**RESEARCH ARTICLE**

# *In-silico* Molecular Docking Studies of Methyl Oxadiazole Hybrids Inhibiting Acetylcholinesterase for Alzheimer's Disease Treatment

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***Received: 11th October, 2023; Revised: 13th January, 2024; Accepted: 22nd February, 2024; Available Online: 25th March, 2024***

## ABSTRACT

Memory loss and cognitive decline are the main signs of Alzheimer's disease (AD), a neurodegenerative brain illness that affects millions worldwide. AD is linked to aberrant beta-amyloid, low acetylcholine, oxidative stress, inflammation, and T protein aggregation. Low acetylcholine levels are one of the most important factors in Alzheimer's disease since they are essential for cognitive processing and memory. This is why we've concentrated on ACHEIs and the cholinergic system. We used *in-silico* testing to find new and effective oxadiazole acetylcholinesterase inhibitors. This study created, docked, and predicted numerous novel oxadiazole scaffolds to find Alzheimer's disease cholinesterase inhibitors. Offline tools like Protein Data Bank for PBD protein file downloads and Marvin Sketch for chemical structure representation enhance internet resources like PubChem, Swiss ADMET, and PyRx 0.9 for molecular docking research. We used Swiss Protein Data Bank Viewer for protein synthesis and https://plip-tool.biotec.plip.index.html for active site pocket prediction. Study results suggest 108 oxadiazole hybrids were used. Most compounds had zero or one Lipinski rule of five (RO5) violation. ADME research shows that all of these medicines have perfect pharmacokinetic features, including blood-brain barrier penetration. The docking tests demonstrate that our compounds have high target receptor binding energies of 8.1 to 12.3 kcal/mol. Similar to donepezil (12.76 K/cal), 2, 19, and 36 had 12 kcal/mol binding energies, 4, 11, and 32 had 11.5 kcal/mol, while compound 18 had 12.7 kcal/mol. Finally, our medications highly react with amino acid residues like Arg393, Arg525, Ala528 Asp400, and others. This binding approach is similar to donepezil, the gold standard. ADMET projections suggest these medications will have safer toxicological and pharmacokinetic profiles. The research aims to produce innovative AChE medications that restore brain acetyl choline levels, relieve Alzheimer's disease symptoms and promote cognitive development.

**Keywords:** Alzheimer's disease, Oxadiazole derivatives, Acetylcholinesterase, Molecular docking, Pharmacokinetic studies, Inhibitory activity.

International Journal of Pharmaceutical Quality Assurance (2024); DOI: 10.25258/ijpqa.15.1.63

**How to cite this article:** Magesh M, Gandhimathi R. *In-silico* Molecular Docking Studies of Methyl Oxadiazole Hybrids Inhibiting Acetylcholinesterase for Alzheimer's Disease Treatment. International Journal of Pharmaceutical Quality Assurance. 2024;15(1):403-413.

**Source of support:** Nil.

**Conflict of interest:** None

## INTRODUCTION

Cognitive decline and memory loss result from Alzheimer's disease (AD). AD has no effective treatment, maybe due to its unclear source.[1] AD is characterized by extracellular amyloid-beta (A) plaque, neurofibrillary tangles, gliosis, synapse loss, and inflammation. There are several explanations. There are various Alzheimer's theories[2] Several ideas have been proposed, such as the β-amyloid hypothesis, oligomer hypothesis, tau hypothesis, $Ca^{2+}$ dysregulation theory, presenilin hypothesis, and lysosome hypothesis.[3-4] AD requires low acetylcholine. Esterase inhibitors can optimize acetylcholine levels to prevent deterioration.[5] Excess A-amyloid peptides may cause synaptotoxicity, neurotoxicity, and neurodegeneration, such as amyloid plaques. Inflammation and neurodegenerative diseases like Alzheimer's are linked to CaSR imbalance.[6] Variations in presenilin genes, which catalyze -secretase, enhance AD risk. Presenilins cut APP. Finally, lysosome theory argues that autophagy-lysosomal pathway problems result from mutations in pH genes.[7-8] The illness is linked to AChE and BChE. They increase neurotoxicity by accelerating Alzheimer's-like A peptide aggregation formation.[9] AD patients have low acetylcholine, abnormal amyloid, T protein aggregation, inflammation, and oxidative stress. The majority of Alzheimer's disease research today targets AChE inhibitors.[10]

Acetylcholinesterase is type-B carboxylesterase. Common carboxylesterase type B ancestor. This serine hydrolase degrades acetylcholine and choline esters.[11-12] Skeletal muscle,

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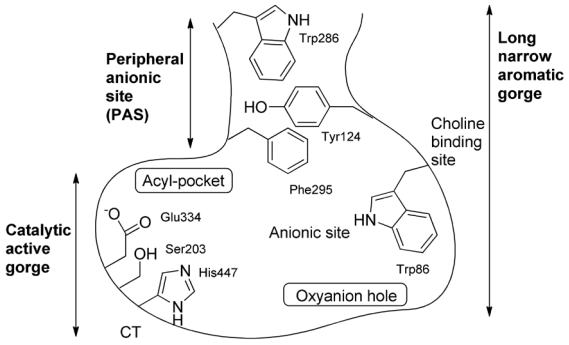



**Figure 1:** Representation of AChE's binding site

neurons, and hematopoietic cells produce acetylcholinesterase (AChE), a powerful enzyme, due to its rapid catalysis. Acetylcholinesterase needs three amino acids—Glu334, His447, and Ser203—to catalyze its 20-angstrom active site. A Tyr33712-bounding site is outside. Either can contain AChE inhibitors. Kinetic studies demonstrate that AChE has two active sites: an acidic catalytic machinery site and an anionic choline-binding pocket site. The catalytic triad (Ser203, Glu334, and His447) converts acetylcholine to acetate and choline at the ecstatic site.[13] Although other serine proteases have serine and histidine, their third amino acid residue is often aspartate. The catalytic triad of AChE is oppositely chiral to other proteases. A nucleophilic water molecule and histidine attack the acyl-enzyme to release choline and the enzyme. Acetic acid, the independent enzyme, acetylcholine's positive quaternary amine, and cation substrates and inhibitors make up the c process's anionic site. The research identified lipophilic, apolar anionic active site aromatic compounds.[14,15]

