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Modular and Computational Access to Innocuous Multistep Metal-Free Synthesis of 1,3,4-Oxadiazoles as Enzyme Inhibitors

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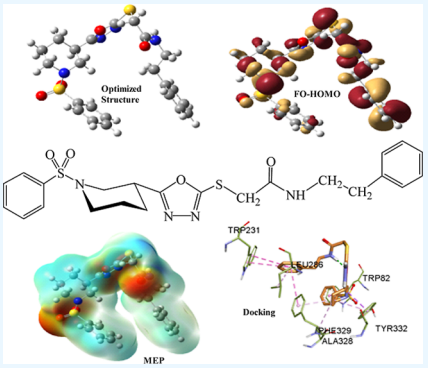
ABSTRACT: An array of 1,3,4-oxadiazole hybrids, **7a−s**, structurally intriguing cores with potential in natural product synthesis and drug discovery, have been synthesized using innovative comparable conventional and microwave-assisted protocols. The synthesis was performed by the reaction of secondary amine-based acetamides, **6a−s**, as the electrophile and piperidine-based oxadiazoles as the nucleophile, **3**, under the metal-free reaction conditions. High yield in minimum time with highest purity was obtained by the microwave-irradiated method instead of the conventional one. The structural elucidations were made through infrared, ^{1}H NMR, ^{13}C NMR, and elemental analysis studies. The whole array of synthesized compounds, **7a−s**, was evaluated for their potential against α-glucosidase and butyryl cholinesterase (BChE) enzymes. Natural bond orbital and structural optimizations were made by using the B3LYP method and the basis set of 6-311++G(d,p). Frontier molecular orbitals and molecular electrostatic potential were calculated at the same level of selected compounds as potential candidates against BChE and α-glucosidase enzymes utilizing the time-dependent density functional theory. Fifteen compounds out of 19 were observed to be active against α-glucosidase enzyme in comparison with acarbose as the reference standard and 7 against the BChE enzyme compared to eserine as the reference standard. The highest potential of compound **7j** against BChE is well correlated by the higher binding interaction with target protein as −10.2, calculated by docking studies. The recruited compounds against both enzymes could be the best anti-enzymatic drugs and part of drugs discovery programs after further analysis.



1. INTRODUCTION

In the realm of medicinal chemistry, heterocyclic molecules combining nitrogen and oxygen are widely used.[1] Oxadiazole-based heterocyclic compounds have received a lot of attention from researchers in recent decades because of their importance in medical formulation.[2] Among the different isomers of oxadiazoles, 1,3,4-oxadiazole has been shown to be particularly active as an antibacterial,[3,4] antifungal,[5] anticancer,[6,7] anti-enzymatic,[8] anti-proliferative,[9] anti-tubercular,[10] and analgesic[11] agent. α-Glucosidase inhibitors are medications that slow the digestion of carbs into sugar and thus increase the time taken for glucose to be absorbed. Compounds with a high anti-glucosidase inhibitory activity can help regulate postprandial glucose levels and enhance glycemic control in diabetics.[12,13] Butyryl cholinesterase (BChE) levels are critical to monitor in Alzheimer's disease (AD), particularly in the late stages, because BChE levels rise at this time.[14] The maintaining of this enzyme's level is also vital in type 2 diabetes mellitus.[15] So, in the given current situation, synthetic chemists have an obligation to produce BChE inhibitors to address a very widespread issue caused by BChE enzyme. This will result in a wider range of therapy options and a better understanding of AD drug development.[16,17]

Through the application of an efficient computational chemistry approach, one can gather the most detailed and comprehensive information regarding the interactions of compounds. This method enables researchers to validate their structure−activity relationship analyses of synthesized compounds. Before conducting laboratory experiments, scientists can also use computer analysis to determine and optimize the properties, activities, and anticipated outputs of their synthesized molecules.[18−20] Structures, dipole moments, vibrational frequencies, nuclear magnetic resonance, chemical shifts, optical characteristics, molecular electrostatic potentials (MEPs), molecular processes, and thermodynamic properties of organic molecules are accurately analyzed using density functional theory techniques. The location of each atom within the synthesized molecules and their structural optimization with minimum energy in space along with highest occupied molecular orbital (HOMO)−lowest unoccupied molecular

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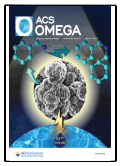

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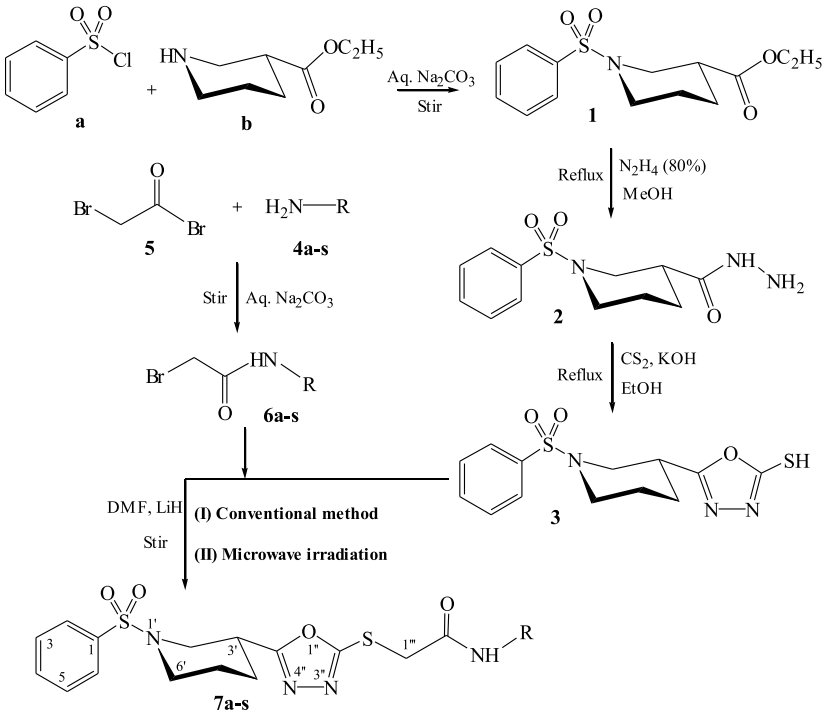
Scheme 1. Synthesis of *N*-(Substituted)-2-{5-[1-(phenylsulfonyl)piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (7a−s)



orbital (LUMO) studies were studied by the Gaussian 09W program 6-311++G(d,p) basis set, over polarized functions by B3LYP.[21]

The current study uses two alternative techniques to synthesize *N*-substituted acetamide derivatives of 1,3,4-oxadiazoles. Microwave-assisted synthesis is one approach, and normal synthesis is the other. In terms of yield and time savings, the microwave-assisted method outperformed the others. The availability of the heterocyclic oxadiazole and azinane as a single entity with the combination of acetamides may account for the produced compounds' prospective biological uses.

2. RESULTS AND DISCUSSION

The goal of this study is to find new and biologically active compounds for the addition of new hybrids to the 1,3,4-oxadiazole library utilizing two alternative approaches: traditional and microwave-assisted synthetic techniques. A series of *N*-(substituted)-2-{5-[1-(phenylsulfonyl)piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamides, **7a−s**, were synthesized according to the protocol given in Scheme 1 and explored for their biological applications. Different substituents for the whole synthesized library of compounds are given in Table 1. The parent compound **3** was obtained after three consecutive reaction steps presented in Scheme 1. In the first step, compound **1** was obtained by the reaction of benzene sulfonyl chloride (a) with ethyl piperidine-3-carboxylate (b). The reaction of **1** with hydrazine resulted into compound **2**. At the third step, the refluxed reaction of compound **2** with KOH and CS_2 was carried out to obtain compound **3**. Different primary amines, **4a−s**, were reacted with bromoacetyl bromide (**5**) in aqueous medium at basic pH to synthesize acetamides, **6a−s**. The hybrids of 1,3,4-oxadiazole, **7a−s**, were synthesized at the last stage by combining compound **3** with **6a−s** using two methods: traditional and microwave-aided methods. The data for reaction time and percent yield was collected for the same amount of the reactants and solvent on stirring. The targeted compounds, **7a−s**, were synthesized in 900−1800 min by traditional methods and in 30−70 s by microwave-aided methods, with high yields (Table 2). After keeping all the parameters under the same condition, the different results justified the superiority of the microwave-assisted method. The mechanism of action of microwaves is clearly based on superheating which converts the maximum amount of reactants into products in a short time. Superheating helps the maximum number of molecules achieve activation energy of the reaction and form the maximum amount of products.

2.1. Chemistry. Compound **7g** was considered for discussion of structural elucidation, and structures of the whole library of compounds were confirmed by following the similar pattern. The structural elucidation through ^{1}H NMR and ^{13}C NMR (Figures 1−3) has been explained and given in the Supporting Information.

2.2. α-Glucosidase Inhibition Studies. The α-glucosidase inhibition potential of all the synthesized compounds, **7a−s**, was measured in units of percent inhibition and IC_{50} in comparison to that of acarbose as the standard drug (Table 3). The whole library of the synthesized compounds was found to be active against α-glucosidase enzyme with variable potential except **7d**, **7k**, **7p**, and **7r**. Fifteen compounds out of 19 were the active ones. The least activity of **7d** (2,6-dimethylphenyl), **7k** (2-ethylphenyl), **7p** (cyclohexyl), and **7r** (benzyl) may be due to their least interactive structure (Table 1). Among all the synthesized compounds bearing dimethylphenyl groups, compound **7e** (3,5-dimethylphenyl) bearing two methyl groups at both *meta* positions remained the most active one with an IC_{50} value of 41.76 ± 0.01 μM which is comparable to that of the reference standard of 38.25 ± 0.12 μM. The compound **7i** (2-methoxy-5-chlorophenyl) was the second most active compound which showed the activity almost half of that of the reference. It presented an IC_{50} value of 57.41 ± 0.04 μM. The 13 compounds **7a−c**, **7f−h**, **7j**, **7l−o**, **7q**, and **7s**

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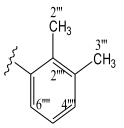
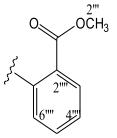
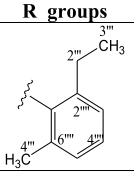
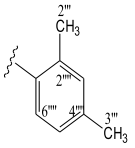
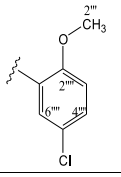
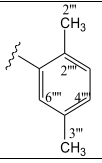
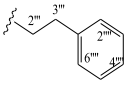
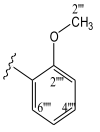
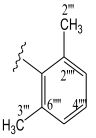
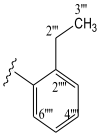
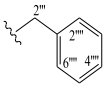
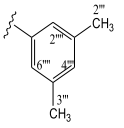
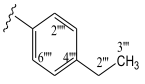
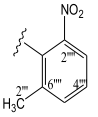
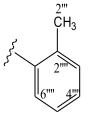
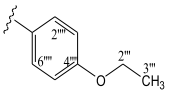
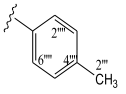
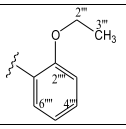
Table 1. Different Alkyl/Aralkyl/Aryl Groups

C #	R groups	C #	R groups	C #	R groups
7a		7h		7o	
7b		7i		7p	
7c		7j		7q	
7d		7k		7r	
7e		7l		7s	
7f		7m			
7g		7n			

were found to be the active ones with variable potential ranging from moderately weak to low.

