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IN-SILICO ASSESSMENT OF NOSTROCARBOLINE AS A DUAL CHOLINESTERASE INHIBITOR FOR NEURODEGENERATER

Chitransh Khare*[1], Dr. Sandip Prasad Tiwari[2], Mr. Dipak Bhadre[3]

*[1]Student, Faculty of Pharmacy, Kalinga University Raipur (C.G.).

[2]Principal and Professor, Faculty of Pharmacy, Kalinga University Raipur (C.G.).

[3]Assistant Professor, Faculty of Pharmacy, Kalinga University Raipur (C.G.).

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***Corresponding Author**
Chitransh Khare
Student, Faculty of Pharmacy, Kalinga University Raipur (C.G.).

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ABSTRACT

Neurodegenerative disorders, such as Alzheimer's disease, are characterized by progressive neuronal loss, cognitive decline, and memory impairment, often associated with cholinergic dysfunction. Therapeutic strategies targeting acetylcholinesterase (AChE) and butyryl cholinesterase (BChE) have shown promise in improving cognitive performance. Nostocarboline, a β-carboline alkaloid isolated from freshwater cyanobacteria, has been reported to exhibit inhibitory activity against both AChE and BChE. This study employed an in-silico approach to evaluate Nostocarboline's potential as a dual cholinesterase inhibitor. Molecular docking simulations were conducted to assess binding affinities, interaction profiles, and stability within enzyme active sites. Molecular dynamics simulations analysed the conformational stability of ligand–enzyme complexes over time. Pharmacokinetic and ADMET analyses evaluated drug-likeness, blood–brain barrier permeability, and toxicity. Results demonstrated strong binding interactions with catalytic and peripheral anionic site residues of both enzymes, favourable stability in dynamic simulations, and acceptable pharmacokinetic properties. These findings suggest that Nostocarboline could serve as a promising lead compound for further development as a dual cholinesterase inhibitor in the management of neurodegenerative disorders, warranting experimental validation.

KEYWORDS: Nostocarboline; Acetylcholinesterase (AChE); Butyryl cholinesterase (BChE); Dual inhibition; Neurodegenerative disorders; Molecular docking; Molecular dynamics simulation; ADMET; Drug-likeness.

1. INTRODUCTION

Neurodegenerative disorders are progressive conditions characterized by the gradual loss of neuronal structure and function, ultimately leading to neuronal death. Common examples include Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, Batten disease, and Creutzfeldt–Jakob disease. Although these diseases have different clinical features, they share common pathogenic mechanisms such as oxidative stress and chronic inflammation, which contribute to neuronal damage. Since neurons have limited regenerative capacity, most neurodegenerative diseases remain incurable, and current treatments mainly focus on symptom management rather than disease reversal.Memory impairment is a major feature of neurodegeneration. Amnesia, defined as partial or complete loss of memory, may occur due to brain injury, neurological disorders, trauma, or certain drugs. It is classified into retrograde amnesia, involving loss of previously stored memories, and anterograde amnesia, characterized by difficulty in forming new memories. Damage to brain regions such as the hippocampus and medial temporal lobe is closely associated with these deficits.Studies have shown that Nostocarboline exhibits inhibitory activity against both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) in the micromolar range. Dual inhibition is important because BChE activity increases in advanced stages of neurodegenerative diseases. Therefore, Nostocarboline may serve as a promising candidate for further investigation as a dual cholinesterase inhibitor for managing neurodegenerative disorders associated with memory impairment.

The neurodegenerative disorders are classified as follows:

1. Alzheimer's disease: Alzheimer's disease (AD) is the most common cause of dementia and is characterized by progressive cognitive decline and memory impairment. It primarily affects elderly individuals and gradually interferes with daily activities and independent living.

- **Cause:** Accumulation of **beta-amyloid plaques** (outside cells) and **tau tangles** (inside cells). It involves a loss of acetylcholine and is influenced by genes like *APP* or *APOE-ε4*.

