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IN SILICO-STRUCTURE BASED DRUG DESIGN; MOLECULAR DOCKING STUDIES, ADME STUDIES OF NOVEL GALANT-AMINE DERIVATIVE AS NEURO-PROTECTIVE AGENTS

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Abstract: The identification and development of novel therapeutic medicines has been transformed by the discipline of in silico drug design. The development of neuroprotective drugs for the treatment of neurodegenerative illnesses like Alzheimer's is one such exciting application. The neuroprotective effects of galantamine, a well-known acetylcholinesterase inhibitor, have been extensively researched. A thorough analysis of in silico structure-based drug design is presented in this presentation, with particular attention paid to molecular docking and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) investigations of new galantamine derivatives.Alzheimer's disease (AD) poses a significant global health challenge with limited therapeutic options. Acetyl cholinesterase (Ache) inhibitors represent a cornerstone in AD treatment by enhancing cholinergic neurotransmission.

Index Terms - Computer-Aided Drug Design, Alzheimer's, Molecular Docking, Acetylcholinesterase, ADMET

I. INTRODUCTION

Neurological disorders encompass a broad spectrum of conditions affecting the central nervous system (CNS), which includes the brain, spinal cord, and peripheral nerves. These disorders result from various abnormalities in the structure or function of the nervous system, leading to disruptions in the transmission of electrical signals, biochemical imbalances, or degeneration of neural tissues. This detailed exploration will cover several major neurological disorders, their pathophysiology, clinical manifestations, and current scientific perspectives on diagnosis and treatment.

Alzheimer'sdisease:

Alzheimer's disease (AD), first identified and named by German scientist Alois Alzheimer in 1907, is a degenerative neurological condition characterized by the progressive loss of cognitive function. Globally, around 47 million individuals are impacted by this ailment, with predictions indicating astaggering 62% increase in cases by 2050. AD is marked by the gradual deterioration of neurons within the central nervous system and the dysfunction of nerve cells. Early-onset AD (EOAD), comprising only 1–2% of AD cases, typically exhibits hereditary autosomal dominant traits, with key genes such as amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) implicated in its manifestation. Mutations in these genes have been identified in familial AD cases, suggesting a genetic basis for the disorder. Various risk factors, including neuritic plaques, trisomy 21, and rapid synaptic loss, contribute to the development of AD. Clinically, AD is primarily diagnosed based on progressive

cognitive decline, memory loss, impairment in daily activities, and a range of neuropsychiatric symptoms such as apathy, agitation, anxiety, and hallucinations. The "cholinergic hypothesis" has gained traction as prominent the origin understanding and treating AD, suggesting that cholinergic dysfunction plays a crucial role in cognitive decline. Studies have demonstrated a link between cholinergic activity and amyloid processing, with muscarinic receptor activity influencing the amyloidogenic pathway. The "amyloid cascade hypothesis," proposed in 1992, posits amyloid- beta (Aβ) accumulation as a central event triggering neurodegeneration. Other hypotheses, including the oligomeric and metallic hypotheses, offer further insights into the mechanisms underlying AD progression.

Recent research has highlighted the role of endogenous metal ions, particularly copper (II),iron (III),and zinc (II),in exacerbating neurodegenerative processes by promoting Aβ aggregation and toxicity. Additionally, AD is associated with deficits in the neurotransmitter acetylcholine (ACh) and oxidative stress resulting from glutamatergic transmission dysregulation.

Acetylcholinesterase (AChE) inhibition has emerged as a therapeutic approach for AD, as well as other disorders like dementia, myasthenia gravis, glaucoma, and Parkinson's disease, due to its role in regulating memory and cognition within cholinergic synapses. Alzheimer's disease (AD), first identified and named by German scientist Alois Alzheimer in 1907, is a degenerative neurological condition characterized by the progressive loss of cognitive function. Globally, around 47 million individuals are impacted by this ailment, with predictions indicating a staggering 62% increase in cases by 2050. AD is marked by the gradual deterioration of neurons within the central nervous system and the dysfunction of nerve cells. Early-onset AD (EOAD), comprising only1–2% of AD cases, typically exhibits hereditary autosomal dominant traits, with key genes such as amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) implicated in its manifestation. Mutations in these genes have been identified in familial AD cases, suggesting a genetic basis for the disorder. Various risk factors, including neuritic plaques, trisomy 21, and rapid synaptic loss, contribute to the development of AD.

