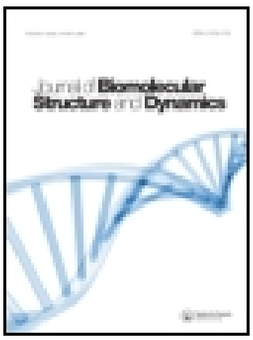

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Benzenesulfonamide derivatives as potent acetylcholinesterase, α-glycosidase, and glutathione S-transferase inhibitors: biological evaluation and molecular docking studies

Parham Taslimi[a], Mesut Işık[b], Fikret Türkan[c], Mustafa Durgun[d], Cüneyt Türkeş[e], İlhami Gülçin[f] and Şükrü Beydemir[g,h]

[a]Department of Biotechnology, Faculty of Science, Bartın University, Bartın, Turkey; [b]Department of Pharmacy Services, Vocational School of Health Services, Harran University, Şanlıurfa, Turkey; [c]Department of Medical Services and Techniques, Vocational School of Health Services, Iğdır University, Iğdır, Turkey; [d]Department of Chemistry, Faculty of Arts and Sciences, Harran University, Şanlıurfa, Turkey; [e]Department of Biochemistry, Faculty of Pharmacy, Erzincan Binali Yıldırım University, Erzincan, Turkey; [f]Department of Chemistry, Faculty of Sciences, Atatürk University, Erzurum, Turkey; [g]Department of Biochemistry, Faculty of Pharmacy, Anadolu University, Eskişehir, Turkey; [h]The Rectorate of Bilecik Şeyh Edebali University, Bilecik, Turkey

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ABSTRACT

Sulfonamide derivatives exhibit a wide biological activity and can function as potential medical molecules in the development of a drug. Studies have reported that the compounds have an effect on many enzymes. In this study, the derivatives of amine sulfonamide (**1i-11i**) were prepared with reduced imine compounds (**1-11**) with $NaBH_4$ in methanol. The synthesized compounds were fully characterized by spectral data and analytical. The effect of the synthesized derivatives on acetylcholinesterase (AChE), glutathione S-transferase (GST) and α-glycosidase (α-GLY) enzymes were determined. For the AChE and α-GLY, the most powerful inhibition was observed on **10** and **10i** series with K_I value in the range 2.26 ± 0.45–3.57 ± 0.97 and 95.73 ± 13.67–102.45 ± 11.72 μM, respectively. K_I values of the series for GST were found in the range of 22.76 ± 1.23–49.29 ± 4.49. Finally, the compounds have a stronger inhibitor in lower concentrations by the attachment of functional electronegative groups such as two halogens (-Br and -Cl), -OH to the benzene ring and $-SO_2NH_2$. The crystal structures of AChE, α-GLY, and GST in complex with selected derivatives **4** and **10** show the importance of the functional moieties in the binding modes within the receptors.

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α-Glycosidase; acetylcholinesterase; glutathione S-transferase; molecular docking; sulfonamide derivatives

1. Introduction

Primary sulfonamides of type RSO_2NH_2 constitute an important class of drugs. Sulfonamides are one of the oldest antimicrobial drugs and have been used for the treatment of humans and animals for nearly 80 years. It is clear that most of the drugs used in medical chemistry have SO_2NH_2 group in their structure. It should also be noted that these drugs are aromatic/heterocyclic sulfonamides. Examples include sulfamethoxazole as antimicrobial sulfonamides, acetazolamide as carbonic anhydrase inhibitors, glibenclamide and glipizide as sulfonylureas, selective serotonin receptor agonists as sumatriptan, celecoxib as selective cyclo-oxygenase COX-2 inhibitor. Sulfonamide derivatives exhibit a wide biological activity and can function as potential medical molecules in the development of a drug. Their derivatives have very important different pharmacological properties such as anti-inflammatory, anti-bacterial, anti-tumor and anti-HIV activities, enzymatic inhibition towards the cyclooxygenase (COX) enzymes COX-1 and COX-2, and the carbonic anhydrase (CA) isozymes (Fahim & Ismael, 2019; Fahim & Shalaby, 2019; Fares et al. 2020; Hameed et al., 2017; Lin et al., 2008; Saluja et al., 2014; Supuran et al., 2003).

Diabetes mellitus (DM) is a metabolic disorder associated with complications (Türkeş, Demir, et al., 2019), like retinopathy, nephropathy, diabetic neuropathy, cardiomyopathy, etc. Diabetes, known for its disruptive effects, has been known to cause inflammation and oxidative stress at hippocampus, leading to neurological complications and neurodegeneration (Alipour et al., 2012; Saravanan & Ponmurugan, 2012). The cognitive disorder and hippocampal synaptic neurotransmission occur as a result of diabetes with cholinergic neurons dysfunction (Patel et al., 2015; Sherin et al., 2012). The cholinergic neuron dysfunction is characterized by the change in the activity of acetylcholinesterase (AChE) and cholineacetyltransferase (ChAT) enzyme. The AChE has been carried great importance for understanding and illuminating the most vital mechanisms responsible for the proper cholinergic function (Kuhad et al., 2008; Schmatz et al., 2009). Interestingly, AChE is also associated with various complications and oxidative stress involved in the progression and pathogenesis of central neural disorders like diabetes

CONTACT Şükrü Beydemir sukrubeydemir@anadolu.edu.tr; beydemirs@gmail.com Department of Biochemistry, Faculty of Pharmacy, Anadolu University, Eskişehir, 26470, Turkey

mellitus, neurodegenerative diseases (Alzheimer's disease, etc.) and stroke (Kamboj et al., 2008; Kuhad et al., 2008; Mushtaq et al. 2014). Many studies have reported that new benzene sulfonamides containing 1,3,5-triazine and 1,3-diaryltriazene structural motifs have inhibition effects on AChE, α-glycosidase (α-GLY) and carbonic anhydrase enzymes (Işık, 2020; Lolak et al., 2020).

