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In Silico Design and Evaluation of Triazine Based 4-Thiazolidinone (TBT) Analogues as Anti Alzheimer's Agents through BACE 1 Inhibition

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ABSTRACT

Alzheimer's disease (AD) is a worldwide public health issue with an ageing problem. There is no effective medication or treatment that can stop the AD from progressing and lack of information regarding early detection, diagnosis and treatment of AD indications. Over the last two decades, advances in the understanding of illness pathophysiology and an increase in disease burden have driven research into novel therapies. In our study, we predicted potential BACE1 inhibitor molecules for AD treatment using a computational approach, i.e. molecular docking, and ADMET studies. The chemical structures of compounds drawn by chemoffice 16.0 and screened for pharmacokinetics and Receptor-ligand binding studies using Swiss ADME server and autodock vina tool respectively. Some of the prepared analogues exhibited good BACE1 inhibitory activity in which Compound TBT11 exhibited the most potent BACE1 inhibitory activity than the standard donepezil drug by comparing their binding affinity. The binding affinity of TBT11 was found to be -10.4 kcal/mol. Our results clearly demonstrate that 1,2,4-Triazine-4-thiazolidinone subordinates open up another road in the field of AD.

Keywords: BACE1 Inhibition; Alzheimer's Agents; APP Protein; Molecular Docking; ADMET; Amyloid Plaque; Co-Crystallized Ligands; Binding Energies; Swiss ADME Server; Binding Energy

Introduction

Alzheimer's disease (AD) is one of the most difficult neurodegenerative illnesses, affecting primarily people over the age of 65. The disease's confusing character makes its management all the more challenging [1,2]. More than 50 million people are suffering around the world, with the figure expected to rise to 150 million by 2050 [3]. The disease's multi-factorial nature, with numerous interrelated etiologies, prompted the development of multi-target directed ligands (MTDLs). In the field of neurodegenerative illnesses, MTDLs have become a very important topic of research for both academia and industry [3,4]. The MTDL design consists of two or more pharmacophore moieties that are responsible for addressing numerous targets that are involved in disease etiology [4-6]. Identifying potent BACE1 inhibitors has become a major explored therapeutic technique in the fight against AD, in addition to finding medicines to combat the disease [6,7]. The metabolic stability and pharmacokinetic features of peptidomimetic BACE1 inhibitors such as hydroxy ethylene, hydroxymethyl-carbonyl,

hydroxyethyl-amine, and others are absent. Nonpeptide inhibitors are produced because they are smaller, have better metabolic stability, and penetrate the blood-brain barrier better [8]. Many scaffolds have been developed during the last few decades, including aminoimidazole, acyl guanidine, aminothiazoline, amino/iminohydantoin, aminooxazoline, and 2-aminopyridine [9]. The success of these compounds shows that BACE1 inhibitors may be useful in the fight against AD. The mechanistic pathway of β-secretase enzyme via APP cleavage shown in the (Figures 1 & 2). β-secretase cleaved the APP (Amyloid precursor protein) in a 99 amino acid contacting protein fragment which further undergoes proteolytic cleavage by γ-secretase to form neurotoxic αβ-oligomers that cause Plaquing as well as induced glutaminergic neurons to increase the influx of Ca^{2+} which destabilized the calcium homeostasis along with mitochondrial dysfunction which reduce the production of ATP and increase the production of ROS (Reactive Oxygen Species) as well as initiate apoptosis by opening of MPTP and cytochrome C. Another mechanistic path suggested that hyperphosphorylated Tau alter the Drp-1 by complexation which cause mitochondrial fission, result apoptosis.

