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Synthesis and biological evaluation of bromophenol derivatives with cyclopropyl moiety: Ring opening of cyclopropane with monoester

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ABSTRACT

Trans-(1R*,2R*,3R*)-Ethyl 2-(3,4-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylate (**6**) and its *cis* isomer **7** were obtained from the reaction of the methyl isoeugenol (**5**) with ethyl diazoacetate. The reduction and bromination reactions of the ester **6** and **7** together with the hydrolysis of all esters were carried out. Opening ring of cyclopropane was observed in the reaction of **7** with bromine. The opening of cyclopropane ring with COOR and synthesis of esters, alcohols and acids (**6–26**) are new. These obtained bromophenol derivatives (**6–26**) were effective inhibitors of the cytosolic carbonic anhydrase I and II isoforms (hCA I and II) and acetylcholinesterase (AChE) enzymes with Ki values in the range of 7.8 ± 0.9–58.3 ± 10.3 nM for hCA I, 43.1 ± 16.7–150.2 ± 24.1 nM for hCA II, and 159.6 ± 21.9–924.2 ± 104.8 nM for AChE, respectively. Acetylcholinesterase inhibitors are the most popular drugs applied in the treatment of diseases such as Alzheimer's disease, Parkinson's disease, senile dementia, and ataxia, among others.

1. Introduction

Phenol and bromophenol compounds exhibit biological activities such as cytotoxic, antibacterial, enzyme inhibitor, anti-cancer and antimicrobial activities [1]. Compound **1** is natural bromophenol compound exhibiting antioxidant and carbonic anhydrase inhibitor activities (Fig. 1) [1c,2]. Milnacipran (**2**) including cyclopropane moiety and amine functional groups is an antidepressant drug. Several papers have been published on **2** and its derivatives [3]. We reported that derivatives of compounds **3** and **4** were synthesized and all compounds synthesized including **3** and **4** exhibited important carbonic anhydrase isoenzymes I, II, IX, and XII inhibitory effects [4].

Acetylcholine (ACh), an important cholinergic neurotransmitter which takes part in memory and learning and also breaks into acetic acid and choline in vertebrates by the action of a key hydrolase enzyme which called acetylcholinesterase (AChE, E.C.3.1.1.7) [5]. The active part of AChE enzyme has three binding subsites, including the catalytic anionic site, the catalytic triad, and peripheral anionic site. The catalytic anionic site of this enzyme hydrolyzes ACh and also the peripheral anionic site of this enzyme has an inductive efficacy on beta amyloid plaques organization. Inducing self-regulation, cellular metabolism, and oxidative stress cause loss of cholinergic cells and therefore decrement of ACh level [6]. Some structures with the capability of inhibiting BChE and AChE can also balance the AChE and BChE levels in addition to reducing beta amyloid protein plaques. Synthesis and Design of molecules that can inhibit AChE enzyme activities have newly gained higher interest since AChE inhibitors are the significant molecules utilized to treat myasthenia gravis and Alzheimer's disease (AD) [7].

Carbonic anhydrase (CA, E.C.4.2.1.1) enzymes are ubiquitous zinc comprising metalloenzymes present in eukaryotes and prokaryote cells that act as impressive catalysts for the reversible hydration of carbon dioxide (CO_2) and water into bicarbonate (HCO_3^-) and proton (H^+), a reaction that supports several physiological and biochemical functions [8]. Seven genetically distinct CA families (α-, β-, γ-, δ-, η-, ζ- and θ-CAs) are known to date, as well as multiple isozymes in most organism cells [9]. In humans, sixteen various CA isoforms, which all belong to the α-CAs have been explained, with several catalytic activity, subcellular organ/tissue distribution and localization CA II is a zinc metalloenzyme that catalyzes the reversible interconversion of CO_2 and water to a H^+ and HCO_3^- [10]. CA II isoform is plentiful in most cells, and has a key role in multiple processes including epithelial ion transport, respiration, gas exchange, vascular regulation, and intra- and extracellular pH control [11]. The activation or inhibition of the many

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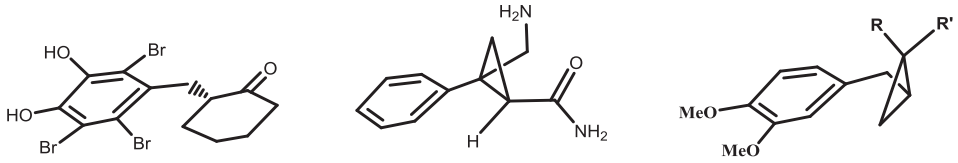


1 2 3 R = H, R' = COOEt 4 R = COOEt, R' = H

Fig. 1. Some biological active compounds.

hCA isoforms was widely evaluated due to their potential use for several biomedical applications. For example, inhibitors targeting hCA II, IV, XII and XIV are utilized for the treatment of edema, as diuretics, inhibitors targeting hCA II, IV and XII are utilized for the treatment of glaucoma, and those targeting hCA XIV and VII are utilized as antiepileptics [12].

The compounds **2–4** including cyclopropane units are important compounds because of their properties. According to benzene rings in **3** and **4**, the cyclopropane rings are 2,3 positions. Isomers of **3** and **4**, in which structure cyclopropane rings are in 1,2 positions like **2**, may be important compounds. Therefore, bromophenol derivatives (**6–26**) were synthesized and then their biological properties were investigated.

2. Results and discussion

2.1. Synthesis

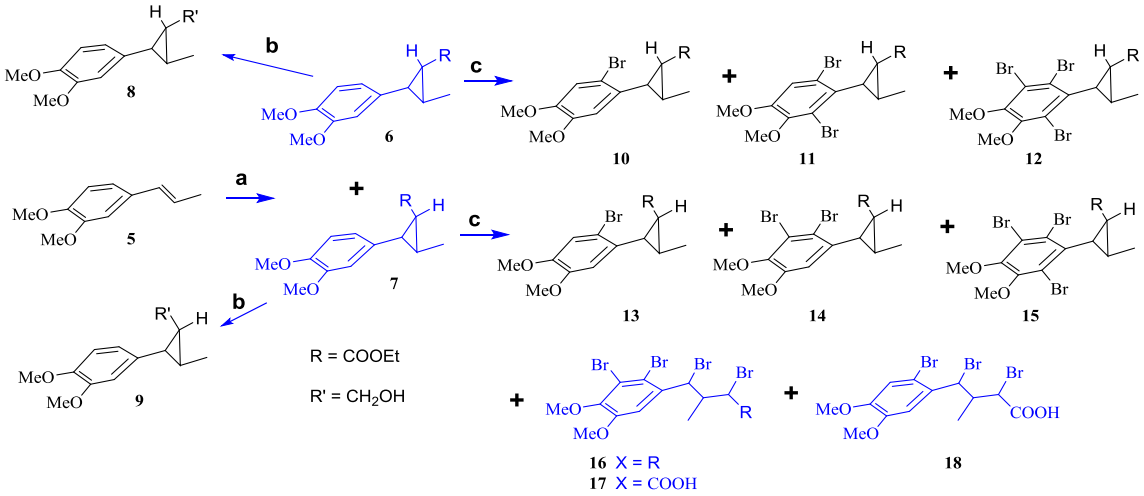
To synthesize compounds whose structures are benzene derivatives with cyclopropyl unit, methyl isoeuganol (**5**) was used as starting material. Reaction of **5** with ethyl diazoacetate by known method [4,13] gave two isomeric ester products as *cis* and *trans* (Scheme 1). Isomeric product **6** was accepted as *trans* (ester and phenyl groups in the cyclopropane ring are *trans*) because it is major product and more stable than *cis* product **7**.

Compounds including cyclopropyl methanol are both biologically active [4] and compounds which can be rearranged [14]. Therefore, reductions of esters **6** and **7** with $LiAlH_4$ were performed, and alcohols **8** and **9** were obtained from these reactions, respectively (Scheme 1). It is important to synthesize the brominated derivatives of **6** and **7** because of their biological activity and structure properties [4]. Electron-rich structures such as phenyl rings with OMe are easily brominated with molecular bromine [1b,1g–k,4,15]. To synthesize monobromides of esters **6** and **7**, each of them was reacted with bromine (approximately 1.0 equiv.) at room temperature (RT) in CH_2Cl_2. From these reactions, monobromides **10** and **13** were obtained in high yields. Bromine atoms on rings of the monobromides should be at C2 because of directors of groups on benzene rings in the electrophilic aromatic substitution reactions.

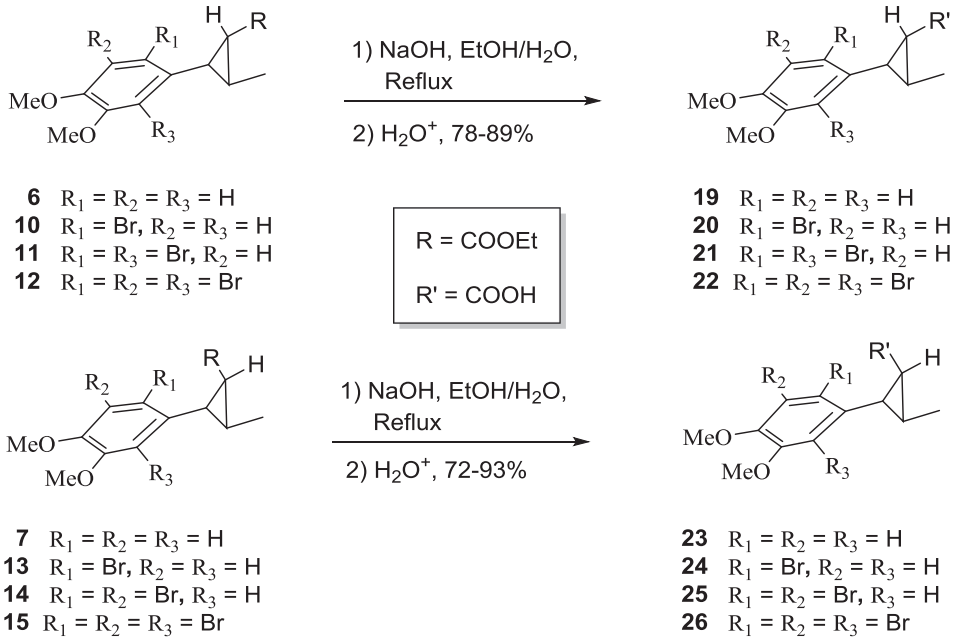
After the compound **6** (1.0 equiv.) was reacted with Br_2 (5.7 equiv.) at RT in CH_2Cl_2 for 13 h, two products were obtained from column chromatography (CC) of the reaction mixture. According to their NMR data, they are dibromide and tribromide. In similar conditions, five products were obtained from the bromination of the compound **7**. Depending on their NMR data, there are not cyclopropane rings in three compounds of them. Two products with cyclopropane ring also are a dibromide and a tribromide. Two products without cyclopropane ring, acids, are hydrolysis products while the other is ester (Scheme 1) (see Scheme 2).