2.3. Butyryl Cholinesterase (BChE) Inhibition Studies. The BChE inhibition potential of all the synthesized compounds, **7a**−**s**, was measured in units of percent inhibition and IC_{50} in comparison to that of eserine as the standard drug (Table 3). Seven compounds out of 19 were found to be active against BChE enzyme with variable potential. The five compounds, **7a** (2,3-dimethylphenyl), **7b** (2,4-dimethylphenyl), **7e** (3,5-dimethylphenyl), **7l** (4-ethylphenyl), and **7m** (4-ethoxyphenyl), remained the least active with higher IC_{50} values. The compound **7s** (2-methyl-6-nitrophenyl) was found to present moderately high inhibition potential. The compound **7j** (phenylethyl) presented the highest inhibition potential with an IC_{50} value of 12.15 ± 0.09 μM in comparison with the standard with an IC_{50} of 0.85 ± 0.0001 μM. The highest activity by compound **7j** may be because of no substitution at the phenyl ring. The non-substituted phenyl ring may not hinder the interaction of the synthesized compound with the active site of enzyme and so showed better inhibition.

2.4. Computational Studies. The compounds showing the highest, the least, and the intermediate biological potential against BChE and α-glucosidase enzymes were selected for their computational studies to justify the difference in their way of interaction against respective enzymes. The optimized structures of all the selected compounds relevant to BChE and α-glucosidase enzymes are presented in Table 4. The structurally optimized array of compounds was then investigated by comprehensive computational studies and is presented in Figure 4.

2.5. FMO Analysis. Molecular orbital analysis in terms of their energy gap between the HOMO and LUMO is widely employed to find the electronic properties and also useful to gauge the chemical reactivity of synthesized compounds.[22] The HOMO and LUMO are called FMOs and are designated with specific energies and also certain specific energy gaps. These energy gaps provide valuable information about the chemical behavior including stability and reactivity. The presence of electron-donating or electron-withdrawing groups affects the HOMO−LUMO energy gap and changes the reactivity or interacting ability. Thus, the calculation of such energy gaps may inform about the inhibition potential of the synthesized compounds.[23] The small HOMO−LUMO energy gap is characterized by high polarization, high reactivity, and low stability. Such molecules are termed soft ones. The high energy gap makes the molecules less reactive because a high-energy LUMO is unable to add electrons into it. In contrast to

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Table 2. Comparison of Conventional and Microwave-Assisted Methods

	reaction yield (%)		reaction time	
compounds	microwave	conventional	microwave (s)	conventional (min)
7a	91	72	42	1380
7b	95	74	32	1440
7c	89	79	69	1320
7d	87	82	60	1260
7e	94	78	35	1800
7f	89	84	45	1500
7g	92	70	35	1320
7h	91	82	33	1200
7i	93	85	68	1080
7j	96	86	60	1620
7k	86	75	52	960
7l	93	68	38	1260
7m	95	63	30	1140
7n	91	59	49	900
7o	82	68	70	1680
7p	84	59	55	1520
7q	88	53	60	1800
7r	81	62	47	1180
7s	91	49	45	1020

compounds with small HOMO−LUMO energy gap, those with high HOMO−LUMO energy gap are stable and chemically tougher.[24] So, it is clear from the given results shown in Figure 4 that compound **7j** was found to be more stable with highest HOMO−LUMO energy gap and highest BChE inhibition potential. Compound **7s**, presented in Figure 4, possessed the least HOMO−LUMO energy gap, thus being soft and reactive with less BChE inhibition potential. The minimum HOMO−LUMO energy gap was achieved by the presence of the NO_2 substituent present at the phenyl ring of acetamide in compound **7s**. The backbone of the whole structure of all three selected compounds relevant to inhibition potential of BChE is similar, while the presence of different substituents at the phenyl ring of the acetamide ring differentiated all these three compounds as presented in Table 1 and Figure 4. The presence of the NO_2 substituent made compound **7s** reactive because NO_2 is a highly electron-withdrawing group which decreases the energy gap of the HOMO and LUMO of compound **7s**, making it more reactive. Similarly, among the whole array of compounds selected for their computational studies relevant to the inhibition potential of α glucosidase enzyme, compound **7e** presented in Figure 4 was found to be less reactive because it possessed electron-donating groups substituted at the phenyl ring of acetamide (Table 1).

2.6. MEP Analysis. The molecular site, rich in electron density and feasibility for possible nucleophilic and electrophilic reactions, could be better understandable by the use of MEP analysis. The MEP studies are also well suited to understand the phenomenon of drug−receptor and enzyme−substrate interaction. With the help of the B3LYP method and the basis set of 6-311++G(d,p), MEPs were computed in optimal geometry to estimate the reactive regions of electrophilic and nucleophilic attacks for the molecules under study.[25,26] Different hues represent various electrostatic potential levels on the surface. The possible increase or decrease is indicated by the colors red, orange, yellow, green, and blue. Positive regions (blue) are related with nucleophilic reactivity, while negative regions (red and yellow) are connected with electrophilic reactivity on the MEP of the same set of compounds for FMO studies (Figure 5).[27] The sulfonyl group appeared to be covered by the negative charge, and the positive region was above the other groups. The

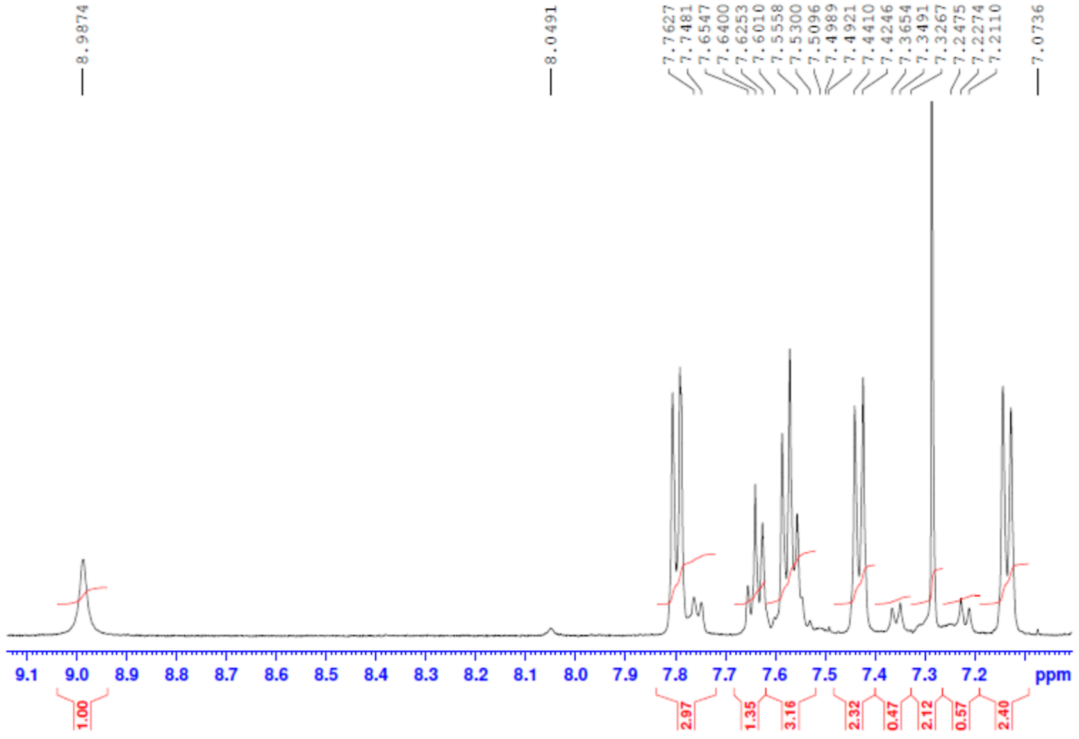

Figure 1. ^{1}H NMR spectra (aromatic region) of compound **7g**.

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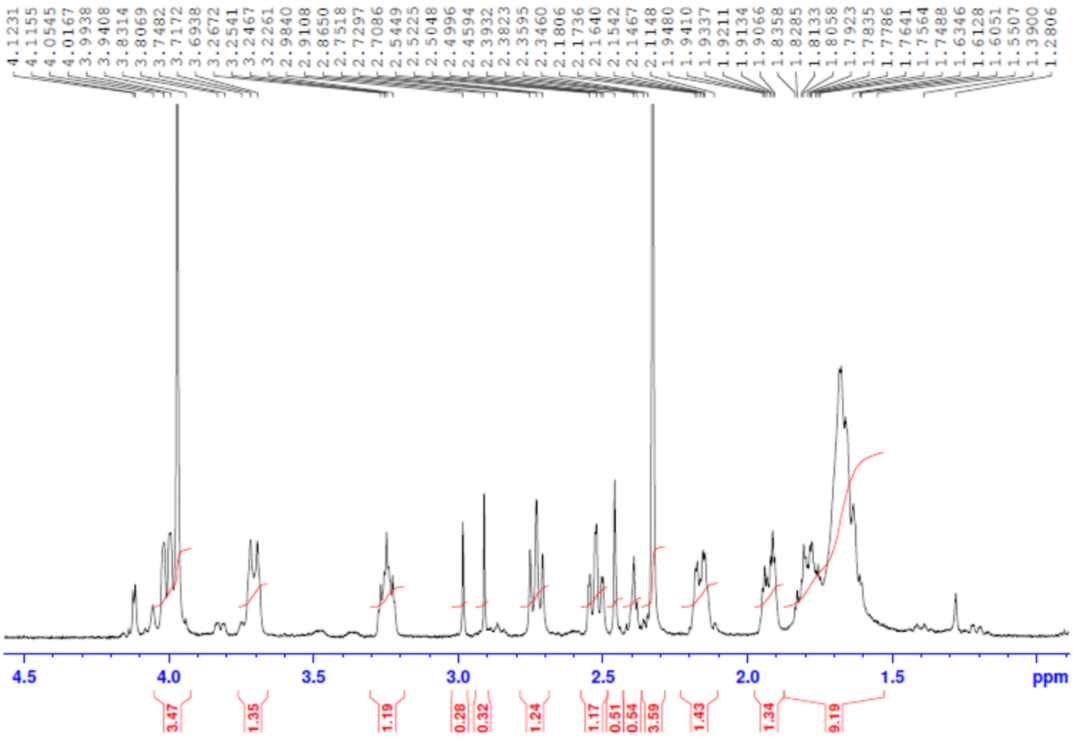

Figure 2. ^{1}H NMR spectra (aliphatic region) of compound **7g**.

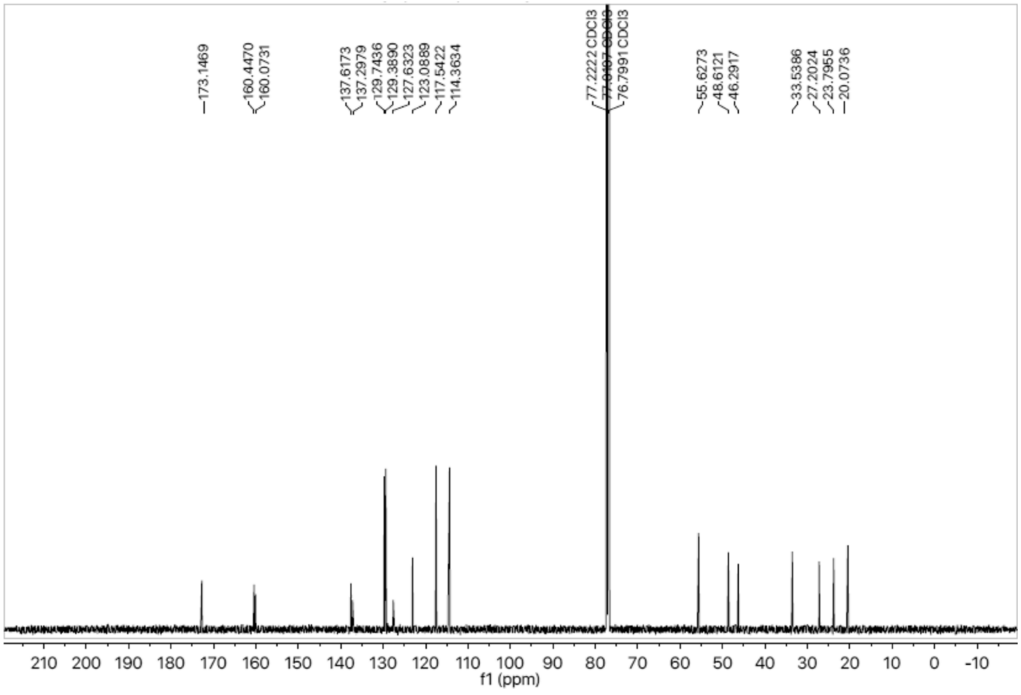

Figure 3. ^{13}C NMR spectra of compound **7g**.

sulfonyl group has the highest electronegativity, and therefore, other sections of the molecules are more reactive.