The α-GLY inhibitor compounds are used as oral antidiabetic drugs for the therapy of type 2 diabetes. They act by hampering the digestion of carbohydrate molecules such as starch. The carbohydrates typically turn into simple sugars that are absorbed through the intestine (Topal, 2019). These inhibitors act as competitive inhibitors of the α-GLY required for carbohydrate digestion (Bhandari et al., 2008; Gao et al., 2008). The α-GLYs hydrolyze carbohydrates to glucose and other monosaccharide molecules in the small intestine. The inhibition activity of these enzymatic systems helps to reduce carbohydrate digestion. Fewer amounts of glucose are absorbed because carbohydrates do not break down into glucose molecules. In diabetic patients, the short-term effect of these drugs is by inhibiting the enzyme by lowering high blood glucose levels (Adisakwattana et al., 2009; Shinde et al., 2008). The currently used synthetic enzyme inhibitors cause gastrointestinal side effects such as abdominal bloating, diarrhea, abdominal bloating and so natural α-amylase and α-GLY inhibitors from dietary plants can be utilized as an effective treatment for use post-meal hyperglycemia treatment with minimal side effects (Jung et al., 2006).

Glutathione S-transferase (GST) is one of the detoxification enzymes group (Verma et al., 2019), and it is the most exist and important enzyme groups in the liver. GST enzyme families provide the addition of glutathiones to oxidative stress products due to their detoxifying effects (Selim et al., 2019; Türkan, 2019). The detoxification of the xenobiotic compounds of GST enzymes takes place thanks to the binding of -SH group present antioxidants GSH to hydrophilic compounds of the substrate present (Balcı et al., 2019). Various factors such as environmental factors, DM, and cancer cause oxidative stress in the body. As a result, the accumulation of free radicals in the tissues increases rapidly. As a result of these conditions, especially tissue damage occurs, and the activity of GST enzyme is reduced (Turkan, 2019; Türkan, 2018).

It is known that diabetic animals and Alzheimer patients have different levels of enzyme activity and oxidative damage occurs in each tissue or cell (Bhor et al., 2004; Işık, 2017; Kakkar et al., 1995). Therefore, it is important to determine the drugs that decrease or maintain the activity of important metabolic enzymes such as AChE, α-GLY, and GST. In this study, the effects of sulfonamide derivatives (**1**-**11**, and **1i**-**11i**) that we synthesized in our previous studies on AChE, α-GLY and GST were investigated, and then determined kinetics properties of its. Molecular docking scores and binding modes of some derivatives with the receptors were determined by molecular docking. Moreover, the relationship between the structure and activity of the compounds was evaluated.

2. Materials and methods

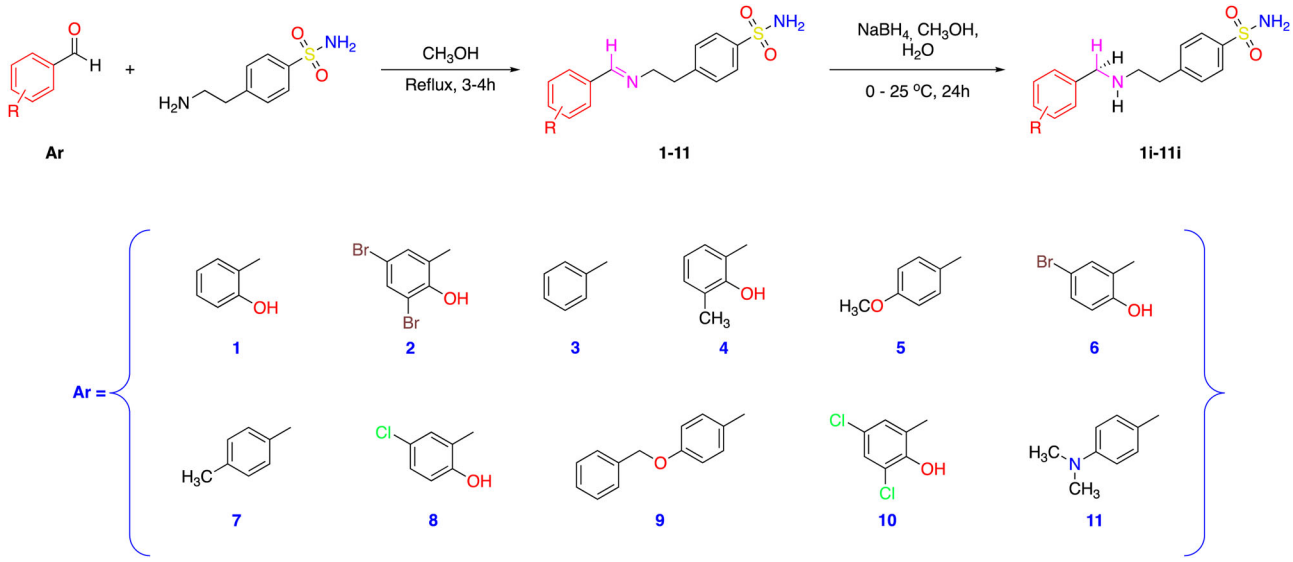
All the chemicals were obtained from commercial suppliers (Sigma-Aldrich, Merck) and used without further purification.

2.1. General method for the synthesis of imine derivatives (1-11), and amine derivatives (1i-11i)

Sulfonamide derivatives (**1**-**11**) and (**1i**-**11i**) were resynthesized and characterized as previously described (Scheme 1) (Durgun et al., 2015). Briefly, *First route;* for the synthesis of imine derivatives (**1**-**11**), the benzaldehyde derivatives (1.0 mmol) in 30 mL of MeOH were added dropwise to the appropriate 4-(2-aminoethyl)benzenesulfonamide (for **1**-**11**) (1.0 mmol) previously dissolved in 30 mL of MeOH. A catalytic amount of formic acid was added to the reaction medium and refluxed for 3–4 h. After evaporation of the solvent, the resulting solid was washed with ice-cold ethanol. The final products were recrystallized from ethanol/methanol and dried under vacuum at room temperature. The imine derivatives (**1**-**11**) obtained are 4-(2-((2-Hydroxybenzylidene)amino) ethyl)benzenesulfonamide **(1)**, 4-(2-((3,5-Dibromo-2-hydroxybenzylidene)amino)ethyl)benzenesulfonamide **(2),** 4-(2-((benzylidene)amino)ethyl)benzenesulfonamide **(3),** 4-(2-((2-hydroxy-3-methylbenzylidene)amino)ethyl)benzenesulfonamide **(4),** 4-(2-((4-methoxybenzylidene)amino)ethyl)benzenesulfonamide **(5),** 4-(2-((5-bromo-2-hydroxybenzylidene)amino)ethyl)benzenesulfonamide **(6),** 4-(2-((4-methylbenzylidene)amino)ethyl)-benzenesulfonamide **(7),** 4-(2-((5-chloro-2-hydroxybenzylidene) amino)ethyl)benzenesulfonamide **(8),** 4-(2-((4-(benzyloxy)benzylidene)amino)ethyl)benzenesulfonamide **(9),** 4-(2-((3,5-dichloro-2-hydroxybenzylidene)amino)ethyl)benzenesulfonamide **(10),** and 4-(2-((4-(dimethylamino)benzylidene)amino)ethyl)benzenesulfonamide **(11),** respectively.

