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Synthesis, characterization, biological evaluation, and molecular docking studies of some piperonyl-based 4-thiazolidinone derivatives

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Abstract

Heterocyclic compounds are of particular importance among pharmacologically active compounds. In this study, some piperonyl-based 4-thiazolidinone derivatives (**2a–i**) were synthesized and characterized by spectroscopic assays. All molecules were tested as enzyme inhibitory factors. These compounds were effective inhibitors of the enzymes acetylcholinesterase (AChE), α-glycosidase (α-Gly), and the human carbonic anhydrase I and II isoforms (hCA I and II), with K_i values in the range of 8.90–66.51 nM for α-Gly, 94.8–289.5 nM for hCA I, 106.3–304.6 nM for hCA II, and 0.55–2.36 nM for AChE. The synthesized molecules were also studied theoretically. Molecular docking calculations were performed to investigate the interaction between the target protein and molecules. CA inhibitor compounds have been clinically used for almost 60 years as antiglaucoma and diuretic drugs. The inhibition of the AChE enzyme results in the blockage of ACh hydrolysis. On the contrary, the design of inhibitor compounds or/and modulators for AChE is of major interest as it is one of the most popular tools to prevent Alzheimer's disease.

KEYWORDS
acetylcholinesterase, carbonic anhydrase, enzyme inhibition, molecular docking, piperonyl-based 4-thiazolidinone, α-glycosidase

1 | INTRODUCTION

Heterocyclic compounds are of particular importance among pharmacologically active compounds.[1,2] They gave a new dimension to drug discovery by allowing the development of a simple and efficient method of synthesis of compounds containing multiple heterocyclic rings. Thiazole compounds have also been the molecules of interest for many years due to their various biological activities.[3] In particular, 4-thiazolidinone derivatives have drawn attention because they have a wide range of biological properties.[4] In addition to existing in the structure of many natural products, they also form the core structure of many pharmacologically active compounds.[5] Examples of such derivatives are antibacterial,[6] antiviral[7]/anti-HIV,[8] anticancer,[9,10] anti-inflammatory,[11] analgesic activity, anticonvulsant, antidepressant, antidiabetic activity, and hypoglycemic agents.[12]

Cognitive dysfunctions, such as deficit in learning, memory, speed of information processing, visual perception, mental flexibility, and sustained attention are associated with diabetes. Cholinergic neurotransmission is vital in regulating cognitive function, in particular, learning and memory.[13] Cholinesterases, namely acetylcholinesterase (AChE) and butyrylcholinesterase, are important in cholinergic neurotransmission. Acetylcholine (ACh) is synthesized from choline and acetyl coenzyme A in the presynaptic neuron and released into the synaptic space to stimulate neurotransmission. However, the hydrolytic action of AChE terminates ACh-mediated neurotransmission. AChE is highly substrate-specific; however, the

enzyme hydrolyzes ACh at a rate of >10,000 molecules per second, and this enzyme is present in neurons.[14]

Diabetes mellitus (DM) is determined by alterations and hyperglycemia in carbohydrate, lipid, and protein metabolisms, caused by defects in insulin action or generation. Postprandial hyperglycemia is a common deficiency that occurs early in diabetes and can give rise to diverse secondary complications, like elevated risk for cardiovascular diseases, cataracts, atherosclerosis, neuropathy, retinopathy, nephropathy, and impaired wound healing. Ingesting a carbohydrate molecule diet triggers high amounts of blood glucose due to the rapid absorption of carbohydrate molecules, which is helped by glycoside hydrolysis, like α-glycosidase (α-Gly) enzyme; this important enzyme is available in the epithelial mucosa of the small intestine, which releases absorbable monosaccharide molecules.[15]

Plenty of organism cells possess numerous isoenzymes of carbonic anhydrase (CA), which is a family of zinc metalloenzymes that catalyze the reversible hydration of CO_2 to HCO_3^- and H^+ molecules. This reaction is involved in diverse vital physiological mechanisms, and the deregulation of CA enzyme activities is associated with disturbances and diseases like epilepsy, cancer, glaucoma, and obesity.[16] Human carbonic anhydrase inhibitors (hCAIs) have several therapeutic applications. For example, hCA II and VII inhibitors are utilized as antiepileptic drugs, while some anti-inflammatory and antitumor CAIs target the isoforms hCA IX and XII. Also, hCA II, IV, and XII inhibitors are utilized in glaucoma and diuretics.[17]

CA enzyme inhibitors mostly include a hydrophilic core bearing a heteroatom, which may interact with Zn, and a hydrophobic moiety that provides access to the active site of the enzyme.[18] Although thiazolidinone derivatives having these properties have the potential for inhibition of other enzymes, like AChE and α-Gly enzymes, very few studies have been conducted on these in the past.[19]

The aim of the study was to investigate the inhibitory potential of a series of piperonyl-based 4-thiazolidinone derivatives against AChE, α-Gly, and human carbonic anhydrase I and II (hCA I and II) isoforms experimentally and theoretically.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

For the synthesis of 4-thiazolidinones, first, imines were prepared by reacting piperonylamine with related aromatic aldehydes.[19] At this stage, the imine was synthesized very practically with only stirring of reactants and was used in the cyclization reaction without further purification. For the cyclization reaction, refluxing in EtOH, which is the most accepted method in 4-thiazolidinone synthesis, was used (Figure 1).[20]

The comparison of yields with yields of known molecules in the literature is shown in Table 1. Though **2a**, **2d**, **2e**, **2g**, and **2i** are known molecules in the literature, **2b**, **2c**, **2f**, and **2h** were newly synthesized in the literature as far as we know.

