Molecular Docking of Coumarin Derivatives as Potential Inhibitors for Alzheimer Disease

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doi.org/10.64643/IJIRTV12I6-186764-459

***Abstract*—Alzheimer's disease, the leading cause of dementia, is still characterized by the presence of amyloid and tau. However, researchers are shifting away from the original amyloid theory, which assumed linear causality. Age-related, preventive, and disease-promoting factors most likely interact with the disease basic mechanisms.**

Coumarin, known as 2H-1-benzopyran-2-one, serves as a fundamental structure in many natural and synthetic compounds that exhibit a wide range of biological activities, including anticancer effects, antioxidant properties, and inhibition of both carbonic anhydrase and acetylcholinesterase (AChE). Derivatives of coumarin, which are naturally found in plants, have shown great potential due to their varied pharmacological effects. Additionally, modifications made at the 7 positions of the coumarin structure significantly influence its ability to inhibit AChE.

The molecular docking was embedded utilizing atomic working environment program. The current work utilized protein (PDB ID: 4EY7) which has recombinant human re-crystallized with donepezil downloaded from Protein Data Bank. The 4EY7 protein represents a promising target for drug development at Alzheimer's disease because of its involvement in the amyloid-β aggregation process.

Molecular docking simulation was used to identify potential inhibitors of Alzheimer's disease from a set of thirty-six Coumarin derivatives. Overall structural fragments contributed to the activity by different types of interactions like hydrogen bonding, hydrophobic, and aromatic stacking interactions. Based on the docking score five drugs were found to be more active & showed promising binding against the protein (4EY7) as compared to others & can be further studied & evaluated in more detail for their use against Alzheimer's disease.

I. INTRODUCTION

- Alzheimer's disease (AD) is a severely neurodegenerative brain condition that is a leading cause of dementia and can be life-threatening. Key symptoms of dementia include a decline in memory, language, thinking abilities, and other cognitive functions.[1]
- It is a progressive brain disorder characterized by the decline of presynaptic markers in the cholinergic system, which is linked to memory and the capacity to perform everyday tasks. This condition is termed progressive because its symptoms deteriorate over time. [2].
- Since the identification of amyloid β (Aβ) and tau as the key components of plaques and tangles, research has yielded extensive insights into the molecular events that contribute to disease progression. [3].
- However, the underlying causes of Alzheimer's disease remain largely unknown, and effective treatments are still lacking. While the pathological changes associated with Alzheimer's are essential for diagnosis and can lead to symptoms in some patients, various factors contribute to symptom onset in individuals over the age of 75.[3]
- Neuronal damage first seems to occur in the hippocampus and entorhinal Cortex, both of which are important for memory formation. As the disease progress, it impacts regions in the cerebral cortex that govern language, reasoning, and social interactions.
- Ultimately numerous other brain areas and adjacent neurons become impaired and cease to function properly. In the advanced stages of Alzheimer's, the damage is extensive leading to considerable shrinkage of brain tissue. [4].
- Molecular docking involves examining how various molecular structures, such as drugs and enzymes or proteins, associate with each other.
- Essentially, docking is a molecular modeling approach used to anticipate the interaction

between a protein (enzyme) and small molecules (ligands).

- The aim of docking studies is to predict the target three-dimensional structures. This technique is commonly employed to forecast how small therapeutic molecules align with their protein targets, which helps in estimating the molecules' affinity and activity.
- The primary goal of these studies is to fine-tune the shape of both the ligand and the protein, along with their orientation in relation to each other, in order to minimize the total free energy of the system.
- Molecular Docking various Software use like Autodock, Marvin View, Kingdraw, Bio Discovery, Pymol.

II. LITERATURE OF REVIEW: -

1. Kamilia M. Amin1: Design and synthesis of novel coumarin derivatives as potential acetylcholinesterase inhibitors for Alzheimer's disease (2021) Twenty novel coumarin derivatives were designed, synthesized, and screened for anti-AD activity. Compounds 5b, d 13c, and 16a, b showed promising anti-AD activity. In vivo scopolamine-induced dementia improved cognitive functions in mice. The compounds exhibited good lipophilicity and moderate BBB penetration, resembling the native co-crystallized ligand donepezil
2. Samina Khan Yusufzai: - Molecular docking studies of coumarin hybrids as potential acetylcholinesterase, butyrylcholinesterase, monoamine oxidase A/Band β-amyloid inhibitors for Alzheimer's disease (2018) Alzheimer's disease (AD) is the leading cause of dementia worldwide, causing irreversible cognitive, social, and physical deterioration, depression, anxiety, and abnormal behavior. Coumarin and its derivatives are valuable resources for developing anti-Alzheimer medications, with some compounds showing promising action due to their unique properties.
3. Ujjwala Supe, Jayant Supe: - Alzheimer: A disease of brain (2018) Reviewed here are certain main causes, effects and preventions of this deadly disease within our scope of general observation. To start with the interesting story of describing this disease first in 1906 and subsequently, discussed are main causes, risk factors involved and different early warning signs of Alzheimer. A few simple symptoms, causes and some effective treatment is concluded in this article.
4. Johanna C Meyer: - Overview of Alzheimer's disease and its management (2016) Alzheimer's disease is a complex dementia affecting older adults, causing cognitive decline and requiring reliance on others. Current medications temporarily alleviate symptoms, but they don't stop the decline. Preventive measures like higher education and cardiovascular health could postpone the disease's onset. The World Health Organization's Director-General, Margaret Chan, emphasizes the urgent need for new drug development.
5. Gaba Madan: - An Overview of Molecular Docking (2010) This review focuses on molecular docking and scoring, highlighting its applications in identifying new lead candidates. Challenges include developing reliable scoring functions, and innovative algorithms are expected to improve current methods. Protein flexibility and induced-fit movements will become more important in designing new lead candidates. Validated studies are crucial for docking program development.

III. ALZHEIMER'S DISEASE: -

Epidemiology: -

It is estimated that over 18 million people globally will suffer from Alzheimer's disease, with projections indicating that the number will reach 70 million by 2050. According to a report by the Alzheimer's Association in 2018, Alzheimer's is officially recognized as the sixth leading cause of death in the United States. [1]. Alzheimer's disease is the most prevalent type of dementia, comprising 60-80% of all cases and primarily impacting individuals aged 85 and above, with an incidence rate of 25-50%. At present, a new case of dementia develops in the U.S. every 70 seconds, totalling approximately 450,000 new cases annually. [5]

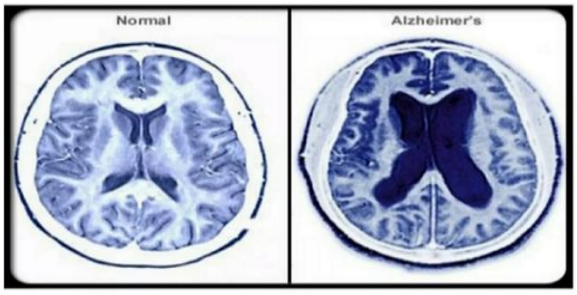


Figure 1

Pathophysiology: -

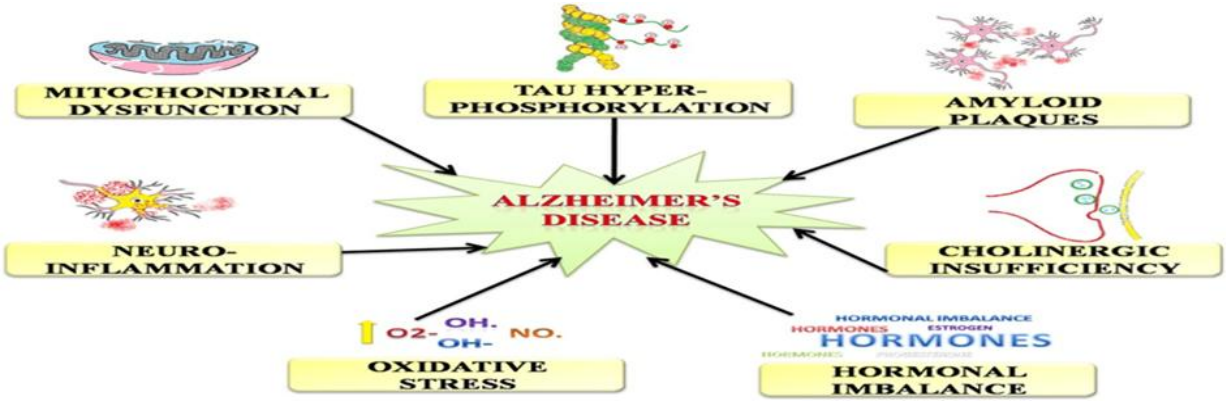


Figure 2

The pathophysiology of Alzheimer's disease (AD) involves several factors, such as the build-up of extracellular beta-amyloid (Aβ) plaques, the formation of intracellular neurofibrillary tangles, oxidative damage to neurons, and inflammatory responses. It is generally accepted that the increased production of Aβ peptide, the primary constituent of amyloid plaques, plays a crucial role in the disease's development. Since the initial identification of the neurotoxic effects of Aβ peptide, numerous studies have explored the cellular and molecular abnormalities caused by it.