According to NMR, HRMS and elemental analyses data, the structures of esters (**6**, **7** and **10–16**), alcohol (**8** and **9**) and acids (**17** and **18**) were determined. Also, acids of these esters may exhibit biological activities such as carbonic anhydrase inhibitor activity. Therefore, reactions of esters (**6**, **7** and **10–16**) with an aqueous solution of NaOH in EtOH and then their acidifications yielded the corresponding acids **19–26** in high yields (Scheme 1).

The exact configuration of the 2-(2,6-dibromo-3,4-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylic acid (**21**) and 2-methyl-3-(2,3,6-tribromo-4,5-dimethoxyphenyl)cyclopropane-1-carboxylic acid (**26**) were unambiguously confirmed by X-ray diffraction analysis (Fig. 2). These analyzes also confirm the structures of esters **6** and **7**. Compound **21** crystallized in the monoclinic space group $P2_1/n$ with four molecules per unit cell. In the case of **26,** structure crystallized in the triclinic space group *P*-1with two molecules in the unit cell. C—C (cyclopropane) distances are in the range of 1.485(4)–1.530(4) Å and all have the single bond character. C-Br bonds are between 1.881 and 1.902(4) Å. **21** and **26** contain six asymmetric carbon atoms, stereogenic centers are as follows; C7(*R*,*S*), C8(*R*,*S*) and C9(*R*,*R*). In the solid state, structures are stabilized *via* effective intermolecular O—H···O



Scheme 1. Synthesis, reduction and bromination of esters with cyclopropane[a]. [a]**Reagents and conditions**: (**a**) N_2CHCO_2Et, Cu/heat, hexane, 130 °C, 32 h, 30% for **6** and 13% for **7** (**b**) $LiAlH_4$, THF and then H_3O^+, 0 °C 2 h then RT, 20 h, 75% for **8** and 74% for **9**, (c) Bromination in different condition. Percent yields of products depend on the conditions. See experimental section.



6 $R_1 = R_2 = R_3 = H$
10 $R_1 = Br, R_2 = R_3 = H$
11 $R_1 = R_3 = Br, R_2 = H$
12 $R_1 = R_2 = R_3 = Br$

19 $R_1 = R_2 = R_3 = H$
20 $R_1 = Br, R_2 = R_3 = H$
21 $R_1 = R_3 = Br, R_2 = H$
22 $R_1 = R_2 = R_3 = Br$

7 $R_1 = R_2 = R_3 = H$
13 $R_1 = Br, R_2 = R_3 = H$
14 $R_1 = R_2 = Br, R_3 = H$
15 $R_1 = R_2 = R_3 = Br$

23 $R_1 = R_2 = R_3 = H$
24 $R_1 = Br, R_2 = R_3 = H$
25 $R_1 = R_2 = Br, R_3 = H$
26 $R_1 = R_2 = R_3 = Br$

Scheme 2. Synthesis of acids **19–26** from esters **6**, **7**, and **10–15.**

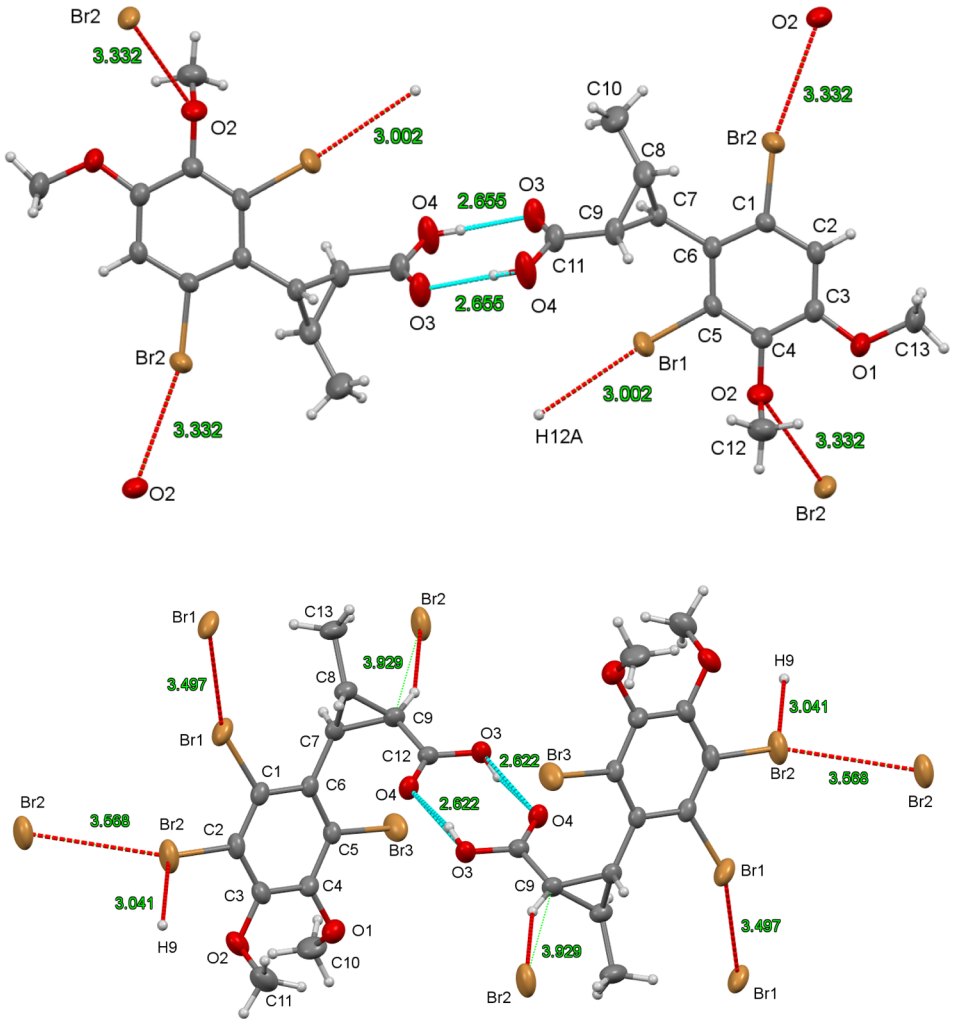
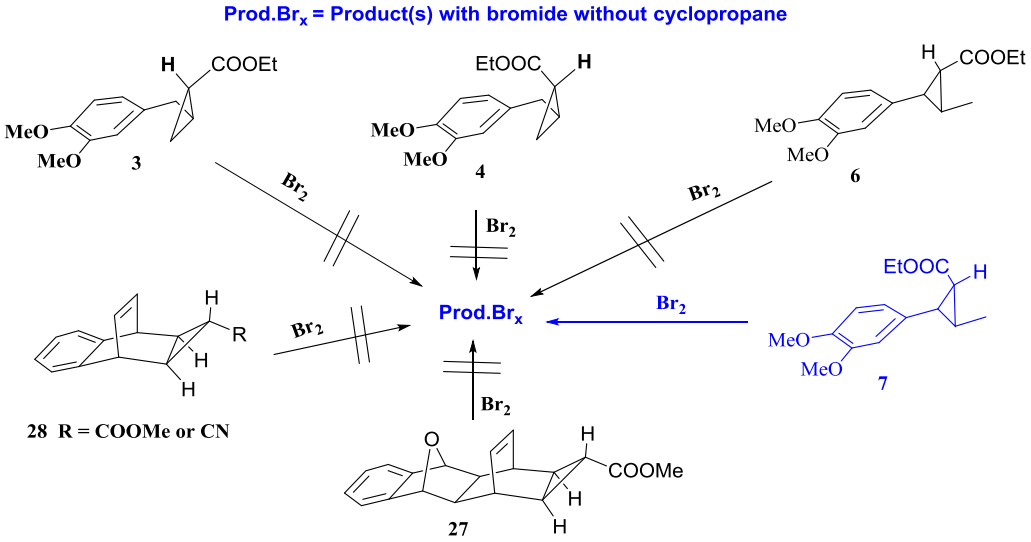


Fig. 2. Ortep drawings of dimeric synthons **21** (up) and **26** (down) with atom numbering scheme. Intermolecular Br···O, Br···C and Br···Br interactions of < 4 A° are shown. Thermal ellipsoids are drawn with 40% probability.



Scheme 3. Behaviors of some compounds **3, 4, 6, 7, 27 and 28** with molecular bromine.

[$D\cdots A$ = 2.655(3), 2.622(3) Å] interactions, which lead to the formation of dimeric synthons (Fig. 2). Along with that non-covalent Br···O, Br···C, and Br···Br halogen interactions have a contribution in the formation of a stable structure (Fig. 2).

When one of the groups in the rings of cyclopropane is ester and at the *cis* positions, we reported that the chemical shifts of CO resonate at higher fields than that of *trans* positions [4,16]. The same effects were also determined in the carbonyl groups in the synthesized esters **19–21** and acids **22–25**. By opening ring, formation of the compounds without cyclopropane ring in the bromination of ester **6** was observed (Scheme 1). Probable, ester **7** is unstable than **6** because of strain. The products without cyclopropane ring were not met in the bromination of compounds **3**, **4**, **6**, **27** and **28** (Scheme 3) [4,17].

2.2. Biological assay

In this study, we obtained the effects of novel bromophenol derivatives (**6–26**) against hCA I, hCA II, and AChE enzymes. The CA isozymes are involved in multiple physiological and biochemical mechanisms such as bone resorption, calcification, acid-base regulation, gluconeogenesis, ureagenesis, and tumorigenicity, thus representing interesting biological aims for the design of CA inhibitors (CAIs) with many biomedical applications [18]. The ubiquitous isoform hCA I is involved in cerebral edema and retinal, and its inhibition can be a noteworthy factor for fighting these conditions [19]. Indeed, hCA II isoform involved in edema, epilepsy, glaucoma and among others [20]. We report the inhibition effects of these derivatives on the activity of hCA I, hCA II and AChE enzymes under *in vitro* conditions. The following results are presented in Table 1 and Fig. 3.

In the last decade, a lot of work has been done on the synthesis of CAIs belonging to various classes, such as coumarins, sulfonamides, carboxylic acids, heterocyclic derivatives, phenols, dithiocarbamates, etc [21]. Out of these, sulfonamide compounds and their bioisosteres like the sulfamides and the sulfamates are powerful active site coordinating CAIs, which, in deprotonated form, bind to the Zn^{2+} ion present within the active site of enzyme [22]. The slow cytosolic isoform hCA I was inhibited by the investigated novel bromophenol derivatives (**6–26**), with K_i values ranging between 7.8 ± 0.9 and 58.3 ± 10.3 nM. Furthermore, (1S*,2R*,3R*)-ethyl 2-methyl-3-(2,3,6-tribromo-4,5-dimethoxyphenyl)cyclopropanecarboxylate (**15**), (1R*,2R*,3R*)-Ethyl 2-(2-bromo-4,5-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylate (**10**), and (1R*,2R*,3R*)-(2-(3,4-dimethoxyphenyl)-3-methylcyclopropyl)methanol (**8**) which demonstrated the most powerful hCA I isoenzyme inhibition properties with K_i values of 7.8 ± 0.9, 8.4 ± 2.3 and 9.1 ± 1.6 nM. In addition, it is known that the molecules, that had affinity against CA isoenzymes. The standard and clinically used drug acetazolamide (AZA) demonstrated a K_i value of 81.7 ± 21.1 nM (Table 1). Thus, the investigated compounds showed better inhibitory profiles compared to AZA, a clinically used CA inhibitor. The hCA I isoform is present in many tissues and in red blood cells but its physiological function is still unknown; however, it is known that hCA I is associated with cerebral edema and retinal, and the inhibition of CA I can be beneficial in curing such conditions [23]. It was reported in a recent study, some bromophenol derivatives with S including natural products inhibited hCA I isoenzyme with Ki values in ranging of 53.8 ± 12.5–234.7 ± 46.8 nM [24].

