Synthesis and Biological Evaluation of Thiazole-Based Derivatives as Potential Acetylcholinesterase Inhibitors

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ABSTRACT: Nineteen new thiazole-based derivatives were synthesized and their structures characterized with analytical and spectral data. The *in vitro* assessment of their acetylcholinesterase (AChE) inhibitory activity revealed that compounds **10** and **16** produced potent AChE inhibitory activities with IC_{50} values of 103.24 and 108.94 nM, respectively. Compounds **13**, **17**, **18**, **21**, **23**, **31**, and **33** displayed moderate activity with 25−50% relative potency compared to the known potent AChE inhibitor donepezil. Molecular docking studies of the active compounds docked within the active site cavity of AChE showed a binding orientation similar to that of donepezil, with good predicted binding affinities. These compounds could therefore be considered as potential lead compounds for the development of new and potentially improved AChE inhibitors.
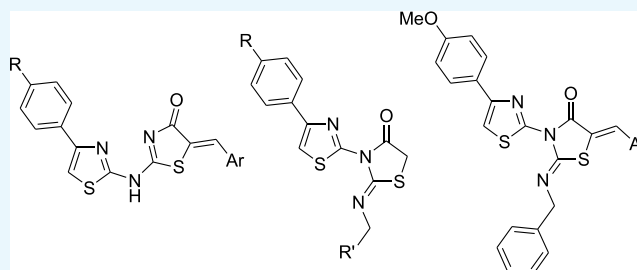
1. INTRODUCTION

Alzheimer's disease (AD) is the most predominant form of neurodegenerative disorder in the elderly worldwide.[1−3] AD is a slowly progressive brain disease that begins many years before symptoms emerge.[4] The early clinical symptoms of AD include difficulties in remembering recent conversations, names, or events in addition to apathy and depression. Later symptoms include confusion, disorientation, impaired communication, poor judgment, behavioral changes, and deterioration of speaking, swallowing, and walking capabilities.[5] Although the reasons for the development and etiology of AD have not yet been fully explored, AD patients are characterized by histopathological brain changes including extracellular deposition of amyloid β-protein (Aβ) in amyloid plaques[6] and by intraneuronal neurofibrillary tangles consisting of aggregated hyperphosphorylated τ-protein.[7] To date, there is no cure for AD. Currently approved therapeutics for AD only offer symptomatic relief without the ability of slowing down disease progression.[8] The formation of Aβ and τ-proteins is associated with the progressive loss of muscarinergic neurons and increased acetylcholinesterase (AChE) enzyme activity, consequently lowering the levels of brain acetylcholine (ACh).[9] The AChE inhibitors rivastigmine, donepezil, galantamine, and tacrine (Figure 1) and the N-methyl-D-aspartate receptor antagonist memantine are the most commonly used symptomatic therapies for AD with limited success.[10]

Structural modifications of the currently used clinical AChE inhibitors resulted in the exploration of the importance of the incorporation of thiazole moieties as essential building blocks for the optimization of AChE inhibitory activity (Figure 2).[11] The acridine−thiazole hybrid derivative **A** showed potent AChE inhibitory activity with IC_{50} = 6.5 nM, exemplifying the
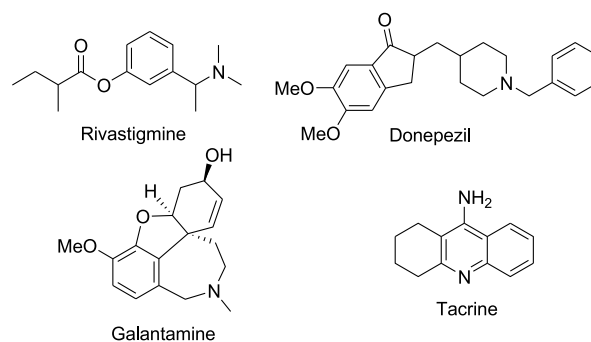

Figure 1. Currently used AChE inhibitors as anti-AD drugs.

importance of the acridine moiety of tacrine incorporated into this structure.[12] However, the acridine moiety is known to cause hepatotoxicity, which has led to the removal of tacrine from the pharmaceutical market.[10] In addition, the benzofuranylthiazole derivatives **B** and **C** displayed moderate dual AChE and butyrylcholinesterase (BuChE) inhibitory activities (IC_{50}: 3.85 μM and 9.25 μM, respectively).[13] Coumarylthiazole derivatives containing aryl urea/thiourea groups, represented by compound **D** (IC_{50} = 4.58 μM), were also reported as moderate AChE inhibitors.[14] Furthermore, the
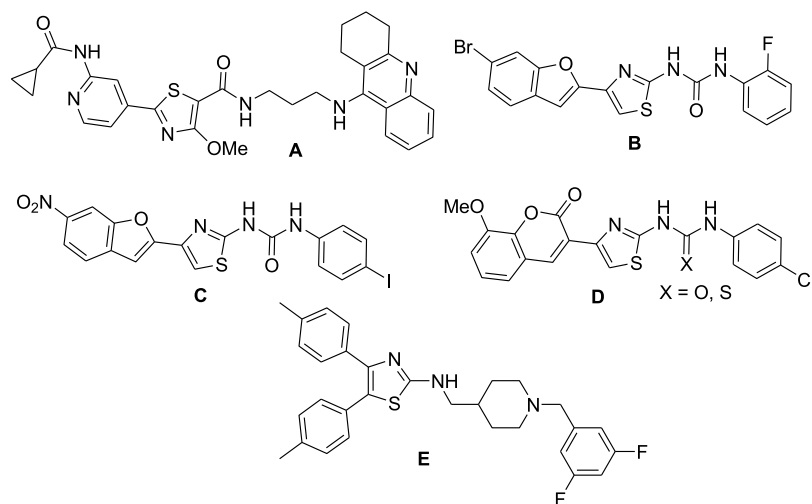
Figure 2. Thiazole-based AChE inhibitors (**A**−**E**) reported in the literature.

benzylpiperidine-linked diarylthiazole derivative **E** exhibited promising AChE inhibitory activity with an IC$_{50}$ value of 0.30 μM.[15] In continuation for the search of improved thiazole-based AChE inhibitors without the acridine moiety, we synthesized a series of thiazole−thiazolidine-incorporated derivatives (Schemes 1 and 2, Table 1). The thiazolidine

**Scheme 1. Synthesis of Compounds 8−21 and 23**
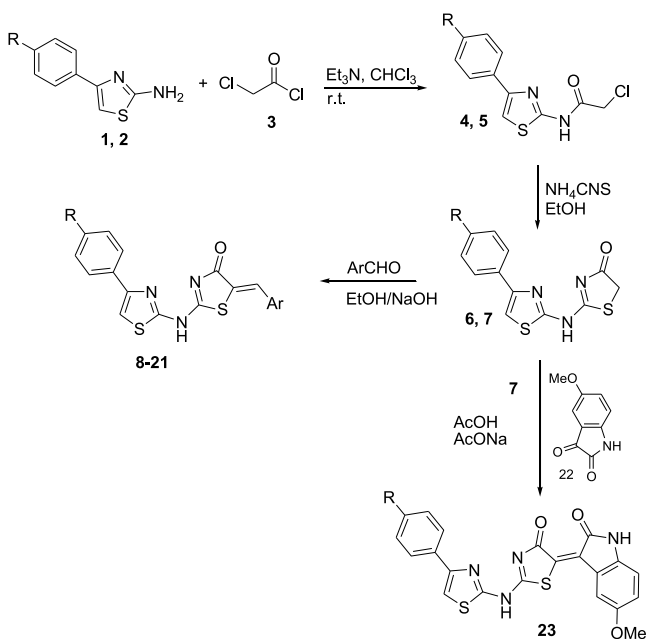
moiety acts as a bioisosteric replacement of the urea/thiourea moieties, as seen in compounds **B**−**D**, and the biological effect thereof was explored using an AChE inhibitory assay (Table 2).