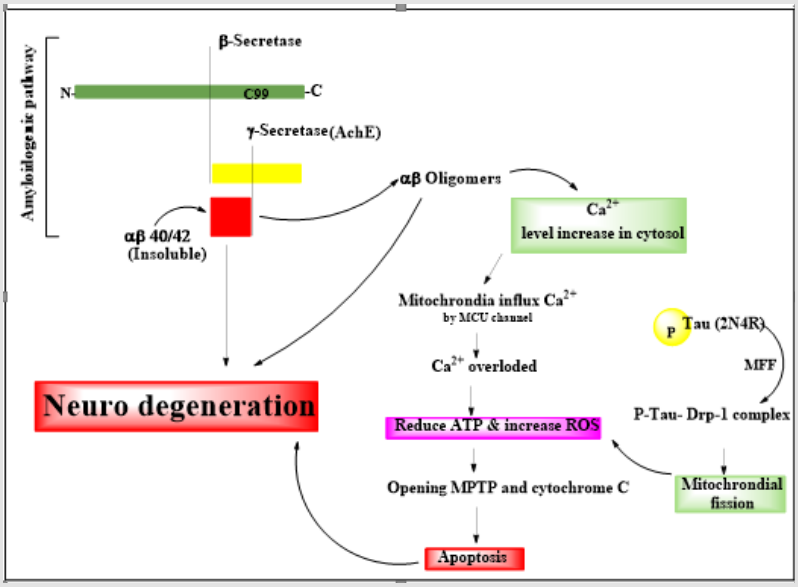

Figure 1: Mechanistic pathway of β-secretase enzyme via APP cleavage and pathogenesis of Alzheimer's diseases.

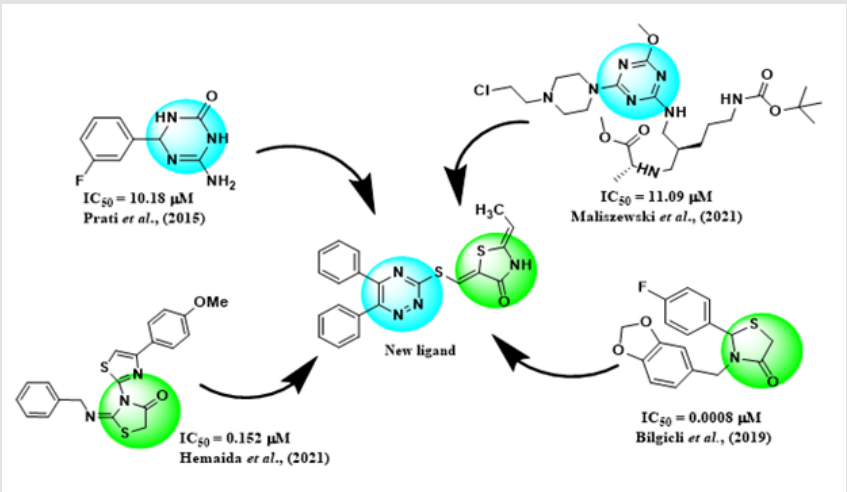

Figure 2: The structural rationality behind the designing of new inhibitors. Based on the clubbing with thiazolidine-4-one with the core scaffold, Triazine moiety.

Triazine is an important aromatic heterocyclic compound which build-up the thiazolidinone (TBT) linked scaffolds which are very effective in Alzheimer disease as multi-targeted agents [9-11]. Triazine as a core moiety required to stop the APP cleavage by the inhibition beta secretase enzyme. The mechanism of action suggests that the triazine inhibits the β-secretase enzyme pathway which prevent the chevage of amyloid precursor protein (APP) found on the extracellular neuronal cell [12,13]. Due to the cleavage of APP that generate the amyloid plaque which deposit on the neuronal cell. This plaque is toxic to neuronal cells that leads to the dementia afterword cause the Alzheimer disease [13,14]. Importance of 4-thiazolidinone was now a days play a crucial role in several diseases due to its sulphur containing heterocyclic scaffold showed a potentiality against ROS (reactive oxygen species). In our study, we tried to investigate the potential of anti-Alzheimer activity of some novel triazine linked thiazolidinone hybrids against β-secretase enzyme. As a feature of the in-silico examination we have arranged novel ligands and performed docking studies in Discovery Studio Version 2.5 on β-secretase protein (PDB ID: 1w51). Donepezil served as reference ligand, which is as of now accessible in market as inhibitor of Alzheimer agent [15,16].

