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Naphthoquinones and anthraquinones: Exploring their impact on acetylcholinesterase enzyme activity

Hatice Esra Duran[1] | **Şükrü Beydemir**[2,3]

[1]Department of Medical Biochemistry, Faculty of Medicine, Kafkas University, Kars, Turkey

[2]Department of Biochemistry, Faculty of Pharmacy, Anadolu University, Eskişehir, Turkey

[3]Bilecik Şeyh Edebali University, Bilecik, Turkey

Correspondence
Hatice Esra Duran and Şükrü Beydemir
Department of Basic Medical Sciences, Faculty of Medicine, Kafkas University, 36100 Kars, Turkey. Email: haticeesra4990@gmail.com and beydemirs@gmail.com

Abstract

The identification of novel acetylcholinesterase inhibitors holds significant relevance in the treatment of Alzheimer's disease (AD), the prevailing form of dementia. The exploration of alternative inhibitors to the conventional acetylcholinesterase inhibitors is steadily gaining prominence. Quinones, categorized as plant metabolites, represent a specific class of compounds. In this study, the inhibitory effects of various naphthoquinone derivatives, along with anthraquinone and its derivatives, on the acetylcholinesterase (AChE) enzyme were investigated for this purpose. An in vitro investigation was conducted to examine the effects of these compounds in order to clarify the possible mechanism of inhibition in the interaction between the enzyme and chemicals. In addition, an in silico investigation was carried out to understand the conceivable inhibitor binding process to the enzyme's active site. The acquired outcomes corroborated the in vitro results. The AChE enzyme was found to be effectively inhibited by both naphthoquinones and anthraquinones, with inhibition constant (K_I) values ranging from 0.014 to 0.123 μM (micormolar). The AChE enzyme was inhibited differently by this quinone and its derivatives. Although derivatives of naphthoquinone and anthraquinone exhibited a competitive inhibitory effect, derivatives of anthraquinone exhibited a noncompetitive inhibition effect. Furthermore, because it had the lowest K_I value of any of these substances, 1,5-dihydroxyanthraquinone (**1c**) was shown to be the most potent inhibitor. The findings will add to the body of knowledge on the creation of fresh, potent, and successful treatment approaches.

KEYWORDS

acetylcholinesterase, anthraquinone, enzyme, inhibition, naphthoquinone

Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; AChEIs, acetylcholinesterase inhibitors; AD, Alzheimer's disease; K_I, inhibition constant; THA, tacrine.

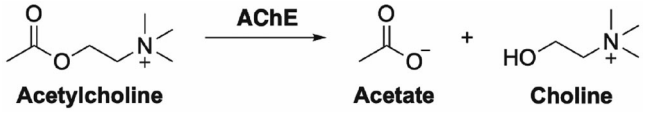

FIGURE 1 Hydrolysis mechanism of acetylcholinesterase enzyme.

1 | INTRODUCTION

Alzheimer's disease (AD) is a neuropathological condition[1] primarily impacting the elderly, manifesting as challenges in thinking, problem-solving, memory loss, and language difficulties.[2,3] AD is marked by various cortical disorders, leading to intellectual dysfunction, impaired daily life activities, diminished learning skills, and memory loss.[4] Several hypotheses have been proposed to elucidate the mechanisms behind AD, with the cholinergic hypothesis standing out as the foremost theory for the treatment of AD.[5]

Acetylcholinesterase (AChE; EC 3.1.1.7) is an essential cholinesterase that regulates[5] and hydrolyzes[6] acetylcholine (ACh) in the central nervous system.[7] ACh, a neurotransmitter in the nervous system, is essential for regulating the physiological and behavioral activities of cholinergic neurons. Reduced levels of ACh are essential for the development and course of disorders connected to these neural processes.[8] The hydrolysis of acetylcholine, which breaks down into acetate and choline, is its main function[9] (Figure 1).

AChE is a vital enzyme involved in the transmission of nerve impulses. Consequently, the inhibition of AChE is considered one of the most rational strategies for the management of AD. In clinical practice, various acetylcholinesterase inhibitors (AChEIs) are utilized, including donepezil, galanthamine, rivastigmine, and tacrine (THA).[10] Nevertheless, these drugs have exhibited adverse effects, including nausea, vomiting, diarrhea, dizziness, and hepatotoxicity.[11] Additionally, they are associated with toxic effects and have limited efficacies.[12] Due to these considerations, it is imperative to identify novel AChEIs that are more reliable and efficacious for the treatment of AD.

In AD, the upregulation of ACh expression in metabolism, resulting from the inhibition of the AChE enzyme, leads to improvements in language skills, attention span, and memory functions.[13,14] Consequently, the development of more potent AChEIs becomes a pivotal approach to mitigate adverse reactions associated with AChEIs, which significantly impact therapeutic outcomes both during and after the treatment of AD.[15]

In the initial studies involving the AChE enzyme, its role in transmitting a nerve impulse from one nerve cell to another was identified. Subsequent research revealed that this functionality also contributes to the generation of bioelectrical current along nerve and muscle fibers. Besides transmitting neural signals among neighboring nerve cells in vertebrates, these signals also play a crucial role in initiating the contraction of muscle cells. The AChE enzyme, by breaking down and clearing harmful chemicals accumulated at the nerve end, serves to eliminate barriers to electron carriers, addressing issues in neural conduction. Dysfunction of the AChE enzyme results in the accumulation of acetylcholine in synaptic spaces, potentially leading to severe conditions such as muscle paralysis and seizures, and even death.[16]

Currently, AChEIs employed in the treatment of AD represent a drug class that has attained a notable degree of success. These drugs, developed as AChEIs, act to inhibit AChE, the enzyme responsible for the hydrolysis of acetylcholine, an essential neurotransmitter in the central nervous system. The inhibition leads to a reduction in the concentration of acetylcholine, contributing to a marked improvement in the patient's behavioral disorders.[17] When ACh undergoes hydrolysis by AChE, the signal transmission between nerve ends is terminated.[18] In conditions associated with memory loss, it has been observed that acetylcholine is rapidly broken down. Inhibiting the enzyme responsible for acetylcholine hydrolysis leads to enhanced nerve conduction. Drugs targeting AChE have been linked to hepatotoxicity and gastrointestinal disorders.[19] Consequently, there is a growing interest in safer natural AChEIs.[20]

Quinones are plant-derived secondary metabolites.[21] Benzoquinones have a variety of pharmacological characteristics and are essential for electron transfer, bioenergetic transport, and oxidative phosphorylation. These substances are necessary building blocks for the synthesis of many different types of pharmaceutical drugs.[22]

Naphthoquinones represent a notable subgroup within the quinone family, finding application in various industrial sectors such as agrochemicals and pharmaceuticals.[23] These compounds serve as fungicides, algicides, and chemical intermediates in the synthesis of pharmaceuticals and dyes. Additionally, naphthoquinones exhibit potential as antifungals, blood clotting agents, antibacterials, and are actively explored for their role as anticancer agents.[24]