- **Symptoms:** Starts with minor memory loss of recent events, progressing to confusion, language issues, and total loss of independence.
- **Management:** Cholinesterase inhibitors (Donepezil) and Memantine manage symptoms; no cure exists.

2. Parkinson's disease: Parkinson's disease (PD) is a progressive movement disorder resulting from degeneration of dopaminergic neurons in the substantia nigra region of the brain. It mainly affects motor function but can also cause cognitive and behavioral changes.

- **Cause:** Death of dopamine-producing neurons in the substantia nigra. Characterized by Lewy bodies (alpha-synuclein protein).
- **Symptoms:** Classic motor signs include resting tremors, muscle rigidity, slow movement (bradykinesia), and balance issues.
- **Management:** Dopamine replacement (Levodopa/Carbidopa) and deep brain stimulation (DBS).

3. Huntington's disease: Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by motor dysfunction, psychiatric disturbances, and cognitive decline.

- **Cause:** An inherited (autosomal dominant) mutation in the HTT gene featuring excessive **CAG repeats**. It primarily damages the basal ganglia.
- **Symptoms:** Involuntary jerky movements (chorea), psychiatric instability (irritability/depression), and progressive dementia.
- **Management:** Symptomatic care using antipsychotics; genetic counseling is vital for families

4. Multiple sclerosis: Multiple sclerosis (MS) is a chronic autoimmune disorder affecting the central nervous system, characterized by inflammation and demyelination of nerve fibers.

- **Cause:** An **autoimmune attack** on the **myelin sheath** (the protective coating of nerves) in the central nervous system.
- **Symptoms:** Vision problems (optic neuritis), muscle weakness, numbness, and fatigue. It often follows a "relapse-remitting" pattern.
- **Management:** Steroids for acute attacks and disease-modifying therapies (Interferons) to prevent relapses.

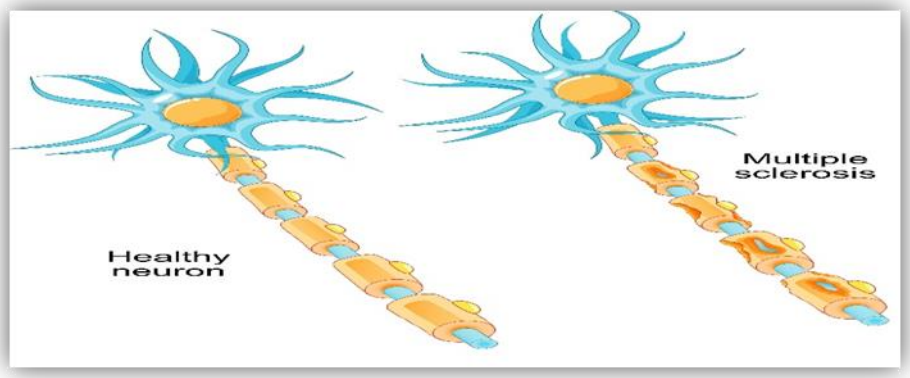


Fig 1: Multiple Sclerosis destroys the myelin sheath, causing signal failure compared to a healthy neuron.

5. Amyotrophic lateral sclerosis: Amyotrophic lateral sclerosis (ALS) is a progressive disorder affecting motor neurons in the brain and spinal cord.

- **Cause:** Progressive death of upper and lower motor neurons. While mostly sporadic, some cases are linked to the *SOD1* mutation.
- **Symptoms:** Muscle twitching (fasciculations), progressive weakness, and eventual respiratory failure. Cognitive function often remains intact.
- **Management:** Riluzole to slow progression; focus is on respiratory and nutritional support.

6. Batten disease: Batten disease is a rare inherited lysosomal storage disorder that primarily affects children.

- **Cause:** A rare, fatal **lysosomal storage disorder** in children where genetic mutations cause fats/proteins (lipopigments) to build up in cells.
- **Symptoms:** Early vision loss, seizures, motor decline, and childhood dementia.
- **Management:** Mostly supportive (seizure control), though enzyme replacement therapy helps some specific types.