Alzheimer diseases associated with multiple factors like neuroinflammation, β-cleavage by β-secretase, GSK3β mediated Tau hyperphosphorylation. Aβ-oligomer mediated oxidative stress and increase in influx of calcium ion in mitochondrial dysfunction. Here two nitrogenous heterocyclic moiety and sulphur containing heterocycles showed a crucial impact on the both inhibition of proteolytic enzymes and reduce the oxidative stress likewise 4-thiazolidinone showed an inhibitory impact on acetylcholinesterase enzyme that mediates inflammatory signals via PS-1 and further γ-secretase which produce Aβ-APP fragments as well as react with ROS (Reactive Oxygen Species) due to its high range of oxidation state of the sulphur. In previous research triazines scaffold showed good interaction with BACE-1 with promising IC50.

Objective

This in-silico experiment was performed to screen and identify Novel Triazine-4-Thiazolidinone hybrid as BACE-1 inhibitors by several methods like Molecular docking and drug-likeness screening etc.

Materials and Methods

Preparation of Proposed Ligand

The 3-Dimensiional structures of triazine based thiazolidinone and its analogues were drawn utilizing Chem3D Pro 16.0 programming package right away (Figure 3). For screening reason, we have also prepared library of 15 analogues (Figure 3). Based on the mechanism of action of triazine based thiazolidinone, it needs to be reduced the activation of BACE1 enzyme and that leads to the prevention of deposition of amyloid beta plaque on neuronal cell so based on the necessity, we have fused triazine based thiazolidinone. Then, at that point, the 3D designs of triazine based thiazolidinone analogues were allow for energy minimization utilizing MM2 force field parameters that comes under molecular mechanics method, to get the steadiest conformity. The energy minimization operation was finished utilizing Chem3D Pro 16.0 programming package (Figure 4). Such energy minimization treatment is vital for eliminate the effect of any conceivable adverse non-bonded connection, bond length, torsional turns, bond angle.

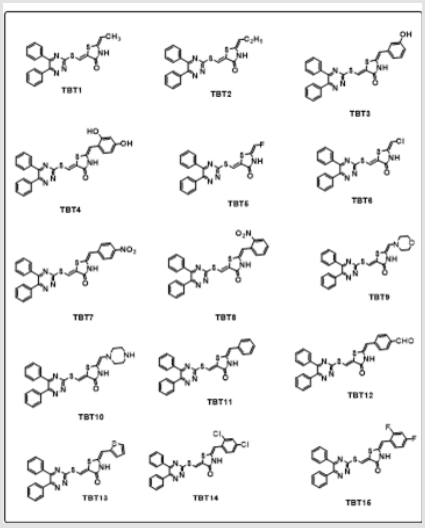

Figure 3: 2D-structure of proposed analogues of triazine based thiazolidinone scaffold.

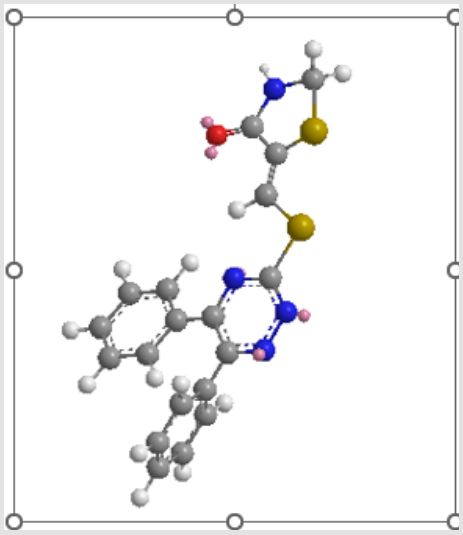

Figure 4: 3D-structure of proposed triazine clubbed with 4-thiazolidinone scaffold.