An important class of substances with a wide range of uses is comprised of anthraquinones. Folk medicine has been using plants like rhubarb and aloe, which contain anthraquinones, for over 4000 years. It has been determined that anthraquinone derivatives have biological properties in fungi, insects, and bacteria in addition to plants. These substances, whether manufactured or found naturally, are widely used in a wide range of products and services, such as paints, cuisines, foodstuffs, medicines, and cosmetics. Furthermore, because of their redox

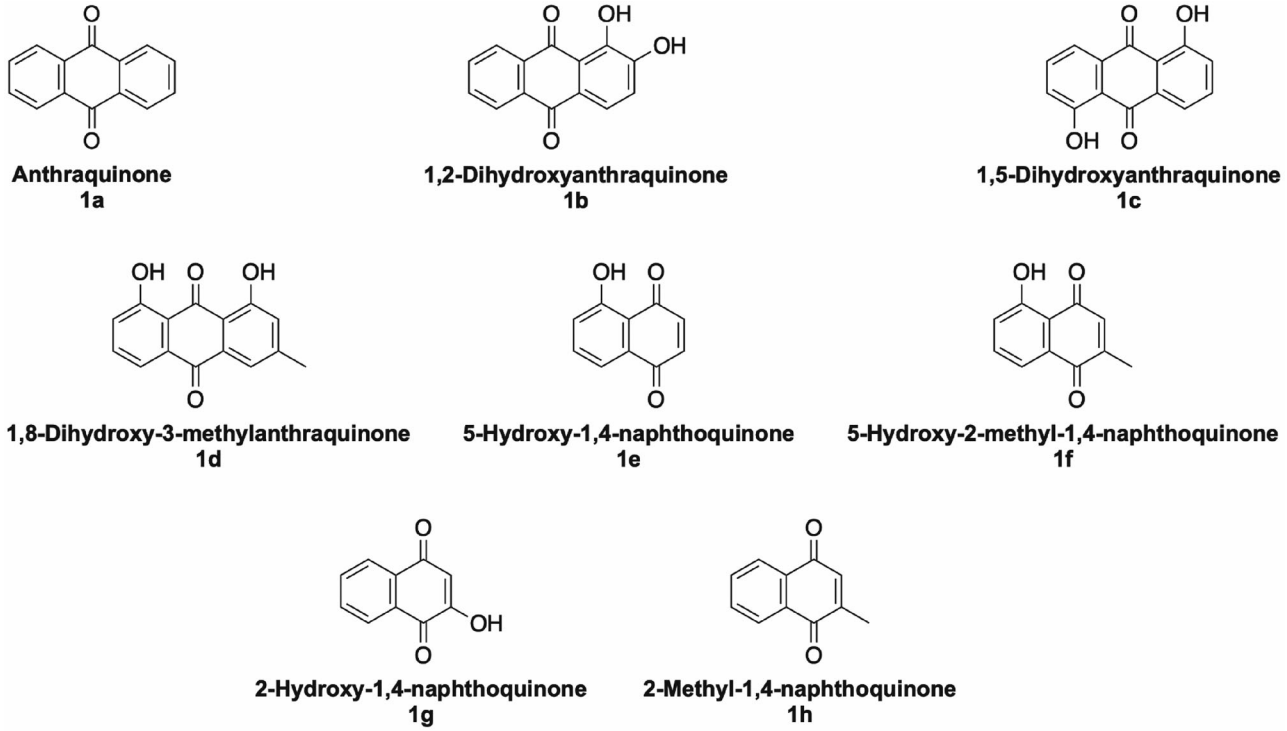

FIGURE 2 Chemical structures of naphthoquinones and anthraquinones used in this study.

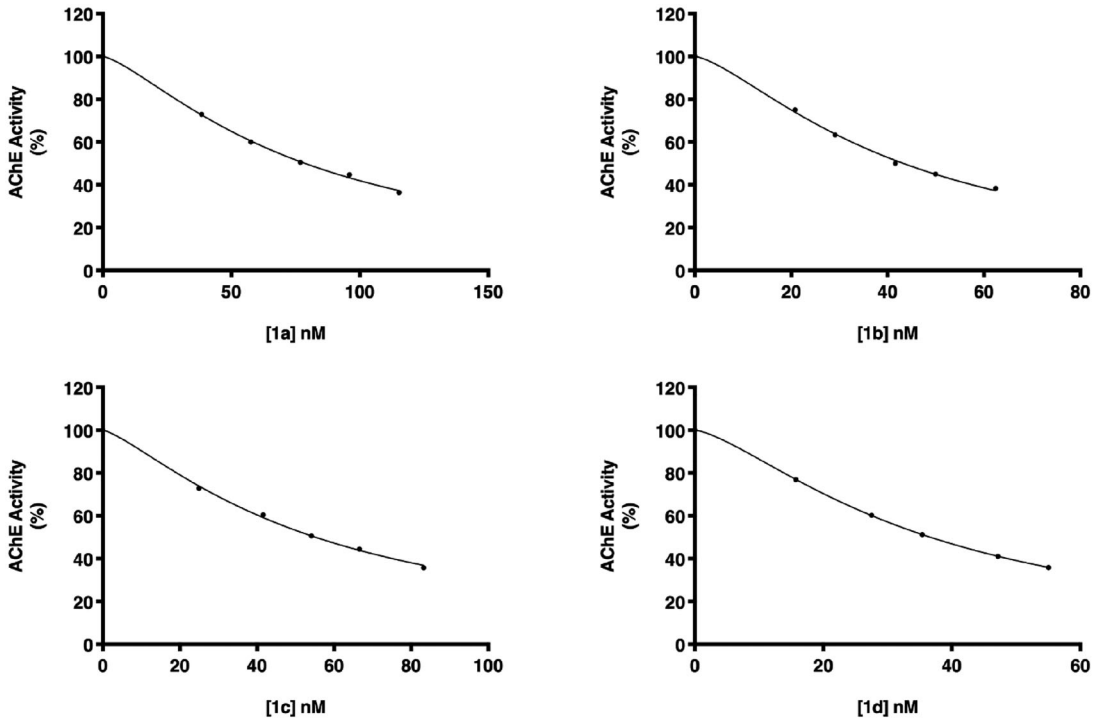

FIGURE 3 IC_{50} graphs of some anthraquinones on the acetylcholinesterase (AChE) enzyme.

potential, anthraquinones act as catalysts in a variety of chemical and biogeochemical processes, especially the reductive destruction of pollutants.[25,26]

The primary goal of this study is to discover new and effective AChEIs. In this study, the in vitro inhibitory effects of quinones