7. Creutzfeldt–Jakob disease: Creutzfeldt–Jakob disease (CJD) is a rare and rapidly progressive prion disease.

- **Cause:** Triggered by **prions** (misfolded proteins) that cause the brain to develop a "spongy" texture (spongiform degeneration).
- **Symptoms:** Extremely rapid mental decline, muscle jerks, and visual impairment, usually leading to death within a year.
- **Management:** No cure; focus is strictly on palliative/comfort care.

1.2 Amnesia

Amnesia is a condition characterized by partial or complete loss of memory, which may arise due to brain injury, neurological disorders, or as a temporary effect of certain sedative or hypnotic drugs. The extent of memory loss depends on the severity and location of the neural damage. Amnesia can significantly impact daily functioning, learning, and quality of life.

Amnesia is of following types:

- **Retrograde Amnesia:** This form involves the inability to recall information or events that occurred prior to a specific incident, such as a traumatic accident or surgery.
- **Anterograde Amnesia:** Anterograde amnesia is characterized by difficulty in forming new memories after the onset of the condition.

Causes and Mechanisms of Amnesia:

1. Head Trauma: **2.** Traumatic Events **3.** Physical Deficiencies

1. **Symptoms:** Impairment of Declarative Memory, specifically Semantic (facts/concepts) and Episodic (personal experiences) recall.

Pharmacological Management of Amnesia

- **Cholinesterase Inhibitors:**These drugs increase acetylcholine levels in the brain by preventing its breakdown. Common agents include: Donepezil (Aricept),Rivastigmine (Exelon) ,Galantamine (Razadyne)
- **Glutamate Regulators:** Drugs such as memantine (Namenda) help normalize glutamate signaling in the central nervous system to prevent excitotoxic neuronal damage.

1.2.1 Role of Anticholinergic Drugs in Memory Modulation: Anticholinergic drugs influence memory by altering activity within neural networks critical for cognitive function. Studies on healthy elderly subjects show that administration of low-dose scopolamine (0.2 mg IV) reduces episodic memory performance and selectively decreases connectivity within cortical networks such as the salience and default mode networks.

1.2.2 Herbal Approaches for Amnesia Prevention: Ayurvedic medicine describes a class of herbs known as Medhya Rasayana, reputed to enhance intelligence and memory. Key herbal agents include: jatamansi, ashwagandha, vacha, jyotishmati, shankhpushpi, amalaki, yashtimadhu, kavach beej, brahmi, mandukparni. These herbs exert neuroprotective effects by:

- Inhibiting acetylcholinesterase (AChE) to increase acetylcholine levels

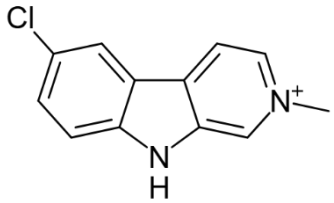
- Enhancing cerebral blood flow, thereby improving oxygen and nutrient delivery to neurons
- Exhibiting antioxidant activity to reduce oxidative stress in brain tissues.

3 Nostocarboline

Marine algae and cyanobacteria are rich sources of bioactive compounds with therapeutic potential. Nostocarboline, a β-carboline alkaloid derived from freshwater cyanobacteria of the genus *Nostoc*, has demonstrated diverse pharmacological properties. Its antioxidant and neuroprotective activities suggest potential applications in neurodegenerative disorders, particularly those associated with cholinergic deficits.

Chemical Properties: Nostocarboline belongs to the carboline alkaloid class and features a tricyclic indole-pyridine structure, a subgroup of indole alkaloids. Structurally, it resembles tryptamine, with an ethylamine chain fused to the indole ring through an additional carbon, forming a rigid three- ring system conducive to biological activity.

