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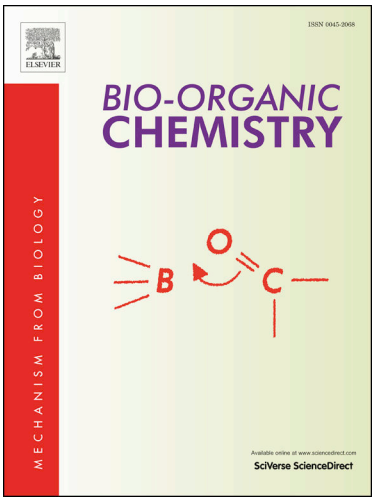

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Novel Propanolamine Derivatives Attached to 2-Metoxifenol Moiety: Synthesis, Characterization, Biological Properties, and Molecular Docking Studies

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ABSTRACT

The synthesis of seven new ß-amino alcohols was designed and performed by starting from eugenol, a natural phenolic compound known to be biologically active. The synthesized compounds were obtained in yields ranging from 54 to 81%. Molecule structures were determined with FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopies. In addition, the inhibitory effects of these substances on acetylcholinesterase (AChE), α-glycosidase (α-Gly), human carbonic anhydrase I (hCA I), and human carbonic anhydrase II (hCA II) enzymes have been investigated. It has been seen that all compounds have a better ability to inhibit compared to existing tried inhibitors. Among these, the best inhibitor against AChE enzyme is **2b** (Ki 62.08 ± 11.67 µM and IC_{50} 90.33), and against α-Gly, **2c** showed the highest effect (Ki 0.33 ± 0.08 µM and IC_{50} 0.28). The best inhibitor against hCA I, and hCA II enzymes is compound **2f**. For hCA I and hCA II, Ki value was measured as 9.68 ± 1.32 and 11.46 ± 2.64 µM and IC_{50} values as 7.37 and 8.26 µM respectively. The interactions of the studied new propanolamine derivatives with the enzymes were done by molecular docking calculations and their biological activities were compared to the experimental tests. Studied enzymes in molecular docking calculations are acetylcholinesterase (AChE) is PDB ID: 4M0E, α-glycosidase (α-Gly) is PDB ID: 1R47, human carbonic anhydrase isoenzyme I (hCA I) PDB ID: 3LXE is human carbonic anhydrase isoenzyme II (hCA II) is PDB ID: 5 AML.

Keywords: Eugenol; propanol amine; β-amino alcohols; enzyme inhibition; molecular docking

1. INTRODUCTION

It is well known that when drugs enter the body, they are converted into metabolites by various enzymes and excreted from the organism [1]. Thus, when designing the synthesis of compounds having high potential to be a drug active substance, referencing to the molecule structures found in existing drugs or natural products [2] are favorably supports the process. Because the metabolites of such compounds have already been tested and their positive or negative aspects have been investigated in detail [3,4].

The β-amino alcohol structures also known as β-hydroxylamin or 1,2-amino alcohol are considered as significant pharmacofores [5] due to be present in the structure of many pharmacologically active natural or synthetic compounds [6,7]. These compounds have an undeniable importance especially in the synthesis of substances such as synthetic amino acids, β-blockers and insecticidal agents [8]. Currently, there are 82 aminoalcohol-derived compounds in the FDA approved drug list, while 119 drug candidates are pending the approval. There are also 23 amino alcohols used as a nutritional supplement in the food industry [9]. Eugenol is an essential oil and widely used in industries such as medicine, food and cosmetics [10]. This natural phenolic compound, which has been used an antibacterial since ancient times, has important effects on human health [11].

Based on this, the synthesis of new β-amino alcohol derivatives carrying the 2-methoxyphenol group, which is also found in the eugenol compound, was designed and carried out (Scheme 1). Their structures were determined by ^{1}H NMR and ^{13}C NMR spectroscopies. The inhibitory effects of these substances on acetylcholinesterase (AChE), α-glycosidase (α-Gly), human carbonic anhydrase I (hCA I), and human carbonic anhydrase II (hCA II) enzymes were investigated.

Scheme 1

The role of carbonic anhydrase (CA) in human physiological is vital such as electrolytes secretion, intracellular pH regulation, lipogenesis, gluconeogenesis, and bone resorption and consequently interests the medicinal chemists for drug discovery of anticancer, antiglaucoma, antineuropathic pain, antiepileptic and antiobesity agents [12,13]. α-Glycosidase is a primary target of type-2 diabetes mellitus (T2DM) therapy and drug discovery. The three main clinically practiced drugs (Acarbose, Miglitol, and Voglibose) for T2DM are α-glycosidase and work by reduction of post-prandial hyperglycemia. The unfortunate side effects including hepatotoxicity limit their use and impact, calling to design better inhibitors for α-glycosidase [14,15]. AD is

the single most complex neurodegradation challenge of 21st century. Presently, 40 million are suffering from dementia worldwide mainly caused by AD, the number is expected to increase two-fold after every two decades. Multitarget drug discovery strategies have been studied for last twenty years to yield potential candidates for Alzheimer's disease (AD), citing cholinesterase enzymes including acetylcholinesterase and butyrylcholinesterase to be the major targets of Cholinergic pathway associated to dementia in AD and Parkinson's diseases (PD) [16,17].

Many of the theoretical studies conducted today have started to guide experimental studies [18–21]. Theoretical studies reduce the duration and cost of experimental studies. This provides great convenience to researchers. These theoretical studies allow us to find the optimized structures of molecules, the atom or groups of atoms to interact with the enzyme, and find the active regions of the enzymes. Today, molecular docking is the most common among the theoretical methods. With this method, the comparison of the biological activities of the molecules with the enzymes is calculated by finding the numerical values [18]. Using this method, the conditions for the methoxyphenol derivatives studied to become drugs in the future will be examined. Many parameters are obtained for this study by molecular docking calculations [22]. Numerical values of these parameters will be checked to see if they are within the limits of being a drug. These analyzes are called ADME analysis [23–25]. In this analysis, the conditions of molecules to be drugs are examined.

In the present study, we determined the synthesis and characterization of novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) and effects of these derivatives on CA isoenzymes (hCA I and II), cholinergic enzyme (AChE), and digestive enzyme (α-glycosidase). Furthermore, the metabolic enzyme inhibition profiles of novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) were compared to acetazolamide, tacrine, and acarbose as standard inhibitors for metabolic enzymes. Also, with molecular docking studies, the conditions of molecules to be drugs are examined.

2. MATERIALS AND METHODS

2.1.Synthesis of 2-methoxy-4-(oxiran-2-ylmethyl)phenol (1)

To the stirred solution of eugenol (1) (0,5 g, 3 mmol) in $CHCl_3$, was added dropwise the solution of *m*-CPBA (meth-achloroperbenzoic acid) (1.29 g, 7.5 mmol) of $CHCl_3$ (20 mL). The reaction mixture was stirred at 80 °C for 24 hours and then cooled to room temperature and filtered. The

filtrate was transferred to the separatory funnel and extracted with $NaHCO_3$(aq) (2x10 mL) and then water (2x10 mL) respectively. The organic phase was dried with $MgSO_4$ and concentrated in a rotary evaporator. The crude product was analyzed with ^1H and ^{13}C NMR spectra and was used in the subsequent reactions without any additional purification (Scheme 2).