Pathophysiology: Alzheimer's disease is a progressive neurodegenerative disorder characterized by the accumulation of beta-amyloid plaques and neurofibrillary tangles in the brain. These pathological changes lead to synaptic dysfunction, neuronal loss, and impaired neurotransmission.

Clinical Manifestations:

AD typically presents with memory loss, cognitive decline, and behavioral changes. As the disease progresses, individuals may experiencedifficultiesinlanguage,executivefunction,andeventually,activities of daily living.

Diagnosis and Treatment: Diagnosis involves clinical assessments, neuroimaging, and biomarker analysis. While there is no cure for AD, current treatments focus on symptomatic relief, including cholinesterase inhibitors and N-methyl-D-aspartate(NMDA)receptorantagonists.Ongoingresearchexplores disease-modifying therapies targeting beta-amyloid and tau protein.

- **Parkinson'sdisease(PD):**

Pathophysiology: Parkinson's disease is characterized by the degeneration of dopaminergic neurons in the substantia nigra, leading to a decrease in dopamine levels. Accumulation of alpha-synuclein inclusions, known as Lewy bodies, contributes to neuronal dysfunction.

Clinical Manifestations: Motor symptoms include tremors, bradykinesia, rigidity, and postural instability. Non-motor symptoms such as cognitive impairment, autonomic dysfunction, and mood disorders also occur.

Diagnosis and Treatment: Diagnosis relies on clinical evaluation, and neuroimaging may be used to rule out other conditions. Treatment involves dopamine replacement therapies, such as levodopa, and other medications targeting motor and non-motor symptoms. Deep brain stimulation (DBS) is a surgical intervention for refractory cases.

- ***MultipleSclerosis(MS):***

Pathophysiology: Alzheimer's disease is a progressive neurodegenerative disorder characterized by the accumulation of beta-amyloid plaques and neurofibrillary tangles in the brain. These pathological changes lead to synaptic dysfunction, neuronal loss, and impaired neurotransmission.

Clinical Manifestations:
AD typically presents with memory loss, cognitive decline, and behavioral changes. As the disease progresses, individuals may experience difficulties in language, executive function, and eventually, activities of daily living.

Diagnosis and Treatment: Diagnosis involves clinical assessments, neuroimaging, and biomarker analysis. While there is no cure for AD, current treatments focus on symptomatic relief, including cholinesterase inhibitors and N-methyl-D-aspartate (NMDA)receptorantagonists.Ongoingresearchexplores disease-modifying therapies targeting beta-amyloid and tau protein.

MultipleSclerosis(MS):

Pathophysiology: Multiple sclerosis is an autoimmune disorder characterized by demyelination and inflammation in the CNS. Immune cells target myelin, leading to disrupted nerve signals and neurodegeneration.

Clinical Manifestations: MS presents with a wide range of symptoms, including fatigue, sensory disturbances, muscle weakness, and impaired coordination. Symptoms vary based on the location and extent of demyelination.

Diagnosis and Treatment: Diagnosis involves clinical and imaging criteria, including magnetic resonance imaging (MRI).

Epilepsy:

Pathophysiology: Epilepsy is characterized by abnormal neuronal activity leading to recurrent seizures. Causes may include genetic factors, brain injuries, or structural abnormalities.

Clinical Manifestations: Seizure types vary, ranging from generalized tonic- clonic seizures to focal seizures with or without impaired awareness. Other manifestations include auras, loss of consciousness, or automatisms.

Diagnosis and Treatment: Diagnosis involves a thorough medical history, electroencephalogram (EEG), and imaging studies. Antiepileptic drugs (AEDs) are the primary treatment, aiming to control seizures with minimal side effects. For refractory cases, surgical interventions like respective surgery or neurostimulation may be considered.

Amyotrophic Lateral Sclerosis(ALS):

Pathophysiology: ALS is a progressive neurodegenerative disorder affecting motor neurons in the brain and spinal cord. The exact etiology is not fully understood, but genetic and environmental factors play a role.

Clinical Manifestations: Initial symptoms include muscle weakness, twitching, and spasticity, progressing to paralysis and respiratory failure. Cognitive and behavioral changes may also occur in some cases.

Diagnosis and Treatment: Diagnosis relies on clinical and electrophysiological assessments, with no specific diagnostic test. Treatment involves supportive care, including respiratory support, physical therapy, and medications to manage symptoms. Riluzole is an FDA-approved drug that may slow disease progression.