Pharmacological Effects:



- **Butyrylcholinesterase (BChE):** IC50 = 13.2 µM
- **Acetylcholinesterase (AChE):** IC50 = 5.3 µM

3. EXPERIMENTAL: In-Silico Evaluation of Nostocarboline:

3.1 Bioactivity Score: The drug-likeness and potential biological activity of Nostocarboline were evaluated using the online tool **Molinspiration** The molecular structure of Nostocarboline was submitted in SMILES format for assessment. Bioactivity scores provide a quantitative estimate of the likelihood that a compound can interact with various biological targets. Nostocarboline demonstrated a high enzyme inhibition score of **0.98**, falling well within the 0.50–1.0 range indicative of significant bioactivity. This result suggests strong potential as an enzyme inhibitor, supporting its suitability for further computational studies targeting acetylcholinesterase (AChE) and butyryl cholinesterase (BChE)

Table 1: Molinspiration Bioactivity Scores for Nostocarboline.

S.NO	PROPERTIES	SCORE
1.	GPCR ligand	-0.08
2.	Ion channel modulator	0.61
3.	Kinase inhibitor	-0.29
4.	Nuclear receptor ligand	-1.77
5.	Protease inhibitor	-0.65
6.	Enzyme inhibitor	0.98

3.2 Molecular Docking Studies

Molecular docking simulations were performed using **AutoDock 4.2**, supported by **Python 2.7** and **MGLTools**, to investigate the binding interactions of Nostocarboline with AChE and BChE. The crystal structures of AChE (PDB ID: 4EY7) and BChE (PDB ID: 4BDS) were obtained from the Protein Data Bank. Proteins were pre-processed by removing heteroatoms, adding polar hydrogens, and assigning Gasteiger charges. Ligands were allowed flexible torsions during docking. Active site pockets were identified using LigPlot and validated via the Computed Atlas of Surface Topography of Proteins (CASTp) server. Docking employed the Lamarckian Genetic Algorithm to optimize binding poses, and results were visualized using Discovery Studio Visualizer 4.1. Nostocarboline exhibited strong binding to both AChE and BChE with multiple non-covalent interactions.

For **AChE, key interactions included:**

Van der Waals interactions: Tyr124, Arg296
Hydrogen bond: Phe338
Carbon–hydrogen bonds: Ser293, Phe295, Phe338
Pi–donor hydrogen bonds: Trp286, Phe297, Tyr341, Tyr337
Pi–Pi stacking: Phe338
Pi–alkyl interactions: Val294

➢ **Van der Waals interactions:** Asp70, Gly78, Tyr332, Trp430, Tyr440
➢ **Hydrogen bonds:** Asp70, Ser79
➢ **Carbon–hydrogen bonds:** Asn83, Thr120, Tyr440
➢ **Pi–Pi stacking:** Trp82
➢ **Alkyl interactions:** His438
➢ **Pi–alkyl interactions:** Ala328, Met437

In BChE, the ligand formed

These interactions highlight the compound's versatility and ability to engage key residues within the catalytic and peripheral anionic sites of both enzymes, suggesting potential dual inhibitory activity.

Table 2: Docking Interactions and Binding Energies.

S.NO	Target	Binding Energy (kcal/mol)	Inhibition Constant (µM)	Key Interactions
1	AChE	-7.21	5.23	Tyr124, Arg296 (vdW); Phe338 (H-bond); Ser293, Phe295, Phe338 (C–H bond); Trp286, Phe297, Tyr341, Tyr337 (Pi–donor H-bond); Phe338 (Pi–Pi stacked); Val294 (Pi–alkyl)
2	BChE	-7.06	6.70	Asp70, Gly78, Tyr332, Trp430, Tyr440 (vdW); Asp70, Ser79 (H-bond); Asn83, Thr120, Tyr440 (C–H bond); Trp82 (Pi–Pi stacked); His438 (Alkyl); Ala328, Met437 (Pi–alkyl)

3.3 In-Silico ADME Predictions: Pharmacokinetic and drug-likeness properties were evaluated using **SwissADME** .Nostocarboline showed favorable characteristics:

- **Molecular weight:** 217.67 g/mol
- **Lipophilicity (XLOGP3):** 3.08
- **Solubility (ESOL Log S):** -3.77 (classified as soluble)
- **Gastrointestinal absorption:** High
- **Blood–brain barrier permeability:** Yes
- **No violations** in Lipinski, Ghose, Veber, Egan, or Muegge rules

Table 3: ADME Properties of Nostocarboline.

