IDENTIFICATION OF SERPENTINE AS PROMISING BACE 1 INHIBITORS: A COMPUTATIONAL APPROACH TO EXPLORE NOVEL STRATEGIES FOR ALZHEIMER'S THERAPY

A Dissertation

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by

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DECLARATION

I, Sushankita Srivastava 24/MSCBIO/08 hereby certify that the work which is being presented in the thesis entitled **"Identification of Serpentine as Promising BACE 1 Inhibitors: A Computational Approach to Explore Novel Strategies for Alzheimer's Therapy"** in partial fulfillment 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 2024 to 2026 under the supervision of Prof. Pravir Kumar.

The matter presented in the thesis has not been submitted by me for the award of any other degree of this or any other Institute.

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CERTIFICATE BY THE SUPERVISOR

This is to certify that the Dissertation Project titled **"Identification of Serpentine as Promising BACE 1 Inhibitors: A Computational Approach to Explore Novel Strategies for Alzheimer's Therapy"** which is being submitted by Sushankita Srivastava 24/MSCBIO/08, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Science is a record of the work carried out by the student under my supervision. To the best of my knowledge, this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

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"IDENTIFICATION OF SERPENTINE AS PROMISING BACE 1 INHIBITORS: A COMPUTATIONAL APPROACH TO EXPLORE NOVEL STRATEGIES FOR ALZHEIMER'S THERAPY"

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ABSTRACT

Aim: This study aims to identify and characterize serpentine as potential BACE1 inhibitors by in-silico approach as an alternate therapeutic approach towards Alzheimer's. It is a neurodegenerative condition involving multiple factors and currently there is no cure. It is primarily driven by abnormal production and buildup of amyloid β peptides that are formed by sequential processing of APP mediated by the action of BACE1 and γ-secretase. While BACE 1 has been identified as potential therapeutic target molecule and many drug candidates have been tested in clinical trials but they show limited cognitive benefits and many cases produced off-target side effects. Due to this, the attention is shifted toward naturally occurring molecules that may offer safer and more effective inhibition of BACE 1. In this study, serpentine, an indole alkaloid found in Catharanthus roseus and its stereoisomers were evaluated using an integrated insilico screening approach. A PubChem similarity search with 90 percent Tanimoto similarity threshold produced 116 serpentine related compounds, which were further shortlisted through ADME based filtering to select drug like candidates. Molecular docking was performed that utilized Lamarckian genetic algorithm with Verubecestat as the reference molecule. Eleven shortlisted compounds show stronger binding affinities than the reference inhibitor, with serpentine (PubChem CID 73073) showing the highest affinity. Analysis of protein ligand interactions revealed the involvement of BACE 1 residues, including Tyr71, Gln73 and Thr232. Conclusively, this novel findings indicate that serpentine and its stereoisomers may serve as promising lead molecules for designing future BACE1-focused treatments for Alzheimer's disease and is strongly advised for in vivo analysis.

Result: During the course of our study, initially 116 related compounds were produced and further shortlisted based on ADME analysis left us with 14 compounds which were all BBB permeable. Docking analysis of these compounds identified eleven with binding affinities higher than the reference, Verubecestat (-7.946kcal/mol), with the highest affinity of -9.329 in kcal/mol.

Conclusion: Among the eleven identified compounds, Compound 1 was the most effective treatment for Alzheimer's disease, with the highest binding affinity and being BBB permeable. We suggest validating these findings through in vivo experiments.

List of Publications

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LIST OF ABBREVIATIONS

APP	Amyloid Precursor Protein
Aβ	Amyloid beta
BBB	Blood-Brain Barrier
NFT	Neurofibrillary Tangles
AD	Alzheimer Disease
FDA	Food and Drug Administration
BACE1	Beta-site Amyloid Precursor Protein Cleaving Enzyme 1
IC50	Half Maximal Inhibitory Concentration
PS1	Presenilin 1
PS2	Presenilin 2
CSF	Cerebrospinal Fluid
AchE	Acetycholinesterase enzyme
Ach	Acetylcholine
CNS	Central Nervous System
ADMET	Absorption, Distribution, Metabolism, Excretion, Toxicity
NMDA	N-methyl-D-aspartate
SDF	Structural Data File
HPLC	High Performance Liquid Chromatography
TPSA	Topological Polar Surface Area
CADD	Computer aided drug design
LGA	Lamarckian genetic algorithm
SMILES	Simplified molecular input line entry system
GI	Gastrointestinal Absorption
PDB	Protein Data Bank
CID	Compound Identity Number

ROS	Reactive Oxygen Species
LPS	Lipopolysachharide
PK	Pharmacokinetics
UHPLC	Ultra High Performance Liquid Chromatography
PDBQT	Protein Data Bank, Partial charge and Atom Type
GUI	Graphical User Interface
Asp	Aspartate
Tyr	Tyrosine
Leu	Leucine
Gln	Glutamine
Thr	Threonine
PAINS	Pan Assay Interference compounds
UCSF Chimera	University of California, San Francisco Chimera

1. INTRODUCTION

Alzheimer's disease (AD) is the major contributor to dementia, particularly in individuals with an age above 65 years [1]. It gradually progresses and interlinks multiple pathological changes in the brain [1]. The condition is primarily marked by the extracellular buildup of amyloid-beta (Aβ) peptides whereas intracellular accumulation of tau proteins which become excessively phosphorylated [1]. Aβ aggregates to form neuritic plaques and hyperphosphorylated tau give rise to neurofibrillary tangles. These two abnormalities are considered as the main hallmark of AD. The medial temporal lobe (mainly hippocampus which involves in memory formation) is most affected initially. As the disease advances, these pathological changes spread to various neocortical areas. The combined impact leads to a gradual decline in thinking, memory and behaviour problems [2].

AD is a multifactorial disorder. It is caused by protein misfolding, acetylcholinestrase deficiency, oxidative stress, neuroinflammation, disrupted glutamate activity, reduced insulin response, changes in gut bacteria, and impaired mitochondria function. There are various hypothesis related to this. The amyloid cascade hypothesis suggested that AD starts when BACE1 enzyme cuts amyloid precursor protein (APP) which is subsequently processed by γ-secretase within the membrane leads to Aβ40 and Aβ42 production [1]. These accumulate outside the cells and form plaques. Aβ42 can clump easily and trigger oxidative stress [1].

BACE1 is an aspartyl proteases belong to pepsin family. In neurons, it is found on the plasma membrane and in endosomes [3]. Since BACE 1 initiates the amyloidogenic pathway, it became a potential therapeutic target. Several inhibitors were developed which lower Aβ levels in early studies. However in large clinical trials, they did not show meaningful cognitive benefits. Some even produce adverse effects like liver toxicity, mood alterations which lead to early termination of trials [4].

Serpentine is a monoterpenoid indole alkaloid found in Catharanthus roseus. It is a medicinal plant that has a diverse range of bioactive phytochemicals. This includes well studied alkaloids such as vinblastine, ajamalicine, and serpentine which arise from coordinated biosynthetic pathways [5]. Among these, serpentine has neuroactive properties which at low micromolar concentration inhibit acetylcholinesterase, this suggest its ability in providing neuroprotection [6].

This study aimed to identify serpentine and its structural stereoisomers with enhanced inhibitory potential against BACE1 using computational workflow. A structurally similar compound library was screened using PubChem and all docking scores were evaluated relative to the reference molecule (Verubecestat). The objective was to identify compounds that could block BACE 1 more effectively and provide a better treatment option for AD. The analysis included similarity based screening, ADME evaluation, molecular docking and detailed visualization of protein ligand interactions.

2. REVIEW OF LITERATURE

2.1 Alzheimer's Disease: Pathophysiology & Current Therapies

Alzheimer's Disease (AD) is a gradual, permanent and incurable condition, and is considered to be the most frequent cause of dementia [7]. Though it occurs mostly in elderly individuals, it is not an inevitable result of aging, rather a disorder in which functional and cognitive impairment occurs slowly, often long before clinical illness becomes evident. Current understanding suggests that AD follows a very long preclinical course before actual symptoms arise, where a number of pathological changes build up, which explains why diagnosis is delayed until neuronal damage is significant [8].
Alzheimer's disease (AD) is an advancing neurodegenerative disease and a dominant form of dementia in aged people [9]. 50 million people are suffering from dementia globally and 50-70% cases are due to AD. Its occurrence increases with age affecting 10% of people who are older than 65 years and roughly 50% of those who are above 85 and it is expected that cases will increase from 9.3% in 2020 to 16.0% in 2050 [10]. The occurrence of AD doubles every 5 years after the age of 65, and it is slightly higher in females [1] [10]. It is a crucial worldwide concern which continues to rise. Global estimates also show that nearly 130 million people might get affected by 2050, especially in low to middle income countries. Apart from its epidemiological effect, AD's prolonged duration, progressive impairment and additional care needs put a heavy burden on families, health facilities and society [11].

Pathologically, two main important features of AD are extracellular β-amyloid plaques and hyperphosphorylated tau protein which make the intracellular neurofibrillary tangles. These (lesions) are associated with synaptic abnormalities, activation of microglial cells, neuronal loss and degeneration of pyramidal neurons, suggesting that AD does not follow a single molecular path but rather occurs due to a wider neurodegenerative cascade [8]. The advancement of the disease is further accompanied by features such as blood-brain barrier disruption, inflammatory alterations and metabolic changes. All these mechanisms together weaken synapses, disrupt neuronal transmission, eventually causing extensive neurodegeneration [11].

Clinically, people with AD mainly show memory related cognitive issues. Early signs include depression or anxiety, altered sleeping habits and pulling away from social activities. Clinical symptoms of AD typically start with subtle episodic and temporary memory impairment, including learning and remembering new information. Later, as the illness progresses, language, visual abilities and direction are all affected and behavioral changes along with growing dependence in everyday activities become more noticeable [12]. End stages may also include symptoms like impaired mobility, convulsions, substantial functional deterioration and hallucinations. The progressive pattern of these symptoms indicates underlying expansion of synaptic loss throughout limbic and cortical networks [13]. As the condition advances, symptoms get deteriorate and may lead to serious memory loss, hallucinations, delusional thinking, and noticeable changes in behavior and emotions. Some individuals may experience difficulties in skills like recognizing places or objects, speaking, decision making or movement [14][15]. Regrettably, there is no cure for AD yet, and individuals are diagnosed at a late and more severe stage and live for an average time of 4 to 8 years [16].
Different ideas have been suggested to explain how AD develops as it is complex in nature. AD can be subdivided into two main types: familial which contributes to 1-5% of AD cases and sporadic forms over 95% of cases [14]. Familial AD is linked to rare inherited changes in amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes, showing symptoms from age 30 to 65 and advancing quickly [17]. Whereas, sporadic AD also known as late onset AD, usually occurs

after the age of 65 and is influenced by a combination of genetic risks, environmental factors, and various other factors[18].

The pathogenesis of AD includes various interconnected mechanisms at molecular level that collectively contribute to dysfunction of neurons and their death:

- **Amyloid Cascade Hypothesis**

  Amyloid mediated neurodegeneration mechanism is still the most widely accepted theory for explaining AD pathogenesis involving accumulation of β-amyloid protein. The amyloid precursor protein, also known as APP is a type-1 membrane spanning protein which is expressed in different types of cells and undergoes two diverse cleavage pathways in the central nervous system (CNS) [19].

  The first one is non-amyloidogenic pathway in which a soluble sAPPα and a transmembrane C83 fragment are produced upon cleavage of APP by α-secretase. Subsequently, C83 undergoes second round of cleavage by γ-secretase producing p3 and the APP intracellular domain. This route does not generate β-amyloid peptides [20].

  Amyloidogenic pathway, on the other hand involves β-secretase or BACE1, which splits APP into a membrane-bound C99 segment and a soluble sAPPβ fragment. Now γ-secretase produces amyloid-beta protein by cleaving C99, directly connects it to synthesis of plaque-forming peptides [21].

  Although this hypothesis is the dominant model for AD, it has faced some criticism with evidences indicating that amyloid-beta accumulation is solely not responsible for disease progression. However, APP processing and dysregulation of amyloid are still considered the central mechanisms for therapeutic development [22].

  Role of Secretases

  α-secretase, among other secretes, is involved in non-amyloidogenic and protective pathway as it does not allow APP processing towards amyloid-beta production. In contrast, β-secretase plays a direct role in amyloidogenic route, making BACE1 a primary focus for molecular and pharmacological study in AD. γ-secretase which works in both the pathways, is also a critical factor for determining the amount of amyloid-beta as it carries out the final cleavage of C99 to generate amyloid-beta peptides [23].

