INTERACTION OF ESEROLINE WITH BACE1: AN *IN- SILICO* APPROACH FOR ALZHEIMER'S THERAPY

A Thesis Submitted
In Partial Fulfilment of the Requirements for the Degree of

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BIOTECHNOLOGY

by

ISHA PRABHAKAR
(23/MSCBIO/74)

Under the Supervision of
PROF. PRAVIR KUMAR
Professor and Dean of International Affairs
Department of Biotechnology

Delhi Technological University

Department of Biotechnology

DELHI TECHNOLOGICAL UNIVERSITY
(Formerly Delhi College of Engineering)
Shahbad Daulatpur, Main Bawana Road, Delhi-110042, India

May, 2025

DELHI TECHNOLOGICAL UNIVERSITY

(Formerly Delhi College of Engineering)
Shahbad Daulatpur, Main Bawana Road, Delhi-42

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I, Isha Prabhakar, bearing Roll No. 23/MSCBIO/74 hereby certify that the work which is being presented in the thesis entitled " **INTERACTION OF ESEROLINE WITH BACE1: AN *IN- SILICO* APPROACH FOR ALZHEIMER'S THERAPY** " in partial fulfilment of the requirements for the award of the Degree of Master of Science , submitted in the Department of Biotechnology , Delhi Technological University is an authentic record of my own work carried out during the period from January 2025 to May 2025 under the supervision of Prof. Pravir Kumar.

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DELHI TECHNOLOGICAL UNIVERSITY

(Formerly Delhi College of Engineering)
Shahbad Daulatpur, Main Bawana Road, Delhi-42

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Certified that **ISHA PRABHAKAR** (23/MSCBIO/74) has carried out their search work presented in this thesis entitled **"INTERACTION OF ESEROLINE WITH BACE1: AN *IN- SILICO* APPROACH FOR ALZHEIMER'S THERAPY"** for the award of **Master of Science** from Department of Biotechnology, Delhi Technological University, Delhi, under my supervision. The thesis embodies results of original work, and studies are carried out by the student herself and the contents of the thesis do not form the basis for the award of any other degree to the candidate or to anybody else from this or any other University/Institution.

Date:

Prof. Pravir Kumar
Professor and Dean IA
Department of Biotechnology
Delhi Technological University
Delhi - 110042

Prof. Yasha Hasija
Head of Department
Department of Biotechnology
Delhi Technological University
Delhi - 110042

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Isha Prabhakar

23/MSCBIO/74

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ABSTRACT

Alzheimer's disease continues to be a challenging neurological disorder, primarily due to amyloid-ß plaques which accumulate and disrupt brain function. An enzyme that plays a central role in the development of these plaques is BACE1. It initiates the cleavage of APP, setting off a cascade of events. In my attempt to understand potential inhibitors, I ran a molecular docking study to observe how Eseroline, a derivative of physostigmine, might interact with BACE1. I used AutoDock 4.2 to run the simulations, and while the binding energy came out to roughly - 4.79 kcal/mol, which is not particularly strong, but it is definitely worth noting as it still suggested a degree of affinity.

What stood out was the interaction with ARG43, a residue located in the pro-domain of BACE1. This region isn't part of the mature catalytic site, so at first glance, it might not seem relevant but that's precisely what makes it interesting. There's a chance that this kind of binding could impact how the protein matures or stabilizes, which isn't something to overlook. These results are preliminary and entirely based on computational data, but they do raise some intriguing questions. Could Eseroline be influencing BACE1 in an indirect but meaningful way? Possibly. It's something that deserves more attention if we're seriously exploring new angles for Alzheimer's treatment.

LIST OF PUBLICATIONS

1. Poster:

Isha Prabhakar[1], Pravir Kumar[1], "*Exploring Eseroline's Binding Affinity to BACE1 via Computational Docking for Alzheimer's Disease Therapeutic Potential"*

Presented at: SNCI, Jamia Hamdard

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LIST OF ABBREVIATIONS

Abbreviation	Full Form
AD	Alzheimer's Disease
Aß	Amyloid-beta
ACh	Acetylcholine
AChE	Acetylcholinesterase
AICD	Amyloid Precursor Protein Intracellular Domain
ADME	Absorption, Distribution, Metabolism, and Excretion
APP	Amyloid Precursor Protein
BBB	Blood-Brain Barrier
BACE1	β-site APP Cleaving Enzyme 1
BChE	Butyrylcholinesterase
CNS	Central Nervous System
GI	Gastrointestinal
HBD	Hydrogen Bond Donor
HBA	Hydrogen Bond Acceptor
LGA	Lamarckian Genetic Algorithm
LogP	Logarithm of the Partition Coefficient
MMFF94	Merck Molecular Force Field 94
MW	Molecular Weight
NMDA	N-methyl-D-aspartate
PDB	Protein Data Bank
PDBQT	Protein Data Bank, Partial Charges & Torsions
PyRx	Python Prescription – Virtual Screening Tool
RMSD	Root Mean Square Deviation
SDF	Structure Data File

TPSA	Topological Polar Surface Area
3D	Three Dimensional

CHAPTER – 1

INTRODUCTION

Alzheimer's disease (AD) is a hazardous health crisis, characterized by a progressive decline in cognitive function and memory, ultimately leading to a loss if independence [1]. A defining pathological feature of AD is the aggregation of extracellular amyloid-ß (Aß) plaques in the brain, which disrupts neuronal communication and contributes to neurodegeneration [2]. The formation of these Aß peptides is triggered by ß-site amyloid precursor protein cleaving enzyme 1 (BACE1), which cleaves the amyloid precursor protein (APP). BACE1 is therefore a prime therapeutic target for AD [3].

However, the development of effective BACE1 inhibitors has been challenging due to issues such as poor BBB penetration, off-target effects, and toxicity. Therefore, the discovery of novel compounds that can selectively and effectively modulate BACE1 activity is crucial.

This study investigates Eseroline, a metabolite of physostigmine, as a potential BACE1 inhibitor. While eseroline is known for its interactions within the cholinergic nervous system and has potential neurotoxic effects, its molecular structure presents possibilities for BACE1 interaction. Computational docking was employed to examine the binding affinity and interaction profile of Eseroline with BACE1, providing a structural basis for further research [4].