S,NO	PROPERTIES	VALUE
1	Formula	C12H10ClN2+
2	MW	217.67
3	Heavy atoms	15
4	Aromatic heavy atoms	13
5	Rotatable bonds	0
6	H-bond donors	19.67
7	H-bond acceptors	3.08
8	TPSA	High
9	GI absorption	217.67
10	BBB permeant	Yes
11	Bioavailability score	0.55
12	Lipinski violations	0

3.4 Boiled Egg Diagram: It is generated via SwissADME, visually illustrates Nostocarboline's ability to penetrate the blood-brain barrier (BBB) and achieve passive gastrointestinal absorption. Nostocarboline lies within the **BBB-permeant region**, indicating

efficient CNS delivery. This property is critical for neuroactive compounds targeting AChE and BChE in neurodegenerative disorders.

3.5 RESULTS

3.5.1 Bioactivity Score

The bioactivity of Nostocarboline was evaluated using the Molinspiration bioactivity prediction tool. The analysis indicated an enzyme inhibition score of 0.98, suggesting a strong likelihood of biological activity. According to Molinspiration classification, compounds with bioactivity scores ranging from 0.50 to 1.00 are considered highly active. Therefore, the obtained score highlights the significant enzyme inhibitory potential of Nostocarboline.The Molinspiration bioactivity assessment is based on the presence of specific molecular fragments and structural features within the compound. These fragments contribute to the prediction of interaction with biological targets such as enzymes. The high bioactivity score obtained in this study suggests that Nostocarboline may serve as a promising enzyme inhibitor. Consequently, this quantitative evaluation provides valuable insight into the pharmacological significance of Nostocarboline and supports its potential application in drug discovery and development.

Table 4: Molinspiration activity score.

PROPERTIES	NOSTOCARBOLINE
GPCR ligand	-0.08
Ion channel modulator	0.61
Kinase inhibitor	-0.29
Nuclear receptor ligand	-1.77
Protease inhibitor	-0.65
Enzyme inhibitor	0.98

3.5.2 Molecular Docking

Molecular docking analysis was performed to investigate the interaction of Nostocarboline with the target enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). The docking results revealed that Nostocarboline forms several significant interactions within the active sites of both enzymes, indicating its potential inhibitory activity.In the case of AChE, van der Waals interactions were observed with Tyr124 and Arg296. Hydrogen bonding occurred with Phe338, while carbon–hydrogen bonds were formed with Ser293, Phe295, and Phe338. π-donor hydrogen bond interactions were identified with Trp286, Phe297, Tyr341, and Tyr337. Additionally, strong π–π stacking with Phe338 and a π-alkyl interaction with Val294 contributed to the stabilization of the ligand within the binding pocket.For BChE,

Nostocarboline exhibited van der Waals interactions with Asp70, Gly78, Tyr332, Trp430, and Tyr440. Hydrogen bonds were formed with Asp70 and Ser79, while carbon–hydrogen bonds involved Asn83, Thr120, and Tyr440. π–π stacking was observed with Trp82, along with alkyl interaction with His438 and π-alkyl interactions with Ala328 and Met437, enhancing ligand–enzyme stability.