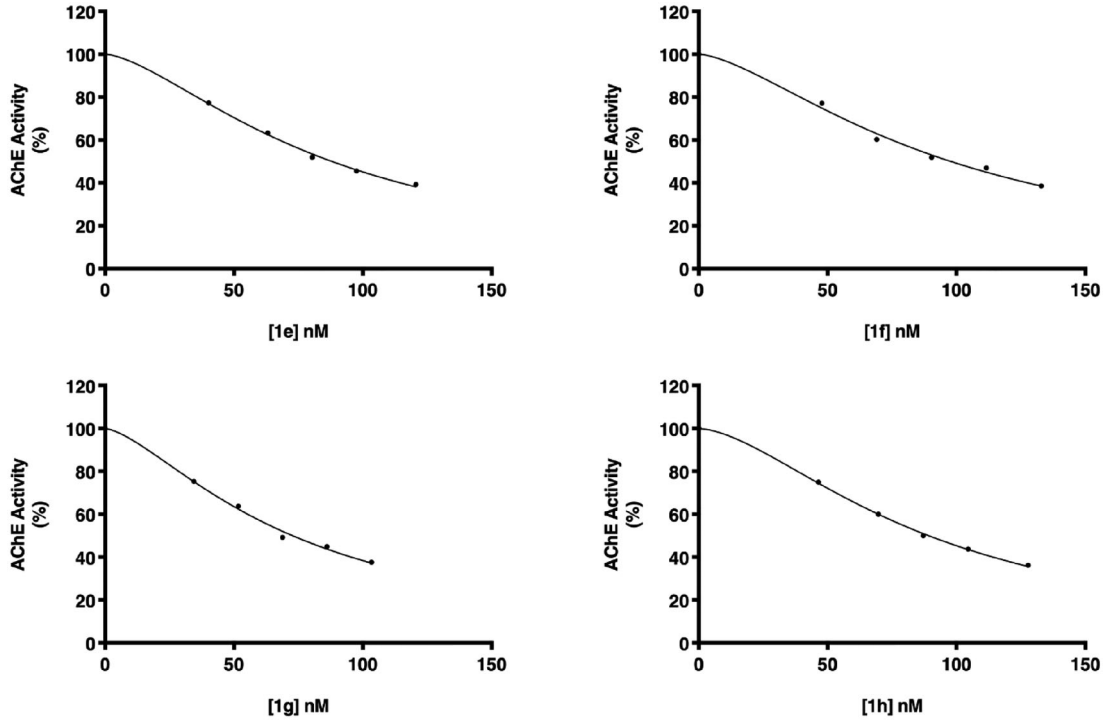

FIGURE 4 IC_{50} graphs of some naphthoquinones on the acetylcholinesterase (AChE) enzyme.

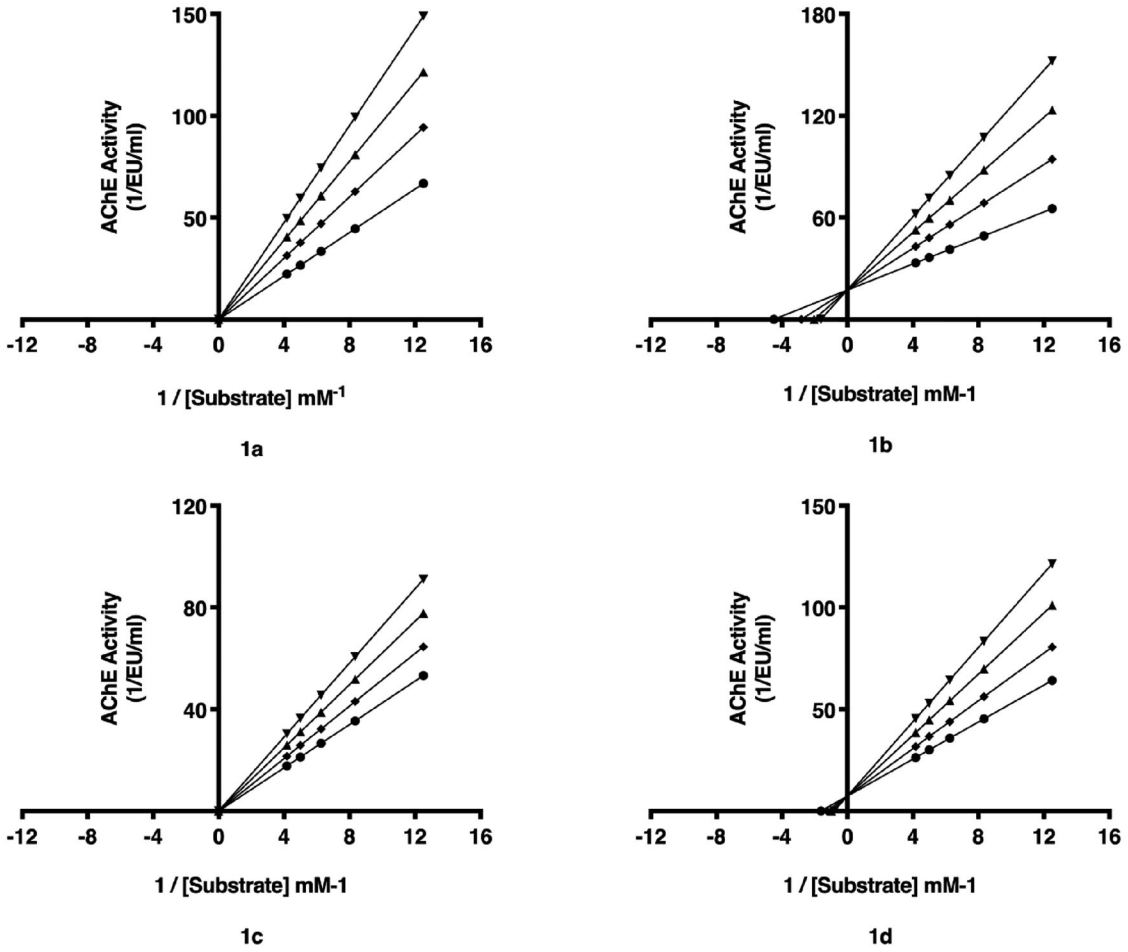

FIGURE 5 Lineweaver–Burk plots of some anthraquinones on the acetylcholinesterase (AChE) enzyme.