In addition, hCA II isozyme, the physiologically dominant isoenzyme, is another enzyme, which is associated with various disease conditions like edema, epilepsy, altitude sickness, and glaucoma [25]. Furthermore, it has also emerged in the past few years that these enzymes can be used as potential target for designing anti-infective drugs with a novel mechanism of action [26]. The hCA II was also efficiently inhibited by the novel bromophenol derivatives (**6–26**) investigated here. These compounds appeared to strongly inhibit hCA II, with K_i values ranging from 43.1 ± 16.7 nM to 150.2 ± 24.1 nM. These values are better than those of the clinically used drugs acetazolamide (K_i of 152.3 ± 33.3 nM). All the investigated these novel bromophenol derivatives (**6–26**) demonstrated marked inhibition against hCA II, but the compounds of (1R*,2R*,3R*)-2-(2-bromo-4,5-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylic acid (**20**) and (1R*,2R*,3R*)-ethyl 2-(2-bromo-4,5-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylate (**10**) showed excellent inhibitions profile against cytosolic hCA II with K_i values of 43.1 ± 16.7 and 48.3 ± 13.3 nM, respectively (Table 1). It was reported that hCA I isoenzyme was effectively inhibited by some bromophenol derivatives with S including natural products with Ki values between 42.8 ± 9.4 and 200.5 ± 57.3 nM [24].

The inhibitory effects of the synthesized novel bromophenol derivatives (**6–26**) on AChE are shown in Table 1. AChE is one of the important cholinesterase enzymes. Its structure possessing narrow and deep channel which is constituted of five binding zones, (a) acyl binding site, (b) peripheral anionic site existing at the gorge entry (c) oxyanion hole (d) choline binding pocket and (e) catalytic triad located at the bottom of gorge, where the hydrolysis of ACh occurs anticholinesterases or AChEIs inhibit cholinesterase, raising the level and length of ACh action [27]. A variety of utilization of AChE inhibitors is popular in medicine and agriculture [28]. AChE inhibitors traditionally utilized for medical goals include carbamates and organophosphates [29]. In diseases such as AD and myasthenia gravis, in which

Table 1
Human carbonic anhydrase isoenzymes I, and II (hCA I and hCA II) isoenzymes, and AChE enzyme inhibition values of novel bromophenol derivatives (**6–26**).

Compounds	IC_{50} (nM)						K_i (nM)		
	hCA I	r^2	hCA II	r^2	AChE	r^2	hCA I	hCA II	AChE
6	25.1	0.9837	96.2	0.9336	304.8	0.9837	21.6 ± 1.1	116.1 ± 2.1	254.8 ± 29.7
7	21.4	0.9204	63.8	0.943	433.9	0.9902	12.7 ± 2.9	75.3 ± 1.7	303.9 ± 43.8
8	6.8	0.9435	51.3	0.9367	1102.7	0.9621	9.1 ± 1.6	61.6 ± 1.1	734.8 ± 92.6
9	30.4	0.9830	80.3	0.9728	783.0	0.9811	39.4 ± 4.4	107.2 ± 1.6	557.1 ± 36.7
10	11.2	0.9864	46.8	0.9431	384.0	0.9693	8.4 ± 2.3	48.3 ± 1.3	279.7 ± 32.8
11	33.6	0.9898	97.6	0.9346	554.7	0.9247	37.3 ± 10.4	150.2 ± 2.4	426.9 ± 65.0
12	27.7	0.9789	92.4	0.9252	305.9	0.9921	18.8 ± 3.3	120.6 ± 3.5	236.0 ± 24.8
13	17.4	0.9917	77.8	0.9476	438.7	0.9583	14.2 ± 3.3	89.1 ± 2.3	388.9 ± 50.8
14	12.2	0.9917	56.4	0.9152	1243.8	0.9890	10.7 ± 2.9	61.7 ± 2.0	924.2 ± 104.8
15	13.9	0.9771	51.3	0.9475	1092.0	0.9702	7.8 ± 0.9	55.2 ± 1.4	893.6 ± 99.5
16	27.8	0.9950	102.1	0.9306	822.7	0.9811	27.2 ± 11.7	92.9 ± 1.8	634.9 ± 101.7
17	20.7	0.9909	64.7	0.9481	192.8	0.9638	21.4 ± 7.0	98.0 ± 2.6	159.6 ± 21.9
18	17.1	0.9888	57.7	0.9297	394.9	0.9424	13.9 ± 1.5	83.0 ± 2.8	293.1 ± 48.9
19	49.4	0.9902	89.3	0.9614	594.2	0.9836	58.3 ± 10.3	100.4 ± 2.4	429.5 ± 94.2
20	17.6	0.9841	56.3	0.9397	669.7	0.9902	18.9 ± 8.6	43.1 ± 1.7	554.0 ± 92.6
21	21.6	0.9778	121.5	0.9298	478.9	0.9782	18.9 ± 3.0	143.0 ± 3.1	368.2 ± 37.1
22	35.6	0.9871	108.3	0.9283	413.4	0.9630	27.1 ± 4.3	105.1 ± 2.4	283.8 ± 24.8
23	21.5	0.9778	77.8	0.9312	904.7	0.9721	18.1 ± 3.6	89.3 ± 1.5	748.6 ± 118.4
24	16.3	0.9893	59.7	0.9393	490.6	0.9882	14.3 ± 1.7	70.4 ± 1.9	447.9 ± 74.0
25	17.1	0.9970	46.5	0.9027	736.7	0.9377	12.4 ± 5.3	62.9 ± 1.9	593.9 ± 58.2
26	20.7	0.9952	55.4	0.9109	416.3	0.9728	24.5 ± 11.0	85.1 ± 1.9	333.1 ± 48.1
AZA*	107.7	0.9432	155.4	0.9594	–	–	81.7 ± 21.1	152.3 ± 3.33	–
TAC**	–	–	–	–	159.6	0.9773	–	–	110.7 ± 11.9

* AZA (acetazolamide) was used as a positive control for human carbonic anhydrase I and II isoforms (hCA I and II).
** TAC (tacrine) was used as a positive control for acetylcholinesterase enzyme.

cholinergic function is defective, organophosphates/carbamates provide therapeutic options due to high effectiveness as AChEIs [30]. Theseinhibitors are also utilized as pesticides for the deletion of insects that pose a threat to agriculture, gardening, and public health [31]. The AChE inhibition profiles of the compounds evaluated here were quite interesting [32]. Overall, the novel bromophenol derivatives (**6–26**) had excellent inhibitory activity with K_i values ranging from 159.63 ± 21.88 nM to 924.23 ± 104.83 nM. Furthermore, tacrine, used as a standard AChE inhibitor in this study, demonstrated K_i value of 110.73 ± 11.93 nM toward AChE. As these results show, the inhibition of AChE of novel bromophenol derivatives (**6–26**) is much better than standard drug. The compounds of 2,4-dibromo-4-(2,3-dibromo-4,5-dimethoxyphenyl)-3-methylbutanoic acid (**17**) and (1R*,2R*,3R*)-ethyl 2-(2,5,6-tribromo-3,4-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylate (**12**) showed excellent inhibitions profile against AChE with K_i values of 159.63 ± 21.88 and 236.04 ± 24.81 nM, respectively (Table 1 and Fig. 3). In a previous study, which performed by our group, some bromophenol derivatives with S including natural products inhibited AChE with Ki values between 0.9 ± 0.2–18.5 ± 5.1 nM [24].

3. Conclusion

Reaction of the methyl isoeugenol (**5**) with ethyl diazoacetate gave isomeric products *trans*-**6** and *cis*-**7** by catalysis Cu powder. Each of them was reduced with $LiALH_4$ and the corresponding alcohols **8** and **9** were obtained. Esters **6** and *cis*-**7** were reacted with molecular bromine to give the corresponding mono-, di- and tribromides **10–15** at different conditions. Also, the products without cyclopropane ring were observed in the reactions of **7** with bromine. Probably, these products **16–18** were occurred because ester **7** is rather unstable. Opening ring of cyclopropane substituted monoester group with bromine is new. According to our knowledge, observation of this opening ring is first. By base catalyzed-hydrolysis, acids **19–26** were obtained from esters **6**, **7** and **10–15**. Characterizations of all the new products **6–26** were performed by spectroscopic methods, and their structures were determined by NMR, HRMS, elemental analysis and X-ray crystallographic analysis.

These molecules represent a promising structural scaffold that can be further explored in order to generate other synthetics with enhanced inhibitory potential as well as selectivity against hCA I, hCA II and AChE enzymes. The indicated bromophenol derivatives constitute strong drug candidates against the diseases including glaucoma, epilepsy, periodic paralysis, idiopathic intracranial hypertension, altitude sickness, and heart failure (as CA inhibitors), to treat postural tachycardia syndrome, myasthenia gravis, and AD (as cholinergic enzymes inhibitors). In our future studies we will be designing and synthesizing similar molecules with potent biological activities and further dissecting these molecules efficiencies and biological activities by using *in vivo* and *in vitro* disease models.

4. Experimental protocols

4.1. Chemistry

General experimental procedures. Solvents were purified and dried by known methods. For all compounds, values as well as Mp, IR Spectra, ^1H and ^{13}C NMR spectra, chemical shift, elemental analyses, and CA inhibitory properties of samples were performed as explained previously [1k,15a]. PLC (preparative thick-layer chromatography) was used as 1 mm of silica gel 60 PF (Merck, Darmstadt, Germany) on glass plates. HRMS data were obtained by LC-MS-TOF electrospray ionization technique (1200/6210, Agilent).

4.1.1. Reaction of methyl isoeugenol (5) with ethyl diazoacetate

While a mixture of methyl isoeugenol (**5**) (7.13 g, 40 mmol) and Cu powder (1.84 g) at 130 °C was magnetically stirred, ethyl diazoacetate (4.56 g, 40 mmol) in hexane (10 mL) was added dropwise during 8 h, and then the reaction mixture was stirred at same condition. After completion of the addition, the brown reaction mixture was cooled to RT and then hexane in the mixture was removed. The reaction mixture was submitted to CC (silica gel, 160 g) eluting with hexane/ethyl acetate (96/4). The products **6** (3.14 g, 11.9 mmol, 30%) and **7** (1.36 g, 5.1 mmol, 13%) were obtained from the chromatography, respectively.

