MASTER OF SCIENCE (BIOTECHNOLOGY) NAVNEET 2022

AN APPROACH TO TARGET ALZHEIMER'S DISEASE THROUGH MOLECULAR DOCKING

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE

REQUIREMENTS FOR THE AWARD

OF THE DEGREE

OF

MASTER OF SCIENCE

IN

BIOTECHNOLOGY

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CANDIDATE'S DECLARATION

I Navneet, Roll Number: 2K20/MSCBIO/19, student of M.Sc. Biotechnology, hereby declare that the work which is presented in the Major Project entitled "**An approach to target Alzheimer's disease through molecular docking**" in the fulfillment of the requirement for the award of the degree of Master of Science in Biotechnology and submitted to the Department of Biotechnology, DTU, is an authentic record of my own carried out during the period from Jan to May 2022, under the supervision of **Prof Pravir Kumar**.

I have not applied for any other degree at this or any other University based on the information contained in this report. The following details about the related study have been approved in the SCI/SCI Scopus Index Conference:

Title of the Paper: "Putative microRNAs in the pathogenesis of Alzheimer's diseases"
Author Names: Navneet, Pravir Kumar
Name of Conference: 2022 8th International Conference on Advanced Computing and Communication Systems (ICACCS)– IEEE Conference
Date and Venue: 25th -26th March 2022, Virtual at Sri Eshwar college of engineering, Coimbatore, Tamil Nadu, India
Registration: Done
Status of Paper: Acceptance Received
Date of Paper Communication: 27 Feb 2022
Date of Paper Acceptance: 06 March 2022
Date of Paper Publication: NA

Date: Navneet (2K20/MSCBIO/19)

DEPARTMENT OF BIOTECHNOLOGY

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To the best of my understanding, the above work has never been presented in part or in full for a degree at this institute or anywhere else. I also verify that the student's publishing and indexing information is accurate.

Place: Delhi

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ACKNOWLEDGEMENT

I would like to express my gratitude and respect toward my guide, **Prof Pravir Kumar**, He gives me the opportunity to do this thesis work and provided precious support to this project work. His energy, dedication, and determination have had a huge impact on me and made this thesis a work of ease. This thesis is made only with his guidance.

I would also like to thank **Mr. Rohan Gupta** for his support and guidance throughout my work. Also, I want to thank Delhi Technological University for providing me with possibilities during my academic career.

Finally, my thanks go to all the people who have supported me during my entire study.

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ABSTRACT

Alzheimer's disease is described as a nervous system illness that worsens with time. In the world's increasing aging people, it is the most common cause of dementia. The increasing number of Alzheimer's disease cases poses a massive load on families or communities. Despite different attempts to study more about the genesis of Alzheimer's disease, little progress has been made till now. And for the detection and prognosis of Alzheimer's disease, circulatory miRNAs are the most specific favorable prospects in the search for simply attainable and non-invasive biomarkers. Few of them have been recognized as AD-specific miRNAs, and their targets appear to be involved in pathophysiological processes that underpin AD. And now the currently available drugs are very limited for the effective therapy of Alzheimer's disease thus the discovery of new & effective therapeutics is required for AD. Recent computational endeavors to predict novel and effective drugs and targets are reliable and less time-consuming. In computer-assisted drug design, molecular docking is an important technology. PB-DOCK online site gives the detailed docking result and confers how the ligands make a bond with the specific target, which is invaluable in lead molecule optimization. In CB-DOCK, I have used target protein 1sgz Beta-Secretase from AD, which is collected from RCSC PDB databank in PDB format, and then carried CB-DOCK dockings with the test ligands collected from PubChem in SDF-MDL MOL format then converted into PDB format through **Open Bable GUI** software, which is freely available on the internet. After that, I proceeded with the docking of the rasagiline, Entacapone, and mirtazapine drugs. Results further indicated that these test ligands bind significantly to the Beta-secretase and may play a role in its inhibition. These ligands have been identified as potential beta-secretase inhibitors and new anti-Alzheimer drugs in this study.

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1. Introduction

It is a very complicated neurodegenerative disease which mainly distinguishes by an increased decline of abilities such as a way of talking, way of thinking, the behavior of a person, etc. And through this information, Alzheimer's disease reports for almost 80% of all dementia diagnoses and it has been responsible for the main cause of mental illness. It is about more than forty-five million people all around the world affected by Alzheimer's disease and their number is evaluated to approximate one hundred thirty-one million in the next 5-6 decades according to a new report [1] [2] [3]. And the Alzheimer's disease cases are kept on rising just because it is probably brought out by the pathological heterogeneity features of Alzheimer's patients. And it has been broadly described that there are two pathologies in Alzheimer's disease such as β- amyloid plaque accumulation and neurofibrillary tangles of hyperphosphorylated [4] [5] [6]. Correspondingly inspire the important advancement in molecular medicine. Active Alzheimer's disease therapy is still not able to stop the patient from the ongoing and irreversible cognitive decline. It has been seen that the negative influence of which is the growing people with an aging population in different countries [7]. The possible biomarkers are fruitful tools for Alzheimer's disease prevention, and its detection. Now it is important for serious decile form of dementia and for Alzheimer's patients to get a diagnosis and early detection with specific administration. Several studies have been done till now through researchers to know the possible evidence and understand the molecular etiology of Alzheimer's diseases [8] [9]. Some of which converted into favorable therapy approaches. For now, different biomarkers in cerebrospinal fluid have been broadly characterized which includes Aβ, net total tau levels, and other different new candidate biomarkers [10]. Besides, it has been illustrated that greater than a single biomarker will be more specific to

give out the possibility of Alzheimer's disease to mild cognitive impairment. For now, few reports described that CSF and PET biomarkers were hired for a certain type of Alzheimer's disease in scientific clinical cases such as increasingly continuous neurodegenerative disease (AD). Although due to the uncontrol infection of CSF collection, this approach is markedly redistricted in the clinical operation. Plasma and urine are also searched out by the researchers to know the other biomarker for easy detection of Alzheimer's disease. Metallothionein (MTI) and several other genes were the possible targets for AD, and this has been reported through various studies. One another research has proposed GRIKI was linked to Alzheimer's diseases stages through WGCNA analysis. In earlier studies, researchers normally focused on a single analysis method or specific gene. That is why except for WGCNA other ways were also used in this research in response to detecting multiple possible biomarkers linked with the onset of Alzheimer's disease.

Moreover, amyloid-beta inhibit the destruction of hyperphosphorylated tau by the proteasome. The amyloidogenic pathway is occur due to a variation that substitutes the actual pathway in which alpha-secretase acts on the amyloid precursor protein accompanied by gamma-secretase developing harmless p-3 peptide but the amyloidogenic pathway indulged in the collapsing of amyloid precursor protein by Beta-secretase accompanied by gamma-secretase and results in the development of an Aβ plaque [11]. The extracellular domain of APP encounters proteolytic cleavage through β–site amyloid precursor protein cleaving enzyme or beta-secretase accompanied by cleavage of the transmembrane domain of beta-amyloid precursor protein by gamma-secretase. With each and every site of cleavage and different peptides being developed, it is getting more apparent that different amyloid precursor protein-derived peptides beyond Amyloid-beta. [12]. Available drug for the treatment of AD is not satisfactory and researchers are always in search of new drug targets for AD. Few available drugs and targets for AD are described in table 1.

