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Novel carvacrol based new oxypropanolamine derivatives: Design, synthesis, characterization, biological evaluation, and molecular docking studies

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ABSTRACT

Carvacrol, as a natural product used for many years in the treatment of various diseases, therefore it was chosen as the starting compound for this study. Novel carvacrol based new oxypropanolamine derivatives were synthesized and characterized by spectroscopic methods. All new compounds were tested as metabolic enzyme inhibitory agents. Their clinical usage of carvacrol has been established as diuretics, antiepileptics, and anti-glaucoma factors, in the management of gastric, duodenal ulcers, mountain sickness, osteoporosis, idiopathic intracranial hypertension, or neurological disorders. The in vitro anti-hyperglycemic screening results showed that the compound **3d** exhibits the maximum inhibitory effect against α-glycosidase enzyme (IC_{50}: 904.10 nM). In addition, the compounds **3d** (IC_{50}: 29.74 nM and 23.64 nM) and **3e** (IC_{50}: 31.28 nM and 26.11 nM) were found to have a significant response to inhibit carbonic anhydrase I, and II isoenzymes (hCA I and II), respectively. The novel carvacrol based oxypropanolamine compounds were effective inhibitors of the hCA I and II isozymes, and acetylcholinesterase with Ki values in the range of 27.18−44.84 nM for hCA I, 25.62−38.71 nM for hCA II, and 99.83 −146.25 nM for AChE, respectively.

1. Introduction

Natural products are always the main inspiration for chemistry, biology, and medicine [1,2]. Their complex treatment mechanisms are not always completely understandable, thus their core structures attract the attention of scientists [3,4]. Carvacrol, a monoterpenic phenol produced by numerous aromatic plants, mainly oregano and thyme is currently used as a preservative and food flavoring and as a fragrance in cosmetic formulations. Recently, important researches have been carried out in an effort to determine the biological effects of carvacrol for its potential use in clinical applications as well [5]. In traditional medicine, carvacrol has been used as an antimicrobial agent and furthermore it is the most effective agent among other essential oils using for this purpose [6]. Moreover, some results from *in vivo* and in vitro studies show that carvacrol has a wide variety of pharmacological and biological properties, including analgesic, antiallergic, antiarthritic, antibiotic, anticarcinogenic, anticholesterol, antidiabetic, anti-endotoxemic, antifungal, anti-inflammatory, antileishmanial, antimicrobial, antioxidant, antitoxins, antiviral, cardioprotective, gastroprotective, hepatoprotective, insecticidal, nematocidal, neuroprotective, and trypanocidal effects [7]. Although, the research on the information on the toxicology of Carvacrol is limited, findings from the study in the metabolism have showed that carvacrol was discarded after 24 h in large quantities in urine as glucoronide and sulfate conjugates [8].

The 1,2-amino alcohol core is a common structure encountered in a number of natural products like amino acids (serine, threonine, and hydroxyproline), hormones (adrenaline and noradrenaline).

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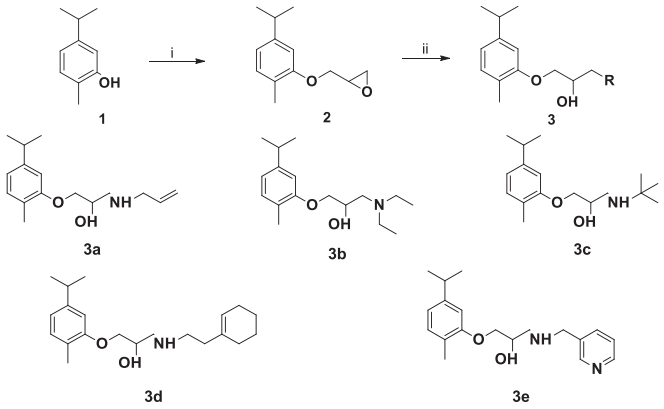

Scheme 1. The procedure for the synthesis of **2** and **3a-e**. (i) epichlorohydrin, NaOH/water, 85 °C, 0.5 h; (ii) Amine compound, saturated K_2CO_3 solution, room temperature, 8–12 h.

Furthermore, it can be encountered in the glycosidase inhibitor nojirimycin, the antimalarial agent febrifugine, the anticancer agent hapalosin, amino sugars such as antibiotic neomycin. Due to the variety of biological activity that it offers, it has also taken place in synthetic drug structures like Randolazine (antianginal), Zanamivir (influenza), Docetaxel (combat metastatic cancers) [9]. On the other hand, the substructure of 1,2-amino alcohols oxypropanolamines have been known as β-adrenoceptor antagonists [10] particularly in cardiovascular disease since the 1960s, and also in the treatment of many diseases such as thyrotoxicosis, angina pectoris, hypertension, chronic pulmonary diseases [11], skin inflammation [12] and diuretic [13].

Carbonic anhydrases (CAs, E.C.4.2.1.1) are zinc-containing enzymes, which perform a very important reaction: the reversible hydration of CO_2 and water to proton and bicarbonate ions [14,15]. So far, twelve catalytically active CA isoenzymes have been identified that based on the several cellular distribution can be gathered in four various groups: mitochondrial (CAs VA and VB), cytosolic (CAs I, II, III, VII and XIII), membrane associated (CAs IV, IX, XII and XIV), and secretory (CA VI) CAs [16,17]. These isoenzymes differ also for tissue distribution and catalytic efficiency. Various CA isoenzymes play significant roles in diverse pathological mechanisms related to epilepsy, cancer, glaucoma, obesity, etc. Thus, these isoenzymes have become relevant aims for the synthesis and design of inhibitors with biological applications [18–20].

The α-glycosidase as a catabolic important enzyme hydrolyzes carbohydrate molecules to crop energy sugars necessary for some physiological functions. This enzyme provides energy sources to hold healthy functioning. In conflict, glucose molecule absorption in patients with type-2 diabetes mellitus (T2DM) can cause clinically important difficulties because the high activity of this enzyme enhances plasma Mellitus glucose amounts [21–23]. The glucose has been recorded to improve memory in humans and animals. Studies that focused on animals have revealed that glucose can improve memory through the facilitation of acetylcholine (ACh) molecule synthesis and release in the brain cells. This glucose-relevant memory progress has prompted research in elder age [24]. These findings have recorded that the memory improving of glucose depends on each single's blood glucose regulation. Indeed, some researchers have investigated the effect of glucose molecule on memory in patients with Alzheimer's disease (AD) [25]. The acetylcholinesterase (AChE) enzyme catalyzes the hydrolysis of the neurotransmitter ACh to choline and acetate in a synaptic cleft. So far, AChE inhibition is one of the most successful methods for the treatment of AD [26].

Referring to the previous studies [27–32] on the synthesis of compounds having biological activity, in order that the structure of the compound to be similarly synthesized is similar to the metabolites, natural products or present drugs, the higher the likelihood of showing biological activity. In this regard, the study treats carvacrol-derived oxypropanol amines as molecules which can show high biological activity. In this study, synthesis, characterization, molecular docking, and metabolic enzymes inhibitory properties of novel carvacrol based new oxypropanolamine derivatives (**3a-e**) have been investigated.

2. Materials and methods

2.1. Chemistry

The oxyrane (**2**) derivative of carvacrol was prepared by the treatment of carvacrol with epichlorohydrin and then the ring was opened with various amine compounds. Primary or secondary amines having different steric effects and bearing aliphatic, olefinic or aromatic groups were selected. The synthetic route was given in Scheme 1.

2.1.1. Synthesis of 2-((5-isopropyl-2-methylphenoxy)methyl) oxirane (2)

Carvacrol (1 g, 6.6 mmol) and epichlorohydrin (10 mL) were dissolved in methanol (10 mL) and sodium hydroxide (0.24 g, 6.6 mmol) in water (10 mL) was added dropwise over a period of 30 min to the solution under vigorous stirring at 85 °C. The mixture was further continued to be stirred for another 15 min at the same temperature. The organic phase was mixed with ethyl acetate (20 mL) and washed with brine (2 × 15 mL), dried over $MgSO_4$, and

Table 1
The enzyme inhibition results of Carvacrol based novel oxypropanolamine derivatives (**3a-e**) against human carbonic anhydrase isoenzymes I and II (hCA I and II), acetylcholinesterase (AChE), and α-glycosidase (α-Gly) enzymes.