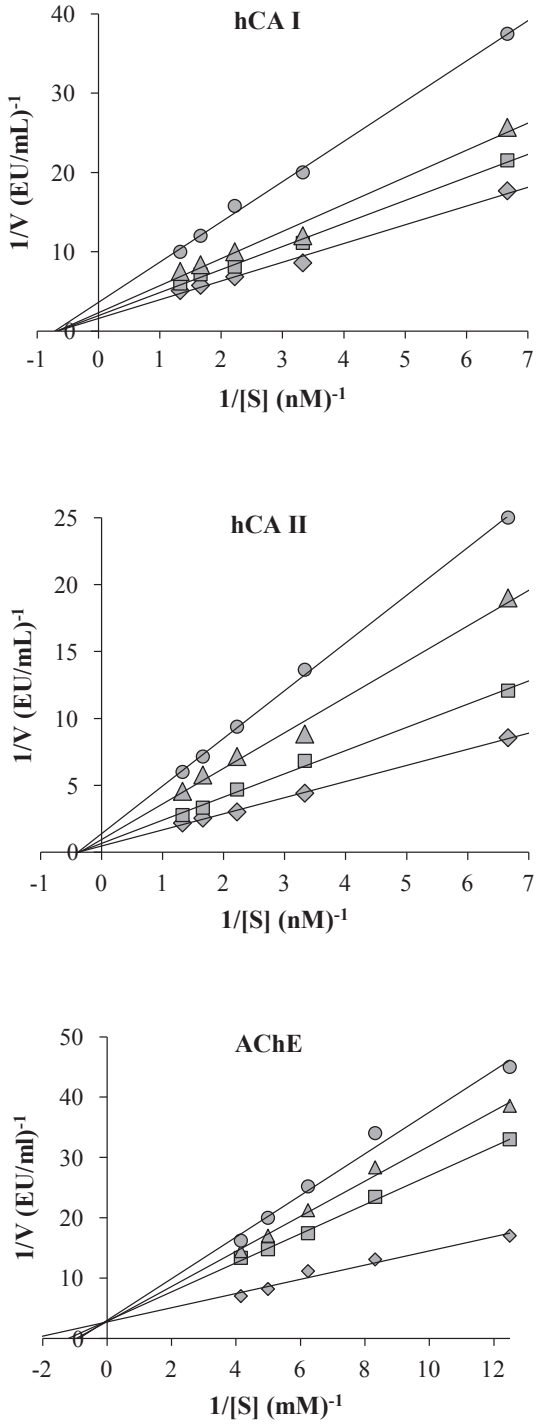


Fig. 3. Determination of Lineweaver-Burk graphs for excellent inhibitors for hCA I (**15**) and hCA II (**20**), AChE (**17**) enzymes.

4.1.1.1. (1R,2R*,3R*)-Ethyl 2-(3,4-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylate **(6)***. Pale blue oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, A part of AB system, J = 7.9 Hz, aromatic, 1H), 6.64–6.59 (m, aromatic, 2H), 4.17 (q, J = 7.1 Hz, OCH_2, 2H), 3.86 (s, OCH_3, 3H), 3.84 (s, OCH_3, 3H), 2.37 (dd, J = 6.4, 5.2 Hz, cyclopropane, 1H), 1.94 (dd, J = 9.2, 5.0 Hz, cyclopropane, 1H), 1.69–1.58 (m, cyclopropane, 1H), 1.34 (d, J = 6.2 Hz, CH_3, 3H), 1.28 (t, J = *7.11, Hz*, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.93 (CO), 149.13 (C), 147.80 (C), 133.37 (C), 118.00 (CH), 111.49 (CH), 110.08 (CH), 60.67 (OCH_2), 56.21 (OCH_3), 56.06 (OCH_3), 32.32, 29.41, 25.37, 14.61, 12.22; IR (cm^{-1}, CH_2Cl_2): 3787, 3695, 3661, 2938, 1718, 1519, 1465, 1350, 1265, 1235, 1181, 1103, 1027, 895, 843, 796; HRMS (APCI – Tof) calcd for $[C_{15}H_{21}O_4 + H]^+$: m/z = 265.1440; found: 265.1447.

4.1.1.2. (1S,2R*,3R*)- Ethyl 2-(3,4-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylate **(7)***. ^{1}H NMR (4.00 MHz, $CDCl_3$): δ 6.82–6.73 (m, aromatic, 3H), 3.90 (q, J = 7.0 Hz, OCH_2, 2H), 3.85 (s, OCH_3, 3H), 3.84 (s, OCH_3, 3H), 2.30 (dd, J = 9.2, 6.9 Hz, cyclopropane, 1H), 2.07–1.97 (m, cyclopropane, 1H), 1.78 (dd, J = 9.2, 5.1 Hz, cyclopropane, 1H), 1.26 (d, J = 6.1 Hz, $CHCH_3$, 3H), 1.02 (t, J = 7.0 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.19 (CO), 148.54 (C), 147.87 (C), 129.53 (C), 121.38 (CH), 112.52 (CH), 110.80 (CH), 60.34 (OCH_2), 56.02 (OCH_3), 56.00 (OCH_3), 34.21, 30.25, 20.11, 17.95, 14.40; IR (cm^{-1}, CH_2Cl_2):3787, 3695, 3661, 3058, 2686, 1722, 1518, 1465, 1265, 1237, 1177, 859, 734, 704; Elemental Anal. Calcd (%) for $C_{15}H_{20}O_4$ requires C 68.16, H, 7.63; Found: C 67.72, H, 7.59.

4.1.2. Synthesis of Alcohol 8: Standard procedure for synthesis of alcohol from reaction of ester with $LiAlH_4$

A stirred solution of ester **6** (77 mg, 0.29 mmol) in dry tetrahydrofuran (THF) (5 mL) was cooled at 0 °C and then $LiAlH_4$ (90 mg, 2.4 mmol) was added in portions over a period of 15 min. After the reaction mixture was stirred at the same temperature for 2 h, cold bath was removed, and it was allowed to stir for 20 h at RT. The grey mixture was cooled to 0 °C, and hydrolyzed by the slow addition of water. The mixture was filtered (inorganic salts) and the solvent evaporated. The residue was cooled to 0 °C, $CHCl_3$ (20 mL) and a solution of NH_4Cl (5%, 15 mL) were added. After organic phase was separated, aqueous phase was extracted with $CHCl_3$ (2 × 10 mL). The combined organic phases were washed with water (10 mL), dried over Na_2SO_4 and the solvent was evaporated, to leave the alcohol **8** (57 mg, 75%) as a pale grey liquid. (1*R**,2*R**,3*R**)-(2-(3,4-dimethoxyphenyl)-3-methylcyclopropyl) methanol **(8)**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 (d, A part of AB system, J = 8.4 Hz, aromatic, 1H), 6.60–6.57 (m, aromatic, 2H), 3.92–3,85 (m, CH_2, 1H), 3.85 (s, OCH_3, 3H), 3.84 (s, OCH_3, 3H), 3.71–3.62 (m, CH_2, 1H), 1.52–1.38 (m, 3H), 1.27–1.23 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.13 (C), 147.31 (C), 135.61 (C), 117.64 (CH), 111.64 (CH), 109.70 (CH), 62.54 (OCH_2), 56.26 (OCH_3), 56.03 (OCH_3), 29.52, 29.26, 21.49, 13.20; IR (cm^{-1}, CH_2Cl_2): 3787, 3661, 3057, 2937, 1518, 1465, 1265, 1235, 1192, 1141, 1027, 896, 857, 800, 732; HRMS (APCI – Tof) calcd for $[C_{13}H_{18}O_3]^+$: m/z = 222.1256; found: 222.1279.

4.1.3. Synthesis of Alcohol 9

The standard procedure described above for the synthesis of **8** was applied. Ester **7** (320 mg, 1.2 mmol), $LiAlH_4$ (120 mg, 3.2 mmol) and THF (12 mL) were used in the reaction. Alcohol **9** (197 mg, 74%) was obtained as a pale orange viscous liquid. **(1*S**,2*R**,3*R**)-(2-(3,4-dimethoxyphenyl)-3-methylcyclopropyl)methanol (9)**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77–6.69 (m, aromatic, 3H), 3.84 (s, OCH_3, 3H), 3.82 (s, OCH_3, 3H), 3.48 (dd, J = 11.6, 5.8 Hz, A part of AB system, CH_2, 1H), 3.27 (dd, J = 11.6, 8.0 Hz, B part of AB system, CH_2, 1H), 1.91 (dd, J = 7.8, 5.4 Hz, cyclopropane, 1H), 1.37–1.10 (m, cyclopropane and CH_3, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.92 (C), 147.32 (C), 134.71 (C), 119.79 (CH), 111.63 (CH), 111.37 (CH), 62.92 (OCH_2), 55.92 (OCH_3), 55.82 (OCH_3), 33.85, 18.32, 16.97, 9.64: IR (cm^{-1}, CH_2Cl_2): 3787, 3058, 2891, 2382, 1720, 1597, 1518, 1465, 1265, 1140, 813, 735, 704; HRMS (APCI – Tof) calcd for $[C_{13}H_{18}O_3]^+$: m/z = 222.1256; found: 222.1282.

4.1.4. Bromination of esters

*4.1.4.1. Bromination of ester **6** by 5.7 equiv. bromine at RT: Standard procedure for bromination of esters*. A stirring solution of ester **6** (0.65 g, 2.46 mmol) in CH_2Cl_2 (20 mL) was prepared at RT and then a solution of bromine (2.25 g, 14.1 mmol, 5.7 equiv.) in CH_2Cl_2 (10 mL) was added dropwise at RT over 5 min. After the reaction mixture was stirred for 13 h, volatile compounds of the reaction mixture were removed at

evaporator. The residue was subjected to CC on silica gel (SiO_2, 65 g) and eluted using EtOAc/hexane (3.5:96.5). Dibromide **12** (126 mg, 0.3 mmol, 12%) and tribromide **11** (435 mg, 0.87 mmol, 36%) were obtained from CC as liquid.

4.1.4.2. (1R,2R*,3R*)-Ethyl 2-(2,6-dibromo-3,4-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylate **(11)***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (s, aromatic, 1H), 4.30–4.15 (m, OCH_2, 2H), 3.84 (s, OCH_3, 3H), 3.81 (s, OCH_3, 3H), 2.21 (dd, J = 5.4, 7.0 Hz, cyclopropane, 1H), 1.91 (dd, J = 5.4, 9.4 Hz, cyclopropane, 1H), 1.68–1.60 (m, cyclopropane, 1H), 1.44 (d, J = 6.2 Hz, CH_3, 3H), 1.30 (t, J = 7.1 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.19 (CO), 152.65 (C), 146.37 (C), 130.96 (C), 123.47 (C), 121.12 (C), 116.27 (CH), 60.67 (OCH_2), 60.64 (OCH_3), 56.49 (OCH_3), 34.23, 31.29, 27.78, 14.75, 12.13; IR (cm^{-1}, CH_2Cl_2): 3787, 2931, 2379, 1725, 1580, 1478, 1420, 1304, 1213, 1183, 831, 739; Elemental Anal. Calcd (%) for $C_{15}H_{18}Br_2O_4$ requires C 42.68, H, 4.30; Found: C 42.74, H, 4.28.

