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Research Article

Screening of Some Sulfonamide and Sulfonylurea Derivatives as Anti-Alzheimer's Agents Targeting BACE1 and PPARγ

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In the last few decades, Alzheimer's disease (AD) has emerged as a serious global problem, and it has been considered as the most common type of dementia. PPARγ and beta-secretase 1 (BACE1) are considered as potential targets for Alzheimer's disease management. In the same time, sulfonylureas and sulfonamides have been confirmed to have PPARγ agonistic activity. Aiming to obtain new anti-AD agents, thirty-five compounds of sulfonamide and sulfonylurea derivatives having the same essential pharmacophoric features of the reported PPARγ agonists have been subjected to virtual screening. Docking studies revealed that five compounds (1, 2, 3, 4, and 5) have promising affinities to PPARγ. They were also docked into the binding site of BACE1. In addition, ADMET and physicochemical properties of these compounds were considered. Additionally, these compounds were further evaluated against BACE1 and PPARγ. Compound 2 showed IC_{50} value of 1.64 μM against BACE1 and EC_{50} value of 0.289 μM against PPARγ.

1. Introduction

Alzheimer's disease (AD) is one of the most well-known neurodegenerative diseases, and it is characterized by a series of various mental conditions such as memory loss and other cognitive impairments [1]. Today, 50 million people are suffering from AD, and 5.4 million of them are Americans. Currently, a new case appear every 67 seconds, and by 2050, each new case of AD is expected to appear every 33 seconds, with an approximate prevalence range between 11 million and 16 million patients [2]. AD is a major health issue for all communities.

Physiological deregulations associated with disease progression have been identified, such as loss of synapses and synaptic activity, structural and functional mitochondrial defects, inflammatory responses, development of extracellular neuritis plaques, and neuronal losses [3]. The neurological disorders of AD occur extracellular, essentially in amyloid-β peptide (Aβ), or intracellular by aggregation of phosphorylated tau proteins.

There are many AD treatments comprising 105 drugs, of which twenty-five are in phase I, fifty-two are in phase II, and twenty-eight are in phase III [4]. The approved drug treatments include the following: (i) cholinesterase

inhibitors as donepezil, rivastigmine, and galantamine [5, 6] and (ii) memantine that uncompetitively blocks the NMDA receptor and can act as a neuroprotective [7]. Additionally, there are many potential future drug treatments: (i) anti-amyloid treatment, targeting amyloid-β (Aβ), gamma-secretase, or beta-secretase (as AZD3293 and MK-8931) [8]; (ii) immunization against Aβ as AN 1792, which was stopped because of meningoencephalitis in 6% of subjects [9]; (iii) monoclonal antibodies as bapineuzumab, which is a monoclonal antibody targeting Aβ, examined in patients with mild to moderate AD during phase III clinical trial [7]; (iv) tau-targeted therapy currently in clinical trials as methylthioninium (phase II clinical trial), and it has showed advantages for patients with AD after fifty weeks therapy [10].

The β-secretase enzyme, which is known as β-site amyloid precursor protein cleaving enzyme 1 (BACE1), initiates the production of the toxic amyloid-β (Aβ) that plays an important role in Alzheimer's disease [11]. BACE1 is a crucial therapeutic target for reducing cerebral Aβ concentrations in AD because of its vital role in the generation of Aβ. Nevertheless, BACE1 also acts as a housekeeping enzyme, and it is implicated in the treating of many other proteins that are responsible for appropriate neuronal tissue function [12]. In addition, recent studies on multitarget directed ligands have provided insight and hope on the use of natural products in targeting AD via BACE-beta amyloid mechanism [13].

Studies have shown that an altered insulin pathway can affect the deposition of amyloid-β protein and the phosphorylation of tau protein, both leading factors in the development of AD [14]. Hence, drugs used for type 2 diabetes mellitus (T2DM) as sulfonylurea receptor SUR agonists and peroxisome proliferator-activated receptors (PPARɣ) agonists may represent a promising candidate to fight against AD [15].

Sulfonylureas (SUs) are one of the most well-known groups of antidiabetic drugs that stimulate insulin secretion by interacting with the pancreatic ATP-sensitive potassium channels (KATP) [16], which are also found in neurons [17]. It was reported that glibenclamide treatment of mice decreased hippocampal A., inhibited neuronal apoptosis, and improved synaptic plasticity of the hippocampus [18]. Also, a combination of metformin and sulfonylurea has been reported to decrease the risk of dementia by 35% over eight years [19]. Recently, it has been reported that the incidence of dementia is decreased in T2DM patients when receiving SUs treatments [20, 21].

New sulfonamides were designed and synthesized aiming to produce multifunctional agents against Alzheimer's disease. Their investigation resulted in the identification of promising leads that can help in further development of new promising candidates [22].

PPARγ plays an essential role in the metabolism of glucose and in the processing of fatty acids, making it a key target for the production of antihyperglycemic agents [23]. They also enhance skeletal muscle sensitivity, inhibit hepatic gluconeogenesis, boost glycemic control, and decrease circulating insulin levels [24]. It has been reported that PPARγ agonists can suppress proinflammatory molecules in peripheral immune cells and resident glial cells; hence, PPARγ agonists are considered to be active against Alzheimer's disease. In addition, these agonists showed significant effects in neurodegenerative CNS disorders in animals [25]. PPARγ agonists were also reported to have a role in neurons inflammatory disorders because of their potential to suppress NFkB-mediated signals at numerous sites [26].

Moreover, it has been confirmed before that sulfonylureas and sulfonamides have the PPARγ agonistic activity [27, 28]. Additionally, it was reported that some sulfonamide derivatives showed bioactivity against BACE1, indicating their expected potential as promising anti-AD active agents [29].

In the normal physiological conditions, PPARγ can be expressed in the brain at low levels. A full analysis of gene expression has lately shown that mRNA levels are high in patients with AD [30]. This indicates that PPARγ plays a vital role in the modulation of the AD pathophysiology. The drugs currently used are primarily aimed at symptomatic treatment. Such agents have a limited therapeutic efficacy over rather short periods. Therefore, the development of new therapeutic approaches is critical [31].

In this work, our rationale focused on investigating some recorded sulfonylureas and sulfonamides on PPARγ and BACE1. Accordingly, we have performed virtual screening using docking studies for tens of sulfonamides and sulfonylureas against PPARγ and BACE1. The most promising compounds were further tested *in vitro* against PPARγ and BACE1.

1.1. Rational of Molecular Design. Studying the structure-activity relationships of PPARγ agonists revealed that they have five basic structural features for binding to PPARγ. The features include an acidic head, a linker attached to an aromatic scaffold (spacer group), a linker, and a heteroaromatic lipophilic tail [32, 33] (Figure 1). Thiazolidinediones (TZDs) class is the most famous class of compounds reported as high-affinity agonists to PPARγ [34, 35].

Also, it was reported that sulfonylureas and sulfonamides have PPARγ agonistic activity. Accordingly, in this study, moieties of sulfonylurea and sulfonamide serve as acid heads required for the agonistic action of PPARγ. In our compounds, the sulfonyl (SO_2) group acts as a single atom spacer between an acid head and an aromatic group. The para-disubstituted phenyl group acts as an aromatic spacer, which is essential for ideal PPARγ agonism [36]. Many different linkers between the lipophilic tail and an aromatic spacer have been utilized in our compounds. These linkers are important for the agonistic action of PPARγ. Eventually, various heteroaromatic nuclei were used to serve as the lipophilic tail necessary for PPARγ.

Based on the above considerations and to obtain new anti-AD agents, thirty-five reported sulfonamide and sulfonylurea derivatives [37–39] having the same essential pharmacophoric features of the reported PPARγ agonists (Figure 2) have been screened using virtual screening via docking studies (Figure 3). Based on docking studies, the

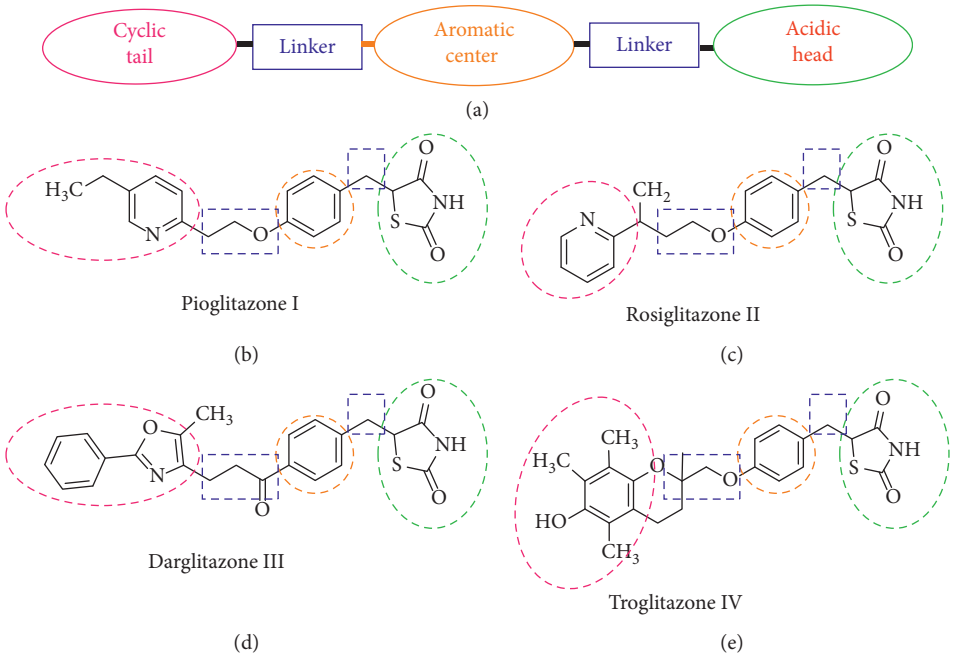


Figure 1: The basic essential pharmacophoric features of PPARγ agonists and some reported compounds.