2-methoxy-4-(oxiran-2-ylmethyl)phenol (1): Colorless oily; yield 0.52g, 95%; ^1H NMR (300 MHz, Chloroform-*d*) δ 6.81 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.73 (d, *J* = 1.7 Hz, 1H), 6.69 (dd, *J* = 8.0, 1.7 Hz, 1H), 3.80 (d, *J* = 1.5 Hz, 3H), 3.10 (ddtd, *J* = 5.4, 4.2, 2.7, 1.4 Hz, 1H), 2.83 – 2.68 (m, 3H), 2.52 (tt, *J* = 4.6, 3.1, 2.7, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.94, 144.66, 129.20, 121.77, 114.81, 112.02, 56.06, 53.16, 47.15, 38.50.

Scheme 2

2.2.Synthesis of propyl amine derivatives (2a-g)

To the mixture of 2-methoxy-4-(oxyran-2-ylmethyl) phenol (**1**) (0.18 g, 1 mmol) and amine derivative (1.40 mmol), Na_2CO_3 (0.18 g, 1.40 mmol) was added and it was stirred at room temperature for 24 hours. At the end of the reaction, after removed excess amine in vacuum, the residue was dissolved with dichloromethane (30 mL) and washed with brine (20 mL) and water (2x20 mL), respectively. The organic phase was dried with $MgSO_4$ and concentrated in a rotary evaporator. Purification methods for each compound are described in the experimental section. The structures were characterized by ^1H NMR, ^{13}C NMR and FT-IR spectrums. General reaction equation and structures of synthesized compounds are given in Scheme 3.

Scheme 3

4-(3-(Diethylamino)-2-hydroxypropyl)-2-methoxyphenol (2a): Hexane was added to the crude product and the viscose substance (**2a**) was separated from the mixture by centrifugation. Brown viscose liquid; yield 0.18g, 72%; FT-IR *ν* (cm^{-1}) = 1035 (CO stretching), 1121 (CN stretching), 1268 (CO stretching), 2969 (CH stretching), 3374 (OH stretching); ^1H NMR (300 MHz, Chloroform-*d*) δ 6.83 (d, *J* = 8.0 Hz, 1H), 6.78 (s, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 3H), 3.83 – 3.71 (m, 1H), 2.84 – 2.07 (m, 10H), 1.00 (td, *J* = 7.1, 0.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.63, 144.29, 130.68, 122.01, 114.48, 112.10, 68.27, 59.23, 56.08, 47.29 (2C), 41.32, 12.20 (2C).

4-(3-(Tert-butylamino)-2-hydroxypropyl)-2-methoxyphenol (2b): Hexane and ether (1: 1) solvents were added to the crude product. Separation of the insoluble particles by filtration,

pure **2b** was obtained. Brown solid; yield 0.16g, 63%; mp: 116-118 ºC; FT-IR *v* (cm^{-1}) = 1032 (CO stretching), 1085 (CN stretching), 1268 (CO stretching), 2961 (CH stretching), 3294 (OH stretching); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.74 (d, *J* = 1.8 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.55 (dd, *J* = 8.0, 1.8 Hz, 1H), 3.71 (s, 3H), 3.61 – 3.50 (m, 1H), 2.74 – 2.13 (m, 6H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.73, 144.38, 130.42, 122.08, 114.61, 112.04, 71.57, 56.07, 50.85, 47.73, 41.61, 29.20 (3C).

4-(3-(Allylamino)-2-hydroxypropyl)-2-methoxyphenol (2c): To the obtained crude product, DCM was added and insoluble beige solid (**2c**) was filtered off. Beige solid; yield 0.19g, 81%; mp: 114-116 ºC; FT-IR *v* (cm^{-1}) = 1034 (CO stretching), 1082 (CN stretching), 1269 (CO stretching), 2923 (CH stretching), 3307 (OH stretching); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.83 (d, *J* = 8.0 Hz, 1H), 6.78 – 6.56 (m, 2H), 5.99 – 5.74 (m, 1H), 5.24 – 5.00 (m, 2H), 3.87 (s, 3H), 3.95 – 3.76 (m, 1H), 3.48 – 2.97 (m, 4H), 2.75 (dd, *J* = 12.1, 3.1 Hz, 1H), 2.68 (d, *J* = 5.8 Hz, 2H), 2.54 (dd, *J* = 12.1, 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.81, 144.50, 135.22, 129.93, 122.08, 117.86, 114.70, 112.09, 70.66, 56.07, 53.83, 51.99, 41.50.

4-(3-(Butylamino)-2-hydroxypropyl)-2-methoxyphenol (2d): After dissolving the crude product in a mixture of ether: DCM (50:50) by heating, the solution was left in the freezer overnight. Pure **2d** was obtained by filtration of the settled solid. Pale brown solid; yield 0.15g, 61%; mp: 111-113 ºC; FT-IR *v* (cm^{-1}) = 1035 (CO stretching), 1076 (CN stretching), 1250 (CO stretching), 2928 (CH stretching), 3173 (OH stretching); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.81 (d, *J* = 7.9 Hz, 1H), 6.73 (d, *J* = 1.9 Hz, 1H), 6.67 (dd, *J* = 8.0, 1.9 Hz, 1H), 3.98 – 3.68 (m, 4H), 2.85 – 2.41 (m, 9H), 1.46 (p, *J* = 6.9 Hz, 2H), 1.32 (ddd, *J* = 16.0, 12.9, 7.0 Hz, 2H), 0.89 (t, *J* = 7.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.85, 144.56, 130.11, 122.08, 114.73, 112.11, 70.77, 56.05, 54.83, 49.53, 41.59, 32.11, 20.61, 14.22.

4-(2-Hydroxy-3-(isopropylamino)propyl)-2-methoxyphenol (2e): The light yellow viscous material obtained after extraction was loaded onto a pad of 5cm silica gel prepared in a glass micropipette and eluted with hexane, ether, DCM and MeOH solvents respectively. The MeOH fraction gave pure **2e.** Light brown solid; yield 0.14, 58%; mp: 133-135 ºC; FT-IR *v* (cm^{-1}) = 1034 (CO stretching), 1082 (CN stretching), 1268 (CO stretching), 2923 (CH stretching), 3307 (OH stretching); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.82 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 1.7 Hz, 1H), 6.67 (dd, *J* = 8.0, 1.7 Hz, 1H), 3.85 (s, 3H), 3.88 – 3.75 (m, 1H), 2.78 (dt, *J* = 4.1, 1.1 Hz, 1H), 2.74 (dd, *J* = 3.2, 0.9 Hz, 1H), 2.67 (dd, *J* = 6.3, 2.5 Hz, 2H), 2.48 (ddd, *J* = 12.0, 9.1,

1.0 Hz, 1H), 1.05 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.91, 146.86, 130.39, 122.06, 114.79, 112.22, 69.75, 56.05, 56.00, 52.19, 49.21, 41.27, 22.55.

