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Original Research Article

Exploring of some benzoquinone derivatives impact on Acetylcholinesterase enzyme activity

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Abstract

The discovery of acetylcholinesterase inhibitors is important for the treatment of Alzheimer's disease, which is the most common type of dementia. Due to the side effects of commonly used acetylcholinesterase inhibitors, studies aimed at discovering new inhibitors are increasing. Therefore, in this study, the effects of some benzoquinone derivatives, 1,4-benzoquinone (**1a**), 2,6-dichloro-1,4-benzoquinone (**1b**), and 2,6-dimethyl-1,4-benzoquinone (**1c**) on AChE enzyme were investigated. In vitro studies were conducted to understand the possible inhibition mechanism in the interaction of enzyme-benzoquinone compounds, and the effects of these compounds were examined. The quinones examined were found to exhibit effective inhibition of the AChE enzyme. IC_{50} values were determined to be 48-187 nM, and KI values ranged from 54 ± 0.007 nM to 262 ± 0.016 nM. These benzoquinones exhibited different inhibition mechanisms. While 1,4-benzoquinone (**1a**) and 2,6-dimethyl-1,4-benzoquinone (**1c**) showed competitive inhibition effects, 2,6-dichloro-1,4-benzoquinone (**1b**) exhibited noncompetitive inhibition effects. Additionally, among the compounds whose effects were examined, 2,6-dimethyl-1,4-benzoquinone (**1c**) showed the most effective inhibitor property with the lowest KI value. The findings will add to the body of knowledge on creating fresh, potent, and successful treatment approaches.

Keywords: AChE; enzyme; inhibition; benzoquinone;

Introduction

Alzheimer's Disease (AD) is a neuropathological condition that predominantly affects the elderly [1]. It can encompass difficulties in thinking or problem-solving, memory loss, and language-related challenges. AD is characterized by multiple cortical dysfunctions such as impairment in intellectual functions, inability to perform daily life activities, decline in learning skills, and memory loss [2,3]. Various hypotheses have been proposed to explain AD. Among these, the cholinergic hypothesis stands out as the most significant hypothesis for AD treatment [4].

Acetylcholinesterase (AChE) is an important cholinesterase type responsible for the regulation [5] and breakdown [6] of acetylcholine (ACh) in the central nervous system. [7]. AChE is primarily responsible for the hydrolysis of acetylcholine into acetate and choline [8] (Figure 1).

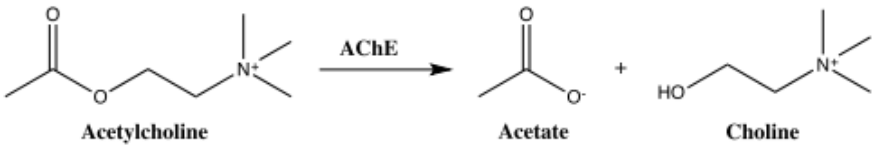

Figure 1. Hydrolysis mechanism of AChE enzyme.

Increased expression of ACh in metabolism due to the inhibition of the AChE enzyme leads to improved cognitive abilities such as language skills, attention span, and memory functions in Alzheimer's disease [9,10]. Therefore, the development of effective acetylcholinesterase inhibitors (AChEIs) could be a critical approach for the treatment of AD and to prevent adverse reactions such as gastrointestinal and

hepatotoxicity reactions that significantly affect therapeutic targets induced by Acetylcholinesterase inhibitors AChEIs during treatment. In the initial studies on the AChE enzyme, it was found to be involved in carrying nerve impulses from one nerve cell to another (Figure 2) [11].

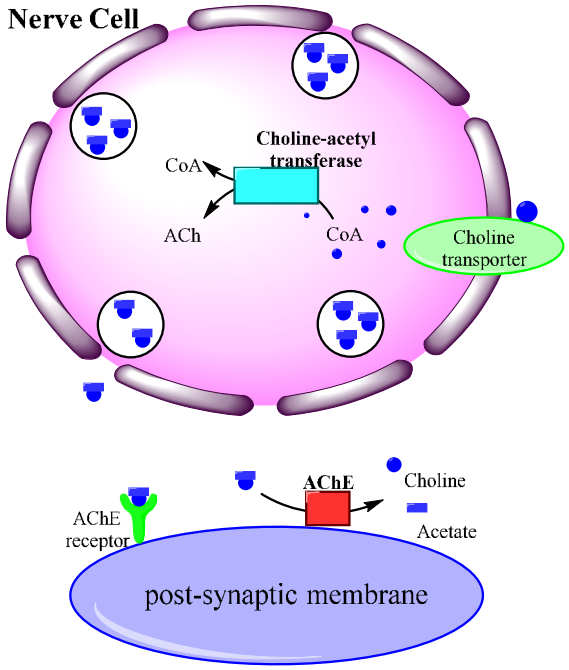

Figure 2. Function of AChE enzyme.

