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Synthesis, characterization, crystal structure and bioactivities of novel enamine and pyrrole derivatives endowed with acetylcholinesterase, α-glycosidase and human carbonic anhydrase inhibition effects

Abel Maharramov [1], Malahat Kurbanova [1], Parham Taslimi [2], Yeliz Demir [3], Aytan Safarova [1], Elnur Huseyinov [1], Afsun Sujayev [1], Saleh H. Alwasel [5] and İlhami Gulcin [6,*]

[1]*Baku State University, Organic Chemistry Department, Z. Khalilov 23, Baku, 1148, Azerbaijan*
[2]*Bartin University, Faculty of Science, Department of Biotechnology, 74100-Bartin, Türkiye*
[3]*Ardahan University, Nihat Delibalta Göle Vocational High School, Department of Pharmacy Services, 75000-Ardahan, Türkiye*
[4]*Azerbaijan National Academy of Sciences, Laboratory of Organic chemistry, Institute of Chemistry of Additives, 1029-Baku, Azerbaijan*
[5]*King Saud University, College of Science, Department of Zoology, Riyadh, Saudi Arabia*
[6]*Ataturk University, Faculty of Science, Department of Chemistry, 25240-Erzurum, Türkiye*

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Abstract: Presented research work is devoted to the synthesis of new heterocyclic compounds containing the ethyl ester fragment of acetate and glycine and the study of their crystal structure and biological activity. (Z)-Ethyl 2-(3-oxo-1,3-diphenylprop-1-enylamino)acetate (**1**) was first obtained on the base of the reaction of dibenzene methane with glycine ethyl ester hydrochloride in the presence of *Y(OTF)3* catalyst in aqueous medium. At the same time, ethyl-3,5-diphenyl-1*H*-pyrrole-2-carboxylate (**2**) was synthesized from the interaction of enamine with *tert*-BuOK in the presence of *tert*-BuOH/DMFA solvent. The structure of new compounds has been studied by 1H, ^{13}C NMR. In addition, the crystal structure of ethyl-3,5-diphenyl-1H-pyrrole-2-carboxylate (**2**) is presented. The monoclinic, yellow crystals, with sizes 0.20 × 0.10 × 0.10 mm^3, one striped: a = 10.5340(6) E, b = 7.5101(5) E, c = 20.2352(15) Å, β = 102.131(2)°, V = 1565.09(18) E^3, space group P2$_1$/c, Z= 4, ds = 1.236 mg/m^3, μ = 0.080 mm^{-1} were obtained. The crystalline compound keeps crystallographically independent molecules in the central bicyclic moiety. Compound **2** holds complex three-organic compound system consisting of pyrrole and benzol rings. In this study, the IC_{50} and K_i values of the compounds were calculated to compare their inhibition profiles on acetylcholinesterase (AChE), α-glycosidase and hCA I, and II isozymes. These compounds demonstrated Ki values in the low micromolar range for studied enzymes. The best inhibitor for hCA I and II isoenzymes and AChE was the (**1**) with Ki values of 47.21±5.06, 35.77±3.53 and 103.94±15.36 μM, respectively. On the other hand, compound **2** showed the best inhibition profile against α-glycosidase with Ki of 63.76±7.12 μM.

Keywords: Enamine; acetylcholinesterase; pyrrole; carbonic anhydrase; α-glycosidase

* Corresponding author: E-Mail: igulcin@atauni.edu.tr, Phone: + 90 4442314375; Fax: + 90 4422310941.

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Synthesis, characterization and bioactivity of novel enamine and pyrrole derivatives

1. Introduction

Pyrrole and pyrrole derivatives from nitrogenous heterocycles are biologically active compounds[1]. They can be found in many natural compounds. That's why these compounds are in the interest of researchers. Pyrrole and its derivatives have a special place among the pentagonal heterocyclic compounds. It's known that many important physiologically active natural organic compounds like chlorophyll, hemoglobin, vitamin B_{12}, Crisprine A, Lamellarin D and Lettowainthine contain pyrrole ring. The antibacterial, antidiabetic, antimicrobial and other biological properties of pyrroles make them more popular[2]. In the modern time, the five substituted optically active derivatives of pyrrole is the most widely used drug to lower blood cholesterol[3]. 3,5-Disubstituted-1H-pyrrole-2-carboxylate was synthesized in the literature by microwave irradiation of 1,3-disubstituted propene-2-on and ethyl nitroacetate in the presence of triethylphosphite ($P(OEt)_3$) and diethylamine[4]. Another method is the treatment of ethyl-2-nitro-5-oxo-3,5-diarylpentanoate with triethylphosphite exposed microwave irradiation[5]. Also, it was obtained pyrrole-2-carboxypyrroles by electrocyclic ring closure of chalcones and glycine esters or amides[6]. Although many researchers have synthesized similar pyrroles. We obtained 3.5-dialkyl (phenyl)-pyrrole-2-ethylcarboxylates from the reaction of enamines and glycine ethyl ester hydrochloride in the presence of *tert*-BuOK/*tert*-BuOH for the first time.