Active regions of most human AChE isoforms include the acyl binding pocket, omega loop, oxyanion hole, mid-aromatic gorge, and catalytic triad (CT) comprising Ser203, Glu334, and His447 (Figure 1). Acetylcholinesterase inhibitors work influences their irreversibility, pseudo-irreversibility, or reversibility.[16-18]

The treatment of protozoan and neurological illnesses calls for the development of novel therapeutic scaffolds based on oxadiazoles. Oxadiazole compounds have a wide range of therapeutic uses, including antimalarial, antitrypanosomal, antibacterial, antiviral, anticancer, antileishmanial, and anti-prion medications. It is also informed to act against AD, inflammatory disorders, and diabetes mellitus. Recent research has demonstrated that anti-TDP-43 aggregation is advantageous in ALS disease models. Oxadiazole derivatives may be the most productive source of new hybrid and dimeric multitarget lead and therapeutic potential. It is widely known that oxadiazole compounds have the potential to inhibit acetylcholinesterase and acetylcholine dehydrogenase. This research initiative aims to discover innovative drug-like compounds that block the acetylcholinesterase enzyme as potential Alzheimer's disease treatments.[19,20] We developed and evaluated a variety of oxadiazoles for this inquiry when keeping in attention the importance of these analogs. To develop a potent inhibitor of the AChE enzyme, we set out to model a variety of potential candidates (Table 1). Then, using computer docking techniques, the mode of interaction between these substances and the active area of AChE was investigated.

## MATERIALS AND METHODS

### Devices and Materials

Docking is often utilized in modern drug research to explore the interaction between the desired lead chemical substance, its protein receptors, and the targeted ligand receptor. The investigation was conducted electronically using computational techniques. We employ the programs like Protein Data Bank (accessible at public domain websites like www.rcsb.org/pdb) and Marvin sketch for depicting chemical structures in addition to internet resources. and PyRx V0.9 served as a platform for Auto dock vina.[21]

### Preparation of Protein

With the help of the offline software RCSB.com, we have AChE (PDB: 4EY6 Resolution 2.40A). After crystallization, we improved the protein's energy by supplying the missing hydrogens, protonating, ionizing, and adjusting its charge. The energy budget was made as efficient as possible with the Swiss-PDB Viewer.

### Active Site Identification

Active site pocket was determined atplip-tool is a technique for locating proteins that contain useful amino acids. There is a Google offline tool. Based on this, we deduced the protein's activation status.

### Ligand Preparation

Using the Marvin sketch tool, the molecules are created in both 2D and 3D. The compound was drawn, optimized in three dimensions in Marvin Sketch, and saved as SDF formate.

### ADMET Prediction *In-silico*

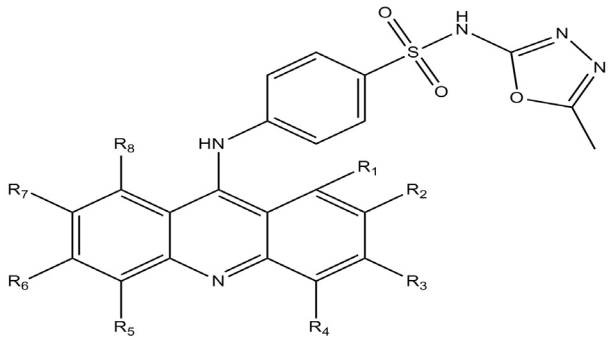
Swiss ADME prediction, a computer tool, was used to estimate the ADME properties of potential medications. We determined the TPSA, count of H bond acceptors (n-ON), number of H bond donors (n-OHNH), CNS activity, proportion of oral absorption by people, distribution constant of the molecule in 1-octanol in water, and number of n-ON and n-OHNH hydrogen bond acceptor and donor sites. The information provided here can be used to better understand the ADME characteristics of any medicine or synthetic compound. Additionally, it was discovered that there were pharmacological parallels, violations of the thumb rule (RO5), and breaches of the three-to-one rule. A particular molecule should possess five ideal qualities including MW of 500, a count of 5 H bond donors, and a count of 10 H bond acceptors.[22-23]

## RESULTS AND DISCUSSION

### *In-silico* Molecular Docking Studies

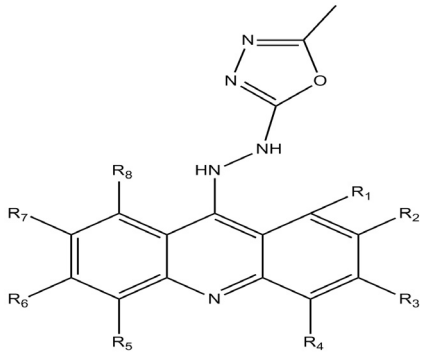
Totally 108 oxadiazole scaffolds used in our study were created after a review of the literature on oxadiazole derivative research and docking studies. PyRx V0.9 has been applied for

