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Novel Acridine Derivative Inhibiting Acetylcholinesterase: In Silico Molecular Docking Studies For Alzheimer's Disease Treatment

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative brain disorder that causes diminished memory and cognitive decline, and it affects millions of people throughout the world. In particular, acetylcholinesterase (AChE) inhibitors have been studied as a means of studying the cholinergic system, since low acetylcholine levels, T protein aggregation, oxidative stress, inflammatory processes, and abnormal beta-amyloid, are all related to AD. For the aim of ADMET experiments for cholinesterase inhibitors against Alzheimer's disease, a series of new acridine scaffolds were developed, docked, and predicted in this research. When compared to normal Donepezil, the proposed compound showed improved docking studies in the binding region of acetylcholinesterase enzyme when utilizing the Pyrex docking program. Compound 19 (12.3 Kcal/mol) was the most widely proposed new acridine derivative, and its inhibitory activity against AChE was mediated by two hydrogen bonding interactions. Pharmacokinetic and drug-like properties were predicted in vitro using Swiss ADME software. The pharmacokinetic characteristics of the synthetic compounds suggest that they may be effective cholinesterase inhibitors in the treatment of Alzheimer's disease.

KEYWORDS: Alzheimer's disease, Acridine derivatives, Acetylcholinesterase, Molecular docking, Pharmacokinetic studies, Inhibitory activity

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative neurological condition characterized by cognitive decline and memory loss [1]. It affects an ever-increasing number of individuals. Neurodegeneration, a decline in brain function, delusions, anxiety, inaction, and despair are some of the hallmarks of Alzheimer's disease [2-4]. Due to the absence of effective therapies, a proper diagnosis of AD is crucial. Imaging techniques like as PET and MRI are often used to identify cases of AD. High-quality images with excellent soft-tissue contrast and enhanced spatial analysis may be obtained using MRI with no risks to the patient [2]. In contrast to positron emission tomography (PET), which uses radiotracers to detect and track alteration in neurotransmitters, metabolism rate, flow of blood in BBB, etc.[5],

Uncertainty over the cause of Alzheimer's disease may explain why there is no effective treatment available. Based on the defining aspects of Alzheimer's disease, such as the existence of extracellular amyloid-beta (A) plaques and tangles of neurofibrillary cells in the interior of cells, in addition to gliosis, the degeneration of synapses, and inflammation, many theories have been proposed to explain the illness [6-9]. The causes of Alzheimer's disease have been the subject of several theories. The A-amyloid hypothesis, the A-amyloid oligomer hypothesis, the tau hypothesis, the Ca2+ regulation theory, the presenilin is hypothesis, and the lysosome hypothesis are all examples of such theories.

Overproduction of A -amyloid peptide is thought to cause synaptotoxicity, neurotoxicity, and neurodegeneration in the form of amyloid plaques [10]. aberrant neurofibrillary structures are thought to occur due to aberrant phosphorylation of tau (tubulin-associated unit), as proposed by the tau hypothesis. In healthy cells, tau proteins connect to microtubules, increasing their stability and encouraging their polymerization [11]. These receptors belong to the G type protein-coupled receptor (GPCR) family C, the calcium-sensing receptor (CaSR) mediates calcium homeostasis and regulates intracellular signaling [12], providing support for the Ca2+ dysregulation hypothesis.

Inflammation and neurodegenerative diseases including Alzheimer's have been linked to CaSR dysregulation [13,14]. Genetic variations in genes producing presenilins, the catalytic component of -secretase, have been linked to an increased risk of developing Alzheimer's disease (AD) [15]. Presenilins are responsible for cleaving the amyloid precursor protein (APP). Finally, a lysosome hypothesis postulates that defects in the autophagy-lysosomal pathway are caused by mutations in genes controlling lysosomal pH [16].

Mainly two enzymes are linked to AD namely called butyrylcholinesterase enzyme (BChE) and Acetylcholinesterase enzyme (AChE). They have been shown to increase neurotoxicity by speeding up the assembly of A peptides into Alzheimer's disease-like aggregates [17]. In AD patients, Low acetylcholine levels, aberrant -amyloid levels, T aggregation of proteins, inflammatory processes, and oxidative damage [18]. The cholinergic system, namely acetylcholinesterase (AChE) inhibitors, is now the main focus of Alzheimer's disease research.

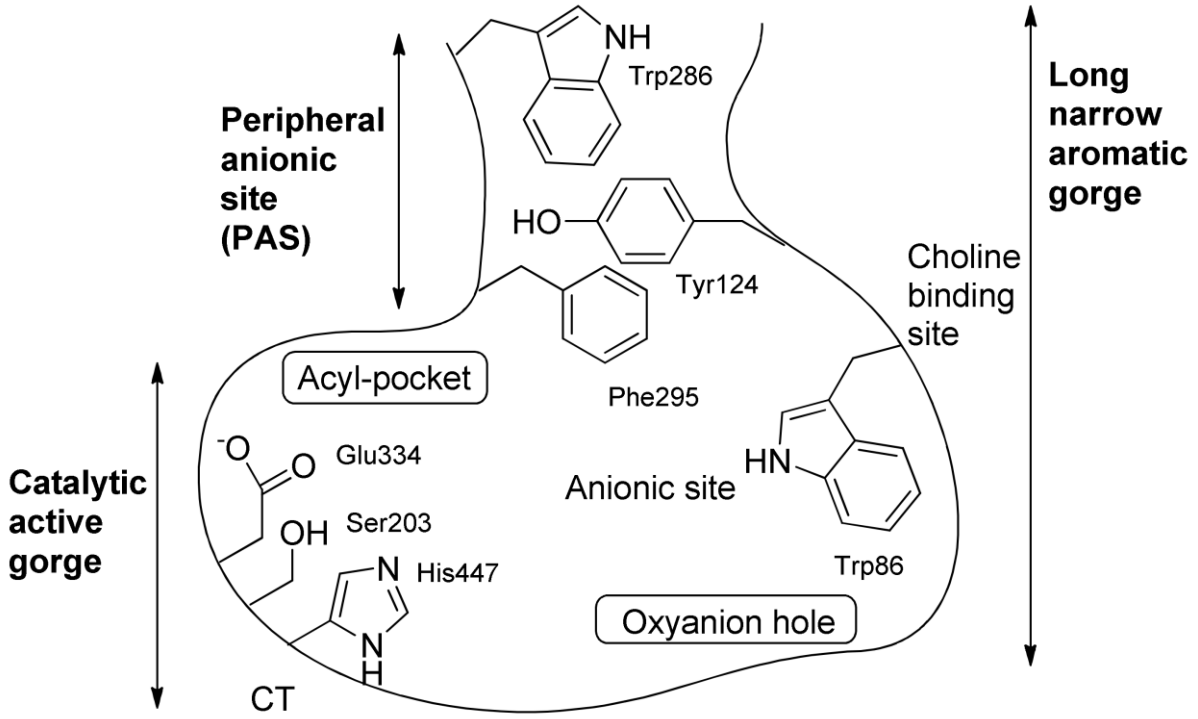
Acetylcholinesterase (AChE) is a type-B carboxylesterase enzyme. Carboxylesterase type B refers to a group of proteins that have common ancestry [19]. Neurotransmitters acetylcholine and other choline esters are broken down by this serine hydrolase [20]. Acetylcholinesterase (AChE) is an enzyme produced by many cell types, including skeletal muscle, neurons, and hematopoietic cells, and is notable for its high catalytic efficiency. The catalytic triad of