2.7. Molecular Docking Studies. To validate the docking protocol, first, bound co-crystal ligands within both target proteins were docked, and we found that rmsd was less than allowed 2 Å. Figure 6 and Table 5 show the binding energy in terms of the chemguass4 score for all selected compounds against BChE target proteins. Analysis of the chemguass4 score revealed that compound **7j** owing to −10.2 has higher binding interaction with BChE target protein followed by **7s** (−10) and **7e** (−9.7). Detailed binding interactions of each selected compound with the amino acid residue of BChE are depicted in Table 5. Compound **7j** was found to interact with six different amino acid residues including Trp82, Tyr332, Trp231, Phe329, Ala328, and Leu286, present in the active site of the enzyme. This molecule interacted through its three major sides including the benzene sulfonyl group, piperidine ring, and phenylethyl group. The benzene sulfonyl group

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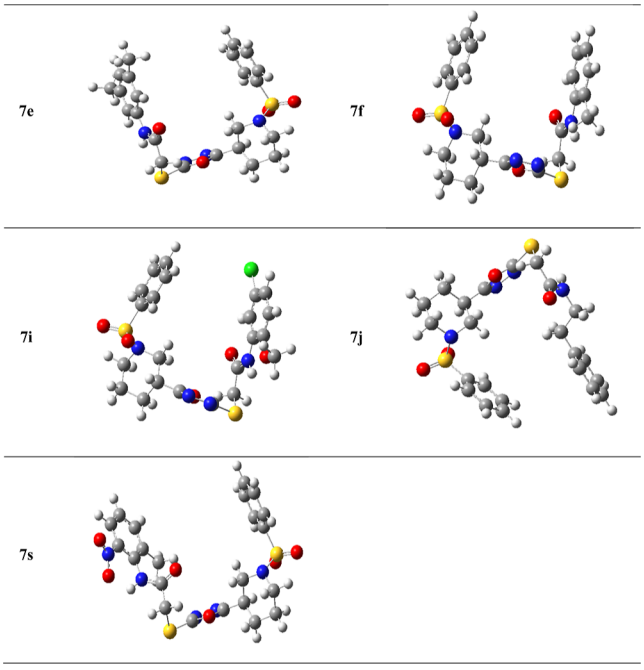
Table 3. % Inhibition and IC_{50} for Anti-Enzymatic Potential of Synthesized Compounds[a]

	α-glucosidase		BChE	
compound	inhibition (%) at 0.5 mM	IC_{50} (μM)	inhibition (%) at 0.5 mM	IC_{50} (μM)
7a	95.65 ± 0.89	170.89 ± 0.15	75.32 ± 0.35	284.5 ± 0.13
7b	96.09 ± 0.17	170.15 ± 0.06	76.51 ± 0.44	283.3 ± 0.17
7c	98.53 ± 0.18	144.22 ± 0.03	40.76 ± 0.27	
7d	31.71 ± 0.19		48.51 ± 0.15	
7e	98.71 ± 0.13	41.76 ± 0.01	66.82 ± 0.32	375.4 ± 0.12
7f	68.97 ± 0.24	384.69 ± 0.05	47.23 ± 0.14	
7g	95.82 ± 0.19	157.89 ± 0.08	46.75 ± 0.18	
7h	95.21 ± 0.21	161.11 ± 0.07	35.52 ± 0.23	
7i	96.82 ± 0.25	57.41 ± 0.04	38.81 ± 0.17	
7j	95.45 ± 0.49	140.63 ± 0.09	97.93 ± 0.38	12.15 ± 0.09
7k	30.61 ± 0.05		44.24 ± 0.32	
7l	92.39 ± 0.57	157.34 ± 0.06	93.71 ± 0.28	274.6 ± 0.13
7m	95.17 ± 0.39	212.84 ± 0.02	72.41 ± 0.17	328.1 ± 0.18
7n	91.29 ± 0.25	183.39 ± 0.08	43.72 ± 0.15	
7o	98.42 ± 0.63	191.72 ± 0.13	38.31 ± 0.29	
7p	41.32 ± 0.20		26.47 ± 0.39	
7q	95.30 ± 0.12	187.50 ± 0.19	36.32 ± 0.16	
7r	29.94 ± 0.74		37.74 ± 0.48	
7s	94.25 ± 0.42	187.36 ± 0.15	67.19 ± 0.39	123.3 ± 0.15
standard	**92.23 ± 0.14[a]**	**38.25 ± 0.12[a]**	**82.82 ± 1.09[b]**	**0.85 ± 0.0001[b]**

[a]Note: a = acarbose, b = eserine.

Table 4. Optimized Structures of Selected Compounds against Butyryl Cholinesterase (7e, 7j, and 7s) and α-Glucosidase (7e, 7f, and 7i)



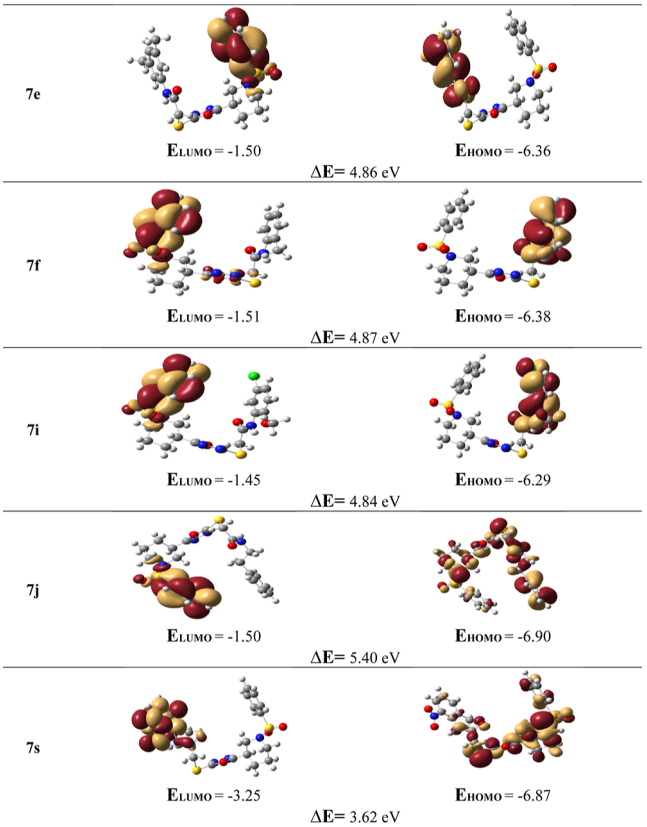


Figure 4. Frontier orbital (HOMO–LUMO) views, corresponding energies, and energy gap of titled compounds with variable potential against BChE (**7e**, **7j**, and **7s**) and α-glucosidase (**7e**, **7f**, and **7i**).

presented dipole–dipole and π–π interactions with Trp82 and Phe329. The piperidine ring of the molecule showed π-alkyl interactions with Tyr332, Phe329, Ala328, and Leu286. The phenylethyl group illustrated π–π interactions with Trp231 and Phe329. The distances of these interactions also provided information about the strength of these interactions. The strong interaction of compound **7j** with the active site confirms its higher potential against BChE. Compound **7s** was found to interact with 10 different amino acid residues including Gly117, Trp82, Tyr332, Trp231, Phe329, Ala328, His438, Gly116, Pro285, and Leu286, present in the active site of the enzyme. This molecule also interacted through three major sides like those of **7j**. The benzene sulfonyl group presented H-

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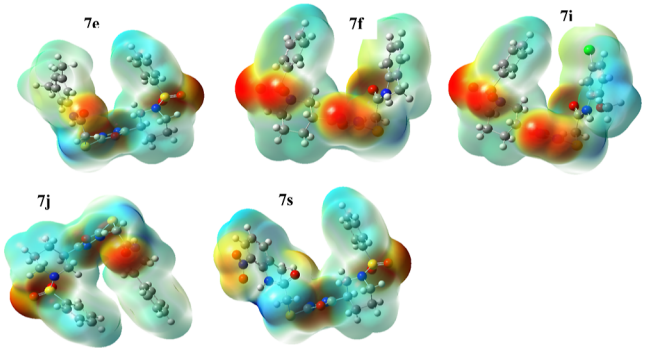

Figure 5. MEPs of compounds **7e**, **7f**, **7i**, **7j**, and **7s**.

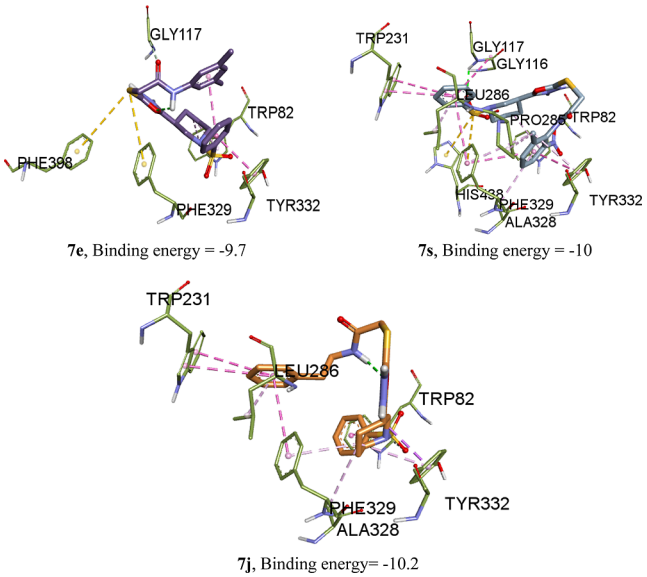

Figure 6. Binding energy and binding interaction of compounds **7e**, **7s**, and **7j** with BChE enzyme.

bonding, π-S, π-alkyl, and $\pi-\pi$ interactions with Gly117, His438, Trp231, Gly116, Leu286, and Phe329. The piperidine ring of the molecule exhibited π-alkyl interactions with Pro285 and Trp82. The variable part, the 2-methyl-6-nitrophenyl group, showed π-alkyl and $\pi-\pi$ interactions with Tyr332, Ala328, and Phe329. Although the interactions were greater in number for **7s** as compared to those for **7j**, the distances of these interactions were large and so resulted in a little low binding potential. Compound **7e** presented low potential as compared to **7j** and **7s**. It only interacted with five different amino acid residues including Gly117, Phe398, Trp82, Tyr332, and Phe329, present in the active site of the enzyme. These interactions were also characterized by large interaction distances and so resulted in lower inhibition potential. The benzene sulfonyl group interacted with Tyr332 through $\pi-\pi$ interaction, the piperidine ring with Trp82 through π−alkyl interaction, thioether functionality with Phe329 and Phe398 through π−S interactions, and amidic carbonyl with Gly117 through dipole−dipole interaction. Thus, the nature and number of interactions play a great role in the bioactivity potential of the molecules.

