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NGS and Drug Development Pipeline for Alzheimers Disease

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Abstract: ***Alzheimer's disease is a form of dementia characterized by the gradual and irreversible loss of cognitive abilities, primarily affecting memory, thinking, and behaviour.Globally, there are more than 50 million people that suffer from Alzheimer's.Alzheimer's disease, a complex and devastating neurodegenerative disorder, represents a profound challenge to modern neuroscience and medicine. Defined by the accumulation of abnormal protein aggregates, such as beta-amyloid plaques and tau tangles, within the brain, it inexorably disrupts essential neuronal connections and communication. This relentless deterioration leads to a gradual deterioration of cognitive functions, memory loss, and ultimately, a profound loss of independence for afflicted individuals. Unravelling the intricate molecular and cellular mechanisms underlying Alzheimer's remains an urgent scientific endeavour, offering hope for novel treatments and preventive strategies to confront this formidable adversary of the human brain. In this study, the variability of the human γ-secretase, 5FN5protein sequence was compared and evaluated with the reference sequence using MMDB, BLAST, and COBALT. RasMol was utilized to identify the domain and function of the human γ secretase for the analysis of structural properties. Molecular docking was performed to study the interaction of 5FN5 molecule and the associated ligandusing PyMOL. In the computer-aided drug designing approach, molecular docking was performed for 5FN5 protein, and CB-Dock was used to find optimized conformations between 5FN5 protein and E2012 drug, resulting in the minimum energy that bound to a particular protein. E2012 was found to be the accurate drug ligand for the binding site of gamma secretase with docking score of –9, acting as a modulator for 5FN5 protein.***
Keywords: Alzheimer's disease, dementia,β-amyloid, gamma secretase inhibitors, E2012, Multiple sequence alignment, homology modelling, structure Analysis, CB-Dock

I. INTRODUCTION

Alzheimer's disease (AD) is a complex and chronic neurodegenerative disease, it in the main impacts the brain, leading to a gradual decline in cognitive abilities, memory loss, and changes in behaviour. AD is the most common cause of dementia, accounting for approximately 60-80% of all cases around the world [1].Alzheimer's has affected over 40 million people worldwide [2]. AD is the fourth greatest cause of death in the United States, trailing after heart disease, cancer, and stroke, and it is a serious public health issue impacting the entire world [3].Alzheimer's disease involves two major proteins: *β*-amyloid protein and tau protein.These proteins become abnormal and toxic to the brain, by formingbeta-amyloid plaques and neurofibrillary tangles.Beta-amyloid plaques are present in between the neurons. These plaques are the clumps, formed by the buildupof insoluble fragments of a protein called amyloid-beta [4].On the other hand, the abnormal Tau protein accumulates, and forms twisted fibers, known asneurofibrillarytangles inside the neurons. As the level of abnormal*β*-amyloid reaches the critical point, there will be rapid spread of Tau throughout the Brain [5].Theseplaques and tangles disrupt the normal functioning of brain cells and lead to their degeneration and eventual death.

β-amyloid (Aβ) forms plaques outside the cells and tau forms tangles inside the neurons. Both the proteins damage nerve cells causing them to die. But *β*-amyloid protein and tau protein may not be the only factors involved in Alzheimer's disease [6].There are other factors to be considered.Sometimes, vascular system may fail to deliver sufficient blood and nutrients to the brain, the brain may lack glucose needed to power its activity [7]. Chronic inflammation sets in as microglial cells fail to clear away debris, furthermore astrocytes react to distressed microglia. Eventually, nerve cells lose their ability to communicate. As all the neurons die, it causes the brain to shrink. In Alzheimer's, Hippocampus is the first part of the brain to be affected. The hippocampus is a region of the brain that is in responsible for memory and learning. Initially, there will be memory loss, impaired decision-making, and language problems [8].

As more and more neurons die, and more areas of the brain are affected, the symptoms of Alzheimer's become worse and more numerous. This is sometimes known as a gradual progression of symptoms. The brain of a person with Alzheimer's disease also has lower levels of a certain neurotransmitter which allows messages to pass between the Nerve cells.

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Lower levels of neurotransmitters may cause the remaining cells to communicate with each other less effectively and it may lead to greater problems with memory and thinking. Consequently, a person with Alzheimer's disease loses the ability to remember, think, make decisions, and function independently [9].The symptoms of Alzheimer's disease typically start with mild memory loss and confusion, which gradually worsen over time. As the disease progresses, individuals may experience difficulties with language, problem-solving, and everyday tasks. Behavioural changes, mood swings, and loss of independence are also common as the disease advances [10].

The main drug treatment for Alzheimer's disease aim to increase the levels of neurotransmitters in the remaining neurons helping to preserve brain function for a while. As Alzheimer's disease progresses, it becomes very much difficult to remember things.Research indicates that abnormalities in the processing and clearance of beta-amyloid protein play a central role in the development and progression of Alzheimer's disease [11].Normally, the brain has mechanisms to remove excess beta-amyloid, but in Alzheimer's disease, this clearance process becomes impaired, leading to the accumulation of beta-amyloid plaques. These plaques trigger inflammation and oxidative stress, further damaging neurons and promoting neurodegeneration.While there is currently no cure for Alzheimer's disease, various treatments and interventions can help manage symptoms and improve quality of life for affected individuals. These may include medications to temporarily alleviate cognitive symptoms, behavioural therapies, and support from caregivers. Ongoing research aims to develop disease-modifying therapies that target the underlying mechanisms of Alzheimer's disease, with the goal of slowing down or halting its progression [12].