2. RESULTS AND DISCUSSION

2.1. Chemical Synthesis. The required precursors 4-arylthiazol-2-amines **1** and **2** were prepared *via* condensation of thiourea and the appropriate aryl methyl ketone in the presence of iodine.[16] The reaction of compounds **1** and **2** with chloroacetyl chloride **3** and triethylamine in chloroform at room temperature yielded the corresponding 2-chloro-*N*-

Scheme 2. Synthesis of Compounds 28−33
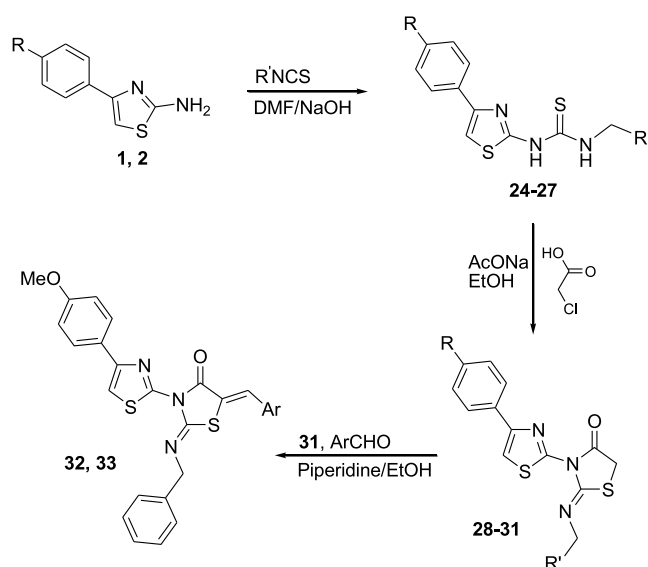
thiazolyl acetamide derivatives **4** and **5**,[17,18] which were reacted with ammonium thiocyanate to yield the corresponding dihydrothiazol-4-one analogues **6**[19] and **7**.[20] Compounds **6** and **7** were condensed with various aromatic aldehydes in the presence of sodium hydroxide to yield the corresponding 5-arylidene derivatives **8−21**, and compound **7** was condensed with 5-methoxyindoline-2,3-dione in acetic acid in the presence of sodium acetate to yield compound **23** (Scheme 1, Table 1).

The aminothiazole derivatives **1** and **2** were reacted with ethyl or benzyl isothiocyanate in *N,N*-dimethylformamide (DMF) to yield the corresponding thiourea derivatives **24**, **25**,[21] **26**, and **27**. The thiourea derivatives **24−27** were then reacted with chloroacetic acid in the presence of sodium acetate to yield the thiazolidin-4-one derivatives **28−31**. The reaction of compound **31** with 3,4-dimethoxybenzaldehyde or 2,4-dichlorobenzaldehyde in ethanol in the presence of a catalytic amount of piperidine yielded the corresponding 5-arylidene analogues **32** and **33**, respectively (Scheme 2, Table 1).

Table 1. Melting Points, Yield Percentages, Molecular Formulae, and Molecular Weights of Compounds 8, 10–21, 23, 24, and 26–33

comp. no.	R	R′/Ar	melting point (°C)	yield (%)	mol. formula (Mol. Wt.)
8	CH_3	$4\text{-}CH_3C_6H_4$	314–316	90	$C_{21}H_{17}N_3OS_2$ (391.51)
10	CH_3	$3,4\text{-}(CH_3O)_2C_6H_3$	290–292	85	$C_{22}H_{19}N_3O_3S_2$ (437.53)
12	CH_3	$2,4\text{-}Cl_2C_6H_3$	322–325	84	$C_{20}H_{13}Cl_2N_3OS_2$ (446.37)
13	CH_3	thiophen-2-yl	328–330	90	$C_{18}H_{13}N_3OS_3$ (383.51)
14	CH_3	5-bromothiophen-2-yl	320–322	86	$C_{18}H_{12}BrN_3OS_3$ (462.41)
15	OCH_3	$4\text{-}CH_3C_6H_4$	308–310	90	$C_{21}H_{17}N_3O_2S_2$ (407.51)
16	OCH_3	$4\text{-}CH_3OC_6H_4$	322–325	90	$C_{21}H_{17}N_3O_3S_2$ (423.51)
17	OCH_3	$3,4\text{-}(CH_3O)_2C_6H_3$	293–295	80	$C_{22}H_{19}N_3O_4S_2$ (453.53)
18	OCH_3	$4\text{-}ClC_6H_4$	325–328	80	$C_{20}H_{14}ClN_3O_2S_2$ (427.93)
19	OCH_3	$2,4\text{-}Cl_2C_6H_3$	328–330	90	$C_{20}H_{13}Cl_2N_3O_2S_2$ (462.37)
20	OCH_3	thiophen-2-yl	325–327	80	$C_{18}H_{13}N_3O_2S_3$ (399.51)
21	OCH_3	5-bromothiophen-2-yl	288–290	80	$C_{18}H_{12}BrN_3O_2S_3$ (478.41)
23			335–338	65	$C_{22}H_{16}N_4O_4S_2$ (464.52)
24	CH_3	CH_3	220–222	79	$C_{13}H_{15}N_3S_2$ (277.41)
26	OCH_3	CH_3	210–212	69	$C_{13}H_{15}N_3OS_2$ (293.41)
27	OCH_3	C_6H_5	215–217	79	$C_{18}H_{17}N_3OS_2$ (355.48)
28	CH_3	CH_3	208–210	64	$C_{15}H_{15}N_3OS_2$ (317.43)
29	CH_3	C_6H_5	198–200	66	$C_{20}H_{17}N_3OS_2$ (379.5)
30	OCH_3	CH_3	215–215	66	$C_{15}H_{15}N_3O_2S_2$ (333.43)
31	OCH_3	C_6H_5	210–212	68	$C_{20}H_{17}N_3O_2S_2$ (395.5)
32		$3,4\text{-}(CH_3O)_2C_6H_3$	217–218	79	$C_{29}H_{25}N_3O_4S_2$ (543.66)
33		$2,4\text{-}Cl_2C_6H_3$	189–191	80	$C_{27}H_{19}Cl_2N_3O_2S_2$ (552.49)

Table 2. *In Vitro* AChE Inhibitory Potency of Compounds 8, 10, 12–21, 23, and 28–33 and Donepezil

compound no.	R	R′/Ar	IC_{50} $(nM)^a$	relative potency (%)
8	CH_3	$4\text{-}CH_3C_6H_4$	500.56 ± 14	10.99
10	CH_3	$3,4\text{-}(CH_3O)_2C_6H_3$	103.24 ± 2.8	53.27
12	CH_3	$2,4\text{-}Cl_2C_6H_3$	335.79 ± 9.1	16.38
13	CH_3	thiophen-2-yl	173.75 ± 4.7	31.66
14	CH_3	5-bromothiophen-2-yl	379.81 ± 10	14.48
15	OCH_3	$4\text{-}CH_3C_6H_4$	374.70 ± 10	14.68
16	OCH_3	$4\text{-}CH_3OC_6H_4$	108.94 ± 3	50.49
17	OCH_3	$3,4\text{-}(CH_3O)_2C_6H_3$	175.93 ± 4.8	31.26
18	OCH_3	$4\text{-}ClC_6H_4$	193.48 ± 5.3	28.43
19	OCH_3	$2,4\text{-}Cl_2C_6H_3$	731.33 ± 20	7.52
20	OCH_3	thiophen-2-yl	259.64 ± 7.1	21.18
21	OCH_3	5-bromothiophen-2-yl	187.83 ± 5.1	29.28
23			151.0 ± 4.1	36.42
28	CH_3	CH_3	478.20 ± 13	11.50
29	CH_3	C_6H_5	187.86 ± 5.1	29.28
30	OCH_3	CH_3	346.40 ± 9.4	15.88
31	OCH_3	C_6H_5	152.45 ± 4.1	36.08
32		$3,4\text{-}(CH_3O)_2C_6H_3$	450.4 ± 12	12.21
33		$2,4\text{-}Cl_2C_6H_3$	187.9 ± 5.1	29.27
donepezil			55.0 ± 0.004	100

^{a}Values are expressed as the mean ± standard error of the mean of three experiments.

