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Synthesis, biological activity and docking calculations of bis-naphthoquinone derivatives from Lawsone

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ABSTRACT

Some metabolic enzyme inhibitors can be used as Multi-target-Directed-Ligands (MTDL) in Medicinal chemistry therefore, synthesis and determination of alternative inhibitors are essential. In this study, novel bis-napthoquinone derivatives **(5a-o)** were synthesized through a multi-component cascade reaction of two molecules of 2-hydroxy-1,4-naphthoquinone with an aromatic aldehyde in basic media using triethylamine as a catalyst. This novel heterocyclic derivatives **(5a-o)** are applied to inhibit the carbonic anhydrase (hCA I and hCA II) isoform in low levels of nano molecules with Ki values exist between 4.62 ± 1.01 to 70.45 ± 9.03 nM for hCA I and for hCA II which is physiologically dominant K_is values are in the range of 5.61 ± 1.04 to 73.26 ± 10.25 nM. Further these novel derivatives (**5a-o**) efficiently inhibit AChE with Ki values in the range of 0.13 ± 0.02 to 3.16 ± 0.56 nM. The compounds are also applied for BChE with Ki values varying between 0.50 ± 0.10 to 9.23 ± 1.15 nM. For α-glycosidase, the most efficient Ki values of **5e** and **5f** are 76.14 ± 9.60 and 95.27 ± 12.55 nM respectively. Finally, molecular docking calculations against enzymes (acetylcholinesterase, butyrylcholinesterase, and the human carbonic anhydrase I and II) are compared using biological activities of heterocyclic derivatives. After these calculations, an ADME/T analysis is performed to study the future medicinal use of heterocyclic derivatives from lawsone.

1. Introduction

2-Hydroxy-1,4-naphthoquinone is the principal natural dye in the leaves of henna [1]. Today, semipermanent hair dyes containing henna as well as its pure dye ingredient, widely used and has become increasingly popular due to their natural origin [2]. Naturally occurring tricyclic quinone alkaloids possess extensive biological properties ranging from antimicrobial capacity to cytotoxicity [3]. Among them, the benzo[*g*]quinoline-5,10-dione skeleton is ubiquitous in a wide variety of naturally occurring and synthetic compounds that exhibit important biological activities (Fig. 1). Thus ongoing exploration of the chemical space afforded by natural products [4] continues to be attractive means of identifying new inhibitors. A case in point is conocurvone **(1)**, [5] has been shown to an inhibitor of both HIV integrase and HIV mediated cell fusion [6] and biological active bis-naphthoquinone derivatives bilawsone **(2)** and biramentaceone **(3)** isolated from natural products [7–10]. Bis-naphthoquinones **(4)** have also been reported as anti-parasitic agents [11]. Hence, the synthesis of the benzo[*g*]imidazo[1,2-*a*]quinolinediones could be a valuable strategy to discover new bioactive compounds.

Naphthoquinone compounds have been the subjects of much interest for a number of years due to their capability as intermediates in the synthesis of heterocycle compounds [12]. Benzoxanthenes and xanthenes have been reported to possess various biochemical and therapeutic properties, such as antibacterial [13], antiviral [14], and anti-inflammatory activity [15], as well as photodynamic therapy [16]. The other useful applications of these heterocycles are as dyes [17], fluorescent materials for visualization of biomolecules [18], and in laser

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technologies [19]. Some procedures have been developed for the synthesis of aryl-5*H*-dibenzo[*b,i*]xanthene-5,7,12,14(13*H*)-tetraone and 3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-triones such as p-toluene sulfonic acid (*p*-TSA) [20], pyrrolidonium hydrogensulfate [21], (4-sulfobutyl) *tris*(4-sulfophenyl)phosphonium hydrogensulfate. Because of these significant features, there has been a continuous interest in the synthesis of these types of compounds and consequently numerous approaches have been reported for their synthesis [22].

Carbonic anhydrases (CAs) isoenzymes are metalloenzymes and responsible for the reversible hydration of carbon dioxide (CO_2) into bicarbonate (HCO_3^-). This fundamental reaction involved in various physiological and pathological processes [23,24]. In recent years, CAs have been recognized as important drug targets for different pathologies such as glaucoma, epilepsy, and cancer. The design of powerful and selective inhibitors has been an extraordinary goal leading to the discovery of new drugs [25,26].

Acetylcholine (ACh) is one of the key neurotransmitters in the human body that acts as a chemical messenger to transmit signals through the nerve synapse [27]. Disruption of central cholinergic conduction has been associated with multiple diseases, including Alzheimer's disease (AD), Parkinson's disease, schizophrenia, and epilepsy. In both the central and peripheral nervous systems, the termination of impulse conduction occurs through rapid ACh hydrolysis by the acetylcholinesterase (AChE) enzyme [28,29]. AChE converts ACh into choline and acetic acid, causing the cholinergic neuron to return to a resting state. The enzyme is inactivated by several inhibitors leading to acetylcholine accumulation and impairment of neurotransmission caused by over-stimulation of nicotinic and muscarinic receptors [30,31]. Among the many drug targets of type 2-diabetes Mellitus (T2DM), starch-digesting enzymes such as α-amylase and intestinal α-glycosidase aim to achieve inhibition of these enzymes and thus control postprandial hyperglycemia [32,33]. α-Glycosidases are digestive enzymes belonging to a family called glycosides found in the brush edge membrane of small intestine cells, which are involved in the final stage of carbohydrate digestion. These enzymes exclusively catalyze the hydrolysis of the α-1,2, α-1,4 and α-1,6-glucosidic bonds in oligosaccharides, thereby releasing absorbable monosaccharides [34,35].

Many properties of molecules can be calculated with theoretical calculations. As a result of these calculations, information about many properties of molecules is obtained. By comparing the numerical values of the parameters obtained as a result of these calculations, the biological activities of molecules can be compared [36–37]. When all these calculations are made before experimental procedures, the time to determine molecules with higher biological activity will be shorter [38]. In this direction, it saves both time and money in determining molecules with higher biological activity. The biological activities of the molecules are compared with the parameters found as a result of the calculations made by the molecular docking method. For molecular docking calculations, numerical values of biological activities against many enzymes were calculated. After these calculations, ADME/T (Absorption, Distribution, Metabolism, Excretion and Toxicity) analysis was performed for heterocyclic derivatives from Lawsone. With this analysis, the potential of this molecule to be used as a medicine was investigated. It was made to predict behaviors in human metabolism as a result of ADME/T analysis. The numerical values of these parameters provide information about their future drug availability [39,40].

The literature [41–45] discloses that rationale of some selected reported inhibitors with current work in the context of hCA I & II, AChE & BChE and α-glycosidase inhibition is shown in the Fig. 2 which possesses potential metabolic liabilities and/or moderate potencies.

AD (Alzheimer's disease) is the most complex neurodegenerative disorder challenge of 21st century which is characterized by memory impairment, speech impairment, dymentia and cognitive dysfunction. Recent studies evidenced that human carbonic anhydrases (hCAs), cholinesterase (AChE and BChE), and α-glycosidase inhibitors serve as an important target for AD treatment [44].

Keeping in view the importance of these metabolic enzymes inhibitors in biological studies along with previously reported inhibitor structures, we have decided to synthesize a series of novel fused ring heterocyclic Lawson derivatives **(5a-o)** and studied the applications against carbonic anhydrases (hCA I and II), cholinesterase (AChE and BChE), and α-glycosidase enzyme. The novel bis-napthoquinone derivatives **(5a-o)** can act as Multi-Target-Directed Ligands rather than 'one drug-one target' approach in modern Medicinal chemistry. The molecular docking study of the synthesized compounds is also reported.

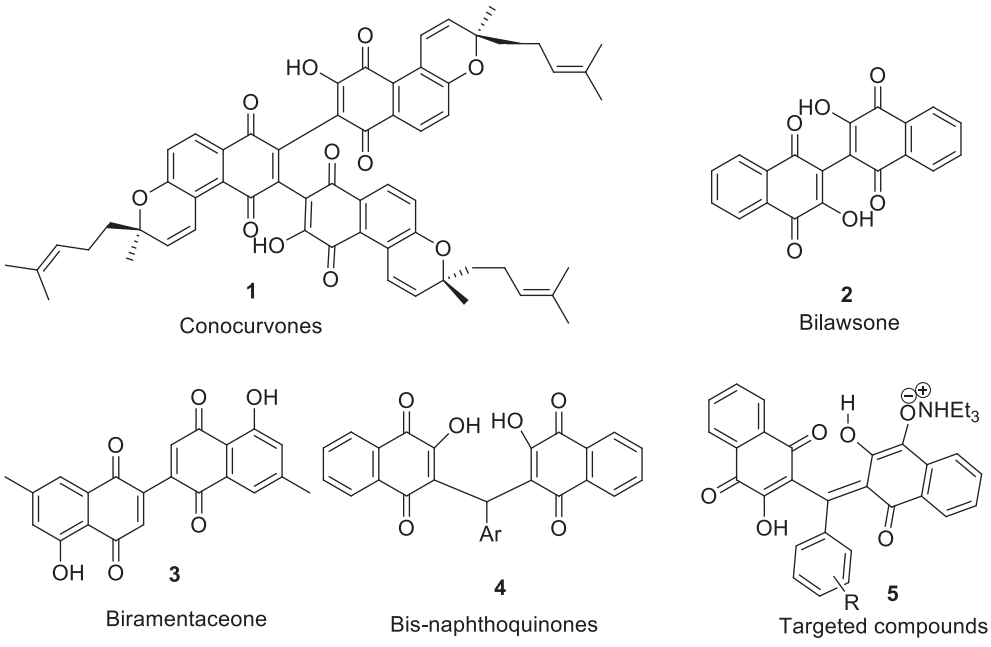


Fig. 1. Structures of naturally occurring naphthoquinone derivatives and our target compound.