1.1 Beta-Secretase

The BACE1 gene encodes BACE 1, also called β-site cleaving enzyme 1 (BACE1), membrane-associated with different enzymes. BACE1 expression is mostly seen in neurons.

The extracellular protein domain of the protein comprises a couple of active sites of aspartate residues and may regulate in the form of dimer; the cytoplasmic tail is needed for proper development & effective inside cell trafficking but has no effect on activity. It is generated as the enzyme, and endoproteolytic elimination takes place in the Golgi apparatus after BACE exits the endoplasmic reticulum. In addition, extra sugars are added to the pro-peptide to enhance its molecular mass. As a result, the tail got palmitoylated [13].

1.2 Role of BACE1 in AD

BACE1 is the prime enzyme in neurons that produces amyloid peptides. Two consecutive breakdowns of the APP are required to produce the forty or forty-two amino acid lengthy peptides of amyloid that assemble in the brains of AD patients. BACE1 cleaves APP extracellularly, resulting in a soluble fragment and abounded fragment called C99 [14].

The intracellular domain of APP is released when β secretase breaks C99 inside its transmembrane domain, resulting in amyloid-. Gamma-secretase removes a piece of the amyloid peptide because it breaks amyloid precursor protein nearer to the membrane of the cell than beta-secretase 1. Primary cleavage of amyloid precursor protein through secretase than BACE1 inhibits the formation of Aβ, resulting in P3.

Unlike amyloid precursor protein and the presenilin involved in β-secretase, there are no familiar mutations in the BACE1 gene that affects initial-onset familial AD, a rare type of the illness.

Nevertheless, the stage of this enzyme is more in late-onset sporadic AD, which is significantly more frequent. Beta secretase 2 is a close relative of beta secretase1, although there has been no evidence of APP cleavage in vivo [15].

BACE's breakage of amyloid precursor protein and other transmembrane proteins has no recognized physiological function; nevertheless, several investigations have found that BACE1 is indulged in myelination. The beta subunit called VGSC is a substrate for beta-secretase 1 in a similar way to how APP is processed. An individual residue variation in amyloid precursor protein, on the other hand, decreases beta-secretase 1 capacity to break it and make Aβ, lowering the likelihood of AD and other diseases. The inflammatory state influences BACE1 expression: cytokines lower PPAR1, a BACE1 mRNA inhibitor, during Alzheimer's disease [16].

2. PATHOGENESIS

Alzheimer's disease occurs due to the aggregation of intracellular neurofibrillary tangles and Aβ plaques which consist of hyperphosphorylated microtubule-associated τ. And the plaque which is mentioned above develops initially in the different regions of the brain and subsequent stages develop over the hippocampus region, basal ganglia & neocortex. In severe cases, amyloid β is found in the mesencephalon region, over the cerebellar cortex, and brain stem lowering as well. Amyloid β activates the τ-tangle development concentration which is detected in the coeruleus and transentorhinal region of the cerebrum. Areas, where severe stages of Alzheimer's disease are seen, are the neocortex and hippocampus region. In the progression of these diseases, Aβ and NFTs play a most important role in it.

Pathogenesis of amyloid initiates with the modified breakage of the precursor protein of amyloid which is a structural group of amino acids on the plasma membrane through the β-secretases

(BACE1) enzymes and to form immixture Amyloid β fibrils. After this the Aβ gets oligomerized disperse into the synaptic cleft and obstructs through synaptic signaling, therefore, it polymerizes into an immixture of amyloid fibrils that are deposited into the plague. Activation of kinases is occurring through polymerization which results in hyperphosphorylation of the microtubule-linked with τ protein. The deposition of plague and tangles is going along with the microglia recruitment surrounding plagues and this process influence or promotes the microglial activation and local inflammatory response [17] [18].

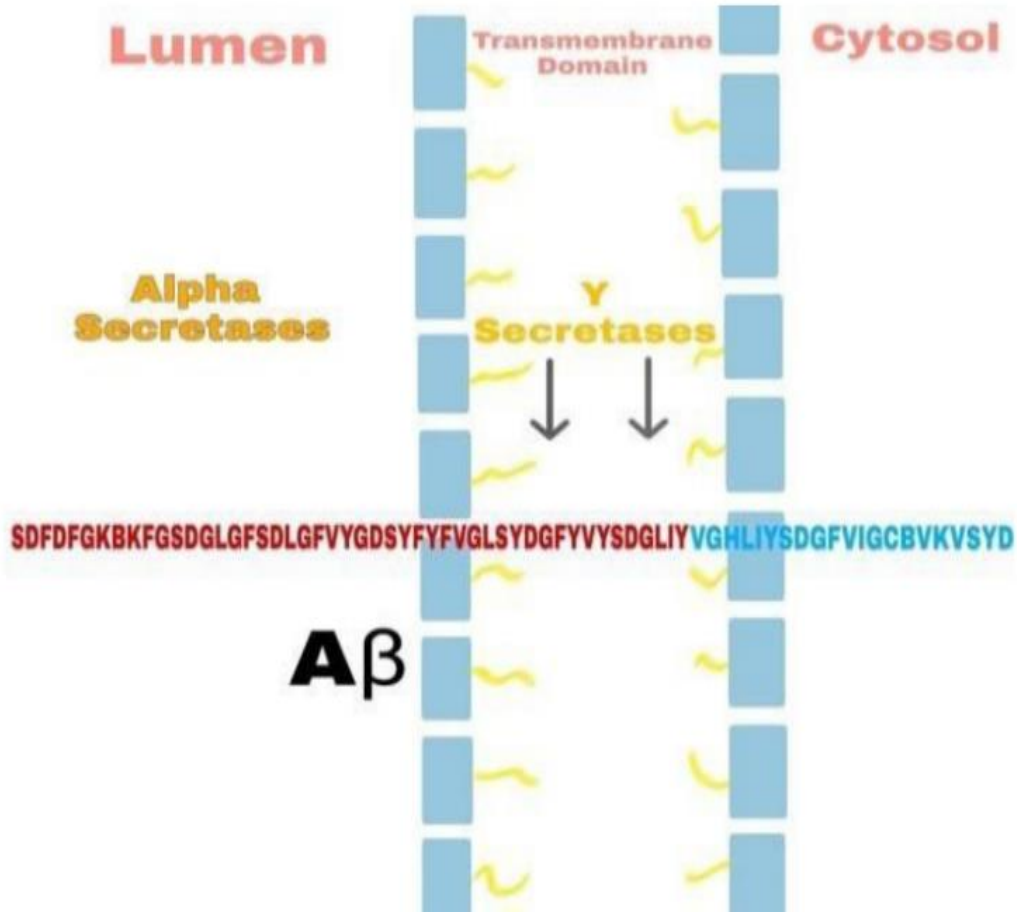

Fig 1: Outline of amyloid-beta pathogenesis

The amyloid precursor protein is linked with the group of associated proteins which includes mammalian APP like amyloid precursor proteins 1 and 2. It is a structural transmembrane protein