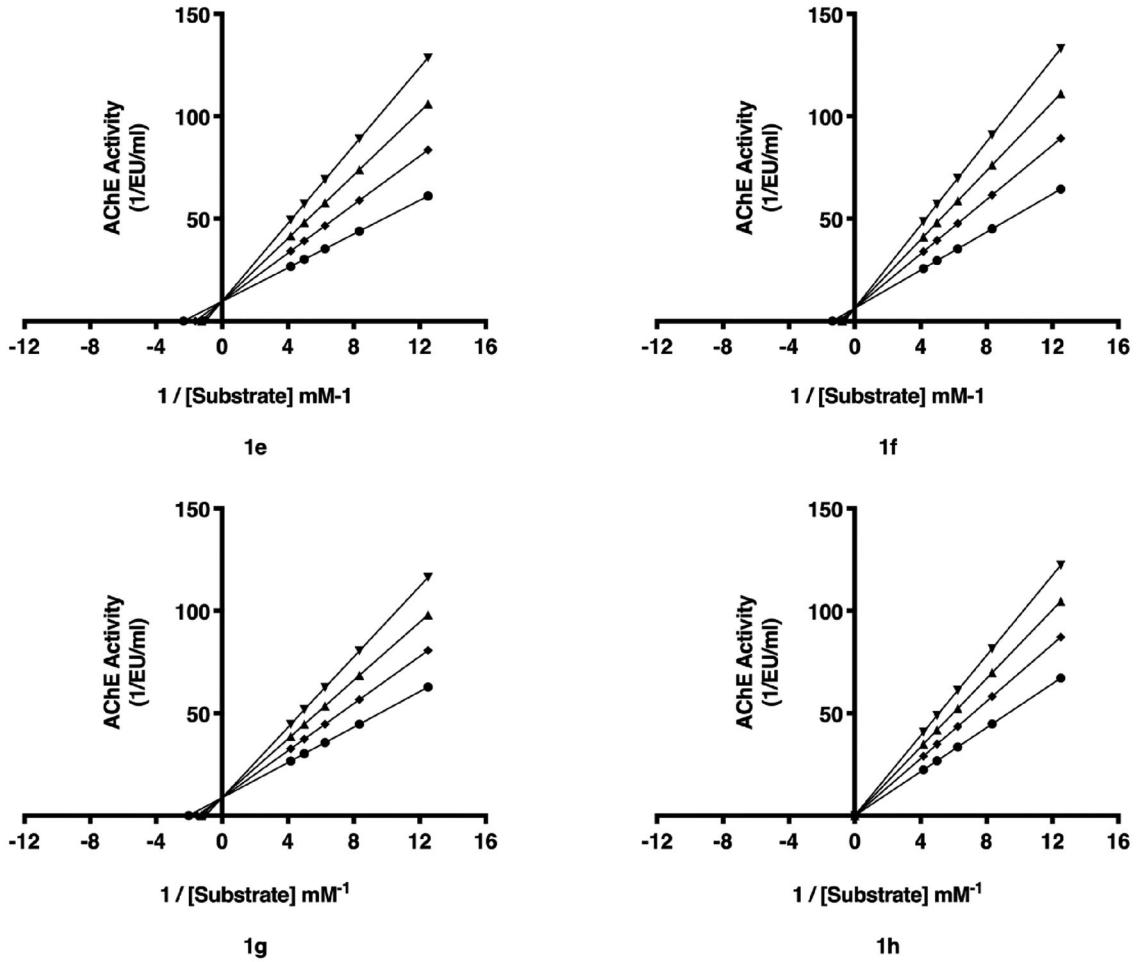

FIGURE 6 Lineweaver–Burk plots of some naphthoquinones on the acetylcholinesterase (AChE) enzyme.

(anthraquinone [**1a**], 1,2-dihydroxyanthraquinone [**1b**], 1,5-dihydroxyanthraquinone [**1c**], 1,8-dihydroxy-3-methylanthraquinone [**1d**], 5-hydroxy-1,4-naphthoquinone [**1e**], 5-hydroxy-2-methyl-1,4-naphthoquinone [**1f**], 2-hydroxy-1,4-naphthoquinone [**1g**], and 2-methyl-1,4-naphthoquinone [**1h**]) (Figure 2) were investigated on AChE, and in silico studies were also carried out.

2 | MATERIALS AND METHODS

2.1 | Chemicals

AChE from *Electrophorus electricus* (C2888, Type V-S) and all chemicals used in the study were were sourced from Sigma-Aldrich.

2.2 | AChE enzyme activity measurement

AChE enzyme activity was assessed utilizing a modified version of the Ellman method.[27,28] The inhibitory effect of quinones and their derivatives was spectrophotometrically examined at 412 nm, employing acetylthiocholine iodide (ATChI) and 5,5-dithiobis (2-nitrobenzoic) acid as substrates.[29,30]

2.3 | In vitro inhibition studies

At least five distinct inhibitor concentrations were used to evaluate the quinones' and their derivatives' inhibitory effects on AChE. As in our earlier research,[31–33] the IC_{50} values of the quinones were determined using the Activity (%) − [Compound] graphs (Figures 3 and 4) for each derivative. The inhibition constant (K_I) values and inhibition types were found using Lineweaver and Burk curves[34–36] (Figures 5 and 6).

2.4 | In silico molecular docking analysis

The analysis and design of in silico figures were performed using the Schrödinger Small-Molecule Drug Discovery Suite 2023–4 for Mac, provided by Schrödinger.[37] The

TABLE 1 IC_{50} and K_I values and inhibition types of naphthoquinone and anthraquinone derivatives (**1a–h**) on AChE enzyme.

Inhibitor ID	Inhibitor	IC_{50} (nM)*	R^2	K_I (nM)[a]	R^2
1a	Anthraquinone	78.82 ± 0.99	0.9988	93.73 ± 15.94	0.9168
1b	1,2-Dihydroxyanthraquinone	55.22 ± 0.84	0.9984	117.30 ± 23.92	0.9598
1c	1,5-Dihydroxyanthraquinone	43.33 ± 0.63	0.9983	34.54 ± 3.88	0.9773
1d	1,8-Dihydroxy 3-methylanthraquinone	36.69 ± 0.05	0.9999	54.81 ± 7.59	0.9662
1e	5-Hydroxy-1,4-naphthoquinone	88.01 ± 1.25	0.9982	92.00 ± 9.72	0.9799
1f	5-Hydroxy-2-methyl-1,4-naphthoquinone	97.79 ± 2.71	0.9930	112.50 ± 23.46	0.9322
1g	2-Hydroxy-1,4-naphthoquinone	72.83 ± 1.59	0.9959	104.20 ± 13.38	0.9710
1h	2-Methyl-1,4-naphthoquinone	89.30 ± 0.67	0.9994	155.60 ± 21.48	0.9730
THA	Tacrine	430.10 ± 1.45	0.9998	155.29 ± 0.82	0.9999

Abbreviations: AChE, acetylcholinesterase; K_I, inhibition constant.
[a]The test results were indicated as mean ± standard error of mean.