At the same time, the β-enamines that we used as another component in this study are important synthetics for a number of active compounds, such as enzymes inhibitors[7], dopamine auto receptors, agonists, anticonvulsants[8], and etc. Enamines are of particular importance because they are used as intermediates in the formation of the taxol chain[9]. They are also used in the synthesis of polyunsaturated pyrrole and other heterocycles and various colored pigments[10]. Because of easy nucleophilic and electrophilic attack properties enamines were used in the synthesis of different heterocycles and natural compounds. In addition to the short reaction time, high yield, and simplicity of the process, many researchers have focused on synthesizing enamines in a pure way without toxic catalysts[11].

Carbonic anhydrases (CAs, E.C.4.2.1.1) present in all organisms over the phylogenetic trees and are encoded by at least eight different genetic families[12-15]. CAs catalyzes an important biological reaction reversible hydration of carbon dioxide (CO_2) to produce hydronium ions (H_3O^+) and bicarbonate (HCO_3^-)[16-18]. CAs acted in numerous biological processes, starting with pH regulation and ending with metabolism. Abnormal levels or activities of CA isoenzymes are related to numerous human disorders[19-21]. Hence, it is significant to discover a potent approach that can inhibit the CA isoforms involved in many diseases[22,23]. Pharmacological applications of CA inhibitors (CAIs) have found place in many fields such as acid-base disequilibria, ulcers, glaucoma and neurological disorders. Most of α-CA isoforms available in mammals and humans. Recently, highly effective as CAIs like sulfonamides has been used as non-selective inhibitors. Hence, the design and synthesis of new and selective CAIs had a great importance.[24-26].

Alzheimer's disease (AD) is a multifactorial and highly prevalent neurodegenerative disease, and globally cause of dementia in elder people worldwide[27]. Great interest was gathered due to the increasingly rejuvenation of the crowd attached to the disease[28,29]. Because cholinergic pathways are associated with AD progression and cholinergic loss has a correlation with the severity of dementia in AD, some of the pharmacotherapies available for this disease contain acetylcholinesterase inhibitors (AChEIs) that used for the symptoms treatment[30-32]. AChEIs are effective and feasible strategies to increase ACh levels in the brain for AD treatment. Also, AChEIs are clinically used to treat glaucoma, myasthenia gravis, neuromuscular disturbance, and AD. Moreover, cholinesterase inhibitors have extensive usage as pesticides, which can generate toxic responses in human and mammals[33-35].

On the other hand, diabetes mellitus (DM) is one a major global problem for public health and well-known metabolic disorder, which is characterized as an unusual postprandial enhance of blood glucose level. The control of postprandial hyperglycemia is known one of significant therapy method of DM[36-38]. α-Glycosidase hydrolyses the glycosidic bond between two or more carbohydrates. It exists in intestinal chorionic epithelium, which is accountable for the depreciation of carbohydrates. A lot of researches on development of effective hypoglycemic methods have provided discoveries of molecular therapy targets including α-glycosidase inhibition. α-Glycosidase inhibitors (AGIs) fall under the third class of oral hypoglycemic factors. Recently a growing interest has been observed in design and synthesis of bioactive compounds due to their potential and powerful antidiabetic potencies [40-42].

The aim of the present study was to find out the inhibition properties of a novel enamine and pyrrole derivatives against hCA isoenzymes, acetylcholinesterase and α-glycosidase enzymes that linked to some global diseases including diabetes mellitus, glaucoma and Alzheimer's disease.