acetylcholinesterase consists of three amino acids (Glu334, His447, and Ser203) and is located at an active site that is 20 angstroms deep. Beyond Tyr337, a neighboring binding location may be found on the periphery.

Both of these locations are accessible to AChE inhibitors [21]. Studies of AChE's kinetics have shown that it has two distinct active sites, an ecstatic site for the catalytic machinery and an anionic site for the choline-active binding region [22]. The ecstatic site, degrade to choline and acetate contains a trioenzyme such as His447, Ser203 and Glu334. histidine and Serine are found in other proteases that contain serine, while aspartate is always found in the third position. Furthermore, the chirality of AChE's catalytic triad is inverted with respect to that of other proteases [23]. The acyl-enzyme is attacked by a nucleophilic water molecule, with help from the histidine, to release the choline and the acyl-enzyme. The acetic acid and the independent enzyme are produced as a consequence of this reaction [24].

Acetylcholine's positive quaternary amine, along with other cation substrates and inhibitors, participate in the c process at the anionic site. The anionic site, which scientists discovered has aromatic chemicals at the active site, is lipophilic and apolar [22].

Scheme 1 illustrating the components of the active site shared by a large number of human AChE isoforms: the acyl binding pocket; the omega loop; the oxyanion hole; the middle of the aromatic region; Ser203, Glu334, and His447, also known as the catalytic triad (CT); the anionic subsite (AS) consisting of Gly448, Glu202, Ile451, Tyr133, and Trp86 [25-27]. Reversible, pseudo-irreversible, and irreversible acetylcholinesterase inhibitors are distinguished by their respective mechanisms of action [28].



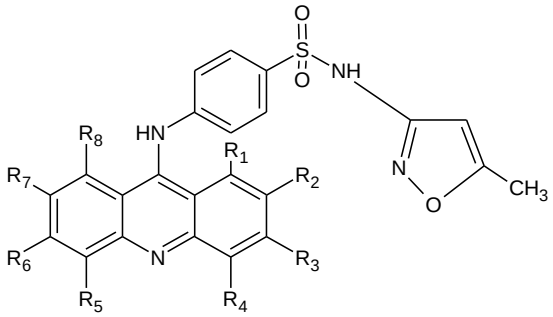
Scheme 1. Illustration of the ligand-AChE interaction.

New therapeutic scaffolds based on acridines are highly sought after in the fight against protozoan and neurological diseases [29]. Some of the various therapeutic uses for acridine derivatives [30-37] include antimalarial, antitrypanosomal, antiviral, antibacterial, cancer prevention, antileishmanial, and anti-prion medications. It has also been suggested that they

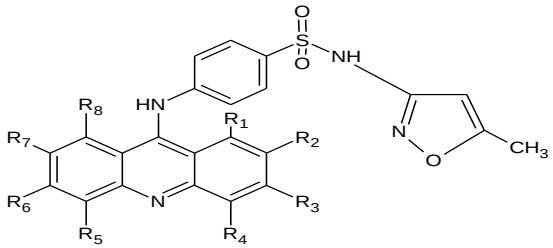
have anti-inflammatory, anti-Alzheimer's, and anti-diabetic characteristics [38-42]. Recently, it has been discovered that anti-TDP-43 aggregation is helpful in ALS disease models. Acridine derivatives may be the most promising source of novel multitarget lead and therapeutic candidates, including hybrid and dimeric forms.

Inhibition of acetylcholine dehydrogenase and acetylcholinesterase by acridine derivatives has been extensively documented [43-45]. Previously we study the binding site of the BuChE protein molecules docked with novel acridine and oxadiazole derivates molecules [46-49]. New drug-like compounds that block the acetylcholinesterase enzyme are the subject of this study, which aims to find effective treatments for Alzheimer's disease. We created and analyzed a variety of acridines for this investigation, bearing in mind the significance of these scaffolds. To this end, we set out to simulate a number of possible inhibitors of the AChE enzyme. Then, the nature of the interaction between these compounds and the AChE active site was investigated by in silico molecular dock techniques.

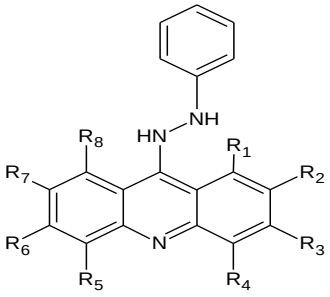
NOVEL ACRIDINE DERIVATIVATIVES



C1: R_2= CH_3	C10: **R_6**= NH_2	C19: R_2, R_4= CH_3	C28: R_3, R_6= OCH_3
C2: R_3= CH_3	C11:R_7= **R_3**= Cl	C20: R_2, R_3= OCH_3	C29: R_4, R_6= OCH_3
C3: **R_4**= CH_3	C12: **R_4**= Cl	C21: R_3, **R_4**= OCH_3	C30: R_4, R_7= OCH_3
C4: R_2=OCH_3	C13: **R_6**= Cl	C22: R_2, R_4= OCH_3	C31: R_3, **R_4**= Cl
C5: **R_3**= OCH_3	C14: R_7= Cl	C23: R_4, R_6= OCH_3	C32: R_4, R_6= Cl
C6: **R_4**= OCH_3	C15:R_5=OH	C24: R_6, R_7= OCH_3	C33: R_6, R_7= Cl
C7: **R_6**= OCH_3	C16: **R_6**= OH	C25: R_2, R_7= OCH_3	C34: R_4, R_7= Cl
C8: R_2-R_7=H	C17: R_2, R_3= CH_3	C26: R_2, R_6= OCH_3	C35: R_3, **R_6**= NH_2
C9: R_3= NH_2	C18: R_3, **R_4**= CH_3	C27: R_3, R_7= OCH_3	C36: R_5, **R_6**= OH