5FN5 is a protein structure identifier for Human g-secretase. g secretase is a protease enzyme located within the cell membrane. It is responsible for cleaving various substrates. Gamma secretase plays a crucial role in cellular processes by cleaving various substrates, including Notch and amyloid precursor protein (APP). Abnormal cuts of Notches are usually implicated in cancer, while abnormalities in cleaving β-amyloid precursor protein will lead to Alzheimer’s disease. There are gamma secretase inhibitors for Alzheimer’s such as L-685,458, DAPT [13], E2012, and begacestatwhich may work efficiently and could be one of the effectivetreatments for Alzheimer’s disease [14].5FN5 is a membrane protein that comes under the group of hydrolases. Understanding the structural characteristics and dynamics of gamma secretase in the apo-state ensemble, including class 3, is important for gaining insights into its functional mechanisms, regulation, and potential therapeutic targets. It helps to investigate the behaviour and interactions of the enzyme in its natural state, leading to a better understanding of its biological functions and potential implications in diseases like Alzheimer's disease and cancer. This human gamma secretase, 5fn5 is present and is expressed in humans. 5FN5 is composed of 4 macromolecules: Nicastrin, Presenilin-1, Gamma-secretase subunit APH-1A, and Gamma-secretase subunit PEN-2.This study is performed to identify the 5FN5(gamma secretase) inhibitors for Alzheimer’s disease [15].

II. MATERIALS AND METHODS

The study utilized the National Center for Biotechnology Information (NCBI) to obtain the amino acid sequences in FASTA format. NCBI serves as a valuable bioinformatics resource in the field of biology and biotechnology, offering access to a vast array of biological information and tools. In this research study, National Center for Biotechnology Information (NCBI) was used as a resource to retrieve the sequences[16].Later on, BLAST (Basic Local Alignment Search Tool) program was used to determine sequence similarity. BLAST only does "local" alignments.BLAST is designed to analyze and compare biological sequences. It is a powerful tool for identifying regions of similarity between different sequences, such as DNA, RNA, or protein sequences. BLAST helps in determining the degree of similarity between a query sequence and subject sequence [17].

After that, the Protein Data Bank (PDB) was used to access the repository of 5FN5, which contains information about the experimentally determined 5FN5 protein structures, the study of protein function, interactions, and structure-based drug design. Ligands were found in the literature and were downloaded in SDF format using PubChem. It is the world's largest publicly accessible chemical data archive. The PDB collects and curates data from various sources, including X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, and electron microscopy. Each structure in the PDB is assigned a unique alphanumeric identifier called the PDB ID, which is used to refer to a specific entry[18].Moreover,MMDB(Molecular Modeling Database) was used to retrieve the comprehensive information on experimentally determined 3D structure of 5FN5 molecule,including its atomic coordinates, protein-ligand interactions, secondary structure annotations, and related metadata, facilitating detailed analysis and investigations on 5FN5, Cryo-EM structure of gamma secretase in class 3 of the apo- state ensemble[19]. Each chain of 5FN5 molecule was run in BLAST and Multiple sequence alignment was performed using COBALT (Constraint-Based Alignment Tool). COBALT incorporates pairwise constraints from various sources to generate accurate and reliable alignments, making it particularly useful for studying the evolution and relationships between proteins[20].RasMolwas used to visualize the 3D structure of 5FN5.

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RasMol usually helps in visualizing the three-dimensional structures of molecules, such as proteins, nucleic acids, and small molecules, which are typically obtained from experimental techniques like X-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy. With RasMol, users can rotate, zoom, and manipulate the molecular models to better understand their structure and function [21].PyMOL is a software that provides a range of tools and features that enable users to manipulate molecular models, view them in various representations (e.g., cartoon, surface, sticks), measure distances and angles, create publication-quality images, and conduct structural analyses. Hence PyMOLwas used to gain insights into the structure-function relationships of biomolecules and to aid in the study of protein-ligand interactions [22].The method then conducts docking using the widely-used Autodock Vina program. Through careful optimization, CB-Dock achieved an impressive ~70% success rate for top-ranking docking poses with RMSD within 2 Å from the X-ray pose, outperforming other blind docking tools in benchmark tests. Additionally, CB-Dock provided a 3D visualization ofprotein-ligand interactions of 5FN5 and E2012 of the results and it is freely accessible at CB-Dock website [23].

III. RESULTS AND DISCUSSIONS

In this study, BLASTP was run to check the sequence similarity, the molecular 3D structure of 5FN5 (Human γ-secretase) was visualized and studied using software tools such as RasMol, and Pymol. Next generation sequencing and multiple sequence alignment was achieved through COBALT. Using Pubchem, a potential modulator for 5FN5 was identified. Finally, molecular docking was performed using the CB-Dock.