  Formation of Amyloid-beta Peptides

  Amyloid-beta fragments which are generated from APP also show variation. Peptides produced by γ-secretase cleavage may vary from 37 to 42 amino acids in length, with longer fragments like Aβ40 and 42 being more likely to undergo self-aggregation and form fibrils [24]. Consequently, there are several biological effects due to this trait. A shift towards aggregation and buildup of Aβ42 could occur due to familial mutations in APP synthesing and associated genes, leading to senile plaque development in brain tissue [25].

  With further advancements in our understanding, it is being widely recognized that both soluble oligomeric and insoluble plaques are responsible for amyloid-beat toxicity. While both of both of them are connected to hyperphosphorylation of tau and oxidative stress, oligomers obtained from AD neurons can cause serious implications like long-term potentiation, disruption of dendritic spines and synaptic dysregulation [26].

- **Cholinergic Hypothesis-**

  According to cholinergic hypothesis of AD, low levels of acetylcholine lead to abnormal cholinergic neurotransmission. Acetycholinesterase (AchE) enzyme degrades acetylcholine (Ach) in synaptic cleft [1]**.**

- **Other Mechanisms:**

  While amyloid-beta plays a major role in AD, additional processes also influence the progression

of this disease. Most often these processes are inked to amyloid-toxicity. For instance, buildup of beta-amyloid can cause abnormal production of reactive oxygen species, mitochondrial impairment, resulting in neuronal damage [27]. Oxidative stress may also boost phosphorylation of tau protein and APP processing by amyloidogenic pathway which further enhances the degeneration. In a same way, gradual damage of neurons, synaptic dysfunction and cytokine storm are all outcomes of neuroinflammation mediated by microglial cells. Neuroinflammation is quite significant since microglia also aid in elimination of amyloid, suggesting that in AD inflammation can be both beneficial as well as adverse [28].

Together, these pathways show AD is caused by combining network of amyloid deposits, secretase activity, aggregation of proteins and oxidative damage, rather than a single event.

The majority of current therapeutic strategies manage only symptoms. Various FDA approved medications like donepezil, rivastigmine, galantamine, memantine and namzaric have been used in symptomatic treatment. Donepezil, rivastigmine, galantamine and namzaric are AchE enzyme inhibitor and memantine is a NMDA receptor antagonist [1][29]. Combinational treatments such as acetylcholinesterase inhibitors like rivastigmine, donepezile along with memantine offer some boost in function or cognition, however the root cause of the disease is still not corrected [30]. This limitation is primarily due to the multifaceted pathway of AD involving accumulation of amyloid, neuronal inflammation, vascular injury, mitochondrial failure and tau phosphorylation which intensify over time. Many potential medications have also been unsuccessful due to poor bioavailability, low BBB penetration and low specificity towards target. Hence, instead of depending solely on single-pathway treatment, research is shifting in the direction of early biomarker based detection, prevention and multi-targeted therapies [31]. New drugs which are currently under review including sodium oligomannate, aducanumab, lecanemab and donanemab, they are designed to alter the alzheimer's development by providing targeted therapy[14][16].

Overall, the present literature highlights the complex and degenerative nature of AD with several societal and clinical implications. Its pathophysiology, slow development and lack of actual treatment make it a critical issue in neurosciences compelling for development of early diagnosis and multimodal therapeutic strategies.

2.2 BACE 1 as Therapeutic Target in AD

BACE1, which is a membrane bound type I aspartyl protease, is arranged in a way that it allows controlled intracellular processing, opposed to a extracellular release. It is produced through a proteolytic processing and movement via acidic compartments where its catalytic property is preferred. It consists of a cytoplasmic tail, a transmembrane region and large catalytic domain. Its enrichment in endosomes and golgi apparatus can be correlated to its tendency for acidic pH and its substrate cleavage[32][3].

Although, BACE1 is structurally a member of aspartic proteases of pepsin family, its differs from related enzymes over the fact that it has an elongated lumen and flexible flap which modulates the substrates access to the active site. The flap orientation and the pair of conserved amino acids at the catalytic site lay the foundation for developing BACE1 inhibitors. Within cells, BACE1 is not just involved in amyloid processing, it performs breakdown of several substrates related to synaptic arrangement and axonal function [33].

BACE1 is involved in amyloid-beta production by cleaving APP protein to produce soluble sAPPβ and C99, by γ-secretase action it will going to generate Aβ peptides, mainly Aβ40 and Aβ42, which forms the amyloid plaques. Since, cleavage at this β-site is the rate determining step, BACE1 is

considered to play a central role in amyloid pathway[3]. Because of its molecular placement, BACE1 has emerged as a well-known target for AD therapy. Early clinical investigations revealed the significant inhibition of Aβ production is possible by lowering BACE1 catalytic activity which reduces the further downstream synthesis. The reasoning is straight, γ-secretase cannot produce Aβ, if its substrate, C99 is eliminated at the source [34].

However, BACE1 is not completely harmful. Since this enzyme is involved in processing of number of natural substrates which are part of myelination and synaptic communication, its total inhibition can have severe consequences. This dual nature is significant, as therapeutic strategy now involves decreasing APP levels and at the same time maintaining sufficient BACE1 function [35].

2.3 Existing BACE1 Inhibitors: Known Compounds and Limitations

Since BACE1 is involved in upstream step of the pathogenesis, its inhibition becomes compelling and use of BACE1 inhibitors becomes more reasonable in preclinical phase than in later dementia as preventing amyloid synthesis early should greatly reduce plaque production before synaptic loss becomes more prevalent. The clearest evidence are the biomarker studies which shows significant Aβ reduction without associated clinical benefit once damage is done [36]. However, the very same evidence also suggests that over inhibition can have serious implications due to the role of BACE1 in several other biological processes like synaptic maintenance. Hence, inhibition does not always yield favorable results, indicating that age, timing and the degree of inhibition are all important factors [37].

Current BACE1 inhibitors are categorized into two main classes, natural and synthetic, with main focus is towards synthetic chemistry initiatives. The 1st Gen BACE1 inhibitors mainly composed of peptidomimetics, which demonstrated strong inhibition but was limited due to poor oral exposure and reduced BBB penetration. In order to maintain interactions at the catalytic site while enhancing CNS-drug like characteristics, development switched towards non-proteinous molecules like acyl guanidine, aminopyridines, and analogues of aminothiadiazine dioxide [38]. Many synthetic drugs cleared preclinical and clinical trials, which includes LY2811376, LY2886721, erubecestat, and some other compounds which showed significant reduction in Aβ levels [39].

- **LY2811376**
  It was made by Eli Lilly and it was the first inhibitor which goes for clinical trials. In phase I trial it showed decrease in amyloid beta level in both plasma and CSF but due to its toxicological profile it has been discontinued as it causes damage to eye pigment epithelium in rats [39][40].
- **LY2886721**
  It was also made by Eli Lilly and it's a second generation inhibitor. In phase I trial it showed safer, well tolerated and reduce amyloid beta in a dose dependent manner. But in phase II trial it showed some off target effects (abnormal increase in liver enzyme) which lead to its discontinuation [39][41][42].
- **BI 1181181**
  It was discovered by Vitae Pharmaceuticals and manufactured by Boehringer Ingelheim. Three phase I trials were done. Two of the three phase I trial revealed that its single dose was well tolerated and can reduce the Aβ level. Third phase I trial was done which evaluate the safety of different doses of this drug which was then discontinued as it showed some skin reactions [39][43][44].
- **JNJ-54861911 (Atabecestat)**
  It was made by Janssen. It has reached phase II/III trials. There it evaluated the safety, tolerance, pharmacokinetics and pharmacodynamics profiling. It showed BBB penetration

and reduction in Amyloid beta level in phase I trial. But in phase II/III trial, it was discontinued as it showed some liver toxicity and T cell mediated inflammatory response [39][45][45].

- **LY3314814 (AZD3293, Lanabecestat)**
  It was developed by AstraZeneca and Eli Lilly. It is a BACE1 and BACE2 inhibitor. It showed safer and well tolerated reduction in Aβ level in phase I. A phase II/III trial known as AMARANTH trial was done. These finding lead to termination of LY3314814 as it was not able to reduce cognitive decline and disease progression and lead to cognitive worsening and depigmentation in epidemis and hair [39][46][47].
- **MK-8931 (MK-8931-009, Verubecestat)**
  It was made by Merck. It is a BACE1 and BACE2 inhibitor. Three phase I trial were done which revealed reduction in Aβ protein by interacting with the catalytic dyad of BACE1. Phase II/III trials were done and then terminated as it showed no benefit in improving cognitive decline and it leads to sleep disturbance, skin rash, weight loss. So it was discontinued [39][48][49].
- **E2609 (Elenbecestat)**
  It was made by both Biogen and Eisai Co. Ltd. It is a selective BACE1 inhibitor. Phase I/II/III trials were done. In preclinical trial it showed reduction in Aβ level. Phase III trial was terminated of unfavourable risk-benefit ratio and no evidence of potential inhibition. It showed adversed effects like contact dermatitis, headache, upper respiratory infection [39][50][51][52].

Moreover, synthetic inhibitors have shown several side-effects, for instance LY2811376 was discontinued after demonstrating renal toxicity in studies. Similarly, LY2886721 was also halted, when it was observed that it disturbs enzyme levels in liver. Verubecestat was also stopped due to ineffectiveness poor cognitive results in individuals. All these outcomes suggest that synthetic drugs cannot provide a long-term solution without severe implications highlighting the need for natural alternatives [53].

Natural inhibitors

Although they have been mentioned in several research, natural compounds as inhibitors are far less advanced than synthetic counterparts. Natural BACE1 inhibitors and combination of natural and synthetic BACE1 and AChE inhibitors are being tested, majority of the progress have come from tailored small molecules rather than naturally derived compounds [54].

2.4 Serpentine: Chemical and Pharmacological Importance

Catharanthus roseus belongs to Apocynaceae family has medicinal properties and it secretes various terpenoid indole alkaloids such as vincristine, vinblastine, or ajmalicine. It shows anticancer activity which is linked to vincristine, vinblastine. Serpentine, a monoterpene alkaloid with a characteristic indole moiety (indole alkaloid) is mainly obtained from *Catharanthus roseus* and *Rauwolfia serpentina* and has also been found in stem barks and roots. These plants have been used for ages in traditional medicines for conditions like neurological issues including anxiety and mental illness, hypertension and snakebites. These ethnomedicinal properties highlight the significance of serpentine and other alkaloids in studies focusing on disorders of nervous and cardiovascular systems [55][56][57].

Its molecular formula is C21H21N2O3 and consists of an indole nucleus, with a classical tryptophan or tryptamine derived fused pyrrole and benzene rings. The indole family usually shows many variations in its structures including many hydroxyl, methyl and carbonyl substituents in the

skeleton, which directly alter its hydrogen bonding capabilities and reactivity [58]. The physiochemical properties of indole alkaloids show a very strong preference for organic solvents and exhibit poor solubility in water in its free base form. This preference is largely influenced by the existence of basic nitrogen atom and a huge heteroaromatic rings, making these compounds ideal for chromatographic and acid base extraction. These structural characteristics also describe the usage of rigorous UHPLC, HPLC and other chromatographic methods for accurate identification of several alkaloids. Hence, serpentine is not just a bioactive compound obtained naturally but also allows modifications, optimization using current medicinal chemistry techniques whose core with heterocyclic rings and oxygenated replacements are critical for its biological activity [59][56].

The medicinal significance of serpentine can be most effectively understood with larger alkaloid profiling, since *Rauwolfia* is closely linked to CNS and cardiovascular functions. Its roots have been used traditionally to treat schizophrenia, epilepsy and sleeplessness, indicating strong CNS link. Current research also highlight inhibitory activity towards acetylcholinesterase and antipsychotic properties in alkaloids from *Rauwolfia* which shows its role in modulating neurological communication. In this reference, serpentine emerges as a biologically active alkaloid with immense scope as neuroprotective agent, despite the scarcity of serpentine based studies [60]. Serpentine from *Catharanthus roseus* at low concentration (IC50 0.27 μg/ml) act as invitro inhibitor of AchE enzyme so help in symptomatic control of AD [6].

Many *Rauvolfia* extracts exhibit strong antioxidant capabilities, such as ROS scavenging by root extracts, while methanol and hydro alcohol based extracts show wide antioxidant behaviors. Since, oxidative stress can cause both brain damage and chronic inflammation, this activity becomes more significant. Monoterpene alkaloids, *Rauwolfia* and *Catharanthus* extracts have also been shown to possess anti-inflammatory properties such as suppressing nitric oxide generation by LPS mediated activation of macrophages. Its CNS related medicinal properties are also supported by the fact that these classes of compounds are linked to ion-channel activity and anti-AChE effects. All things considered, serpentine can be best comprehended as a main pharmacological bioactive indole based alkaloid with strong significance in neurochemistry and inflammation [61][62].