4.1.4.3. (1R,2R*,3R*)-Ethyl 2-(2,5,6-tribromo-3,4-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylate **(12)***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31–4.15 (m, OCH_2, 2H), 3.88 (s, OCH_3, 3H), 3.87 (s, OCH_3, 3H), 2.28 (dd, J = 5.5, 7.1 Hz, cyclopropane, 1H), 1.93 (dd, J = 5.5, 9.4 Hz, cyclopropane, 1H), 1.68–1.58 (m, cyclopropane, 1H), 1.45 (d, J = 6.2 Hz, CH_3, 3H), 1.31 (t, J = 7.1 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.89 (CO), 151.18 (C), 150.80 (C), 136.54 (C), 124.85 (C), 122.72 (C), 121.86 (C), 61.08 (OCH_2), 61.02 (OCH_3), 60.78 (OCH_3), 36.07, 32.08, 28.59, 14.74, 12.12; IR (cm^{-1}, CH_2Cl_2): 3787, 2937, 2382, 1721, 1455, 1390, 1349, 1265, 1183, 1111, 1075, 1036, 1009, 966, 891, 857, 821, 734; Elemental Anal. Calcd (%) for $C_{15}H_{17}Br_3O_4$ requires C 35.96, H, 3.42; Found: C 36.02, H, 3.43.

4.1.4.4. Bromination of ester 6 by 1.38 equiv. bromine at RT. Reaction of ester **6** (228 mg, 0.86 mmol) with bromine (110 mg, 0.69 mmol, 1.38 equiv.) in CH_2Cl_2 (10 mL) for 26 min. and separation of the residue were performed according to standard procedure described 4.1.4.1. Monobromide **10** (268 mg, 91%) was obtained as pale blue liquid.

4.1.4.5. (1R,2R*,3R*) - Ethyl 2-(2-bromo-4,5-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylate **(10)***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, aromatic, 1H), 6.52 (s, aromatic, 1H), 4.25–4.15 (m, CH_2, 2H), 3.83 (s, OCH_3, 6H), 2.54–248 (m, cyclopropane, 1H), 1.90 (dd, J = 9.2, 5.2 Hz, cyclopropane, 1H), 1.61–1.50 (m, cyclopropane, 1H), 1.40 (d, J = 6.2 Hz, CH_3, 3H), 1.30 (t, J = 7.1 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.84 (CO), 148.48 (C), 148.42 (C), 131.67 (C), 116.20 (CH), 115.73 (CH), 111.30 (CH), 60.74 (OCH_2), 56.41 (OCH_3), 56.36 (OCH_3), 33.12, 28.00, 24.89, 14.65, 12.31; IR (cm^{-1}, CH_2Cl_2):3787, 3695, 3661, 3058, 1718, 1510, 1436, 1376, 1349, 1264, 1210, 1184, 1163, 1104, 1035, 973, 857, 808, 734, 703; HRMS (APCI – Tof) calcd for $[C_{15}H_{19}{}^{79}BrO_4 + H]^+$: m/z = 343.0545; found: 343.0578.

4.1.4.6. Bromination of ester 7 by 8 equiv. bromine at RT. Reaction of ester **7** (1.0 g, 3.79 mmol) with bromine (4.86 g, 30.4 mmol, 8.0 equiv.) in CH_2Cl_2 (50 mL) for 13 h and separation of the residue were performed according to standard procedure described 4.1.4.1. Dibromide **14** (176 mg, 11%), tribromide **15** (532 mg, 28%), tetrabromide **16** (88 mg, 4%), tetrabromo acid **17** (55 mg, 2.6%) and tribromo acid **18** (180 mg, 10%) were obtained from CC.

4.1.4.7. (1S,2R*,3R*)-Ethyl 2-(2,6-dibromo-3,4-dimethoxyphenyl)-3-methylcyclopropanecarboxylate **(14)***. Liquid (pale yellow); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (s, aromatic, 1H), 4.00–3.89 (m, OCH_2, 2H), 3.86 (s, OCH_3, 3H), 3.82 (s, OCH_3, 3H), 2.31 (t, J = 8.0, Hz, benzylic and cyclopropane, 1H), 2.00–1.94 (m, cyclopropane, 2H), 1.33 (d, J = 5.2, Hz, CH_3, 3H), 1.07 (t, J = 7.1 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.01 (CO), 151.78 (C), 146.44 (C), 134.20 (C), 121.29 (C), 118.96 (C), 113.76 (CH), 60.50 (OCH_3), 60.33 (OCH_2), 56.39 (OCH_3), 36.90 (CH), 30.17 (CH), 21.94 (CH), 17.32 (CH_3) 13.89 (CH_3); IR (cm^{-1}, CH_2Cl_2): 3787, 3058, 2380, 1718, 1464, 1420, 1376, 1265, 1179, 984, 856, 772, 735, 704; Elemental Anal. Calcd (%) for $C_{15}H_{18}Br_2O_4$ requires C 42.68, H, 4.30; Found: C 42.68, H, 4.27.

4.1.4.8. (1S,2R*,3R*)-Ethyl 2-methyl-3-(2,3,6-tribromo-4,5-dimethoxyphenyl) cyclopropanecarboxylate **(15)***. Liquid (pale yellow); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01–3.91 (m, OCH_2, 2H), 3.88 (s, OCH_3, 6H), 2.19–2.11(m, cyclopropane, 1H), 2.04 (t, J = 7.8, cyclopropane, 1H), 2.00–1.84 (m, cyclopropane, 1H), 1.41 (d, J = 6.0 Hz, CH_3, 3H), 1.12 (t, J = 7.1 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.83 (CO), 150.85 (C), 134.71 (C), 129.84 (C), 115.20 (C), 114.51 (C), 94.57 (CH), 61.08 (OCH_2), 60.95 (OCH_3), 60.59 (OCH_3), 37.71, 32.60, 28.46, 17.82, 14.26; IR (cm^{-1}, CH_2Cl_2): 3787, 3058, 2380, 1722, 1457, 1392, 1289, 1265, 1180, 1116, 1077, 974, 902, 852, 777, 736, 704; Elemental Anal. Calcd (%) for $C_{15}H_{17}Br_3O_4$ requires C 35.96, H, 3.42; Found: C 35.99, H, 3.44.

*4.1.4.9. Ethyl 2,4-dibromo-4-(2,3-dibromo-4,5-dimethoxyphenyl)-3-methylbutanoate **(16)***. Liquid (pale yellow); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, aromatic, 1H), 5.67 (d, J = 10.7 Hz, Benzylic, 1H), 5.33–5.31 (m, COCHBr, 1H), 4.33–4.23 (m, CH_2, 1H), 3.91 (OMe, 3H), 3.89 (OMe, 3H), 2.84–2.75 (m, CH, 1H), 1.34 (t, J = 7.1 Hz, CH_3, 1H), 0.89 (d, J = 6.6 Hz, CH_3, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.55 (CO), 153.21 (C), 147.96 (C), 136.48 (C), 117.34 (C), 112.90 (C), 112.16 (CH), 62.71 (OCH_2), 60.58 (OCH_3), 58.10 (CHBr), 53.90 (OCH_3), 44.31 (CHBr), 29.68 (CH), 14.10 (CH_3), 13.25(CH_3); HRMS (APCI – Tof) calcd for $[C_{15}H_{19}{}^{79}Br_2{}^{81}Br_2{}^{x}BrO_4 + H\text{-}H^{x}Br]^+$: m/z = 500.8735; found: 500.8757.

*4.1.4.10. 2,4-dibromo-4-(2,3-dibromo-4,5-dimethoxyphenyl)-3-methylbutanoic acid **(17)***. Mp: 86–88 °C; White; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (s, aromatic, 1H), 5.59 (d, CHBr, J = 7.84 Hz, 1H), 4.31 (d, CHBr, J = 9.16 Hz, 1H), 3.90 (s, OCH_3, 1H), 3.87 (s, OCH_3, 1H), 2.69–2.58 (m, CH, 1H), 1.37 (d, J = 6.84 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 171.51 (CO), 153.01 (CO), 148.29 (CO), 133.50 (CO), 122.30 (CO), 115.46 (CO), 110.06 (CH), 85.30 (CHBr), 60.60 (OCH_3), 54.46 (OCH_3), 50.27 (CH), 45.18 (CHBr), 15.57 (CH_3); HRMS (APCI – Tof) calcd for $[C_{13}H_{14}{}^{79}Br_2{}^{81}Br_2{}^{x}BrO_4 + H\text{-}H^{x}Br]^+$: m/z = 472.8422; found: 472.8436.

*4.1.4.11. 2,4-Dibromo-4-(2-bromo-4,5-dimethoxyphenyl)-3-methylbutanoic acid **(18)***. Mp: 170–172 °C; White; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (s, aromatic, 1H), 6.84 (s, aromatic, 1H), 5.47 (d, J = 9.0 Hz, CHBr, 1H), 4.34 (d, J = 10.6 Hz, CHBr, 1H), 3.889 (s, OMe, 3H), 3.885 (s, OMe, 3H), 2.68–2.57 (m, methylenic CH, 1H), 1.31 (d, J = *6.77 Hz*, 3H); ^{13}C NMR (100 MHz, $CDCl_3$: 171.48 (CO), 150.19 (C), 149.17 (CH), 127.29, 115.28 (CH), 113.01 (C), 109.66 (**C**H), 84.41 (CHBr), 56.34 (OMe), 56.26 (OMe), 50.64 (C_3H), 46.20 (CHBr), 14.51 (CH_3); IR (cm^{-1}, CH_2Cl_2): 3787, 3087, 2402, 1786, 1600, 1508, 1381, 1307, 1263, 1210, 1169, 934, 735; HRMS (APCI – Tof) calcd for $[C_{13}H_{15}{}^{79}Br_2{}^{81}Br^{x}BrO_4 + H\text{-}H^{x}Br]^+$: m/z = 394.9317; found: 394.9342.

4.1.4.12. Bromination of ester 7 by 1 equiv. bromine at RT. Reaction of ester **7** (132 mg, 0.50 mmol) with bromine (80 mg, 0.50 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) for 27 min. and separation of the residue were performed according to standard procedure described 4.1.4.1. Monobromide **13** (268 mg, 87%) was obtained as pale yellow liquid. **(1S*,2R*,3R*) - Ethyl 2-(2-bromo-4,5-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylate (13):** ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (s, aromatic, 1H), 6.73 (s, aromatic, 1H), 4.00–3.87 (m, CH_2, 2H), 3.86 (s, OCH_3, 3H), 3.83 (s, OCH_3, 3H), 2.26 (t, J = 8.3 Hz, cyclopropane, 1H), 2.01–1.89 (m, cyclopropane, 2H), 1.32 (d, J = 6.3 Hz, CH_3, 3H), 1.09 (t, J = 7.5, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.19 (CO), 148.40 (C), 147.79 (C), 128.66 (C),

116.15 (CH), 115.11 (CH), 113.89 (CH), 60.22 (OCH_2), 56.10 (OCH_3), 56.05 (OCH_3), 35.04, 29.89, 21.63, 17.66, 14.18; IR (cm^{-1}, CH_2Cl_2): 3787, 3058, 2380, 1718, 1509, 1440, 1383, 1264, 1209, 1163, 953, 860, 788, 733; HRMS (APCI – Tof) calcd for $[C_{15}H_{19}{}^{79}BrO_4 + H]^+$: m/z = 343.0545; found: 343.0585.