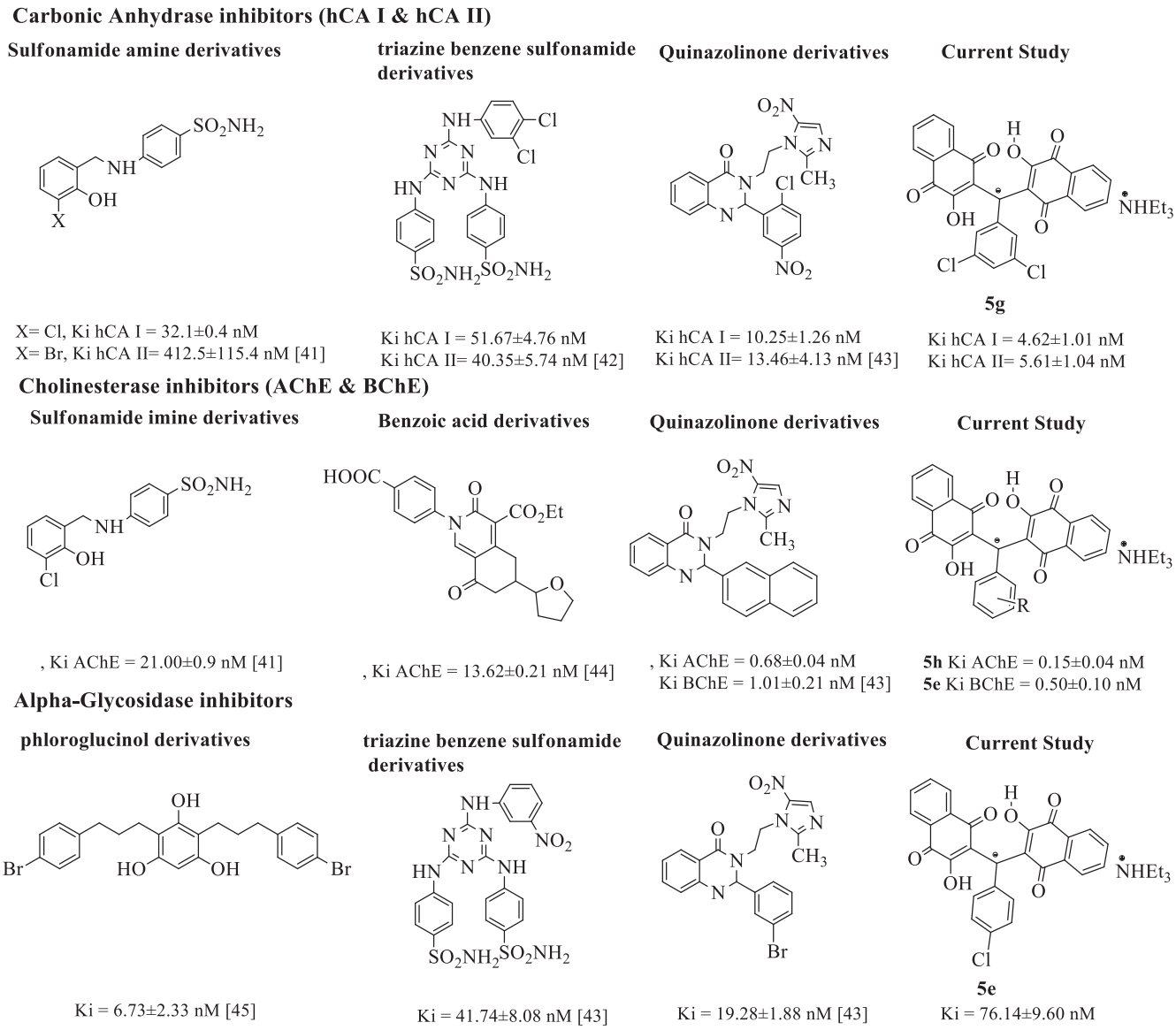


Fig. 2. Selected hCA I & II, AChE & BChE and α-Glycosidase inhibitors with current study.

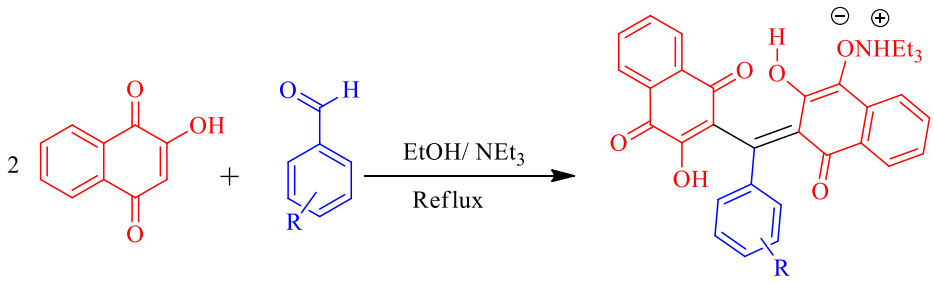
2. Result and discussion

2.1. Chemistry

Different bis-naphthoquinone **(5a-o)** were prepared by optimizing at different solvent conditions. The methodology was developed to get targeted biologically active compounds in good yield with economically and easily available precursors. Ethanol was selected as best solvent to react 2-hydroxy-1,4-naphthoquinone **(6)** with different aromatic aldehydic compounds **(7)** by using triethylamine as basic catalysts to get the targeted bis-naphthoquinone bis-naphthoquinones **(5a-o)** Scheme 1. Different substituted aldehydes yielded the different derivatives of this series in different yield which depicted the scope of the reaction and the reactivity of respective aldehydes with 2-hydroxy-1,4-naphthoquinone **(6).**

The structural formula of synthesized bis-naphthoquinone was confirmed by applying spectroscopic techniques for elucidation of structures like IR, NMR etc. The IR spectra of this series indicated the required functionalities in targeted compound. The C—H stretching and carbonyl groups were confirmed by absorption band at 3026 cm^{-1} and 1657 cm^{-1} respectively. Other functional groups in different aldehyde derivatives were also indicated with IR spectra of the respective compounds. The presence of absorption bands for C═C and aromatic region also facilitated the structure of targeted compounds. Broad absorption band at 3674 and 3157 cm^{-1} represent the existence of O—H and N—H stretching respectively in compound **(5a)**.

In ^{1}H NMR spectrum broad singlets at 14.21 ppm and 11.44 ppm confirm the presence of two OH groups as proton is attached with heteroatom of compound **5a**. These aromatic protons have been assigned according to their chemical shift with different multiplicity and oupling constant. ^{13}C NMR spectrum also confirms the aliphatic, aromatic and carbonyl carbons in respective chemical shift. Spectrum confirms the aliphatic carbons of ethyl group of ammonium ion at 8.441 ppm and 20.832 ppm of compound **5a**. ^{13}C NMR (DEPT-135) confirms the primary, secondary and tertiary carbons in targeted bis-naphthoquinone and **(5a-o)**. Elemental analysis confirms the observed percentage of elements in targeted compounds which is in good aggrement to the calculated values.



6 **7** **5a-o**

5a, R = H
5b, R = 4-Me
5c, R = 4-OMe
5d, R = 2-Cl
5e, R = 4-Cl
5f, R = 3-Cl
5g, R = 3,5-Dichloro
5h, R = 4-Br

5i, R = 4-I
5j, R = 4-NO_2
5k, R = 3-NO_2
5l, R = 2-NO_2
5m, R = 2-OH
5n, R = Oxolol
5o, R = 2-CN

Scheme 1. Synthesis of bis-naphthoquinone derivatives in basic media.

3. Biological evaluation

3.1. hCA I and II isoenzymes inhibition results

CAs have involvement in plenty of biological roles like ureagenesis, acid/base balance, gluconeogenesis, fluid secretion, and thus pH regulation, gastric acid production, and transport of CO_2 from tissue cells to the lung cells (bicarbonate form) through the blood. Due to their critical involvement in the regulation of these processes, CAs played a key role in the pathophysiology of diverse diseases like renal tubular acidosis, glaucoma, hemolytic anemia, osteoporosis, colorectal cancer, neuropathic pain, etc. [46,47]. The CA inhibitors can be therapeutic applications for the therapy of several clinical disorders. The results presented in Table 1 indicate that novel 2-hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)** had effective inhibition profile against slow cytosolic hCA I isoform. The hCA I isoform was inhibited by these novel 2-Hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)** in low nanomolar levels, the Ki of which differed between 4.62 ± 1.01 and 70.45 ± 9.03 nM. On the other hand, acetazolamide (AZA), considered being a broad-specificity CA inhibitor owing to its widespread inhibition of CAs, showed Ki value of 64.52 ± 9.45 nM against hCA I. Among the inhibitors, the **5g** and **5m** were obtained to be the excellent hCA I inhibitor with Ki of 4.62 ± 1.01 and 5.91 ± 0.92 nM, respectively. The hCA I inhibition effects of novel 2-Hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)** were found to be the greater than that of acetazolamide, which was a clinically standard CA inhibitor. For hCA I, IC_{50} values of AZA as positive control and some novel 2-Hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro -naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)**; the following order: **5g** (5.07 nM) < **5m** (6.94 nM) < **5d** (19.76 nM) < **5h** (21.45 nM) < **AZA** (68.78). Against the physiologically dominant isoform hCA II, the novel 2-hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives

Table 1
Inhibition results of novel compounds (**5a-5o**) on some metabolic enzymes.

Compounds	IC_{50} (nM)					K_i (nM)				
	hCA I	hCA I	AChE	BChE	α-Gly	hCA I	hCA II	AChE	BChE	α-Gly
5a	49.10	45.72	1.26	5.44	159.05	53.16 ± 11.43	41.55 ± 6.12	1.14 ± 0.11	5.03 ± 0.82	153.76 ± 13.67
5b	29.03	33.74	0.83	3.66	193.24	28.14 ± 3.76	30.63 ± 2.56	0.65 ± 0.13	3.24 ± 0.34	200.34 ± 25.12
5c	44.87	40.12	1.93	6.98	187.45	40.21 ± 6.84	36.81 ± 8.21	1.56 ± 0.23	6.45 ± 1.02	158.01 ± 29.10
5d	19.76	24.66	0.18	0.87	142.11	18.34 ± 3.67	21.47 ± 3.07	0.13 ± 0.02	1.14 ± 0.24	131.67 ± 22.90
5e	23.55	30.78	0.28	0.56	81.24	21.46 ± 6.82	28.15 ± 5.21	0.21 ± 0.10	0.50 ± 0.10	76.14 ± 9.60
5f	31.87	34.61	0.87	1.45	104.05	30.92 ± 6.88	37.32 ± 5.82	0.80 ± 0.08	1.32 ± 0.22	95.27 ± 12.55
5g	5.07	6.06	0.56	9.01	145.23	4.62 ± 1.01	5.61 ± 1.04	0.44 ± 0.10	9.23 ± 1.15	135.71 ± 45.12
5h	21.45	27.01	0.21	2.81	204.11	18.45 ± 5.61	25.12 ± 5.84	0.15 ± 0.04	2.41 ± 0.23	183.95 ± 24.16
5i	68.21	68.98	0.97	2.78	176.23	70.45 ± 9.03	73.26 ± 10.25	1.04 ± 0.15	2.45 ± 0.31	164.21 ± 35.71
5j	50.81	48.15	3.13	6.12	231.08	46.98 ± 3.88	50.12 ± 5.30	2.96 ± 0.34	5.98 ± 1.67	245.01 ± 56.31
5k	61.35	56.12	1.26	6.23	188.35	56.71 ± 10.23	58.21 ± 9.67	1.01 ± 0.24	5.98 ± 0.72	153.80 ± 23.67
5l	58.32	63.67	1.05	4.71	156.63	63.18 ± 14.22	60.25 ± 8.35	1.34 ± 0.12	4.20 ± 0.31	145.13 ± 27.04
5m	6.94	8.42	0.86	6.78	134.76	5.91 ± 0.92	8.03 ± 0.96	0.70 ± 0.09	6.21 ± 0.91	126.03 ± 26.91
5n	45.56	38.41	3.78	7.33	256.27	42.67 ± 4.76	35.02 ± 4.72	3.16 ± 0.56	6.92 ± 1.05	223.72 ± 40.52
5o	36.88	41.57	2.90	5.13	189.64	33.68 ± 4.61	44.72 ± 11.10	2.56 ± 0.32	5.01 ± 0.65	211.25 ± 17.08
AZA	68.78	81.33	–	–	–	64.52 ± 9.45	75.36 ± 11.31	–	–	–
TAC	–	–	4.21	9.66	–	–	–	4.64 ± 1.11	9.88 ± 1.27	–
ACR*	–	–	–	–	866.30	–	–	–	–	851.16 ± 68.2

* Acarbose (ACR), AZA, TAC, and ACR were as standard compounds for carbonic anhydrases, cholinesterases, and α-glycosidase enzymes, respectively).