2.2 | Biological results

After synthesis and characterization of molecules, biochemical factors were investigated and their effects on different enzymes were investigated. It was found that they inhibited some important metabolic enzymes well, and the results are presented in Table 2. The hCA I isozyme was inhibited by the piperonyl-based 4-thiazolidinone derivatives (**2a–i**), with K_i values between 94.8 ± 14.7 and 289.5 ± 50.6 nM. In addition, **2f** and **2e** exhibited good hCA I isoform inhibition with K_i values of 94.8 ± 14.7 and 105.9 ± 23.6 nM, respectively. The standard drug acetazolamide (AZA) had a K_i value of 354.4 ± 42.5 nM. Indeed, the investigated synthesized compounds had better inhibitory profiles compared to the AZA molecule (Table 2). Among the clinically utilized CAIs are methazolamide, AZA, saccharin, ethoxzolamide, dorzolamide, and brinzolamide. CAIs of the sulfamate type have been clinically utilized for several decades as antiobesity drugs, antiglaucoma, and diuretics agents, and recently, a number of studies reported that CA inhibition exhibits profound antitumor effects inhibiting new hypoxia-inducible isoenzymes CA XII and IX, which are overexpressed in many hypoxic tumors.[24,25] In addition, various proof-of-concept studies have determined the involvement of several CA isozymes in arthritis and neuropathic pain, with the CAIs of the coumarin/sulfonamide type showing considerable effects in vivo and in vitro, in animal models of these diseases. Hence, the field of synthesis, drug design, and in vivo evaluations of diverse types of CAIs is a highly dynamic one, with a large number of interesting new chemotypes that act on these various enzymes constantly emerging.[26,27] The results clearly showed that hCA II was significantly inhibited by the synthesized piperonyl-based 4-thiazolidinone derivatives (**2a–i**). These compounds had strong hCA II inhibition with K_i values ranging from 106.3 ± 26.9 to 304.6 ± 36.0 nM. The K_i values of the synthesized molecules are better than those of the standard drug AZA (K_i: 368.4 ± 33.6 nM). All the evaluated synthesized molecules showed potent inhibition against hCA II, but the compounds **2f** and **2e** showed a significant inhibition profile against hCA II with K_i values of 106.3 ± 26.9 and 126.8 ± 30.6 nM (Table 2).

The inhibitory effects of the synthesized piperonyl-based 4-thiazolidinone derivatives (**2a–i**) on AChE enzyme are presented in Table 2. The AChE inhibition profiles of the molecules investigated here are really interesting. Overall, these compounds had excellent inhibitory activity with K_i values ranging from 0.55 ± 0.08 to 2.36 ± 0.47 nM. In addition, tacrine, utilized as a control AChEI in this paper, demonstrated a K_i value of 107.12 ± 22.0 nM toward AChE. The inhibition of AChE of the synthesized piperonyl-based 4-thiazolidinone derivatives (**2a–i**) is much better than standard drugs. The compounds **2d** and **2a** showed excellent inhibition profile against AChE with K_i values of 0.55 ± 0.08 and 0.65 ± 0.11 nM, respectively (Table 2). The IC_{50} values of these compounds can be written in the following order: **2d** (0.84 nM, r^2: 0.9843) < **2a** (0.94 nM, r^2: 0.9683) < **2c** (1.05 nM, r^2: 0.9406) < **2i** (1.23 nM, r^2: 0.9694) < **2b** (1.83 nM, r^2: 0.9779) < **2f** (1.95 nM, r^2: 0.9842) < **2h** (2.60 nM, r^2: 0.9916) < **2g** (2.77 nM, r^2: 0.9578) < **2e** (2.81 nM, r^2: 0.9750).

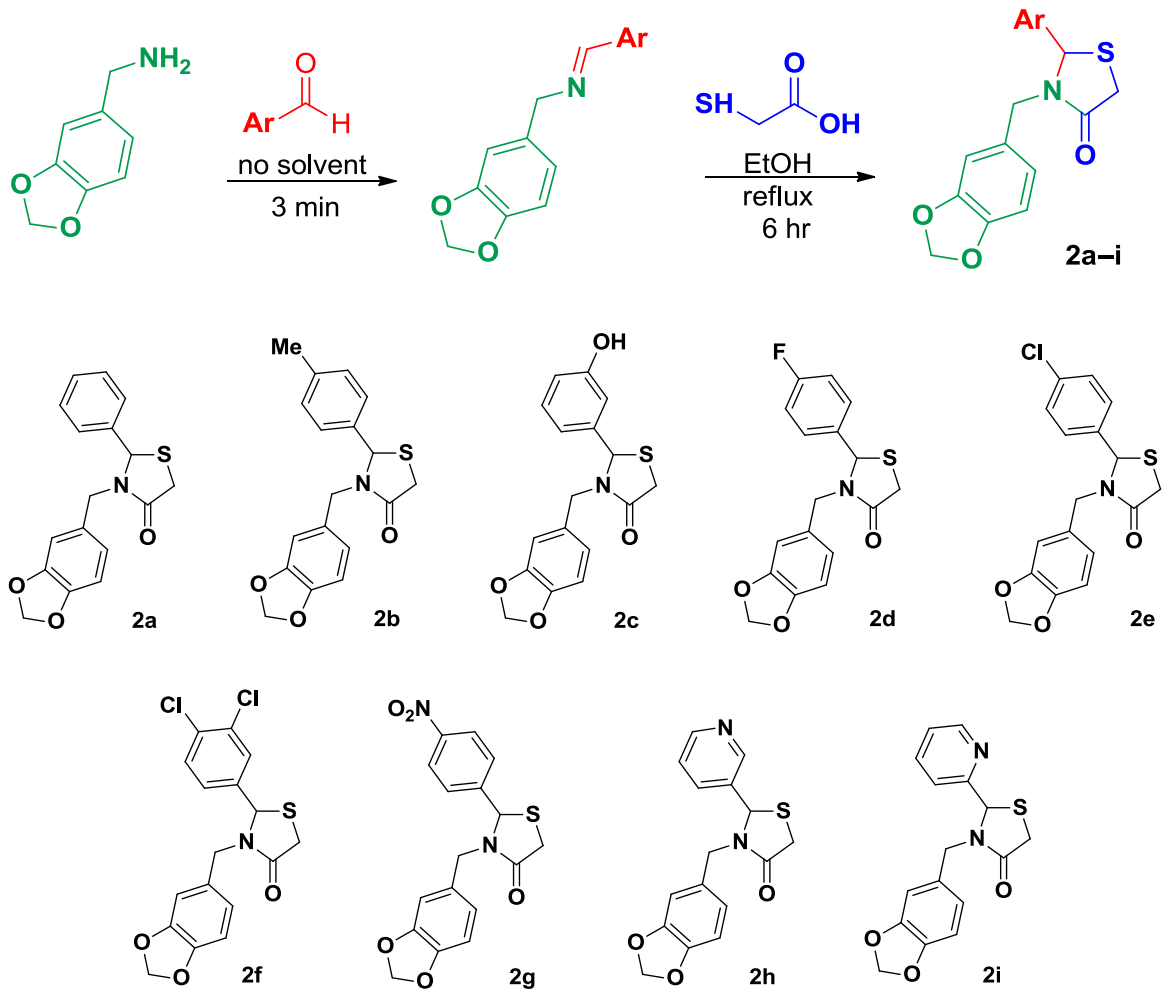

FIGURE 1 Synthesis of 4-thiazolidinones (**2a–i**) from piperonylamine and aromatic aldehyde derivatives