*4.1.5. General procedure for base-catalyzed hydrolysis of esters **6, 7, 10–15** to acids **19–26***

A mixture of ester (0.5 mmol), ethyl alcohol (7 mL), water (15 mL) and NaOH (400 mg) was refluxed for 20 h, and then the reaction mixture was allowed to stand for 5 h at room temperature. After the mixture was cooled to 0 °C, it was acid with HCl (37%) until pH = 1.0–2.0. The mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and then the solvent was evaporated. Residue was crystallized from ethyl acetate/hexane

4.1.5.1. (1R,2R*,3R*)- 2-(3,4-Dimethoxyphenyl)-3-methylcyclopropane-1-carboxylic acid **(19)***. Mp: 66–68 °C; Pale yellow (82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, A part of AB system, J = 8.8 Hz, aromatic, 1H), 6.65–6.61 (m, aromatic, 2H), 3.87 (s, OCH_3, 3H), 3,85 (s, OCH_3, 3H), 2.43 (dd, J = 7.3, 5.2 Hz, cyclopropane, 1H), 1.96 (dd, J = 9.2, 4.9 Hz, cyclopropane, 1H), 1.80–1.70 (m, cyclopropane, 1H), 1.39 (d, J = 6,2 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.39 (CO), 149.16 (C), 147.98 (C), 132.78 (C), 118.18 (CH), 111.48 (CH), 110.16 (CH), 56.21 (OCH_3), 56.09 (OCH_3), 33.42, 29.05, 26.18, 12.27; IR (cm^{-1}, CH_2Cl_2): 3787, 3661, 2934, 1689, 1591, 1518, 1440, 1333, 1254, 1232, 1188, 1143, 1104, 1072, 1027, 955, 884, 798, 736; HRMS (APCI – Tof) calcd for $[C_{13}H_{16}O_4 + H]^+$: m/z = 237.1127; Found: 237.1148.

4.1.5.2. (1R,2R*,3R*)-2-(2-Bromo-4,5-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylic acid **(20)***. Mp: 108–110 °C; Pale yellow (78%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (s, aromatic, 1H), 6.54 (s, aromatic, 1H), 3.85 (s, OCH_3, 6H), 2.59–245 (m, cyclopropane, 1H), 1.94 (dd, J = 9.1, 5.2 Hz, cyclopropane, 1H), 1.73–1.62 (m, cyclopropane, 1H), 1.46 (d, J = 6.2 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.28 (CO), 148.64 (C), 148.46 (C), 131.16 (C), 116.22 (C), 115.75 (CH), 111.37 (CH), 56.43 (OCH_3), 56.37 (OCH_3), 34.15, 27.69, 25.93, 12.33; IR (cm^{-1}, CH_2Cl_2): 3787, 3057, 2378, 1694, 1510, 1440, 1264, 1210, 1164, 896, 732, 704; HRMS (APCI – Tof) calcd for $[C_{13}H_{15}{}^{79}BrO_4 + H]^+$: m/z = 343.0545; Found: 343.0585.

4.1.5.3. (1R,2R*,3R*)-2-(2,6-dibromo-3,4-dimethoxyphenyl)-3-methylcyclopropane-1-carboxylic acid **(21)***. Mp: 108–110 °C; Grey (85%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (s, aromatic, 1H), 3.86 (s, OCH_3, 3H), 3.82 (s, OCH_3, 3H), 2.26 (dd, J = 5.4, 7.2 Hz, cyclopropane, 1H), 1.97 (dd, J = 5.4, 9.4 Hz, cyclopropane, 1H), 1.79–1.69 (m, cyclopropane, 1H), 1.51 (d, J = 6.2 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.92 (CO), 152.77 (C), 146.41 (C), 130.51 (C), 123.45 (C), 121.15 (C), 116.32 (CH), 60.66 (OCH_3), 56.50 (OCH_3), 35.00, 30.94, 28.76, 12.18; IR (cm^{-1}, CH_2Cl_2): 3787, 3661, 3057, 2686, 2398, 1698, 1586, 1425, 1265, 896, 774, 732; HRMS (APCI – Tof) calcd for $[C_{13}H_{14}{}^{79}Br^{81}BrO_4 + H]^+$: m/z = 394.9317; Found: 394.9362.

4.1.5.4. (1R,2R*,3R*)-2-Methyl-3-(2,3,6-tribromo-4,5-dimethoxyphenyl)cyclopropane-1-carboxylic acid **(22)***. Mp: 139–141 °C; Pale yellow (89%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.887 (s, OCH_3, 3H), 3.885 (s, OCH_3, 3H), 2.33 (dd, J = 7.2, 5.6 Hz, cyclopropane, 1H), 1.99 (dd, J = 9.9, 5.6 Hz, cyclopropane, 1H), 1.79–1.69 (m, cyclopropane, 1H), 1.52 (d, J = 6.2 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.04 (CO), 151.31 (C), 150.84 (C), 136.04 (C), 124.86 (C), 122.73 (C), 121.96 (C), 61.10 (OCH_3), 61.05 (OCH_3), 36.78, 31.74, 29.55, 12.20; IR (cm^{-1}, CH_2Cl_2): 3787, 3057, 2685, 2389, 1697, 1434, 1265, 896, 775, 734, 704; HRMS (APCI – Tof) calcd for $[C_{13}H_{13}{}^{79}Br_2{}^{81}BrO_4 + H]^+$: m/z = 472.8422; Found: 472.8481.

4.1.5.5. (1S,2R*,3R*)-2-(3,4-Dimethoxyphenyl)-3-methylcyclopropanecarboxylic acid **(23)***. 72% White; Mp: 75–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80–6.70 (m, aromatic, 3H), 3.84 (s, OCH_3, 3H), 3,81 (s, OCH_3, 3H), 2.39–2.31 (m, cyclopropane, 1H), 2.05–1.92 (m, cyclopropane, 1H), 1.76–1.70 (m, cyclopropane, 1H), 1.25 (d, J = 6,0 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.31 (CO), 148.51 (C), 147.95 (C), 128.89 (C), 121.51 (CH), 112.36 (CH), 110.87 (CH), 56.02 (OCH_3), 55.96 (OCH_3), 35.41, 29.89, 21.30, 17.96; IR (cm^{-1}, CH_2Cl_2): 3787, 3058, 2885, 2381, 2269, 1608, 1427, 1265, 1172, 1041, 896, 734, 705; HRMS (APCI – Tof) calcd for $[C_{13}H_{12}O_4 + H]^+$: m/z = 237.1127; Found: 237.1151.

4.1.5.6. (1S,2R*,3R*)-2-(2-Bromo-4,5-dimethoxyphenyl)-3-methylcyclopropanecarboxylic acid **(24)***. 93% White; Mp: 154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (s, aromatic, 1H), 6.66 (s, aromatic, 1H), 3.84 (s, OCH_3, 3H), 3.81 (s, OCH_3, 3H), 2.43 (dd, J = 6.6, 5.0 Hz, cyclopropane, 1H), 1.99–1.85 (m, cyclopropane, 2H), 1.31 (d, J = 6.0 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.99 (CO), 148.58 (C), 147.86 (C), 128.14 (C), 116.37 (C), 115.30 (CH), 113.86 (CH), 56.28 (OCH_3), 56.23 (OCH_3), 36.19, 29.54, 22.89, 17.86; IR (cm^{-1}, CH_2Cl_2): 3786, 3058, 2685, 1693, 1597, 1510, 1440, 1382, 1264, 1209, 1163, 1105, 977, 940, 897, 868, 790, 733, 703; Elemental Anal. Calcd (%) for $C_{13}H_{15}BrO_4$ requires C 49.54, H, 4.80; Found: C 49.49, H, 4.81.

4.1.5.7. (1S,2R*,3R*)-2-(2,3-dibromo-4,5-dimethoxyphenyl)-3-methylcyclopropanecarboxylic acid **(25)***. 86% White; Mp: 156–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (s, aromatic, 1H), 3.83 (s, OCH_3, 6H), 2.38 (t, J = 8.0 Hz, cyclopropane, 1H), 2.0–1.92 (m, cyclopropane, 2H), 1.34 (d, J = 5.6 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.90 (CO), 152.04 (C), 146.84 (C), 133.70 (C), 121.58 (C), 119.48 (C), 114.30 (CH), 60.74, 56.43, 37.92, 29.75, 23.42, 17.79; IR (cm^{-1}, CH_2Cl_2): 3787, 3057, 2561, 1684, 1425, 1375, 1265, 896, 777, 733, 704; Elemental Anal. Calcd (%) for $C_{13}H_{14}Br_2O_4$ requires C 39.62, H, 3.58; Found: C 39.57, H, 3.60.

4.1.5.8. (1S,2R*,3R*)-2-Methyl-3-(2,3,6-tribromo-4,5-dimethoxyphenyl)cyclopropanecarboxylic acid **(26)***. 84% Pale yellow; Mp: 176–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 3.88 (s, OCH_3, 6H), 2.15–1.80 (m, cyclopropane, 3H), 1.40 (d, J = 6.0 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.72 (CO), 150.97 (C), 150.72 (C), 150.35 (C), 134.15 (C), 134.08 (C), 134.05 (C), 61.12 (OCH_3), 61.01 (OCH_3), 38.40, 32.32, 29.49, 17.86; IR (cm^{-1}, CH_2Cl_2): 3787, 3086, 2881, 2735, 2638, 2551, 1693, 1450, 1391, 1360, 1291, 1229, 973, 898, 737, 703; HRMS (APCI – Tof) calcd for $[C_{13}H_{13}{}^{79}Br2{}^{81}BrO_4 + H]^+$: m/z = 472.8422; found: 472.8471.