(5a-o) demonstrated K_is varying from 5.61 ± 1.04 to 73.26 ± 10.25 nM (Table 1). These novel 2-hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)** were observed to have high inhibition effects toward hCA II isoenzymes. On the other hand, standard compound AZA showed Ki of 75.36 ± 11.31 nM against hCA II. The **5g** and **5m** had shown the most inhibition effect with Ki values of 5.61 ± 1.04 and 8.03 ± 0.96 nM, respectively. For hCA II, IC_{50} values of AZA as positive control and some novel compounds synthesized in this study; the following order: **5g** (6.06 nM) < **5m** (8.42 nM) < **5d** (24.66 nM) < **AZA** (81.33 nM). The active site of CA contains a zinc ion bound with the hydroxide ion (OH^-) and shares the same catalytic activity. The CA enzyme has three histidine residues (His 94, His 96 and His 119), and the side chain residues form coordinate bonds with the zinc ion. The active site of CA contains a special pocket for CO_2, and the first step in its catalysis action involves the nucleophilic attack of the zinc-bound hydroxide ion on CO_2. The most active classes of CAIs identified today are the sulfonamides and their bioisosters, sulphamates and sulfamides [48,49].

3.1.1. AChE inhibition results

The important group of drugs used for the therapy of AD is cholinesterase inhibitors (ChE-Is). The first ChE-I recorded for symptomatic therapy of AD was tacrine. The ChE-Is currently available in the market are rivastigmine, donepezil, and galantamine as tacrine is no longer in use, due to its hepatotoxicity [50]. Indeed, conforming to mechanism of action the ChE-Is classified as short-acting or reversible agents such as tacrine, donepezil, and galantamine, as intermediate-acting or pseudo-irreversible factor like rivastigmine [51,52]. All of novel 2-hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)** had significantly higher AChE inhibitory activity than that of standard AChE inhibitors such as Tacrine. Furthermore, the Ki values of novel 2-hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)** and standard compound (tacrine) are summarized in Table 1. As can be seen from the results obtained in Table 1, these novel 2-hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)** effectively inhibited AChE, with Ki values in the range of 0.15 ± 0.04 to 3.16 ± 0.56 nM. However, all of these novel derivatives (**5a-o**) had almost similar inhibition profiles. The most active **5h** showed Ki values of 0.15 ± 0.04 nM. For AChE, IC_{50} values of TAC as positive control and some novel compounds were studied in this study the following order: **5d** (0.18 nM) < **5h** (0.21 nM) < **5e** (0.28 nM) < **TAC** (4.21 nM). For BChE, IC_{50} values of TAC as positive control and novel 2-hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)** the following order: **5e** (0.56 nM) < **5d** (0.87 nM) < **5f** (1.45 nM) < **TAC** (9.66 nM). Additionally, the novel compounds effectively inhibited BChE, with Ki values in the range of 0.50 ± 0.10 to 9.23 ± 1.15 nM. However, all of these novel 2-Hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)** had almost similar inhibition profiles. The most active **5e** and **5d** effectively inhibited BChE, with Ki values of 0.50 ± 0.10 to 1.14 ± 0.24 nM. AChE inhibitors are the most promising therapeutics for AD treatment as these prevent the loss of ACh and slow the progression of the disease [53].

3.1.2. α-Glycosidase inhibition results

Type-2 diabetes mellitus can be successfully treated with α-glycosidase inhibitors that have the ability to delay and reduce postprandial blood glucose levels. α-Glycosidase plays a role in carbohydrate metabolism and has an important function in diabetes, cancer and viral infections [54]. This metabolic enzyme has various biological activities and is considered an attractive drug target. Currently, a number of α-glycosidase inhibitors have been discovered and studied. Anti-diabetic drugs used in clinical practice, like voglibose, acarbose, and miglitol, competitively inhibit α-glycosidase in the brush edge of the small intestine, which then interrupt the hydrolysis of carbohydrate and ameliorate postprandial hyperglycemia [55,56]. For enzyme glycosidase, novel 2-hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)** have IC_{50} values in the range of 81.24–256.27 nM and Ki in the range of 76.14 ± 9.60–245.01 ± 56.31 nM (Table 1). The results have clearly documented that all of these novel 2-hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)** have shown the inhibitory effects of α-glycosidase efficient acarbose (IC_{50}: 866.30 nM) as a standard glycosidase inhibitor. In fact, the most effective Ki values of **5e** and **5f** were with Ki values of 76.14 ± 9.60 and 95.27 ± 12.55 nM, respectively. For α-glycosidase, IC_{50} values of ACR as positive control and some novel 2-hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)** the following order: **5e** (81.24 nM) < **5f** (104.05 nM) < **5m** (134.76 nM) < **ACR** (866.30 nM).

4. Docking studies

Nowadays, with the spread of theoretical studies, molecules docking have begun to be used to compare the biological activities of molecules. With molecular docking calculations, it has become easier to discover more active and effective molecules before experimental studies. It has been observed that the results of the theoretical calculations and the experimental results are in great harmony with each other [57]. The biological activities of the molecules are compared with the parameters found by molecular docking calculations. A comparison is made with the numerical value of these parameters. These parameters are given in Table 2.

As a result of molecular docking calculations, the most important parameter among many parameters calculated to compare the biological activity of molecules is the Docking score. With the numerical value of this parameter, the biological activities of molecules are interpreted. It should be well known that the molecule with the most negative numerical value of this parameter of heterocyclic derivatives from Lawsone has the highest biological activity value. In molecular docking calculations, it is seen that as the interaction between molecules and enzymes increases, the biological activity values of molecules increase [58–61]. These interactions have many interactions such as hydrogen bonds, polar and hydrophobic interactions, π-π and halogen [62–65]. These interactions are given in Figs. 3, 4, 5, 6, and 7. In the molecular docking calculations made, many parameters are calculated except the docking scores parameter. These parameters are used to describe the type and amount of interactions such as Glide H-bond, Glide evdw, and Glide ecoul [57]. Apart from these, there are parameters such as Glide emodel, Glide energy, Glide einternal, and Glide posenum that provide information about the exposure between molecule and enzyme [74].

After the molecular docking calculations made, ADME/T analysis was performed for the molecules to be used as drugs in the future. With this analysis, he theoretically examines the effects and responses of molecules when heterocyclic derivatives from Lawsone enter human metabolism as a drug. As a result of the AMDE/T analysis, many parameters were obtained and these are given in the Table 3. Each parameter obtained numerical values of the reactions of molecules in different tissues and organs are obtained. These numerical values are valued and guide future experimental studies. The two most important parameters among the parameters found are RuleOfFive [66–67] and RuleOfThree [68]. These two parameters are very important as they contain many parameters. Apart from these, there are also two important parameters such as QPPCaco and QPPMDCK. The QPPCaco

Table 2
Numerical values of the docking parameters of molecule against enzymes.

AChE	Docking Score	Glide ligand efficiency	Glide hbond	Glide evdw	Glide ecoul	Glide emodel	Glide energy	Glide einternal	Glide posenum
5a	–	–	–	–	–	–	–	–	–
5b	−2.35	−0.06	−0.16	−12.84	4.66	−14.70	−8.18	20.79	159
5c	−3.22	−0.08	−0.14	−23.37	5.10	−23.35	−18.27	22.12	395
5d	−5.49	−0.14	0.00	−34.69	−5.13	−28.07	−39.82	37.08	77
5e	–	–	–	–	–	–	–	–	–
5f	−3.17	−0.08	−0.06	−31.77	7.66	−22.04	−24.11	20.12	171
5g	−2.98	−0.07	0.00	−31.25	2.23	4.02	−29.02	67.78	165
5h	–	–	–	–	–	–	–	–	–
5i	–	–	–	–	–	–	–	–	–
5j	–	–	–	–	–	–	–	–	–
5k	–	–	–	–	–	–	–	–	–
5l	−3.02	−0.07	0.00	−27.16	0.29	−7.39	−26.86	63.05	359
5m	–	–	–	–	–	–	–	–	–
5n	–	–	–	–	–	–	–	–	–
5o	–	–	–	–	–	–	–	–	–
BChE	Docking Score	Glide ligand efficiency	Glide hbond	Glide evdw	Glide ecoul	Glide emodel	Glide energy	Glide einternal	Glide posenum
5a	0.35	0.01	0.00	−17.61	1.12	−9.16	−16.49	17.46	346
5b	−1.03	−0.03	0.00	−9.58	−2.77	−4.08	−12.35	24.81	60
5c	−1.07	−0.03	−0.06	−16.56	−1.57	−15.51	−18.12	19.92	87
5d	−1.16	−0.03	−0.32	−20.82	−3.62	−15.43	−24.44	24.40	151
5e	−1.71	0.02	0.00	−25.70	−4.52	−15.46	−26.21	27.02	40
5f	−1.12	−0.03	0.00	−17.53	−2.15	2.84	−19.68	45.79	369
5g	−0.80	−0.02	0.00	−11.14	−0.98	6.95	−12.12	58.40	331
5h	–	–	–	–	–	–	–	–	–
5i	–	–	–	–	–	–	–	–	–
5j	−0.75	−0.02	0.00	−26.22	−2.95	−19.56	−29.17	19.73	320
5k	0.02	0.00	0.00	−14.12	0.57	−10.59	−13.55	7.03	263
5l	−0.27	−0.01	0.00	−14.76	−2.03	9.83	−16.79	53.34	389
5m	–	–	–	–	–	–	–	–	–
5n	–	–	–	–	–	–	–	–	–
5o	−0.57	−0.01	0.00	−18.96	0.06	−6.34	−18.91	25.76	325
α-Gly	Docking Score	Glide ligand efficiency	Glide hbond	Glide evdw	Glide ecoul	Glide emodel	Glide energy	Glide einternal	Glide posenum
5a	–	–	–	–	–	–	–	–	–
5b	−1.17	−0.03	0.00	−21.17	−0.04	−16.61	−21.21	24.21	357
5c	−0.58	−0.01	0.00	−20.51	−0.63	−6.50	−21.14	29.65	42
5d	−1.65	−0.04	0.00	−19.65	−4.66	−6.91	−24.30	37.22	319
5e	−2.29	0.01	0.00	−25.77	−5.87	−18.67	−24.91	21.11	12
5f	0.89	0.02	0.00	−21.75	0.00	−10.49	−21.75	23.77	2
5g	0.26	0.01	0.00	−26.29	−1.64	−17.52	−27.94	23.90	58
5h	0.73	0.02	0.00	−21.27	−0.05	−8.63	−21.32	25.97	194
5i	–	–	–	–	–	–	–	–	–
5j	−0.01	0.00	0.00	−10.97	−1.35	−4.04	−12.32	23.79	46
5k	−0.44	−0.01	0.00	−24.23	−5.20	9.89	−29.43	81.28	142
5l	–	–	–	–	–	–	–	–	–
5m	–	–	–	–	–	–	–	–	–
5n	–	–	–	–	–	–	–	–	–
5o	–	–	–	–	–	–	–	–	–
hCA I	Docking Score	Glide ligand efficiency	Glide hbond	Glide evdw	Glide ecoul	Glide emodel	Glide energy	Glide einternal	Glide posenum
5a	−3.43	−0.09	0.00	−17.21	1.84	−15.56	−15.38	22.51	182
5b	−5.33	−0.13	0.00	−14.52	1.23	−21.48	−13.29	26.41	218
5c	–	–	–	–	–	–	–	–	–
5d	−2.95	−0.07	−0.16	−29.35	0.73	−23.93	−28.61	37.97	180
5e	−4.35	−0.11	0.00	−16.74	0.59	−6.44	−16.15	23.32	76
5f	–	–	–	–	–	–	–	–	–
5g	–	–	–	–	–	–	–	–	–
5h	−3.99	−0.10	0.00	−16.76	1.16	−10.85	−15.60	25.45	15
5i	–	–	–	–	–	–	–	–	–
5j	–	–	–	–	–	–	–	–	–
5k	–	–	–	–	–	–	–	–	–
5l	–	–	–	–	–	–	–	–	–
5m	−0.80	−0.02	0.00	−31.32	−2.30	−25.78	−33.63	24.71	14
5n	–	–	–	–	–	–	–	–	–
5o	−2.46	−0.06	−0.03	−23.53	−0.90	−4.27	−24.43	51.42	26
hCA II	Docking Score	Glide ligand efficiency	Glide hbond	Glide evdw	Glide ecoul	Glide emodel	Glide energy	Glide einternal	Glide posenum
5a									
5b									
5c									
5d	−2.19	−0.05	0.00	−19.84	−2.20	1.73	–22.04	56.88	9
5e	–	–	–	–	–	–	–	–	–
5f	–	–	–	–	–	–	–	–	–