with extracellular domains. Amyloid precursor protein gives rise to amyloid genic fragments via distinctive breakage by enzymes. The studies of provisionally transfected cell lines display that the Amyloid β pathogenesis hypothesis mediates the living condition of the cell growth the cell, its motility, and the neurite outgrowth and roles assigned to the excretion of mixable ectodomains over normal breakage of the APP. The significance of the APP has been spotlighted through various studies where brain irregularities have been described in animals injected with amyloid precursor protein ectodomains intracerebral and APP RNAi injections which have shown upgraded synaptic density [19]. Transmembrane glycoprotein is encoded by the APP and this glycoprotein is breaking either by an amyloidogenic pathway (diseased state) or through the non-amyloidogenic pathway (normal state). Amyloid precursor protein contains several seven seventy amino acids of which Amyloid β also contains twenty-eight residues with few extra fourteen residues from the domain transmembrane of the Amyloid precursor protein. Towards the cleavage site, α-secretase breaks & release a huge mixture of ectodomains amyloid precursor protein sα into the medium and the terminal pieces of C83 which again breaks through the enzyme γ- secretase at residue 711 which leads to secreting truncated amyloid precursor proteinsβ.[20] [21] [22] [23].

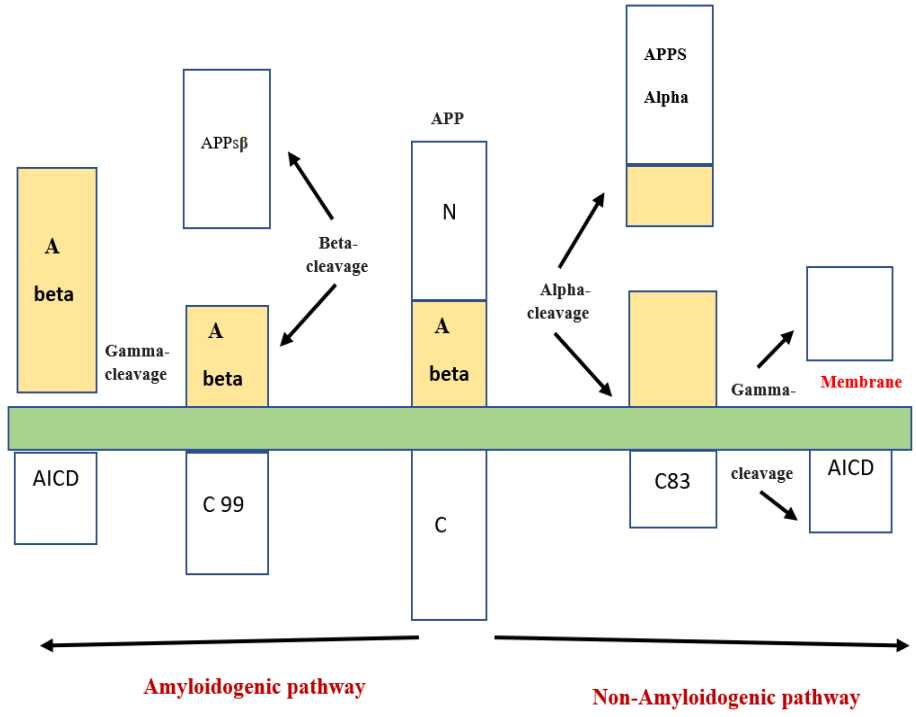

Fig 2 BACE1 (β-secretase) and -secretase cleave PP sequentially to produce Aβ.

3. Regulation of APP expression and BACE1

Elevated Amyloid Precursor Protein expression may enhance the production of Aβ, synaptic failure, lead to neuron toxification, and finally cause dementia, based on mounting data [24] [25]. Several microRNAs have been involved in the control of Amyloid Precursor Protein expression; for example, miR- 106a/520c has been shown to attach to the 3'untranslational region of protein APP and inhibit its expression in human cell lines [26] [27]. The miR-20 family was later discovered to control APP expression through the attachment of the Amyloid Precursor Protein 3'UTR by a group of researchers. Furthermore, the expression level of Amyloid Precursor Protein is reduced in conjunction with miR-20 excess expression in the cells of neurons [28] [29].

The distribution of Amyloid Precursor Protein through BACE1 is the earliest and rate-limit stage for the development of Amyloid β, and elevated expression of BACE1 levels and activities of

enzymes has been seen in sporadic Alzheimer's diseases brains. Several microRNAs that regulate the appearance of BACE1 and its function have been discovered [30] [31] [32]. The expression amount of the microR29a/b1 concentration declined dramatically with increased concentration of BACE1 appearance in sporadic Alzheimer's Diseases, according to several investigations of microRNA expression profiles of sporadic in patients of AD. MiR-107 is another well-measured microRNA. In AD patients, miR-107 expression reduced dramatically as BACE1 levels rose [33] [34] [35] [36]. In a cell culture reporter test, it was discovered that miR-107 controlled BACE1 expression by identifying and binding the 30UTR of BACE1 [37] [38] [33] [40]. Further, it was shown that miR-107 amount was inversely associated with mRNA BACE1 amount, resulting in Aβ deposition. Furthermore, several studies have linked miR-107 to the prevention of toxification of neurons and blood-brain barrier disruption caused by Aβ and making miR-107 a viable therapeutic aim for scientists and researchers [41]

Table: Available drugs and targets of Alzheimer's disease

S. No	Available medicine	Target	Mechanism of action
1	Tacrine, Donepezil	Acetylcholinesterase	Acetylcholinesterase inhibitor
2	Piaglitazone, Rosiglitazone, tartaric Acid	BACE	beta-site APP cleaving
3	Memantine, Nameda, Axura and Akatinol, Ebixa	N-methyl D-aspartate	N-methyl D-aspartate antagonist

BACE may occupy an unexpectedly central place. This is due to the fact that BACE cleavage of APP produces not only the C-terminal fragment of APP, which is the immediate precursor of Aβ. The Aβ peptide has been implicated as a central mediator of AD based on extensive genetic and biochemical data. It has been implicated that Aβ can generate a sulfuryl radical involving methionine 35, as well as its direct effects on post-synaptic structures. Other key downstream mediators along with APP are insulin receptors and tau. This study involves docking of β-secretase with some ligands like rasagiline, entacapone, and mirtazapine to find out potent β-secretase inhibitors using CB-DOCK [42] [43] [44].