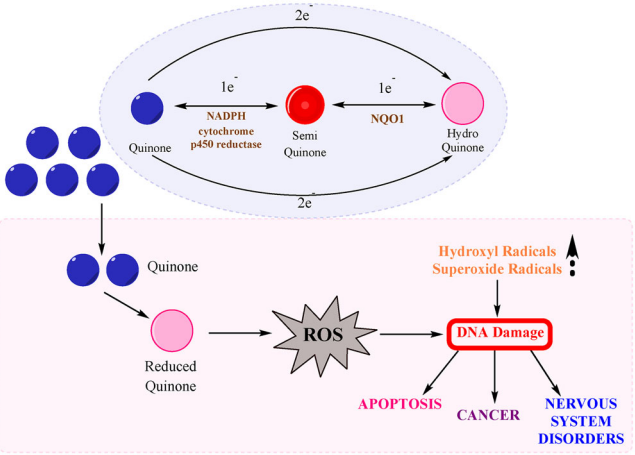

FIGURE 7 The relationship of quinones with oxidative stress.

software panels utilized were Maestro,[38,39] LigPrep,[40,41] Protein Preparation Wizard,[42,43] Receptor Grid Generation,[44] Ligand Docking,[45] and Prime MM-GBSA.[46] Initially, the crystal structure of AChE (PDB: 4BDT, species *Homo sapiens*)[47] was obtained from the Protein Data Bank.[48,49] The structure was downloaded, prepared, and optimized using the Maestro software.[50] The anthraquinones (**1a–d**) and naphthoquinones (**1e–h**) were constructed using the ChemDraw software and were suitably optimized for docking using the LigPrep tool.[51,52] The Epik tool[53] was utilized under default conditions with the OPLS force field[54] at a pH of 7.0 ± 2.0. The Receptor Grid Generation tool[55,56] was employed to generate the grid box for 4BDT. Furthermore, the Ligand Docking tool was used in conjunction with the Glide extra precision (XP) option[57,58] to dock the quinones (**1a–h**) within the enzyme's binding site. The docking scores were then utilized to evaluate the binding affinity of these compounds (**1a–h**) concerning the binding site of 4BDT. The MM-GBSA solvation method,[59,60] employing the VSGB energy model and the OPLS4 force field, was used to calculate the binding energies for the optimal poses of AChE with the quinones (**1a–h**) obtained from the Glide XP docking.

2.5 | Statistical studies

Analysis of the data and drawing of graphs were realized using GraphPad Prism version 8 for Mac (GraphPad Software). The inhibition constants were calculated by SigmaPlot version 12 for Windows (Systat Software). The fit of enzyme inhibition models was compared using the extra sum-of-squares *F* test and the AICc approach. The results were exhibited as mean ± standard error of the mean (95% confidence intervals). Differences between datasets were considered statistically significant when the *p*-value was less than 0.05.

3 | RESULTS AND DISCUSSION

Numerous investigations have shown that Alzheimer's sufferers' brains exhibit specific changes in particular neurotransmitter systems. The cholinergic system, which is the foundation of AD, is affected by the most notable abnormalities arising from these modifications. It is still unclear exactly what causes AD and how it progresses. The cholinergic hypothesis serves as the foundation for symptomatic treatment, which aims to improve cognitive performance in AD by enhancing central cholinergic function.[61] Primarily associated with the cholinergic hypothesis, AD is connected to cholinesterases, which include AChE and choline acetyltransferase (ChAT) enzymes. The biochemical properties of cholinesterases in the AD brain are sensitive to inhibitors, altering the optimal pH of the brain and causing differences from the normal brain. Therefore, agents that inhibit cholinesterase can offer selective advantages over AChEIs.[62] Studies have indicated a positive association between common drugs and methods of AChE inhibition in laboratory animals and humans with AD.[63]

TABLE 2 ADME-related parameters[a] of some naphthoquinone and anthraquinone derivatives (**1a–h**) and clinically used reference inhibitor tacrine.

Compound-ID	#stars	#rtvFG	CNS	MW	Dipole	SASA	Volume	donorHB	accptHB	QPlogPC16	QPlogPoct	QPlogPw	QPlogPo/w	QPlogS	QPPCaco	QPlogBB	QPPMDCK	QPlogKp	#metab	QPlogKhsa	HOA	PSA	Rule of Five	Rule of Three
1a	3	0	0	200.2	0.2	377.2	606.2	0	4	6.7	8.8	7.1	0.9	−1.3	1036	−0.3	514	−2.5	0	−0.7	86	56.4	0	0
1b	3	2	−2	232.2	3.2	405.1	662.3	0	8	7.3	12.1	11.3	−1.5	0.3	103	−1.1	43	−4	0	−1.6	54	113.4	0	0
1c	4	0	−2	232.2	0.6	401.6	659.1	0	8	7.3	11.8	11.3	−1.5	0.4	112	−1.1	47	−4.6	0	−1.6	55	115.6	0	0
1d	2	0	−2	244.2	11.8	433.5	715.4	0	8	7.4	15.0	11.1	−1.2	−0.2	111	−1.2	46	−4	0	−1.4	57	115.6	0	0
1e	3	0	−1	168.1	4.7	332.4	516.4	0	6	5.6	9.0	8.7	−1.3	0.4	200	−0.8	87	−4.3	0	−1.5	60	92.8	0	0
1f	2	0	−1	180.1	10.3	362.9	571.6	0	6	5.7	11.5	8.5	−0.7	−0.3	259	−0.8	115	−4	0	−1.3	66	89.4	0	0
1g	3	2	−1	168.1	4.2	336.7	520.7	0	6	5.6	9.0	8.7	−1.3	0.5	180	−0.9	77	−4.4	0	−1.5	60	90.9	0	0
1h	2	0	0	164.1	7.5	348.5	543.6	0	4	5.4	8.8	6.4	0.1	−0.8	849	−0.3	414	−3	0	−0.9	80	59.8	0	0
THA[b]	0	0	1	198.3	4.2	430.7	709.9	1.5	2	6.9	10.7	6.4	2.6	−3.1	2931	0.0	1582	−1.8	3	0.1	100	34.2	0	0

[a]Various computational pharmacodynamic and pharmacokinetic parameters of synthesized compounds in this research were predicted, such as number of property or descriptor values that fall outside the 95% range of similar values for known drugs. (#stars; 0–5), number of reactive functional groups (#rtvFG; 0–2), central nervous system activity (CNS; −2 inactive, +2 active), molecular weight of the compound (MW; 130.0–725.0), computed dipole moment of the compound (dipole; 1.0–12.5), total solvent accessible surface area (SASA; 300.0 –1000.0), total solvent-accessible volume in cubic angstroms using a probe with a 1.4 Å radius (volume; 500.0–2000.0), number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution (donorHB; 0.0–6.0), number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution (accptHB; 2.0–20.0), hexadecane/gas partition coefficient (QPlogPC16; 4.0–18.0), octanol/gas partition coefficient (QPlogPoct; 8.0–35.0), water/gas partition coefficient (QPlogPw; 4.0–45.0), octanol/water partition coefficient (QPlogPo/w; −2.0 to 6.5), aqueous solubility (QPlogS; −6.5 to 0.5), apparent Caco-2 cell permeability in nm/s (QPPCaco; <25 poor, great >500), brain/blood partition coefficient (QPlogBB; −3.0 to 1.2), apparent MDCK cell permeability in nm/s (QPPMDCK; <25 poor, great >500), skin permeability (QPlogKp; −8.0 to −1.0), number of likely metabolic reactions (#metab; 1–8), prediction of binding to human serum albumin (QPlogKhsa; −1.5 to 1.5), human oral absorption (HOA; <25% poor, high >80%), van der Waals surface area of polar nitrogen and oxygen atoms (PSA; 7.0–200.0), number of violations of Lipinski's rule of five (max. 4), and number of violations of Jorgensen's rule of three (max. 3).