The structures of the newly synthesized compounds were confirmed by elemental analyses, ^1H NMR, ^{13}C NMR, and electron ionization mass spectrometry (EI-MS) spectral data.

2.2. *In Vitro* AChE Inhibitory Activity. The *in vitro* AChE inhibitory activity of the target compounds 8, 10, 12–21, 23, and 28–33 was investigated following the previously described modification of Ellman's spectrophotometric method[22,23] using donepezil hydrochloride as the reference drug (positive control). The IC_{50} values of AChE inhibitory activities and their relative potencies to donepezil hydrochloride are summarized in Table 2. The IC_{50} values ranged from 500.56

to 103.24 nM and their relative potencies from 10.99 to 53.27%. The optimum AChE inhibitory activity was attained by compounds 10 and 16 with IC_{50} values of 103.24 nM and 108.94 nM, respectively, and relative potencies of more than 50%. Compounds 13, 17, 18, 21, 23, 31, and 33 displayed moderate AChE inhibitory activities with 25–50% relative potencies. Meanwhile, the relative potencies of compounds 8, 12, 14, 15, 19, 20, 28, 29, 30, and 32 were less than 25%.

Within the 2-(4-arylthiazol-2-ylamino)-5-(4-methylbenzylidene)-4,5-dihydrothiazole-4-one derivatives 8–21, it could be concluded that the AChE inhibitory activity is mainly

dependent on the nature of the arylidene substituents; the 4-methoxy- and 3,4-dimethoxybenzylidene substituents are optimal for activity, while the 4-methyl- and 2,4-dichlorobenzylidene substituents caused a sharp deterioration of the activity. The thiophen-2-yl, 5-bromothiophen-2-yl, and the 4-chlorobenzylidene substituents retained moderate activities. The activity of the 5-methoxyindolin-2-one analogue 23 is higher than that of the thiophen-2-yl, 5-bromothiophen-2-yl, and the 4-chlorobenzylidene analogues. In addition, it could also be concluded that the 4-aryl substituents (CH_3 and OCH_3) are almost equipotent.

In the 2-substituted imino-3-(4-arylthiazol-2-yl)thiazolidin-4-ones 28−31, the AChE inhibitory activities of the benzyl analogues 29 and 31 were superior to those of their ethyl analogues 28 and 30. Contrary to the activity of compounds 8−22, the activity of the 2,4-dichlorobenzylidene derivative 33 was found to be higher than that of its 3,4-dimethoxybenzylidene analogue 32.

2.3. Molecular Docking Studies. In order to obtain structural insights regarding the binding interactions and orientation of the most active AChE inhibitors within each series, molecular docking experiments were performed on representative active compounds 10, 13, 16, 23, and 31 (relative potencies = 31.66% to 53.27%, Table 2) using the X-ray crystal structure of AChE co-crystallized with the potent AChE inhibitor donepezil (PDB code: 4EY7, www.rcsb.org). Molecular Operating Environment (MOE) software[24] was used to conduct the docking experiments, score the molecules according to their binding affinity, and determine potential binding interactions. To confirm if the docking parameters and computational procedure could reproduce the experimental results, the co-crystallized ligand, donepezil, was redocked (Figure 3). The docking pose obtained was comparable to the
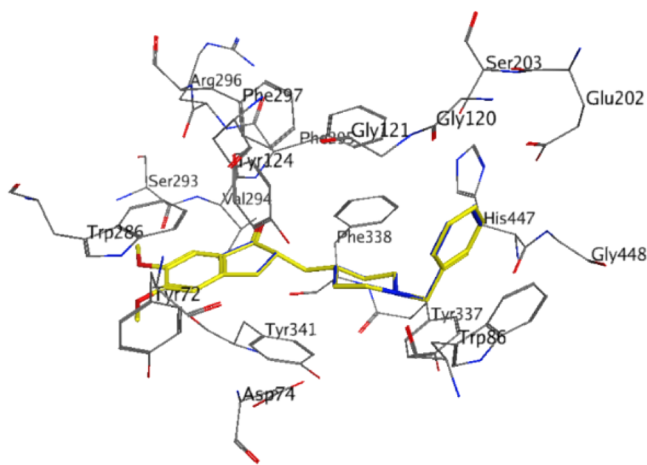

Figure 3. Co-crystallized pose of donepezil (yellow) vs the docked experimental pose of donepezil (blue) within the AChE active site. A very low rmsd value of 0.23 Å was obtained, indicating the accuracy and repeatability of the docking procedure.

co-crystallized one, with a root-mean squared deviation (rmsd) of 0.23 Å and a binding affinity of −15.50 kcal/mol. In addition, compounds 8, 14, 19, 28, and 32 with some of the lowest relative potencies in the series (7.52 to 14.48%, Table 2) were also docked to observe any particular interactions or reduction in predicted binding affinity that could rationalize the reduced potency.

The results from the docking experiments revealed that compounds 10, 13, 16, 23, and 31 were able to bind in a comparable position and manner within the AChE active site to that of the co-crystallized ligand, donepezil. Figures 4−9
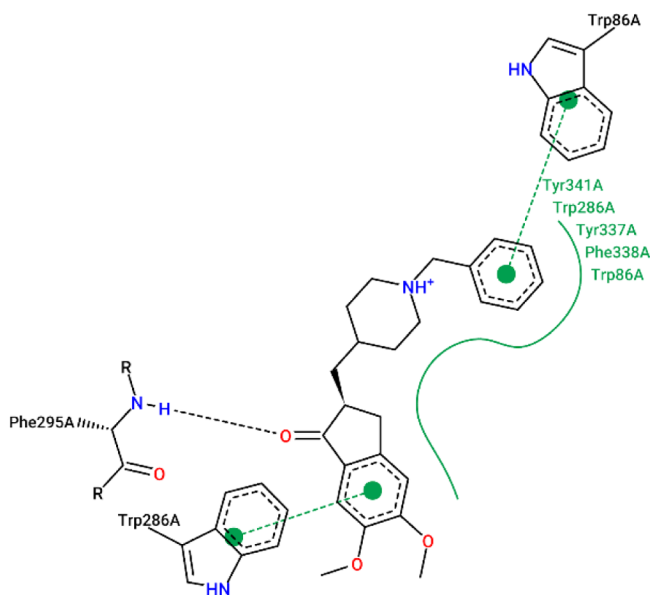

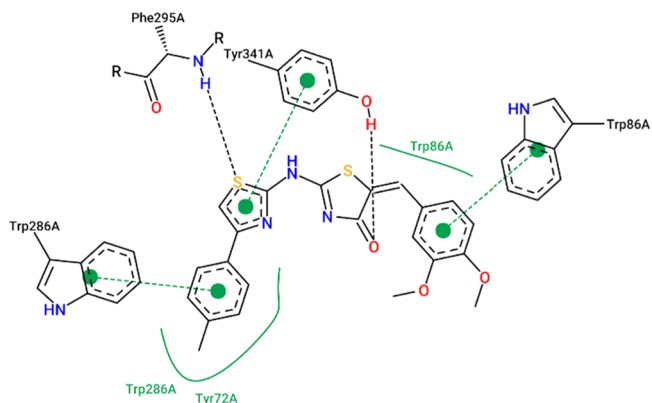**Figure 4.** Interaction map of donepezil within the active site of AChE (BA = −15.50 kcal/mol).