C37: R_2= CH_3	C46: **R_6**= NH_2	C55: R_2, R_4= CH_3	C64: R_3, R_6= OCH_3
C38: R_3= CH_3	C47:R_7= **R_3**= Cl	C56: R_2, R_3= OCH_3	C65: R_4, R_6= OCH_3
C39: **R_4**= CH_3	C48: **R_4**= Cl	C57: R_3, **R_4**= OCH_3	C66: R_4, R_7= OCH_3
C40: R_2=OCH_3	C49: **R_6**= Cl	C58: R_2, R_4= OCH_3	C67: R_3, **R_4**= Cl
C41: **R_3**= OCH_3	C50: R_7= Cl	C56: R_4, R_6= OCH_3	C68: R_4, R_6= Cl
C42: **R_4**= OCH_3	C51:R_5=OH	C60: R_6, R_7= OCH_3	C69: R_6, R_7= Cl
C43: **R_6**= OCH_3	C52: **R_6**= OH	C61: R_2, R_7= OCH_3	C70: R_4, R_7= Cl
C44: R_2-R_7=H	C53: R_2, R_3= CH_3	C62: R_2, R_6= OCH_3	C71: R_3, **R_6**= NH_2
C45: R_3= NH_2	C54: R_3, **R_4**= CH_3	C63: R_3, R_7= OCH_3	C72: R_5, **R_6**= OH



C73: R_2= CH_3	C82: **R_6**= NH_2	C91: R_2, R_4= CH_3	C100: R_3, R_6= OCH_3
C74: R_3= CH_3	C83:R_7= **R_3**= Cl	C92: R_2, R_3= OCH_3	C101: R_4, R_6= OCH_3
C75: **R_4**= CH_3	C84: **R_4**= Cl	C93: R_3, **R_4**= OCH_3	C102: R_4, R_7= OCH_3
C76: R_2=OCH_3	C85: **R_6**= Cl	C94: R_2, R_4= OCH_3	C103: R_3, **R_4**= Cl
C77: **R_3**= OCH_3	C86: R_7= Cl	C95: R_4, R_6= OCH_3	C104: R_4, R_6= Cl
C78: **R_4**= OCH_3	C87:R_5=OH	C96: R_6, R_7= OCH_3	C105: R_6, R_7= Cl
C79: **R_6**= OCH_3	C88: **R_6**= OH	C97: R_2, R_7= OCH_3	C106: R_4, R_7= Cl
C80: R_2-R_7=H	C89: R_2, R_3= CH_3	C98: R_2, R_6= OCH_3	C107: R_3, **R_6**= NH_2
C81: R_3= NH_2	C90: R_3, **R_4**= CH_3	C99: R_3, R_7= OCH_3	C108: R_5, **R_6**= OH

Methods

Nowadays, molecular dock studies is a common method used in drug discovery to learn more about how a potential lead compound would interact with a certain ligand receptor on a protein target. Using bioinformatics tools, the research was conducted virtually. In addition to databases like PubChem and molecular docking software like PyRx 0.9 available online, we also make use of offline programmes like Protein Data Bank (available at public domain websites like www.rcsb.org/pdb) and Marvin sketch for drawing chemical structures [50].

Preparation of protein

We obtained AChE (PDB: 4EY6) with a resolution of 2.40 Å using the offline program at the protein data bank. Following crystallization, we optimized the protein's energy by adding missing hydrogens, protonating it, ionizing it, and optimizing its charge. The Swiss-Protein Data Bank Viewer was used to optimize the energy budget. Protein quality may be checked using the Ramachandran chart [51]

Active site identification

We used the website plip biotech to get the ligand-protein interaction profile is a method for identifying proteins that contain functional amino acids. A Google offline tool is available. We inferred the protein's activation state based on this [52].

Ligand Preparation

Using the Marvin sketching software, the molecules are built in both three and two dimensions. The process began with a drawing of the molecule, moved on to 3D optimising in Marvin sketch, and culminated in a PDB file [53].

In silico ADMET Prediction

Estimates of the pharmacokinetic properties (ADMET) of possible drugs were made using a computer program called Swiss ADME prediction. A human's ability to orally absorb a molecule may be estimated by determining its surface area that is polar (PSA), the no. of acceptors of hydrogen bonds (n-ON), the no. of donors of hydrogen bonds (n-OHNH), the overall activity in the central nervous system, and its percentage of oral absorption, and the distribution of the constant in 1-octyl methanol in water (log P o/w), the researchers were able to conclude that the compound was able to inhibit the activity of the central nervous system. and n-ON and n-OHNH hydrogen bond acceptor and donor numbers, we were able to determine the molecule's ability to cross the blood-brain barrier. The ADME properties of any drug or synthetic molecule may be better understood with the help of the data presented here. It was also found that there were pharmacological similarities, breaches of the rule of five, and violations of the rule of three. A molecule with a specificity of five with a molecular weight of five hundred, a count of 5 H-bond donors, and a count of 10 acceptors has an optimal distribution [54].

Results and Discussion

INSILICO MOLECULAR DOCKING STUDIES

Our investigation's 108 acridine scaffold were designed after reviewing the research on acridine derivatives in the literature, and they have been used in molecular docking studies. In order to foresee the protein's potential interactions with its inhibitors, molecular docking was performed using PyRx 0.9. Molecular docking was used to examine acetylcholinesterase's binding mode competence with 108 acridine derivatives. The synthetic molecules were anchored next to the native ligand. Docking values between 8 and 12

kcal/mol for our engineered medicines suggested an acceptable affinity for interacting to a target receptor mentioned in Table 2.