2.5 Structural Stereoisomerism and Its Biological Importance

Compounds that have same atomic composition but differ in their spatial orientation are known as stereoisomers, and in medicinal chemistry, this property has a significant influence on biological recognition and activity of the compound [63]. Since enzymes, transport proteins and receptors recognize the 3-D arrangement of their binding molecule as unique identity, stereoisomers of the same compound show different properties. This implies that one stereoisomer of a drug may be less toxic, more specific and highly active as compared to the other [64]

These differences are important for binding and specificity towards proteins, because stereo-specific interactions with enzymes and receptors can alter both pharmacodynamic and pharmacokinetic properties. Additionally, several enantiomers follow diverse metabolic routes, which directly change toxicity, exposure and elimination from the body. Toxicity is often seen in one isomer than others, mostly when undesirable stereoisomer forms toxic byproducts or binds with off-target proteins. Hence, for alkaloids obtained from *Catharanthus* and *Rauvolfia*, stereoisomers of each compound are very critical as they show different activity and preference for target [65].

Stereoisomers are important for computational drug identification because binding pockets in proteins can differentiate between stereoisomers and generally favors a particular docking pose and interaction patterns. Hence, screening stereosisomers of compounds becomes imperative as

different stereoisomers can show unique properties and improved binding. Moreover, alkaloids interact with hydrogen bonding, pi-sigma interactions, hydrophobic interactions, whose arrangement may vary among stereoisomers [66].

Stereosisomer based ADMET analysis is also important as stereoselective variations in binding, metabolism can change its efficacy and toxicity. Therefore, stereoisomer-focused docking, ADMET profiling becomes essential steps in definitive lead compound selection rather than optional enhancements [65].

2.6 Computational Approaches in Drug Discovery

The strategy that has completely transformed the current drug discovery process by greatly reducing the time, expense, and experimental burden involved in identifying promising therapeutic candidates is Computer aided drug design (CADD). A typical CADD method starts with identification and retrieval of target protein, followed by target processing and ligand preparation. Thereafter, molecular docking, binding affinity calculation, PK profiling and drug-likeness tests are conducted. This approach allows a proper lead candidate selection prior to any in-vitro synthesis and biochemical assays [67].

The foundation for this structure based drug design strategy is molecular docking. It is an in-silico method that involves predicting the preferred binding arrangement of a ligand molecule in a site of target protein which is generally an active site which is followed by estimating the thermodynamic feasibility of the complex using a scoring system [68]. One of the most common, free available docking tool is AutoDock Vina which effectively identifies an optimal conformation of ligand and docking site by a combination empirical scoring matrix and gradient optimization technique [69].

Before performing docking, protein preparation and ligand preparation are two essential processes to be done to prevent steric hindrances and imprecise electrostatic interactions which may lead to inaccurate docking results. UCSF Chimera is commonly used software for this purpose, acting as vital component in both pre-docking processing and post-docking analysis. For preparation, it is utilized to analyze the protein/receptor's tertiary structure, eliminate solvent molecules, add missing H atoms and identify heteroatoms. Its user friendly GUI allows researchers and students to easily work with it making it a top choice among other competitors. During post-docking inspection, chimera makes it easier to visualize protein-ligand docking output and detect important interactions between them such as hydrogen bonds, stacking interactions, hydrophobic contacts and many more [70].

A crucial post docking screening that determines if a drug follows a feasible PK behavior for therapeutic use is ADMET profiling (Adsorption, Distribution, Metabolism, Excretion and Toxicity). SwissADME is a publicly available web-based bioinformatic tool that allows detailed predictions of several pharmacological properties like water solubility, lipophilicity, cytochrome P450 interactions and many others. Among these properties, Blood-brain permeability is a very important factor mainly for drug candidates which target protein of CNS such as BACE1 inhibitors [71].

Drug-likeness is another evaluation for filtering compounds, which is mainly governed by Lipinski's rule of five, states that an oral drug should have molecular weight < 500 Da and a computed logP score of less than 5 with no more than 5 hydrogen bond donors and 10 hydrogen bond acceptor. Compounds which meet these criteria have higher chance of demonstrating good bioavailability [72].

The combination of docking, ADMET analysis and drug-likeness as coherent in-silico method significantly improves the likelihood of finding good and relevant drug candidates. This approach guarantees that only those compounds which show optimal binding affinity and acceptable PK characteristics move forward for additional research before experimental confirmation.

2.7 Research Gaps and Study Rationale

Although our knowledge on AD and its molecular mechanism has been advanced tremendously, developing successful therapeutic strategies is still a challenging task. Most of the current approaches manage symptoms and do not prevent or stop the disease at its root cause. BACE1 is an important protein which is involved in a crucial stage of amyloid-β production and has been a major focus for therapeutic approaches aimed at inhibiting it. However, many BACE1 inhibitors had minimal success because of toxicity, poor PK properties and serious cognitive consequences, emphasizing the need for identification and development of safer and potent inhibitors.

Natural products have emerged as an important source for bioactive compounds which have neuroprotective capabilities. Among these, serpentine which is an indole alkaloid extracted from *Rauvolfia serpentine* and *Catharanthus roseus* has gained significant attention due to its biological activity and relevance in CNS [57]. Despite this, the potential of serpentine in inhibiting BACE1 remain greatly underexplored. Since, stereochemistry can affect recognition, binding affinity and PK behavior, evaluation of its stereoisomers may offer essential insights about its therapeutic prospective.

Therefore, in-silico techniques such as docking and PK studies may allow useful and cost-effective methods for early evaluation of strong drug candidates against BACE1.

3. METHODOLOGY

3.1. Target structure retrieval

The three-dimensional (3D) structure of human BACE 1 bound to compound 0211 (PubChem CID: 89836206) was retrieved from the Protein Data Bank (PDB) database (https://www.rcsb.org/) using PDB ID: 5DQC [73]. This particular structure of compound on PDB has a resolution of 2.47Å and was determined by X-ray diffraction. This structure of BACE1 was chosen in this study as it was co-crystallized with a small inhibitor molecule with clearly defined and appropriate active site geometry, making it very suitable for molecular docking. The presence of complexed compound inside the active site facilitated constructing the grid box for docking site. Finally, both the distinct flap and catalytic pair residues (Asp32 and Asp228) were preserved in this structure which was very crucial for determining inhibitor binding and specificity [74].

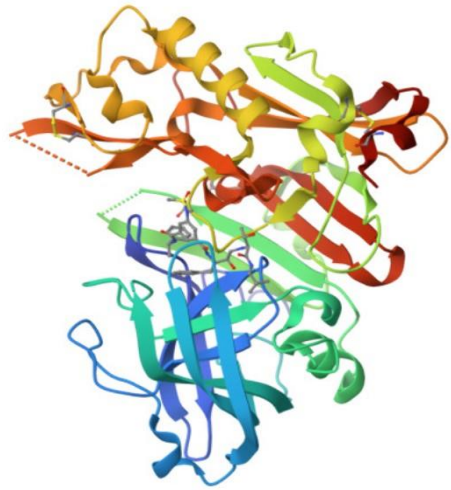


Fig.1. Human BACE 1 in complex with compound 0211

3.2. Selection of ligands

- Reference selection: There are several BACE 1 inhibitors out of which Verubecestat (PubChem CID 51352361) is selected as a reference molecule for comparative docking [73]. Its structure is obtained from the PubChem database in SDF format.

- Serpentine is used as a primary ligand and all the molecules which are structurally similar to it was searched from PubChem database using structure similarity search tool with a similarity threshold ≥ 90%. All the structures were retrieved and saved in SDF format.

- Ligand screening based on ADME analysis: In ADME, the letter A means absorption of compound in the body, D is for distribution of compound in the body, M is for metabolism compound and E is for excretion of compound. These criteria play an important role during research and manufacturing of pharmaceutical compounds. There are some important parameters that need to be analysed during drug development like BBB permeability, Lipinski rule of five, PAINS and Brenk.

SwissADME (http://www.swisssimilarity.ch/) is a web based tool which was used to analyse the pharmacokinetic and drug likeliness properties of all compounds. These screened compounds were then sent to SwissADME and the major parameters (BBB permeability, Lipinski violations, PAINS and Brenk) were used which helped in shortlisting the compounds. The shortlisted compounds were further used for molecular docking.

3.3. Preparation of target protein and ligands

The BACE1 three dimensional structure was obtained from the Protein Data Bank and downloaded in PDB format. UCSF Chimera 1.19 integrated with autodock vina extension was used to clean the target protein by removing any water molecules, heteroatoms and the native ligand from the structure (Compound 0211 in this case). Then, addition of polar hydrogens was done and Gasteiger charges were assigned.

Similarly, the 3D structures of all the shortlisted ligands as well as the reference ligand Verubecestat were taken from PubChem (https://pubchem.ncbi.nlm.nih.gov/) as SDF file format. The directory containing all ligand files was opened and energy minimization along with addition of hydrogens and charges within the UCSF Chimera was done.

The AutoDock Vina extension will automatically produce PDBQT files format for both the receptor and ligands during the docking process.

3.4. Molecular docking

UCSF Chimera 1.19 is used for molecular docking. It is a molecular visualization and analysis software. It can be integrated with the AutoDock Vina extension which uses gradient based local search genetic algorithm, a type of Lamarckian genetic algorithm (LGA) to perform docking directly inside the interface. This combination allows preparation of receptors and ligands, execution of docking runs, and visualization of binding poses within a single software [70]. The target protein in PDB format was uploaded. A grid box was generated using center coordinates of x = -0.696967, y = -20.3531 & z = 31.8785 having the dimensions of 25 Å x 25 Å x 25 Å and docking was performed subsequently. Each ligand (reference molecule Verubecestat) and shortlisted compounds in SDF format is docked individually. Separate output files for each ligand in PDBQT format were saved and an excel file containing binding affinities of all the ligands was produced as a result of docking.

3.5. Protein-ligand complex analysis

BOVIA Discovery Studio is a software suite developed by Dassault Systems BIOVIA [75]. Discovery Studio 2025 Client was used for the creation of 2D and 3D confirmations of ligand interactions. The ligand output file and target protein file were both in PDBQT format. A structural visualization of the reference ligand - target protein interaction as well as interactions of filtered ligands with protein was carried out followed by its extraction in both 2D and 3D formats. Interacting residues and bonds were a major focus of observation.

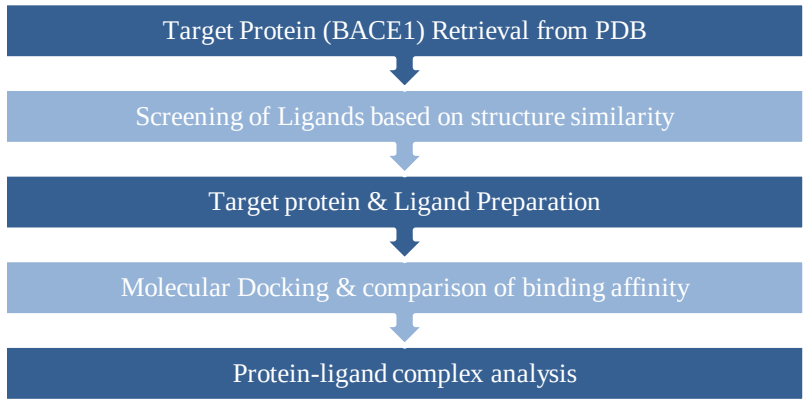


Fig.2. Workflow depicting methodology of molecular docking

4. RESULTS AND DISCUSSION

4.1. Preliminary screening and ADME analysis

Compounds structurally similar to serpentine were first identified using PubChem. By applying a Tanimoto similarity ≥ 90%, a total of 116 candidate molecules were obtained. These compounds then further filtered through ADME screening using SwissADME, where we applied certain filters such as BBB permeability, Lipinski's rules, and PAINS and Brenk alerts. After this evaluation, 11 compounds were shortlisted (Table 1); they were BBB permeable and showed no Lipinski violations, PAINS alerts, or Brenk alerts.