Figure 5. Interaction map of compound 10 within the active site of AChE (BA = −14.87 kcal/mol).

show the binding orientations, binding interactions, and binding affinities of donepezil and the active compounds (Table 3). The molecules were able to span from the catalytic anionic site (CAS) through the narrow active site gorge into the peripheral anionic site (PAS) of AChE. Important $\pi-\pi$ interactions were observed for all the test compounds with Trp86 (within the CAS) and Trp286 (within the PAS), similar to donepezil. Interestingly, the thiazole−thiazolidine moiety within these structures was able to form a number of interactions with the residues lining the active site gorge of AChE (Figures 4−9, Table 3). In addition, the compounds presented with binding affinities (from −13.34 to −14.87 kcal/mol) that are within a close range to that of the potent AChE inhibitor donepezil (−15.50 kcal/mol). Table 3 illustrates the relationship between the predicted binding affinities and experimental IC_{50} values of the most potent AChE inhibitors within this series. A definite trend between the binding affinity
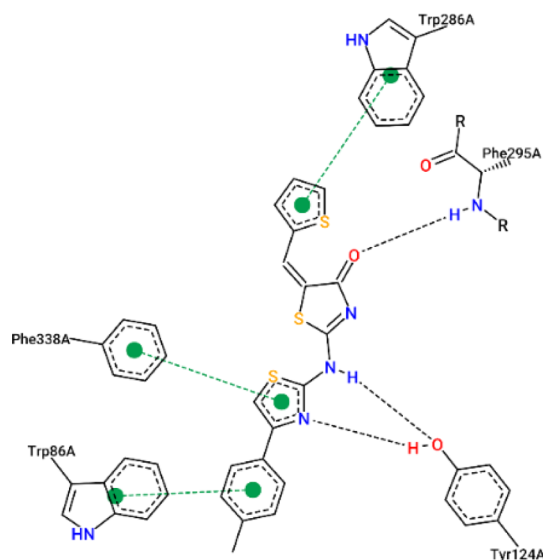
Figure 6. Interaction map of compound **13** within the active site of AChE (BA = −13.34 kcal/mol).

and the experimental IC$_{50}$ value of the test compounds is observed.

Additionally, the lower potency agents **8**, **14**, **19**, **28**, and **32** confirmed the structure−activity relationship observations made in the biological section. The predicted binding affinities of the compounds were slightly reduced (from 12.38 to 13.22 kcal/mol) when compared to that of the more potent compounds (Table 3), which is in correlation with the biological activities. In general, the interactions with Trp86 and Trp286 were retained, the thiazole−thiazolidine moiety also showed similar integrations with the residues within the active site gorge (including Tyr341, Tyr337, Tyr124, Phe295, and Phe338) as the more active compounds. This is to be expected as the least active compound **8** still showed an improved IC$_{50}$ value of 500.56 ± 14 when compared to that of the known thiazole derivatives in the literature (see Scheme 1, compounds **B−D**).

3. CONCLUSIONS

Nineteen new thiazole-based derivatives were synthesized and evaluated as potential AChE inhibitors for the treatment of AD. The most active AChE inhibitory compounds were **10** and **16**, which also represented the lowest IC$_{50}$ values with relative

potencies of more than 50% in comparison to the potent AChE inhibitor donepezil. Docking studies within the AChE active site revealed that compounds **10**, **13**, **16**, **23**, and **31** showed binding orientations similar to that of donepezil and presented with key interactions that explain their potent AChE activity observed. The thiazole moiety was also found to form important interactions with the amino acid residues lining the active site gorge of AChE. The results suggest that these new thiazole derivatives, especially **10** and **16**, may serve as new lead compounds for further development of potent thiazole-based AChE inhibitors that do not incorporate the hepatotoxic acridine moiety.

4. MATERIALS AND METHODS

4.1. General Information. Melting points (°C) were measured in open glass capillaries using a Stuart-SMP30 electro-thermal melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on a JEOL ECA-500 II NMR spectrometer at 500.16 MHz for ^{1}H and 125.77 MHz for ^{13}C; the chemical shifts are expressed in δ (ppm) downfield from tetramethylsilane as the internal standard; and the coupling constants (J) are expressed in Hz. Deuteriodimethyl sulfoxide (DMSO-d_6) and deutero-chloroform (CDCl$_3$) were used as solvents. Elemental analyses (C, H, N, and S) were in good agreement with the proposed structures within ±0.4% of the theoretical values (Table S1, Supporting Information). Monitoring the reactions and checking the purity of the final products were carried out by thin layer chromatography using silica-gel-precoated aluminum sheets (60 F$_{254}$, Merck) and visualization with ultraviolet light (UV) at 365 and 254 nm. The reference drug donepezil hydrochloride (CAS 120011-70-3) was purchased from Sigma-Aldrich Chemie GmbH, Germany. Compounds **9**, **11**,[20] and **25**[21] were prepared following the previously reported procedures.

4.2. General Procedure for the Synthesis of Compounds 8, 10, and 12−21. The appropriate aromatic aldehyde (10 mmol) was added to a solution of thiazolidinone **6** or **7** (10 mmol) and sodium hydroxide (1.0 g) in ethanol (30 mL), and the mixture was stirred at room temperature for 4 h. The precipitate formed was filtered, dried, and crystallized with ethanol.

4.2.1. 2-[4-(p-Tolylthiazol-2-yl)amino]-5-(4-methylbenzy-lidene)-4,5-dihydrothiazole-4-one (8). ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 3H, CH$_3$), 2.33 (s, 3H, CH$_3$), 7.18 (d, 2H, Ar-H, J = 7.6 Hz), 7.28 (d, 2H, Ar-H, J = 8.2 Hz), 7.37 (s, 1H, thiazole-
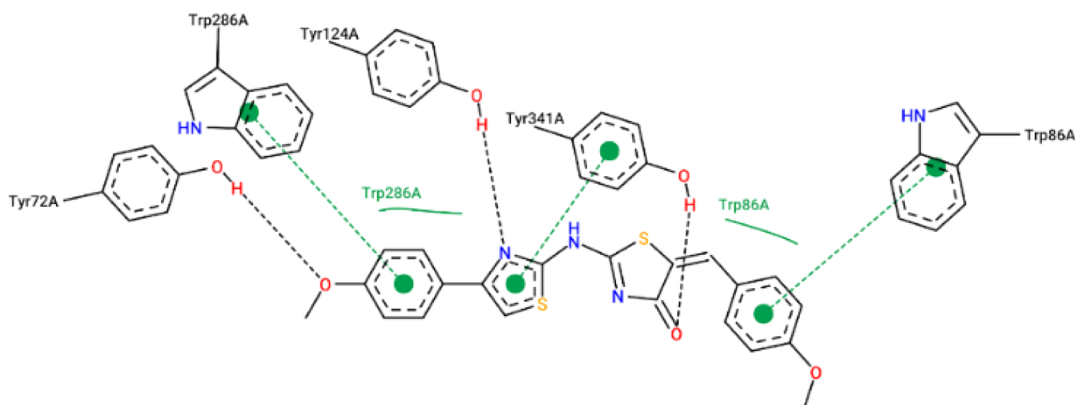