[b]Tacrine.

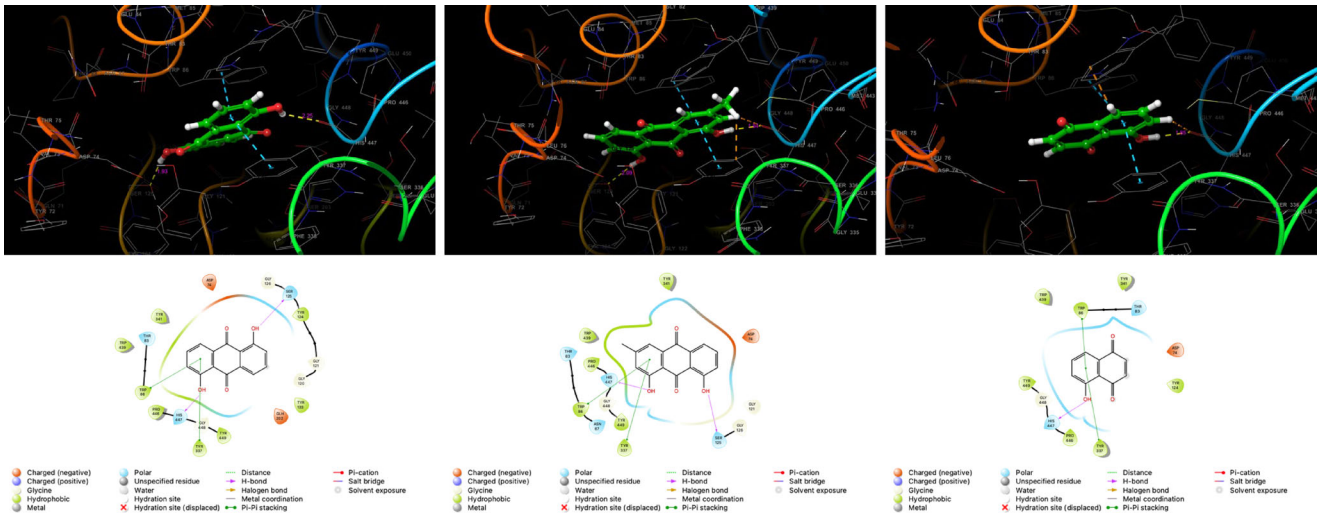

FIGURE 8 The binding sites of acetylcholinesterase (AChE) (PDB: 4BDT) with the 3D and 2D docked poses of the 1,5-dihydroxyanthraquinone (**1c**) (left), 1,8-dihydroxy 3-methylanthraquinone (**1d**) (middle), and 5-hydroxy-1,4-naphthoquinone (**1e**) (right).

TABLE 3 Pharmacokinetic properties[a] of some naphthoquinone and anthraquinone derivatives (**1a–h**) and clinically used reference inhibitor tacrine.

Compound ID	GI absorption	BBB permeant	P-gp substrate	CYP inhibitor				
				CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
1a	High	Yes	No	Yes	Yes	No	No	No
1b	High	Yes	No	Yes	No	No	No	Yes
1c	High	Yes	No	Yes	No	No	No	Yes
1d	High	Yes	No	Yes	No	No	No	Yes
1e	High	Yes	No	No	No	No	No	No
1f	High	Yes	No	Yes	No	No	No	No
1g	High	Yes	No	Yes	No	No	No	No
1h	High	Yes	No	Yes	No	No	No	No
THA	High	Yes	Yes	Yes	No	No	No	Yes

Abbreviations: CYP, cytochromes P450; GI, gastrointestinal; MW, molecular weight; THA, tacrine.

[a]Various pharmacokinetic parameters, such as the GI absorption, human gastrointestinal absorption; BBB permeant, blood–brain barrier permeation; P-gp substrate, prediction of being substrate or non-substrate of P-glycoprotein; CYP inhibitor, prediction of being inhibitor or non-inhibitor of cytochromes P450 five major isoforms (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4); and log K_p, prediction of the skin permeability coefficient of targeted compounds in this research, were predicted using SwissADME platform.

AChE is primarily responsible for the quick hydrolysis of ACh in the presynaptic area, which lowers the concentration of ACh and stops nerve impulses from being sent in cholinergic synapses. As a result, AChEIs, which reduce or completely block acetylcholine hydrolysis, are essential for treating a wide range of illnesses. Currently, a number of synthetic medications known as AChEIs, such as THA, rivastigmine, and donepezil, are used in clinical settings to treat cognitive impairment and memory loss linked to AD.[64] Data from the literature suggest that a variety of negative effects are linked to synthetic AChEIs that are often employed in therapeutic settings. Sulfonamides, on the other hand, are said to not cause these negative effects.[65] As a result, sulfonamides are valued in the context of AD as a noteworthy class of bioactive chemicals with a variety of biological effects.[66]

Free radicals are significant because they both directly and indirectly influence how many diseases occur.[67,68] According to reports, oxidative stress is linked to numerous illnesses of the respiratory and urinary systems, as well as neurological system problems, cancer, diabetes, atherosclerosis, and myocardial infarction.[69] A number of research on this topic have found that as people age, their lipid peroxidation increases and their enzyme activity significantly shifts.[70] Among the factors contributing to the body's increased production of free oxygen

TABLE 4 Drug-likeness descriptors[a] of some naphthoquinone and anthraquinone derivatives (**1a–h**) and clinically used reference inhibitor tacrine.

Compound ID	Ghose	Veber	Egan	Muegge	Bioavailability score
1a	Yes	Yes	Yes	Yes	0.55
1b	Yes	Yes	Yes	Yes	0.55
1c	Yes	Yes	Yes	Yes	0.55
1d	Yes	Yes	Yes	Yes	0.55
1e	No; 1 violation: atoms <20	Yes	Yes	No; 1 violation: MW <200	0.55
1f	Yes	Yes	Yes	No; 1 violation: MW <200	0.55
1g	No; 1 violation: atoms <20	Yes	Yes	No; 1 violation: MW <200	0.85
1h	Yes	Yes	Yes	No; 1 violation: MW <200	0.55
THA	Yes	Yes	Yes	No; 1 violation: MW <200	0.55

Abbreviations: MW, molecular weight; THA, tacrine.

[a]Drug-likeness parameters, such as the Ghose (Amgen), Veber (GSK), Egan (Pharmacia), and Muegge (Bayer) methods and bioavailability score (Abbot) of targeted compounds in this research, were predicted using SwissADME platform.

TABLE 5 Medicinal chemistry pattern recognition methods[a] of some naphthoquinone and anthraquinone derivatives (**1a–h**) and clinically used reference inhibitor tacrine.