3. CONCLUSIONS

A series to contribute in the library of the hybrids of 1,3,4-oxadiazole for biological benefits was synthesized, and structure conformation was achieved with the help of spectral data. The microwave-assisted approach was found to be more efficient in terms of short time and high yield. The synthesized hybrids were found to be excellent against enzyme inhibition. All the compounds, **7a**−**s**, were found to be active against α-glucosidase except four compounds **7d**, **7k**, **7p**, and **7r**. Compound **7e** presented comparable activity to that of reference and **7i** as 50% inhibition potential in comparison of standard drug, acarbose. Seven compounds **7a**, **7b**, **7e**, **7j**, **7l**, **7m**, and **7s** were found to be BChE inhibitors. Compound **7s** was moderately high, and **7j** was the most active one against BChE, and their inhibition potential was compared with that of the standard drug, eserine. Structural optimization, FMO,

Table 5. Detailed Binding Interactions of Selected Ligands with Butyryl Cholinesterase

distance	type of bond	interacting amino acid residue	distance	type of bond	interacting amino acid residue
		7e			
3.47	dipole−dipole	A:GLY117:CA	3.67	$\pi-\pi$ stacked	A:TYR332
5.24	π−sulfur	A:PHE329	4.64	π−alkyl	A:TRP82
5.86	π−sulfur	A:PHE398	5.20	π−alkyl	A:TRP82
		7s			
2.50842	conventional hydrogen bond	A:GLY117:HN	5.51895	amide−π stacked	A:GLY116
5.24797	π−sulfur	A:PHE329	5.15047	alkyl	A:PRO285
4.41469	π−sulfur	A:HIS438	4.71122	π−alkyl	A:TRP82
3.88837	$\pi-\pi$ stacked	A:TYR332	5.30952	π−alkyl	A:PHE329
5.0144	$\pi-\pi$ T-shaped	A:TRP231	4.23246	π−alkyl	A:TYR332
5.02436	$\pi-\pi$ T-shaped	A:TRP231	5.06494	π−alkyl	A:ALA328
5.21105	$\pi-\pi$ T-shaped	A:PHE329	4.93686	π−alkyl	A:LEU286
5.13156	$\pi-\pi$ T-shaped	A:PHE329			
		7j			
3.79659	dipole−dipole	A:TRP82:CD1	4.93732	$\pi-\pi$ T-shaped	A:PHE329
3.63382	$\pi-\sigma$	A:TYR332	4.90553	alkyl	A:ALA328
3.63496	$\pi-\pi$ stacked	A:TRP82	4.12184	π−alkyl	A:PHE329
4.43235	$\pi-\pi$ stacked	A:TRP82	4.18734	π−alkyl	A:TYR332
5.07627	$\pi-\pi$ T-shaped	A:TRP231	4.89832	π−alkyl	A:LEU286
5.0992	$\pi-\pi$ T-shaped	A:TRP231			

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MEP, and docking studies for binding energy calculations were made to justify the anti-enzymatic potential of synthesized compounds. The most active compounds against the two enzymes, after further investigation, might be used in drug discovery programs as anti-enzymatic agents.

4. EXPERIMENTAL SECTION

Sigma-Aldrich and Alfa Aesar provided the various chemicals required to synthesize the targeted molecules. The reaction conditions were monitored using thin layer chromatography with pre-coated silica gel G-25-UV254 aluminum plates. Thin layer chromatography was carried out in a solvent system based on *n*-hexane and ethyl acetate, and the results were observed under a UV light with a wavelength of 254 nm. The KBr pellet method was used to analyze the infrared (IR) spectra of the compounds in order to identify functional groups using a JASCO-320 A spectrometer. A Bruker spectrometer running at 500 MHz was used to record ^{1}H NMR spectra and that at 100 MHz to record ^{13}C NMR spectra. The melting points were recorded using the Griffin and George melting point instrument and an open capillary tube.

4.1. Synthesis of Ethyl 1-(Phenylsulfonyl)piperidine-3-carboxylate (1). Ethyl 1-(phenylsulfonyl)piperidine-3-carboxylate (**1**) was synthesized by the reaction of benzene sulfonyl chloride (**a**) with ethyl piperidine-3-carboxylate (**b**) in an equimolar ratio at room temperature in the aqueous medium for 5−6 h. 18% Sodium carbonate solution was used to maintain the pH of the reaction at 9−10. The reaction progress and product formation were confirmed by thin layer chromatography. At completion of the reaction, the pH of the reaction mixture was maintained neutral by using dilute HCl. To obtain the precipitates of the synthesized compound, cold distilled water was added. Then, filtration, washing, and drying of precipitates were performed.

4.2. Synthesis of 1-(Phenylsulfonyl)piperidine-3-carbohydrazide (2). 1-(Phenylsulfonyl)piperidine-3-carbohydrazide (**2**) was synthesized by refluxing compound **1** with hydrazinium hydroxide in an equimolar ratio in a methanol solvent for 8−9 h. Thin layer chromatography was used for the confirmation of product formation. After completion of the reaction, the excess methanol was evaporated followed by the addition of chilled water. The obtained product was then filtered, washed, and dried.

4.3. Synthesis of 5-[1-(Phenylsulfonyl)piperidin-3-yl]-1,3,4-oxadiazole-2-thiol (3). For complete dissolution of KOH and compound **2** in ethanol, an equimolar amount of compound **2** (0.314 mol) and potassium hydroxide (0.314 mol) was refluxed for half an hour. The equimolar CS_2 was added, and the entire mixture was refluxed for another 5−6 h. Thin layer chromatography was used to examine the reaction's completeness. After the reaction was completed, the reaction mixture was filled with cold distilled water. The pH of the reaction mixture was then maintained at 5−6 by adding dilute HCl to protonate the sulfur atom directly attached to the oxadiazole ring. After this, the precipitates were filtered and washed before being dried.

4.4. Synthesis of *N*-(Substituted)-2-bromoacetamides (6a−s). Different alkyl/aralkyl/aryl amines (**4a−s**; 0.03 mol) were vigorously stirred with 2-bromoacetyl bromide (**5**; 0.03 mol) in a 250 mL conical flask in distilled water for 5 min and then set to stirring for further 60 min. During the reaction, 18% Na_2CO_3 solution was used to adjust pH to 9−10. After stirring, formed precipitates were filtered, washed with distilled water, and dried.

4.5. General Conventional and Microwave-Assisted Procedures for the Synthesis of *N*-Alkyl/Aralkyl/Aryl Acetamide Derivatives of Compound 3 (7a−s). Conventional synthesis. The targeted compounds, **7a−s**, were synthesized by dissolving compound **3** in a round bottom flask in *N*,*N*-dimethyl formamide. Then, equimolar LiH was added, and it was stirred for half an hour. An equimolar amount of all the synthesized electrophiles, **6a−s**, was added subsequently and placed under stirring for 900−1800 min at room temperature. The reaction completion was confirmed by using thin layer chromatography. After reaction completion, chilled distilled water was added upon continuous stirring for maximum yield. After this addition, filtration and washing of obtained products were performed. Chloroform was used for the extraction of a few compounds. Microwave-assisted synthesis. The targeted compounds, **7a−s**, were synthesized by dissolving compound **3** in a round bottom flask in *N*,*N*-dimethyl formamide. Then, equimolar LiH was added, and it was stirred for half an hour. An equimolar amount of all the synthesized electrophiles, **6a−s**, was added subsequently and microwave-irradiated for 30−70 s upon stirring. The reaction completion was confirmed by using thin layer chromatography. After reaction completion, chilled distilled water was added upon continuous stirring for maximum yield. After this addition, filtration and washing of obtained products were performed. Chloroform was used for the extraction of a few compounds.

*4.5.1. N-(2,3-Dimethylphenyl)-2-{5-[1-(phenylsulfonyl)-piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (**7a**).* Off-white amorphous solid; yield: 91%; mp 140−142 °C; molecular formula: $C_{23}H_{26}N_4O_4S_2$; molecular mass: 486.61 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3349 (N−H stretching), 3042 (C−H), 1665 (C═O), 1342 (−SO_2 stretching), 1529 (C═C stretching), 1568 (C═N stretching), 1241, and 1079 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.68 (s, 1H, N−H), 7.76 (d, J = 7.2 Hz, 2H, H-2, H-6), 7.66 (t, J = 6.4 Hz, 1H, H-4), 7.58 (t, J = 7.8 Hz, 2H, H-3, H-5), 7.14 (t, J = 9.1 Hz, 1H, H-5), 7.05 (d, J = 8.7 Hz, 2H, H-4‴′, H-6‴′), 4.05 (s, 2H, H-1‴), 4.01 (d, J = 11.5 Hz, 1H, H_{eq}-2′), 3.80 (d, J = 11.6 Hz, 1H, H_{eq}-6′), 3.27−3.22 (m, 1H, H-3′), 2.83 (t, J = 9.5 Hz, 1H, H_{ax}-2′), 2.63−2.58 (m, 1H, H_{ax}-6′), 2.30 (s, 3H, H-2‴), 2.20 (s, 3H, H-3‴), 2.19−2.13 (m, 1H, H_{eq}-4′), 1.94−1.90 (m, 1H, H_{ax}-4′), 1.89−1.86 (m, 1H, H_{eq}-5′), 1.72−1.64 (m, 1H, H_{ax}-5′);^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 172.1 (carbonyl carbon), 164.3 (C-2″), 162.1 (C-5″), 143.2 (C-1),136.4 (C-3‴′),135.7 (C-1‴′),129.8 (C-2& C-6),128.1 (C-4),127.9 (C-3 & C-5),126.4 (C-2‴′),125.7 (C-4‴′), 124.4 (C-5‴′), 122.9 (C-6‴′),51.7 (C-2′), 47.6 (C-6′), 42.4 (C-3′), 35.6 (C-1‴), 29.2 (C-4′), 26.3 (C-5′), 18.8 (C-3‴), 15.2 (C-2‴); Anal. Calcd. for $C_{23}H_{26}N_4O_4S_2$: C, 56.77; H, 5.39; N, 11.51; O, 13.15; S, 13.18. Found: C, 56.43; H, 5.27; N, 11.49; O, 13.08; S, 13.11.

*4.5.2. N-(2,4-Dimethylphenyl)-2-{5-[1-(phenylsulfonyl)-piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (**7b**).* Reddish sticky solid; yield: 95%; mp 141−143 °C; molecular formula: $C_{23}H_{26}N_4O_4S_2$; molecular mass: 486.61 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3356 (N−H stretching), 3046 (C−H), 1653 (C═O), 1349 (−SO_2 stretching), 1521 (C═C stretching), 1565 (C═N stretching), 1230, and 1082 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.65 (s, 1H, N−H), 7.75 (d, J = 8.2 Hz, 2H, H-2, H-

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6), 7.70 (s, 1H, H-3‴′), 7.64 (t, J = 6.7 Hz, 1H, H-4), 7.56 (t, J = 7.4 Hz, 2H, H-3, H-5), 7.02 (d, J = 10.3 Hz, 2H, H-5‴′, H-6‴′), 4.05 (s, 2H, H-1‴), 4.01 (d, J = 11.8 Hz, 1H, H_{eq}-2′), 3.73 (d, J = 12.1 Hz, 1H, H_{eq}-6′), 3.27−3.22 (m, 1H, H-3′), 2.70 (t, J = 10.7 Hz, 1H, H_{ax}-2′), 2.52−2.48 (m, 1H, H_{ax}-6′), 2.30 (s, 3H, H-2‴), 2.22 (s, 3H, H-3‴), 2.19−2.13 (m, 1H, H_{eq}-4′), 1.94−1.90 (m, 1H, H_{ax}-4′), 1.82−1.75 (m, 1H, H_{eq}-5′), 1.69−1.63 (m, 1H, H_{ax}-5′);^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 171.8 (carbonyl carbon), 164.3 (C-2″), 162.1 (C-5″), 142.8 (C-1), 135.1 (C-1‴′), 133.9 (C-2‴′), 130.8 (C-4‴′), 129.3 (C-2 & C-6), 127.7 (C-4), 127.5 (C-3 & C-5), 126.9 (C-5‴′), 124.7 (C-3‴′), 122.7 (C-6‴′), 51.3 (C-2′), 47.4 (C-6′), 42.3 (C-3′), 35.7 (C-1‴), 28.9 (C-4′), 26.1 (C-5′), 19.2 (C-3‴), 15.7 (C-2‴); Anal. Calcd. for $C_{23}H_{26}N_4O_4S_2$: C, 56.77; H, 5.39; N, 11.51; O, 13.15; S, 13.18. Found: C, 56.43; H, 5.27; N, 11.49; O, 13.08; S, 13.11.