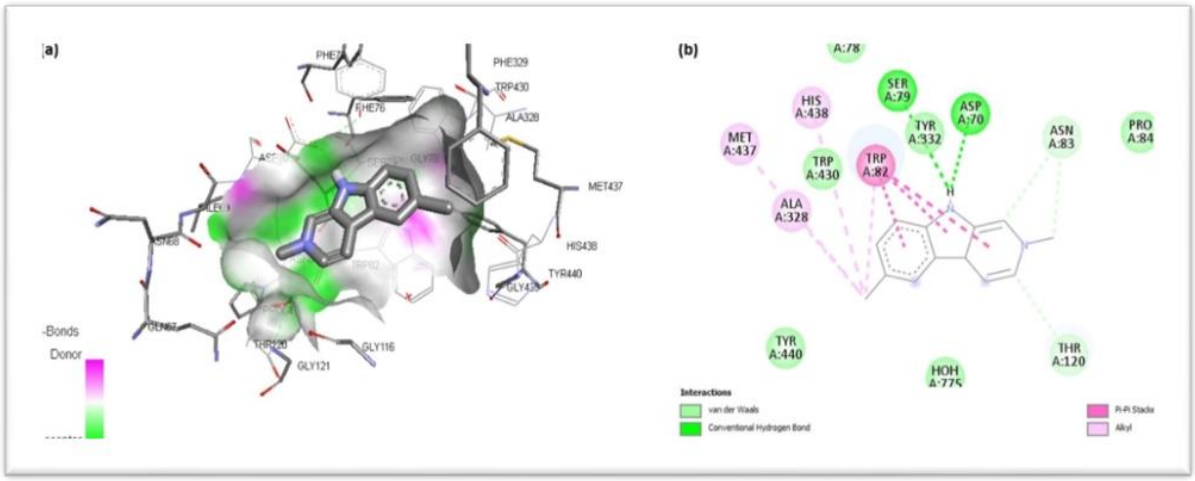


Figure 3: Docking interaction of Nostocarboline with acetylcholinesterase (a) 2D interaction (B) 3D interaction.

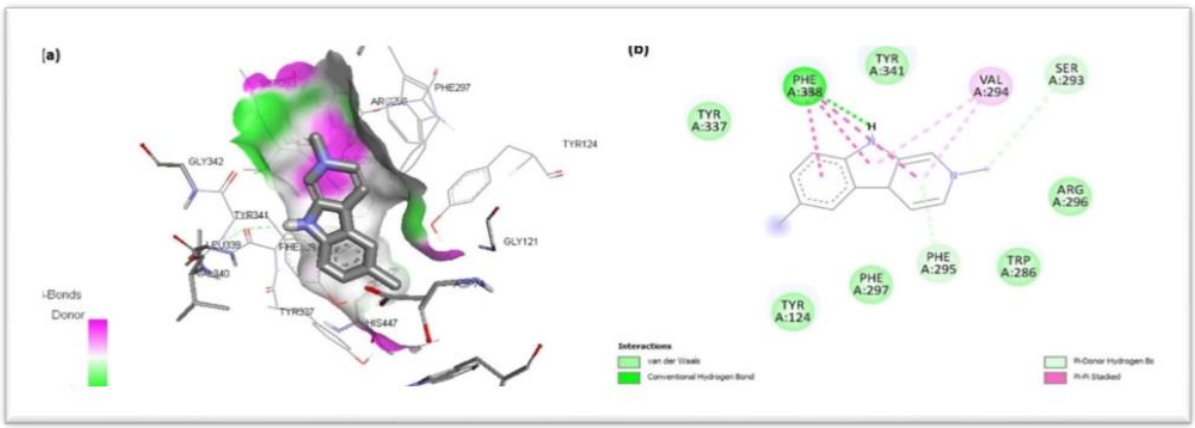


Figure 4: Docking interaction of Nostocarboline with acetylcholinesterase (a) 2D interaction (B) 3D interaction.

Table 5: Docking interactions of Nostocarboline with COX-2.

Target	Binding Energy (kCal/mol)	Inhibition Constant (μM)	Interactions
AchE	-7.21	5.23	**van der waals interaction:** Tyr 124, Arg 296, **Hydrogen bond** : Phe 338, **Carbon Hydrogen bond:** Ser 293, Phe

			295, Phe 338 **Pi donor hydrogen bond :** Trp 286, Phe 297, Tyr 341, Tyr 337 **Pi-Pi stacked :** Phe 338 Pi-alkyl: Val 294
BchE	-7.06	6.70	**van der waals interactions:** Asp 70, Gly 78,Tyr 332, Trp 430, Tyr 440 **Hydrogen bond:** Asp 70, Ser 79 **Carbon Hydrogen bond** : Asn 83, Thr 120, Tyr 440 **Pi-Pi stacked bonding:** Trp 82 **Alkyl bond:** His 438 **Pi-alkyl:** Ala 328, Met 437