The designed compounds were docked the docking energies are compared to the standard drug donepezil. Table 2 shows that our proposed compounds have significant binding energies with the target receptor, with docking values ranging from 8.1 to 12.3 kcal/mol. Binding energies of 12 kcal/mol were observed for compounds 1, 19, and 36. Docking results for compounds 3, 12, and 33 (11.5 K/cal) are similar to those for donepezil (12.76 K/cal), as are those for compound 18. The residual molecule has good to moderate action, which is above and above that of the standard drug. Important ligand-binding domain amino acids found in human inhibitors of AChE have also been identified. Substitutional bonds The acetylcholinesterase inhibitor's ligand-binding domain was evaluated in conjunction with the ligands. Certain amino acids in the part of acetylcholinesterase (AChE) inhibitors that bind to ligands, as well as this part as a whole, have been linked to the reduction of ligand interactions between AChE and its inhibitors. Previous studies have shown that these particular amino acids play a recurring role in engaging with AChE inhibitors during ligand interactions, hence serving a pivotal role in obstructing the ligand-binding region of Acetylcholinesterase inhibitors. Figures 1–8 illustrate many instances of non-covalent interactions. The aforementioned interactions include hydrogen bonding, π–π stacking, van der Waals forces, and electrostatic interactions.

Table 2: docking energies of designing compounds

Ligand	Binding Affinity	Ligand	Binding Affinity	Ligand	Binding Affinity	Ligand	Binding Affinity
1	**-12**	28	-10.4	55	-9.2	82	-10.3
2	-10.7	29	-11.3	56	-8.1	83	-10.3
3	**-11.5**	30	-10.1	57	-8.5	84	-10.2
4	-11.4	31	-11.4	58	-8.3	85	-10.3
5	-10.9	32	-11.2	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	-10.6	38	-8.9	65	-8.3	92	-9.6
12	**-11.5**	39	-9	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	**-11.9**	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

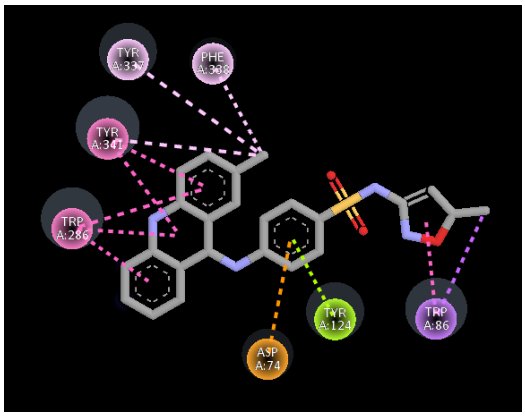


Figure 1: Compound 1 binding to the active protein region of the AChE protein (4EY6), as shown in a 2D structure.

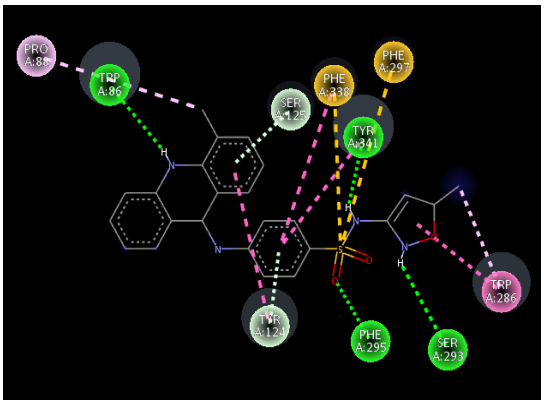


Figure 2: Compound 3 binding to the active protein region of the AChE protein (4EY6), as shown in a 2D structure.

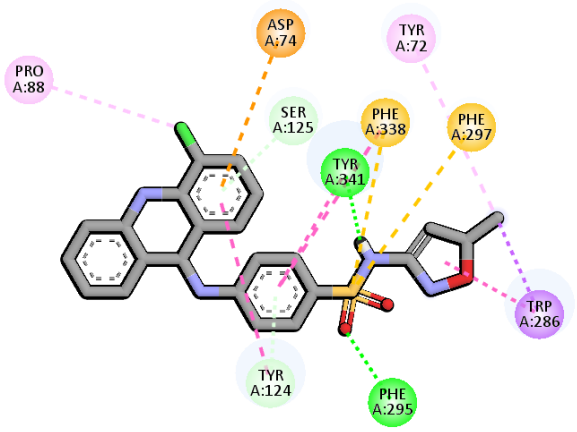


Figure 3: Compound 12 binding to the active protein region of the AChE protein (4EY6), as shown in a 2D structure.

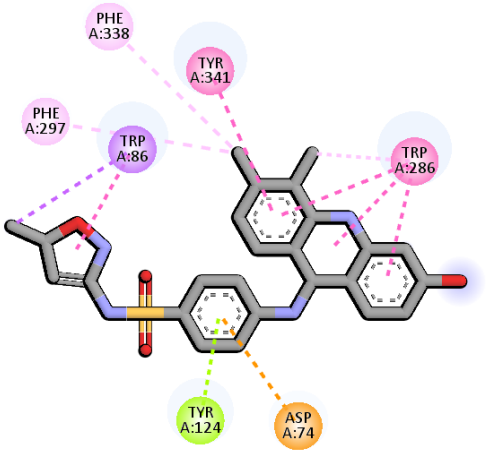


Figure 4: Compound 18 binding to the active protein region of the AChE protein (4EY6), as shown in a 2D structure.

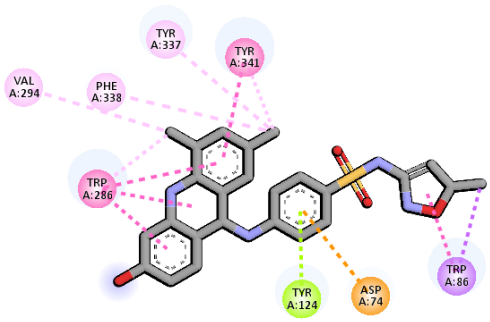


Figure 5: Compound 19 binding to the active protein region of the AChE protein (4EY6), as shown in a 2D structure.

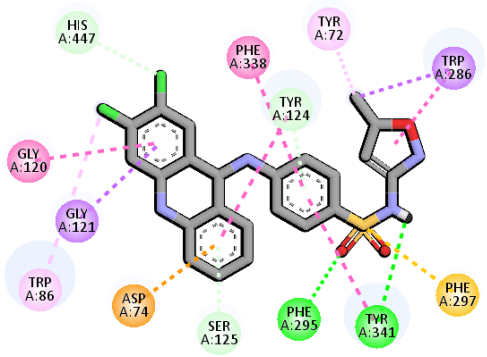


Figure 6: Compound 33 binding to the active protein region of the AChE protein (4EY6), as shown in a 2D structure.