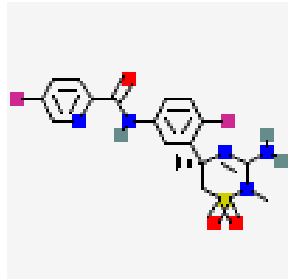
Table 1: Tabular Representation of Of Shortlisted Compounds

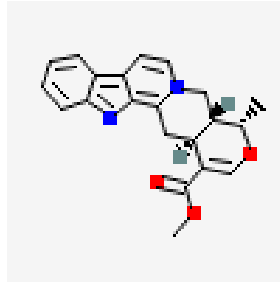
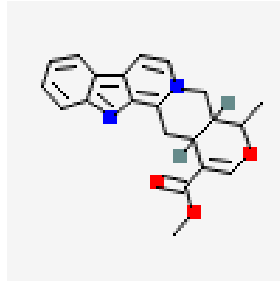
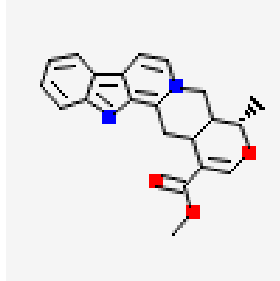
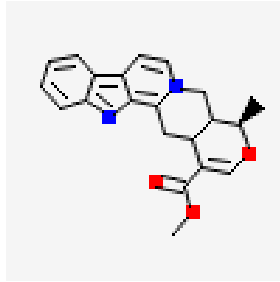
PubChem CID	Compound Name
73073	methyl (15R,16S,20S)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
371944	methyl 16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
23039	methyl (16S)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
166534427	methyl (16R)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
682644	methyl (15R,16R,20S)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
1150940	methyl (15R,16R,20R)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
5321258	methyl (15R)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
5459309	methyl (15R,16S,20R)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
6326642	methyl (15S,16S,20R)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
6541180	methyl (15S,16R,20S)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
44722335	methyl (15R,20S)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate

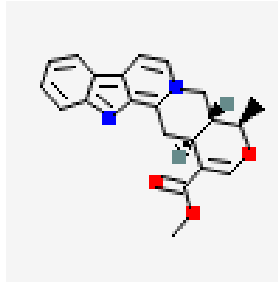
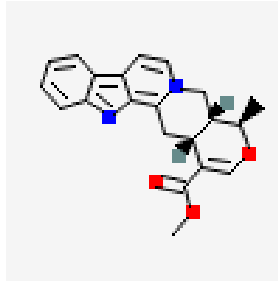
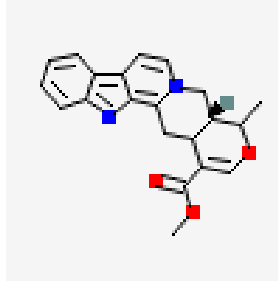
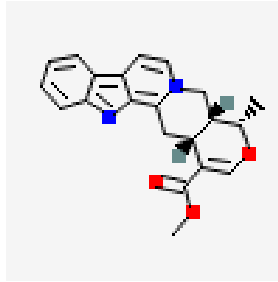
4.2. Molecular docking analysis

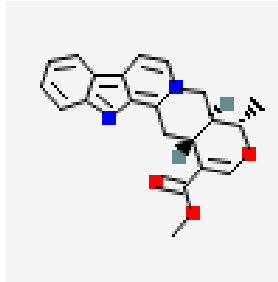
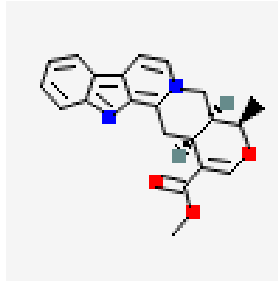
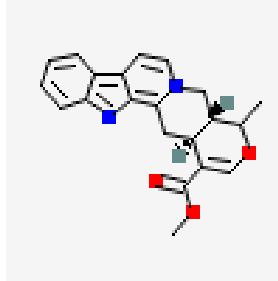
Docking analysis of these 14 compounds help in the selection of 11 compounds that showed binding affinity more than that of the reference, i.e., Verubecestat. The binding affinity of Verubecestat was found to be -7.946kcal/mol. The binding energies of the shortlisted compounds ranges from –8.493kcal/mol to –9.329 kcal/mol. The docking outcome of Compound 1 with PubChem CID 73073 exhibited relatively largest binding affinity of -9.329 in kcal/mol (Table 2).

Table 2: Tabular Representation of 2D Chemical Structures, Binding Affinities and Interactions of Ligands

Compound Name	PubChem CID	2D Chemical Structure	Binding Affinity (kcal/mol)	Interacting residues
Reference (Verubecestat)	51352361		-7.946	Asp32, Gly23, Tyr71, Thr231, Thr72, Arg235, Gln73

Compound 1 (Serpentine)	73073		-9.329	Thr232, Gln73, Leu30, Tyr71
Compound 2	371944		-8.759	Gln73, Lys321, Asn233, Tyr71
Compound 3	23039		-8.493	Leu30, Trp115, Tyr71, Gln73, Thr232
Compound 4	166534427		-8.974	Gly11, Lys321, Gln73, Arg307, Tyr71

Compound 5	682644		-9.066	Gly11, Gln73, Arg235, Tyr71
Compound 6	1150940		-8.78	Gln73, Lys321, Asn233, Tyr71
Compound 7	5321258		-8.901	Gln73, Gly11, Tyr71, Arg235
Compound 8	5459309		-8.936	Val332, Asp228, Asp32, Tyr71, Gly230, Phe108, Thr231, Thr232

Compound 9	6326642		-8.869	Leu30, Trp115, Tyr71, Gln73, Thr232
Compound 10	6541180		-8.746	Tyr71, Gln73, Lys321
Compound 11	44722335		-8.798	Gly11, Gln73, Tyr71, Arg235

4.3. Visualization of docked ligands

BIOVIA Discovery Studio 2025 Client was used for the visualization of both the 2D and 3D binding of the ligands to the BACE 1 protein. The interacting amino acid residues for all eleven selected compounds, as well as for the reference molecule, were identified (Table 2).

Figure 3 illustrates the 2D interaction of Verubecestat with the target protein. Figures 4–14 shows the 2D interaction diagram for Compounds 1 to 11, respectively, each highlighting their key binding residues within the receptor.

