Journal of Molecular Structure 1286 (2023) 135514

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

Eco-friendly and potential colin esterase enzyme inhibitor agent sulfonyl hydrazone series: Synthesis, Bioactivity Screening, DFT, ADME properties, and Molecular Docking study

Ummuhan Ozdemir Ozmen [a,*], Burak Tuzun [b], Esra Bilen Ayan [a], Bekir Sıtkı Cevrimli [c]

[a] Department of Chemistry, Faculty of Science, Gazi University, 06500, Ankara, Turkey
[b] Department of Plant and Animal Production, Technical Sciences Vocational School of Sivas, Sivas Cumhuriyet University, Sivas, Turkey
[c] Department of Chemistry, Vocational School of Technical Sciences, Gazi University, 06500, Ankara, Turkey

ARTICLE INFO

Keywords:
Sulfonylhydrazone
Green chemistry
Choline esterase enzyme inhibition
Molecular docking
ADME/T

ABSTRACT

In this study, new compounds containing the sulfonamide group and having inhibitory activity on cholinesterase enzymes (AChE, BChE) were synthesized. For this purpose, three new sulfonylhydrazone compounds were synthesized from different alkylsulfonic acid hydrazide and N'-(4-diethylamino) salicylaldehyde and designed by the green chemistry method in shorter time and more environmentally friendly. The structures of the synthesized compounds were characterized by elemental analysis (CHNS), ^{1H}NMR , ^{13C}NMR , and FT-IR. The effects of the synthesized sulfonylhydrazone derivatives (4Dea-salesh, 4Dea-salpsh, 4Dea-salbsh) on acetylcholinesterase and butyrylcholinesterase enzymes were investigated. According to the results, all synthesized compounds showed inhibitory effect on AChE and BChE enzymes. In particular, 4Dea-salbsh exhibited the best activity with an IC_{50} value of 9.549±0.75 μM on AChE. The Molecules were optimized by B3LYP, HF, and M062X methods with 6–31++g(d,p) basis sets. Then, their activities against biological materials namely acetylcholinesterase (AChE) (PDB ID: 4M0E and 1OCE) and butyrylcholinesterase (BChE) (PDB ID: 5NN0 and 6R6V), were compared. Molecular docking studies were performed to evaluate the binding interactions between the compounds and the enzymes. Subsequently, ADME/T properties were investigated to test the drug properties.

1. Introduction

Throughout our lives, we constantly need enzymes. Even in the smallest life activity, metabolic activity takes place. Enzymes take care of that, and each of them is very important for living beings. Acetylcholinesterase (AChE; EC.:3.1.1.7) is one of these enzymes. Acetylcholinesterase breaks down and removes chemicals that have accumulated in the nerve terminal. In this way, an environment suitable for electron transporters is created, ensuring that nerve conduction is not disrupted [1]. AChE is involved in catalysing the hydrolysis process of the neurotransmitter acetylcholine (ACh) and is of great biological importance [2]. Cholinesterases are divided into 2 groups based on their substrate selectivity for acetylcholine and butyrylcholine. Acetylcholinesterase (AChE, acetylcholine acetylhydrolase, EC 3.1.1.7) is a true cholinesterase; butyrylcholinesterase (BChE, acylcholine acylhydrolase, EC 3.1.1.8) is known as pseudocholinesterase, serum cholinesterase or nonspecific cholinesterase. Another important distinguishing feature between AChE and BChE is that AChE is inhibited and BChE is activated at high substrate concentrations [3]. While AChE is found in high concentration in the brain, nerve cells, muscles, and erythrocytes, BChE; is found in the serum, pancreas, liver, and central nervous system, and these enzymes are also quite common in animals [4]. The main function of AChE is to terminate cholinergic neurotransmission, but the actual physiological function of BChE is not yet known [5]. Cholinesterases also play a role in cell regeneration, differentiation, stress response to various factors, and amyloid formation [6]. Alzheimer's disease results from the decrease of neurotransmitters in the brain, and the neurotransmitter that decreases the most in this disease is ACh. Recently, research has focused on the inhibition of cholinesterase, which is considered the only valid target for the clinical treatment of Alzheimer's disease (AD) [7].