Compounds	IC_{50} (nM)								K_i (nM)			
	hCA I	r^2	hCA II	r^2	AChE	r^2	α-Gly	r^2	hCA I	hCA II	AChE	α-Gly
3a	41.05	0.9817	35.71	0.9748	136.05	0.9682	984.62	0.9382	44.84 ± 10.53	38.71 ± 5.17	99.83 ± 14.75	1007.56 ± 111.8
3b	36.93	0.9933	34.96	0.9590	184.73	0.9505	1065.73	0.9194	34.12 ± 8.58	31.74 ± 9.33	125.06 ± 25.82	945.72 ± 94.71
3c	40.55	0.9427	33.04	0.9681	157.77	0.9835	1013.63	0.9724	42.65 ± 6.08	36.30 ± 7.18	119.85 ± 34.81	904.88 ± 101.88
3d	29.74	0.9605	23.64	0.9532	195.04	0.9533	904.10	0.9821	27.18 ± 6.86	25.62 ± 6.11	146.25 ± 17.22	896.61 ± 78.63
3e	31.28	0.9872	26.11	0.9831	190.17	0.9073	1000.05	0.9120	30.57 ± 8.60	27.93 ± 4.13	138.60 ± 26.02	1026.80 ± 147.3
AZA[a]	57.36	0.9790	64.08	0.9903	–	–	–	–	51.83 ± 7.83	60.77 ± 14.07	–	–
TAC[b]	–	–	–	–	208.03	0.9628	–	–	–	–	177.15 ± 39.05	–
ACR[c]	–	–	–	–	–	–	22800	–	–	–	–	12600 ± 78

[a] Acetazolamide (AZA) was used as a control for hCA I and II isoenzymes.
[b] Tacrine (TAC) was used as a control for AChE enzyme.
[c] Acarbose (ACR) was used as a control for α-glycosidase enzyme which obtained from references [61] and [62].

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filtered. The residue was vaporized under vacuum at 90–100 °C to remove excess epichlorohydrin. The oily residue was passed through silica gel column chromatography with a mixture of hexane: ethyl acetate (97:3) to provide pure oxirane **2** (1.22 g, 89%).

2.1.2. General synthesis of propan-2-ol amine derivatives (3a-e)

A mixture of the oxirane **2** (1 mmol), amine derivative (3 mmol) and aqueous saturated solution of K_2CO_3 solution (2 mL) was vigorously stirred at room temperature for 8–12 h. The reaction was monitored with TLC. After the completed conversion, the reaction mixture was extracted with ethyl acetate (10 mL) and water (2 × 10 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography with hexane: ethyl acetate (97:3). The product was analyzed by ^{1}H and ^{13}C NMR.

2.1.3. 1-(Allylamino)-3-(5-isopropyl-2-methylphenoxy)propan-2-ol (3a)

Colorless viscous liquid, Yield 1.34 g (86%); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.06 (d, *J* = 7.6 Hz, 1H), 6.76 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.70 (d, *J* = 1.6 Hz, 1H), 6.00–5.83 (m, 1H), 5.23 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.16 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.20–4.08 (m, 1H), 4.04 (dd, *J* = 9.2, 5.3 Hz, 1H), 3.97 (dd, *J* = 9.2, 5.4 Hz, 1H), 3.44 (s, 2H), 3.34 (dd, *J* = 6.2, 1.4 Hz, 2H), 2.94 (dt, *J* = 12.2, 6.9 Hz, 1H), 2.89–2.79 (m, 2H), 2.19 (s, 3H), 1.24 (d, *J* = 6.9 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.78, 148.29, 135.85, 130.75, 124.18, 118.76, 117.28, 109.83, 70.67, 68.47, 52.30, 51.57, 34.35, 24.36 (2C), 16.12.

2.1.4. 1-(Diethylamino)-3-(5-isopropyl-2-methylphenoxy)propan-2-ol (3b)

Light yellow viscous liquid, Yield 1.22 g (74%); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.06 (d, *J* = 7.5 Hz, 1H), 6.75 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.72 (d, *J* = 1.5 Hz, 1H), 4.20–3.91 (m, 3H), 2.80–2.93 (m, *J* = 6.9 Hz, 1H), 2.78–2.49 (m, 4H), 2.21 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 6H), 1.07 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.01, 148.17, 130.65, 124.32, 118.55, 109.79, 70.62, 66.24, 56.36, 47.50 (2C), 34.36, 24.37 (2C), 16.07, 12.21 (2C).

2.1.5. 1-(Tert-butylamino)-3-(5-isopropyl-2-methylphenoxy) propan-2-ol (3c)

Colorless viscous liquid, Yield 1.45 g (88%); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.10 (dd, *J* = 7.6, 0.7 Hz, 1H), 6.85–6.54 (m, 2H), 4.17–4.04 (m, 3H), 4.03–3.90 (m, 1H), 2.99–2.85 (m, 3H), 2.85–2.73 (m, 1H), 2.24 (s, 3H), 1.28 (d, *J* = 6.9 Hz, 6H), 1.18 (d, *J* = 1.2 Hz, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.94, 148.30, 130.76, 124.21, 118.68, 109.79, 70.91, 68.88, 50.70, 45.25, 34.41, 29.24 (3C), 24.42, 24.36, 16.23.

2.1.6. 1-((2-(Cyclohex-1-en-1-yl)ethyl)amino)-3-(5-isopropyl-2-methylphenoxy)propan-2-ol (3d)

Brown viscous liquid, Yield 1.57 g (80%); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.05 (d, *J* = 7.7 Hz, 1H), 6.74 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.70 (s, 1H), 5.46 (s, 1H), 4.22–3.84 (m, 3H), 3.07–2.61 (m, 4H), 2.18 (s, 3H), 2.05–1.86 (m, 7H), 1.70–1.50 (m, 6H), 1.23 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.83, 148.36, 135.40, 130.71, 124.22, 123.17, 118.67, 109.79, 70.69, 68.48, 52.14 (2C), 47.80, 34.34, 28.37, 25.46, 24.34 (2C), 23.14, 22.66, 16.11.

2.1.7. 1-(5-Isopropyl-2-methylphenoxy)-3-((pyridin-3-ylmethyl) amino)propan-2-ol (3e)

Yellow viscous liquid, Yield 1.45 g, 78%; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.57 (dd, *J* = 1.6, 0.8 Hz, 1H), 8.50 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.70 (ddd, *J* = 7.8, 4.8, 1.6 Hz, 1H), 7.27 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.04 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.75 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.68 (d, *J* = 1.6 Hz, 1H), 4.27–4.06 (m, H), 4.06–3.96 (m, 2H), 3.86 (s, 2H), 3.06–2.70 (m, 3H), 2.23 (s, 1H), 2.15 (s, 3H), 2.04 (d, *J* = 0.6 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.84, 149.54, 148.40, 148.28, 136.53, 135.80, 130.79, 124.16, 123.91, 118.77, 109.86, 70.79, 68.92, 52.01, 51.38, 34.36, 24.40, 24.35, 16.14.