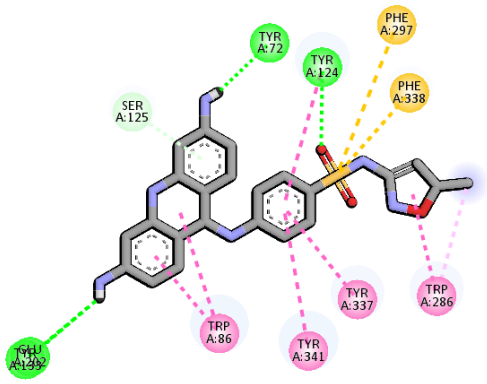


Figure 7: Compound 35 binding to the active protein region of the AChE protein (4EY6), as shown in a 2D structure.

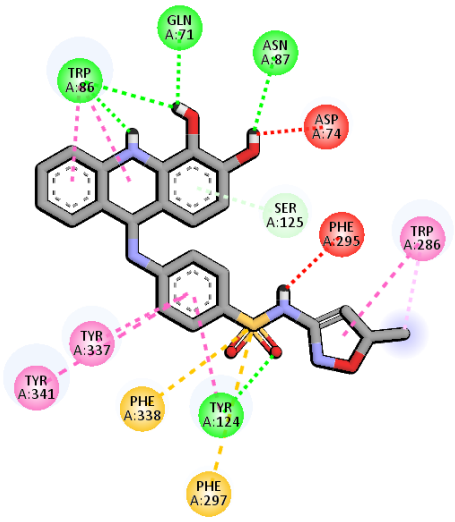


Figure 8: Compound 38 binding to the active protein region of the AChE protein (4EY6), as shown in a 2D structure.

INSILICO ADME STUDIES

The suggested ligands' in-silico ADMET properties were explored using SWISS ADME software. The molecular weights of the suggested compounds are from 230 to 480. It was determined that there was somewhere about 1 hydrogen bond donor. There were four estimated hydrogen bond acceptors. It was speculated that between one and three metabolic processes would be possible, and that the octanol/water coefficient of partition should be between 2.5 and 3. The Lipinski five-paragraph rule was not violated. All of them cross the blood-brain barrier (BBB) and are easily absorbed after being taken orally. This means that almost every property of the compounds falls within the acceptable range. Table 3 lists the compounds' individual in-silico ADMET properties

Table 3. Designed compound ADMET characteristics in silico

Code	MW	H-bond acceptors	H-bond donors	GI absorption	TPSA	iLOGP	Lipinski violations	BBB permeant
1	444.51	5	2	Low	105.5	2.85	0	No
2	444.51	5	2	Low	105.5	3	0	No
3	444.51	5	2	Low	105.5	3.08	0	No
4	460.51	6	2	Low	114.73	2.69	0	No
5	460.51	6	2	Low	114.73	3.11	0	No
6	460.51	6	2	Low	114.73	2.96	0	No
7	460.51	6	2	Low	114.73	3.11	0	No
8	460.51	6	2	Low	114.73	2.69	0	No
9	445.49	5	3	Low	131.52	2.24	0	No
10	445.49	5	3	Low	131.52	2.24	0	No
11	464.92	5	2	Low	105.5	2.82	0	No
12	464.92	5	2	Low	105.5	2.93	0	No
13	464.92	5	2	Low	105.5	2.82	0	No
14	464.92	5	2	Low	105.5	2.73	0	No
15	446.48	6	3	Low	125.73	2.81	0	No
16	446.48	6	3	Low	125.73	2.38	0	No
17	474.53	6	3	Low	125.73	3.1	0	No
18	474.53	6	3	Low	125.73	2.73	0	No
19	474.53	6	3	Low	125.73	2.75	0	No
20	506.53	8	3	Low	144.19	2.69	1	No
21	506.53	8	3	Low	144.19	2.99	1	No
22	506.53	8	3	Low	144.19	2.7	1	No
23	490.53	7	2	Low	123.96	3.17	0	No
24	490.53	7	2	Low	123.96	2.71	0	No
25	490.53	7	2	Low	123.96	3.47	0	No
26	490.53	7	2	Low	123.96	3.43	0	No
27	490.53	7	2	Low	123.96	3.43	0	No
28	490.53	7	2	Low	123.96	3.34	0	No
29	490.53	7	2	Low	123.96	3.17	0	No

30	490.53	7	2	Low	123.96	3.18	0	No
31	499.37	5	2	Low	105.5	2.84	0	No
32	499.37	5	2	Low	105.5	3.18	0	No
33	499.37	5	2	Low	105.5	2.9	0	No
34	499.37	5	2	Low	105.5	3.09	0	No
35	460.51	5	4	Low	157.54	2	0	No
36	462.48	7	4	Low	145.96	2.46	0	No
37	223.27	2	2	High	50.94	1.98	0	Yes
38	239.27	3	2	High	60.17	2.06	0	Yes
39	239.27	3	2	High	60.17	2.21	0	Yes
40	239.27	3	2	High	60.17	1.8	0	Yes
41	239.27	3	2	High	60.17	2.21	0	Yes
42	243.69	2	2	High	50.94	2.12	0	Yes
43	243.69	2	2	High	50.94	2.18	0	Yes
44	243.69	2	2	High	50.94	2.24	0	Yes
45	225.25	3	3	High	71.17	1.84	0	Yes
46	225.25	3	3	High	71.17	1.65	0	Yes
47	237.3	2	2	High	50.94	2.19	0	Yes
48	237.3	2	2	High	50.94	2.33	0	Yes
49	269.3	4	2	High	69.4	2.19	0	Yes
50	269.3	4	2	High	69.4	2.32	0	Yes
51	269.3	4	2	High	69.4	2.43	0	Yes
52	269.3	4	2	High	69.4	2.31	0	Yes
53	269.3	4	2	High	69.4	2.19	0	Yes
54	269.3	4	2	High	69.4	2.42	0	Yes
55	269.3	4	2	High	69.4	2.5	0	Yes
56	269.3	4	2	High	69.4	2.5	0	Yes
57	269.3	4	2	High	69.4	2.46	0	Yes
58	269.3	4	2	High	69.4	2.31	0	Yes
59	269.3	4	2	High	69.4	2.18	0	Yes
60	278.14	2	2	High	50.94	2.2	0	Yes
61	278.14	2	2	High	50.94	2.31	0	Yes
62	278.14	2	2	High	50.94	2.24	0	Yes
63	239.28	2	4	High	102.98	1.06	0	No
64	241.25	4	4	High	91.4	-0.34	0	No
65	299.37	1	2	High	36.95	3.2	0	Yes
66	299.37	1	2	High	36.95	3.23	0	Yes
67	299.37	1	2	High	36.95	3.23	0	Yes
68	315.37	2	2	High	46.18	3.11	0	Yes
69	315.37	2	2	High	46.18	3.27	0	Yes
70	315.37	2	2	High	46.18	3.07	0	Yes
71	315.37	2	2	High	46.18	3.27	0	Yes

