Journal of Biomolecular Structure and Dynamics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tbsd20

Design, synthesis, characterization, biological evaluation, and molecular docking studies of novel 1,2-aminopropanthiols substituted derivatives as selective carbonic anhydrase, acetylcholinesterase and α-glycosidase enzymes inhibitors

Afat Huseynova, Ruya Kaya, Parham Taslimi, Vagif Farzaliyev, Xadija Mammadyarova, Afsun Sujayev, Burak Tüzün, Umit M. Kocyigit, Saleh Alwasel & İlhami Gulçin

To cite this article: Afat Huseynova, Ruya Kaya, Parham Taslimi, Vagif Farzaliyev, Xadija Mammadyarova, Afsun Sujayev, Burak Tüzün, Umit M. Kocyigit, Saleh Alwasel & İlhami Gulçin (2022) Design, synthesis, characterization, biological evaluation, and molecular docking studies of novel 1,2-aminopropanthiols substituted derivatives as selective carbonic anhydrase, acetylcholinesterase and α-glycosidase enzymes inhibitors, Journal of Biomolecular Structure and Dynamics, 40:1, 236-248, DOI: 10.1080/07391102.2020.1811772

To link to this article: https://doi.org/10.1080/07391102.2020.1811772

JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS
2022, VOL. 40, NO. 1, 236–248
https://doi.org/10.1080/07391102.2020.1811772

Design, synthesis, characterization, biological evaluation, and molecular docking studies of novel 1,2-aminopropanthiols substituted derivatives as selective carbonic anhydrase, acetylcholinesterase and α-glycosidase enzymes inhibitors

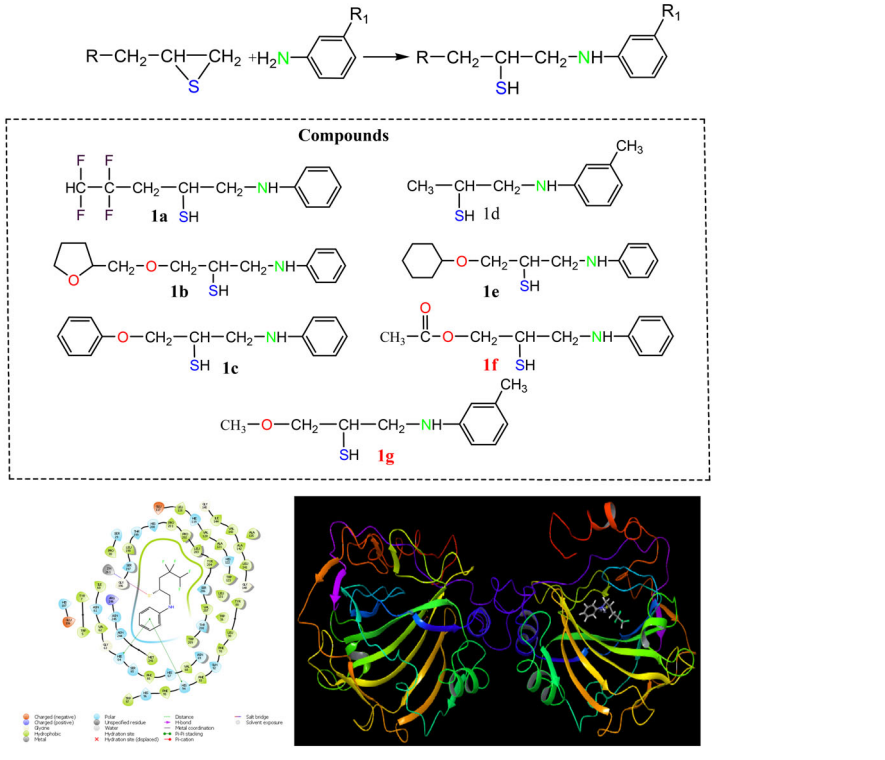
Afat Huseynova[a], Ruya Kaya[b,c], Parham Taslimi[d], Vagif Farzaliyev[e], Xadija Mammadyarova[e], Afsun Sujayev[e], Burak Tüzün[f], Umit M. Kocyigit[g], Saleh Alwasel[h] and İlhami Gulçin[c]

[a]Laboratory of 'Fine Organic Synthesis' of Baku State University, Baku, Azerbaijan; [b]Agri Ibrahim Cecen University Central Research and Application Laboratory, Agri, Turkey; [c]Faculty of Science, Department of Chemistry, Atatürk University, Erzurum, Turkey; [d]Department of Biotechnology, Faculty of Science, Bartin University, Bartin, Turkey; [e]Laboratory of Theoretical Bases of Synthesis and Action Mechanism of Additives, Institute of Chemistry of Additives, Azerbaijan National Academy of Sciences, Baku, Azerbaijan; [f]Department of Chemistry, Faculty of Science, Sivas Cumhuriyet University, Sivas, Turkey; [g]Department of Basic Pharmaceutical Sciences, Division of Biochemistry, Faculty of Pharmacy, Sivas Cumhuriyet University, Sivas, Turkey; [h]Department of Zoology, College of Science, King Saud University, Riyadh, Saudi Arabia

Communicated by Ramaswamy H. Sarma

ABSTRACT

In the article, various substituted derivatives of 1,2-aminopropanthiol (**1a–g**) have been prepared by a general and efficient method, in one-steps, starting from available thiirane and aromatic amines (aniline, *o*-toluidine) as a convenient source of sulfur and nitrogen. The synthesized compounds were fully characterized by spectral and analytical data. Seven novel compounds are synthesized. The biochemical properties indicating their potential for constituting an anti-Alzheimer's disease substance were also recorded revealing strong carbonic anhydrase I, and II, α-glycosidase, and acetylcholinesterase inhibitory effects. These synthesized novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) were found to be effective inhibitors for the α-glycosidase, human carbonic anhydrase I and II, and acetylcholinesterase enzymes, with K_i values in the range of 11.47 ± 0.87–24.09 ± 6.37 μM for α-glycosidase, 29.30 ± 4.67-79.01 ± 4.49 μM for hCA I, 14.27 ± 2.82-30.85 ± 12.24 μM for hCA II and 5.76 ± 1.55–55.39 ± 2.27 μM for AChE, respectively. In the last step of this study, molecular docking calculations were obtained in order to compare the biological activities of indicated molecules against the enzymes of acetylcholinesterase, butyrylcholinesterase and α-glycosidase.



ARTICLE HISTORY
Received 18 May 2020
Accepted 13 August 2020

KEYWORDS
Thiirane; aniline; 1,2-aminopropanthiol; enzyme inhibition; molecular docking

CONTACT Parham Taslimi parham_taslimi_un@yahoo.com; ptaslimi@bartin.edu.tr Faculty of Science, Department of Biotechnology, Bartin University, Bartin 74100, Turkey

1. Introduction

Aminothiols are among the recently studied group of sulfur-containing organic compounds. Aminothiol derivatives exhibit a wide range of biological activities and can function as potential medicinal molecules in the development of a drug. In recent years, due interest has been allocated to them in connection with their versatile use in medicine, as well as intermediates of organic synthesis (Guillaume et al., 2008). Aminothiols constitute an important class of compounds for medicinal and synthetic chemistry. Some of them (e.g. cysteine, homocysteine) are used as drugs in medicine. The synthetic aminothiol, amifostine, was originally developed as a radioprotector and has been extensively used as a chemical radioprotector for the normal tissues in cancer radiotherapy and chemotherapy (Vijayaraghavan et al., 2009).

Aminothiols and their derivatives also exhibit a variety of other physiological activity. These compounds can be used to create blockers, autoimmunomodulators, antiseptics and hypomicimic agents. They can serve as key compounds for the synthesis of various nitrogen and sulfur-containing heterocyclics, allowing them to be widely used as drugs in pharmacological practice. Aminothiols are the sinton for fine organic compounds in the making physiologically active compounds (Maharramov et al., 2017).

Alzheimer's disease (AD) occurs as a result of decreases in neurotransmitters in the brain. The neurotransmitter which exhibits the highest decreases in AD is also commonly observed in dementia and other neurodegenerative diseases. AD was found to be a dysfunction of memory. The decrease in the level of acetylcholine (ACh) in the brain is the biggest biochemical factor of this disease (Akıncıoğlu et al., 2015; Ekiz et al., 2018; Göçer et al., 2013; Kocyigit et al., 2017). A comprehensive treatment of this disease has not been fully developed. The treatments applied today are merely aiming at alleviating the symptoms.

Acetylcholinesterase (AChE; E.C.3.1.1.7) is a nonspecific enzyme that hydrolyzes lipolrophic ACh in tissues that is free or in combination with phospholipids. AChE inhibitors such as Rivastigmine, Galantamine and Donepezil are generally used for this purpose (Akıncıoğlu et al., 2015; Göçer et al., 2015). Recent studies have reported that the amount of butyrylcholinesterase (BChE; E.C.3.1.1.8) in the brains of Alzheimer's patients is higher than the amount in healthy brains (Massoulié et al., 1993). Therefore, it is estimated that BChE inhibition may also be associated with AChE-inhibiting drugs.

It is believed that the control of postprandial hyperglycemia is important in the treatment of diabetes mellitus. α-Glycosidase (E.C.3.2.1.20), secreted from the intestinal chorionic epithelium, is an enzyme responsible for the breakdown of carbohydrates. In the 1980s, α-glycosidase inhibitors emerged as a new class of antidiabetic drugs. These antidiabetic drug class of α-glycosidase inhibitors slows down the digestion and absorption process of carbohydrates by competitively blocking α-glycosidase activity. As a result, the peak concentration of postprandial blood glucose is reduced and blood sugar levels are brought under control. α-Glycosidase inhibitors may offer several advantages and have been proposed by the Third Asia-Pacific Region Guidelines for Diabetes Treatment as the first treatment method for reducing postprandial hyperglycemia (Li et al., 2008; Yin et al., 2014). Various side effects of the currently used drugs have made the discovery of new inhibitors important.

In order to help the experimental studies, theoretical calculations have been developed. Theoretical calculations of the biological activities of the molecules will provide more comprehensive information about the mechanisms involved in the activities of these molecules. The most important factor in the interaction of molecules with enzymes is the chemical interactions (Tüzün, 2020). As these interactions increase, the biological activities of the molecules increase (Tüzün & Kaya, 2018). Accordingly, three enzymes that are acetylcholinesterase for ID 4M0E (AChE) (Cheung et al., 2013), Butyrylcholinesterase for ID 5NN0 (BChE) (Košak et al., 2017), α-glycosidase for ID 1R47 (α-Gly) (Tan et al., 2014), were used to interact with the molecules. The probability of using the studied molecules as medicines in the future has been investigated.