(*continued on next page*)

Table 2 (*continued*)

AChE	Docking Score	Glide ligand efficiency	Glide hbond	Glide evdw	Glide ecoul	Glide emodel	Glide energy	Glide einternal	Glide posenum
5g	–	–	–	–	–	–	–	–	–
5 h	–	–	–	–	–	–	–	–	–
5i	–	–	–	–	–	–	–	–	–
5j	–	–	–	–	–	–	–	–	–
5k	–	–	–	–	–	–	–	–	–
5l	–	–	–	–	–	–	–	–	–
5m	–	–	–	–	–	–	–	–	–
5n	–	–	–	–	–	–	–	–	–
5o	0.14	0.00	−0.11	−21.39	3.05	−12.25	−18.34	25.19	323

Fig. 3. Presentation interactions of molecule **5d** with AChE enzyme.

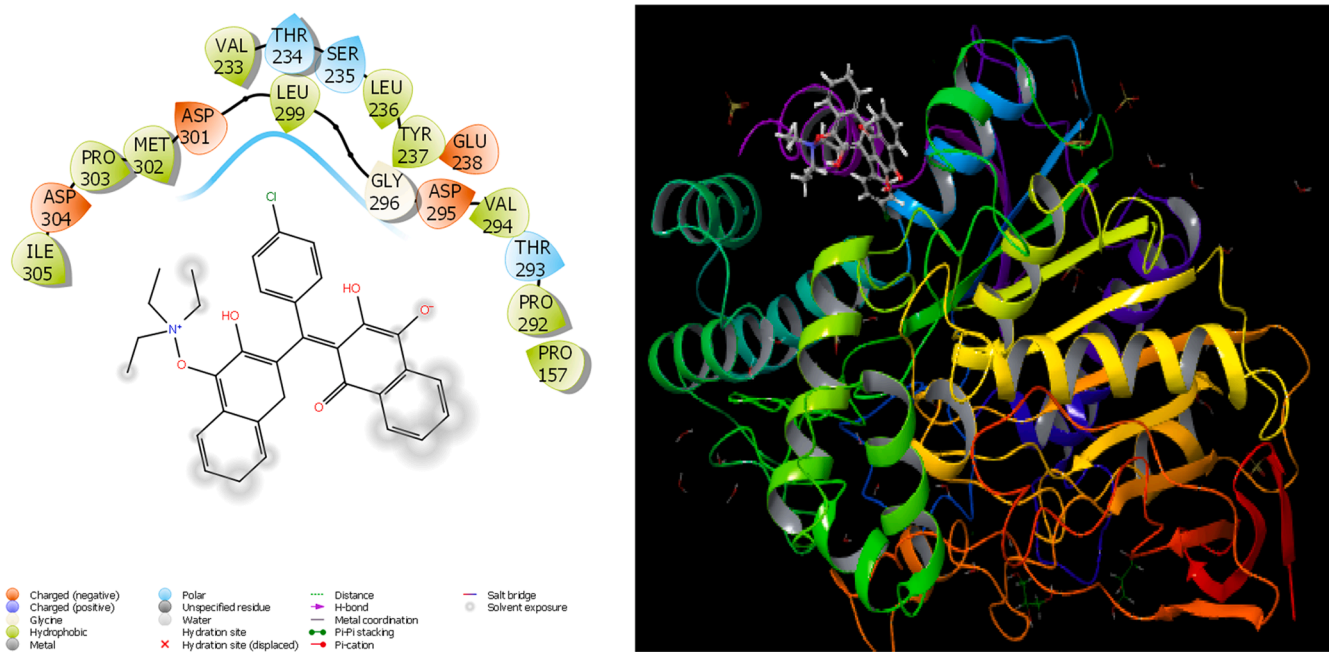


Fig. 4. Presentation interactions of molecule **5e** with BChE enzyme.

parameter indicates the passage of molecules from the gut-blood cell in nm/*sec*. On the other hand, the parameter of QPPMDCK shows the passage of the brain-blood barrier in nm/*sec* unit.

5. Conclusion

In the present study, a series of fifteen bis-naphthoquinone derivatives were synthesized and their structures were confirmed by

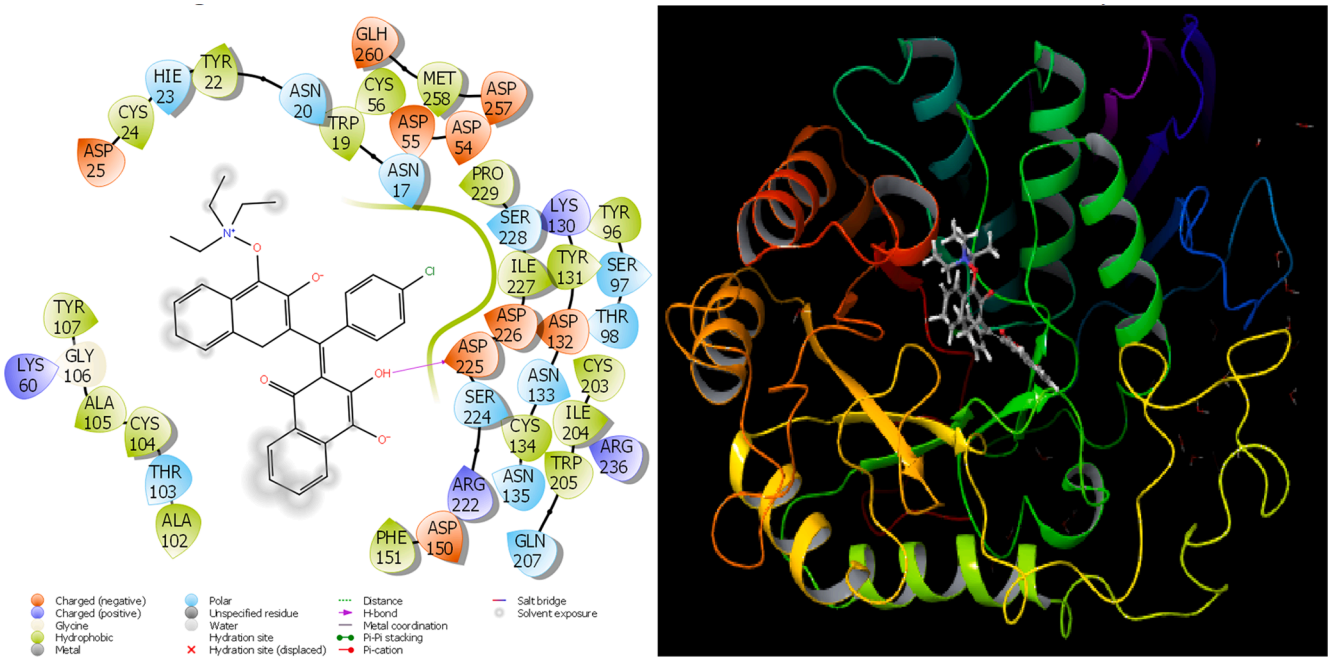


Fig. 5. Presentation interactions of molecule **5e** with α-Gly enzyme.

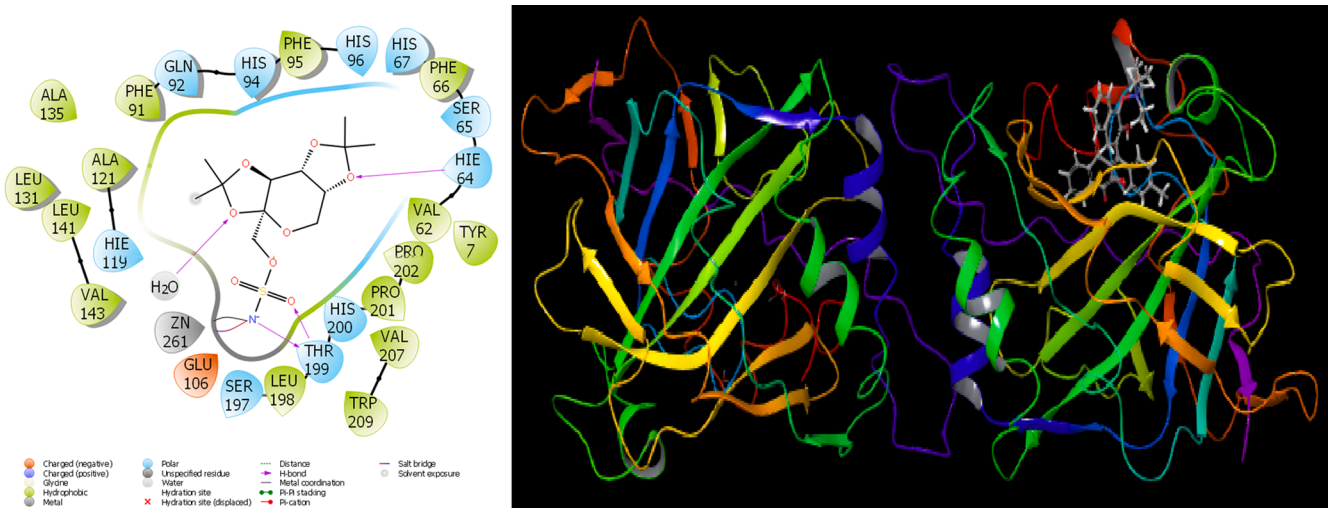


Fig. 6. Presentation interactions of molecule **5b** with hCA I enzyme.

different spectral techniques. The novel compounds **(5a-o)** reported here were tested against several metabolic enzymes such as carbonic anhydrases (hCA I and II), cholinesterase (AChE and BChE), and α-glycosidase. Among the series, the compound **5g** showed great inhibition potency against hCA I and hCA II with Ki of 4.62 ± 1.01 and 5.61 ± 1.04 nM respectively. For AChE inhibition the compound **5h** displayed higher potency as compared with other derivatives with Ki of 0.15 ± 0.04 nM and compound **5e** showed high potency for BChE with Ki value 0.50 ± 0.10 nM. On the other hand, α-GLY was also greatly inhibited by most of the compounds, but **5e** was the best compound to inhibit this enzyme among them with a Ki of 76.14 ± 9.60 nM. One of the most important findings of the current study is that all of the synthesized compounds showed a better inhibition profile than the used standard drugs ACR, TAC, and AZA for the enzymes α-GLY, AChE, BChE, hCA I and II respectively. Further molecular docking studies were also carried out to discover the harmony between theoretical calculations and experimental findings. Later, after examining the interactions of these derivatives from Lawsone with enzymes, ADME/T analysis was performed to investigate the drug properties. As a result of this analysis, it is thought that the use of **5g, 5m, 5d, 5h, 5f** and **5e** molecules of bis-naphthoquinone derivatives are theoretically appropriate for further experimental studies. In future studies, these compounds **(5a-o)** have the potential to be used in further research for the treatment of many diseases such as diabetes, Alzheimer's disease, heart failure, ulcer, and epilepsy.