Amyloid plaque: -

Amyloid precursor protein (APP) breakdown is the primary origin of β-amyloid-42, which is a protein found on the cell membrane or within cells. Intracellular vesicles have been observed in cells throughout the body, including those in the nervous system, according to research conducted by Haass et al. in 1991 and Kang et al. in 1987. [6]. Aβ is produced through the proteolytic cleavage of amyloid precursor protein (APP) via α-secretase, with abnormal processing occurring through β- and γ-secretases. This results in an imbalance between the production and clearance of the Aβ peptide, leading to the formation of insoluble and proteolysis-resistant fibrils known as senile plaques. These plaques disrupt neuronal transmission at synapses, ultimately causing failure in information transfer and resulting in neuronal cell death. [2]

Neurofibrillary tangles: -

Neurofibrillary tangles (NFT) consist of clumps of atypical filaments that build up in neurons. These abnormal filaments linked to NFT have been detected in cell bodies, dendrites, and axons.

Inflammatory mediators: -

Brain inflammation is a key pathological feature of Alzheimer's disease (AD). However, the typical signs of inflammation, such as swelling, heat, and pain, are absent in the brain, which leads us to describe this as chronic inflammation rather than acute. The inflammatory response is primarily mediated by microglia, astrocytes, and neurons. [7].

Cholinergic neurotransmission: -

Cholinergic neurotransmission could potentially be a focused area for â-amyloid to impact, given its

sensitivity to this particular neurotransmitter. Research has demonstrated a decrease in both choline absorption and acetylcholine release in controlled laboratory conditions. This information is relevant to the current discussion. The alterations in the brain of individuals with Alzheimer's disease primarily affect pyramidal neurons, leading to a loss of these cells during the progression of the disease. Tangle formation is a significant contributor to the accumulation of amyloid precursor protein (APP) and subsequent potential for its misprocessing, resulting in elevated levels. The production of beta-amyloid protein is influenced by neurotransmitter acetylcholine (ACh) in the early stages of the disease. [8]

Hormonal balance: -
Alzheimer's disease is a progressive condition characterized by memory loss, with notable differences between genders. Research indicates a higher prevalence of Alzheimer's disease among women. Variations in life expectancy between males and females may contribute to the heightened risk of Alzheimer's disease (AD). Hormones have the ability to impact various aspects of the central nervous system. The brain, spinal cord, and peripheral nerves are affected by estrogen and progesterone receptors present in these regions.

Blood brain barrier and cerebrovascular: -
Around one-third of patients with AD might show different types of brain vascular lesions. These are usually overlooked as random discoveries during an autopsy. Alzheimer’s disease affects the blood vessels in the brain, causing changes in the cells lining the blood vessels and the muscles around them. This leads to blockages in both large and small blood vessels. Small vessel disease is connected to conditions like infarction, bleeding, and changes in the white matter of the brain. Furthermore, the protein amyloid β plays a role in the breakdown of both larger arteries and tiny blood vessels in the brain that make up the blood-brain barrier.

Stages: -
1. Mild Cognitive impairment
2. Mild Alzheimer
3. Moderate Alzheimer
4. Severe Alzheimer

1. Mild Cognitive impairment: -
Some individuals who have trouble remembering things may have a condition known as mild cognitive impairment (MCI). Older individuals with MCI may experience challenges with movement and sense smell. People with MCI have a higher chance of getting Alzheimer's, but not everyone with MCI gets it. They might even get back their usual capacity to think.

2. Mild Alzheimer: -
This is the beginning phase, when the disease is typically identified for the first time and can last for 2 to 4 years. During this time, loved ones may start to notice a decrease in abilities. In the patient’s thinking skills. People often face more memory loss and other problems with thinking. Challenges can arise such as getting lost, struggling with managing money and paying bills, and repeating actions. Asking more questions, needing more time to do regular tasks, and showing changes in personality and behaviour. Many individuals receive a diagnosis during this phase.

3. Moderate Alzheimer: -
Patients frequently encounter heightened challenges related to memory and may require assistance with daily tasks. This period can extend for a duration of 2 to 10 years, representing the lengthiest phase of the disease. Damage happens in parts of the brain that manage language, thinking, awareness, and feeling processing. Memory loss and confusion worsen, and smells, leading to problems for individuals. Identifying and acknowledging loved ones.

4. Severe Alzheimer: -
In the advanced phase of the illness, there is a progressive deterioration in cognitive function and a significant decline in physical abilities. This phase typically lasts for a period ranging from 1 to 3 years. In the end, when Alzheimer’s disease becomes severe, the brain is damaged to a point where a person can no longer communicate effectively rely entirely on others for their care. Towards the end of their life, the individuals may become fully dependent on others for assistance. Spending most or all of the time in bed while the body shuts down.

Symptoms: -
Memory issues often serve as one of the initial indicators of cognitive decline associated with

Alzheimer's disease. Some individuals experiencing memory difficulties may be diagnosed with a condition known as mild cognitive impairment (MCI).

- Growing issues with short-term memory and confusion
- Trouble identifying family and friends
- Reduced attention span and a sense of restlessness
- Challenges with reading, writing, and numerical concepts
- Possible disregard for personal hygiene
- Decreased appetite
- Changes in personality, such as aggression and notable mood fluctuations
- Increasing need for help with everyday activities.
- Difficulty with speech comprehension or usage
- Loss of control over urination or bowel movements
- Failure to recognize oneself or family members
- Extreme disorientation
- Growing immobility and extended sleep periods

Risk factor: -

1. Age
2. Family History
3. Health problems
4. Education
5. Other risk factors

1. Age: -

The primary risk factor for Alzheimer's disease is getting older, but it is not a normal aspect of aging. Most individuals are diagnosed with Alzheimer's at 65 years or older, but it can also occur in those under 65, though this is uncommon. Age is not the sole risk factor for developing Alzheimer's disease. Different research has demonstrated that growing older can weaken the body's ability to fix itself, even in the brain. As people get older, their chances of having heart problems like high bold pressure, heart disease, and high cholesterol go up.

2. Family History: -

People with a parent or sibling who has Alzheimer's are at a higher risk of developing the disease compared to those without a first-degree relative who has it. In case of Alzheimer's disease that arise before the age of 65, chromosome mutations may play a role. This uncommon type of the disease is unknown as Familial Alzheimer's disease and impacts fewer than 10% of individuals affected by Alzheimer's. Neurological symptoms that may manifest later in the illness includes seizures, increased muscle tones, muscle spasms, incontinence, and lack of speech.

3. Health Problems: -

Researcher have noticed a strong connection between the heart health and brain health of someone with Alzheimer's disease. Suffering from heart disease, high blood pressure, or high cholesterol can raise the chances of getting Alzheimer's disease even more. This occurs when blood vessels in the brain are harmed, leading to reduced blood flow and potential severe damage to brain tissues. several risk factors that elevate the likelihood of cardiovascular disease re also linked to a greater chance of developing Alzheimer's and other dementia-related conditions. Individuals with mild cognitive impairment are at a higher risk for progressing to Alzheimer's and other forms of dementia compared to those without MCI, due to the memory issues associated with MCI. Nearly 50% of individuals who consult a doctor regarding MCI symptoms will go on to develop dementia within 3 to 4 years.

4 Education: -

Individual with less formal education face a greater risk of developing Alzheimer's and other forms of dementia compared to those with higher educational attainment. Some researchers suggest that increased years of education contribute to a "cognitive reserve," which helps people adapt to brain changes that might lead to Alzheimer's or other types of dementia symptoms. Alzheimer's disease is a degenerative neurological condition that gradually impairs memory, cognitive function, and the capacity to perform daily tasks.

5. Other risk factors: -

Recent studies indicate that there are other important factors to consider, even though they are not necessarily the direct cause of dementia. These factors may include: - Loss of hearing, depression that is not being treated (although this can also be a sign of dementia). The study found that we can reduce our risk of loneliness or social isolation, as well as a sedentary lifestyle, by making changes to the factors within our control. Dementia may be greatly decreased.