2. Materials and methods

2.1. Measurements

The purity of the synthesized compounds was determined by paraphrase chromatography on a Tsvet-104 chromatograph, column 200×0.3 cm, temperature-210-P., the column was purged with water vapor at a pressure of $P_{H2O} = 14709.98 - 19613.30$. By the amount of sample supplied 0.1mkl. As the adsorbent, a 37% silicone brand elastomer was used. 'SE-301' deposited on a solid carrier. Chromaton 'N-AW' C grain size $0.5 - 0.15$ mm. TLC was performed on Sulifol U-254 plates. Ethyl alcohol and hexane were used as eluent in a ratio of 1:5. In all cases, the manifestation of iodine vapor was formed by one spot. The chemical structure of the synthesized compounds was confirmed by using IR, ^{1}H, ^{13}C NMR spectroscopy. The IR spectra were taken on the instrument Nicolet IS-10. NMR experiments were 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 tetramethylsilane (TMS).

2.2. Synthesis of substituted 1,2-aminopropanthiols (1a–g) general procedure

In a ampoule with a capacity of 100 mL was placed 15.8 g (0.2 mol) aniline and 20.4 g (0.1 mol) of 1,2-epithio-3-hydroxy-5,5,6,6-tetrafluorhexane. The ampoule was heated for 12 h in a water bath. Then the ampoule ruptured, an excess of aniline was distilled off, and the reaction product was subjected to vacuum distillation. The extracts were combined with the organic part, washed with warm water, dried with $MgSO_4$, then the solvent was distilled off and (9.9 g) 75% of compound (**1a**) was isolated by vacuum distillation. In a similar

way, other substituted 1,2-aminothiols (**1b**, **1c**, **1d**, **1e**, **1f** and **1g**) were obtained.

2.2.1. 1-(P-Toluidino)-4,4,5,5-tetrafluoropentane-2-thiol (1a)

Yield: 75%, b.p. 110–111 °C/0.3 mm Hg, d_4^{20} =1.5050, R_f = 0.47, ^{1}H-NMR ($CHCl_3$, 300 MHz): 2.5 (s, 1H - CH), 1.9 (d, 2H, CH_2), 5.69 (s, 1H – CHF_2), 7.1-7.2 (s, 4H - Ar-H), 8.06 (s, 1H - NH), 2.34 (s, 3H, CH_3-Ph), 1.5 (s, 1H - SH). ^{13}C-NMR (75 MHz, $CHCl_3$): 22.4, 24.3, 34.8, 60.5, 113.4, 114, 126.8, 129.8, 130.5, 144.6. IR (KBr, υ, cm^{-1}): 1120–1110, 1365–1350, 3360–3340, 3050, 2545–2540, 1460–1445, 1510–1500, 1610–1590. Found, %: N-5.18; S-11.94. $C_{11}H_{13}F_4NS$. Calculated (%): N-5.24; S-11.99.

2.2.2. 1-(Phenylamino)-3-((tetrahydrofuran-2-yl)methoxy)-propane-2-thiol (1b)

Yield: 65%, b.p. 95–96 °C/0.2 mm Hg, d_4^{20} =1.5680, R_f = 0.31, ^{1}H-NMR ($CHCl_3$, 300 MHz): 3.1 (s, 1H - CH), 6.58-7.08 (s, 4H - Ar-H), 1.5 (s, 1H - SH), 8.06 (s, 1H - NH). 3.80; 3.70 (d, 2H-CH_2), 3.44, 3.19 (d, 2H-CH_2), 3.76, 3.51 (d, 2H-CH_2), 3.63; 3.38 (d, 2H-CH_2), 3.80, 3.70 (d, 2H-CH_2), 4.07 (t, 1H-CH), 1.90, 1.80 (d, 2H- CH_2), 1.93; 1.68 (d, 2H-CH_2). ^{13}C-NMR (75 MHz, $CHCl_3$): 25.9, 32.4, 37, 56.8, 71.2, 74.9, 75, 84.2, 113.5, 117.2, 147. IR (KBr, υ, cm^{-1}): 1115, 1355, 3365–3345, 3030, 2530, 1440–1425, 1515, 1605–1575. Found, %: N – 5.22; S – 11.95. $C_{14}H_{21}O_2NS$. Calculated (%): N – 5.24; S – 11.98.

2.2.3. 1-(P-Toluidino)propane-2-thiol (1c)

Yield: 70%, b.p. 109–110 °C/0.2 mm, d_4^{20} = 1.5720, R_f = 0.37, ^{1}H-NMR ($CHCl_3$, 300 MHz): 3.1 (s, 1H - CH), 6.58-7.08 (s, 4H - Ar-H), 1.5 (s, 1H - SH), 8.06 (s, 1H - NH). 3.80; 3.70 (d, 2H-CH_2), 3.44, 3.19 (d, 2H-CH_2), 3.76; 3.51 (d, 2H-CH_2), 3.63, 3.38 (d, 2H-CH_2), 3.80; 3.70 (d, 2H-CH_2), 4.07 (t, 1H-CH), 1.90, 1.80 (d, 2H- CH_2), 1.93, 1.68 (d, 2H-CH_2). ^{13}C-NMR (75 MHz, $CHCl_3$): 31.4, 33.2, 34.1, 36.2, 60.8, 66.8, 113.5, 117.2, 129.6, 147.6. IR (KBr, υ, cm^{-1}): 1100, 1335, 3360, 2240, 1490, 1525, 1615–1570. Found, %: N – 5.38; S – 12.29. $C_{15}H_{17}ONS$. Calculated (%): N – 5.41; S – 12.35.

2.2.4. 1-(Phenylamino)-3-(tetrahydro-2H-pyran-4-yl)propane-2-thiol (1d)

Yield: 80%, b.p.: 96–97 °C/0.2 mm, d_4^{20} = 1.5660, R_f = 0.56, ^{1}H-NMR ($CHCl_3$, 300 MHz): 2.7 (s, 1H - CH), 6.40-7.28 (s, 4H - Ar-H), 1.5 (s, 1H - SH), 3.12 (s, 1H - NH), 1.28 (s, 3H- CH_3). ^{13}C-NMR (75 MHz, $CHCl_3$): 29, 54, 62, 72, 74, 113, 117, 129, 146. IR (KBr, υ, cm^{-1}): 3030, 3344, 2545–2540, 1610, 1590, 1510, 1500, 1460, 1445, 1334, 1125. Found, %: N – 7.69; S – 17.63. $C_{10}H_{15}NS$. Calculated (%): N – 7.73; S – 17.68.

2.2.5. 2-Mercapto-3-(phenylamino)propyl acetate (1e)

Yield: 78%, b.p. 75–76 °C/0.1 mm, d_4^{20} = 1.5242, R_f = 0.48, ^{1}H-NMR ($CHCl_3$, 300 MHz): 2.87 (t, 1H - CH), 6.5–7.8 (s, 4H - Ar-H), 1.5 (s, 1H - SH), 8.01 (s, 1H - NH), 3.9, 3.6 (d, 2H-CH_2), 3.24, 3.09 (d, 2H-CH_2), 2.87 (d, 1H-CH), 2.05 (d, 1H-CH). ^{13}C-NMR (75 MHz, $CHCl_3$): 39.2, 56.5, 67.7, 70.6, 74.1, 113, 117, 147.4. IR (KBr, υ, cm^{-1}): 1120, 1365, 3340, 3050, 2540, 1445, 1510, 1610, 1570. Found, %: N – 5.24; S – 12.02. $C_{15}H_{23}ONS$. Calculated (%): N – 5.28; S – 12.08.

2.2.6. 1-Phenoxy-3-(phenylamino)propane-2-thiol (1f)

Yield: 60%, b.p. 111–112 °C/0.3 mm, d_4^{20} = 1.5480, R_f = 0.29, ^{1}H-NMR ($CHCl_3$, 300 MHz): 1.93 (s, 3H, CH_3), 2.19–2.51 (s,4H, $2CH_2$), 8.02 (s, 2H, NH), 4.29 (s,1H, CH), 1.5 (s, 1H - SH); 6.82–7.27 (4H, m, Ar). IR (KBr, υ, cm^{-1}): 3175, 3198, 3020, 2978, 2240, 1620, 1604, 1445, 720, 680. Found, %: N – 6.19; S –14.17. $C_{11}H_{15}O_2NS$. Calculated %: N – 6.22; S – 14.22.

2.2.7. 1-(P-Toluidino)-3-methoxypropane-2-thiol (1g)

Yield: 84%, b.p. 105–106 °C/0.3 mm, d_4^{20} = 1.5661, R_f = 0.56, ^{1}H-NMR ($CHCl_3$, 300 MHz): 3.11 (s, 1H - CH), 3.19, 3.44, 3.51, 3.76 (d, 2H, CH_2), 6.31–6.84 (s, 4H - Ar-H), 1.5 (s, 1H - SH), 8.06 (s, 1H - NH), 2.32 (s, 3H, CH_3-Ph), 3.24 (s, 3H, CH_3O). ^{13}C-NMR (75 MHz, $CHCl_3$): 24.3, 36.7, 56.8, 58.9, 76.8, 113.4, 126.8, 129.8, 144.6. IR (KBr, υ, cm^{-1}): 1120–1110, 1365–1350, 3360–3340, 3050, 2545–2540, 1460–1445, 1510–1500, 1610–1590. Found, %: N, 6.56; S, 15.06. $C_{11}H_{18}ONS$. Calculated (%): N – 6.60; S – 15.09.

2.3. Carbonic anhydrases, cholinesterase and α-glycosidase inhibition

The inhibitory effect of novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) on AChE activity was performed according to spectrophotometric method of Ellman et al. (1961) as described previously (Behcet et al., 2018). α-Glycosidase inhibition effect of novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) was evaluated according to the method of Tao et al. (2013). The absorbance o samples were recorded at 405 nm (Taslimi et al., 2018).

In the present work, hCA I, and II isoenzymes were purified by Sepharose-4B-L-Tyrosine-sulfanilamide affinity column chromatography, CA isoenzymes activity was determined according to the spectrophotometric method of Verpoorte et al. (1967) as described in details in our previous studies. p-Nitrophenylacetate (p-NPA) was used as substrate for the enzymatic reaction (Türker et al., 2018). One CA enzyme unit adopted the amount of CA, which had absorbance difference at 348 nm over a 3 min at 25 °C. For determination of inhibition kinetics of novel 1,2-aminopropanthiols substituted derivatives (**1a–g**), an activity (%) and [1,2-Aminopropanthiols] graph was drawn. From these graphs, half maximal inhibitor concentrations (IC_{50}) for novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) were determined. Also, for K_is, three different concentrations of novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) were used (Yiğit et al., 2018). Then, Lineweaver–Burk graphs were drawn according to these measurements (Lineweaver & Burk, 1934). K_is of novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) were determined from Lineweaver–Burk graphs as previously described (Aktas et al., 2020; Burmaoglu et al., 2020). Quantity of protein during the purification processing,

Bradford's technique was utilized (Bradford, 1976), and bovine serum albumin was used as the standard protein (Gulçin et al., 2018). Sodium dodecyl sulphate-polyacrylamide gel electrophoresis was employed for visualizing the image of isoenzymes (Atmaca et al., 2018).