2.2. Biological studies

The purification of both cytosolic CA isoenzymes (CA I and II) were performed with a simple one-step procedure by a Sepharose-4B-L tyrosine-sulphanilamide affinity chromatoghraphy. The protein quantity in the column effluents were evaluated spectrophotometrically at 280 nm. For purity of both isoenzymes sodium

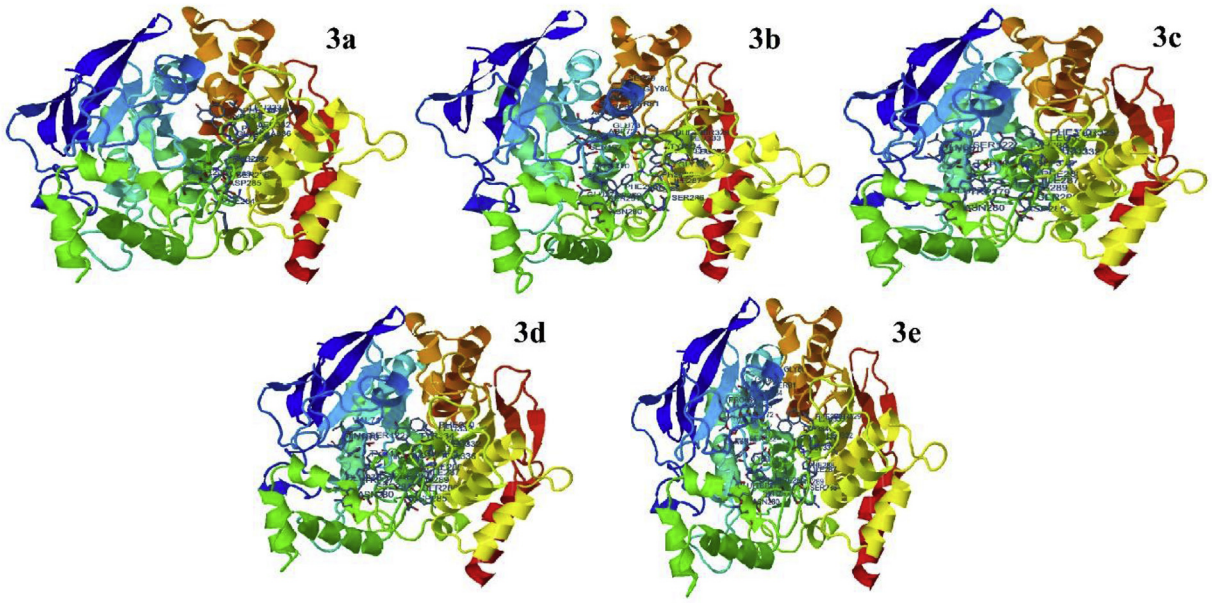

Fig. 1. Demonstration of the interaction of 1OCE protein with the studied molecules.

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dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was applied. The CA inhibitory effects of new carvacrol based novel oxypropanolamine derivatives (**3a-e**) were performed according to Verpoorte et al. [33] as described in former studies [34–36] and measured at 348 nm spectrophotometrically using the p-nitrophenylacetate as the main substrate [37]. For AChE, the inhibitory effect of novel carvacrol based new oxypropanolamine derivatives (**3a-e**) was calculated according to Ellman's method [38]. Briefly, 100 μL of Tris/HCl buffer (1 M, pH 8.0), 780 μL of sample solution dissolved in deionized water at different concentrations, and 20 μL of AChE solution were mixed and incubated for 10 min at 25 °C. Then, 50 μL of DTNB (0.5 mM) was added. Then reaction was initiated by the addition of 50 μL of AChI. The hydrolysis of these substrates was monitored spectrophotometrically by formation of the yellow 5-thio-2-nitrobenzoate anion as the result of the reaction of DTNB with thiocholine, released by enzymatic hydrolysis of AChI, with an absorption maximum at a wavelength of 412 nm compatible to former studies [39,40] and measured at 412 nm spectrophotometrically using acetylthiocholine iodide molecule as a main substrate for the enzymatic reaction. 5,5′-Dithio-bis(2-nitro-benzoic) acid was utilized for the measurement of the AChE activity [41,42]. For α-glycosidase, inhibitory effect of indicated compounds on α-glycosidase enzyme activity was measured using p-nitrophenyl-D-glycopyranoside (p-NPG) as molecule as the substrate, according to the assay of Tao et al. [43]. Initially, 400 μL of phosphate buffer was mixed with 40 μL of the homogenate solution in phosphate buffer (0.15 U/mL, pH 7.4). Also, 100 μL of *p*-NPG in phosphate buffer (5 mM, pH 7.4) after preincubation was added and again incubated at 30 °C. The absorbances were spectrophotometrically measured at 405 nm, conforming to former studies [44–46].

2.3. Molecular docking

The study compared the inhibition values of five molecules against some enzymes performed and compared. In order to compare the enzyme inhibition values of the molecules, the molecules were first optimized using the Gaussian package program in HF/6-31++g basis set [47–49]. Then, they molecules were computed in the Docking Server using the optimized structures obtained. The interaction of each molecule against enzymes was examined. The names of the protein molecules studied are AChE for ID 1OCE, α-Glycosidase for ID 1XSI, hCA I for ID 2CAB, hCA II for ID 4R5B. The interactions of these proteins with the five studied was compared by working in DockingServer.

3. Results and discussion

3.1. Chemistry

Carvacrol, as a natural product used for many years in the treatment of various diseases, was chosen as the starting compound for this study. After obtained oxirane derivative **2** from the treatment of carvacrol with epichlorohydrin, the oxirane ring was opened with various amines. Although having a steric effect, the highest yield (88%) was obtained with the reaction of tert-butyl amine (**3c**). The other highest yield was obtained from allylamine with 86% (**3a**). In the presence of cyclohexylene ethylamine 80% yield was observed (**3d**). The other primary amine containing a pyridine group gave 78% yield (**3e**). As expected, the lowest yield between of them was obtained from diethylamine with 74% (**3b**). Biological activity studies of the oxypropanolamines derivatives **(3a-e)** were subsequently performed.

3.2. Biological results

Carvacrol based novel oxypropanolamine derivatives (**3a-e**) were tested to evaluate their inhibitory effects towards the hCA I and II isoenzymes, AChE, and α-glycosidase enzymes. The chemical structure of these compounds is given in Scheme 1 and their AChE, α-glycosidase, and CA I, and II isoforms inhibition data are summarized in Table 1.

CA inhibitors (CAIs), such as acetazolamide (AZA), are used as anti-glaucoma drugs to lower intraocular pressure, but it has been found out that some of these drugs act as vasodilators of retinal arteries [50]. The hCA I isoenzyme was inhibited by these compounds; with Ki values which found between 27.18 ± 6.86 and

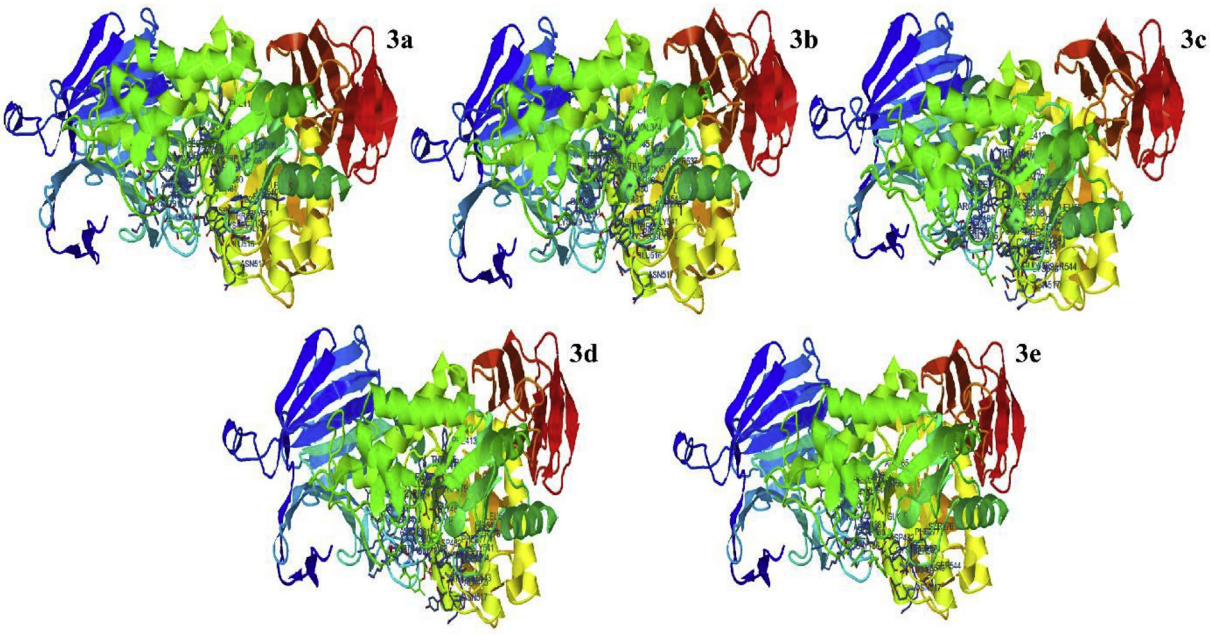

Fig. 2. Demonstration of the interaction of 1XSI protein with the studied molecules.