Without acetylcholine, our memory would not work correctly, making it difficult to focus and process information. Therefore, Alzheimer's disease is frequently linked to a deficit of this chemical. According to research, the concentration of acetylcholine in the bodies of those with this type of senile dementia patients is 73% lower than that of healthy individuals with an average level of this neurotransmitter [12].

In further studies, it has been determined that the AChE enzyme is also involved in generating bioelectrical currents along nerve and muscle fibers besides its initial function. Apart from transmitting neural signals between adjacent nerve cells in vertebrates, it also plays a role in initiating the contraction of muscle cells in response to these signals. The AChE enzyme clears harmful chemicals accumulated at the nerve terminal by breaking them down. Thus, it eliminates obstacles to electron carriers, alleviating disruptions in neural transmission. Loss of AChE enzyme function leads to the accumulation of ACh in the synaptic clefts. Consequently, conditions such as muscle paralysis, seizures, and even death can occur [13].

The body's insufficient supply of acetylcholine inhibits nerve signals and weakens muscular contractions, which can cause paralysis. Acetylcholine deficiency also impacts the development of myasthenia gravis, an autoimmune muscular disease. Next comes exhaustion, drooping eyelids, difficulty swallowing, respiratory issues, and double vision [12].

Today, acetylcholinesterase inhibitors are used as a drug class in the treatment of Alzheimer's disease, showing a certain level of success. Drugs developed as AChE inhibitors inhibit the AChE enzyme, which hydrolyzes acetylcholine, a major neurotransmitter in the central nervous system, decreasing its levels. This inhibition results in a significant regression in the patient's behavioral disturbances [14]. ACh is a neurotransmitter that facilitates communication between two nerve cells. When ACh is hydrolyzed by AChE, the transmission between nerves ceases. It has been observed that ACh is rapidly degraded in diseases related to memory loss. Inhibition of the enzyme that breaks down ACh has been found to strengthen the transmission between nerves. It has been observed that AChE drugs cause disorders such as hepatotoxicity and gastrointestinal issues. Therefore, safer natural AChE

inhibitors have come to the forefront. These inhibitors are dopaminergic, serotonergic, and adrenergic aminotetralin derivatives [15].

Quinones are plant-derived secondary metabolites [16]. Benzoquinones are compounds with critical biological functions in oxidative phosphorylation, electron transfer processes, and bioenergetic transport. They exhibit various pharmacological properties such as antiviral, anti-inflammatory, antimicrobial, and anticancer activities. These compounds are used as potential synthetic building blocks in the design and synthesis of various heterocyclic drug molecules [17].

This study investigated the effects of certain benzoquinones (Figure 3) on AChE enzyme activity.

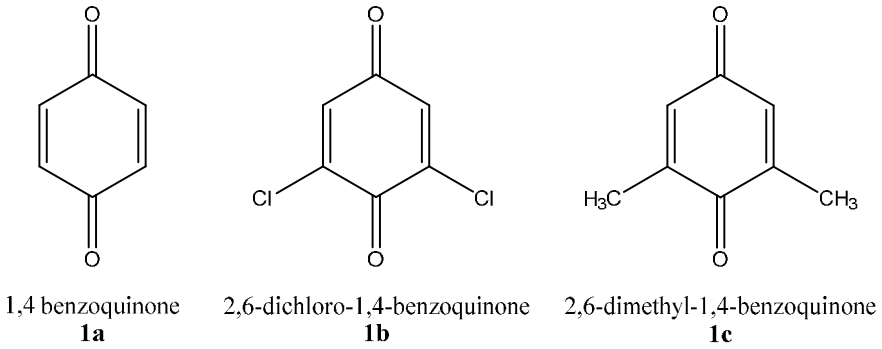

Figure 3. Chemical structures of the benzoquinones used in this study.