2.4. Docking studies

Theoretical studies are widely used to comment on the biological activities of molecules. In this study, the activities of molecules against enzymes were compared. For this comparison, the molecules were first optimized using the Gaussian package program with HF/6-31++g basis set (Frisch et al., 2009). After optimizing structures of 1,2-aminopropanthiol derivatives, files with the *.sdf extension were created. In the next process, it was calculated by using Maestro Molecular Modeling platform (version 12.2) by Schrödinger, LLC (Schrodinger, 2019) to examine the interactions of molecules and enzymes. This program consists of many modules. In the first module, enzymes, which are Human Acetylcholinesterase for ID 4M0E (AChE) (Cheung et al., 2013), Butyrylcholinesterase for ID 5NN0 (BChE) (Košak et al., 2017), α-Glycosidase for ID 1R47 (α-Gly) (Tan et al., 2014), were prepared for interaction with molecules by the protein preparation module (Friesner et al., 2006; Schrodinger, 2019). With the help of this module, water molecules in the structure of enzymes were removed, and then the loads and binding methods of the enzymes were characterized. A grid box of default size ($20 \times 20 \times 20$ Å^3) of the protein structure was centered on 1,2-aminopropanthiol derivatives position. A minimization of the protein of the enzymes was performed using the default constraint of 0.30 RMSD (root-mean-squared deviation) and the OPLS3e force field. The active sites of the enzyme were then determined using this module. Small proteins in this active region were given freedom of movement for interactions. In the next step, 1,2-aminopropanthiol derivatives were used to prepare for interaction the LigPrep module (Sastry et al., 2013; Schrodinger, 2019). Physiological pH values of high-energy isomers of 1,2-aminopropanthiol derivatives were determined. The Glide ligand was interacted with the docking module (Taslimi et al., 2020) to interact with prepared 1,2-aminopropanthiol derivatives and enzymes. Function score of the glide ligand was selected as the default.

The probability of using the studied molecules as medicines in the future has been investigated. For this study, ADME analysis (Absorption, distribution, metabolism, excretion and toxicity) of the molecules was performed. The Qikprop module (Schrödinger, 2020) of the Schrödinger software of molecules was used for ADME analysis. As a result of calculations made with The Qik-prop module, many parameters of the molecules were obtained. The numerical values of these parameters have provided a lot of information about their ability to be medicines (Zengin et al., 2018). The ability of 1,2-aminopropanthiol derivatives to be used as drugs depends on the numerical values of these parameters in a certain range.

3. Results and discussion

3.1. Chemistry

There are certain fundamental and applied issues in science that have not been justified merely by approaches limited to one scientific field, and for many years, satisfactory results have not been achieved. There is a need for a comprehensive scientific approach to such issues, and the most successful scientific results of the recent years are reflected in the research findings that science has gained through multidisciplinary (interdisciplinary) approaches.

From this point of view, this new research article focuses on the modern problems common to medicine and other related fields—biological activity (Taslimi et al.). Potentially such problems occur in the environment which practically include organisms. In this regard, the expansion of scientific studies on the study of new synthesis methods of both antioxidant and biological active compounds with combined effects is of great importance.

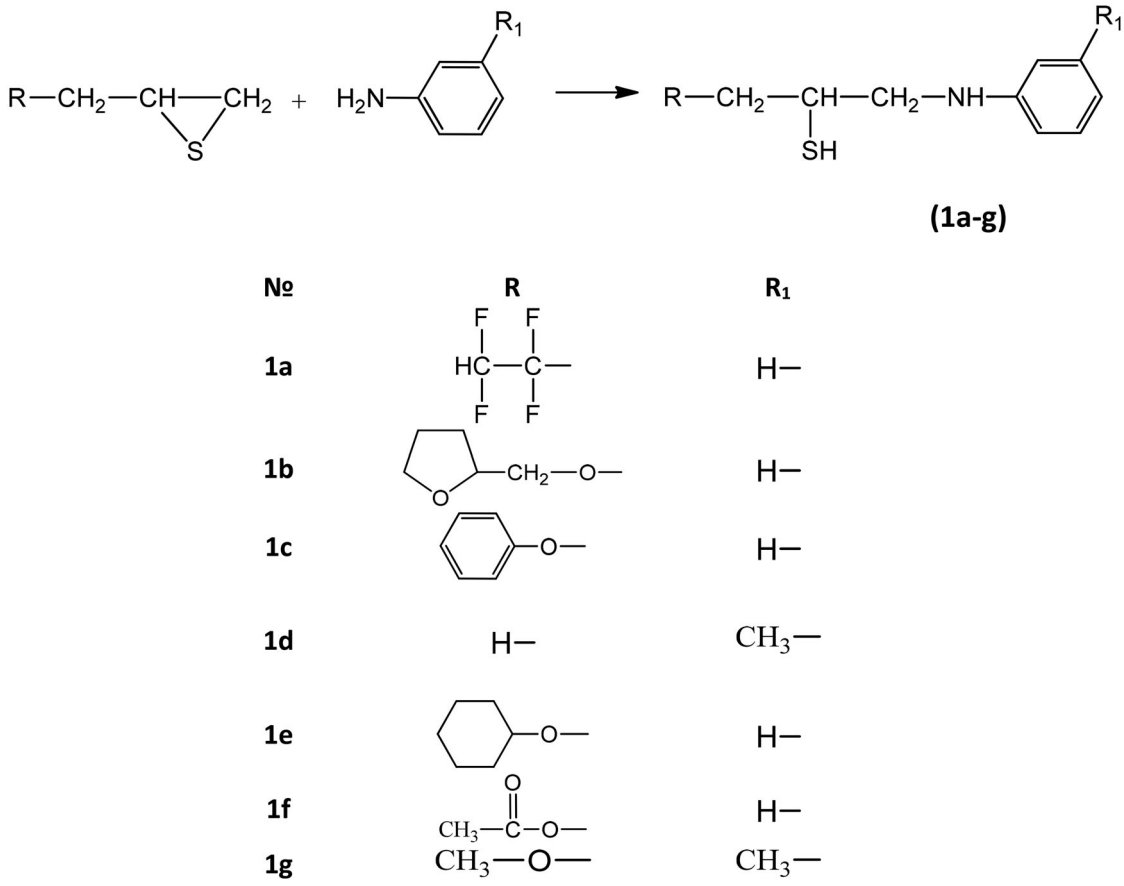
According to literature (Karimov et al., 2020; Mammadov et al., 2019), aminothiol derivatives exhibit a wide biological activity and can function as potential medical molecules in the development of potential drugs. It was shown that heterocyclic compounds containing nitrogen and sulfur are effective antimicrobial and antioxidant additives. For this purpose, in continuation of research in the field of the synthesis of aminothiols, the new 1,2-aminopropanthiols (**1a–g**) belonging to new and more effective antioxidants were synthesized for the first time.

The reaction is carried out in an aqueous medium according to the Scheme 1.

1,2-Aminothiols (**1a–g**) were obtained by reacting various thiiranes with aromatic amines-aniline, *o*-toluidine at a ratio of reactants thiirane: amine (1:2) for 12 h at 90–100 °C in ampoule. The yield of substituted 1,2-aminothiols was 60–84%. Synthesized 1,2-aminothiols (**1a–g**) were colorless liquids. When storing, the liquid turned yellow. They are insoluble in water, dissolve well in organic solvents (acetone, ether, ethanol, etc.) and have a high boiling point and thermal stability, that is, along with other operational properties, they are also thermally stable. The physicochemical characteristics, the data of elemental analysis and molecular refraction of the esters (**1a–g**) were given in the corresponding description of the experiment. The purity of the synthesized 1,1-aminothiols (**1a–g**) was confirmed by elemental analysis, thin-layer and gas-liquid chromatography, and the structure of the compounds was proved by IR, ^{1}H, and ^{13}C NMR spectroscopies. IR and NMR spectra were recorded on a Bruker spectrophotometer.

3.2. Biochemical studies

The CA isoenzymes inhibitors are utilized to design novel classes of drugs for glaucoma and epilepsy (Sujayev et al., 2018). Additionally, novel CA inhibitors have been required to expand as therapeutic factors. Some researchers have studied the inhibition of hCAs with catecholamines, thiourea derivatives, bromophenols, anions, uracil derivatives and sulphonamides (Taslimi et al., 2017). In addition, chalcones and



Scheme 1. Derivatives of substituted 1,2-aminopropanthiols (**1a–g**).

pyrazoles have also been studied to inhibit hCAs. The results presented in Table 1 indicate that novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) had effective inhibition against hCA I isoform. The hCA I isoform was inhibited by novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) in nanomolar levels, the K_i of which obtained between 29.30 ± 4.67 and 79.01 ± 4.49 μM. Indeed, acetazolamide (AZA), as a broad-specificity CA inhibitor showed K_i value of 136.48 ± 11.87 μM against hCA I. Among the inhibitors, **1b** and **1g** were observed to be the effective hCA I inhibitors with K_i of 29.30 ± 4.67 and 38.77 ± 5.88 μM, respectively. The hCA I inhibition effects of novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) were found to be the greater than AZA. For hCA I, IC_{50} values of AZA as positive control and some novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) were as the following order: **1g** (24.66 μM, r^2: 0.9965) < **1c** (31.94 μM, r^2: 0.9906) < **1a** (36.67 μM, r^2: 0.9417) < **1b** (37.46 μM, r^2: 0.9485) < AZA (112.54 μM, r^2: 0.9240). Against the hCA II isoform, the novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) demonstrated varying K_i values from 14.27 ± 2.82 to 30.85 ± 12.24 μM (Table 1). These novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) were observed to have high inhibition effects toward hCA II. Additionally, AZA showed K_i of 170.64 ± 25.76 μM against hCA II. **1a** and **1c** exhibited the highest inhibition effect with K_i values of 14.27 ± 2.82 and 16.69 ± 1.60 μM, respectively. For hCA II, IC_{50} values of AZA and some novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) are as the following order: **1g** (16.78 μM, r^2: 0.9716) < **1e** (19.69 μM, r^2: 0.9825) < **1c** (23.49 μM, r^2: 0.9858) < **1b** (26.35 μM, r^2: 0.9546) < AZA (148.78 μM, r^2: 0.9545).