Multiple drugs utilized in the therapy of Alzheimer's disease (AD) are based on the established cholinergic hypothesis, where the target is to increase the concentration of the ACh molecule in the synaptic cleft by the deterrence of cholinesterase (ChE) activities. AChE inhibitors (AChEIs) prevent the separation of the cholinesterase enzyme, increasing the synaptic availability of ACh in the brain and subsequently boosting cholinergic neurotransmission in forebrain regions, which results in compensating for the loss of function of brain cells. Due to this, AChE inhibition has been documented as a critical treatment route of AD. In addition, AChEIs belong to myriad classes of functional and structural groups of molecules. Also, the multiple side effects of the present AD drugs have spurred the designing of new AChEIs for pharmacological usage.[30]

TABLE 1 Obtained yields and comparison with the literature

Compound	Yield (%)[a]	Conventional yield (%)[b]
3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-phenylthiazolidin-4-one (**2a**)	87	90[21]
3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(*p*-tolyl)thiazolidin-4-one (**2b**)	84	–
3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(3-hydroxyphenyl)thiazolidin-4-one (**2c**)	80	–
3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(4-fluorophenyl)thiazolidin-4-one (**2d**)	91	70[22]
3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(4-chlorophenyl)thiazolidin-4-one (**2e**)	98	68[23]
3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(3,4-dichlorophenyl)thiazolidin-4-one (**2f**)	92	–
3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(4-nitrophenyl)thiazolidin-4-one (**2g**)	87	92[22]
3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(pyridin-3-yl)thiazolidin-4-one (**2h**)	76	–
3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(pyridin-2-yl)thiazolidin-4-one (**2i**)	74	69[22]

[a]Isolated yields.
[b]Yields in the literature.

TABLE 2 The enzyme inhibition results of synthesized piperonyl-based 4-thiazolidinone derivatives (**2a–i**) against human carbonic anhydrase isoenzymes I and II (hCA I and II), acetylcholinesterase (AChE), and α-glycosidase (α-Gly) enzymes

Compounds	IC_{50} (nM)								K_i (nM)			
	hCA I	r^2	hCA II	r^2	AChE	r^2	α-Gly	r^2	hCA I	hCA II	AChE	α-Gly
2a	185.9	.9615	227.8	.9817	0.94	.9683	28.6	.9514	204.7 ± 25.8	254.8 ± 37.9	0.65 ± 0.11	35.77 ± 8.52
2b	205.1	.9811	240.9	.9715	1.83	.9779	36.9	.9790	190.8 ± 35.2	236.6 ± 21.5	1.25 ± 0.17	31.53 ± 6.04
2c	137.9	.9605	154.3	.9844	1.05	.9406	11.5	.9633	145.0 ± 16.8	185.9 ± 16.4	0.85 ± 0.07	14.84 ± 2.64
2d	123.5	.9901	128.1	.9599	0.84	.9843	25.3	.9815	128.4 ± 17.4	157.7 ± 26.9	0.55 ± 0.08	19.05 ± 2.33
2e	120.9	.9424	134.8	.9725	2.81	.9750	56.0	.9958	105.9 ± 23.6	126.8 ± 30.6	2.36 ± 0.47	66.51 ± 9.50
2f	91.0	.9756	98.4	.9390	1.95	.9842	31.8	.9351	94.8 ± 14.7	106.3 ± 26.9	1.58 ± 0.37	39.84 ± 5.08
2g	195.8	.9853	218.7	.9847	2.77	.9578	5.9	.9684	183.2 ± 24.9	204.7 ± 41.5	2.20 ± 0.25	8.90 ± 1.04
2h	216.9	.9640	205.2	.9721	2.60	.9916	20.6	.9550	266.8 ± 41.3	250.9 ± 59.5	2.05 ± 0.12	27.42 ± 4.81
2i	264.3	.9889	306.6	.9611	1.23	.9694	18.8	.9687	289.5 ± 50.6	304.6 ± 36.0	0.95 ± 0.09	24.53 ± 3.77
AZA[a]	317.3	.9813	334.3	.9504	–	–	–	–	354.4 ± 42.5	368.4 ± 33.6	–	–
TAC[b]	–	–	–	–	118.55	.9610	–	–	–	–	107.12 ± 22.0	–
ACR[c]	–	–	–	–	–	–	22,800	–	–	–	–	12,600 ± 780

[a]Acetazolamide (AZA) was used as a control for hCA I and II.
[b]Tacrine (TAC) was used as a control for AChE enzyme.
[c]Acarbose (ACR) was used as a control for α-glycosidase enzyme.[28,29]

For this metabolic enzyme, the synthesized piperonyl-based 4-thiazolidinone derivatives (**2a–i**) had IC_{50} values in the range of 5.9–56.0 nM and K_i values in the range of 8.90 ± 1.04–66.51 ± 9.50 nM (Table 2). The results clearly showed that all synthesized derivatives (**2a–i**) showed more efficient α-Gly inhibitory effects than acarbose (IC_{50}: 22,800 nM)[28,29] as a control α-Gly inhibitor. However, the most effective K_i values were obtained by **2g** and **2c** with K_i values of 8.90 ± 1.04 and 14.84 ± 2.64 nM, respectively. The IC_{50} values of these compounds exhibited the following order: **2g** (5.90 nM, r^2: 0.9684) < **2c** (11.05 nM, r^2: 0.9633) < **2i** (18.80 nM, r^2: 0.9687) < **2h** (20.60 nM, r^2: 0.9550) < **2d** (25.30 nM, r^2: 0.9815) < **2a** (28.60 nM, r^2: 0.9514) < **2f** (31.80 nM, r^2: 0.9351) < **2b** (36.90 nM, r^2: 0.9790) < **2e** (56.0 nM, r^2: 0.9958). Diverse types of α-Gly inhibitors have been clinically used to inhibit α-Gly activity for medicinal aims like voglibose, acarbose, and miglitol compounds. Inhibitors of this enzyme are designed and orally taken, acting as an antidiabetic drug by preventing the digestion of carbohydrate molecules and by delaying the absorption of sugar. This allows plasma glucose to be maintained at a steady level. However, due to the numerous side effects of these drugs, medicinal chemists are continuously trying to discover new α-Gly inhibitors.[31]