2. Experimental

2.1. Measurements

^{1}H NMR and ^{13}C NMR spectra were performed on a 400-spectrophotometer using in DMSO-d_6. Chemical shifts values are recorded in ppm taking tetramethyl silane (TMS) as the internal standard and J values are given in hertz. The signal types are indicated by the following letters: s=singlet, m= multiplets, t = triplet and d = doublet. Also, X-ray structure analysis was used for confirmation of structure of compound **2**. NMR experiments have been performed on a Bruker FT NMR spectrometer AVANCE 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) with BVT 3200 variable-temperature unit in 5 mm sample tubes using Bruker Standard software (Topspin 3.1). The ^{1}H and ^{13}C chemical shifts were referenced to internal TMS. The NMR grade DMSO-d_6 (99.7%, including 0.3% H_2O) was used for both synthesized compounds.

Flash column chromatography was realized using by glass columns with flash grade silica gel (70-230 mesh). Reactions tracking were watched by thin layer chromatography (TCL) and visualized by UV light. All organic extracts were dehydrated over oven-dried $MgSO_4$. The structure of the synthesized compounds was confirmed by the diffraction spectrum "Bruker APEX II CCD" (T = 296 K, λMoKα-radiation, graphite monochromator, φ- and ω-scanning, 2θmax = 46°). The additional information about NMR and X-ray structure analysis of the investigated compounds are provided as Supporting Information. Dibenzoylmethane (98% Sigma Aldrich), glycine ethyl ester hidrochloride (ethyl glycinate hydrochloride) (≥98.5% Sigma Aldrich), yttrium(III) trifluoromethanesulfonate (trifluoromethanesulfonic acid yttrium(III) salt, yttrium triflate, 98% Sigma Aldrich), potassium tert-butoxide (potassium *tert*-butylate, potassium t-butoxide (≥98% Sigma Aldrich).

2.2. Crystallography

Suitable crystals of (**2**) were selected for data collection, which was performed on a D8-QUEST diffractometer equipped with graphite-monochromatic Mo Ka radiation. The structures were solved by direct methods using SHELXS-97[43]. They refined by full-matrix least-squares methods on F2 using SHELXL-97 from within the WINGX[44]. All non-hydrogen atoms were refined with anisotropic parameters. Molecular diagrams were created using MERCURY[45]. Also, supramolecular analyses were performed and the diagrams were prepared with the aid of PLATON[46]. Detailed information of crystal structure determinations and data collection are summarized in Table S1 (see supporting information file).

2.3. Synthesis

*2.3.1. (Z)-Ethyl 2-(3-oxo-1,3-diphenylprop-1-enylamino)acetate (**1**)*

The 1 mL of dibenzoylmethane was mixed with 10 mmol glycine ethyl ester hydrochloride in aqueous medium in the presence of 5 mol% *Y(OTF)3* for 6 hours at 25°C. The course of the reaction was monitored by TLC. Then mixture was twice extracted with 10 mL diethyl ether. The reaction products were separated by column chromatography. Eluent n-hexane: ethyl acetate 10:1. Melting point: 128-130°C. ^{1}H NMR (300 MHz, DMSO-d6), δ [ppm]: 1.07 (3H, t, CH_3), 4.02 (k, 2H, CH_2O), 4.84 (d, 2H, CH_2), 5.83 (s, 1H, CH), 7.22-8.37 (m, 10H, 2Ar-H), 11.38 (t, 1H, NH). ^{13}C NMR (DMSO-d_6), δ [ppm]: 14.28 CH_3, 46.33 CH_2N, 61.35 CH_2O, 93.60 CH=, 128.76 CH_{ar}, 128.91 CH_{ar}, 129.17 CH_{ar}, 131.44 CH_{ar}, 133.28 CH_{ar}, 135.07 CH_{ar}, 130.17 C_{ar}, 134.43 C_{ar}, 166.13 N-C=, 169.97 COO, 196.03 CO.

*2.3.2. Ethyl 3,5-diphenyl-1H-pyrrole-2-carboxylate (**2**)*

The 0.85 g enamine ($C_6H_5COCH{=}CCH_3NHCO_2C_2H_5$) and 0.67 g of *tert*-BuOK were added to a round bottom flask in 5 mL of *tert*-BuOH and 10 mL DMFA and was mixed for 4-5 hours at 80°C.

Then, the mixture was allowed and extracted twice with 30 mL diethyl ether and washed with water. After expulsion, the mixture was separated by column chromatography. Eluent n-hexane: ethyl acetate (10:1). Yellow crystals were obtained. Melting point: 140-144°C, yield 45-50%. ^{1}H NMR (300 MHz, DMSO-d_6), δ [ppm]: 1.18 (t, 3H, CH_3); 4.17 (k, 2H, CH_2O), 6.74 (s, 1H, CH=); 7.30-7.90 (m, 10H, 10Ar-H), 11.94 (s, 1H, NH). ^{13}CNMR (DMSO-d_6), δ [ppm]: 14.54 CH_3, 60.07 CH_2O, 110 CH_{pyr}, 118.71 C_{pyr} – CO, 125.83 CH_{ar}, 127.00 CH_{ar}, 127.94 CH_{ar}, 130.17 CH_{ar}, 131.16 C_{ar}, 132.74 C_{ar}, 133.01 CH_{ar}, 133.42 CH_{ar}, 135.71 C_{pyr}-C-NH_2, 136.14 C_{pyr}-NH_2, 161.02 COO.

2.4. Biological Assay

2.4.1. Carbonic Anhydrase Purification and Inhibition Assays

Affinity chromatography is a common and efficient method for separation of biochemical mixture based on a highly specific interaction between enzyme and substrate[47]. Sepharose-4B-L-Tyrosine-sulfanilamide (SBTS) material was used as a selective affinity matrix for retention of hCAs[48-50]. The most putative reaction catalyzed by hCAs is the conversion of p-nitrophenylacetate (PNA) into p-nitrophenol (PNP) and acetate. The hCAs activities were spectrophotometrically determined according to prior methods[51,52]. One hCA unit is a quantity of hCA, which had absorbance change of PNA to PNP at 348 nm over 3 min at 25 °C[54-56]. During SBTS affinity chromatography processes, the quantity of hCAs was identified at 280 nm[57,58] and the quantity of protein was measured at 595 nm[59] as described previously[60-62]. Bovine serum was used as the standard protein[63-64]. The purity checking of hCA isozymes was performed at two different acrylamides concentrations (10 and 3%) for running and the stacking gel, respectively, containing 0.1% sodium dodecyl sulphate according to Laemmle procedure[65] and described in prior studies[66-69].

2.4.2. Acetylcholinesterase Inhibition Assay

The determination of novel enamine and pyrrole derivatives inhibition on AChE activity were conducted in line with spectrophotometric procedure recommended by Ellman et al.[70] as described previously[71,72]. In both reactions, the substrates utilized were acetylthiocholine iodide (AChI) was conducted with maximum absorption at wavelength of 412 nm[73-77].

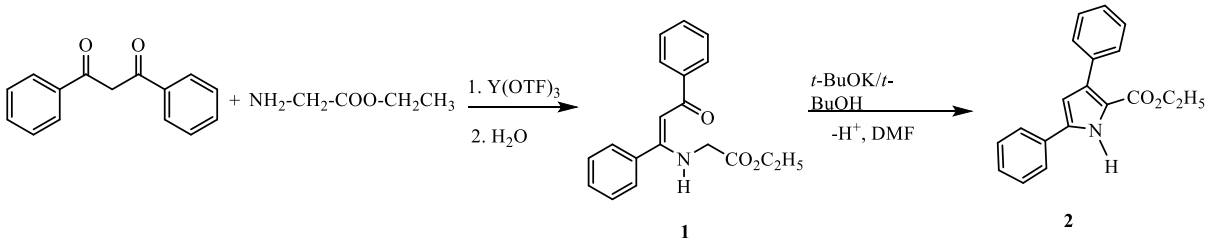
2.4.3. α-Glycosidase Inhibition Assay

α-Glycosidase inhibition effect of novel enamine and pyrrole derivatives was realized using p-nitrophenyl-D-glycopyranoside (pNPG) as the substrate, according to the prior procedure of Tao et al.[78]. The absorbances were spectrophotometrically recorded at 405 nm. The IC_{50} was calculated from activity (%) versus novel enamine and pyrrole derivatives concentration plots[79-81].

3. Results and Discussion

3.1. Chemistry

New pyrrole and enamine derivatives containing ethyl ether fragment of acetate and glycyl acid, synthesized on the basis of two-component condensation, are a class of physiologically and pharmacologically favorable heterocyclic compounds. Taking into account the successful application of analogues of these compounds containing different functional groups in medicine, we have synthesized their new derivatives. First, (Z)-ethyl 2-(3-oxo-1,3-diphenylprop-1-enylamino)acetate (**1**) was obtained as a result of the reaction of dibenzoylmethane with glycine ethyl ester hydrochloride under the catalytic effect of $Y(OTF)_3$ in aqueous medium. Then enamine was taken as the object of study. It was dissolved in butyl alcohol and added to it *tert*-BuOK. The final result is crystals of ethyl-3,5-diphenyl-1H-pyrrole-2-carboxylate (**2**). The reaction scheme can be described as follows (Scheme 1)