After opening the SDF file that was downloaded from PubChem, it opened in the RasMol software. In this study, RasMolwas used to visualize the 3D structure of 5FN5 molecule. The molecule was visualized using various commands such as Cartoon, shapely, wireframe, backbone, sticks, ball and stick, and ribbon. The results obtained from RasMol are as follows:

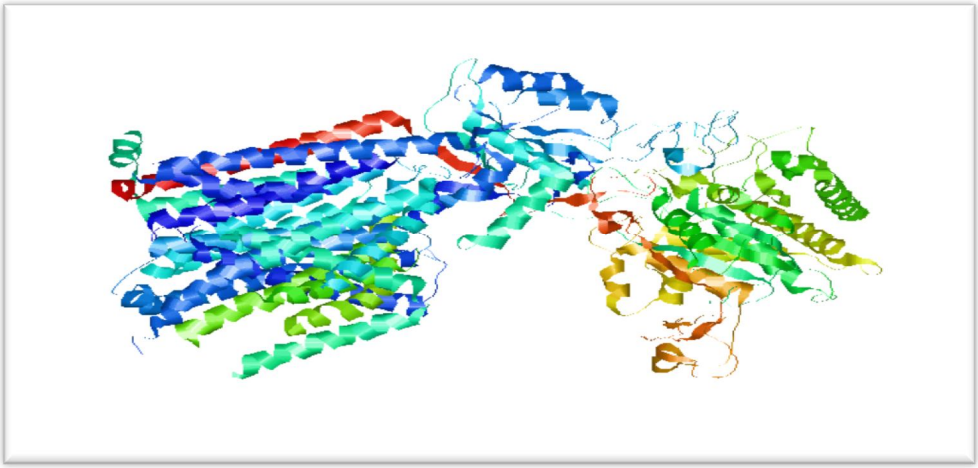


Figure 1:This is the structure of 5FN5 gamma secretase visualized by RasMol through Cartoon. The cartoon command on the RasMol command line represented the currently selected residues of 5FN5 gamma secretase as a deep ribbon structure.



Figure 2:InRasMol, Shapely colour scheme represented different colours for all 20 amino acids and nucleic acid residues present in 5FN5 molecule.

Results obtained from Shapely in RasMol

Table 1: This table provides the list of amino acids residues observed using Shapely colour scheme in RasMol.

Sl. No.	Observed amino acids	Assigned colour
1.	Isoleucine (ILE)	Dark green
2.	Alanine (ALA)	Light-green
3.	Lysin (LYS)	Blue
4.	Glutamic acid (GLU)	Red brown
5.	Leucin (LEU)	Olive green
6.	Phenylalanine (PHE), Proline (PRO), Tryptophan (TRP)	Dark grey
7.	Histidine	Pale blue
8.	Serine (SER), Glutamine (GLN)	Orange
9.	Argenine (ARG)	Dark blue
10.	Aspirine (ASP), Threonine (THR)	Dark red

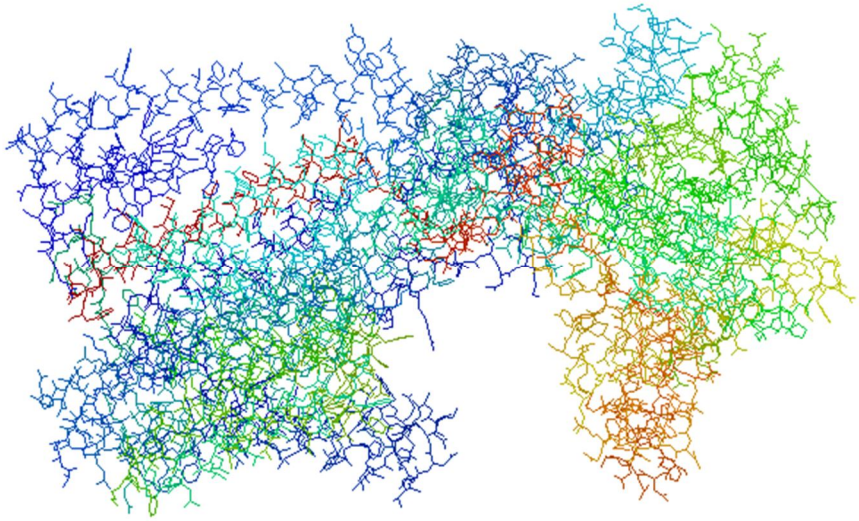


Figure 3:This is a wireframe command in RasMol, displaying the bonds within the selected or chosen region of the molecule using cylinders, lines, or depth-cued vectors.

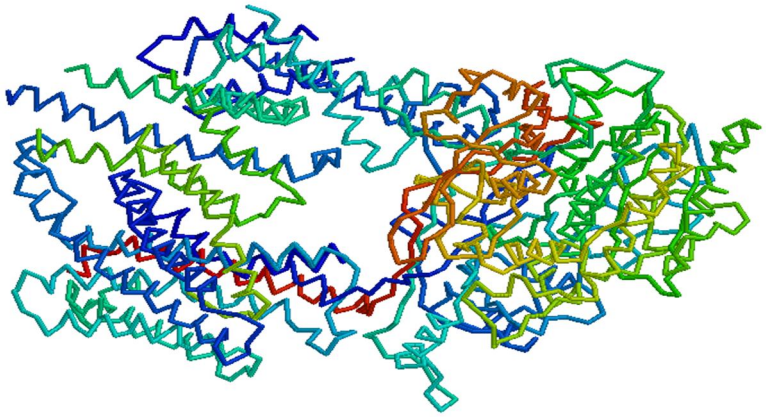


Figure 4: This is a structure of 5FN5 represented using Backbone command in RasMol represents the sugar phosphate backbone of the nucleic acid.