Second route; for the synthesis of amine derivatives (**1i**-**11i**), sodium borohydride ($NaBH_4$) (6.0 mmol) was added portionwise to imino-compounds (**1**-**11**) (1.0 mmol) in methanol (30 mL) at 0 °C. The mixture was stirred at room temperature for 24 h. Then half of the solvent in the reaction mixture was evaporated and ice water was poured onto it. The resulting fine white precipitate was filtered and recrystallized from absolute dichloromethane and dried under vacuum. The amine derivatives (**1i**-**11i**) obtained are 4-(2-[(2-hydroxybenzyl) amino]ethyl)benzenesulfonamide (**1i**), 4-(2-[(3,5-dibromo-2-hydroxybenzyl)amino]ethyl)benzenesulfonamide (**2i**), 4-(2-(benzylamino)ethyl)benzenesulfonamide (**3i**), 4-(2-[(2-hydroxy-3-methylbenzyl)amino]ethyl)benzenesulfonamide (**4i**), 4-(2-[(4-methoxybenzyl)amino]ethyl)benzenesulfonamide (**5i**), 4-(2-[(5-bromo-2-hydroxybenzyl)amino]ethyl)benzenesulfonamide (**6i**), 4-(2-[(4-methylbenzyl)amino]ethyl)benzenesulfonamide (**7i**), 4-(2-[(5-chloro-2-hydroxybenzyl)amino]ethyl)benzenesulfonamide (**8i**), 4-(2-[(4-(benzyloxy)benzyl)amino]ethyl)benzenesulfonamide (**9i**), 4-(2-[(3,5-dichloro-2-hydroxybenzyl)amino]ethyl)benzenesulfonamide (**10i**), 4-(2-[(4-(dimethylamino)benzyl)amino]ethyl)benzenesulfonamide (**11i**), respectively.

Experimental details for imine (**1**-**11**) and amine (**1i**-**11i**) derivatives, data, and spectral analysis of sulphonamide



Scheme 1. The synthetic routes of sulfonamide derivatives.

derivatives have been presented in our previous studies (Durgun et al., 2015).

2.2. Measurement of metabolic enzymes activities

The AChE inhibitory effect of the compounds was determined according to the procedure of Ellman *et al.* (Ellman et al., 1961; Tripathy et al., 2017). It was recorded spectrophotometrically at 412 nm using acetylthiocholine iodide as substrate for the enzymatic reaction according to previous studies. 5,5 Dithio-bis (2-nitro-benzoic) acid compound was used to measure AChE activity (Gündoğdu et al., 2019; Işık, Demir, et al., 2020). In addition, the inhibitory effect of these compounds on α-GLY enzyme activity was carried out using the p-nitrophenyl-D-glycopyranoside (p-NPG) substrate according to the analysis of Tao et al. (2013). First, 200 mL of phosphate buffer was mixed with 40 mL of homogenate solution in phosphate buffer (0.15 U/mL, pH 7.4). After preincubation, 50 µL p-NPG in phosphate buffer (5 mM, pH 7.4) was added and incubated again at 30 °C. Absorbances were measured spectrophotometrically at 405 nm according to previous studies (Taslimi et al. 2018; Taslimi & Gulçin, 2017; Zengin et al., 2018). The GST activity was measured with using CDNB as a key substrate compound. The method system included a phosphate buffer, GSH and CDNB (Gulçin et al., 2018).

2.3. In vitro inhibition studies

The inhibition effects of resynthesized sulfonamide derivatives (**1**-**11** and **1i**-**11i**) were determined with at least five different inhibitor concentrations on AChE, α-GLY, and GST. IC_{50}s of the synthesized analogues were calculated from Activity (%)–[Compound] graphs for each derivative (Akbaba et al., 2013; Demir, 2019; Türkeş et al., 2013). The inhibition types and K_I values were found by Lineweaver and Burk's curves (Demir, 2020; Türkeş et al., 2014). The experiments were repeated in triplicate for each compound concentration used, as in our previous studies (Türkeş et al., 2015, 2016).

2.4. Molecular docking study

For the present study, the 3D X-ray protein structures of the receptors with the inclusion of AChE (PDB code: 4EY5, 2.30 Å), α-GLY (PDB code: 5NN8, 2.45 Å), and GST (PDB code: 2GSS, 1.90 Å) were retrieved from the Protein Data Bank (Türkeş, Beydemir, et al., 2019). The refined enzymes were subjected to energy minimization by the OPLS3e force field (Sastry et al., 2013) using the Protein Preparation Wizard (Türkeş & Beydemir, 2020) of the Schrödinger Suite 2019-2 (Schrödinger, LLC, New York, NY, 2019). The 2D structures of the ligands (**1-11** and **1i**-**11i**) were drawn using ChemDraw (Durgun et al., 2020) and prepared by the LigPrep module (Beydemir et al., 2019) with default settings using the OPLS3e force field (Türkeş, 2019b) with Epik (Demir et al., 2020). Receptor Grid Generation panel (Türkeş, 2019c) in the Maestro module was used to prepare the docking grid. The docking calculations were carried out in the SP (standard precision) mode (Türkeş, Arslan, et al., 2019; Türkeş et al., 2020) of Schrodinger Glide (Türkeş, 2019a). Also, the Prime MMGBSA module (Işık, Beydemir, et al., 2020; Istrefi et al., 2020) was used to calculate binding free energies corresponding with the selected ligands. 3D and 2D representations of the ligand-receptor interactions are summarized in Figures 1–3.