The enzyme can be inactivated by various inhibitors, leading to ACh accumulation and also disrupted neurotransmission caused by hyperstimulation of muscarinic and nicotinic receptors (Gulçin et al., 2017; Maharramov et al., 2019). Reversible AChE inhibitors are extensively utilized for the treatment of neurodegenerative diseases, while irreversible inhibitors are associated with toxic effects. Indeed, irreversible AChE inhibitors (AChEIs) include chemical warfare factors and many organophosphorus molecules used as insecticides and pesticides (Türkan et al., 2018; Yiğit et al., 2018). All of novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) had significantly higher AChE inhibitory activity than tacrine as control molecule. Furthermore, the K_i values of novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) and tacrine are summarized in Table 1. As can be observed from the results recorded in Table 1 and Figure 1, novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) effectively inhibited AChE, with K_i values in the range of 5.76 ± 1.55 to 55.39 ± 2.27 μM. Thus, all of these novel compounds had almost similar inhibition profiles. The most active **1e** and **1c** showed K_i values of 5.76 ± 1.55 and 10.13 ± 3.74 μM. For AChE, IC_{50} values of TAC (Tao et al., 2013) and some novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) are as the following order: **1g** (25.48 μM, r^2: 0.9825) < **1a** (27.50 μM, r^2: 0.9965) < **1b** (31.79 μM, r^2: 0.9578) < TAC (70.87 nM, r^2:

Table 1. Inhibition results of novel 1,2-aminopropanthiols (**1a–g**) derivatives on carbonic anhydrase, acetylcholinesterase and α-glycosidase enzymes.

	IC_{50} (μM)								K_i (μM)			
Compounds	hCA I	r^2	hCA II	r^2	AChE	r^2	α-Gly	r^2	hCA I	hCA II	AChE	α-Gly
1a	36.67	0.9417	31.5	0.9657	27.50	0.9965	40.52	0.9835	40.18 ± 11.89	14.27 ± 2.82	33.23 ± 7.85	19.30 ± 7.60
1b	37.46	0.9485	26.35	0.9546	31.79	0.9578	40.06	0.9857	29.30 ± 4.67	17.53 ± 6.42	22.62 ± 1.70	15.02 ± 3.48
1c	31.94	0.9906	23.49	0.9858	44.71	0.9706	42.00	0.9938	47.41 ± 2.74	16.69 ± 1.60	10.13 ± 3.74	15.72 ± 2.25
1d	49.5	0.9593	50.58	0.9447	60.37	0.9487	50.58	0.9446	56.35 ± 17.87	26.85 ± 5.76	55.39 ± 2.27	24.09 ± 6.37
1e	38.72	0.9947	19.69	0.9825	52.50	0.9508	27.83	0.9835	45.30 ± 17.59	24.20 ± 3.96	5.76 ± 1.55	22.21 ± 3.37
1f	37.56	0.9704	33.00	0.9963	50.22	0.9958	31.64	0.9786	79.01 ± 4.49	30.85 ± 12.24	42.59 ± 1.75	11.47 ± 0.87
1g	24.66	0.9965	16.78	0.9716	25.48	0.9825	14.90	0.9897	38.77 ± 5.88	20.13 ± 3.41	20.41 ± 0.25	17.08 ± 3.50
AZA*	112.54	0.9240	148.78	0.9545	–		–	–	136.48 ± 11.87	170.64 ± 25.76	–	–
TAC**	–	–	–	–	70.87	0.9549	–	–			57.90 ± 7.63	–

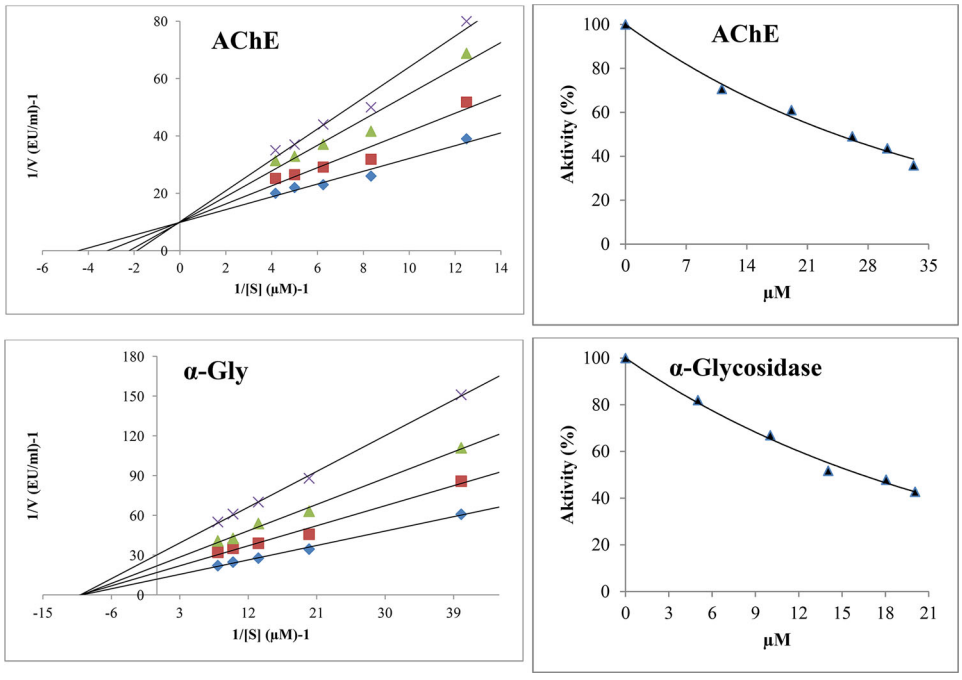


Figure 1. Determination of Lineweaver–Burk graphs for excellent inhibitors of alpha glycosidase and AChE enzymes.

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

		1a	1b	1c	1d	1e	1f	1g
AChE	Docking score	−5.35	−6.73	–	−6.27	–	–	–
	Glide ligand efficiency	−0.31	−0.37	–	−0.57	–	–	–
	Glide h-bond	−0.46	−0.32	–	−0.57	–	–	–
	Glide evdw	−23.25	−31.46	–	−21.32	–	–	–
	Glide ecoul	−5.02	−4.45	–	−2.63	–	–	–
	Glide emodel	−36.29	−45.02	–	−32.93	–	–	–
α-Gly	Docking Score	−3.99	−4.05	–	–	−3.66	−4.17	−4.10
	Glide ligand efficiency	−0.23	−0.23	–	–	−0.20	−0.28	−0.29
	Glide h-bond	−0.30	−0.58	–	–	−0.33	−0.29	−0.57
	Glide evdw	−19.01	−23.86	–	–	−19.50	−21.15	−18.85
	Glide ecoul	−7.45	−7.04	–	–	−8.57	−10.14	−9.98
	Glide emodel	−33.08	−35.98	–	–	−32.08	−40.15	−35.31
hCA I	Docking Score	−7.64	−7.57	–	–	−7.50	−5.22	–
	Glide ligand efficiency	−0.45	−0.42	–	–	−0.42	−0.35	–
	Glide h-bond	−0.12	−0.21	–	–	−0.13	−0.32	–
	Glide evdw	−18.47	−18.48	–	–	−18.52	−25.24	–
	Glide ecoul	−7.94	−9.94	–	–	−7.98	−5.92	–
	Glide emodel	−51.76	−64.13	–	–	−55.53	−48.59	–
hCA II	Docking Score	−5.79	−7.02	−1.06	−6.33	–	–	–
	Glide ligand efficiency	−0.34	−0.39	−0.06	−0.58	–	–	–
	Glide h-bond	−0.19	−0.63	−0.07	−0.38	–	–	–
	Glide evdw	−15.30	−18.89	−31.61	−11.83	–	–	–
	Glide ecoul	−11.16	−9.88	−4.43	−10.39	–	–	–
	Glide emodel	−45.08	−51.23	−49.75	−43.32	–	–	–

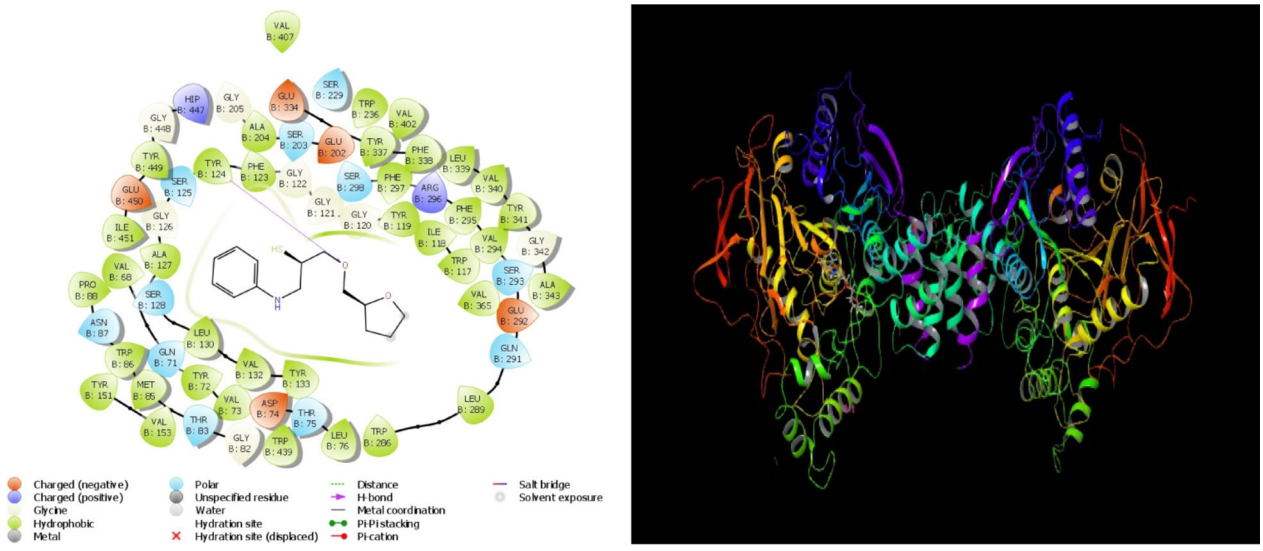


Figure 2. Demonstration of interactions between AChE enzyme and molecule with highest biological activity.