CHAPTER – 2

LITERATURE REVIEW

2.1 Alzheimer's disease

Alzheimer's disease (AD) is often described as slow yet relentless decline in mental functioning. This disease causes neurodegeneration which causes loss of memory, intellectual abilities and independence of the patient [1]. At the biological level, the disease is characterized by two major features— clumps of amyloid-ß (Aß) proteins outside nerve cells and twisted strands of tau protein within neurons. This disrupts the proper cell signalling which in turn leads to brain shrinkage and ultimately neuronal death. The available treatments, such as cholinesterase inhibitor or NMDA receptor antagonists, can help to ease the symptoms but not completely cure the disease [5]. This fact was encouraged scientists to explore a variety of mechanisms like blocking specific enzymes involved in Aß production, developing immunotherapies that help clear protein deposits, etc. AD is a disease which is caused by many overlapping factors like oxidative stress, inflammation, mitochondrial failure and protein misfolding. So, a single treatment approach is not enough. Instead, early diagnosis and a combination of treatment strategies seem to hold the most promise.

2.2 Amyloid-beta

One of the central suspects in Alzheimer's pathology is the amyloid-beta (AP) peptide, especially the Aß42 [6] variant, which is notorious for clumping and damaging neurons and is formed via non-amyloidogenic pathway [7]. These peptides are formed when APP is cut by two enzymes—BACE1 and γ-secretase [8].

APP processing by secretases occurs via 2 pathways: -

- Amyloidogenic Pathway – APP is cleaved by BACE1 followed by γ-secretase to form Aß42 which forms amyloid plaques.

- Non-amyloidogenic Pathway – Cleavage by α-secretase followed by γ- secretase to form Aß40 which is not involved in plaque formation.

Both pathways release AICD, which is the intracellular domain of APP.

The shorter forms of Aß are harmless but sometimes some forms like Aß42 can aggregate together to form toxic clusters that interrupt the brain functions. According to researches these oligomers can:

- disrupt the delicate interneural signalling
- imbalance the calcium signalling
- activate various immune cells, for e.g., microglia which triggers inflammation [9]

The brain's ability to clear Aß plaques becomes less efficient with age which accelerates the deposition of Aß plaques in the brain. Various clinical trials have shown mixed results upon targeting Aß with either BACE1 inhibitors or monoclonal antibodies. Researches are still going on to refine these therapies as well as to find combination with other treatments to increase the effectiveness of the treatment [10], [11].

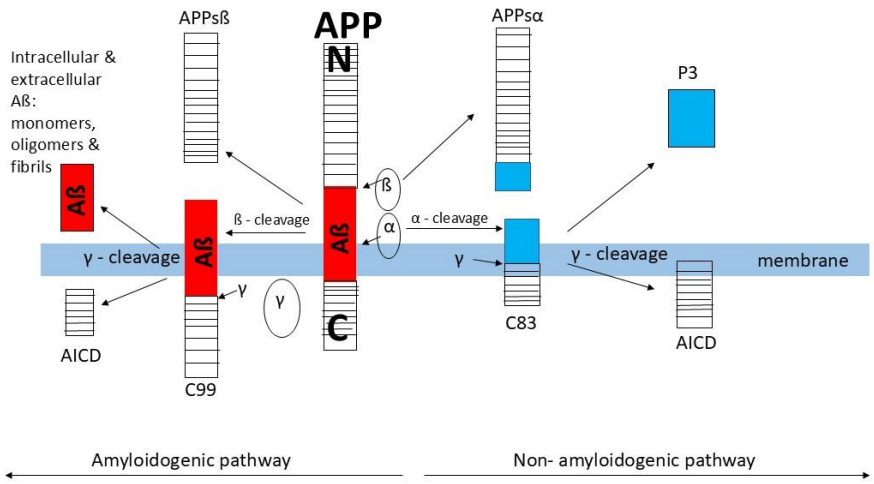

Fig.1 Processing of APP by secretases via amyloidogenic and Non-amyloidogenic pathways

2.3 BACE1

BACE1 is embedded in cell membranes [12] and is involved in the process of amyloid-ß formation. It slices APP molecule to produce first piece of amyloid protein (AP) [13]. So, BACE1 has become a primary target for Alzheimer's drug development [14]Elevated BACE1 activity has been found in the brains of AD patients, strongly linking it to disease progression [15]. On a structural level, BACE1 has a distinctive active site that allows for precise drug targeting. However, this enzyme is involved in more than just Aß production. It also plays roles in neuron communication and the maintenance of myelin. This makes complete inhibition risky, potentially harming healthy brain functions. So, researchers are trying to design inhibitors that either partially block BACE1 or target them specifically in brain [16], [17]. This approach aims to strike a balance between effectiveness and safety of the patient [18], [19].

2.4 Beta-secretase Inhibitors

Beta-secretase Inhibitors are drugs that block BACE1 and in turn amyloid-ß. Many molecules like, aspartic protease, have been designed [20]. While early results were encouraging showing reductions in AP levels many of these drugs didn't make it past late-stage trials. In some cases, they were linked to worsened cognitive function or unpleasant side effects [21]. These outcomes have made it clear that BACE1 inhibition is not as straightforward as it once seemed. Current research is more cautious, focusing on developing inhibitors that are selective, less toxic, and better at reaching the brain.[22], [23]. Scientists are using advanced modelling tools [24]to predict how potential drugs will behave and to design molecules that hit the right targets without unintended effects [25]. Various natural compounds[26] and their synthetic derivatives are also being explored and tested, out of which some have displayed decent lab-based simulations [27], [28], [29], [30], [31], [32]. Some researches are also going on to investigate the use of non-peptide BACE1 inhibitors [33]

2.5 Physostigmine

Physostigmine is a natural compound which is obtained after extraction from Calabar beans [34]It was one of the first cholinesterase inhibitors studied for Alzheimer’s treatment. Its

mechanism involves blocking acetylcholinesterase, enzyme which breaks down acetylcholine, i.e., a neurotransmitter necessary for learning and memory abilities of the brain. Physostigmine inhibits this reaction which helps in maintaining higher acetylcholine levels in the brain. Even after all this, its use was restricted due to its short action duration and significant side effects, especially in the digestive system. Its chemical structure served as the basis for development of better drugs like rivastigmine and eseroline. Recently, physostigmine and its analogues have been revisited as potential multitarget agents. Computational studies now explore how they might inhibit not only AChE but also BACE1, offering a dual-action approach in treating AD [35].