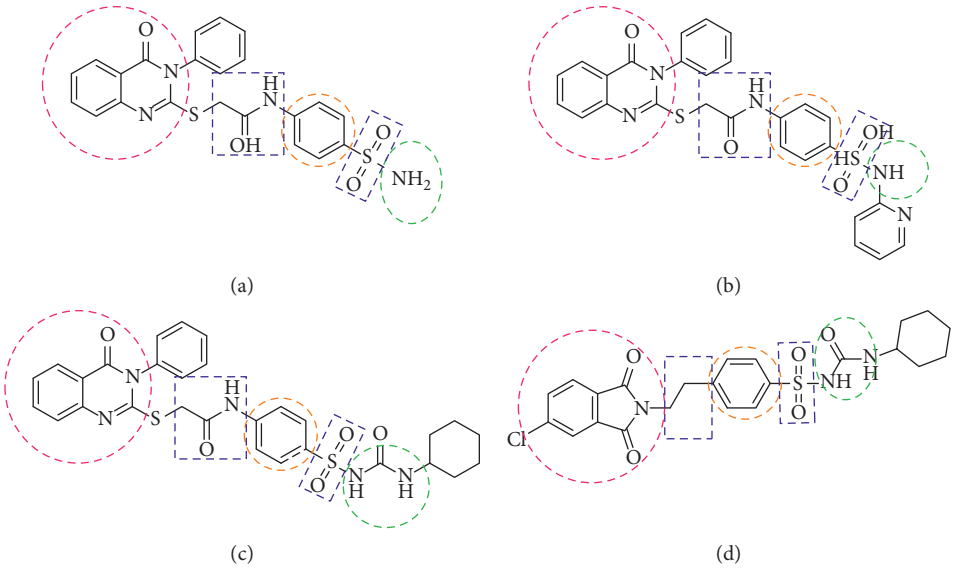


Figure 2: Sulfonamide and sulfonylurea derivatives having the same essential pharmacophoric features of the reported PPARγ agonists.

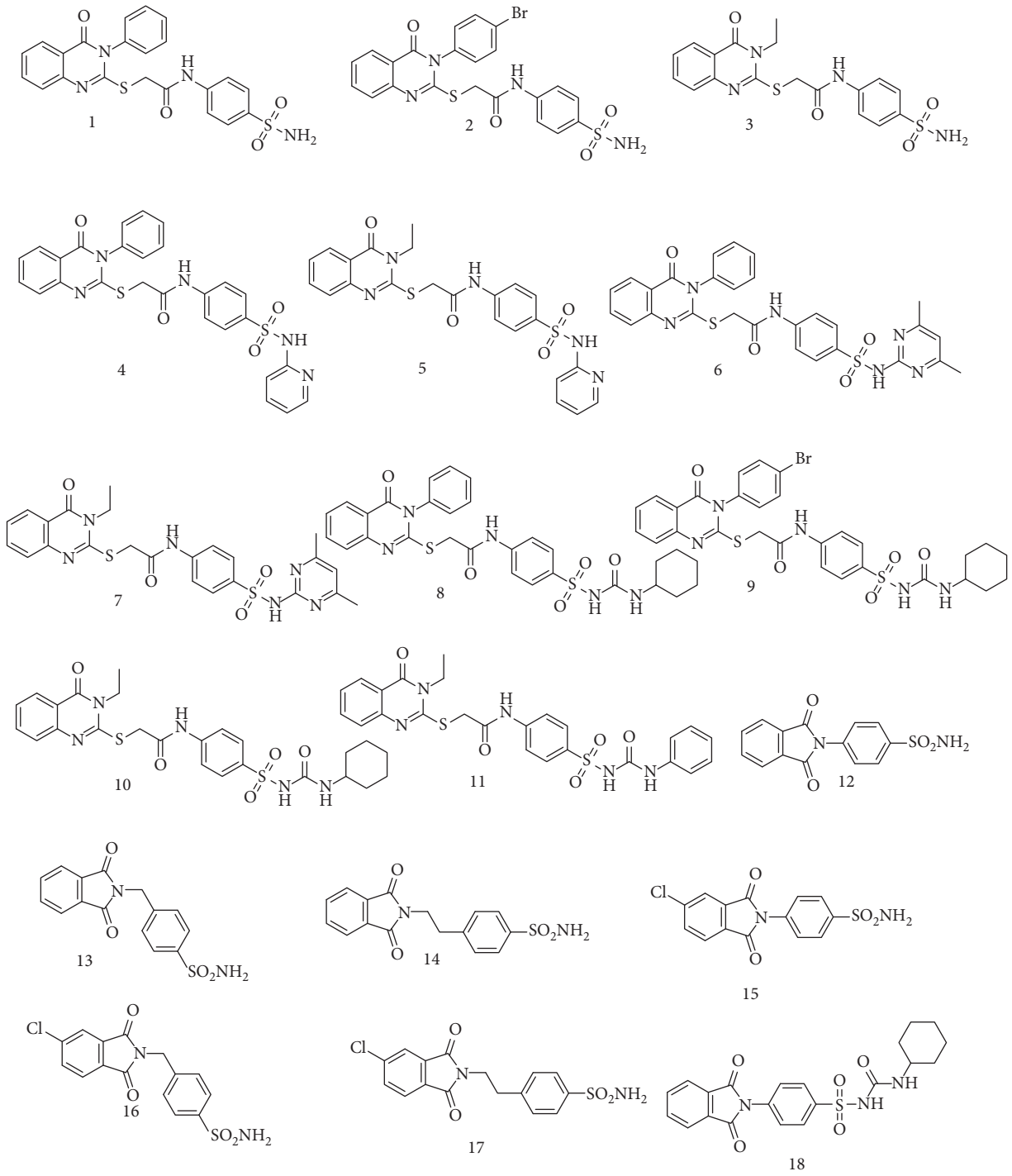
most promising candidates were subjected to further *in silico* and *in vitro* studies. The *in silico* studies include docking against BACE1, ADMET, and physiochemical properties. The *in vitro* studies comprise the PPARγ-ligand binding assay and BACE1 inhibitory activities.

2. Experimental

2.1. Virtual Screening via Docking Studies

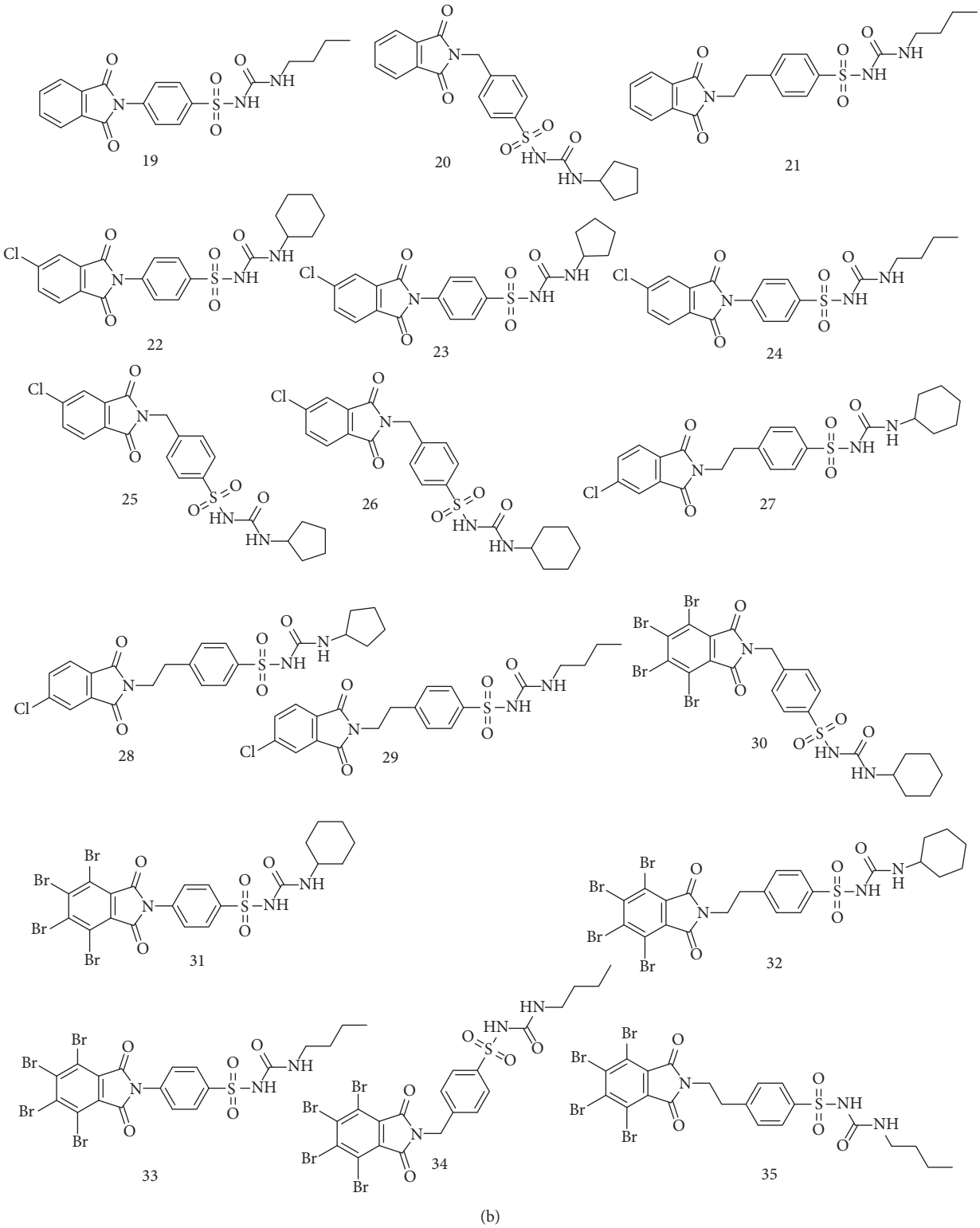
2.1.1. Preparation of the Target Molecules. The target molecules, PPARγ (PDB ID: 1FM6 resolution 2.1 Å, https://www.rcsb.org/structure/1FM6) and BACE1 (PDB ID: 2qk5, resolution 2.2, https://www.rcsb.org/structure/2QK5), were downloaded from the Protein Data Bank. MOE software was used in the performance of the docking analysis [40]. In this procedure, the free energies and binding modes of the analyzed compounds against PPARγ and BACE1were detected. The active sites of both targets were prepared by a sequence of several steps including deleting water molecules, protonation of each amino acid chain, and hiding the hydrogen atoms.