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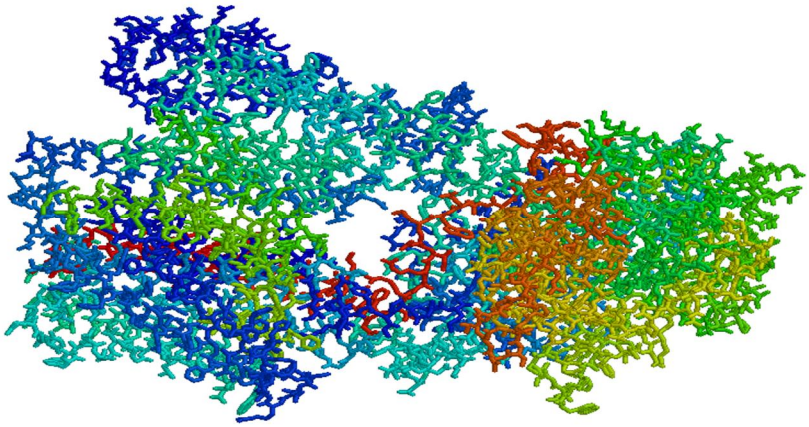


Figure 5:Sticks in the RasMol software, the "stick" representation is a visualization mode that displays the molecular structure of 5FN5 using lines to represent the covalent bonds between atoms. Each bond is represented as a thin line, giving a simplified view of the molecular connectivity. This representation is particularly useful for visualizing the overall structure of the molecule and the arrangement of atoms and bonds.

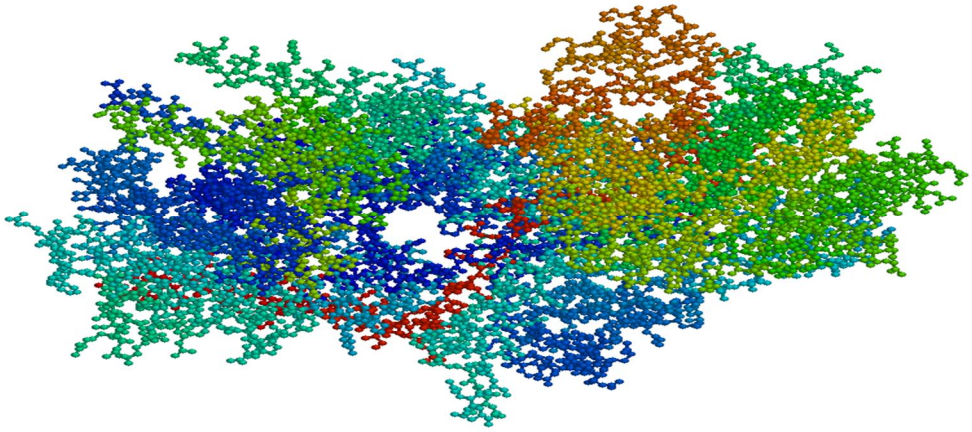


Figure 6:Representation of the 5FN5 protein in Ball and stick model

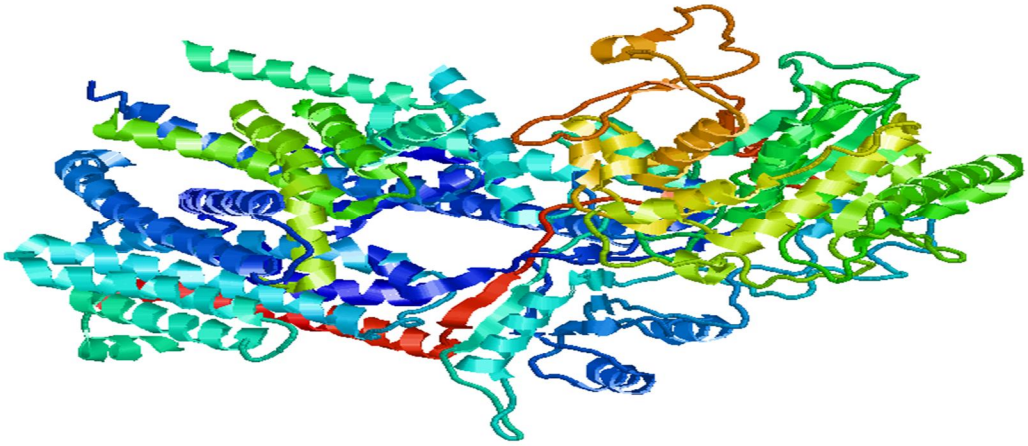


Figure 7:The molecular visualization of 3D Structure of 5FN5 Human γ-secretase. The N Chain is represented in blue coloured ribbons whereas the C terminal is represented in red coloured ribbon structures.

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IV. HOMOLOGY MODELLING

BLASTP determines the regions of similarity between the sequences. It compares the protein sequence with other sequences in the database and computes the applicable mathematics. Closer the E-value is to Zero, the more "significant" is the match. In this case, different proteins from different organisms shows the significant similarity to the query sequence.



select all 100 sequences selected — GenPept | Graphics | Distance tree of results | Multiple alignment | MSA Viewe