Scheme 1. Synthesis of (Z)-ethyl 2-(3-oxo-1,3-diphenylprop-1-enylamino)acetate (**1**) and ethyl-3,5-diphenyl-1H-pyrrole-2-carboxylate **(2)**

3.2. X-ray structural determination

X-ray crystallographic analysis was performed by double crystallization of novel compound **2** in ethyl alcohol. The crystalline form and structure of compound **2** have been given in the Figure 1, but the selected difference between bond length and valence angle has been given in Supplemental Information. Crystalline compound **2** keep crystallographically independent molecules in the central bicyclic fragment. The compound **2** keep complex three-organic compound system consisting of pyrrole and benzol rings. Hydrogen bonds for A_A [Å and °] were given in Table 2. In bicyclic fragment the cycles of pyrrole take a shape of symmetric platform. In this instance, benzol cycle in practice directs to the cycle of pyrrole perpendicularly.

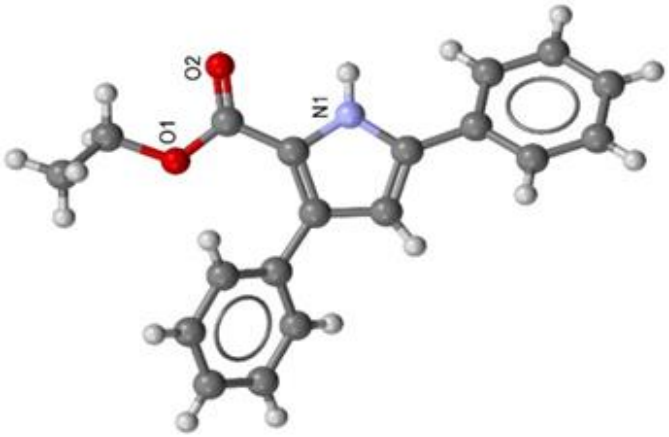


Figure 1. The molecular structure of the compound **2**

Table 2. Hydrogen bonds for A_A [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N1)...O(1)#1	0.90	2.09	2.947(3)	158.2

Symmetry transformations used for generation of equivalent atoms: #1 -x+1,-y,-z+1

3.3. Enzymes Inhibition Results

In this study, the affinity chromatographic technique, in which the biological molecules contained in a complex mixture and desired to be purified are purified by using specific ligands by making use of some molecular properties of the proteins[82,83]. The hCAs were efficiently and successfully purified using the SBTS affinity chromatography method[84-86]. Classical inhibitors of CAs have been clinically employed as diuretic and anti-glaucoma drug in diabetics affected patients. Many researches have been studied on sulfonamides as CA inhibitors. They can be widespread used for treating diabetes, cancer, epilepsy and obesity[87,88]. In present study, the ubiquitous cytosolic hCA I was moderately inhibited by synthesized compounds. Both compounds exhibited K_is in the low micromolar range. The order of the K_is of the indicated compounds was **2** (K_i: 47.21±5.06 µM) > **1** (K_i: 85.07±10.04 µM). Based on the IC_{50} and K_i values of compounds **1** and **2** had less than inhibitory activity in comparison with the standard drug AZA (K_i: 27.04±2.43 µM) (Table 3).

Table 3. The inhibition results of both compounds for hCAs, acetylcholinesterase (AChE) and α-glycosidase 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**
1	78.05	0.9704	58.94	0.9820	206.43	0.9614	54.98	0.9036	85.07±10.04	66.01±8.47	154.87±15.85	63.76±7.12
2	39.54	0.9726	30.15	0.9688	128.36	0.9881	91.11	0.9742	47.21±5.06	35.77±3.53	103.94±15.36	93.54±11.20
AZA	21.42	0.9432	25.32	0.9631	-	-	-	-	27.04±2.43	35.51±3.32	-	-
TAC	-	-	-	-	118.20	0.9547	-	-	-		107.25±18.61	-
ACR	-	-	-	-	-	-	31.64	0.9202	-		-	45.21±5.34

AZA: Acetazolamide; TAC: Tacrine; ACR: Acarbose were used as a positive control for hCAs, AChE and α-glycosidase (α-Gly) enzymes