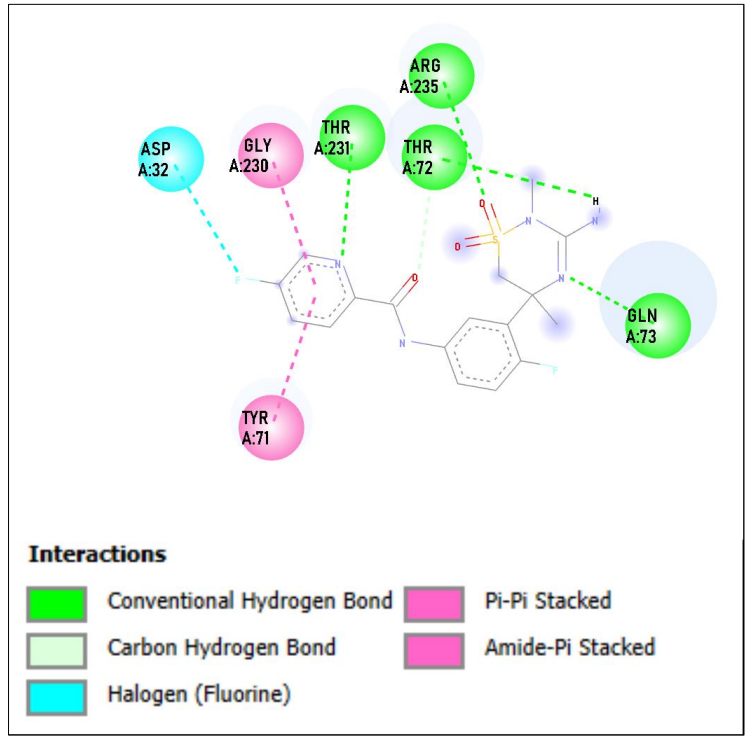


Fig.3. Interactions with Verubecestat

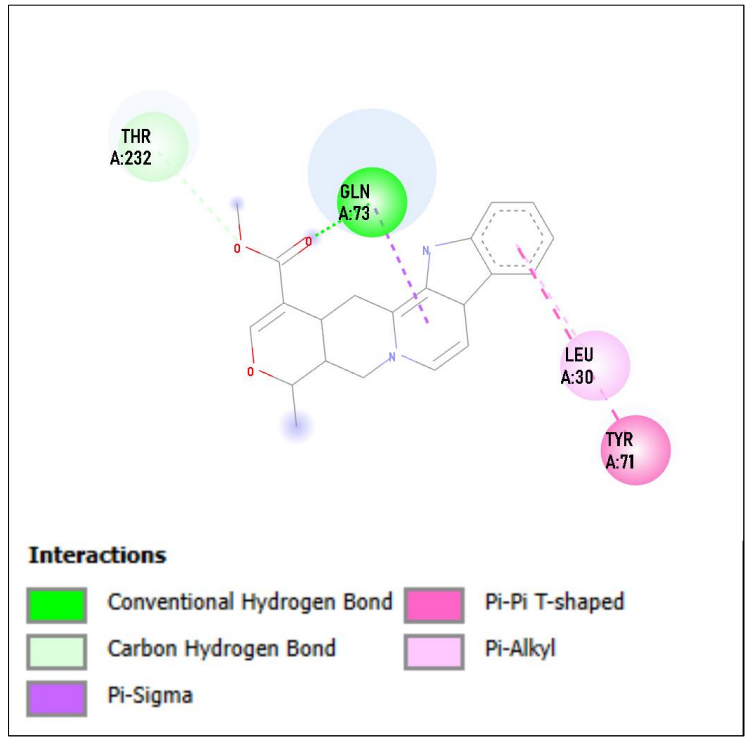


Fig.4. Interactions involving Compound 1

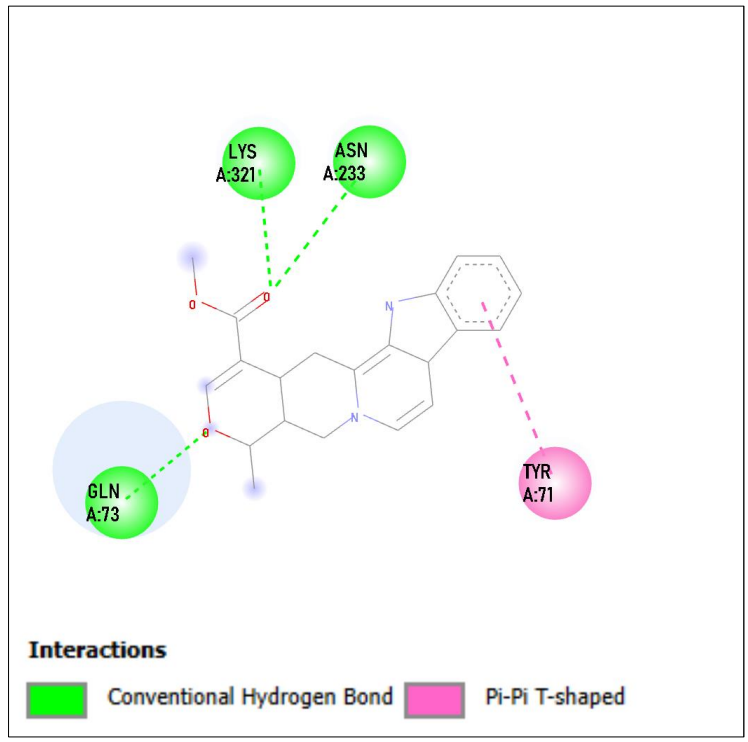


Fig.5. Interactions involving Compound 2

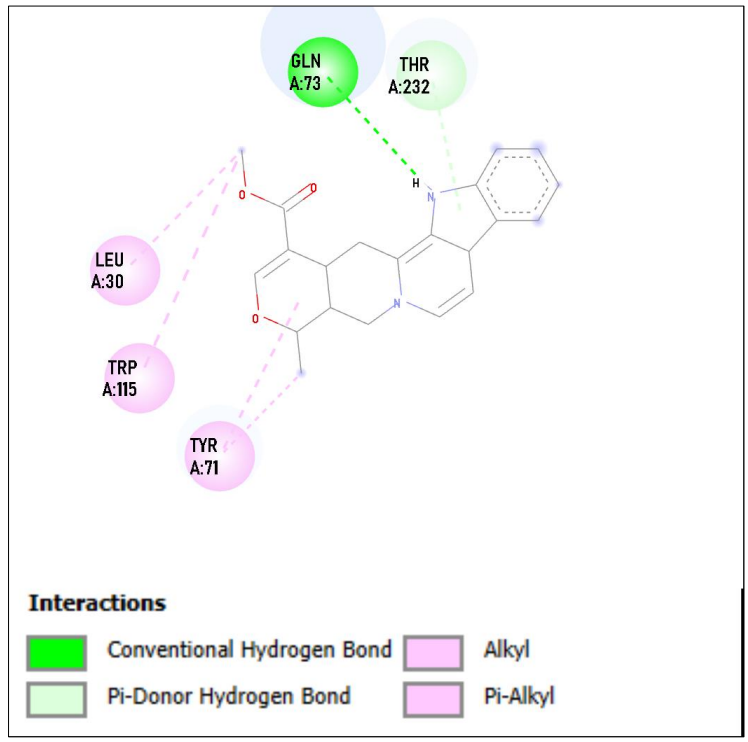


Fig.6. Interaction involving Compound 3

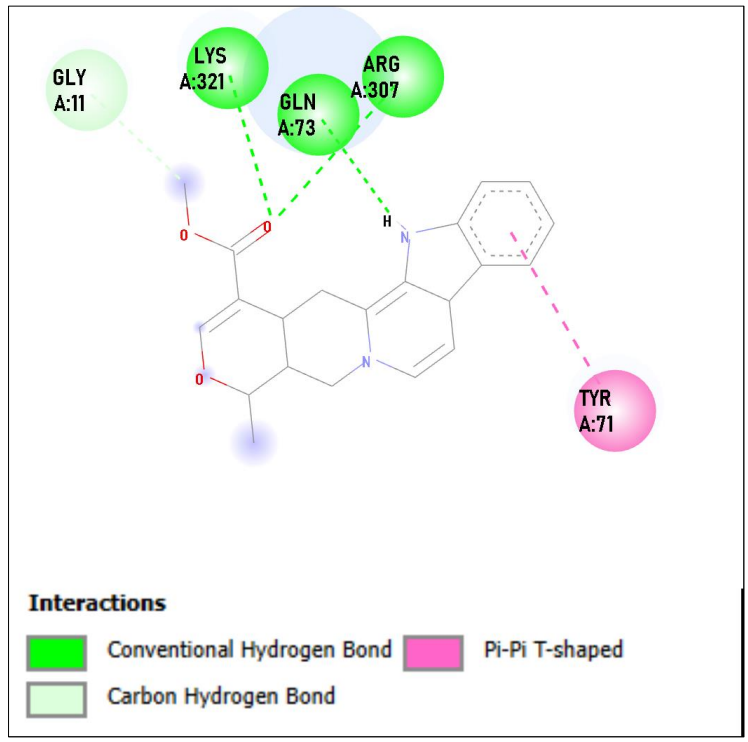


Fig.7. Interactions involving Compound 4

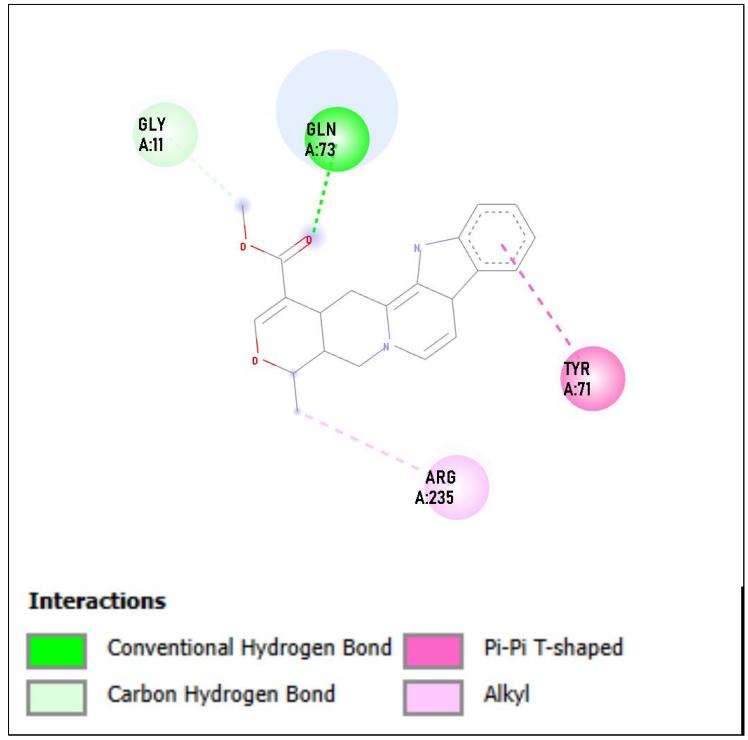


Fig.8. Interactions involving Compound 5

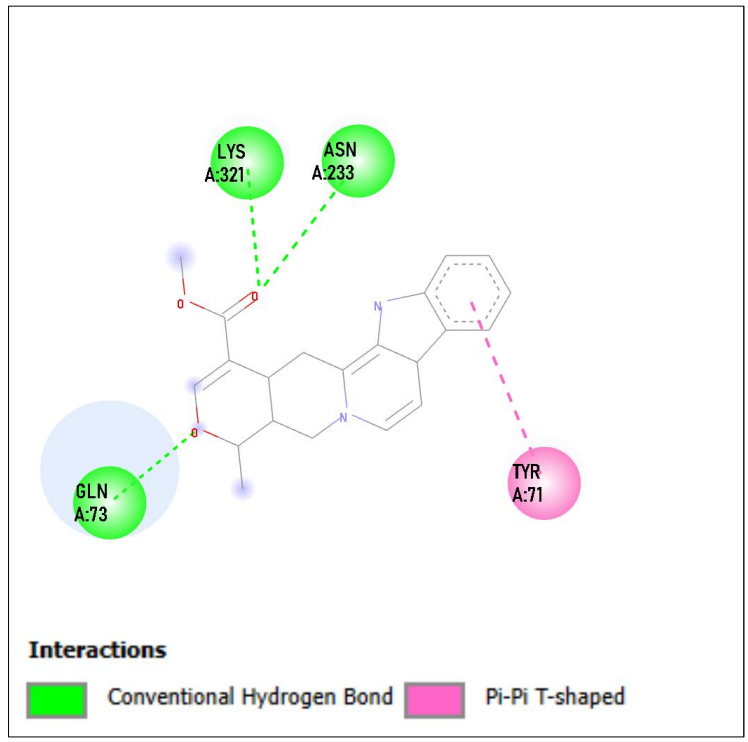


Fig.9. Interactions involving Compound 6

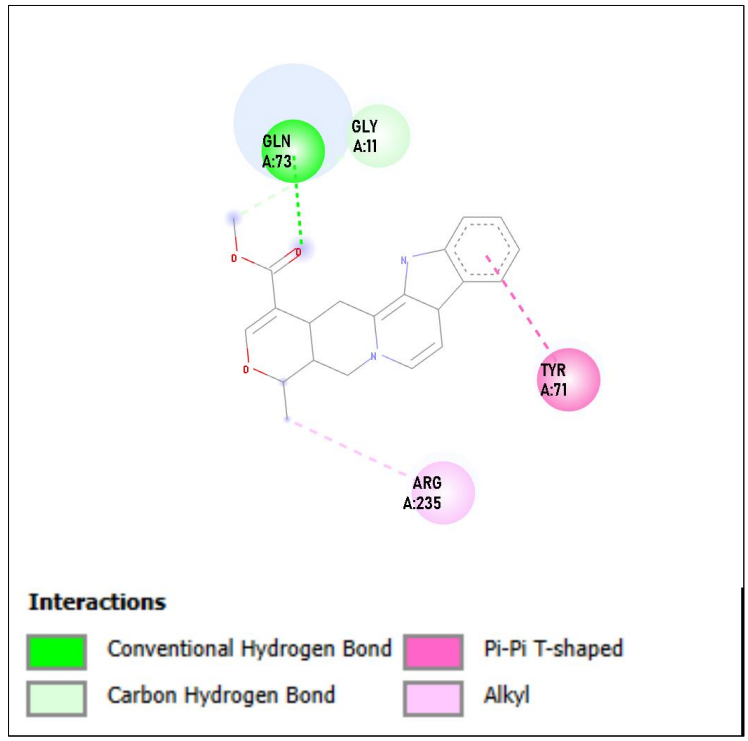


Fig.10. Interactions involving Compound 7

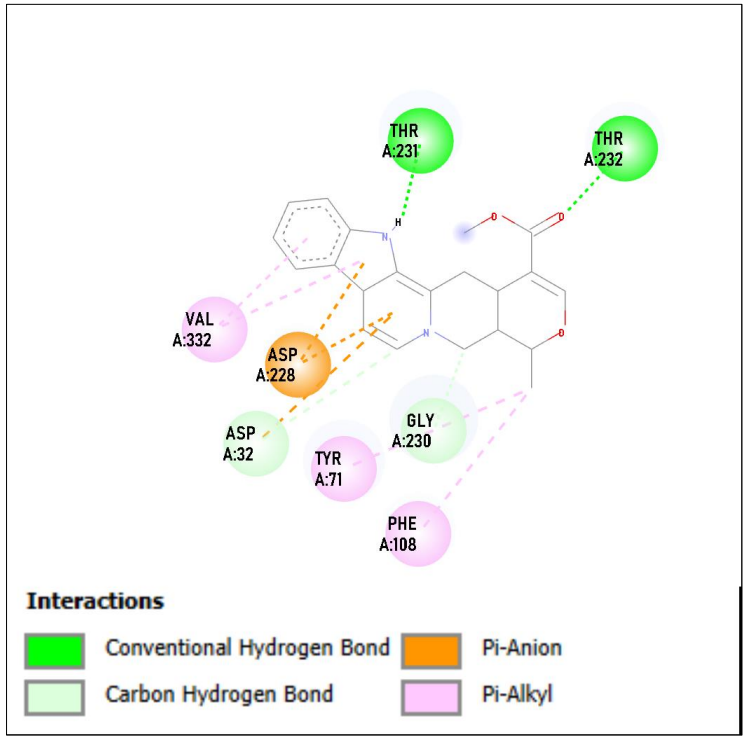


Fig.11. Interactions involving Compound 8

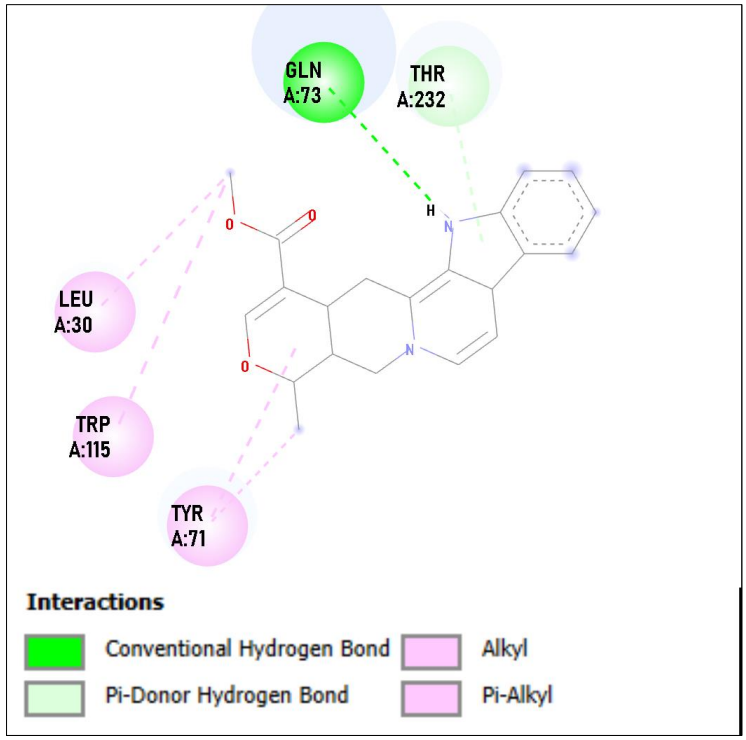


Fig.12. Interactions involving Compound 9

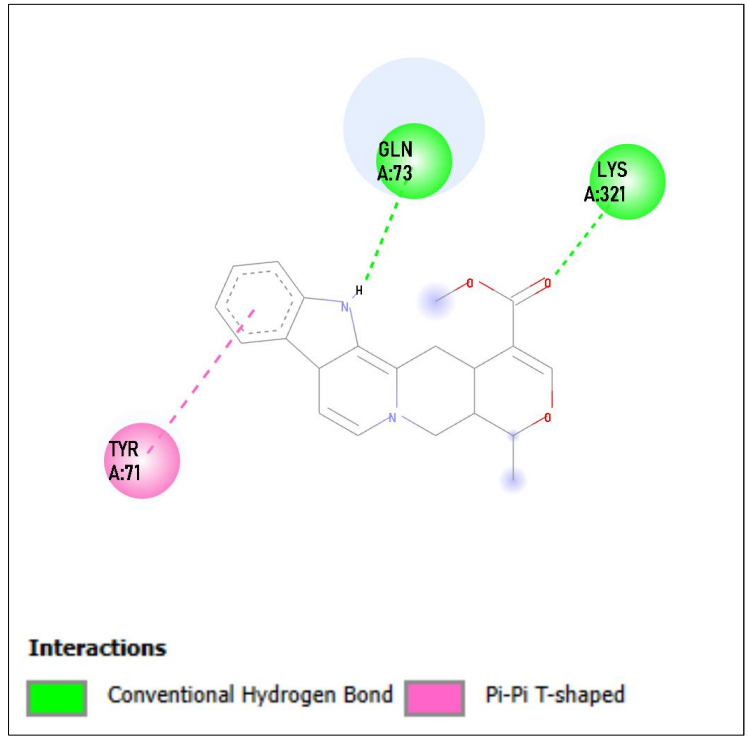


Fig.13. Interactions involving Compound 10

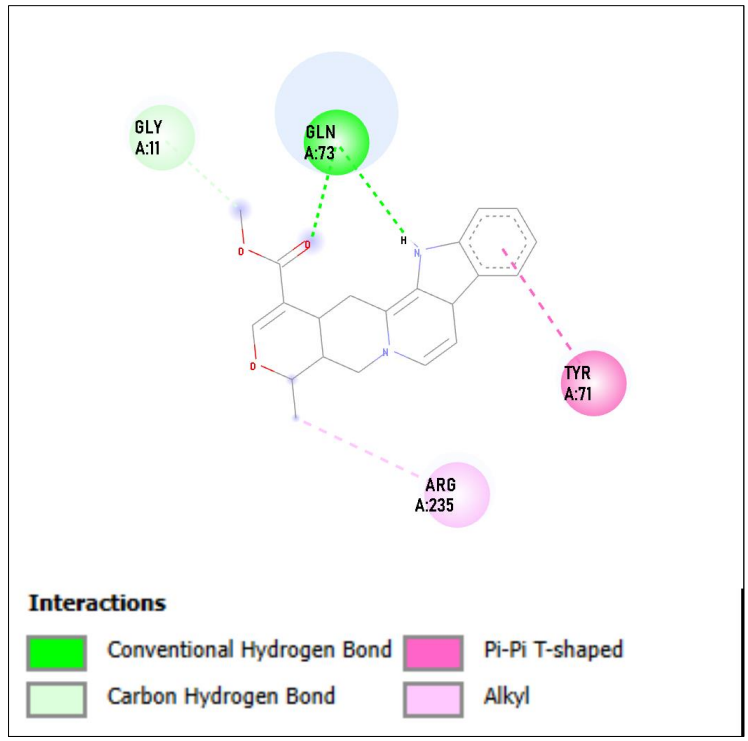


Fig.14. Interactions involving Compound 11

4.4. Detailed ADME analysis

SwissADME analysis of the 11 shortlisted compounds showed favourable results across several drug likeness parameters. All eleven molecules were expected to cross the BBB and had no Lipinski rule violations, indicating good potential for drug development. They also showed zero PAINS alerts, suggesting a low risk of false positive activity, and zero Brenk alerts, further supporting their suitability. Additional ADME parameters such as TPSA, GI absorption, consensus logP, and logKp were also evaluated to assess their overall viability (Table 3). This study was successful to find a replacement for Verubecestat as eleven compounds with better binding affinities were discovered.

Table 3. ADME Analysis of Compound 1-11

S. No	BBB permeable	Lipinski violation	TPSA value	Consensus logP	Gastrointestinal absorption (GI)	log Kp (cm/s)
1	Yes	0	High	2.87	High	-6.59
2	Yes	0	High	2.87	High	-6.59
3	Yes	0	High	2.87	High	-6.59
4	Yes	0	High	2.87	High	-6.59
5	Yes	0	High	2.87	High	-6.59
6	Yes	0	High	2.87	High	-6.59
7	Yes	0	High	2.87	High	-6.59
8	Yes	0	High	2.87	High	-6.59
9	Yes	0	High	2.87	High	-6.59
10	Yes	0	High	2.87	High	-6.59
11	Yes	0	High	2.87	High	-6.59

5. CONCLUSION

This study highlights the growing importance of computational approaches in accelerating drug discovery for complex neurodegenerative conditions such as Alzheimer's disease. Through a multilayered in silico pipeline combining molecular docking, ADME profiling, and virtual screening, eleven compounds were identifies as promising BACE1 inhibitors, all having higher binding affinities ranges from 8.493kcal/mol to –9.329 kcal/mol than the reference compound Verubecestat (-7.946 kcal/mol).

Among these, Compound 1 (Serpentine) named (methyl (15R,16S,20S)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20] henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate) turned out to be the best possible alternative as it had the maximum binding affinity (-9.329 kcal/mol) among all eleven compounds. Analysis showed the involvement of BACE1 residues, including Tyr71, Leu30, Gln73 and Thr232. Tyr71 is the flap molecule of BACE1 so by this interaction, it locks the flap molecule in close conformation and prevent APP entering the catalytic site.

From a pharmacokinetic point of view, all eleven candidates demonstrated blood-brain barrier permeability, a non-negotiable criterion for any therapeutic targeting the central nervous system. Furthermore, the shortlisted compounds have not violated Lipinski's Rule of Five, and all were found to be free of PAINS and Brenk structural alerts, which suggest a low chance of off-target interactions and a favorable overall drug-likeness profile. These findings support BACE1 inhibition as a viable disease modifying strategy in Alzheimer's therapeutics, particularly when candidate molecules can simultaneously achieve high target affinity and acceptable pharmacological safety margins.

The in-silico methods used many of which rely on machine learning tools highlight both the efficiency and modern nature of this approach. Such computational techniques greatly reduce the time, cost, and effort involved in early drug discovery. However, it is important to note that a compound’s behaviour in the human body can be very different from what is predicted by computer models. Moreover, effective treatment for Alzheimer’s may require strategies beyond BACE 1 inhibition alone. Therefore, we suggest that the current computational findings should be further validated by in-vivo experiments to confirm their real world potential.

In conclusion, this work contributes meaningfully to the landscape of BACE1 targeted drug discovery and showed the practical value of in silico methodologies in identifying pharmacokinetically viable lead compounds. Serpentine, in particular stands out as a strong foundation for further preclinical development, with the long-term objective of producing a disease altering treatment capable of slowing the pathological progression of AD.

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List of Publications

1. Conference paper:

Title of paper- "Computational Analysis of Serpentine and its structural stereoisomers as promising BACE1 Inhibitors"
Author Names- Sushankita Srivastava and Pravir Kumar
Name of Conference- 5th International Conference on Innovative Sustainable Computational Technologies (CISCT – 2026)
Date of Conference- 24th -25th July, 2026 at Graphic Era (Deemed to be University).
Indexing- IEEE
Status of paper- Accepted
Date of Acceptance- 7th May, 2026

2. Poster:

Sushankita Srivastava[1], Pravir Kumar[1], "In silico Analysis of Serpentine as potential BACE 1 inhibitor: Novel approach for Alzheimer's therapy"

Presented at: SNCI, Jamia Hamdard, New Delhi

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[5th International Conference on Innovative Sustainable Computational Technologies] Decision on Paper ID 393 - Computational Analysis of Serpentine and its structural stereoisomers as promising BACE 1 Inhibitors

5 messages

Microsoft CMT <noreply@msr-cmt.org> Thu, May 7, 2026 at 3:08 PM
To: Sushankita Srivastava <sushankitasrivastava_24mscbio08@dtu.ac.in>

Dear Sushankita Srivastava,