2.6 Eseroline

Eseroline is a semi-synthetic derivative of physostigmine [36]and has garnered interest for its potential dual role in Alzheimer's therapy. Initially studied for its mild opioid properties, eseroline was later found to inhibit AChE, making it relevant in the context of cholinergic-based treatments. Unlike its parent compound, eseroline has a different pharmacological profile and is being examined for its broader therapeutic effects. ln silico studies indicate that eseroline can form stable interactions with key regions of BACE1, especially the catalytic aspartate residues and flap domains. These findings suggest that it can be used as a scaffold for designing multitargeting ligands. Although concerns about its toxicity remain, researchers are interested in modifying its structure to reduce side effects while preserving its therapeutic potential.

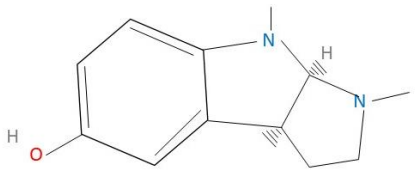

Fig.2 Chemical structure of Eseroline

2.7 Cholinesterase Inhibitors

Cholinesterase inhibitors (ChEls) have long been the standard option for treating the symptoms of Alzheimer's, particularly during the early to middle stages [37]. These drugs majorly block enzymes involved in breakdown of acetylcholine like, acetylcholinesterase and butyrylcholinesterase. This helps in prolonging the action of this neurotransmitter which is usually in low amounts in AD patient's brain. Popular ChEls like donepezil, rivastigmine, and galantamine each have varied modes of action. Rivastigmine, for e.g., targets both AChE and BChE whereas galantamine acts on nicotinic receptors as well. Although they are effective, these drugs have side effects like nausea, fatigue and slowed heart rate. Researchers are constantly searching for new natural or synthetic compound which is both effective as well as safe. Compounds like huperzine A [38] and eseroline are among the ones being tested using in silico techniques like molecular docking and other predictive technologies [39], [40], [41].

2.8 Neurodegeneration

Neurodegeneration in Alzheimer's disease is the result of several harmful processes acting in parallel over time.

One of the earliest and most damaging steps is the deposition of Aß oligomers, which interfere with neural signals transmission [42]. These oligomers can: -

- disrupt receptor function
- imbalance calcium levels
- trigger inflammation via activation of glial cells.

Tau pathology adds to the damage by breaking down the neuron's internal support system, which impairs the movement of nutrients and other essentials along the axon part of the neurons[43]. Inflammatory responses, oxidative stress, and mitochondrial dysfunction also worsen the situation which eventually leads to neural death [44].

Emerging areas of interest include the role of insulin resistance, gut-brain interactions, and impaired autophagy. New therapies are being designed which aim to address not just amyloid

and tau pathology but also these secondary mechanisms that contribute to brain damage [44], [45], [46].

2.9 Amyloid Cascade Hypothesis

It is a central theory in Alzheimer's pathology. It states that the deposition of amyloid-ß, especially Aß42 form, is a trigger that initiates a cascade of harmful events. These events include tau tangles, synaptic failure, inflammation, and ultimately loss of neurons and cognitive abilities. This idea has inspired the development of drugs which are designed to reduce Aß production, prevent its aggregation, or boost its clearance from the brain [47] [5].

Therapies such as BACE1 inhibitors, γ-secretase modulators, are all based on this model [48].

However, the limited success of these drugs has led to new questions. Some researchers believe amyloid build-up might be a symptom rather than the root cause, or that treatment needs to begin much earlier.

Recent updates to the hypothesis account for the role of soluble Aß forms, inflammation, and timing of intervention making it a more comprehensive framework for understanding and treating AD [49], [50].

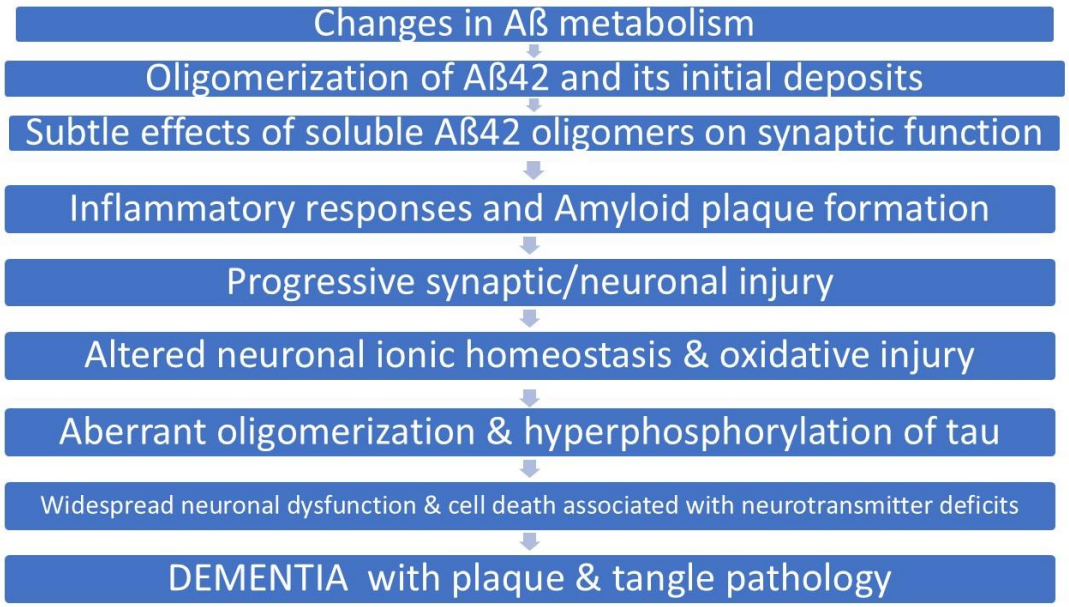

Fig.3 Amyloid Cascade Hypothesis

2.10 Computational Drug Discovery

The integration of computational techniques has revolutionized drug discovery especially in fields like neurology where the brain's complexity causes traditional research practices to be time consuming and expensive. In the case of Alzheimer's disease, these tools are particularly used to model and predict the interaction of potential drug candidates with targets such as BACE1[51], [52], γ-secretase and AChE. Various techniques like virtual screening, molecular docking and pharmacophore modelling allow researchers to test thousands of compounds in their computers before switching to lab work [53]. Softwares like PyRx, AutoDock, Schrödinger, etc help in simulating the binding or fitting of molecules into the enzyme's active sites, estimate their binding energies and even predict their side effects [54]. Recently, artificial intelligence and machine learning have also been integrated into these research studies offering even greater accuracy in predicting absorption, distribution, metabolism and toxicity which are commonly referred to as ADMET properties [55].