2.1.2. Energy Minimization. The energy of the target receptors was minimized using the energy minimization



(a)

Figure 3: Continued.



(b)

Figure 3: Structures of the reported sulfonamides and sulfonylureas.

algorithm of the MOE tool. The following parameters were utilized for energy minimization: gradient: 0.05, force field: MMFF94X + solvation, and chiral constraint: current geometry. Energy minimization was terminated when the root mean square gradient falls below 0.05. The initial and final energy of protein were calculated (in kcal/mol) by GizMOE using MMFF94X force field with the conjugant gradient method. The minimized structure was used as the template for docking. Then, the binding active sites of the target receptors were defined.

2.1.3. Calculating the Active Site Sequence. Active sites present in the target receptors were identified from the following parameters: compute, surfaces and maps, molecular surface, create, and isolate.

2.1.4. Preparation of Ligand Molecule. The next step involves the preparation of the tested compound for docking. This step starts by drawing these compounds using ChemBioDraw Ultra 14.0. The created file was saved as MDL-SD format. Then, the saved file was opened using MOE. Next, several processes were carried out including protonation of the 3D structures of the tested compounds and rosiglitazone, minimization of the potential energy, and validation process.

2.1.5. Docking Process. The binding of the ligand molecule with the target molecules was carried out using MOE program to find the correct conformation (with the rotation of bonds, the structure of molecule is not rigid) and configuration (with the rotation of whole molecule, the structure of the molecule remains rigid) of the ligand, so as to obtain minimum energy structure. The parameters used for docking were as follows: total runs = 30, gradient = 0.01, no. of return poses = 1000, iteration limit = 500, potential energy grid: ON, rescoring1: London dG, and refinement: force field. The output from MOE was further analyzed with Discovery Studio 4.0 software [41, 42].

2.2. In Silico ADMET Analysis. The ADMET model of Discovery Studio software version 4.0 was used to access the drug-like properties of the tested compounds. Lipinski's rule of five was used as a standard [43]. This rule explains different properties of a drug molecule, as well as its solubility, absorption, interaction, metabolism, excretion, and toxicity were also predicted. In this study, the protocol of ADMET descriptor module of the small molecules was applied as following steps.

2.2.1. Ligand Preparation. The tested compounds were drawn using ChemBioDraw Ultra 14.0 and saved as MDL-SD format. This file was opened using Discover Studio software version 4.0. The ligand geometry was minimized by applying the force field algorithm, and the ligand preparation protocol was achieved using the following parameters: change ionization: true, generate tautomer: true, generate isomer: true, fixed bad valences: true, generate coordinates: 3D, parallel processing: false, and then run [44].

2.2.2. Drug-Likeness Prediction. From the protocol of small molecules, ADMET descriptors were used. Then, the prepared ligands in the previous step were applied. Also, the different descriptors including aqueous solubility, blood–brain barrier penetration, cytochrome P450 2D6 enzyme inhibition, hepatotoxicity, and plasma protein binding level were applied [44].

2.3. BACE1 Assay. The inhibition activity of tested compounds to BACE1 was determined via manufacturer's protocol from Invitrogen Kit (L0724) [45]. IC_{50} (concentration of compound required to displace 50% of titrated ligand) was calculated, and each experiment was repeated twice.

2.4. PPARγ-Ligand Binding Assay. The binding affinity of the tested compounds to PPARγ was determined via the fluorescence polarization assay technique [46]. The Polar Screen™ PPARγ-competitor assay kit (Invitrogen, Carlsbad, CA) was used in this technique. According to the manufacturer's instructions, the procedure of determination of binding affinity was conducted. EC_{50} (concentration of compound required to displace 50% of titrated ligand) was calculated [47], and each experiment were repeated twice.

2.5. Computational Determination of the Essential Physicochemical Properties. The essential physicochemical properties of the tested compounds (1, 2, 3, 4, and 5) were determined using Discovery Studio 4.0 software. First, the compounds were prepared by the application of force fields via CHARMM and MMFF94. Then, the different molecular descriptors were predicted from the general purpose protocol [38, 44, 48].

3. Results and Discussion

3.1. Virtual Screening

3.1.1. Docking Studies against PPARγ. The receptor-based drug design (docking) approach [49–56] was used to analyse the binding mode of the reported compounds with the PPARγ. According to the literature survey, the PPARγ cavity consists of three main parts: an entrance, arm I, and arm II. Arm I contains four polar residues such as Ser289, Tyr473, His323, and His449 involved in hydrogen bonding. Arm II comprises of Ile281, Ile 341, Leu353, and Val339, while the entrance consists of Leu330 Leu333, Arg288, and Ser342 [57] (Figure 4).

The results of virtual screening using docking studies revealed that some of the analyzed compounds exhibited similar orientations inside the putative binding sites of PPARγ. The binding energies of these compounds against PPARγ are illustrated in Table 1. The results indicated that there are five compounds that have promising binding affinity toward PPARγ. Then, the binding mode of the most promising members was discussed in detail as follows.

Rosiglitazone (the co-crystalized ligand) showed a binding mode with an affinity value equal to −24.44 kcal/mol. Thiazolidinedione nucleus was directed into the polar site of the receptor. Thiazolidinedione formed two hydrogen bonding interactions with Ser289 and His449. The pyridine moiety formed hydrophobic interactions with Arg288 and Val339. The central phenyl ring formed hydrophobic interactions with Leu330 and Cys285 (Figures 5 and 6).

Compound 1 showed a binding mode like that of the co-crystalized ligand (rosiglitazone), with binding energy of

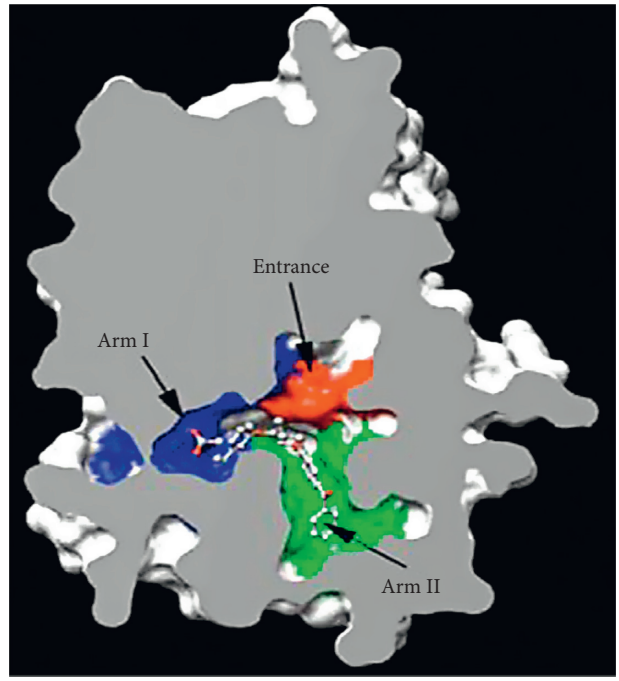


Figure 4: PPARγ cavity showing the three main parts: arm I arm II, and an entrance [57].

Table 1: The docking binding free energies of the screened compounds against PPARγ.

Comp.	Binding free energy (kcal/mol)	Comp.	Binding free energy (kcal/mol)
1	−18.05	19	−12.26
2	−28.62	20	7.88
3	−24.35	21	12.17
4	−17.96	22	−13.43
5	−20.86	23	−13.21
6	8.06	24	−13.88
7	−15.04	25	−10.08
8	−11.75	26	−17.94
9	−5.29	27	−17.34
10	−6.17	28	13.05
11	−8.19	29	−11.24
12	−10.80	30	−9.99
13	−14.23	31	−13.89
14	−8.85	32	−8.63
15	−7.59	33	−17.12
16	−14.25	34	−16.02
17	−15.57	35	−16.60
18	−12.23	Rosiglitazone	− 24.44

−18.05 kcal/mol. The sulfonamide group was directed into the polar part of PPARγ forming two hydrogen bonds with Cys285 and Ser289. 3-Phenylquinazolin-4(3*H*)-one moiety was oriented in the hydrophobic pocket forming hydrophobic interactions with Leu333, Glu343, Arg288, Cys285, and Ile341. Also, it has formed a hydrogen bond with Ser342. The phenyl spacer formed hydrophobic interaction with Ile326, Leu330, Cys285, and Arg288. Moreover, the amide moiety formed a hydrogen bond with Arg288 (Figures 7 and 8).