Figure 7. Interaction map of compound **16** within the active site of AChE (BA = −14.58 kcal/mol).
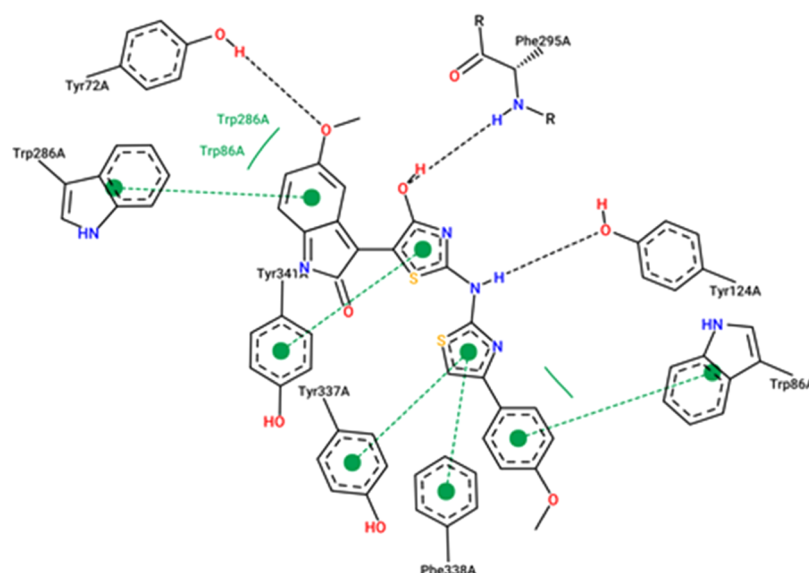
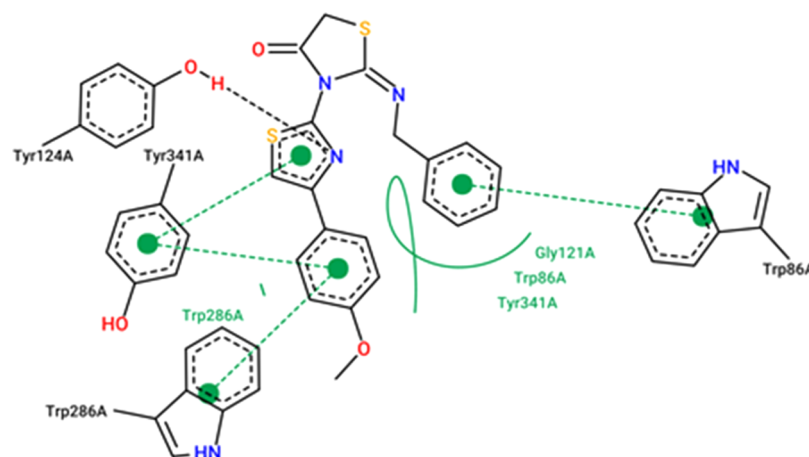**Figure 8.** Interaction map of compound **23** within the active site of AChE (BA = −13.85 kcal/mol).

Figure 9. Interaction map of compound **31** within the active site of AChE (BA = −13.80 kcal/mol).

Table 3. Experimental IC$_{50}$ Values, Binding Affinities, and Binding Interactions of the Representative Most Active Docked Compounds within This Series

compound	AChE IC$_{50}$ (nM)	predicted binding affinity (kcal/mol)	binding interactions
donepezil	55.0 ± 0.004	−15.50	Trp86, Phe295, Trp286
10	103.24 ± 2.8	−14.87	Trp86, Tyr341, Phe295, Trp286
16	108.94 ± 3.0	−14.85	Trp86, Tyr341, Tyr124, Trp286, Tyr72
23	151.00 ± 4.1	−13.85	Trp86, Tyr124, Phe295, Phe338, Tyr337, Tyr341, Trp286, Tyr72
31	152.45 ± 4.1	−13.80	Trp86, Tyr124, Tyr341, Trp286
13	173.75 ± 4.7	−13.34	Trp86, Phe338, Tyr124, Trp286

(Ar-C, thiazoline-C, and arylidene-C), 182.0 (C═O). EI-MS, m/z (%): 393.56 (32.80), 100.95 (100).

4.2.2. 2-[4-(p-Tolylthiazol-2-yl)amino]-5-(3,4-dimethoxy-benzylidene)-4,5-dihydrothiazole-4-one (10). ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 3H, CH$_3$), 3.80 (s, 3H, OCH$_3$), 3.82 (s, 3H, OCH$_3$), 7.38 (d, 2H, Ar-H, J = 8.2 Hz), 7.13−7.19 (m, 4H, Ar-H & NH), 7.36 (s, 1H, thiazole-H), 7.40 (s, 1H, CH═C), 7.78 (d, 2H, Ar-H, J = 7.6 Hz). ^{13}C NMR: δ 20.90 (CH$_3$), 55.46 (OCH$_3$), 55.63 (OCH$_3$), 108.73, 148.81, 167.80 (thiazole-C), 112.06, 122.04, 124.60, 125.51, 128.41, 129.15, 130.79, 132.90, 136.22, 149.01, 167.80, 171.98 (Ar-C, thiazoline-C, and arylidene-C), 180.41 (C═O). EI-MS, m/z (%): 438.83 (88), 117.37 (100).

4.2.3. 2-[4-(p-Tolylthiazol-2-yl)amino]-5-(2,4-dichloroben-zylidene)-4,5-dihydrothiazole-4-one (12). ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 3H, CH$_3$), 3.32 (s, 1H, NH), 7.18−7.20 (m, 2H, Ar-H & thiazole-H), 7.46 (s, 1H, CH═C), 7.59−7.61 (m, 2H, Ar-H), 7.61−7.69 (m, 1H, Ar-H), 7.73 (d, 1H, Ar-H, J = 2.0 Hz), 7.77 (d, 2H, Ar-H, J = 7.5 Hz). ^{13}C NMR: δ 20.87 (CH$_3$), 109.29, 149.10, 167.47 (thiazole-C), 117.83, 125.50, 128.09, 129.15, 129.50, 132.52, 132.76, 132.96, 134.54, 136.28, 137.55, 167.47, 170.96 (Ar-C, thiazoline-C, and arylidene-C),

H), 7.42 (s, 1H, CH═C), 7.46 (d, 2H, Ar-H, J = 8.2 Hz), 7.78 (d, 2H, Ar-H, J = 7.6 Hz). ^{13}C NMR: δ 20.83 (CH$_3$), 21.0 (CH$_3$), 108.76, 148.0, 159.50 (thiazole-C), 124.07, 125.44, 129.08, 129.57, 132.17, 132.77, 132.87, 136.13, 137.85, 172.0

179.43 (C=O). EI-MS, *m/z* (%): 444.96 (33.17), 445.99 (23), 446.98 (40.20), 377.20 (100).

4.2.4. 2-[4-(p-Tolylthiazol-2-yl)amino]-5-[(thiophen-2-yl)-methylene]-4,5-dihydrothiazole-4-one (13). ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 3H, CH$_3$), 3.32 (s, 1H, NH), 7.18−7.20 (m, 3H, Ar-H & thiazole-H), 7.40 (d, 1H, thiophene-H, *J* = 3.5 Hz), 7.42 (s, 1H, CH=C), 7.61−7.82 (m, 4H, Ar-H & thiophene-H). ^{13}C NMR: δ 20.89 (CH$_3$), 108.95, 148.99, 167.67 (thiazole-C), 117.46, 125.53, 128.41, 128.88, 129.16, 130.19, 132.22, 132.85, 136.26, 140.80, 171.14 (Ar-C, thiazoline-C, thiophene-C, and arylidene-C), 179.79 (C=O). EI-MS, *m/z* (%): 385.47 (25), 381.76 (42), 147.66 (100).

4.2.5. 2-[4-(p-Tolylthiazol-2-yl)amino]-5-[(5-bromothio-phen-2-yl)methylene]-4,5-dihydrothiazole-4-one (14). ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 3H, CH$_3$), 7.18−7.20 (m, 3H, Ar-H & thiazole-H), 7.25 (d, 1H, thiophene-H, *J* = 4.0 Hz), 7.31 (d, 1H, thiophene-H, *J* = 4.0 Hz), 7.44 (s, 1H, CH=C), 7.54 (s, 1H, NH), 7.78 (d, 2H, A-H, *J* = 7.5 Hz). ^{13}C NMR: δ 20.87 (CH$_3$), 109.08, 149.05, 167.55 (thiazole-C), 114.0, 116.58, 125.50, 129.11, 130.55, 131.72, 132.79, 133.22, 136.25, 142.77, 170.53 (Ar-C, thiazoline-C, thiophene-C, and arylidene-C), 179.42 (C=O). EI-MS, *m/z* (%): 460.93 (30), 462.90 (34%), 77.30 (100).