CA II has significant role in biological processes such as homeostasis balance of pH and CO_2, biosynthetic reactions, calcification, respiration and movement of carbon dioxide/bicarbonate, bone resorption, and tumorigenicity[89,90]. Treatment of glaucoma requires high doses of sulfonamide drugs and this sometimes results in various adverse impacts such as malaise, altered taste, depression, fatigue, and anorexia[91]. Son, we synthesized organic compounds based on non-sulfonamide moiety and investigation their role as inhibitors of hCA II isoenzyme in this study. According to the results, the order of the K_is of the both synthesized compounds was following order: **2** (K_i: 35.77±3.53 µM) and **1** (K_i: 66.01±8.47 µM). Based on the K_i values, compound **1** had less inhibitory activity when compared with AZA (K_i: 35.51±3.32 µM) (Table 3). Also, the compound **2** gave almost close results to AZA, which is a medication used for treatment of some common disease including glaucoma[92,93].

ACh is the most significant neurotransmitter and had great importance in the regulation in body processes[94,95]. Acetylcholinesterase inhibitors (AChEIs) have cholinergic deficit in AD by reestablishing the level of synaptic ACh. AChEIs have inhibited AChE activity and blocked ACh breakdown. Inhibition of AChE activity permits ACh to keep active in the synapse and to accumulate, which can give rise to deadly results such as respiratory failure central nervous system symptoms and coma until death for the most severe cases. So, AChEIs have clinically demonstrated beneficial effects in symptomatic AD treatment[96]. In this study, the inhibition effect of both novel enamine and pyrrole derivatives on AChE activity was investigated. The Lineweaver-Burk plots were used for determination inhibition type and K_i parameters[97,98]. The order of the K_is of the both synthesized compounds was **2** (K_i: 103.94±15.36 µM) and **1** (K_i: 154.87±15.85 µM) (Table 3). Based on the K_i values of compound **1** had less than inhibitory activity in comparison with the standard compound TAC (K_i: 107.25±18.61 µM), but the compound **2** showed potent inhibition effect according to TAC[78].

Increased plasma glucose level is a crucial indicator of hydrolysis of carbohydrates such as starch and sucrose[99,100]. Two important hydrolase enzymes including α-glucosidase and α-amylase primarily catalyze this process. α-Glycosidases are found on the brush edges of enterocytes and perform the hydrolysis of carbohydrate polymers[101,102]. It hydrolyzes sucrose and starch into glucose units, while α-amylases specifically hydrolyzes internal α-1,4-glycosidic bond of starch to yield glucose and maltose. The inhibitors of both digestive enzymes can reduce plasma post-prandial glucose levels in patients with type 2-diabetes[103,104]. The present study was designed to evaluated compounds against α-glucosidase activity. The order of the K_is of the synthesized compounds was **1** (K_i: 63.76±7.12 µM) and **2** (K_i: 93.54±11.20 µM) (Table 2). Based on the IC_{50} and K_i values, both compounds had less than inhibitory effects in comparison with acarbose (K_i: 45.21±5.34 µM), which used to treat type 2-diabetes. Acarbose is a starch blocker and inhibits intestinal enzyme of α-glucosidase that releases glucose from larger carbohydrates[105].

4. Conclusion

(Z)-Ethyl 2-(3-oxo-1,3-diphenylprop-1-enylamino)acetate (**1**) and ethyl-3,5-diphenyl-1H-pyrrole-2-carboxylate (**2**) effectively inhibited the hCA I and II isoenzymes, α-glycosidase and AChE enzymes at the micromolar levels. The inhibition of these enzymes is associated with some global health disturbances. So, both compounds can be acceptable candidate drugs for treatment of disorders including epilepsy, diabetes mellitus, duodenal and gastric ulcers, glaucoma, mountain sickness, Alzheimer's diseases, neurological diseases, and osteoporosis disturbances.

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Supporting Information

Supporting information accompanies this paper on https://www.acgpubs.org/journal/organic-communications

ORCID
Abel Maharramov: 0000-0003-1882-7519
Malahat Kurbanova: 0000-0001-9857-9505
Parham Taslimi: 0000-0002-3171-0633
Yeliz Demir: 0000-0003-3216-1098
Aytan Safarova: 0000-0002-1034-9308
Elnur Huseyinov: 0000-0001-5309-0124
Afsun Sujayev : 0000-0001-6890-2324
Saleh H. Alwasel: 0000-0002-0626-2306
İlhami Gülçin: 0000-0001-5993-1668

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