The binding mode of compound 2 (affinity value of −28.62 kcal/mol) was virtually like that of the co-crystalized ligand where the sulfonamide group was oriented in the hydrophilic region, forming three hydrogen bonding interactions with Tyr473, His449, and Ser289. The 3-(4-bromophenyl) quinazolin-4(3*H*)-one moiety was oriented in the hydrophobic region to form six hydrophobic interactions and two hydrogen bonds with Glu343 and Ser342 (Figures 9 and 10). The mapping surface technique was carried out to show compound 2 occupying the active pocket of PPARγ (Figure 11).

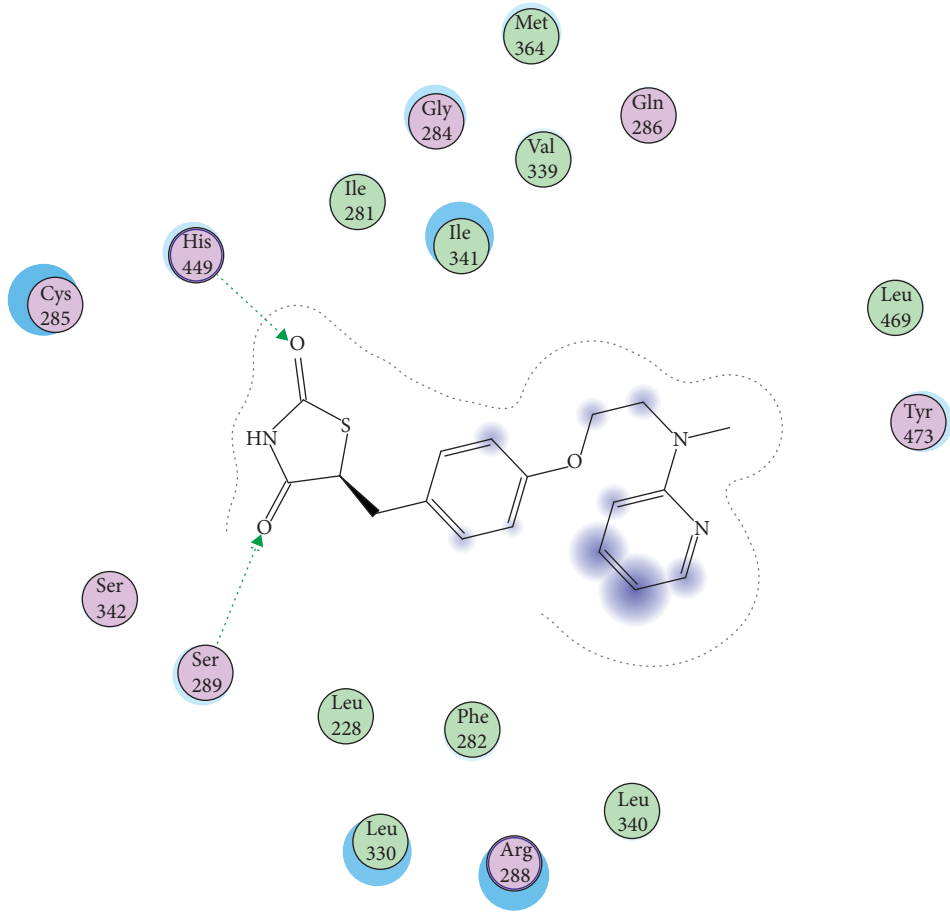


Figure 5: 2D structure of rosiglitazone docked into the active site of PPARγ.

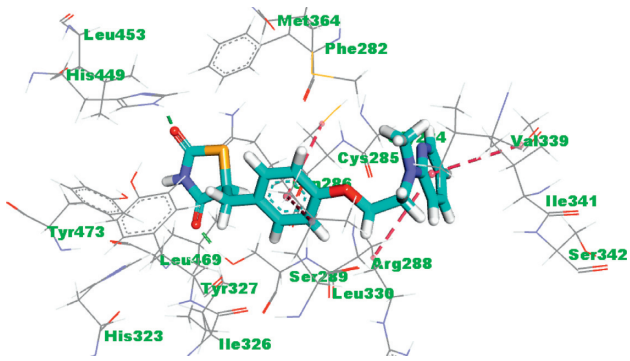


Figure 6: 3D structure of rosiglitazone docked into the active site of PPARγ.

Similarly, compounds 3, 4, and 5 showed binding modes like that of rosiglitazone with affinity values of −24.35, −17.96, and −20.86 kcal/mol, respectively (Figures 12–17).

3.1.2. Docking Studies against BACE1. The best five compounds that showed good affinity to *PPARγ* were selected to be subjected for further docking studies on BACE1. Results of docking studies revealed that the tested compounds have a good binding mode inside the pocket of BACE1 with binding energies ranging from −20.33 to −25.16 (Table 2). The co-crystalized ligand showed a binding mode with an affinity value equal to −25.60 kcal/mol. It has formed five hydrogen bonds with Asp93, Gly95, Asp289, Gly291, and Thr293. In addition, it has showed three hydrophobic interactions with Tyr132, Phe169, and Tyr259 (Figures 18 and 19).

Compound 3 (as a representative example, all figures for the other docked compounds are provided in supplementary data) showed a binding mode like that of co-crystalized ligand with a binding energy of −25.16 kcal/mol. It has formed three hydrogen bonds with Gly95, Arg189, and Thr133. In addition, it has formed four hydrophobic interactions with Tyr132, Trp176, Leu91, and Ile179 (Figures 20 and 21). The mapping surface technique was carried out to show compound 3 occupying the active pocket of BACE1 (Figure 22).

With regard to the binding mode of compounds 1, 2, 4, and 5 against BACE, these compounds exhibited binding modes like that of co-crystalized ligand with a binding energy of −25.16, −24.70, −22.03, −20.33, and −27.02 kcal/mol, respectively. They showed essential hydrogen bonds with the essential amino acids in the active site. Compound 1 formed hydrogen bonds with Arg189, Pro131, Asp289, and Thr133. Compound 2 formed hydrogen bonds with Gln134 and Tyr259. Compound 4 formed hydrogen bonds with

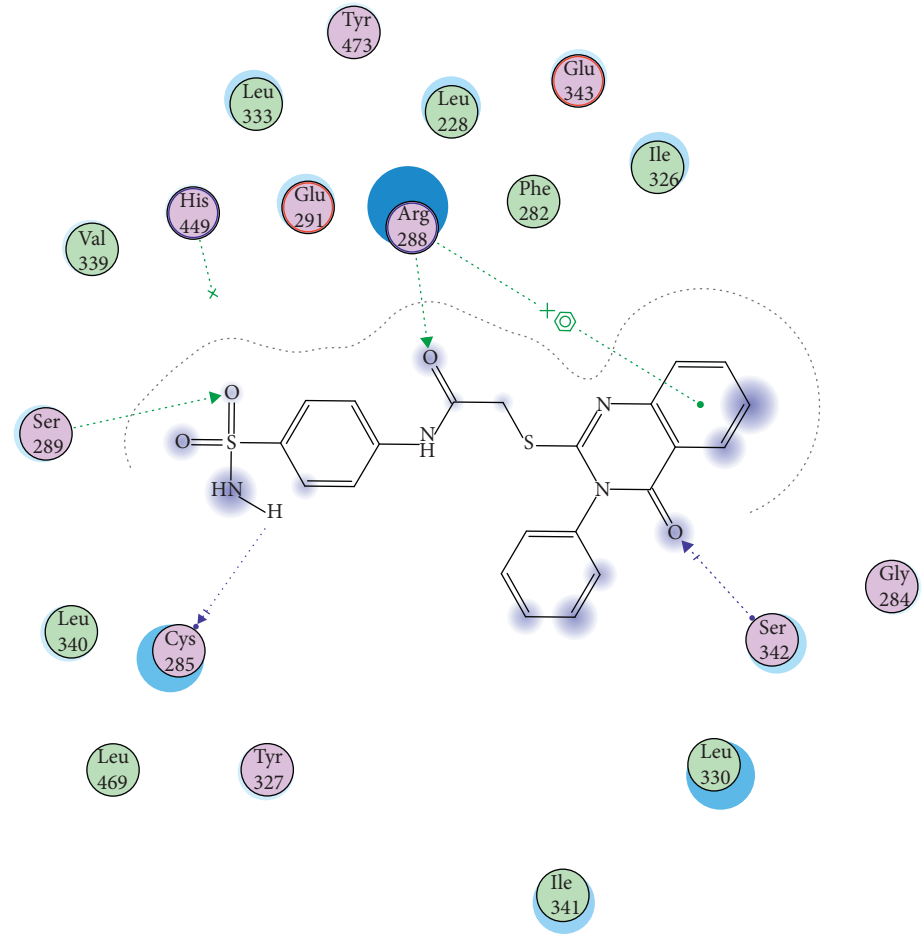


Figure 7: 2D structure of compound 1 docked into the active site of PPARγ.

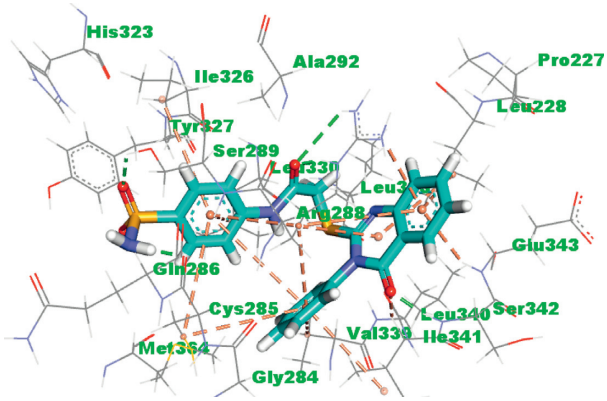


Figure 8: 3D structure of compound 1 docked into the active site of PPARγ.