V. DIAGNOSIS:

In clinical environments, the identification of Alzheimer's disease (AD) primarily relies on a thorough review of medical records, physical and neurological assessments, and neuropsychological testing. Additionally, other potential causes are ruled out through specific additional tests. In specialized settings such as memory disorder clinics, the clinical diagnosis of Alzheimer's disease (AD) has an accuracy rate ranging from 70% to 90% when compared to the pathological diagnosis. [9]

Early diagnosis is crucial because it is during this phase that pharmacological treatment can effectively address reversible conditions and prolong the time before a patient needs hospitalization. Clearly defining the distinction between aging and mild dementia is essential, and this condition is referred to as Mild Cognitive Impairment (MCI). MCI is characterized by noticeable memory loss that is inconsistent with a person's age and educational background. The criteria for diagnosing MCI include:

- Memory concerns supported by a family member
- Other cognitive abilities remaining intact
- Daily activities being performed normally
- Memory loss that is abnormal for their age
- No signs of dementia present

VI. THERAPY / TREATMENT:

Getting treatment early on will make the patient's life better. Using medicine in the beginning of the Treating diseases can help with cognitive issues, slow down deficits, and reduce psychiatric symptoms like agitation, depression, and psychosis. [10] Alzheimer's medication therapy is still in its early stages, and there is currently no cure for the illness. Medicines that target the brain's neurotransmitter systems are now the cornerstone of Alzheimer's disease treatment.

1. Non-Pharmacological therapy
2. Pharmacological therapy

1. Non-Pharmacological Therapy:

Non-pharmacological treatments involve caring for the patient through psychotherapeutic methods and stimulating conversations. Psycho-education plays a crucial role, as it can lead to behavioral changes and reduce the need for symptomatic treatments. Additionally, establishing a structured routine, preventing isolation, providing cognitive stimulation when feasible, and offering emotional support are also essential components. Other nonpharmacological treatments to prevent quality of life or alleviate behavioral issues like depression, sleep problems, agitation, and aggression. Some studies indicate that certain nonpharmacological therapies may help improve or maintain cognitive function, assist in daily activities, and positively impact behaviour, mood, and overall quality of life.

2. Pharmacological Therapy: -

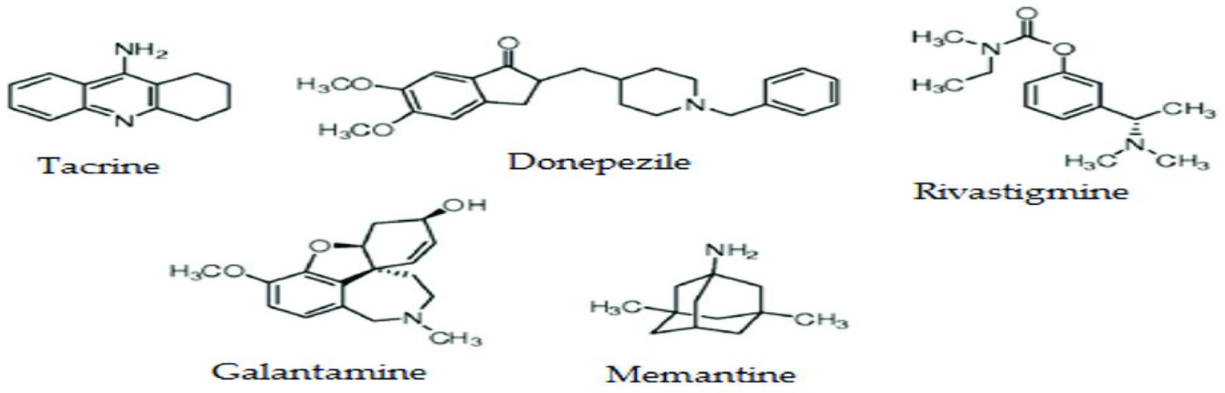
This section examines the clinical efficacy of approved and potential pharmacological therapies for AD. The current treatments only improve symptoms temporarily, lasting six to eighteen months. Pharmacological treatments involve the use of medications to alleviate the symptoms of an illness. Currently, none of the available treatments for Alzheimer's disease (AD) can prevent or reverse the neuronal death and dysfunction that lead to AD symptoms and ultimately result in the disease being fatal. However, numerous drugs and therapies aimed at addressing brain cell death and dysfunction are under investigation globally. The U.S. Food and Drug Administration has approved five medications that provide temporary relief from AD symptoms by enhancing the levels of neurotransmitters in the brain, though their effectiveness can differ among individuals.

Drugs Information: -

Drug	Class and Indication	Mechanism of Action	Adverse effect
Donepezil	Doctors may prescribe a cholinesterase inhibitor to help with mild to moderate symptoms. Moderate-to-severe AD can cause significant symptoms and require careful management.	Helps in maintaining the levels of acetylcholine in the brain by inhibiting its degradation	Nausea, vomiting, diarrhoea

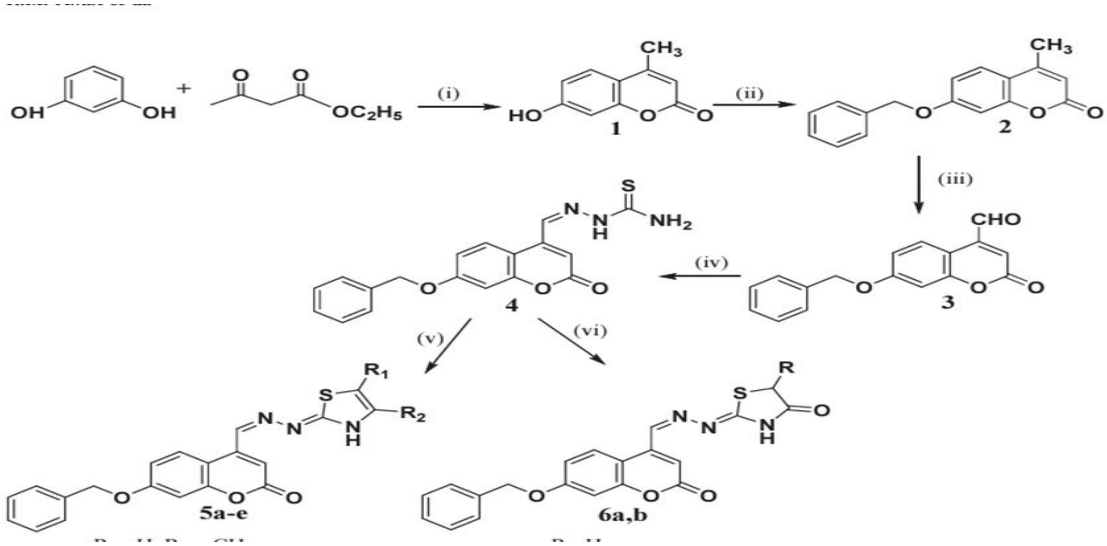
Rivastigmine	Cholinesterase inhibitors are commonly prescribed to manage symptoms associated with mild to moderate Alzheimer's disease.	Inhibits the degradation of acetylcholine and butyrylcholine in the brain, thereby maintaining their levels.	Symptoms such as nausea, vomiting, diarrhoea, reduced appetite, weight loss, and muscle weakness may be experienced
Galantemine	Cholinesterase inhibitors are commonly prescribed to manage symptoms of mild to moderate Alzheimer's disease.	In order to inhibit the degradation of acetylcholine and promote the activation of nicotinic receptors for increased release. Acetylcholine plays a significant role in the brain.	Symptoms such as nausea, vomiting, diarrhoea, decreased appetite, and weight loss may be experienced.
Mamentine	N-methyl-D-aspartate antagonist is prescribed to alleviate symptoms of moderate to severe Alzheimer's disease	Inhibits the degradation of acetylcholine and activates nicotinic receptors to increase the release of acetylcholine in the brain.	Dizziness, Headache, constipation, confusion.
Tacrine	Tacrine is classified as a cholinesterase inhibitor and is prescribed for the management of mild to moderater Alzheimer's disease.	It functions by blocking acetylcholinesterase, leading to elevated level of acetylcholine in the brain, which may enhance cognitive abilities.	Nausea, vomiting, diarrhoea, abdominal pain, Liver damage, Muscle weakness, Dizziness, Headache.