Applications in Neurological Disorders:

Alzheimer's disease: Neuroprotective agents are explored for their potential in slowing the progression of Alzheimer's disease and preserving cognitive function.

Parkinson's disease: Strategies to protect dopaminergic neurons, commonly affected in Parkinson's disease, are a focus of research in the development of neuroprotective agents.

Stroke: Agents that mitigate the damage caused by ischemic stroke or enhance neuronal recovery after a stroke are of particular interest.

Traumatic Brain Injury: Neuroprotective interventions aim to minimize secondary damage following traumatic brain injury, promoting neuronal survival and functional recovery.

Challenges and Future Directions:

Developing effective neuro-protective agents faces challenges, including crossing the blood-brain barrier, targeting specific cellular pathways, and addressing the multifactorial nature of many neurological disorders. Personalized medicine approaches may become more prevalent, tailoring neuroprotective interventions based on individual genetic and environmental factors.

Natural Neuro-protective Compounds:

Some compounds found in plants, herbs, and natural sources exhibit neuroprotective properties. Examples include curcumin from turmeric, resveratrol from grapes, and flavonoids from various fruits and vegetables.

Clinical Trials: Many neuroprotective agents undergo rigorous testing in preclinical and clinical trials to evaluate their safety and efficacy in humans. The development and exploration of neuroprotective agents hold promise for addressing the challenges posed by neurological disorders. The multifaceted nature of these agents, targeting various pathways and mechanisms Continued research in this field is crucial for advancing our understanding and developing effective treatments for neurological conditions. Galantamine is a natural alkaloid compound derived from the bulbs and flowers of several plant species, including the Galanthus nivalis (snowdrop) and Leucojum aestivum (summer snowflake). This compound has gained attention for its pharmacological properties, particularly its role as an acetylcholinesterase inhibitor. Acetylcholinesterase is an enzyme that breaks down the neurotransmitter acetylcholine, and by inhibiting its activity, galantamine increases acetylcholine levels in the brain. Originally used for centuriess in traditional medicine, galantamine has found application in modern medicine.

Mechanismof Action:

Galantamine primarily functions as an acetylcholinesterase inhibitor. By inhibiting this enzyme, galantamine increases the concentration of acetylcholine in the synaptic cleft, enhancing cholinergic neurotransmission.
Additionally, galantamine has been suggested to modulate nicotinic acetylcholine receptors, further influencing cognitive function.

Clinical Use: Alzheimer's Disease: Galantamine is approved for the treatment of mild to moderate Alzheimer's disease. It is prescribed to improve cognitive function, including memory, attention, and overall mental clarity, in individuals with this progressive neurodegenerative disorder.

Mild Cognitive Impairment: Some studies have explored the use of galantamine in individuals with mild cognitive impairment, condition that may precede Alzheimer's disease.

Dosage and Administration: Galantamine is typically administered orally in the form of tablets or extended-release capsules. Dosage may vary based on the specific medical condition, patient

Selection of Nucleus:

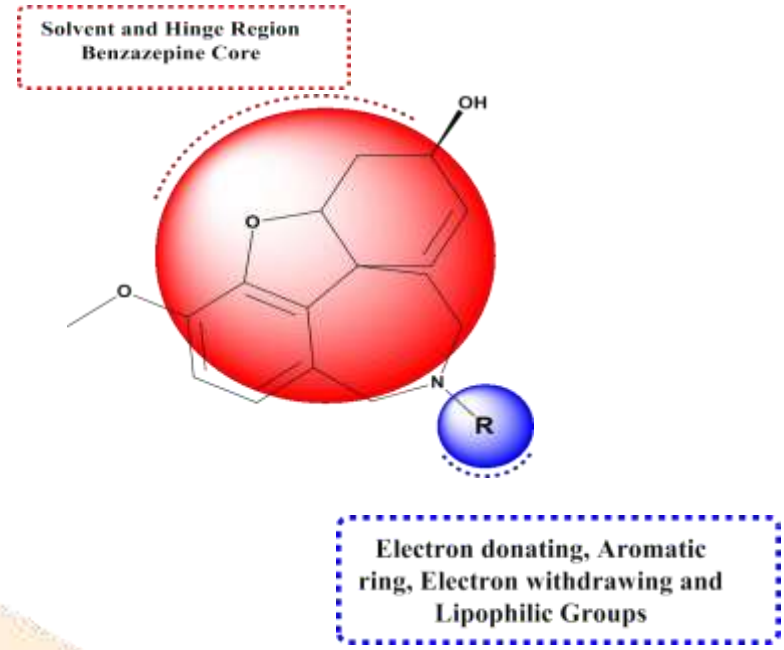
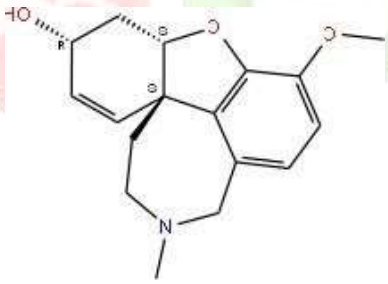
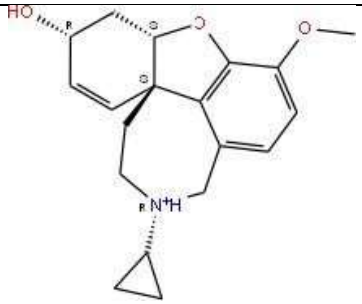
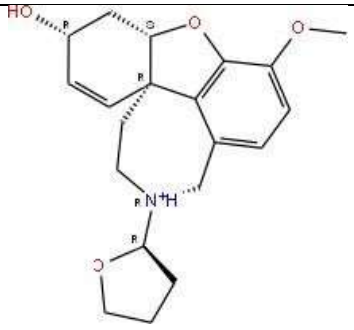
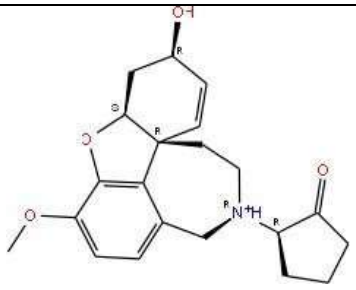
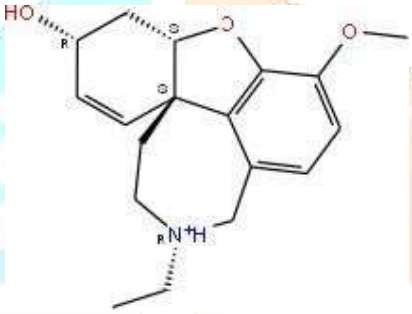
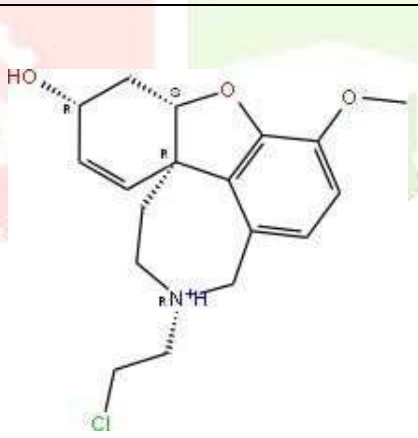
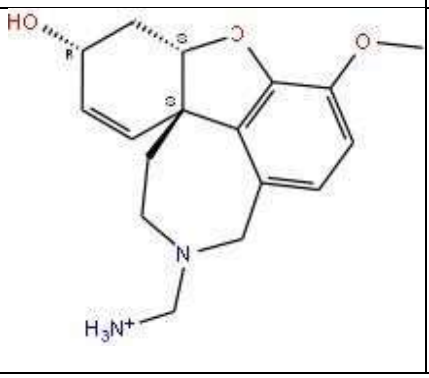
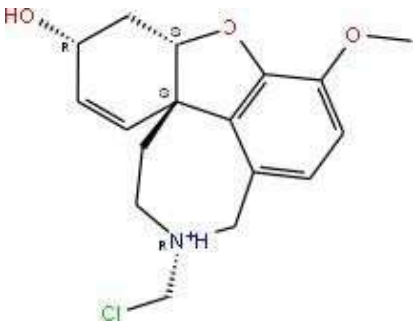
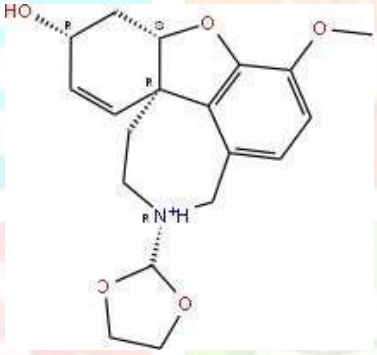
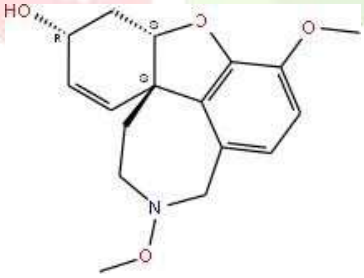
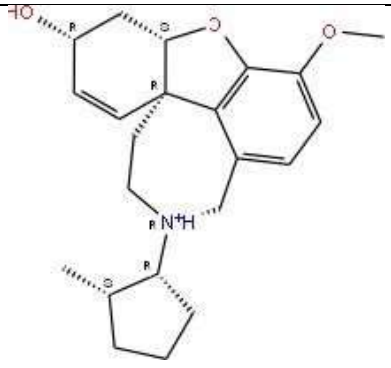