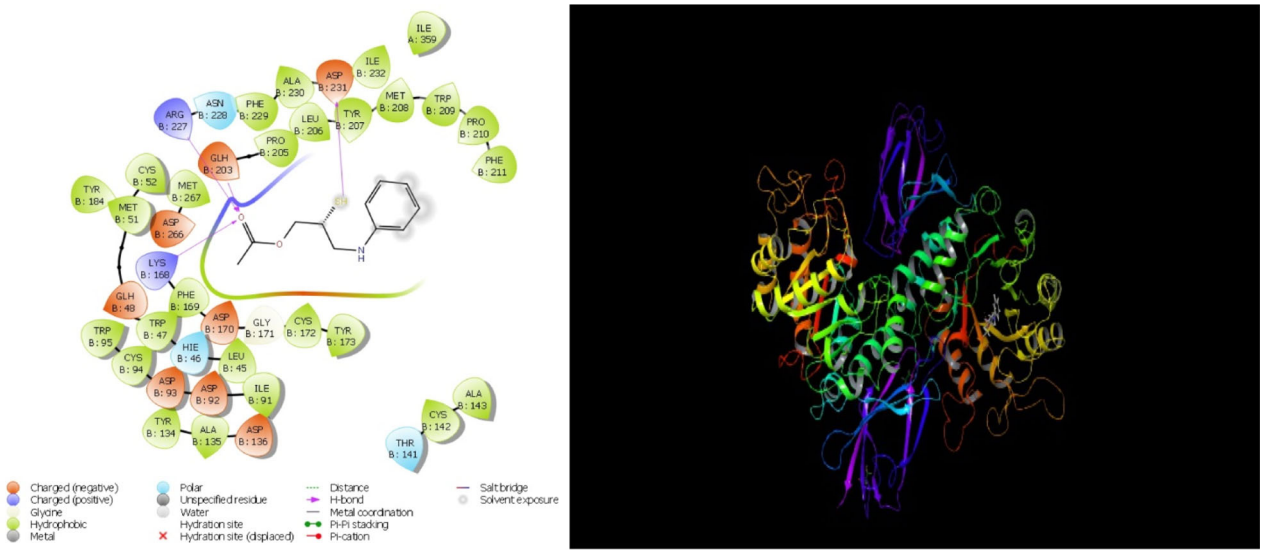


Figure 3. Demonstration of interactions between α-Glycosidase enzyme and molecule with highest biological activity.

0.9549). Like donepezil, AChEIs are approved by the Food and Drug Administration in the United States for the treatment of AD, and have clinical trial data supporting their use in Parkinson's disease and vascular dementia.

For α-glycosidase enzyme, novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) have IC_{50} values in the range of 14.90–50.58 μM and K_is in the range of 11.47 ± 0.87–24.09 ± 6.37 μM (Table 1). For this enzyme, the most effective K_i values of **1f** and **1b** were with K_i values of 11.47 ± 0.87 and 15.02 ± 3.48 μM, respectively. For α-glycosidase, IC_{50} values of acarbose as positive control and some novel 1,2-aminopropanthiols substituted derivatives (**1a–g**) are as the following order: **1g** (14.90 μM, r^2: 0.9897) < **1e** (27.83 μM, r^2: 0.9835) < **1f** (31.64 μM, r^2: 0.9786) < ACR (56.44 μM). Inhibition of α-glycosidases by inhibitors tends to slow the breakdown and release of sugar molecules into the bloodstream and can be utilized as therapeutic factors in the therapy of obesity and diabetes. Indeed, some of the inhibitors are utilized to treat mainly voglibose, acarbose and miglitol.

3.3. Docking results

In the interaction of 1,2-aminopropanthiol derivatives with enzymes, some sections are left blank in Table 2. It was seen that the molecules in these empty sections have no interaction with enzymes. Therefore, these sections were left blank. The interactions are the most important factors affecting the biological activity of molecules (Sayin & üngördü, 2018, 2019; Sayin & karakaş, 2018a, 2018b). These interactions have many different types of interactions such as hydrogen bonds, polar and hydrophobic interactions, π–π and halogen bonds (Jayarajan et al., 2020; Sayin & Karakaş, 2017; Sayin & Üngördü, 2019). As these interactions between the molecule and the enzyme increase, the biological activity

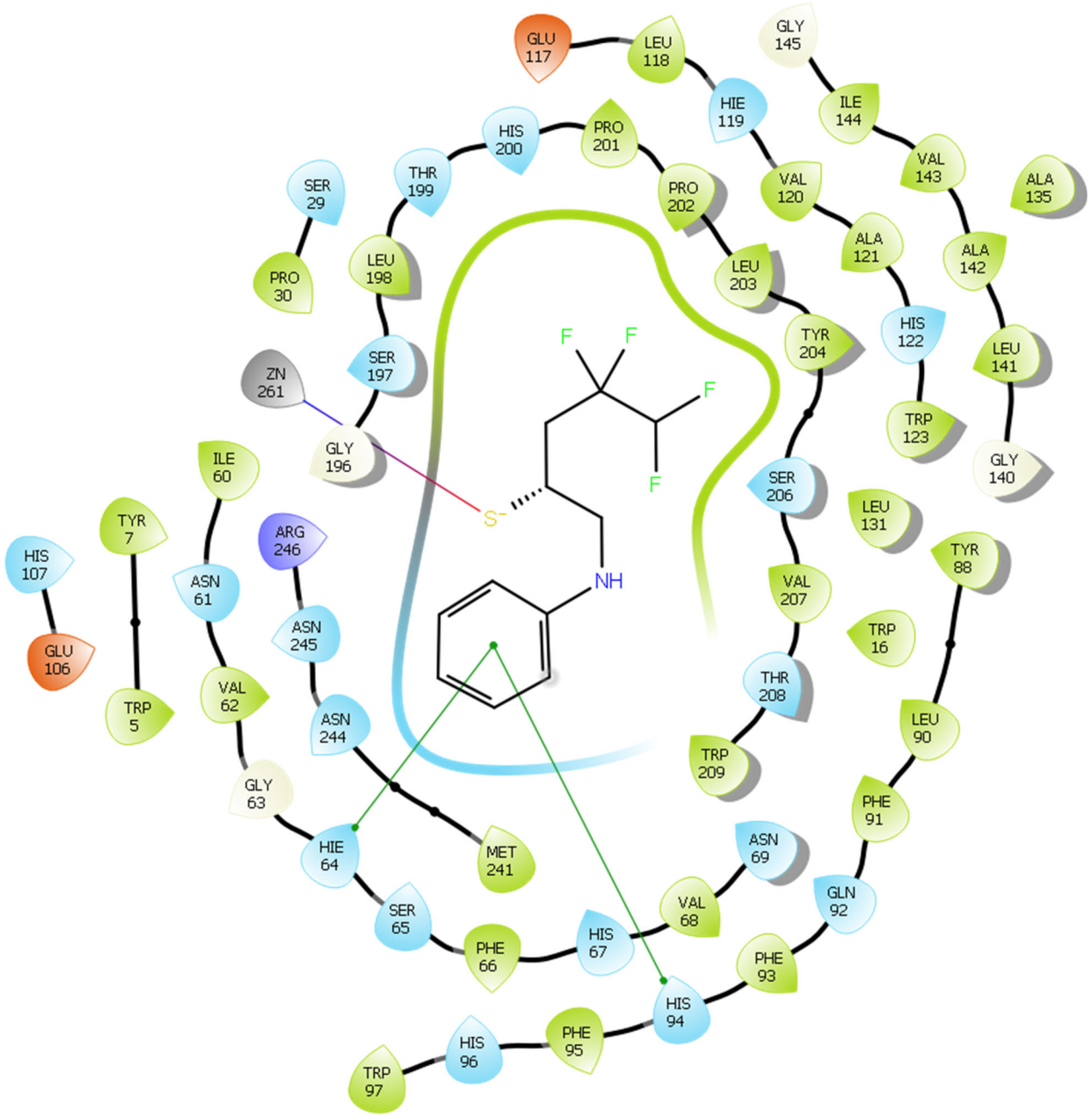


Figure 4. (a) Demonstration of interactions between hCA I enzyme and molecule with highest biological activity. (b) Demonstration of interactions between hCA I enzyme and molecule with highest biological activity.

of the molecule increases (Mamedova et al., 2019; Tüzün & Saripinar, 2020). There are many small protein molecules in enzymes. Since these proteins are composed of heteroatoms, they can form strong interactions. These interactions with molecules are shown in Figures 2–5. In the calculations made, the number of poses consisting of the interactions of enzyme's protein and molecules is 35.

In molecular docking calculations, these parameters are used to explain the biological activities of molecules against enzymes. A comparison of the biological activity of molecules is made according to the numerical values of these parameters, among which the most important parameter is the docking score (Subhani et al., 2015). The biological activity of this molecule, which is the numerically most negative molecule, is generally the highest. In the calculations made, there is more than one stable isomer of a molecule in the preparation process of the molecules. In docking calculations, these isomers can dock at different points in the active region of proteins. When these dockings are sorted according to the numerical values of the Docking score parameter, only the most negative value is considered. Therefore, even if a molecule in docking has different isomers at different points, only the most negative isomer is considered. As a result of the calculations, the most negative value of the docking score parameter against all enzymes is, respectively, the hCA I isoenzymes for the **1a** molecule, the hCA II isoenzymes for the **1b** molecule, the AChE enzymes for the **1b** molecule, and the α-glycosidase enzymes for the **1f** molecule. Another parameter is docking model, which is the energy numerical value of the interaction pose between the

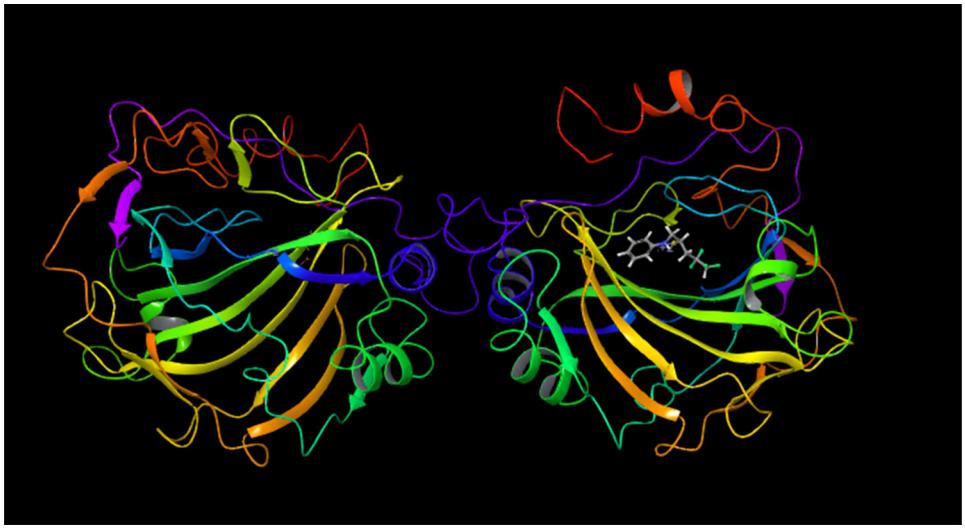


Figure 4. Continued.