3. Results and discussion

3.1. Chemistry

The synthetic routes of sulfonamide derivatives were shown in Scheme 1. Schiff base derivatives (containing sulphonamide group) **1-11** were obtained by the condensation reaction of the 4-aminobenzenesulfonamide and 4-(2-aminoethyl)benzenesulfonamide with the corresponding aromatic aldehyde in methanol with catalytic amounts of formic acid. The derivatives of amine

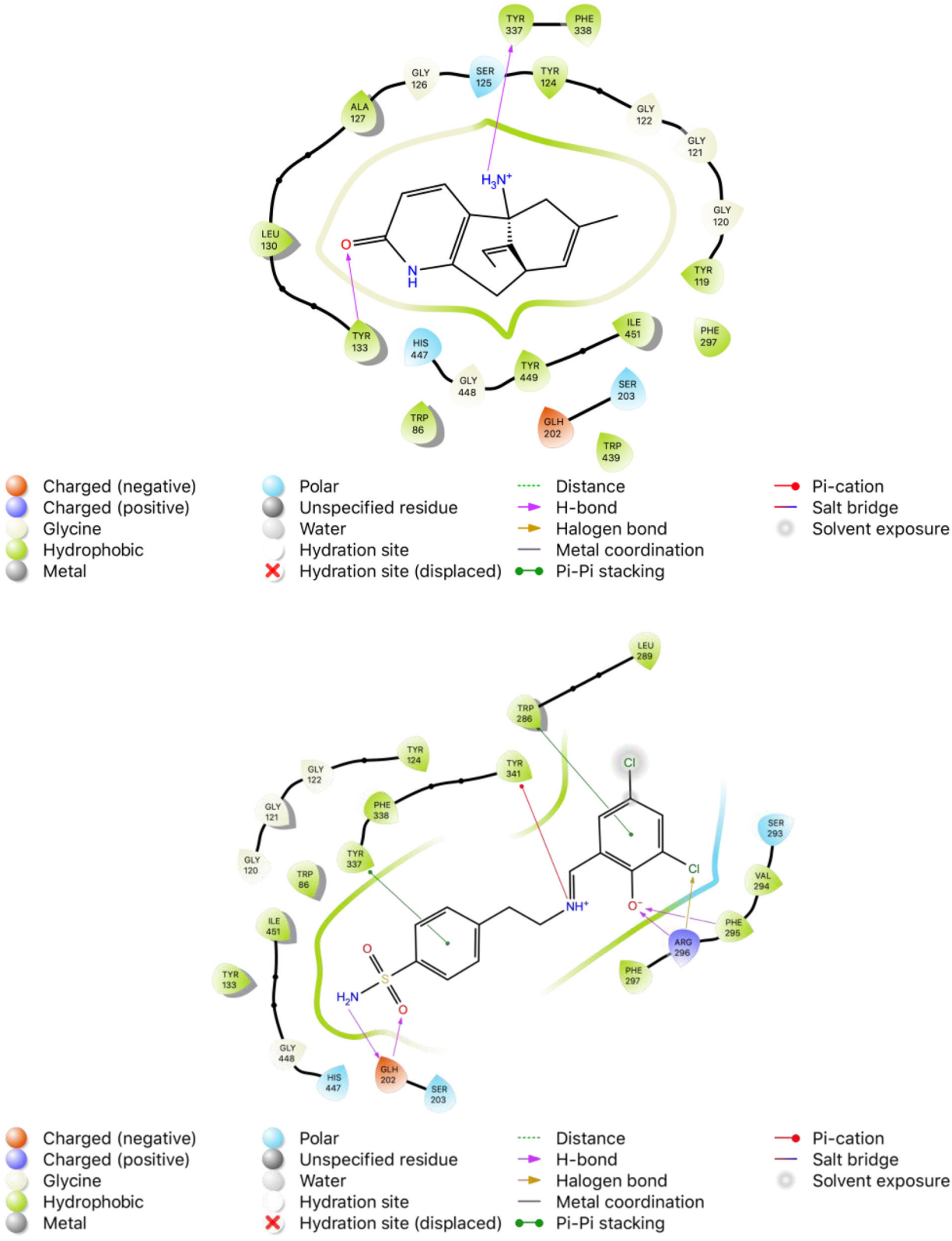


Figure 1. 2D binding modes of native ligand huperzine A (HUP) and compound **10** in the active site of AChE (PDB ID: 4EY5), respectively.

sulfonamide (**1i**-**11i**) were prepared by reduced imine compounds (**1**-**11**) with $NaBH_4$ in methanol. In the study, among the aromatic aldehyde derivatives used for the synthesis of the sulphonamide derivatives were 2-hydroxybenzaldehyde **(1)**, 3,5-dibromo-2-hydroxybenzaldehyde (**2**), benzaldehyde (**3**), 2-hydroxy-3-methylbenzaldehyde (**4**), 4-methoxybenzaldehyde (**5**), 5-bromo-2-hydroxybenzaldehyde (**6**), 4-methylbenzaldehyde (**7**), 5-chloro-2-hydroxybenzaldehyde (**8**), 4-(benzyloxy)benzaldehyde (**9**), 3,5-dichloro-2-hydroxybenzaldehyde (**10**), 4-(dimethylamino) benzaldehyde (**11**).

All the synthesized compounds were fully characterized by spectral data and analytical and all data are consistent