The absorption, distribution, metabolism, and excretion (ADME) properties of Nostocarboline were evaluated to determine its drug-likeness and pharmacokinetic potential. Nostocarboline possesses the molecular formula $C_{12}H_{10}ClN_2^+$ with a molecular weight of 217.67 g/mol**,** indicating a relatively small molecular size that is generally favorable for drug development.The lipophilicity of the compound, represented by XLOGP3 (3.08) and WLOGP (2.8) values, suggests an appropriate balance between hydrophilicity and lipophilicity, which may facilitate effective permeability across biological membranes, including the blood–brain barrier (BBB). The ESOL Log S value of −3.77 indicates that Nostocarboline has good aqueous solubility, which is an important factor influencing drug absorption and bioavailability. Furthermore, the compound demonstrates high gastrointestinal (GI) absorption**,** suggesting efficient uptake after oral administration.Drug-likeness evaluation revealed that Nostocarboline does not violate any of the major pharmaceutical guidelines, including Lipinski, Ghose, Veber, Egan, and Muegge rules, which are commonly used to predict oral bioavailability and drug-like behavior. Overall, these findings indicate that Nostocarboline possesses favorable pharmacokinetic characteristics and may serve as a promising candidate for further drug development studies.

Table 6: ADME properties of Nostocarboline.

Molecule	Nostocarboline
Formula	$C_{12}H_{10}ClN^{2+}$
MW	217.67
#Heavy atoms	15
#Aromatic heavy atoms	13
Fraction Csp3	0.08
#Rotatable bonds	0
#H-bond acceptors	0
#H-bond donors	1

MR	64.41
TPSA	19.67
iLOGP	-1.97
XLOGP3	3.08
WLOGP	2.8
MLOGP	2.44
Silicos-IT Log P	3.31
Consensus Log P	1.93
ESOL Log S	-3.77
ESOL Class	Soluble
Ali Log S	-3.16
Ali Class	Soluble
Silicos-IT LogSw	-4.78
Silicos-IT class	Moderately soluble
GI absorption	High
BBB permeant	Yes
Pgp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
log Kp (cm/s)	-5.44
Lipinski #violations	0
Ghose #violations	0
Veber #violations	0
Egan #violations	0
Muegge #violations	0
Bioavailability Score	0.55
PAINS #alerts	0
Brenk #alerts	1
Leadlikeness #violations	1
Synthetic Accessibility	1.63

3.5.3 BOILED-Egg Model Analysis

The BOILED-Egg model provides a graphical representation used to predict the gastrointestinal absorption and brain penetration ability of a compound. In the present analysis, Nostocarboline is positioned within the region that indicates effective penetration of the **blood–brain barrier (BBB)**. This observation suggests that the molecule possesses physicochemical properties favorable for crossing the protective barrier surrounding the brain.

The BOILED-Egg diagram visually highlights the compound's ability to reach the central nervous system, which is an important consideration for drugs intended to act on neurological

targets. The predicted BBB permeability of Nostocarboline indicates its potential suitability for therapeutic applications related to the **central nervous system (CNS)**. Therefore, the model supports the possibility that Nostocarboline could effectively interact with neural targets and may be further investigated for its role in the treatment of neurodegenerative disorders.