Description	Scientific Name	Max Score	Total Score	Query Cover	E value	Per. Ident	Acc. Len	Accession
nicastrin isoform 1 precursor [Homo sapiens]	Homo sapiens	1471	1471	100%	0.0	100.00%	709	NP_056146.1
KIAA0253 [Homo sapiens]	Homo sapiens	1468	1468	99%	0.0	100.00%	708	BAA13383.1
nicastrin isoform X1 [Pan paniscus]	Pan paniscus	1466	1466	100%	0.0	99.72%	709	XP_003811930.1
NCSTN isoform 1 [Pongo abelii]	Pongo abelii	1460	1460	100%	0.0	99.15%	709	PNJ57011.1
nicastrin isoform X1 [Pongo pygmaeus]	Pongo pygmaeus	1458	1458	100%	0.0	99.01%	709	XP_054307039.1
PREDICTED: nicastrin isoform X2 [Mandrillus leucophaeus]	Mandrillus leucophaeus	1457	1457	100%	0.0	99.01%	709	XP_011825769.1
nicastrin [Trachypithecus francoisi]	Trachypithecus francoisi	1457	1457	100%	0.0	99.01%	709	XP_033054363.1
nicastrin isoform X1 [Papio anubis]	Papio anubis	1457	1457	100%	0.0	98.87%	709	XP_003892964.2
nicastrin precursor [Pongo abelii]	Pongo abelii	1456	1456	100%	0.0	98.73%	709	NP_001125587.1
PREDICTED: nicastrin isoform X1 [Colobus angolensis palliatus]	Colobus angolensis palliatus	1456	1456	100%	0.0	98.87%	709	XP_011813032.1
nicastrin [Rhinopithecus roxellana]	Rhinopithecus roxellana	1456	1456	100%	0.0	98.87%	709	XP_010359051.1
nicastrin [Hylobates moloch]	Hylobates moloch	1455	1455	100%	0.0	98.59%	709	XP_032009875.1
PREDICTED: nicastrin isoform X1 [Cercocebus atys]	Cercocebus atys	1455	1455	100%	0.0	98.73%	709	XP_011923021.1
nicastrin [Macaca thibetana thibetana]	Macaca thibetana thibetana	1455	1455	100%	0.0	98.87%	805	XP_050613458.1

Figure 8:Homology analysis by BLASTP

After retrieving the 5FN5 protein sequence from NCBI, it was transformed into FASTA format and used as a query sequence in BLASTP. BLASTP compares a protein sequence with a database of protein sequences. The BLASTP result displayed a list of hundreds of sequences in the description that were similar to the query sequence. The E-value in the study of the 5FN5 protein (Human gamma secretase protein) was zero, indicating that the query and subject sequences were better aligned.Query coverage was 100%, which indicated that the lengths of the query and subject sequences were the same. According to Per.Ident, the query sequence,Nicastrin isoform 1 precursor [*Homo sapiens*] and KIAA0253 [*Homo-sapiens*] have a 100 percent similarity, whilst other sequences have a similarity ranging from 89.70 percent to 99.72 percent.

V. RESULTS OF COBALT

COBALT was used to perform the multiple sequence alignment and Next generation sequencing (NGS). COBALT helped to view the alignment information and data of 5FN5 protein from individual sequence. The query sequence was retrieved from NCBI in FASTA format and multiple aligned using COBALT. It does not try to employ all accessible constraints, but rather a highscoring consistent subgroup that can vary as the alignment progresses. The COBALT result emphasized the amino acid residues among the sequences, giving us insight into which amino acid is present in the sequences that are common.



Figure 9: Panaroma graphical view representing the consensus sequence of Chain A in 5FN5 protein and coverage and quality of alignment. Blue coloured positions represent gap or insertion, positions where the sequences match the consensus are coloured in grey, while the positions containing a huge proportion of mismatches are coloured in red.



Figure 10: Graphical view of Chain C in 5FN5 on Shapely define traditionally colouring of amino acid colours. Shapely command uses a different set of colours for amino acids and colours differentially the all 6 kinds of nucleotides.

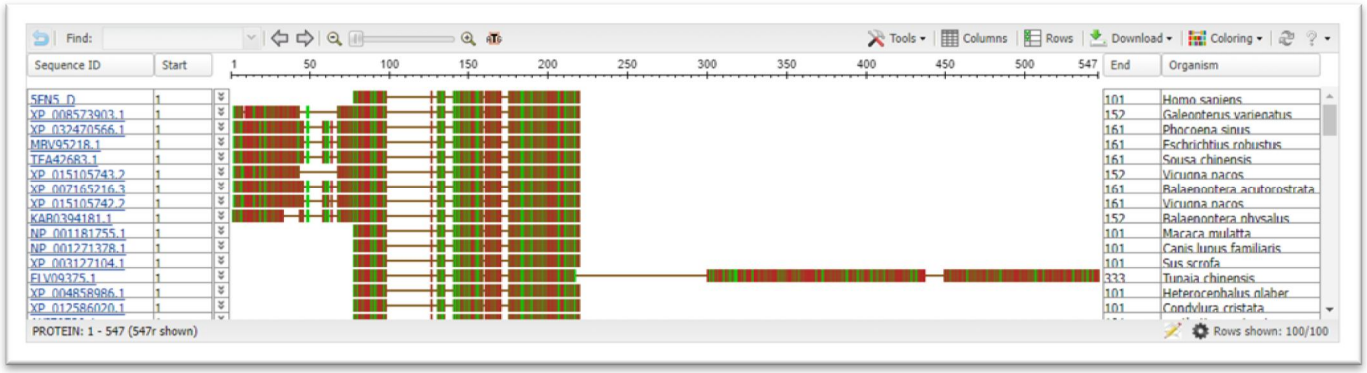


Figure 11: Signal sequence of chain D in 5FN5 reflect on helical potential on biological database sequence

A. PyMOL Result

PyMOL was used to visualize the 3D structure of a protein, to analyze and interpret the protein-protein docking results. PyMOL has various applications: It supports molecular modelling, it is used to dock ligands into the active site, it is frequently employed in drug discovery. In This study, PyMOL was used to visualize the structure of 5FN5 molecule.