Because AChE and α-Gly enzymes are important and they have relationships between them, we have tried inhibition on these enzymes. According to epidemiological studies, patients with type 2 diabetes (T2D) have a higher occurrence of dementia and AD and vice versa. Active research has been performed over the last decade on understanding the mechanisms of AD and T2D. Experimental evidence was found that impairment of insulin might be a mechanistic link between both conditions: not only is T2D caused by insulin deficiency, but also insulin (and leptin) has been shown to regulate neuronal and synaptic functions in the brain.[32] At the same time, AChE may be involved in the parthenogenesis of T2D through suppression of amyloid formation.[33] It was also demonstrated that selective inhibition of BChE in aged rats improved cognitive navigation.[34]

In previous studies, Zengin et al.[13] synthesized and characterized a series of thymol-bearing oxypropanolamine compounds. Their in vitro antibacterial activity on *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus* strains were investigated with the agar well diffusion method. These novel thymol-bearing oxypropanolamine derivatives were effective inhibitors of the α-Gly, hCA I and II isoforms, and AChE, with K_i values in the range of 463.85–851.05 μM for α-Gly, 1.11–17.34 μM for hCA I, 2.97–17.83 μM for hCA II, and 13.58–31.45 μM for AChE, respectively.[13] Also in another study, Bayrak et al.[35] tested novel bromophenols compounds against some important enzymes, like acetylcholinesterase and butyrylcholinesterase enzymes, carbonic anhydrase I and II isoenzymes. The novel bromophenols showed K_i values in the range of 53.75 ± 12.54–234.68 ± 46.76 nM against hCA I; 42.84 ± 9.36 and 200.54 ± 57.25 nM against hCA II; 0.84 ± 0.12–14.63 ± 3.06 nM against AChE; and 0.93 ± 0.20–18.53 ± 5.06 nM against BChE.[35] When we compared these three studies, their obtained results were similar to the inhibitor values in our study, and our results were obtained at the nM level.

2.3 | Molecular docking

Theoretical studies are widespread because they are easy and simple compared with experimental studies. In theoretical studies, when the interactions of protein molecules are examined, the molecules with the strongest interaction with the protein are more stable. In molecular docking studies, synthesized molecules were studied both experimentally and theoretically. The theoretical and experimental

TABLE 3 Molecular energy data for the studied molecules for human carbonic anhydrase I

	2a	2b	2c	2d	2e	2f	2g	2h	2i
Est. free energy of binding (kcal/mol)	−6.62	−4.28	−5.13	−4.83	−3.69	−3.17	−0.89	−4.42	−4.33
Est. inhibition constant K_i (mM)	13.98	732.2	175.11	285.9	1.97	4.71	222.6	579.8	675.02
vdW + H-bond + desolv energy (kcal/mol)	−7.35	−5.83	−6.39	−6.19	−5.07	−3.72	−3.12	−5.58	−5.10
Electrostatic energy (kcal/mol)	+0.00	−0.01	−0.02	−0.01	−0.01	−0.02	−0.01	−0.01	−0.03
Total intermolec. energy (kcal/mol)	−7.35	−5.83	−6.41	−6.21	−5.09	−3.74	−3.13	−5.59	−5.12
Frequency (%)	40	90	50	50	70	90	50	30	30
Interact. surface	626.4	621.94	606.68	597.75	623.61	641.88	624.77	599.84	648.16

studies were compared with each other. Molecular docking calculations were performed to investigate the interaction between target protein and molecule. The interactions of molecules studied with proteins are given in Figures S1–S4.

All calculations at molecular docking were made at pH 7.3. The reason for this is that experimental studies are done with the enzymes found in humans. In this way, more adaptation to the experimental environment was tried.[32]

