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

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).**

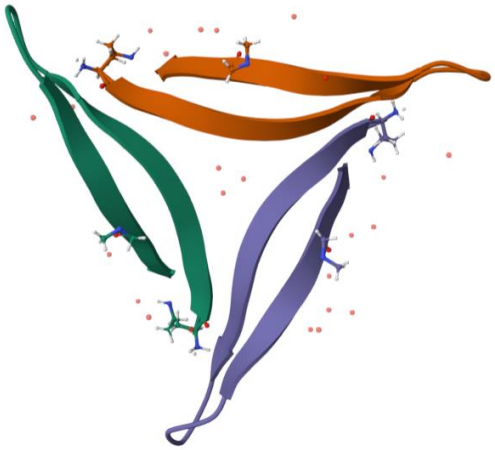

Fig: 3D Structure of the 5HOX protein

- **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**.** Rivastigmine 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**: Rivastigmine | C14H22N2O2 | CID 77991 - PubChem

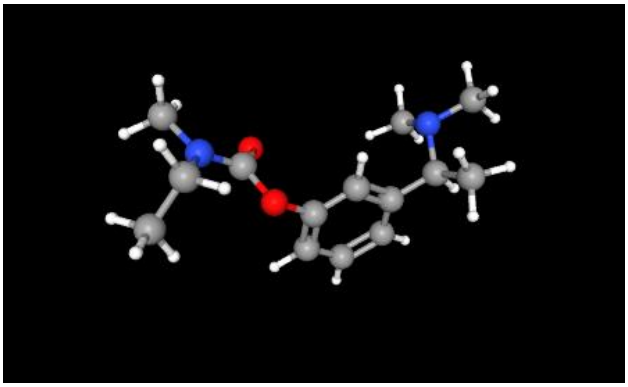

Fig: 3D Structure of Ligand Rivastigmine

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 Rivastigmine 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 (Rivastigmine)**:
    - **Chemical Formula**: $C_{14}H_{22}N_2O_2$
    - **Mechanism of Action**: Rivastigmine is a reversible cholinesterase inhibitor, enhancing cholinergic signaling in the brain.
    - **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 Rivastigmine'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 Rivastigmine.
    - Analyze binding affinities, docking scores, and interaction residues.
4. **Key Observations**:
    - Binds to the hydrophobic pocket of 5HOX.
    - Forms hydrogen bonds with residues like Lysine and hydrophobic interactions with Valine.

Docking Results

- **Binding Affinity**: Rivastigmine 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         -5.6      0.000      0.000
   2         -5.4      2.205      6.556
   3         -5.4      1.879      6.583
   4         -5.3      1.964      2.996
   5         -5.3      3.192      7.258
   6         -5.3      3.024      4.886
   7         -5.3     18.660     22.228
   8         -5.3     21.490     22.461
   9         -5.2     20.764     24.327
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Fig: Docking Analysis

- **Key Interactions**:

- Forms hydrogen bonds with polar residues in 5HOX.
- Stabilized by π-π stacking and hydrophobic interactions near the fibril binding site.

- **Biological Implications**: Rivastigmine may weakly bind to amyloid beta fibrils, providing limited influence on aggregation, with its primary benefit being symptomatic improvement.
- **Docked Molecule Image**:

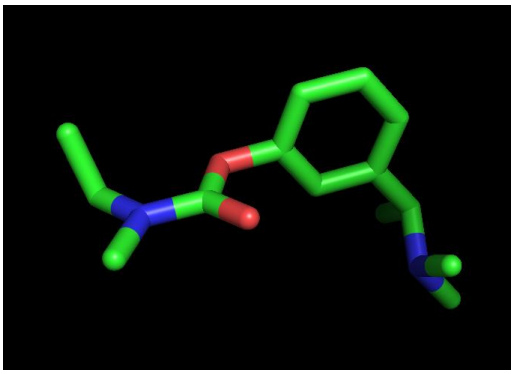

Fig: Docked Molecule

Conclusion

The docking of amyloid beta (5HOX) with Rivastigmine suggests that, beyond its role as a cholinesterase inhibitor, Rivastigmine 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.