4. Materials & Methods

4.1 Design of experiment

Docking is a technique in molecular modeling that anticipate the better orientation of an individual molecule to another where a ligand and a receptor protein are coupled to form a balanced complex. Through utilizing scoring functions, for eg, understating of the better orientation could be utilized to find out the stability of the bond or binding attraction b/w 2 molecules.

In signal transduction, the bonding b/w physiologically appropriate molecules like proteins, and peptides are crucial. Nevertheless, the sort of signal formed could be damaged through the relative movement of the 2 interacting molecules. As a result, docking is important for forecasting the intensity of the signals [45] [46] [47]. Due to its ability to predict the binding configuration of less size-molecule ligands to the correct target binding site, docking is one of the major often used strategies in structure-based drug formation.

The investigation of binding action aids in the logical design of therapy as well as in knowing the concept of fundamental biological processes [48].

4.2 **Software used**

CB-DOCK is the software that was used during the docking process between the protein and ligand. CB-Dock anticipates the binding of the protein region, finds out the mid area and diameters through utilizing a curvature-based cavity detection application, then docks through Auto dock Vin, and through different programs. The high-ranking postures whose root mean squared deviation was between two of the location in the X-ray crystal structure had a 70% success rate in our benchmark testing. It surpassed other popular blind docking technologies and outperformed the classic blind docking approach (40 percent). This software is freely available on the internet and provides a good and detailed docking result. On this open software we need to upload our PDB file of protein and ligand and they must be in PDB format.

4.3 **Selection of target protein**

PDB was used to obtain the X-ray crystal coordinates of beta-secretase (BACE 1). Beta-secretase was chosen for modeling research because its crystal structure reflects the pharmacological target for the formation of novel medications to treat Alzheimer's disease.

4.4 Selection of ligands

Three ligands were selected for this study namely rasagiline**,** entacapone, and mirtazapine against beta-secretase. Every ligand was specifically docked against beta-secretase for getting good results.

4.5 Molecular docking

CB-DOCK docks specific protein chains and selects them for docking. Small compounds found in PDB files were either added to the ligand folder or saved as SDF files. CB-DOCK combines a variety of computational chemistry programs targeted at accurately computing parameters required at various stages of the docking technique, such as precise ligand shape optimization and energy minimization. Each test ligand was docked with the protein separately, as well as the whole protein.

So, in this CB-DOCK online software, protein is added in a specific folder in pdf format and the specific ligand is added in a specific folder in PDB format. After that, we have to set the parameter and then process the docking.

