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Novel eugenol bearing oxypropanolamines: Synthesis, characterization, antibacterial, antidiabetic, and anticholinergic potentials

Hayriye Genç Bilgiçli[a,*], Ali Kestane[a], Parham Taslimi[b], Oguz Karabay[c], Arlinda Bytyqi-Damoni[d], Mustafa Zengin[a], İlhami Gulçin[e]

[a] Sakarya University, Science and Arts Faculty Chemistry Department, 54187-Serdivan Sakarya, Turkey
[b] Department of Biotechnology, Faculty of Science, Bartin University, 74100 Bartin, Turkey
[c] Sakarya University, Faculty of Medicine Infectious Diseases and Clinical Microbiology Department, 54290-Adapazarı Sakarya, Turkey
[d] University of Pristina, Faculty of Education, Department of Chemistry, Pristina, Kosovo
[e] Department of Chemistry, Faculty of Science, Atatürk University, 25240-Erzurum, Turkey

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ABSTRACT

Five oxypropanol amine derivatives that four of them are novel have been synthesized with high yields and practical methods. *in vitro* antibacterial susceptibility of *Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli* and *Staphylococcus aureus* strains to synthesized substances were evaluated with agar well-diffusion method by comparison with commercially available drugs. Most of the bacteria were multidrug resistant. It was concluded that these compounds are much more effective than reference drugs. These eugenol bearing oxypropanolamine derivatives were also effective inhibitors against α-glycosidase, cytosolic carbonic anhydrase I and II isoforms (hCA I and II), and acetylcholinesterase (AChE) enzymes with K_i values in the range of 0.80 ± 0.24–3.52 ± 1.01 μM for hCA I, 1.08 ± 0.15–3.64 ± 0.92 μM for hCA II, 5.18 ± 0.84–12.46 ± 2.08 μM for α-glycosidase, and 11.33 ± 2.83–32.81 ± 9.73 μM for AChE, respectively.

1. Introduction

Eugenol (4-Allyl-2-methoxyphenol) which is inexpensive, easily affordable and pharmacologically active a natural monoterpene compound is the main component of clove buds, (*Syzygium aromaticum*) and it is also found in nutmeg (*Myristic afragrans*), basil (*Ocimum basilicum L.*) and cinnamon (*Cinnamomum zeylanicum*) [1]. Since ancient times this essential oil is also well known for antibacterial, antimicrobial and antioxidant properties. Numerous studies on the antimicrobial effect of eugenol for certain agents are available in the literature [2]. Many molecules having oxypropanol amine moiety are marketed commercially as β-adrenoceptors [3]. They used in especially cardiovascular disease, and also used in the treatment of many diseases such as hypertension, thyrotoxicosis, angina pectoris, chronic pulmonary diseases [4], skin inflammation [5] and diuretic [6]. We have had many previous studies on antibacterial [7] and enzyme activity [8–12]. These experiences have shown us that, natural products having therapeutic properties, and core structures already proven having biological activity are great sources of inspiration for discovering new drugs. Hence, compounds containing eugenol and oxypropanolamine core structures have been studied by considering that they have biological activities.

α-Glycosidase is the key enzyme involved in the digestion of the carbohydrate. The α-Amylase enzyme hydrolyzes the α-linked polysaccharide molecules into oligosaccharide molecules, and α-glycosidase enzymes, membrane-bound enzymes which are located in the brush border of the small intestine, catalyze the final stage in the digestive mechanism of carbohydrate molecule to release absorbable monosaccharides like glucose [13,14]. Thus, inhibitor compounds of α-glycosidase can reduce range the liberation of absorbable monosaccharide molecules from dietary complex carbohydrates, delaying the absorption of glucose molecule into the bloodstream and so prevent any sudden rise in meal-induced blood glucose level [15].

Acetylcholinesterase (AChE, E.C. 3.1.1.7) as neural enzyme performs a key role in the functioning of cholinergic neuronal pathways [16]. This enzyme finishes nerve transmission at cholinergic synapses by hydrolysis of the acetylcholine (ACh), which is involved in both learning and memory [17,18]. Conforming to the cholinergic hypothesis, impairment of the cholinergic pathways plays an important role in the development of neurodegenerative diseases such as depression, schizophrenia, Alzheimer's disease (AD) problems with the regulation of traumatic brain injury and sleep [19–21]. The AD is the main reason for dementia disease, and mild to moderate cases are generally treated

* Corresponding author at: Sakarya University, Arts and Science Faculty, Chemistry Department, 54187 Serdivan-Sakarya, Turkey.
E-mail address: hayriyegenc@sakarya.edu.tr (H. Genç Bilgiçli).

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with AChE inhibitors (AChEIs) [22,23]. For example, in Japan, three ChEI (rivastigmine, galantamine, and donepezil) are now available; the effect of these drugs on Japanese AD patients has been reported in previous studies. Thus, AD patients sometimes discontinue ChEI treatment or have to switch to another ChEI because of side effects, a rapid reduction in hospitalization or cognitive function unrelated to AD [24–27].

Conversion of water (H_2O) and carbon dioxide (CO_2) into the proton (H^+) and bicarbonate (HCO_3^-) is an important reaction catalyzed by a superfamily of zinc-containing metalloenzymes, called carbonic anhydrase (CA, E.C.4.2.1.1) isoenzymes [28,29]. Human CA inhibitor compounds clinically use for more than seventy years as antiglaucoma and diuretics drugs [30–33]. Glaucoma is a multifactorial optical illness determined by optical nerve degeneration mainly relevant to high intraocular pressure (IOP), which can give rise to blindness. hCA inhibitor compounds such as acetazolamide, brinzolamide, and dorzolamide are efficient in decreasing IOP after topical administration; Hence, these drugs have the various side effect, new therapeutic factors are needed [34]. The CA IV and CA II isoenzymes commonly involved in aqueous humor secretion. Topical and oral CA inhibitor compounds are also utilized in other ocular diseases, among which cystoid macular oedema [35,36].

In the present study we explain the design, synthesis and evaluation of some of novel eugenol oxypropanolamine derivatives (**2, 3a-e**) as effective α-glycosidase, AChE, hCA inhibitor agents. Another main goal of this study, is compared their inhibitory effects with standard compounds like acetazolamide, tacrine, and acarbose.

2. Materials and methods

2.1. Synthesis of 2-((4-allyl-2-methoxyphenoxy)methyl)oxirane (2)

The route followed for the synthesis of **3a-e** is given in Scheme 1. Sodium hydroxide (0.24 g, 6.6 mmol) in water (10 mL) was added dropwise to a solution of eugenol (1.084 g, 6.6 mmol) and epichlorohydrin (10 mL) in 85 °C over a period of 0.5 h under vigorous stirring. The reaction mixture was kept at the same temperature till the eugenol completely consumed. Then the reaction mixture was solved in ethyl acetate (20 mL) and washed with brine (2x15 mL), dried over $MgSO_4$, and filtered. Organic phase was removed under reduced pressure and oily residue was obtained **2** (1.45 g, 92%).