Sulfonamides, which have broad biological effects, are now widely used to treat or prevent various diseases, as are the best-selling artificial sweeteners such as saccharin [8]. In clinical medicine, they are used as

* Corresponding author.
E-mail address: ummuhan@gazi.edu.tr (U. Ozdemir Ozmen).

https://doi.org/10.1016/j.molstruc.2023.135514
Received 11 February 2023; Received in revised form 21 March 2023; Accepted 4 April 2023
Available online 6 April 2023

anti-cancer agents [9], antimicrobial agents [10] and antiglaucoma agents [11]. In addition, sulfonamide derivatives play an active role as cholinesterase inhibitors in the treatment of AD. Girisha et al. (2009) synthesized piperidine sulfonamide derivatives and investigated their anti-acetylcholinesterase activity in three different materials (mouse, human serum and electric eel) and compared their inhibitory effect on AChE with the neostigmine standard. It was found that some of the inhibitors had values close to the standard [12]. Akincioglu et al. (2017) synthesized new sulfonamide derivatives from β-benzylphenethylamines and investigated the inhibitory activities of these compounds on acetylcholinesterase (AChE), butyrylcholinesterase (BChE) enzymes and compared them with tacrine (TAC) as the standard inhibitor. It was found that the two synthesized compounds showed much better inhibitory effect on AChE enzyme than tacrine [13]. In another study, it was reported that various inhibitors were synthesized for AH, among which compounds containing a hydrazone group showed high activity for AChE and BChE enzymes. The activity differs depending on the substituents attached to the hydrazone group (MeO, Cl, CH_3, OH, NO_2) [14]. Alptüzün et al. (2010) synthesized pyridinylidene hydrazones containing bisphenyl with different chain lengths. Among these compounds, the most promising compound has the longest chain for both AChE and BChE inhibition [15]. Recently, research in the field of cholinesterase inhibition has increased, and it is considered a valid target in clinics for the treatment of Alzheimer's disease (AD). Therefore, there is a need for the synthesis and development of new cholinesterase inhibitor molecules. In our previous studies, various sulfonamides/sulfonylhydrazones and metal complexes were synthesized [16–18] and their spectroscopic properties, anti-cancer, antimicrobial, and anti-carbonic anhydrase activities were investigated [19]. In addition, we investigated the inhibitory properties of AChE and BChE enzymes of sulfonylhydrazone derivatives, which are effectively used in the treatment of AD [20].

In this study, new sulfonylhydrazone compounds (4Dea-salesh, 4Dea-salpsh, 4Dea-salbsh) were synthesized for the first time and characterized by spectroscopic methods (^{1H}NMR , ^{13C}NMR , FT-IR) and elemental analytical measurements. The inhibitory effect of the synthesized compounds on acetylcholinesterase (AChE); and butyrylcholinesterase (BChE) enzymes were investigated by comparing IC_{50} values. In addition, by comparing the IC_{50} values and the AChE selectivity index (SI, IC_{50} of BChE/IC_{50} of AChE) and the BChE selectivity index (SI, IC_{50} of (AChE) / IC_{50} of (BChE), the selective inhibition of AChE or BChE were investigated.

As a result of the theoretical calculations, many chemical and biological properties of the molecules were studied with numerous calculated parameters. In the performed calculations, the optimized structures of the molecules were obtained using the B3LYP, HF, and M062X methods with the 6–31++g(d,p) basis sets [21,22]. Molecular docking calculations were performed to investigate the activities of molecules against biological materials, acetylcholinesterase (AChE) (PDB ID: 4M0E and 1OCE) [23] and butyrylcholinesterase (BChE) (PDB ID: 5NN0 and 6R6V) [24]. Finally, the theoretical drug properties of the molecules were investigated so that they could be used as drugs.

2. Experimental

2.1. Materials

The starting reagents were purchased from commercial sources (Sigma-Aldrich Chemical Company (USA)) and were used without further purification. The solvents were dried according to standard procedures. Ethane/propane/butane sulfonyl chloride, hydrazine hydrate, and N'-(4-diethylamino) salicylaldehyde were commercial products (Purum). All reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using Merck silica gel and visualized by ultraviolet light. Melting points were determined in open capillary tubes on Buchi B-540. Proton nuclear magnetic resonance was determined with a 300-MHz Brucker Ultrashield (Gazi Univ. Department of Chemistry) using DMSO as solvent and TMS as internal standard. FT-IR Spectra were recorded in KBr (ν, in cm-1) using a Mattson 1000 FT-IR spectrophotometer (Gazi Univ. Department of Chemistry). Elemental analyzes were performed according to standard microanalytical procedures (Gazi Univ. Department of Chemistry). Acetylcholinesterase from Electrophorus electrius (AChE) and butyrylcholinesterase from equine serum (BChE) were assayed using enzyme activity assays from Sigma. The inhibition activities of all compounds on AChE and BChE were measured spectrophotometric according to Elman's methods in the multi-plate reader.