**Table 1:** Designed oxadiazole derivatives



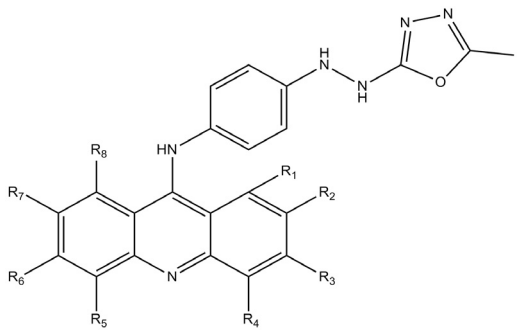

| *Compounds* | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | $R_8$ |
|---|---|---|---|---|---|---|---|---|
| 1. | H | $CH_3$ | H | H | H | H | H | H |
| 2. | H | H | $CH_3$ | H | H | H | H | H |
| 3. | H | H | H | $CH_3$ | H | H | H | H |
| 4. | H | $OCH_3$ | H | H | H | H | H | H |
| 5. | H | H | $OCH_3$ | H | H | H | H | H |
| 6. | H | H | H | $OCH_3$ | H | H | H | H |
| 7. | H | H | H | H | H | $OCH_3$ | H | H |
| 8. | H | H | H | H | H | H | H | H |
| 9. | H | H | $NH_2$ | H | H | H | H | H |
| 10. | H | H | H | H | H | $NH_2$ | H | H |
| 11. | H | H | Cl | H | H | H | H | H |
| 12. | H | H | H | Cl | H | H | H | H |
| 13. | H | H | H | H | H | Cl | H | H |
| 14. | H | H | H | H | H | H | Cl | H |
| 15. | H | H | H | H | OH | H | H | H |
| 16. | H | H | H | H | H | OH | H | H |
| 17. | H | $CH_3$ | $CH_3$ | H | H | H | H | H |
| 18. | H | H | $CH_3$ | $CH_3$ | H | H | H | H |
| 19. | H | $CH_3$ | H | $CH_3$ | H | H | H | H |
| 20. | H | $OCH_3$ | $OCH_3$ | H | H | H | H | H |
| 21. | H | H | $OCH_3$ | $OCH_3$ | H | H | H | H |
| 22. | H | $OCH_3$ | H | $OCH_3$ | H | H | H | H |
| 23. | H | H | H | $OCH_3$ | H | $OCH_3$ | H | H |
| 24. | H | H | H | H | H | $OCH_3$ | $OCH_3$ | H |
| 25. | H | $OCH_3$ | H | H | H | H | $OCH_3$ | H |
| 26. | H | $OCH_3$ | H | H | H | $OCH_3$ | H | H |
| 27. | H | H | $OCH_3$ | H | H | H | $OCH_3$ | H |
| 28. | H | H | $OCH_3$ | H | H | $OCH_3$ | H | H |
| 29. | H | H | H | $OCH_3$ | H | $OCH_3$ | H | H |
| 30. | H | H | H | $OCH_3$ | H | H | $OCH_3$ | H |
| 31. | H | H | Cl | Cl | H | H | H | H |
| 32. | H | H | H | Cl | H | Cl | H | H |
| 33. | H | H | H | H | H | Cl | Cl | H |
| 34. | H | H | H | Cl | H | H | Cl | H |
| 35. | H | H | $NH_2$ | H | H | $NH_2$ | H | H |
| 36. | H | H | H | H | OH | OH | H | H |

Cont...




| *Compounds* | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | $R_8$ |
|---|---|---|---|---|---|---|---|---|
| 37. | H | $CH_3$ | H | H | H | H | H | H |
| 38. | H | H | $CH_3$ | H | H | H | H | H |
| 39. | H | H | H | $CH_3$ | H | H | H | H |
| 40. | H | $OCH_3$ | H | H | H | H | H | H |
| 41. | H | H | $OCH_3$ | H | H | H | H | H |
| 42. | H | H | H | $OCH_3$ | H | H | H | H |
| 43. | H | H | H | H | H | $OCH_3$ | H | H |
| 44. | H | H | H | H | H | H | H | H |
| 45. | H | H | $NH_2$ | H | H | H | H | H |
| 46. | H | H | H | H | H | $NH_2$ | H | H |
| 47. | H | H | Cl | H | H | H | H | H |
| 48. | H | H | H | Cl | H | H | H | H |
| 49. | H | H | H | H | H | Cl | H | H |
| 50. | H | H | H | H | H | H | Cl | H |
| 51. | H | H | H | H | OH | H | H | H |
| 52. | H | H | H | H | H | OH | H | H |
| 53. | H | $CH_3$ | $CH_3$ | H | H | H | H | H |
| 54. | H | H | $CH_3$ | $CH_3$ | H | H | H | H |
| 55. | H | $CH_3$ | H | $CH_3$ | H | H | H | H |
| 56. | H | $OCH_3$ | $OCH_3$ | H | H | H | H | H |
| 57. | H | H | $OCH_3$ | $OCH_3$ | H | H | H | H |
| 58. | H | $OCH_3$ | H | $OCH_3$ | H | H | H | H |
| 59. | H | H | H | $OCH_3$ | H | $OCH_3$ | H | H |
| 60. | H | H | H | H | H | $OCH_3$ | $OCH_3$ | H |
| 61. | H | $OCH_3$ | H | H | H | H | $OCH_3$ | H |
| 62. | H | $OCH_3$ | H | H | H | $OCH_3$ | H | H |
| 63. | H | H | $OCH_3$ | H | H | H | $OCH_3$ | H |
| 64. | H | H | $OCH_3$ | H | H | $OCH_3$ | H | H |
| 65. | H | H | H | $OCH_3$ | H | $OCH_3$ | H | H |
| 66. | H | H | H | $OCH_3$ | H | H | $OCH_3$ | H |
| 67. | H | H | Cl | Cl | H | H | H | H |
| 68. | H | H | H | Cl | H | Cl | H | H |
| 69. | H | H | H | H | H | Cl | Cl | H |
| 70. | H | H | H | Cl | H | H | Cl | H |
| 71. | H | H | $NH_2$ | H | H | $NH_2$ | H | H |
| 72. | H | H | H | H | OH | OH | H | H |