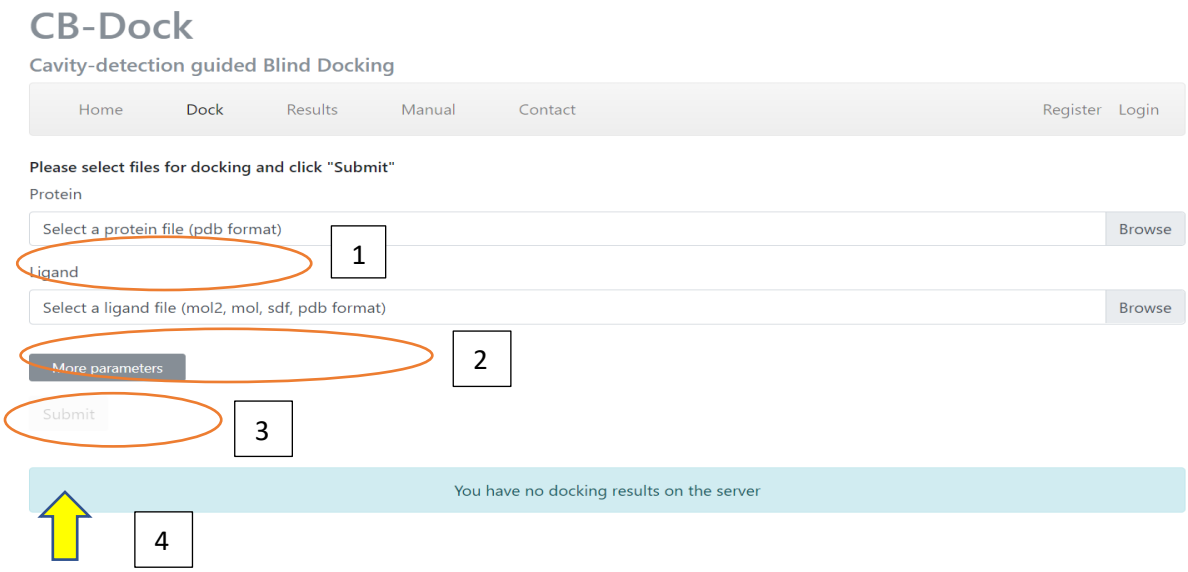

Fig 3: CB-DOCK processing representation

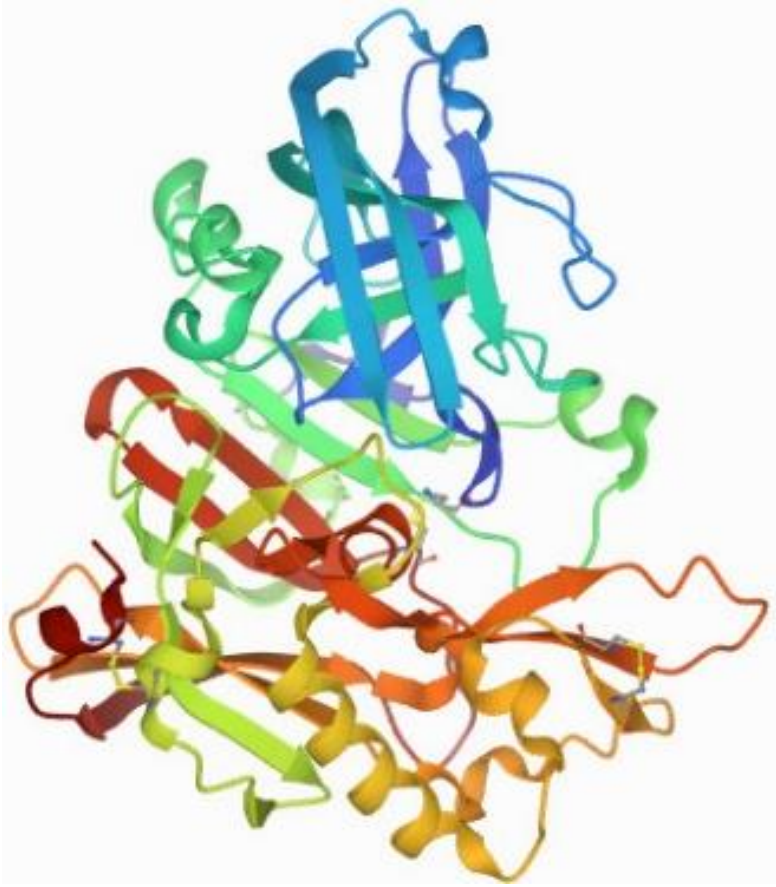

Fig 4: Target protein BACE1

Chemical Structure Depiction

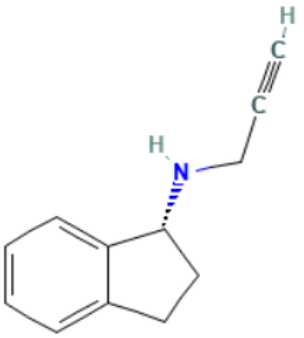

Fig 5 Rasagiline

Chemical Structure Depiction

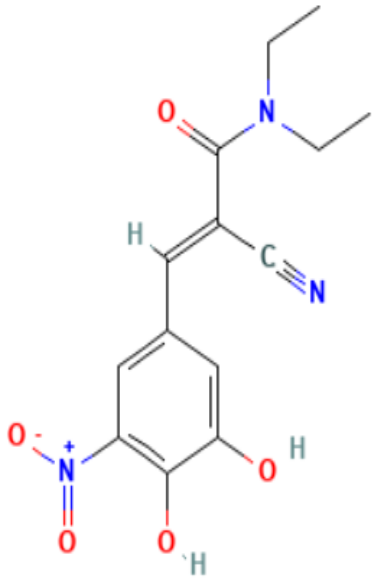

Fig 5(a) Entacapone

Chemical Structure Depiction

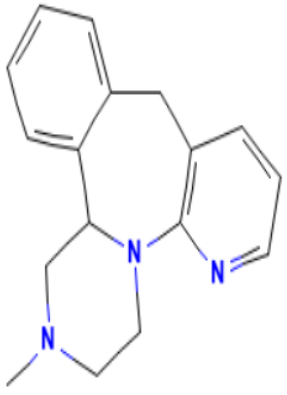

Fig 5 (b) Mirtazapine

5. Docking of Beta secretase with Rasagiline

Binding Modes

Table: 2 The above table represents the binding energy between the protein beta-secretase and ligand.

Vina score	Cavity size	Center			Size		
		x	y	z	x	y	z
-6.4	4510	19	84	37	19	27	33
-6.4	706	-6	84	34	19	19	19
-5.9	2328	-20	84	-3	19	19	28