72	315.37	2	2	High	46.18	3.11	0	Yes
73	300.36	1	3	High	62.97	2.61	0	Yes
74	300.36	1	3	High	62.97	2.61	0	Yes
75	319.79	1	2	High	36.95	3.23	1	Yes
76	319.79	1	2	High	36.95	3.05	1	Yes
77	319.79	1	2	High	36.95	3.23	1	Yes
78	319.79	1	2	High	36.95	3.23	1	Yes
79	301.34	2	3	High	57.18	2.97	0	Yes
80	301.34	2	3	High	57.18	2.58	0	Yes
81	313.4	1	2	High	36.95	3.4	1	Yes
82	313.4	1	2	High	36.95	3.37	1	Yes
83	313.4	1	2	High	36.95	3.34	1	Yes
84	345.39	3	2	High	55.41	3.37	0	Yes
85	345.39	3	2	High	55.41	3.37	0	Yes
86	345.39	3	2	High	55.41	3.39	0	Yes
87	345.39	3	2	High	55.41	3.42	0	Yes
88	345.39	3	2	High	55.41	3.37	0	Yes
89	345.39	3	2	High	55.41	3.54	0	Yes
90	345.39	3	2	High	55.41	3.52	0	Yes
91	345.39	3	2	High	55.41	3.52	0	Yes
92	345.39	3	2	High	55.41	3.55	0	Yes
93	345.39	3	2	High	55.41	3.42	0	Yes
94	345.39	3	2	High	55.41	3.17	0	Yes
95	354.23	1	2	High	36.95	3.36	1	Yes
96	354.23	1	2	High	36.95	3.36	1	Yes
97	354.23	1	2	High	36.95	3.37	1	Yes
98	354.23	1	2	High	36.95	3.48	1	Yes
99	315.37	1	4	High	88.99	2.24	0	No
100	317.34	3	4	High	77.41	2.86	0	Yes
101	368.26	1	2	High	36.95	3.6	1	No
102	368.26	1	2	High	36.95	3.6	1	No
103	368.26	1	2	High	36.95	3.63	1	No
104	384.26	2	2	High	46.18	3.65	1	Yes
105	384.26	2	2	High	46.18	3.73	1	Yes
106	384.26	2	2	High	46.18	3.55	1	Yes
107	384.26	2	2	High	46.18	3.73	1	Yes
108	384.26	2	2	High	46.18	3.65	1	Yes

CONCLUSION

The results obtained while docking acridine scaffold compounds in the binding region of the AChE protein molecule (PDB ID:4EY6) were indistinguishable from the results

obtained when using protein. The measurements of the docking energy revealed that there was a weak but beneficial binding to acetylcholinesterase. Based on the enzyme dock energies results in protein inhibitory activity, compounds 1, 3, 12, 18, 19, 33, 35, & 36 possessed protein activity as inhibitors towards the AChE enzyme that was comparable to that of donepezil. According to the findings of the ADMET prediction, these drugs will also have better pharmacokinetic and toxicology profiles. As a result, the purpose of the research is to clear the path for the development of original AChE medications. According to the findings of this study, further research is likely needed until acridine derivatives can be considered as possible candidates for treatment of Alzheimer's disease.

REFRENCE

1. Kaur, S.; Bansal, Y. Design, Molecular Docking, Synthesis and Evaluation of Xanthoxylin Hybrids as Dual Inhibitors of IL-6 and Acetylcholinesterase for Alzheimer’s Disease. Bioorg. Chem. 2022, 121, 105670.
2. De Mendonça, L.J.C.; Ferrari, R.J. Alzheimer’s Disease Classification Based on Graph Kernel SVMs Constructed with 3D Texture Features Extracted from MR Images. Expert Syst. Appl. 2023, 211, 118633.
3. Lyketsos, C.G.; Carrillo, M.C.; Ryan, J.M.; Khachaturian, A.S.; Trzepacz, P.; Amatniek, J.; Cedarbaum, J.; Brashear, R.; Miller, D.S. Neuropsychiatric Symptoms in Alzheimer’s Disease. Alzheimer’s Dement. 2011, 7, 532–539.
4. Frederiksen, K.S.; Waldorff, F.B.; Waldemar, G. O2-02-02: Physical Activity as a Predictor of Clinical Course in Mild Ad: The Danish Alzheimer’s Intervention Study (Daisy). Alzheimers Dement. 2014, 10, P165.
5. Berger, A. Positron Emission Tomography. BMJ 2003, 326, 1449.
6. Petrella, C.; Di Certo, M.G.; Barbato, C.; Gabanella, F.; Ralli, M.; Greco, A.; Possenti, R.; Severini, C. Neuropeptides in Alzheimer’s Disease: An Update. Curr. Alzheimer Res. 2019, 16, 544–558.
7. Iqbal, K.; Grundke-Iqbal, I. Neurofibrillary Pathology Leads to Synaptic Loss and Not the Other Way around in Alzheimer Disease. J. Alzheimers Dis. 2002, 4, 235–238.
8. Iqbal, K.; Liu, F.; Gong, C.-X. Tau and Neurodegenerative Disease: The Story so Far. Nat. Rev. Neurol. 2016, 12, 15–27.
9. Itagaki, S.; McGeer, P.L.; Akiyama, H.; Zhu, S.; Selkoe, D. Relationship of Microglia and Astrocytes to Amyloid Deposits of Alzheimer Disease. J. Neuroimmunol. 1989, 24, 173–182.
10. Choi, S.H.; Tanzi, R.E. Alzheimer’s Disease: Causes, Mechanisms, and Steps Toward Prevention. In The Oxford Handbook of the Neurobiology of Learning and Memory; Carew, T.J., Ed.; Oxford University Press: Oxford, UK, 2020; ISBN 978-0-19-006916-2.
11. Xu, J.; Wang, F.; Guo, J.; Xu, C.; Cao, Y.; Fang, Z.; Wang, Q. Pharmacological Mechanisms Underlying the Neuroprotective Effects of Alpinia Oxyphylla Miq. on Alzheimer’s Disease. Int. J. Mol. Sci. 2020, 21, 2071.
12. Hendy, G.N.; Guarnieri, V.; Canaff, L. Chapter 3 Calcium-Sensing Receptor and Associated Diseases. In Progress in Molecular Biology and Translational Science; Tao, Y.-X., Ed.; Academic Press: Cambridge, MA, USA, 2009; Volume 89, pp. 31–95.

13. Bandyopadhyay, S.; Jeong, K.-H.; Hansen, J.T.; Vassilev, P.M.; Brown, E.M.; Chattopadhyay, N. Calcium-Sensing Receptor Stimulates Secretion of an Interferon-Induced Monokine (CXCL10) and Monocyte Chemoattractant Protein-3 in Immortalized GnRH Neurons. J. Neurosci. Res. 2007, 85, 882–895.
14. Chiarini, A.; Pra, I.D.; Marconi, M.; Chakravarthy, B.; Whitfield, J.F.; Armato, U. Calcium-Sensing Receptor (CaSR) in Human Brain's Pathophysiology: Roles in Late-Onset Alzheimer's Disease (LOAD). Curr. Pharm. Biotechnol. 2009, 10, 317–326.
15. Kelleher, R.J.; Shen, J. Presenilin-1 Mutations and Alzheimer's Disease. Proc. Natl. Acad. Sci. USA 2017, 114, 629–631.
16. Zhang,W.; Xu, C.; Sun, J.; Shen, H.-M.;Wang, J.; Yang, C. Impairment of the Autophagy–Lysosomal Pathway in Alzheimer's Diseases: Pathogenic Mechanisms and Therapeutic Potential. Acta Pharm. Sin. B 2022, 12, 1019–1040.
17. Carvajal, F.; Inestrosa, N. Interactions of AChE with Aβ Aggregates in Alzheimer's Brain: Therapeutic Relevance of IDN 5706. Front. Mol. Neurosci. 2011, 4, 19.
18. Pitchai, A.; Rajaretinam, R.K.; Mani, R.; Nagarajan, N. Molecular Interaction of Human Acetylcholinesterase with TransTephrostachin and Derivatives for Alzheimer's Disease. Heliyon 2020, 6, e04930.
19. Myers, M.; Richmond, R.C.; Oakeshott, J.G. On the Origins of Esterases. Mol. Biol. Evol. 1988, 5, 113–119.
20. Hormozi Jangi, S.R.; Akhond, M. Introducing a Covalent Thiol-Based Protected Immobilized Acetylcholinesterase with Enhanced Enzymatic Performances for Biosynthesis of Esters. Process Biochem. 2022, 120, 138–155.
21. Riaz, N.; Iftikhar, M.; Saleem, M.; Aziz-ur-Rehman; Hussain, S.; Rehmat, F.; Afzal, Z.; Khawar, S.; Ashraf, M.; al-Rashida, M. New Synthetic 1,2,4-Triazole Derivatives: Cholinesterase Inhibition and Molecular Docking Studies. Results Chem. 2020, 2, 100041.
22. Sussman, J.L.; Silman, I. Acetylcholinesterase: Structure and Use as a Model for Specific Cation—Protein Interactions. Curr. Opin. Struct. Biol. 1992, 2, 721–729.
23. Tripathi, A.; Srivastava, U.C. Acetylcholinesterase: A Versatile Enzyme of Nervous System. Ann. Neurosci. 2010, 15, 106–111.
24. Molecular Architecture and Biological Reactions. Chem. Eng. News Arch. 1946, 24, 1375–1377.
25. El-Sayed, N.A.-E.; Farag, A.E.-S.; Ezzat, M.A.F.; Akincioglu, H.; Gülçin, ˙I.; Abou-Seri, S.M. Design, Synthesis, in Vitro and in Vivo Evaluation of Novel Pyrrolizine-Based Compounds with Potential Activity as Cholinesterase Inhibitors and Anti-Alzheimer's Agents. Bioorg. Chem. 2019, 93, 103312.
26. Wang, L.; Moraleda, I.; Iriepa, I.; Romero, A.; López-Muñoz, F.; Chioua, M.; Inokuchi, T.; Bartolini, M.; Marco-Contelles, J. 5-Methyl- N -(8-(5,6,7,8-Tetrahydroacridin-9-Ylamino)Octyl)-5 H -Indolo[2,3- b]Quinolin-11-Amine: A Highly Potent Human Cholinesterase Inhibitor. MedChemComm 2017, 8, 1307–1317.
27. Kuzu, B.; Tan, M.; Taslimi, P.; Gülçin, ˙I.; Ta¸spınar, M.; Menges, N. Mono- or Di-Substituted Imidazole Derivatives for Inhibition of Acetylcholine and Butyrylcholine Esterases. Bioorg. Chem. 2019, 86, 187–196.

28. McGleenon, B.M.; Dynan, K.B.; Passmore, A.P. Acetylcholinesterase Inhibitors in Alzheimer's Disease. Br. J. Clin. Pharm. 1999, 48, 471–480.
29. Bongarzone S, Bolognesi ML. The concept of privileged structures in rational drug design: focus on acridine and quinoline scaffolds in neurodegenerative and protozoan diseases. Expert opinion on drug discovery. 2011 Mar 1;6(3):251-68.
30. Denny WA. Acridine derivatives as chemotherapeutic agents. Current Medicinal Chemistry. 2002 Sep 1;9(18):1655-65.
31. Girault S, Grellier P, Berecibar A, Maes L, Mouray E, Lemiere P, Debreu MA, Davioud-Charvet E, Sergheraert C. Antimalarial, antitrypanosomal, and antileishmanial activities and cytotoxicity of bis (9-amino-6-chloro-2-methoxyacridines): influence of the linker. Journal of medicinal chemistry. 2000 Jul 13;43(14):2646-54.
32. Gamage SA, Figgitt DP, Wojcik SJ, Ralph RK, Ransijn A, Mauel J, Yardley V, Snowdon D, Croft SL, Denny WA. Structure− activity relationships for the antileishmanial and antitrypanosomal activities of 1 '-substituted 9-anilinoacridines. Journal of medicinal chemistry. 1997 Aug 1;40(16):2634-42.
33. Lyakhov SA, Suveyzdis YI, Litvinova LA, Andronati SA, Rybalko SL, Dyadyun ST. Biological active acridine derivatives. Part 4: Synthesis and antiviral activity of some bis-acridinylated diamides. Die Pharmazie. 2000 Oct 1;55(10):733-6.
34. Denny WA. Acridine derivatives as chemotherapeutic agents. Current Medicinal Chemistry. 2002 Sep 1;9(18):1655-65.
35. Korth C, May BC, Cohen FE, Prusiner SB. Acridine and phenothiazine derivatives as pharmacotherapeutics for prion disease. Proceedings of the National Academy of Sciences. 2001 Aug 14;98(17):9836-41.
36. Collinge J, Gorham M, Hudson F, Kennedy A, Keogh G, Pal S, Rossor M, Rudge P, Siddique D, Spyer M, Thomas D. Safety and efficacy of quinacrine in human prion disease (PRION-1 study): a patient-preference trial. The Lancet Neurology. 2009 Apr 1;8(4):334-44.
37. Klingenstein R, Löber S, Kujala P, Godsave S, Leliveld SR, Gmeiner P, Peters PJ, Korth C. Tricyclic antidepressants, quinacrine and a novel, synthetic chimera thereof clear prions by destabilizing detergent-resistant membrane compartments. Journal of neurochemistry. 2006 Aug;98(3):748-59.
38. Sondhi SM, Singh J, Rani R, Gupta PP, Agrawal SK, Saxena AK. Synthesis, anti-inflammatory and anticancer activity evaluation of some novel acridine derivatives. European Journal of Medicinal Chemistry. 2010 Feb 1;45(2):555-63.
39. Makhaeva GF, Lushchekina SV, Boltneva NP, Serebryakova OG, Rudakova EV, Ustyugov AA, Bachurin SO, Shchepochkin AV, Chupakhin ON, Charushin VN, Richardson RJ. 9-Substituted acridine derivatives as acetylcholinesterase and butyrylcholinesterase inhibitors possessing antioxidant activity for Alzheimer's disease treatment. Bioorganic & Medicinal Chemistry. 2017 Nov 1;25(21):5981-94.
40. Lermontova N, Lukoyanov N, Serkova T, Lukoyanova E, Bachurin S. Effects of tacrine on deficits in active avoidance performance induced by AF64A in rats. Molecular and chemical neuropathology. 1998 Jan;33:51-61.

41. Csuk R, Barthel A, Raschke C, Kluge R, Ströhl D, Trieschmann L, Böhm G. Synthesis of monomeric and dimeric acridine compounds as potential therapeutics in Alzheimer and prion diseases. Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry. 2009 Dec;342(12):699-709.
42. Antosova A, Chelli B, Bystrenova E, Siposova K, Valle F, Imrich J, Vilkova M, Kristian P, Biscarini F, Gazova Z. Structure-activity relationship of acridine derivatives to amyloid aggregation of lysozyme. Biochimica et Biophysica Acta (BBA)-General Subjects. 2011 Apr 1;1810(4):465-74.
43. Dudai Y, Silman I, Shinitzky M, Blumberg S. Purification by affinity chromatography of the molecular forms of acetylcholinesterase present in fresh electric-organ tissue of electric eel. Proceedings of the National Academy of Sciences. 1972 Sep;69(9):2400-3.
44. Lopes JP, Costa JS, Ceschi MA, Gonçalves CA, Konrath EL, Karl AL, Guedes IA, Dardenne LE. Chiral bistacrine analogues: Synthesis, cholinesterase inhibitory activity and a molecular modeling approach. Journal of the Brazilian Chemical Society. 2017;28:2218-28.
45. Jin H, Nguyen T, Go ML. Acetylcholinesterase and butyrylcholinesterase inhibitory properties of functionalized tetrahydroacridines and related analogs. Med. Chem. 2014;4(10):2161-0444.
46. Reka S, Magesh M, Tirupathiswamy N , Dhanalakshmi , Rameshwari ,Meenaloshini , Mahalakshmi D. Molecular docking studies of butyryl cholinesterase inhibitors comprising acridine derivatives. Eur Chem Bull.2023:12(6):159-181.
47. Magesh M , Poornima M , Shalini S, Mohamed imath M, Mohan raj K, Thirusha KM, Mahalakshmi D. In silico evaluation of anti cholinesterase activity of novel acridine scaffolds. Eur Chem Bull.2023:12(6):203-222.
48. Magesh M, Gandhimathi R. Design, synthesis and biological evaluation of substituted oxadiazolebenzamide derivatives as new scaffolds against alzheimer's disease. Eur Chem Bull.2023:12(4):3782-3792.
49. Magesh M. Design, Synthesis And Biological Evaluation Of Substituted Oxadiazole Derivatives As New Scaffolds Against Butyrylcholinesterase. Latin American Journal of Pharmacy. 2023 Apr 24;42(2):198-211.
50. Onkol T, Cakir B, Sahin FM. Synthesis and antinociceptive activity of 2-[(2-Oxobenzothiazolin-3-yl) methyl]-5- aminoalkyl/aryl-1,3,4-thiadiazole. Turk. J. Chem., 2002;28:461
51. L. Kaviarasan, E. Elizabeth, T. K. Praveen, R. Kalirajan, M. Manal, Pulla Prudviraj, and B. Gowramma. 1,3,4-Thiadiazolo (3,2-A) Pyrimidine-6-Carbonitrile Scaffold as PARP1 Inhibitor, Anti-Cancer Agents in Medicinal Chemistry 2021;21(15): 2050–65.
52. Swathi K, Gowramma B, Manal, M. Synthesis, in-silico and invivo evaluation of novel 1, 3, 4-thiadiazole analogues as novel anticancer agents. Letters in Drug Design & Discovery, 2019;16:1–11.
53. Wang HQ, Sun XB, Xu YX, Zhao H, Zhu QY, Zhu CQ. Astaxanthin upregulates heme oxygenase-1 expression through ERK1/2 pathway and its protective effect against beta- amyloid-induced cytotoxicity in SH-SY5Y cells. Brain Res. 2010; 1360: 159–167.

54. Yu H, Yao L, Zhou H, Qu S, Zeng X, Zhou D, et al. Neuroprotection against Aβ25-35- induced apoptosis by Salvia miltiorrhiza extract in SH-SY5Y cells. Neurochem Int. 2014; 75: 89–95.