Gln134, Tyr259, and Thr133. Compound 5 formed hydrogen bonds with Tyr259, Gln134, and Thr292 (supplementary data).

3.2. In Silico ADMET Analysis. ADMET studies are techniques used for the prediction of the pharmacokinetic behavior of new chemical agents [44, 48]. In this procedure, the analyzed compounds and the reference drug (pioglitazone) were subjected for computational determination of absorption level, cytochrome P450 2D6 enzyme inhibition, hepatotoxicity, plasma protein binding level, and solubility level. Discovery Studio 4.0 software was used in this technique (Table 3 and Figure 23).

The results revealed that most of the tested compounds have moderate intestinal absorption. On the other hand, compound 3 has good intestinal absorption, while compound 4 has poor intestinal absorption. The CYP2D6 score predicts the inhibitory and noninhibitory behavior of particular compounds on cytochrome P450 2D6 enzyme. The results showed that all the tested compounds are CYP2D6 noninhibitors. Also, the hepatotoxicity prediction values were in the range from 0.256 to 0.4567. Accordingly, liver dysfunction, the most common side effect of CYP2D6 inhibitors, is unexpected upon administration of such members. The plasma protein binding model predicts the binding ability of a compound to plasma proteins. All the tested compounds have a PPB level of more than 95%. It is widely known that many drug candidates did not reach the final phase of clinical trials due to problems related to their absorption properties [58]. Depending on the computation analysis of the synthesized compounds, it was found that most of the compounds have an ADME aqueous solubility logarithmic level equal to 1 or 2, indicating low-to-moderate aqueous solubility.

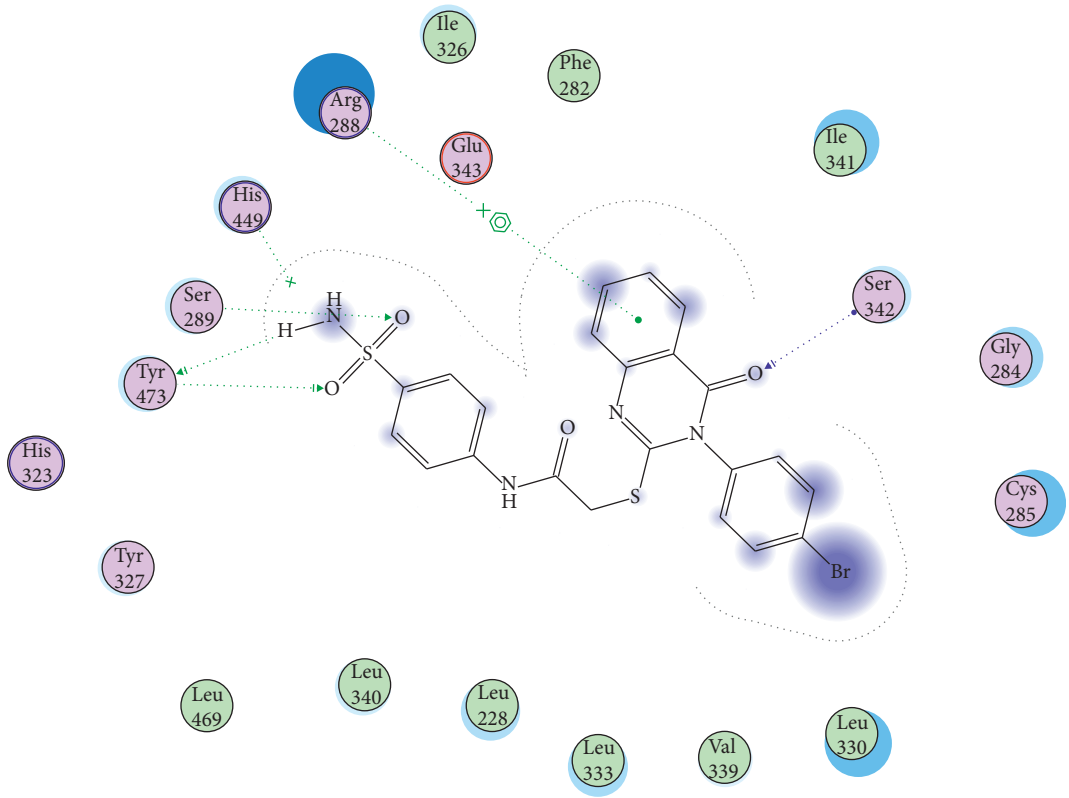


Figure 9: 2D structure of compound 2 docked into the active site of PPARγ.

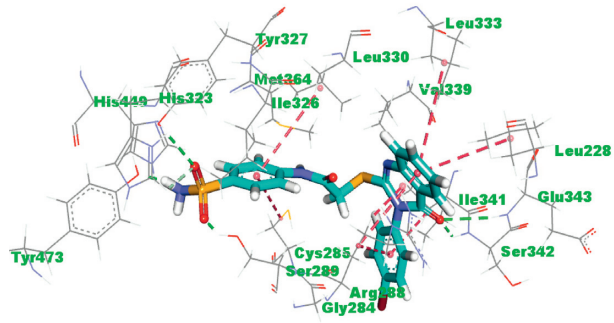


Figure 10: 3D structure of compound 2 docked into the active site of PPARγ.

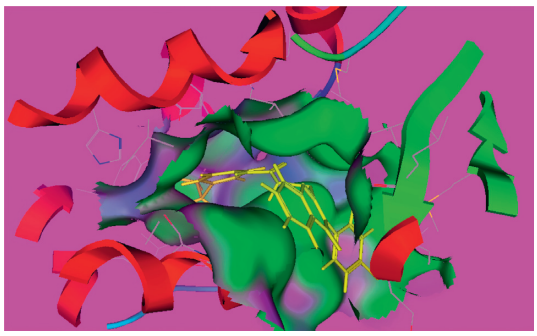


Figure 11: Mapping surface showing compound 2 occupying the active pocket of PPARγ.

3.3. Biological Evaluation

3.3.1. BACE1 Assay. Compounds 1–5 were examined to determine their abilities to inhibit BACE1 according to the manufacturer's protocol from Invitrogen (L0724), and the assay was performed to investigate the activity of the selected compounds against BACE1. The results of inhibition are reported in Table 4 as IC_{50} values. Compound 2 showed a significant inhibition to BACE1 with an IC_{50} value of 1.24 μM when compared with rosiglitazone ($IC_{50} = 1.74\,\mu$M). Compounds 1, 3, 4, and 5 showed a good inhibition to BACE1, and their IC_{50} values are 2.75, 3.59, 3.14, and 2.53 μM, respectively.

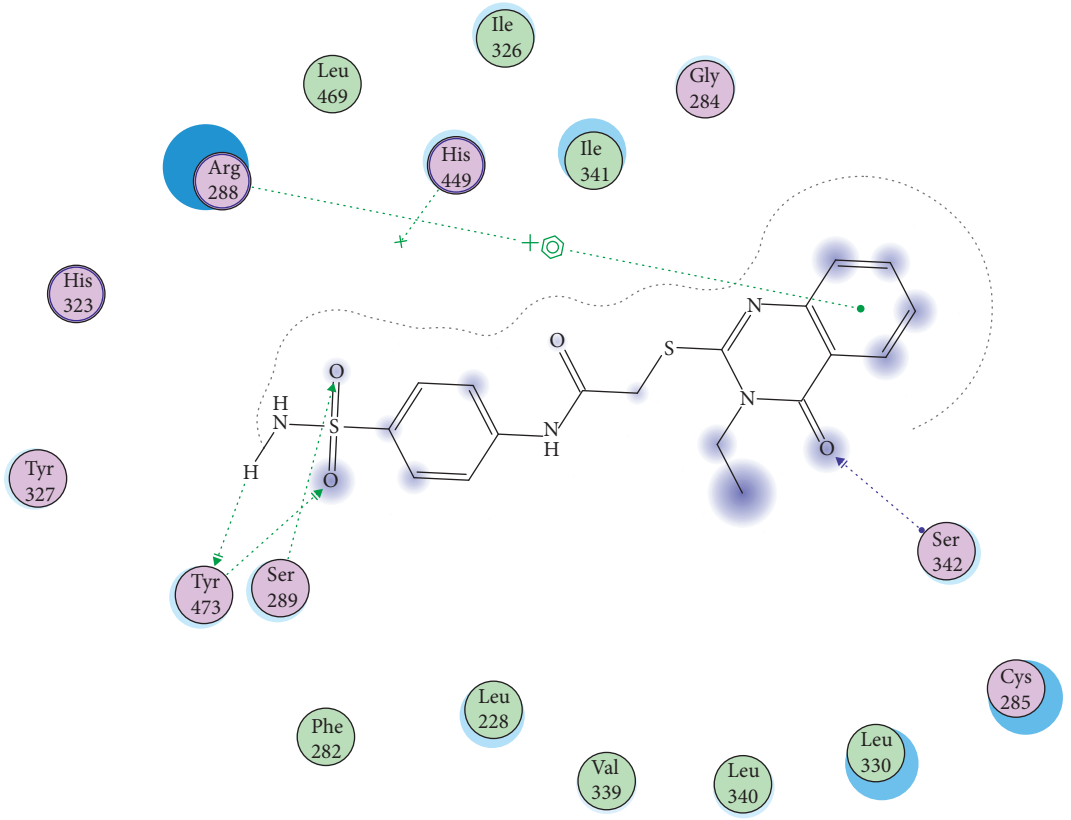


Figure 12: 2D structure of compound 3 docked into the active site of PPARγ.