4-(2-Hydroxy-3-(phenylamino)propyl)-2-methoxyphenol (2f): The obtained crude product was purified over silica gel column eluting with a mixture of DCM / MeOH (30:70). The collected fractions gave the pure **2f** product. Brown solid; yield 0.19g, 70%; mp: 91-93 ºC; FT-IR *v* (cm^{-1}) = 1032 (CO stretching), 1266 (CO stretching), 2919 (CH stretching), 3389 (OH stretching); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.19 (td, *J* = 7.8, 3.6 Hz, 1H), 6.94 – 6.53 (m, 2H), 4.03 (tdd, *J* = 8.2, 5.1, 3.2 Hz, 0H), 3.83 (d, *J* = 5.0 Hz, 1H), 3.29 (dd, *J* = 12.8, 3.5 Hz, 0H), 3.07 (dd, *J* = 12.8, 7.9 Hz, 0H), 2.78 (qt, *J* = 13.5, 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ148.43, 146.88, 144.57, 129.76, 129.56 (2C), 122.20, 118.13, 114.83, 113.58 (2C), 112.10, 71.49, 56.13, 49.54, 41.44.

4-(3-((3-(dimethylamino)propyl)amino)-2-hydroxypropyl)-2-methoxyphenol (2g): The crude product was washed with hexane (3x5mL) and pure **2g** was obtained by separating the viscous layer. Light brown viscous; yield 0.17g, 61%; FT-IR *v* (cm^{-1}) = 1035 (CO stretching), 1080 (CN stretching), 1270 (CO stretching), 2938 (CH stretching), 3307 (OH stretching); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.75 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 1.9 Hz, 1H), 6.62 (dd, *J* = 8.0, 1.9 Hz, 1H), 4.55 (bs, 1H), 3.84 – 3.74 (m, 1H), 3.80 (s, 3H), 2.64 (tdd, *J* = 12.3, 9.6, 5.1 Hz, 5H), 2.45 – 2.25 (m, 4H), 2.20 (s, 6H), 1.63 (p, *J* = 8.5, 7.8 Hz, 2H); ^{13}C NMR (75 MHz) δ 148.43, 146.88, 144.57, 129.75, 129.55 (2C), 122.20, 118.13, 114.83, 113.58 (2C), 112.10, 71.49, 56.13, 49.54, 41.44.

2.3. Biochemical Studies

The inhibitory effects of novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) on both hCA isozymes have been described in Verpoorte et al. [26] and according to an esterase assay using p-nitrophenylacetate (PNA) substrate was recorded spectrophotometrically at 348 nm [27]. On the other hand, the inhibitory effects of AChE and BChE compounds were determined according to the method of Ellman et al. [28]. They were recorded spectrophotometrically at 412 nm using acetylcholine iodide and butyrylcholine iodide and recorded as enzymatic reaction substrates according to previous studies. 5,5-Dithio-bis (2-nitro-benzoic acid) was used to measure AChE and BChE activity [29,30]. In addition, the inhibitory effect of these compounds on the activity of α-glycosidase enzyme was assessed using the p-nitrophenyl-D-glycopyranoside substrate (p-NPG) according to the analysis of Tao et al. [31]. First, 200 liters of phosphate buffer was mixed with 40 liters of homogenate in phosphate buffer

(0.15 U / mL, pH 4.7). In addition, after preincubation, 50 µL of p-NPG was added to phosphate buffer (5 mM, pH 7.4) and incubated again at 30 °C. The absorbance was spectrophotometrically measured at 405 nm [32,33].

In silico studies

There are theoretically many methods and procedures to determine the activity of the methoxyphenol derivatives studied against enzymes. Molecular docking is the most common of these. Molecular docking calculations of methoxyphenol derivatives were done using Maestro Molecular Modeling platform (version 12.0) by Schrödinger, LLC [34]. Protein structures of enzymes were obtained from the Protein Data Bank site. Enzymes used for calculations are acetylcholinesterase (AChE) is PDB ID: 4M0E, α-glycosidase (α-Gly) is PDB ID: 1R47, human carbonic anhydrase isoenzyme (hCA I) is PDB ID: 3LXE is human Carbonic anhydrase isoenzyme II (hCA II) is PDB ID: 5 AML. In molecular docking calculations of methoxyphenol derivatives with enzymes, all calculations were made in the pH 7.0 ± 2.0 range. In order to interact with these enzymes with methoxyphenol derivatives, preparation was done with enzyme protein preparation module [35,36]. Using this module, all the water molecules in the crystal structure of the enzyme were removed. Again, using this module, the binding methods and loads of proteins in the structure of the enzyme were optimized. The active site of proteins was determined. The proteins in the active region were given mobility during interaction. After this process, the molecular structures of the studied methoxyphenol derivatives were drawn using the Gaussian software program [37]. After the molecules drawn, the LigPrep module [38,39] was used for molecular docking calculations. In this module, 3D structures of methoxyphenol derivatives, correct protonation state in physiological pH and molecular geometries of the methoxyphenol derivatives were obtained. After the methoxyphenol derivatives were prepared, calculations were made using the Glide ligand-docking module [40] for molecular docking calculations of enzymes with the studied methoxyphenol derivatives. After calculating the biological activities of molecules against enzymes, the drug properties of methoxyphenol derivatives will be examined. ADME (Absorption, distribution, metabolism, excretion, and toxicity) analysis is performed to examine the drug properties of the methoxyphenol derivatives studied. To make this analysis, the Qik-prop module [41] of Schrödinger software is used. This module provides a lot of information about the conditions of a molecule to become a drug. Many parameters are calculated with the Qik-prop module. A few of these parameters are molecular weight, QP log $p_{o/w}$ donorHB, accptHB, rule of five, and rule of three, etc. [42,43].

3. RESULTS AND DISCUSSION

3.1.Chemistry

In our previous studies oxypropanol amine derivatives starting with natural phenolic compounds such as eugenol [16], thymol [44] and carvacrol [22] were synthesized and a number of their biological properties were investigated. As a result, it has demonstrated that they show superior some antibacterial and inhibitor properties when compared to existing drugs. In this study, unlike the previous ones, 7 new propanol amine derivatives were investigated by advancing the reaction through the double bond of eugenol. At the end of the literature studies for the synthesis of target compounds, the synthesis of propanol amines with a nucleophilic attack of amines on epoxide was found appropriate. Among the methods used to convert the double bond in the eugenol to the oxirane ring, the method with m-CPBA was preferred [45]. This is because it provides high yield (95%), and besides, the resulting benzoic acid by-product is easily separated from the medium by filtration and no additional purification is required to clean the target product **1**. In the second step, it is aimed to open the oxirane ring with different amine compounds. In order to perform the synthesis of α-propanol amine compounds, a reaction method to be performed in basic environment has been determined considering the reaction mechanism [16]. In order to determine the scope of the study, the amine derivatives were selected from existing in different drug structures and having different properties. It was selected from amine groups consisting of primary (n-butyl amine, isopropyl amine), secondary (diethylamine), straight chain (n-butyl amine), branched (isopropyl amine, tert-butylamine), including an unsaturation bond (ally amine), having steric hindrance (tert-butyl amine, diethylamine), aromatic cycle (aniline) and different functional group (3-dimethylaminopropylamine).