Cont...




| *Compounds* | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | $R_8$ |
|---|---|---|---|---|---|---|---|---|
| 73. | H | $CH_3$ | H | H | H | H | H | H |
| 74. | H | H | $CH_3$ | H | H | H | H | H |
| 75. | H | H | H | $CH_3$ | H | H | H | H |
| 76. | H | $OCH_3$ | H | H | H | H | H | H |
| 77. | H | H | $OCH_3$ | H | H | H | H | H |
| 78. | H | H | H | $OCH_3$ | H | H | H | H |
| 79. | H | H | H | H | H | $OCH_3$ | H | H |
| 80. | H | H | H | H | H | H | H | H |
| 81. | H | H | $NH_2$ | H | H | H | H | H |
| 82. | H | H | H | H | H | $NH_2$ | H | H |
| 83. | H | H | Cl | H | H | H | H | H |
| 84. | H | H | H | Cl | H | H | H | H |
| 85. | H | H | H | H | H | Cl | H | H |
| 86. | H | H | H | H | H | H | Cl | H |
| 87. | H | H | H | H | OH | H | H | H |
| 88. | H | H | H | H | H | OH | H | H |
| 89. | H | $CH_3$ | $CH_3$ | H | H | H | H | H |
| 90. | H | H | $CH_3$ | $CH_3$ | H | H | H | H |
| 91. | H | $CH_3$ | H | $CH_3$ | H | H | H | H |
| 92. | H | $OCH_3$ | $OCH_3$ | H | H | H | H | H |
| 93. | H | H | $OCH_3$ | $OCH_3$ | H | H | H | H |
| 94. | H | $OCH_3$ | H | $OCH_3$ | H | H | H | H |
| 95. | H | H | H | $OCH_3$ | H | $OCH_3$ | H | H |
| 96. | H | H | H | H | H | $OCH_3$ | $OCH_3$ | H |
| 97. | H | $OCH_3$ | H | H | H | H | $OCH_3$ | H |
| 98. | H | $OCH_3$ | H | H | H | $OCH_3$ | H | H |
| 99. | H | H | $OCH_3$ | H | H | H | $OCH_3$ | H |
| 100. | H | H | $OCH_3$ | H | H | $OCH_3$ | H | H |
| 101. | H | H | H | $OCH_3$ | H | $OCH_3$ | H | H |
| 102. | H | H | H | $OCH_3$ | H | H | $OCH_3$ | H |
| 103. | H | H | Cl | Cl | H | H | H | H |
| 104. | H | H | H | Cl | H | Cl | H | H |
| 105. | H | H | H | H | H | Cl | Cl | H |
| 106. | H | H | H | Cl | H | H | Cl | H |
| 107. | H | H | $NH_2$ | H | H | $NH_2$ | H | H |
| 108. | H | H | H | H | OH | OH | H | H |

molecular docking to predict the potential interactions between the protein and its inhibitors. Acetylcholinesterase's binding mechanism competency with 108 oxadiazole compounds was investigated using molecular docking. The synthetic ligand was attached close to the protein molecules. For our designed drugs, docking values between 8 and 12 kcal/mol indicated a suitable affinity for binding with a target receptor.

The synthetic molecules were subjected to docking studies along with donepezil, the reference drug, and the natural ligand. With docking values ranging from 8.1 to 12.3 kcal/mol, Table 2 demonstrates that proposed drugs have considerable binding energies with the target receptor. The binding energies of molecules 1, 19, and 36 were 12 kcal/mol. The docking results for compounds 3, 12, and 33 (11.5 K/cal) and compound 18 are comparable to those for donepezil (12.76 K/cal). The leftover molecule's activity is superior to that of normal medications and ranges from good to moderate. The ligand-binding domain of human AChE inhibitors' critical amino acids has also been identified. The AChE inhibitor ligand-binding domain's non-covalent interactions with the analyzed ligands were determined. Active site pockets of AChEI in an enzyme and specific amino acid residues that have frequently remained linked to an active site were detected. These amino acids have been demonstrated to frequently interact with AChE inhibitors and play a key role in inhibiting the enzyme acetylcholinesterase. Hydrogen bonds, van der Waals forces, and columbic forces are only a few examples of the non-covalent interactions seen in Figures 2 to 10.