Materials and methods

Chemicals

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

AChE Enzyme Activity Measurement

AChE enzyme activity was assessed using a modified Ellman method version [18,19]. The inhibitory effect of benzoquinone derivatives was spectrophotometrically examined at 412 nm, employing acetylthiocholine iodide and 5,5-Dithiobis (2-nitrobenzoic) acid as substrates [20,21].

In Vitro Inhibition Studies

At least five distinct inhibitor concentrations were used to evaluate the inhibitory effects of benzoquinone derivatives on the AChE enzyme. As in our earlier research [22,23], the IC_{50} values of the benzoquinones were determined using the Activity (%) − [Compound] graphs for each derivative. The K_I values and inhibition types were found using Lineweaver and Burk curves [24-26].

Results

While the IC50 values of benzoquinone and some of its derivatives were determined from the graph given in Figure 4 for each derivative, the KI values and inhibition types were determined from the graphs given in Figure 5.

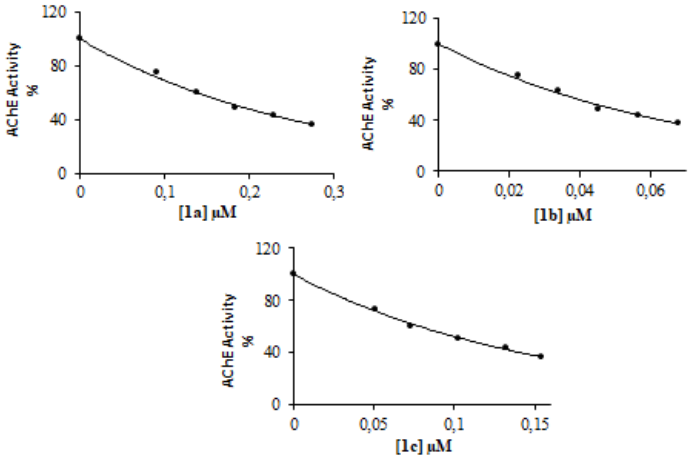

Figure 4. IC_{50} graphs of some benzoquinones on the AChE enzyme.

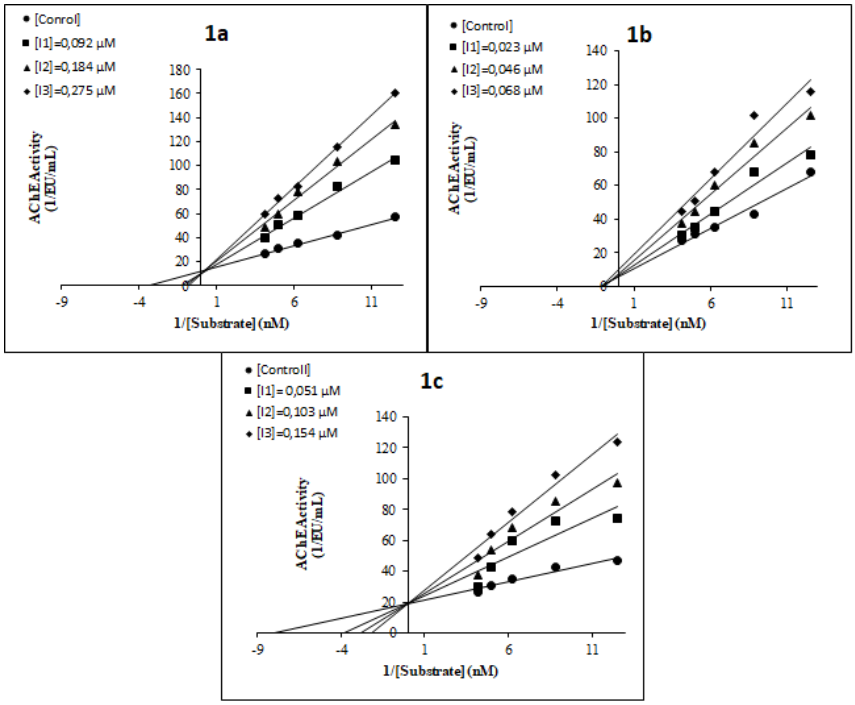

Figure 5. Lineweaver-Burk plots of some benzoquinones on the AChE enzyme.