Many parameters and data are obtained in molecular docking studies. These parameters and data are used to compare molecules. The parameters obtained in molecular docking studies for different proteins are given in Tables 3–6. The first parameter is the estimated free energy of binding; the numerical values obtained for this parameter are: −6.62, −4.28, −5.13, −4.83, −3.69, −3.17, −0.89, −4.42, and −4.33 for hCA I; −6.25, −6.05, −6.05, −6.00, −6.47, −7.86, −5.67,−5.95, and −5.51 for hCA II; −8.80, −8.65, −8.99, −9.15, −9.23, −10.16, −8.36, −8.51, and −8.18 for AChE; and −6.22, −6.04, −5.63, −6.34, −7.16, −6.61, −5.69, −5.55, and −5.65 for α-Gly. The results show that the **2i** molecule has the highest bioactivity for AChE and hCA II proteins. The second parameter is the estimated inhibition constant.[33] The K_i values are, respectively: 13.98, 732.29, 175.11, 285.94, 1.97, 4.71, 222.60, 579.84, and 675.02 for hCA I; 26.00, 36.73, 37.97, 40.04, 18.20, 1.74, 70.12, 43.57, and 92.16 for hCA II; 355.45, 460.25, 257.49, 196.77, 172.95, 35.42, 750.21, 580.69, and 1.01 for AChE; and 27.42, 37.54, 75.00, 22.64, 5.61, 14.25, 66.95, 84.94, and 72.69 for α-Gly. This parameter shows that both drug molecules can inhibit an enzyme and drug molecules can interact with a substrate for the enzyme. If the value of this parameter of one of the studied molecules is greater than the other molecules, the extra drug is needed to prevent enzyme activity.[34] The lowest value for this parameter is **2e** for hCA I and AChE. The third parameter, the vdW H-bond dissolve energy, is −7.35, −5.83, −6.39, −6.19, −5.07, −3.72, −3.12, −5.58, and −5.10 for hCA I; −6.63, −6.30, −6.43, −6.43, −6.71, −8.05, −6.36, −6.16, and −5.94 for hCA II; −9.26, −9.01, −9.60, −9.60, −9.55, −10.35, −9.08, −8.90, and −8.89 for AChE, −6.80, −6.78, −6.70, −7.08, −7.68, −7.22, −6.72, −6.51, and −6.42 for α-Gly. This parameter is the most important parameter for molecular docking. This parameter indicates the position of the studied molecule relative to the target protein. The numerical value of this parameter is negative, indicating that the studied molecules are well bound to an active site on the target protein. The most negative value for this parameter is the **2f** molecule for the enzyme hCA II and AChE. For molecular docking, the last parameter is the electrostatic energy, which is 0.00, −0.01, −0.02, −0.01, −0.01, −0.02, −0.01, −0.01, and −0.03 for hCA I; −0.12, −0.05, −0.25, +0.05, −0.04, −0.10, −0.08, −0.16, and −0.15 for hCA II; −0.01, −0.11, −0.16, +0.02, −0.03, −0.03, +0.02, −0.00, and −0.02 for AChE; and +0.01, +0.11, +0.18, −0.05, +0.00, +0.25, +0.02, +0.08, and +0.05 for α-Gly. If the numerical value of this parameter has a negative value, it indicates that there is a link between the molecule and the protein molecule studied.[36] When the values of the hCA I, hCA II, and AChE enzymes are examined, it is seen that they are, generally, negative for this parameter. But, the enzyme α-Gly generally has positive values.

In this study, the molecules studied interact with enzymes and with many amino acids within the enzyme. These interactions increase the biological activity of the molecules. Figure 2 shows the interactions between the AChE enzyme and the **2f** molecule. The AChE enzyme includes the amino acid, TYR121. The distance

TABLE 4 Molecular energy data for the studied molecules for human carbonic anhydrase II

	2a	2b	2c	2d	2e	2f	2g	2h	2i
Est. free energy of binding (kcal/mol)	−6.25	−6.05	−6.05	−6.00	−6.47	−7.86	−5.67	−5.95	−5.51
Est. inhibition constant K_i (mM)	26.00	36.73	36.97	40.04	18.20	1.74	70.12	43.57	92.16
vdW + H-bond + desolv energy (kcal/mol)	−6.63	−6.30	−6.43	−6.43	−6.71	−8.05	−6.36	−6.16	−5.94
Electrostatic energy (kcal/mol)	−0.12	−0.05	−0.25	+0.05	−0.04	−0.10	−0.08	−0.16	−0.15
Total intermolec. energy (kcal/mol)	−6.75	−6.34	−6.68	−6.38	−6.75	−8.15	−6.44	−6.32	−6.08
Frequency (%)	30	40	60	10	20	10	10	80	80
Interact. surface	586.6	569.2	551.4	544.39	575.8	747.6	547.8	581.4	582.77

TABLE 5 Molecular energy data for the studied molecules for acetylcholinesterase

	2a	2b	2c	2d	2e	2f	2g	2h	2i
Est. free energy of binding (kcal/mol)	−8.80	−8.65	−8.99	−9.15	−9.23	−10.16	−8.36	−8.51	−8.18
Est. inhibition constant K_i (mM)	355.4	460.25	257.49	196.77	172.9	35.42	750.2	580.69	1.01
vdW + H-bond + desolv energy (kcal/mol)	−9.26	−9.01	−9.60	−9.60	−9.55	−10.35	−9.08	−8.90	−8.89
Electrostatic energy (kcal/mol)	−0.01	−0.11	−0.16	+0.02	−0.03	−0.03	0.0	−0.00	−0.02
Total intermolec. energy (kcal/mol)	−9.27	−9.12	−9.77	−9.59	−9.58	−10.38	−9.06	−8.90	−8.91
Frequency (%)	40	30	20	20	10	70	30	40	40
Interact. surface	811.9	845.49	817.95	810.43	874.6	902.81	875.5	807.26	777.33

between TYR121 and the N1 atom in molecule **2f** is 3.19 atomic units. Figure 3 shows the interactions between α-Gly enzyme and **2e** molecule. The α-Gly enzyme includes the amino acid, ASP482. The distance between ASP482 and the N1 atom in molecule **2e** is 3.10 atomic units. Figure 4 shows the interactions between hCA I enzyme and **2a** molecule. The hCA I enzyme includes the amino acid, GLN92. The distance between GLN92 and the N1 atom protein in molecule **2a** is 3.00 atomic units. Lastly, Figure 5 shows the interactions between hCA II enzyme and **2f** molecule. The hCA II enzyme includes the two amino acids, PRO13 and PRO247. The distance between PRO13 and the C8 atom in molecule **2f** is 3.47 atomic units, and the distance between PRO247 and the C10 atom is 3.70 atomic units. When we examine all interactions, it is seen that interactions with heteroatoms in the molecule are more. The interaction of ligands with an amino acid has an important effect on activation. If the amino acid interacts with more the atom on the ligand, the activity of the ligand significantly increases. The smaller the distance between the amino acid and the ligand, the more the interaction. This leads to a stable structure. The stable structure increases the biological activity of the ligand.