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

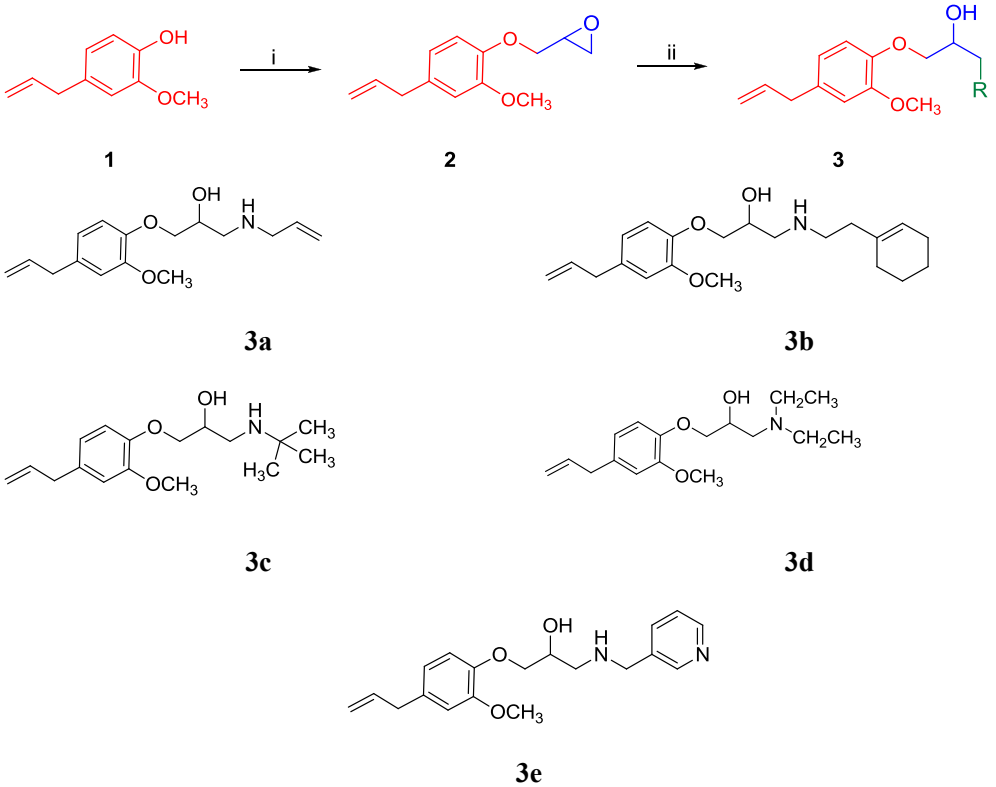
To a solution of **2** (1 mmol) and aqueous saturated solution of K_2CO_3 (2 mL) was added related amine (3 mmol) at room temperature. The mixture was vigorously stirring for 5–24 h untill the reaction was completed according to TLC. Then the mixture was extracted with ethyl acetate (10 mL) and water (2x10 mL). The organic phase was dried over anhydrous MgSO4 and the solvent was removed under reduced pressure. After recrystallization from ether and hexane mixture the product was analyzed by ^1H and ^{13}C NMR.

2.2.1. 1-(4-Allyl-2-methoxyphenoxy)-3-(allylamino)propan-2-ol (3a)

Yield 0.26 g, 95%; ^1H NMR (300 MHz, $CDCl_3$) δ_H 2.70–2.83(dd, 2H, *J* 11.95–4.23 Hz), 3.24–3.26 (d, 1H, *J* 6.63 Hz), 3.29–3.31(d, 2H, *J* 5.68 Hz), 3.80 (s, 3H), 3.94–3.98 (dd, 2H, *J* 6.68 Hz), 4.04–4.11(m, 1H), 5.03–5.05(d, 2H, *J* 8.51 Hz), 5.13–5.19 (d, 2H, *J* 9.18 Hz), 5.83–5.95(m, 2H), 6.66–6.68 (d, 1H, *J* 6.65 Hz), 6.68 (s, 1H), 6.80–6.83 (d, 1H, *J* 8.57 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 40.04, 51.61, 52.53, 55.96, 68.67, 73.14, 112.54, 114.66, 115.89, 116.33, 120.88, 133.80, 136.83, 137.81, 146.78, 149.74.

2.2.2. 1-(4-Allyl-2-methoxyphenoxy)-3-((cyclohex-1-en-1-ylmethyl) amino)propan-2-ol (3b)

Yield 0.31 g, 78%; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.49–1.64 (m, 4H), 1.89–1.97 (dd, 4H, *J* 10.31, 7.23), 2.04–2.13 (t, 2H, 7.81, 5.86 Hz), 2.66–2.83 (m, 3H), 3.30–3.33 (d, 1H, *J* 6.65 Hz), 3.82 (s, 3H),



Scheme1. Synthesis procedure for **2** and **3a-e**. (i) epichlorohydrin, NaOH/water, 85 °C, 0.5 h; (ii) Amine compound, saturated K_2CO_3 solution, room temperature, 5–24 h.

3.94–3.98 (dd, 2H *J* 6.68 Hz), 4.04–4.11 (m, 1H), 5.03–5.05 (d, 2H, *J* 8.51 Hz) 5.43 (s, 1H), 5.83–5.95 (m, 2H), 6.66–6.68 (m, 1H), 6.68 (s, 1H), 6.80–6.83 (d, 1H, *J* 8.57 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 25.46, 28.28, 38.62, 39.97, 42.35, 47.99, 52.08, 56.01, 68.47, 73.17, 112.57, 114.86, 115.89, 120.86, 122.88, 133.89, 135.23, 137.79, 146.81, 149.83.

2.2.3. 1-(4-Allyl-2-methoxyphenoxy)-3-(tert-butylamino)propan-2-ol (3c)

Yield 0.28 g, 98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.10 (s, 9H), 2.66–2.83 (dd, 2H, *J*12.4–3.75 Hz), 3.30–3.33 (d, 1H, *J* 6.65 Hz), 3.82 (s, 3H), 3.94–3.98 (dd, 2H *J* 6.68 Hz), 4.04–4.11 (m, 1H), 5.03–5.05 (d, 2H, *J* 8.51 Hz 5.83–5.95 (m, 2H), 6.66–6.68 (m, 1H), 6.68 (s, 1H), 6.80–6.83 (d, 1H, *J* 8.57 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 29.29, 29.29, 29.29, 40.06, 44.96, 50.37, 56.00, 68.77,73.32, 112.58, 114.73, 115.89, 120.86, 133.82, 137.81, 146.86, 149.83.

2.2.4. 1-(4-Allyl-2-methoxyphenoxy)-3-(diethylamino)propan-2-ol (3d)

Yield 0.25 g, 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H1.00–1.05 (t, 6H, *J* 7.12 Hz), 2.52–2.65(q, 4H, *J* 7.12 Hz), 2.61–2.66 (m, 3H), 3.30–3.33 (d, 1H, *J* 6.65 Hz), 3.82 (s, 3H), 4.00 (s, 1H), 4.00–4.01 (d, 2H *J* 8.97 Hz) 5.03–5.05 (d, 2H, *J* 8.51 Hz), 5.90–5.99 (m, 2H), 6.66–6.68 (m, 1H), 6.68 (s, 1H), 6.80–6.83 (d, 1H, *J* 8.57 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 12.19,12.19, 40.05, 47.45, 56.09, 56.17, 66.40, 72.75, 112.71, 114.66, 115.85, 120.78, 133.68, 137.86, 147.03, 149.87.

2.2.5. 1-(4-Allyl-2-methoxyphenoxy)-3-((pyridin-3-ylmethyl)amino) propan-2-ol (3e)

Yield 0.27 g, 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.74–2.78(dd, 2H, *J* 10.83, 6.53 Hz), 3.26–3.28 (d, 1H, *J* 6.25 Hz), 3.71–3.76(d, 2H, *J* 7.85 Hz), 3.71 (s, 3H), 3.94–3.98 (dd, 2H *J* 6.68 Hz), 4.04–4.11 (m, 1H), 5.03–5.05 (d, 2H, *J* 8.51 Hz), 5.13–5.19 (d, 2H, *J* 9.18 Hz), 5.83–5.95 (m, 2H), 6.66–6.68 (d, 1H, *J* 6.65 Hz), 6.68 (s, 1H), 6.80–6.83 (d, 1H, *J* 8.57 Hz). 7.64 (s, 1H), 8.41–8.49 (d, 2H, *J* 4.81 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 40.01, 51.36, 51.79, 55.91, 68.69, 73.06, 112.51, 112.56, 114.48, 115.92, 120.89, 123.68, 133.83, 135.76, 136.21, 137.76, 146.66, 148.49, 149.61, 149.73.

2.3. Strains and growth conditions

20 strains from each bacteria which were *A. baumannii, P. aeruginosa, E. coli* and *S. aureus* were obtained from stocks of Sakarya University Infectious Diseases and Clinical Microbiology Laboratory. The source of these stocks strains were isolated from laboratory specimens such as urine, blood and pus, which are taken by various clinics for diagnosis from clinics' hospitalized patients'. All of *A. baumannii P. aeruginosa* and *S. aureus* strains and some *E. coli* strains were identified as multidrug resistant (MDR) [37]. Antibiotic susceptibility profiles of all isolates were evaluated by Kirby Bauer's disk diffusion method according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) [38].