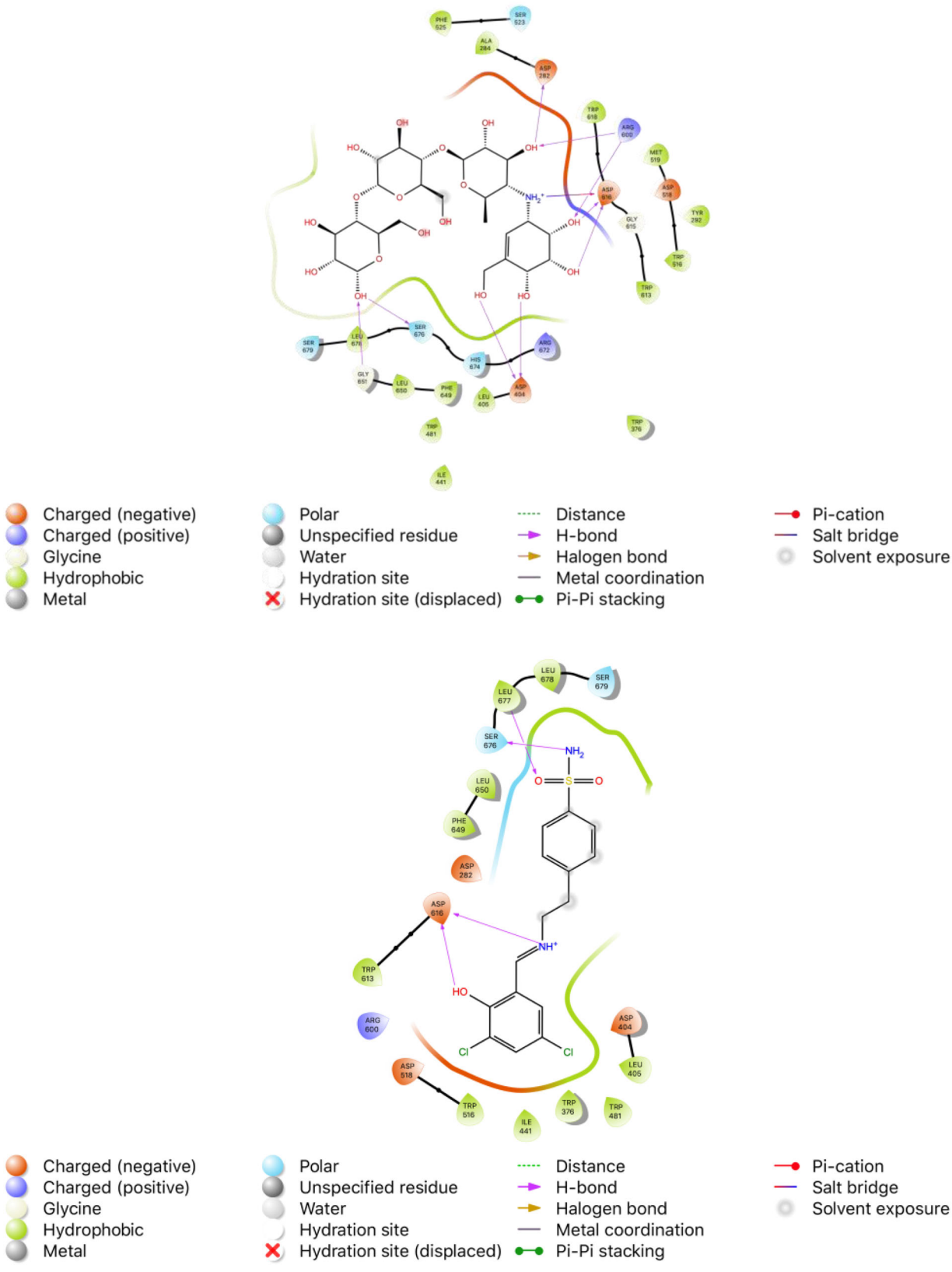


Figure 2. 2D binding modes of native ligand α-acarbose (ACR) and compound **10** in the active site of α-GLY (PDB ID: 5NN8), respectively.

with the literature. When the spectra are examined, data explaining the structure of both imine compounds and amine compounds can be seen. Experimental details for imine (**1**-**11**) and amine (**1i**-**11i**) derivatives, data, and spectral analysis of synthesized sulphonamide derivatives have been presented in our previous studies (Durgun et al., 2014, 2015, 2016).

In general, the FT-IR spectrum of imine compounds is characterized by the presence of a strong band at about 1635 cm^{-1} due to stretching of the C = N bond, while this

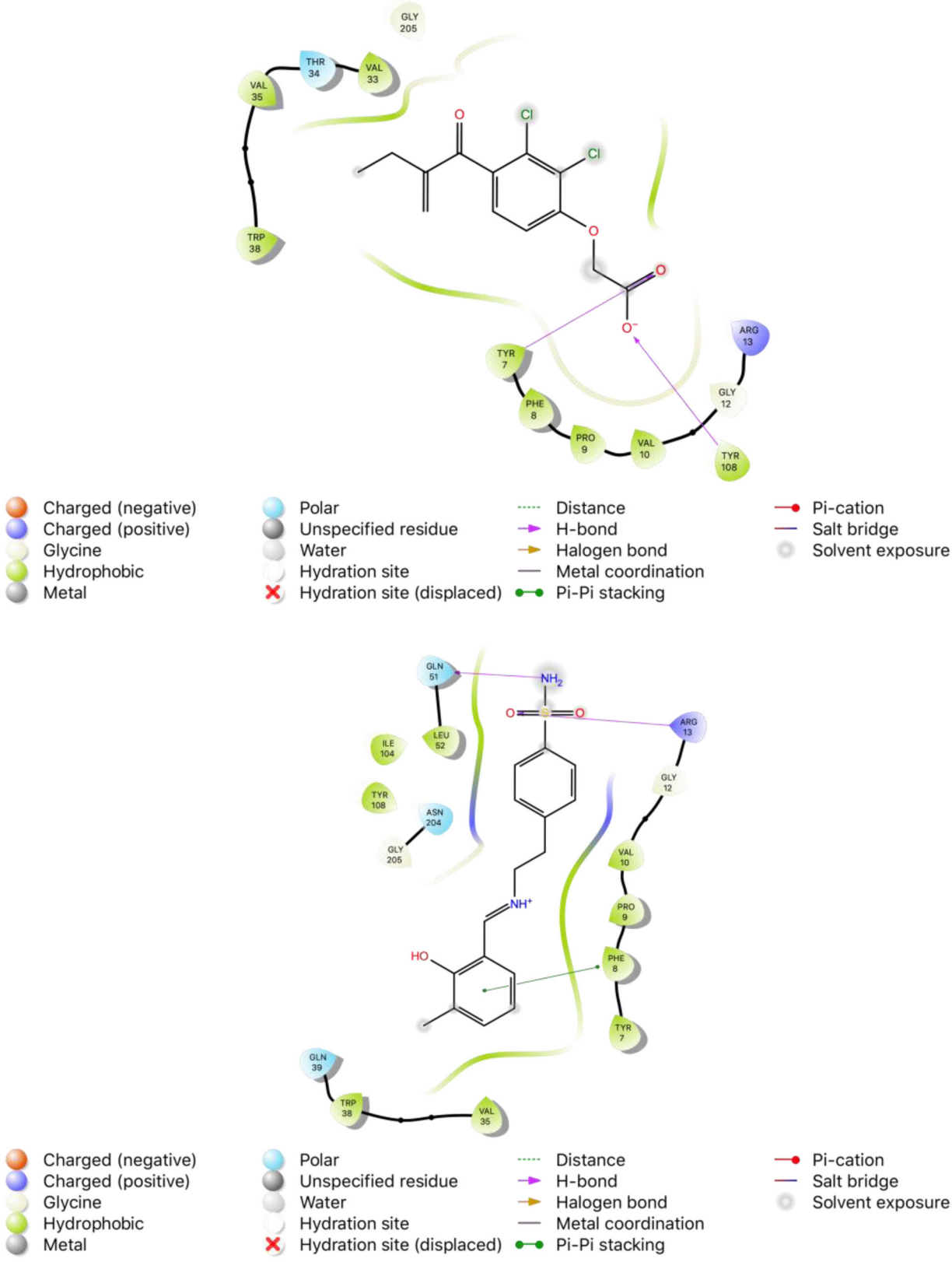


Figure 3. 2D binding modes of native ligand ethacrynic acid (EAA) and compound **4** in the active site of GST (PDB ID: 2GSS), respectively.