3 | CONCLUSIONS

Some piperonyl-based 4-thiazolidinone derivatives (**2a–i**) have been synthesized and evaluated for α-Gly inhibitory potential. AChEI is actually the best available pharmacotherapy for the treatment of AD symptoms, increasing the levels of the acetylcholine neurotransmitter in the cerebral cortex synapses. In addition, the compounds studied in this work can be acceptable candidate drugs, the same as CAIs, for treatment of disorders like epilepsy, gastric and duodenal ulcers, mountain sickness, glaucoma, neurological, and osteoporosis disturbances. Indeed, synthesized piperonyl-based 4-thiazolidinone derivatives (**2a–i**) effectively inhibited some metabolic enzymes like α-Gly, hCA I, hCA II, and AChE enzymes at the nanomolar levels. Also, the biological activity values of some piperonyl-based 4-thiazolidinone derivatives (**2a–i**) against α-Gly, hCA I, hCA II, and AChE enzymes were compared in molecular docking. In the docking study, it was seen that the most important factor affecting the biological activity values of molecules is intermolecular interactions. The most important of these interactions are hydrogen bonds, polar and hydrophobic interactions, π–π, and halogen bonds. In the light of the results obtained, when the obtained tables were examined, values close to the experimental studies were found. Although there is great harmony between experimental and theoretical studies, there are some differences. The reason for the differences between theoretical and experimental studies is that the theoretical studies are conducted in a pure and isolated environment. There are many experimental interventions in experimental studies.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

Melting points (mps) were taken on a Barnstead Electrothermal 9200. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were measured on a spectrometer at VARIAN Infinity Plus 300 and at 75 Hz, respectively. All

TABLE 6 Molecular energy data for the studied molecules for α-glycosidase

	2a	2b	2c	2d	2e	2f	2g	2h	2i
Est. free energy of binding (kcal/mol)	−6.22	−6.04	−5.63	−6.34	−7.16	−6.61	−5.69	−5.55	−5.65
Est. inhibition constant K_i (mM)	27.42	37.54	75.00	22.64	5.61	14.25	66.95	84.94	72.69
vdW + H-bond + desolv energy (kcal/mol)	−6.80	−6.78	−6.70	−7.08	−7.68	−7.22	−6.72	−6.51	−6.42
Electrostatic energy (kcal/mol)	+0.01	+0.11	+0.1	−0.05	+0.00	+0.25	+0.02	+0.08	+0.05
Total intermolec. energy (kcal/mol)	−6.79	−6.67	−6.53	−7.13	−7.68	−6.97	−6.69	−6.43	−6.37
Frequency (%)	20	30	10	20	40	30	10	10	40
Interact. surface	600.72	601.94	608.6	605.80	628.13	626.37	602.47	571.59	601.19

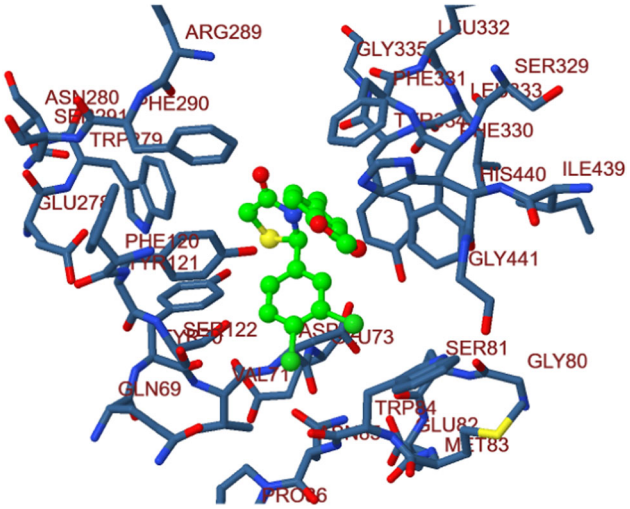

FIGURE 2 Molecular interactions between the acetylcholinesterase enzyme and **2g**

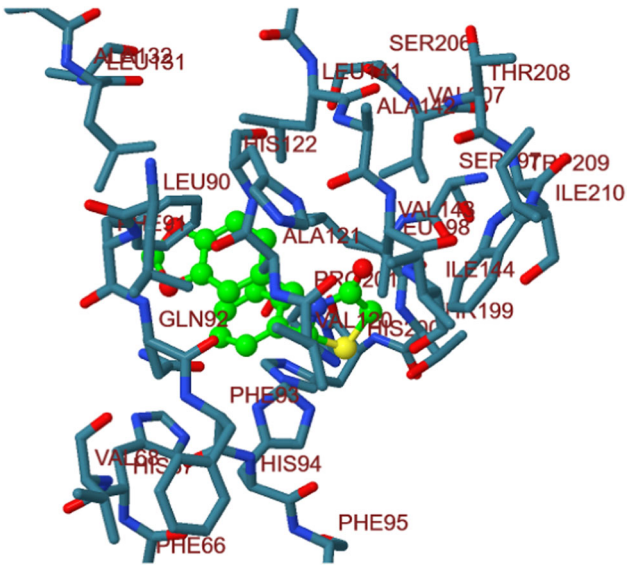

FIGURE 4 Molecular interactions between the human carbonic anhydrase I enzyme and **2a**

the chemical substances used for synthesis of compounds were provided commercially (Merck, Sigma-Aldrich, and Fluka).

The InChI codes of the investigated compounds are provided as Supporting Information.

4.1.2 | General methods for imine synthesis[19]

For imine synthesis, 3 mmol piperonylamine and 3 mmol aromatic aldehyde were mixed in a beaker by a baguette for 3 min. The expected imine product was obtained in quantitative yield and used for further reaction without any purification.

4.1.3 | General methods of 4-thiazolidinone synthesis[20]

To a solution of imine (3 mmol) in ethanol (15 ml), 2-mercaptoacetic acid (3 mmol) was added and the reaction mixture was heated under reflux for 6 hr. The mixture was concentrated under vacuum and diluted with EtOAc. The organic phase was washed (5× water), dried over $MgSO_4$ and the solvent was removed in a vacuum. The crude product was crystallized from warm EtOH to give pure 4-thiazetidinone derivatives (Figure 1).