Different methods such as column chromatography, crystallization, precipitation and washing with solvents have been tried to purify the target products from the crude products. When DCM is added to the substance obtained from the reaction with allyl amine, the product (2e) collapses and easily separated by filtration. Unfortunately, purification with such a simple process for other products has not been possible. For this reason, compound **2e** (81%) was obtained with the highest yield among other products. The product of **2f** obtained in the synthesis with aniline was successfully purified by column chromatography (70%). However,

column chromatography could not be applied for other substances. This is because these compounds degrade in column conditions in a short time. The reason for not occurring of degrading of **2f** is that delocalization of unpaired electrons in the nitrogen with the ring increases the stability and makes the compound more stable in acidic or basic conditions. Synthesis of the product made with isopropyl amine (**2e**) was purified (58%) by rapid passing of hexane, ether, DKM and MeOH solvents respectively, over very little silica gel pad prepared in a 150 mm glass micropipette. Among the methods tested to purify of other compounds precipitation with different solvents was successful. Thus, the synthesis of target compounds was carried out in 54-81% yields. The structures of the compounds are clarified with ^{1}H NMR, ^{13}C NMR and FT-IR. Inhibition effects of the synthesized compounds on acetylcholinesterase (AChE), α-glycosidase (α-Gly), human carbonic anhydrase I (hCA I), and human carbonic anhydrase II (hCA II) enzymes were investigated.

3.2.**Biochemistry results**

3.2.1. hCA I and II isoenzymes inhibition results

The strong CA inhibitors acetazolamide (AZA) and methazolamide have been used clinically as weak diuretic factors, in the prevention of altitude sickness and therapy of glaucoma [46–48]. The results presented in Table 1 and indicate that novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) had effective inhibition profile against hCA I isoform. The hCA I isoform was inhibited by these novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) in low micromolar levels, the Ki of which differed between 9.68±1.32 and 33.78±6.08 μM. Indeed, acetazolamide (AZA) as a broad-specificity CA inhibitor showed Ki value of 57.64±5.41 μM against hCA I. Among the inhibitors, the **2f** and **2g** were obtained to be the excellent hCA I inhibitor with Ki of 9.68±1.32 and 16.06±3.77 μM, respectively. The hCA I inhibition effects of novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) were found to be the greater than that of acetazolamide. For hCA I, IC_{50} values of AZA as positive control and some novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**); the following order: **2f** (7.37 μM, r^2: 0.9562) < **2g** (12.37 μM, r^2: 0.9611) < **2a** (13.65 μM, r^2: 0.9384) < **2b** (17.26 μM, r^2: 0.9889) < **AZA** (45.46 μM, r^2: 0.9585). CA Inhibitor (CAI) compounds of several human isozymes have found clinical applications for the management of diseases like ocular hypertension in epilepsy; obesity, glaucoma, hypoxic cancers and recently they were proved beneficial in neuropathic pain too. The major hurdle in CAI development and design is related to the isozyme selectivity issue, which thrived to novel chemotypes [44,49–

51]. Against the physiologically dominant isoform hCA II, the novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) demonstrated K_is varying from 11.46±2.64 to 26.86±5.08 μM (Table 1). These novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) were observed to have high inhibition effects toward hCA II. Also, control AZA showed Ki of 79.75±8.34 μM against hCA II. The **2f** and **2a** had shown the most inhibition effect with Ki values of 11.46±2.64 and 14.74±4.11 μM, respectively. For hCA II, IC_{50} values of AZA as control and other compounds synthesized in this study; the following order: **2f** (8.26 μM, r^2: 0.9361) < **2a** (10.25 μM, r^2: 0.9838) < **2g** (10.53 μM, r^2: 0.9836) < **2b** (14.38 μM, r^2: 0.9683) < **AZA** (60.33 μM, r^2: 0.9364).

3.2.2. AChE inhibition results

To date, many AChE inhibitor compounds have been approved for the therapy of AD, like rivastigmine, donepezil, huperzine-A, physostigmine, galantamine, tacrine, and these drugs are capable to prevent the degradation of ACh and also increase its level in the cholinergic synapses, which can improve cognitive deficits [52–55]. Thus, the adverse effects like vomiting, bradycardia, nausea, and weight loss have limited their clinical efficacy. In this case, it is necessary to develop new AChE inhibitor compounds with a better therapeutic effect and less toxic side effects. Recently, there is a major interest in the extension of selective AChE inhibitors [56–58]. All of novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) had significantly higher AChE inhibitory activity than that of standard AChE inhibitors such as Tacrine. Furthermore, the Ki values of novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) and tacrine are summarized in Table 1. As can be seen from the results obtained in Table 1, these novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) effectively inhibited AChE, with Ki values in the range of 62.08±11.67 to 123.76±22.06 μM. However, all of these novel molecules (**2a-g**) had almost similar inhibition profiles. The most active **2b** showed Ki values of 62.08±11.67 μM. For AChE, IC_{50} values of TAC as TAC and other compounds were studied in this study the following order: **2b** (90.33 μM, r^2: 0.9208) < **2f** (103.25 μM, r^2: 0.9627) < **2e** (111.84 μM, r^2: 0.9370) < **2c** (113.47 μM, r^2: 0.9835) < **TAC** (198.24 μM, r^2: 0.9077). Recently, the development of new AChE inhibitors has become the focus of research.

3.2.3. α-Glycosidase inhibition results

α-Glycosidase inhibition helps to slowly release monosaccharide molecules after food. In T2DM, postprandial blood sugar is caused by insulin resistance [59,60]. α-Glycosidase inhibitors are used as therapeutic drugs to control post-meal blood sugar conditions. Many organisms naturally produce α-glycosidase inhibitors, and several inhibitors have been reported so far, some of which have previously been used for therapeutic purposes [61]. For enzyme glycosidase, novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) have IC_{50} values in the range of 0.28-2.34 μM and Ki in the range of 0.33±0.08-2.55±0.28 μM (Table 1). The results have clearly documented that all of these novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) have shown the inhibitory effects of α-glycosidase efficient acarbose (IC_{50}: 5.44 μM) as a standard glycosidase inhibitor. In fact, the most effective Ki values of **2c** and **2f** were with Ki values of 0.33±0.08 and 1.03±0.10 μM, respectively. For α-glycosidase, IC_{50} values of ACR as positive control and some novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) the following order: **2c** (0.28 μM, r^2: 0.9034) < **2f** (0.84 μM, r^2: 0.9731) < **2a** (0.95 μM, r^2: 0.9343) < **ACR** (5.44 nM).