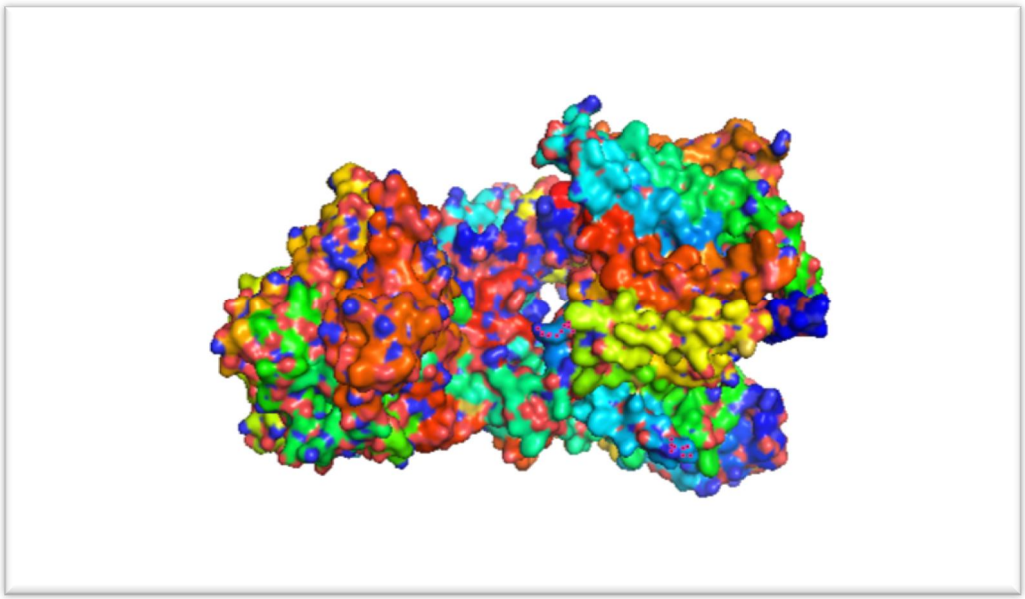


Figure 12: Molecular surface representation of 5FN5 performed usingPymol

B. Molecular Docking Results of Cb-Dock

In this research, we have docked the 5FN5 molecule with(3E)-1-[(1S)-1-(4-fluorophenyl)ethyl]-3-[[3-methoxy-4-(4-methylimidazol-1-yl)phenyl]methylidene]piperidin-2 (also known as E2012). E2012 is a Human γ-secretase modulator that is currently being evaluated as a new potential treatment for Alzheimer's disease. E2012 has shown some potential to reduce the production of β-amyloid protein by modulating the function of 5FN5 gamma secretase.

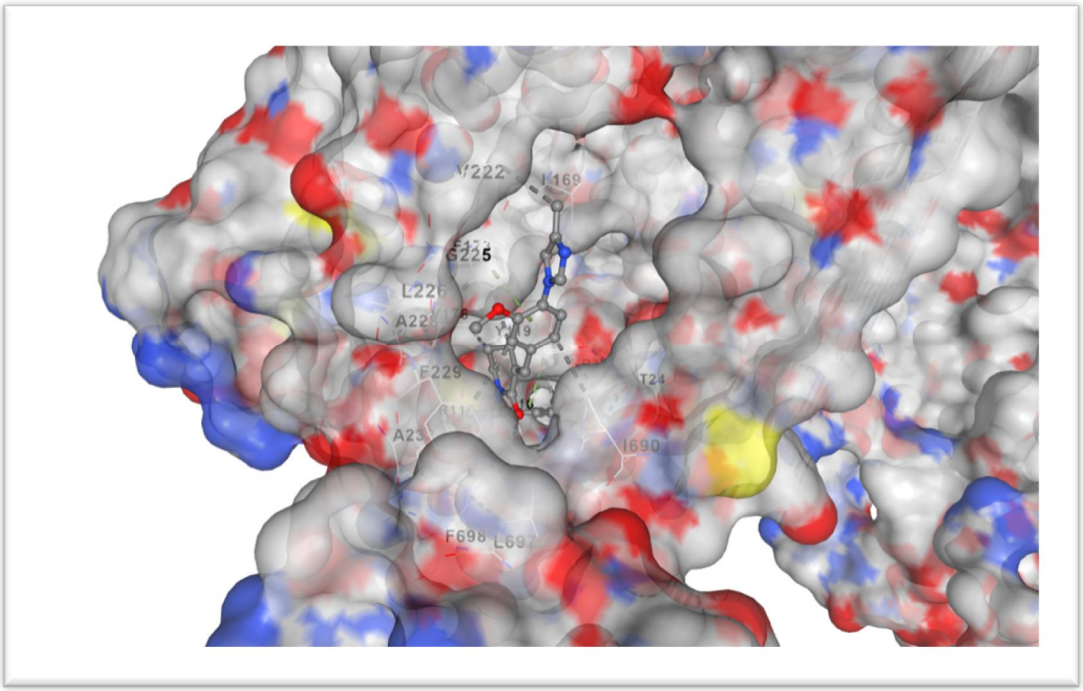


Figure 13:Protein and ligand interaction (Molecular docking):The 'Structure-based Docking' result of 5FN5 (Human γ-secretase) interaction with E2012 drug ligand.