6. Experimental

6.1. Materials and methods

All chemicals and solvents were purchased from Aldrich, Fluka, and Merck-Schuchatdt. These novel synthesized compounds were synthesized through the optimized procedure. Melting points were determined on cover slips by using a Fisher-Johns melting point apparatus and are

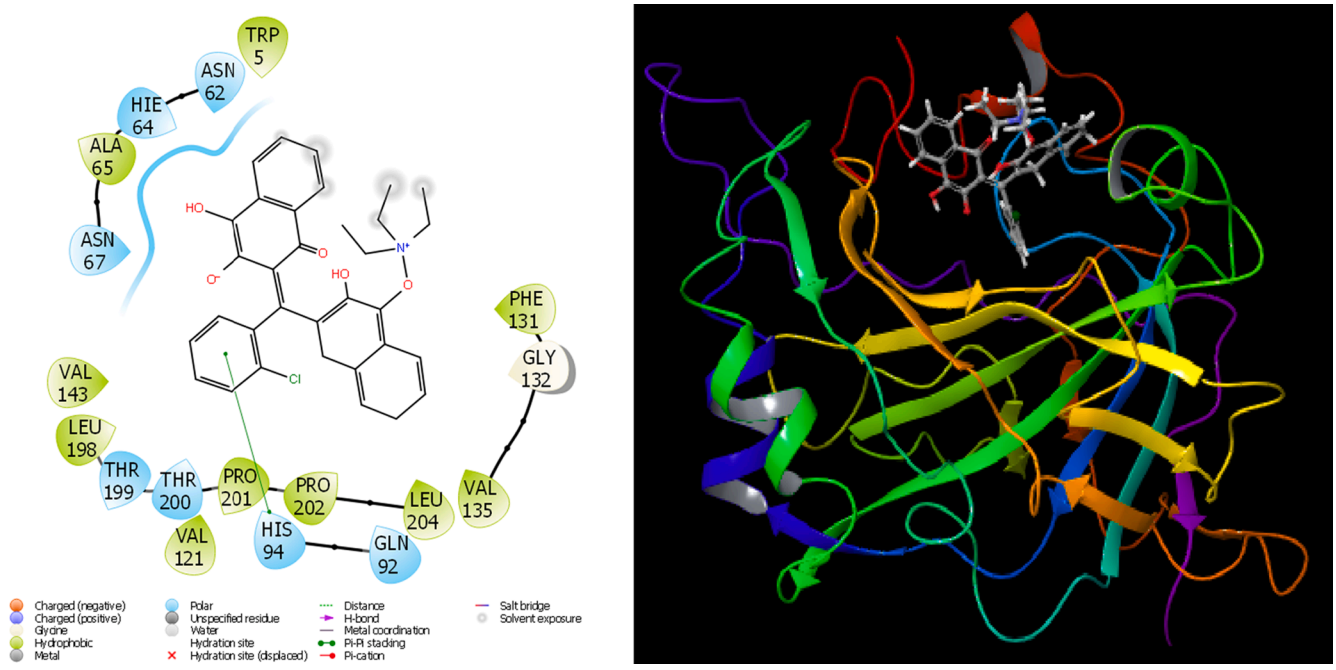


Fig. 7. Presentation interactions of molecule **5g** with hCA II enzyme.

Table 3
ADME properties of molecule.

	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	5m	5n	5o	Referance Range
mol_MW	–	–	–	–	–	–	–	–	569	569	569	569	–	–	–	130–725
dipole (D)	–	–	–	–	–	–	–	–	23.1	23.1	19.6	14.2	–	–	–	1.0–12.5
SASA	–	–	–	–	–	–	–	–	790	790	790	769	–	–	–	300–1000
FOSA	–	–	–	–	–	–	–	–	257	257	257	255	–	–	–	0–750
FISA	–	–	–	–	–	–	–	–	195	195	195	148	–	–	–	7–330
PISA	–	–	–	–	–	–	–	–	338	338	338	366	–	–	–	0–450
WPSA	–	–	–	–	–	–	–	–	0	0	0	0	–	–	–	0–175
volume (A^3)	–	–	–	–	–	–	–	–	1563	1563	1564	1541	–	–	–	500–2000
donorHB	–	–	–	–	–	–	–	–	2	2	2	2	–	–	–	0–6
accptHB	–	–	–	–	–	–	–	–	7.3	7.3	7.3	7.3	–	–	–	2.0–20.0
glob (Sphere = 1)	–	–	–	–	–	–	–	–	0.8	0.8	0.8	0.8	–	–	–	0.75–0.95
QPpolrz (A^3)	–	–	–	–	–	–	–	–	52.6	52.6	52.6	52.0	–	–	–	13.0–70.0
QPlogPC16	–	–	–	–	–	–	–	–	16.8	16.8	16.8	16.4	–	–	–	4.0–18.0
QPlogPoct	–	–	–	–	–	–	–	–	29.5	29.5	28.2	26.3	–	–	–	8.0–35.0
QPlogPw	–	–	–	–	–	–	–	–	12.9	12.9	12.9	12.7	–	–	–	4.0–45.0
QPlogPo/w	–	–	–	–	–	–	–	–	5.0	5.0	5.0	5.2	–	–	–	−2.0–6.5
QPlogS	–	–	–	–	–	–	–	–	−6.1	−6.1	−6.1	−5.7	–	–	–	−6.5–0.5
CIQPlogS	–	–	–	–	–	–	–	–	−9.2	−9.2	−9.2	−9.2	–	–	–	−6.5–0.5
QPlogHERG	–	–	–	–	–	–	–	–	−6.0	−6.0	−6.0	−5.9	–	–	–	*
QPPCaco (nm/*sec*)	–	–	–	–	–	–	–	–	141	141	139	393	–	–	–	**
QPlogBB	–	–	–	–	–	–	–	–	−2.0	−2.0	−2.0	−1.5	–	–	–	−3.0–1.2
QPPMDCK (nm/*sec*)	–	–	–	–	–	–	–	–	60	60	59	180	–	–	–	**
QPlogKp	–	–	–	–	–	–	–	–	−2.9	−2.9	−2.9	−1.9	–	–	–	Kp in cm/hr
IP (ev)	–	–	–	–	–	–	–	–	5.9	5.9	5.9	6.0	–	–	–	7.9–10.5
EA (eV)	–	–	–	–	–	–	–	–	1.9	1.9	1.9	1.9	–	–	–	−0.9–1.7
#metab	–	–	–	–	–	–	–	–	6	6	6	6	–	–	–	1–8
QPlogKhsa	–	–	–	–	–	–	–	–	0.9	0.9	0.9	0.9	–	–	–	−1.5–1.5
Human Oral Absor.	–	–	–	–	–	–	–	–	3	3	3	2	–	–	–	–
Per. Human Oral Absor.	–	–	–	–	–	–	–	–	82	82	82	78	–	–	–	***
PSA	–	–	–	–	–	–	–	–	131	131	131	121	–	–	–	7–200
RuleOfFive	–	–	–	–	–	–	–	–	1	1	1	2	–	–	–	Maximum is 4
RuleOfThree	–	–	–	–	–	–	–	–	1	1	1	1	–	–	–	Maximum is 3
Jm	–	–	–	–	–	–	–	–	0.0	0.0	0.0	0.0	–	–	–	–

* corcern below −5.

** a < 25 is poor and a > 500 is great.

*** b < 25 is poor and b > 80 is high.

uncorrected. Elemental (C, H, N) analyses were performed on a Leco CHNS-9320 (USA) elemental analyzer and were in full agreement with the proposed structures within ± 0.4% of the theoretical limits, except where noted otherwise. Infrared (IR) spectra (KBr discs) were run on Shimadzu Prestige-21 FT-IR spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in DMSO-d_6 on Bruker (Rhenistetten-Forchheim, Germany) AM 300 spectrometer, operating at 300 MHz and using TMS as an internal standard. The chemical shifts (δ) are reported in parts per million (ppm) and coupling constants in Hz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 300 MHz with the same internal standard. The progress of the reaction and purity of the products were checked on TLC plates coated with Merck silica gel 60 $GF_{254,}$ and the spots were visualized under ultraviolet light at 254 and 366 nm and / or spraying with iodine vapours.

7. Synthesis of tetriethyl-ammonium salts of bis-naphthoquinone derivatives; (5a-o)

2-hydroxy-1,4-naphthoquinone (2 eq, 0.57 mmol) was dissolved in EtOH along with triethylamine (1 eq) and reaction material was stimulated for 5 mins at room temperature. Then appropriate benzaldehyde (1 eq, 0.28 mmol) was added and the reaction mixture was warmed to reflux for 6 h. After sometime course of the reaction was monitored with the help of TLC to make sure that aromatic aldehyde is consumed. The crude material was cooled and filtered at room conditions to get crude solid material. Crude mixture was purified by washing with ethanol (2 × 5 mL) and dried to get pure desired product.

*7.1. 2-Hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-p-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium; (**5a**)*

Yield, 75%; Dark yellow solid; Solubility ($CHCl_3$); with M.P. 220–222 °C; **IR (KBr, cm^{-1}),** 3655, 3597, 3049, 3024, 2967, 2985, 1705, 1611, 983, 945; **^{1}H NMR (300 MHz, $CDCl_3$); δ, ppm,** 14.19 (broad singlet, OH,1H),11.39 (broad singlet, OH, 1H), 8.20 (dd, H-C_5& C_8,2H, *J* = 7.6 Hz, 0.9 Hz), 8.01 (dd, H—C′$_5$& C′$_8$, 2H, *J* = 6.2 Hz, 1.3 Hz), 7.71 (td, H-C_6 & C_7,2H, *J* = 7.5 Hz, 1.5 Hz),7.59 (td, H—C′$_6$& C′$_7$,2H, *J* = 7.5 Hz, 1.5 Hz),7.14 (d, H-Ph,2H, *J* = 8.1 Hz), 6.96 (d, H-Ph,2H, *J* = 8.1 Hz), 6.88 (singlet, H-$^+$NHEt$_3$,1H), 2.99 (q, H-CH_2,6H, *J* = 7.5 Hz), 2.25 (singlet, H-Methyl group,3H),1.09 (t, H-CH_3,9H, 7.3 Hz); **^{13}C NMR (400 MHz, $CDCl_3$); δ, ppm,** 185.02, 184.01, 161.99, 138.02, 134.03, 133.56, 132.99, 131.71, 130.98, 129.04, 127.19, 126.78, 125.29, 124.10, 76.97, 45.80, 33.49, 21.01, 8.44; **^{13}C NMR (400 MHz, DEPT-135, $CDCl_3$); δ, ppm,**+133.76, +131.67, +128.35, +127.21, +126.88, +125.34, −45.81, +33.54, +20.84, +8.45. **MS (ESI)** m/e: 538.60 [M + H]$^+$, Anal. Calcd for $C_{33}H_{31}NO_6$ (%): C, 73.73; H, 5.81; N, 2.61; found (%): C, 73.65; H, 5.76; N, 2.52.