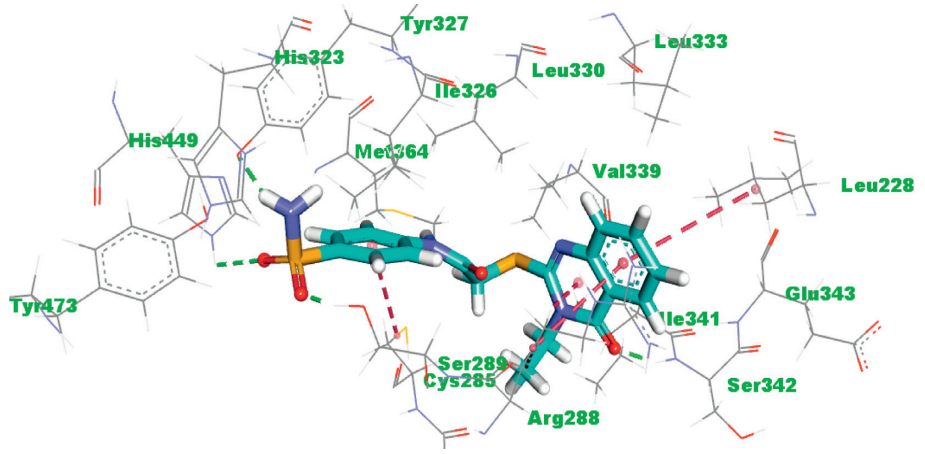


Figure 13: 3D structure of compound 3 docked into the active site of PPARγ.

3.3.2. PPARγ-Ligand Binding Assay. Compounds with promising computational PPARγ affinities (1, 2, 3, 4, and 5) were examined to determine their binding affinities to PPARγ. The fluorescence polarization assay technique [46] was carried out to assess binding affinities of the selected compounds with PPARγ-LBD. Rosiglitazone, as one of the most active PPARγ agonist, was used as a positive control. The results of binding are reported in Table 5 as EC_{50} values.

Compound 2 exhibited a significant binding affinity to PPARγ with an EC_{50} value of 0.289 μM when compared with rosiglitazone ($EC_{50} = 0.292\,\mu$M). Compounds 1, 3, 4, and 5 showed high PPARγ binding affinities of 0.399, 0.462, 0.473, and 0.426, respectively. Interestingly, the PPARγ binding affinity of the most active compounds was consistent with that of computational PPARγ affinity.

3.4. Computational Determination of the Essential Physicochemical Properties. Calculated partition coefficient (*c* log P), molecular polar surface area, molecular solubility, molecular volume, molecular weight, hydrogen bond acceptors,

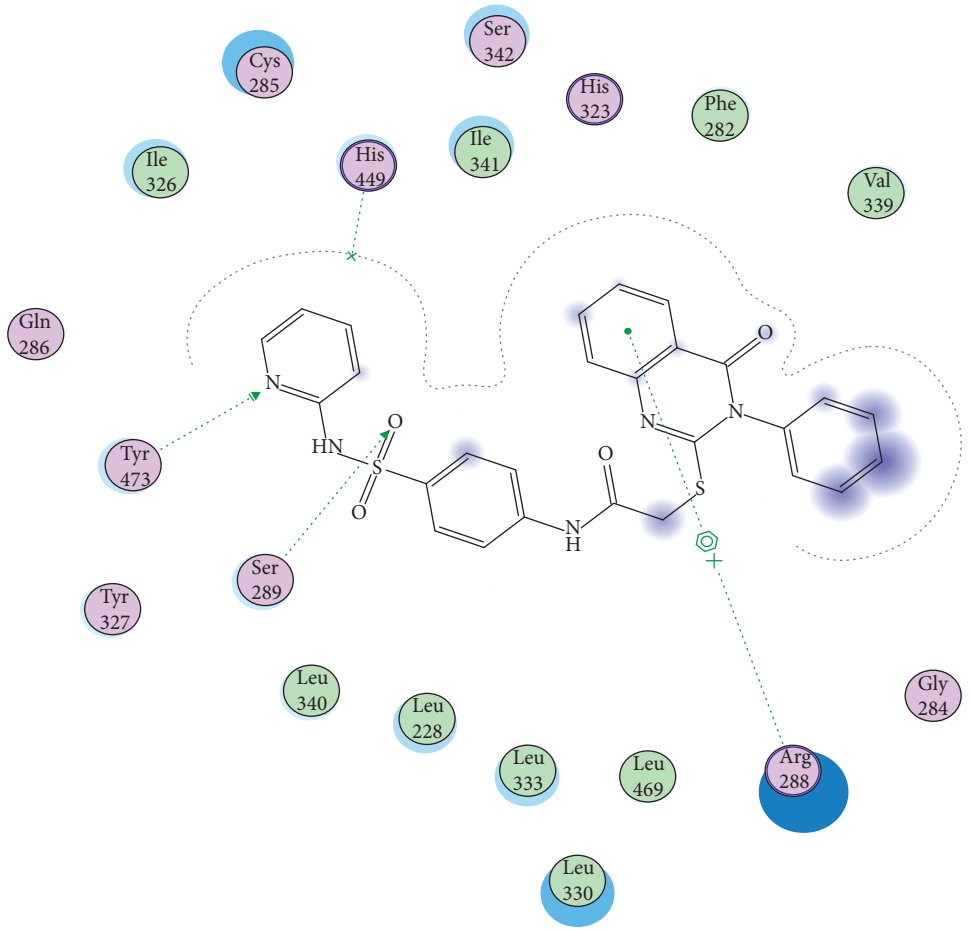


Figure 14: 2D structure of compound 4 docked into the active site of PPARγ.

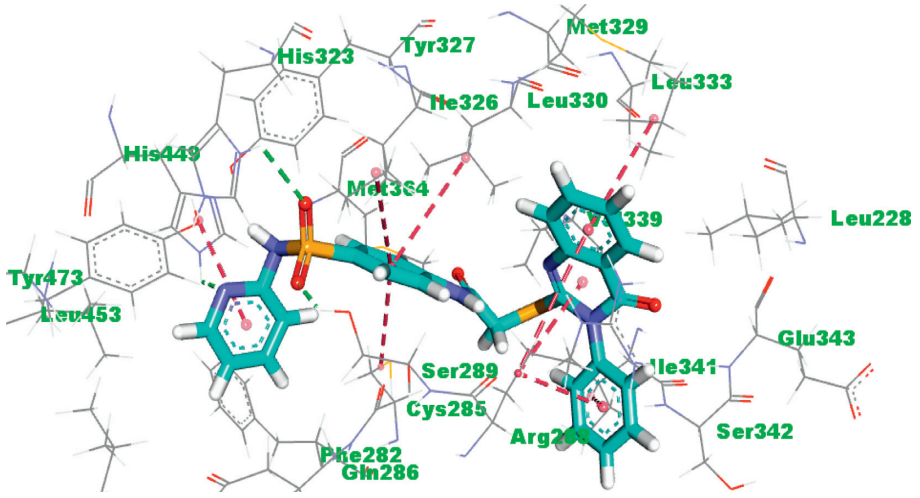


Figure 15: 3D structure of compound 4 docked into the active site of PPARγ.

and hydrogen bond donors correlation were determined using Discovery Studio 4.0 software.

The relationship between the lipophilic character of the analyzed compounds and their biological activities was measured through the correlation of PPARγ affinity with the c log P values for all the compounds. The c log P value expresses the degree of lipophilicity of the chemical compounds. An increase in this value indicates an increase in the lipophilic character of the tested compound. It is worthwhile to note that the c log P values for the analyzed compounds