Structure of Drugs: -



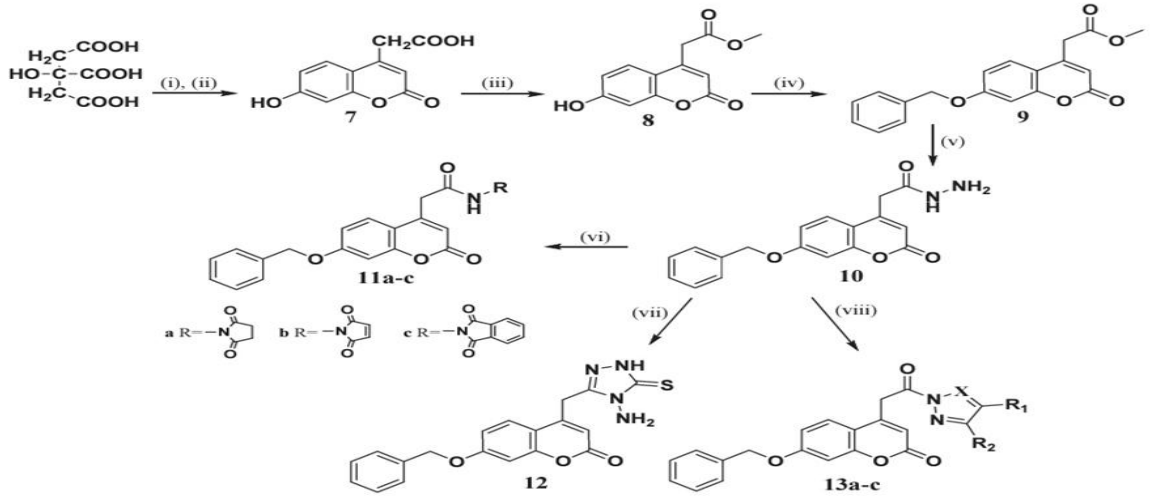
Scheme used in synthesis of structures:-

SCHEME 1



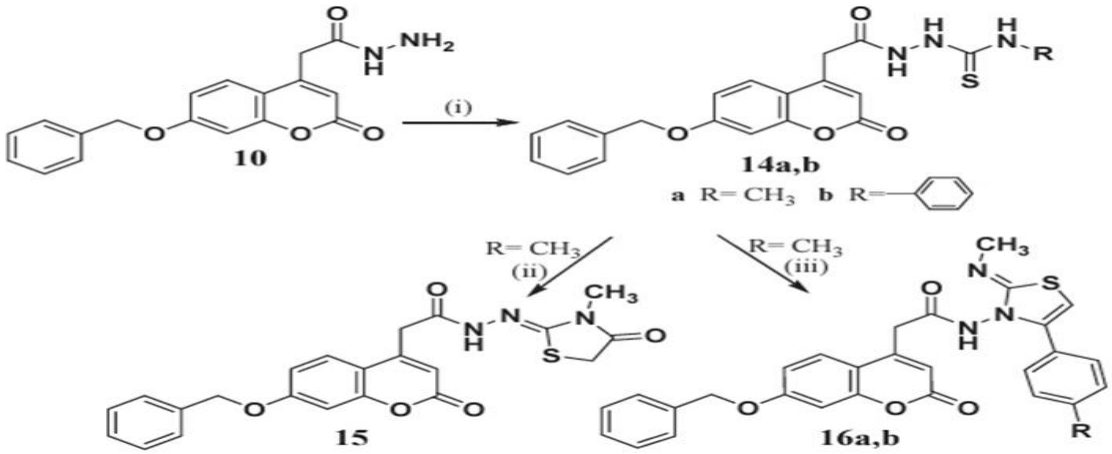
Sr. No.	Drug ID	R 1	R 2
1.	A 1	H	CH_3
2.	A 2	H	C_6H_5
3.	A 3	H	C_6H_4-p-Br
4.	A 4	H	C_6H_4-p-Br
5.	S 1	CH_3	C_2H_5
6.	S 2	CH_3	C_6H_5
7.	S 3	CH_3	C_6H_4-O-Cl
8.	S 4	CH_3	C_6H_4-Br
9.	S 5	OCH_3	C_2H_5
10.	S 6	CH_3COOH	OCH_3
11.	S 7	C_6H_5-p-NH_2	H
12.	S 8	CH_3	C_6H_5OH
13.	S 9	H	-
14.	S 10	CH_2COOH	-
15.	S 11	NH_2	-
16.	S 12	C_2H_4OH	-

SCHEME 2



Sr. No.	Drug ID	X	R 1	R 2
1.	A 1	-	$C_4H_5O_2N$	-
2.	A 2	-	$C_4H_3O_2N$	-
3.	A 3	-	$C_8H_5O_2N$	-
4.	S 1	-	CH_2C00H	-
5.	S 2	-	$C_8H_4O_2ClN$	-
6.	S 3	-	$C_8H_5O_2Br_2N$	-
7.	A 4	=O	H	CH_3
8.	A 5	C- CH_3	H	CH_3
9.	A 6	C- NH_2	CN	H
10.	S 4	OH	CH_3	CN
11.	S 5	C_2H_5	OH	NH_2
12.	S 6	NO_2	Cl	CH_3

SCHEME 3



Sr. No,	Drug ID	R
1.	A 1	CH_3
2.	A 2	C_6H_6
3.	S 1	C_6H_4-p-Br
4.	S 2	CH_2COOH
5.	A 3	H
6.	A 4	OCH_3
7.	S 3	C_2H_5
8.	S 4	OH

VII. MOLECULAR DOCKING

Introduction: -

Molecular docking is a structure-based drug design approach that simulates how molecules interact and estimates the binding mode and affinity between receptors and ligands. Docking is often utilized to determine how drug candidates bind to their protein targets, helping to assess the potential affinity and activity of small molecules. It is crucial in the rational design of drugs. The goal of molecular docking is to find an ideal conformation for both the protein and ligand, as well as their relative orientation, in order to minimize the overall system's free energy. Molecular acknowledgment is essential for facilitating key biomolecular interactions, including those between enzymes and substrates, drugs and proteins, and drugs and nucleic acids.[11]

This method entails forecasting the atomic-level interaction between a small molecule and a protein. It allows scientists to investigate how small molecules, including nutraceuticals, behave within the binding site of a specific protein, thereby providing insights into the essential biochemical processes involved in this interaction. These algorithms are based on natural selection and are used to find the best pose for a protein conformation. They use biologically inspired operators like mutation, crossover, and selection. [11]

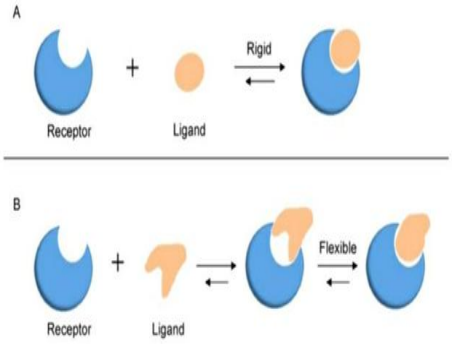


Figure 3

Principle of Molecular Docking: -

Docking is a technique that analyses how designed compounds fit into target cavities and interact with various residues. In the computational drug discovery, docking typically occurs between small molecules and macromolecules, particularly in the context of protein-ligand interactions, which is referred to as molecular docking. In recent years, docking has also been applied to interactions between two macromolecules, such as protein-protein docking.

During the 1980s, molecular modelling utilized force fields, which evolved to study molecular processes like ligand binding to target proteins. Two primary approaches have been developed for this purpose: rigid body docking and flexible docking. In rigid body

docking, ligands and targets are treated as distinct entities that interact based on their shape and size. [12]

Types of Molecular Docking: -

a. Lock and key
b. Rigid docking
c. Flexible docking

1. Lock and Key:-

This method is utilized to identify complexes that exhibit a high level of shape compatibility between the ligand and the receptor. In this technique, both the ligand and the receptor are treated as rigid entities, resulting in a constrained search space. Ligand flexibility can be accommodated by employing a pre-determined collection of ligand conformations or by permitting some degree of atom-atom overlap between the protein and the ligand (Meng et al., 2011)

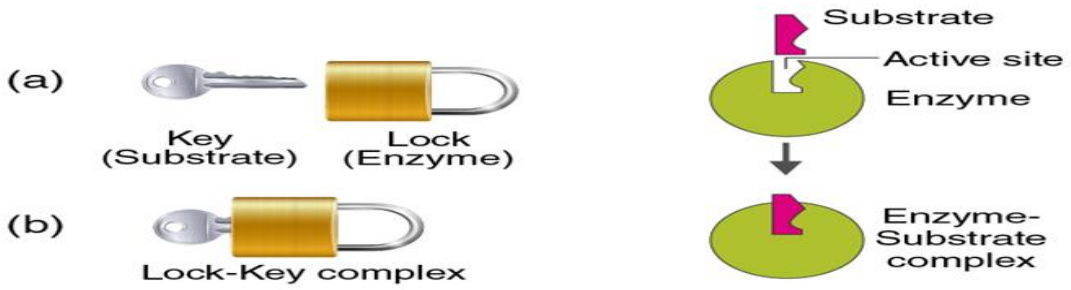


Figure 1

2. Rigid Docking: -

Assuming the compounds are stiff, we aim to reposition one of the compounds in three-dimensional space to achieve the optimal alignment with the other compounds based on a scoring system. The ligand's shape may be determined with or without the influence of receptor binding. This approach relies on induced-fit mechanics and takes into account the flexibility of both the ligand and the receptor as they adjust their shapes to achieve an optimal, low-energy complex. However, to enhance precision and manage computational time more effectively, the receptor is kept stationary while allowing the ligand to remain flexible.