4.2. Crystal structure determination

For the crystal structure determination, single-crystal of the compounds **21** and **26** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). Graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) and oscillation scans technique with Δw = 5° for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement were performed using CrystalClear (Rigaku/MSC Inc., 2005) software [33]. The structures were solved by direct methods using SHELXS-97 [34], which allowed for the location of most of the heaviest atoms, with the remaining non-hydrogen atoms being located from different Fourier maps calculated from successive full-matrix least squares refinement cycles on F^2 using SHELXL-97 [34]. All non-hydrogen atoms were refined using

anisotropic displacement parameters. Hydrogens attached to carbons were located at their geometric positions using appropriate HFIX instructions in SHELXL. The final difference Fourier maps showed no peaks of chemical significance. *Crystal data for* **21**: $C_{13}H_{14}O_4Br_2$, crystal system, space group: monoclinic, $P2_1/n$; (no: 14); unit cell dimensions: $a = 8.8446(2)$, $b = 17.1561$ (3), $c = 9.7113(2)$ Å, $\alpha = 90$, $\beta = 92.872(2)$, $\gamma = 90°$; volume: 1471.73(5) Å^3; Z = 4; calculated density: 1.78 g/cm^3; absorption coefficient: 5.514 mm^{-1}; F (0 0 0) = 766; θ-range for data collection 2.4–28.3°; refinement method: full matrix least-square on F^2; data/parameters: 2904/177; goodness-of-fit on F^2: 1.025; final R-indices [I > 2σ(I)]: $R_1 = 0.031$, w$R_2 = 0.075$; largest diff. peak and hole: 1.034 and −0.850 e Å^{-3}. *Crystal data for* **26**: $C_{13}H_{13}O_4Br_3$, crystal system, space group: triclinic, P-1; (no: 2); unit cell dimensions: $a = 6.990(2)$, $b = 9.512$ (2), $c = 13.715(3)$ Å, $\alpha = 109.50(4)$, $\beta = 93.47(5)$, $\gamma = 106.80(5)°$; volume: 810.3(3) Å^3; Z = 2; calculated density: 1.94 g/cm^3; absorption coefficient: 7.476 mm^{-1}; F(0 0 0) = 456; θ-range for data collection 2.3–28.6°; refinement method: full matrix least-square on F^2; data/parameters: 2571/185; goodness-of-fit on F^2: 1.073; final R-indices [I > 2σ(I)]: $R_1 = 0.057$, w$R_2 = 0.192$; largest diff. peak and hole: 1.190 and −0.820 e Å^{-3}.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge on quoting the depository numbers CCDC-1894216 (for **21**) and CCDC-1894470 (for **26**) (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

4.3. Inhibition assay

4.3.1. hCA isoenzymes purification studies

Both hCA isoenzymes purification studies were performed according to previous studies [35]. For this purpose, human erythrocytes were centrifuged at 10.000*g* for 30 min. Then precipitate and the serum were separated. Then, serum pH was adjusted to 8.7 with solid Tris. Sepharose-4B-L-Tirozyne-sulfanylamide affinity column balanced with Tris-HCl/Na_2SO_4 (25 mM/0.1 M, pH 8.7). Adjusted human erythrocyte sample was applied to the Sepharose-4B-L-Tirozyne-sulfanylamide affinity column. The affinity gel was washed with Tris-HCl/Na_2SO_4 (25 mM/22 mM, pH: 8.7). The hCA I, and hCA II isoenzymes were eluted with NaCl (1.0 M)/sodium phosphate (0.25 M; pH 6.3) and sodium acetate (0.1 M)/$NaClO_4$ (0.5 M, pH 5.6), respectively. Column flow rate was 20 mL/h and was 4 mL fractions were collected. All procedures were performed at 4 °C. The protein content during the purification steps was identified using by Bradford method at 595 nm with slight modification. In this study, bovine serum albumin was used as standard protein [36].

4.3.2. hCA isoenzymes inhibition studies

CA inhibitory effects of novel bromophenol derivatives (**6–26**) on both CA isoenzymes were measured according to Verpoorte et al. [37] described in previous studies [38] using p-nitrophenylacetate (PNA) substrate. For this purpose esterase activity was determined by absorbance changing at 348 nm of PNA to p-nitrophenolate conversion over a period of 3 min at 25 °C using a spectrophotometer. The enzymatic reaction performed containing 0.4 mL of Tris-SO_4 buffer solutions (0.05 M, pH 7.4), 0.36 mL PNA (3 mM), 0.22 mL water and 0.2 mL of enzyme solution in total volume of 1 mL. -The enzyme solution was not added to the control sample. A reference measurement was obtained by preparing the mixture without the enzyme solution. All measurements were recorded in triplicate. The Ki values were determined from a series of experiments using three different novel sulfonamides and 4-nitrophenylacetate as the substrate at five different concentrations to construct Lineweaver–Burk curves as described previously [39].

4.3.3. AChE inhibition study

Acetylcholinesterase enzyme inhibition assay was determined on commercially available purified AChE from electric gel (*Electrophorus electricus*) based on the method of Ellman et al. [40] as described previously [41]. Acetylthiocholine iodide (AChI) was utilized as substrate for the enzymatic reaction. 5,5′-Dithio-bis(2-nitro-benzoic) acid (DTNB) was utilized for the evaluation of the AChE activity. Briefly, 50 µL DTNB and 100 µL of Tris/HCl solution (1.0 M, pH 8.0), 770 µL of sample solution dissolved in distilled water at disparate concentrations and 30 µL AChE (5.32×10^{-3} U) solution were incubated and mixed for 10 min at 25 °C. AChI was used as substrates for this study. Finally, 50 µL of AChI was added and reaction started. For the measurement of the AChE activity, DTNB was applied. The enzymatic hydrolysis of this substrate was recorded spectrophotometrically by the creating of yellow 5-thio-2-nitrobenzoate anion as the result of the product of thiocholine with DTNB in 5 min at 412 nm. The half maximal inhibitory concentration (IC_{50}) of each novel bromophenol derivatives (**6–26**) was calculated from graphs. IC_{50} values are measure of the effectiveness of novel bromophenol derivatives (**6–26**) in inhibiting AChE, and both CA isoenzymes. For the calculation of Ki values, three diverse novel bromophenol derivatives (**6–26**) concentrations were utilized. Ki values reflect the binding affinity of novel bromophenol derivatives (**6–26**) to AChE. In this experiment, AChI were used as substrate at five different concentrations for AChE [42].

Declaration of Competing Interest

The authors report no financial and non-financial conflict of interest.

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References

[1] (a) G.W. Gribble, Chem. Soc. Rev. 28 (1999) 335–346;
(b) H.T. Balaydin, I. Gulcin, A. Menzek, G. Goksu, E. Sahin, J. Enzyme Inhib. Med. Chem. 25 (2010) 685–695;
(c) H.T. Balaydin, M. Senturk, A. Menzek, Bioorg. Med. Chem. Lett. 22 (2012) 1352–1357;
(d) K. Li, X.M. Li, J.G. Gloer, B.G. Wang, J. Agric. Food Chem. 59 (2011) 9916–9921;
(e) X.J. Duan, X.M. Li, B.G. Wang, J. Nat. Prod. 70 (2007) 1210–1213;
(f) F.Z. Kucukbay, H. Kucukbay, M. Tanc, C.T. Supuran, J. Enzyme Inhib. Med. Chem. 31 (2016) 1198–1202;
(g) H.T. Balaydin, M. Senturk, S. Goksu, A. Menzek, Eur. J. Med. Chem. 54 (2012) 423–428;
(h) Y. Cetinkaya, H. Gocer, I. Gulcin, A. Menzek, Arch. Pharm. 347 (2014) 354–359;
(i) T. Artunc, Y. Cetinkaya, H. Gocer, I. Gulcin, A. Menzek, E. Sahin, C.T. Supuran, Chem. Biol. Drugs Des. 87 (2016) 594–607;
(k) C. Bayrak, P. Taslimi, I. Gulcin, A. Menzek, Bioorg. Chem. 72 (2017) 359–366;
(m) I. Gulcin, Arch. Toxicol. 86 (3) (2012) 345–391.
[2] J.S. Choi, H.J. Park, H.A. Jung, H.Y. Chung, J.H. Jung, W.C. Choi, J. Nat. Prod. 63 (2000) 1705–1706.
[3] (a) S. Ono, K. Ogawa, K. Yamashita, T. Yamamoto, Y. Kazuta, A. Matsuda, S. Shuto, Chem. Pharm. Bull. 50 (2002) 966–968;
(b) Y. Kazuta, R. Tsujita, K. Yamashita, S. Uchino, S. Kohsaka, A. Matsuda, S. Shuto, Bioorg. Med. Chem. 10 (2002) 3829–3848;
(c) S. Shuto, H. Takada, B.D. Mochizuk, R. Tsujita, Y. Hase, S. Ono, N. Shibuya, M. Akira, J. Med. Chem. 38 (1996) 2964–2968.
[4] M. Boztas, Y. Cetinkaya, M. Topal, I. Gulcin, A. Menzek, E. Sahin, M. Tanc, C.T. Supuran, J. Med. Chem. 58 (2015) 640–650.
[5] (a) M. Zengin, H. Genc, P. Taslimi, P.A. Kestane, E. Guclu, A. Ogutlu, O. Karabay, I. Gulcin, Bioorg. Chem. 81 (2018) 119–126;
(b) U. Atmaca, A. Yıldırım, P. Taslimi, S.T. Celik, I. Gulcin, C.T. Supuran, M. Celik, J. Biochem. Mol. Toxicol. 32 (2018) e22173;
(c) S. Okten, M. Ekiz, U.M. Kocyigit, A. Tutar, I. Celik, M. Akkurt, M. Gokalp, P. Taslimi, I. Gulcin, J. Mol. Struct. 1175 (2019) 906–915.
[6] (a) B. Yigit, M. Yigit, P. Taslimi, Y. Gok, I. Gulcin, Arch. Pharm. 351 (2018) 1800146;
(b) G. Gondolova, P. Taslimi, A. Medjidov, F. Farzaliyev, A. Sujayev,