Table 1

Molecular Docking results

In this study, the interaction of the methoxyphenol derivatives with the proteins of the enzymes was examined and the biological activity values of the molecules were compared [22]. As a result of the calculations, using the numerical values of the obtained parameters have been made a comparison. Many parameters are obtained, among which the most important parameter is the docking score [23–25]. The numerical value of this parameter is the highest, the biological activity value of the negative molecule. Therefore, biological activity can be ordered according to the numerical value of this parameter. Many parameters other than this parameter are obtained from docking calculations, but these parameters are used to explain the interactions of molecules with enzymes. The interactions of methoxyphenol derivatives with enzymes in this study are given in **Figure 1, 2, 3,** and **4**. Some parameters obtained from these interactions of methoxyphenol derivatives with enzymes are given in **Table 2**.

Table 2 and Figure 1, 2, 3, and 4

Many parameters are obtained from interactions of studied methoxyphenol derivatives with enzymes. Among these, the most important parameter for molecular docking calculations is Docking Score. Molecules with the highest biological activity value according to the

numerical value of this parameter; It is the 2b molecule for AChE and α-Gly enzymes, the compound **2f** for hCA I and hCA II isoenzymes in **Figure 5**.

Figure 5

The interactions of molecules with enzymes are very important because, as the interaction of molecules with enzymes increases, the biological activities of molecules increase [62–64]. After molecular docking calculations of the biological activities of the molecules, the ability of these molecules to be advanced drugs was investigated. As a result of the calculations in the Qik-prop module for this study, many parameters were obtained. These parameters give information about the possibility of molecules to be drugs [23].

ADME properties of molecules were examined with the parameters obtained as a result of calculations. Many parameters of the molecules are examined and these parameters are given in the supplementary file Table S1. The parameter given in the Table S1 gives a lot of information about molecules. The parameter range for the parameters given in Table S1. It is believed that if the parameters obtained were in this range, these molecules met the condition of being a drug. These parameters include a parameter known as the 5 rules of Pfizer, but also used as the 5 rules of Lipinski in molecular docking [24]. In this rule, the number of hydrogen bonding atoms in the molecule will not be more than 5 (nitrogen and oxygen atoms for one or more hydrogen atoms attached to it). However, the number of atoms accepting hydrogen bonds in the molecule will not exceed 10 (number of nitrogen and oxygen atoms). In addition, its molecular weight should be below 500 Da and the lipophilicity coefficient (log p) should be below 5. Small molecules that follow these rules are thought to have potential to become drugs. Another parameter is Solute as Donor-Hydrogen Bonds, which is estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution [25]. Another parameter is Solute as Acceptor-Hyrogen Bonds, which is estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution [23]. The properties of a parameter molecule such as drug molecule are examined. Given the parameters in Table 2, the biological activity of the compound **2f** for hCA I, and hCA II isoenzymes was high, but the numerical values of Apparent Caco-2 Permeability (nm / sec) and Apparent MDCK Permeability (nm / sec) were above normal.

4. CONCLUSIONS

In conclusion, synthesis of novel propanolamine derivatives attached to 2-metoxifenol moiety (**2a-g**) were reported, which designed to target inhibitor against hCA I, and hCA II isoenzymes and AChE, and α-glycosidase enzymes. All of the compounds have showed significant sub-micromolar inhibition towards all metabolic enzymes. Especially compound **2f** for cytosolic hCA I, and II isoenzymes, compound **2b** for AChE cholinergic enzyme and **2c** for α-glycosidase enzyme. Theoretical study results obtained from molecular docking studies have support experimental study results. The results may useful for designing and synthesizing of novel metabolic enzyme inhibitors, which had further potential lead candidates for the design of novel drugs to treat some diseases including glaucoma, epilepsy, AD, leukemia, and T2DM in the future.

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Table 1. The enzyme inhibition results of novel compounds (**2a-g**) against human carbonic anhydrase isoenzymes I and II (hCA I and II), acetylcholinesterase (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**
2a	13.65	0.9384	10.25	0.9838	125.04	0.9488	0.95	0.9343	16.34±4.74	14.74±4.11	111.45±23.45	1.14±0.13
2b	17.26	0.9889	14.38	0.9683	90.33	0.9208	1.37	0.9375	21.45±2.06	17.08±3.66	62.08±11.67	1.83±0.23
2c	20.34	0.9682	16.06	0.9770	113.47	0.9835	0.28	0.9034	26.44±6.57	20.36±1.87	74.34±16.94	0.33±0.08
2d	19.26	0.9581	14.88	0.9604	155.38	0.9598	1.93	0.9950	22.67±5.71	18.45±7.28	123.76±22.06	2.34±0.40
2e	28.51	0.9964	22.35	0.9739	111.84	0.9370	2.34	0.9623	33.78±6.08	26.86±5.08	87.46±10.77	2.55±0.28
2f	7.37	0.9562	8.26	0.9361	103.05	0.9627	0.84	0.9731	9.68±1.32	11.46±2.64	78.08±15.83	1.03±0.10
2g	12.37	0.9611	10.53	0.9836	134.87	0.9205	1.14	0.9698	16.06±3.77	15.82±4.88	103.37±9.63	1.47±0.22
AZA*	45.46	0.9422	60.33	0.9364	-	-	-	-	57.64±5.41	79.75±8.34	-	-
TAC**	-	-	-	-	198.24	0.9077	-	-	-	-	167.05±23.64	-
ACR***	-	-	-	-	-	-	5.44	0.9642	-	-	-	7.45±1.04

*Acetazolamide (AZA) was used as a control for hCA I, and II isoenzymes.