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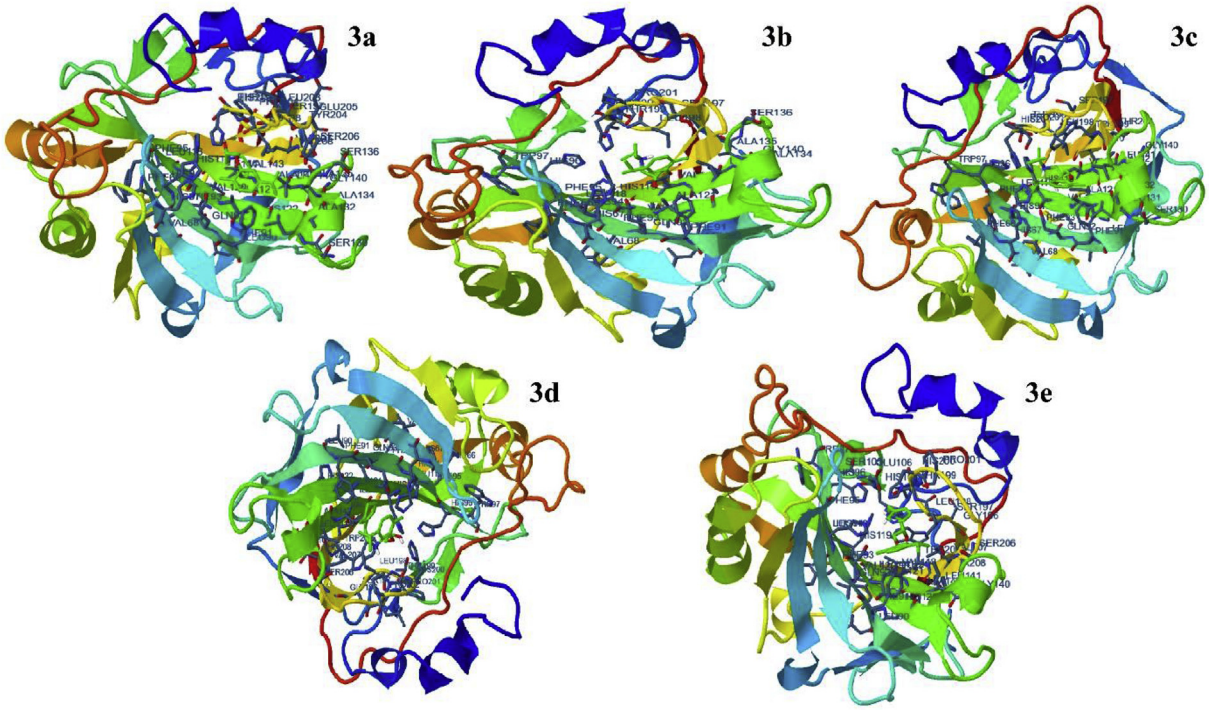

Fig. 3. Demonstration of the interaction of 2CAB protein with the studied molecules.

44.84 ± 10.53 nM. In addition, 1-((2-(cyclohex-1-en-1-yl)ethyl) amino)-3-(5-isopropyl-2-methylphenoxy)propan-2-ol (**3d**), and 1-(5-isopropyl-2-methylphenoxy)-3-((pyridin-3-ylmethyl)amino) propan-2-ol **(3e)** were recorded the most powerful hCA I isoform inhibition properties with Ki values of 27.18 ± 6.86 and 30.57 ± 8.60 nM, respectively. The control and clinically used drug AZA demonstrated a Ki value of 51.83 ± 7.83 nM. Hence, the investigated novel molecules showed better inhibition profiles when compared to AZA (Table 1).

CAIs have diverse therapeutic applications. For instance, hCA II, and, IV and XII inhibitors are utilized as glaucoma and in diuretics. The hCA II and VII inhibitors are utilized as anti-epileptic drugs, whereas certain anti-inflammatory and antitumor CAIs are isoforms hCA IX and XII [51,52]. The results clearly showed that hCA II was impressively inhibited by the carvacrol based novel oxypropanolamine derivatives (**3a-e**). These compounds had strong hCA II inhibition with Ki values ranging from 25.62 ± 6.11 to 38.71 ± 5.17 nM. Ki values of novel molecules appear to be better than those of the standard used drug AZA (Ki: 60.77 ± 14.07 nM). All the evaluated novel molecules showed potent inhibition against hCA II, but the compounds of 1-((2-(cyclohex-1-en-1-yl)ethyl) amino)-3-(5-isopropyl-2-methylphenoxy)propan-2-ol (**3d**), and 1-(5-isopropyl-2-methylphenoxy)-3-((pyridin-3-ylmethyl)amino) propan-2-ol **(3e)** showed significant inhibition profile against hCA II with Ki values of 25.62 ± 6.11 and 27.93 ± 4.13 nM (Table 1).

There is much considerable concern in the mechanism of action for different compounds against neurodegenerative diseases. Principally in AD, some organic compounds have shown the capability to address the etiology of neurological disturbances as they deteriorate their molecule physiology by regulating therapeutic goals with decreased in the risk of AD with age [53]. Also, the inhibitors of these enzymes can decrease inflammation by behaving as anti-inflammatory factors and by reducing the risk of oxidative stress. Indeed, there are some accessible reports in the literature for diverse isoflavones, flavonols, flavones, curcuminoids, anthocyanidins, and stilbenes for a beneficial role in inhibiting AChE enzyme. On the other hand, several plants extracts were found rich in phytochemicals principally alkaloids having a potential or capacity to inhibit AChE [54,55]. The inhibitory effects of these compounds on AChE enzyme are shown in Table 1. The AChE inhibition profiles of the molecules investigated here were really interesting. Overall, these compounds had excellent inhibitory activity with Ki values in ranging from 99.83 ± 14.75 nM to 146.25 ± 17.22 nM. Additionally, tacrine, utilized as a control AChEI in this paper, demonstrated Ki value of 177.15 ± 39.05 nM toward AChE. The inhibition of AChE of Carvacrol based novel oxypropanolamine derivatives (**3a-e**) is much better than standard drug. The compounds of 1-(allylamino)-3-(5-isopropyl-2-methylphenoxy)propan-2-ol (**3a**), and 1-(tert-butylamino)-3-(5-isopropyl-2-methylphenoxy)propan-2-ol (**3c**) showed excellent inhibition profile against AChE with Ki values of 99.83 ± 14.75 and 119.85 ± 34.81 nM, respectively (Table 1). Various drugs utilized in the therapy of AD are based on the appointed cholinergic hypothesis, where the target is to enhance the concentration of ACh level in the synaptic cleft by the inhibition of cholinesterase activity. AChEIs prevent the breakdown of the cholinesterase enzyme, augmenting the synaptic accessibility of ACh in the brain and subsequently boosting cholinergic neurotransmission in forebrain regions that result in compensating the loss of functioning of brain cells. Owing to this, AChE inhibition has been documented as a critical treatment route of AD [56,57].

One of the most beneficial therapeutics was proposed as maintaining blood glucose at normal levels after a meal. This approach may gradually help avoid chronic hyperglycemia, reduce insulin resistance and consequently appear crucial in the hydrolysis of polysaccharides to obtain glucose more suitable for absorption. Hyperglycemia in patients with T2DM was attributed to starch breakdown by pancreatic α-amylase and glucose uptake by intestinal α-glycosidase [58,59].