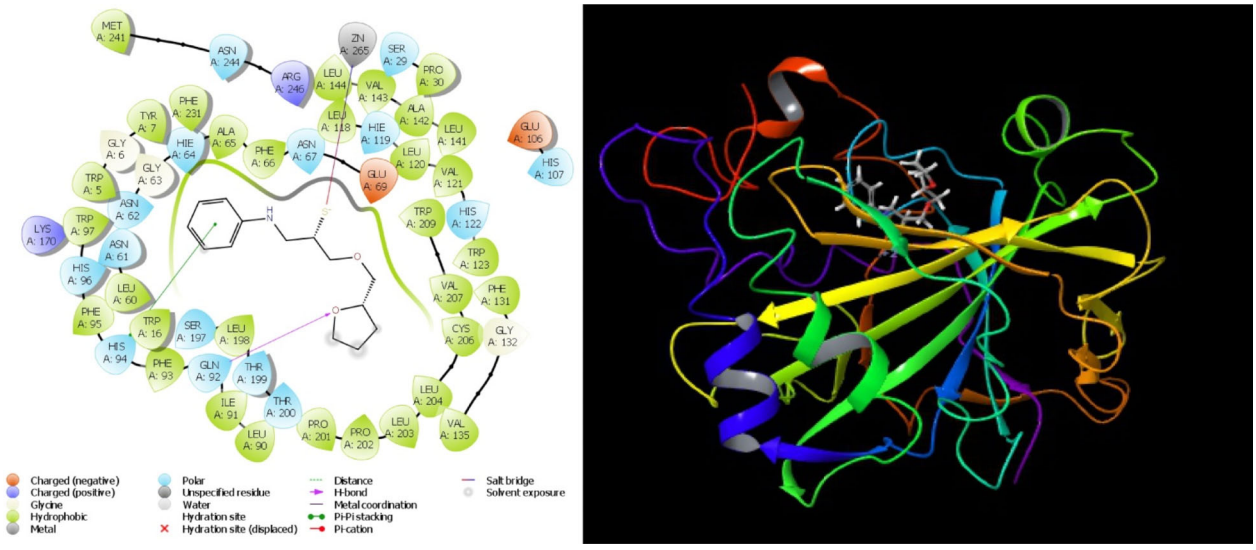


Figure 5. Demonstration of interactions between hCA II enzyme and molecule with highest biological activity.

molecule and the enzyme. Glide ligand efficiency parameter gives information about the effectiveness of molecules. The Glide h-bond parameter of 1,2-aminopropanthiol derivatives predicts the number of hydrogen bonds formed between molecules and enzymes. The Glide evdw parameter gives information about the number of Van der Waals interactions resulting from the interaction (Sever et al., 2019). The Glide ecoul parameter predicts Coulomb interactions that occur in the interaction of 1,2-aminopropanthiol derivatives with enzymes (Wang et al., 2019). These parameters are used to explain the interactions of molecules with enzymes and also used to compare the biological activities of 1,2-aminopropanthiol derivatives.

As a result of docking calculations, many interactions occur between molecules and enzymes. In the AChE enzyme, a hydrogen bond interaction occurs between the O atom in the center of the **1b** molecule and the TYR124 protein. Hydrophobic interactions with the enzyme occurs in the tetrahydrofuran ring side of the molecule. However, hydrogen bonding occurs between the α-Gly enzyme and the molecule **1f**, between carbonyl oxygen and GLH203, ARG227, and LYS168 proteins. Again, a hydrogen bond is formed between the hydrogen atom attached to the sulfur atom in the **1f** molecule and the ASP231 protein. Pi–pi stacking occurs between the enzyme hCA I and the molecule **1a**, between the benzene ring and the HIS94 and HIE64 proteins. Plus, the salt-bridge interaction occurs between the sulfur atom and the ZN261 protein. These interactions are shown in more detail in Figure 4a, b. In this docking study, the numerical value of the docking score between this molecule and this enzyme is the most negative. Finally, pi–pi stacking occurred between the hCA II enzyme and the molecule **1b**, between the benzene ring and the HIS94 enzyme. A hydrogen bond interaction occurred between the tetrahydrofuran ring and GLN92. Salt bridge interaction occurs between sulfur atom and ZN265 protein.

After interactions of 1,2-aminopropanthiol derivatives with enzymes, the future drug properties of these derivatives were investigated. For this, ADME analysis of 1,2-aminopropanthiol derivatives was performed. Many parameters of 1,2-

Table 3. ADME properties of molecules.

	1a	1b	1c	1d	1e	1f	1g	Reference range
Solute Molecular Weight	267	267	259	167	265	225	211	130–725
Solute Dipole Moment (D)	2.1	4.1	3.8	1.9	3.5	7.2	3.6	1.0–12.5
Solute Total SASA	483	562	546	405	574	481	479	300–1000
Solute Hydrophobic SASA	86	284	62	121	295	130	255	0–750
Solute Hydrophilic SASA	10.8	10.8	10.8	10.8	10.8	81.5	10.8	7.0–330
Solute Carbom Pi SASA	202	202	407	202	202	202	146	0–450
Solute Weakly Polar SASA	184	66	66	71	65	67	67	0–175
Solute Molecular Volume (A^3)	797	944	913	641	973	792	782	500–2000
Solute as Donor-Hydrogen Bonds	1.8	1.8	1.8	1.8	1.8	1.8	1.8	0.0–6.0
Solute as Acceptor-Hydrogen	1.5	4.9	2.3	1.5	3.2	3.5	3.2	2.0–20.0
Solute Globularity (Sphere =1)	0.9	0.8	0.8	0.9	0.8	0.9	0.9	0.75–0.95
QP Polarizability (A^3)	24	28	30	19	30	24	23	13.0–70.0
QP log p for hexadecane/gas	7.0	9.3	10.4	6.5	9.5	8.4	7.4	4.0–18.0
QP log p for octanol/gas	11.2	14.1	13.5	9.1	13.8	12.8	11.2	8.0–35.0
QP log p for water/gas	5.2	8.2	7.2	5.4	6.8	7.6	6.4	4.0–45.0
QP log p for octanol/water	4.3	3.5	4.5	2.9	4.3	2.6	3.1	−2 to 6.5
QP log S aqueous solubility	−4.1	−3.7	−4.4	−2.5	−4.6	−3.1	−3.1	−6.5 to 0.5
QP log S-conformation indepent	−4.2	−3.1	−4.2	−2.2	−3.6	−2.7	−2.6	−6.5 to 0.5
LogHERG	−4.8	−5.3	−6.2	−4.3	−5.3	−4.7	−4.5	(corcern below −5)
Apparent Caco-2 Permeability (nm/sec)	7818	7818	7818	7818	7818	1669	7818	[a]
QP log BB for brain/blood	0.6	0.1	0.2	0.4	0.2	−0.4	0.3	−3 to 1.2
Apparent MDCK Permeability (nm/sec)	10000	10000	10000	10000	10000	1993	10000	[a]
QP log Kp for skin Permeability (Jm)	−0.4	−0.2	0.4	−0.6	−0.3	−1.7	−0.6	Kp in cm/h
Solute Ionization Potential (eV)	9.4	9.0	9.1	9.2	9.0	9.3	9.0	7.9–10.5
Solute Electron Affinity (eV)	0.3	−0.1	0.0	0.0	−0.1	0.2	−0.1	0.9–1.7
No. of Primary Metabolites	4	6	5	4	4	4	6	1.0–8.0
QP log K has Serum protein Binding	0.1	−0.1	0.3	−0.2	0.3	−0.2	−0.2	−1.5 to 1.5
Qual. Model for Human Oral Absorption	3	3	3	3	3	3	3	–
% Human Oral Absorption in GI (±20%)	100	100	100	100	100	100	100	[b]
Solute CdW Polar SA (PSA)	12.6	28.8	20.3	12.6	19.7	54.0	20.7	7–200
Lipinski Rule of 5 Violations	0	0	0	0	0	0	0	Maximum is 3
Jorgensen Rule of 3 Violations	0	0	0	0	0	0	0	Maximum is 3

[a] <25 is poor and >500 is great.
[b] <25% is poor and >80% is high.

aminopropanthiol derivatives were obtained from ADME analysis in Table 3. These parameters provide information on the ability of 1,2-aminopropanthiol derivatives to be employed as drugs. The numerical values of these parameters are expected to be within a certain range. If the numerical values of the parameters are outside these ranges, 1,2-aminopropanthiol derivatives are not expected to be used as drugs in the future. Among these parameters; there are many parameters such as Solute Molecular Weight (Sağlık et al., 2019), Solute CdW Polar SA, logHERG (Sağlık et al., 2019), Apparent Caco-2 Permeability, QP log BB for brain/blood (Ertas et al., 2019), Apparent MDCK Permeability, Lipinski Rule of 5 Violations (Gunduz et al., 2020), Jorgensen Rule of 3 Violations (Jorgensen & Duffy, 2002; Lipinski et al., 1997), etc. These parameters provide information on how 1,2-aminopropanthiol derivatives behave in human metabolism. The Solute Molecular Weight parameter gives information about the weights of molecules. The Solute CdW Polar SA parameter is Van der Waals surface area of polar nitrogen and oxygen atoms and carbonyl carbon atoms. The logHERG parameter is IC_{50} value for blockage of HERG K^+ Channel. Apparent Caco-2 Permeability parameter is Caco 2 cells constitute a model for the gut-blood barrier. The QP log BB for brain/blood parameter is Predicted brain/blood partition coefficient for orally delivered drugs. Apparent MDCK Permeability parameter is MDCK cells are considered to be a good mimic for the blood–brain barrier. Lipinski Rule of 5 Violations and Jorgensen Rule of 3 Violations is a combination of many parameters.

4. Conclusion

In conclusion, 1,2-aminopropanthiol exhibits a wide biological activity and can function as potential medical molecules in the development of a drug. In this study, the derivatives of 1,2-aminopropanthiol (**1a–g**) were prepared with thiirane compounds with aromatic amines. Especially, the evaluation of the inhibitory efficacy of compound **1e** against acetyl and butyrylcholinesterase enzymes also indicates the anti-AD potential. The results were remarkably striking because of the much stronger inhibitory effect compared to standard drugs. In view of the obtained molecular docking results, the biological activity values of the molecules against the enzymes were found to be consistent with the experimental results. Interactions between molecule and enzyme were the most important factors affecting biological activity values. Additionally, antidiabetic and anticholinergic properties of these compounds were determined in this study.

Acknowledgements

This research was made possible by TUBITAK ULAKBIM, High Performance and Grid Computing Center (TR-Grid e-Infrastructure). S. Alwasel would like to extend his sincere appreciation to the Researchers Supporting Project (RSP-2019/59), King Saud University, Saudi Arabia, for support. This work was carried out with the support of the Science Development Fund under the President of Azerbaijan Republic-EIF/GAM-4-BGM-GIN-2017-3(29)-19/05/4-M-07.

Disclosure statement

The authors declare that there are no conflicts of interest.

Funding

This work is supported by the Scientific Research Project Fund of Sivas Cumhuriyet University under the project number RGD-020.