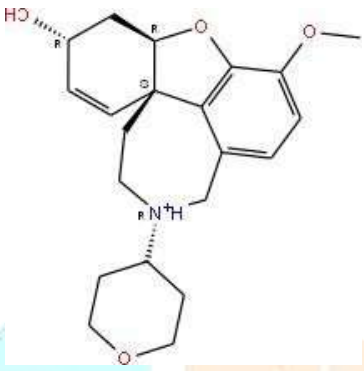
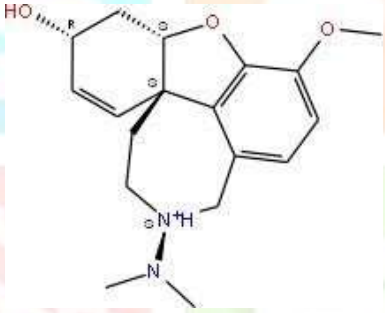
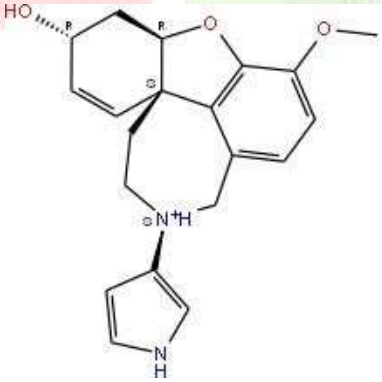
Figure 1 .Selection of nucleus

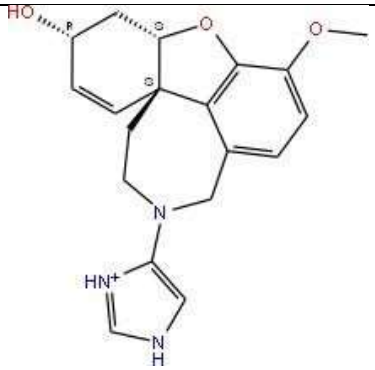
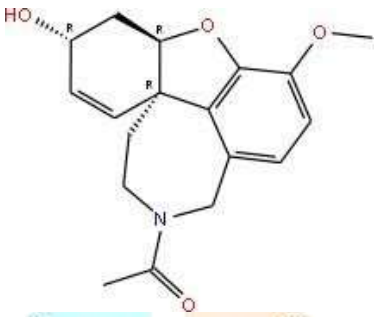
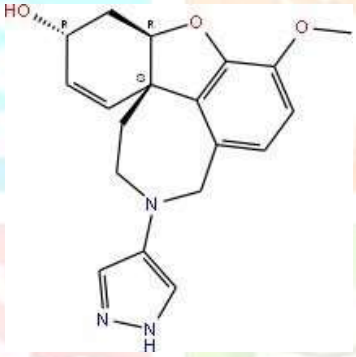
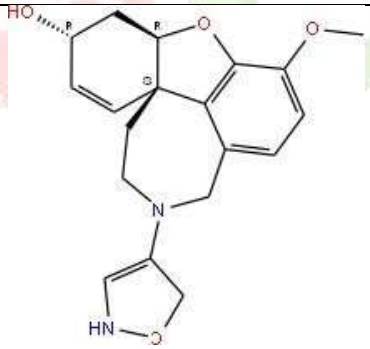
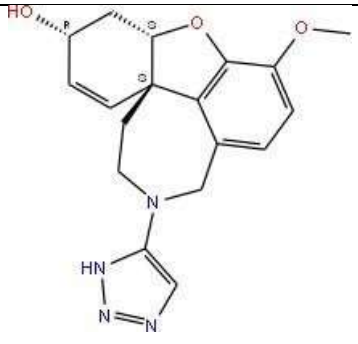
Table: 1. Designed Molecules, ADMET predicted analysis and Docking studies