After obtained the isolates were stored at −20 °C in skimmed milk. Each strain was sub cultured on 5% blood agar at 37 °C for two consecutive days prior to the study. From strains obtained in the second passage, bacterial suspensions were prepared in tryptone soya broth (TSB) (Oxoid, Basingstoke, UK), and adjusted to a turbidity equal to McFarland 0.5 (1.5×10^8 cfu/ml) (DIN EN 1040, 2005). All strains were studied with an agar well-diffusion method [39].

2.4. Agar well-diffusion method

Each Mueller-Hinton agar plate was inoculated with microorganism by swabbing throughout the entire surface of the sterile agar. This procedure was repeated by streaking 2 more times, rotating the plate approximately 60 °C each time to ensure even distribution of the inoculum. As a final step, the rim of the agar was also swabbed. Once the agar was solidified, it was punched with eight-millimeter diameter wells and filled with 50 µL of the test material. The concentration of the employed chemical compound extracts was 10 mg/ml in DMSO. They are incubated at 37 °C for 18 to 24 h. Subsequently, the plates were examined for bacterial growth inhibition and the inhibition zone diameter (IZD) was measured with a ruler to the nearest millimeter.

2.5. Biochemical studies

CA inhibitory effects of novel eugenol oxypropanolamine derivatives (**2** and **3a-e**) was measured according to Verpoorte et al. [40] and conforming to previous studies [41–43] and measured at 348 nm spectrophotometrically using p-nitrophenylacetate substrate.

AChE inhibitory effect of novel eugenol oxypropanolamine derivatives (**2** and **3a-e**) was measured according to Ellman et al. [44] and conforming to previous studies [45–48] and measured at 412 nm spectrophotometrically using acetylthiocholine iodide as a substrate for the enzymatic reaction. 5,5′-Dithio-bis(2-nitro-benzoic) acid compound was used for the measurement of the AChE activity [49].

Inhibitory effect of novel eugenol oxypropanolamine derivatives (**2** and **3a-e**) on α-glycosidase enzyme activity was performed using p-nitrophenyl-D-glycopyranoside (*p*-NPG) as the substrate, conforming to the method of Tao et al. [50] (Tao et al., 2013). Firstly, 200 µL of phosphate buffer was mixed with 40 µL of the homogenate solution in phosphate buffer (0.15 U/mL, pH 7.4). Also, 50 µL of *p*-NPG in phosphate buffer (5 mM, pH 7.4) after preincubation was added and again incubated at 30 °C. The absorbances were spectrophotometrically measured at 405 nm, according to previous studies [51,52].

3. Results and discussion

Oxypropanolamines containing eugenol structure have been designed, synthesized and their biological activities were explored. The compounds **3a, 3b, 3d** and **3e** have been synthesized for the first time and **3c** [53] has been already known as β-adrenergic blocking agent drug. Methoxyphenoxymethyl oxirane derivative **2** was synthesized with a high yield by the reaction between eugenol and epichlorohydrin. Then, to obtain target oxypropanolamine derivatives (**3a-e**), the oxirane ring of **2** was opened with different amine compounds. Some biological activities such as enzyme inhibition and antibacterial activities of synthesized compounds **2** and **3a-e** were examined.

Antibacterial susceptibilities of 20 each of *Acinetobacter baumannii, Pseudomonas. aeruginosa, Escherichia coli*, and *Staphylococcus aureus* strains against **2** and **3a-e** were examined. Most strains were MDR (except some of *E. coli* strains). The antibacterial effects of oxypropanolamines against these strains were given in Tables 1–4.

Against *A. baumannii* isolates all compounds had greater than an average of 15 mm IZD, except **2**. Mean IZDs of **3a-e** compounds were determined as in the range of 18–21 mm.

The mean zones of inhibition ranged between 14 mm and 24 mm for *P. aeruginosa* except the intermediates **2** and bearing pyridine derivative **3e**. While **2** had not antibacterial activity against *P. aeruginosa* strains, **3e** were found to be effective for only 5 (20%) them (Table 2).

Against *E. coli* **3a-e** have in the range of 18 – 26 mm inhibition zone. The similar poor antibacterial activity of the intermediate **2** and pyridine bearing derivative **3e** also determined here. On the other hand **3a** and **3c** have ≥20 mm IZD in all tested *E.coli* stains (Table 3).

The average IZD of **3a-e** on *S.aureus* is ≥ 20 mm. Three phenoxypropanolamine derivatives having the strongest antibacterial effects on *S. aureus* with 26.8 mm, 25.9 mm and 24.4 mm IZD are **3b**, **3a**, and **3d** respectively (Table 4).

Five eugenol oxypropanolamine derivatives (**2, 3a-e**) were tested to evaluate their inhibitory effects towards the hCA I and II isoenzymes, AChE, and α-glycosidase enzymes. CA isoforms play important roles in a diversity of physiological mechanisms including electrolyte secretion in a diversity of organs and tissues, calcification, biosynthetic reactions (ureagenesis, lipogenesis, and gluconeogenesis are among them), pH

Table 1
The results of the disk sensitivity test and the inhibition zone of compounds **3a-e** against *A. baumannii*.

Strains	2	3a	3b	3c	3d	3e	CAZ	AK	CIP	IPM	CN	SAM	TZP
1	10	21	21	25	17	15	0	10	0	0	20	0	0
2	10	22	17	20	20	20	0	0	0	0	20	0	0
3	0	20	21	20	20	20	0	0	0	15	0	0	0
4	0	20	20	20	20	20	0	0	0	15	0	0	0
5	17	20	20	20	20	15	0	0	0	16	0	0	0
6	16	17	20	21	17	20	0	0	0	14	0	0	0
7	15	25	22	30	23	20	0	20	0	15	15	0	0
8	24	20	20	20	20	20	0	0	0	10	0	0	0
9	10	22	25	21	20	15	0	10	0	0	20	0	0
10	0	22	25	20	20	22	0	0	0	0	0	0	0
11	25	22	20	20	22	15	0	10	0	0	20	0	0
12	0	22	20	22	17	17	0	0	0	0	15	0	0
13	0	20	20	22	20	15	0	0	0	0	20	0	0
14	10	20	20	17	20	21	0	0	0	0	17	0	0
15	15	21	20	20	20	20	0	0	0	0	15	0	0
16	0	25	22	17	20	17	0	0	0	0	20	0	0
17	15	20	25	25	19	20	0	0	0	0	10	0	0
18	20	22	20	15	17	18	0	10	0	0	25	0	0
19	15	25	20	22	20	22	0	0	0	0	20	0	0
20	15	22	22	25	20	15	0	0	0	0	0	0	0
Average	11	21	21	21	20	18	0	3	0	4, 3	12	0	0

CAZ: ceftazidime, CIP: ciprofloxacin, IPM:Imipenem, AK:Amikacin, CN: Gentamicin TZP: Piperacillin/Tazobactam, SAM: Ampicillin/sulbactam.

Table 2
The results of the disk sensitivity test and the inhibition zone of compounds 3a-e against *P. aeruginosa*.

Strains	2	3a	3b	3c	3d	3e	CAZ	AK	CIP	IPM	CN	SAM	TZP
1	0	15	20	12	15	0	0	0	0	10	0	20	0
2	0	25	15	15	12	0	0	0	0	10	0	10	0
3	0	17	10	17	17	0	0	0	0	10	0	12	0
4	0	23	20	10	15	0	0	0	0	10	0	18	0
5	0	12	18	16	15	10	0	0	0	0	0	16	0
6	0	17	17	16	20	0	0	10	0	15	0	20	0
7	0	15	21	17	17	0	0	15	0	15	0	20	0
8	0	13	20	15	0	0	0	10	0	15	0	20	0
9	0	12	21	18	18	0	0	12	0	15	0	20	0
10	0	10	21	17	16	0	0	15	0	15	0	20	0
11	0	15	20	30	16	0	0	12	0	15	0	20	0
12	0	16	16	10	10	0	0	12	0	12	0	20	0
13	0	15	20	16	11	15	0	0	0	10	0	17	0
14	0	10	24	12	20	12	0	12	0	12	0	20	0
15	0	10	22	15	20	12	0	10	0	15	0	20	0
16	0	15	25	25	15	0	0	14	0	16	0	20	0
17	0	15	22	16	15	0	0	15	0	15	0	15	0
18	0	12	15	0	10	0	0	10	0	16	0	20	0
19	0	12	17	19	17	0	0	16	0	16	0	20	0
20	0	17	17	18	11	20	0	8	0		0	20	0
Average	0	15	19	16	15	3	0	9	0	13	0	18	0

CAZ: ceftazidime, CIP: ciprofloxacin, IPM:Imipenem, AK:Amikacin, CN: Gentamicin TZP: Piperacillin/Tazobactam, SAM: Ampicillin/sulbactam.

Table 3
The results of the disk sensitivity test and the inhibition zone of compounds **3a-e** against *E. coli*.

Strains	2	3a	3b	3c	3d	3e	CAZ	AK	CIP	IPM	CN	SAM	TZP
1	0	23	18	22	16	15	8	15	0	20	0	8	15
2	0	25	20	26	20	16	20	15	12	25	12	0	20
3	0	25	23	25	17	15	15	12	20	18	10	0	15
4	0	19	18	19	20	10	20	15	15	22	8	15	22
5	0	21	19	22	20	16	12	17	0	35	15	0	25
6	0	20	20	25	20	15	17	15	16	20	12	0	20
7	0	25	20	22	21	15	16	12	0	22	15	0	17
8	0	20	22	22	18	10	18	15	0	30	12	16	25
9	0	15	22	20	15	0	15	17	0	30	15	12	20
10	0	20	17	18	15	0	0	14	0	20	0	8	18
11	0	20	22	24	22	12	17	22	25	27	17	0	25
12	0	22	20	32	20	15	17	17	25	20	15	0	17
13	0	25	22	25	16	12	0	15	0	20	0	0	17
14	0	21	20	20	17	0	25	15	17	25	15	0	22
15	0	17	0	21	17	0	0	17	0	30	17	0	25
16	0	20	20	25	20	15	0	15	0	30	12	0	25
17	0	25	18	30	20	12	18	15	25	20	14	0	20
18	0	22	17	25	17	15	0	17	0	25	0	0	20
19	15	22	18	21	17	15	20	20	22	25	15	0	25
20	20	18	17	22	16	15	25	25	30	30	17	0	28
Average	2	21	19	23	18	11	13	16	10	25	11	3	21

CAZ: ceftazidime, CIP: ciprofloxacin, IPM:Imipenem, AK:Amikacin, CN: Gentamicin TZP: Piperacillin/Tazobactam, SAM: Ampicillin/sulbactam.

Table 4
The results of the disk sensitivity test and the inhibition zone of compounds **3a-e** against *S. aureus*.

Strains	2	3a	3b	3c	3d	3e	VA	TEC	CIP	OX	E	CN	SXT
1	15	22	25	27	20	19	16	14	17	12	20	16	20
2	15	23	21	21	19	20	16	15	20	10	0	15	0
3	10	20	26	23	17	21	15	15	22	10	20	17	25
4	12	21	25	21	20	21	17	15	20	10	25	18	20
5	12	22	26	22	20	15	18	15	20	8	24	20	20
6	12	20	24	22	20	21	18	15	22	0	20	15	12
7	17	23	27	25	20	25	18	18	25	10	0	20	25
8	15	25	22	25	20	18	18	18	20	12	20	18	22
9	10	27	25	22	17	22	15	15	10	12	20	20	15
10	15	21	25	25	30	20	15	15	23	0	20	17	22
11	10	21	25	14	20	20	17	17	27	0	22	20	20
12	15	21	25	22	18	21	15	15	20	0	20	15	10
13	12	22	22	15	23	20	15	15	22	0	20	15	20
14	10	20	21	22	17	18	15	17	22	0	20	17	20
15	14	20	22	25	20	17	16	15	22	10	20	15	20
16	20	25	20	25	30	19	15	16	25	0	25	18	20
17	15	22	21	25	21	19	20	15	10	0	0	20	25
18	10	23	31	15	20	20	18	17	20	0	22	17	20
19	20	22	25	25	20	20	17	15	0	0	0	12	0
20	10	20	25	25	20	16	16	15	22	0	24	20	24
Average	13	22	24	22	21	20	17	16	19	5	17	17	18

VA: Vancomycin, TEC: Teicoplanin, CIP: ciprofloxacin, OX: Oxacillin, E: Erythromycin, P:Penicillin, SAM: Ampicillin/sulbactam, CN: Gentamicin, CRO:Ceftriaxone, SXT: Trimethoprim-sulfamethoxazole.

and CO_2 homeostasis, tumorigenicity, and bone resorption and many others [54]. Inhibition effect of CAs is becoming increasingly popular as a research subject, which is due to their abnormal levels associated with different diseases such as osteoporosis, cancer, glaucoma, and some neurological disturbances [55]. The chemical structure of these eugenol oxypropanolamine derivatives (**2** and **3a-e**) is given in Scheme 1 and their AChE, α-glycosidase, and CA I and II isoforms inhibition data are summarized in Table 5. The following results are presented in Table 1. The hCA I isoenzyme was inhibited by these compounds; with Ki values were found between 0.80 ± 0.24 and 4.17 ± 0.94 μM. In addition, 1-(4-allyl-2-methoxyphenoxy)-3-(diethylamino)propan-2-ol (**3d**), and 1-(4-allyl-2-methoxyphenoxy)-3-(allylamino)propan-2-ol (**3a**) recorded the most powerful hCA I isoform inhibition properties with Ki values of 0.80 ± 0.24 and 0.88 ± 0.18 μM, respectively. The control and clinically used drug acetazolamide (AZA) demonstrated a Ki value of 4.17 ± 0.94 μM. Hence, the investigated novel molecules showed better inhibitory profiles when compared to AZA molecule (Table 5 and Fig. 1).

Inhibition of the diverse CA isoforms involved in drug development, mainly with sulfonamide compounds, the most extensively utilized class of CA inhibitor compounds, has significant physiological results which motivate their use as pharmacological factors as mentioned earlier [56]. But the use of CA inhibitors (CAIs) as antiglaucoma and diuretics factors has been well-established for decades, their applications as antiobesity and antiepileptics drugs are more recent, and only the last decade has seen important advances which have validated CAs as antitumor drug aims [57]. The results clearly showed that hCA II was

Table 5
The enzyme inhibition results of novel eugenol oxypropanolamine derivatives (**2, 3a-e**) against human carbonic anhydrase isoenzymes I and II (hCA I and II), achethylcholinesterase (AChE) and α-glycosidase (α-Gly) enzymes.

Compounds	IC_{50} (μM)								K_i (μM)			
	hCA I	r^2	hCA II	r^2	AChE	r^2	α-Gly	r^2	hCA I	hCA II	AChE	α-Gly
2	1.08	0.9827	3.62	0.9743	15.94	0.9481	12.84	0.9804	0.93 ± 0.12	3.27 ± 0.86	11.33 ± 2.83	10.52 ± 3.04
3a	0.98	0.9911	1.83	0.9682	22.05	0.9105	8.73	0.9649	0.88 ± 0.18	2.21 ± 0.17	16.73 ± 4.03	9.03 ± 2.15
3b	2.04	0.9690	3.84	0.9802	48.20	0.9690	9.34	0.9812	2.87 ± 0.42	3.02 ± 0.32	32.81 ± 9.73	7.92 ± 1.05
3c	3.84	0.9852	4.08	0.9527	31.93	0.9738	4.71	0.9280	3.52 ± 1.01	3.64 ± 0.92	24.05 ± 5.16	5.18 ± 0.84
3d	0.81	0.9730	1.04	0.9810	29.94	0.9884	11.73	0.9832	0.80 ± 0.24	1.08 ± 0.15	20.66 ± 8.10	11.04 ± 3.41
3e	0.90	0.9478	1.72	0.9791	34.04	0.9625	16.20	0.9424	0.98 ± 0.20	2.27 ± 0.48	27.41 ± 3.62	12.46 ± 2.08
AZA*	4.81	0.9943	5.22	0.9158	–	–	–	–	4.17 ± 0.94	5.15 ± 1.01	–	–
TAC**	–	–	–	–	51.20	0.9054	–	–	–	–	34.12 ± 10.83	–
ACR***	–	–	–	–	–	–	22.80	–	–	–	–	12.60 ± 0.78

* Acetazolamide (AZA) was used as a control for hCA I and II.
** Tacrine (TAC) was used as a control for AChE enzyme.
*** Acarbose (ACR) was used as a control for α-glycosidase enzyme.[63,64].

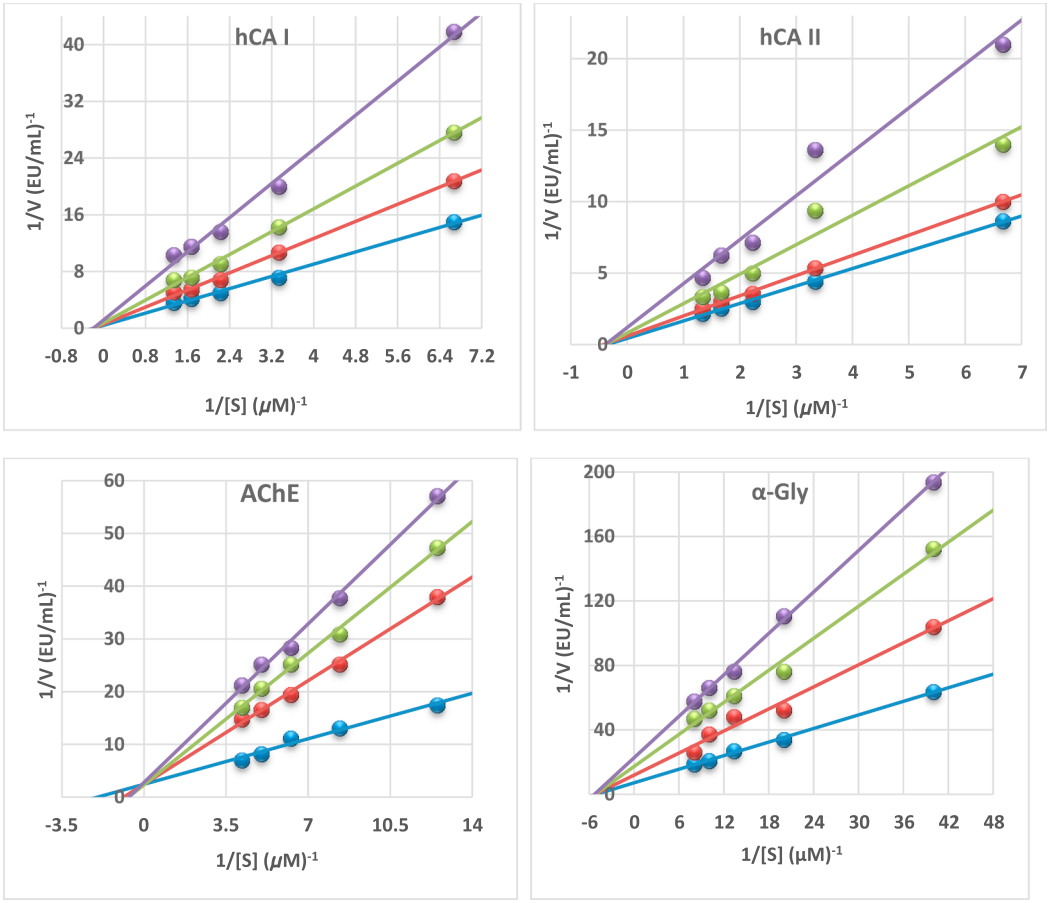


Fig. 1. Determination of Lineweaver-Burk graphs for excellent inhibitors of hCA I (1-(4-allyl-2-methoxyphenoxy)-3-(diethylamino)propan-2-ol (3d)) and hCA II (1-(4-allyl-2-methoxyphenoxy)-3-(diethylamino)propan-2-ol (3d)) isoenzymes, achethylcholinesterase (AChE) (phenoxymethyl oxirane derivatives (2)) and α-glycosidase (α-Gly) (1-(4-allyl-2-methoxyphenoxy)-3-(*tert*-butylamino)propan-2-ol (3c)) enzymes.

impressively inhibited by the novel eugenol oxypropanolamine derivatives (**2** and **3a-e**). These compounds had strong hCA II inhibition with Ki values ranging from 1.08 ± 0.15 μM to 3.64 ± 0.92 μM. Ki values of novel molecules are better than those of the standard used drug AZA (Ki: 5.15 ± 1.01 μM). All the evaluated novel molecules showed potent inhibition against hCA II, but the compounds of 1-(4-allyl-2-methoxyphenoxy)-3-(diethylamino)propan-2-ol (**3d**), and 1-(4-allyl-2-methoxyphenoxy)-3-(allylamino)propan-2-ol (**3a**) showed significant inhibition profile against hCA II with Ki values of 1.08 ± 0.15 and 2.21 ± 0.17 μM (Table 5 and Fig. 1).

An extensive level of evidence shows that AChEI can improve cognitive function and interfere with the advance of the AD, and recently these inhibitor compounds such as rivastigmine, tacrine, galantamine, donepezil, and huperzine A, have been used as first-line drugs in clinical practice [58]. Thus, modulation of cholinergic function by AChEIs is used as a pharmacological strategy for therapy of other disturbances such as glaucoma and Myasthenia Gravis [59–61]. The inhibitory effects of these compounds on AChE enzyme are shown in Table 5. The AChE inhibition profiles of the molecules investigated here were really interesting. Overall, these compounds had excellent inhibitory activity

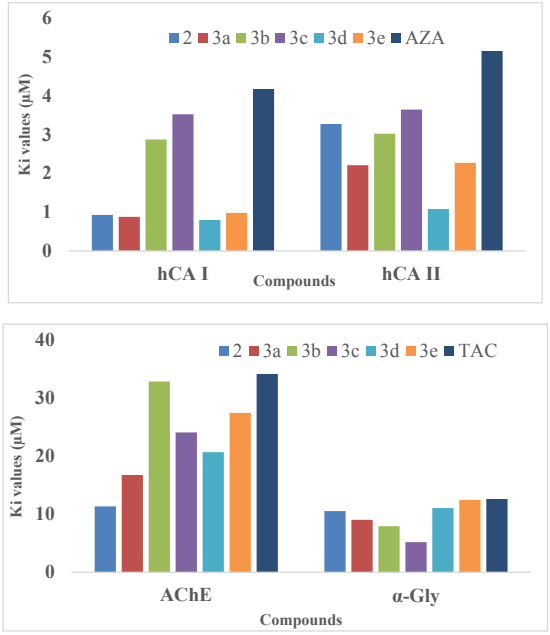


Fig. 2. Ki values of hCA I and II, AChE, and α-glycosidase enzymes.

with Ki values ranging from 11.33 ± 2.83 μM to 32.81 ± 9.73 μM. Additionally, tacrine, utilized as a control AChEI in this paper, demonstrated Ki value of 34.12 ± 10.83 μM toward AChE. The inhibition of AChE of novel eugenol bearing oxypropanolamine derivatives (**2** and **3a-e**) is much better than standard drugs. The compounds of phenoxymethyl oxirane derivatives (**2**), 1-(4-allyl-2-methoxyphenoxy)-3-(allylamino)propan-2-ol (**3a**) showed excellent inhibition profile against AChE with Ki values of 11.33 ± 2.83 and 16.73 ± 4.03 μM, respectively (Table 5 and Fig. 1).

The inhibitor compounds of α-glycosidase have wide-ranging applications in illuminating the α-glycosidase mechanism of action at in evolving chemotherapeutic agents and molecular levels for the cure of carbohydrate-mediated diseases like cancer, diabetes, hepatitis, obesity, HIV, and cardiovascular diseases [62]. The process of inhibition action of this enzyme is based on their capability to bind competitively to the carbohydrate-binding area of this enzyme. For this metabolic enzyme, the novel eugenol oxypropanolamine derivatives (**2** and **3a-e**) had IC_{50} values in the range of 4.71–16.20 and Ki values in the range of 5.18 ± 0.84–12.46 ± 2.08 μM (Table 5 and Fig. 1). The results clearly showed that all novel derivatives (**2** and **3a-e**) recorded efficient α-glycosidase inhibitory effects than that of acarbose (IC_{50}: 22.80 μM) [63,64] as a control α-glycosidase inhibitor. However, the most effective Ki values were obtained by 1-(4-allyl-2-methoxyphenoxy)-3-(*tert*-butylamino)propan-2-ol (**3c**) and 1-(4-allyl-2-methoxyphenoxy)-3-((cyclohex-1-en-1-ylmethyl)amino)propan-2-ol (**3b**), with Ki values of 5.18 ± 0.84 and 7.92 ± 1.05 μM, respectively. (See Fig. 2).

4. Conclusions

Five oxypropanolamine derivatives that four of them are novel have been synthesized, isolated and characterized by ^{1}H NMR and ^{13}C NMR and some biological properties of them like antibacterial and enzyme activity have been investigated. They have shown powerful antibacterial effects on some MDR Gram-negative (*A. baumannii, P. aeruginosa,* and *E. coli*) and Gram-positive (*S. aureus*) bacteria. The intermediate **2** and the having pyridine side chain **3e** generally exhibit lower antibacterial activity while other compounds **3a**, **3b**, **3c** and **3d** have similar and higher antibacterial activities.

Today, bacterial infections due to antibiotics are a serious threat to humanity. There are very few alternative therapies available for such bacterial infections. For this reason, every new alternative to be developed against multiple drug resistant bacteria (MDR) bacteria is required. We believe that these newly developed products can be used as antiseptic agents in skin and soft tissue infections. However, this study was conducted with *in vitro* tests. Therefore, in vivo and toxicity tests are required. Bacteria used in this study are MDR bacteria. Therefore, the antibiotics that can be used in these bacteria are very limited. For this reason, we think that these results obtained with oxypropanolamine derivatives are very important. However, our results need to be continued with *in vitro* tests.

As we recorded above, novel compounds studied in the work can be acceptable candidate drugs, the same as CAIs, for therapy of some diseases like epilepsy, gastric and duodenal ulcers, glaucoma, mountain sickness, osteoporosis, or neurological disturbances. All novel above compounds effectively inhibited some metabolic enzymes like α-glycosidase, hCA I, hCA II, and AChE enzymes at the micromolar levels. On the other hand, T2DM is a metabolic difficulty created by high blood glucose content and can reason other health disturbances, such as weakness, high blood pressure, neuropathy, nephropathy retinopathy, cardiovascular disease, gangrene, and other dysfunctions.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.102931.

References

[1] K.G. Lee, T. Shibamoto, Antioxidantproperty of aroma extract isolated from clovebuds [*Syzygium aromaticum* (L.) Merr et Perry], Food Chem. 74 (4) (2001) 443–448.
[2] A. Marchese, R. Barbieri, E. Coppo, I.E. Orhan, M. Daglia, S.F. Nabavi, M. Izadi, M. Abdollahi, S.M. Nabavi, M. Ajami, Antimicrobial activity of eugenol and essential oils containing eugenol: a mechanistic viewpoint, Crit. Rev. Microbiol. 43 (6) (2017) 668–689.
[3] I.J. Chen, J.L. Yeh, Y.C. Lo, S.H. Sheu, Y.T. Lin, Capsinolol: the first β-adrenoceptor blocker with an associated calcitonin gene-related peptide releasing activity in the heart, Br. J. Pharmacol. 119 (1) (1996) 7–14.
[4] G. Bazylak, L.J. Nagels, A novel potentiometric approach for detection of beta-adrenergics and beta-adrenolytics in high-performance liquid chromatography, Il Farmaco 58 (8) (2003) 591–603.
[5] J.B. Wechsler, C.L. Hsu, P.J. Bryce, IgE-mediated mast cell responses are inhibited by thymol-mediated, activation-induced cell death in skin inflammation, J. Allergy. Clin. Immunol. 133 (6) (2014) 1735–1743.
[6] V. Cecchetti, A. Fravolini, F. Schiaffella, O. Tabarrini, G. Bruni, G. Segre, o-Chlorobenzenesulfonamidicderivatives of (aryloxy) propanolamines as. beta.-blocking/diureticagents, J. Med. Chem. 36 (1) (1993) 157–161.
[7] H. Genç, O. Karabay, 2-aminoindanbiguanide chloride and acetate salts against resistant gram-negative bacilli, Annu. Res. Rev. Biol. 4 (9) (2014) 1353–1360.
[8] H. Genç, M. Zengin, E. Yavuz, N. Gençer, O. Arslan, Synthesis and tyrosinase inhibitory properties of novel isoquinoline urea/thiourea derivatives, Artif. Cells Nanomed. Biotechnol. 42 (3) (2014) 178–185.
[9] A. Bytyqi-Damoni, H. Genç, M. Zengin, S. Beyaztas, N. Gençer, O. Arslan, In vitro effect of novel β-lactam compounds on xanthine oxidase enzyme activity, Artif. Cells Blood Subst. Biotechnol. 40 (6) (2012) 369–377.
[10] D. Demir, N. Gençer, O. Arslan, H. Genç, M. Zengin, In vitro inhibition of polyphenol oxidase by some new diarylureas, J. Enzyme Inhib. Med. Chem. 27 (1) (2012) 125–131.
[11] H. Genc, B. Ceken, Ç. Bilen, Z. Sackes, N. Gencer, O. Arslan, Synthesis and biological evaluation of new 4-thiazolidinone derivatives as carbonic anhydrase inhibitors, Lett. Org. Chem. 14 (2) (2017) 80–85.
[12] A. Atahan, N. Gencer, C. Bilen, E. Yavuz, H. Genc, F. Sonmez, M. Zengin, M. Ceylan, M. Kucukislamoglu, Synthesis, biological activity and structure-activity relationship of novel diphenylurea derivatives containing tetrahydroquinoline as carbonic anhydrase I and II inhibitors, Chem. Select 3 (2) (2018) 529–534.
[13] F. Türker, D. Barut Celepci, A. Aktaş, P. Taslimi, Y. Gök, M. Aygün, İ. Gulçin, Metacyanobenzyl substituted benzimidazole: synthesis, characterization, crystal structure and carbonic anhydrase, α-glycosidase, butyrylcholinesterase, acetylcholinesterase inhibitory properties, Arch. Pharm. 351 (7) (2018) 2–11.
[14] P. Taslimi, C. Çağlayan, F. Farzaliyev, O. Nabiyev, A. Sujayev, F. Türkan, R. Kaya, İ. Gulçin, Synthesis and discovery of potent carbonic anhydrase, acetylcholinesterase, butyrylcholinesterase and α- glycosidase enzymes inhibitors: the novel N, N′-bis-cyanomethylamine and alkoxymethylamine derivatives, J. Biochem. Mol. Toxic. 32 (4) (2018) 1–9.
[15] S. Burmaoglu, A.O. Yilmaz, P. Taslimi, O. Algul, D. Kılıç, İ. Gulçin, Synthesis and biological evaluation of phloroglucinol derivatives possessing α-glycosidase, acetylcholinesterase, butyrylcholinesterase, carbonic anhydrase inhibitory activity, Arch. Pharm. 351 (2) (2018) 1–12.
[16] İ. Gulçin, P. Taslimi, Sulfonamide inhibitors: a patent review 2013-present, Expert Opin. Ther. Pat. 28 (7) (2018) 541–549.

[17] B. Yiğit, M. Yiğit, D. Barut Celepci, Y. Gök, A. Aktaş, M. Aygün, P. Taslimi, İ. Gulçin, Novel benzylic substituted imidazolinium, tetrahydropyrimidinium and tetrahydrodiazepinium salts-potent carbonic anhydrase and acetylcholinesterase inhibitors, Chem. Select 3 (27) (2018) 7976–7982.

[18] B. Yiğit, M. Yiğit, P. Taslimi, Y. Gök, İ. Gulçin, Schiff bases and their amines: synthesis, and discovery of carbonic anhydrase and acetylcholinesterase enzymes ınhibitors, Arch. Pharm. 351 (9) (2018) 1800146.

[19] P. Taslimi, İ. Gulçin, Antioxidant and anticholinergic properties of olivetol, J. Food Biochem. 42 (3) (2018) e12516.

[20] A. Behcet, T. Çağlılar, D. Barut Celepci, A. Aktaş, P. Taslimi, Y. Gök, M. Aygün, R. Kaya, İ. Gulçin, Synthesis characterization and crystal structure of 2-(4-hydroxyphenyl)ethyl and 2-(4-nitrophenyl)ethyl substituted benzimidazolium bromide salts: their inhibitory properties against carbonic anhydrase and acetylcholinesterase, J. Mol. Struct. 1170 (2018) 160–169.

[21] C. Yamali, H.İ. Gül, A. Ece, P. Taslimi, İ. Gulçin, Synthesis, molecular modeling and biological evaluation of 4-[5-aryl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl] benzenesulfonamides towards acetylcholinesterase, carbonic anhydrase I and II enzymes, Chem. Biol. Drug Des. 91 (4) (2018) 854–866.

[22] F. Erdemir, D. Barut Celepci, A. Aktaş, P. Taslimi, Y. Gök, H. Karabıyık, İ. Gulçin, 2-Hydroxyethyl substituted NHC precursors: synthesis, characterization, crystal structure and carbonic anhydrase, α-glycosidase, butyrylcholinesterase, and acetylcholinesterase inhibitory properties, J. Mol.Struct. 1155 (1028) (2018) 797–806.

[23] I. Gulçin, M. Abbasova, P. Taslimi, Z. Huyut, L. Safarova, A. Sujayev, V. Farzaliyev, S. Beydemir, S.H. Alwasel, C.T. Supuran, Synthesis and biological evaluation of aminomethyl and alkoxymethyl derivatives as carbonic anhydrase, acetylcholinesterase and butyrylcholinesterase inhibitors, J. Enzyme Inhib. Med. Chem. 32 (1) (2017) 1174–1182.

[24] A. Akıncıoğlu, E. Kocaman, H. Akıncıoğlu, R.E. Salmas, S. Durdağı, İ. Gülçin, C.T. Supuran, S. Göksu, The synthesis of novel sulfamides derived from β-benzylphenethylamines as acetylcholinesterase, butyrylcholinesterase and carbonic anhydrase enzymes inhibitors, Bioorg. Chem. 74 (2017) 238–250.

[25] N. Öztaşkın, P. Taslimi, A. Maraş, S. Göksu, İ. Gülçin, Novel antioxidant bromophenols with acetylcholinesterase, butyrylcholinesterase and carbonic anhydrase inhibitory actions, Bioorg. Chem. 74 (2017) 104–114.

[26] Ç. Bayrak, P. Taslimi, İ. Gülçin, A. Menzek, The first synthesis of 4-phenylbutenone derivative bromophenols including natural products and their inhibition profiles for carbonic anhydrase, acetylcholinesterase and butyrylcholinesterase enzymes, Bioorg. Chem. 72 (2017) 359–366.

[27] U.M. Kocyigit, Y. Budak, M.B. Gürdere, Ş. Tekin, T. Kul Köprülü, F. Ertürk, K. Özcan, İ. Gülçin, M. Ceylan, Synthesis, characterization, anticancer, antimicrobial and carbonic anhydrase inhibition profiles of novel (3aR,4S,7R,7aS)-2-(4-((E)-3-(3-aryl)acryloyl) phenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione derivatives, Bioorg. Chem. 70 (2017) 118–125.

[28] H. Göcer, A. Akıncıoğlu, S. Göksu, I. Gülçin, Carbonic anhydrase inhibitory properties of phenolic sulfonamides derived from dopamine related compounds, Arab. J. Chem. 10 (3) (2017) 398–402.

[29] K. Aksu, B. Özgeriş, P. Taslimi, A. Naderi, İ. Gülçin, S. Göksu, Antioxidant activity, acetylcholinesterase and carbonic anhydrase inhibitory properties of novel ureas derived from phenethylamines, Arch. Pharm. 349 (12) (2016) 944–954.

[30] F. Özbey, P. Taslimi, İ. Gulcin, A. Maraş, S. Goksu, C.T. Supuran, Synthesis, acetylcholinesterase, butyrilcholinesterase, carbonic anhydrase inhibitory and metal chelating properties of some novel diaryl ether, J. Enzyme Inhib. Med. Chem. 31 (S2) (2016) 79–85.

[31] H. Genç, R. Kalin, Z. Köksal, N. Sadeghian, U.M. Kocyigit, M. Zengin, İ. Gülçin, H. Özdemir, Discovery of potent carbonic anhydrase and acetylcholinesterase inhibitors: 2-aminoindan β-lactam derivatives, Int. J. Mol. Sci. 17 (2016) 1736–1748.

[32] B. Özgeriş, S. Göksu, L. Köse Polat, İ. Gülçin, R.E. Salmas, S. Durdagi, F. Tümer, C.T. Supuran, Acetylcholinesterase and carbonic anhydrase inhibitory properties of novel urea and sulfamide derivatives incorporating dopaminergic 2-aminotetralin scaffolds, Bioorg. Med. Chem. 24 (10) (2016) 2318–2329.

[33] A. Akıncıoğlu, H. Akıncıoğlu, I. Gülçin, S. Durdağı, C.T. Supuran, S. Göksu, Discovery of potent carbonic anhydrase and acetylcholine esterase inhibitors: Novel sulfamoylcarbamates and sulfamides derived from acetophenones, Bioorg. Med. Chem. 23 (13) (2015) 3592–3602.

[34] A. Yıldırım, U. Atmaca, A. Keskin, M. Topal, M. Çelik, İ. Gülçin, C.T. Supuran, N-Acylsulfonamides strongly inhibit human carbonic anhydrase isoenzymes I and II, Bioorg. Med. Chem. 23 (10) (2015) 2598–2605.

[35] M. Boztaş, Y. Çetinkaya, M. Topal, İ. Gülçin, A. Menzek, E. Şahin, M. Tanc, C.T. Supuran, Synthesis and carbonic anhydrase isoenzymes I, II, IX, and XII inhibitory effects of dimethoxy-bromophenol derivatives incorporating cyclopropane moieties, J. Med. Chem. 58 (2) (2015) 640–650.

[36] A.P. Magiorakos, A. Srinivasan, R.B. Carey, Y. Carmeli, M.E. Falagas, C.G. Giske, S. Harbarth, J.F. Hindler, G. Kahlmeter, B. Olsson-Liljequist, D.L. Paterson, L.B. Rice, J. Stelling, M.J. Struelens, A. Vatopoulos, J.T. Weber, D.L. Monnet, Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance, Clin. Microbiol. Infect. 18 (3) (2012) 268–281.

[37] CLSI, Performance Standarts for Antimicrobial Susceptibility Testing; Eighteenth Informational Supplement. CLSI document M100-S18, Clinical and Laboratory Standarts Institute, Wayne, PA, 2008.

[38] Deutsches Institut fur Normung. DIN EN 1040, Chemical Disinfectants and Antiseptics Quantitative Suspension Test for the Evaluation of Basic Bactericidal Activity of Chemical Disinfectants and Antiseptics Test Method and Requirements (Phase 1), Beuth, Berlin, Germany, 2005.

[39] J.A. Verpoorte, S. Mehta, J.T. Edsall, Esterase activities of human carbonic anhydrases B and C, J. Biol. Chem. 242 (1967) 4221–4229.

[40] M. Güney, A. Coşkun, F. Topal, A. Daştan, İ. Gülçin, C.T. Supuran, Oxidation of cyanobenzocycloheptatrienes: Synthesis, photooxygenation reaction and carbonic anhydrase isoenzymes inhibition properties of some new benzotropone derivatives, Bioorg. Med. Chem. 22 (13) (2014) 3537–3543.