Preparation of Target

The crystal structure of β-secretase catalyst (PDB ID: 1w51) was brought from RCSB Protein Data Bank. The reasoning of choosing PDB ID: 1w51 was the presence of β-secretase enzyme in 1w51 which was viewed as bound in its active binding site. The protein file was ready by excluding Co-crystalised ligands and other atoms such as water from the design. Only amino acid chain A and B were saved for additional docking studies. PyMOL (version 2.5) programming tool was used for setting up the objective [17-19].

Docking

All the prepared analogues were docked to β-secretase enzyme (PDB ID: 1w51) using AutoDock Vina software. This package utilizes grids to pre-compute the binding interactions at multiple positions within the region of interest where score values are put into tables. By adding together table entries, binding energies for each position may be calculated rather quickly. To cover the limiting pocket, the grid enclose co-ordinate was set so that the focal point of the case was X: 69.497, Y: 49.083, Z: 7.359 and the aspect was X: 76, Y: 54, Z: 52 (8). AutoDock Vina utilizes flexible docking with rigid protein while at the same time permitting rotatable bonds for torsional rotation. PyMOL and Biovia Discovery Studio 4.1 were analysed the pose of the conformer different-different binding free energy using output file with the respective BACE1. This was done for confirming that ligands were docked at the appropriate region of interest after docking [20,21].

Pharmacokinetics and Drug-likeness Investigation

Pharmacokinetics, toxicities, and drug-likeness parameters of all TBTs analogues were screened using online Swiss ADME server. Initially, Pharmacokinetic characteristics are generally assessed during the development of a novel medicine. When there is a wide library of chemicals to consider but access to physical samples is limited. This website calculates key ADME-Tox and drug characteristics [22,23].

Results and Discussion

Binding energy of TBT analogues

Table 1: Binding affinity and DBEST of all TBT analogues compared to standard donepezil.

Analogues	Binding affinity	DBEST
TBT1	-8.7	-0.3
TBT2	-8.4	-0.6
TBT3	-9.4	0.4
TBT4	-9.1	0.1
TBT5	-9.4	0.4
TBT6	-9	0
TBT7	-9.9	0.9
TBT8	-9.1	0.1
TBT9	-9.7	0.7
TBT10	-8.8	-0.2
TBT11	-10.4	1.4
TBT12	-9.6	0.6
TBT13	-9	0
TBT14	-9.4	0.4
TBT15	-10.4	1.4
donepezil	-9	0

Donepezil was used as the standard in our research. As a result, the binding energy of donepezil was used to compare the binding

affinity of all TBTs (Table 1). summarises the binding energy. The binding energy difference between all TBTs and the standard was computed using the formula below. Difference between Binding energy of standard (Std) and TBTs (DBEST) = Binding energy of Std - Binding energy of TBTs. The numbers were used to construct a scatter plot after computing binding energy differences for all TBTs. In summary, the higher the DBEST value, the higher the binding affinity of TBT compared to standard. Except for TBT1, TBT2, and TBT10, all TBTs were shown to be better bound to the target than the parent molecule, as demonstrated by targeted docking. We chose all TBTs except TBT1, TBT2, and TBT10 for further investigation since a positive DBEST result suggests a better interaction than the standard (donepezil). TBT11 and TBT15 had the highest DBEST values since then (Table 1). The deviation of binding affinity of TBT analogues from donepezil shown in (Figure 5).