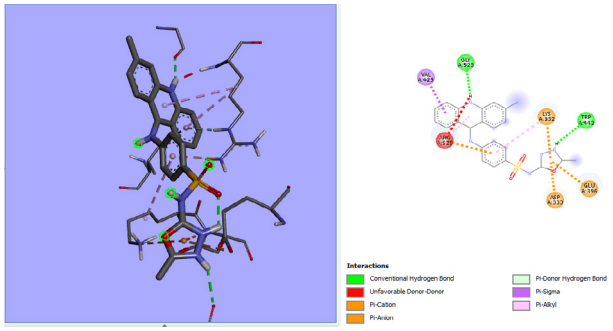



**Figure 2:** Molecular view of the interaction between compound 2 with the active site of AChE protein (4EY6)

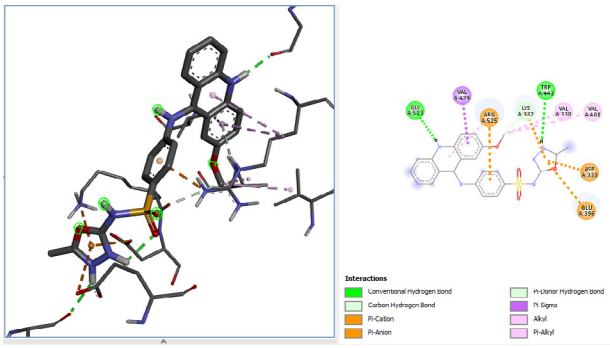



**Figure 3:** Molecular view of the interaction between compound 4 with the active site of AChE protein (4EY6)

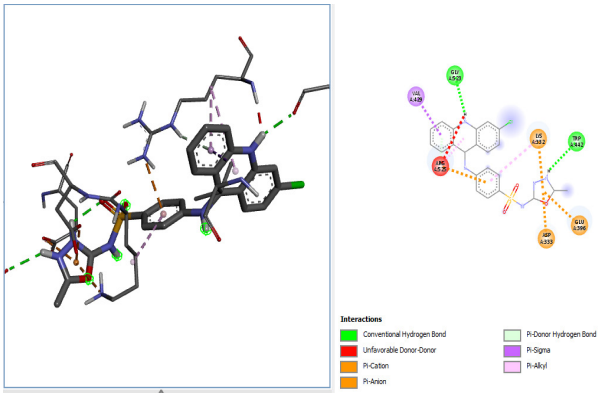



**Figure 4:** Molecular view of the interaction between compound 11 with the active site of AChE protein (4EY6)

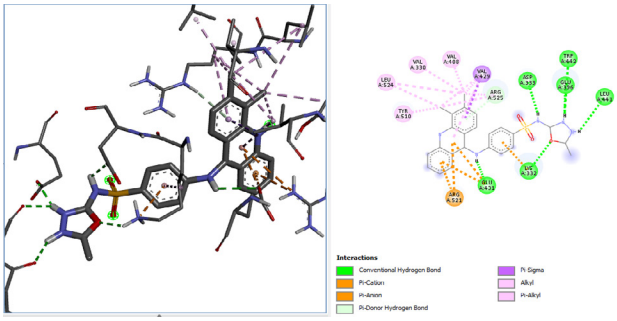



**Figure 5:** Molecular view of the interaction between compound 18 with the active site of AChE protein (4EY6)

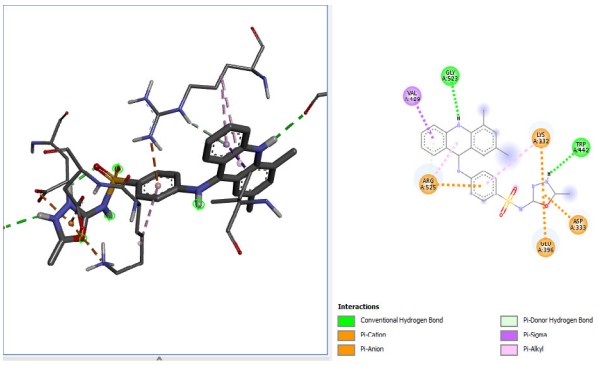



**Figure 6:** Molecular view of the interaction between compound 19 with the active site of AChE protein(4EY6)

## *In-silico* Admet Studies

SWISS ADME is a platform where we investigated the designed ligands' pharmacokinetic characteristics. The recommended molecules range in MW from 225.25 to 481. There were found to be 1 to 4 hydrogen bond donors are present in the designed compounds. Almost all the designed molecules have hydrogen bond acceptors within a range of 1-5, but rarely few molecules contain 6. The predicted gastric absorption rate of designed compounds was also found to be good except few. The topological polar surface area (TPSA) is important when

**Table 2:** designed compound docking score

| *Ligand* | *Binding affinity (Kcal/Mole)* | *Ligand* | *Binding affinity (Kcal/Mole)* | *Ligand* | *Binding affinity (Kcal/Mole)* | *Ligand* | *Binding affinity (Kcal/Mole)* |
|---|---|---|---|---|---|---|---|
| 1 | -10 | 28 | -10.4 | 55 | -9.2 | 82 | -10.3 |
| 2 | -12 | 29 | -11.3 | 56 | -8.1 | 83 | -10.3 |
| 3 | -11.1 | 30 | -10.1 | 57 | -8.5 | 84 | -10.2 |
| 4 | -11.5 | 31 | 10.9 | 58 | -8.3 | 85 | -10.3 |
| 5 | -10.9 | 32 | -11.4 | 59 | -8.4 | 86 | -10.3 |
| 6 | -11.4 | 33 | -11.5 | 60 | -8 | 87 | -10.5 |
| 7 | -10.8 | 34 | -11.3 | 61 | -8 | 88 | -10.7 |
| 8 | -10.5 | 35 | -11.7 | 62 | -8.5 | 89 | -10.2 |
| 9 | -11 | 36 | -12.1 | 63 | -8.5 | 90 | -10.2 |
| 10 | -11.4 | 37 | -8.8 | 64 | -8.1 | 91 | -10.8 |
| 11 | -11.5 | 38 | -8.9 | 65 | -8.3 | 92 | -9.6 |
| 12 | 10.3 | 39 | 11.5 | 66 | -8.6 | 93 | -9.5 |
| 13 | -11.4 | 40 | -8.7 | 67 | -8.5 | 94 | -10.1 |
| 14 | -11.4 | 41 | -8.5 | 68 | -8.7 | 95 | -10 |
| 15 | -11.1 | 42 | -8.4 | 69 | -8.6 | 96 | -9.6 |
| 16 | -11.4 | 43 | -8.5 | 70 | -8.6 | 97 | -9.6 |
| 17 | -12 | 44 | -8.7 | 71 | -8.4 | 98 | -9.3 |
| 18 | -12.7 | 45 | -8.5 | 72 | -9 | 99 | -9.2 |
| 19 | -12.3 | 46 | -8.4 | 73 | -10.6 | 100 | -9.5 |
| 20 | -10.7 | 47 | -8.5 | 74 | -10.4 | 101 | -10 |
| 21 | -11.1 | 48 | -8.7 | 75 | -10.4 | 102 | -9.7 |
| 22 | -11 | 49 | -8.5 | 76 | -10.3 | 103 | -10.3 |
| 23 | -10.9 | 50 | -8.8 | 77 | -9.6 | 104 | -10.4 |
| 24 | -10.7 | 51 | -8.7 | 78 | -9.9 | 105 | -10.1 |
| 25 | -11.1 | 52 | -8.5 | 79 | -9.6 | 106 | -10.6 |
| 26 | -10.9 | 53 | -9.3 | 80 | -9.6 | 107 | -10.6 |
| 27 | -10.7 | 54 | -9.3 | 81 | -10.3 | 108 | -11.1 |
| 109 Standard (Donepezil) | | | -12.76Kcal/Mole | | | | |