Thank you for your submission to 5th International Conference on Innovative Sustainable Computational Technologies.

We are pleased to inform you that your paper, ID 393, entitled "Computational Analysis of Serpentine and its structural stereoisomers as promising BACE 1 Inhibitors", has been ACCEPTED WITH MINOR REVISIONS for presentation at the conference.

Computational Analysis of Serpentine and its structural stereoisomers as promising BACE 1 Inhibitors

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***Abstract*—Alzheimer disease is a neurodegenerative condition involving multiple factors and currently there is no cure. It is primarily driven by abnormal production and buildup of amyloid β peptides, which are formed by sequential processing of APP mediated by BACE1 and γ-secretase. While BACE 1 has been identified as potential therapeutic target molecule and many drug candidates have been tested in clinical trials but they show limited cognitive benefits and many cases produced off-target side effects. Due to this, the attention is shifted toward naturally occurring molecules that may offer safer and more effective inhibition of BACE 1. In this study, serpentine, an indole alkaloid found in *Catharanthus roseus* and its stereoisomers were evaluated using an integrated insilico screening approach. A PubChem similarity search with 90 percent Tanimoto similarity threshold produced 116 serpentine related compounds, which were further shortlisted through ADME based filtering to select drug like candidates. Molecular docking was performed that utilized Lamarckian genetic algorithm with Verubecestat as the reference molecule. Eleven shortlisted compounds show stronger binding affinities than the reference inhibitor, with serpentine (PubChem CID 73073) showing the highest affinity. Analysis of protein ligand interactions revealed the involvement of BACE 1 residues, including Tyr71, Gln73 and Thr232. Conclusively, this novel findings indicate that serpentine and its stereoisomers may serve as promising lead molecules for designing future BACE1-focused treatments for Alzheimer's disease.**

Keywords*—*Alzheimer's disease, BACE 1, amyloid β, Serpentine, ADME, Binding affinity, Ligand interactions, insilico analysis, computational tools.

I. Introduction

Alzheimer's disease (AD) is the major contributor to dementia, particularly in individuals with an age above 65 years [1]. It gradually progresses and interlinks multiple pathological changes in the brain [1]. The condition is primarily marked by the extracellular buildup of amyloid-beta (Aβ) peptides whereas intracellular accumulation of tau proteins which become excessively phosphorylated [1]. Aβ aggregates to form neuritic plaques and hyperphosphorylated tau give rise to neurofibrillary tangles. These two abnormalities are considered as the main hallmark of AD. The medial temporal lobe (mainly hippocampus which involves in memory formation) is most affected initially. As the disease advances, these pathological changes spread to various neocortical areas. The combined impact leads to a gradual decline in thinking, memory and behaviour problems [2].

AD is a multifactorial disorder. It is caused by protein misfolding, acetylcholinestrase deficiency, oxidative stress, neuroinflammation, disrupted glutamate activity, reduced insulin response, changes in gut bacteria, and impaired mitochondria function. There are various hypothesis related to this. The amyloid cascade hypothesis suggested that AD starts when BACE1 enzyme cuts amyloid precursor protein (APP) which is subsequently processed by γ-secretase within the membrane leads to Aβ40 and Aβ42 production [1]. These accumulate outside the cells and form plaques. Aβ42 can clump easily and trigger oxidative stress [1].

BACE1 is an aspartyl proteases belong to pepsin family. In neurons, it is found on the plasma membrane and in endosomes [3]. Since BACE 1 initiates the amyloidogenic pathway, it became a potential therapeutic target. Several inhibitors were developed which lower Aβ levels in early studies. However in large clinical trials, they did not show meaningful conginitive benefits. Some even produce adverse effects like liver toxicity, mood alterations which lead to early termination of trials [4].

Serpentine is a monoterpenoid indole alkaloid found in Catharanthus roseus. It is a medicinal plant that has a diverse range of bioactive phytochemicals. This includes well studied alkaloids such as vinblastine, ajamalicine, and serpentine which arise from coordinated biosynthetic pathways [5]. Among these, serpentine has neuroactive properties which at low micromolar concentration inhibit acetylcholinesterase, this suggest its ability in providing neuroprotection [6].

This study aimed to identify serpentine and its structural stereoisomers with enhanced inhibitory potential against BACE1 using computational workflow. A structurally similar compound library was screened using PubChem and all docking scores were evaluated relative to the reference molecule (Verubecestat). The objective was to identify compounds that could block BACE 1 more effectively and provide a better treatment option for AD. The analysis included similarity based screening, ADME evaluation, molecular docking and detailed visualization of protein ligand interactions.

II. Literature Review

Alzheimer's disease (AD) is an advancing neurodegenerative disease and a dominant form of dementia in aged people [7]. 50 million people are suffering from dementia globally and 50-70% cases are due to AD. Its occurrence increases with age and it is expected that cases will increase from 9.3% in 2020 to 16.0% in 2050 [8]. The occurrence of AD doubles every 5 years after the age of 65, and it is slightly higher in females [1][8]. AD is a complex condition that leads to gradual memory impairment and difficulties in everyday functioning. It has an impact on individuals as well as their families and society. Individuals with AD show a significant buildup of amyloid-β (Aβ)

plaques and neurofibrillary tangles (NFTs) within their brains, followed by neuroinflammation, synaptic dysfunction, mitochondrial and bioenergetic disturbances which together may cause the death of neurons [9][10].