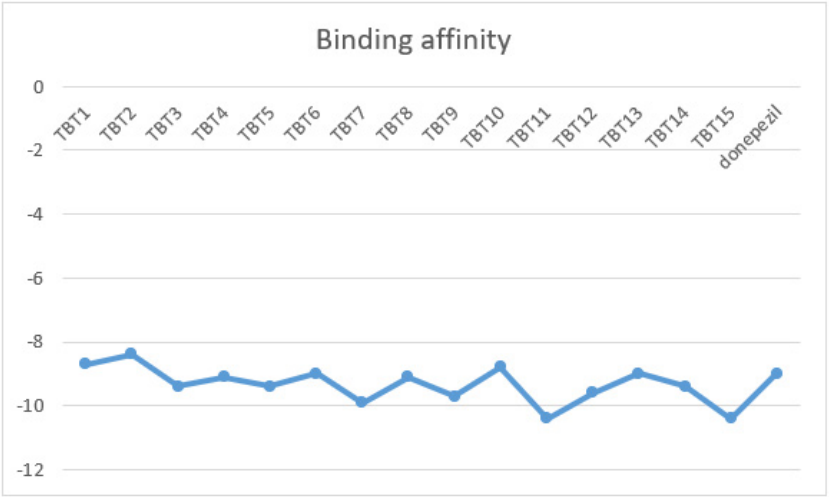

Figure 5: Deviation of binding affinity of TBTs analogues from donepezil.

Binding interaction of TBT analogues

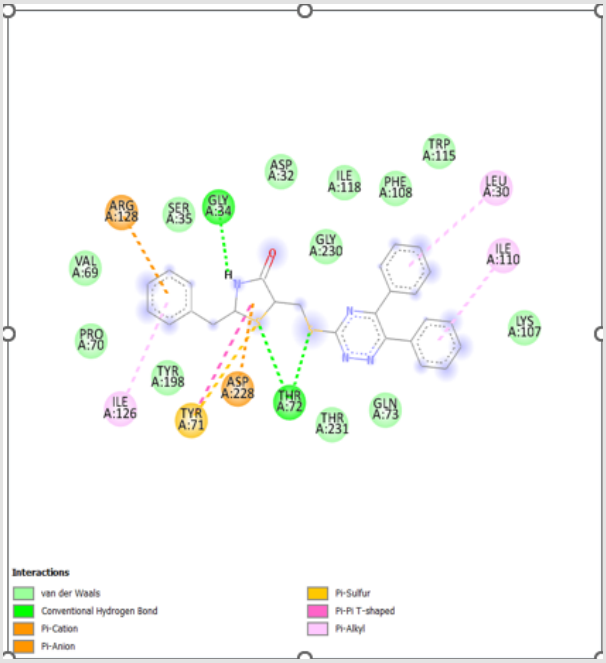

Figure 6: Binding interactions of TBT 11.

According to Patel et al the binding site of BACE (β-secretase) is located within a 2.55 Å comprising of TYR71, ASP228, GLY34, ASP32, VAL69, TYR198, THR72, GLN73, THR232, GLY230, and ILE110 of chain A. The crystal structure of BACE extracted from PDB reveals that TYR71, ILE110, GLN73, GLY230, ASP228 and THR72 are crucial for binding. Most of our TBTs, as well as the Standard, showed their interaction with these amino acids, indicating that these amino acids are also significant in interacting with TBT analogues, according to our findings. TBT11 and TBT15 are of particular relevance since their binding affinity is -10.4 kcal/mol and they interact with eight and nine amino acid residues, respectively, whereas most other TBTs do not. TBT15 has nine interactions that include hydrogen bonds, hydrophobic bonds, halogen bonds, and others (Table 2). It also interacted with the amino acids TYR71, ARG128, ILE126, GLY34, ASP228, THR231, THR72, LEU30, and ILE110, which were critical for interaction. Except for THR231, TBT11 has eight interactions with the same amino acid residue as TBT15 (Figure 6). TBT7, another possibility, could be a potential hit because it has the second highest binding affinity (-9.9 kcal/mol) and a 66.66 percent similarity. TYR198, ARG128, ILE110, GLY34, ASP228, THR72, LEU30, and ILE110 were among the eight amino acid residues with which it interacted (Table 2). 3.3