M. Huseyinova, O. Sahin, B. Yalcin, F. Turkan, I. Gulcin, J. Biochem, Mol. Toxicol. 32 (2018) e22197.
[7] (a) B. Yigit, M. Yigit, P. Taslimi, D. Barut Celepci, Y. Gok, A. Aktas, M. Aygun, I. Gulcin, ChemistrySelect 3 (27) (2018) 7976–7982;
(b) I. Gulcin, P. Taslimi, Exp. Opin. Therap. Pat. 28 (7) (2018) 541–549;
(c) I. Gulcin, P. Taslimi, J. Food Biochem. 42 (8) (2018) e12516.
[8] (a) A. Behcet, T. Caglılar, D. Barut Celepci, A. Aktas, P. Taslimi, Y. Gok, M. Aygun, R. Kaya, I. Gulcin, J. Mol. Struct. 1170 (2018) 160–169;
(b) A. Yıldırım, U. Atmaca, A. Keskin, M. Topal, M. Celik, I. Gulcin, C.T. Supuran, Bioorg. Med. Chem. 23 (10) (2015) 2598–2605.
[9] (a) A. Akincioglu, H. Akincioglu, I. Gulcin, S. Durdagi, C.T. Supuran, S. Goksu, Bioorg. Med. Chem. 23 (13) (2015) 3592–3602;
(b) M. Kucuk, I. Gulcin, Environ. Toxicol. Pharmacol. 44 (2016) 134–139;
(c) F. Topal, I. Gulcin, A. Dastan, M. Guney, Int. J. Biol. Macromol. 94 (2017) 845–851.
[10] (a) U.M. Kocyigit, Y. Budak, M.B. Gurdere, S. Tekin, T. Kul Koprulu, F. Erturk, K. Ozcan, I. Gulcin, M. Ceylan, Bioorg. Chem. 70 (2017) 118–125;
(b) A. Aktas, P. Taslimi, I. Gulcin, Y. Gok, Arch. Pharm. 350 (6) (2017) e1700045.
[11] (a) K. Oktay, L. Polat Kose, K. Sendil, M.S. Gultekin, I. Gulcin, Med. Chem. Res. 26 (8) (2017) 1619–1627;
(b) N. Oztaskin, P. Taslimi, A. Maras, S. Guksu, I. Gulcin, Bioorg. Chem. 74 (2017) 104–114;
(c) A. Akincioglu, E. Kocaman, H. Akıncıoglu, R.E. Salmas, S. Durdagı, I. Gulcin, C.T. Supuran, S. Goksu, Bioorg. Chem. 74 (2017) 238–250.
[12] (a) I. Gulcin, M. Abbasova, P. Taslimi, Z. Huyut, L. Safarova, A. Sujayev, V. Farzaliyev, S. Beydemir, S.H. Alwasel, C.T. Supuran, J. Enzyme Inhib. Med. Chem. 32 (1) (2017) 1174–1182;
(b) U.M. Kocyigit, Y. Budak, M.B. Gurdere, F. Erturk, B. Yencilek, P. Taslimi, I. Gulcin, M. Ceylan, Synth. Commun. 47 (24) (2017) 2313–2323;
(c) F. Erdemir, D. Barut Celepci, A. Aktas, P. Taslimi, Y. Gok, H. Karabiyik, I. Gulcin, J. Mol. Struct. 1155 (2018) 797–806.
[13] (a) A. Menzek, N. Saracoglu, M. Kraweic, W.H. Watson, M. Balci, J. Org. Chem. 60 (1995) 829–832;
(b) A. Menzek, M. Karakaya, Turk J. Chem. 28 (2004) 141–148;
(c) M.D. Gheorghiu, E. Olteanu, J. Org. Chem. 52 (1987) 5158–5162.
[14] (a) A. Menzek, Tetrahedron 56 (2000) 8505–8512;
(b) A. Menzek, B. Gokmen, Helv. Chim. Acta 86 (2003) 324–329.
[15] (a) Y. Cetinkaya, A. Menzek, E. Sahin, H.T. Balaydin, Tetrahedron 67 (2011) 3483–3487;
(b) M.E. Sengul, A. Menzek, M. Balci, Turk. J. Chem. 30 (2006) 131–138;
(c) U. Coruh, A. Menzek, S. Garcia-Granda, Acta Cryst. E 61 (2005) o1869–o1871.
[16] Y. Adiloglu, E. Sahin, A. Tutar, A. Menzek J. Heterocyc. Chem. 55 (2018) 1917–1927.
[17] (a) A. Menzek, N. Saracoglu, A. Dastan, M. Balci, R. Abbasoglu, Tetrahedron 53 (1997) 14451–14461;
(b) A. Menzek, A. Altundas, U. Çoruh, N. Akbulut, E.M. Vazquez Lopez, T. Hokelek, A. Erdönmez, Eur. J. Org. Chem. (2004) 1143–1148.
[18] (a) C. Caglayan, I. Gulcin, J Biochem Mol Toxicol. 32 (1) (2018) e22010;
(b) T. Dastan, U.M. Kocyigit, S. Durna Dastan, C. Kilickaya, P. Taslimi, O. Cevik, M. Koparir, A. Cetin, C. Orek, I. Gulcin, J. Biochem. Mol. Toxicol. 31 (11) (2017) e21971;
(c) C. Yamali, H.I. Gul, A. Ece, P. Taslimi, I. Gulcin, Chem. Biol. Drugs Des. 91 (4) (2018) 854–866.
[19] M. Senturk, I. Gulcin, A. Dastan, O.I. Kufrevioglu, C.T. Supuran, Bioorg. Med. Chem. 17 (8) (2009) 3207–3211.
[20] T.A. Coban, S. Beydemir, I. Gucin, D. Ekinci, A. Innocenti, D. Vullo, C.T. Supuran, Bioorg. Med. Chem. 17 (16) (2009) 5791–5795.
[21] A. Innocenti, S.B. Ozturk Sarıkaya, I. Gulcin, C.T. Supuran, Bioorg. Med. Chem. 18 (6) (2010) 2159–2164.
[22] A. Innocenti, I. Gulcin, A. Scozzafava, C.T. Supuran, Bioorg. Med. Chem. Lett. 20 (18) (2010) 5050–5053.
[23] (a) S.B. Ozturk Sarıkaya, F. Topal, M. Senturk, I. Gulcin, C.T. Supuran, Bioorg. Med. Chem. Lett. 21 (14) (2011) 4259–4262;
(b) A. Akıncıoglu, Y. Akbaba, H. Gocer, S. Goksu, I. Gulcin, C.T. Supuran, Bioorg. Med. Chem. 21 (6) (2013) 1379–1385.
[24] C. Bayrak, P. Taslimi, H.S. Kahraman, I. Gulcin, A. Menzek, A, Bioorg. Chem. 85 (2019) 128–139.
[25] K. Aksu, M. Nar, M. Tanc, D. Vullo, I. Gulcin, S. Goksu, F. Tumer, C.T. Supuran, Bioorg. Med. Chem. 21 (11) (2013) 2925–2931.
[26] P. Taslimi, A. Sujayev, S. Mamedova, P. Kalın, I. Gulcin, N. Sadeghian, S. Beydemir, O.I. Kufrevioglu, S.H. Alwasel, V. Farzaliyev, S. Mamedov, J. Enzyme Inhib. Med. Chem. 32 (1) (2017) 137–145.
[27] S. Burmaoglu, A.O. Yilmaz, P. Taslimi, O. Algul, D. Kılıc, I. Gulcin, Arch. Pharm. 351 (2) (2018) e1700314.
[28] P. Taslimi, A. Sujayev, E. Garibov, N. Nazarov, Z. Huyut, S.H. Alwasel, I. Gulcin, J. Biochem. Mol. Toxicol. 31 (7) (2017) e21897.
[29] P. Taslimi, S. Osmanova, I. Gulcin, S. Sardarova, V. Farzaliyev, A. Sujayev, R. Kaya, F. Koc, S. Beydemir, S.H. Alwasel, O.I. Kufrevioglu, J. Biochem. Mol. Toxicol. 31 (9) (2017) e21931.
[30] (a) U.M. Kocyigit, P. Taslimi, H. Gezegen, I. Gulcin, M. Ceylan, J. Biochem. Mol. Toxicol. 31 (9) (2017) e21938;
(b) H. Tohma, A. Altay, E. Koksal, A.C. Goren, İ. Gulcin, J. Food Measure. 13 (2) (2019) 1607–1619.
[31] (a) H. Genc Bilgicli, A. Kestane, P. Taslimi, O. Karabay, A. Bytyqi-Damoni, M. Zengin, İ. Gulcin, Bioorg. Chem. 88 (2019) 102931;
(b) N. Oztaskin, R. Kaya, A. Maras, E. Sahin, I. Gulcin, S. Goksu, Bioorg. Chem. 87 (2019) 91–102.
[32] (a) P. Taslimi, H. Akincioglu, I. Gulcin, J. Biochem. Mol. Toxicol. 31 (11) (2017) e21973;
(b) F. Turkan, A. Cetin, P. Taslimi, M. Karaman, I. Gulcin, Bioorg. Chem. 86 (2019) 420–427;
(c) K. Kucukoglu, H.I. Gul, P. Taslimi, I. Gulcin, C.T. Supuran, Bioorg. Chem. 86 (2019) 316–321.
[33] Rigaku/MSC, Inc., 9009 New Trails Drive, TheWoodlands, TX 77381.
[34] G.M. Sheldrick, Acta Cryst. A 64 (2008) 112–122.
[35] (a) H. Gocer, A. Akıncıoglu, S. Goksu, I. Gulcin, C.T. Supuran, J. Enzyme Inhib. Med. Chem. 30 (2) (2015) 316–320;
(b) A. Atasever, H. Ozdemir, I. Gulcin, O.I. Kufrevioglu, Food Chem. 136 (2) (2013) 864–870;
(c) Y. Akbaba, A. Akıncıoglu, H. Gocer, S. Goksu, I. Gulcin, C.T. Supuran, J. Enzyme Inhib. Med. Chem. 29 (1) (2014) 35–42;
(d) O. Hisar, S. Beydemir, I. Gulcin, O.I. Kufrevioglu, C.T. Supuran, J. Enzyme Inhib. Med. Chem. 20 (1) (2005) 35–39.
[36] (a) B. Ozgeris, S. Goksu, L. Polat Kose, I. Gulcin, R.E. Salmas, S. Durdagi, F. Tumer, C.T. Supuran, Bioorg. Med. Chem. 24 (10) (2016) 2318–2329;
(b) L. Polat Kose, I. Gulcin, A.C. Goren, J. Namiesnik, A.L. Martinez-Ayala, S. Gorinstein, Ind. Crops Prod. 74 (2015) 712–721;
(c) I. Gulcin, A. Scozzafava, C.T. Supuran, H. Akıncıoglu, Z. Koksal, F. Turkan, S. Alwasel, J. Enzyme Inhib. Med. Chem. 31 (6) (2016) 1095–1101.
[37] J.A. Verpoorte, S. Mehta, J.T. Edsall, J. Biol. Chem. 242 (1967) 4221–4229.
[38] (a) M. Nar, Y. Cetinkaya, I. Gulcin, A. Menzek, J. Enzyme Inhib. Med. Chem. 28 (2) (2013) 402–406;
(b) O. Hisar, S. Beydemir, I. Gulcin, S. AraSHisar, T. Yanık, O.I. Kufrevioglu, Turk. J. Vet. Anim. Sci. 29 (2005) 841–845;
(c) K. Aksu, B. Ozgeris, P. Taslimi, A. Naderi, I. Gulcin, S. Goksu, Arch. Pharm. 349 (12) (2016) 944–954.
[39] (a) H. Lineweaver, D. Burk, J. Am. Chem. Soc. 56 (1934) 658–666;
(b) Y. Akbaba, E. Bastem, F. Topal, I. Gulcin, A. Maras, S. Goksu, Arch. Pharm. 347 (12) (2014) 950–957;
(c) P. Taslimi, I. Gulcin, N. Oztaskın, Y. Cetinkaya, S. Goksu, S.H. Alwasel, C.T. Supuran, J. Enzyme Inhib. Med. Chem. 31 (4) (2016) 603–607.
[40] G.L. Ellman, K.D. Courtney, V. Andres, R.M. Featherston, Biochem. Pharmacol. 7 (1961) 88–95.
[41] (a) P. Taslimi, C. Caglayan, I. Gulcin, J. Biochem. Mol. Toxicol. (2017) e21995;
(b) Y. Sarı, A. Aktas, P. Taslimi, Y. Gok, C. Caglayan, I. Gulcin, J. Biochem. Mol. Toxicol. 32 (1) (2018) e22009;
(c) U.M. Kocyigit, Y. Budak, M.B. Gurdere, F. Erturk, B. Yencilek, P. Taslimi, I. Gulcin, M. Ceylan, Arch. Physiol. Biochem. 124 (1) (2018) 61–68.
[42] (a) B. Yigit, R. Kaya, P. Taslimi, Y. Isık, M. Karaman, M. Yigit, I. Ozdemir, I. Gulcin, J. Mol. Struct. 1179 (2019) 709–718;
(b) A. Bicer, P. Taslimi, G. Yakalı, I. Gülcin, M.S. Gültekin, G.T. Cin, Bioorg. Chem. 82 (2019) 393–404;
(c) S. Burmaoglu, O.A. Yilmaz, M.F. Polat, O. Algul, R. Kaya, I. Gulcin, Bioorg. Chem. 85 (2019) 191–197.