Clinically, people with AD mainly show memory related cognitive issues. Early signs include depression or anxiety, altered sleeping habits and pulling away from social activities. As the condition advances, symptoms get deteriorate and may lead to serious memory loss, hallucinations, delusional thinking, and noticeable changes in behavior and emotions. Some individuals may experience difficulties in skills like recognizing places or objects, speaking, decision making or movement [11][12]. Regrettably, there is no cure for AD yet, and individuals are diagnosed at a late and more severe stage and live for an average time of 4 to 8 years [10].

Various FDA approved medications like donepezil, rivastigmine, galantamine, memantine and namzaric have been used in symptomatic treatment . Donepezil, rivastigmine, galantamine and namzaric are AchE enzyme inhibitor and memantine is a NMDA receptor antagonist [1][13]. These drugs might reduce or manage symptoms temporarily but they do not halt the disease's advancement over time and possibly cause several adverse effects. New drugs which are currently under review including sodium oligomannate, aducanumab, lecanemab and donanemab, they are designed to alter the alzheimer's development by providing targeted therapy [11][10].

Different ideas have been suggested to explain how AD develops as it is complex in nature. AD can be subdivided into two main types: familial which contributes to 1-5% of AD cases and sporadic forms over 95% of cases [11]. Familial AD is linked to rare inherited changes in amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes, showing symptoms from age 30 to 65 and advancing quickly [14]. Whereas, sporadic AD also known as late onset AD, usually occurs after the age of 65 and is influenced by a combination of genetic risks, environmental factors, and various other factors [15].

BACE1 (β-site amyloid cleaving enzyme1) was identified in 1999 and functions as an aspartyl protease belonging to the pepsin family. This type I transmembrane protein is abundantly present in the brain [3]. BACE 1 at the subcellular level is present on the cell membrane and inside endosomal vesicles. Its catalytic site contains two aspartate residues. Post translational modifications are present that help in lipid raft localization, phosphorylation and degradation [3].

BACE 1 cleaves the membrane-associated protein known as amyloid precursor protein (APP) along with γ-secretase and resulting in Aβ that clumps inside the brain. Amyloid deposits occur before the neurofibrillary tangles formation which results from hyperphosphorylation of tau protein. This damages the neuronal communication by damaging synaptic connection [3].

BACE 1 is used as potential target for drug repurposing to identify new therapeutic molecules. There are various BACE 1 inhibitors were discovered like verubecestat, lanabecestat, atabecestat, etc. These inhibitors effectively reduce Aβ level in CSF in animal models and clinical trials, increase glucose metabolism and insulin sensitivity as well as body weight reduction. Thus, they help in delaying the onset of AD and slow down its progression. BACE 1 inhibitors have both on target and off target effects this results in termination of trials [4].

Catharanthus roseus belongs to Apocynaceae family has medicinal properties and it secretes various terpenoid indole alkaloids such as vincristine, vinblastine, or ajmalicine. It shows anticancer activity which is linked to vincristine, vinblastine. Serpentine is a monoterpenic indole alkaloid which has anti-hypertensive and anti neuroinflammatory properties [5][16]. According to cholinergic hypothesis of AD, low levels of acetylcholine lead to abnormal cholinergic neurotransmission. Acetycholinesterase (AchE) enzyme degrades acetylcholine (Ach) in synaptic cleft. AchE inhibitor has been investigated and found that these alkaloids act as a potential AchE inhibitor. Serpentine at low concentration (IC_{50} 0.27 μg/ml) act as invitro inhibitor of AchE enzyme so help in symptomatic control of AD [6].

III. Materials And methods

A. Target structure retrieval

The three-dimensional (3D) structure of human BACE 1 bound to compound 0211 (PubChem CID: 89836206) was obtained from the Protein Data Bank (PDB) database (https://www.rcsb.org/) using PDB ID: 5DQC [17]. This particular structure of compound on PDB has a resolution of 2.47Å and was determined by X-ray diffraction.

B. Selection of ligands

- Reference selection: There are several BACE 1 inhibitors out of which Verubecestat (PubChem CID 51352361) is selected as a reference molecule for comparative docking [17]. Its structure is obtained from the PubChem database in SDF format.
- Serpentine is used as a primary ligand and all the molecules which are structurally similar to it was searched from PubChem database using structure similarity search tool with a similarity threshold ≥ 90%. All the structures were retrieved and saved in SDF format.
- Ligand screening based on ADME analysis: In ADME, the letter A means absorption of compound in the body, D is for distribution of compound in the body, M is for metabolism compound and E is for excretion of compound. These criteria play an important role during research and manufacturing of pharmaceutical compounds. There are some important parameters that need to be analysed during drug development like BBB permeability, Lipinski rule of five, PAINS and Brenk.

SwissADME (http://www.swisssimilarity.ch/) is a web based tool that was used to evaluate the pharmacokinetic and drug likeliness properties of all compounds. These screened compounds were then sent to SwissADME and the major parameters (BBB permeability, Lipinski violations, PAINS and Brenk) were used which helped in shortlisting the compounds. The shortlisted compounds were further used for molecular docking.

C. Preparation of target protein and ligands

The three dimensional structure of BACE1 was obtained from the Protein Data Bank and downloaded in PDB format. UCSF Chimera 1.19 integrated with autodock vina extension was used to clean the target protein by removing any water molecules, heteroatoms and the native ligand from the structure (Compound 0211 in this case). Then, addition of polar hydrogens was done and Gasteiger charges were assigned.

Similarly, the 3D structures of all the shortlisted ligands as well as the reference ligand Verubecestat were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) as SDF file format. The directory containing all ligand files was opened and energy minimization along with addition of hydrogens and charges within the UCSF Chimera was done.

The AutoDock Vina extension will automatically produce PDBQT files format for both the receptor and ligands during the docking process.

D. Molecular docking

UCSF Chimera 1.19 is used for molecular docking. It is molecular visualization and analysis software. It can be integrated with the AutoDock Vina extension which uses gradient based local search genetic algorithm, a type of Lamarckian genetic algorithm (LGA) to perform docking directly inside the interface. This combination allows preparation of receptors and ligands, execution of docking runs, and visualization of binding poses within a single software [18]. The target protein in PDB format was uploaded. A grid box was generated using center coordinates of x = -0.696967, y = -20.3531 & z = 31.8785 with the dimensions of 25 Å x 25 Å x 25 Å and docking was performed subsequently. Each ligand (reference molecule Verubecestat) and shortlisted compounds in SDF format is docked individually. Separate output files for each ligand in PDBQT format were saved and an excel file containing binding affinities of all the ligands was produced as a result of docking.

E. Protein-ligand complex analysis

BOVIA Discovery Studio is a software suite developed by Dassault Systems BIOVIA [19]. Discovery Studio 2025 Client was used for the creation of 2D and 3D confirmations of ligand interactions. The ligand output file and target protein file were both in PDBQT format. A structural visualization of the reference ligand - target protein interaction as well as interactions of filtered ligands with protein was carried out followed by its extraction in both 2D and 3D formats. Interacting residues and bonds were a major focus of observation.

IV. Results And Discussion

A. Preliminary screening and ADME analysis

Compounds structurally similar to serpentine were first identified using PubChem. By applying a Tanimoto similarity $\geq$ 90%, a total of 116 candidate molecules were obtained. These compounds then further filtered through ADME screening using SwissADME, where we applied certain filters such as BBB permeability, Lipinski's rules, and PAINS and Brenk alerts. After this evaluation, 11 compounds were shortlisted (Table I); they were BBB permeable and showed no Lipinski violations, PAINS alerts, or Brenk alerts.

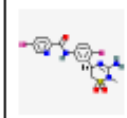
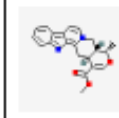
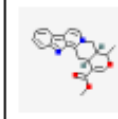
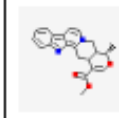
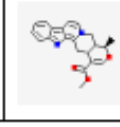
TABLE I. Tabular Representation Of Shortlisted Compounds

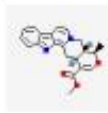
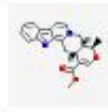
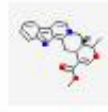
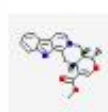
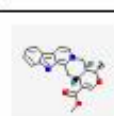
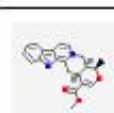
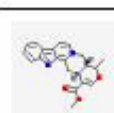
PubChem CID	Compound Name
73073	methyl (15R,16S,20S)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
371944	methyl 16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
23039	methyl (16S)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
166534427	methyl (16R)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
682644	methyl (15R,16R,20S)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
1150940	methyl (15R,16R,20R)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
5321258	methyl (15R)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
5459309	methyl (15R,16S,20R)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
6326642	methyl (15S,16S,20R)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
6541180	methyl (15S,16R,20S)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate
44722335	methyl (15R,20S)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate

B. Molecular docking analysis

Docking analysis of these 14 compounds help in the selection of 11 compounds that showed binding affinity more than that of the reference, i.e., Verubecestat. The binding affinity of Verubecestat was found to be -7.946kcal/mol. The binding affinities of the shortlisted compounds vary from –8.493kcal/mol to –9.329 kcal/mol. The docking outcome of Compound 1 with PubChem CID 73073 exhibited relatively largest binding affinity of -9.329 in kcal/mol (Table II).

TABLE II. Tabular Representation of 2D Chemical Structures, Binding Affinities And Interaction Residues of Ligand

Compound Name	PubChem CID	2D Chemical Structure	Binding Affinity (kcal/mol)	Interacting residues
Reference (Verubecestat)	51352361		-7.946	Asp32, Gly23, Tyr71, Thr231, Thr72, Arg235, Gln73
Compound 1 (Serpentine)	73073		-9.329	Thr232, Gln73, Leu30, Tyr71
Compound 2	371944		-8.759	Gln73, Lys321, Asn233, Tyr71
Compound 3	23039		-8.493	Leu30, Trp115, Tyr71, Gln73, Thr232
Compound 4	166534427		-8.974	Gly11, Lys321, Gln73, Arg307, Tyr71

Compound 5	682644		-9.066	Gly11, Gln73, Arg235, Tyr71
Compound 6	1150940		-8.78	Gln73, Lys321, Asn233, Tyr71
Compound 7	5321258		-8.901	Gln73, Gly11, Tyr71, Arg235
Compound 8	5459309		-8.936	Val332, Asp228, Asp32, Tyr71, Gly230, Phe108, Thr231, Thr232
Compound 9	6326642		-8.869	Leu30, Trp115, Tyr71, Gln73, Thr232
Compound 10	6541180		-8.746	Tyr71, Gln73, Lys321
Compound 11	44722335		-8.798	Gly11, Gln73, Tyr71, Arg235

C. Visualization of docked ligands

BIOVIA Discovery Studio 2025 Client was used for the visualization of both the 2D and 3D binding of the ligands to the BACE 1 protein. The interacting amino acid residues for all eleven selected compounds, as well as for the reference molecule, were identified (Table II).

Figure 1 illustrates the 2D interaction of Verubecestat with the target protein. Figures 2–12 shows the 2D interaction diagram for Compounds 1 to 11, respectively, each highlighting their key binding residues within the receptor.