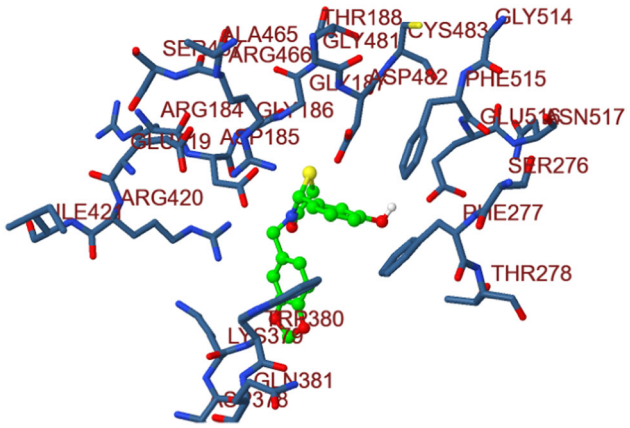

FIGURE 3 Molecular interactions between the α-glycosidase enzyme and **2i**

*3-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-(p-tolyl)thiazolidin-4-one (**2b**)* Bright crystal, yield 84%, mp 98–100°C; ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.24–7.02 (m, 4H, Ar–***H*** for tolyl), 6.71 (dd, J = 7.9, 0.8 Hz, 1H, Ar–***H*** for piperonyl), 6.63 (d, J = 1.7 Hz, 1H, Ar–***H*** for piperonyl), 6.50 (dd, J = 7.9, 1.7 Hz, 1H, Ar–***H*** for piperonyl), 5.95

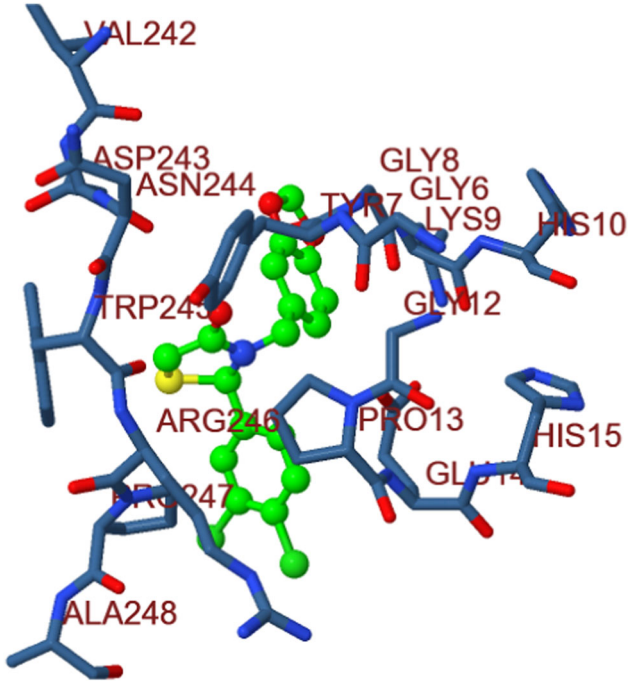

FIGURE 5 Molecular interactions between the human carbonic anhydrase II enzyme and **2f**

(d, J = 0.6 Hz, 2H, –Ar–O–C***H***$_2$–O), 5.37 (d, J = 2.0 Hz, 1H, –N–C***H***(Ar)–S), 5.04 (d, J = 14.6 Hz, 1H, –N–C(O)–C***H***$_2$–S), 3.93–3.83 (m, 1H, –Ar–C***H***$_2$–N), 3.73 (d, J = 15.5 Hz, 1H, –Ar–C***H***$_2$–N), 3.42 (d, J = 14.6 Hz,1H, –N–C(O)–C***H***$_2$–S), and 2.37 (s, 3H, Ar–C***H***$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.37 (–***C***═O), 148.21 (Ar–***C***–O), 147.52 (Ar–***C***–O), 139.44 (Ar–***C***), 136.28, 130.03 (2C, Ar–***C***), 129.36 (Ar–***C***), 127.38 (2 C, Ar–***C***), 122.22 (Ar–***C***), 109.07 (Ar–***C***), 108.46 (Ar–***C***), 101.39 (–O–***C***H$_2$–O), 62.71 (–N–***C***H(Ar)–S), 46.10 (Ar–***C***H–N), 33.34 (–C(O)–***C***H$_2$–S), and 21.51 (Ar–***C***H$_3$); LC–MS (*m/z*): calculated for ($C_{18}H_{17}NO_3S$) 327.09 and found 328 $[M+H]^+$.

*3-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-(3-hydroxyphenyl)thiazolidin-4-one (**2c**)*

Bright crystal, yield 80%, mp 150–152°C; ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.58 (s, 1H, –O***H***), 7.15 (t, J = 7.8 Hz, 1H, Ar–***H*** for hydroxyphenyl), 6.81 (dd, J = 7.8, 0.6 Hz, 1H, Ar–***H*** for piperonyl), 6.75–6.59 (m, 4H, Ar–***H*** for piperonyl and hydroxyphenyl), 6.52 (dd, J = 7.7, 1.6 Hz, 1H, Ar–***H*** for piperonyl), 5.97 (d, J = 1.0 Hz, 2H, –Ar–O–C***H***$_2$–O), 5.43 (d, J = 1.7 Hz, 1H, –N–C***H***(Ar)–S), 4.77 (d, J = 15.0 Hz, 1H, –N–C(O)–C***H***$_2$–S), 3.85 (dd, J = 15.6, 1.8 Hz, 1H, –Ar–C***H***$_2$–N), 3.73 (d, J = 15.6 Hz, 1H, –Ar–C***H***$_2$–N), and 3.48 (d, J = 15.0 Hz, 1H, –N–C(O)–C***H***$_2$–S); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.48 (–***C***═O), 158.51 (Ar–***C***), 148.16 (Ar–***C***–O), 147.36 (Ar–***C***–O), 141.97 (Ar–***C***), 130.66 (Ar–***C***), 130.12 (Ar–***C***), 121.88 (Ar–***C***), 118.04 (Ar–***C***), 116.48 (Ar–***C***), 113.92 (Ar–***C***), 108.89 (Ar–***C***), 108.78 (Ar–***C***), 101.71 (–O–***C***H$_2$–O), 62.24 (–N–***C***H(Ar)–S), 45.99 (Ar–***C***H–N), and 32.45 (–C(O)–***C***H$_2$–S); LC–MS (*m/z*): calculated for ($C_{17}H_{15}NO_4S$) 329.07 and found 330 $[M+H]^+$.