**Tacrine (TAC) was used as a control for AChE enzyme.

***Acarbose (ACR) was used as a control for α-glycosidase enzyme.

Table 2. Numerical values of the parameters obtained from interaction of enzymes studied with enzymes

		2a	2b	2c	2d	2e	2f	2g
AChE	**Docking Score**	-7.52	-8.13	-8.12	-6.78	-7.74	-6.91	-8.04
	Glide hbond	-0.14	-0.31	-0.43	-0.46	-0.37	-0.41	-0.53
	Glide emodel	-62.97	-59.03	-71.13	-69.81	-68.81	-52.95	-89.52
	Glide ligand efficiency	-0.41	-0.45	-0.47	-0.37	-0.45	-0.34	-0.44
α-Gly	**Docking Score**	-4.94	-6.26	-5.62	-3.95	-5.89	-4.87	-4.10
	Glide hbond	-0.36	-0.65	-0.63	-0.33	-0.71	-0.57	-0.38
	Glide emodel	-51.34	-51.30	-55.17	-50.64	-48.84	-38.69	-65.81
	Glide ligand efficiency	-0.27	-0.34	-0.33	-0.18	-0.34	-0.24	-0.20
hCA I	**Docking Score**	-4.79	-4.89	-4.35	-2.63	-5.13	-6.11	-2.44
	Glide hbond	-0.50	-0.49	-0.47	0.00	-0.40	-0.45	-0.32
	Glide emodel	-40.37	-41.08	-39.02	-32.21	-41.20	-48.05	-33.70
	Glide ligand efficiency	-0.26	-0.27	-0.25	-0.14	-0.30	-0.30	-0.12
hCA II	**Docking Score**	-4.60	-4.00	-4.09	-2.71	-3.98	-4.83	-2.57
	Glide hbond	-0.23	0.00	0.00	-0.19	0.00	-0.29	0.00
	Glide emodel	-39.76	-38.55	-37.66	-33.10	-38.37	-41.62	-37.08
	Glide ligand efficiency	-0.25	-0.22	-0.24	-0.15	-0.23	-0.24	-0.12

* Apparent Caco-2 Permeability and Apparent MDCK Permeability are <25 poor and >500 great