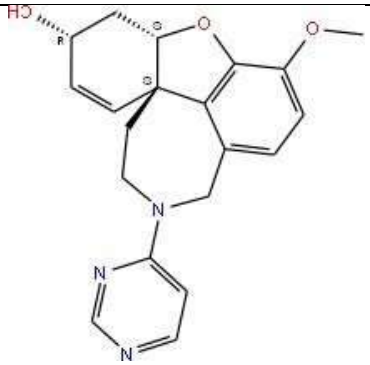
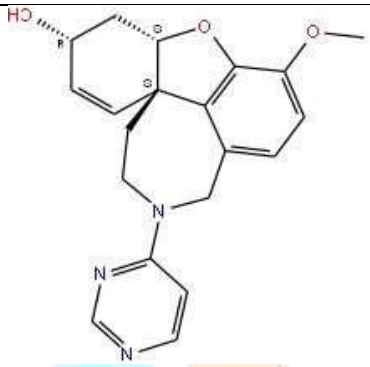
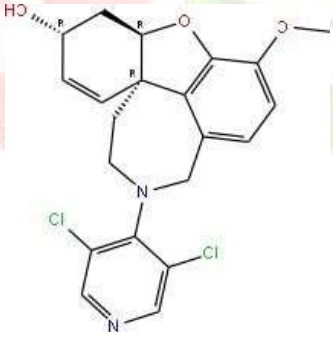
Sr. No.	Code	Molecules	Lipinski Rule	Bioavailability Score	Log *P*	GI abs	BBB Permeation	Tox. Class	Glide Score
1.	Ref.		Yes	0.55	2.64	High	Yes	3	-10.24
2.	MT01		Yes	0.55	2.32	High	Yes	3	-12.5

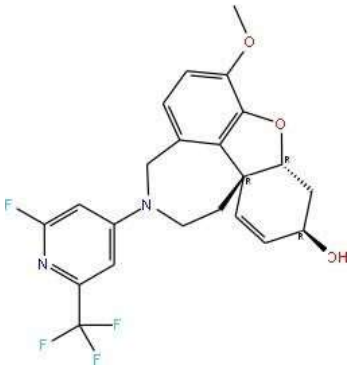
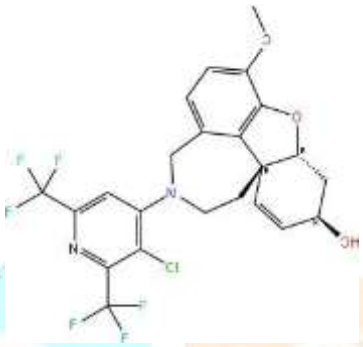
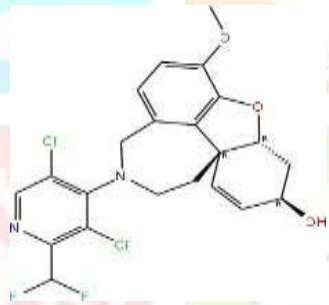
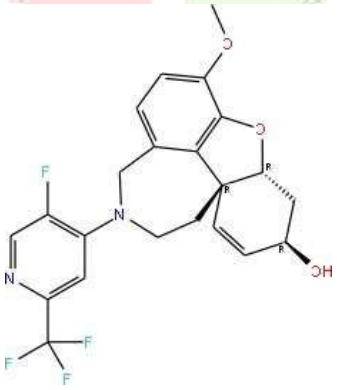
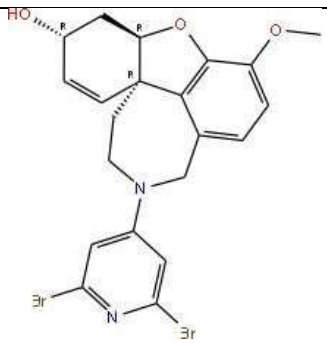
3.	MT02		Yes	0.55	2.30	High	Yes	3	-12.26
4.	MT03		Yes	0.55	1.82	High	Yes	4	-11.76
5.	MT04		Yes	0.55	2.02	High	Yes	3	-11.55
6.	MT05		Yes	0.55	1.63	High	No	3	-10.82
7.	MT06		Yes	0.55	1.89	High	No	4	-12.18