2.2. Preparation of new sulfonylhydrazone compounds (4Dea-salesh, 4Dea-salpsh, 4Dea-salbsh)

The one-pot synthesis method for sulfonylhydrazone is a synthesis method that reduces chemical waste during synthesis, reduces synthesis cost and time, and increases productivity. Synthesis time is shortened and yield loss is minimized because the two-step synthesis process is carried out in one vessel and at the same time. For these reasons, the one-pot synthesis method is a synthesis method suitable for environmental and green chemistry applications. All compounds were synthesized according to the following general procedure [20].

The synthesis of the targeted compounds was carried out in one pot and in two steps (Fig. 1.).

In the first step, a cold ethanol solution of hydrazine hydrate (1.2 mmol) was added to an ethanol solution of alkylsulfonyl chlorides (ethane, propane, or butane) at 0 °C (1.0 mmol). (2.0 mmol) Triethylamine was catalyzed by stirring for 1 h at room temperature and alkylsulfonic acid hydrazide compounds were synthesized.

In the second step, new sulfonylhydrazone derivatives were synthesized by adding the solution of N'-(4-diethylamino) salicylaldehyde compound in ethanol under HCl catalysis (pH∼4) (1.44 mmol) to the alkylsulfonic acid hydrazide compound in the obtained solution medium and mixing it under reflux for 10–12 h at 50–65 °C. The reaction was monitored by TLC using hexane/ethyl acetate (1:1) as eluent. The synthesized compounds were purified by crystallization in a solvent mixture of ethanol and distilled water.

2.2.1. 4-diethylamino salicylaldehydeethanesulfonylhydrazone (4Dea-salesh)

Yield: 67%; Orange; m.p. 176 °C; IR (KBr): 3172 (w, υN—H), 2977 (w, υC—H), 11,628 (m, υC═N), 1337 (m, υasSO$_2$*), 1129(s,* υsSO$_2$*) cm^{-1}; ^{1}H NMR,300 MHz (DMSO-d$_6$) δ 1.10 (t, 3H,* CH$_2$—CH$_3$*), 1.20 (s, 6H,* N(CH$_2$—CH$_3$)$_2$*,3.05(t,4H,* N(CH$_2$—CH$_3$)$_2$ *3.20(m, 2H,* SO$_2$—CH$_2$*), 6.10 (dd, 1H ArH),7.46 (d, 1H, ArH), 8.22(s, 1H, ArH); 9.61 (s, 1H, HC—N), 10.76 (s,1H, OH, 11.25(s, 1H, NH); ^{13}C NMR,300 MHz (DMSO-d$_6$): δ 8.54* (CH$_2$—CH$_3$)*, 12.51* (N(CH$_2$CH$_3$)$_2$)*, 43.84* N(CH$_2$—CH$_3$)$_2$*, 45.62* (SO$_2$—CH$_2$)*, 97.02; 104.03 ve 106.36 (CH$_{ar}$), 132.99 (HC—N), 150,90* C—N(CH$_2$—CH$_3$)$_2$*, 160,56 (C—OH); Anal. Calcd for* C$_{13}$H$_{21}$N$_3$O$_3$S*: C, 52.15; H, 7.07; N, 14.04; S, 10.71; Found: C, 51.47; H, 6.88; N, 13.36; S, 9.94.*

2.2.2. 4-diethylamino salicylaldehydepropanesulfonylhydrazone (4Dea-salpsh)

Yield: 74%; yellow; m.p. 112 °C; IR (KBr): 3186 (w, υN—H), 2977 (w, υC—H), 1625 (m, υC—N), 1312(m, υasSO$_2$*), 1134 (s,* υsSO$_2$*) cm^{-1}; ^{1}H NMR,300 MHz (DMSO-d$_6$) δ 0.98(t, 3H,* CH$_2$—CH$_3$*), 1.09 (t, 6H,* N(CH$_2$—CH$_3$)$_2$*, 1.69 (m,2H),3.15 (t,4H, N(CH2-CH3),3.20(m,2H,* SO$_2$—CH$_2$*,6.09(s, 1H, ArH), 6.24(d, 1H, ArH), 7.25 (d, 1H, ArH); 8.10 (s, 1H, HC—N), 10.20(s,1H, OH, 10.60 (s, 1H, NH); ^{13}C NMR,300 MHz (DMSO-d$_6$): δ 13.02* (CH$_2$—CH$_3$) *and* CH$_2$—CH$_2$—CH$_3$*, 39.18,* N(CH$_2$—CH$_3$)$_2$*, 40.82* (SO$_2$—CH$_2$)*, 97,53; 104,53, 106,88 (CH$_{ar}$), 133.51 (HC—N, 15,.40* (C—N(CH$_2$—CH$_3$)$_2$)*, 161.15 (C—OH)); Anal. Calcd for* C$_{14}$H$_{23}$N$_3$O$_3$S*: C, 53.65; H, 7.40; N, 13.41; S, 10.23; Found: C, 52.87; H, 6.99; N, 13.00; S, 10.04.*

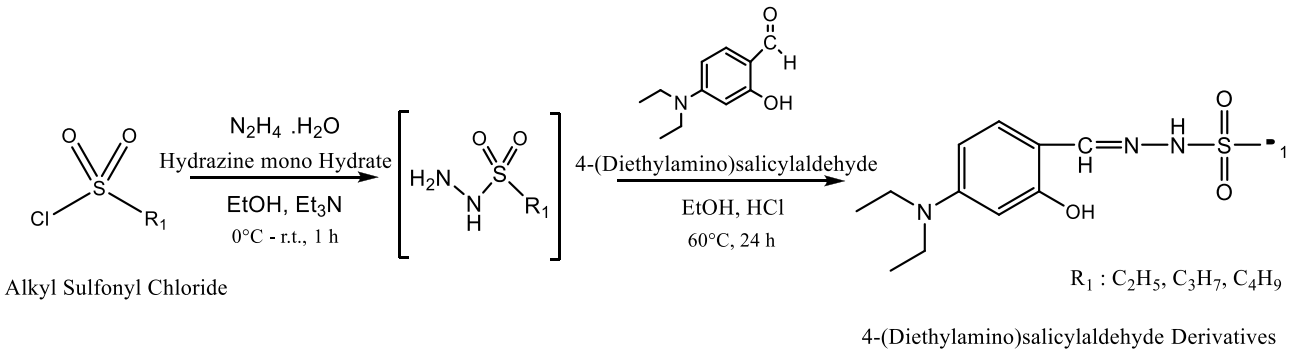


Fig. 1. Preparation of sulfonylhydrazone series in two steps and in one pot method.

2.2.3. 4-diethylamino salicylaldehydebutaneesulfonylhydrazone (4Dea-salbsh)

Yield: 78%; Orange; m.p. 81 °C; IR (KBr): 3186(w, υN—H), 2970(w, υC—H), 11,634 (m, υC—N), 1317 (m, $\upsilon asSO_2$*), 1130 (s,* υsSO_2*)* cm^{-1}*;* ^1H *NMR,300 MHz (DMSO-*d_6*)* δ *0.97(t, 3H,* CH_2—CH_3*), 1.09 (t, 6H,* N(CH_2—CH_3)$_2$*, 1.40 (m,2H,*CH_2—CH_3 *1.65 (m,2H,* CH_2—CH_2—CH_3*, 3.15 (t, 4H,* N(CH_2—CH_3)$_2$*, 3.20 (m, 2H,* SO_2—CH_2*), 6.12 (s, 2H, ArH) 6.25 (d, 2H, ArH), 7.45 (d, 2H, ArH); 8.13(s, 1H, HC—N), 10.25(s,1H, OH, 10.60 (s, 1H, NH);* ^{13}C *NMR,300 MHz (DMSO-*d_6*):* δ *12,14* (CH_2—CH_3) *and* CH_2—CH_2—CH_2—CH3*, 40.18* (N(CH_3)$_2$)*, 43.48* (SO_2—CH_2)*, 96.65; 103.66 ve 106.00 (*CH_{ar}*), 106.00 (HC—N), 150,53* C—N(CH_2—CH_3)$_2$*, 160,27 (C—OH); Anal. Calcd for* $C_{15}H_{25}N_3O_3S$*: C, 55.02; H, 7.70; N, 12,83; S, 9,79; Found: C, 53.87; H, 7.09; N, 12.00; S, 9.04.*