strong band was not observed for amine compounds. In addition, in the ^{1}H NMR spectrum of imine compounds, a single peak was observed at about 8.50 ppm attributed to the chemical shift of azomethine (CH = N), while this peak (CH = N) was not observed in the ^{1}H NMR spectrum of amine compounds. The amine compounds showed a new peak at about 3.75 ppm due to the presence of the -CH_2- group. In the ^{13}C-NMR spectrum, signals at about 163 ppm were attributed to the azomethine group (CH = N) for amine derivatives. These signals are not observed for amine derivatives. Also,

Table 1. IC_{50} values of compounds (**1**-**11**) and (**1i**-**11i**).

Compound ID	AChE (IC_{50}, μM)	r^2	α-GLY (IC_{50}, μM)	r^2	GST (IC_{50}, μM)	r^2
1	47.04	0.9485	374.90	0.9584	34.22	0.9682
1i	53.84	0.9730	401.54	0.9745	30.16	0.9542
2	27.93	0.9772	285.94	0.9084	39.64	0.9812
2i	24.66	0.9889	277.31	0.9783	52.15	0.9802
3	63.77	0.9622	684.04	0.9627	29.42	0.9457
3i	84.82	0.9424	674.93	0.9714	29.04	0.9892
4	105.63	0.9689	1054.80	0.9488	30.12	0.9904
4i	90.27	0.9733	994.84	0.9917	31.97	0.9588
5	95.52	0.9810	694.11	0.9904	38.03	0.9780
5i	74.83	0.9903	734.19	0.9788	38.29	0.9876
6	23.67	0.9508	384.06	0.9309	41.08	0.9612
6i	19.63	0.9745	362.28	0.9694	38.78	0.9852
7	39.78	0.9644	513.04	0.9783	39.66	0.9841
7i	43.72	0.9278	524.88	0.9905	50.43	0.9436
8	20.85	0.9738	304.82	0.9490	55.48	0.9908
8i	19.26	0.9384	298.55	0.9388	51.25	0.9438
9	58.73	0.9480	489.08	0.9128	52.18	0.9480
9i	52.61	0.9594	505.34	0.9718	40.05	0.9627
10	3.85	0.9913	102.83	0.9889	33.23	0.9814
10i	5.93	0.9558	98.46	0.9493	41.04	0.9487
11	35.53	0.9406	305.88	0.9511	37.58	0.9508
11i	29.54	0.9694	354.72	0.9605	35.56	0.9804
TAC[a]	146.95	0.9788	–	–	–	–
ACR[b]	–	–	22.80	–	–	–

[a]Tacrine.
[b]Acarbose.

Table 2. K_I values of compounds (**1**-**11**) and (**1i**-**11i**).

Compound ID	AChE (K_I, μM)	α-GLY (K_I, μM)	GST (K_I, μM)
1	35.54 ± 5.94	398.34 ± 35.76	28.98 ± 1.12
1i	41.84 ± 6.08	453.15 ± 46.88	24.83 ± 2.32
2	21.65 ± 3.56	306.11 ± 23.08	34.32 ± 3.03
2i	18.73 ± 5.78	256.07 ± 19.45	44.74 ± 4.15
3	46.76 ± 11.65	712.54 ± 76.07	24.41 ± 1.09
3i	61.25 ± 7.88	704.36 ± 56.97	22.76 ± 1.23
4	82.46 ± 14.74	1154.65 ± 243.66	23.78 ± 1.16
4i	79.66 ± 12.55	1005.84 ± 111.53	26.93 ± 1.17
5	77.47 ± 9.58	754.76 ± 70.50	30.28 ± 2.78
5i	68.36 ± 10.76	776.23 ± 85.63	30.95 ± 2.95
6	18.56 ± 2.57	405.82 ± 46.11	34.46 ± 3.11
6i	15.87 ± 1.87	377.87 ± 26.73	31.46 ± 3.01
7	30.23 ± 8.74	547.74 ± 63.76	32.32 ± 3.48
7i	34.74 ± 10.78	504.82 ± 46.88	42.98 ± 4.47
8	15.76 ± 3.57	326.78 ± 54.64	49.29 ± 4.49
8i	13.46 ± 2.24	306.90 ± 40.65	43.09 ± 4.16
9	38.57 ± 8.53	505.72 ± 77.11	44.62 ± 4.63
9i	40.56 ± 7.44	546.05 ± 80.35	33.13 ± 1.98
10	2.26 ± 0.45	95.73 ± 13.67	27.02 ± 1.26
10i	3.57 ± 0.97	102.45 ± 11.72	35.85 ± 3.37
11	25.40 ± 4.56	325.90 ± 56.88	30.74 ± 2.35
11i	23.21 ± 3.66	341.76 ± 30.64	29.08 ± 1.84
TAC[a]	111.25 ± 14.76	–	–
ACR[b]	–	12.60 ± 0.78	–

[a]Tacrine.
[b]Acarbose.

the amine compounds showed a new peak at about 50 ppm due to the presence of the -CH_2- group.

3.2. Biological evaluation

It is known that DM and Alzheimer's disease (AD) have an increase in the activity of AChE (E.C.3.1.1.7), which can lead to changes in cholinergic neurotransmission (Kamboj et al., 2008; Mushtaq et al. 2014; Taslimi & Gulçin, 2018). Changes in the activity or expression of the AChE, which is important for neurodegenerative disorders, may play a key role in determining of neurotoxicity as biomarkers (Işık et al., 2015). AChE inhibitors are widely used in the elimination of the neurotoxic effect caused by the change of the cholinergic hypothesis. Multiple β-amyloid (Aβ) neurotoxic products on disease development have reduced by the effect of AChE inhibitors, which have important functions such as protection of cells from oxidative damage and production of endogen antioxidant in the symptomatic treatment of AD (Bartolini et al., 2003; García-Ayllón, 2011; Göçer et al., 2015). AChE inhibitors used in treatment can slow the excessive hydrolysis of ACh and prevent AD progression. As a result, it provides relaxation and improves cognitive function (Blennow, 2010; Işık, 2019).

