In silico screening of multi target drug for Alzheimer's disease and Parkinson's disease using pharmacophore-based drug discovery approach

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TABLE OF CONTENTS

ABSTRACT . . . . . **i**

ÖZET . . . . . **iii**

ACKNOWLEDGEMENTS . . . . . **v**

DEDICATION . . . . . **vi**

LIST OF TABLES . . . . . **vii**

LIST OF FIGURES . . . . . **viii**

LIST OF SYMBOLS/ABBREVIATIONS . . . . . **xii**

1. OBJECTIVE **1**

1.1 STATEMENT OF AIM 2

2. INTRODUCTION **3**

2.1 Parkinson disease 3

2.2 Alzheimer's disease 4

2.2.1 Tau Protein 6

2.3 Parkinson disease treatment 8

2.4 Alzheimer treatment 9

2.5 Target protein 10

2.5.1 Monoamine oxidase B PDB coed (2V5Z) 10

2.5.2 Acetyl cholinesterase PDB code (1EVE) 11

2.6 Inhibitors 11

2.6.1 Ropinirole 11

2.6.2 Selegiline 12

2.6.3 Trihexyphenidyl 12

2.6.4 Opicapone 12

2.6.5 Pimavanserin 13

2.6.6 Pramipexole 13

2.6.7 Procyclidine 13

2.6.8 Dehydroascorbic Acid 14

2.6.9 Dihydroergocristine 15

2.6.10 Donepezil 15
2.6.11 Dihydro-alpha-ergocryptine 16
2.6.12 Lisuride 16
2.6.13 Galantamine 17
2.6.14 Huperzine A 17
2.6.15 Huperzine B 18
2.6.16 Isocarboxazid 18
2.6.17 Memantine 19
2.6.18 Pargyline 20
2.6.19 Phenelzine 20
2.6.20 Physostigmine 21
2.6.21 Rivastigmine 21
2.6.22 Tranylcypromine 22
2.6.23 Viloxazine 23
2.6.24 Ajmaline 23
2.6.25 Apomorphine 24
3. Material and Method **29**
3.1 Target Proteins 30
3.1.1 Active site for Acetylcholinesterase (1EVE) 30
3.1.2 Active site for Monoamine oxidase B (2V5Z) 31
3.2 Inhibitors selection 33
3.3 Pharmacophore Modeling Screening 38
3.3.1 Pharmacophore of anti-Alzheimer drugs (2V5Z-Target) 40
3.3.2 Pharmacophore of anti Parkinson drugs (2V5Z-Target) 41
3.3.3 Pharmacophore of anti-Alzheimer drugs(1EVE-Target) 42
3.3.4 Pharmacophore of anti Parkinson drugs acetylcholinesterase (1EVE-Target) 43
3.4 Lipinski rule of 5 47
3.5 Docking studies 48
4. Result and Discussion **49**

4.1 Molecular docking of acetylcholinesterase (1EVE) and the top 5 Anti-Alzheimer's compounds 49
4.1.1 ZINC03830630 49
4.1.2 ZINC03830629 49
4.1.3 ZINC03831223 49
4.1.4 ZINC11592603 50
4.1.5 ZINC03831061 50
4.2 Molecular docking of acetylcholinesterase (1EVE) and the top 5 anti-Parkinson's compounds 54
4.2.1 ZINC03881345 54
4.2.2 ZINC04026555 54
4.2.3 ZINC11616656 54
4.2.4 ZINC11592603 55
4.2.5 ZINC02033589 55
4.3 Molecular docking of 2V5Z and the top 5 anti-Parkinson's compounds 60
4.3.1 ZINC03881345 60
4.3.2 ZINC04026555 60
4.3.3 ZINC11616656 60
4.3.4 ZINC03830768 60
4.3.5 ZINC03812892 61
4.4 Molecular docking of Monoamine oxidase B (2V5Z) and the top 5 anti-Alzheimer's compounds. 65
4.4.1 ZINC02033589 65
4.4.2 ZINC01530604 65
4.4.3 ZINC00537877 65
4.4.4 ZINC00538275 66
4.4.5 ZINC00538505 66
4.5 ADMET studies 71
4.6 Cross docking 75
5. CONCLUSIONS **80**

REFERENCES **89**

In silico screening of multi target drug for Alzheimer's disease and Parkinson's disease using pharmacophore-based drug discovery approach

ABSTRACT

Research on neurodegenerative diseases (NDD), commonly known as Alzheimer's and Parkinson's disease are the most important concern in this aging society. Among the other causes the main suspected reasons are the production and precipitation of the beta amyloid plaques as well as the decrease of acetyl and butyryl choline neurotransmitter in the brain. This eventually results in dementia in older people. APOE (apolipoprotein) alleles (genes) are very important for the genetic determination of Alzheimer disease (AD). Those individuals carrying APOE 4 allele have the high risk of getting AD comparing with the people having more common 3 and 2 alleles. MK-8931(secretase inhibitor), CSP-1103, Pioglitazone, Saracatinib, Aducanumab, Solanezumab, etc. are the drugs generally categorized as disease-modifying drugs which help to postpone the symptoms. However, modifying drugs can entirely reduce the possibility of Alzheimer disease (AD) evolution. Whereas, Parkinson's disease (PD) is a type of degenerative disorder which occurs in the central nervous system (CNS) that mainly influence the motor system. Mutations in specific genes like SNCA, LRRK2, GBA, PRKN, PINK1, PARK7, etc. are the reason for about 5-10 % of PD cases. In this study, we are aiming to obtain some more potent novel inhibitors than that of the current approved drugs for Alzheimer's (target enzyme acetylcholine esterase enzyme pdb code: 1EVE) and Parkinson's disease (target enzyme monoamine oxidase enzyme pdb code: 2V5Z) using molecular modeling and in silico screening methods. Molecular modeling and docking studies are performed in this research to obtain the preferable candidates have inhibitory effect against both diseases. Wherefore, pharmacophore approach was applied by using zinc pharma database compounds to achieve the aim of this study. After several screening analysis techniques, cross docking procedure was applied on the final 15 compounds that obtained from (AD) and (PD). All compounds shown a significant

binding energy with target protein, 12 compounds have had a dual effecting on both diseases and only 3 compounds were identified a selectivity against 1EVE target of acetylcholinesterase enzyme. Eventually all compounds were subjected to ADME assay and Toxicity by using ADMET SAR tool.

Keywords: Alzahaimer disease,Parkinson disease ,PharmaGist, drug design

TEZİN TÜRKÇE ADI

ÖZET

Genel olarak Alzheimer ve Parkinson hastalıkları diye bilinen nörodejeneratif hastalıklar üzerine yapılan araştırmalar yaşlanan toplumları ilgilendiren en önemli konulardır. Diğer nedenlerin yanında bu hastalıklarda beyinde beta amiloid plakaların oluşması ve yumaklaşması, asetil ve bütril kolin nörotransmiterlerinin azalması şüphelenilen nedenlerdir. Netice olarak bu olgu ileri yaşlarda demans (bunama) olarak ortaya çıkar. APOE (apolipoprotein) allelleri (genleri) Alzheimer hastalığının genetik tespitinde çok önemlidir. APOE 4 alleli taşıyan bireyler 3 ve 2 alleli taşıyanlardan daha yüksek riskte Alzheimer hastası olma olasılıkları vardır. MK-8931 (sekretaz inhibitörü), CSP-1103, Pioglitazone, Saracatinib, Aducanumab, Solanezumab v.b. gibi ilaçlar genellikle hastalık seyrini değiştiren ilaçlar olarak sınıflandırılırlar ve hastalığın ortaya çıkmasını ötelerler. Bununla beraber bu ilaçlar hastalığın gelişimini tamamen azaltma yönündedir. Diğer taraftan Parkinson hastalığı merkezi sinir sisteminde özellikle motor sistemini etkileyen nörodejeneratif bir bozukluktur. SNCA, LRRK2, GBA, PRKN, PINK1, PARK7, v.b. gibi spesifik genlerde oluşan mutasyonlar 5-10 % oranında Parkinson hastalığına neden olabilirler. Bu çalışmamızda in siliko tarama yöntemiyle Alzheimer için ilgili 1EVE kodlu asetil kolin, Parkinson için 2V5Z kodlu monoamin oksidaz B enzimleri hedef olarak kullanılarak bilinen ruhsatlı ilaçlardan daha etkili ilaçlar tasarlanmıştır. Moleküler modelleme ve doklama çalışmaları gerçekleştirilerek her iki hastalığa karşı etkili olabilecek ilaç adayları önerilmiştir. Çalışmamızda ilaç adayları "zinc pharmer" veri bankasından farmakofor modelleme yöntemiyle seçilmiştir. Birkaç tarama tekniği, çapraz doklama işlemi uygulanarak 15 final bileşiği seçilmiştir. Bütün bileşiklerin hedef proteinlere anlamlı bağlanma enerjilerine sahip olduğu görülmüştür. 12 bileşik her iki hedefe de iyi bağlanmakla birlikte, 3 bileşik seçimli olarak sadece 1EVE hedef proteini asetilkolinesteraz enzimine daha iyi bağlandığı bulunmuştur. Sonuç olarak ADMET SAR programıyla bütün bileşiklerin ADME ve toksikoloji testlerini geçtiği

görülmüştür. **Anahtar Sözcükler: Alzheimer hastalığı, Parkinson hastalığı, ilaç tasarımı, Pharma gist.**

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I introduce this work to my kind parent (Mohammed and khawlah)

LIST OF TABLES

Table 2.1 2D structure of the known inhibitors. 25
Table 2.2 Experimental value of the the knowing inhibitors. 26
Table 2.3 Experimental value of the the knowing inhibitors. 27
Table 2.4 Experimental value of the the knowing inhibitors. 28
Table 3.1 Docking results for Acetylcholinesterase and known inhibitors for Alzheimer's. All the final drugs are approved drugs and filtered using drugbank(Wishart et al., 2018). 34
Table 3.2 Showing docking results for Acetylcholinesterase and known inhibitors for Parkinson's. All the final drugs are approved drugs and filtered using drugbank(Wishart et al., 2018). 35
Table 3.3 Showing docking results for Monoamine oxidase B and known inhibitors for Alzheimer's. All the final drugs are approved drugs and filtered using drugbank(Wishart et al., 2018). 36
Table 3.4 Showing docking results for Monoamine oxidase B and known inhibitors for Parkinson's. All the final drugs are approved drugs and filtered using drugbank(Wishart et al., 2018). 37
Table 3.5 Total compound screened. 47
Table 3.6 Pharmacophore screening and Lipinski rule of 5. 48
Table 4.1 ADME. 72
Table 4.2 Metabolism. 73
Table 4.3 Toxicity. 74
Table 4.4 Cross docking result1 76
Table 4.5 Cross docking result-2 76
Table 4.6 Cross docking result-3 77
Table 4.7 Cross docking result-4 78
Table 4.8 Cross docking result-5 79
Table 5.1 Cross Docking showing Active compounds. 81
Table 5.2 2D and 3D interaction ZINC038881345, ZINC11616656 and ZINC03830768are. 81

LIST OF FIGURES

Figure 2.1 The diagram shows the mutation occurring in SNCA(Jankovic, 2008) 4

Figure 2.2 APP metabolism, A oligomerization and signaling participation in the mechanisms of synaptic destruction in Alzheimer(Opare Asamoah Botchway and Iyer, 2017). 7

Figure 2.3 Crystal structure of Monoamine oxidase B code 2V5Z (Accelrys: Materials Studio is a Software Environment for Molecular Modeling, 2009) 10

Figure 2.4 Crystal structure of acetyl cholinesterase code 1EVE (Accelrys: Materials Studio is a Software Environment for Molecular Modeling, 2009) 11

Figure 3.1 Schematic showing the work flow of the research 29

Figure 3.2 Image showing the binding sites in AChE, Using Discovery Studio 30

Figure 3.3 Image showing the binding sites in MOA B, Using Discovery Studio 32

Figure 3.4 workflow of Pharma Gist 39

Figure 3.5 Pharmacophore obtained for target protein 2V5Z and anti-Alzheimer drugs from pharma Gist. 40

Figure 3.6 Pharmacophore obtained for target protein 2V5Z and anti-Parkinson from pharma Gist. 41

Figure 3.7 Pharmacophore obtained for target protein acetylcholinesterase (1EVE) and anti-Alzheimer drugs from pharma Gist 42

Figure 3.8 Pharmacophore obtained for target protein acetylcholinesterase 1EVE and anti Parkinson drugs from Pharma Gist 43

Figure 3.9 The pharmacophore feature of the ligand Donepezil visualized in Biovia DS 2016 where the three cyan spheres are the hydrophobic features, and the green spheres is the Hydrogen acceptor. 44

Figure 3.10 The pharmacophore feature of the ligand safinamide visualized in Biovia DS 2016 where the cyan spheres is the Hydrophobic feature, and the green spheres is the Hydrogen acceptor. 45
Figure 3.11 The pharmacophore feature of the ligand visualized in Biovia DS 2016 where the cyan spheres is the hydrophobic feature, the orange spheres is the aromatic feature and the green spheres is the Hydrogen acceptor. 46
Figure 4.1 Complex showing interaction between 1EVE with ZINC03830629 at amino acid residues- ASN85 TYR70, using AutoDock tools. . 51
Figure 4.2 Complex showing interaction between 1EVE with ZINC03831223 at amino acid residues- PHE 288 using AutoDock tools. 52
Figure 4.3 Complex showing interaction between 1EVE with ZINC03831061 at amino acid residues- ARG289, using AutoDock tools. 53
Figure 4.4 Complex showing interaction between 1EVE with ZINC03881345 at amino acid residues- ARG289, using AutoDock tools. 56
Figure 4.5 Complex showing interaction between 1EVE with ZINC04026555 at amino acid residues- PHE 288 using AutoDock tools. 57
Figure 4.6 Complex showing interaction between 1EVE with ZINC11616656 at amino acid residues- PHE 288, HIS 440 SER 200 using AutoDock tools. 58
Figure 4.7 Complex showing interaction between 1EVE with ZINC02033589at amino acid residues- ARG289 using AutoDock tools. 59
Figure 4.8 Complex showing interaction between 2V5Z with ZINC04026555 at amino acid residues- SER 59 TYR 60,using AutoDock tools.. 62
Figure 4.9 Complex showing interaction between 2V5Z with ZINC03830768 at amino acid residues- SER 59 TYR 60, using AutoDock tools. 63
Figure 4.10 Complex showing interaction between 2V5Z with ZINC11616656 at amino acid residues- GLN 206, using AutoDock tools. 63
Figure 4.11 Complex showing interaction between 2V5Z with ZINC03881345 at amino acid residues- SER59, using AutoDock tools. 64

Figure 4.12 Complex showing interaction between 2V5Z with ZINC03812892 at amino acid residues- TYR 60, using AutoDock tools.. 64
Figure 4.13 Complex showing interaction between 2V5Z with ZINC02033589at amino acid residues- SER59, TYR60 TYR326 using AutoDock tools. 67
Figure 4.14 Complex showing interaction between 2V5Z with ZINC01530604 at amino acid residues- TYR 435, MET 436 SER59 using AutoDock tools. 68
Figure 4.15 Complex showing interaction between 2V5Z with ZINC00537877 at amino acid residues- TYR188, using AutoDock tools. 69
Figure 4.16 Complex showing interaction between 2V5Z with ZINC00538275 at amino acid residues- SER 59 TYR 60, using AutoDock tools. 70
Figure 4.17 Complex showing interaction between 2V5Z with ZINC00538505 at amino acid residues- SER 59, TYR 60 TYR 435, using AutoDock tools. 70
Figure 5.1 2D interaction of the compound ZINC03830768 with Acetyl-cholinesterase (1eve) in the biding pocket. 82
Figure 5.2 3D Interaction between the protein residues and the Binding pocket of Acetyl-cholinesterase (1eve) and ZINC03830768. 82
Figure 5.3 2d interaction of the compound ZINC03830768 With monoamine oxidase B (2v5z) in the biding pocket. 83
Figure 5.4 3D Interaction between the protein residues and the Binding pocket of monoamine oxidase B (2v5z) and ZINC03830768 . . . 83
Figure 5.5 2D interaction of the compound ZINC11616656 with Acetyl-cholinesterase (1eve) in the biding pocket. 84
Figure 5.6 3D Interaction between the protein residues and the Binding pocket of Acetyl-cholinesterase (1eve) and ZINC11616656 84
Figure 5.7 2D interaction of the compound ZINC11616656 With monoamine oxidase B (2v5z) in the biding pocket. 85
Figure 5.8 3D Interaction between the protein residues and the Binding pocket of monoamine oxidase B (2v5z) and ZINC11616656. . . . 85

Figure 5.9 2D interaction of the compound ZINC03881345 with Acetyl-cholinesterase (1eve) in the biding pocket. 86
Figure 5.10 3D Interaction between the protein residues and the Binding pocket of Acetyl-cholinesterase (1eve) and ZINC03881345 86
Figure 5.11 2D interaction of the compound ZINC03881345 with Acetyl-cholinesterase (2v5z) in the biding pocket. 87
Figure 5.12 3D Interaction between the protein residues and the Binding pocket of Acetyl-cholinesterase (2v5z) and ZINC03881345 87
Figure 5.13 Biovia DS ADMET Predication for the three best candidate compound 88

LIST OF SYMBOLS/ABBREVIATIONS

MAO B	Monoamine oxidase A
AChE	Acetylcholinesterase
PDB	Protein Data Bank
AD	alzheimer's disease
PD	parkinson disease

1. OBJECTIVE

Alzheimer's disease is a chronic neurodegenerative disease that commonly starts gradually worsens over time. It leads to brain cells to corrupt and die. Alzheimer disease is The main causative of dementia- an uninterrupted decline in thoughtful, behavior and social skills that disorders a person's ability to function independently. Up-to-date around 44 million people live with dementia worldwide presently. APOE-e4 gene is related with high level probabilities of people over 55 years developing Alzheimer's. Cholinesterase inhibitors are approved for symptomatic relief Include: Rivastigmine, Donepezil, and Tacrine. various types of drug, interim can be used singly or in collections with a cholinesterase inhibitor (Hurtado-Puerto, Russo and Fregni, 2018).

Parkinson disease (PD) is a disorder associated with movement. It caused as a result of chemical compound known as dopamine when doesn't secreted in the brain. Parkinson generally doesn't occur in families however; occasionally it can be considered genetic. Exterior elements as well can participate in the progress of the disease. The symptoms like quivering of hands, legs and face, stiffness of arms and legs, loss of balance. The disease is started from the age of 60 but also may happen at an earlier age and it affects the men more than women(Davie, 2008a).

PD is the second most public age-related age neurodegenerative disorder after Alzheimer's disease (AD). PRKN, PARK7, SNCA, PINK1 and LRRK2 are genes that responsible of this disorder, where those genes like SNCA and LRRK2 have the liability for displaying autosomal dominant traits in patients because of mutations in these genes. Other genes PINK1, PARK7, and PRKN demonstrate autosomal recessive trait in the patients. (http:/michaeljfon.org/understandingparkinsons/living-with-

pd/topic.ph?genetics). A new gene TMEM230 mutation is detected that has a role in dopamine wrapping in neurons and mutation in this gene cause failure in dopamine wrapping in the neurons finally resulting in PD(Mendez, 2012).

Presently, there no specific analysis still available for Parkinson. A precise form of scan which is Dopamen Transporte DAT Scan which usages the principle of Single-Photon Emission Computerized Tomography SPECT may also be complete to classify the disease. in the most cases symbols of symptoms are sufficient to recognize DAT and PD is not essential (Jankovic, 2008). Until now, There is no therapy for Parkinson's disease. Convinced drugs help in carrying the disease to control.

Most common for controlling PD :

- MAO B Inhibitors
- Dopamine agonists
- Anticholinergics
- Carbidopa levodopa
- Catechol O-Methyltransferase Inhibitors
- Amatadines.(Todd et al., 2013)

1.1 STATEMENT OF AIM

a. Screening of the known inhibitors with binding energy of -8.0 kcal/mol or lower for selection of known inhibitors).

b. Finding potential known inhibitors for Parkinson's Alzheimer's finalizing the target proteins (2V5Z 1EVE

c. Using the selected known inhibitors for the pharmacophore modeling and screening a35 million compounds to obtain novel potential inhibitors for Parkinson's Alzheimer's target.

d. Applying Lipinski rule of 5 for filtering the screened molecules.

e. Performing Cross docking to study the specificity of the proteins and ligand

f. Structure based screening for the interaction (inhibitory action) of ligands with the target proteins using Virtual Screening as well as docking studies.

2. INTRODUCTION

2.1 Parkinson disease

Parkinson is the most important neurodegenerative disorder that occurs in Central Nervous System that mostly affects the motor system (Abou-Sleiman, Muqit and Wood, 2006) .Strenuously, its effect on performing daily activities and person displays signs of shaking, inflexibility, slow movement and walking problems. Likewise, thoughtful and behavioral complications can occur (Sveinbjornsdottir, 2016). Parkinson may rise because of genetic and environmental influences but the real cause is not clear (Kalia and Lang, 2015). External elements can also be accountable for Parkinson as long term contact to pesticides and chemicals and also head wounds can be the reason (Barranco Quintana et al., 2013). Genetic reasons have also the responsibility for developing of the disease. LRRK2 gene is the cause heredity in Parkinson and it has sporadic PD where almost (5 %) of persons with family background have a chance of receiving this disease because of mutation in particular gene (Davie, 2008a).However, mutation in the (GBA) gene then the individual has the highest chance of receiving Parkinson disease. Mutation in particular genes are the motive for around (5-10 %) of this disease cases(Lesage and Brice, 2009). LRRK2, SNCA, GBA, PRKN, PARK7, VPS35, EIF4G1, PINK1, DNAJC13 and CHCHD2 are the genes that involved in this process.(Gasser, 2005). Still GBA1 gene is current in (less then 1 %)of the world's population (Stoker, Torsney and Barker, 2018).SNCA is an important mutation because of this gene encodes for the protein alpha-syncline, that existing as a main factor in Lowy bodies that accumulated in the brains of the patients.

Currently, there is no treatment for Parkinson's disease (Jankovic, 2008). The drug

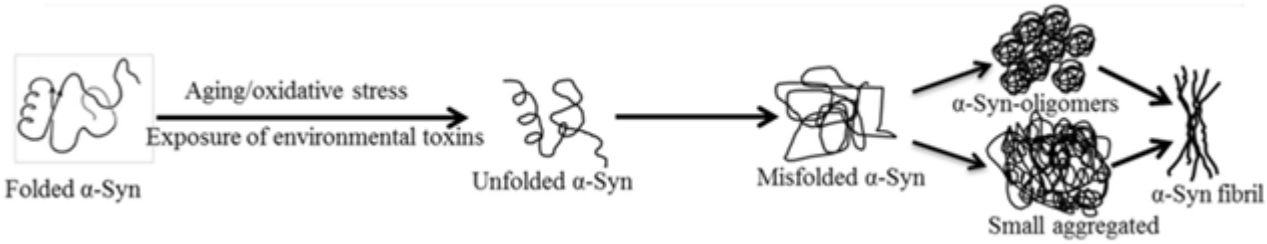


Figure 2.1 The diagram shows the mutation occurring in SNCA(Jankovic, 2008)

used presently for cure of the disease is Levodopa (L-DOPA), its anti-Parkinson's drug. Dopamine agonists are complexes that assistance in the activation of dopamine receptors (Samii, Nutt and Ransom, 2004). They're known for many types D1, D2 and D3 which are also recognized as biased agonists and they characteristically trigger signaling pathway(Möller et al., 2017). These compounds aid in starting the signaling pathways by -arrestins and G-proteins which are trimetric and modification gene transcription (Davie, 2008b).