2.11 Molecular Docking

Molecular docking is a technique which is used to predict how two molecules, typically a drug (ligand) and a protein (target) will bind or fit together. In Alzheimer's research, it's mainly used to identify compounds that might block the action of disease-related enzymes like BACE1 and AChE [56]. Docking software creates 3D models of how a potential drug might nestle into the active site of a protein, mimicking the lock-and key nature of biochemical interactions[57]. These models are scored based on predicted strength and stability of binding. Tools like AutoDock 4.2, SwissDock, and PyRx are commonly used for such studies. To improve accuracy, these studies are often followed by molecular dynamics simulations and energy calculations like MM-GBSA[58].[21], [22], [59].

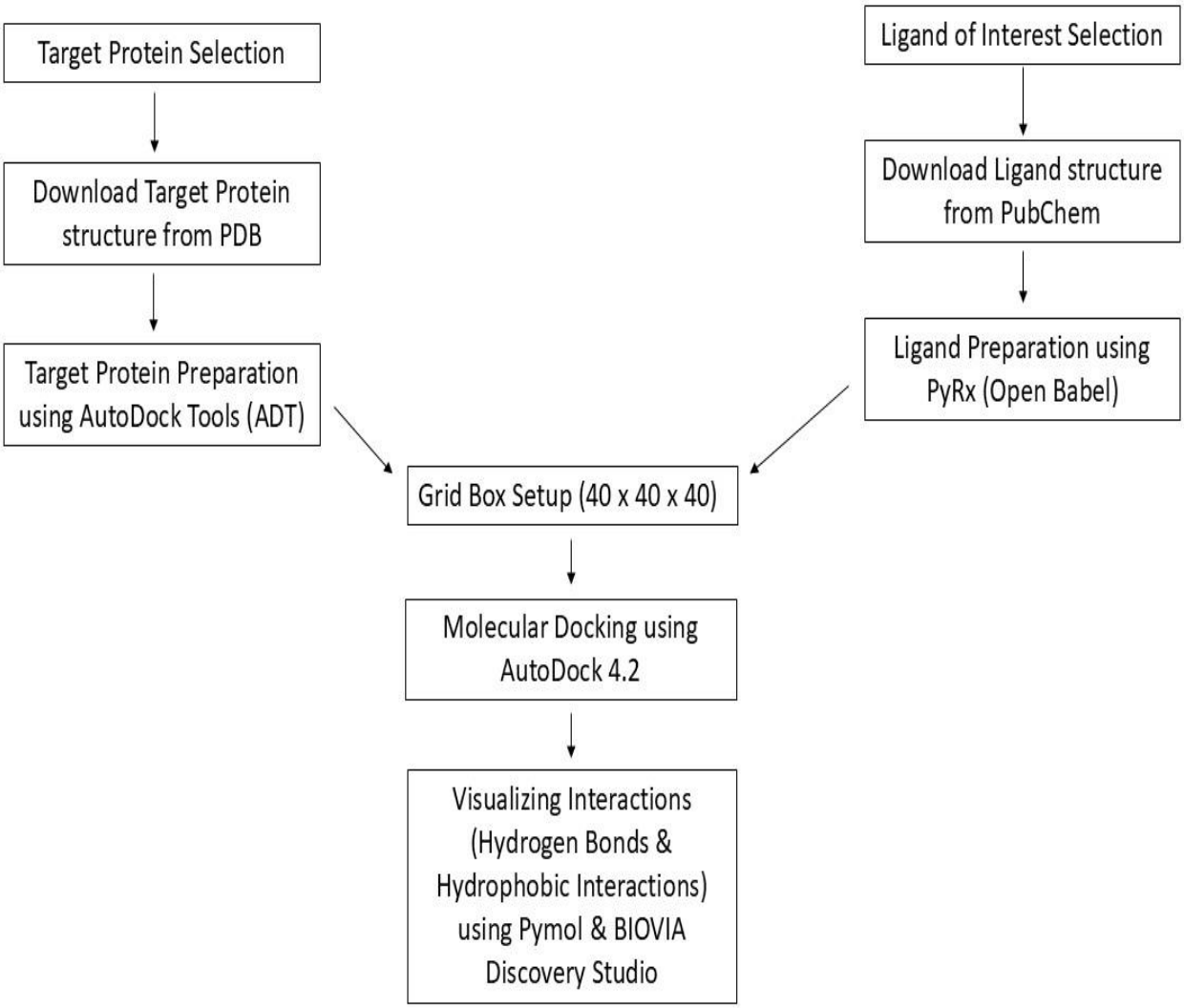

Fig.4 Overview of Molecular Docking methodology used in this study

CHAPTER – 3

MATERIALS & METHOD

3.1 Software Tools Used

The following software tools were employed throughout the study to perform molecular docking and data analysis on a Windows 10 (64-bit) system: -

- **PyRx (Latest Version)** – Utilized for ligand preparation. Ligand was energy-minimized and optimized using the integrated Open Babel engine. It also enabled conversion of molecular formats.
- **AutoDock 4.2** – Used to perform molecular docking simulations between the ligand and the receptor protein. The Lamarckian Genetic Algorithm (LGA) was selected to predict the most favourable binding conformations and calculate binding affinities.
- **AutoDockTools (ADT, Version 1.5.7)** – Applied for protein preparation, including the removal of water molecules, addition of polar hydrogens, Gasteiger charge assignment, and grid box configuration. It also facilitated visualization and analysis of docking results.
- **BIOVIA Discovery Studio Visualizer (Latest Version)** – Employed for visual inspection of docked complexes. It was used to analyse protein–ligand interactions such as hydrogen bonding and hydrophobic contacts.
- **PyMOL (Latest Version)** – Used to visualize 3D structures of proteins and ligands. It also aided in high-resolution rendering of docking poses for publication-quality images.
- **Microsoft Excel (Office 365)** – Utilized for compiling docking scores and organizing tabular results
- **SwissADME** – Used to predict various properties like physiochemical, pharmacokinetics, drug likeliness, lipophilicity, water solubility, and others which are useful in determining the effectiveness of a drug

3.2 Ligand Preparation

The three-dimensional coordinates of Eseroline were obtained from the PubChem database in SDF format. The structure was then transformed into PDB format using PyRx and Open Babel. To ensure a stable conformation, energy minimization was done using the MMFF94 force field. Finally, structure was saved in the PDBQT format with rotatable bonds to allow for conformational flexibility during docking. Fig.5 shows the structure of Eseroline.