Based on the obtained information in Table 2, the types of inhibition were determined.

Table 2. IC_{50} and KI values of benzoquinone derivatives on AChE enzyme and types of inhibition.

Inhibitor ID	Inhibitor	IC_{50} (nM)*	R2	KI (nM)*	R2
1a	1,4-benzoquinone	187 ± 0.9924	0.9978	262 ± 0.016	0.9259
1b	2,6-dichloro-1,4-benzoquinone	48 ± 0.9899	0.9964	102 ± 0.019	0.9608
1c	2,6-dimethyl-1,4-benzoquinone	106 ± 0.9946	0.9963	54 ± 0.007	0.9543

*The test results were indicated as mean ± standard error of mean.

Our results revealed compound 2,6-dimethyl-1,4-benzoquinone (1c) exhibited the highest inhibitory effect (KI: 54 ± 0.007 nm) compared to other benzoquinone derivatives. Based on the inhibition types determined for quinone derivatives (Figure 5), compound 1,4-benzoquinone (1a) and compound 2,6-dimethyl-1,4-benzoquinone (1c) exhibited competitive inhibition, while compound 2,6-dichloro-1,4-benzoquinone (1b) showed non-competitive inhibition. In addition, KM and Vmax values for specific substrates without inhibitors were calculated using the Lineweaver-Burk plots and were calculated as KM = 0.127, Vmax = 0.053.

Discussion

Numerous studies have shown selective alterations in specific neurotransmitter systems in the brains of Alzheimer's patients. The most striking abnormalities resulting from these changes involve the cholinergic system, which forms the basis of AD. The etiology and exact pathogenesis of AD are still not fully understood. The cholinergic hypothesis provides the rationale for a symptomatic treatment aiming to strengthen the central cholinergic function of AD in the hope of improving cognitive function [1]. AD associated with the cholinergic hypothesis is linked to alterations in cholinesterases such as AChE and choline acetyltransferase (ChAT). The biochemical properties of cholinesterases in the AD brain are sensitive to inhibitors, have altered optimal pH, and appear different from those in normal brains. This suggests that agents inhibiting cholinesterases may have advantages over selective AChE inhibitors [27]. Agents with a common AChE inhibition mechanism positively correlate with cognitive changes in AD patients and laboratory animals [28].

AChE's primary role is to terminate nerve signal transmission at cholinergic synapses by rapidly hydrolyzing ACh in the presynaptic region, thereby reducing the concentration of ACh. Therefore,

AChE inhibitors that inhibit or slow down the hydrolysis of ACh play a crucial role in treating various diseases such as AD, myasthenia gravis, Parkinson's disease, senile dementia, and ataxia. Currently, available synthetic drugs for the treatment of cognitive dysfunction and memory loss associated with AD include a series of AChE inhibitors such as rivastigmine, tacrine, and donepezil [29]. According to the literature, widely used synthetic AChE inhibitors have side effects such as gastrointestinal discomfort and hepatotoxicity, while sulfonamides have been shown to have no side effects [30]. Sulfonamides, which are essential bioactive compounds with many biological effects such as diuretic, antitumor, antithyroid, antibacterial, anti-carbonic anhydrase, antidiabetic, hypoglycemic, and protease inhibitor activities, are beneficial in AD [31].

Quinones are substances that take part in redox cycling activities in biological systems. These processes cause quinones to break down and produce semiquinones, single-electron compounds that subsequently generate hydroquinones, which are two-electron compounds. One electron is transferred during the reduction of quinone by nicotinamide adenine dinucleotide 2′-phosphate (NADPH): cytochrome p450 reductase. In the presence of oxygen (O_2), semiquinone is oxidized to quinone, resulting in O_2 reduction and ROS production. However, NAD(P)H quinone dehydrogenase 1 can use either NADPH or NADH as electron donors and catalyzes the two-electron reduction of quinone to hydroquinone, which generates reactive oxygen species (ROS). Reduced antioxidant pathways cause a shift towards a preoxidative state in diseased situations [32].