In fact, there are many available antidiabetic drugs such as

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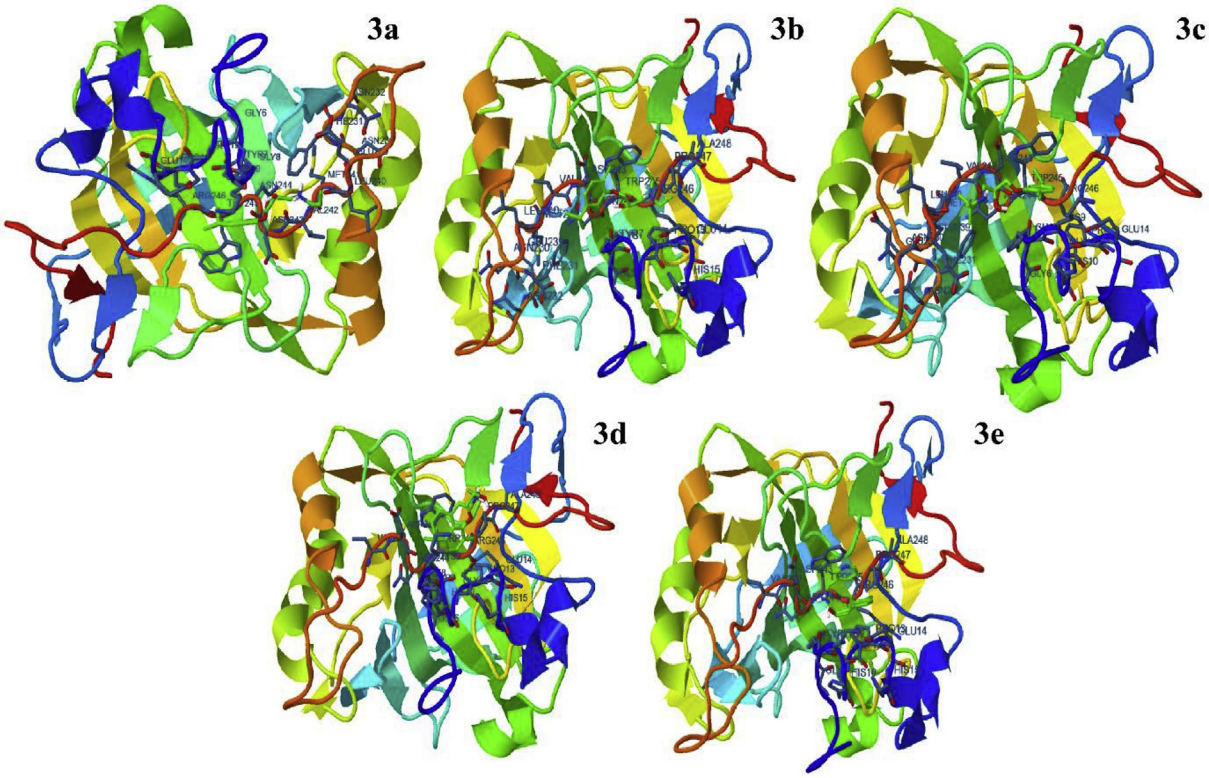

Fig. 4. Demonstration of the interaction of 4R5B protein with the studied molecules.

Table 2
Molecular energy data for studies molecule for hCA I, hCA II, AChE and α-glycosidase enzymes.

	Molecular energy data	3a	3b	3c	3d	3e
hCA I	Estimated Free energy of binding (kCal/mol)	−2.55	−2.41	−1.45	9.58	1.89
	Estimated Ki (mM)	13.56	17.14	86.49	–	–
	vdW + Hbond + desolv energy (kCal/mol)	−4.84	−4.17	−3.21	4.58	−2.71
	Electrostatic Energy (kCal/mol)	−0.14	−0.06	−0.19	−0.13	−0.28
	Total Intermolecular energy (kCal/mol)	−4.98	−4.24	−3.39	4.45	−2.98
	Frequency	%70	%80	%40	%20	%20
	Interact. Surface	615.86	629.83	644.61	645.43	632.59
hCA I	Estimated Free energy of binding (kCal/mol)	−4.68	−4.72	−5.58	−5.38	−5.05
	Estimated Ki (mM)	368.87	348.67	81.18	114.72	199.65
	vdW + Hbond + desolv energy (kCal/mol)	−5.39	−6.28	−5.89	−5.99	−5.61
	Electrostatic Energy (kCal/mol)	−0.42	−0.22	−0.38	0.04	−0.51
	Total Intermolecular energy (kCal/mol)	−5.81	−6.50	−6.27	−5.95	−6.12
	Frequency	%10	510	%20	%20	%10
	Interact. Surface	590.22	601.41	621.23	544.87	571.57
AChE	Estimated Free energy of binding (kCal/mol)	−7.45	−7.37	−8,19	−8.23	−8.38
	Estimated Ki (mM)	3.46	3.99	986.22	923.13	714.61
	vdW + Hbond + desolv energy (kCal/mol)	−7.22	−7.94	−7.92	−8.16	−9.01
	Electrostatic Energy (kCal/mol)	−1.35	−0.50	−0.82	−0.76	−1.36
	Total Intermolecular energy (kCal/mol)	−8.57	−8.44	−8.74	−8.93	−10.37
	Frequency	%10	%20	%10	%10	%20
	Interact. Surface	656.10	920.95	941.99	989.56	1037.67
α-Gly	Estimated Free energy of binding (kCal/mol)	−6.31	−6.24	−6.75	−7.10	−6.14
	Estimated Ki (mM)	23.79	26.62	11.31	6.29	31.80
	vdW + Hbond + desolv energy (kCal/mol)	−5.20	−6.21	−6.01	−7.83	−5.97
	Electrostatic Energy (kCal/mol)	−2.31	−1.70	−1.98	−1.99	−1.41
	Total Intermolecular energy (kCal/mol)	−7.52	−7.91	−7.99	−9.82	−7.38
	Frequency	%20	%10	%10	%20	%10
	Interact. Surface	657.57	671.27	640.28	744.47	680.09

biguanides, sulfonylureas, meglitinides, thiazolidinediones, α-glycosidase inhibitors, incretin mimetics, dipeptidyl peptidase-IV inhibitors and insulin; however, the use of these pharmaceutical drugs may cause undesired and severe side effects [60]. For this metabolic enzyme, the Carvacrol based novel oxypropanolamine derivatives (**3a-e**) had IC_{50} values in the range of 904.10−1065.73 nM and Ki values in the range of 896.61 ± 78.63−1026.80 ± 147.3 nM (Table 1). The results clearly