The inhibition effect and type on AChE of the synthesized sulfonamide derivatives (**1**-**11** and **1i**-**11i**) was determined by Lineweaver-Burk and Michaelis-Menten kinetics. The most powerful inhibition was observed on **10** and **10i** series with a K_I value of 2.26 ± 0.45 and 3.57 ± 0.97 μM, respectively. Additionally, all the other synthesized sulfamides were highly efficient inhibition constants against AChE. IC_{50} values of sulfonamides series were recorded in range of 3.85–105.63 μM. On the other hand, The AChE was very effectively inhibited by sulfonamides series, with K_I in the range from 2.26 ± 0.45 to 82.46 ± 14.7 μM (Tables 1 and 2). The synthesized derivatives have higher AChE inhibitory potential than standard drug tacrine (TAC) with K_I value 111.25 ± 14.76 μM.

In other study, the benzylpiperidine substituted derivatives (**4a-c** and **5a-i**) have been shown to have the potential to inhibit AChE (IC_{50} of **4a** was 8 μM) when the donepezil indanon system is replaced with substitution pyrol or indole ring (Andreani et al., 2001). In the study, Benzophenone derivatives also have high AChE inhibitory potential (Belluti et al., 2009; Singh et al., 2013). Additionally, in another study, a high inhibition effect of sulfonamide derivatives on BChE and AChE has been shown in a series of new biphenyl bis-sulfonamide derivatives that IC_{50} values of the derivatives

Table 3. Molecular docking scores and binding modes of some derivatives (**4** and **10**) with the receptors (4EY5, 5NN8, and 2GSS).

Compound ID	Receptor code	MM-GBSA ΔG Bind (kcal/mol)[a]	Docking Score (kcal/mol)[b]	ΔG vdW (kcal/mol)	ΔG Coulomb (kcal/mol)	Glide Energy (kcal/mol)	Glide Emodel (kcal/mol)	H-bond
10	4EY5 (AChE)	−45.46	−6.62	−38.68	−5.46	−59.28	−44.15	Gln202 (2.13 and 2.26 Å), Phe295 (2.03 Å), Arg296 (2.13 and 2.68 Å)
10	5NN8 (α-GLY)	−45.01	−4.79	−32.48	−15.50	−68.62	−47.98	Asp616 (1.78 and 2.13 Å), Ser676 (2.11 Å), Leu677 (1.95 Å)
4	2GSS (GST)	−47.44	−5.45	−27.30	−4.18	−40.11	−31.48	Arg13 (2.02 Å), Gln51 (1.68 Å)

[a]Molecular Mechanics-Generalized Born Surface Area.
[b]Glide standard precision (SP) mode.

were were in the range of 7.74–400 μM for BChE and 2.27 ± 0.01 to 123.11 ± 0.04 μM for AChE (Mutahir, 2016).

There are many studies on GST enzyme activity in the literature. In the studies conducted by Türkan *et al.*, Avermectin derivative group was found to inhibit the enzyme at millimolar level (Türkan et al., 2018) and some cephalosporin group antibiotics both *in vivo* and *in vitro* (Türkan et al., 2019). Similarly, Gülçin *et al.* studied that the inhibition effects of rosmarinic acid on GST enzymes (Gülçin, Scozzafava, Supuran, Koksal, et al. 2016). The standard inhibitor EA (ethacrynic acid) was used as a reference for GST in the test. K_I constants were calculated as 42.52 nM. In another study, it was reported that caffeic acid phenylethyl ester (CAPE) showed inhibition effects on GST (Gülçin, Scozzafava, Supuran, Akıncıoğlu, et al. 2016). In our study, we found that **3i** molecule inhibit the GST enzyme at micromolar level. As an inhibition study, we calculated IC_{50} and K_I values separately. For **3i** molecule showing the lowest K_I value. K_I value was calculated as 22.76 ± 1.23 μM. For this enzyme, IC_{50} values of some active derivatives the following order: **3i** (29.04 μM, r^2: 0.9892) < **3** (29.42 μM, r^2: 0.9457) < **4** (30.12 μM, r^2: 0.9904) < **1i** (30.16 μM, r^2: 0.9542) < **4i** (31.97 μM, r^2: 0.9588) < **10** (33.23 μM, r^2: 0.9814) < **1** (34.22 μM, r^2: 0.9682).

For the α-GLY as the metabolic enzyme, the active molecules had IC_{50} values from 98.46 to 1054.80 μM and K_I values were from 95.73 ± 13.67 to 1154.65 ± 243.66 μM (Tables 1 and 2). The results of this study showed that all molecules demonstrated powerful α-GLY inhibitory effects that were similar to the result of acarbose (ACR) (IC_{50}: 22.80 μM, K_I: 12,60 μM) (Teng et al., 2017; Torres-Naranjo et al., 2016) as a standard α-GLY inhibitor. Indeed, the most useful K_I value was obtained by a molecule of 10, with K_I value of 95.73 ± 13.67 μM. One of the aims of hyperglycemia reduction is to reduce the activity of α-GLY responsible for carbohydrates hydrolysis. Inhibitors of this metabolic enzyme delay the absorption of sugars in the intestinal tract, thus limiting post-intake plasma glucose excursions. In fact, ACR is an oral α-GLY inhibitor, which recommended for blood glucose control (Aktaş et al., 2019; Biçer et al., 2019; Eruygur et al., 2019). For this enzyme, IC_{50} values of ACR as positive control and some active derivatives the following order: **ACR** (22.80 μM) < **10i** (98.46 μM, r^2: 0.9493) < **10** (102.83 μM, r^2: 0.9889) < **2i** (277.31 μM, r^2: 0.9783) < **2** (285.94 μM, r^2: 0.9084) < **8i** (298.55 μM, r^2: 0.9388) < **8** (304.94 μM, r^2: 0.9490) < **11** (305.88 μM, r^2: 0.9511).