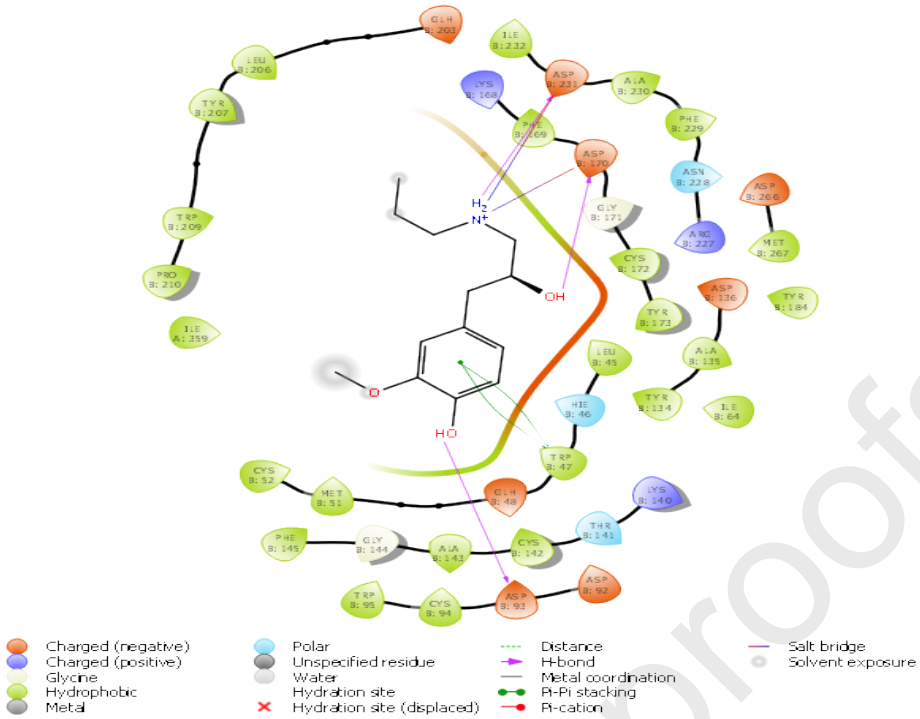


Figure 1. Demonstration of the interaction of α-Gly enzymes with 2b

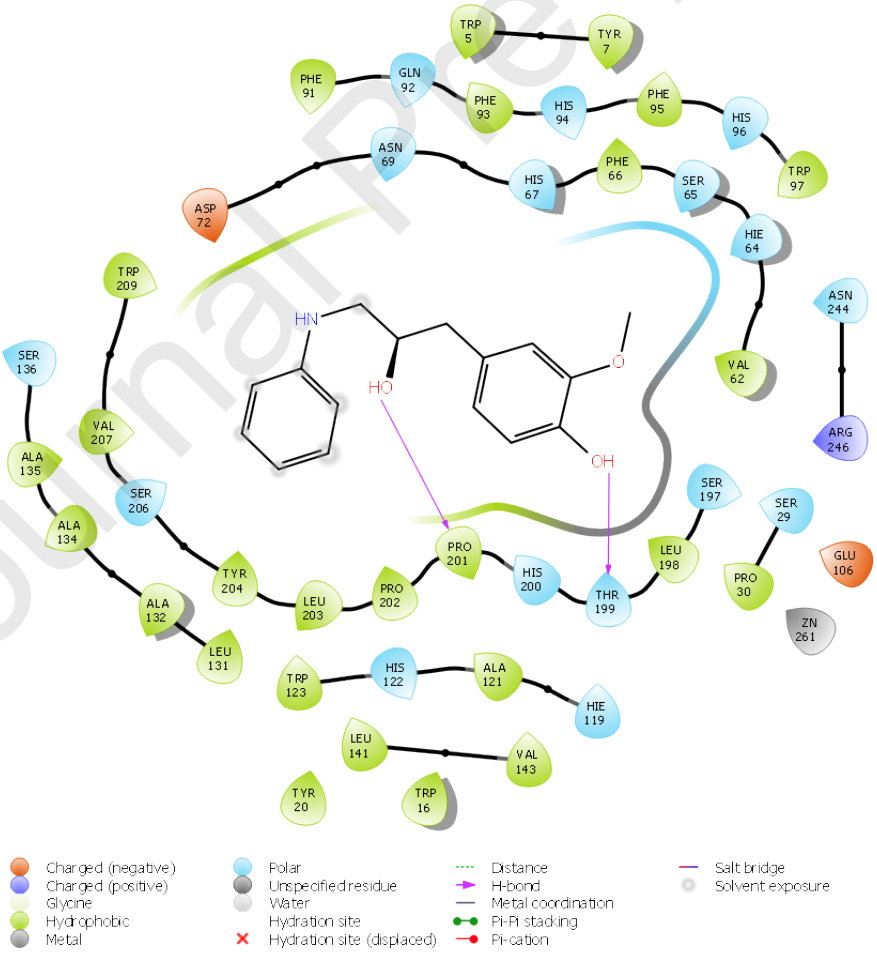


Figure 2. Demonstration of the interaction of hCA I enzymes with 2f

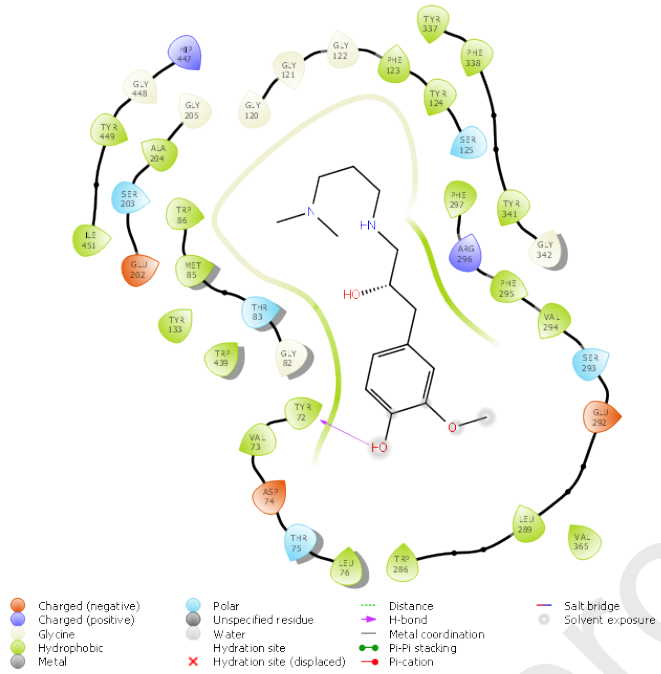


Figure 3. Demonstration of the interaction of AChE enzymes with 2b

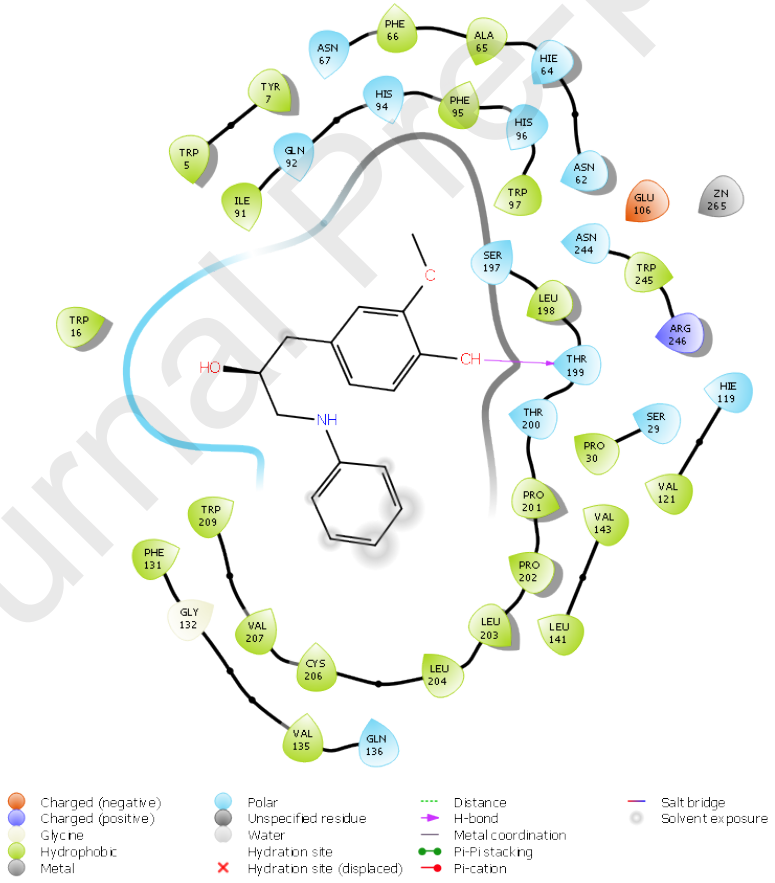


Figure 4. Demonstration of the interaction of hCA II enzymes with 2f

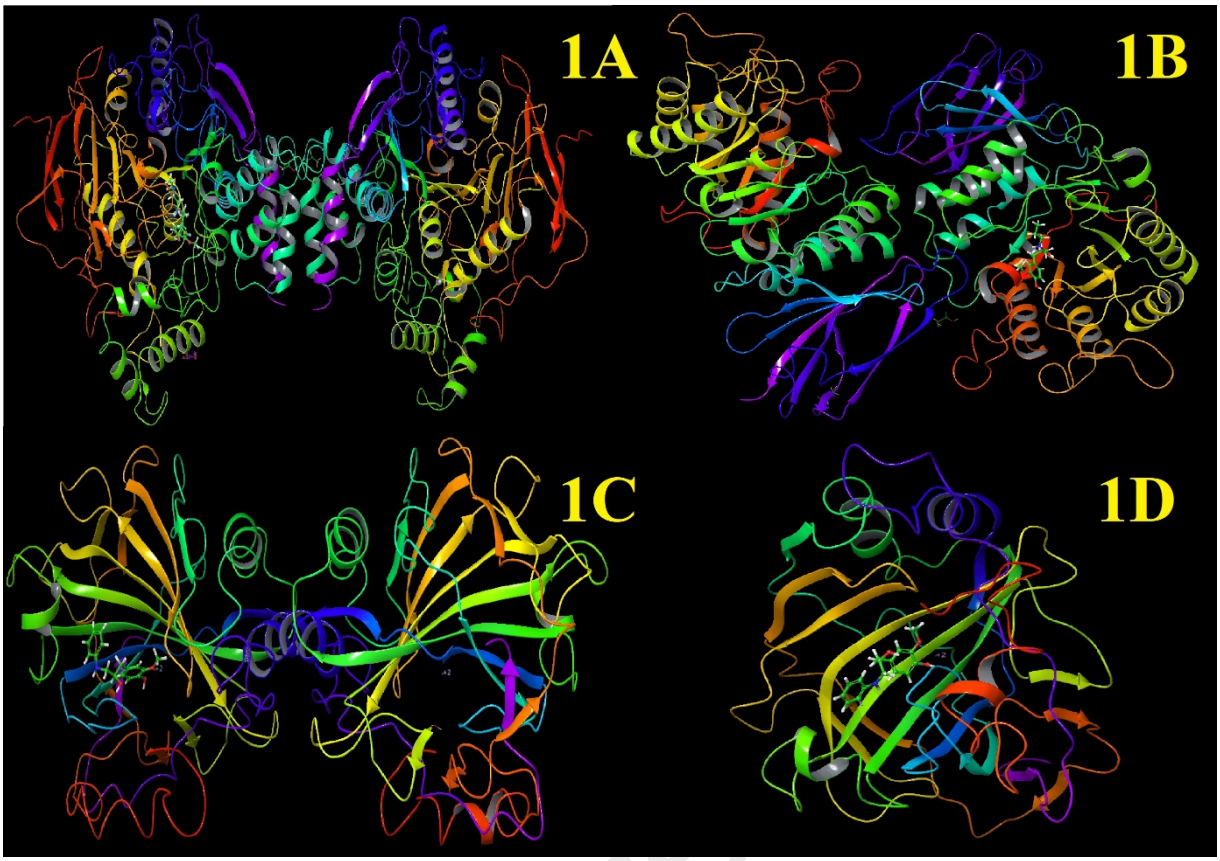
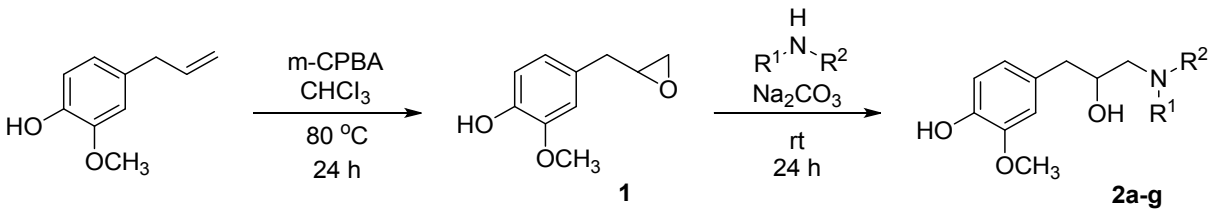
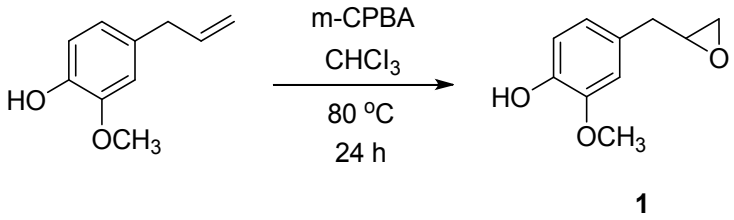