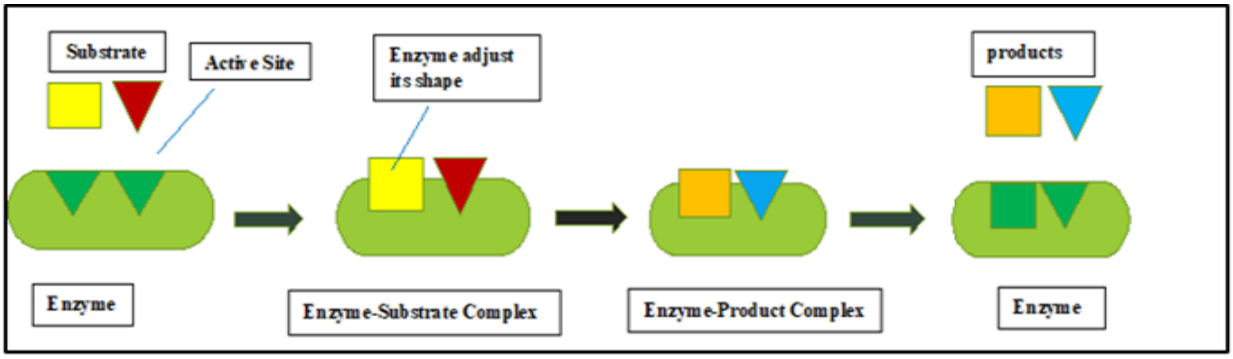


Figure 5

3. Flexible Docking: -

Along with transformations, we assess molecular flexibility to determine the conformations of both the receptor and ligand molecules as they exist within the complex.

This technique also relies on induced fit mechanics, but it emphasizes the importance of side chain flexibility in forming ligand-receptor complexes. Such adjustments enable the receptor to modify its binding site based on the ligand's orientation. One of the benefits of this method is its computational efficiency, as the receptor coordinates remain constant while interactions are managed by tweaking the Van der Waals parameters.

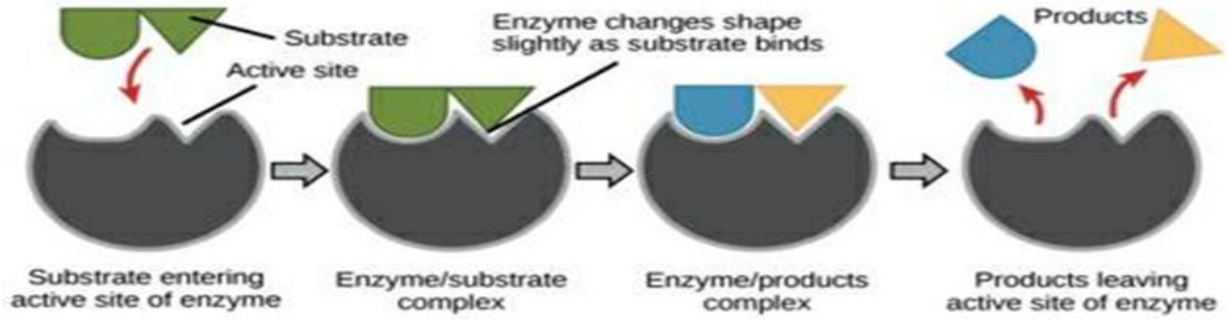
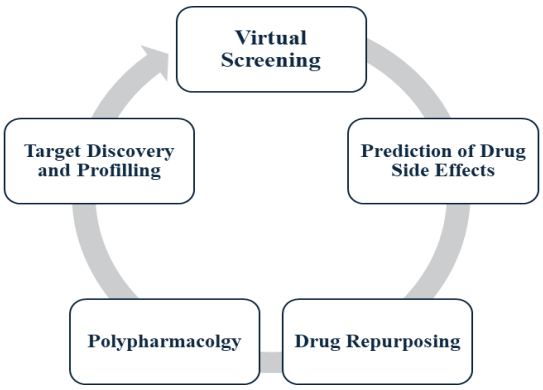


Figure 6

Application: -

- Molecular docking has a multitude of applications in the contemporary landscape, where bioinformatics is increasingly influencing research literature.
- The growth in computational power and advancements in algorithms have expanded the uses of molecular docking to include drug discovery, toxicity prediction, identification of side effect targets, epitope prediction for vaccines, drug repositioning, elucidation of biological mechanisms, bioremediation, and library construction, among others.
- As one of the most effective and widely-used in-silico methods, molecular docking aids in predicting interactions between molecules and biological targets.
- This drug repositioning strategy utilizes molecular docking's computational approach by screening for structural complementarity.
- Additionally, various computational methods, including molecular docking, are employed to assess potential side effects of drugs by analyzing existing databases of drug-related adverse reactions. [13].



a. Virtual Screening: -

- Virtual screening identifies promising candidates and lead compounds from molecular databases using scoring functions. The integration of molecular dynamics and free energy binding estimation techniques with docking has enhanced the effectiveness of virtual screening.

b. Predication of drug side effects: -

- Identifying negative drug effects early is crucial in the drug discovery process. Many drug candidates are known to fail in clinical trials primarily because of adverse reactions from unexpected off-target interactions. Numerous computational methods are available to assist with this task.

c. Drug Repurposing: -

- Drug repurposing is a recognized method in drug discovery that allows for the discovery of new therapeutic uses for existing approved medications, investigational drug candidates, natural substances, or generally pre-synthesized ligands.

d. Polypharmacology: -

- Polypharmacology involves finding molecules that can attach to specific targets in the body and have positive effects for treating various conditions. The pharmaceutical industry has focused on creating very specific drugs to prevent any potential side effects. Molecular docking is a useful tool that helps scientists find out which chemical structures work well together. Moreover, the selection of protein shapes to use for docking can significantly impact the result of the design.

e. Target Discovery and Profiling: -

- Reverse docking facilitates the identification of the biological target associated with a specific molecule, making it a crucial method in the computational discovery and profiling of targets. Numerous docking techniques and algorithms are available for conducting reverse screening of ligands against libraries of protein structures and assessing their binding affinities.

Factors Affecting Molecular Docking: -

1. Intra-molecular forces

- Bond angle
- Bond length
- Dihedral angle

2. Inter-molecular Forces

- Dipolar
- Electrostatic
- Hydrophobiicity
- Vander Wall Forces

Software: -

The following is a list of software used for docking:

- DOCK
- AutoDock
- GOLD
- Mgl tool
- Discovery Studio
- Marvin view
- Kingdraw / Chemdraw
- Open Babel
- Autodock Vina
- Flex-X