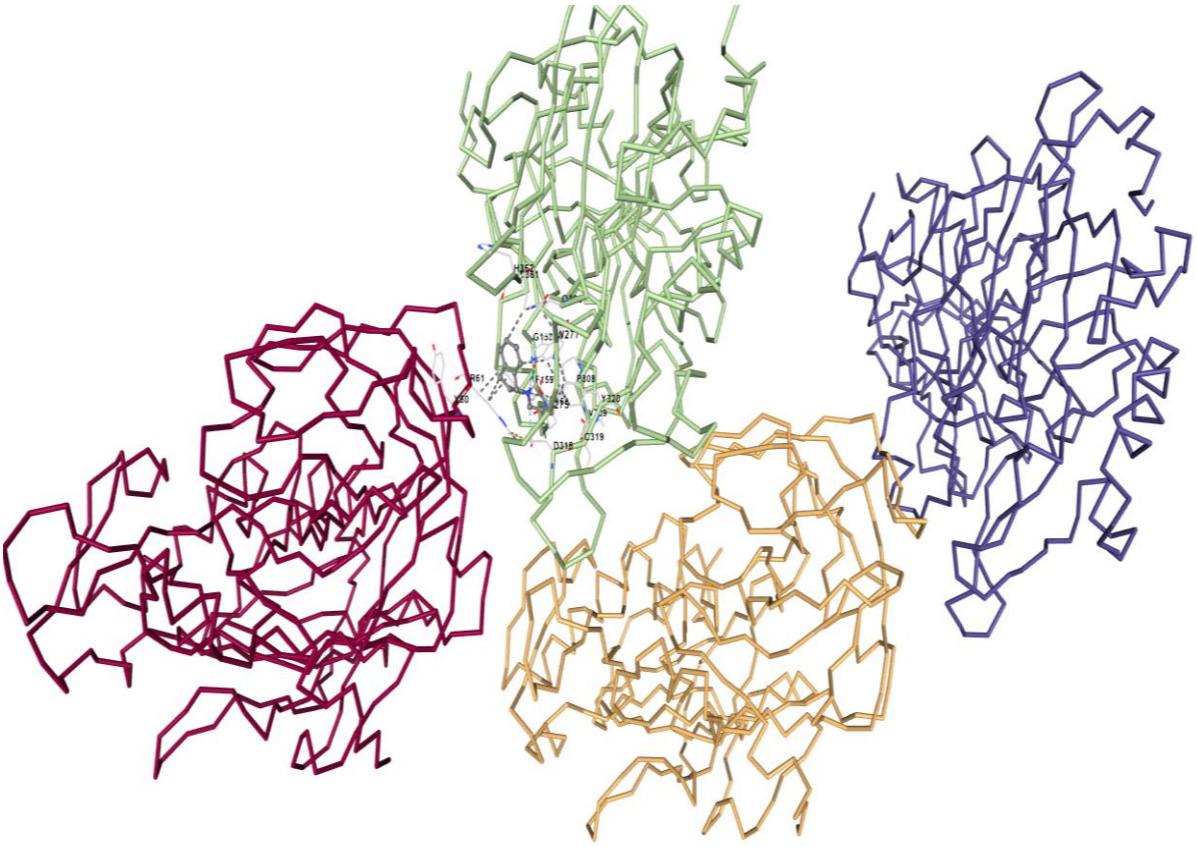

Fig 6: Image shows binding of protein with Ligand

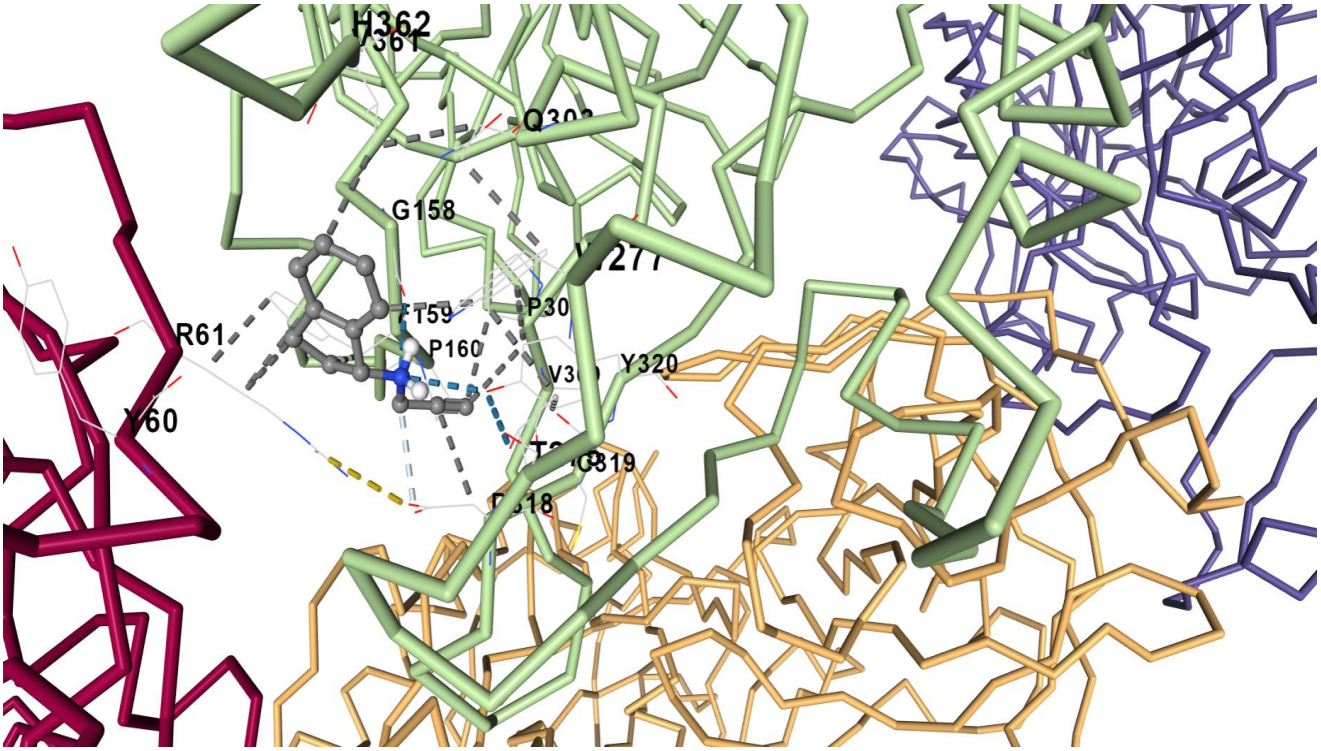

Fig 6a**:** A close look between the ligand and the protein

6. Docking of Beta secretase with Entacapone

Binding Modes

Vina score	Cavity size	Center			Size		
		x	y	z	x	y	z
-7.7	2328	-20	84	-3	21	21	28
-7.2	4510	19	84	37	21	27	33
-6.8	706	-6	84	34	21	21	21

Table: 3

The above table represents the binding energy between the protein beta-secretase and ligand.