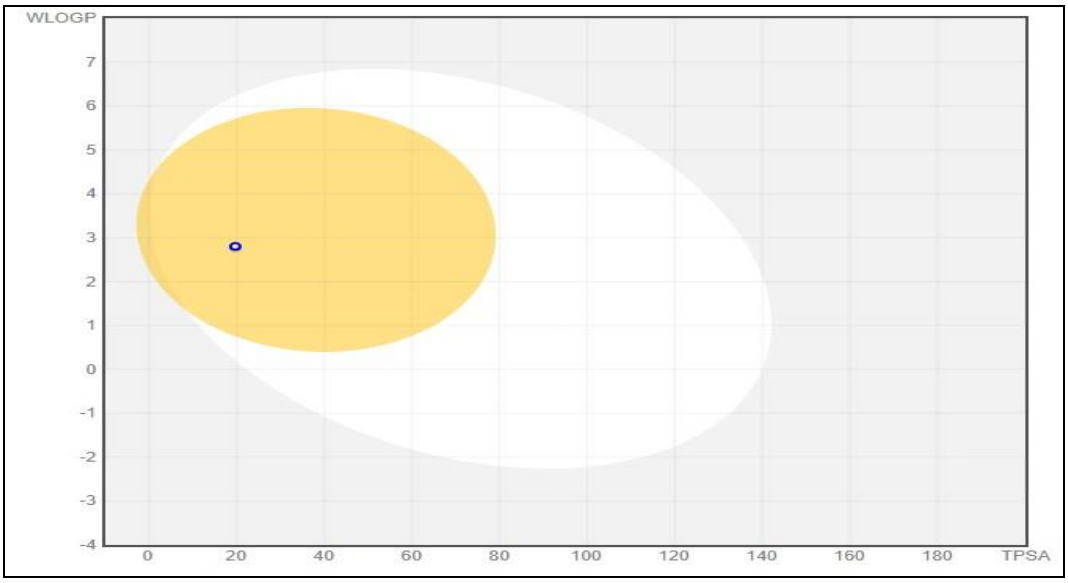


Figure 5: Boiled egg diagram for Nostocarboline.

3.6 DISCUSSION

Bioinformatics and computer-aided drug design have become important tools in modern drug discovery, allowing rapid identification and screening of potential drug candidates while reducing time and cost compared to traditional experimental methods. In this study, an in silico analysis was performed to evaluate the interaction of Nostocarboline with the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) using molecular docking techniques. Molecular docking results showed that Nostocarboline forms stable interactions within the active site of acetylcholinesterase. Important residues such as Tyr124, Phe338, Trp286, Tyr341, and Tyr337 contributed to ligand stabilization through hydrogen bonding and π–π stacking interactions. These interactions indicate that the compound can effectively bind within the enzyme gorge and potentially inhibit its activity.

Similarly, docking with butyrylcholinesterase revealed significant interactions with residues including Asp70, Tyr332, Trp82, and His438 through van der Waals forces, hydrogen bonding, and π–π stacking interactions. These contacts suggest that Nostocarboline can interact with key structural regions of the enzyme and form a stable ligand–protein

complex.Drug-likeness analysis using Molinspiration predicted strong enzyme inhibition potential for Nostocarboline. ADME evaluation also showed favorable pharmacokinetic properties, including suitable lipophilicity, good solubility, high gastrointestinal absorption, and no violations of Lipinski, Ghose, Veber, Egan, or Muegge rules. Additionally, BOILED-Egg analysis suggested the compound may cross the blood–brain barrier, indicating potential central nervous system activity.

Overall, the computational findings suggest that Nostocarboline possesses promising pharmacological properties and may act as a potential cholinesterase inhibitor. However, further in vitro and in vivo studies are required to confirm its therapeutic potential, particularly for neurodegenerative diseases such as Alzheimer's disease.

4. SUMMARY AND CONCLUSION

This study utilized bioinformatics tools and computer-aided drug discovery approaches to evaluate the therapeutic potential of Nostocarboline. Molecular docking analysis with the enzyme Acetylcholinesterase demonstrated several important interactions, including hydrogen bonding, electrostatic forces, and hydrophobic contacts, suggesting that the compound may influence enzyme activity. The drug-likeness assessment using the Molinspiration platform indicated favorable properties, supporting its potential effectiveness as an enzyme inhibitor. In addition, the analysis of ADME characteristics showed a balanced pharmacokinetic profile, which is an essential factor for drug development. Overall, these findings suggest that Nostocarboline could serve as a promising lead compound for future research, particularly for disorders associated with cholinergic imbalance such as Alzheimer's disease. Further experimental and clinical investigations are required to validate its therapeutic potential.

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