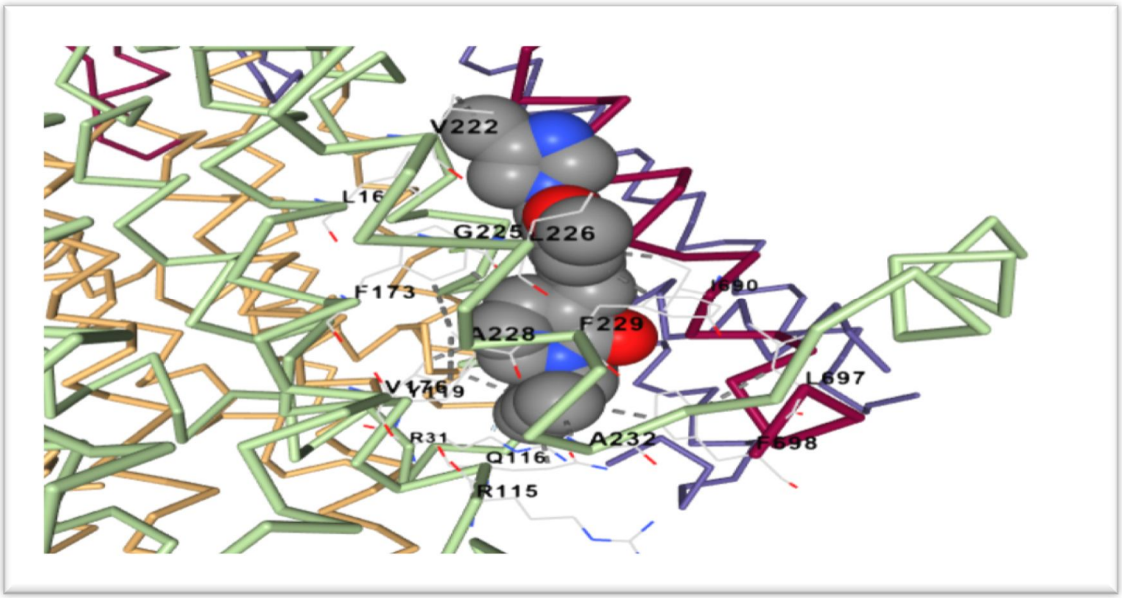


Figure 14:Backbone form receptor showing E2012Drug interacting with 5FN5 target site residue B108(ARG), B167(ILE), B264(PRO), B379(VAL), B429(LYS), B435(LEU), D21(GLY), D25(PHE), D44(VAL), D46(ALA)(protein ligand molecular docking).

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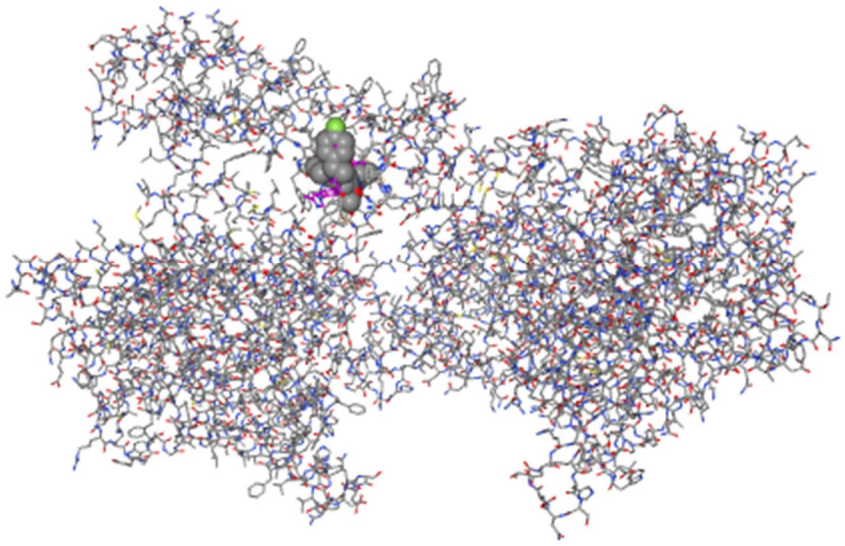


Figure 15:Template-based Blind Docking represent of licorice form protein receptor and ligand shows in spacefill form and contact residue in this Chain A: SER241 ILE242 ASN243
Chain B: PHE176 PHE179 ILE180 GLY183 GLU184 LYS187 LYS239 TYR240
Chain D: PHE94

CurPocket ID	Vina score	Cavity volume (Å^3)	Center (x, y, z)	Docking size (x, y, z)
C2	-9.0	1744	120, 93, 134	26, 26, 26
C1	-7.9	1996	118, 102, 108	26, 26, 26
C5	-7.9	896	143, 121, 116	26, 26, 26
C3	-6.4	1256	135, 138, 119	26, 26, 26
C4	-6.2	1037	107, 166, 126	26, 26, 26

Table 2: Molecular Docking result of 5FN5 Protein with E2012 (docking scores)

VI. CONCLUSION

Alzheimer's Disease is a complex neurodegenerative condition, and the development of effective drugs to treat and cure it has been very challenging. Many drugs have been investigated and tested over the years, but unfortunately, most of them have not resulted in a definitive cure or fully effective treatment for the disease.However, using computational toolkits offers a comprehensive solution for protein sequence analysis, structure visualization, and homology modelling, drug discovery and medical diagnostics.In this research study, Human γ-secterase, 5FN5 was the targeted protein. 5FN5 causes the aberrant cleavage of integral membrane proteins such as notch receptors and APP (β-amyloid precursor protein) leading to Alzheimer's disease. Thus, various drugs were studied for binding with 5FN5 protein.