4.2.6. 2-[4-(4-Methoxyphenylthiazol-2-yl)amino]-5-(4-methylbenzylidene)-4,5-dihydrothiazole-4-one (15). ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 3H, CH$_3$), 3.77 (s, 3H, OCH$_3$), 6.94 (d, 2H, Ar-H, *J* = 8.5 Hz), 7.28 (d, 2H, Ar-H, *J* = 8.5 Hz), 7.33 (s, 1H, thiazole-H), 7.37 (s, 1H, CH=C), 7.45 (d, 2H, Ar-H, *J* = 7.5 Hz), 7.82 (d, 2H, Ar-H, *J* = 7.5 Hz). ^{13}C NMR: δ 21.0 (CH$_3$), 55.14 (OCH$_3$), 107.68, 148.74, 167.74 (thiazole-C), 113.89, 124.14, 126.80, 128.41, 129.04, 129.59, 132.23, 132.78, 158.49, 159.89, 171.75 (Ar-C, thiazoline-C, and arylidene-C), 180.27 (C=O). EI-MS, *m/z* (%): 407.50 (7.21), 100.90 (100).

4.2.7. 2-[4-(4-Methoxyphenylthiazol-2-yl)amino]-5-(4-methoxybenzylidene)-4,5-dihydrothiazole-4-one (16). ^{1}H NMR (DMSO-d_6): δ 3.77 (s, 3H, OCH$_3$), 3.80 (s, 3H, OCH$_3$), 6.94 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.05 (d, 2H, Ar-H, *J* = 9.0 Hz), 7.32 (s, 1H, thiazole-H), 7.36 (s, 1H, CH=C), 7.51 (d, 2H, Ar-H, *J* = 8.5 Hz), 7.81 (d, 2H, Ar-H, *J* = 8.5 Hz). ^{13}C NMR: δ 55.11 (OCH$_3$), 55.31 (OCH$_3$), 107.55, 148.72, 167.76 (thiazole-C), 113.90, 114.54, 124.10, 126.81, 128.08, 128.43, 129.0, 130.66, 158.49, 159.26, 171.83 (Ar-C, thiazoline-C, and arylidene-C), 180.42 (C=O). EI-MS, *m/z* (%): 423.50 (5), 139.04 (100).

4.2.8. 2-[4-(4-Methoxyphenylthiazol-2-yl)amino]-5-(3,4-dimethoxybenzylidene)-4,5-dihydrothiazole-4-one (17). ^{1}H NMR (DMSO-d_6): δ 3.76 (s, 3H, OCH$_3$), 3.77 (s, 3H, OCH$_3$), 3.82 (s, 3H, OCH$_3$), 6.64 (d, 2H, Ar-H, *J* = 9.0 Hz), 7.09 (s, 1H, Ar-H), 7.13−7.15 (m, 2H, Ar-H), 7.32 (s, 1H, thiazole-H), 7.36 (s, 1H, CH=C), 7.81 (d, 2H, Ar-H, *J* = 8.5 Hz). ^{13}C NMR: δ 55.10 (OCH$_3$), 55.41 (OCH$_3$), 55.58 (OCH$_3$), 107.0, 148.76, 167.0 (thiazole-C), 112.02, 112.80, 113.86, 114.0, 122.50, 124.41, 126.77, 128.40, 131.50, 138.0, 148.93, 158.45, 172.0 (Ar-C, thiazoline-C, and arylidene-C), 180.50 (C=O). EI-MS, *m/z* (%): 453.40 (26), 117.45 (100).

4.2.9. 2-[4-(4-Methoxyphenylthiazol-2-yl)amino]-5-(4-chlorobenzylidene)-4,5-dihydrothiazole-4-one (18). ^{1}H NMR (DMSO-d_6): δ 3.77 (s, 3H, OCH$_3$), 6.94 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.35 (s, 1H, thiazole-H), 7.39 (s, 1H, CH=C), 7.53 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.58 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.81 (d, 2H, Ar-H, *J* = 8.0 Hz). ^{13}C NMR: δ 55.09 (OCH$_3$), 107.86, 148.70, 167.50 (thiazole-C), 113.88, 122.56, 126.77, 128.98, 130.59, 132.41, 134.05, 134.53, 149.0, 157.40, 171.50

(Ar-C, thiazoline-C, and arylidene-C), 179.86 (C=O). EI-MS, *m/z* (%): 427.80 (13.03), 111.24 (100).

4.2.10. 2-[4-(4-Methoxyphenylthiazol-2-yl)amino]-5-(2,4-dichlorobenzylidene)-4,5-dihydrothiazole-4-one (19). ^{1}H NMR (DMSO-d_6): δ 3.77 (s, 3H, OCH$_3$), 6.94 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.38 (s, 1H, thiazole-H), 7.59−7.73 (m, 4H, Ar-H & CH=C), 7.82 (d, 2H, Ar-H, *J* = 8.5 Hz). ^{13}C NMR: δ 55.11 (OCH$_3$), 108.14, 148.91, 167.46 (thiazole-C), 113.90, 117.78, 126.81, 128.05, 129.40, 129.47, 132.53, 132.93, 134.50, 137.57, 149.10, 159.80, 170.85 (Ar-C, thiazoline-C, and arylidene-C), 179.41 (C=O). EI-MS, *m/z* (%): 462.87 (100). (26), 117.45 (100).

4.2.11. 2-[4-(4-Methoxyphenylthiazol-2-yl)amino]-5-[(thiophen-2-yl)methylene]-4,5-dihydrothiazole-4-one (20). ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 3H, OCH$_3$), 6.94 (d, 2H, Ar-H, *J* = 8.5 Hz), 7.18 (t, 1H, thiophene-H, *J* = 3.5 Hz), 7.37 (s, 1H, thiazole-H), 7.40 (d, 1H, thiophene-H, *J* = 3.5 Hz), 7.60 (s, 1H, CH=C), 7.73 (d, 1H, thiophene-H, *J* = 3.5 Hz), 7.81 (d, 2H, Ar-H, *J* = 8.5 Hz). ^{13}C NMR: δ 55.09 (OCH$_3$), 107.70, 148.50, 165.80 (thiazole-C), 113.87, 117.26, 126.78, 128.31, 128.39, 128.76, 130.04, 132.28, 140.79, 158.47, 171.95 (Ar-C, thiazoline-C, thiophene-C, and arylidene-C), 179.80 (C=O). EI-MS, *m/z* (%): 399.08 (42), 147.66 (100).

4.2.12. 2-[4-(4-Methoxyphenylthiazol-2-yl)amino]-5-[(5-bromothiophen-2-yl)methylene]-4,5-dihydrothiazole-4-one (21). ^{1}H NMR (DMSO-d_6): δ 3.77 (s, 3H, OCH$_3$), 6.94 (d, 2H, Ar-H, *J* = 8.5 Hz), 7.25 (d, 1H, thiophene-H, *J* = 4.0 Hz), 7.31 (d, 1H, thiophene-H, *J* = 4.0 Hz), 7.36 (s, 1H, thiazole-H), 7.55 (s, 1H, CH=C), 7.81 (d, 2H, Ar-H, *J* = 8.5 Hz). ^{13}C NMR: δ 55.10 (OCH$_3$), 107.95, 149.96, 167.51 (thiazole-C), 112.05, 113.86, 116.47, 126.80, 127.44, 130.39, 131.68, 142.77, 158.50, 163.50, 170.40 (Ar-C, thiazoline-C, thiophene-C, and arylidene-C), 179.40 (C=O). EI-MS, *m/z* (%): 478.74 (16),104.22 (100).