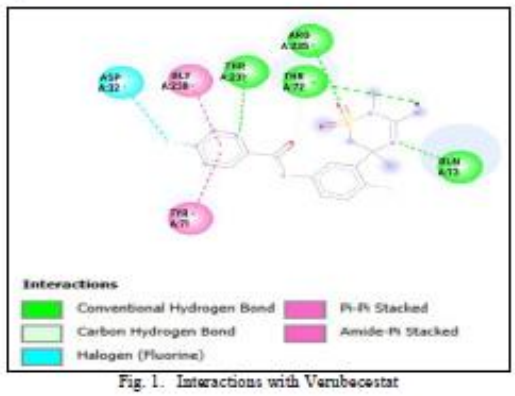


Fig. 1. Interactions with Verubecestat

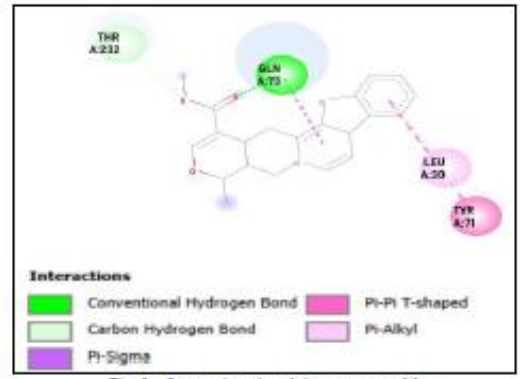


Fig. 2. Interactions involving compound 1

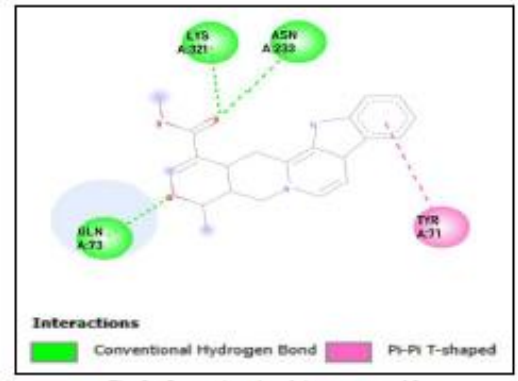


Fig. 3. Interactions involving compound 2

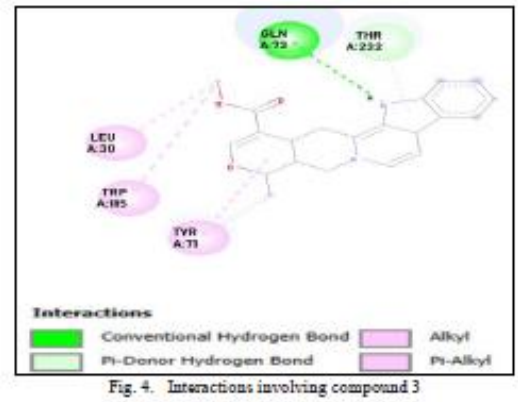


Fig. 4. Interactions involving compound 3

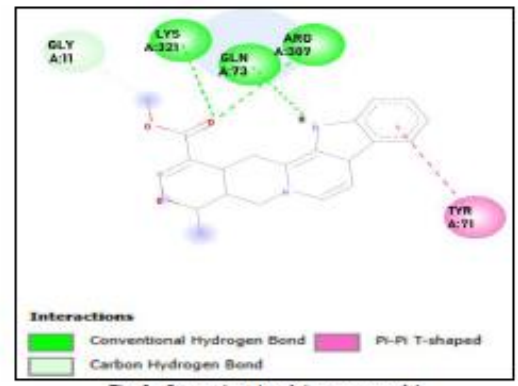


Fig. 5. Interactions involving compound 4

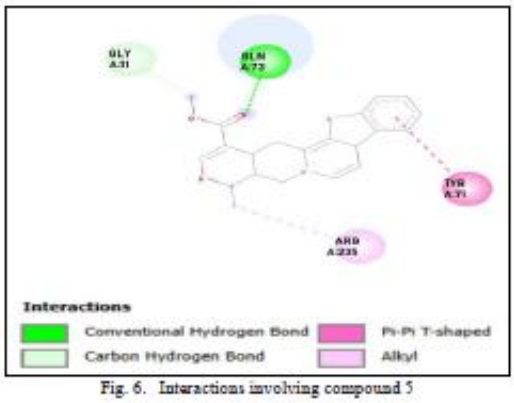


Fig. 6. Interactions involving compound 5

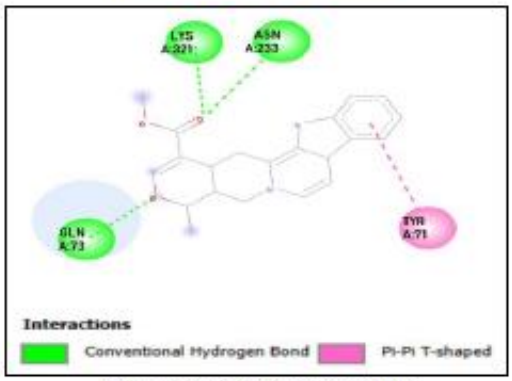


Fig. 7. Interactions involving compound 6

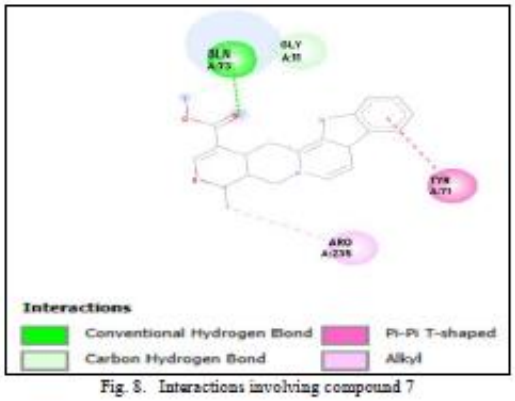


Fig. 8. Interactions involving compound 7

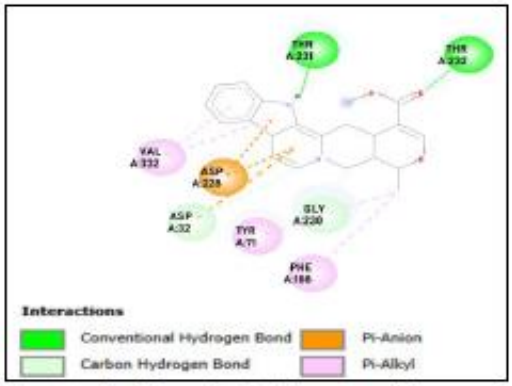


Fig. 9. Interactions involving compound 8

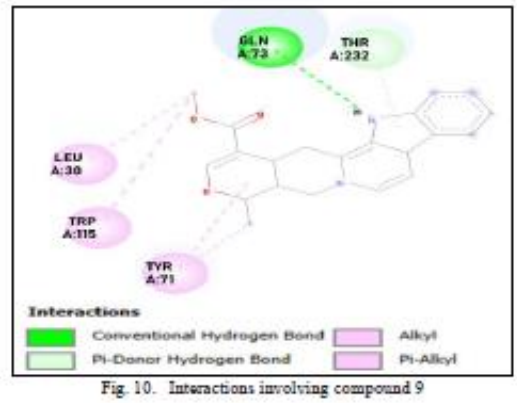


Fig. 10. Interactions involving compound 9

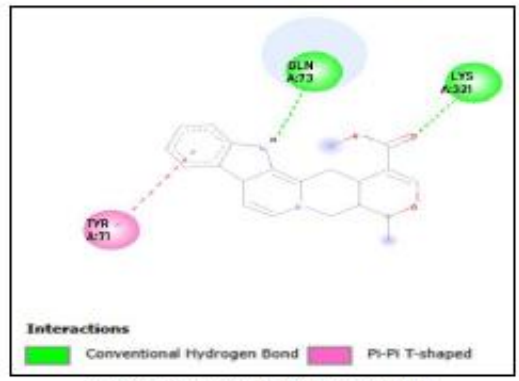


Fig. 11. Interactions involving compound 10

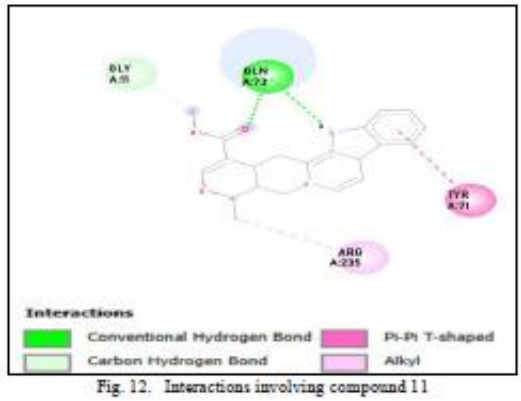


Fig. 12. Interactions involving compound 11

D. Detailed ADME studies

SwissADME analysis of the 11 shortlisted compounds showed favourable results across several drug likeness parameters. All eleven molecules were expected to cross the BBB and had no Lipinski rule violations, indicating good potential for drug development. They also showed zero PAINS alerts, suggesting a low risk of false positive activity, and zero Brenk alerts, further supporting their suitability. Additional ADME parameters such as TPSA, GI absorption, consensus logP, and logKp were also evaluated to assess their overall viability (Table III).

TABLE III. ADME ANALYSIS OF COMPOUND 1-11

S.No.	BBB permeable	Lipinski violation	TPSA value	Consensus logP	Gastrointestinal absorption (GI)	log Kp (cm/s)
1.	Yes	No	High	2.87	High	-6.59
2.	Yes	No	High	2.87	High	-6.59
3.	Yes	No	High	2.86	High	-6.59
4.	Yes	No	High	2.87	High	-6.59
5.	Yes	No	High	2.87	High	-6.59
6.	Yes	No	High	2.87	High	-6.59
7.	Yes	No	High	2.87	High	-6.59
8.	Yes	No	High	2.86	High	-6.59
9.	Yes	No	High	2.87	High	-6.59
10.	Yes	No	High	2.86	High	-6.59
11.	Yes	No	High	2.87	High	-6.59

V. CONCLUSION

BACE1 inhibition remains a promising strategy for developing new Alzheimer's treatments. In our analysis, eleven compounds showed stronger performance compared to the reference inhibitor, with Compound 1 displaying the maximum binding affinity. The in-silico methods used many of which rely on machine learning tools highlight both the efficiency and modern nature of this approach. Such computational techniques greatly reduce the time, cost, and effort involved in early drug discovery. However, it is important to note that a compound's behaviour in the human body can be very different from what is predicted by computer models. Moreover, effective treatment for Alzheimer's may require strategies beyond BACE 1 inhibition alone. Therefore, we suggest that the current computational findings should be further validated by in-vivo experiments to confirm their real world potential.

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This is to certify that Prof./Dr./Ms./Mr. Ms. Sushankita Srivastava
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EDUCATION

Program	Institute	%/CGPA	Year of Completion
M.Sc. Biotechnology	Delhi Technological University, New Delhi		2026
B.Sc. (H) Botany	Deen Dayal Upadhyaya College, University of Delhi, New Delhi	9.608	2024
XII (CBSE)	South Delhi Public School, New Delhi	88.4	2018
X (CBSE)	South Delhi Public School, New Delhi	8.8	2016

ACHIEVEMENTS

- Awarded with University Gold Medal from University of Delhi for securing highest marks (9.608) in B.Sc. (H) Botany.
- Qualified in CSIR NET 2025 with 94.14 percentile.
- Qualified in GATE (XL) 2026 with score 612.
- Qualified in GATE (BT) 2026 with score 353.

SKILLS

Technical skills:
Gram staining, DNA isolation, SDS-PAGE, BCA protein assay, Media preparation, Plant tissue culture, Microscopy, Centrifugation, Paper Chromatography, Thin Layer Chromatography (TLC), UV Spectrophotometry, Colorimetry.
Basic Bioinformatics (Database searching and retrieval of sequences, NCBI-BLAST), Molecular Docking (UCSF Chimera), Primer designing using PRIMER-BLAST. Basic R programming and python.

Professional skills:
Communication, Teamwork, Time Management, Presentation Skills, Canva.

INTERNSHIP & WORKSHOP

Panacea Biotech Trainee - Vaccine R&D July 2025	• Gained exposure in both Analytical and Downstream processing (DSP) departments. • Learned buffer preparation and observed TFF and Ion Exchange Chromatography. • Hands- on experience with BCA assay, SDS-PAGE, Western Blotting, ELISA and received demonstrations on HPLC
Ethical Edufabrica Pvt.Ltd® in association with IIT Kharagpur Drug Discovery & Molecular Docking June 2025	• Hands-on experience on Molecular docking using UCSF Chimera and structure visualization using BIOVIA Discovery studio • Learned about SWISS ADME, Target and ligand retrieval and preparation for docking, use of ChemSketch tool and Protox tool for drug discovery.
Nextgenhelper, New Delhi Bioinformatics Bootcamp: Biology to Bytes(basic to advanced analysis) 09th - 30th September 2025	• Learned about basic bioinformatics, NCBI-BLAST, basics of network biology. • Basics of R programming, R studio, Python.

Deen Dayal Upadhyaya College, DU 2-days Workshop on Plant Tissue Culture 12th – 13th April 2024	• Gained experience in Plant Tissue Culture • Learned MS media preparation and working under sterile condition. • Hands-on experience with Laminar Airflow Cabinet, Inoculation of explants in the media.

EXPERIENCE & CO-CURRICULUM ACTIVITIES

Symposium 15th – 16th April 2026	• Presented Research work at National Symposium on "Bridging Neurochemistry and Neuroscience: Molecular insights into Brain function" organised by SNCI & Department of Toxicology, Jamia Hamdard, New Delhi.
Poster Presentation in G20 Event 28th August 2024	• Won second prize in poster presentation on topic " Agricultural Methods and its compatibility with Bio-fertilizers" in G20 event on "Novel Initiatives in Indo-us Education Sector: Exploring Indian Knowledge System" organized by Cultural Council (University of Delhi) with Deen Dayal Upadhyaya College (University of Delhi), New Delhi
National Service Scheme, DTU	• Director of Design Team – Jul 2025 • Member of Design Team – Aug 2024
BioSoc, Biotechnological Society, DTU	• Member of Design Team – Oct 2024 - Present
Invictus, Annual Technical Fest, DTU	• Co-head of Creative Team - 2025

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