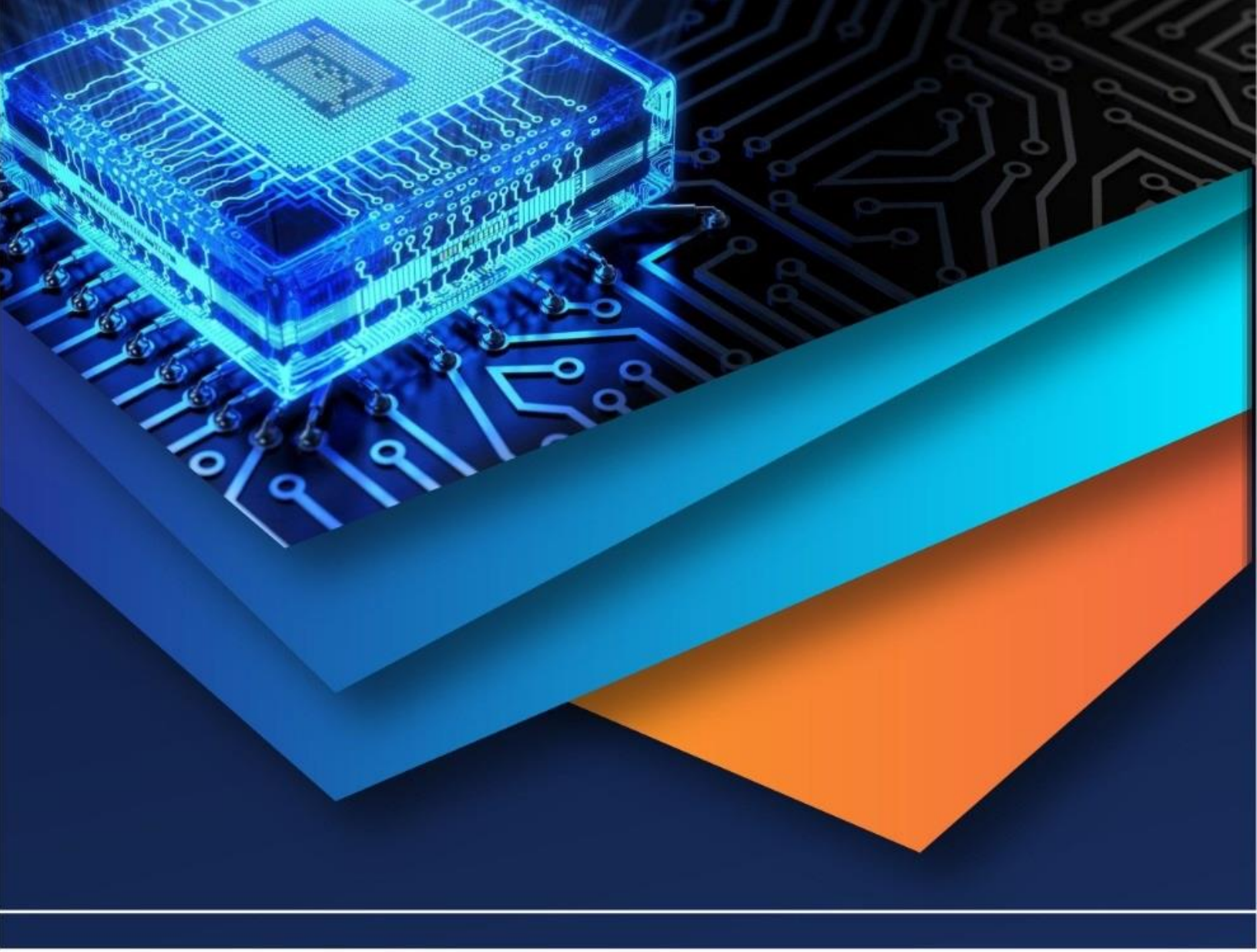
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After docking the various drugs,(3E)-1-[(1S)-1-(4-fluorophenyl)ethyl]-3-[[3-methoxy-4-(4-methylimidazol-1-yl)phenyl]methyl idene]piperidin-2 (also known as E2012) was found to be the accurate therapeutic drug for 5FN5 protein. From the obtained results using RasMol, BLASTP, PubChem, COBALT, PyMOL, and CB-Dock, and after analyzing the molecular docking results, the structure-based docking images, and template-based docking image displayed better protein–ligand (5FN5 – E2012) interaction and docking table showed significant docking score of –9 which is a good docking score for the binding of E2012 drug ligand to the binding site of 5FN5 protein. Hence, we can conclude that E2012 can be one of the novel compounds with modulatory activity for preventing 5FN5,human gamma secretase that plays a crucial role in Alzheimer's disease. By providing valuable insights into protein structure-function relationships, this CADD approach can contribute to advancing our understanding of such complex abnormal functioning of proteins in and around the neurons insidethe biological systems and support to the development of new therapeutic strategies for other disorders as well.

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