The information supplied indicates that research was done on how some quinones affected the AChE enzyme. 1,4 benzoquinone (1**a**) and 2,6-dimethyl benzoquinone (**1c**) showed competitive inhibition by the inhibitory types found for benzoquinone and certain derivatives. Upon analysis of these results, it becomes evident that the chemicals under investigation can cause inhibition of an enzyme via binding to the enzyme-substrate complex or the free enzyme. The methyl groups in 2,6-dimethyl benzoquinone (**1c**) were likewise shown to exhibit a substantial inhibitory impact, and based on KI values, this compound had the most inhibitory implications compared to the other compounds. Except for the groups affixed to the ring structure, the benzoquinones' chemical structures that were the inhibition investigation's focus were identical. Inhibition rates, however, differed significantly. This discovery concludes that the AChE enzyme is strongly inhibited by the presence of methyl groups linked to the benzoquinone structure. Furthermore, it is noted that compound 2,6-dichloro-1,4-benzoquinone (**1b**) has efficient inhibitory activity due to the presence of chlorine groups in it.

Significantly varied inhibition rates were found for the quinones under examination despite their nearly identical chemical structures, except for the groups linked to the ring structure. Compound 2,6-dichloro-1,4-benzoquinone (**1b**) showed a more significant inhibitory impact than the others when evaluated based on IC_{50} values, but compound **1a** demonstrated a lesser inhibitory effect. In light of this, the AChE enzyme is effectively inhibited when a methyl group is linked to the benzoquinone molecule. For every inhibitor, KI values were ascertained in addition to IC_{50} values. The *KI* values were determined as follows: 2,6-dichloro-1,4-benzoquinone (**1b**) < 2,6-dimethyl-1,4-benzoquinone (**1c**) < 1,4-benzoquinone (**1a**). These compounds, which exhibit potential inhibitory properties for AChE, were found to reduce enzyme activity at low concentrations.

Studies concentrating on inhibiting the AChE enzyme have significantly increased recently. Aydin et al.'s work [33] involved synthesizing a few pyrimidine derivative chemicals and examining their inhibitory effects. At the nanomolar level, every substance utilized in the investigation exhibited an inhibitory effect. After synthesizing imidazole-based benzenesulfonamide derivatives and analyzing their inhibitory properties, Tugrak et al. [34] found that these compounds exhibited nanomolar inhibition. Sulfaguanidine (SG1-4) and sulfisoxazole (SO1-4) derivatives were synthesized by Lolak et al. [35], who then investigated the compounds' inhibitory properties and found that they had an effect at the nanomolar level. In another study conducted by our team (2024), the impact of naphthoquinones and anthraquinones on the AChE enzyme was examined, and 1,5-dihydroxyanthraquinone was determined to be the most effective inhibitör [36].

These days, protein research is heavily concentrated, especially in antibodies, vaccinations, natural interferons, and different types of metabolic enzymes. These constituents are essential to several

pathological processes. Though medicine has benefited most from the insights acquired from these investigations, other fields have also benefited. These goods' continuous investigation and application highlight how scientific and medical research is a dynamic and ever-changing field [37].

Conclusion

Due to scientific advancements, a new era has emerged, mainly in medicine, genetics, and other health-related fields. These fields are working to understand the mechanisms behind various diseases and provide the most accurate diagnoses, allowing for promptly initiating necessary treatments. Technological developments have increased our understanding of proteins, enabling researchers to comprehend disease pathways better.

Standard chemicals employed as selective AChE inhibitors were less effective than benzoquinone and several derivatives. Because of their ability to inhibit metabolic enzymes and remove free radicals that cause cellular damage, the study may offer valuable information to the literature for synthesizing substituted molecules for inhibitory medications used to treat disorders. More potent medications can be produced based on the findings of specific investigations conducted in our laboratories. Furthermore, these chemicals might garner more attention because of their unique interactions with the targeted enzyme. This discovery may pave the way for novel pharmaceutical therapies and offers particular potential for improving therapy choices for Alzheimer's disease.

Abbreviations

AD, Alzheimer's disease; AChEIs, Acetylcholinesterase inhibitors; ACh, acetylcholine; AChE, Acetylcholinesterase; KI, Inhibition constant; IC50, concentration of inhibitor that cuts half of the activity of the enzyme; nM, nanomolar; choline acetyltransferase. ChAT; NADPH, nicotinamide adenine dinucleotide 2′-phosphate; ROS, reactive oxygen species.

Declaration of interest

The authors declare no conflict of interest.

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