Compounds ID	PAINS	Brenk	Lead-likeness	SA score
1a	1 Alert	0 Alert	No; 1 violation: MW <250	2.07
1b	2 Alerts	1 Alert	No; 1 violation: MW <250	2.35
1c	1 Alert	0 Alert	No; 2 violations: MW <250, XLOGP3 >3.5	2.31
1d	1 Alert	0 Alert	No; 1 violation: XLOGP3 >3.5	2.47
1e	1 Alert	0 Alert	No; 1 violation: MW <250	2.31
1f	2 Alerts	0 Alert	No; 1 violation: MW <250	2.41
1g	1 Alert	0 Alert	No; 1 violation: MW <250	2.42
1h	1 Alert	0 Alert	No; 1 violation: MW <250	2.37
THA	0 Alert	0 Alert	No; 1 violation: MW >350	2.08

Abbreviations: MW, molecular weight; THA, tacrine.

[a]Medicinal chemistry pattern recognition method, such as the PAINS, pan assay interference structure alert filter; Brenk, structural alert filter; Lead-likeness, lead-likeness criteria; and SA score, synthetic accessibility score (ranges from 1: very easy, to 10: very difficult) of targeted compounds in this research, were predicted using SwissADME platform.

radicals are stress, alcohol, cigarettes, obesity, and air pollution. Both cellular enzymatic antioxidant systems and non-enzymatic antioxidant mechanisms can neutralize reactive oxygen species (ROS).[71,72]

Quinones are compounds engaging in redox cycling processes within cellular systems, leading to their degradation and the generation of a semi-cell (bearing a single electron), subsequently forming hydroquinone (carrying two electrons). The reduction of quinone by nicotinamide adenine dinucleotide 2′-phosphate (NADPH): cytochrome p450 reductase involves the transfer of a single electron. The semiquinone undergoes oxidation back to quinone in the presence of oxygen (O_2), resulting in the reduction of O_2 and the production of ROS.[73,74] Nonetheless, NAD(P)H quinone dehydrogenase 1 utilizes either NADPH or NADH as electron donors and facilitates the reduction of quinone (involving two electrons) to hydroquinone, resulting in the production of ROS. In pathological conditions, a shift toward a preoxidative state occurs due to a reduction in antioxidant mechanisms, an elevation in preoxidation markers, or both. The sustained elevation of oxidative stress may lead to tissue and cellular damage through various mechanisms, including lipid peroxidation, DNA damage, and protein damage[75] (Figure 7).

Medicines known as AChEIs are the first class of drugs used to treat AD, glaucoma, myasthenia gravis, and other neuromuscular conditions. But there is a catch: when acetylcholine (ACh) levels rise, the symptoms of these conditions get worse. As a result, there is a great deal of focus on the investigation of new AChEIs in an effort to advance the care of these illnesses.[76,77]

In line with this information, the effects of some naphthoquinones and anthraquinones on the AChE enzyme were examined in vitro by comparing them with the reference drug THA. Table 1 provides a summary of the quinones inhibitory results. In this study, K_I parameters of quinone derivatives were determined by Lineweaver–Burk plots. The AChE enzyme was inhibited by all quinones at nanomolar (nM) levels; the range of K_I values was 54.81 ± 7.59 to 155.60 ± 21.48 nM. THA, the reference standard agent, had a K_I value of 155.29 ± 0.82 μM. In the results, it was determined that **1c** with K_I values of 34.54 ± 3.88 nM had the highest inhibitory effect compared to other quinone derivatives (Table 1).

According to the inhibition types determined for quinone derivatives, both naphthoquinones and anthraquinones exhibited competitive inhibition. Analyzing these findings, it is evident that the compounds under examination can bind to either the free enzyme or the enzyme–substrate complex, thereby inducing enzyme inhibition. Additionally, it is observed that hydroxy groups exert a notable inhibitory effect in **1c**. It was noted that the chemical structures of both naphthoquinones and anthraquinones, subjects of the inhibition study, were precisely identical, except for the groups attached to the ring structure. However, their inhibition rates exhibited significant differences. When compared according to IC_{50} values, compound **1c** showed more inhibition effect than others. In light of this observation, it can be inferred that the presence of hydroxy groups attached to the anthraquinone structure imparts a potent inhibitory effect on the AChE enzyme. Besides the IC_{50} values, K_I values were determined for each inhibitor. In this regard, it was discovered that the quinones' inhibitory strength sequence was as follows: 1,5-dihydroxyanthraquinone (**1c**) > 1,8-dihydroxy-3-methylanthraquinone (**1d**) > 5-hydroxy-1,4-naphthoquinone (**1e**) > anthraquinone (**1a**) > 2-hydroxy-1,4-naphthoquinone (**1g**) > 5-hydroxy-2-methyl-1,4-naphthoquinone (**1f**) > 1,2-dihydroxyanthraquinone (**1b**) > 2-methyl-1,4-naphthoquinone (**1h**).

To better understand the interaction of the anthraquinones (**1a–d**) and naphthoquinones (**1e–h**) with 4BDT, the most potent AChEIs **1c**, **1d**, and **1e** were docked in the binding sites of this enzyme. For the redocking computation, the structure of the crystal ligand, HUW (PubChem Ref.: 71463576, Huprine W) in the active site was used. The docked pose of HUW overlapped with the pose in the x-ray crystal structure (PDB ID: 4BDT)[47] at a root mean square deviation (RMSD) value of 0.77 Å. After that, in the present docking study, the docking pattern of HUW was compared with that of **1c** (K_I: 34.54 ± 3.88 nM), **1d** (K_I: 54.81 ± 7.59 nM), and **1e** (K_I: 92.00 ± 9.72 nM), the most potent compounds in this series (**1a–h**). The binding interactions of the inhibitors with ChE are displayed in Figure 8. It is essential to emphasize and consider that the conformations in Figure 8 are distinguished by many diverse interactions, including but not limited to hydrogen bonding and π–π stacking that transpire within the corresponding enzyme-binding pockets. In simpler terms, these particular conformations involve highly complex and intricate molecular interactions between the ligands and the enzyme-binding pockets, which in turn serve to stabilize and maintain the ligands securely within the confines of the pockets.