*4.5.3. N-(2,5-Dimethylphenyl)-2-{5-[1-(phenylsulfonyl)-piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (**7c**).* Creamy solid; yield: 89%; mp 136−138 °C; molecular formula: $C_{23}H_{26}N_4O_4S_2$; molecular mass: 486.61 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3345 (N−H stretching), 3031 (C−H), 1669 (C═O), 1322 (−SO_2 stretching), 1531 (C═C stretching), 1571 (C═N stretching), 1230, and 1089 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.68 (s, 1H, N−H), 7.78 (d, J = 7.8 Hz, 2H, H-2, H-6), 7.73 (s, 1H, H-6‴′), 7.64 (t, J = 6.7 Hz, 1H, H-4), 7.56 (t, J = 7.5 Hz, 2H, H-3, H-5), 7.07 (d, J = 7.6 Hz, 1H, H-3‴′), 6.91 (d, J = 7.3 Hz, 1H, H-4‴′), 4.06 (s, 2H, H-1‴), 4.01 (d, J = 11.7 Hz, 1H, H_{eq}-2′), 3.73 (d, J = 11.5 Hz, 1H, H_{eq}-6′), 3.24−3.16 (m, 1H, H-3′), 2.70 (t, J = 10.3 Hz, 1H, H_{ax}-2′), 2.52−2.42 (m, 1H, H_{ax}-6′), 2.30 (s, 3H, H-2‴), 2.22 (s, 3H, H-3‴), 2.17−2.13 (m, 1H, H_{eq}-4′), 1.93−1.90 (m, 1H, H_{ax}-4′), 1.79−1.75 (m, 1H, H_{eq}-5′), 1.66−1.61 (m, 1H, H_{ax}-5′); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 172.3 (carbonyl carbon), 164.3 (C-2″), 162.1 (C-5″),142.6 (C-1), 135.9 (C-1‴′), 133.1 (C-5‴′), 130.8 (C-2‴′), 129.5 (C-2 & C-6), 128.3 (C-4), 127.7 (C-3 & C-5), 126.3 (C-4‴′), 123.1 (C-3‴′),121.9 (C-6‴′), 51.5 (C-2′), 47.8 (C-6′), 42.1 (C-3′), 35.6 (C-1‴), 29.1 (C-4′), 25.9 (C-5′), 19.8 (C-3‴), 16.1 (C-2‴); Anal. Calcd. for $C_{23}H_{26}N_4O_4S_2$: C, 56.77; H, 5.39; N, 11.51; O, 13.15; S, 13.18. Found: C, 56.43; H, 5.27; N, 11.49; O, 13.08; S 13.11.

*4.5.4. N-(2,6-Dimethylphenyl)-2-{5-[1-(phenylsulfonyl)-piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (**7d**).* Dark-brown amorphous solid; yield: 87%; mp 132−134 °C; molecular formula: $C_{23}H_{26}N_4O_4S_2$; molecular mass: 486.61 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3351 (N−H stretching), 3038 (C−H), 1657 (C═O), 1339 (−SO_2 stretching), 1525 (C═C stretching), 1568 (C═N stretching), 1235, and 1080 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.38 (s, 1H, N−H), 7.80 (d, J = 7.1 Hz, 2H, H-2, H-6), 7.64 (t, J = 7.4 Hz, 1H, H-4), 7.57 (t, J = 7.8 Hz, 2H, H-3, H-5), 7.12 (t, J = 6.2 Hz, 1H, H-4‴′), 7.08 (d, J = 7.5 Hz, 2H, H-3‴′, H-5‴′), 4.05 (s, 2H, H-1‴), 4.01 (d, J = 11.7 Hz, 1H, H_{eq}-2′), 3.71 (d, J = 11.6 Hz, 1H, H_{eq}-6′), 3.23−3.17 (m, 1H, H-3′), 2.72 (t, J = 10.3 Hz, 1H, H_{ax}-2′), 2.59−2.51 (m, 1H, H_{ax}-6′), 2.23 (s, 3H, H-2‴), 2.18−2.13 (m, 1H, H_{eq}-4′), 1.94−1.91 (m, 1H, H_{ax}-4′), 1.68−1.61 (m, 4H, H_{eq}-5′, H-3‴); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 172.5 (carbonyl carbon),164.3 (C-2″), 162.1 (C-5″),143.1 (C-1), 136.5 (C-1‴′), 131.7 (C-2‴′ & C-6‴′), 129.6 (C-2 & C-6), 128.4 (C-4), 127.6 (C-3 & C-5),126.1 (C-3‴′ & C-5‴′),125.1 (C-4‴′), 51.2 (C-2′),47.6 (C-6′), 42.5 (C-3′),35.5 (C-1‴), 29.2 (C-4′), 26.3 (C-5′), 19.5 (C-2‴& C-3‴); Anal. Calcd. for $C_{23}H_{26}N_4O_4S_2$: C, 56.77; H, 5.39; N, 11.51; O, 13.15; S, 13.18. Found: C, 56.43; H, 5.27; N, 11.49; O, 13.08; S, 13.11.

*4.5.5. N-(3,5-Dimethylphenyl)-2-{5-[1-(phenylsulfonyl)-piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (**7e**).* White solid; yield: 94%; mp 148−150 °C; molecular formula: $C_{23}H_{26}N_4O_4S_2$; molecular mass: 486.61 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3343 (N−H stretching), 3035 (C−H), 1659 (C═O), 1331 (−SO_2 stretching), 1534 (C═C stretching), 1566 (C═N stretching), 1232, and 1074 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.91 (s, 1H, N−H), 7.79 (d, J = 7.1 Hz, 2H, H-2, H-6), 7.65 (t, J = 6.4 Hz, 1H, H-4), 7.56 (t, J = 7.8 Hz, 2H, H-3, H-5), 7.18 (s, 1H, H-2‴′, H-6‴′), 6.78 (s, 1H, H-4‴′), 4.01 (d, J = 6.6 Hz, 1H, H_{eq}-2′), 3.99 (s, 2H, H-1‴), 3.71 (d, J = 11.5 Hz, 1H, H_{eq}-6′), 3.27−3.21 (m, 1H, H-3′), 2.73 (t, J = 10.7 Hz, 1H, H_{ax}-2′), 2.52−2.43 (m, 1H, H_{ax}-6′), 2.30 (s, 3H, H-2‴), 2.19−2.14 (m, 1H, H_{eq}-4′), 1.94−1.90 (m, 1H, H_{ax}-4′), 1.82−1.75 (m, 1H, H_{eq}-5′), 1.74−1.65 (m, 4H, H_{eq}-5′, H-3‴); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 171.8 (carbonyl carbon),164.3 (C-2″), 162.1 (C-5″),143.2 (C-1), 137.6 (C-1‴′), 134.9 (C-3‴′ & C-5‴′), 130.1 (C-2 & C-6), 128.7 (C-4), 127.5 (C-3 & C-5), 125.9 (C-4‴′),124.2 (C-2‴′ & C-6‴′), 51.7 (C-2′), 47.4 (C-6′),42.4 (C-3′), 35.6 (C-1‴),29.1 (C-4′), 26.3 (C-5′), 20.7 (C-2‴& C-3‴); Anal. Calcd. for $C_{23}H_{26}N_4O_4S_2$: C, 56.77; H, 5.39; N, 11.51; O, 13.15; S, 13.18. Found: C, 56.43; H, 5.27; N, 11.49; O, 13.08; S, 13.11.

*4.5.6. 2-{5-[1-(Phenylsulfonyl)piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}-N-o-tolylacetamide (**7f**).* Light-yellowish solid; yield: 89%; mp 128−130 °C; molecular formula: $C_{22}H_{24}N_4O_4S_2$; molecular mass: 472.61 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3339 (N−H stretching), 3055 (C−H), 1656 (C═O), 1338 (−SO_2 stretching), 1523 (C═C stretching), 1569 (C═N stretching), 1245, and 1085 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.76 (s, 1H, N−H), 7.92 (d, J = 8.2 Hz, 1H, H-3‴′), 7.78 (d, J = 7.8 Hz, 2H, H-2, H-6), 7.63 (t, J = 7.1 Hz, 1H, H-4), 7.56 (t, J = 7.8 Hz, 2H, H-3, H-5), 7.22 (d, J = 7.6 Hz, 1H, H-6‴′), 7.20 (t, J = 7.6 Hz, 1H, H-4‴′), 7.18 (t, J = 7.4 Hz, 1H, H-5‴′), 4.05 (s, 2H, H-1‴), 4.01 (d, J = 11.4 Hz, 1H, H_{eq}-2′), 3.73 (d, J = 11.1 Hz, 1H, H_{eq}-6′), 3.27−3.22 (m, 1H, H-3′), 2.70 (t, J = 10.5 Hz, 1H, H_{ax}-2′), 2.56−2.48 (m, 1H, H_{ax}-6′), 2.19 (s, 3H, H-2‴), 2.19−2.15 (m, 1H, H_{eq}-4′), 1.94−1.90 (m, 1H, H_{ax}-4′), 1.83−1.75 (m, 1H, H_{eq}-5′), 1.67−1.59 (m, 1H, H_{ax}-5′); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 171.9 (carbonyl carbon), 164.3 (C-2″), 162.1 (C-5″), 143.2 (C-1), 137.1 (C-1‴′),132.4 (C-2‴′),129.8 (C-2 & C-6),128.3 (C-4),127.5 (C-3 & C-5),126.3 (C-3‴′),125.3 (C-5‴′), 124.7 (C-4‴′), 123.1 (C-6‴′),51.7 (C-2′), 47.6 (C-6′), 42.4 (C-3′), 35.6 (C-1‴), 29.2 (C-4′), 26.3 (C-5′), 18.4 (C-2‴); Anal. Calcd. for $C_{22}H_{24}N_4O_4S_2$: C, 55.91; H, 5.12; N, 11.86; O, 13.54; S, 13.57. Found: C, 55.86; H, 5.10; N, 11.75; O, 13.48; S, 13.51.

*4.5.7. 2-{5-[1-(Phenylsulfonyl)piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}-N-p-tolylacetamide (**7g**).* Dark-brown; yield: 92%; mp 133−135 °C; molecular formula: $C_{22}H_{24}N_4O_4S_2$; molecular mass: 472.61 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3345 (N−H stretching), 3046 (C−H), 1666 (C═O), 1344 (−SO_2 stretching), 1525 (C═C stretching), 1561 (C═N stretching), 1237, and 1074 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.98 (s, 1H, N−H), 7.76 (d, J = 7.3 Hz, 2H, H-2, H-6), 7.64 (t, J = 7.3 Hz, 1H, H-4), 7.55 (t, J = 7.8 Hz, 2H, H-3, H-5), 7.44 (d, J = 8.2 Hz, 2H, H-2‴′, H-6‴′), 7.21 (d, J = 8.2 Hz, 2H, H-3‴′, H-5‴′), 4.01 (d, J = 11.4 Hz, 1H, H_{eq}-2′), 3.83 (s, 2H, H-1‴), 3.74 (d, J = 11.1 Hz, 1H, H_{eq}-

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6′), 3.26−3.22 (m, 1H, H-3′), 2.72 (t, J = 10.5 Hz, 1H, H_{ax}-2′), 2.54−2.45 (m, 1H, H_{ax}-6′), 2.34 (s, 3H, H-2‴), 2.18−2.14 (m, 1H, H_{eq}-4′), 1.93−1.90 (m, 1H, H_{ax}-4′), 1.83−1.75 (m, 1H, H_{eq}-5′), 1.63−1.60 (m, 1H, H_{ax}-5′); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm) 173.1 (carbonyl carbon), 160.4 (C-2″), 160.0 (C-5″), 137.6 (C-1), 137.1 (C-1‴′), 129.7 (C-4‴′), 129.3 (C-2 & C-6), 127.6 (C-4), 123.0 (C-3 & C-5), 117.5 (C-3‴′ & C-5‴′), 114.3 (C-2‴′ & C-6‴′), 55.6 (C-2′), 48.6 (C-6′), 46.2 (C-3′), 33.5 (C-1‴), 27.2 (C-4′), 23.7 (C-5′), 20.0 (C-2‴); Anal. Calcd. for $C_{22}H_{24}N_4O_4S_2$: C, 55.91; H, 5.12; N, 11.86; O, 13.54; S, 13.57. Found: C, 55.86; H, 5.10; N, 11.75; O, 13.48; S, 13.51.