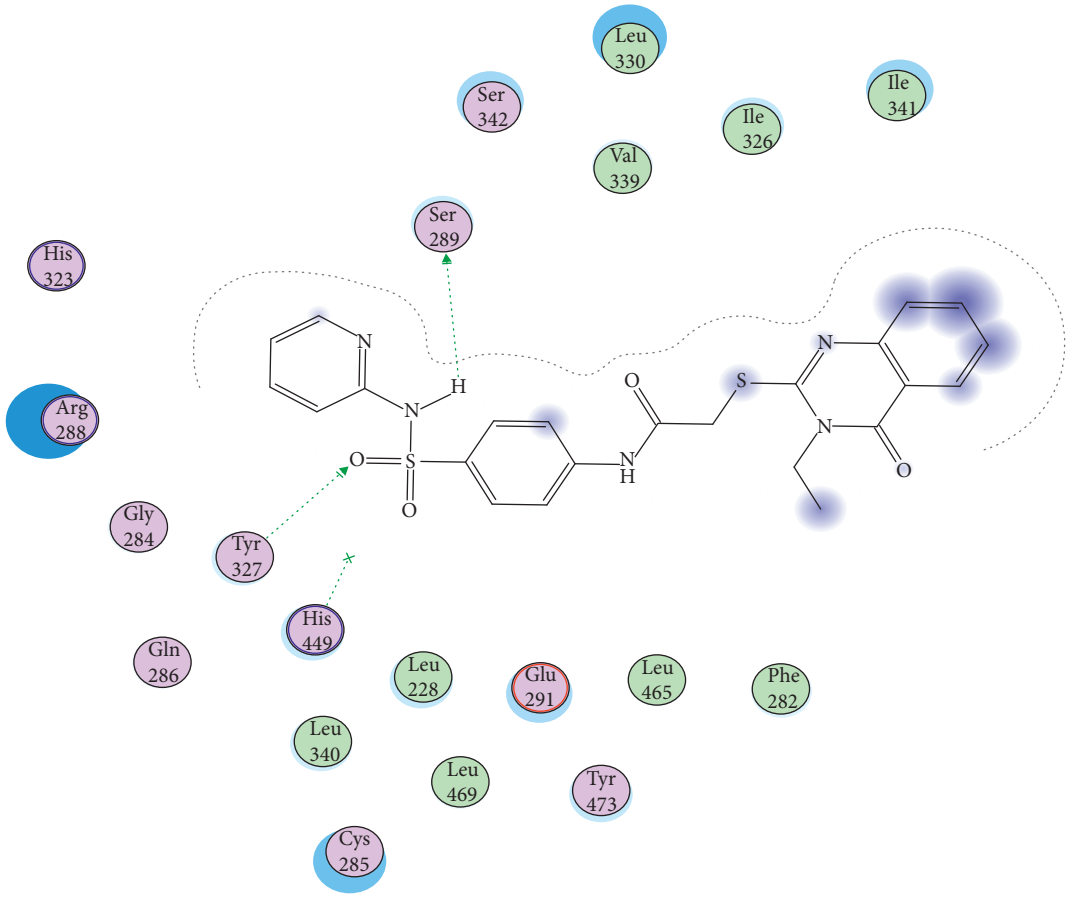


Figure 16: 2D structure of compound 5 docked into the active site of PPARγ.

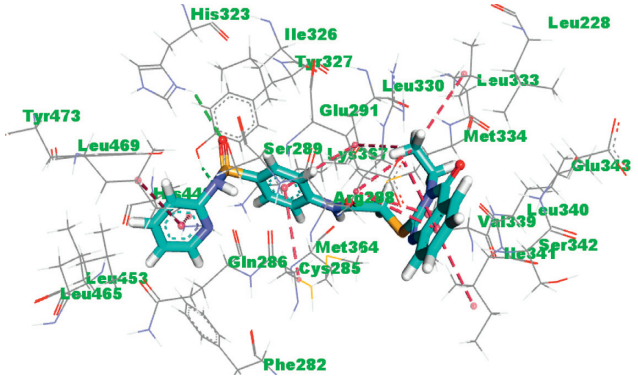


Figure 17: 3D structure of compound 5 docked into the active site of PPARγ.

Table 2: The docking binding free energies of the screened compounds against BACE1.

Comp.	Binding free energy (kcal/mol)
1	−24.70
2	−22.03
3	−25.16
4	−20.33
5	−27.02
Co-crystalized ligand	−25.60

range from 1.927 to 4.325. These values may explain the variation in their biological activity compared with their lipophilicity. Interestingly, the c log P values for the most active compounds lied in the ideal range of lipophilicity [59], which facilitate BBB penetration and consequently can treat AD disease. Based on these results, we noted a correlation between the PPARγ affinity of the target compounds and their lipophilic characters.

In addition, the molecular solubility of the compounds ranges from −7.026 to −4.449, which indicate that these

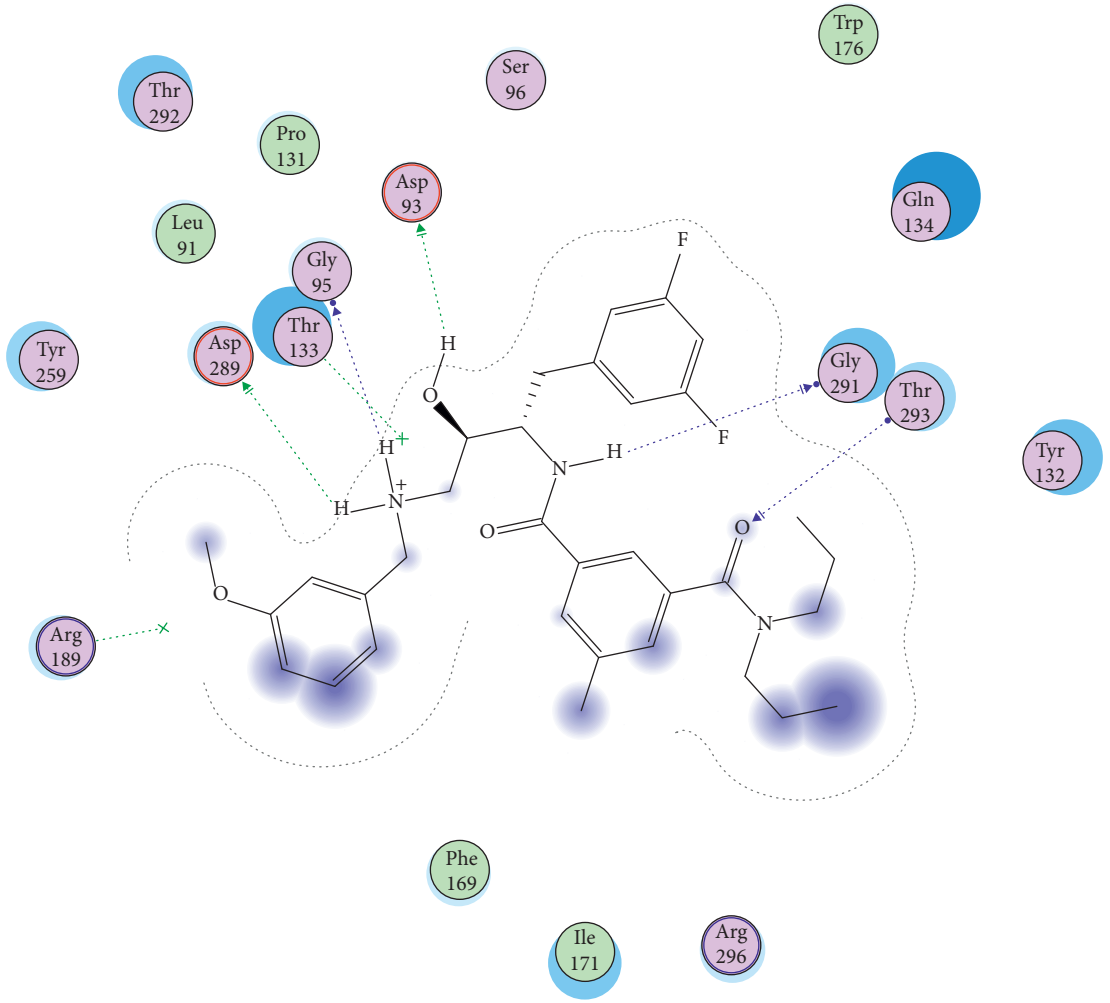


Figure 18: 2D structure of the co-crystalized ligand docked into the active site of BACE1.

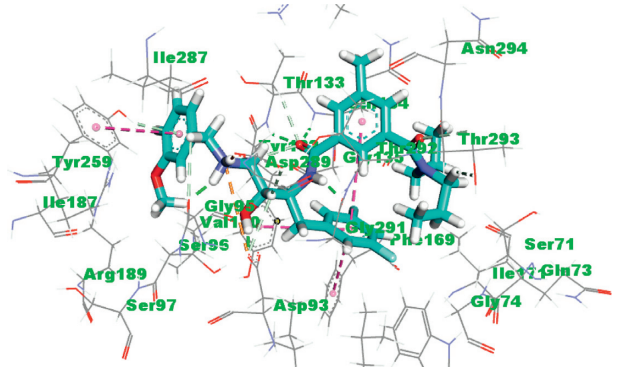


Figure 19: 3D structure of the co-crystalized ligand docked into the active site of BACE1.

compounds have good water solubility for some extent. Moreover, the total polar surface area (TPSA) is another key property linked to drug bioavailability; the passively absorbed molecules with TPSA > 140 have low oral bioavailability [60]. The tested compounds showed acceptable values of TPSA. Moreover, molecular volume (M.V) descriptor determines transport characteristics of molecules, such as intestinal absorption [61]. It was observed that the analyzed compounds exhibited good molecular volume values.