*7.2. 2-Hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-phenyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium; (**5b**)*

Yield, 78%; Orange red solid; Solubility ($CHCl_3$); with M.P. 205–207 °C; **IR (KBr, cm^{-1}),** 3651, 3586, 3169, 3010, 1667, 1603, 992, 956; **^{1}H NMR (300 MHz, $CDCl_3$); δ, ppm,** 14.19 (broadsinglet, OH,1H),11.39 (broadsinglet, OH,1H), 8.19 (dd, H-C_5& C_8, 2H, *J* = 6.4 Hz, 0.7 Hz), 7.99 (dd, H—C′$_5$& C′$_8$, 2H, *J* = 6.2 Hz, 1.3 Hz), 7.69 (td, H-C_6& C_7, 2H, *J* = 6.3 Hz, 1.2 Hz),7.59 (td, H—C′$_6$& C′$_7$, 2H, *J* = 6.3 Hz, 1.1 Hz),7.29 (d, H-Ph,2H, *J* = 7.9 Hz), 7.17 (t, H-Ph,2H, *J* = 7.8 Hz), 7.03 (t, H-Ph, 1H, *J* = 7.1 Hz), 6.89 (singlet, H-$^+$NHEt$_3$,1H), 2.94 (q, H-CH_2, 6H, *J* = 7.3 Hz),1.09 (t, H-CH_3,9H, 7.3 Hz); **^{13}C NMR (400 MHz, $CDCl_3$); δ, ppm,** 185.02, 184.09, 134.10, 133.43, 132.12, 129.95, 128.13, 127.65, 127.07, 125.25, 125.02, 123.32, 76.78, 46.13, 34.05, 8.53; **^{13}C NMR (400 MHz, DEPT-135, $CDCl_3$); δ, ppm,** +133.83, +131.76, +127.78, +127.29, +126.90, +125.40, +124.84, −45.83, +33.10, +8.47. **MS (ESI)** m/e: 552.63 [M + H]$^+$, Anal. Calcd for $C_{34}H_{33}NO_6$ (%): C, 74.03; H, 6.03; N, 2.54; found (%):C, 74.01; H, 6.02; N, 2.49.

*7.3. 2-Hydroxy-3-[(3-hydroxy-1,4-dihydro-naphthalen-2-yl)-(4-methoxy-phenyl)-methylene]-4-oxo-3,4-dihydro-naphthalene-1-olatetriethylammonium; (**5c**)*

Yield, 65%; Ruby red solid; Solubility ($CHCl_3$); with M.P. 210–212 °C; **IR (KBr, cm^{-1}),** 3640, 3612, 3182, 3023, 2947, 1672, 1604, 998, 961; **^{1}H NMR (300 MHz, $CDCl_3$); δ, ppm,** 14.19 (broadsinglet, OH,1H),11.39 (broadsinglet, OH,1H), 8.20 (d, H-C_5& C_8, 2H, *J* = 7.7 Hz), 8.02 (d, H—C′$_5$& C′$_8$, 2H, *J* = 7.5 Hz), 7.64 (t, H-C_6& C_7, 2H, *J* = 7.5 Hz),7.55 (t, H—C′$_6$& C′$_7$,2H, *J* = 7.5 Hz),7.20 (d, H-Ph,2H, *J* = 7.9 Hz), 6.84 (singlet, H-$^+$NHEt$_3$,1H,), 6.69 (d, H-Ph,2H, *J* = 7.9 Hz), 3.73 (singlet, H-OMethyl,3H,), 2.99 (q, H-CH_2,6H, *J* = 7.1 Hz),1.09 (t, H-Me,9H, 7.3 Hz); **^{13}C NMR (400 MHz, $CDCl_3$); δ, ppm,** 184.99, 184.03, 162.67, 156.87, 134.21, 133.54, 132.87, 131.53, 130.78, 127.98, 127.09, 124.56, 123.91, 112.97, 76.89, 55.29, 45.67, 33.09, 8.32; **^{13}C NMR (400 MHz, DEPT-135, $CDCl_3$); δ, ppm,** +133.78, +131.68, +128.24, +126.90, +125.35, +113.17, +77.24, +55.39, −45.87, +33.11, +8.46. **MS (ESI)** m/e: 568.63 [M + H]$^+$, Anal. Calcd for $C_{34}H_{33}NO_7$ (%): C, 71.94; H, 5.86; N, 2.47; found (%):C, 71.88; H, 5.79; N, 2.42.

*7.4. 3-[(2-Chloro-phenyl)-(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-methylene]-2-hydroxy-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium; (**5d**)*

Yield, 81%; Light yellow solid; Solubility ($CHCl_3$); with M.P. 205–206 °C; **IR (KBr, cm^{-1}),** 3653, 3634, 3161, 2977, 1674, 1542, 1367, 1067, 981; **^{1}H NMR (300 MHz, $CDCl_3$); δ, ppm,** 14.22 (broadsinglet, OH,1H),11.49 (broadsinglet, OH,1H), 8.21 (d, H-C_5& C_8,2H, *J* = 7.5 Hz), 8.02 (d, H-C_6& C_7,2H, *J* = 7.5 Hz), 7.65 (td, H—C′$_5$& C′$_8$,2H, *J* = 6.3 Hz, 1.5 Hz),7.60 (td, H—C′$_6$& C′$_7$,2H, *J* = 6.3 Hz, 1.2 Hz),7.39 (dd, H-Ph,1H, *J* = 4.8 Hz, 2.1 Hz), 7.22 (d, H-Ph,1H, *J* = 2.1 Hz), 7.05–7.09 (m, H-Ph, 2H), 6.79 (singlet, H-$^+$NHEt$_3$, 1H), 2.89 (q, H-CH_2,6H, *J* = 7.2 Hz),1.09 (t, H-CH_3,9H, 7.2 Hz);**^{13}C NMR (400 MHz, $CDCl_3$); δ, ppm,** 185.03, 184.11, 162.53, 140.03, 134.21, 133.44, 132.12, 130.83, 130.21, 129.14, 128.34, 127.19, 124.55, 123.87, 76.67, 46.06, 33.64, 8.32; **^{13}C NMR (400 MHz, DEPT-135, $CDCl_3$); δ, ppm,**+133.98, +131.82, +128.80, +127.68, +126.92, +125.45, −45.91, +33.45, +8.44**. MS (ESI)** m/e: 573.05 [M + H]$^+$, Anal. Calcd for $C_{33}H_{30}ClNO_6$ (%): C, 69.29; H, 5.29; N, 2.45; found (%): C, 69.22; H, 5.21; N, 2.38.

*7.5. 3-[(4-Chloro-phenyl)-(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-methylene]-2-hydroxy-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium; (**5e**)*

Yield, 88%; Pale yellow solid; Solubility ($CHCl_3$); with M.P. 240–242 °C; **IR (KBr, cm^{-1}),** 3645, 3565, 3031, 2927, 1692, 1621, 1399, 982, 899; **^{1}H NMR (300 MHz, $CDCl_3$); δ, ppm,** 14.11 (broadsinglet, OH,1H),11.19 (broadsinglet, OH,1H), 8.21 (dd, H-C_5& C_8,2H, *J* = 6.4 Hz, 1.2 Hz), 8.02 (dd, H—C′$_5$& C′$_8$,2H, *J* = 6.2 Hz, 1.3 Hz), 7.71 (td, H-C_6& C_7,2H, *J* = 6.4 Hz, 1.1 Hz),7.61 (td, H—C′$_6$& C′$_7$,2H, *J* = 6.5 Hz, 0.9 Hz),7.19 (d, H-Ph,2H, *J* = 8.6 Hz), 7.09 (d, H-Ph,2H, *J* = 8.6 Hz), 6.91 (singlet, H-$^+$NHEt$_3$,1H), 2.99 (q, H-CH_2,6H, *J* = 7.3 Hz),1.12 (t, H-CH_3,9H, 7.3 Hz); **^{13}C NMR (400 MHz, $CDCl_3$); δ, ppm,** 185.21, 184.28, 161.51, 140.24, 134.22, 133.97, 132.06, 130.56, 129.12, 128.16, 127.35, 125.88, 124.79, 122.39, 76.93, 44.75, 33.56,8.39; **^{13}C NMR (400 MHz, DEPT-135, $CDCl_3$); δ, ppm,**+133.88, +131.82, +128.78, +127.68, +126.92, +125.45, −45.91, +33.45, +8.45**. MS (ESI)** m/e: 573.05 [M + H]$^+$, Anal. Calcd for $C_{33}H_{30}ClNO_6$ (%): C, 69.29; H, 5.29; Cl, N, 2.45; found (%): C, 69.23; H, 5.24; N, 2.37.

7.6. 3-[(3-Chloro-phenyl)-(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-methylene]-2-hydroxy-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium; (5f)

Yield, 72%; Light yellow solid; Solubility ($CHCl_3$); with M.P. 235–236 °C; **IR (KBr, cm^{-1}),** 3691, 3578, 3076, 2917, 1681, 1623, 1356, 972, 940; **^{1}H NMR (300 MHz, $CDCl_3$); δ, ppm,** 15.59 (singlet broad, OH,1H),8.88 (broadsinglet, OH,1H), 8.01 (dd, H-C_5& C_8,2H, J = 6.7 Hz, 0.9 Hz), 7.67 (dd, H—C′$_5$& C′$_8$,2H, J = 6.6 Hz, 1.0 Hz), 7.81 (td, H-C_6& C_7,2H, J = 6.2 Hz, 1.4 Hz),7.71 (td, H—C′$_6$& C′$_7$,2H, J = 6.2 Hz, 1.3 Hz),7.21 (t, H-Ph,1H, J = 7.0 Hz), 7.11 (dd, H-Ph,1H, J = 1.0 Hz, 0.9 Hz), 7.11–7.14 (m, H-Ph,2H), 6.71 (singlet, H-$^+$NHEt$_3$,1H), 32.95 (q, H-CH_2,6H, J = 7.3 Hz), 1.10 (t, H-CH_3,9H, 7.3 Hz);**^{13}C NMR (400 MHz, $CDCl_3$); δ, ppm,** 184.23, 183.21, 145.08, 133.87, 133.45, 133.03, 132.58, 131.15, 130.73, 126.89, 126.54, 126.04, 125.54, 1254.65, 121.78, 45.38, 32.68, 8.76; **^{13}C NMR (400 MHz, DEPT-135, $CDCl_3$); δ, ppm,**+134.27, +132.41, +131.13, +126.89, +126.21, +125.64, +124.64, −46.17, +33.45, +9.12. **MS (ESI)** m/e: 573.05 $[M + H]^+$, Anal. Calcd for $C_{33}H_{30}ClNO_6$ (%): C, 69.29; H, 5.29; Cl, N, 2.45; found (%): C, 69.21; H, 5.25; N, 2.41.