*4.5.8. Methyl 2-(2-(5-(1-(Phenylsulfonyl)piperidin-3-yl)-1,3,4-oxadiazol-2-ylthio)acetamido)benzoate (**7h**).* Dark-brown amorphous solid; yield: 91%; mp 141−143 °C; molecular formula: $C_{23}H_{24}N_4O_6S_2$; molecular mass: 516.59 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3342 (N−H stretching), 3038 (C−H), 1675 (C═O), 1352 (−SO_2 stretching), 1519 (C═C stretching), 1566 (C═N stretching), 1234, and 1084 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.63 (s, 1H, N−H), 8.04 (d, J = 8.0 Hz, 1H, H-6‴′), 7.75 (d, J = 8.7 Hz, 2H, H-2, H-6), 7.64 (t, J = 7.4 Hz, 1H, H-4), 7.63−7.57 (m, 4H, H-3, H-5, H-3‴′, H-4‴′), 7.18 (t, J = 7.2 Hz, 1H, H-5‴′), 4.77 (s, 3H, H-3‴), 4.02 (d, J = 11.4 Hz, 2H, H_{eq}-2′), 3.88 (s, 2H, H-1‴), 3.75 (d, J = 11.1 Hz, 1H, H_{eq}-6′), 3.27−3.23 (m, 1H, H-3′), 2.79 (t, J = 9.8 Hz, 1H, H_{ax}-2′), 2.59−2.58 (m, 1H, H_{ax}-6′), 2.12−2.08 (m, 1H, H_{eq}-4′), 1.94−1.90 (m, 1H, H_{ax}-4′), 1.87−1.76 (m, 1H, H_{eq}-5′), 1.64−1.60 (m, 1H, H_{ax}-5′); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 172.0 (carbonyl carbon), 171.0 (C-2‴), 164.3 (C-2″), 162.1 (C-5″),144.2 (C-1‴′), 143.1 (C-1), 134.3 (C-3‴′), 131.1 (C-5‴′), 129.8 (C-2 & C-6), 128.1 (C-4), 127.4 (C-3 & C-5), 123.2 (C-4‴′), 120.7 (C-6‴′), 117.0 (C-2‴′), 52.9 (C-3‴), 51.7 (C-2′), 47.4 (C-6′), 42.2 (C-3′), 35.6 (C-1‴), 29.2 (C-4′), 26.3 (C-5′); Anal. Calcd. for $C_{23}H_{24}N_4O_6S_2$: C, 53.47; H, 4.68; N, 10.85; O, 18.58; S, 12.41. Found: C, 53.41; H, 4.62; N, 10.76; O, 18.51; S, 12.35.

*4.5.9. N-(5-Chloro-2-methoxyphenyl)-2-{5-[1-(phenylsulfonyl)piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}-acetamide (**7i**).* White amorphous solid; yield: 93%; mp 150−152 °C; molecular formula: $C_{22}H_{23}ClN_4O_5S_2$; molecular mass: 523.03 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3347 (N−H stretching), 3032 (C−H), 1657 (C═O), 1347 (−SO_2 stretching), 1537 (C═C stretching), 1563 (C═N stretching), 1247, and 1088 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 9.20 (s, 1H, N−H), 8.40 (s, 1H, H-6‴′), 7.74 (d, J = 7.8 Hz, 2H, H-2, H-6), 7.63 (t, J = 7.2 Hz, 1H, H-4), 7.58 (t, J = 7.2 Hz, 2H, H-3, H-5), 7.02 (d, J = 6.3 Hz, 1H, H-3‴′), 6.79 (d, J = 8.7 Hz, 1H, H-4‴′), 4.06 (s, 3H, H-2‴), 4.02 (d, J = 9.4 Hz, 1H, H_{eq}-2′), 3.87 (s, 2H, H-1‴), 3.75 (d, J = 10.4 Hz, 1H, H_{eq}-6′), 3.27−3.21 (m, 1H, H-3′), 2.70 (t, J = 10.8 Hz, 1H, H_{ax}-2′), 2.52−2.50 (m, 1H, H_{ax}-6′), 2.19−2.14 (m, 1H, H_{eq}-4′), 1.94−1.90 (m, 1H, H_{ax}-4′), 1.82−1.76 (m, 1H, H_{eq}-5′), 1.64−1.59 (m, 1H, H_{ax}-5′); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 171.9 (carbonyl carbon), 164.3 (C-2″), 162.1 (C-5″), 147.6 (C-2‴′), 142.9 (C-1),131.9 (C-4‴′), 129.8 (C-2 & C-6), 128.5 (C-4), 127.8 (C-3 & C-5),127.9 (C-1‴′), 127.1 (C-6‴′), 125.1 (C-5‴′), 115.9 (C-3‴′),57.5 (C-2‴), 51.4 (C-2′), 47.8 (C-6′), 42.2 (C-3′), 35.6 (C-1‴), 29.3 (C-4′), 25.9 (C-5′); Anal. Calcd. for $C_{22}H_{23}ClN_4O_5S_2$: C, 50.52; H, 4.43; Cl, 6.78; N, 10.78; O, 15.30; S, 12.26. Found: C, 50.47; H, 4.37; Cl, 6.73; N, 10.69; O, 15.26; S, 12.21.

*4.5.10. N-Phenethyl-2-{5-[1-(phenylsulfonyl)piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (**7j**).* Light-orange solid; yield: 96%; mp 122−123 °C; molecular formula: $C_{23}H_{26}N_4O_4S_2$; molecular mass: 486.61 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3348 (N−H stretching), 3043 (C−H), 1667 (C═O), 1347 (−SO_2 stretching), 1523 (C═C stretching), 1565 (C═N stretching), 1235, and 1085 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.65 (s, 1H, N−H), 7.79 (d, J = 6.8 Hz, 2H, H-2, H-6), 7.68 (t, J = 7.3 Hz, 1H, H-4), 7.60 (t, J = 7.7 Hz, 2H, H-3, H-5), 7.30 (d, J = 7.3 Hz, 2H, H-2‴′, H-6‴′), 7.27−7.23 (m, 1H, H-4‴′), 7.20−7.16 (m, 2H, H-3‴′, H-5‴′), 4.22 (s, 2H, H-1‴), 3.89 (d, J = 9.4 Hz, 1H, H_{eq}-2′), 3.56 (d, J = 10.4 Hz, 1H, H_{eq}-6′), 3.49 (q, J = 10.9 Hz, 2H, H-2‴), 3.30−3.26 (m, 1H, H-3′), 3.14 (t, J = 9.0 Hz, 2H, H-3‴), 2.88 (t, J = 6.8 Hz, 1H, H_{ax}-2′), 2.71−2.60 (m, 2H, H_{ax}-6′), 2.13−2.08 (m, 1H, H_{eq}-4′), 1.92−1.87 (m, 1H, H_{ax}-4′), 1.75−1.72 (m, 1H, H_{eq}-5′), 1.70−1.65 (m, 1H, H_{ax}-5′); ^{13}C NMR (CDCl3, 100 MHz, δ/ppm): 172.1 (carbonyl carbon), 164.3 (C-2″), 162.1 (C-5″), 143.1 (C-1), 141.8 (C-1‴′), 131.5 (C-3‴′ & C-5‴′), 129.7 (C-2 & C-6), 128.7 (C-4), 128.1 (C-3 & C-5), 127.5 (C-2‴′ & C-6‴′),127.1 (C-4‴′), 51.3 (C-2′), 47.6 (C-6′), 42.3 (C-3′), 35.6 (C-1‴),33.1 (C-3‴), 29.5 (C-4′), 28.6 (C-2‴), 26.3 (C-5′); Anal. Calcd. for $C_{23}H_{26}N_4O_4S_2$: C, 56.77; H, 5.39; N, 11.51; O, 13.15; S, 13.18. Found: C, 56.43; H, 5.27; N, 11.49; O, 13.08; S, 13.11.

*4.5.11. N-(2-Ethylphenyl)-2-{5-[1-(phenylsulfonyl)-piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (**7k**).* Brown sticky solid; yield: 86%; mp 116−118 °C; molecular formula: $C_{23}H_{26}N_4O_4S_2$; molecular mass: 486.61 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3352 (N−H stretching), 3041 (C−H), 1659 (C═O), 1336 (−SO_2 stretching), 1524 (C═C stretching), 1561 (C═N stretching), 1238, and 1081 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.71 (s, 1H, N−H), 7.79 (d, J = 6.4 Hz, 2H, H-2, H-6), 7.69 (t, J = 7.3 Hz, 1H, H-4), 7.63 (t, J = 7.7 Hz, 2H, H-3, H-5), 7.37 (d, J = 6.4 Hz, 1H, H-3‴′), 7.28 (d, J = 6.4 Hz, 1H, H-6‴′), 7.23−7.19 (m, 2H, H-4‴′, H-5‴′), 4.22 (s, 2H, H-1‴), 3.89 (d, J = 9.4 Hz, 1H, H_{eq}-2′), 3.56 (d, J = 10.4 Hz, 1H, H_{eq}-6′), 3.30−3.26 (m, 1H, H-3′), 2.88 (t, J = 6.8 Hz, 1H, H_{ax}-2′), 2.71−2.60 (m, 3H, H_{ax}-6′, H-2‴), 2.14−2.08 (m, 1H, H_{eq}-4′), 1.92−1.87 (m, 1H, H_{ax}-4′), 1.75−1.72 (m, 1H, H_{eq}-5′), 1.70−1.65 (m, 1H, H_{ax}-5′), 1.17 (t, J = 7.55 Hz, 3H, H-3‴); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 172.1 (carbonyl carbon), 164.3 (C-2″), 162.1 (C-5″),146.5 (C-1‴′),143.2 (C-1), 129.9 (C-2 & C-6),128.7 (C-4),127.9 (C-3 & C-5),127.4 (C-3‴′),127.1 (C-2‴′), 125.3 (C-5‴′), 124.7 (C-4‴′), 121.1 (C-6‴′),51.7 (C-2′), 47.5 (C-6′), 42.4 (C-3′), 35.6 (C-1‴), 29.3 (C-4′), 26.3 (C-5′), 24.1 (C-2‴), 14.2 (C-3‴); Anal. Calcd. for $C_{23}H_{26}N_4O_4S_2$: C, 56.77; H, 5.39; N, 11.51; O, 13.15; S, 13.18. Found: C, 56.43; H, 5.27; N, 11.49; O, 13.08; S, 13.11.