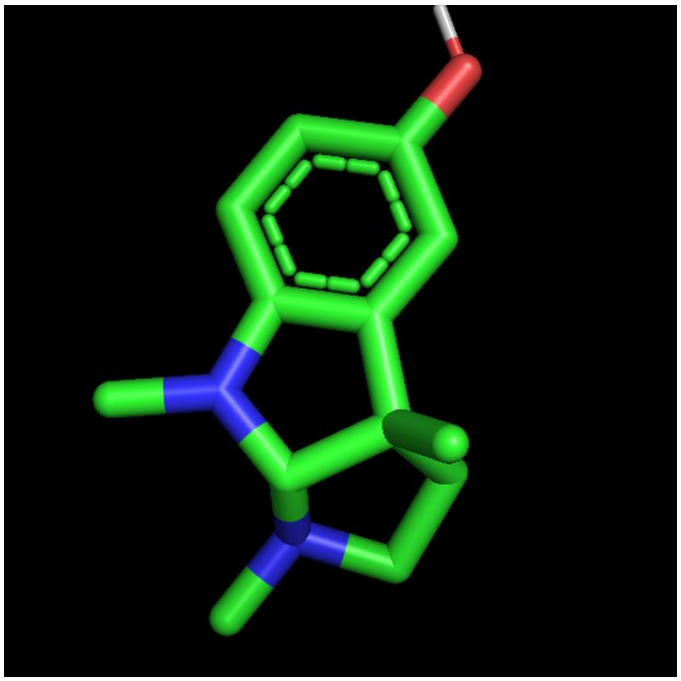

Fig.5 Structure of Eseroline

3.3 Protein Preparation

BACE1 (PDB ID: 1FKN) was retrieved from the RCSB PDB. Before proceeding, all water molecules were eradicated, addition of polar hydrogens and Gasteiger charges were done, and then structure was saved in PDBQT format using Auto Dock Tools (ADT). Fig.6 shows the structure of BACE1 downloaded from PDB. Fig.7 shows the structure of BACE1 prepared for docking.

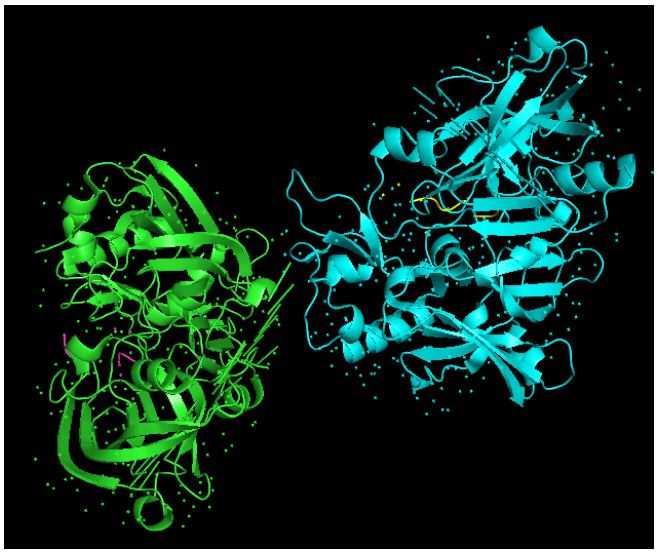

Fig.6 Structure of BACE1 obtained from PDB

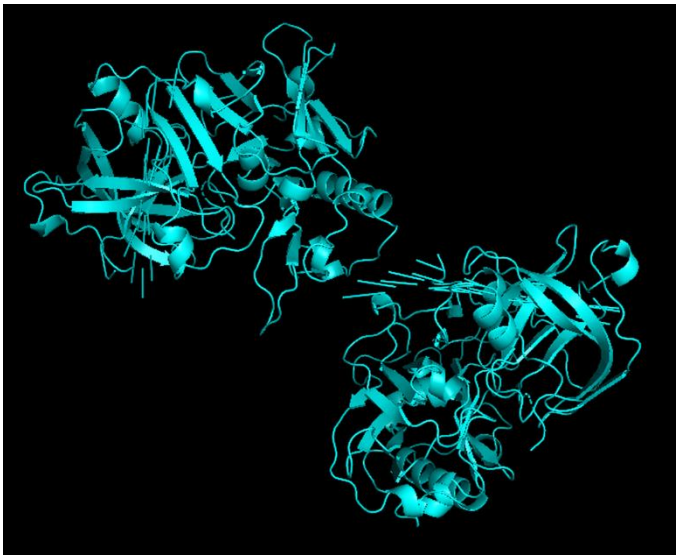

Fig.7 Structure of BACE1 prepared for docking

3.4 Docking Simulation

Docking simulations were conducted using AutoDock 4.2, which utilizes the Lamarckian Genetic Algorithm (LGA). 40 x 40 x 40 grid box was defined around the BACE1 active site to specify the search space. Docking parameters were optimized to ensure thorough exploration of potential binding modes. Fig.8 shows the grid box parameters used.

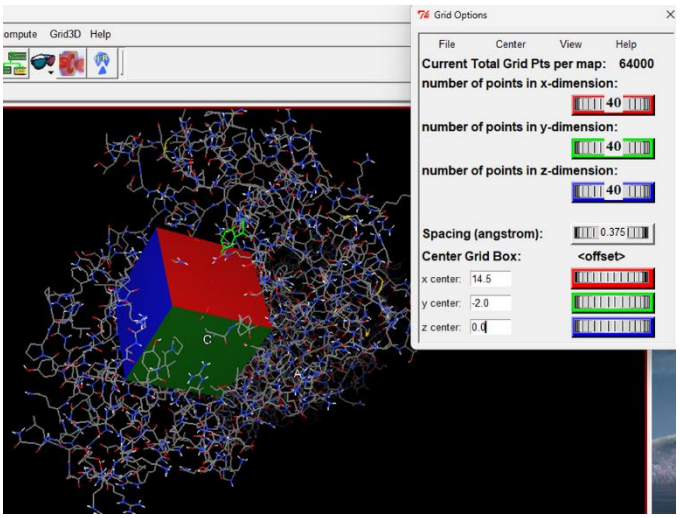

Fig.8 Grid Box setup used for docking

3.5 Analysis

The resulting binding energy (kcal/mol) was calculated to assess the strength of the interaction between Eseroline and BACE1. Key molecular interactions, including hydrogen bonds and hydrophobic contacts, were identified and visualized using BIOVIA Discovery Studio.

3.6 ADME analysis

This web tool is used to predict various properties like physiochemical, pharmacokinetics, drug likeliness, lipophilicity, water solubility, and others which are useful in determining the effectiveness of a drug. Boiled egg made for eseroline represents the p-gp substrate, BBB of the compound in Fig.9.