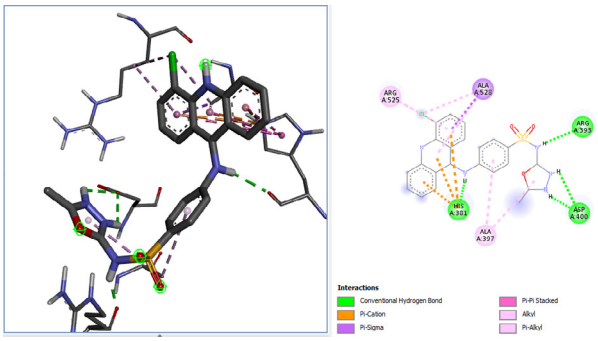



**Figure 7:** Molecular view of the interaction between compound 32 with the active site of AChE protein (4EY6)

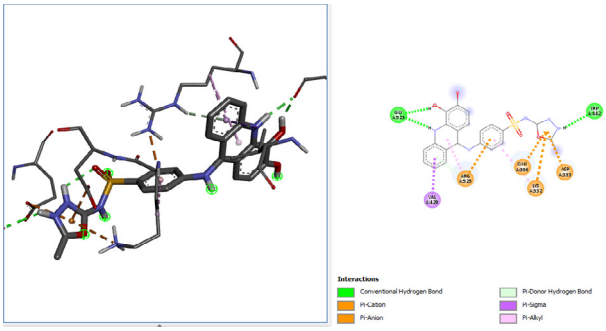



**Figure 8:** Molecular view of the interaction between compound 36 with the active site of AChE protein (4EY6)

crossing the blood-brain barrier (BBB). The TPSA values of our compounds were in a satisfactory range, indicating almost all the molecules can easily cross the blood-brain barrier. Meanwhile the, acetylcholinesterase inhibitors are used to treat and manage Alzheimer's disease they have to cross the blood-brain barrier readily. Our designed molecules have been found to have excellent BBB penetrability. It was predicted that there would be one to three possible metabolic processes and that the 1-octyl alcohol and water partition coefficient would range between 2.5 and 3. The five-rule of Lipinski was upheld.