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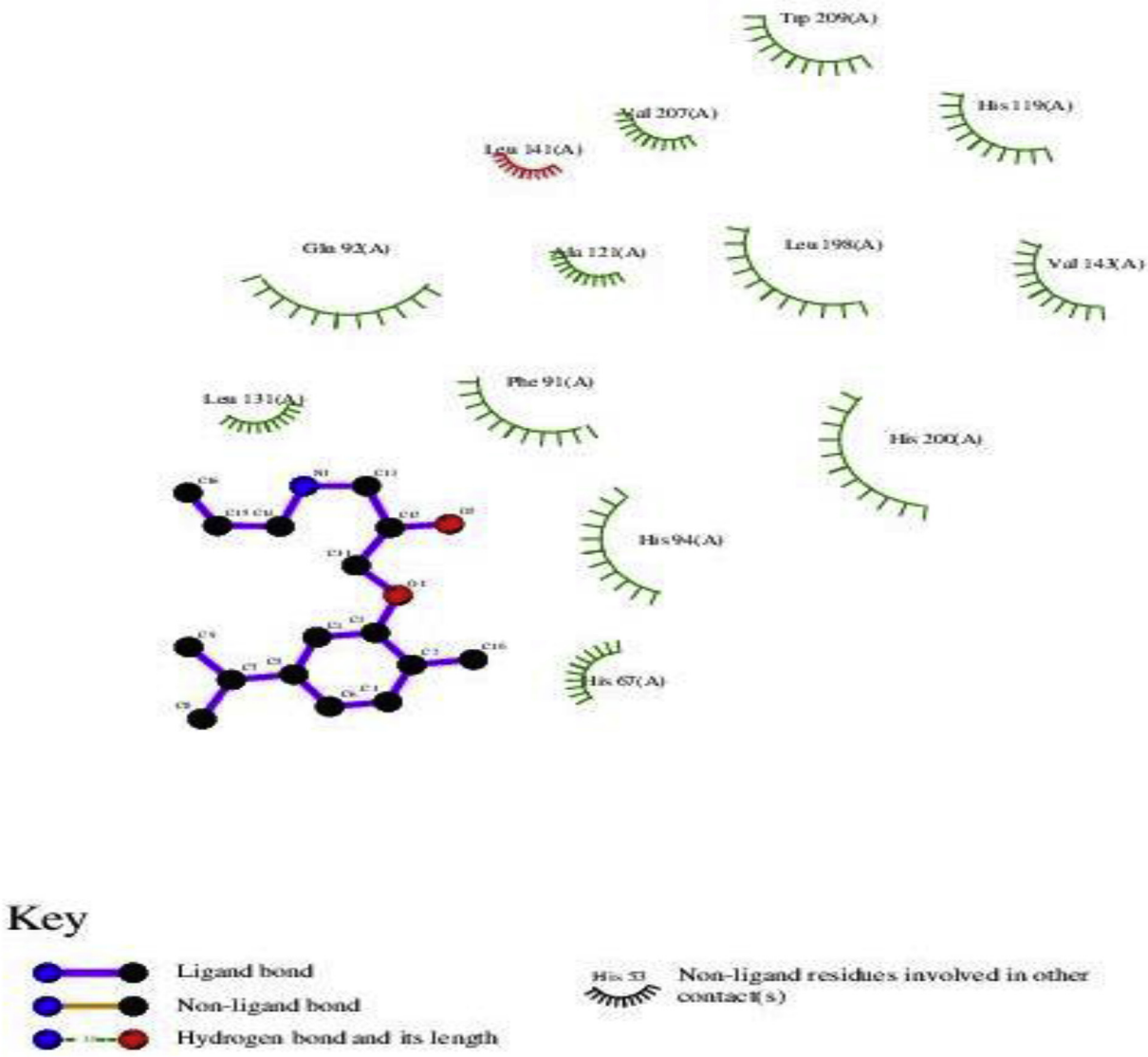

Fig. 5. Showing of interactions between hCA I isoenzyme and novel oxypropanolamine derivative of **3a**.

showed that all novel derivatives (**3a-e**) were recorded efficient α-glycosidase inhibitory effects than that of acarbose (IC_{50}: 22800 nM) [61,62] as a control α-glycosidase inhibitor. However, the most effective Ki values were obtained by 1-((2-(cyclohex-1-en-1-yl)ethyl)amino)-3-(5-isopropyl-2-methylphenoxy)propan-2-ol (**3d**) and 1-(tert-butylamino)-3-(5-isopropyl-2-methylphenoxy) propan-2-ol (**3c**), with Ki values of 896.61 ± 78.63 and 904.88 ± 101.88 nM, respectively. One remedial approach for treating diabetes diseases involves regulating postprandial hyperglycemia by inhibiting the α-glycosidase enzyme in the digestive tract, prolonging the overall digestion of carbohydrate. Also, carbohydrate digestion should decrease consequently to prevent spikes and the rate of glucose absorption in the postprandial blood glucose and insulin levels. Utilizing these enzyme inhibitors has become a promising therapeutic mechanism for decreasing the risks of carbohydrate-mediated diseases and diabetes, hyperlipoproteinemia, and obesity [63].

In the previous studies, Aksu et al. (2013) A series of novel sulfamides incorporating the dopamine scaffold were synthesized and inhibition of six α-CAs, that are CA I, CA II, CA VA, CA IX, CA XII and CA XIV, and two β-CAs from *Candida glabrata* and *Mycobacterium tuberculosis* with these sulfamides was investigated. All CA isozymes were inhibited in the low micromolar to nanomolar range by the dopamine sulfamide analogues [17]. Zengin et al. (2018) a series of thymol bearing oxypropanolamine compounds were synthesized and characterized. Their in vitro antibacterial activity on *A. baumannii*, *P. aeruginosa*, *E. coli* and *S. aureus* strains were investigated with agar well diffusion method. These novel thymol bearing oxypropanolamine derivatives were effective inhibitors of the α-glycosidase, hCA I and II isoforms, and AChE with Ki values in the range of 463.85—851.05 μM for α-glycosidase, 1.11—17.34 μM for hCA I, 2.97—17.83 μM for hCA II, and 13.58—31.45 μM for AChE, respectively [22]. Also in the other study, Biçer et al. (2019) the newly synthesized bis-thiomethylcyclohexanone compounds showed Ki values of in range of 39.14—183.23 nM against hCA I, 46.03—194.02 nM against hCA II isoenzyme, 4.55—32.64 nM against AChE and 12.77—37.38 nM against BChE. As a result, novel bis-thiomethylcyclohexanone compounds can have promising anti

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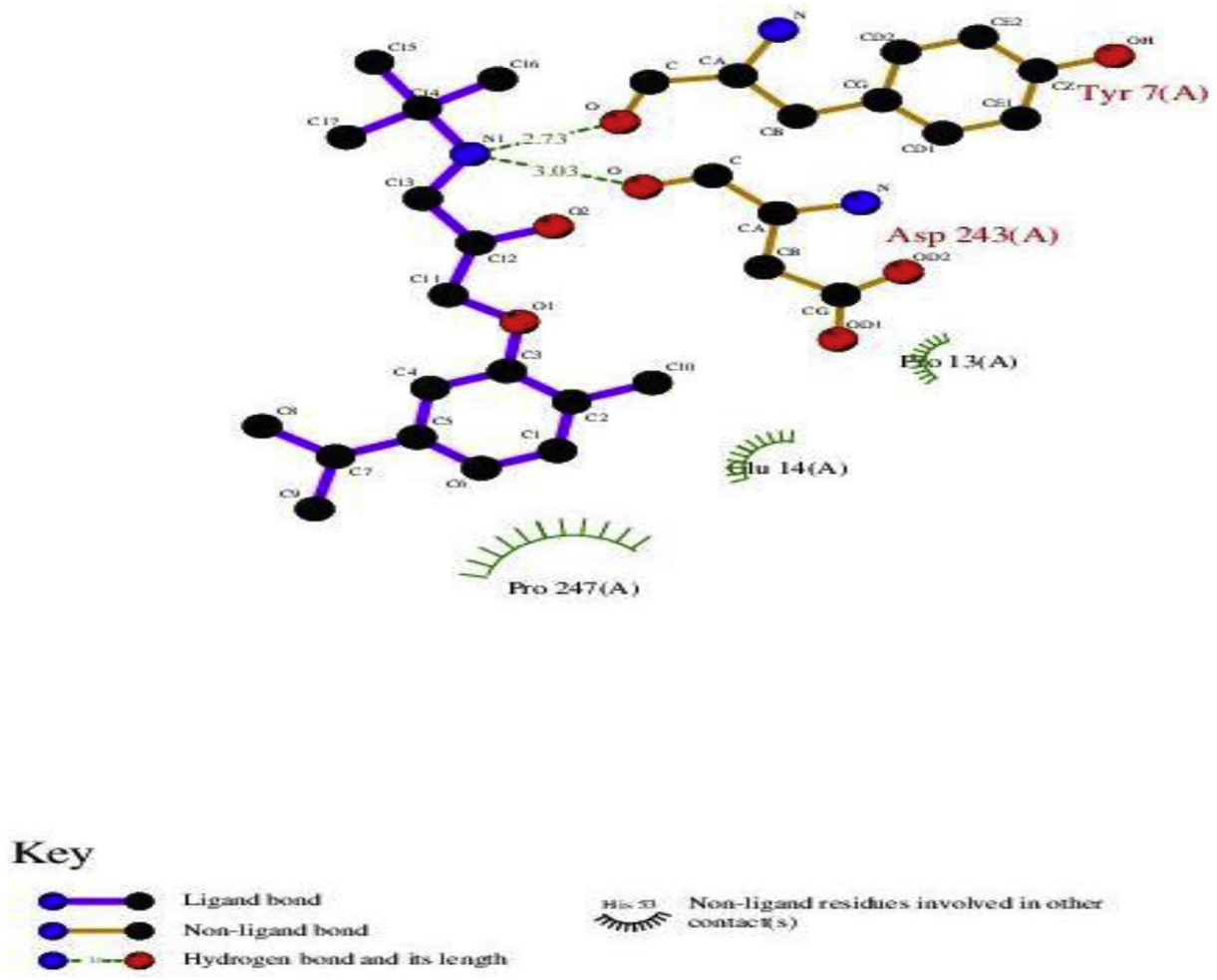

Fig. 6. Showing of interactions between hCA II isoenzyme and novel oxypropanolamine derivative of **3c**.

Alzheimer drug potential and record novel hCA I, and hCA II enzymes inhibitor [25]. When we compared these three studies, they were obtained results similar to the inhibitor values in our study, and our results were obtained at nM level.

3.3. Molecular docking

Theoretical studies are the simplest and fastest method used to determine the biological activities of molecules. The most important of theoretical studies is molecular docking. In docking studies, the interaction of enzymes formed by proteins and studied molecules are examined. In this study, both the experimental and theoretical approaches are studied. The theoretical study was compared against the experimental findings. The enzymes formed by the combination of proteins and ligands were studied. The interactions of the studied with the enzymes are shown in Figs. 1–4. In molecular docking, all calculations were made at pH 7.3. The reason for making calculations at this pH is because of the pH value at which these enzymes are most active in metabolisms. By working at this pH, it was ensured that the experimental values and theoretical values were compatible with each other [64].

Many parameters and data were obtained from the interaction of molecules with studied enzymes. For this study, the first parameter Est. Free Energy of Binding, where the numerical values for this parameter can be sorted as follows: 2.55, −2.41, −1.45, 9.58, 1.89 for hCA I, −4.68, −4.72, −5.58, −5.38, −5.05 for hCA II, −7.45, −7.37, −8,19, −8.23, −8.38 for AChE, −6.31, −6.24, −6.75, −7.10, −6.14 for α-Gly. The results show that 3d is the most active molecule for α-glycosidase. This result is consistent with the experimental result. The next parameter is Est. Inhibition constant (Ki) where the values for this parameter [65], can be sorted as follows: 13.56, 17.14, 86.49 for hCA I, 368.87, 348.67, 81.18, 114.72, 199.65 for hCA II, 3.46, 3.99, 986.22, 923.13, 714.61 for AChE, 23.79, 26.62, 11.31, 6.29, 31.80 for α-glycosidase. This parameter shows that both drug molecules can inhibit an enzyme and drug molecules can interact with a substrate for the enzyme. If the value of this parameter of one of the studied molecules is greater than the other molecules, extra drug is needed to prevent enzyme activity [66]. The lowest value for this parameter is the AChE enzyme 3a molecule. This result is consistent with the experimental results. The next parameter is vdW + Hbond + desolve Energy, whose numerical values are listed as follows: 4.84, −4.17, −3.21, 4.58, −2.71 for hCA I, −5.39, −6.28, −5.89, −5.99, −5.61 for hCA II, −7.22, −7.94, −7.92, −8.16, −9.01 for AChE, −5.20, −6.21, −6.01, −7.83, −5.97 for α-glycosidase. The numerical values of this parameter are very important parameter for molecular docking calculations. This parameter is an important parameter used to determine the position of enzyme proteins relative to the ligand studied. If this value has a negative value, it shows good binding to the active site in the enzyme. The most negative value for this parameter is the 3d molecule for the enzyme

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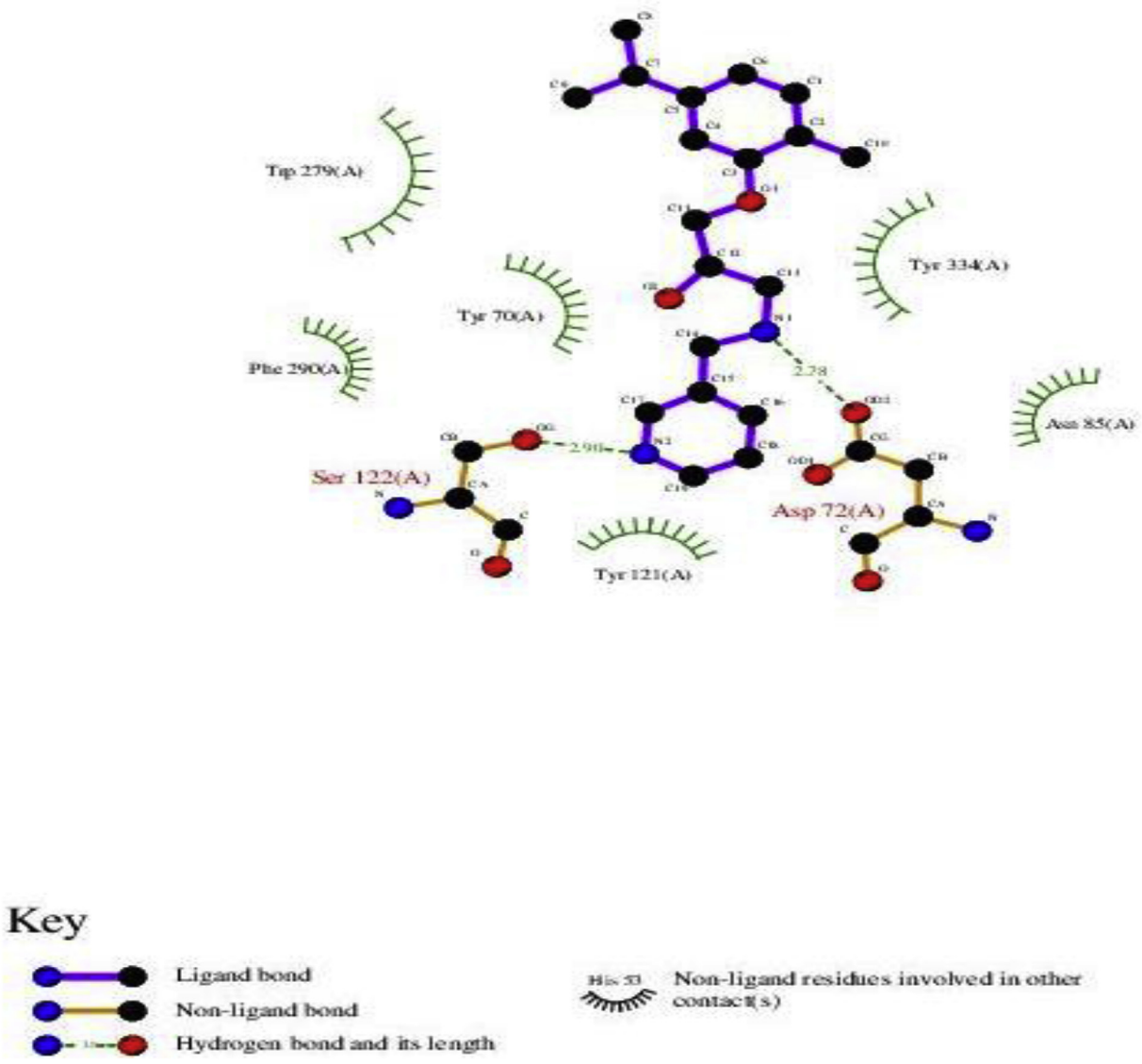

Fig. 7. Showing of interactions between AChE enzyme and novel oxypropanolamine derivative of **3e**.

α-glycosidase. Final parameter for molecular docking calculations is Electrostatic energies are −0.14, −0.06, −0.19, −0.13, −0.28 for hCA I, −0.42, −0.22, −0.38, 0.04, −0.51 for hCA II, −1.35, −0.50, −0.82, −0.76, −1.36 for AChE, −2.31, −1.70, −1.98, −1.99, −1.41 for α-glycosidase. If the numerical value of this parameter has a negative value, it shows that there is chemical interaction between molecules and proteins that make up the enzyme [67]. The numerical value of this parameter is obtained as a negative for all enzymes. This indicates that all enzymes are in chemical interaction with proteins (Table 2).

There are many interactions between molecules and enzymes. These interactions allow the molecule to bind to the protein. These interactions increase the biological activity of the molecule. Thus, the interactions between the hCA I isoenzyme, and the molecule 3a are shown in Fig. 5. The hCA I is composed of several amino acid, which named as His-94, His-119, and His-200. The distance between the His-94 protein and the N1 atom in novel oxypropanolamine derivative of **3a** is 3.54 atomic units. The distance between the His-94 protein and the H21 atom in novel oxypropanolamine derivative of **3a** is 3.58 atomic units. The distance between the His-94 protein and the H20 atom in novel oxypropanolamine derivative of **3a** is 2.89 atomic units. However, the distance between the His-119 protein and the H20 atom in molecule 3a is 3.52 atomic units. The distance between the HIS-200 protein and the H21 atom in novel oxypropanolamine derivative of **3a** is 2.90 atomic units. On the other hand, the interactions between the enzyme hCA II and the novel oxypropanolamine derivative of **3c** are shown in Fig. 6. The hCA II is composed of several proteins, the names of which are Tyr-7 and Asp-243. The distance between the Tyr-7 protein and the N1 atom in novel oxypropanolamine derivative of **3c** is 2.73 atomic units. The distance between the Asp-243 protein and the N1 atom in molecule 3c is 3.03 atomic units. Moreover, the interactions between the enzyme AChE and the molecule 3e are shown in Fig. 7. The enzyme AChE is composed of several proteins, the names of which are Ser-122, Tyr-334 and Asp-72. The distance between the Ser-122 protein and the N2 atom in novel oxypropanolamine derivative of **3e** is 2.90 atomic units. The distance between the TYR-334 protein and the H21 atom in novel oxypropanolamine derivative of **3e** is 3.11 atomic units and the H20 atom in novel oxypropanolamine derivative of **3e** is 3.11 atomic units. The distance between the ASP122 protein and the N1 atom in molecule 3e is 2.78 atomic units and the H20 atom in molecule 3e is 2.38 atomic units

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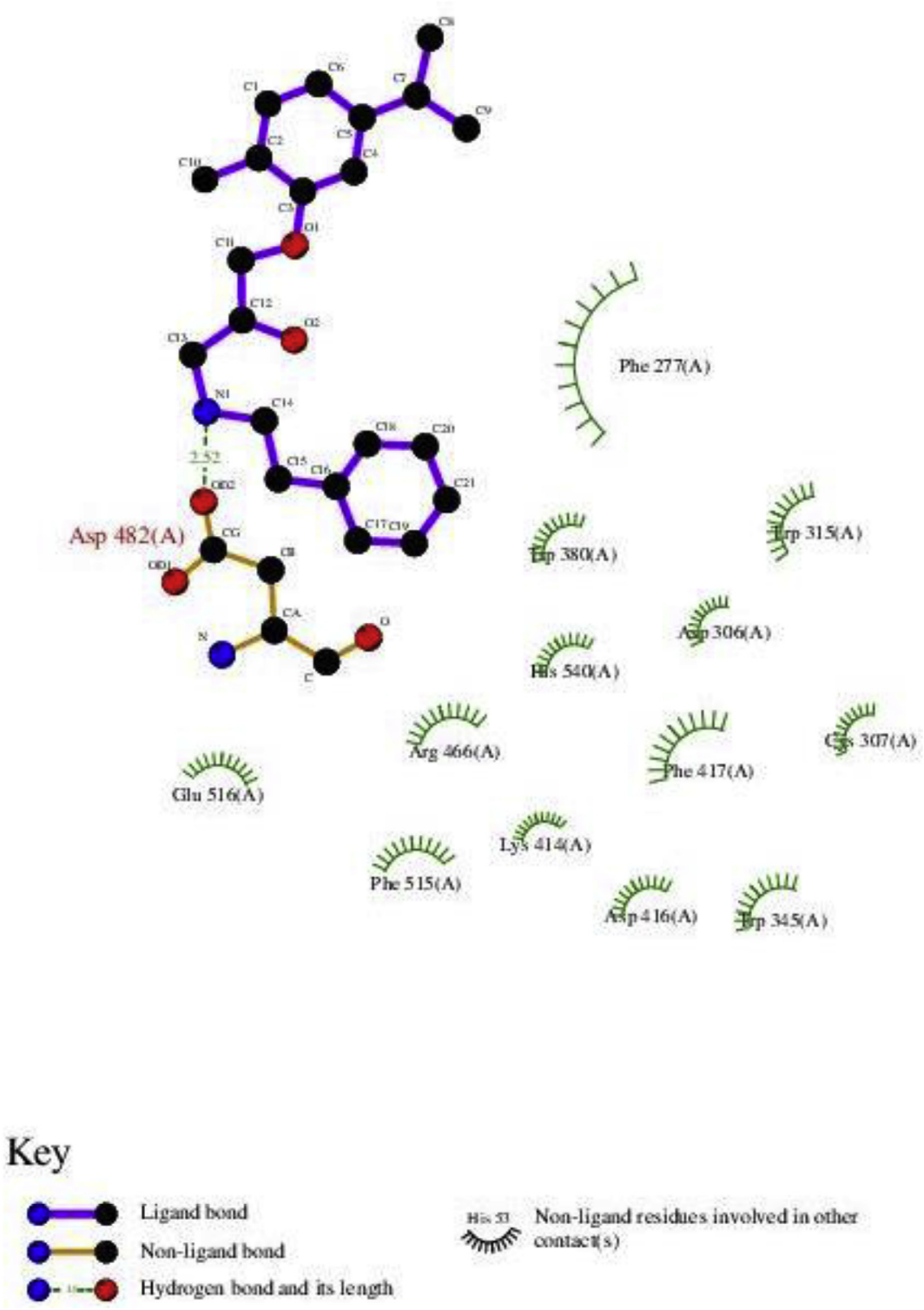

Fig. 8. Showing of interactions between α-Gly enzyme and novel oxypropanolamine derivative of **3d**.

and the H21 atom in molecule 3e is 2.96 atomic units. The interactions between the α-glycosidase and the molecule 3d are shown in Fig. 8 whereby the enzyme α-glycosidase is composed of several proteins, the names of which are Asp-482 and Phe-515. The distance between the Asp-482 protein and the N1 atom in novel oxypropanolamine derivative of **3d** is 2.52 atomic units and the H20 atom in molecule 3d is 2.75 atomic units and the H21 atom in molecule 3d is 3.37 atomic units. The distance between the Phe-515 protein and the H20 atom in novel oxypropanolamine derivative of **3d** is 3.23 atomic units.

In the light of the above information, the obtained data indicate that all interactions between the enzyme and the molecule are mostly between heteroatoms. One of the most important factors affecting the biological activity of the molecule is the interaction

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between molecules and proteins. As this interaction increases, the biological activity of the molecule increases, too. Furthermore this interaction increases, as the distance between the molecule and the enzyme decreases.

4. Conclusions

The results showed that experimental and theoretical results are similar. The reason some of the differences is that the theoretical studies are conducted in pure and isolated environment. There are many experimental attempts to cause these differences in experimental studies. As we explained above, novel molecules studied in the work can be used in selective candidate drugs, the same as hCAIs, for therapy of some diseases such as: glaucoma, epilepsy, mountain sickness, osteoporosis, gastric and duodenal ulcers, or neurological disturbances. All these molecules effectively inhibited important enzymes such as hCA I, hCA II, α-glycosidase, and AChE enzymes at the nanomolar levels. Inhibitors of α-glycosidase defer the break of starch in the little intestine and reduce the postprandial blood glucose deviation levels in diabetic patients. Henceforth, the restraint of α-glycosidase conspicuous chemicals has been set up as a practical and proficient methodology to diminish the dimensions of postprandial hyperglycemia. Several antidiabetic commercial drugs such as acarbose, voglibose, and miglitol are currently available in the market in use for the treatment of α-amylase and α-glycosidase enzyme inhibition in diabetes mellitus. Hence, findings indicate that these molecules can be candidate drugs as potential inhibitors for some diseases. Their clinical use has been established as diuretics, antiepileptics, and anti-glaucoma factors, in the management of gastric, duodenal ulcers, mountain sickness, osteoporosis, idiopathic intracranial hypertension and neurological disorders.

Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molstruc.2019.127297.

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