*4.5.12. N-(4-Ethylphenyl)-2-{5-[1-(phenylsulfonyl)-piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (**7l**).* Off-white solid; yield: 93%; mp 124−126 °C; molecular formula: $C_{23}H_{26}N_4O_4S_2$; molecular mass: 486.61 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3342 (N−H stretching), 3041 (C−H), 1658 (C═O), 1344 (−SO_2 stretching), 1517 (C═C stretching), 1559 (C═N stretching), 1233, and 1082 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 9.01 (s, 1H, N−H), 7.78 (d, J = 7.3 Hz, 2H, H-2, H-6), 7.63 (t, J = 7.4 Hz, 1H, H-4), 7.56 (t, J = 7.8 Hz, 2H, H-3, H-5), 7.46 (d, J = 8.3 Hz, 2H, H-2‴′, H-6‴′), 7.17 (d, J = 11.5 Hz, 2H, H-3‴′, H-5‴′), 4.01 (d,

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J = 10.3 Hz, 1H, H_{eq}-2′), 3.98 (s, 2H, H-1‴), 3.71 (d, J = 10.4 Hz, 1H, H_{eq}-6′), 3.26−3.22 (m, 1H, H-3′), 2.72 (t, J = 10.8 Hz, 1H, H_{ax}-2′), 2.61 (q, J = 7.6 Hz, 2H, H-2‴), 2.54−2.49 (m, 1H, H_{ax}-6′),2.17−2.14 (m, 1H, H_{eq}-4′), 1.94−1.90 (m, 1H, H_{ax}-4′), 1.82−1.74 (m, 1H, H_{eq}-5′), 1.70−1.62 (m, 1H, H_{ax}-5′), 1.23 (t, J = 7.6 Hz, 3H, H-3‴); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 171.9 (carbonyl carbon),164.3 (C-2″), 162.1 (C-5″), 145.4 (C-4‴′), 143.1 (C-1), 142.1 (C-1‴′), 129.3 (C-2 & C-6), 128.9 (C-4), 127.6 (C-3 & C-5), 126.5 (C-3‴′ & C-5‴′), 120.4 (C-2‴′ & C-6‴′), 51.3 (C-2′), 47.6 (C-6′), 42.3 (C-3′), 35.6 (C-1‴), 29.2 (C-4′),28.1 (C-2‴), 26.3 (C-5′), 16.2 (C-3‴); Anal. Calcd. for $C_{23}H_{26}N_4O_4S_2$: C, 56.77; H, 5.39; N, 11.51; O, 13.15; S, 13.18. Found: C, 56.43; H, 5.27; N, 11.49; O, 13.08; S, 13.11.

*4.5.13. N-(4-Ethoxyphenyl)-2-{5-[1-(phenylsulfonyl)-piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (**7m**).* White solid; yield: 95%; mp 124−126 °C; molecular formula: $C_{23}H_{26}N_4O_5S_2$; molecular mass: 502.61 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3331 (N−H stretching), 3039 (C−H), 1654 (C═O), 1334 (−SO_2 stretching), 1515 (C═C stretching), 1562 (C═N stretching), 1243, and1084 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.94 (s, 1H, N−H), 7.78 (d, J = 7.6 Hz, 2H, H-2, H-6), 7.63 (t, J = 7.2 Hz, 1H, H-4), 7.56 (t, J = 7.8 Hz, 2H, H-3, H-5), 7.44 (d, J = 8.9 Hz, 2H, H-2‴′, H-6‴′), 6.88 (d, J = 9.0 Hz, 2H, H-3‴′, H-5‴′), 4.06−3.99 (m, 3H, H_{eq}-2′, H-2‴), 3.97 (s, 2H, H-1‴), 3.69 (d, J = 11.6 Hz, 1H, H_{eq}-6′), 3.26−3.21 (m, 1H, H-3′), 2.72 (t, J = 10.8 Hz, 1H, H_{ax}-2′), 2.54−2.49 (m, 1H, H_{ax}-6′), 2.16−2.13 (m, 1H, H_{eq}-4′), 1.93−1.89 (m, 1H, H_{ax}-4′), 1.82−1.74 (m, 1H, H_{eq}-5′), 1.67−1.61 (m, 1H, H_{ax}-5′), 1.44 (t, J = 6.8 Hz, 3H, H-3‴); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 171.9 (carbonyl carbon), 164.3 (C-2″), 162.1 (C-5″), 145.4 (C-4‴′), 143.1 (C-1), 142.1 (C-1‴′), 129.3 (C-2 & C-6), 128.7 (C-4), 127.9 (C-3 & C-5), 126.5 (C-3‴′ & C-5‴′), 120.4 (C-2‴′ & C-6‴′), 51.3 (C-2′), 47.6 (C-6′), 42.3 (C-3′), 35.6 (C-1‴), 29.2 (C-4′),28.1 (C-2‴), 26.3 (C-5′), 16.2 (C-3‴); Anal. Calcd. for $C_{23}H_{26}N_4O_5S_2$: C, 54.96; H, 5.21; N, 11.15; O, 15.92; S, 12.76. Found: C, 54.90; H, 5.17; N, 11.10; O, 15.86; S, 12.69.

*4.5.14. N-(2-Ethoxyphenyl)-2-{5-[1-(phenylsulfonyl)-piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (**7n**).* Light-brown sticky liquid; yield: 91%; mp 120−122 °C; molecular formula: $C_{23}H_{26}N_4O_5S_2$; molecular mass: 502.61 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3347 (N−H stretching), 3044 (C−H), 1662 (C═O), 1342 (−SO_2 stretching), 1519 (C═C stretching), 1575 (C═N stretching), 1233, and 1081 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 9.02 (s, 1H, N−H), 8.32 (d, J = 7.9 Hz, 1H, H-3‴′), 7.78 (d, J = 8.2 Hz, 2H, H-2, H-6), 7.62 (t, J = 7.2 Hz, 1H, H-4), 7.55 (t, J = 7.6 Hz, 2H, H-3, H-5), 7.15−6.90 (m, 3H, H-4‴′, H-5‴′, H-6‴′), 4.17 (q, J = 10.9, 2H, H-2‴), 4.12−4.01 (m, 3H, H-1‴, H_{eq}-2′), 3.74 (d, J = 10.9 Hz, 1H, H_{eq}-6′), 3.23−3.19 (m, 1H, H-3′), 2.64 (t, J = 9.2 Hz, 1H, H_{ax}-2′), 2.47−2.43 (m, 1H, H_{ax}-6′), 2.19−2.13 (m, 1H, H_{eq}-4′), 1.93−1.89 (m, 1H, H_{ax}-4′), 1.80−1.75 (m, 1H, H_{eq}-5′), 1.64−1.59 (m, 1H, H_{ax}-5′), 1.49 (t, J = 7.3 Hz, 3H, H-3‴); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm) 169.7 (carbonyl carbon), 164.1 (C-2″), 161.7 (C-5″), 148.1 (C-2‴′),143.2 (C-1), 129.4 (C-2 & C-6), 128.4 (C-4),127.7 (C-3 & C-5),127.1 (C-1‴′),125.4 (C-4‴′),121.3 (C-6‴′), 120.2 (C-5‴′), 114.1 (C-3‴′), 62.2 (C-2‴), 51.3 (C-2′), 47.1 (C-6′), 41.9 (C-3′), 35.6 (C-1‴), 29.3 (C-4′), 26.3 (C-5′), 15.7 (C-3‴); Anal. Calcd. for $C_{23}H_{26}N_4O_5S_2$: C, 54.96; H, 5.21; N, 11.15; O, 15.92; S, 12.76. Found: C, 54.90; H, 5.17; N, 11.10; O, 15.86; S, 12.69.

*4.5.15. N-(2-Ethyl-6-methylphenyl)-2-{5-[1-(phenylsulfonyl)piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}-acetamide (**7o**).* Greenish solid; yield: 82%; mp 120−122 °C; molecular formula: $C_{24}H_{28}N_4O_4S_2$; molecular mass: 500.61 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3331 (N−H stretching), 3038 (C−H), 1654 (C═O), 1345 (−SO_2 stretching), 1535 (C═C stretching), 1563 (C═N stretching), 1245, and 1088 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.39 (s, 1H, N−H), 7.78 (d, J = 7.1 Hz, 2H, H-2, H-6), 7.64 (t, J = 7.5 Hz, 1H, H-4), 7.56 (t, J = 7.2 Hz, 2H, H-3, H-5), 7.19 (t, J = 7.9 Hz, 1H, H-4‴′), 7.10 (d, J = 6.9 Hz, 2H, H-3‴′, H-5‴′), 4.06 (s, 2H, H-1‴), 3.99 (d, J = 11.7 Hz, 1H, H_{eq}-2′), 3.72 (d, J = 11.5 Hz, 1H, H_{eq}-6′), 3.28−3.23 (m, 1H, H-3′), 2.73 (t, J = 10.2 Hz, 1H, H_{ax}-2′), 2.55−2.50 (m, 3H, H_{ax}-6′, H-2‴), 2.18−2.13 (m, 4H, H_{eq}-4′, H-4‴), 1.95−1.91 (m, 1H, H_{ax}-4′), 1.83−1.80 (m, 1H, H_{eq}-5′), 1.67−1.61 (m, 1H, H_{ax}-5′), 1.11 (t, J = 7.5 Hz, 3H, H-3‴); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 172.1 (carbonyl carbon), 164.3 (C-2″), 162.1 (C-5″),143.0 (C-1), 141.6 (C-3‴′), 136.7 (C-1‴′), 129.6 (C-2 & C-6), 128.4 (C-4), 127.8 (C-3 & C-5), 127.1 (C-4‴′),125.1 (C-5‴′), 123.5 (C-2‴′), 122.1 (C-6‴′), 51.2 (C-2′), 47.6 (C-6′), 42.5 (C-3′), 35.5 (C-1‴), 29.2 (C-4′), 28.3 (C-2‴), 26.3 (C-5′), 19.8 (C-3‴), 18.4 (C-4‴); Anal. Calcd. for $C_{24}H_{28}N_4O_4S_2$: C, 57.58; H, 5.64; N, 11.19; O, 12.78; S, 12.81. Found: C, 57.51; H, 5.58; N, 11.13; O, 12.73; S, 12.78.

*4.5.16. N-Cyclohexyl-2-{5-[1-(phenylsulfonyl)piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (**7p**).* Light-yellow solid; yield 84%; mp 141−143 °C; molecular formula: $C_{21}H_{28}N_4O_4S_2$; molecular mass: 464.60 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3337 (N−H stretching), 3039 (C−H), 1654 (C═O), 1344 (−SO_2 stretching), 1527 (C═C stretching), 1558 (C═N stretching), 1244, and 1088 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.90 (s, 1H, N−H), 7.76 (d, J = 7.6 Hz, 2H, H-2, H-6), 7.63 (t, J = 7.1 Hz, 1H, H-4), 7.58 (t, J = 7.6 Hz, 2H, H-3, H-5), 4.01 (d, J = 10.9 Hz, 1H, H_{eq}-2′), 3.84 (s, 2H, H-1‴), 3.72 (d, J = 10.7 Hz, 1H, H_{eq}-6′), 3.67−3.65 (m, 1H, H-1‴′), 3.24−3.21 (m, 1H, H-3′), 2.70 (t, J = 10.3 Hz, 1H, H_{ax}-2′), 2.54−2.47 (m, 1H, H_{ax}-6′), 2.19−2.14 (m, 1H, H_{eq}-4′), 1.94−1.90 (m, 1H, H_{ax}-4′), 1.83−1.80 (m, 1H, H_{eq}-5′), 1.77−1.74 (m, 2H, H-4‴′), 1.70−1.65 (m, 2H, H_{eq}-3‴′, H_{eq}-5‴′), 1.63−1.60 (m, 1H, H_{ax}-5′), 1.59−1.56 (m, 2H, H_{ax}-3‴′, H_{ax}-5‴′), 1.39−1.33 (m, 2H, H_{eq}-2‴′, H_{eq}-6‴′), 1.20−1.16 (m, 2H, H_{ax}-2‴′, H_{ax}-6‴′); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 172.1 (carbonyl carbon), 164.7 (C-2″), 162.3 (C-5″), 142.1 (C-1), 141.0 (C-3‴′), 136.1 (C-1‴′), 130.2 (C-2 & C-6), 129.4 (C-4), 127.6 (C-3 & C-5), 127.1 (C-4‴′), 123.1 (C-5‴′), 122.1 (C-2‴′), 121.4 (C-6‴′), 51.1 (C-2′), 47.4 (C-6′), 41.7 (C-3′), 35.1 (C-1‴), 29.6 (C-4′), 26.4 (C-5′); Anal. Calcd. for $C_{21}H_{28}N_4O_4S_2$: C, 54.29; H, 6.07; N, 12.06; O, 13.77; S, 13.80. Found: C, 54.22; H, 6.03; N, 12.01; O, 13.70; S, 13.71.