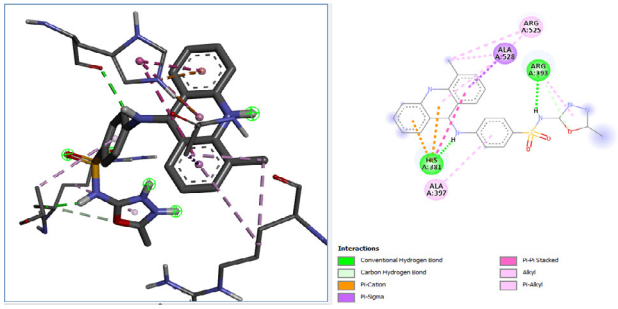


**Figure 9:** Molecular view of the interaction between compound 39 with the active site of AChE protein (4EY6)

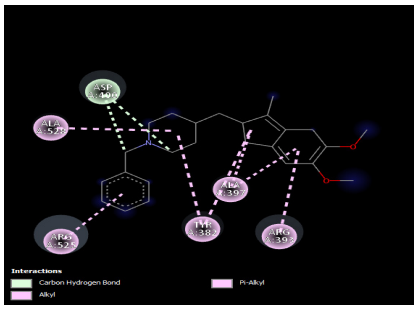


**Figure 10:** 2D view of the interaction between standard donepezil with the active site of AChE protein (4EY6)

**Table 3:** *In-silico* ADMET properties of designed compounds

| *Code* | *MW* | *H-bond acceptors* | *H-bond donors* | *GI absorption* | *TPSA* | *iLog P* | *Lipinski violations* | *BBB permeant* |
|---|---|---|---|---|---|---|---|---|
| 1 | 459.51 | 5 | 2 | Low | 65.5 | 2.85 | 0 | Yes |
| 2 | 459.51 | 5 | 2 | Low | 65.5 | 3 | 0 | Yes |
| 3 | 459.51 | 5 | 2 | Low | 65.5 | 3.08 | 0 | Yes |
| 4 | 475.51 | 6 | 2 | Low | 74.73 | 2.69 | 0 | Yes |
| 5 | 475.51 | 6 | 2 | Low | 74.73 | 3.11 | 0 | Yes |
| 6 | 475.51 | 6 | 2 | Low | 74.73 | 2.96 | 0 | Yes |
| 7 | 475.51 | 6 | 2 | Low | 74.73 | 3.11 | 0 | Yes |
| 8 | 475.51 | 6 | 2 | Low | 64.73 | 2.69 | 0 | Yes |
| 9 | 460.49 | 5 | 3 | Low | 61.52 | 2.24 | 0 | Yes |
| 10 | 460.49 | 5 | 3 | Low | 61.52 | 2.24 | 0 | Yes |
| 11 | 479.92 | 5 | 2 | Low | 65.5 | 2.82 | 0 | Yes |
| 12 | 479.92 | 5 | 2 | Low | 65.5 | 2.93 | 0 | Yes |
| 13 | 479.92 | 5 | 2 | Low | 65.5 | 2.82 | 0 | Yes |
| 14 | 479.92 | 5 | 2 | Low | 65.5 | 2.73 | 0 | Yes |
| 15 | 461.48 | 6 | 3 | Low | 65.73 | 2.81 | 0 | Yes |
| 16 | 461.48 | 6 | 3 | Low | 65.73 | 2.38 | 0 | Yes |
| 17 | 489.53 | 6 | 3 | Low | 65.73 | 3.1 | 0 | Yes |
| 18 | 489.53 | 6 | 3 | Low | 65.73 | 2.73 | 0 | Yes |
| 19 | 489.53 | 6 | 3 | Low | 65.73 | 2.75 | 0 | Yes |
| 20 | 521.53 | 8 | 3 | Low | 64.19 | 2.69 | 1 | Yes |
| 21 | 521.53 | 8 | 3 | Low | 64.19 | 2.99 | 1 | Yes |
| 22 | 521.53 | 8 | 3 | Low | 64.19 | 2.7 | 1 | Yes |
| 23 | 505.53 | 7 | 2 | Low | 63.96 | 3.17 | 0 | Yes |
| 24 | 505.53 | 7 | 2 | Low | 63.96 | 2.71 | 0 | Yes |
| 25 | 505.53 | 7 | 2 | Low | 63.96 | 3.47 | 0 | Yes |
| 26 | 505.53 | 7 | 2 | Low | 63.96 | 3.43 | 0 | Yes |
| 27 | 505.53 | 7 | 2 | Low | 63.96 | 3.43 | 0 | Yes |
| 28 | 505.53 | 7 | 2 | Low | 63.96 | 3.34 | 0 | Yes |
| 29 | 505.53 | 7 | 2 | Low | 63.96 | 3.17 | 0 | Yes |
| 30 | 505.53 | 7 | 2 | Low | 63.96 | 3.18 | 0 | Yes |
| 31 | 505.37 | 5 | 2 | Low | 65.5 | 2.84 | 0 | Yes |
| 32 | 514.37 | 5 | 2 | Low | 65.5 | 3.18 | 0 | Yes |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 33 | 514.37 | 5 | 2 | Low | 65.5 | 2.9 | 0 | Yes |
| 34 | 514.37 | 5 | 2 | Low | 65.5 | 3.09 | 0 | Yes |
| 35 | 475.51 | 5 | 4 | Low | 67.54 | 2 | 0 | Yes |
| 36 | 478.48 | 7 | 4 | Low | 65.96 | 2.46 | 0 | Yes |
| 37 | 238.27 | 2 | 2 | High | 50.94 | 1.98 | 0 | Yes |
| 38 | 254.27 | 3 | 2 | High | 60.17 | 2.06 | 0 | Yes |
| 39 | 254.27 | 3 | 2 | High | 60.17 | 2.21 | 0 | Yes |
| 40 | 254.27 | 3 | 2 | High | 60.17 | 1.8 | 0 | Yes |
| 41 | 254.27 | 3 | 2 | High | 60.17 | 2.21 | 0 | Yes |
| 42 | 258.69 | 2 | 2 | High | 50.94 | 2.12 | 0 | Yes |
| 43 | 258.69 | 2 | 2 | High | 50.94 | 2.18 | 0 | Yes |
| 44 | 258.69 | 2 | 2 | High | 50.94 | 2.24 | 0 | Yes |
| 45 | 239.25 | 3 | 3 | High | 71.17 | 1.84 | 0 | Yes |
| 46 | 240.25 | 3 | 3 | High | 71.17 | 1.65 | 0 | Yes |
| 47 | 252.3 | 2 | 2 | High | 50.94 | 2.19 | 0 | Yes |
| 48 | 252.3 | 2 | 2 | High | 50.94 | 2.33 | 0 | Yes |
| 49 | 284.3 | 4 | 2 | High | 69.4 | 2.19 | 0 | Yes |
| 50 | 284.3 | 4 | 2 | High | 69.4 | 2.32 | 0 | Yes |
| 51 | 284.3 | 4 | 2 | High | 69.4 | 2.43 | 0 | Yes |
| 52 | 284.3 | 4 | 2 | High | 69.4 | 2.31 | 0 | Yes |
| 53 | 284.3 | 4 | 2 | High | 69.4 | 2.19 | 0 | Yes |
| 54 | 284.3 | 4 | 2 | High | 69.4 | 2.42 | 0 | Yes |
| 55 | 284.3 | 4 | 2 | High | 69.4 | 2.5 | 0 | Yes |
| 56 | 284.3 | 4 | 2 | High | 69.4 | 2.5 | 0 | Yes |
| 57 | 284.3 | 4 | 2 | High | 69.4 | 2.46 | 0 | Yes |
| 58 | 284.3 | 4 | 2 | High | 69.4 | 2.31 | 0 | Yes |
| 59 | 284.3 | 4 | 2 | High | 69.4 | 2.18 | 0 | Yes |
| 60 | 284.14 | 2 | 2 | High | 50.94 | 2.2 | 0 | Yes |
| 61 | 293.14 | 2 | 2 | High | 50.94 | 2.31 | 0 | Yes |
| 62 | 293.14 | 2 | 2 | High | 50.94 | 2.24 | 0 | Yes |
| 63 | 254.28 | 2 | 4 | High | 102.98 | 1.06 | 0 | Yes |
| 64 | 256.25 | 4 | 4 | High | 91.4 | -0.34 | 0 | Yes |
| 65 | 314.37 | 1 | 2 | High | 36.95 | 3.2 | 0 | Yes |
| 66 | 314.37 | 1 | 2 | High | 36.95 | 3.23 | 0 | Yes |
| 67 | 314.37 | 1 | 2 | High | 36.95 | 3.23 | 0 | Yes |
| 68 | 330.37 | 2 | 2 | High | 46.18 | 3.11 | 0 | Yes |
| 69 | 330.37 | 2 | 2 | High | 46.18 | 3.27 | 0 | Yes |
| 70 | 330.37 | 2 | 2 | High | 46.18 | 3.07 | 0 | Yes |
| 71 | 330.37 | 2 | 2 | High | 46.18 | 3.27 | 0 | Yes |
| 72 | 330.37 | 2 | 2 | High | 46.18 | 3.11 | 0 | Yes |
| 73 | 315.36 | 1 | 3 | High | 62.97 | 2.61 | 0 | Yes |
| 74 | 315.36 | 1 | 3 | High | 62.97 | 2.61 | 0 | Yes |
| 75 | 334.79 | 1 | 2 | High | 36.95 | 3.23 | 1 | Yes |
| 76 | 334.79 | 1 | 2 | High | 36.95 | 3.05 | 1 | Yes |
| 77 | 334.79 | 1 | 2 | High | 36.95 | 3.23 | 1 | Yes |
| 78 | 334.79 | 1 | 2 | High | 36.95 | 3.23 | 1 | Yes |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 79 | 316.34 | 2 | 3 | High | 57.18 | 2.97 | 0 | Yes |
| 80 | 316.34 | 2 | 3 | High | 57.18 | 2.58 | 0 | Yes |
| 81 | 328.4 | 1 | 2 | High | 36.95 | 3.4 | 1 | Yes |
| 82 | 328.4 | 1 | 2 | High | 36.95 | 3.37 | 1 | Yes |
| 83 | 328.4 | 1 | 2 | High | 36.95 | 3.34 | 1 | Yes |
| 84 | 360.39 | 3 | 2 | High | 55.41 | 3.37 | 0 | Yes |
| 85 | 360.39 | 3 | 2 | High | 55.41 | 3.37 | 0 | Yes |
| 86 | 345.39 | 3 | 2 | High | 55.41 | 3.39 | 0 | Yes |
| 87 | 360.39 | 3 | 2 | High | 55.41 | 3.42 | 0 | Yes |
| 88 | 360.39 | 3 | 2 | High | 55.41 | 3.37 | 0 | Yes |
| 89 | 360.39 | 3 | 2 | High | 55.41 | 3.54 | 0 | Yes |
| 90 | 360.39 | 3 | 2 | High | 55.41 | 3.52 | 0 | Yes |
| 91 | 360.39 | 3 | 2 | High | 55.41 | 3.52 | 0 | Yes |
| 92 | 360.39 | 3 | 2 | High | 55.41 | 3.55 | 0 | Yes |
| 93 | 360.39 | 3 | 2 | High | 55.41 | 3.42 | 0 | Yes |
| 94 | 360.39 | 3 | 2 | High | 55.41 | 3.17 | 0 | Yes |
| 95 | 369.23 | 1 | 2 | High | 36.95 | 3.36 | 1 | Yes |
| 96 | 369.23 | 1 | 2 | High | 36.95 | 3.36 | 1 | Yes |
| 97 | 369.23 | 1 | 2 | High | 36.95 | 3.37 | 1 | Yes |
| 98 | 369.23 | 1 | 2 | High | 36.95 | 3.48 | 1 | Yes |
| 99 | 330.37 | 1 | 4 | High | 88.99 | 2.24 | 0 | Yes |
| 100 | 332.34 | 3 | 4 | High | 77.41 | 2.86 | 0 | Yes |
| 101 | 383.26 | 1 | 2 | High | 36.95 | 3.6 | 1 | Yes |
| 102 | 383.26 | 1 | 2 | High | 36.95 | 3.6 | 1 | Yes |
| 103 | 383.26 | 1 | 2 | High | 36.95 | 3.63 | 1 | Yes |
| 104 | 399.26 | 2 | 2 | High | 46.18 | 3.65 | 1 | Yes |
| 105 | 399.26 | 2 | 2 | High | 46.18 | 3.73 | 1 | Yes |
| 106 | 399.26 | 2 | 2 | High | 46.18 | 3.55 | 1 | Yes |
| 107 | 399.26 | 2 | 2 | High | 46.18 | 3.73 | 1 | Yes |
| 108 | 399.26 | 2 | 2 | High | 46.18 | 3.65 | 1 | Yes |