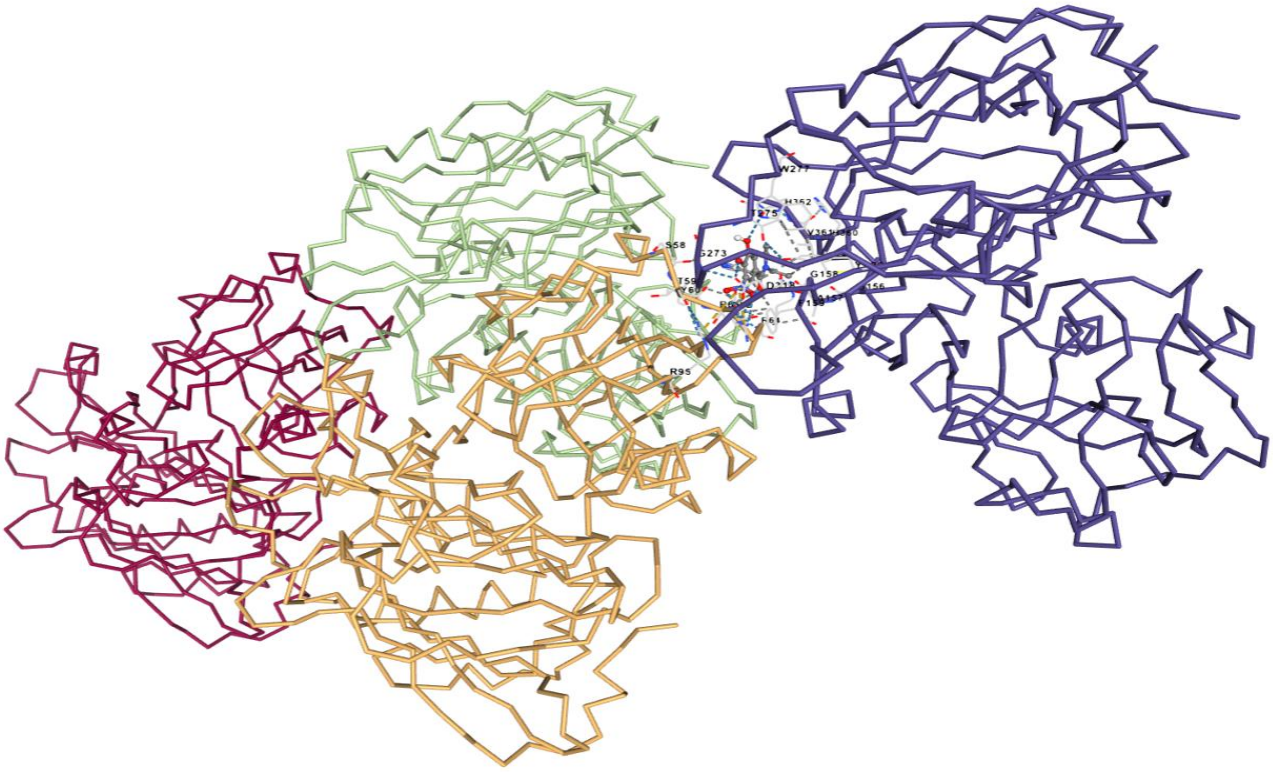

Fig7: Image shows binding of protein with Ligand

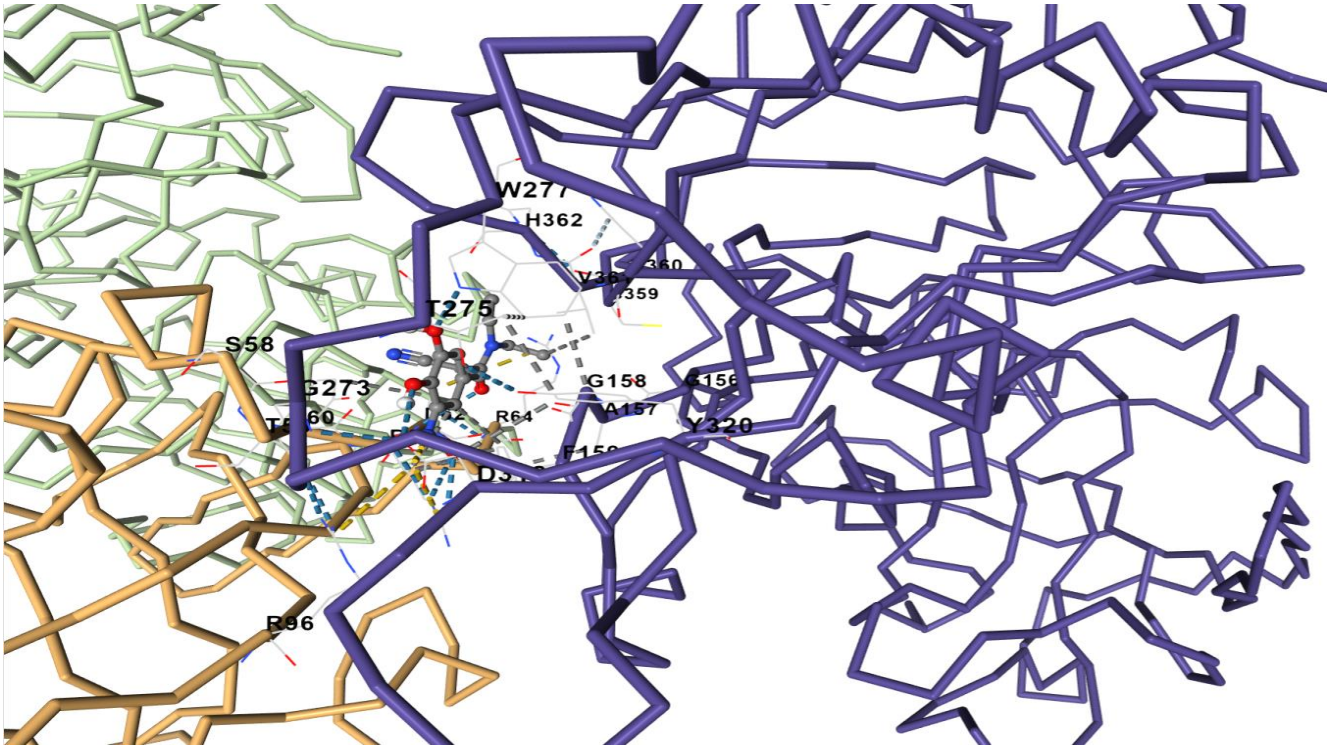

Fig7a: A close look between the ligand and the protein

7. Docking of Beta secretase with Mirtazapine

Binding Modes

Vina score	Cavity size	Center			Size		
		x	y	z	x	y	z
-8.6	4510	19	84	37	19	27	33
-8.5	2328	-20	84	-3	19	19	28
-7.9	706	-6	84	34	19	19	19

Table: 4

The above table represents the binding energy between the protein beta-secretase and ligand.