*4.5.17. N-(2-Methoxyphenyl)-2-{5-[1-(phenylsulfonyl)-piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (**7q**).* Sticky brown solid; yield: 88%; mp 125−127 °C; molecular formula: $C_{22}H_{24}N_4O_5S_2$; molecular mass: 488.58 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3355 (N−H stretching), 3052 (C−H), 1669 (C═O), 1349 (−SO_2 stretching), 1525 (C═C stretching), 1561 (C═N stretching), 1245, and 1089 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 9.07 (s, 1H, N−H), 8.31 (d, J = 6.8 Hz, 1H, H-3‴′), 7.77 (d, J = 7.2 Hz, 2H, H-2, H-6), 7.63 (t, J = 7.3 Hz, 1H, H-

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4), 7.56 (t, J = 7.8 Hz, 2H, H-3, H-5), 7.09 (t, J = 7.7 Hz, 1H, H-4‴′), 6.96 (t, J = 7.8 Hz, 1H, H-5‴′), 6.80 (d, J = 7.4 Hz, 1H, H-6‴′), 4.07 (s, 2H, H-1‴), 4.02 (d, J = 10.3 Hz, 1H, H_{eq}-2′), 3.89 (s, 3H, H-2‴), 3.75 (d, J = 11.0 Hz, 1H, H_{eq}-6′), 3.26−3.21 (m, 1H, H-3′), 2.69 (t, J = 11.1 Hz, 1H, H_{ax}-2′), 2.50−2.45 (m, 1H, H_{ax}-6′), 2.18−2.14 (m, 1H, H_{eq}-4′), 1.93−1.90 (m, 1H, H_{ax}-4′), 1.89−1.74 (m, 1H, H_{eq}-5′), 1.65−1.56 (m, 1H, H_{ax}-5′); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 171.1 (carbonyl carbon), 164.1 (C-2″), 161.7 (C-5″), 147.9 (C-2‴′), 143.2 (C-1), 129.4 (C-2 & C-6), 128.4 (C-4), 127.9 (C-3 & C-5), 127.3 (C-1‴′),125.8 (C-4‴′), 122.1 (C-6‴′), 119.8 (C-5‴′), 116.1 (C-3‴′), 61.1 (C-2‴), 51.3 (C-2′), 47.1 (C-6′), 41.9 (C-3′), 35.6 (C-1‴), 29.3 (C-4′), 26.3 (C-5′); Anal. Calcd. for $C_{22}H_{24}N_4O_5S_2$: C, 54.08; H, 4.95; N, 11.47; O, 16.37; S, 13.13. Found: C, 54.04; H, 4.91; N, 11.42; O, 16.31; S, 13.06.

*4.5.18. N-Benzyl-2-{5-[1-(phenylsulfonyl)piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}acetamide (**7r**).* White amorphous solid; yield: 81%; mp 129−131 °C; molecular formula: $C_{22}H_{24}N_4O_4S_2$; molecular mass: 472.58 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3351 (N−H stretching), 3056 (C−H), 1661 (C═O), 1345 (−SO_2 stretching), 1530 (C═C stretching), 1566 (C═N stretching), 1239, and 1089 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.61 (s, 1H, N−H), 7.78 (d, J = 6.7 Hz, 2H, H-2, H-6), 7.64 (t, J = 7.1 Hz, 1H, H-4), 7.57 (t, J = 7.6 Hz, 2H, H-3, H-5), 7.31 (d, J = 7.3 Hz, 2H, H-2‴′, H-6‴′), 7.26−7.23 (m, 1H, H-4‴′), 7.19−7.15 (m, 2H, H-3‴′, H-5‴′), 4.15 (s, 2H, H-1‴), 3.85 (d, J = 10.1 Hz, 1H, H_{eq}-2′), 3.55 (d, J = 10.7 Hz, 1H, H_{eq}-6′), 3.48 (s, 2H, H-2‴), 3.29−3.26 (m, 1H, H-3′), 2.81 (t, J = 6.7 Hz, 1H, H_{ax}-2′), 2.70−2.61 (m, 2H, H_{ax}-6′), 2.14−2.09 (m, 1H, H_{eq}-4′), 1.91−1.85 (m, 1H, H_{ax}-4′), 1.75−1.72 (m, 1H, H_{eq}-5′), 1.70−1.65 (m, 1H, H_{ax}-5′); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 171.6 (carbonyl carbon), 165.1 (C-2″), 163.4 (C-5″), 143.9 (C-1), 141.1 (C-3‴′), 136.9 (C-1‴′), 130.3 (C-2 & C-6), 128.7 (C-4), 127.9 (C-3 & C-5), 127.7 (C-4‴′), 124.5 (C-5‴′), 121.9 (C-2‴′), 121.3 (C-6‴′), 51.4 (C-2′), 47.7 (C-6′), 42.0 (C-3′), 35.9 (C-1‴), 32.7 (C-2‴), 29.1 (C-4′), 26.7 (C-5′); Anal. Calcd. for $C_{22}H_{24}N_4O_4S_2$: C, 55.91; H, 5.12; N, 11.86; O, 13.54; S, 13.57. Found: C, 55.86; H, 5.10; N, 11.75; O, 13.48; S, 13.51.

*4.5.19. N-(2-Methyl-6-nitrophenyl)-2-{5-[1-(phenylsulfonyl)piperidin-3-yl]-1,3,4-oxadiazol-2-ylthio}-acetamide (**7s**).* Yellowish amorphous solid; yield: 91%; mp 179−181 °C; molecular formula: $C_{22}H_{23}N_5O_6S_2$; molecular mass: 517.58 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3346 (N−H stretching), 3055 (C−H), 1671 (C═O), 1346 (−SO_2 stretching), 1531 (C═C stretching), 1566 (C═N stretching), 1240, and 1088 (C−O−C bond stretching); ^{1}H NMR ($CDCl_3$, 500 MHz, δ (ppm)): 8.75 (s, 1H, N−H), 7.79 (d, J = 7.2 Hz, 2H, H-2, H-6), 7.65 (t, J = 7.4 Hz, 1H, H-4), 7.57 (t, J = 7.2 Hz, 2H, H-3, H-5), 7.18 (t, J = 7.8 Hz, 1H, H-4‴′), 7.11 (d, J = 6.9 Hz, 2H, H-3‴′, H-5‴′), 4.06 (s, 2H, H-1‴), 3.98 (d, J = 11.2 Hz, 1H, H_{eq}-2′), 3.74 (d, J = 10.5 Hz, 1H, H_{eq}-6′), 3.23−3.18 (m, 1H, H-3′), 2.73 (t, J = 10.2 Hz, 1H, H_{ax}-2′), 2.55−2.50 (m, 1H, H_{ax}-6′), 2.18−2.13 (m, 4H, H_{eq}-4′, H-2‴), 1.95−1.91 (m, 1H, H_{ax}-4′), 1.83−1.78 (m, 1H, H_{eq}-5′), 1.67−1.61 (m, 1H, H_{ax}-5′); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 172.5 (carbonyl carbon), 164.3 (C-2″), 162.1 (C-5″), 143.1 (C-1), 136.5 (C-1‴′), 135.1 (C-6‴′), 134.1 (C-3‴′), 131.9 (C-2‴′), 129.6 (C-2 & C-6), 128.4 (C-4), 127.6 (C-3 & C-5), 126.5 (C-5‴′), 124.7 (C-4‴′), 51.2 (C-2′), 47.6 (C-6′), 42.1 (C-3′), 35.4 (C-1‴), 29.3 (C-4′), 26.7 (C-5′), 18.4 (C-2‴); Anal. Calcd. for $C_{22}H_{23}N_5O_6S_2$: C, 51.05; H, 4.48; N, 13.53; O, 18.55; S, 12.39. Found: C, 51.01; H, 4.42; N, 13.49; O, 18.51; S, 12.31.

4.6. α-Glucosidase Inhibition Assay. Pierre's procedure was utilized to carry out the α-glucosidase assay with minimal modifications.[28] In a phosphate buffer with a pH of 6.8, 10 μL of α-glucosidase enzyme was introduced, followed by 10 μL of the test material, which was incubated for 10 min at 37 °C. The absorbance was measured at 400 nm at first and then after 20 mi of incubation. The tests were repeated three times, with acarbose serving as a positive control. Equation 1 was used to calculate the % inhibition. Control is the absorbance in the absence of the test sample, and test is the absorbance in the presence of the test sample in eq 1.

$$\text{inhibition (\%)} = \frac{\text{control-test}}{\text{control}} \times 100 \quad (1)$$

4.7. Butyryl Cholinesterase Inhibition Assay. The approach was utilized to execute the BChE activity that had previously been described.[29] To begin, a 60 μL Na_2PO_4 buffer solution with a pH of 7.7 and a concentration of 50 mM was combined with 10 μL of the test chemical and 10 μL of the BChE pre-incubated enzyme. The absorbance was measured after mixing at 405 nm. All of the contents were incubated at 37 °C for 10 min. After this, 10 μL of butyryl choline chloride (0.5 mM well^{-1}) and 10 μL of 5,5′-dithiobis-(2-nitrobenzoic acid) (0.5 mM) were added, and the reaction was started. After 15 min of incubation at 37 °C, the absorbance at 405 nm was measured using a 96-well plate recorder (Synergy HT, BioTek, USA). Eserine was used as the standard drug. Calculation of % inhibition was performed by using eq 1.

4.8. Statistical Analysis. All the calculations were made in triplicate, and the triplicate data was subjected to statistical analysis by Microsoft Excel 2010. Results were presented as mean ± SEM.

4.9. Computational Studies. GaussView 6.0.16 software was used to create the molecular structure, which was then optimized. Full molecular geometry optimization of the molecule was performed using the 6-311++G(d,p) basis set and density functional theory at the B3LYP level with the aid of the Gaussian 06W software package. Gaussian 06W software was used to determine the MEP, maximum occupied molecular orbital, and LUMO energies using the optimized structure of compounds (Table 4). Following complete optimization of all the structures, the total energy (kcal mol^{-1}), highest occupied molecule, and other data were computed.[30,31]

4.10. Generation and Preparation of Structures of Compounds. Three compounds **7e**, **7s**, and **7j** were selected for docking against BChE. The 2D structure of these compounds was first generated using ChemDraw[32] Professional v 15.0 and then imported into Discovery Studio for generating the 3D structure and energy minimization.[33] The conformers of each ligand were generated using OMEGA 3.0.0.[34] OMEGA generates energy-minimized molecular structures with their tautomers, ionization states, ring conformations, and stereoisomers to produce broad chemical and structural diversity from a single input structure. Therefore, we have used all its utilities to prepare our data set for molecular docking simulations.

4.11. Selection and Preparation of Target Protein Structures. The protein structure of target protein, butyryl cholinesterase, was downloaded from the Protein Data Bank using PDB ID.[34] The PDB2ECEPTOR tool in OpenEye was

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used for preparation of all target protein structures which removes water molecules and heteroatoms and assigns charges and adds hydrogens and missing residues (if any). After preparation of target structures, the active site was defined using co-crystal ligands and a centroid on all residues within 10 Å co-crystal ligands for each targeted protein.

4.12. Molecular Docking Studies. After generation of pre-requisite compounds and target protein structures, molecular docking studies were carried out to find out the putative binding interaction. FRED v3.2.0 from OpenEye Scientific Software was used for performing molecular docking calculations.[34] FRED requires a set of input conformers for each compound which was generated by OMEGA 3.0.0. Default parameters of FRED were used for docking calculation which generated 10 poses for each ligand, and pose with lowest chemguass4 was selected for further analysis. Binding interactions of best docked poses were visualized using Discovery Studio client v16.1.0.[35]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c07612.

NMR spectra of synthesized compounds and chemistry for structure elucidation (PDF)

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Notes

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