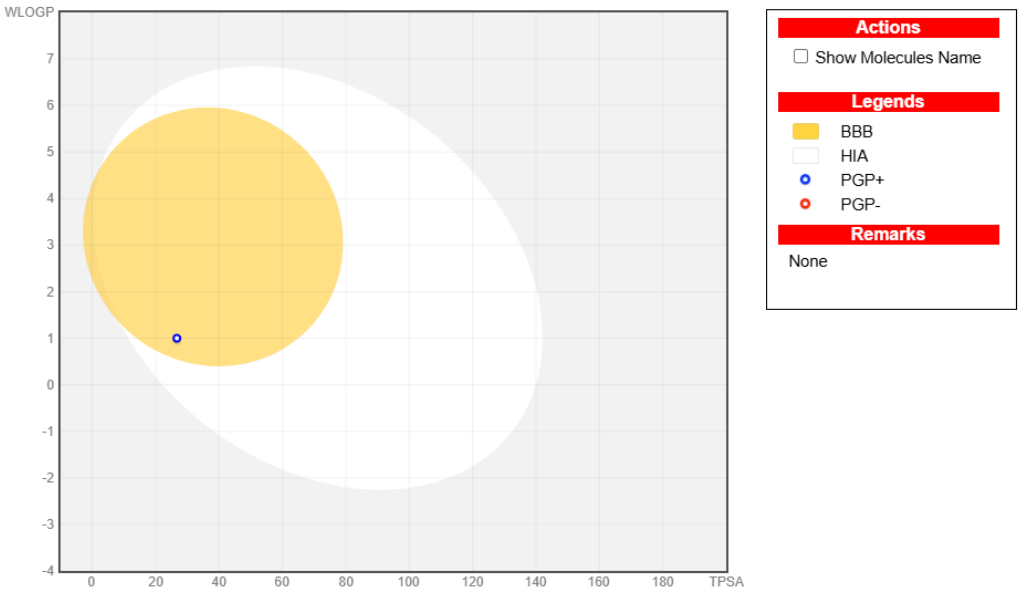

Fig.9 Boiled egg for eseroline

CHAPTER – 4

RESULTS

4.1 Docking Results

The molecular docking simulations of Eseroline with BACE1 yielded a predicted binding affinity of -4.79 kcal/mol, suggesting a stable and moderate degree of interaction between the two molecules.

Interestingly, the compound was found to interact with ARG43P, a residue located within the pro-domain region of BACE1. This region is not part of the catalytic active site, which is typically defined by the aspartic acid residues ASP32 and ASP228, responsible for substrate cleavage. Although ARG43 does not directly participate in enzymatic activity, its location in the pro-domain implies potential relevance in protein folding, maturation, or structural regulation. Fig.10 shows the selected binding pose of Eseroline with BACE1.

Fig.10 Selected binding pose of Eseroline's binding with BACE1

The selected binding pose, representing the most energetically favourable configuration, demonstrated stable binding of eseroline within the BACE1. Fig.11 shows the binding of Eseroline with BACE1 up close at ARG43P.

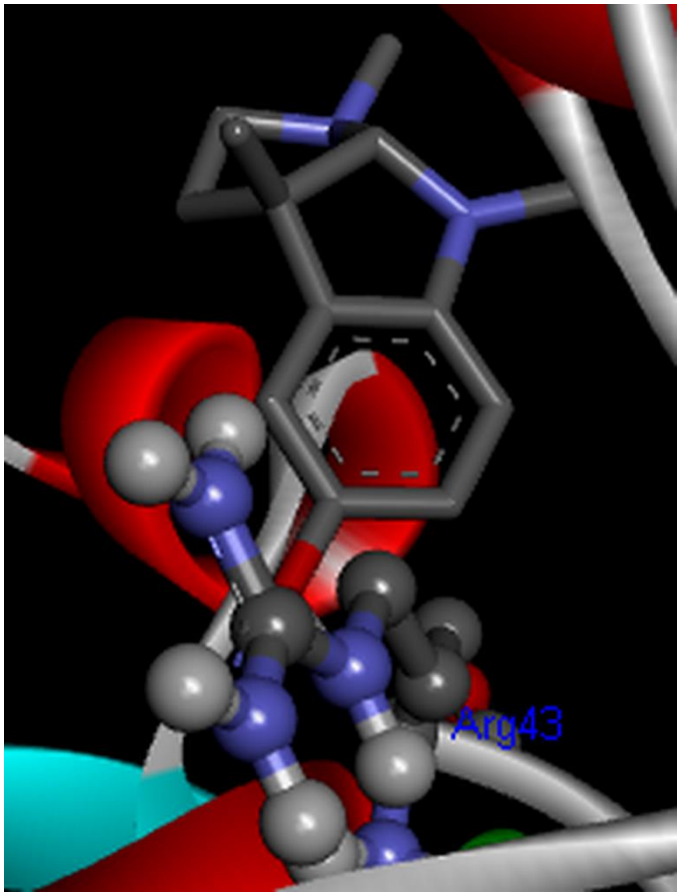

Fig.11 Close up view of binding of Eseroline with BACE1 at ARG43P

In this pose, eseroline was observed to form four hydrogen bonds with specific amino acid residues, namely ASP259, LYS256, ARG43P and SER182. Hydrogen bonds are illustrated in Fig.12. These particular hydrogen bonding interactions are considered significant, as these residues are located either within or in close proximity to the catalytic cleft of BACE1, the site of its enzymatic activity.