A structure-activity relationship (SAR) was attempted to be established based on the positions of the compounds in different substituents and compounds. *In vitro* effect studies have shown that sulfonamide derivatives inhibit the activity of AChE and α-GLY enzyme. These results are important for understanding the structural activity relationship (SAR) created based on their position in different substituents and compounds. *In vitro* effect studies have shown that both bromo and chloro derivatives best inhibit the activity of the AChE and α-GLY enzyme. The compounds **10** and **10i** are the most active compound and showed potential inhibitory activity compared to others. When all the compounds were examined, it was seen that the most active compounds were bromo and chloro containing sulfonamide compounds. That is, **10**, **10i**, **8**, **8i**, **6**, **6i**, **2**, and **2i** compounds exhibited potential inhibitory activity compared to others. Inhibition activities of other compounds were found to be very low compared to sulfonamide compounds containing bromo and chloro. Another remarkable feature in the compounds is that the presence of the -OH and sulfonamide (-SO_2NH_2) moiety in the compounds also increases activity and is clear in molecular docking. Finally, the compounds have a stronger inhibitor in lower concentrations by the attachment of functional electronegative groups such as two halogens (-Br and -Cl), -OH to the benzene ring and -SO_2NH_2.

3.3. Molecular docking study

Re-docking of the native ligands, including (5R,9R,11E)-5-amino-11-ethylidene-5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[b]pyridin-2(1H)-one ($C_{15}H_{18}N_2O$; HUP; huperzine A) (Cheung et al., 2012), 1,4-deoxy-4-((5-hydroxymethyl-2,3,4-trihydroxycyclohex-5,6-enyl)amino)fructose ($C_{25}H_{43}NO_{18}$; ACR; α-acarbose) (Roig-Zamboni et al., 2017), and 2-[2,3-dichloro-4-(2-methylidenebutanoyl)phenoxy]acetic acid ($C_{13}H_{12}Cl_2O_4$; EAA; ethacrynic acid) (Oakley et al., 1997) into the catalytic pockets of AChE, α-GLY, and GST, respectively, was performed as a means of validating our docking parameters. The RMSD values of the binding poses of the co-crystallized ligands were computed as <1.5 Å using the Superposition tool in Maestro (Ece, 2020; Karimov et al., 2020). The results of molecular docking studies confirmed that synthesized compounds (**1**-**11**) successfully accommodated within the binding pockets of AChE, α-GLY, and GST (Table 3). Compounds **10** (for both AChE and α-GLY) and **4** (for GST) determined as competitive inhibitors were chosen for molecular docking simulations to verify its inhibition results by researching its major interactions within the active sites of receptors.

According to the literature, the HUP displays two interactions, H-bond interaction with Tyr133 and Tyr337, and the docking score was −10.34 kcal/mol in the catalytic domain of 4EY5. For the most active compound **10** (K_I=2.26 ± 0.45 μM) the docking score (–6.62 kcal/mol) was found low to the co-crystallized ligand. Compound **10** has shown functional interactions with the active site residues of the AChE (MM-GBSA ΔG bind: −45.46 kcal/mol), i.e. Gln202, Trp286, Phe295, Arg296, Tyr337, and Tyr341. Gln202, Phe295, Arg296 residues formed H-bond interactions and Trp286 and Tyr337 composed Pi-Pi stacking with benzene rings. Also, Tyr341 formed Pi-cation interaction with -NH moiety of the compound (Figure 1).

Unsurprisingly, the docking modes into 5NN8 determined for the two ligands were as both ACR and derivative **10** displayed similar interactions with Asp616 and Ser676. The 5NN8 complexed with ACR shows H-bonds with Asp282, Asp404, Arg600, Asp616, Gly651, and Ser676. Apart from this, ACR showed hydrophobic interactions with Ala284, Tyr292, Trp376, Leu405, Ile441, Trp481, Phe525, Trp516, Met519, Trp613, Trp618, Phe649, Leu650, and Leu678. The docking score was −7.50 kcal/mol. Compound **10** (K_I =95.73 ± 13.67 μM) formed four H-bonds with α-GLY amino acids (Docking score: −4.79 kcal/mol, MM-GBSA ΔG bind: −45.01 kcal/mol), including Asp616, Ser676, Leu677. Also, the analogue **10** composed a hydrophobic cloud with Trp376, Leu405, Ile441, Trp481, Trp516, Trp613, Phe649, Leu650, Leu677, and Leu678 (Figure 2).

EAA, which is previously reported as the native ligand, and analogue **4** (K_I =23.78 ± 1.16 μM), which is the most active analogue of the series, were analyzed in terms of interactions with GST. Surprisingly, the docking scores into 2GSS determined for the EAA and compound **4** were −5.09 kcal/mol, and −5.45 kcal/mol, respectively. Within 2GSS active site, compound **4** showed two H-bond with Arg13, and Gln51, and also, Pi-Pi stacking was composed between the phenyl ring and Phe8 amino acid (MM-GBSA ΔG bind: −47.44 kcal/mol) while, EAA establishes H-bond with Tyr7 and Tyr108. Hydrophobic interaction was monitored between derivative 4 and Tyr7, Phe8, Pro9, Val10, Val35, Trp38, Leu52, Ile104, and Tyr108 (Figure 3).

4. Conclusion

As a result, the derivatives have a stronger inhibitor in lower concentrations by the attachment of functional electronegative groups such as two halogens (-Br and -Cl), -OH to the benzene ring and -SO_2NH_2. Because, we think that this compound, which has an electron density, can inhibit the enzyme by making it easier to bind to the functional groups of amino acids (Tables 1–3, Figures 1–3). Patients with the neurodegenerative disease treated with these inhibitors present undesirable effects like nausea, diarrhea, gastrointestinal anomalies, and hepatotoxicity. α-GLY inhibition is a logical process in the effective management of type 2 diabetes. Various inhibitors of this enzyme class are in clinical utilize but are riddled with potency, efficacy, and safety challenges. Additionally, novel effective α-GLY inhibitors are under evaluation.

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ORCID

Parham Taslimi http://orcid.org/0000-0002-3171-0633
Mesut Işık http://orcid.org/0000-0002-4677-8104
Fikret Türkan http://orcid.org/0000-0002-0538-3157
Mustafa Durgun http://orcid.org/0000-0003-3012-7582
Cüneyt Türkeş http://orcid.org/0000-0002-2932-2789
İlhami Gülçin http://orcid.org/0000-0001-5993-1668
Şükrü Beydemir http://orcid.org/0000-0003-3667-6902

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