7.7. 3-[(3,5-Dichloro-phenyl)-(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-methylene]-2-hydroxy-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium; (5g)

Yield, 72%; Fluorescent yellow solid; Solubility ($CHCl_3$); with M.P. 220–222 °C; **IR (KBr, cm^{-1}),** 3674, 3561, 3216, 2912, 1657, 1621,965, 832;**^{1}H NMR (300 MHz, $CDCl_3$); δ, ppm,** 14.11 (broadsinglet, OH,1H),11.19 (broadsinglet, OH,1H), 8.22 (dd, H-C_5& C_8,2H, J = 7.6 Hz, 1.0 Hz), 7.97 (dd, H-C_6& C_7,2H, J = 6.4 Hz, 1.2 Hz), 7.69 (td, H—C′$_5$& C′$_8$,2H, J = 6.1 Hz, 1.4 Hz),7.59 (td, H—C′$_6$& C′$_7$,2H, J = 7.4 Hz, 1.3 Hz),7.21 (d, H-Ph,2H, J = 1.1 Hz), 7.09 (d, H-Ph,1H, J = 1.0 Hz), 6.90 (singlet, H-$^+$NHEt$_3$,1H), 3.11 (q, H-CH_2,6H, J = 7.4 Hz),1.22 (t, H-CH_3,9H, 7.4 Hz); **^{13}C NMR (400 MHz, $CDCl_3$); δ, ppm,** 185.42, 184.12, 144.61, 135.00, 134.65, 134.11, 132.08, 131.67, 127.22, 125.78, 125.44, 125.13, 121.77, 76.91, 45.78, 34.54, 8.23; **^{13}C NMR (400 MHz, DEPT-135, $CDCl_3$); δ, ppm,** +134.11, +131.96, +126.97, +125.94, +125.58, +125.10, +77.31, −46.10, +33.73, +8.44. **MS (ESI)** m/e: 607.49 $[M + H]^+$, Anal. Calcd for $C_{33}H_{29}Cl_2NO_6$ (%): C, 65.35; H, 4.82; N, 2.31; found (%): C, 65.32; H, 4.75; N, 2.24.

7.8. 3-[(4-Bromo-phenyl)-(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-methylene]-2-hydroxy-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium;(5h)

Yield, 56%; Dark yellow solid; Solubility ($CHCl_3$); with M.P. 196–197 °C; **IR (KBr, cm^{-1}),** 3645, 3576, 3278, 3157, 2924, 1689, 1623, 945, 824;**^{1}H NMR (300 MHz, $CDCl_3$); δ, ppm,** 14.09 (broadsinglet, OH,1H),11.19 (broadsinglet, OH,1H), 8.21 (d, H-C_5& C_8,2H, J = 7.6 Hz, 0.8 Hz), 8.02 (dd, H—C′$_5$& C′$_8$,2H, J = 7.6 Hz, 1.0 Hz), 7.71 (td, H-C_6& C_7,2H, J = 7.6 Hz, 1.4 Hz),7.61 (td, H—C′$_6$& C′$_7$, 2H, J = 7.4 Hz, 1.4 Hz),7.31 (d, H-Ph,2H, J = 8.4 Hz), 7.21 (d, H-Ph,2H, J = 8.4 Hz), 6.91 (singlet, H-$^+$NHEt$_3$,1H), 2.98 (q, H-CH_2,6H, J = 7.4 Hz),1.17 (t, H-CH_3,9H, 7.3 Hz); **^{13}C NMR (400 MHz, $CDCl_3$); δ, ppm,** 185.65, 184.65, 141.34, 134.56, 133.12, 132.56, 131.78, 131.45, 129.30, 127.09, 125.55, 124.22, 119.98, 76.67, 45.35, 33.29, 8.98; **^{13}C NMR (400 MHz, DEPT-135, $CDCl_3$); δ, ppm,** +133.81, +131.28, +130.63, +129.22, +126.92, +125.45, −45.92, +33.53, +8.41. **MS (ESI)** m/e: 617.50 $[M + H]^+$, Anal. Calcd for $C_{33}H_{30}BrNO_6$ (%): C, 64.29; H, 4.90; N, 2.27; found (%):C, 64.21; H, 4.82; N, 2.26.

7.9. 3-[(4-Iodo-phenyl)-(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-methylene]-2-hydroxy-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium; (5i)

Yield, 72%; Pale yellow solid; Solubility ($CHCl_3$); with M.P. 277–279 °C; **IR (KBr, cm^{-1}),** 3634, 3576, 3234, 2956, 1678, 1632, 1356, 987, 824; **^{1}H NMR (300 MHz, $CDCl_3$); δ, ppm,** 14.09 (broadsinglet, OH,1H),11.19 (broadsinglet, OH,1H), 8.21 (d, H-C_5& C_8,2H, J = 7.6 Hz), 8.01 (d, H—C′$_5$& C′$_8$,2H, J = 7.4 Hz), 7.71 (td, H-C_6& C_7,2H, J = 6.3 Hz, 1.4 Hz),7.61 (td, H—C′$_6$& C′$_7$,2H, J = 6.3 Hz, 1.2 Hz),7.31 (d, H-Ph,2H, J = 8.3 Hz), 7.21 (d, H-Ph,2H, J = 8.3 Hz), 6.91 (singlet, H-$^+$NHEt$_3$,1H), 2.98 (q, H-CH_2,6H, J = 7.2 Hz),1.09 (t, H-CH_3,9H, 7.3 Hz); **^{13}C NMR (400 MHz, $CDCl_3$); δ, ppm,** 185.12, 184.23, 161.34, 141.67, 134.45, 133.12, 132.34, 131.19, 130.46, 129.83, 128.39, 126.05, 125.16, 123.90, 76.15, 45.65, 33.25, 8.60; **^{13}C NMR (400 MHz, DEPT-135, $CDCl_3$); δ, ppm,**+133.91, +131.82, +130.63, +129.26, +126.92, +125.45, −45.92, +33.53, +8.44. **MS (ESI)** m/e: 664.50 $[M + H]^+$, Anal. Calcd for $C_{33}H_{30}INO_6$ (%): C, 59.74; H, 4.56; N, 2.11; found (%): C, 59.68; H, 4.50; N, 2.05.

7.10. 2-Hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-(4-nitro-phenyl)-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium; (5j)

Yield, 76%; Orange yellow solid; Solubility ($CHCl_3$); with M.P. 182–183 °C; **IR (KBr, cm^{-1}),** 3623, 3576, 3217, 2938, 1665, 1619, 1366, 998, 917; **^{1}H NMR (300 MHz, $CDCl_3$); δ, ppm,** 14.21 (broadsinglet, OH,1H),11.11 (broadsinglet, OH,1H), 8.39 (dd, H-C_5& C_8,1H, J = 8.7 Hz, 1.0 Hz), 8.19 (dd, H-C_6& C_7,2H, J = 7.6 Hz, 1.0 Hz), 8.11 (d, H-Ph,1H, J = 8.7 Hz),7.94 (dd, H-Ph,2H, J = 7.6 Hz, 1.2 Hz),7.71 (td, H—C′$_5$& C′$_8$,2H, J = 7.4 Hz, 1.4 Hz), 7.59 (td, H—C′$_6$& C′$_7$,2H, J = 7.5 Hz, 1.3 Hz), 7.34 (dd, H-Ph,1H, J = 8.9 Hz, 0.9 Hz) 6.98 (singlet, H-$^+$NHEt$_3$,1H), 2.98 (q, H-CH_2,6H, J = 7.1 Hz),1.10 (t, H-CH_3,9H, 7.4 Hz); **^{13}C NMR (400 MHz, $CDCl_3$); δ, ppm,** 189.87, 185.23, 184.56, 161.44, 150.03, 145.44, 133.88, 133.32, 131.96, 131.43, 130.21, 128.76, 126.34, 124.79, 124.23 123.56, 121.58, 76.64, 46.06, 34.65, 8.26; **^{13}C NMR (400 MHz, DEPT-135, $CDCl_3$); δ, ppm,**+134.16, +132.12, +131.52, +128.12, +126.95, +125.61, +124.32, +122.99, −46.10, +34.30, +8.13. **MS (ESI)** m/e: 583.60 $[M + H]^+$, Anal. Calcd for $C_{33}H_{30}N_2O_8$ (%): C, 68.03; H, 5.19; N, 4.81; found (%): C, 67.97; H, 5.10; N, 4.74.

7.11. 2-Hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-(3-nitro-phenyl)-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium; (5k)

Yield, 79%; Orange brown solid; Solubility ($CHCl_3$); with M.P. 174–175 °C; **IR (KBr, cm^{-1}),** 3634, 3543, 3126, 2965, 1654, 1631, 1363, 1120, 879; **^{1}H NMR (300 MHz, $CDCl_3$); δ, ppm,** 14.29 (broadsinglet, OH,1H),11.31 (broadsinglet, OH,1H), 8.19 (d, H-C_5& C_8,2H, J = 6.6 Hz), 8.21 (singlet, H-Ph,1H,), 7.96 (d, H—C′$_5$& C′$_8$,2H, J = 7.6 Hz), 8.01 (d, H-Ph,1H, J = 8.0 Hz),7.71 (t, H-C_6& C_7,2H, J = 7.5 Hz),7.61 (t, H-Ph,C′$_6$& C′$_7$,3H, J = 7.5 Hz), 7.29 (t, H-Ph,1H, J = 8.0 Hz), 6.98 (singlet, H-$^+$NHEt$_3$,1H), 2.97 (q, H-CH_2,6H, J = 7.2 Hz),1.21 (t, H-CH_3,9H, 7.3 Hz); **^{13}C NMR (400 MHz, $CDCl_3$); δ, ppm,** 185.12, 184.02, 162.87, 149.12, 144.36, 133.99, 133.21, 132.56, 131.89, 131.54, 129.23, 126.16, 125.73, 123.98, 122.23, 121.93, 76.33, 45.59, 33.03, 8.76; **^{13}C NMR (400 MHz, DEPT-135, $CDCl_3$); δ, ppm,**+134.10, +133.89, +132.10, +128.67, +126.56, +125.61, +122.47, +120.29, −46.24, +33.79, +8.37. **MS (ESI)** m/e: 583.60 $[M + H]^+$, Anal. Calcd for $C_{33}H_{30}N_2O_8$ (%): C, 68.03; H, 5.19; N, 4.81; found (%): C, 67.99; H, 5.12; N, 4.77.