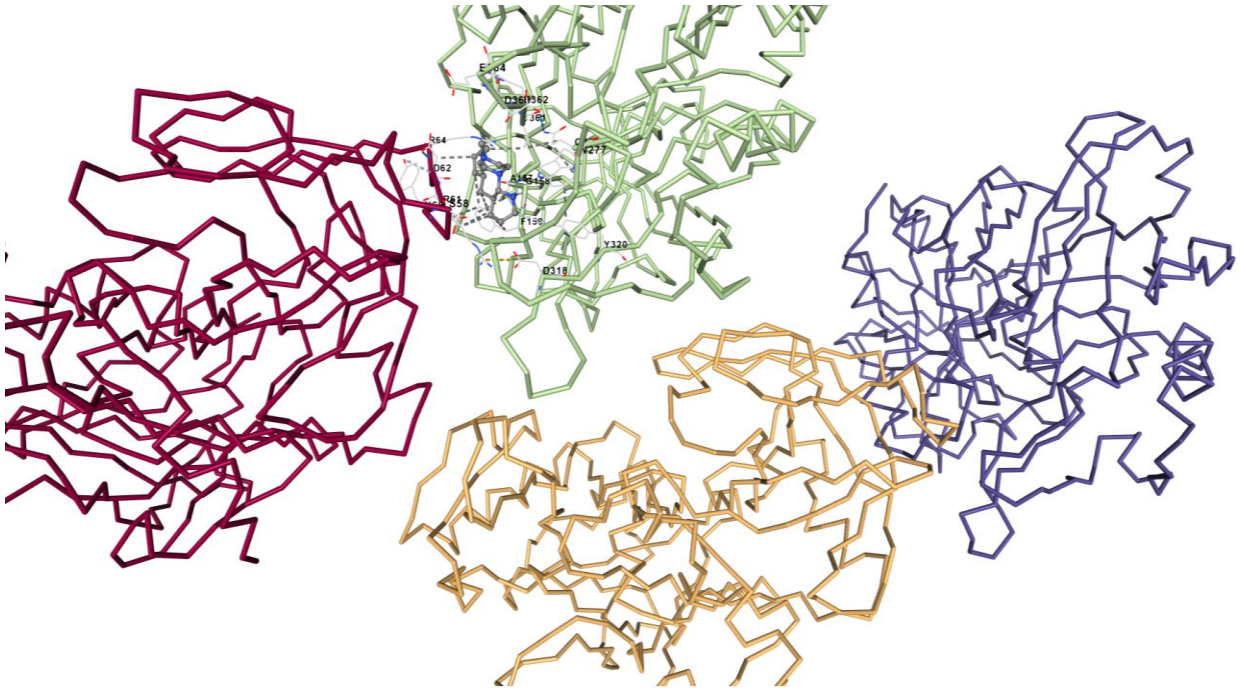

Fig8: Image shows binding of protein with Ligand

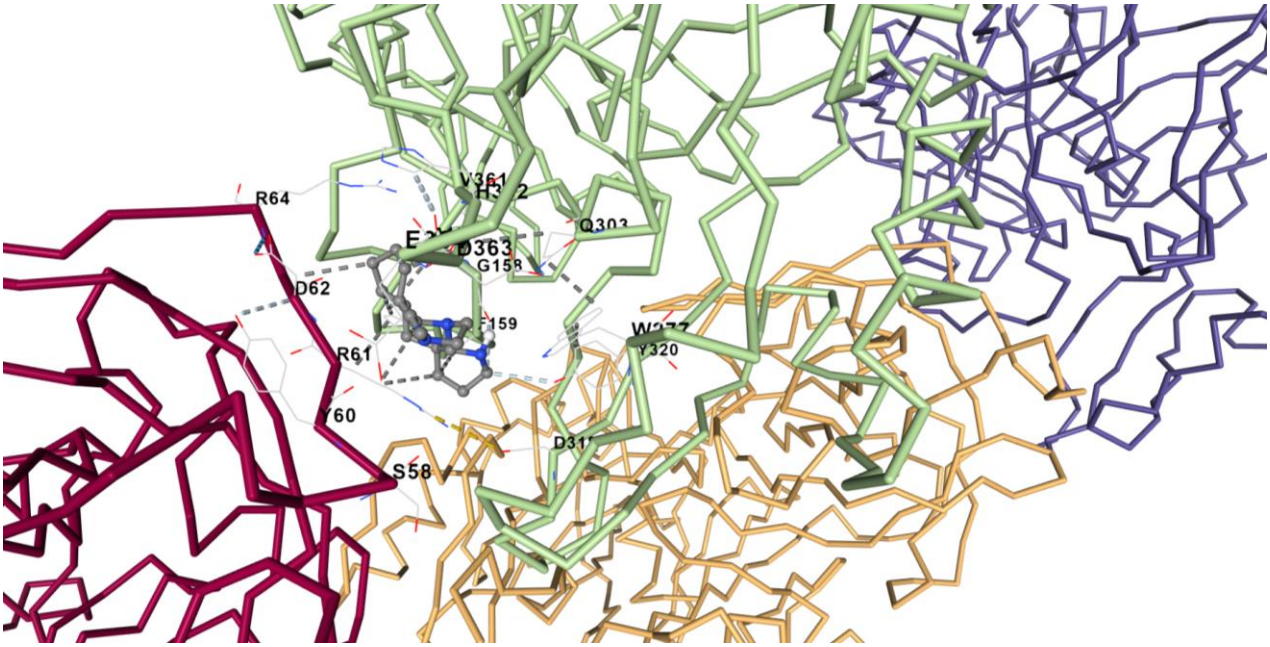

Fig8a: A close look between the ligand and the protein

Table 5: The top best-docked energy results from CB-DOCK Server

S.no	Protein	Ligand	Minimum binding energy (k/cal mol)
1	Beta-secretase	Rasagiline	-6.4
2	Beta-secretase	Entacapone	-7.7
3	Beta-secretase	Mirtazapine	-8.6

8. Results and Discussion

The structure of β-secretase (BACE 1) was derived from the protein data bank (Fig:4). The structure of ligand rasagiline, entacapone, and mirtazapine from PubChem was shown in Figures 4,4a,4b, and they are used for docking study against β -secretase (BACE 1). I have docked every single test ligand specifically, rasagiline, entacapone, and mirtazapine, with our target BACE 1 individually and with the complete protein resulting in PB-DOCK Server. Binding energy was shown in Tables 1, 2,3 but the final and maximum binding energy is shown in table 4. We have found that mirtazapine has the least binding energy in comparison to other ligands (rasagiline and entacapone drug). The binding energy of entacapone is lesser than rasagiline but they are both taken as less (table 4). The initial parameter that is formed as a result of docking is binding energy. It offers an indication of the intensity and affinity of the ligand-target binding. The weaker the contact, the higher the binding energy, and vice versa. The goal of this research is to find the ligand with the lowest binding energy.; thus, the mirtazapine has shown the best affinity among the other ligands. Among the test ligand in this study, mirtazapine shows the least binding energy of -8.6 kcal/mol with 1sgz protein. Rasagiline has a high binding energy of -6.4 kcal/mol among all the ligand molecules. Based on this data and through this study, among the three test ligands, mirtazapine binds significantly to the beta-secretase and may play a role in its inhibition. We found that these ligands dock Beta-secretase (1sgz) and the best docking result with each of the test ligands are shown in fig 2,3,4 which were derived by PB-DOCK Server. Figure 2-4 shows that these three test ligands interact with beta-secretase. These findings are needed to undergo in vitro and in vivo studies for the development of a complete understanding of these possible efficient inhibitors (Mirtazapine) of BACE1 for the effective treatment of AD.

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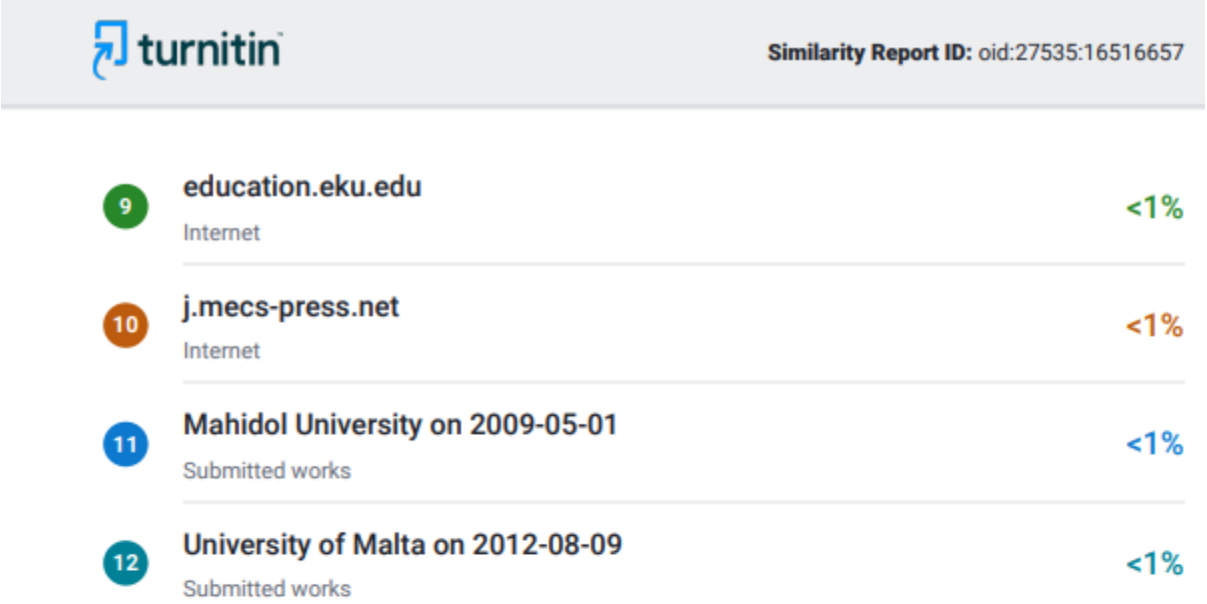
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CANDIDATE'S DECLARATION

I Navneet, Roll Number: 2K20/MSCBIO/19, student of M.Sc. Biotechnology, hereby declare that the work which is presented in the Major Project entitled "**An approach to target Alzheimer's disease through molecular docking**" in the fulfillment of the requirement for the award of the degree of Master of Science in Biotechnology and submitted to the Department of Biotechnology, DTU, is an authentic record of my own carried out during the period from Jan to May 2022, under the supervision of **Prof Pravir Kumar**.

I have not applied for any other degree at this or any other University based on the information contained in this report. The following details about the related study have been approved in the SCI/SCI Scopus Index Conference:

Title of the Paper: "Putative microRNAs in the pathogenesis of Alzheimer's diseases"
Author Names: Navneet, Pravir Kumar
Name of Conference: 2022 8th International Conference on Advanced Computing and Communication Systems (ICACCS)– IEEE Conference
Date and Venue: 25th -26th March 2022, Virtual at Sri Eshwar college of engineering, Coimbatore, Tamil Nadu, India
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