[41] K. Aksu, M. Nar, M. Tanç, D. Vullo, İ. Gülçin, S. Göksu, F. Tümer, C.T. Supuran, Synthesis and carbonic anhydrase inhibitory properties of sulfamides structurally related to dopamine, Bioorg. Med. Chem. 21 (11) (2013) 2925–2931.

[42] A. Akıncıoğlu, Y. Akbaba, H. Göçer, S. Göksu, İ. Gülçin, C.T. Supuran, Novel sulfamides as potential carbonic anhydrase isoenzymes inhibitors, Bioorg. Med. Chem. 21 (6) (2013) 1379–1385.

[43] G.L. Ellman, K.D. Courtney, V. Andres, R.M. Featherston, A new and rapid colorimetric determination of acetylcholinesterase activity, Biochem. Pharmacol. 7 (1961) 88–95.

[44] N. Öztaşkın, Y. Çetinkaya, P. Taslimi, S. Göksu, İ. Gülçin, Antioxidant and acetylcholinesterase inhibition properties of novel bromophenol derivatives, Bioorg. Chem. 60 (2015) 49–57.

[45] A. Sujayev, E. Garibov, P. Taslimi, İ. Gülçin, S. Gojayeva, V. Farzaliyev, S.H. Alwasel, C.T. Supuran, Synthesis of some tetrahydropyrimidine-5-carboxylates, determination of their metal chelating effects and inhibition profiles against acetylcholinesterase, butyrylcholinesterase and carbonic anhydrase, J. Enzyme Inhib. Med. Chem. 31 (6) (2016) 1531–1539.

[46] H.İ. Gül, M. Tuğrak, H. Sakagami, P. Taslimi, İ. Gülçin, C.T. Supuran, Synthesis and bioactivity studies on new 4-(3-(4-substitutedphenyl)-3a,4-dihydro-3h-indeno[1,2-c]pyrazol-2-yl) benzenesulfonamides, J. Enzyme Inhib. Med. Chem. 31 (6) (2016) 1619–1624.

[47] B. Turan, K. Sendil, E. Sengul, M.S. Gultekin, P. Taslimi, İ. Gulcin, C.T. Supuran, The synthesis of some β-lactams and investigation of their metal chelating activity, carbonic anhydrase and achetylcholinesterase inhibition profiles, J. Enzyme Inhib. Med. Chem. 31 (S1) (2016) 79–88.

[48] E. Garibov, P. Taslimi, A. Sujayev, Z. Bingöl, S. Çetinkaya, İ. Gulcin, S. Beydemir, V. Farzaliyev, S.H. Alwasel, C.T. Supuran, Synthesis of 4,5-disubstituted-2-thioxo-1,2,3,4-tetrahydropyrimidines and investigation of their acetylcholinesterase, butyrylcholinesterase, carbonic anhydrase I/II inhibitory and antioxidant activities, J. Enzyme Inhib. Med. Chem. 31 (S3) (2016) 1–9.

[49] Y. Tao, Y. Zhang, Y. Cheng, Y. Wang, Rapid screening and identification of α-glucosidase inhibitors from mulberry leaves using enzyme-immobilized magnetic beads coupled with HPLC/MS and NMR, Biomed. Chrom. 27 (2013) 148–155.

[50] P. Taslimi, H.E. Aslan, Y. Demir, N. Oztaskin, A. Maraş, İ. Gulçin, S. Beydemir, S. Goksu, Diarilmethanon, bromophenols and diarilmetan compounds: Discovery of potent aldose reductase, α-amylase and α-glycosidase inhibitors as new therapeutic approach in diabetes and functional hyperglycemia, Int. J. Biol. Macromol. 119 (2018) 857–863.

[51] I. Gulçin, P. Taslimi, A. Aygün, N. Sadeghian, E. Bastem, O.I. Kufrevioglu, F. Turkan, F. Şen, Antidiabetic and antiparasitic potentials: inhibition effects of some natural antioxidant compounds on α-glycosidase, α-amylase and human glutathione S-transferase enzymes, Int. J. Biol. Macromol. 119 (2018) 741–746.

[52] W. Kunz, H. Jacobi, K. Koch, Basic phenyl and naphthyl ethers and thio ethers and their derivatives, 1966 Patent BE 1966-691159 A.

[53] F. Topal, İ. Gulcin, A. Dastan, M. Guney, Novel eugenol derivatives: potent acetylcholinesterase and carbonic anhydrase inhibitors, Int. J. Biol. Macromol. 94 (2017) 845–851.

[54] P. Taslimi, A. Sujayev, S. Mamedova, P. Kalın, I. Gulcin, N. Sadeghian, S. Beydemir, Ö.İ. Küfrevioglu, S.H. Alwasel, V. Farzaliyev, S. Mamedov, Synthesis and bioactivity of several new hetaryl sulfonamides, J. Enzyme Inhib. Med. Chem. 32 (1) (2017) 137–145.

[55] H.I. Gul, E. Mete, P. Taslimi, I. Gulcin, C.T. Supuran, Synthesis, carbonic anhydrase I and II inhibition studies of the 1,3,5-trisubstituted-pyrazolines, J. Enzyme Inhib. Med. Chem. 32 (1) (2017) 189–192.

[56] H.I. Gül, A. Demirtas, G. Ucar, P. Taslimi, İ. Gülçin, Synthesis of mannich bases by two different methods and evaluation of their acetylcholine esterase and carbonic anhydrase inhibitory activities, Lett. Drug Des. Discov. 14 (5) (2017) 573–580.

[57] M. Işık, S. Beydemir, A. Yılmaz, M.E. Naldan, H.E. Aslan, İ. Gülçin, Oxidative stress and mRNA expression of acetylcholinesterase in the leukocytes of ischemic patients, Biomed. Pharmacother. 87 (2017) 561–567.

[58] P. Taslimi, H. Akıncıoğlu, İ. Gulçin, Synephrine and phenylephrine act as α-amylase, α-glycosidase, acetylcholinesterase, butyrylcholinesterase and carbonic anhydrase enzymes inhibitors, J. Biochem. Mol. Toxicol. 31 (11) (2017) e21973.

[59] P. Taslimi, C. Caglayan, İ. Gulçin, The impact of some natural phenolic compounds on carbonic anhydrase, acetylcholinesterase, butyrylcholinesterase, and α-glycosidase enzymes: an antidiabetic, anticholinergic, and antiepileptic study, J. Biochem. Mol. Toxicol. 31 (12) (2017) e21995.

[60] P. Taslimi, E. Sujayev, F. Turkan, E. Garibov, Z. Huyut, F. Farzaliyev, S. Mamedova, I. Gulçin, Synthesis and investigation of the conversion reactions of pyrimidine-thiones with nucleophilic reagent and evaluation of their acetylcholinesterase, carbonic anhydrase inhibition and antioxidant activities, J. Biochem. Mol. Toxicol. 32 (2) (2018) e22019.

[61] P. Taslimi, S. Osmanova, C. Çağlayan, F. Turkan, S. Sardarova, F. Farzaliyev, E. Sujayev, N. Sadeghian, I. Gulçin, Novel amides of 1,1-bis-(carboxymethylthio)-1-arylethanes: Synthesis, characterization, and acetylcholinesterase, butyrylcholinesterase, and carbonic anhydrase ınhibitory properties, J. Biochem. Mol. Toxicol. (2018) e22191.

[62] P. Taslimi, I. Gulçin, Antidiabetic potential: in vitro inhibition effects of some natural phenolic compounds on α-glycosidase and α-amylase enzymes, J. Biochem. Mol. Toxicol. 31 (10) (2017) e21956.

[63] M. Torres-Naranjo, A. Suarez, G. Gilardoni, L. Carcuthe, P. Flores, V. Morocho, Chemical constituents of Muehlenbeckia tamnifolia (Kunth) Meisn (Polygonaceae) and its in vitro α-Amilase and α-Glucosidase inhibitory activities, Molcules 21 (2016) 1461–1465.

[64] H. Teng, L. Chen, T. Fang, B. Yuan, Q. Lin, Rb2 inhibits α-glucosidase and regulates glucose metabolism by activating AMPK pathways in HepG2 cells, J. Funct. Foods 28 (2017) 306–313.