In pharmaceutical development, assessing the physicochemical and pharmacokinetic properties of target compounds through in silico methods holds great importance.[78,79] These methods serve as an invaluable tool in creating and advancing novel drug molecules. To comprehensively evaluate drug-likeness in these naphthoquinone and anthraquinone derivatives (**1a–h**), a meticulous analysis was conducted utilizing in silico physiochemical properties and ADME predictions for all compounds (**1a–h**). The QikProp module of

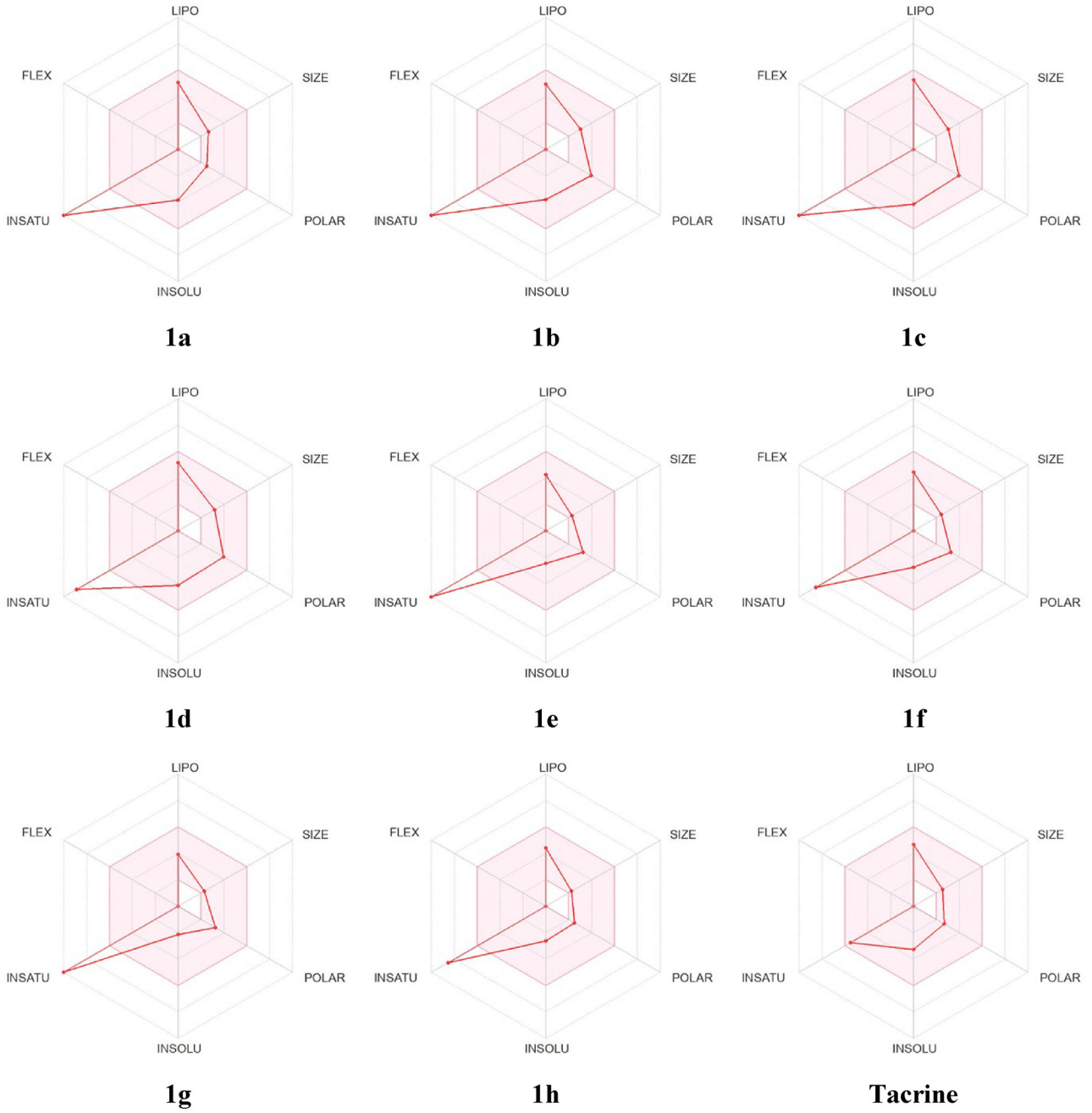

FIGURE 9 Diagrams showing "drug-likeness" descriptors for some naphthoquinone and anthraquinone derivatives (**1a–h**) and clinically used reference inhibitor tacrine. The red-colored zone has been identified as a feasible physicochemical domain to enhance oral bioavailability. LIPO, lipophilicity; SIZE, molecular weight; POLAR, polarity; INSOLU, insolubility; INSATU, saturation; FLEX, flexibility.

the Schrödinger Suite[80,81] and SwissADME platform[82] was employed for this purpose. The findings from this assessment have been meticulously compiled and are presented in Tables 2–5 and Figure 9. A critical aspect of this evaluation involved the calculation of the parameters associated with Lipinski's rule of five[83] and Jorgensen's rule three,[84] which is widely recognized as a primary criterion for predicting drug-likeness and the potential for high oral absorption of a molecule. Remarkably, all compounds (**1a–h**) exhibited Lipinski's and Jorgensen's rules, which are considered acceptable. This significant discovery strongly suggests that these compounds possess drug-like properties and hold great promise regarding their potential to be developed into orally active drugs.

In recent times, there has been a substantial increase in the number of studies focusing on the inhibition of the AChE enzyme. In a study by Aydin et al.,[85] some pyrimidine derivative compounds were synthesized, and the inhibition effect of these synthesized compounds was investigated. All of the compounds used in the study

showed an inhibition effect at the nanomolar level. Tugrak et al.[86] synthesized imidazole-based benzenesulfonamide derivatives and examined their inhibition effects and determined that these compounds showed an inhibition effect at the nanomolar level. Lolak et al.[87] synthesized sulfaguanidine (**SG1–4**) and sulfisoxazole (**SO1–4**) derivatives and examined their inhibition effects and determined that these compounds showed an inhibition effect at the nanomolar level.

The progression of scientific knowledge has ushered in a new era, particularly in the realms of medicine, genetics, and various health disciplines. This advancement empowers the elucidation of the developmental mechanisms underlying diverse diseases, facilitating prompt and accurate diagnoses and the initiation of necessary treatments. The focal point of extensive research by scientists for many years, this subject continues to be actively investigated.

Contemporary studies are extensively focused on proteins, particularly in the fields of antibodies, vaccines, natural interferons, and various metabolic enzymes. These components play pivotal roles in numerous disease processes. The insights gained from these studies have found applications in various fields, with medicine being a primary beneficiary. The ongoing exploration and utilization of these products underscore the dynamic and evolving landscape of scientific and medical research.[88]

4 | CONCLUSIONS

A number of quinones and their derivatives were more effective than standard compounds used as selective AChEIs. As a result, the study may provide promising information for the synthesis of alternative molecules to inhibitory drugs used in the treatment of diseases, due to their effects in removing free radicals that cause cellular damage and their inhibitory capacity on metabolic enzymes. More effective drugs can be obtained in line with the results of some studies researched in our laboratories. Additionally, these compounds may attract more attention due to their dystopic interactions on the targeted enzyme. This research holds particular promise for advancing treatment options in the context of AD, and may open doors to the development of innovative pharmaceutical interventions.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Hatice Esra Duran https://orcid.org/0000-0003-2080-0091

Şükrü Beydemir https://orcid.org/0000-0003-3667-6902

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