Finally, the Lipinski rule of five was applied for the compounds. It was found that all compounds have a molecular weight less than 500 except compounds 2 and 4; all compounds have a hydrogen bond acceptor group less than

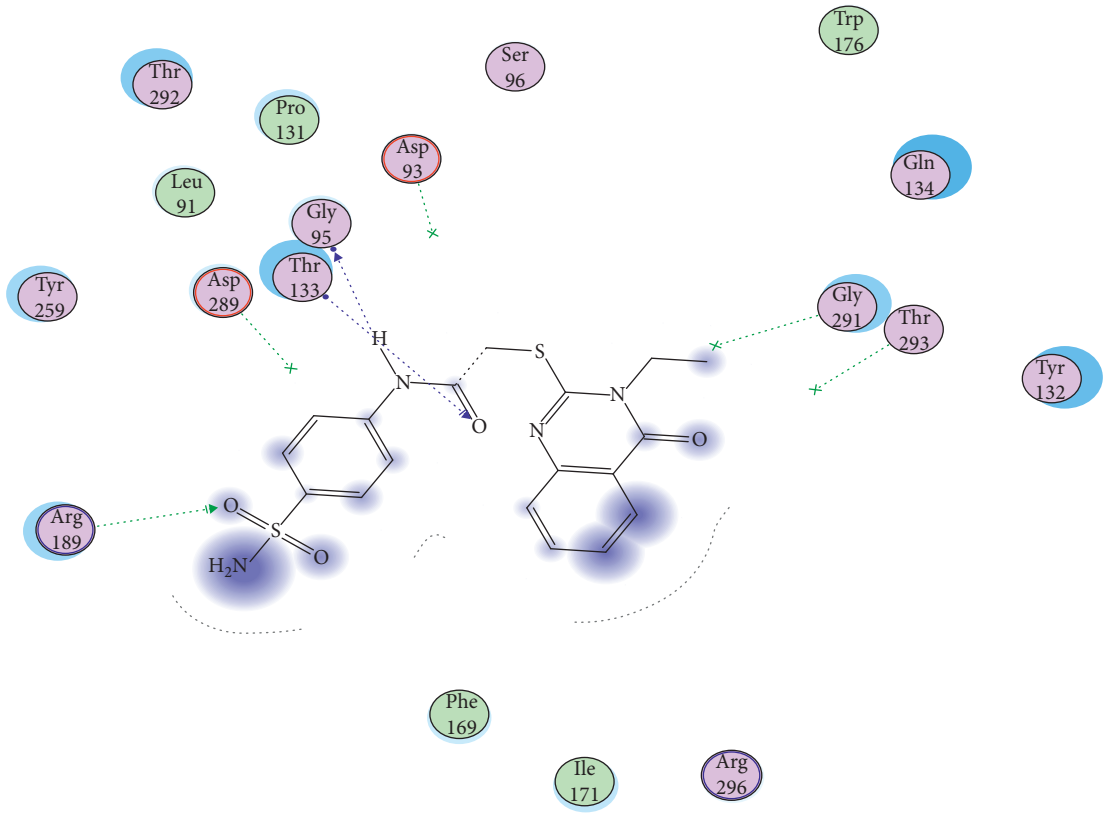


Figure 20: 2D structure of compound 3 docked into the active site of BACE1.

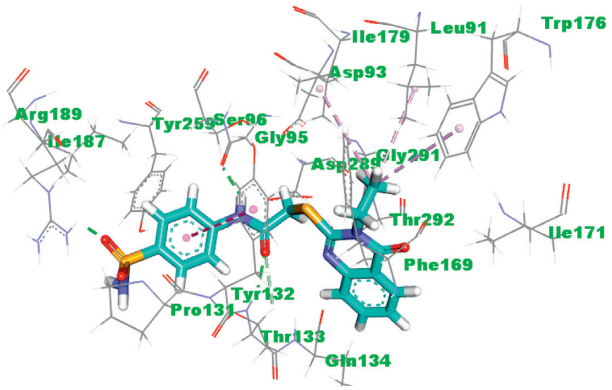


Figure 21: 3D structure of compound 3 docked into the active site of BACE1.

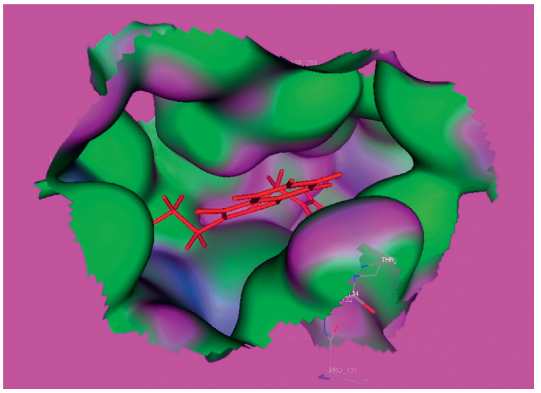


Figure 22: Mapping surface showing compound 3 occupying the active pocket of BACE1.

Table 3: Predicted ADMET for the designed compounds and reference drug.

Comp.	Absorption level[a]	CYP2D6[b]	Hepatotoxicity probability[c]	PPB[d]	Solubility[e]
1	1	0	0.398	2	2
2	1	0	0.348	2	1
3	0	0	0.452	2	2
4	2	0	0.4567	2	2
5	1	0	0.256	2	2
Pioglitazone	1	0	0.245	2	3

Absorption levels: 0 = good, 1 = moderate, 2 = poor, and 3 = very poor. [b]CYP2D6: cytochrome P2D6, 0 = noninhibitor, and 1 = inhibitor. [c]Hepatotoxicity probability: value > 0.5 means toxic and value < 0.5 means nontoxic. [d]PBB, plasma protein binding: 0 means less than 90%, 1 means more than 90%, and 2 means more than 95%. [e]Solubility level: 1 = very low, 2 = low, 3 = good, and 4 = optimal.

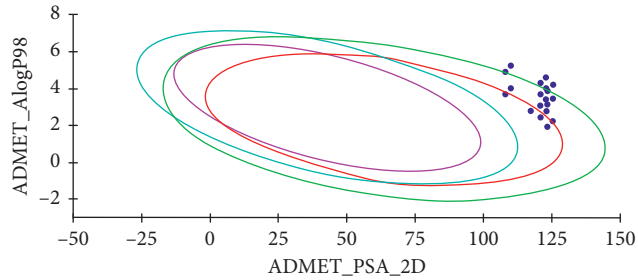


Figure 23: ADMET plot for the analyzed compounds.

Table 4: BACE1 inhibitory activities of the tested compounds and rosiglitazone.

Comp.	BACE1 IC_{50} (μM)
1	2.75
2	1.24
3	3.59
4	3.14
5	2.53
Rosiglitazone	1.74

Table 5: PPARγ binding affinities of the tested compounds and rosiglitazone.

Comp.	PPARγ EC_{50} (μM)
1	0.399
2	0.289
3	0.462
4	0.473
5	0.426
Rosiglitazone	0.292

Table 6: *c* log P molecular polar surface area, molecular solubility, molecular volume, molecular weight, hydrogen bond acceptors, and hydrogen bond donors of the analyzed compounds.

Comp.	*c* Log p[a]	Mol. solubility[b]	MPSA[c]	M.V.[d]	M. Wt[e]	H-acceptors[f]	H-donors[g]
1	3.154	−5.854	155.6	327.22	466.533	8	3
2	3.903	−7.026	155.6	348.83	545.429	8	3
3	1.927	−4.449	155.6	299.43	418.49	8	3
4	4.325	−7.215	154.51	387.58	543.617	9	2
5	3.098	−5.807	154.51	358.09	495.574	9	2

[a]Octanol-water partition coefficient log P. [b]Molecular solubility. [c]Molecular polar surface area. [d]Molecular volume. [e]Molecular weight. [f]Hydrogen bond acceptors. [g]Hydrogen bond donors.

10, and all compounds have a hydrogen bond donor group less than 5. These indicate that these compounds are likely to be orally bioavailable (Table 6).

4. Conclusion

Thirty-five sulfonamide and sulfonylurea derivatives have been screened using docking studies for their inhibition to PPARγ, and then, the promising molecules were also docked into BACE1 as a potential target for anti-AD agents. Five compounds showed promising affinities against BACE1 and PPARγ with binding energies ranging from −17.96 to −28.62 Kcal/mol. The ADMET studies were tested *in silico* using Discovery Studio 4.0 software. The results revealed that the tested compounds have a CYP2D6 noninhibitory effect, moderate aqueous solubility, and intestinal absorption. The physicochemical properties were determined *in silico*. It was found that the *c* log *P* values for the tested compounds range from 1.927 to 4.325. These values may explain the variation in their biological activity compared with their lipophilicity. Interestingly, the *c* log *P* values for the most active compounds lied in the ideal range of lipophilicity, which facilitate BBB penetration and consequently can treat AD disease. Moreover, the compounds were in consistence with the Lipinski rule of five, which indicates their oral bioavailability. Finally, additional *in vitro* studies were carried out for these compounds to estimate their activity on both PPARγ and BACE1. The results revealed the promiscuity of these compounds (1, 2, 3, 4, and 5) to target both PPARγ and BACE1, which are potential targets in treatment of AD. Compound 2 showed a good activity on both targets, and its EC_{50} value is 0.289 μM against PPARγ and EC_{50} value is 1.24 μM against BACE1. Finally, we can say that the most active candidates may serve as useful lead compounds in search for powerful anti-AD agents.

Abbreviations

AD: Alzheimer's disease
ADMET: Absorption, distribution, metabolism, excretion, and toxicity
Aβ: Amyloid-β peptide
BACE1: Beta-secretase 1
c log P: Calculated partition coefficient
CHARMM: Chemistry at harvard macromolecular mechanics
CNS: Central nervous system
EC_{50}: The concentration of a drug which induces a response halfway between the baseline and maximum after a specified exposure time
IC_{50}: Concentration of compound required to displace 50% of titrated ligand
CYP2D6: Cytochrome P450 2D6
KATP: Pancreatic ATP-sensitive potassium channels
MOE: Molecular operating environments
MMFF94: Merckmolecular force field 94
M.V: Molecular volume
M.Wt.: Molecular weight
NFkB: Nuclear factor kappa-light-chain-enhancer of activated B cells
PPARγ: Peroxisome proliferator-activated receptor gamma
SUs: Sulfonylureas
PDB: Protein data bank
PBB: Plasma protein binding
TZDs: Thiazolidinediones
T2DM: Type 2 diabetes mellitus
TPSA: Total polar surface area
2D structures: Two-dimensional structure.

Data Availability

The data used in this study are given within the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Ning Li and Yan Wang are the first authors and contributed equally to this work.

Supplementary Materials

Only for reviewing consideration and not for publication the manuscript contains all the essential figures. However, the supplementary data file comprises the 2D structures of the most promising compounds docked into the active site of BACE1. (*Supplementary Materials*)

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