VIII. METHOD AND PREPARATION:

1. Ligand preparation: -

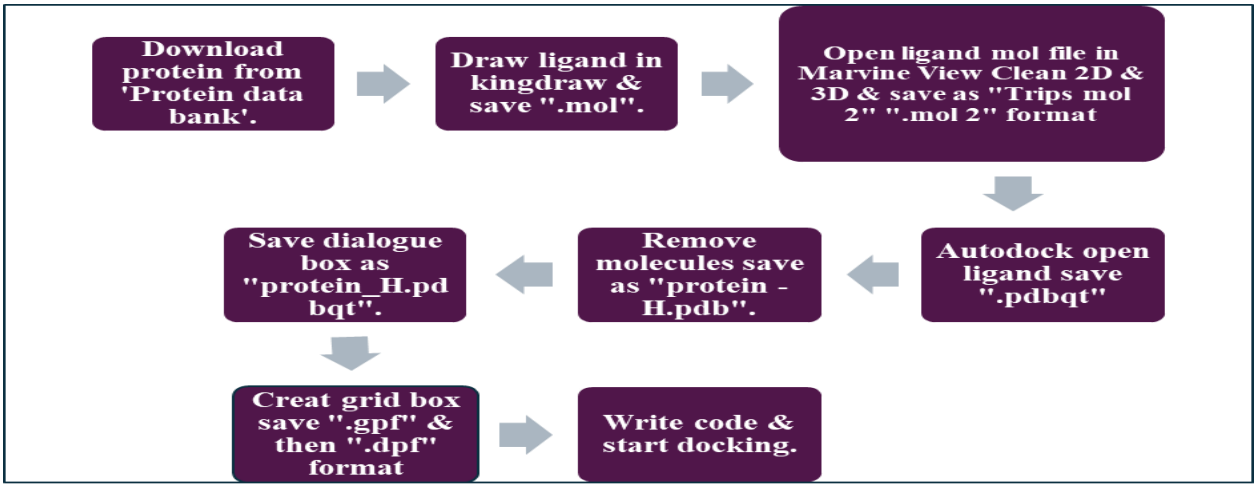
This research involves heterocyclic compounds and functional groups that are recognized for their significance in drug discovery. The chemical structures proposed in above mentioned synthetic scheme were created virtually with kingdraw software. To prepare the ligands, all thirty-six were transformed into '. mol2' format using Marvin View. The optimization of the '. mol2' ligands were performed using autodock tools and saved in '. pdbqt' format.

2. Target protein preparation:

Crystal Structure of Recombinant Human Acetylcholinesterase in Complex with Donepezil. PDB ID: - 4EY7. The protein was prepared for docking by removing water molecules, heteroatoms, and ligand groups through the scripting feature of Discovery Studio 4.0. The altered protein was subsequently saved in '.pdb' format and with name "protein_edited.pdb".

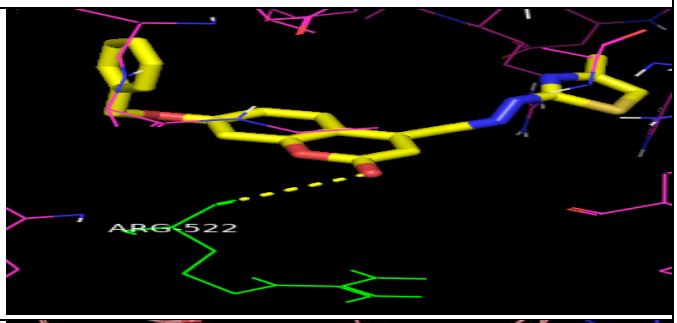
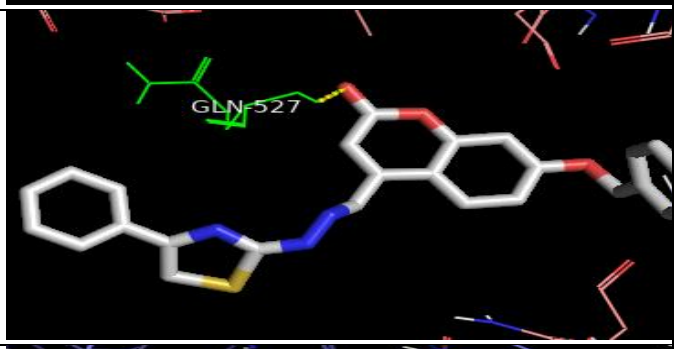
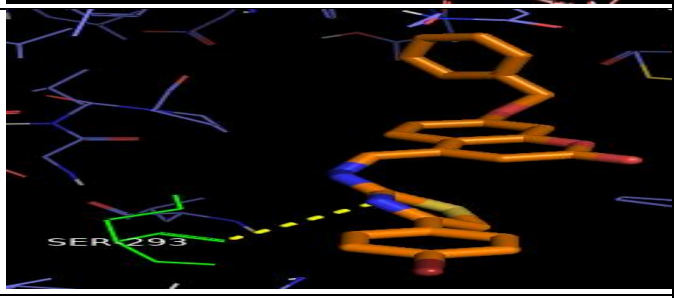
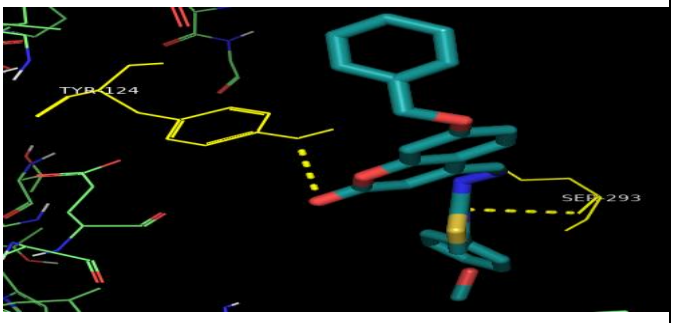
3. Preliminary molecular docking: -

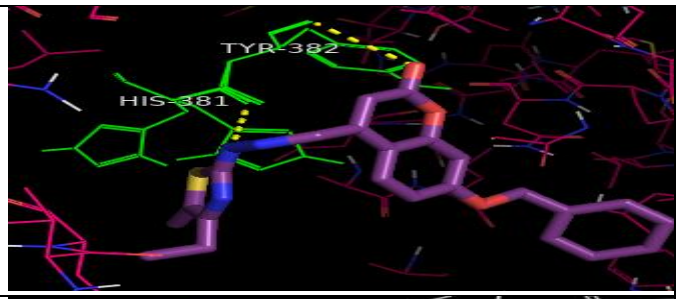
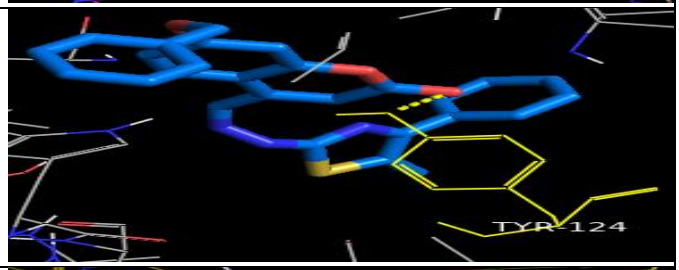
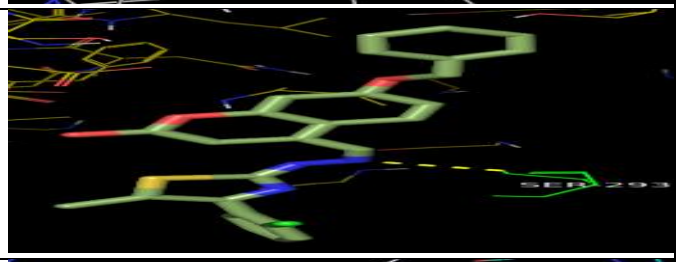
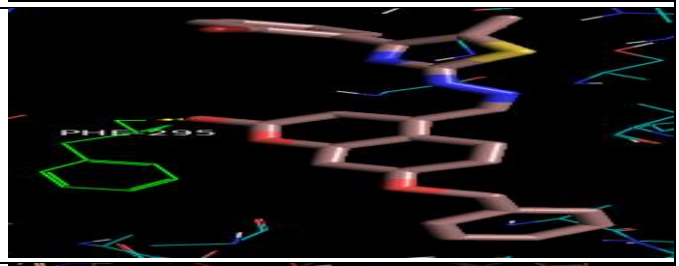
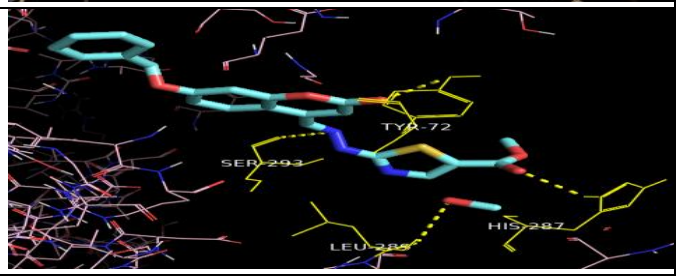
Molecular docking analysis utilized 'AutoDock Vina' to assess hydrogen bond interactions and binding affinities. Following the minimization process, the grid box resolution for PDB ID: 4EY7 was defined at -0.057, -49.711 and 3.277 for the x, y, and z coordinates, respectively, with a resolution of 4 Å. The grid dimensions were established at 66 × 98 × 126 Å.