2.2 Alzheimer's disease

Alzheimer is a disease referred as the deposition and production of the beta amyloid plaques. It is the main cause of dementia. Dementia is a broader term for conditions caused by brain injuries or other diseases that negatively affect memory, thinking and behavior. These changes interfere with daily living. It is categorized clinically by advanced and slow drop in cognitive function and neuropath logically by the attendance of neuropil threads, precise neuron loss, and synapse loss also to the identify of senile plaques and neurofibrillary (Murphy and LeVine, 2010). furthermore, its considered irreversible, advanced disorder that slowly terminates the memory and thinking skills and finally, the capacity to perform the simplest tasks. In addition, the generation of (A) amyloid- peptide by enzymatic cleavages of the(-amyloid) precursor protein has been at the core of Alzheimer disease study. However, A is 38- 43 amino acid long peptide that is resulting from APP through serial cleavages by and Y secretase enzyme actions. The site of cleavage for additional APP treating enzyme, alpha secretase lies within the (A) sequence and thus prevents (A) creation. The terminal fragment of amino acid generated through alpha and beta secretase

is termed secreted APP alpha or beta. The fragments of carboxyterminal (CTF) made by alpha or beta secretase are called (CTF 83) and (CTF 99), respectively. In another hands, Y secretase cleavage of (CTF 83) and (CTF 99) will outcome in the creating of (p3) and (AB), respectively. Alpha Secretase action is refereed by the enzymes from disinterring and metalloproteinase domain proteins ADAM. In the same context (ADAM 9,10 ,17 and 19) being the best probable candidates. There are four proteins are usually essential for this complex:, nicastrin (Nct), presenilin enhancer 2 (Pen2), presenilin (PS) 1 or 2 and anterior defective 1 (Aph-1) (Beattie, Collins and McInnes, 1997).

2.2.1 Tau Protein

Tau is protein that has a high soluble microtubule connected protein tau (MAPT)). Its encoded by the 16 exons comprising microtubule-related protein tau MAPT gene in chromosome 17q21. Though, the another splicing of exons(2,3,10), six main tau isoforms are existing in the human brain . This protein, mostly effective in the distal rations of the axons, proposals stability and flexibility to microtubules. Also, has the capability to regulator the stability of the microtubules by phosphorylation and isoforms. The diverse kinases like Protein Kinase C Glycogen Synthase Kinase 3 (GSK-3), Protein Kinase N1 controls phosphorylation of TAU. Wherefore, kinase has the activation condition, they cause microtubule trouble(Opare Asamoah Botchway and Iyer, 2017).

A couple of studies have known the creation of neurofibrillary tangles being produced by the hyper phosphorylation of the Tau. In another hand, other researchs have suggest that the activation of cascades and cleavage of tau in the brain of patients has alzahaimer can cause the neurofibrillary tangles.

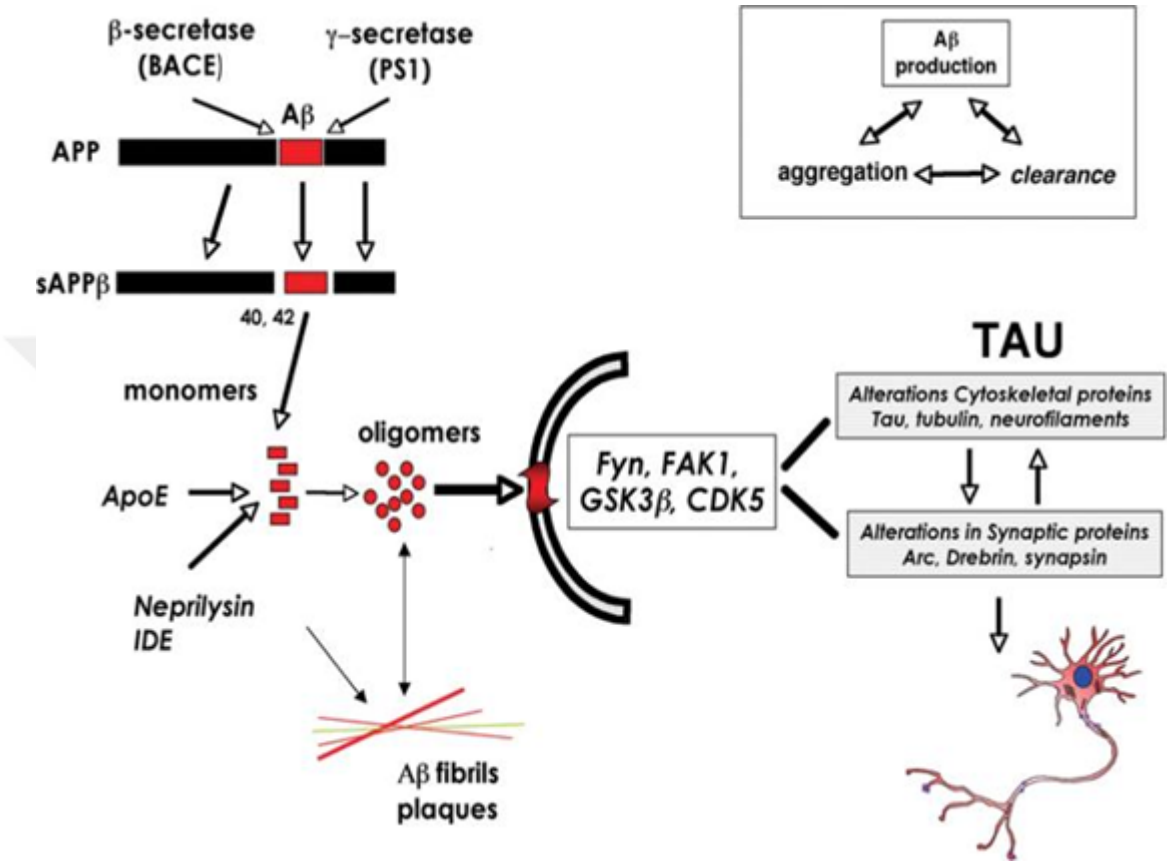


Figure 2.2 APP metabolism, A oligomerization and signaling participation in the mechanisms of synaptic destruction in Alzheimer(Opare Asamoah Botchway and Iyer, 2017).

2.3 Parkinson disease treatment

Curing choices were restricted in the past days. The most earliest treatments was performed (anticholinergic alkaloids) was getting from the plant beladonna and it was revealed in the 18 century through (Charcot, Erb) and others. In 1939 a surgery was established which was assisted in regulated tremors. It's constant and enhanced over 20 year. The surgical procedure before this was lesioning of the corticospinal pathway with paralysis disease. While all treatments were caring they had unsure effects with tremors (Lanska, 2010, pp. 501-546).Nowadays for cureing of Parkinson disease the best normally used drug is (Carbidopa levodopa). The Progress of levodopa was accepted only in the middle of 20 century. Controlling of this disease was altered and healthier with the assistance of levodopa. Its a natural chemical that permits through the brain and gets adapted to dopamine. A carbidopa when mixed with levodopa will avoids levodopa from receiving transformed to dopamine outer the brain that lead to decrease the side effects as nausea. many type of drug as (dopamine) agonists which impersonator the occurrence of dopamine in the brain. It may be smaller than levodopa but they can last longer than levodopa and also can be give along with levodopa to decrease side effects from Levodopa. For instance, Dopamine agonist contains (Requip), (Mirapex), (Neupro). A medication is like to Carbidopa-Levodopa but the reply may alter. the development of Parkinson influence levodopa may lead to fear involuntary actions may also be skilled. A Drugs as (Azilec) (Eldepryl, Zelapar) and (Xadago) that identified as (MAO B) inhibitor help in preventing a brain "enzyme monoamine oxidase B" by stopping the interruption of dopamine. The MAO B enzyme effects metabolism of dopamine in a brain.. A Standard side effects can be "nausea or insomnia". However, DBS has significantly helped in decreasing the non-motor indications such as Depression and Anxiety. The Difficulties as sleep , musculoskeletal hurt, urinary indications, gastrointestinal signs, weight loss condensed with the assistance of DBS. In addition, the neurotransmitter acetylcholine will be released to other brain areas, as neocortex to help grave cognitive operative. Furthermore, A new technique coming up is the Dedicated Ultrasound Subthalamotomy which is eliminating a specific area in

the brain. Meanwhile, this is not ideal over “DBS” since DBS is reversible also a well method for parkinson cure. Nevertheless, It might be a conceivable innovation method where patients would be cured for Parkinson disease without the requirement of opening the skull. Eventually, this process is yet to be advanced and extra study going on it(Gardner, 2013).

2.4 Alzheimer treatment

Donepezil, Rivastigmine, and Galantamine are cholinesterase inhibitors that used in the curing Alzheimer. Likewise, aricept is another cholinesterase inhibitor that avoids the breakdown of Acetylcholine, which is a chemical messenger required for learning and memory. Alzheimer symptoms may be hold at bay for an average of (6 to 12) months in unevenly half of the patients by protection acetylcholine levels elevation. However, namenda, is another public treatment for this disease. Its tries to protect the nerve cell of brain beside “glutamate”, which is a chemical messenger that released in additional amounts by cells injured via Alzheimer disorders. When the glutamate connect to a patient cell brain, its lets calcium to clearly enter the cells, leading to degeneration of cell. The treatment is going ahead to improve biomarkers, a substances that can be measure in the brain and body then serves as signals for the attendance of alzheimer’s disease. TAU injection, “AADvac1”, is a vaccine presently being investigated for the treatment of Alzheimer. Its working by activating the immune system to vilify the imperfect tau protein that ruin the nerve cells of brain, thus stopping the development of this disease. The Initial clinical trial of the AAIC confirmed vital enhancement in the cognitive skills of the clinical trial members., nowadays, CSP-1103 is subjected Phase3 of clinical trial. Moreover, , a Pioglitazone, is another drug type that currently bears the brand term ”Actos”. Regarding of the disease-modifying medications, its core aim does not lie in treating this disease totally but slightly slow down the worsening. In other hand, the previous drugs help postponement the inevitability, these medications delay the disease, its advantage is only temporal. Finally, In future disease adapting drugs will be talented to completely frustrate the concatenation of alzahaimer disorder(Gardner, 2013).

2.5 Target protein

2.5.1 Monoamine oxidase B PDB coed (2V5Z)

It has been categorized as oxidoreductase because of its ability to oxidize materials like monoamines. It is also recognized as monoamine oxidase B. A yeast species namely Komagataella pastoris, an expression system, has been designated for 2V5Z protein expression of resulting from Homo sapiens. X-RAY diffraction method is utilized to determine the 3 dimensional structure of 2V5Z protein. the resolution is 1.6 Å with R Value Free: 0.227 and R Value Work: 0.208. It fits to the flavin having monoamine oxidase family. This protein contains two chains A and B and 520 amino acid. it is encoded by MAO B gene without any mutations have been detected(Binda et al., 2007).

Figure 2.3 Crystal structure of Monoamine oxidase B code 2V5Z (Accelrys: Materials Studio is a Software Environment for Molecular Modeling, 2009)

2.5.2 Acetyl cholinesterase PDB code (1EVE)

It has been categorized as Serine Hydrolase because of the existence of a nucleophiic serine in the active site that used for the hydrolysisthe substrates. X-RAY diffraction technique of crystal form the resolution is 2.5 Å. This protein, also known as acetyl cholinesterase, is encoded by the gene ACH. In addition, No mutations have been identified in gene(Kryger, Silman and Sussman, 1999).

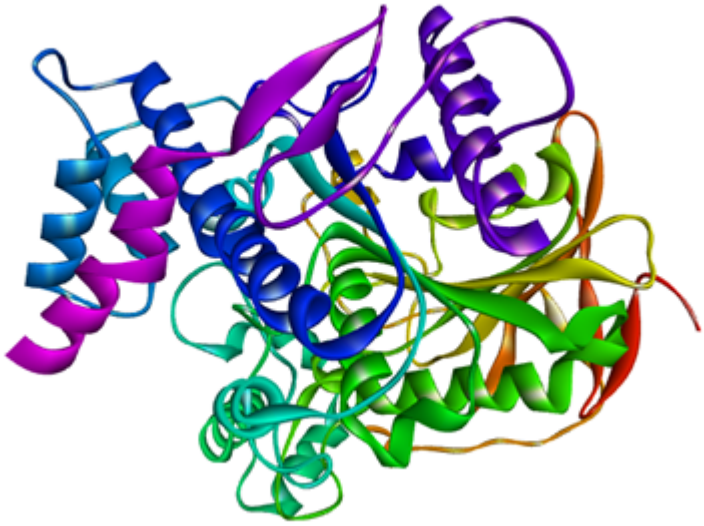


Figure 2.4 Crystal structure of acetyl cholinesterase code 1EVE (Accelrys: Materials Studio is a Software Environment for Molecular Modeling, 2009)

2.6 Inhibitors

2.6.1 Ropinirole

As a member of tertiary amine and indolones, which plays an important role as a dopamine agonist, an antiparkinsonian drug, a central nervous system drug and an antidyskinesia agent. It has known by its I.U.P.A.C Term as 4 - [2-(Dipropylamino) Ethy-l] – 1.3 - Dihydroindol – 2 – one. This is useful in PD therspy and restless legs syndrome. Low serum enzyme level is associated with cure This drug was highly effective and approved by FDA for PD(Kvernmo, Houben and Sylte, 2008).

2.6.2 Selegiline

2.6.2 : This complex has been given the I.U.P.A.C Term (2 R) – N – Methyl – 1 – Phenyl – N - Prop – 2 – Ynylpropan – 2 – Amine. An irreversible selective inhibitor of Kind B Monoamine Oxidase. In addition, it has prescribed in the remediation of depressive, and as an assistant treatment in conjunction with "Levodopa and Carbidopa" in the cure of Parkinson Disease(Engberg, Elebring and Nissbrandt, 1991).

2.6.3 Trihexyphenidyl

This complex named as a (I.U.P.A.C) Term as follow 1 – Cyclohexyl – 1 – Phenyl – 3 – Piperidin – 1 – Ylpropan – 1 – ol. The "Trihexyphenidyl" consider as an oral anticholinergic factor that utilized mostly in the symptomatic treatment of "Parkinson Disease" and the symptoms of movement disorders, some of the high overdose cases may cause of red face, atonic states of bowels and bladder, dryness of mucous membranes, mydriasis, and hyperthermia. Major outcomes are irritation, distraction, and hallucinations. An overdose may be deadly, especially for children. Pre-existence symptoms are respiratory depression and cardiac arrest (Overington, Al-Lazikani and Hopkins, 2006)

2.6.4 Opicapone

"Opicapone" are known by its (I.U.P.A.C) Term as 5 - [3 - (2, 5 – Dichloro – 4, 6 – Dimethyl – 1 – Oxidopyridin – 1 – Ium – 3 - Yl) - 1, 2, 4 – Oxadiazol – 5 - Yl] – 3 – Nitrobenzene - 1, 2 - Diol This case under investigation as drug in US and is elective inhibitor of (COMT) Catechol - O - Methyltransferase It is a small molecule and has been placed in Approved and Investigational groups. It's synonym is Opicapona. It belongs to various categories such as Anti-Dyskinesia Agents, Anti-Parkinson Drugs, Central Nervous System Agents, COMT Inhibitors, Cytochrome P-450 CYP2C19 inducers, Cytochrome P-450 CYP2C8 inhibitors, Cytochrome P-450 Enzyme Induc-

ers and Inhibitors, Dopamine Agents, Enzyme Inhibitors, Nervous System, Oxazoles. Dyskinesia was the most serious adverse event frequently associated with opicapone administration. The reported incidence was 24 % in a placebo-controlled trial (vs 8 % with placebo) and 16 % in the comparative trial (versus 4 % with placebo and 8 % with entacapone). Some other adverse events include dizziness, dry mouth, as well as constipation . Affected organisms are Humans and other mammals. (B. et al., 2006).

2.6.5 Pimavanserin

This complex named as a (I.U.P.A.C) Term as follow 1 - [(4 - Fluorophenyl) Methyl] – 1 - (1 – Methylpiperidin – 4 - Yl) – 3 - [[4 - (2 - Methylpropoxy) Phenyl] Methyl] Urea. It is a type of small molecule and has been placed in the "Approved and Investigational" groups. It belongs to various categories such as (anti-dyskinesia agents, anti-Parkinson drugs, antipsychotic Agents, central nervous system agents, central nervous system depressants, Neurotoxic Agents, Neurotransmitter Agents, Psycholeptics, Serotonin Agents, Serotonin Receptor Antagonists, Serotonin 5-HT2 Receptor Antagonists (Nordstrom et al., 2008).

2.6.6 Pramipexole

This complex named as a (I.U.P.A.C) Term as follow (6S) – 6 – N – Propyl - 4, 5, 6, 7 – Tetrahydro - 1, 3 – Benzothiazole - 2, 6 - Diamine ('Dopamine agonists for restless legs syndrome?', 2011)

2.6.7 Procyclidine

Procyclidine plays a vital role in Anti-Parkinson drug as muscarinic antagonist, which is able to cross BBB along with antidyskinesia agent. It is known by its (I.U.P.A.C) Term as 1 – Cyclohexyl – 1 – Phenyl – 3 – Pyrrolidin – 1 – Ylpropan – 1 – ol. It contains of "Propan – 1 – Ol" exchanged by a Cyclohexyl and a Phenyl set

at site (1) and a Pyrrolidin – 1 - Yl set at site (3) It is a type of small molecule and has been placed in the Approved group. It's synonyms are 1-cyclohexyl-1-phenyl-3-pyrrolidin-1-yl-propan-1-ol hydrochloride, 1-Cyclohexyl-1-phenyl-3-pyrrolidino-1-propanol, Prociclidina, Procyclidin, Procyclidinum, Tricyclamol. It belongs to various categories such as Tachycardia producing Agents, Anti-Dyskinesia Agents, Anti-Parkinson Drugs, Anticholinergic Agents, Central Nervous System Agents, Cholinergic Agents, Muscarinic Antagonists, Neurotransmitter Agents, Pyrrolidines, Tertiary Amines. Affected organisms are Humans and other mammals (Overington, Al-Lazikani and Hopkins, 2006).

2.6.8 Dehydroascorbic Acid

This complex named as a (I.U.P.A.C) Term as follow (5R) – 5 - [(1S) – 1, 2 - Dihydroxyethyl] Oxolane – 2, 3, 4 – Trione. The formula of molecular are "C6H6O6". The acid of dehydroascorbic mean ascorbic acid in an inverted oxidized form. This is a lactone of "2, 3 – diketogulonic acid" with antiscorbutic action in human in case of oral ingestion. The dehydroascorbic acid are prepared from ascorbic acid oxidation. This response is changeable, while Dehydroascorbic Acid can be irreversible in state of undergo hydrolysis to (2, 3 - Diketogulonicacid. Both the Dehydroascorbic acid and the Ascorbic acid in the body have similar biological action as the antivirals, while the Dehydroascorbic acid also has neuroprotective symptoms.

It is a small molecule and has been placed in an experimental group. Affected organisms are Humans and other mammals. It's synonyms are dehydro-L-ascorbic acid, DHAA, L-dehydroascorbate, L-dehydroascorbic acid, L-threo-2,3-hexodiulosonic acid, -lactone, L-threo-hexo-2,3-diulosono-1,4-lactoneoxidized ascorbic acid oxidized vitamin C. It belongs to the various categories such as Acids, Acyclic, Carbohydrates, Growth Substances, Hydroxy Acids, Lactones, Sugar Acids, Vitamins, Micronutrients, food and beverages,Urinary Acidifying Agents(National Center of Biotechnology Information, 2017).

2.6.9 Dihydroergocristine

This complex named as a (I.U.P.A.C) Term as follow 2R, 4R, 7R) – N - [(1S, 2S, 4R, 7S) – 7 – Benzyl – 2 – Hydroxy – 5.8 – Dioxo – 4 - (Propan – 2 - yl) – 3 – Oxa – 6.9 – Diazatricyclo [7.3.0.0^{2},^{6}] Dodecan – 4 - yl] – 6 – Methyl – 6.11 – Diazatetracyclo [7.6.1.0^{2}, ^{7}.0^{12}, ^{16}] Hexadeca – 1 (16), 9, 12, 14 – Tetraene – 4 - Carboximidic Acid. It's molecular formula is C35H41N5O5. It derives from a hydride of an ergotaman. It is a small molecule and it has been placed in the approved and experimental groups. It's synonyms are 9,10-dihydroergocristine, DHEC. It belongs to the various categories such as Adrenergic Agents, Adrenergic Antagonists, Cardiovascular Agents, Alkoids, Cytochrome P-450 CYP3A AND CYP3A4 Substrates, BSEP/ABCB11Substrates, Ergotamine, Neurotransmitter Agents, Peripheral vasodilators, Vasodilating Agents, Ergot Alkaloid and Derivatives. Studies related to acute and chronic toxicity as well as teratogenesis and fertility has proven that dihydroergocristine is a non-toxic and very well tolerated drug (National Center for Biotechnology Information, 2016).

2.6.10 Donepezil

Donepezil or 2 - [(1 – Benzylpiperidin – 4 - Yl) Methyl] - 5, 6 – Dimethoxy - 2, 3 – Dihydroinden – 1 – One or "C24H29N03" are derivative of Indian and piperidine which is a particular and reversible inhibitor of Acetylcholinesterase. In addition, it is much eclectic for the CNS hence are useful in treating minor Dentia in AD. It is having neurocognitive enhancing activity and reversibly blocks acetylcholinesterse, hence incases activity by blocking neurotransmitter acetylcholine hydrolysis. Donepezil decreases sedation related with the cancer treatment and assists in relieving patients with neurocognitive function during their radiation therapy. It is an oral inhibitor and have minimum rate of serum elevations during therapies. It is a small molecule and has been placed in the approved group. It's synonyms are Domepezil, Donepezil, Donepezilo, Donepezilum. Affected organisms are Humans and other mammals. It belongs to the various categories such as Anto Dementia

Drugs, Bradycardia-Causing Agents, Central Nervous System Agents and Depressants, Cholinergic Agents, Cholinesterase inhibitors, Cytochrome P-450 CYP2C9, CYP 2D6, CYP 3A and CYP 3A4 Substrates, Enzyme inhibitors, Indenes, Muscle Relaxants, Neurotransmitter Agents. Symptoms of overdose include severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved (Zhou et al., 2009).