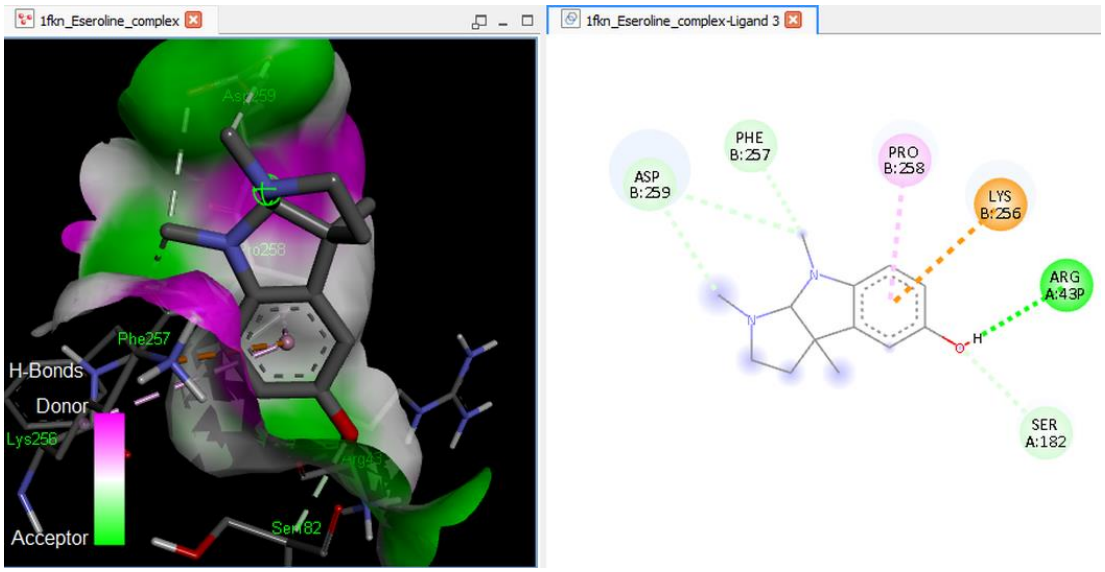

Fig.12 Hydrogen bonds

In addition to the polar interactions mediated by hydrogen bonds, eseroline was also predicted to participate in hydrophobic interactions with residues such as PHE257 and ARG43P. Hydrophobic interactions are illustrated in Fig.13.

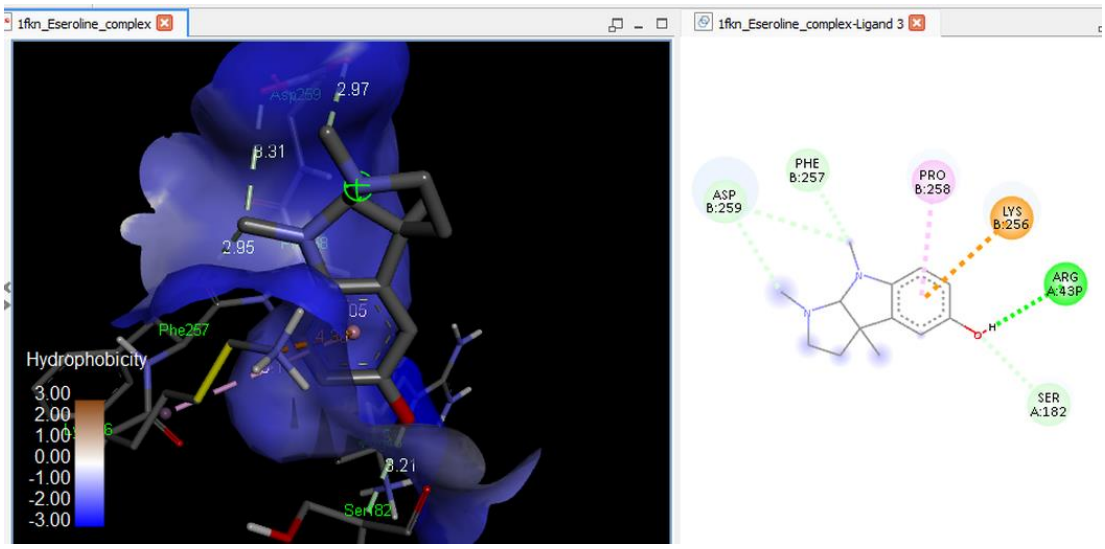

Fig. 13 Hydrophobic interactions

These nonpolar contacts are believed to enhance the affinity of eseroline for the hydrophobic environment of the BACE1 binding pocket. Furthermore, the limited accessibility of the

binding site to solvent molecules implies that eseroline may adopt a tight binding conformation, potentially capable of effectively occluding access for APP and thus inhibiting BACE1's enzymatic function.

The calculated RMSD values between the top-ranked docked poses were consistently below 2 Å, providing evidence for the reproducibility and convergence of the docking simulations. While the predicted binding affinity of eseroline with BACE1 is moderate, the spatial orientation of eseroline within the active site and the nature of the predicted molecular interactions suggest a degree of structural complementarity. Table 1 presents the top-ranked docking poses of eseroline with BACE1, along with corresponding binding energies and RMSD values.

TABLE I. DOCKING RESULTS OF ESEROLINE WITH BACE1 SHOWING BINDING ENERGIES AND RMSD VALUES

Rank	Sub-Rank	Run	Binding Energy	Cluster RMSD[a]	Reference RMSD[a]	Grep Pattern
1	1	6	-4.79	0.00	37.49	RANKING
1	2	8	-4.79	0.02	37.49	RANKING
1	3	10	-4.79	0.03	37.48	RANKING
1	4	5	-4.79	0.02	37.48	RANKING
1	5	1	-4.79	0.01	37.49	RANKING
1	6	2	-4.79	0.05	37.46	RANKING
1	7	4	-4.78	0.02	37.48	RANKING
1	8	3	-4.78	0.04	37.46	RANKING
1	9	7	-4.78	0.02	37.48	RANKING
1	10	9	-4.78	0.05	37.45	RANKING

[a] RMSD – stands for Root Mean Square Deviation

These findings suggest that Eseroline does not inhibit BACE1 through direct interaction with its active site but may exert influence by engaging peripheral or regulatory regions of the enzyme. This could point toward an allosteric or indirect modulation mechanism, highlighting the need for further in vitro or in vivo validation.

4.2 ADME Properties Analysis

ADME analysis of Eseroline shows significant results are shown below in Table II. All properties of ADME such as pharmacokinetics, drug likeliness, water solubility, and other properties are mentioned.

TABLE II. ADME AND DRUG-LIKELINESS PROPERTIES OF ESEROLINE PREDICTED BY SWISSADME

Property	Value	Interpretation
Molecular Formula	$C_{13}H_{18}N_2O$	—
Molecular Weight (MW)	218.29 g/mol	Drug-like (within Lipinski range)
TPSA (Å²)	26.71	Suggests good cell membrane permeability
H-Bond Donors / Acceptors	1 / 2	Acceptable for oral bioavailability
Rotatable Bonds	0	Rigid structure, favourable for binding
LogP (Consensus)	1.66	Moderate lipophilicity
Water Solubility (ESOL)	–2.50 (Soluble)	Acceptable for oral administration
GI Absorption	High	Suitable for oral drugs
BBB Permeability	Yes	May cross the blood-brain barrier
CYP2D6 Inhibitor	Yes	Could affect drug metabolism
Bioavailability Score	0.55	Moderate
Rule Violations (Lipinski, etc.)	0	Drug-like compound
PAINS / Brenk Alerts	0 / 0	No structural toxicity flags
Synthetic Accessibility	2.96	Easy to synthesize

CHAPTER – 5

DISCUSSION

The moderate binding affinity of Eseroline for BACE1 suggests a potential interaction. The formation of hydrogen bonds with key active site residues and hydrophobic interactions indicates a degree of structural complementarity that may facilitate binding. The low solvent accessibility of the binding pocket suggests that Eseroline could potentially interfere with the binding of APP to BACE1.