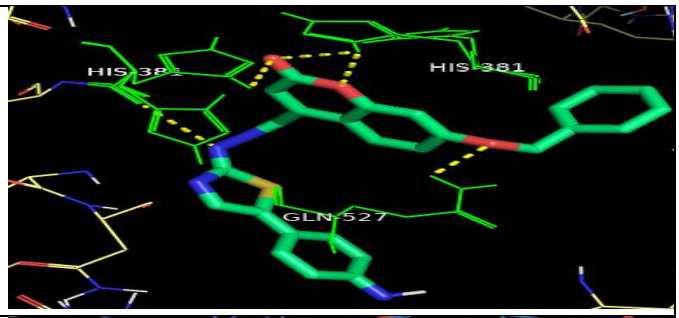
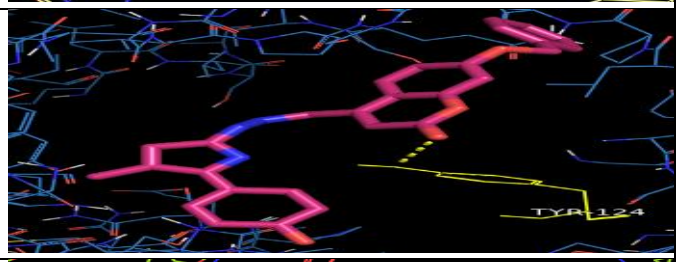
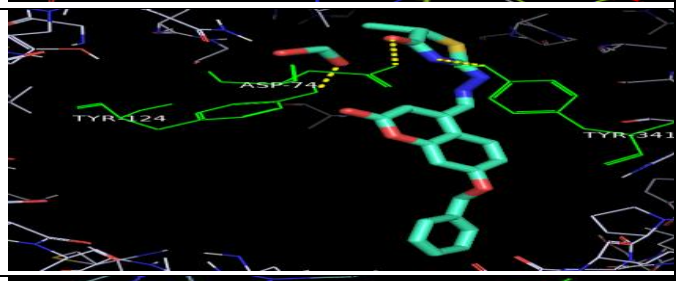
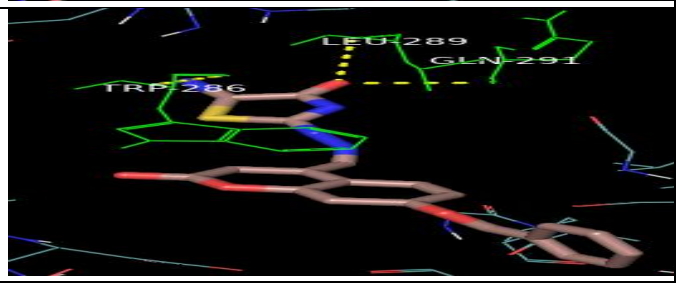


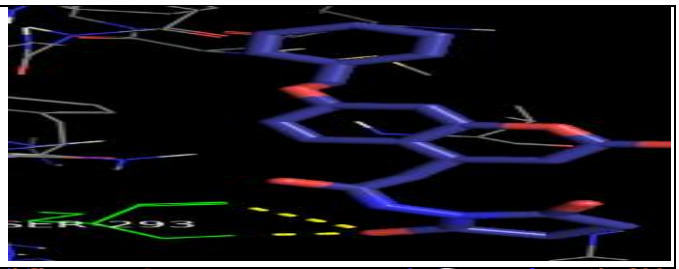
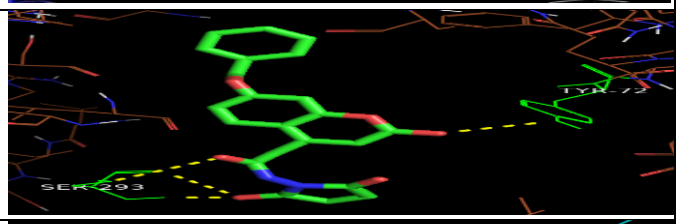
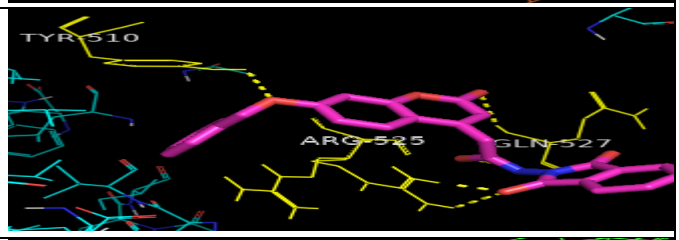
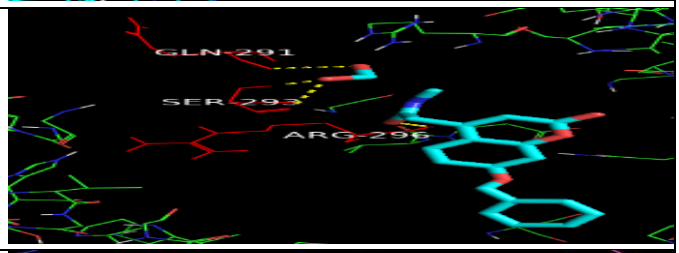
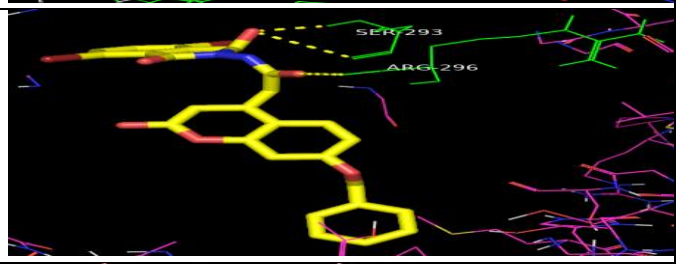
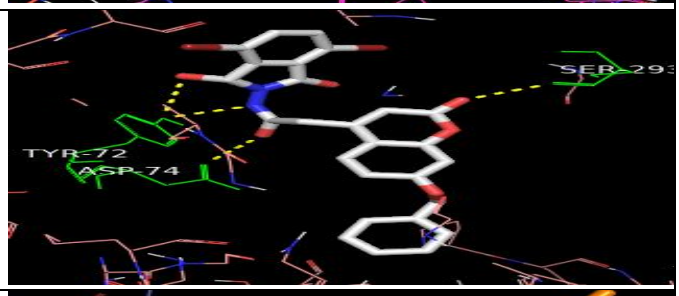
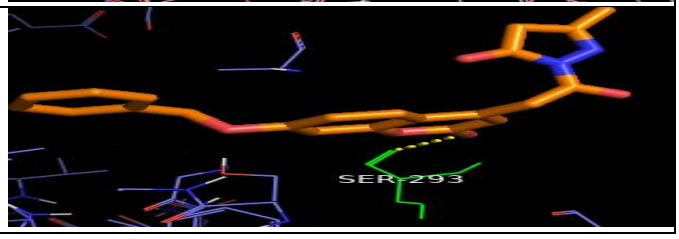
IX. RESULT

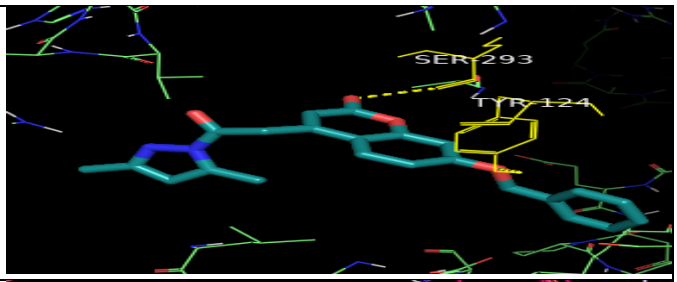
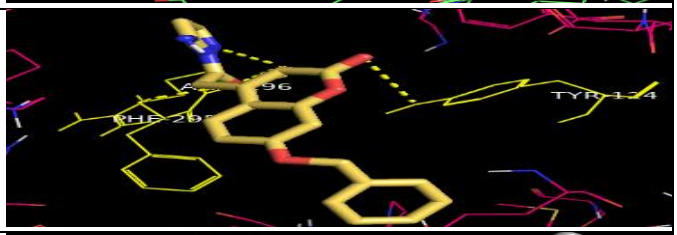
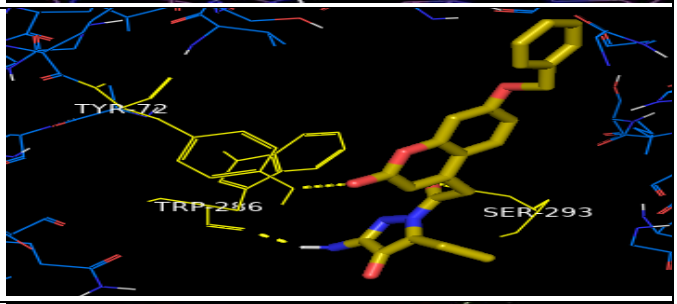
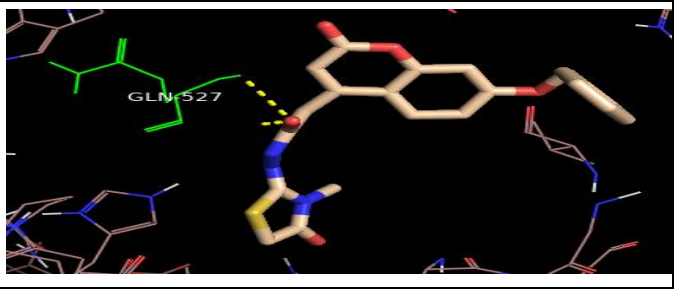
Molecular Docking study was performed on thirty-six derivatives of Coumarin on binding pocket of Crystal structure of Recombinant Human Acetylcholinesterase in Complex with Donepezil (PDB ID: - 4EY7).