Figure 5. Demonstration of the interaction of 1A (AChE enzymes with **2b**), 1B (α-Gly enzymes with **2b**), 1C (hCA I isoenzymes with **2f**), and 1D (hCA II isoenzymes with **2f**)



Scheme 1. General synthesis of new 2-metoxifenol propanolamine derivatives



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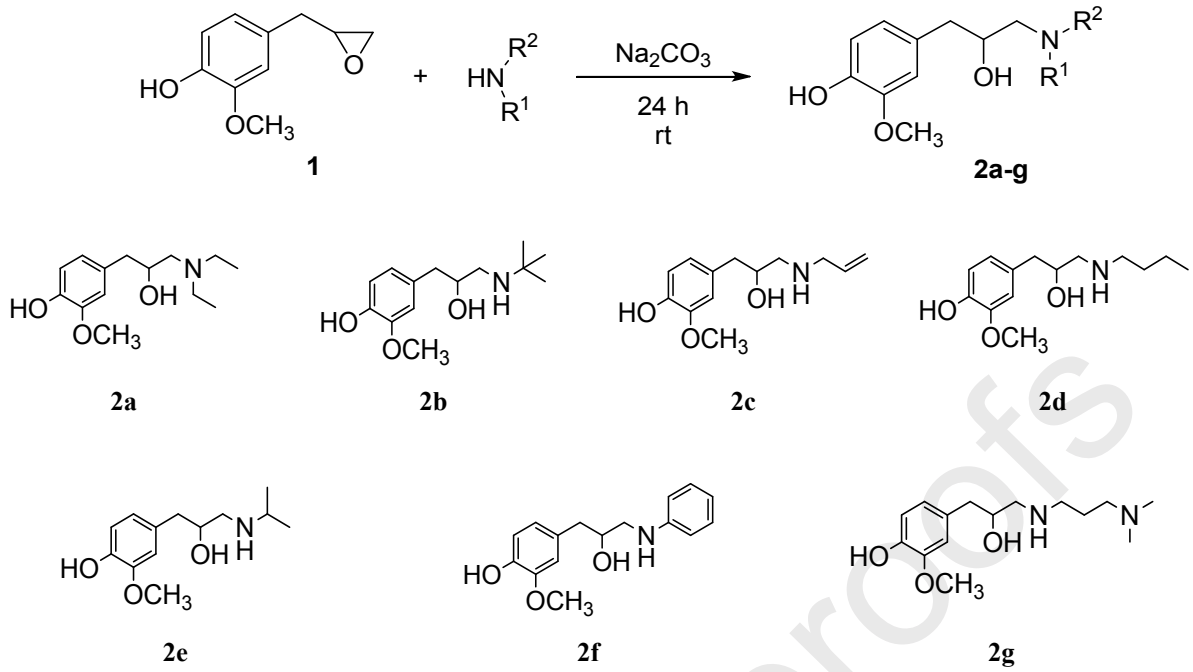
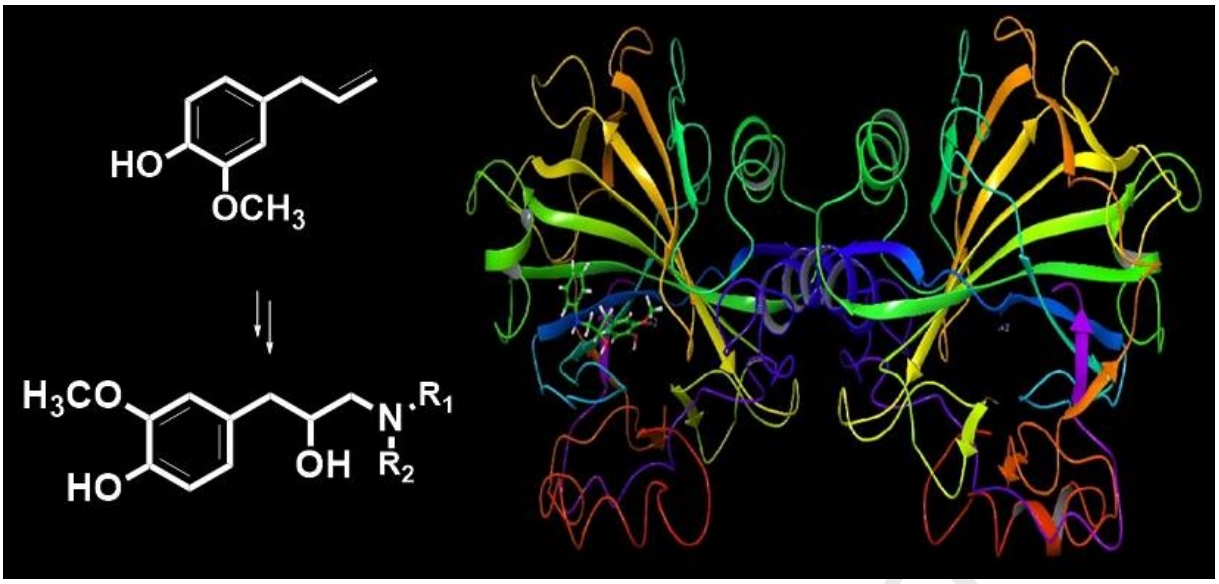
Scheme 2. Synthesis of 2-methoxy-4-(oxiran-2-ylmethyl)phenol



Scheme 3. Synthesis of hydroxypropyl amine derivatives (**2a-g**)

Highlights

- A series of seven new ß-amino alcohol derivatives were synthesized and characterized.
- They are effective inhibitors against α-glycosidase and AChE.
- The compounds also effectively inhibit hCA I and II isoenzymes.
- Experimental results were compared with molecular docking calculations.



Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: