves in the amyloid beta fibril.
   - Stabilized by hydrogen bonds and hydrophobic contacts.

Docking Results

- **Binding Affinity**: Donepezil demonstrates moderate binding affinity, suggesting it can interact with amyloid beta fibrils.

```
mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1        -7.6      0.000      0.000
   2        -7.4     13.491     16.944
   3        -7.4     14.078     15.664
   4        -7.3      4.146      8.793
   5        -7.3      4.230      9.464
   6        -7.3      6.946      8.394
   7        -7.3     14.555     16.960
   8        -7.3      9.522     13.644
   9        -7.2     13.553     16.752
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Fig: Docking Analysis

- **Key Interactions**:
    - Hydrogen bonding with amino acid residues.
    - Stabilization via hydrophobic contacts in the fibril core.
- **Biological Implications**: Donepezil's binding may hinder fibril elongation or aggregation, complementing its role in symptomatic relief.
- **Docked Molecule Image**:

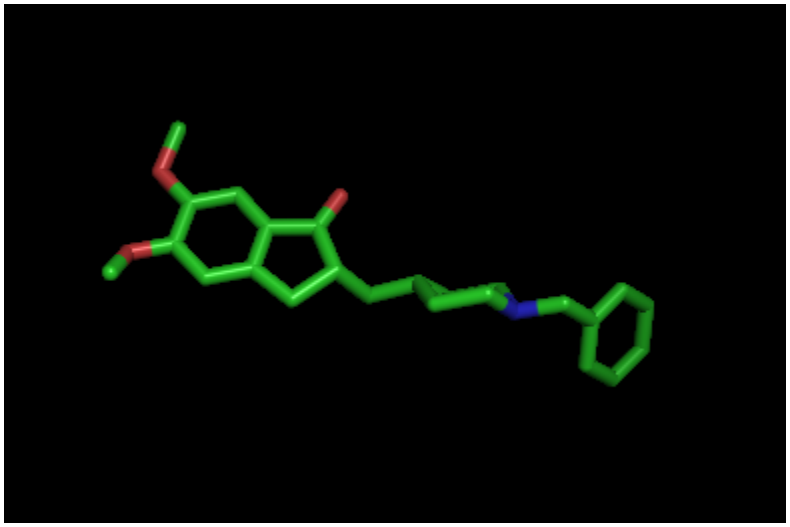

Fig: Docked Molecule

Conclusion

The docking of amyloid beta (5HOX) with Donepezil suggests that, beyond its role as a cholinesterase inhibitor, Donepezil may interact with amyloid beta fibrils, potentially disrupting their aggregation. This secondary mechanism could provide additional therapeutic benefits in Alzheimer’s disease. Further experimental studies and in vivo validation are required to confirm these findings.