2.6.11 Dihydro-alpha-ergocryptine

This complex named as a (I.U.P.A.C) Term as follow (6aR, 9R, 10aR) – N - [(1S, 2S, 4R, 7S) – 2 – Hydroxy – 7 - (2 - Methylpropyl) – 5.8 – Dioxo – 4 – Propan – 2 – Yl – 3 – Oxa – 6.9 – Diazatricyclo [7.3.0.02,6] Dodecan – 4 - Yl] – 7 – Methyl - 6, 6a, 8, 9, 10, 10a – Hexahydro - 4H – Indolo [4, 3 - Fg] Quinoline – 9 – Carboxamide. Alpha - Dihydroergocryptine confirmed drug produce is as a part of an ergoloid mixture. It is a type of small molecule. It has been placed in the Approved groups. It's synonyms are 9,10-dihydro–ergocryptine, alpha-Dihydroergocriptine, dihydro–ergocryptine, - dihydroergocryptine. It belongs to the categories such as Cytochrome P-450 CYP3A Substrates, Cytochrome P-450 CYP3A4 Substrates. Al-pha-dihydroergocryptine does not have effect in fertility and it does not present mutagenic potential (National Center of Biotechnology Information, 2017)

2.6.12 Lisuride

Lisuride acts on D2 receptors or in other words, it is a dopamine agonist along with serotonin agonist. Its (I.U.P.A.C) Term is 3 - [(6aR, 9S) – 7 – Methyl - 6, 6a, 8, 9 – Tetrahydro - 4H – Indolo [4, 3 - Fg] Quinolin – 9 - Yl] - 1, 1 – Diethylurea. It is a monocarboxylic acid amide, which is involved in Anti-Parkinson drug. It is also an antidyskinesia agent, which is derived from ergoline.

It is a type of small molecule. It has been placed in Approved and Investiga-

tional groups. It's synonyms are Lisurid, Lisurida, Lisuridium, N'-((8alpha)-9,10-Didehydro-6-methylergolin-8-yl)-N,N-diethylurea. It belongs to the various categories such as Hypertension producing Agents, Alkaloids, Analgesics, Anti-Dyskinesia Agents, Anti-Parkinson Drugs, Antidepressive Agents, Antimigraine Preparations, Central Nervous System Agents, Central Nervous System Depressants, Dopamine Agents, Dopamine Agonists, Dopamine Antagonists, Ergolines, Cytochrome P-450 CYP2D6 , CYP3A and CYP3A4 Substrates, Neuro-transmitter Agents, Prolactine Inhibitors, Serotonin Agents(National Center for Biotechnology Information, 2016).

2.6.13 Galantamine

The "Galantamine" or (1S, 12S, 14R) – 9 – Methoxy – 4 – Methyl – 11 – Oxa – 4 -Azatetracyclo [8.6.1.01.12.06, 17] Heptadeca – 6 (17), 7, 9, 15 – Tetraen – 14 – Ol or "C17H21NO3" is derived from "Norbelladine". It is an inhibitor which is found in "GALANTHUS" and other "AMARYLLIDACEAE". It is found to be useful in AD as well as in other CNS related disorders (Preissner et al., 2009). It is a type of small molecule. It has been placed in Approved and Investigational groups. It's synonyms are Lisurid, Lisurida, Lisuridium, N'-((8alpha)-9,10-Didehydro-6-methylergolin-8-yl)-N,N-diethylurea. It belongs to the various categories such as Hypertension producing Agents, Alkaloids, Analgesics, Anti-Dyskinesia Agents, Anti-Parkinson Drugs, Antidepressive Agents, Antimigraine Preparations, Central Nervous System Agents, Central Nervous System Depressants, Dopamine Agents, Dopamine Agonists, Dopamine Antagonists, Ergolines, Cytochrome P-450 CYP2D6 , CYP3A and CYP3A4 Substrates, Neuro-transmitter Agents, Prolactine Inhibitors, Serotonin Agents. Affected organisms are Humans and other mammals.

2.6.14 Huperzine A

This complex named as a (I.U.P.A.C) Term as follow (1R, 9R, 13E) – 1 – Amino – 13 – Ethylidene – 11 – Methyl – 6 – Azatricyclo [7.3.1.02, 7] Trideca – 2 (7), 3, 10 – Trien – 5 – one. While its formula from molecular aspect are "c15h18n2o". The

"Huperzine A" are a normaly generating sesquiterpene alkaloid exist in the abstract of the "Firmoss Huperzia Serrata" Which they proved to show neuroprotective action. It has a role as an EC 3.1.1.7 (acetylcholinesterase) inhibitor, a neuroprotective agent and a plant metabolite. It is a sesquiterpene alkaloid, a Pyridone, a primary amino complex and an organic heterotricyclic complex It is a small moecule and has been placed in the approved and experimental groups. It's synonyms are Huperzine A, selagine, L-huperzin A. It belongs to various categories such as Central Nervous System Agents, Cholinergic Agents, Cholinesterase inhibitors, Enzyme inhibitors, Neuroprotective Agents, Neurotransmitter Agents, Protective Agents and Terpenes. This compound has no toxicity. It's affected organisms are Humans and other mammals (Li et al., 2007).

2.6.15 Huperzine B

It has been given the (I.U.P.A.C) Term as (1R, 9R, 10R) – 16 – Methyl - 6, 14 – Diazatetracyclo [7.5.3.01, 10.02, 7] Heptadeca – 2 (7), 3, 16 – Trien – 5 – One. While its formula from molecular aspect are "C16H20N2O". Huperzine B is novel acetylcholinesterase inhibitors(Zhang and Tang, 2000) . It is a small molecule and has been placed in the investigational group. It's synonyms are fordimine, huperzine B. It's affected organisms are Humans and other mammals.

2.6.16 Isocarboxazid

Isocarboaxide also known by its (I.U.P.A.C) Term as N' – Benzyl – 5 – Methyl - 1, 2 – Oxazole – 3 – Carbohydra – Zide, While its formula from molecular aspect are "c12h13n3o2".it is an inhibitor which is very useful in treatment of acute and other classes of depressions. Along with it has shown positive effects with panic and phobic disorders. It has shown significant effect in anti-depression by chronic inhibition of MAO B. It is a small molecule and has been placed in the Approved group. It's synonyms are Isocarboxazid, Isocarboxazida, Isocarboxazide, Isocarboxazidum. It belongs to the various categories such as Hypertension Producing Agents, Seizure

Threshold Reducing Agents, Central Nervous System Agents and Depressants, Hypotensive Agents, Isoxazoles, Monoamine Oxidase inhibitors, Psychotropic drugs, Psychoanaleptics, Serotonin Agents and Modulators. Long-term toxicity studies to evaluate the carcinogenic, mutagenic and fertility impairment potential have not been conducted. Affected organisms are Humans and other mammals. (KENNEDY et al., 2006).

2.6.17 Memantine

This complex named as a (I.U.P.A.C) Term as follow 3, 5 – Dimethyladamantan – 1 – Amine. While its formula from molecular aspect are "c12h21n". The "memantine" considered as an oral "n – Methyl – D - aspartate receptor antagonist. Furthermore, it considered in the research for the curing of Alzheimer's disease and Dementia. It is a small molecule and has been placed in the Approved and Investigational Groups. It's synonyms are 1-Amino-3,5-dimethyladamantane, 1,3-Dimethyl-5-adamantanamine, Memantinum, Memantine, Memantina, 3,5-Dimethyl-1-adamantanamine, 3,5-Dimethyl-1-aminoadamantane, 3,5-Dimethyltricycl-o(3.3.1.1(3,7))decan-1-amine.
It belongs to various categories such as Adamantane, Amantadine, Anti-Dementia-Drugs, Anti-Dyskinesia Agents, Anti-Parkinson Drugs, Central Nervous System Agents, Cholinesterase inhibitors, Cycloparaffins, Cytochrome P-450 CYP2A6 and CYP2B6 inhibitors, Dopamine Agents, Excitatory Amino Acid Agents, Neurotransmitter Agents, Psychoanaleptics. Side effects include pain, abnormal crying, leg pain, fever, increased apetite. Adverse drug reactions include: dizziness, confusion, headache, hallucinations, tiredness. Less common side effects include: vomiting, anxiety, hypertonia, cystitis, and increased libido. Doses of up to 400 mg have been tolerated. Affected organisms are Humans and other mammals (KENNEDY et al., 2006).

2.6.18 Pargyline

This complex named as a (I.U.P.A.C) Term as follow Benzyl (Methyl) (Prop – 2 – Yn – 1 - Yl) Amine, which is a MAO inhibitor exhibiting antidepressant activity. It's a selective inhibitor of (M.A.O. B), which in turn are responsible for inactivation of nor-epinephrine and dopamine (Catecholamines, which cause general physiological changes for physical activity) which increases the concentration and binding to postsynaptic receptors. These increased simulation of receptors causes down-regulation of central receptors thereby contributing in antidepressing activity. It is a small molecule and has been placed in the Approved group. It's synonyms are Pargilina, Pargyline, Pargylinum. It belongs to various categories such as Hypertension Producing Agents, Seizure Threshold reducing Agents, Amines, Antihypertensive Agents, Benzene derivatives, Benzyl Compounds, Benzylamines, Cardiovascular Agents, Central Nervous System Depressants, Enzyme inhibitors, Monoamine Oxidase Inhibitors and Diuretics. Affected organisms are Humans and other mammals (A.A., C.-U. and P.S., 2006).

2.6.19 Phenelzine

This complex named as a (I.U.P.A.C) Term as follow 2 – Phenylethylhydrazine. While its formula from molecular aspect are (C8H12N2). The phenelzine are a Monamine Oxidase Inhibitor "moa Inhibitor" utilized in cure of intense depression, panic disorder, social anxiety disorder and phobic disorder. It is a small molecula and has been placed in the Approved group. It's synonyms are 2-Phenethylhydrazine, beta phenylethylhydrazine, beta-Phenylethylhydrazine, Fenelzin, Nardelzine, Nardil, Phenelzine, Phenelzine Sulfate, Phenethylhydrazine, Sulfate. It belongs to various categories such as Agents that produce hypertension, Agents that reduce seizure threshold, Central Nervous System Depressants, Cytochrome P-450 CYP3A, CYP3A4, CYP3A5,CYP3A7 inhibitors, Cytochrome P-450 Enzyme inducers and inhibitors, Enzyme inhibitors, Hydrazines, Hypotensive Agents, Monoamine oxidase inhibitors, Psychoanaleptics, Psychotropic Drugs, Serotonin Agents and Modula-

tors. Phenelzine, as must of the monoamine oxidase inhibitors, can cause transient, mild and asymptomatic aminotransferase elevations. It has also been reported to be associated with cases of liver injury after 1-3 months of treatment. Affected organisms are Humans and other mammals (Nolen, 2003).

2.6.20 Physostigmine

Physostigmine is used as a cholinergic agent, which is rapidly absorbed in membranes and a veterinary medication. This complex also named as a (I.U.P.A.C) Term as follow [(3aR, 8bS) - 3, 4, 8b – Trimethyl - 2, 3a – Dihydro - 1H – Pyrrolo [2, 3 - b] Indol – 7 - Yl] N - Methylcarbamate. It's chemical formula is C15H21N3O2. It has a vital involments as a miotic, that is an inhibitor to cure poisoning. It can be used as topical medication and it also exhibits the property to cross BBB hence is used in treating CNS related disorders and severe anticholinergic toxicity It is a small molecule and has been placed in the Approved and Investigational groups. Its synonyms are Eserine, Physostigmine, Physostol. It belongs to various categories such as Acids, Acyclic, Alkaloids, Antidotes, Antoglaucoma preparations and Miotics, Autonomic Agents and Carbamates, Cholinergic Agents, Enzyme inhibitors, Indole Alkaloids, Neirotransmitter Agents, Opthalmologicals, Parasympathomimetics, Peripheral Nervous System Agents, Phenylcarbamates, Sensory Organs. Side effects include increased sweating, loss of bladder control, muscle weakness, nausea, vomiting, diarrhea, or stomach cramps or pain, shortness of breath, tightness in chest, or wheezing, slow or irregular heartbeat, unusual tiredness or weakness, watering of mouth, blurred vision or change in near or distant vision, and eye pain. Affected organisms are Humans and other mammals (Nguyen et al., 1999).

2.6.21 Rivastigmine

This complex named as a (I.U.P.A.C) Term as follow [3 - [(1S) – 1 - (Dimethylamino) Ethyl] Phenyl] N – Ethyl – N – Methylcarbamate. It's molecular formula is "C14H22N2O2". Rivastigmine is an oral Acetylcholi-nesterase inhibitor, which

are elective for the “central nervous system” which are utilize in case of the curing of “dementia in Alzheimer Parkinson disease” It is a small molecule and has been placed in the Approved and Investigational groups. It’s synonyms are (S)-3-(1-(Dimethylamino)ethyl)phenyl ethylmethylcarbamate, Rivastigmina, Rivastigmine, m-(S)-1-(Dimethylamino)ethyl)phenyl ethylmethylcarbamate. It belongs to various categories such as Acids, Acyclic, Anti-Dementia Drugs, Bradycardia-Causing Agents, Carbamates, Central Nervous System Agents, Cholinergic Agents, Cholinesterase inhibitors, Cytochrome P-450 CYP3A and CYP3A4 Substrates, Enzyme inhibitors, Neuroprotective Agents, Neurotransmitter Agents, Phenylcarbamates, Protective Agents, Psychoanaleptics. Affected organisms are Human and other mammals (Kennedy et al., 1999).

2.6.22 Tranylcypromine

This complex named as a (I.U.P.A.C) Term as follow (1R, 2S) – 2 – Phenylcyclopropan – 1 – Amine. Its chemical formula is C9H11N. The “Propylamine” are prepared from the side chain of Amphetamine cyclization. This inhibitor of “Monoamine Oxidase” are operative in curing of the most important cases of dysthymic disorder, depression, and uncommon depression. In addition, it is valuable in the cases of “Panic and Phobic Disorders”. The tranylcypromine therapy are connected with infrequent cases of clinically apparent acute liver injury. It is a small molecule and has been placed in the Approved and Investigational groups. It’s synonyms are Transamine, Tranylcypromin, Tranylcypromine, Tranylcyprominum, Tranilcipromina, Racemic Tranylcypromine, trans-2-phenylcyclopropylamine, trans-DL-2-Phenylcyclopropylamine, dl-tranylcyp-romine. In overdosage, some patients exhibit insomnia, restlessness and anxiety, progressing in severe cases to agitation, mental confusion and incoherence. Hypotension, dizziness, weakness and drowsiness may occur, progressing in severe cases to extreme dizziness and shock. A few patients have displayed hypertension with severe headache and other symptoms. Rare instances have been reported in which hypertension was accompanied by twitching or myoclonic fibrillation of skeletal muscles with hyperpyrexia, sometimes progress-

ing to generalized rigidity and coma. Affected organisms are Humans and other mammals (Chen, Ji and Chen, 2002).

2.6.23 Viloxazine

This complex named as a (I.U.P.A.C) Term as follow 2 - [(2 - Ethoxyphenoxy) Methyl] Morpholine. While its formula from molecular aspect are "C13H19NO3". The viloxazine are a norepinephrine reuptake elective inhibitor "NRI", which was prescribed in some European Countries as a drug for the Antidepressant cases. It is a small molecule and has been placed in the Approved, Investigational and Withdrawn groups. It's synonyms are 2-((2-Ethoxyphenoxy)methyl)morpholine, Viloxazina, Viloxazinum. It belongs to vario-us groups such as Adrenergic Agents, Adrenergic Uptake inhibitors, Antidepressive Agents, Central Nervous System Agents, Central Nervous System Depressants, Cytochrome P-450 CYP1A2 Inhibitors, Cytochrome P-450 Enzyme Inhibitors, Membrane Transport Modulators, Morpholines, Neurotransmitter Agents, Neurotransmitter Uptake Inhibitors, Oxazines, Psychoanaleptics, Psychotrop-ic Drugs. Common adverse effects are nausea and vomiting. Other side effects are dry mouth, dizziness, headache, drowsiness, sleep disturbances, bad taste, anorexia, heartburn and indigestion, constipation, diarrhoea, ataxia, tremor, dyskinesia, paraesthesia, confusion, restlessness, irritability, hypomania and mania, sweating, palpitation, tachycardia, increased and decreased blood pressure, pruritus and skin rashes. NO affected organisms have been reported (Pinder et al., 1977).

2.6.24 Ajmaline

This complex named as a (I.U.P.A.C) Term as follow (1R, 9R, 10S, 12R, 13S, 14R, 16S, 17S, 18R) – 13 – Ethyl – 8 – Methyl - 8, 15 – Diazahexacyclo [14.2.1.01,9.02,7.010,15.012,17] Nonadeca - 2, 4, 6 – Triene - 14, 18 – Diol or "C20H26N2O2" is also known as Gilurytmal and Raugalline. It is found in the roots of Rauwolfia serpentina, as an alkaloid. An antiarrhythmic agent change the form and sill of cardiac action possibilities. It is a type of small molecule. It has been placed in the approved and

experimental groups [drugbank]. Its synonyms are Ajmaline Hydrochloride, Aritmina, Cardiorythmine, Gilurtymal, Rauverid, Serenol, Tach-malin, Wolfina [pubchem]. It belongs to the various categories such as Alkaloids, Antiarrhythmic agents, Antiarrhythmics class 1 and class 1a and class 1c, Cardiac therapy, Cardiovascular Agents, Indole Alka-loids, Indoles, Membrane Transport Modulators, Potential QTC-Prolonging Agents, Secologanin Trypta-mine Alkaloids, Sodium channel blockers, Voltage-Gated Sodium Channel Blockers (Barajas-Martínez et al., 2008).

2.6.25 Apomorphine

This complex named as a (I.U.P.A.C) Term as follow (6aR) – 6 – Methyl - 5, 6, 6a, 7 – Tetrahydro - 4H – Dibenzo [De, g] Guinoline - 10, 11 – Diol or Apokyn (Trade Term) [Pubchem]. This complex is dopamine D2 agonist which is a derivative. It is highly effective as an antidote for poisoning along with it, it it is highly useful in treatment and diagnosis of PD but due to its side effects its use is limited [drugbank]. It is given subcutaneously and is used in advanced Parkinson disease. It does not show the lifting of serum enzyme during the cure; whereas, it has not been involved in the cases of sever liver injury It is a type of small molecule. It has been placed in the Approved and Investigational groups .It's syno-nyms are Apokinon, Apomorphin Teclapharm, Apomorphine Chloride, Apomorphine Hydrochloride, Apomorphine Hydrochloride Anhydrous, Apomorphine Hydrochloride, Britaject. It belongs to various categories such as Alkaloids, Anti-Parkinson Agents (Dopamine Agonist), Anti-Parkinson Drugs, Apor-phines, Autonomic Agents, Benzylisoquinolines, Central Nervous System Agents, Central Nervous Sys-tem Depressants, Dopamine Agents, Dopamine Agonists, Drugs used in Erectile Dysfunction, Gastrointes-tinal Agents, Genito Urinary System and Sex Hormones, Hypotensive Agents, Isoquinolines, Serotonin Agents (Berlin et al., 2000).

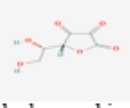
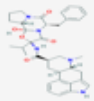
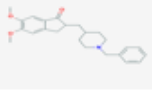
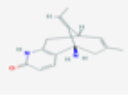
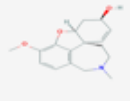
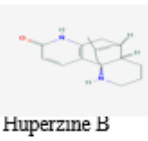
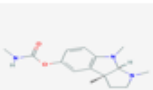
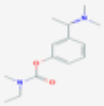
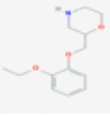
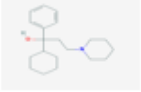
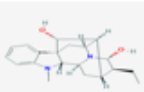
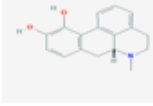
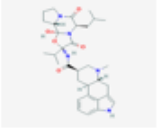
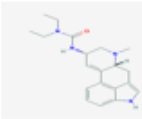
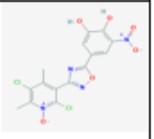
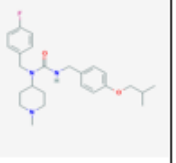
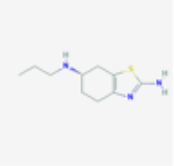
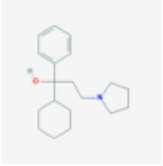
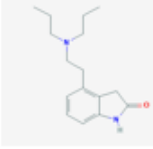
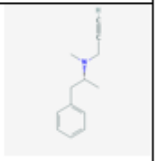
 Dehydroascorbic Acid	 Dihydroergocristie	 Donepezil	 Huperzine A	 Galantamine
 Huperzine B	 Isocarboxazid	 Memantine	 Pargyline	 Phenelzine
 Physostigmine	 Rivastigmine	 Tranylcypromine	 Viloxazine	 Trihexyphenidyl
 Ajmaline	 Apomorphine	 Dihydro-alpha-ergocryptine	 Lisuride	 Opicapone
 Pimavanserin	 Pramipexole	 Procyclidine	 Ropinirole	 Selegiline

Table 2.1 2D structure of the known inhibitors.

No	Drug name	Structure ID	Experimental values	Reference
1.	Dihydroergocristine	DB13345	IC50 value of ~25μM of AChE	(Lei *et al.*, 2015)
2.	Viloxazine	DB09185	IC50 value 298 ± 84 nm of Mao B	(Allain *et al.*, 1992)
3.	Physostigmine	DB00981	IC50 value 22 nm AChE	(Jackisch *et al.*, 2009)
4.	Memantine	DB01043	IC50 1.04 +/- 0.26 mM of Mao B	(Parsons, 1996)
5.	Galantamine	DB00674	IC50 value 575 nM of AChE	(Samochocki, 2003)
6.	Huperzine B	DB03348	IC50 8.0 μM of AChE	(Murray *et al.*, 2013)
7.	Dehydroascorbic Acid	DB08830	IC50 value 2474 μM	(Dosunmu and Owusu-Apenten, 2017)
8.	Pargyline	DB01626	IC50 value 13 μM of Mao B	(Barkhuizen, Petzer and Petzer, 2013)
9.	Isocarboxazid	DB01247	IC50 value 4.8 μM of Mao B	(Barbui *et al.*, 2011)
10.	Tranylcypromine	DB00752	Ki value of 242.7 μM of Mao B	(Schmidt and McCafferty, 2007)

Table 2.2 Experimental value of the the knowing inhibitors.

No	Drug name	Structure ID	Experimental values	Reference
11.	Phenelzine	DB00780	IC50 value 0.033 uM of Mao B	(Bonnet, 2006)
12	Donepezil	DB00843	Ic50 14 nM Of AChE	(Ogura *et al.*, 2000)
13	Huperzine A	DB04864	IC50 is 82 nM of AChE	(Ma *et al.*, 2003)
14	Tacrine	DB00382	IC50 is 302 nM of AChE In another study, IC 50 is 95 nM of AChE	(Ma *et al.*, 2003) (Jackisch *et al.*, 2009)
15	Rivastigmine	DB00989	IC50 is 9120 nM of AChE	(Jackisch *et al.*, 2009)
16	Lisuride	DB00589	Ic50 2.1 nM in treatment of Parkinson, Ic50 1 mM MAOB	(Calne, 1989)
17	Ropinirole	DB00268	IC50 of 1.2 uM antiParkinson's	(Fda and Cder, 2005)

Table 2.3 Experimental value of the the knowing inhibitors.

No	Drug name	Structure ID	Experimental values	Reference
18	Selegiline	DB01037	IC50 5.5±0.26 nM Of Mao B	('Sembragiline: a novel, selective monoamine oxidase type B inhibitor for the treatment of Alzheimer's disease', 2017)
19	Apomorphine	DB00714	IC50 93 mM Of Mao B	(Grünblatt *et al.*, 1999)
20	Pramipexole	DB00413	IC50 6.2 nM Of Mao B	('Compositions and methods of using (r)-pramipexole', 2015)
21	Trihexyphenidyl	DB00376	IC50 0.026 µM,of AChE	(Brocks, 1991)
22	Pimavanserin	DB05316	Parkinson ki value 16nM Acetylcholinesterase Inhibitor	(Hacksell *et al.*, 2014)
23	Procyclidine	DB00387	IC50 0.070 and Ki 0.019 of AChE	(Syvälahti, Kunelios and Laurén, 1988)
24	Ajmaline	DB01426	IC50 43.2 nM Of Mao B	(Harmer, Valentin and Pollard, 2011)
25	Dihydro-alpha-ergocryptine	DB11274	Ki 0.25 nM	(Tittler, Weinreich and Seeman, 1977)
26	Opicapone	DB11632	IC50 of 1483 nM Of Mao B	(Manuel and Lopes, 2013)

Table 2.4 Experimental value of the the knowing inhibitors.

3. Material and Method

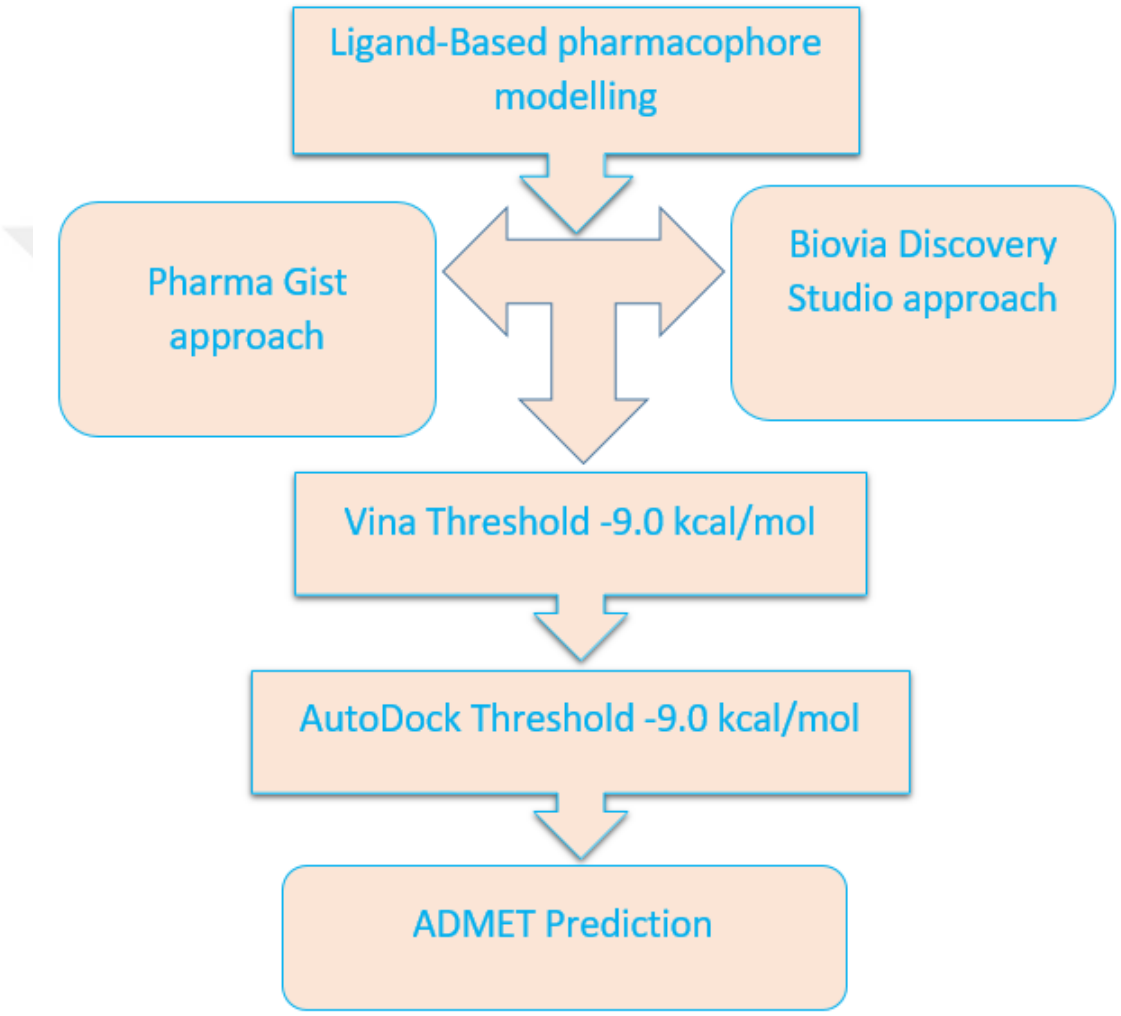


Figure 3.1 Schematic showing the work flow of the research

3.1 Target Proteins

For AChE MAOB structures, PDB was used with pdb ID as 1EVE 2V5Z respectively. Details of the target are mentioned in 5.1 5.2 section. The heteroatoms in the proteins were removed so that we obtain clean protein structures, using , Discovery Studio Visualizer.

3.1.1 Active site for Acetylcholinesterase (1EVE)

As illustrate in literature, AChE has two binding sites-including catalytic anionic sites and peripheral anionic sites. These sites include mainly two residues- TRP84 (at the bottom) , TRP 279 (at the top) TYR121 (in middle gorge). Also, PHE330 (midway down the gorge, between peripheral and anionic site) is also suggested as an additional binding site (Kryger, Silman and Sussman, 1999)

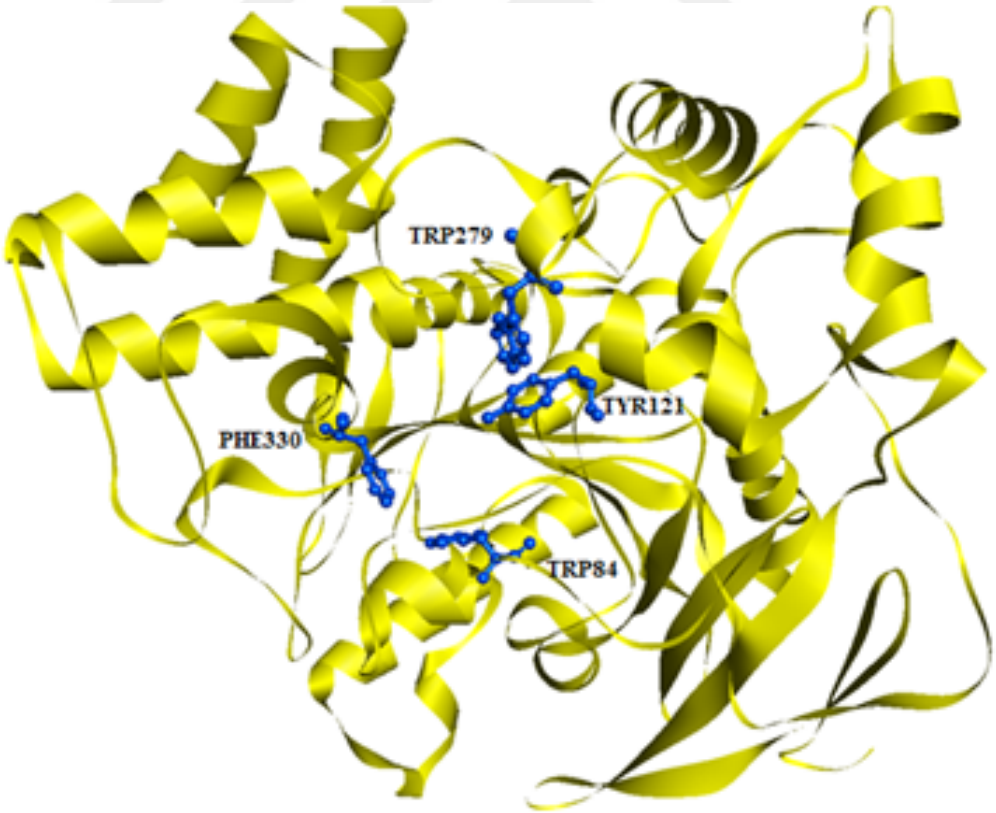


Figure 3.2 Image showing the binding sites in AChE, Using Discovery Studio

Predicted residues in Pocket 1
GLN-A 69 TYR-A70 VAL-A71 ASP-A72 ASN-A85
PRO-A86 TYR-A121 SER-A122 TRP-A84 GLY-A123
TRP-A279 GLU-A73 SER-A81 GLY-A118 GLY-A117
SER-A124 LEU-A127 TYR-A130 GLN-A74 TYR-A334
MET-A83 GLY-A119 LEU-A282 ARG-A289 PHE-A290
SER-A286 PHE-A330 GLU-A82 PHE-A288 GLY-A335
PHE-A331 GLU-A199 ILE-A287 ASP-A285 SER-A200
TRP-A233 HIS-A440 ALA-A336 GLY-A441 LEU-A358
TYR-A116

3.1.2 Active site for Monoamine oxidase B (2V5Z)

This protein structure is in complex with an inhibitor Safinamide, the protein is bound to this inhibitor. Hence while computing the grid for docking, the active site residues which illustrate the binding to the Safinamide were considered. In addition, Safinamide was taking into the account as a reference inhibitor. The residues considered for active site were GLN 206 (Chain A)(Binda et al., 2007).

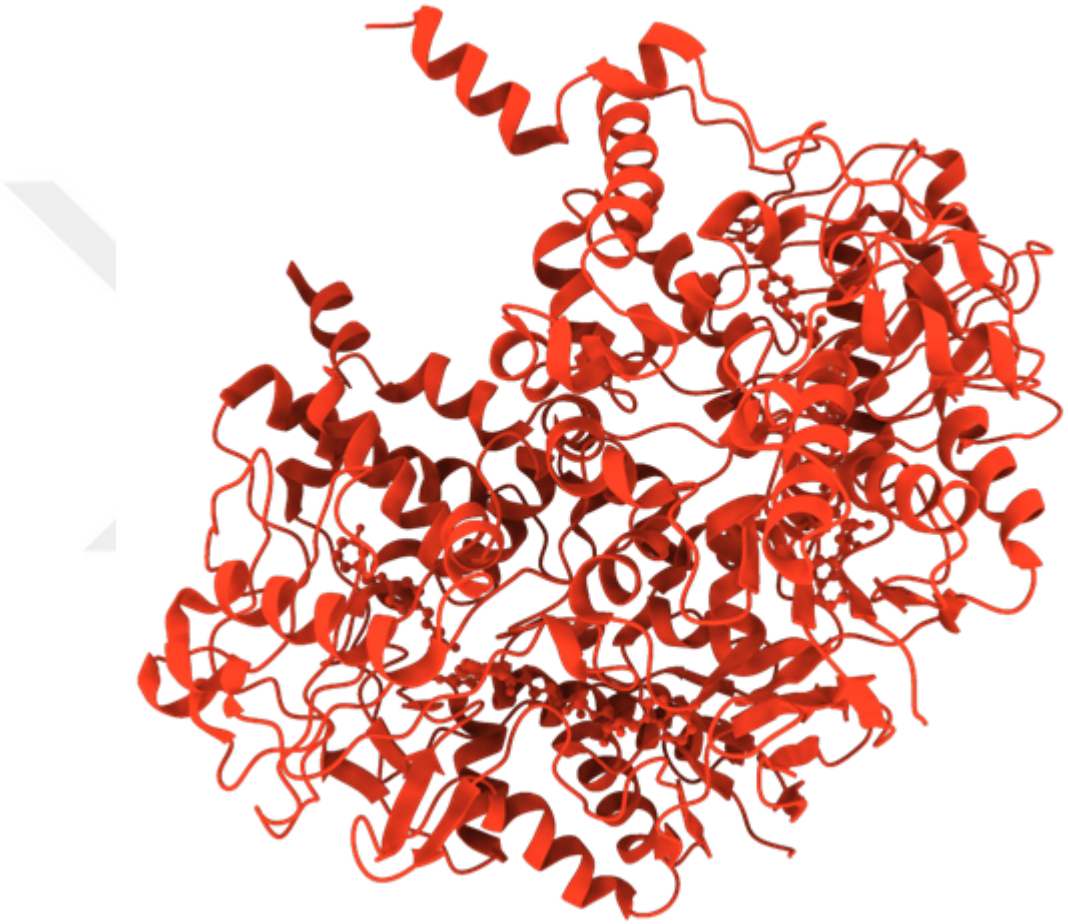


Figure 3.3 Image showing the binding sites in MOA B, Using Discovery Studio

3.2 Inhibitors selection

As for choosing of well-known inhibitors, which will be used in pharmacophore modeling and screening was done via docking studies. In this, all the ligands were docked with their corresponding targets and molecules showing binding energy of -8kcal/mol or less than that were selected. Refer 'Table3.1 , 3.2, 3.3, 3.4' for the docking and selecting process. Drugs/molecules highlighted in red were filtered out from the list of final known ligands. All the ligands were energy minimized using Chemaxon-MARVIN VIEW. For docking AutoDock Vina (Trott and Olson, 2010)was used.

Drug name	Category	Structure ID	Binding Energy
Dihydroergocristie	Accepted,	DB13345	-12.1 Kcal/mol
Galantamine	Accepted	DB00674	-9.5 Kcal/mol
Huperzine B	Trail	DB03348	-9.9 Kcal/mol
Isocarboxazid	Accepted	DB01247	-9 Kcal/mol
Donepezil	Accepted	DB00843	-11.2 Kcal/mol
Huperzine A	Accepted	DB04864	-9.7 Kcal/mol
Tacrine	Accepted	DB00382	-8.6 Kcal/mol
Rivastigmine	Accepted	DB00989	-7.9 Kcal/mol
Viloxazine	Accepted	DB09185	-7.5 Kcal/mol
Memantine	Accepted	DB01043	-7.6 Kcal/mol
Dehydroascorbic Acid	Trail	DB08830	-6 Kcal/mol
Pargyline	Accepted	DB01626	-7 Kcal/mol
Tranylcypromine	Accepted,	DB00752	-6.8 Kcal/mol
Phenelzine	Accepted	DB00780	-6.3 Kcal/mol

Table 3.1 Docking results for Acetylcholinesterase and known inhibitors for Alzheimer's. All the final drugs are approved drugs and filtered using drugbank(Wishart et al., 2018).

Drug	Category	Structure	Binding energy/ Kcal/mol
Lisuride	Accepted,	DB00589	-9.8
Ropinirole	Accepted,	DB00268	-8.5
Apomorphine	Accepted,	DB00714	-10.5
Trihexyphenidyl	Accepted	DB00376	-9.7
Pimavanserin	Accepted,	DB05316	-10.4
Procyclidine	Accepted	DB00387	-9.8
Ajmaline	Accepted	DB01426	-11.6
Dihydro-alpha-ergocryptine	Accepted	DB11274	-13.3
Opicapone	Accepted,	DB11632	-12.2
Tacrine	Accepted	DB00382	-8.6
Donepezil	Accepted	DB00843	-11.2
Huperzine A	Accepted	DB04864	-9.7
Selegiline	Accepted,,	DB01037	-7.8
Pramipexole	Accepted,	DB00413	-6.7
Rivastigmine	Accepted,	DB00989	-7.9

Table 3.2 Showing docking results for Acetylcholinesterase and known inhibitors for Parkinson's. All the final drugs are approved drugs and filtered using drugbank(Wishart et al., 2018).

Drug name	Category	Structure ID	Binding Energy
Physostigmine	Accepted	DB00981	-9 Kcal/mol
Galantamine	Accepted	DB00674	-9 Kcal/mol
Huperzine B	Trail	DB03348	-9.6 Kcal/mol
Isocarboxazid	Accepted	DB01247	-8.5 Kcal/mol
Donepezil	Accepted	DB00843	-11 Kcal/mol
Huperzine A	Accepted	DB04864	-9.7 Kcal/mol
Tacrine	Accepted,	DB00382	-9 Kcal/mol
Rivastigmine	Accepted,	DB00989	-7.6 Kcal/mol
Dihydroergocristine	Accepted	DB13345	-3 Kcal/mol
Viloxazine	Accepted	DB09185	-7.3 Kcal/mol
Tranylcypromine	Accepted	DB00752	-6.4 Kcal/mol
Phenelzine	Accepted	DB00780	-5.9 Kcal/mol
Dehydroascorbic Acid	Trail	DB08830	-5.8 Kcal/mol
Pargyline	Accepted	DB01626	-6.8 Kcal/mol
Memantine	Accepted	DB01043	-7.8 Kcal/mol

Table 3.3 Showing docking results for Monoamine oxidase B and known inhibitors for Alzheimer's. All the final drugs are approved drugs and filtered using drugbank(Wishart et al., 2018).

Drug	Category	Structure	Binding energy
Lisuride	Approved	DB00589	-9.6
Ropinirole	Approved	DB00268	-8.2
Apomorphine	Approved	DB00714	-11.2
Trihexyphenidyl	Approved	DB00376	-9.1
Pimavanserin	Approved	DB05316	-8.9
Procyclidine	Approved	DB00387	-9
Ajmaline	Approved	DB01426	-10.8
Opicapone	Approved	DB11632	-8.3
Tacrine	Approved	DB00382	-9
Donepezil	Approved	DB00843	-11.4
Huperzine A	Approved	DB04864	-9.7
Selegiline	Approved	DB01037	-7
Pramipexole	Approved	DB00413	-6.9
Dihydro-alpha-ergocryptine	Approved	DB11274	-3.3
Rivastigmine	Approved	DB00989	-7.6

Table 3.4 Showing docking results for Monoamine oxidase B and known inhibitors for Parkinson's. All the final drugs are approved drugs and filtered using drugbank(Wishart et al., 2018).

3.3 Pharmacophore Modeling Screening

Pharma Gist (Dror et al., 2009) was used to generate pharmacophores in which 3D compounds were used as input and a multiple pharmacophore candidates where obtained. For pharmacophore modeling, the Pharma Gist was used, which is one of the primary webserver for producing 3 dimensional Pharmacophores from drug-like compound's database. These drug-like compounds are known to bind the target protein .Pharma Gist uses an effective technique for searching the highest scoring pharmacophores. For all input ligands, various flexible alignments are detected for the candidate pharmacophores. Along with this, it is also able to identify pharmacophores to all the input ligands. Algorithm: Different test cases (mainly from FlexS benchmark) are used for assessment of Pharma Gist outcomes Complexes of identical target with different inhibitors are then classified into 12 different cases. Then theses complexes are then validated with respect to the reference pharmacophore created for all test set. The pharmacophore with maximum score as detected was similar to the reference (Sanders et al., 2012) The workflow of Pharma Gist is showing below:

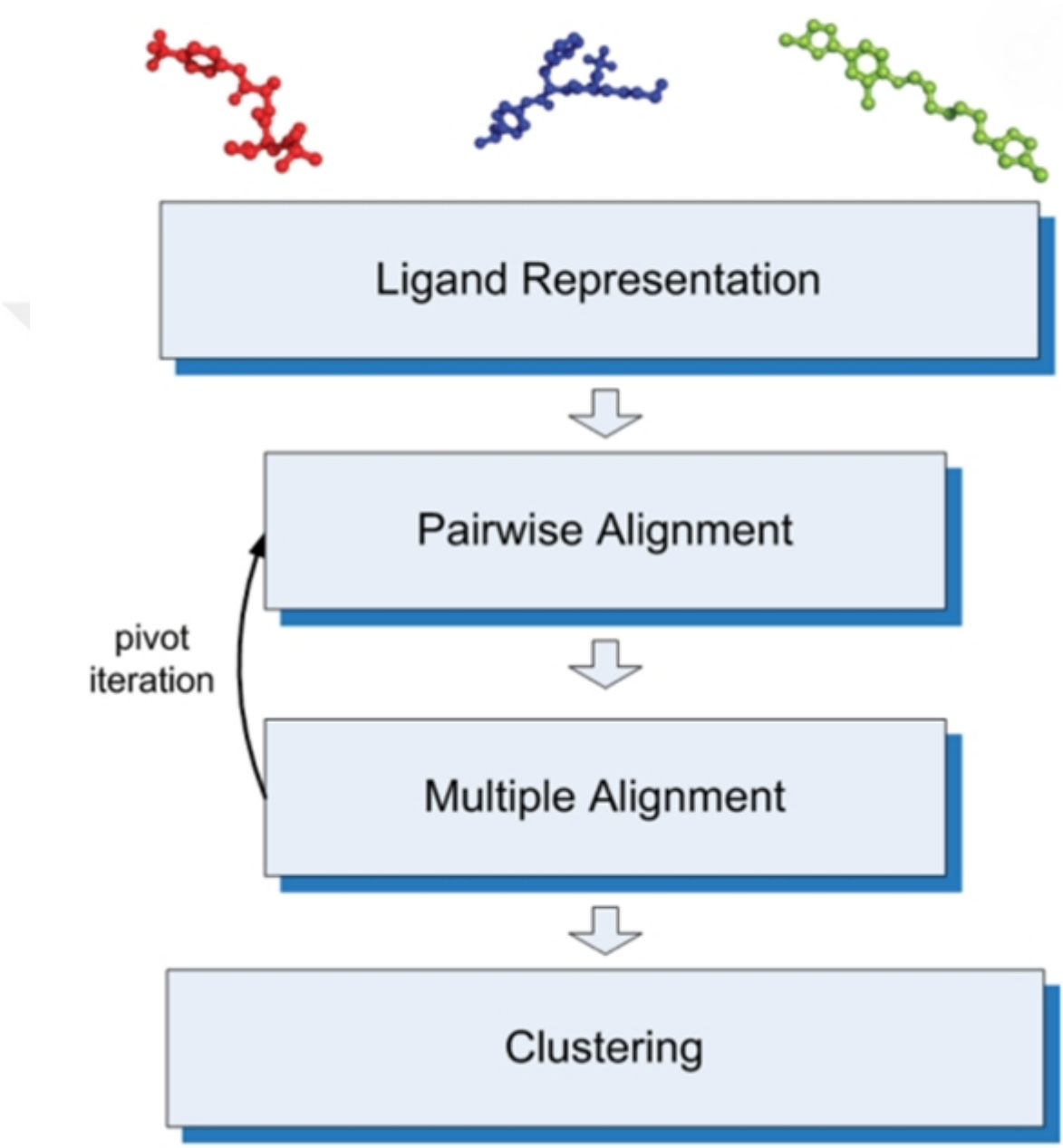


Figure 3.4 workflow of Pharma Gist

Results obtained from Pharma Gist are given below.

3.3.1 Pharmacophore of anti-Alzheimer drugs (2V5Z-Target)

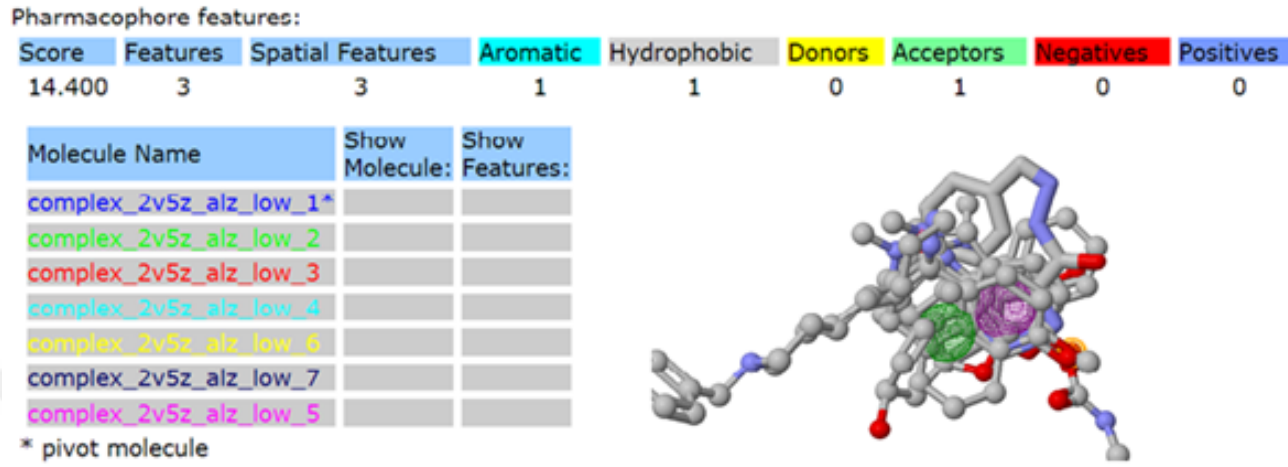


Figure 3.5 Pharmacophore obtained for target protein 2V5Z and anti-Alzheimer drugs from pharma Gist.

3.3.2 Pharmacophore of anti Parkinson drugs (2V5Z-Target)

Pharmacophore features:

Score	Features	Spatial Features	Aromatic	Hydrophobic	Donors	Acceptors	Negatives	Positives
14.400	3	3	1	1	0	1	0	0

Molecule Name	Show Molecule:	Show Features:
complex_2v5z_parkinson_low_1*		
complex_2v5z_parkinson_low_2		
complex_2v5z_parkinson_low_6		
complex_2v5z_parkinson_low_8		
complex_2v5z_parkinson_low_9		
complex_2v5z_parkinson_low_11		
complex_2v5z_parkinson_low_4		
complex_2v5z_parkinson_low_7		

* pivot molecule

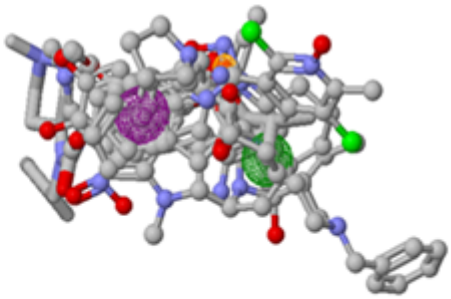


Figure 3.6 Pharmacophore obtained for target protein 2V5Z and anti-Parkinson from pharma Gist.

3.3.3 Pharmacophore of anti-Alzheimer drugs(1EVE-Target)

Pharmacophore features:

Score	Features	Spatial Features	Aromatic	Hydrophobic	Donors	Acceptors	Negatives	Positives
7.200	4	4	0	3	0	1	0	0

Molecule Name	Show Molecule:	Show Features:
complex_1eve_alz_low_1*		
complex_1eve_alz_low_3		
complex_1eve_alz_low_4		
complex_1eve_alz_low_5		
complex_1eve_alz_low_7		
complex_1eve_alz_low_10		
complex_1eve_alz_low_8		
complex_1eve_alz_low_2		

* pivot molecule

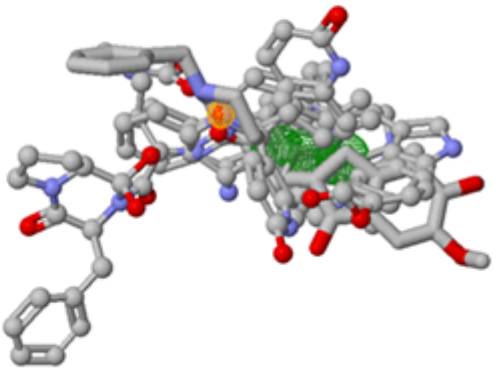


Figure 3.7 Pharmacophore obtained for target protein acetylcholinesterase (1EVE) and anti-Alzheimer drugs from pharma Gist

3.3.4 Pharmacophore of anti Parkinson drugs acetylcholinesterase (1EVE-Target)

Pharmacophore features:

Score	Features	Spatial Features	Aromatic	Hydrophobic	Donors	Acceptors	Negatives	Positives
6.965	3	3	0	2	0	1	0	0

Molecule Name	Show Molecule:	Show Features:
complex_1eve_parkinson_low_1*		
complex_1eve_parkinson_low_2		
complex_1eve_parkinson_low_3		
complex_1eve_parkinson_low_5		
complex_1eve_parkinson_low_6		
complex_1eve_parkinson_low_11		
complex_1eve_parkinson_low_12		
complex_1eve_parkinson_low_13		
complex_1eve_parkinson_low_4		
complex_1eve_parkinson_low_10		
complex_1eve_parkinson_low_14		
complex_1eve_parkinson_low_9		
complex_1eve_parkinson_low_7		

* pivot molecule

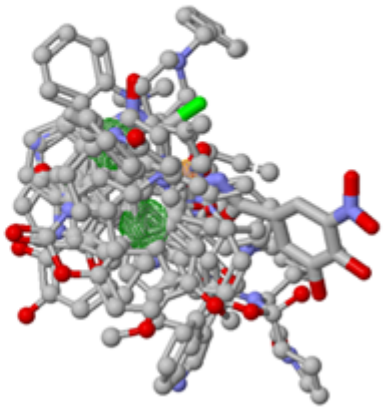


Figure 3.8 Pharmacophore obtained for target protein acetylcholinesterase 1EVE and anti Parkinson drugs from Pharma Gist

The pharmacophore that was generated from the software Pharma Gist was visualized in biovia (DS)

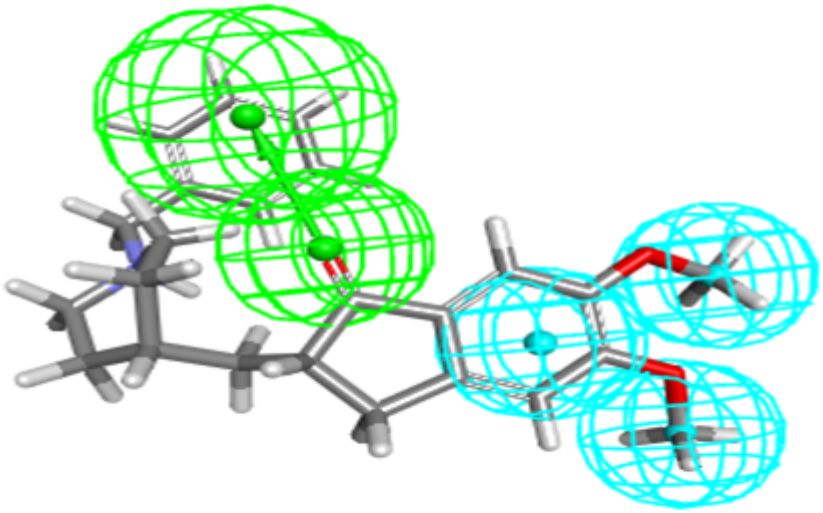


Figure 3.9 The pharmacophore feature of the ligand Donepezil visualized in Biovia DS 2016 where the three cyan spheres are the hydrophobic features, and the green spheres is the Hydrogen acceptor.

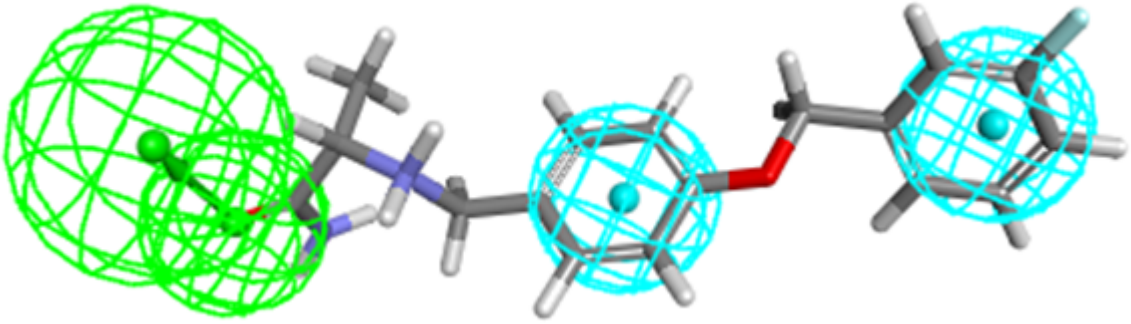


Figure 3.10 The pharmacophore feature of the ligand safinamide visualized in Biovia DS 2016 where the cyan spheres is the Hydrophobic feature, and the green spheres is the Hydrogen acceptor.

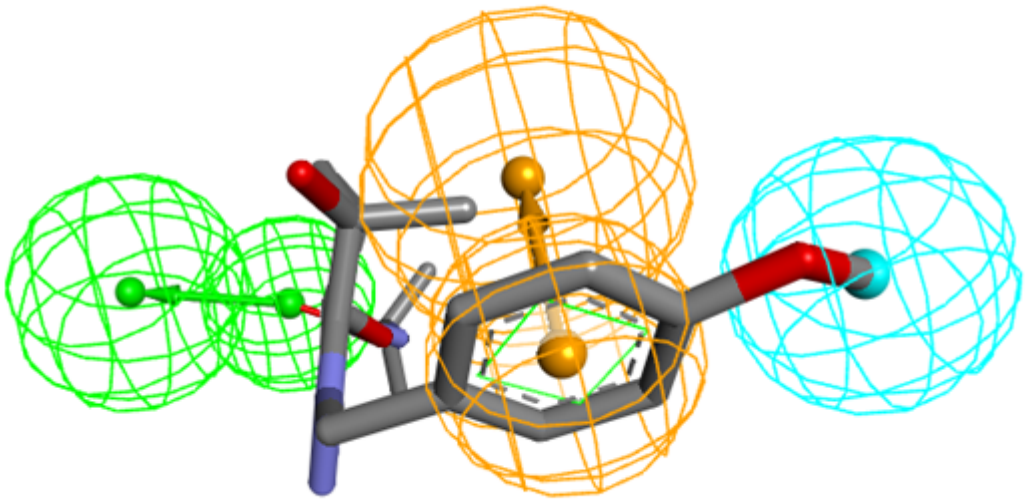


Figure 3.11 The pharmacophore feature of the ligand visualized in Biovia DS 2016 where the cyan spheres is the hydrophobic feature, the orange spheres is the aromatic feature and the green spheres is the Hydrogen acceptor.

	1EVE and Alzheimer	1EVE and Parkinson	2V5Z and Alzheimer	2V5Z and Parkinson
Total compounds screened	137	1682	453	1243

Table 3.5 Total compound screened.

Pharmacophore Based Screening of Zinc Database

Zinc drug database was used so as to screen the database with drug like compounds of ZINC using ZINC pharmer (Schachat, Andrew P., MD; Sadda, SriniVas R., MD; Hinton, David R., MD; Wilkinson, C.P., MD; Wiedemann, Peter, 2017)

3.4 Lipinski rule of 5

After screening molecules were screened for Lipinski rule of 5 which says that poor absorption (or permeation) is more likely when:

- The compound has less than 5 H-bond donors
- The compound has less than 10 H-bond acceptors
- The compound molecular weight is less than 500
- The compound LogP is less than 5

KNIME was used (Berthold et al., 2009) for filtering compounds on the basis of Lipinski rule of 5.

	1EVE and Alzheimer	1EVE and Parkinson	2V5Z and Alzheimer	2V5Z and Parkinson
Total compounds screened	137	1682	453	1243
Lipinski Rule Pass	136	1556	413	1132
Lipinski Rule Fail	1	126	40	111

Table 3.6 Pharmacophore screening and Lipinski rule of 5.

3.5 Docking studies

Autodock vina was used for multiple docking for both the proteins. Compounds that was screened after lipinskii rule of 5 were used as ligand. Autodock vina is a approach for molecular docking founded on virtual screening approach. Active sites for both of the proteins were outlined previously in the research. Docking for all the compounds with respect to the protein was performed using Autodock Vina Then top 5 compounds (based on the binding energy) were again docked with their respective targets using AutoDock software that concern with docking of one molecule with one target protein. This was accomplished to cross verify the docking and interactions.

4. Result and Discussion

4.1 Molecular docking of acetylcholinesterase (1EVE) and the top 5 Anti-Alzheimer's compounds

Docking result for acetylcholinesterase 1EVE and top 5 molecules

4.1.1 ZINC03830630

No INTERACTION

4.1.2 ZINC03830629

1. Interaction bond length: TYR 70 :O→ N23/2.835Å, ASN 85 :OD1→ 024/2.431Å. 2.Binding Energy : -11.16 3.Conclusion: Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC03830629 may give the desired result but with lesser efficiency.

4.1.3 ZINC03831223

1.Interaction bond length:PHE 288: HN→ O21/1.787Å. 2.Binding Energy: -10.91 3.Conclusion: Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC03831223 may give the desired result but with lesser efficiency.

4.1.4 ZINC11592603

No INTERACTION

4.1.5 ZINC03831061

1.Interaction bond:ARG 289:HN [U+F0E0]O21/2.068Å. 2.Binding Energy:-10.01. 3.Conclusion:Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC03831061 may give the desired result but with lesser efficiency.

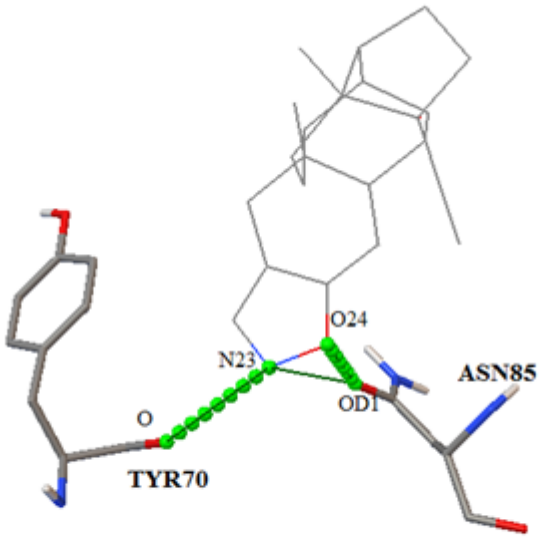


Figure 4.1 Complex showing interaction between 1EVE with ZINC03830629 at amino acid residues- ASN85 TYR70, using AutoDock tools.

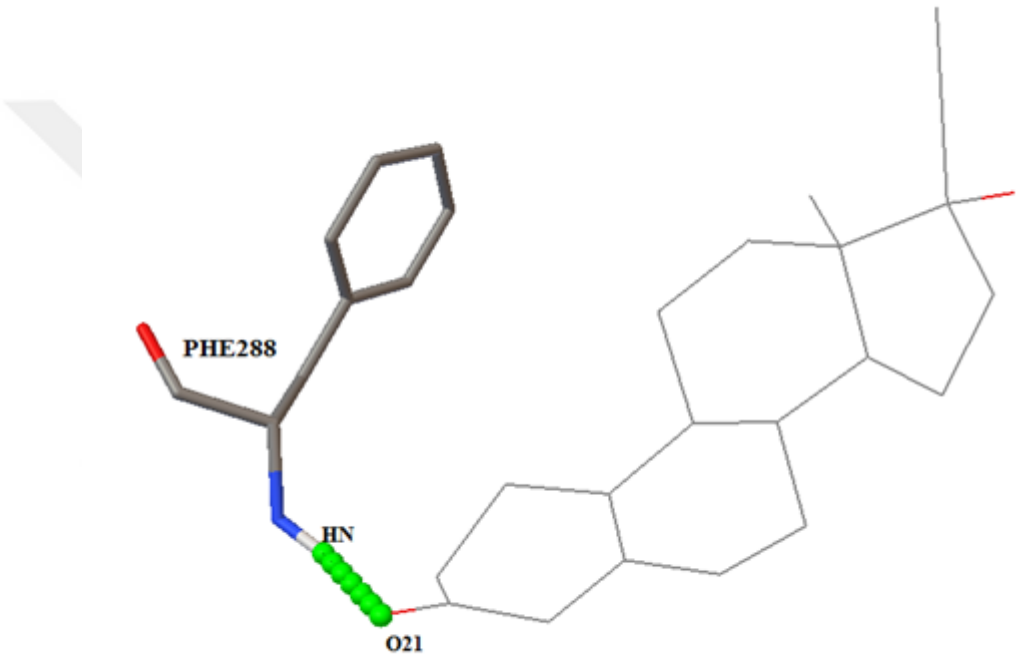


Figure 4.2 Complex showing interaction between 1EVE with ZINC03831223 at amino acid residues- PHE 288 using AutoDock tools.

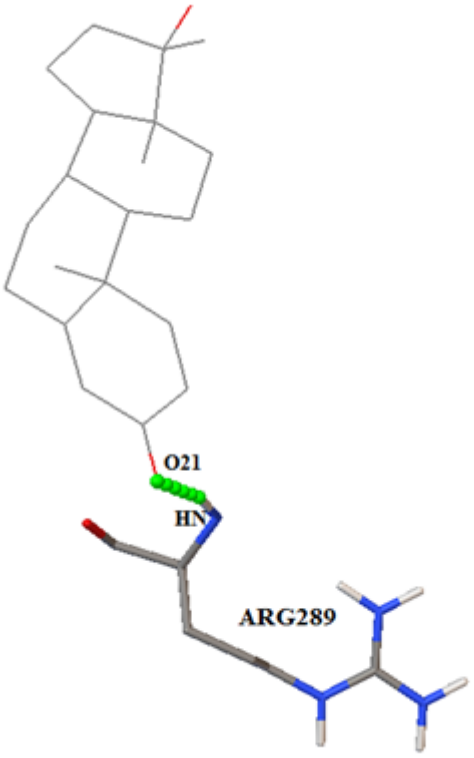


Figure 4.3 Complex showing interaction between 1EVE with ZINC03831061 at amino acid residues- ARG289, using AutoDock tools.

4.2 Molecular docking of acetylcholinesterase (1EVE) and the top 5 anti-Parkinson's compounds

Docking result for acetylcholinesterase (1EVE) and top 5 molecules

4.2.1 ZINC03881345

1.Interaction bond:ARG 289: HN→ O27/2.071Å. 2.Binding Energy:-11.86. 3.Conclusion:Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC03881345 may give the desired result but with lesser efficiency.

4.2.2 ZINC04026555

1.Interaction bond:PHE 288: HN→ O26/2.062Å. 2.Binding Energy:-12.27. 3.Conclusion:Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC04026555 may give the desired result but with lesser efficiency.

4.2.3 ZINC11616656

1.Interaction bond:PHE 288: HN→ O27/1.887Å, HIS 440: HE2→ O26/2.051Å, SER 200: HG→ O26/2.03Å

2.Binding Energy:-12.31 3.Conclusion:Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC11616656 may give the desired result but with lesser efficiency.

4.2.4 ZINC11592603

No INTERACTION

4.2.5 ZINC02033589

1.Interaction bond:ARG 289: HN→ O32/2.204Å 2.Binding Energy:-12.86 3.Conclusion:Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC11616656 may give the desired result but with lesser efficiency.

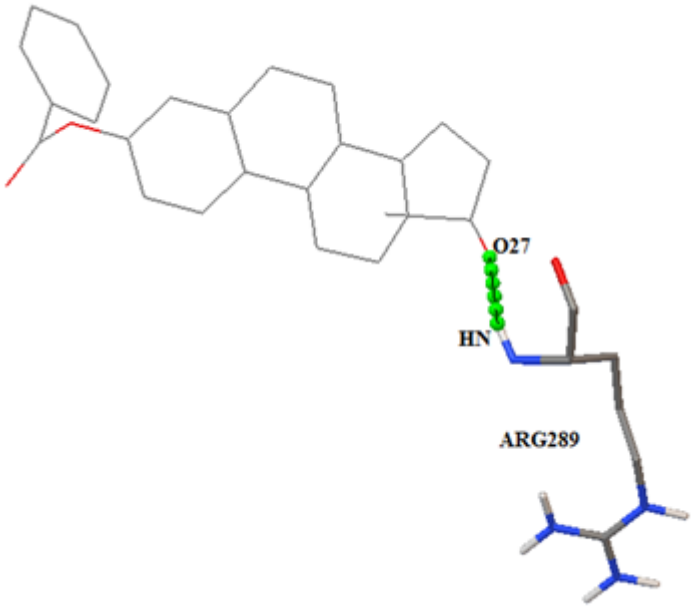


Figure 4.4 Complex showing interaction between 1EVE with ZINC03881345 at amino acid residues- ARG289, using AutoDock tools.

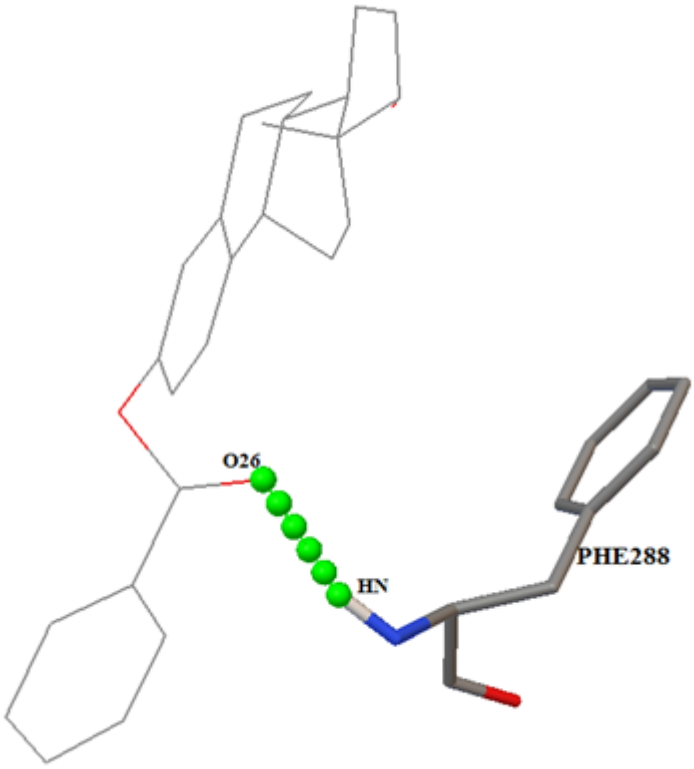


Figure 4.5 Complex showing interaction between 1EVE with ZINC04026555 at amino acid residues- PHE 288 using AutoDock tools.

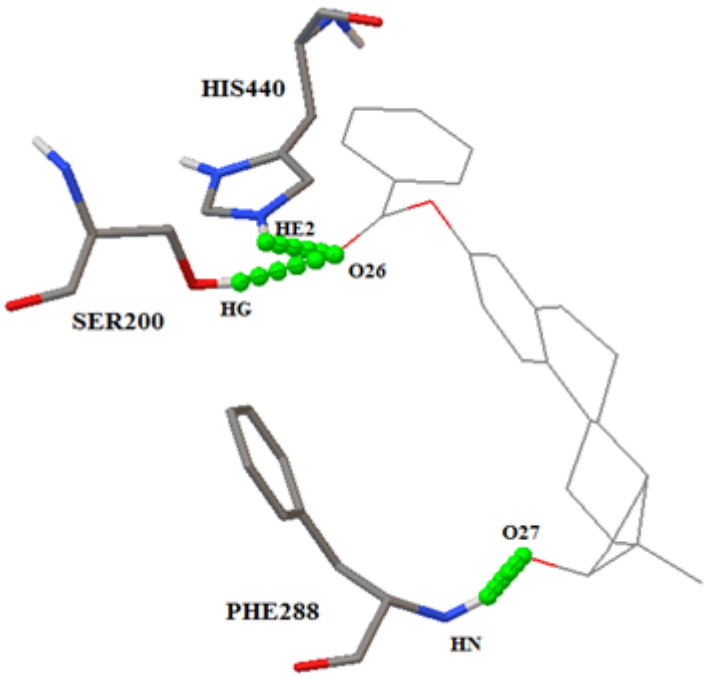


Figure 4.6 Complex showing interaction between 1EVE with ZINC11616656 at amino acid residues- PHE 288, HIS 440 SER 200 using AutoDock tools.

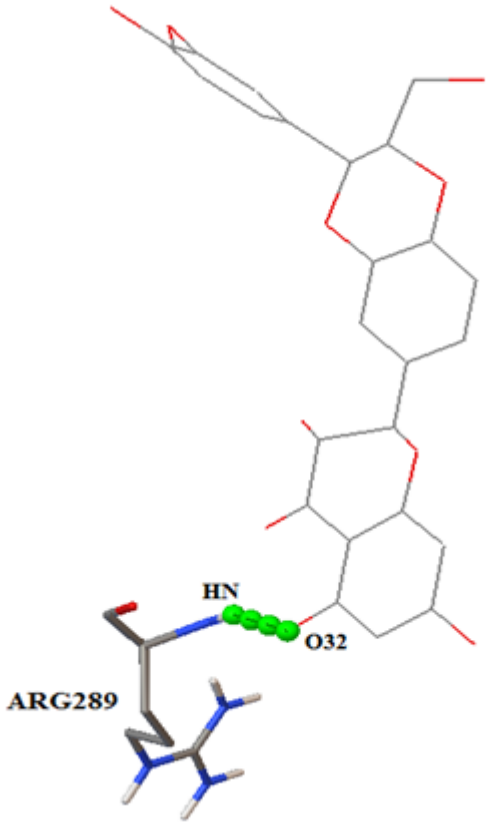


Figure 4.7 Complex showing interaction between 1EVE with ZINC02033589at amino acid residues- ARG289 using AutoDock tools.

4.3 Molecular docking of 2V5Z and the top 5 anti-Parkinson's compounds

Docking result for Monoamine oxidase B (2V5Z) and top 5 molecules

4.3.1 ZINC03881345

1.Interaction bond:SER 59: HN→ O27/2.064Å 2.Binding Energy:-14.06 3.Conclusion:Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC03881345 may give the desired result but with lesser efficiency.

4.3.2 ZINC04026555

1.Interaction bond:SER 59: HN→ O27/2.027Å, TYR 60: HN→ O27/1.790Å.

2.Binding Energy:-13.44 3.Conclusion:Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC04026555 may give the desired result but with lesser efficiency.

4.3.3 ZINC11616656

1.Interaction bond: GLN 206: OE1→ O27/2.872Å 2.Binding Energy:-13.18 3.Conclusion:Interactions are occurring at the exact active site (refer active site report); therefore we can say that the ligand activity will be as desired. Therefore, we can say that the ZINC11616656 may give the desired result with efficiency.

4.3.4 ZINC03830768

1.Interaction bond:SER 59: HN→ O27/1.653Å, TYR 60: HN→ O27/1.956Å.

2.Binding Energy:-13.25. 3.Conclusion:the interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC03830768 may give the desired result but with lesser efficiency.

4.3.5 ZINC03812892

1.Interaction bond:TYR 60: HN→ O35/2.091Å 2.Binding Energy:-12.57 3.Conclusion:Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC03812892 may give the desired result but with lesser efficiency.

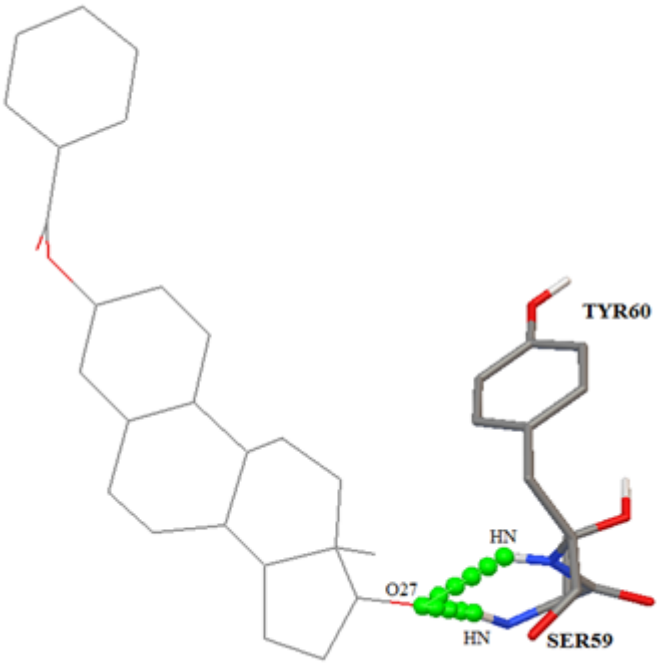


Figure 4.8 Complex showing interaction between 2V5Z with ZINC04026555 at amino acid residues- SER 59 TYR 60,using AutoDock tools..

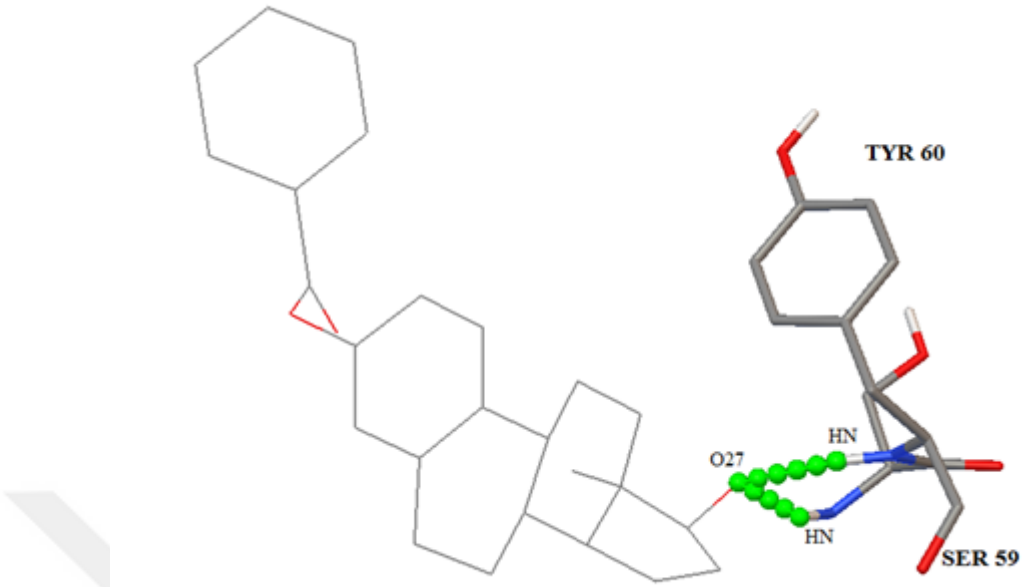


Figure 4.9 Complex showing interaction between 2V5Z with ZINC03830768 at amino acid residues- SER 59 TYR 60, using AutoDock tools.

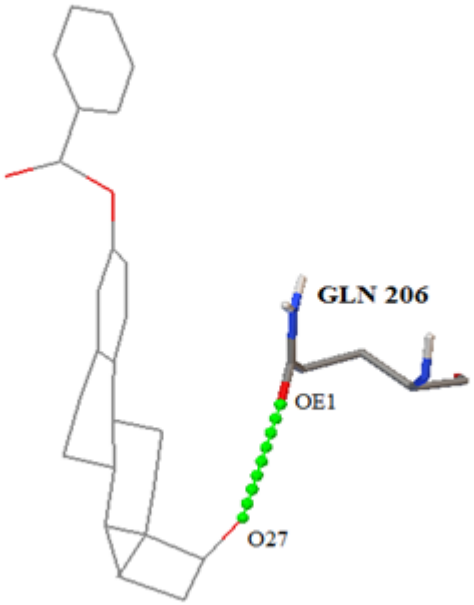


Figure 4.10 Complex showing interaction between 2V5Z with ZINC11616656 at amino acid residues- GLN 206, using AutoDock tools.

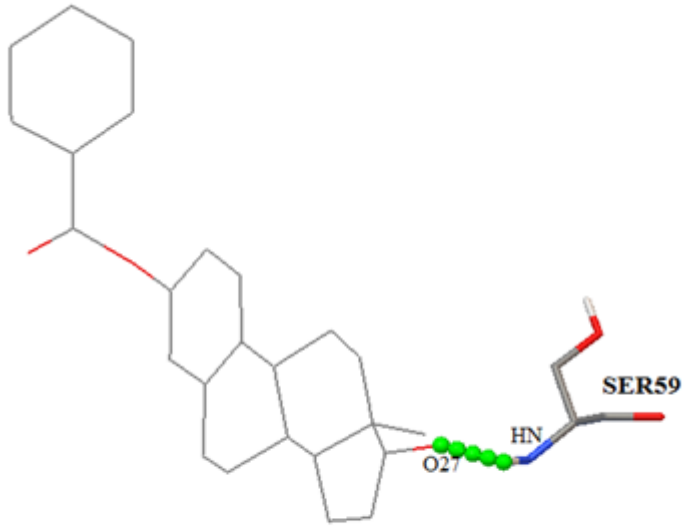


Figure 4.11 Complex showing interaction between 2V5Z with ZINC03881345 at amino acid residues- SER59, using AutoDock tools.

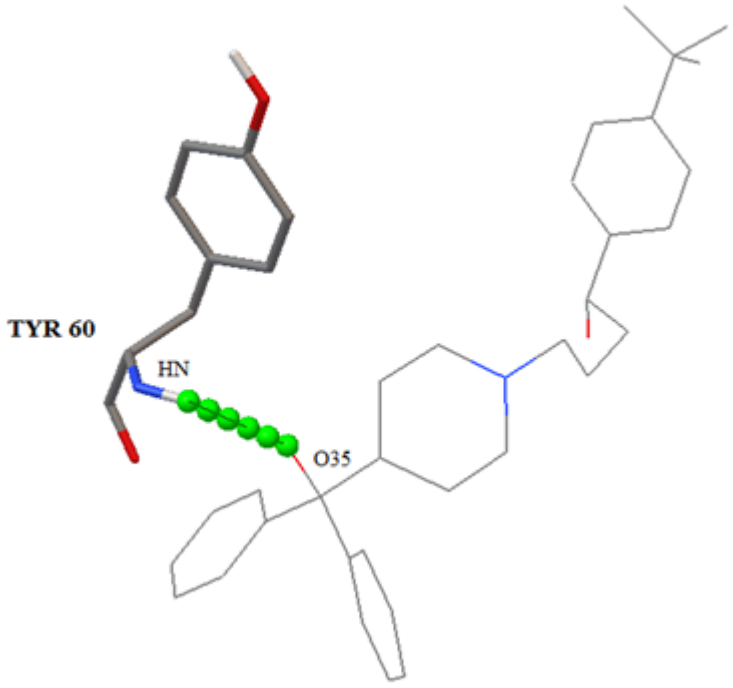


Figure 4.12 Complex showing interaction between 2V5Z with ZINC03812892 at amino acid residues- TYR 60, using AutoDock tools..

4.4 Molecular docking of Monoamine oxidase B (2V5Z) and the top 5 anti-Alzheimer's compounds.

Docking result for Monoamine oxidase B (2V5Z) and top 5 molecules

4.4.1 ZINC02033589

1.Interaction bond:TYR60 : HN→ O35/2.129Å ,SER59 : HN→ O35/1.872Å, TYR326 : HH → O31/1.581Å

2.Binding Energy:-12.67. 3.Conclusion: The interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC11616656 may give the desired result but with lesser efficiency.

4.4.2 ZINC01530604

1.Interaction bond:SER 59: HN→ O28/1.964 Å ,TYR 435 : HH→ O32/2.032 Å ,MET 436 : HN→ O24/2.023Å

2.Binding Energy:-11.18 3.Conclusion:Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC01530604 may give the desired result but with lesser efficiency.

4.4.3 ZINC00537877

1.Interaction bond:TYR188: HH→ O27/2.107Å 2.Binding Energy:-11.09 3.Conclusion:Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC00537877 may give the desired result but with lesser efficiency.

4.4.4 ZINC00538275

1.Interaction bond:SER59: HN→ O33/1.19Å, TYR 60: HN→ O33/2.138Å

2.Binding Energy:-12.62 3.Conclusion:Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC00538275 may give the desired result but with lesser efficiency.

4.4.5 ZINC00538505

1.Interaction bond:SER59: HN→ O25/Å, TYR 60: HN→ O24/Å, TYR 435: HH→ O24/Å

2.Binding Energy:-10.17 3.Conclusion:Interactions are not occurring at the exact active sites (refer active site report); also, we found that interaction occurred in the same pocket of active sites. Therefore we can say that the ZINC00538505 may give the desired result but with lesser efficiency.

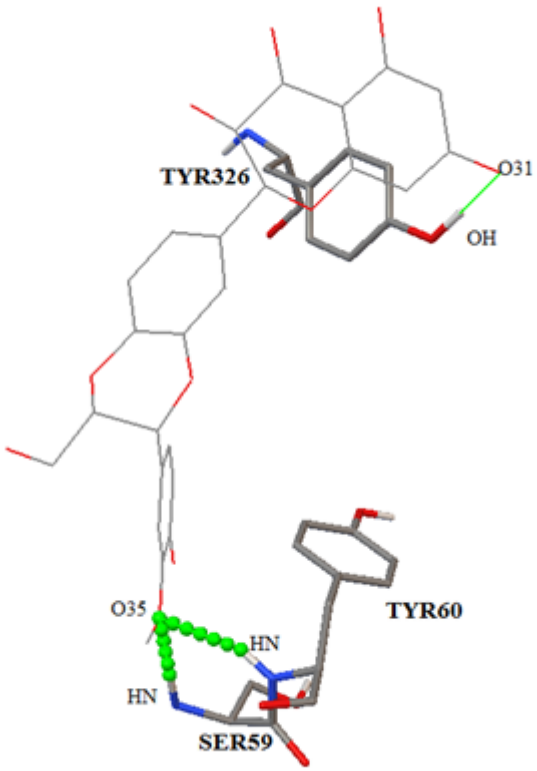


Figure 4.13 Complex showing interaction between 2V5Z with ZINC02033589at amino acid residues- SER59, TYR60 TYR326 using AutoDock tools.

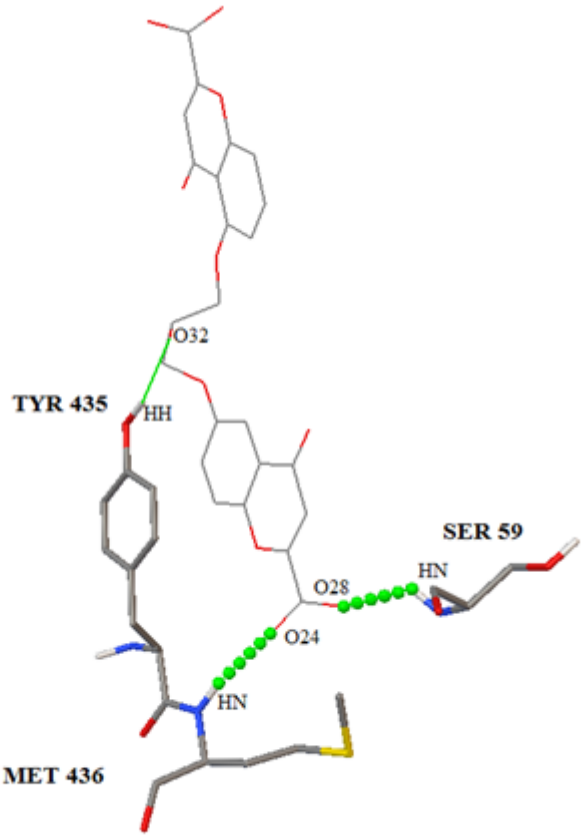


Figure 4.14 Complex showing interaction between 2V5Z with ZINC01530604 at amino acid residues- TYR 435, MET 436 SER59 using AutoDock tools.

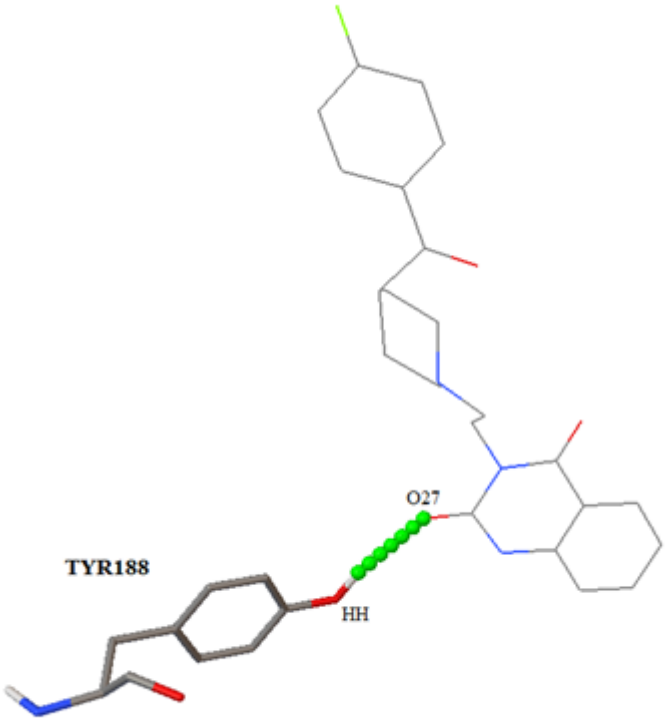


Figure 4.15 Complex showing interaction between 2V5Z with ZINC00537877 at amino acid residues- TYR188, using AutoDock tools.

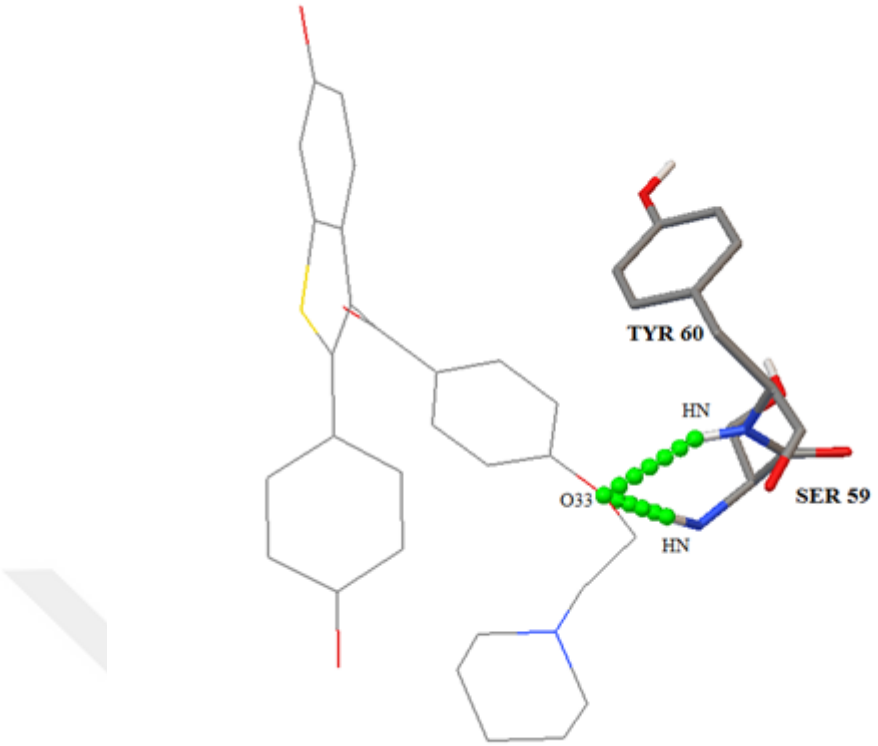


Figure 4.16 Complex showing interaction between 2V5Z with ZINC00538275 at amino acid residues- SER 59 TYR 60, using AutoDock tools.

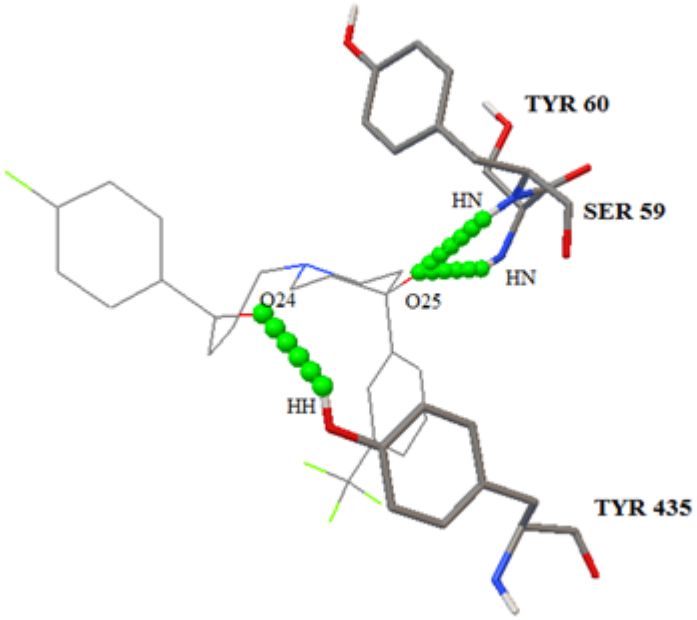


Figure 4.17 Complex showing interaction between 2V5Z with ZINC00538505 at amino acid residues- SER 59, TYR 60 TYR 435, using AutoDock tools.

4.5 ADMET studies

The ADMET studies of compound is the study of its pharmokinetic properties, which describe the drug journey inside the human bloodstream and the time of its existence in it. The concentration of the drug in the blood is determine according to this process to make sure its not toxic but yet its functional. For performed ADMET test admetSAR was applied (Cheng et al., 2012) and KNIME CDK workflow.

Ligends used in Table 4.7 Cytochrome P450 and the Drug Response: CYP activity can change with respect to drugs which can change the rate of degradation of Drugs from the human body. Increases activity of CYP can lead to fast clearing of the drug from body and reverse will accumulate the drug in human body. CYP proteins have different families like CYP1, CYP2, CYP3 and CYP4 which are vital in terms of metabolism, especially CYP3A4.

ADME	logS	logP	LogD	MW	S_HBD	S_HBA	T_PSA	P(BBB+)	P(HIA+)	Caco-2
ZINC03830629	-1.151	0.517	0.295	337.20	1	1	46.26	0.9781	1	0.8866
ZINC03830630	-1.151	0.517	0.295	337.20	1	1	46.26	0.9781	1	0.8866
ZINC03831061	-4.818	2.809	0.269	300.21	1	2	37.3	9	1	0.8737
ZINC03831223	-4.366	3.042	-3.798	298.19	1	2	37.3	0.9413	1	0.8572
ZINC03881345	-7.764	3.376	3.23	376.20	1	2	46.53	0.9155	1	0.7741
ZINC04026555	-7.764	3.376	3.23	376.20	1	2	46.53	0.9155	1	0.7741
ZINC11616656	-7.764	3.376	3.23	376.20	1	2	46.53	0.9155	1	0.7741
ZINC02033589	-2.951	1.149	1.133	482.12	5	3	155.14	0.7675	0.9698	0.5808
ZINC01530604	3.397	1.726	-3.978	466.05	1	5	179.37	0.8335	0.7708	0.5884
ZINC00537877	-3.629	3.453	3.452	396.17	2	1	76.37	0.5878	0.9522	0.6847
ZINC00538275	-4.478	5.167	4.45	474.17	3	1	99.44	0.8206	0.9368	0.8128
ZINC00538505	-3.648	2.29	1.247	410.17	2	2	41.74	0.8773	0.9424	0.527
ZINC03830768	-7.764	3.376	3.23	376.20	1	2	46.53	0.9155	1	0.7741
ZINC03812892	-4.96	6.862	6.774	472.32	3	2	44.9	0.5328	0.7841	0.5786
ZINC11592603	-4.742	3.009	-3.448	298.19	1	2	37.3	0.9413	1	0.8572

Table 4.1 ADME.

Metabolism	CYP450 2C9 Substrate	CYP450 2D6 Substrate	CYP450 3A4 Substrate	CYP450 1A2 Inhibitor	CYP450 2C19 Inhibitor	CYP450 3A4 Inhibitor	CYP Inhibitory Promiscuity
ZINC11616656	Not-substance	Not-substance	substance	inhibition	NOT	NOT	WEAK
ZINC02033589	Not-substance	Not-substance	Not-substance	NOT	NOT	inhibition	STRONG
ZINC01530604	Not-substance	Not-substance	Not-substance	NOT	NOT	NOT	WEAK
ZINC00537877	Not-substance	Not-substance	Not-substance	NOT	inhibition	NOT	STRONG
ZINC0538275	Not-substance	Not-substance	Not-substance	NOT	inhibition	inhibition	STRONG
ZINC00538505	Not-substrate	Substrate	Not-Substrate	NOT	NOT	NOT	WEAK
ZINC03812892	Non-substance	substance	substance	NOT	NOT	NOT	WEAK
ZINC03830629	Not-substance	Not-substance	substance	inhibition	inhibition	inhibition	STRONG
ZINC03830630	Not-substrate	Not-substrate	Substrate	inhibition	inhibition	inhibition	STRONG
ZINC03831061	Not-substance	Not-substance	substance	NOT	NOT	NOT	WEAK
ZINC11592603	Not-substance	Not-substance	substance	NOT	inhibition	NOT	WEAK
ZINC03831223	Not-substance	Not-substance	substance	NOT	Inhibitor	NOT	WEAK
ZINC03881345	Not-substance	Not-substance	Substrate	Inhibitor	NOT	NOT	WEAK
ZINC03830768	Not-substance	Not-substance	substance	Inhibitor	NOT	NOT	WEAK
ZINC04026555	Not-substance	Not-substance	substance	inhibition	NOT	NOT	WEAK

Table 4.2 Metabolism.

Toxicity	hERG Inhibitors	AMES Toxicity	Carcinogens	Fish Toxicity
ZINC11616656	Weak	Not Found	Not Found	STRONG
ZINC02033589	Weak	Not Found	Not Found	STRONG
ZINC01530604	Weak	Not Found	Not Found	STRONG
ZINC00537877	Weak	Not Found	Not Found	STRONG
ZINC0538275	Weak	Not Found	Not Found	STRONG
ZINC00538505	Weak	Not Found	Not Found	STRONG
ZINC03812892	Weak	Not Found	Not Found	WEAK
ZINC03830629	Weak	Not Found	Not Found	STRONG
ZINC03830630	Weak	Not Found	Not Found	STRONG
ZINC03831061	Weak	Not Found	Not Found	STRONG
ZINC11592603	Weak	Not Found	Not Found	STRONG
ZINC03831223	Weak	Not Found	Not Found	STRONG
ZINC03881345	Weak	Not Found	Not Found	STRONG
ZINC03830768	Weak	Not Found	Not Found	STRONG
ZINC04026555	Weak	Not Found	Not Found	STRONG

Table 4.3 Toxicity.

Ligends used in Table 4.3, hERG Inhibitors: If compound is strong inhibitor of hERG, then it may cause cardiac arrest hence non-inhibitor or weak inhibitor are preferred AMES Toxicity: It is a teat to check the mutagenic potential of the chemical compounds

4.6 Cross docking

Cross-docking is a way of finding out the best structure (compound/molecule/potential drug) among multiple structures/screened structures available for a target protein. So cross-docking study was conducted on a data of 15 ligand-receptor complexes that is molecular docking studies for all the ligands with 2 protein targets. Results are given in table below:

Inhibitors	1EVE	2V5Z
ZINC03881345	Binding energy = -11.86 kcal/mol Ki value= 2.02 nM ARG 289: HN→ O27/2.071Å	Binding energy = -14.06 kcal/mol Ki value= 49.76 pM SER 59: HN→ O27/2.064Å
ZINC11616656	Binding energy = -12.31 kcal/mol Ki value= 952.29 pM PHE 288: HN→ O27/1.887Å HIS 440: HE2→ O26/2.051Å SER 200: HG→ O26/2.03Å	Binding energy = -13.18 kcal/mol Ki value= 215.83 pM GLN 206: OE1→ O27/2.872Å
ZINC03830768	Binding energy = -11.95kcal/mol Ki value= 1.73 nM PHE 288: HN→ O27/2.1 Å (Interaction is occurring in the same pocket of active site)	Binding energy = -13.25 kcal/mol Ki value= 193.28 pM SER 59: HN→ O27/1.653Å TYR 60: HN→ O27/1.956Å

Table 4.4 Cross docking result1

Inhibitors	1EVE	2V5Z
ZINC03812892	Binding energy = -12.93kcal/mol Ki value= 331.20 pM PHE 288: HN→ O34/1.83 Å (Interaction is occurring in the same pocket of active site)	Binding energy = -12.57 kcal/mol Ki value= 614.69 pM TYR 60: HN→ O35/2.091Å
ZINC03830630	No interaction	Binding energy = -11.76kcal/mol Ki value= 2.41 nM MET436 : HN→ O24/1.819 Å (Interaction is occurring in the same pocket of active site)
ZINC03830629	Binding energy = -11.16 kcal/mol Ki value= 6.55 nM TYR 70 :O→ N23/2.835Å ASN 85 :OD1→ 024/2.431Å	No interaction

Table 4.5 Cross docking result-2

Inhibitors	1EVE	2V5Z
ZINC03831223	Binding energy = -10.91kcal/mol Ki value= 10.03 nM PHE 288: HN→ O21/1.787Å	Binding energy = -11.79kcal/mol Ki value= 2.28 nM SER 59: HN→ O29/2.038Å TYR 60: HN→ O22/1.754Å (Interaction is occurring in the same pocket of active site)
ZINC03831061	Binding energy = -10.01 kcal/mol Ki value= 46.18 nM ARG 289:HN →O21/2.068	Binding energy = -10.24kcal/mol Ki value= 31.07 nM MET436 : HN→ O24/1.924 Interaction is occurring in the same pocket of active site)
ZINC04026555	Binding energy = -12.27 kcal/mol Ki value= 1.02 nM PHE 288: HN→ O26/2.062Å	Binding energy = -13.44 kcal/mol Ki value= 141.58 pM SER 59: HN→ O27/2.027Å TYR 60: HN→ O27/1.790Å

Table 4.6 Cross docking result-3

Inhibitors	1EVE	2V5Z
ZINC02033589	Binding energy = -12.86 kcal/mol Ki value= 376.35 pM ARG 289: HN→ O32/2.204Å	Binding energy = -12.67 kcal/mol Ki value= 519.30 pM TYR60 : HN→ O35/2.129Å SER59 : HN→ O35/1.872Å TYR326 : HH → O31/1.581Å
ZINC01530604	Binding energy = -10.86kcal/mol Ki value= 10.90 nM SER 200: HG→ O30/2.056Å GLY 119: HN→ O28/1.869 Å PHE 288: HN→ O25/1.982 Å TYR 121 : HH→ O56/1.969 Å HIS 440 : HE2→ O30/2.194 Å (Interaction is occurring in the same pocket of active site)	Binding energy = -11.18 kcal/mol Ki value= 6.35 nM SER 59: HN→ O28/1.964 Å TYR 435 : HH→ O32/2.032 Å MET 436 : HN→ O24/2.023Å
ZINC00537877	Binding energy = -11.51kcal/mol Ki value= 3.49 nM TYR 121: HH→ O27/1.791Å (Interaction is occurring at active site)	Binding energy = -11.09 kcal/mol Ki value= 7.39 nM TYR188: HH→ O27/2.107Å

Table 4.7 Cross docking result-4

Inhibitors	1EVE	2V5Z
ZINC00538275	Binding energy = -13.03kcal/mol Ki value= 230.40 pM TYR 70: O→ O32/2.643Å (Interaction is occurring in the same pocket of active site)	Binding energy = -12.62 kcal/mol Ki value= 564.06 pM SER59: HN→ O33/1.19Å TYR 60: HN→ O33/2.138Å
ZINC00538505	Binding energy = -10.44kcal/mol Ki value= 22.41 nM TYR 121: OD2→ N23/1.828Å (Interaction is occurring at active site)	Binding energy = -10.17 kcal/mol Ki value= 34.84 nM SER59: HN→ O25/Å TYR 60: HN→ O24/Å TYR 435: HH→ O24/Å

Table 4.8 Cross docking result-5

5. CONCLUSIONS

Identification of novel inhibitors is reported for both diseases (1EVE 2V5Z). From literature number of inhibitors were available so in order to find the best we performed docking studies that is interaction analysis for each inhibitors found and the target protein. The inhibitors that gave good interaction from the binding energy point of respect and formed hydrogen bonds with the target protein were selected to build pharmacophore models. Docking studies showed 8 inhibitors for Alzheimer's (3 for 1EVE target protein and 5 for 2V5Z target) and 9 inhibitors for Parkinson's disease (4 targeting 1EVE 5 targeting 2V5Z); out of these it was found 4 common inhibitors for both the targets. The built pharamacophore model was selected based on scoring parameters as per the server used (PharmaGist) and then selected can be used for screening ZINC database. The screened ZINC molecules were again virtually screened with both the targets to find top 5 molecules that were showing best binding energy. Then, all the best inhibitors were docked as per the Alzheimer's and Parkinson'sdisease to find out their inhibitory activity. For studying the selectivity of compounds with the targets, cross docking was performed.

Also, compounds -ZINC03830630, ZINC03830629ZINC11592603 showed selectivity for only 1 target protein that is 1EVE. Also molecules ZINC038881345, ZINC11616656 and ZINC03830768 Showed best binding energy, number of interaction with target protein (more than 2 Hydrogen Bond) along with following ADMET properties.All the three compounds shows ADMET results like highly soluble, lipophilic with 90 % accuracy of crossing Blood brain barrier along with non-inhibitor of CYP 450 3A4, which states that compound will be easily metabolized.Also, all the molecules are carcinogenic and mutagenic free.

COMPOUNDS	1EVE	2V5Z
ZINC03831223	✓	✓
ZINC03831061	✓	✓
ZINC03881345	✓	✓
ZINC04026555	✓	✓
ZINC11616656	✓	✓
ZINC02033589	✓	✓
ZINC01530604	✓	✓
ZINC00537877	✓	✓
ZINC00538275	✓	✓
ZINC00538505	✓	✓
ZINC03830768	✓	✓
ZINC03812892	✓	✓

Table 5.1 Cross Docking showing Active compounds.

	logS	logP	LogD	P(BBB+)	CYP450 3A4 Inhibitor	HeARG Inhibitors	1EVE			2V5Z		
							Binding energy	Ki value	No of H Bonds	Binding energy	Ki value	No of H Bonds
ZINC03881345	-7.76	3.376	3.23	0.9155	Non-Inhibitor	Weak inhibitor	-11.86 kcal/mol	2.02 nM	1	-14.06 kcal/mol	49.76 pM	1
ZINC11616656	-7.76	3.376	3.23	0.9155	Non-Inhibitor	Weak inhibitor	-12.31 kcal/mol	952.29 pM	3	-13.18 kcal/mol	215.83 pM	1
ZINC03830768	-7.76	3.376	3.23	0.9155	Non-Inhibitor	Weak inhibitor	-11.95 kcal/mol	1.73 nM	1	-13.25 kcal/mol	193.28 pM	2

Table 5.2 2D and 3D interaction ZINC038881345, ZINC11616656 and ZINC03830768are.

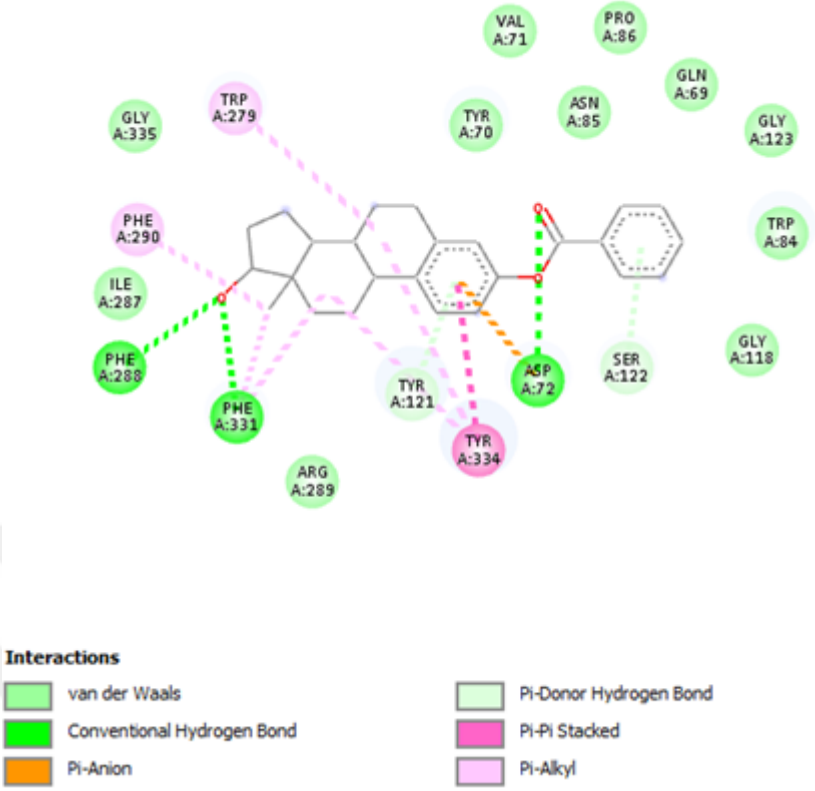


Figure 5.1 2D interaction of the compound ZINC03830768 with Acetyl-cholinesterase (1eve) in the biding pocket.

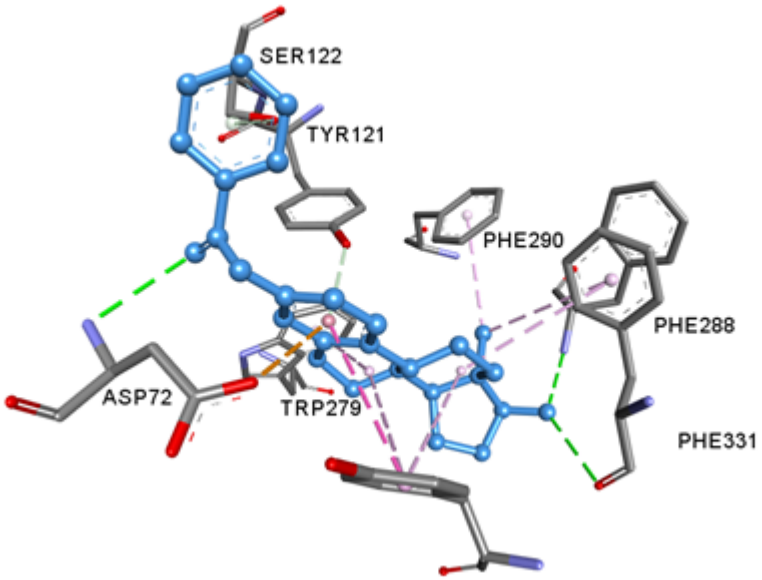


Figure 5.2 3D Interaction between the protein residues and the Binding pocket of Acetyl-cholinesterase (1eve) and ZINC03830768.

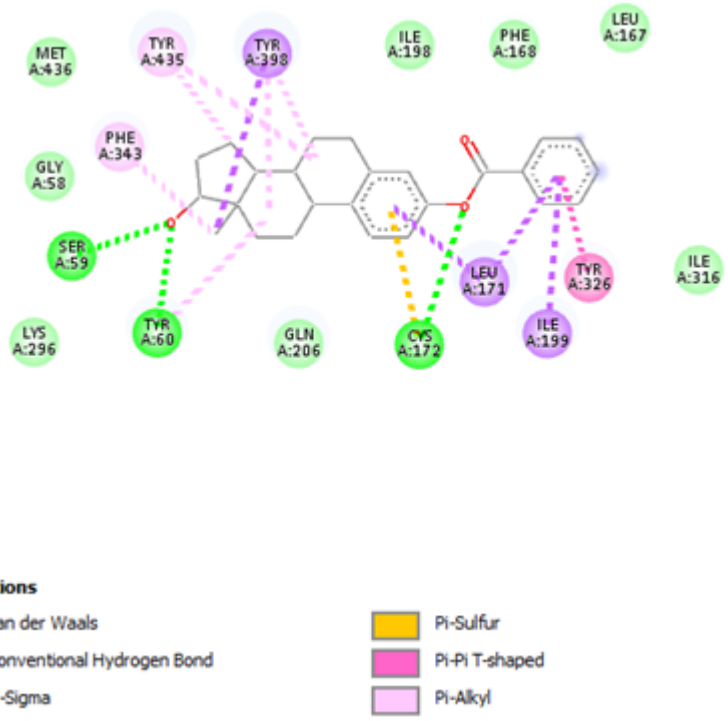


Figure 5.3 2d interaction of the compound ZINC03830768 With monoamine oxidase B (2v5z) in the biding pocket.

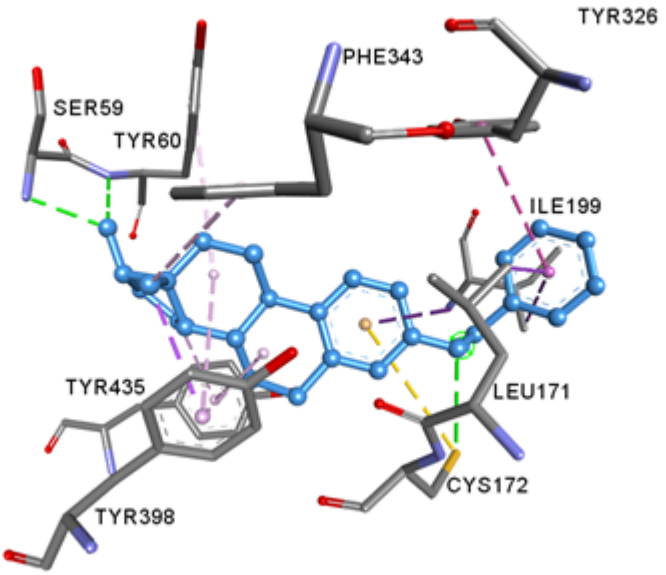


Figure 5.4 3D Interaction between the protein residues and the Binding pocket of monoamine oxidase B (2v5z) and ZINC03830768

Figure 5.5 2D interaction of the compound ZINC11616656 with Acetyl-cholinesterase (1eve) in the biding pocket.

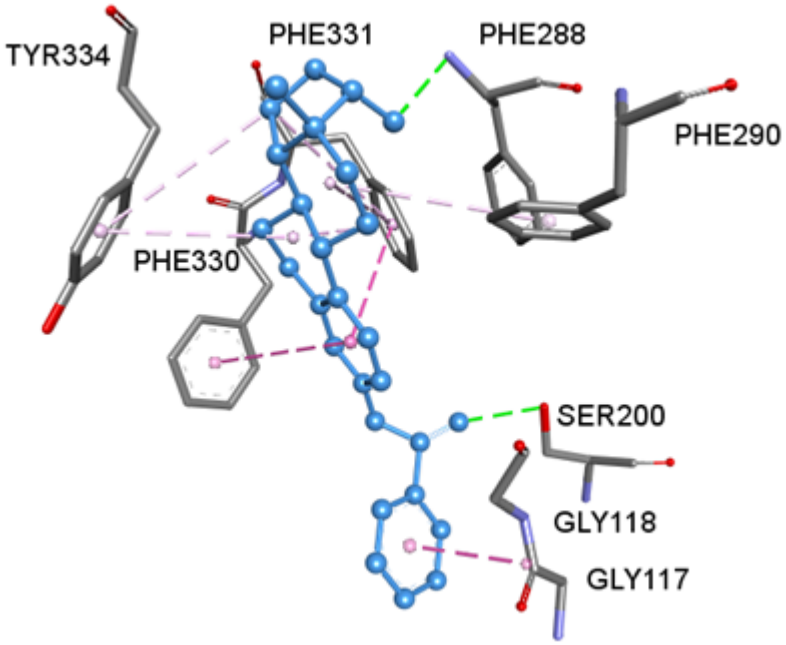


Figure 5.6 3D Interaction between the protein residues and the Binding pocket of Acetyl-cholinesterase (1eve) and ZINC11616656

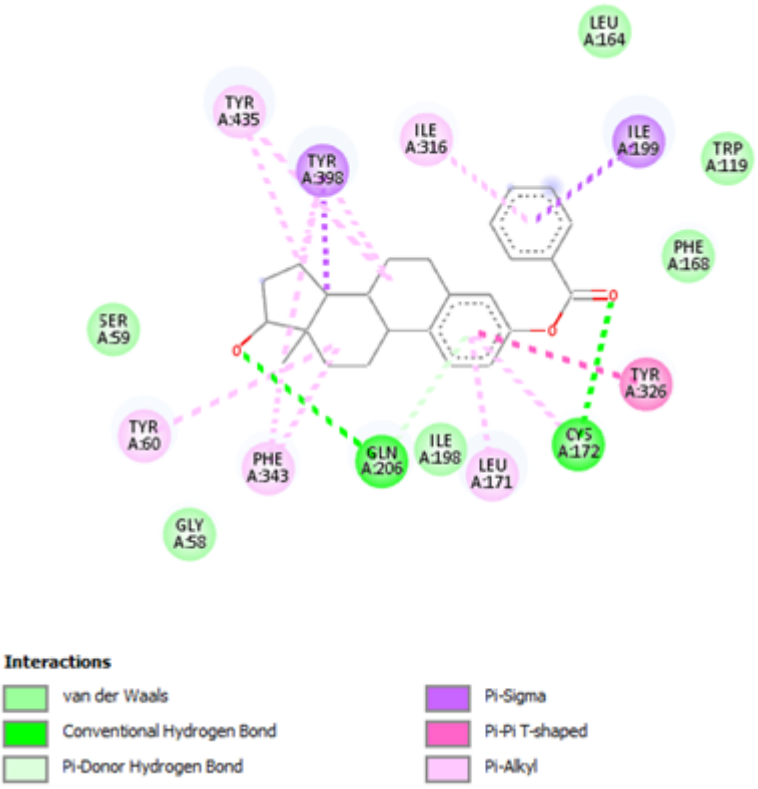


Figure 5.7 2D interaction of the compound ZINC11616656 With monoamine oxidase B (2v5z) in the biding pocket.

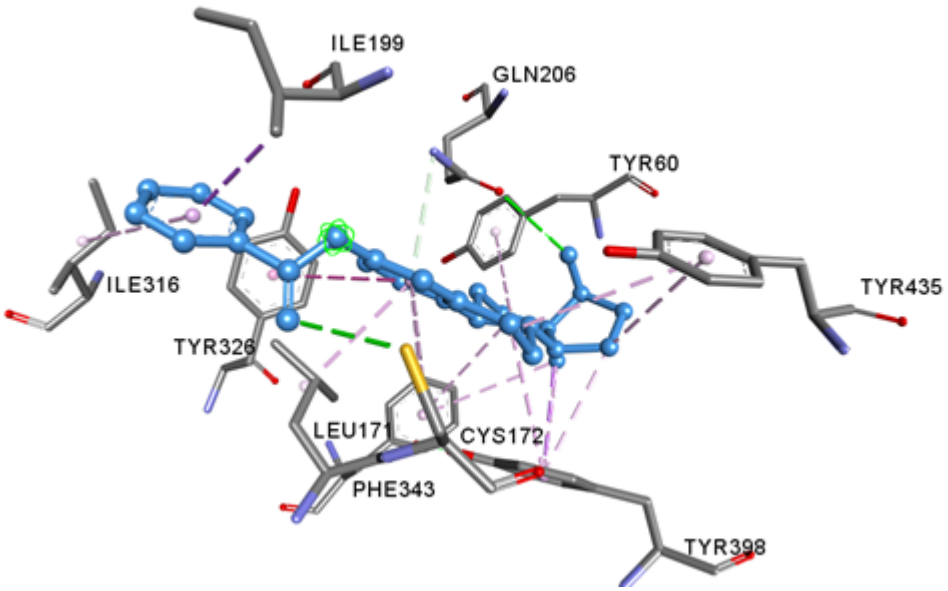


Figure 5.8 3D Interaction between the protein residues and the Binding pocket of monoamine oxidase B (2v5z) and ZINC11616656.

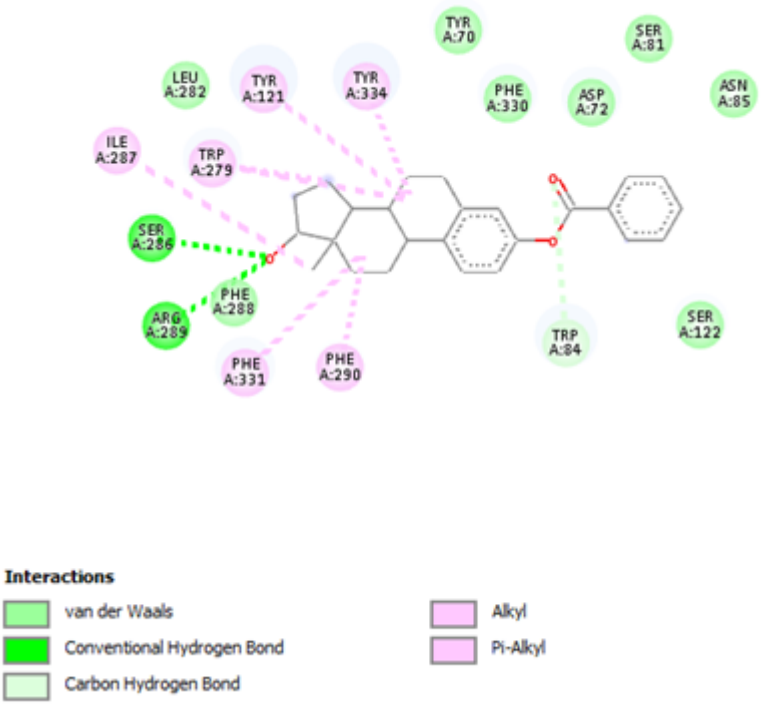


Figure 5.9 2D interaction of the compound ZINC03881345 with Acetyl-cholinesterase (1eve) in the biding pocket.

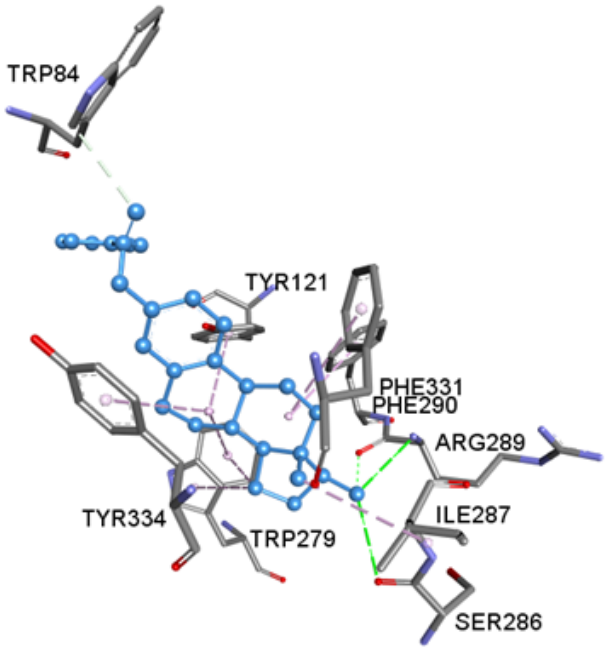


Figure 5.10 3D Interaction between the protein residues and the Binding pocket of Acetyl-cholinesterase (1eve) and ZINC03881345

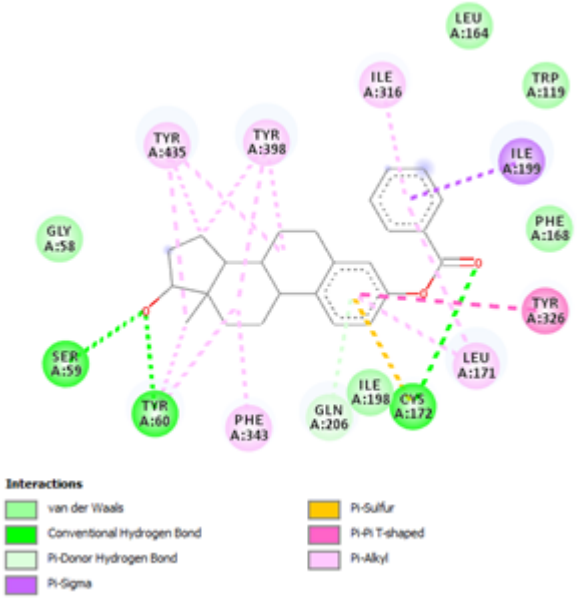


Figure 5.11 2D interaction of the compound ZINC03881345 with Acetyl-cholinesterase (2v5z) in the biding pocket.

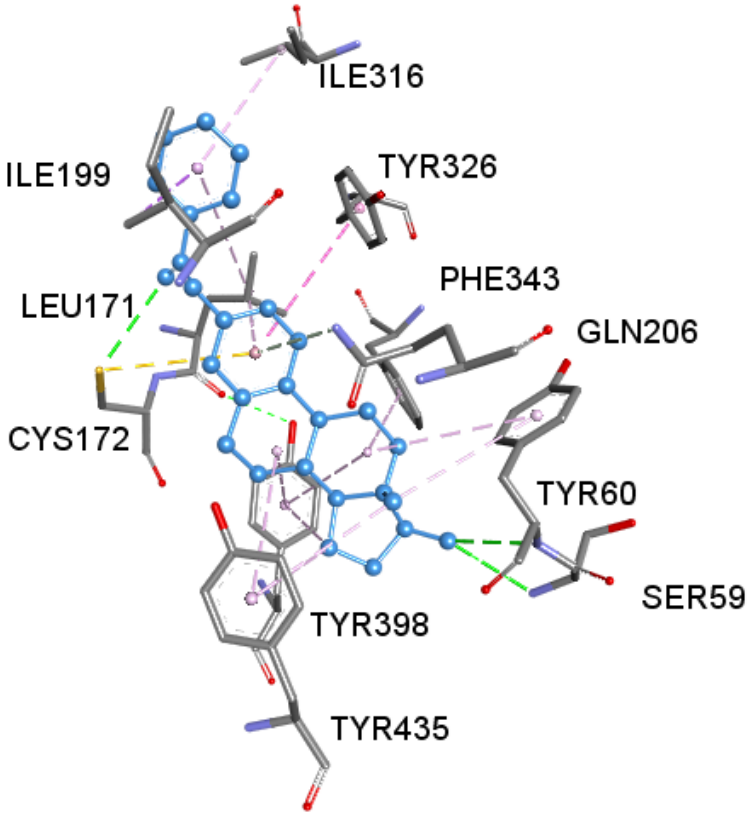


Figure 5.12 3D Interaction between the protein residues and the Binding pocket of Acetyl-cholinesterase (2v5z) and ZINC03881345

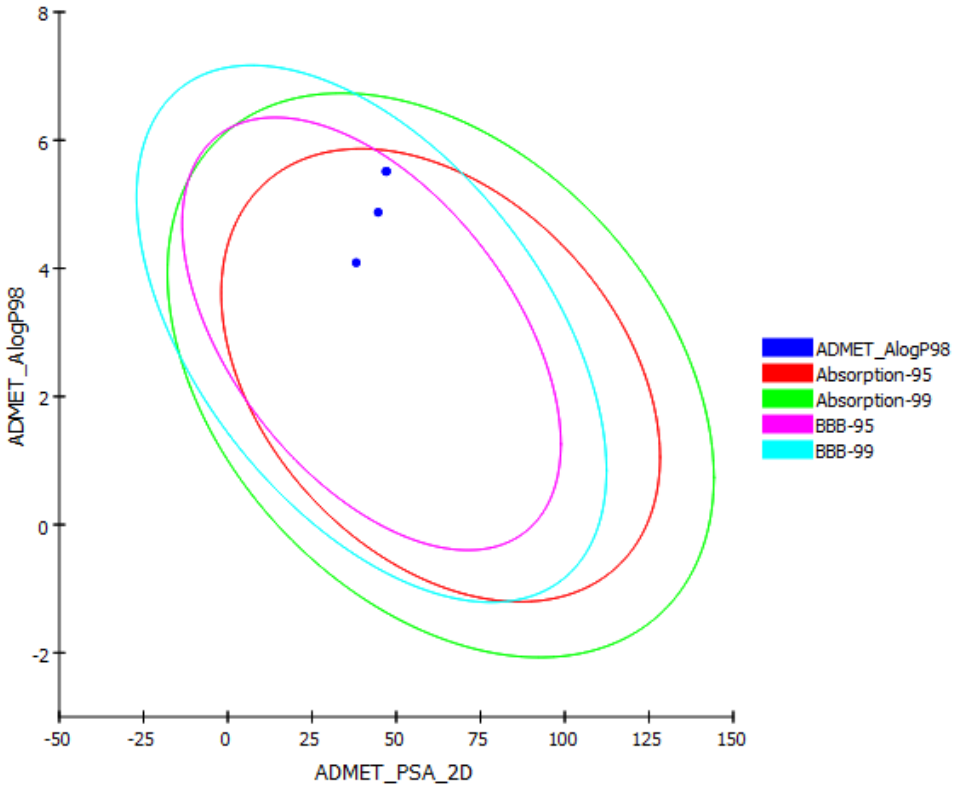


Figure 5.13 Biovia DS ADMET Predication for the three best candidate compound

REFERENCES

A.A., P., C.-U., P. and P.S., M. (2006) 'Transdermal selegiline: The new generation of monoamine oxidase inhibitors', CNS Spectrums.

Abou-Sleiman, P. M., Muqit, M. M. K. and Wood, N. W.(2006) 'Expanding insights of mitochondrial dysfunction in Parkinson's disease', Nature Reviews Neuroscience. doi: 10.1038/nrn1868.

Accelrys: Materials Studio is a Software Environment for Molecular Modeling (2009) 'Dassault Systèmes BIOVIA', Discovery. doi: 10.1099/vir.0.019695-0.

B., T. et al. (2006) 'Predictive factors for thrombosis and major bleeding in an observational study in 181 patients with heparin-induced thrombocytopenia treated with lepirudin', Blood. doi: 10.1182/blood-2006-02-001057 LK - http://resolver.ebscohost.com/openurl?sid=EMBASEissn=00064971id=doi:10.1182%Fblood-2006-02-001057atitle=Predictive+factors+for+thrombosis+and+major+bleeding+in+an+observ induced+thrombocytopenia+treated+with+lepirudinstitle=Bloodtitle=Bloodvolume=10 1496date=2006auinit1=Bauinitm=.

Barajas-Martínez, H. M. et al.(2008) 'Lidocaine-induced brugada syndrome phenotype linked to a novel double mutation in the cardiac sodium channel', Circulation Research. doi: 10.1161/CIRCRESAHA.108.172619.

Barranco Quintana, J. L. et al.(2013) 'Parkinson's Disease and Tea: A Quantitative Review', Journal of the American College of Nutrition. doi: 10.1080/07315724.2009.10719754.

Beattie, V., Collins, B. and McInnes, B.(1997) 'Deep and surface learning: a simple or simplistic dichotomy?', Accounting Education. Taylor Francis Group , 6(1), pp. 1–12. doi: 10.1080/096392897331587.

Berlin, I. et al.(2000) 'Dopaminergic drug response and the genotype (Taq IA polymorphism) of the dopamine D2 receptor', The International Journal of Neuropsychopharmacology, 3(1), p. S1461145700001711. doi: 10.1017/S1461145700001711.

Berthold, M. R. et al.(2009) 'KNIME - the Konstanz information miner (Version 2.0 and Beyond)', ACM SIGKDD Explorations Newsletter. doi: 10.1145/1656274.1656280.

Binda, C. et al. (2007) 'Structures of human monoamine oxidase B complexes with selective noncovalent inhibitors: Safinamide and coumarin analogs', Journal of Medicinal Chemistry. doi: 10.1021/jm070677y.

Chen, X., Ji, Z. L. and Chen, Y. Z.(2002) 'TTD: Therapeutic Target Database', Nucleic Acids Research, 30(1), pp. 412–415. doi: 10.1093/nar/30.1.412.

Cheng, F. et al.(2012) 'AdmetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties', Journal of Chemical Information and Modeling. doi: 10.1021/ci300367a.

Davie, C. A. (2008a) 'A review of Parkinson's disease', British Medical Bulletin. doi: 10.1093/bmb/ldn013.

Davie, C. A.(2008b) 'A review of Parkinson's disease', British Medical Bulletin, 86(1), pp. 109–127. doi: 10.1093/bmb/ldn013.
'Dopamine agonists for restless legs syndrome?' (2011) Drug and Therapeutics Bulletin. doi: 10.1136/dtb.2011.02.0027.

Dror, O. et al.(2009) 'Novel approach for efficient pharmacophore-based virtual screening: Method and applications', Journal of Chemical Information and Modeling. doi: 10.1021/ci900263d.

Engberg, G., Elebring, T. and Nissbrandt, H.(1991) 'Deprenyl (selegiline), a selective MAO-B inhibitor with active metabolites; effects on locomotor activity, dopaminergic neurotransmission and firing rate of nigral dopamine neurons', J Pharmacol Exp Ther.

Gardner, J. (2013) 'A history of deep brain stimulation: Technological innovation and the role of clinical assessment tools', Social Studies of Science. doi: 10.1177/0306312713483678.
Gasser, T. (2005) 'Genetics of Parkinson's disease.', Current opinion in neurology, 18(4), pp. 363–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16003110 (Accessed: 5 May 2019).

Hurtado-Puerto, A. M., Russo, C. and Fregni, F.(2018) 'Alzheimer's disease', in Neuromethods. doi: 10.1007/978-1-4939-7880-9$_9$.

Jankovic, J. (2008) 'Parkinson ' s disease[U+202F]: clinical features and diagnosis Parkinson ' s disease[U+202F]: clinical features and diagnosis', Journal of Neurology Neurosurgery Physiatry. doi: 10.1136/jnnp.2007.131045.

Kalia, L. V and Lang, A. E.(2015) 'Parkinson's disease', The Lancet, 386(9996), pp. 896–912. doi: 10.1016/S0140-6736(14)61393-3.

Kennedy, J. S. et al.(1999) 'Preferential cerebrospinal fluid acetylcholinesterase inhibition by rivastigmine in humans.', Journal of clinical psychopharmacology, 19(6), pp. 513–21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10587286 (Accessed: 5 May 2019).

KENNEDY, S. H. et al. (2006) 'A Trial of Isocarboxazid in the Treatment of Bulimia Nervosa', Journal of Clinical Psychopharmacology. doi: 10.1097/00004714-198812000-00002.

Kryger, G., Silman, I. and Sussman, J. L.(1999) 'Structure of acetylcholinesterase complexed with E2020 (Aricept): Implications for the design of new anti-Alzheimer drugs', Structure. doi: 10.1016/S0969-2126(99)80040-9.

Kvernmo, T., Houben, J. and Sylte, I. (2008) 'Receptor-Binding and Pharmacokinetic Properties of Dopaminergic Agonists', Current Topics in Medicinal Chemistry. doi: 10.2174/156802608785161457.

Lesage, S. and Brice, A. (2009) 'Parkinson's disease: from monogenic forms to genetic susceptibility factors', Human Molecular Genetics, 18(R1), pp. R48–R59. doi: 10.1093/hmg/ddp012.

Li, Y. X. et al.(2007) 'Pharmacokinetics of huperzine A following oral administration to human volunteers', European Journal of Drug Metabolism and Pharmacokinetics. doi: 10.1007/BF03191002.

Mendez, M. F. (2012) 'Early-onset Alzheimer's Disease: Nonamnestic Subtypes and Type 2 AD', Archives of Medical Research. doi: 10.1016/j.arcmed.2012.11.009.

Möller, D. et al.(2017) 'Discovery of G Protein-Biased Dopaminergics with a Pyrazolo[1,5- a]pyridine Substructure', Journal of Medicinal Chemistry. American Chemical Society, 60(7), pp. 2908–2929. doi: 10.1021/acs.jmedchem.6b01857.

Murphy, M. P. and LeVine, H.(2010) 'Alzheimer's Disease and the Amyloid-Peptide', Journal of Alzheimer's Disease. Edited by M. A. Lovell, 19(1), pp. 311–323. doi: 10.3233/JAD-2010-1221.
National Center for Biotechnology Information (2016) '6-CM-H2DCFDA — C27H19Cl3O8 - PubChem', PubChem Compound Database.

National Center of Biotechnology Information(2017) MALACHITE GREEN — C23H25ClN2 - PubChem, PubChem Compound Database. doi: 10.1111/j.1365-2435.2008.01471.x.

Nguyen, P. V. et al. (1999) 'Maturation of Neuromuscular Transmission During Early Development in Zebrafish', Journal of Neurophysiology, 81(6), pp. 2852–2861. doi: 10.1152/jn.1999.81.6.2852.

Nolen, W. A.(2003) '[Classical monoamine oxidase inhibitor: not registered for, but still a place in the treatment of depression].', Nederlands tijdschrift voor geneeskunde, 147(40), pp. 1940–3. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14574774 (Accessed: 5 May 2019).

Nordstrom, A. L. et al. (2008) 'PET analysis of the 5-HT2A receptor inverse agonist ACP-103 in human brain', International Journal of Neuropsychopharmacology. doi: 10.1017/S1461145707007869.

Opare Asamoah Botchway, B. and Iyer, I. C.(2017) 'Alzheimer's Disease – The Past, the Present and the Future', Science Journal of Clinical Medicine. Science Publishing Group, 6(1), p. 1. doi: 10.11648/j.sjcm.20170601.11.

Overington, J. P., Al-Lazikani, B. and Hopkins, A. L. (2006) 'How many drug targets are there?', Nature Reviews Drug Discovery. doi: 10.1038/nrd2199.

Pinder, R. M. et al.(1977) 'Hexoprenaline: A Review of its Pharmacological Properties and Therapeutic Efficacy with Particular Reference to Asthma', Drugs. doi: 10.2165/00003495-197714010-00001.

Preissner, S. et al.(2009) 'SuperCYP: A comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions', Nucleic Acids Research. doi: 10.1093/nar/gkp970.

Samii, A., Nutt, J. G. and Ransom, B. R.(2004) 'Parkinson's disease', The Lancet, 363(9423), pp. 1783–1793. doi: 10.1016/S0140-6736(04)16305-8.

Sanders, M. P. A. et al. (2012) 'From the protein's perspective: The benefits and challenges of protein structure-based pharmacophore modeling', in MedChemComm. doi: 10.1039/c1md00210d.
Schachat, Andrew P., MD; Sadda, SriniVas R., MD; Hinton, David R., MD; Wilkinson, C.P., MD; Wiedemann, Peter, M.(2017) 'Ryan's Retina', in Ryans Retina.

Stoker, T. B., Torsney, K. M. and Barker, R. A. (2018) 'Emerging Treatment Approaches for Parkinson's Disease.', Frontiers in neuroscience. Frontiers Media SA, 12, p. 693. doi: 10.3389/fnins.2018.00693.

Sveinbjornsdottir, S. (2016) 'The clinical symptoms of Parkinson's disease', Journal of Neurochemistry. doi: 10.1111/jnc.13691.

Todd, S. et al.(2013) 'Survival in dementia and predictors of mortality: A review', International Journal of Geriatric Psychiatry. doi: 10.1002/gps.3946.

Trott, O. and Olson, A. J.(2010) 'Software news and update AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading', Journal of Computational Chemistry. doi: 10.1002/jcc.21334.

Wishart, D. S. et al.(2018) 'DrugBank 5.0: A major update to the DrugBank

database for 2018', Nucleic Acids Research. doi: 10.1093/nar/gkx1037.

Zhang, H. Y. and Tang, X. C.(2000) 'Huperzine B, a novel acetylcholinesterase inhibitor, attenuates hydrogen peroxide induced injury in PC12 cells', Neuroscience Letters. doi: 10.1016/S0304-3940(00)01433-6.

Zhou, S.-F. et al.(2009) 'Substrates, Inducers, Inhibitors and Structure-Activity Relationships of Human Cytochrome P450 2C9 and Implications in Drug Development', Current Medicinal Chemistry. doi: 10.2174/092986709789057635.