All of them are readily absorbed after oral administration and pass the blood-brain barrier (BBB). This indicates that almost all of the ligand's properties belong to the allowed range. Each compound's unique ADMET values are listed in Table 3.

## CONCLUSION

Oxadiazole derivatives were docked into the AChE protein molecules' binding site (PDB ID:4EY6), and the results were identical to those obtained by standard. Measurements of docking energy revealed a mild but beneficial interaction with acetylcholinesterase. Our tested compounds are significantly interacting with amino acid residues such as Arg 393, Arg 525, Ala 528 Asp 400. This binding mode is almost similar to that of reference standard donepezil. So it was assumed that those amino acid residues play crucial role in the interaction with cholinesterase inhibitors. According to the enzyme inhibitory test by means of molecular docking, the protein inhibitory activity of 2, 4, 11, 18, 19, 32, 36, and 39 against the AChE enzyme was comparable to donepezil. According to ADMET prediction data, these medications will have safer pharmacokinetic and toxicological profiles. The study's objective is to open the door for the development of new AChE medications in order to improve the neurotransmitter acetylcholine to the optimum level in the brain to suppress the symptoms and develop memory and cognitive thinking to Alzheimer patients. According to the study's findings, these molecules may have potent anti-Alzheimer activity and can be used to prevent the worsening of the condition in Alzheimer's disease and course, more research is necessary before 2-methyl-1,3,4- oxadiazolyl hybrids can be considered as viable treatment for Alzheimer's disease.

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