These computational findings provide preliminary evidence supporting Eseroline's potential as a BACE1 binder. However, it is important to acknowledge the limitations of docking studies. Further studies are necessary to support these results and confirm Eseroline's inhibitory activity and therapeutic potential in Alzheimer's disease.

The results obtained point toward ARG43, a residue located in the pro-domain rather than within the catalytic core, i.e., active site residues (like Asp32 or Asp228). This might not seem significant at first glance because the pro-domain is typically cleaved off as BACE1 matures but it's not completely irrelevant. Regions like this can still influence how a protein folds, stabilizes, or behaves before activation. In fact, the binding energy of about –4.79 kcal/mol, while not remarkably strong, does suggest a non-random interaction.

What's particularly intriguing is that ARG43 isn't just structurally isolated—it might be playing a role in shaping how BACE1 behaves in its early folding or trafficking stages. If Eseroline is capable of binding there consistently, it might hint at an indirect modulation pathway. That sort of mechanism, acting outside the active site, is less likely to disrupt off-target enzymes and could, in theory, offer a gentler way to tweak BACE1 activity. I'll have to emphasize that all of this is computational study. The real test lies in follow-up experiments: for example, mutating ARG43 or altering the pro-domain to observe downstream effects. Until such work is done, this remains a hypothesis worth investigating further but not yet something to draw firm conclusions from.

CHAPTER – 6

CONCLUSION

In this study something quite unexpected came out of the docking analysis with Eseroline. Unlike typical inhibitors that go straight for the catalytic core of BACE1, where residues like Asp32 and Asp228 do their job, Eseroline didn't even go near that region. Instead, it latched onto ARG43, which is part of the pro-domain. That region is usually chopped off as the enzyme matures, so on the surface, it might not seem all that important. But actually, it could be.

Even though ARG43 isn't involved in direct catalysis, it's located in a part of the protein that might influence how the enzyme folds or stabilizes. That sort of peripheral binding might not shut the enzyme down directly, but it could still nudge its behaviour, maybe affecting the way it assembles or behaves under normal biological conditions.

The binding energy was - 4.79 kcal/mol is enough to suggest that there's an interaction worth paying attention to. So rather than working as a classical active site inhibitor, Eseroline might be tweaking things from the side-lines, which is intriguing.

What's worth pointing out here is that previous BACE1 inhibitors, especially those targeting the active site, have run into issues, mostly with off-target effects or toxicity. That's a common problem when we aim for highly conserved active regions. So, a molecule that binds somewhere else, like Eseroline does, could open up a new angle for therapeutic intervention, maybe a bit more subtle, but possibly safer.

We can't draw hard conclusions from docking alone so to back up our claims and assure our findings, we'd need experiments like mutagenesis of ARG43, protein expression studies, etc.

This study points to an interesting hypothesis that deserves further in vivo and in vitro experimentations.

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Prof. Prakash Babu Phanithi
Secretary General (HQ), SNCI

CURRICULUM VITAE

Isha Prabhakar

+(91)8595607132
ishaprabhakar2002@gmail.com
23/MSCBIO/74

EDUCATION

M.Sc.(Biotechnology)	2023-2025	Delhi Technological University, New Delhi	
B.Sc.(Biochemistry)	2020-2023	Sri Venkateswara College, DU	76.5 %
CBSE (Class XII)	2020	St. Cecilia's Public School	95.4 %
CBSE (Class X)	2018	St. Cecilia's Public School	92.6 %

SKILLS

Technical Skills

-Wet Lab Techniques: DNA Isolation, Gel Electrophoresis, UV-Vis Spectrophotometry, ELISA, Cell Culture, Aseptic Techniques, Compound Microscopy

-Scientific Software: MS Word, MS Excel (formulas, pivot tables), MS PowerPoint

Computational & Bioinformatics Skills

-Molecular Docking: AutoDock 4, AutoDockTools (ADT), PyRx, Discovery Studio, PyMOL

-Structural Analysis: Ligand Preparation, Protein Structure Preparation, Active Site Identification, Binding Energy Evaluation, PDB File Analysis

-Data Science: Python (NumPy, Pandas, Matplotlib, Seaborn), Basic SQL

-Data Handling: Data Cleaning, Visualization, Interpretation, Report Preparation

Soft Skills

-Research & Critical Thinking, Problem Solving, Scientific Writing & Documentation, Presentation Skills, Communication & Public Speaking, Team Collaboration, Time Management

RELEVANT EXPERIENCE & PROJECTS

- **Research Project – Alzheimer's Drug Targeting (M.Sc. Project)**

Delhi Technological University | Jan 2024 – Present

- Conducted molecular docking of Eseroline with BACE1 using PyRx and AutoDock 4.

- Analysed binding energies, interaction types (H-bonding, hydrophobic), and visualized results.

- Compiled and interpreted docking data using MS Excel and Discovery Studio.

- Created data-driven visuals and tables for poster and conference submission.

- **Academic Presentations & Analysis**

- Delivered research presentations involving data collection, trend analysis, and graphical representation.

- Used Excel and PowerPoint to summarize scientific outcomes.

CERTIFICATES & ACHIEVEMENTS

- **Certificate of Appreciation – Poster Presentation – Jamia Hamdard & SNCI Delhi Chapter (Apr 2025)**
  Presented research on Alzheimer's therapy in the Young Investigator/Poster Session at the National Symposium on Neurochemistry.
  Certificate of Appreciation_Jamia Hamdard & SNCI Delhi Chapter
- **Hands-on Workshop on Bioinformatics & Molecular Docking – Biosoc-DTU (Apr 2025)**
  Participated in hands-on training focused on molecular docking and computational biology.
  Certificate of Participation_Biosoc-DTU
- **Python Fundamentals Certificate – Coding Blocks (Mar 2025)**
  Completed a foundational programming course covering data types, control flow, loops, functions, and data structures.
  Python Fundamentals_Coding Blocks
- **- Webinar on Offbeat Career Options in Science – Sri Venkateswara College, University of Delhi (Aug 2022)**
  Attended a career-oriented webinar exploring unique paths in scientific research and industry.
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