ORCID

Parham Taslimi http://orcid.org/0000-0002-3171-0633

References

Akıncıoğlu, A., Akıncıoğlu, H., Gülçin, İ., Durdagi, S., Supuran, C., & Göksu, S. (2015). Discovery of potent carbonic anhydrase and acetylcholine esterase inhibitors: Novel sulfamoylcarbamates and sulfamides derived from acetophenones. *Bioorganic & Medicinal Chemistry*, *23*(13), 3592–3602. https://doi.org/10.1016/j.bmc.2015.04.019

Aktas, A., Barut Celepci, D., Gok, Y., Taslimi, P., Akincioglu, H., & Gulcin, İ. (2020). A novel Ag-N-heterocyclic carbene complex bearing the hydroxyethyl ligand: Synthesis, characterization, crystal and spectral structures and bioactivity properties. Crystals, *10*(3), 171. https://doi.org/10.3390/cryst10030171

Atmaca, U., Yıldırım, A., Taslimi, P., Çelik, S., Gülçin, İ., Supuran, C., & Çelik, M. (2018). Intermolecular amination of allylic and benzylic alcohols leads to effective inhibitions of acetylcholinesterase enzyme and carbonic anhydrase I and II isoenzymes. *Journal of Biochemical and Molecular Toxicology*, *32*(8), e22173. https://doi.org/10.1002/jbt.22173

Behcet, A., Çağlılar, T., Celepci, D., Aktaş, A., Taslimi, P., Gök, Y., Aygün, M., Kaya, R., & Gülçin, İ. (2018). Synthesis, characterization and crystal structure of 2-(4-hydroxyphenyl)ethyl and 2-(4-nitrophenyl)ethyl substituted benzimidazole bromide salts: Their inhibitory properties against carbonic anhydrase and acetylcholinesterase. *Journal of Molecular Structure*, *1170*, 160–169. https://doi.org/10.1016/j.molstruc.2018.05.077

Bradford, M. M. (1976). A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Analytical Biochemistry*, *72*(1–2), 248–254. https://doi.org/10.1016/0003-2697(76)90527-3

Burmaoglu, S., Kazancioglu, E. A., Kaya, R., Kazancioglu, M., Karaman, M., Algul, O., & Gulcin, I. (2020). Synthesis of novel organohalogen chalcone derivatives and screening of their molecular docking study and some enzymes inhibition effects. *Journal of Molecular Structure*, *1208*, 127868. https://doi.org/10.1016/j.molstruc.2020.127868

Cheung, J., Gary, E., Shiomi, K., & Rosenberry, T. (2013). Structures of human acetylcholinesterase bound to dihydrotanshinone I and territrem B show peripheral site flexibility. *ACS Medicinal Chemistry Letters*, *4*(11), 1091–1096. https://doi.org/10.1021/ml400304w

Ekiz, M., Tutar, A., Ökten, S., Bütün, B., Koçyiğit, Ü., Taslimi, P., & Topçu, G. (2018). Synthesis, characterization, and SAR of arylated indenoquinoline-based cholinesterase and carbonic anhydrase inhibitors. *Archiv der Pharmazie*, *351*(9), 1800167. https://doi.org/10.1002/ardp.201800167

Ellman, G. L., Courtney, K. D., Andres, V., & Feather-Stone, R. M. (1961). A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochemical Pharmacology*, *7*, 88–95. https://doi.org/10.1016/0006-2952(61)90145-9

Ertas, M., Sahin, Z., Bulbul, E., Bender, C., Biltekin, S., Berk, B., Yurttas, L., Nalbur, A., Celik, H., & Demirayak, Ş. (2019). Potent ribonucleotide reductase inhibitors: Thiazole-containing thiosemicarbazone derivatives. *Archiv der Pharmazie*, *352*(11), 1900033. https://doi.org/10.1002/ardp.201900033

Friesner, R., Murphy, R., Repasky, M., Frye, L., Greenwood, J., Halgren, T., Sanschagrin, P., & Mainz, D. (2006). Extra precision Glide: Docking and scoring incorporating a model of hydrophobic enclosure for protein-ligand complexes. *Journal of Medicinal Chemistry*, *49*(21), 6177–6196. https://doi.org/10.1021/jm051256o

Frisch, M., Trucks, G., Schlegel, H., Scuseria, G., Robb, M., Cheeseman, J., Scalmani, G., Barone, V., Mennucci, B., Petersson, G., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H., Izmaylov, A., Bloino, J., Zheng, G., Sonnenberg, J., Hada, M., … Fox, D. (2009). *Gaussian 09, Revision D.01*. Wallingford, CT: Gaussian, Inc.

Göçer, H., Akincioğlu, A., Göksu, S., Gülçin, İ., & Supuran, C. (2015). Carbonic anhydrase and acetylcholinesterase inhibitory effects of carbamates and sulfamoylcarbamates. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *30*(2), 316–320. https://doi.org/10.3109/14756366.2014.928704

Göçer, H., Akıncıoğlu, A., Öztaşkın, N., Göksu, S., & Gülçin, İ. (2013). Synthesis, antioxidant, and antiacetylcholinesterase activities of sulfonamide derivatives of dopamine-related compounds. *Archiv der Pharmazie*, *346*(11), 783–792. https://doi.org/10.1002/ardp.201300228

Guillaume, M., Delphine, B., Annie-Claude, G., Jocelyne, L., & Mihaela, G. (2008). Efficient synthesis of primary 2-aminothiols from 2-aminoalcohols and methyldithioacetate. *Tetrahedron Letters*, *49*(46), 6553–6555.

Gulçin, İ., Taslimi, P., Aygün, A., Sadeghian, N., Bastem, E., Kufrevioglu, O. I., Turkan, F., & Şen, F. (2018). Antidiabetic and antiparasitic potentials: Inhibition effects of some natural antioxidant compounds on α-glycosidase, α-amylase and human glutathione S-transferase enzymes. *International Journal of Biological Macromolecules*, *119*, 741–746. https://doi.org/10.1016/j.ijbiomac.2018.08.001

Gulçin, İ., Taslimi, P., Huyut, Z., Safarova, L., Abbasova, M., Farzaliyev, V., Sujayev, A., Alwasel, S., Beydemir, Ş., & Supuran, C. (2017). Synthesis and biological evaluation of aminomethyl and alkoxymethyl derivatives as carbonic anhydrase, acetylcholinesterase and butyrylcholinesterase inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *32*(1), 1174–1182. https://doi.org/10.1080/14756366.2017.1368019

Gunduz, S., Budama-Kilinc, Y., Cakir-Koc, R., Zorlu, T., Bicak, B., Kokcu, Y., Ozel, A. E., & Akyuz, S. (2020). In silico design of AVP (4-5) peptide and synthesis, characterization and in vitro activity of chitosan nanoparticles. *Daru*, *28*(1), 139–157. https://doi.org/10.1007/s40199-019-00325-9

Jayarajan, R., Satheeshkumar, R., Kottha, T., Subbaramanian, S., Sayin, K., & Vasuki, G. (2020). Water mediated synthesis of 6-amino-5-cyano-2-oxo-N-(pyridin-2-yl)-4-(p-tolyl)-2H-[1,2′-bipyridine]-3-carboxamide and 6-amino-5-cyano-4-(4-fluorophenyl)-2-oxo-N-(pyridin-2-yl)-2H-[1,2′-bipyridine]-3-carboxamide - An experimental and computational studies with non-linear optical (NLO) and molecular docking analyses. *Spectrochimica Acta. Part A, Molecular and Biomolecular Spectroscopy*, *229*, 117861. https://doi.org/10.1016/j.saa.2019.117861

Jorgensen, W., & Duffy, E. (2002). Prediction of drug solubility from structure. *Advanced Drug Delivery Reviews*, *54*(3), 355–366. https://doi.org/10.1016/S0169-409X(02)00008-X

Karimov, A., Orujova, A., Taslimi, P., Sadeghian, N., Mammadov, B., Karaman, H. S., Farzaliyev, V., Sujayev, A., Tas, R., Alwasel, S., & Gulçin, İ. (2020). Novel functionally substituted esters based on sodium diethyldithiocarbamate derivatives: Synthesis, characterization, biological activity and molecular docking studies. *Bioorganic Chemistry*, *99*, 103762. https://doi.org/10.1016/j.bioorg.2020.103762

Kocyigit, U., Taşkıran, A., Taslimi, P., Yokuş, A., Temel, Y., & Gulçin, İ. (2017). Inhibitory effects of oxytocin and oxytocin receptor antagonist atosiban on the activities of carbonic anhydrase and acetylcholinesterase enzymes in the liver and kidney tissues of rats. *Journal of Biochemical and Molecular Toxicology*, *31*(11), e21972. https://doi.org/10.1002/jbt.21972

Košak, U., Knez, D., Coquelle, N., Brus, B., Pišlar, A., Nachon, F., Brazzolotto, X., Kos, J., Colletier, J. P., & Gobec, S. (2017). N-Propargylpiperidines with naphthalene-2-carboxamide or naphthalene-2-sulfonamide moieties: Potential multifunctional anti-Alzheimer's agents. *Bioorganic and Medicinal Chemistry*, *25*(2), 633–645. https://doi.org/10.1016/j.bmc.2016.11.032

Li, Y., Bai, B., Ye, J., Liu, H., Liu, Y., & Zhang, W. (2008). Reviews on preparation and determination of α-glucosidase inhibitor. *Food Sciences*, *29*, 617–619.

Lineweaver, H., & Burk, D. (1934). The determination of enzyme dissociation constants. *Journal of the American Chemical Society*, *56*(3), 658–666. https://doi.org/10.1021/ja01318a036

Lipinski, C., Lombardo, F., Dominy, B., & Feeney, P. (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*, *23*(1–3), 3–25. https://doi.org/10.1016/S0169-409X(96)00423-1

Maharramov, A., Huseynova, A., Gasımova, Y., Allahverdiyev, M., & Zalov, A. (2017). 1, 2- aminothioly as an anelyticaf reagent for extriction spectrophotometric determination of Copper (II). *International Journal of Innovative Science Engineering and Technology*, *4*, 174–180.

Maharramov, A., Kurbanova, M., Sadigova, A., Kaya, R., Taslimi, P., Sujayev, A., Farzaliyev, V., & Gulcin, İ. (2019). The synthesis and biological evaluation of optically active 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahidro-4H-chromen-3-carbonitriles in the presence of chiral organic catalysts: Antidiabetic and anticholinergics potentials. *Archiv der Pharmazie*, *352*(2), 1800317. https://doi.org/10.1002/ardp.201800317

Mamedova, G., Mahmudova, A., Mamedov, S., Erden, Y., Taslimi, P., Tüzün, B., Tas, R., Farzaliyev, V., Sujayev, A., Alwasel, S., & Gulçin, İ. (2019). Novel tribenzylaminobenzolsulphonylimine based on their pyrazine and pyridazines: Synthesis, characterization, antidiabetic, anticancer, anticholinergic, and molecular docking studies. *Bioorganic Chemistry*, *93*, 103313. https://doi.org/10.1016/j.bioorg.2019.103313

Mammadov, S., Mahmudova, A., Shakhgeldieva, L., Sujayev, A., Ladokhina, N., Zeynalova, L., & Mammadova, S. (2019). Synthesis and biological activity of new sulfonamides. *New Materials, Compounds and Applications*, *3*, 77–86.