7.12. 2-Hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-(2-nitro phenyl)-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl ammonium;(5l)

Yield, 77%; Orange yellow solid; Solubility ($CHCl_3$); with M.P. 196–198 °C; **IR (KBr, cm^{-1}),** 3654, 3572, 3145, 2935, 1702, 1689, 1424, 1073, 946; **^{1}H NMR (400 MHz, $CDCl_3$); δ, ppm,** 15.59 (broadsinglet, OH,1H),8.91 (broadsinglet, OH,1H), 8.02 (dd, H-C_5& C_8,2H, J

= 6.7 Hz, 1.2 Hz), 7.91 (dd, H—C′5& C′8,2H, J = 6.5 Hz, 1.1 Hz), 7.81 (td, H-C6& C7,2H, J = 6.2 Hz, 1.3 Hz),7.71 (td, H—C′6& C′7,2H, J = 6.1 Hz, 1.3 Hz),7.61 (d, H-Ph,1H, J = 7.9 Hz), 7.51 (t, H-Ph,1H, J = 7.4 Hz), 7.39 (d, H-Ph,1H, J = 7.9 Hz), 7.37 (t, H-Ph,1H, J = 7.4 Hz), 6.91 (singlet, H-$^{+}$NHEt$_3$,1H), 2.95 (q, H-CH$_2$,6H, J = 7.3 Hz),1.11 (t, H-CH$_3$,9H, 7.3 Hz); **^{13}C NMR (400 MHz, CDCl$_3$); δ, ppm,** 184.05, 183.99, 148.52, 134.36, 133.92, 133.45, 132.74, 132.24, 131.87, 130.75, 127.59, 126.22, 125.65, 124.45, 121.75, 46.16, 31.47, 9.23; **^{13}C NMR (400 MHz, DEPT-135, CDCl$_3$); δ, ppm,**+134.26, +132.45, +132.13, +130.47, +127.11, +126.12, +125.66, +124.37, −46.26, +40.29, +31.87, +9.13. **MS (ESI)** m/e: 583.60 [M + H]$^{+}$, Anal. Calcd for $C_{33}H_{30}N_2O_8$ (%): C, 68.03; H, 5.19; N, 4.81; found (%): C, 68.01; H, 5.11; N, 4.71.

*7.13. 2-Hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-(2-hydroxy-phenyl)-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium; (**5m**)*

Yield, 86%; Ruby red solid; Solubility (CHCl$_3$); with M.P. 230–231 °C; **IR (KBr, cm^{-1}),** 3637, 3587, 3245, 3046, 2924, 1628, 1578, 1039, 834;**^{1}H NMR (300 MHz, CDCl$_3$); δ, ppm,** 13.88 (broadsinglet, OH,1H),11.41 (broadsinglet, OH,1H), 8.31 (d, 1H, J = 7.9 Hz), 8.09 (t, 1H, J = 4.0 Hz),7.97 (t, 1H, J = 4.7 Hz), 7.81 (d, 1H, J = 7.5 Hz),7.60–7.65 (m, 3H),7.45 (td, 1H, J = 6.5 Hz, 1.3 Hz), 7.33 (d, 1H, 7.5 Hz), 7.13 (t, 2H, J = 3.5 Hz), 7.01 (td, 1H, J = 6.2 Hz, 2.4 Hz), 5.98 (singlet, H-$^{+}$NHEt$_3$,1H), 3.02 (q, H-CH$_2$,6H, J = 7.3 Hz),1.11 (t, H-CH$_3$,9H, 7.3 Hz);**^{13}C NMR (400 MHz, CDCl$_3$); δ, ppm,** 185.08, 184.33, 162.23, 141.87, 134.66, 133.56, 132.08, 131.43, 130.75, 129.44, 127.59, 126.04, 125.66, 123.37, 76.78, 44.42, 33.14, 8.47; **^{13}C NMR (400 MHz, DEPT-135, CDCl$_3$); δ, ppm,**+133.86, +131.82, +130.69, +129.26, +126.94, +125.47, −45.92, +33.54, +8.38. **MS (ESI)** m/e: 554.60 [M + H]$^{+}$, Anal. Calcd for $C_{33}H_{31}NO_7$ (%): C, 71.60; H, 5.64; N, 2.53; found (%):C, 71.54; H, 5.61; N, 2.48.

*7.14. 3-[Benzo[1,3]dioxol-5-yl-(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-methylene]-2-hydroxy-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium; (**5n**)*

Yield, 89%; Fluorescent orange solid; Solubility (CHCl$_3$); with M.P. 258–263 °C; **IR (KBr, cm^{-1}),** 3654, 3597, 3202, 2966, 1669, 1603, 1447, 1025, 893; **^{1}H NMR (300 MHz, CDCl$_3$); δ, ppm,** 14.21 (broadsinglet, OH,1H),11.39 (broadsinglet, OH,1H), 8.21 (dd, H-C5& C8,2H, J = 7.7 Hz, 1.0 Hz), 7.69 (dd, H-C6& C7,2H, J = 7.6 Hz, 0.9 Hz), 7.71 (td, H—C′5& C′8,2H, J = 7.6 Hz, 1.5 Hz),7.61 (td, H—C′6& C′7,2H, J = 7.5 Hz, 1.3 Hz), 6.79 (singlet, H-$^{+}$NHEt$_3$,1H),6.69 (d, H-Ph,1H, J = 1.5 Hz), 6.72 (d, H-Ph,1H, J = 0.9 Hz), 6.59 (d, H-Ph,1H, J = 8.1 Hz) 5.79 (singlet, H-OCH$_2$O,2H,), 2.87 (q, H-CH$_2$,6H, J = 7.3 Hz),1.21 (t,H-CH$_3$,9H, 7.4 Hz); **^{13}C NMR (400 MHz, CDCl$_3$); δ, ppm,** 185.03, 184.67, 148.71, 145.65, 134.65, 133.76, 132.05, 131.47, 126.82, 125.73, 123.39, 121.79, 108.33, 107.83, 100.64, 76.68, 46.24, 33.47, 8.97; **^{13}C NMR (400 MHz, DEPT-135, CDCl$_3$); δ, ppm,**+133.82, +131.77, +126.89, +125.38, +120.01, +108.29, +107.46, +100.49, −45.93, +8.44. **MS (ESI)** m/e: 582.61 [M + H]$^{+}$, Anal. Calcd for $C_{34}H_{31}NO_8$ (%): C, 70.21; H, 5.37; N, 2.41; found (%): C, 70.16; H, 5.29; N, 2.35.

*7.15. 3-[(2-Cyano-phenyl)-(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-methylene]-2-hydroxy-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium; (**5o**)*

Yield, 70%; Orange yellow solid; Solubility (CHCl$_3$); with M.P. 230–232 °C; **IR (KBr, cm^{-1}),** 3637, 3587, 3254, 3206, 2954, 2856, 2138, 1684, 1603, 1064, 966, 937, 899;**^{1}H NMR (300 MHz, CDCl$_3$); δ, ppm,** 13.89 (broadsinglet, OH,1H),11.39 (broadsinglet, OH,1H), 8.21 (dd, H-C5& C8,2H, J = 6.7 Hz, 1.0 Hz), 8.02 (dd,H—C′5& C′8, 2H, J = 6.6 Hz, 1.1 Hz), 7.71 (td, H-C6& C7,2H, J = 6.1 Hz, 1.4 Hz),7.61 (td, H—C′6& C′7,2H, J = 6.2 Hz, 1.3 Hz),7.61 (d, H-Ph,1H, J = 5.8 Hz), 7.29–7.38 (m, H-Ph,2H), 7.21 (t, H-Ph,1H, J = 7.7 Hz), 7.04 (singlet, H-$^{+}$NHEt$_3$,1H), 2.96 (q, H-CH$_2$,6H, J = 7.3 Hz),1.11 (t, H-CH$_3$,9H, 7.3 Hz). **MS (ESI)** m/e: 563.61 [M + H]$^{+}$, Anal. Calcd for $C_{34}H_{30}N_2O_6$ (%): C, 72.58; H, 5.37; N, 4.98; found (%): C, 72.49; H, 5.31; N, 4.92.

8. Enzyme inhibition studies

The inhibitory effects of novel 2-Hydroxy-3-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-*p*-tolyl-methylene]-4-oxo-3,4-dihydro-naphthalen-1-olatetriethyl-ammonium derivatives **(5a-o)** on both hCA (I, II) isozymes have been described in Verpoorte et al. [69] and according to an esterase assay using p-nitrophenyl acetate (PNA) substrate was recorded spectrophotometrically at 348 nm [70]. On the other hand, the inhibitory effects of AChE and BChE compounds were determined according to the method of Ellman et al. [71] They were recorded spectrophotometrically at 412 nm using acetylcholine iodide and butyryl choline iodide and recorded as enzymatic reaction substrates according to previous studies [72,73]. In addition, the inhibitory effect of these compounds on the activity of α-glycosidase enzyme was assessed using the p-nitrophenyl-D-glycopyranoside substrate (p-NPG) according to the analysis of Tao et al. [74] First, 200 microliter of phosphate buffer was mixed with 40 microliter of homogenate in phosphate buffer (0.15 U / mL, pH 4.7). In addition, after preincubation, 50 μL of p-NPG was added to phosphate buffer (5 mM, pH 7.4) and incubated again at 30 °C. According to previous studies, adsorption was measured at 405 nm by spectroscopy [75–76].

9. Molecular docking studies

Molecular docking calculations were used to compare the biological activities of bis-naphthoquinone derivatives from Lawsone. As a result of these calculations, many parameters about the biological activities of molecules have been obtained [77–79]. The numerical values of these parameters of molecules obtained by calculations provide important information about the biological activities of molecules [80,81]. Molecular docking calculations for comparison the biological activities of molecules were made using the Maestro Molecular modeling platform (version 12.2) by Schrödinger. Protein and molecules must be prepared for calculations. In the calculations made, a different process is made for molecules at each stage. First, it was used from Gaussian software program [82] to obtain optimized structures of heterocyclic derivatives from Lawsone, using these structures *.sdf extension files were created. Using these files, all calculations were made with the Maestro Molecular modeling platform (version 12.2) by Schrödinger, LLC [83]. The Maestro Molecular modeling platform (version 12.2) by Schrödinger comes together from many modules. In the first module used, the protein preparation module [84,85] was used to prepare proteins for calculations. The enzymes studied are composed of many small proteins. The crystal structures of these enzymes have been downloaded from the protein data bank site. These enzymes were first minimized and the water molecules in their crystal structures were removed. In the next step, the active sites of the enzymes were determined for calculations, in which freedom of movement was given to all proteins in this active site. Therefore, these proteins have been enabled to interact more easily with molecules. In the next step, the LigPrep module [86,87] was used in preparation for the calculations of the working molecules. Calculations were made to find 3D structures of heterocyclic derivatives from Lawsone at physiological pH values and high-energy isomers in the correct protonation conditions. In the next step, the prepared protein and molecules were docked with each other. The Glide ligand-docking module [88] was used for this step. In this module, OPLS3e method is used in all calculations for docking calculations of molecules and proteins. All calculations have been made at pH 7.0 ± 2.0. Numerical values of many parameters obtained as a result of molecular docking calculations using this module are used. After the docking calculations, ADME/T analysis (absorption, distribution, metabolism, excretion and toxicity)

was performed to examine the future drug properties of the molecule. The Qik-prop module [89] of the Schrödinger software was used for ADME/T analysis.

Declaration of Competing Interest

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 paper.

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Appendix A. Supplementary material

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