Pharmacokinetic and drug likeness analysis

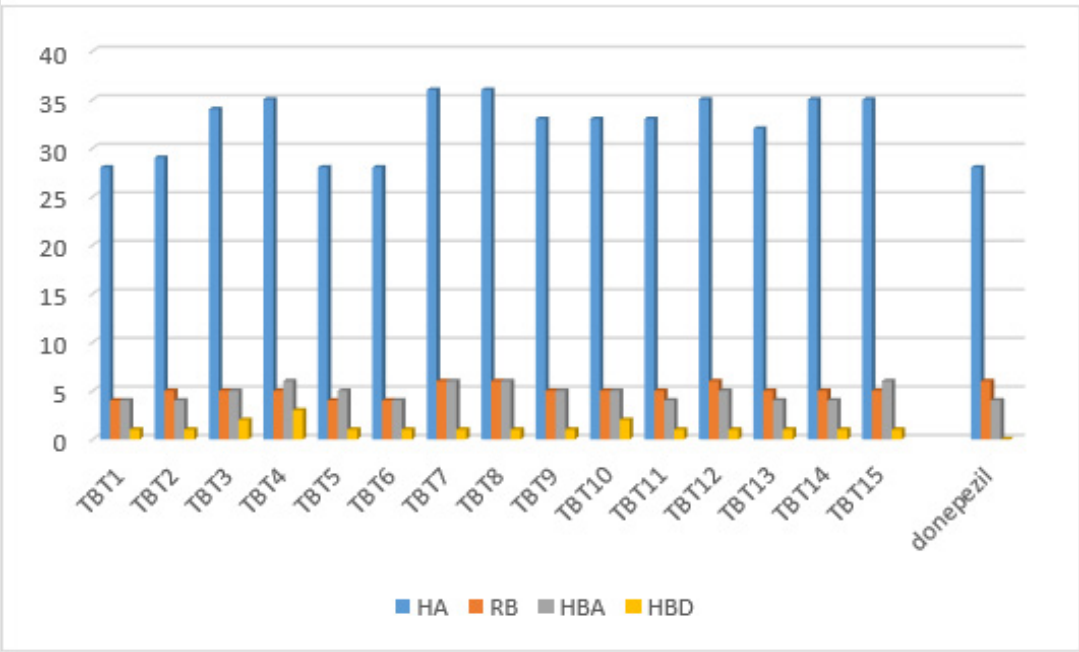

Figure 7: Graphical representation of distribution of HA = no. of heavy atoms, RB = no. Of rotatable bonds, HBA= no. of hydrogen bond acceptor, HBD= no. of hydrogen bond donor.

The in-silico algorithms were built using ligand molecular characteristics (also known as descriptors), such as molecular weight (MW), lipophilicity, hydrogen bond donors, and hydrogen bond acceptors (MW less than 500 Dalton, logP less than 5, H-bond donors less than 5, and H-bond acceptors less than 10). The SwissADME web service was used to conduct a pharmacokinetic (ADME) research of TBT and its analogues (Figure 7). When a drug is taken orally, its absorption in the gastrointestinal tract (GI tract) becomes critical. According to our research all analogues were expected to have good absorption from the GI tract. The LogKp value can be used to determine the degree of skin penetration. Skin permeability was better when Log Kp was higher, and vice versa (Table 3). All of the analogues used in the study did not penetrate the skin layer particularly well, indicating that there was no skin toxicity. The topological polar surface area (TPSA), which was screened by the study of rotatable bonds, the analysis of molecular complexity, and the quantity of stereocenters, was one of the physicochemical and molecular features of analogues. Except for TBT7 and TBT8 (which had one violation), all analogues passed Lipinski's rule, indicating that they had a good chance of becoming an oral medication. Finally, these findings facilitate the synthesis of these analogues, and they will be easy to synthesize, according to Synthetic Accessibility Score data (Table 3).

Table 3: Physicochemical, pharmacokinetic & druglike properties of selected hits.