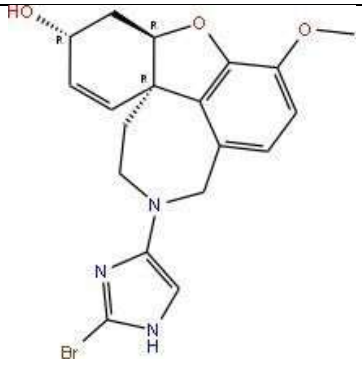
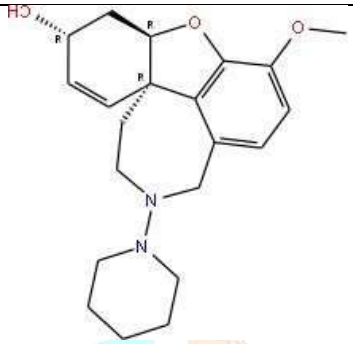
8.	MT07		Yes	0.55	2.35	High	Yes	3	-12.18
9.	MT08		Yes	0.55	2.44	High	No	4	-12.48
10.	MT09		Yes	0.55	2.32	High	No	4	-9.31
11.	MT10		Yes	0.55	2.53	High	No	4	-9.22
12.	MT11		Yes	0.55	2.30	High	No	4	-10.82

13.	MT12		Yes	0.55	2.14	High	No	3	-8.7
14.	MT13		Yes	0.55	2.45	High	Yes	4	-10.73
15.	MT14		Yes	0.55	2.79	High	Yes	4	-8.9
16.	MT15		Yes	0.55	2.40	High	Yes	3	-8.76
17.	MT16		Yes	0.55	2.64	High	Yes	3	-7.2

									
18.	MT17		Yes	0.55	2.55	High	Yes	4	-6.7
19.	MT18		Yes	0.55	2.26	High	No	4	-8.2
20.	MT19		Yes	0.55	2.29	High	Yes	3	-6.83
21.	MT20		Yes	0.55	3.10	High	No	3	-5.47

22.	MT21		Yes	0.55	2.96	High	No	3	-5.14
23.	MT22		Yes	0.55	2.40	High	No	3	-6.83
24.	MT23		Yes	0.55	1.31	High	No	3	-8.51
25.	MT24		Yes	0.55	1.33	High	No	4	-7.7

26.	MT25		Yes	0.55	1.90	High	No	4	-6.5
27.	MT26		Yes	0.55	2.21	High	No	4	-7.4
28.	MT27		Yes	0.55	1.14	High	No	3	-6.3
29.	MT28		Yes	0.55	2.77	High	No	3	-4.4
30.	MT29		Yes	0.55	2.56	High	No	3	-7.6

31.	MT30		Yes	0.55	2.32	High	Yes	3	-4.5
32.	MT31		Yes	0.55	2.21	High	Yes	4	-7

Results:

The series of designed compound is subjected though the ADME & toxicity prediction and further screening of compounds for molecular docking. On completion of the molecular docking based screening process, the resulting conformations poses of the ligands in the binding site of 4EY6 were studied and per residue interaction pattern with in 15 areas from center of grid was studied. Based on glide score top scoring molecules were selected. Compounds which interact most appropriately to 4EY6. A network of hydrogen bonds between the reported inhibitors and PHE338, TYR337, GLY122, SER203, PHE297,GLH202 and TRP86 was observed as well as hydrophobic interactions between the core of the ligands and surrounding lipophillic amino acid residues (eg, withALA204,TYR124,SER125,GLY121andTYR341).

Based on interaction pattern and knowledge based screening top 10 molecules out of 30 have good and dynamic score and interaction that could use for further studies