Massoulié, J., Pezzementi, L., Bon, S., Krejci, E., & Vallette, F. M. (1993). Molecular and cellular biology of cholinesterases. *Progress in Neurobiology*, *41*(1), 31–91. https://doi.org/10.1016/0301-0082(93)90040-Y

Sağlık, B., Çavuşoğlu, B., Osmaniye, D., Levent, S., Çevik, U., Ilgın, S., Özkay, Y., Kaplancıklı, Z., & Öztürk, Y. (2019). In vitro and in silico evaluation of new thiazole compounds as monoamine oxidase inhibitors. *Bioorganic Chemistry*, *85*, 97–108. https://doi.org/10.1016/j.bioorg.2018.12.019

Sağlık, B., Çevik, U., Osmaniye, D., Levent, S., Çavuşoğlu, B., Demir, Y., Ilgın, S., Özkay, Y., Koparal, A., Beydemir, Ş., & Kaplancıklı, Z. (2019). Synthesis, molecular docking analysis and carbonic anhydrase I-II inhibitory evaluation of new sulfonamide derivatives. *Bioorganic Chemistry*, *91*, 103153. https://doi.org/10.1016/j.bioorg.2019.103153

Sastry, G., Adzhigirey, M., Day, T., Annabhimoju, R., & Sherman, W. (2013). Protein and ligand preparation: Parameters, protocols, and influence on virtual screening enrichments. *Journal of Computer-Aided Molecular Design*, *27*(3), 221–234. https://doi.org/10.1007/s10822-013-9644-8

Sayin, K., & Karakaş, D. (2017). Determination of structural, spectral, electronic and biological properties of tosufloxacin boron complexes and investigation of substituent effect. *Journal of Molecular Structure*, *1146*, 191–197. https://doi.org/10.1016/j.molstruc.2017.05.130

Sayin, K., & Karakaş, D. (2018a). Investigation of structural, electronic properties and docking calculations of some boron complexes with norfloxacin: A computational research. *Spectrochimica Acta. Part A, Molecular and Biomolecular Spectroscopy*, *202*, 276–283. https://doi.org/10.1016/j.saa.2018.05.055

Sayin, K., & Karakaş, D. (2018b). Quantum chemical investigation of levofloxacin-boron complexes: A computational approach. *Journal of Molecular Structure*, *1158*, 57–65. https://doi.org/10.1016/j.molstruc.2018.01.016

Sayin, K., & Üngördü, A. (2018). Investigation of anticancer properties of caffeinated complexes via computational chemistry methods. *Spectrochimica Acta. Part A, Molecular and Biomolecular Spectroscopy*, *193*, 147–155. https://doi.org/10.1016/j.saa.2017.12.013

Sayin, K., & Üngördü, A. (2019). Investigations of structural, spectral and electronic properties of enrofloxacin and boron complexes via quantum chemical calculation and molecular docking. *Spectrochimica Acta. Part A, Molecular and Biomolecular Spectroscopy*, *220*, 117102. https://doi.org/10.1016/j.saa.2019.05.007

Schrodinger, L. (2019). Small-Molecule Drug Discovery Suite 2019-4, 2017.

Schrödinger Release 2020-1. (2020). QikProp, Schrödinger, LLC, New York, NY, 2020.

Sever, B., Altıntop, M., Özdemir, A., Tabanca, N., Estep, A., Becnel, J., & Bloomquist, J. (2019). Biological evaluation of a series of benzothiazole derivatives as mosquitocidal agents. *Open Chemistry*, *17*(1), 288–294. https://doi.org/10.1515/chem-2019-0027

Subhani, S., Jayaraman, A., & Jamil, K. (2015). Homology modelling and molecular docking of MDR1 with chemotherapeutic agents in non-small cell lung cancer. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*, *71*, 37–45. https://doi.org/10.1016/j.biopha.2015.02.009

Sujayev, A., Maharramova, G., Taslimi, P., Farzaliyev, V., Durmaz, L., & Gulçin, İ. (2018). Synthesis, characterization, antioxidant, antidiabetic, anticholinergic, and anti-epileptic properties of novel N-substituted tetrahydropyrimidines based on phenylthiourea. *Journal of Biochemical and Molecular Toxicology*, *32*(12), e22221. https://doi.org/10.1002/jbt.22221

Tan, T., Spadiut, O., Gandini, R., Haltrich, D., & Divne, C. (2014). Structural basis for binding of fluorinated glucose and galactose to trametes multicolor pyranose 2-oxidase variants with improved galactose conversion. *PLoS One*, *9*(1), e86736. https://doi.org/10.1371/journal.pone.0086736

Tao, Y., Zhang, Y., Cheng, Y., & Wang, Y. (2013). Rapid screening and identification of α-glucosidase inhibitors from mulberry leaves using enzyme-immobilized magnetic beads coupled with HPLC/MS and NMR. *Biomedical Chromatography*, *27*(2), 148–155. https://doi.org/10.1002/bmc.2761

Taslimi, P., Aslan, H. E., Demir, Y., Oztaskin, N., Maraş, A., Gulçin, İ., Beydemir, S., & Goksu, S. (2018). Diarylmethanon, bromophenol and diarylmethane compounds: Discovery of potent aldose reductase, α-amylase and α-glycosidase inhibitors as new therapeutic approach in diabetes and functional hyperglycemia. *International Journal of Biological Macromolecules*, *119*, 857–863. https://doi.org/10.1016/j.ijbiomac.2018.08.004

Taslimi, P., Erden, Y., Mamedov, S., Zeynalova, L., Ladokhina, N., Tas, R., Tuzun, B., Sujayev, A., Sadeghian, N., Alwasel, S., & Gulcin, I. (2020). The biological activities, molecular docking studies, and anticancer effects of 1-Arylsuphonylpyrazole derivatives. *Journal of Biomolecular Structure and Dynamics*. https://doi.org/10.1080/07391102.2020.1763838.

Taslimi, P., Sujayev, A., Mamedova, S., Kalın, P., Gulçin, İ., Sadeghian, N., Beydemir, S., Kufrevioglu, O. I., Alwasel, S. H., Farzaliyev, V., & Mamedov, S. (2017). Synthesis and bioactivity of several new hetaryl sulfonamides. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *32*(1), 137–145. https://doi.org/10.1080/14756366.2016.1238367

Türkan, F., Huyut, Z., Taslimi, P., & Gülçin, İ. (2018). The in vivo effects of cefazolin, cefuroxime, and cefoperazon on the carbonic anhydrase in different rat tissues. *Journal of Biochemical and Molecular Toxicology*, *32*(3), e22041. https://doi.org/10.1002/jbt.22041

Türker, F., Celepci, D., Aktaş, A., Taslimi, P., Gök, Y., Aygün, M., & Gülçin, İ. (2018). Meta-cyanobenzyl substituted benzimidazolium salts: Synthesis, characterization, crystal structure and carbonic anhydrase, α-glycosidase, butyrylcholinesterase, and acetylcholinesterase inhibitory properties. *Archiv der Pharmazie*, *351*(7), 1800029. https://doi.org/10.1002/ardp.201800029

Tüzün, B. (2020). Investīgatïon of pyrazoly derivatives schïff base līgands and theïr metal complexes used as anti-cancer drug. *Spectrochimica Acta. Part A, Molecular and Biomolecular Spectroscopy*, *227*, 117663https://doi.org/10.1016/j.saa.2019.117663

Tüzün, B., & Kaya, C. (2018). Investigation of DNA–RNA molecules for the efficiency and activity of corrosion inhibition by DFT and molecular docking. *Journal of Bio-and Tribo-Corrosion*, *4*, 69.

Tüzün, B., & Saripinar, E. (2020). Molecular docking and 4D-QSAR model of methanone derivatives by electron conformational-genetic algorithm method. *Journal of the Iranian Chemical Society*, *17*(5), 985–1000. https://doi.org/10.1007/s13738-019-01835-8

Üngördü, A., & Sayin, K. (2019). Quantum chemical calculations on sparfloxacin and boron complexes. *Chemical Physics Letters*, *733*, 136677. https://doi.org/10.1016/j.cplett.2019.136677

Verpoorte, J. A., Mehta, S., & Edsall, J. T. (1967). Esterase activities of human carbonic anhydrases B and C. *Journal of Biological Chemistry*, *242*, 4221–4229.

Vijayaraghavan, R., Gautam, A., & Sharma, M. (2009). CHAPTER 60 - Medical countermeasures and other therapeutic strategies for sulfur mustard toxicity. In R. C. Gupta (ed.), *Handbook of toxicology of chemical warfare agents* (pp. 897–918). New York: Academic Press. https://doi.org/10.1016/B978-012374484-5.00060-2

Wang, J.-L., Li, L., Hu, M.-B., Wu, B., Fan, W.-X., Peng, W., Wei, D.-N., & Wu, C.-J. (2019). In silico drug design of inhibitor of nuclear factor kappa B kinase subunit beta inhibitors from 2-acylamino-3-aminothienopyridines based on quantitative structure-activity relationships and molecular docking. *Computational Biology and Chemistry*, *78*, 297–305. https://doi.org/10.1016/j.compbiolchem.2018.12.021

Yiğit, B., Yiğit, M., Barut Celepci, D., Gök, Y., Aktaş, A., Aygün, M., Taslimi, P., & Gülçin, İ. (2018). Novel benzylic substituted imidazolinium, tetrahydropyrimidinium and tetrahydrodiazepinium salts: Potent carbonic anhydrase and acetylcholinesterase inhibitors. *ChemistrySelect*, *3*(27), 7976–7982. https://doi.org/10.1002/slct.201801019

Yiğit, B., Yiğit, M., Taslimi, P., Gök, Y., & Gülçin, İ. (2018). Schiff bases and their amines: Synthesis and discovery of carbonic anhydrase and acetylcholinesterase enzymes inhibitors. *Archiv der Pharmazie*, *351*(9), 1800146. https://doi.org/10.1002/ardp.201800146Ci

Yin, Z., Zhang, W., Feng, F., Zhang, Y., & Kang, W. (2014). α-Glucosidase inhibitors isolated from medicinal plants. *Food Science and Human Wellness*, *3*(3–4), 136–174. https://doi.org/10.1016/j.fshw.2014.11.003

Zengin, M., Genc, H., Taslimi, P., Kestane, A., Guclu, E., Ogutlu, A., Karabay, O., & Gulçin, İ. (2018). Novel thymol bearing oxypropanolamine derivatives as potent some metabolic enzyme inhibitors - Their antidiabetic, anticholinergic and antibacterial potentials. *Bioorganic Chemistry*, *81*, 119–126. https://doi.org/10.1016/j.bioorg.2018.08.003