ANALOGUES	FORMULA	MW	HA	RB	HBA	HBD	TPSA	xLogP	GI abs	PGP substrate	Log Kp	Lipinski' rule	Bioavailability	Synthetic accessibility
TBT1	$C_{21}H_{16}N_4OS_2$	404.51	28	4	4	1	125.07	5.52	High	No	-4.85	Yes	0.55	3.9
TBT2	$C_{22}H_{18}N_4OS_2$	418	29	5	4	1	125.07	4.5	High	No	-5.66	Yes	-	4.05
TBT3	$C_{26}H_{18}N_4O_2S_2$	482.58	34	5	5	2	145.03	-	-	-	-	-	-	-
TBT4	$C_{26}H_{18}N_4O_3S_2$	498.58	35	5	6	3	165.53	-	-	-	-	-	0.55	-
TBT5	$C_{20}H_{13}FN_4OS_2$	408.47	28	4	5	1	125.07	3.59	High	No	-6.24	Yes	0.55	3.74
TBT6	$C_{20}H_{13}ClN_4OS_2$	424.93	28	4	4	1	125.07	4.12	High	No	-5.97	Yes	0.55	3.73
TBT7	$C_{26}H_{17}N_5O_3S_2$	511.57	36	6	6	1	170.89	5.16	Low	No	-5.76	No (1)	0.55	4.28
TBT8	$C_{26}H_{17}N_5O_3S_2$	511.57	36	6	6	1	170.89	5.16	Low	No	-5.76	No (1)	0.55	4.37
TBT9	$C_{24}H_{21}N_5O_2S_2$	475.59	33	5	5	1	137.54	3.27	High	Yes	-6.9	Yes	0.55	4.27
TBT10	$C_{24}H_{22}N_6OS_2$	474.6	33	5	5	2	140.34	2.95	High	Yes	-7.1	Yes	0.55	4.31
TBT11	$C_{26}H_{18}N_4OS_2$	466.58	33	5	4	1	125.07	5.33	Low	No	-5.36	Yes	0.55	4.25
TBT12	$C_{27}H_{18}N_4O_2S_2$	494.56	35	6	5	1	142.14	4.79	Low	No	-5.92	Yes	0.55	4.29
TBT13	$C_{24}H_{16}N_4OS_2$	472.61	32	5	4	1	-	-	-	-	-	-	-	
TBT14	$C_{26}H_{16}C_{l2}N_4OS_2$	535.47	35	5	4	1	-	-	-	-	-	-	-	
TBT15	$C_{26}H_{16}F_2N_4OS_2$	502.56	35	5	6	1	125.07	-	-	-	-	-	-	
Donepezil	$C_{24}H_{29}NO_3$	379.49	28	6	4	0	38.77	4.28	high	yes	-5.58	Yes	0.55	3.62

Conclusion

In this research, in silico tools such as Molecular docking was used to evaluate the interaction of several anti-Alzheimer's analogues with β-site APP-cleaving enzyme 1 (BACE1). TBT7, TBT11 and TBT15 were modified derivatives that had a higher binding affinity for the target BACE1 due to H-bonding and other interactions. This study finds some amino acid residues required for interaction with drugs that have been changed TYR71, ARG128, ILE126, GLY34, ASP228, THR231, THR72, LEU30, and ILE110 were the primary amino acid residues that showed interaction analogues. All analogues were expected to have good GI tract absorption, escape P-gp, and cause no skin toxicity. TBT11 may be a possible BACE inhibitor in the future, according to the findings of this study. As a result, these analogues should be chosen for further synthesis. The significance of the Synthetic Accessibility Score in the

synthesis of modified analogues was shown. The concept of in silico design of medicinal compounds arose with the goal of drastically reducing the length and cost of research. Our research attempts to develop a more potent medicine than the current one, Donepezil. Our computational research findings will serve as a roadmap for pharmaceutical chemists interested in testing our findings in the lab.

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Nil.

Conflicts of Interest

The authors certify that no actual or potential conflict of interest in relation to this article exists.

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