*3-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-(3,4-dichlorophenyl)thiazolidin-4-one (**2f**)*

Bright crystal, yield 92%, mp 118–120°C; ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.43 (d, J = 8.2 Hz, 1H, Ar–***H*** for 3,4-dichlorophenyl), 7.29 (d, J = 2.1 Hz, 1H, Ar–***H*** for 3,4-dichlorophenyl), 7.05 (dd, J = 8.3, 2.1 Hz, 1H, Ar–***H*** for 3,4-dichlorophenyl), 6.69 (d, J = 7.9 Hz, 1H, Ar–***H*** for piperonyl), 6.59 (d, J = 1.7 Hz, 1H, Ar–***H*** for piperonyl), 6.46 (dd, J = 7.9, 1.8 Hz, 1H, Ar–***H*** for piperonyl), 5.94 (s, 2H, –Ar–O–C***H***$_2$–O), 5.32 (d, J = 1.9 Hz, 1H, –N–C***H***(Ar)–S), 4.98 (d, J = 14.6 Hz, 1H, –N–C(O)–C***H***$_2$–S), 3.86 (dd, J = 15.5, 1.5 Hz, 1H, –Ar–C***H***$_2$–N), 3.72 (d, J = 15.5 Hz, 1H, –Ar–C***H***$_2$–N), and 3.49 (d, J = 14.6 Hz, 1H, –N–C(O)–C***H***$_2$–S); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.23 (–***C***═O), 148.37 (Ar–***C***–O), 147.71 (Ar–***C***–O), 139.86 (Ar–***C***), 133.58 (Ar–***C***), 133.48 (Ar–***C***), 131.30 (Ar–***C***), 129.33 (Ar–***C***), 128.83 (Ar–***C***), 126.63 (Ar–***C***), 122.14 (Ar–***C***), 108.87 (Ar–***C***), 108.53 (Ar–***C***), 101.50 (–O–***C***H$_2$–O), 61.79 (–N–***C***H(Ar)–S), 46.50 (Ar–***C***H–N), and 33.13 (–C(O)–***C***H$_2$–S); LC–MS (*m/z*): calculated for ($C_{17}H_{13}Cl_2NO_3S$) 381.00 and found 382 $[M+H]^+$.

*3-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-(pyridin-3-yl)thiazolidin-4-one (**2h**)*

Bright crystal, yield 76%, mp 121–123°C; ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.62 (dt, J = 5.0, 1.7, 0.8 Hz, 1H, Ar–***H*** for pyridin-3-yl), 8.45 (dd, J = 2.3, 0.8 Hz, 1H, Ar–***H*** for pyridin-3-yl), 7.66 (dd, J = 8.0, 1.7 Hz, 1H, Ar–***H*** for pyridin-3-yl), 7.38 (dd, J = 8.0, 5.0 Hz, 1H, Ar–***H*** for pyridin-3-yl), 6.69 (d, J = 7.9 Hz, 1H, Ar–***H*** for piperonyl), 6.61 (d, J = 1.7 Hz, 1H, Ar–***H*** for piperonyl), 6.44 (dd, J = 8.0, 1.8 Hz, 1H, Ar–***H*** for piperonyl), 5.95 (s, 2H, –Ar–O–C***H***$_2$–O), 5.42 (d, J = 1.9 Hz, 1H, –N–C***H***(Ar)–S), 5.01 (d, J = 14.7 Hz, 1H, –N–C(O)–C***H***$_2$–S), 3.90 (dt, J = 15.7, 1.1 Hz, 1H, –Ar–C***H***$_2$–N), 3.85–3.62 (m, 1H, –Ar–C***H***$_2$–N), and 3.47 (dd, J = 14.7, 2.3 Hz, 1H, –N–C(O)–C***H***$_2$–S); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.26 (–***C***═O), 150.82 (Ar–***C***), 148.90 (Ar–***C***–O), 148.43 (Ar–***C***–O), 147.74 (Ar–***C***), 135.33 (Ar–***C***), 135.24 (Ar–***C***), 128.77 (Ar–***C***), 124.37 (Ar–***C***), 122.14 (Ar–***C***), 108.84 (Ar–***C***), 108.57 (Ar–***C***), 101.48 (–O–***C***H$_2$–O), 60.50 (–N–***C***H(Ar)–S), 46.44 (Ar–***C***H–N), and 33.24 (–C(O)–***C***H$_2$–S); LC–MS (*m/z*): calculated for ($C_{16}H_{14}N_2O_3S$) 314.07 and found 315 $[M+H]^+$.

4.2 | Biological studies

For α-Gly, the inhibitory effect of these compounds on α-Gly enzyme activity was measured using *p*-nitrophenyl-D-glycopyranoside (*p*-NPG) molecule as the substrate, according to the assay of Tao et al.[37] First, 400 µl of phosphate buffer was mixed with 40 µl of the homogenate solution in phosphate buffer (0.15 U/ml, pH 7.4). Also, 100 µl of *p*-NPG in phosphate buffer (5 mM, pH 7.4) after preincubation was added and again incubated at 30°C. The absorbances were spectrophotometrically measured at 405 nm, according to former studies.[38,39] The CA inhibitory effects of the piperonyl-based 4-thiazolidinone derivatives (**2a–i**) for hCA I and II were obtained, according to the method of Verpoorte et al.[40] and according to former studies[41,42] and measured at 348 nm spectrophotometrically using the *p*-nitrophenylacetate as the main substrate.[43] For AChE, the inhibitory effect of the piperonyl-based 4-thiazolidinone derivatives (**2a–i**) was calculated according to Ellman et al.[44] and to former studies[45,46] and measured at 412 nm spectrophotometrically using acetylthiocholine iodide molecule as a main substrate for the enzymatic reaction. 5,5′-Dithio-bis(2-nitro-benzoic) acid molecule was utilized for the measurement of the AChE activity.[35,47,48]

4.3 | Molecular docking

In this study, the nine molecules studied were first optimized using the Gaussian package program in HF/6–31 g++ basis set.[49–51] In the docking study, to compare the biological activities of the molecules against the enzymes, the molecules were first optimized using the Gaussian package program. Files with the extension *.pdb were created using optimized structures. Then the files of the enzymes studied from the RCSB Protein Data Bank site were downloaded and made to interact with the molecules. The names of the protein molecules studied are acetylcholinesterase for PDB ID 1OCE (AChE), α-glycosidase for PDB ID 1XSI (α-Gly), human carbonic anhydrase I for PDB ID 2CAB (hCA I), and human carbonic anhydrase II for PDB ID 4R5B (hCA II). The interaction of these proteins against the nine molecules studied was compared by using DockingServer.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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