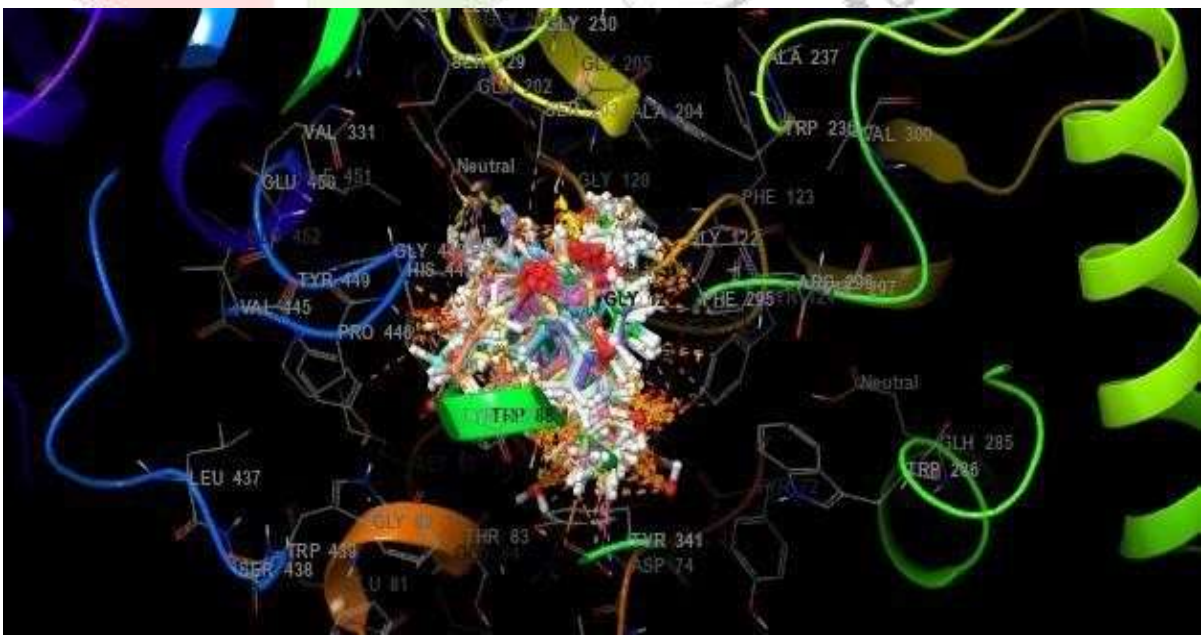


Figure 2.Superimposed view of all the Docked Compounds of series with Molecular target (4EY6)

Figure3.Protein-Ligand 3d and 2d interactions of molecule MT01

Figure 4.Protein-Ligand 3d and 2d interactions of molecule MT02

Figure 5.Protein-Ligand 3d and 2d interactions of molecule MT06

Figure 6 .Protein-Ligand 3d and 2d interactions of molecule MT07

Figure 7. Protein-Ligand 3d and 2d interactions of molecule MT08

Summary and Conclusion:

Summary:

This study explores the potential of novel galantamine derivatives as neuroprotective agents through in silico structure-based drug design techniques. The study begins with molecular docking studies, where in the interaction between the designed derivatives and their target proteins involved in neuro-protection is investigated. Through computational simulations, the binding affinities and interactions between the derivatives and target proteins are analyzed, providing insights into their potential efficacy.

Furthermore, the thesis delves into ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) studies to assess the pharmacokinetic and pharmacodynamic properties of the designed compounds. This comprehensive evaluation aids in predicting the drug-likeness, bioavailability, and safety profiles of the derivatives, crucial factors in the development of effective pharmaceutical agents.

The findings of the research contribute to the field of drug discovery by identifying promising galantamine derivatives with potential neuroprotective properties. Through computational methodologies, valuable insights are gained into the molecular mechanisms underlying their interaction with target proteins, offer in gradational basis for further experimental validation and optimization.

Conclusion:

The thesis demonstrates the efficacy of in silico structure-based drug design approaches in the discovery and optimization of novel neuroprotective agents. The molecular docking studies reveal the favorable binding interactions of the designed galantamine derivatives with their target proteins, highlighting their potential therapeutic utility. Additionally, ADMET studies provide valuable insights into the pharmacokinetic and pharmacodynamic properties of the compounds, guiding their further development towards clinical application.

Moving forward, the identified lead compounds warrant experimental validation through invitro and in-vivo studies to confirm their neuroprotective efficacy and safety profiles. Subsequent optimization based on the computational predictions and experimental data can enhance the potency, selectivity, and overall drug-like properties of the derivatives. Ultimately, the integration of computational and experimental methodologies in drug discovery holds significant promise for the development of effective treatments for neurodegenerative disorders and other diseases.

The findings of this research offer valuable insights into the molecular mechanisms underlying the interaction of galantamine derivatives with target proteins implicate dinneuro protection. Furthermore, the predicted ADMET profiles provide guidance for the selection and optimization of lead compounds with improved drug-like properties. Overall, the integration of in-silico structure-based drug design technique sholds promise for accelerating the discovery and development t of novel neuroprotective agents, addressing the unmet medical needs in the treatment of neurodegenerative diseases

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