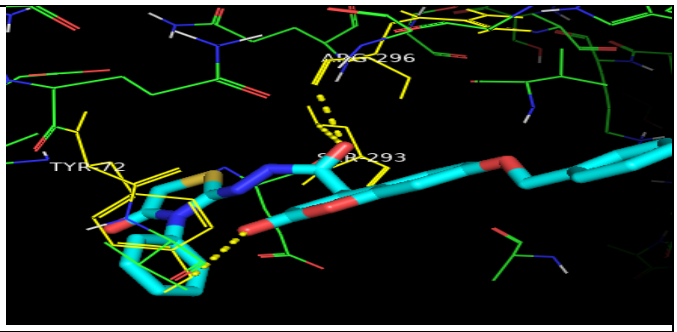
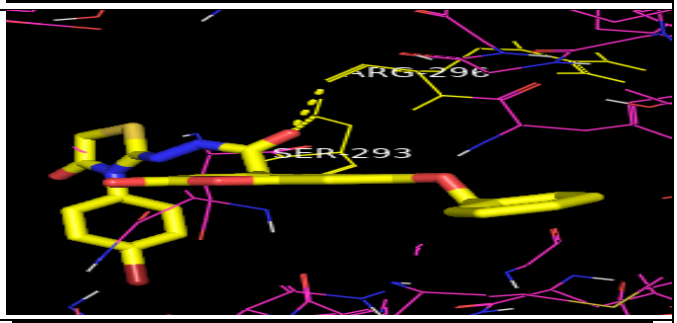
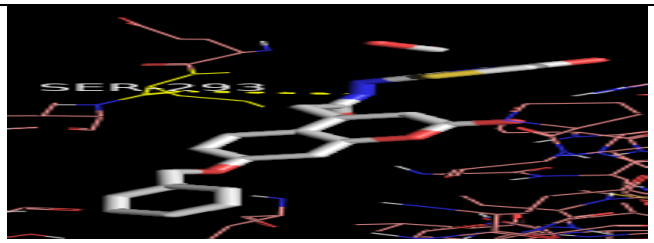
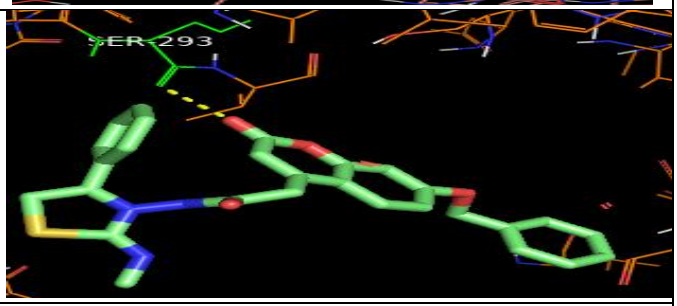
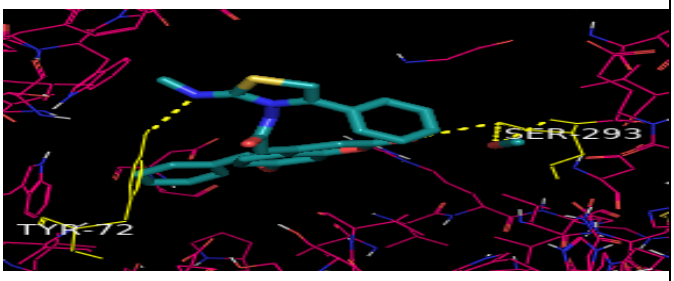
Drug ID	Docking Score	Interaction With Amino Acids	Docking Image
S 1	-9.9	ARG 522	
S 2	-11.0	GLN 527	
S 3	-12.2	SER 293	
S 4	-13.0	TYR 124 SER 293	

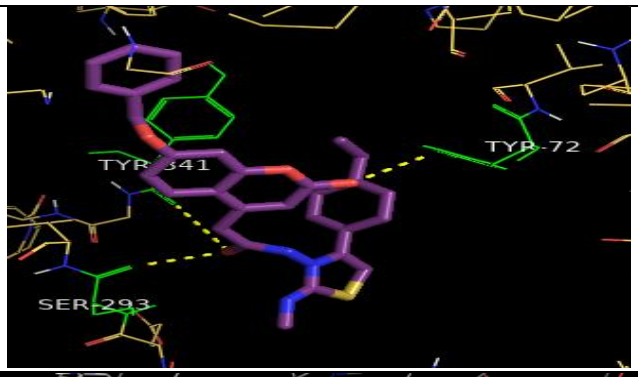
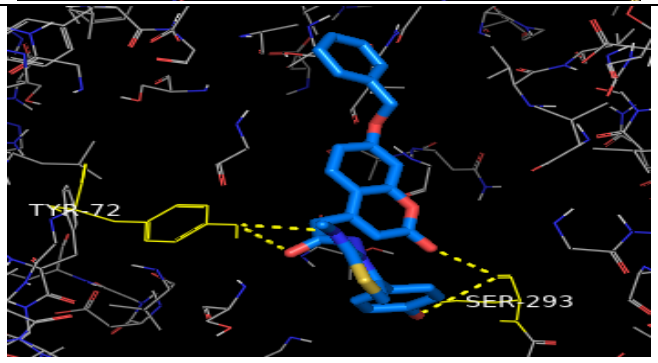
S 5	-12.4	TYR 382 HIS 381	
S 6	-11.4	TYR 124	
S 7	-12.1	SER 293	
S 8	-10.9	PHE 295	
S 9	-10.9	PHE 295	
S 10	-10.4	SER 293 LEU 285 HIS 287 TYR 72	

S 11	-10.4	HIS 381 GLN 527	
S 12	-12.1	TYR 124	
S 13	-9.5	ARG 525 ALA 528 HIS 318	
S 14	-11.1	TYR 124 ASP 74 TRY 341	
S 15	-11.1	TRP 286 LEU 289 GLN 291	
S 16	-10.5	TRP 286 GLN 291 LEU 289	

S 17	-11.2	SER 293	
S 18	-11.2	SER 293 TYR 72	
S 29	-11.1	TYR 510AR G 525 GLN 527	
S 20	-11.4	GLN 291 SER 293 ARG 296	
S 21	-11.9	SER 293 ARG 296	
S 22	-12.0	TYR 72 ASP 74 SER 293	
S 23	-10.9	SER 293	

S 24	-10.9	SER 293 TYR 124	
S 25	-11.7	PHE 296 TYR 124 ARG 296	
S 26	-12.0	HIS 447 GLY 122	
S 27	-11.2	TYR 72 TRP 286 SER 293	
S 28	-11.8	TYR 341 SER 293	
S 29	-10.7	GLN 527	

S 30	-11.4	TYR 72 SER 293 APG 296	
S 31	-11.9	ARG 298 SER 293	
S 32	-11.5	SER 293	
S 33	-11.8	SER 293	
S 34	-12.1	SER 293 TYR 72	

S 35	-11.5	TYR 341 MSER 293 TYR 72	
S 36	-11.5	SER 293 TYR 72	

X. CONCLUSION:

The Present Study used molecular docking simulation to identify potential inhibitors of Alzheimer's disease from a set of thirty-six Coumarin derivatives. Overall structural fragments contributed to the activity by different types of interactions like hydrogen bonding, hydrophobic, and aromatic stacking interactions. Based on the docking score five drugs were found to be more active & showed promising binding against the protein(4EY7) as compared to others & can be further studied & evaluated in more detail for their use against Alzheimer's disease. Thus, the present study may become useful for medical professionals to treat the patients showing symptoms for AD.

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