4.3. Synthesis of 3-{2-([4-(4-Methoxyphenyl)thiazol-2-ylamino]-4-[4,5-dihydro-4-oxothiazol-5-ylidene])}5-methoxyindolin-2-one 23. A mixture of 2-[4-(4-methoxyphenyl)thiazol-2-ylamino]-3,4-dihydrothiazol-4-one **7** (1.53 g, 5.0 mmol), 5-methoxyindoline-2,3-dione **22** (886 mg, 5.0 mmol), and fused sodium acetate (820 mg, 10.0 mmol) in acetic acid (10 mL) was refluxed for 6 h. On cooling, the precipitated crude product was filtered, washed with water, dried, and crystallized from ethanol. ^{1}H NMR (DMSO-d_6): δ 3.56 (s, 3H, OCH$_3$), 3.79 (s, 3H, OCH$_3$), 4.89 (s, 1H, NH), 6.73 (d, 1H, indoline-H, *J* = 8.0 Hz), 6.82−6.84 (m, 1H, indoline-H), 6.94 (s, 1H, thiazole-H), 7.03 (d, 2H, Ar-H, *J* = 8.5 Hz), 7.70 (s, 1H, indoline-H), 7.90 (d, 2H, Ar-H, *J* = 8.0 Hz), 10.38 (s, 1H, indoline-NH). ^{13}C NMR: δ 55.26 (OCH$_3$), 55.29 (OCH$_3$), 108.95, 149.96, 167.51 (thiazole-C), 110.42, 111.53, 114.20, 114.30, 114.40, 127.16, 128.83, 135.99, 151.06, 154.49, 159.51, 171.80 (Ar-C, indoline-C, and arylidene-C), 175.98 (C=O). EI-MS, *m/z* (%): 464.52 (30), 84.40 (100).

4.4. General Procedure for the Synthesis of the 1,3-Disubstituted Thiourea Derivatives 24, 26, and 27. Ethyl or benzyl isothiocyanate (0.025 mol) and sodium hydroxide (1.0 g, 0.025 mol) were added to a solution of the aminothiazoles **1** and **2** (0.025 mol) in DMF (15 mL), and the mixture was stirred for 1 h at room temperature. The reaction mixture was then poured onto ice-water (50 mL) and stirred for 30 min. The separated crude product was filtered, washed with water, dried, and crystallized from ethanol.

4.4.1. 1-Ethyl-3-[4-(p-tolylthiazol-2-yl)]thiourea (24). ^{1}H NMR (DMSO-d_6): δ 1.19 (t, 3H, CH$_2$CH$_3$, *J* = 7.0 Hz), 2.31

(s, 3H, CH$_3$), 3.52 (q, 2H, CH_2CH$_3$, J = 7.0 Hz), 7.22 (d, 2H, Ar-H, J = 7.5 Hz), 7.44 (s, 1H, thiazole-H), 7.72 (d, 2H, Ar-H, J = 7.5 Hz), 9.55 (s, 1H, NH), 11.63 (s, 1H, NH). ^{13}C NMR: δ 13.65 (CH$_2$*C*H$_3$), 20.81 (CH$_3$), 39.50 (*C*H$_2$CH$_3$), 105.74, 148.54, 161.06 (thiazole-C), 125.51, 128.84, 129.3, 131.14, 137.25 (Ar-C), 177.49 (C=S).

4.4.2. 1-Ethyl-3-[4-(4-methoxyphenylthiazol-2-yl)]-thiourea (26). ^{1}H NMR (DMSO-d_6): δ 1.19 (t, 3H, CH$_2$CH_3, J = 7.0 Hz), 3.55 (q, 2H, CH_2CH$_3$, J = 7.0 Hz), 3.77 (s, 3H, OCH$_3$), 6.96 (d, 2H, Ar-H, J = 7.0), 7.35 (s, 1H, thiazole-H), 7.76 (d, 2H, Ar-H, J = 7.5 Hz), 9.60 (s, 1H, NH), 11.61 (s, 1H, NH). ^{13}C NMR: δ 13.85 (CH$_2$*C*H$_3$), 20.81 (CH$_3$), 39.50 (*C*H$_2$CH$_3$), 55.15 (OCH$_3$), 104.54, 148.39, 161.04 (thiazole-C), 114.13, 126.59, 126.93, 159.04 (Ar-C), 177.45 (C=S).

4.4.3. 1-Benzyl-3-[4-(4-methoxyphenylthiazol-2-yl)]-thiourea (27). ^{1}H NMR (DMSO-d_6): δ 3.76 (s, 3H, OCH$_3$), 4.78 (s, 2H, benzylic CH$_2$), 6.87 (d, 2H, Ar-H, J = 9.0), 7.31−7.44 (m, 8H, Ar-H and thiazole-H), 7.58 (d, 2H, Ar-H, J = 9.0 Hz), 10.16 (s, 1H, NH), 11.75 (s, 1H, NH). ^{13}C NMR: δ 48.06 (benzylic CH$_2$), 55.14 (OCH$_3$), 104.61, 148.37, 161.10 (thiazole-C), 114.02, 126.87, 127.50, 127.87, 128.52, 128.68, 137.596, 159.02 (Ar-C), 177.64 (C=S).

4.5. General Procedure for the Synthesis of the 2-Substituted Imino-3-(4-arylthiazol-2-yl)thiazolidin-4-ones 28−31. A mixture of the appropriate thiourea derivative **24−27** (10 mmol), chloroacetic acid (0.95 g, 10 mmol), and fused sodium acetate (1.0 g) in ethanol (50 mL) was heated under reflux and refluxed for 8 h. On cooling, water (15 mL) was added with stirring for 4 h. The precipitated crude product was filtered, washed with water, dried, and crystallized from ethanol.

4.5.1. 2-Ethylimino-3-[4-(p-tolyl)thiazol-2-yl]thiazolidin-4-one (28). ^{1}H NMR (DMSO-d_6): δ 1.14 (t, 3H, CH$_2$CH_3, J = 7.0 Hz), 2.32 (s, 3H, Ar-CH$_3$), 3.76 (q, 2H, CH_2CH$_3$, J = 7.0 Hz), 4.05 (s, 2H, thiazolidine-CH$_2$), 7.24 (d, 2H, Ar-H, J = 7.5 Hz), 7.79 (s, 1H, thiazole-H), 7.84 (d, 2H, Ar-H, J = 7.5 Hz). ^{13}C NMR: δ 12.44 (CH$_2$*C*H$_3$), 20.89 (Ar-CH$_3$), 33.61 (thiazolidine-CH$_2$), 37.76 (*C*H$_2$CH$_3$), 110.11, 151.03, 168.59 (thiazole-C), 125.69, 129.39, 131.30, 137.51 (Ar-C), 161.93 (thiazolidine-C2), 172.46 (C=O). EI-MS, m/z (%): 317.39 (43), 318.50 (62), 56.50 (100).

4.5.2. 2-Benzylimino-3-[4-(p-tolyl)thiazol-2-yl]thiazolidin-4-one (29). ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H, CH$_3$), 4.17 (s, 2H, thiazolidine-CH$_2$), 4.97 (s, 2H, benzylic CH$_2$), 7.25−7.36 (m, 7H, Ar-H), 7.75 (s, 1H, thiazole-H), 7.84 (d, 2H, Ar-H, J = 7.6 Hz). ^{13}C NMR: δ 21.89 (Ar-CH$_3$), 34.01 (thiazolidine-CH$_2$), 46.12 (benzylic CH$_2$), 110.68, 151.55, 168.76 (thiazole-C), 126.12, 128.0, 128.96, 129.84, 131.66, 135.0, 136.41, 138.04 (Ar-C), 162.27 (thiazolidine-C2), 173.17 (C=O). EI-MS, m/z (%): 379.75 (18), 331.22 (100).

4.5.3. 2-Ethylimino-3-[4-(4-methoxyphenyl)thiazol-2-yl]-thiazolidin-4-one (30). ^{1}H NMR (DMSO-d_6): δ 1.14 (t, 3H, CH$_2$CH_3, J = 7.0 Hz), 3.78−3.79 (m, 5H, CH$_2$CH$_3$ & OCH$_3$), 4.05 (s, 2H, thiazolidine-CH$_2$), 6.99 (d, 2H, Ar-H, J = 8.0 Hz), 7.70 (s, 1H, thiazole-H), 7.87 (d, 2H, Ar-H, J = 8.0 Hz). ^{13}C NMR: δ 12.45 (CH$_2$*C*H$_3$), 33.57 (thiazolidine-CH$_2$), 37.76 (*C*H$_2$CH$_3$), 55.21 (OCH$_3$), 108.89, 150.84, 168.53 (thiazole-C), 114.19, 126.80, 127.14, 161.79 (Ar-C), 161.79 (thiazolidine-C2), 172.45 (C=O). EI-MS, m/z (%): 334.92 (10), 333.35 (7), 65.54 (100).

4.5.4. 2-Benzylimino-3-[4-(4-methoxyphenyl)thiazol-2-yl]-thiazolidin-4-one (31). ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 3H,

OCH$_3$), 4.16 (s, 2H, thiazolidine-CH$_2$), 4.95 (s, 2H, benzylic CH$_2$), 6.99 (d, 2H, Ar-H, J = 9.0 Hz), 7.25−7.34 (m, 5H, Ar-H), 7.70 (s, 1H, thiazole-H), 7.87 (d, 2H, Ar-H, J = 9.0 Hz). ^{13}C NMR: δ 33.57 (thiazolidine-CH$_2$), 45.65 (benzylic CH$_2$), 55.20 (OCH$_3$), 109.05, 150.88, 168.23 (thiazole-C), 114.18, 127.13, 127.53, 127.62, 128.0, 128.41, 128.51, 136.02 (Ar-C), 161.76 (thiazolidine-C2), 172.17 (C=O). EI-MS, m/z (%): 396.38 (4), 395.01 (8), 196.81 (100).

4.6. General Procedure for the Synthesis of 5-Arylidene-2-(benzylimino)-3-[4-(4-methoxyphenyl)-thiazol-2-yl]thiazolidin-4-ones 32 and 33. A mixture of compound **31** (791 mg, 2.0 mmol), the appropriate aromatic aldehyde (2.0 mmol), and piperidine (0.1 mL) in ethanol (20 mL) was heated under reflux and refluxed for 3 h, and the solvent was distilled off *in vacuo*. The residue was then washed with water, dried, and crystallized from ethanol.

4.6.1. 2-(Benzylimino)-5-(3,4-dimethoxybenzylidene)-3-[4-(4-methoxyphenyl)thiazol-2-yl]thiazolidin-4-one (32). ^{1}H NMR (CDCl$_3$): δ 3.76 (s, 3H, OCH$_3$), 3.96 (s, 3H, OCH$_3$), 3.97 (s, 3H, OCH$_3$), 5.22 (s, 2H, benzylic CH$_2$), 6.93−6.97 (m, 3H, Ar-H), 7.17 (s, 1H, Ar-H), 7.21−7.23 (m, 2H, Ar-H), 7.26 (s, 1H, CH=C), 7.28−7.35 (m, 2H, Ar-H), 7.53 (d, 2H, Ar-H, J = 7.5 Hz), 7.82 (s, 1H, thiazole-H), 7.87 (d, 2H, Ar-H, J = 8.5 Hz). ^{13}C NMR: δ 46.45 (benzylic CH$_2$), 55.34 (OCH$_3$), 55.98 (OCH$_3$), 56.05 (OCH$_3$), 108.59, 150.89, 168.35 (thiazole-C), 111.25, 111.59, 113.98, 120.5, 125.86, 126.75, 127.26, 127.91, 128.53, 128.93, 133.78, 135.87, 149.0, 149.25, 152.12, 154.60, 159.61 (Ar-C, thiazolidine-C, and CH=C), 166.66 (C=O). EI-MS, m/z (%): 543.37 (28), 198.04 (100).

4.6.2. 2-(Benzylimino)-5-(2,4-dichlorobenzylidene)-3-[4-(4-methoxyphenyl)thiazol-2-yl]thiazolidin-4-one (33). ^{1}H NMR (CDCl$_3$): δ 3.88 (s, 3H, OCH$_3$), 5.21 (s, 2H, benzylic CH$_2$), 6.95 (d, 2H, Ar-H, J = 9.0 Hz), 7.17 (s, 1H, Ar-H), 7.26−7.36 (m, 5H, Ar-H & CH=C), 7.52−7.55 (m, 3H, Ar-H), 7.68 (d, 1H, Ar-H, J = 9.0 Hz), 7.81−7.83 (s, 1H, Ar-H and thiazole-H), 8.10 (s, 1H, Ar-H). ^{13}C NMR: δ 46.62 (benzylic CH$_2$), 55.40 (OCH$_3$), 108.89, 152.24, 168.30 (thiazole-C), 114.09, 127.32, 127.41, 128.59, 129.06, 153.87, 159.65 (Ar-C, thiazolidine-C, and CH=C), 165.84 (C=O). EI-MS, m/z (%): 552.75 (18), 196.32 (100).

4.7. Determination of *In Vitro* AChE Inhibitory Activity. The AChE inhibitory activity of the compounds **8**, **10**, **12−21**, **23**, and **28−33** was measured using Ellman's colorimetric method.[22,23] The concentration needed to inhibit half of the maximum biological response (IC$_{50}$) was determined by constructing an absorbance and/or inhibition (%) curve and examining the effect of four different concentrations. Stock solutions of the compounds and donepezil hydrochloride in DMSO were prepared at concentrations of 0.01−10 μM. AChE was dissolved in 0.1 M phosphate-buffered saline (PBS) (pH 8.0) to obtain a solution of 0.35 U/mL. The compounds were dissolved in DMSO and diluted with the 0.1 M PBS to yield the corresponding test concentrations. AChE (20 μL) was incubated with 10 μL of tested compounds, 130 μL of 0.1 M PBS, and 20 μL of acetylthiocholine iodide (CAS 2260-50-6) for 10 min in 96-well microplates before the addition of 20 μL of 3.33 mM 5,5′-dithio-*bis*-(2-nitrobenzoic acid) (DTNB, CAS # 69-78-3) solution. After the addition of DTNB, the 96-well microplates were read at 412 nm with a microplate reader for 15 min. One triplicate sample without inhibitors was always

present to yield 100% AChE activity. All samples were assayed in triplicate.

4.8. Molecular Docking Method. Computer-assisted docking was carried out using the CHARMM force field and electric human AChE co-crystallized with donepezil (PDB ID: 4EY7), which was recovered from the Brookhaven Protein Database (www.rcsb.org/pdb). Docking simulations were performed on the test compounds using MOE[24] with the following protocol: (1) the AChE enzyme structure was checked for missing atoms, bonds, and contacts. (2) Hydrogens and partial charges were added using the protonate 3D application in MOE. (3) The ligands were imported into MOE and were energy-minimized. (4) Ligands were docked within the AChE active site using the MOE Dock application, and the poses were generated by the Triangle Matcher placement method. (5) The retained best poses were visually inspected, and the interactions with the binding pocket residues were analyzed. To determine the accuracy of this docking protocol, the co-crystallized ligand, donepezil, was redocked into the AChE active site. This procedure was repeated three times, and the best ranked solutions of donepezil exhibited rmsd values of less than 0.5 Å from the position of the co-crystallized ligand. In general, rmsd values smaller than 2.0 Å indicate that the docking protocol is capable of accurately predicting the binding orientation of the co-crystallized ligand.[25,26] This protocol was thus deemed to be suitable for the docking of inhibitors into the active site model of AChE.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c02549.

Elemental analyses' data (C, H, N, and S) of the synthesized compounds **8**, **10−21**, **23**, **24**, and **26−33** (PDF)

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Notes

The authors declare no competing financial interest.

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