2.3. Procedure for choline esterase (AChE-BChE) activity

The AChE/BChE inhibition activity was measured spectrophotometric according to Elman's methods with slight modifications [25]. The total volume of the reaction mixture was 3,00 mL. It contained 2,89 mL Na_2HPO_4 buffer with a concentration of 0.1 M and pH 8. 30 μL test compound (1×10^{-5} - 10 mM well^{-1}) was added, followed by the addition of 10 μL (0.005 unit well^{-1}) enzyme. The contents were pre-incubated for 10 min at room temperature. The reaction began with the addition of 30 μL of 0.01 M substrate (acetylthiocholine iodide/ S-butyrylthiocholine iodide), followed by the addition of 30 μL 5, 5̇-Dithio-bis (2-nitro-benzoic) acid (DTNB) (0.1 mM well^{-1}). After 30 min of incubation at room temperature, absorbance was measured at 412 nm. All experiments were carried out with their respective controls in triplicate. Donepezil (1×10^{-5} - 10 mM well^{-1}) was used as a reference drug

2.4. Theoretical methods

Theoretical calculations provide important information about the chemical and biological properties of molecules. Many quantum chemical parameters are determined by theoretical calculations. The calculated parameters are used to explain the chemical activities of molecules. Numerous programs are used to calculate molecules. These programs are Gaussian09 RevD.01 and GaussView 6.0 [26]. Using these programs, calculations were performed in B3LYP, HF and M06–2x methods with the basis set 6–31++g(d,p) [27]. As a result of these calculations, many quantum chemical parameters were found. Each parameter describes a different chemical property of the molecules. These parameters are HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital), ΔE (HOMO-LUMO energy gap), chemical potential (μ), electrophilicity (ω), chemical hardness (η), global softness (σ), Many parameters such as nucleophilicity (ε), dipole moment, energy value are calculated [28].

$$\chi = -\left(\frac{\partial E}{\partial N}\right)_{\upsilon(r)} = \frac{1}{2}(I + A) \cong -\frac{1}{2}(E_{HOMO} + E_{LUMO})$$

$$\eta = -\left(\frac{\partial^2 E}{\partial N^2}\right)_{\upsilon(r)} = \frac{1}{2}(I - A) \cong -\frac{1}{2}(E_{HOMO} - E_{LUMO})$$

$$\sigma = 1/\eta \;\; \omega = \chi^2/2\eta \;\; \varepsilon = 1/\omega$$

Molecular docking calculations are performed to compare the biological activities of molecules with biological materials. The Maestro Molecular modeling platform program (version 12.8) developed by Schroedinger was used for the molecular docking calculations [29]. The calculations composed of several steps. Each step is performed differently. In the first step, the protein preparation module was used to prepare proteins [30]. In this module, the active sites of proteins were determined. In the next step, the studied molecules are prepared. First, the molecules are optimized in the Gaussian software program, then the LigPrep module is prepared for calculations with optimized structures [31]. The Glide ligand docking module was used to study the interactions between the molecules and the enzyme protein after preparation [32]. All calculations were performed using the OPLS3e method. Finally, ADME/T (absorption, distribution, metabolism, excretion, and toxicity) analysis is performed to investigate the drug potential of the studied molecules. The Qik-prop module of the Schrödinger software was used to predict the effects and reactions of molecules in human metabolism [33].

3. Results and discussion

The synthesis of the sought compounds was carried out in two steps and in a one-pot procedure (Fig. 1). The synthesized sulfonylhydrazone compounds were 4-diethylaminosalicylaldehyde sulfonylhydrazone (4Dea-salesh), 4-diethylaminosalicylaldehydepropanesulfonylhydrazone (4Dea-salpsh), 4-diethylaminosalicylaldehydebutansulfonylhydrazone (4Dea-salbsh), respectively. The results of elemental analysis (C, H, N, S) agreed well with the valuescalculated for the proposed formula. The obtained sharp melting points indicate the purity of the synthesized compounds.

3.1. Characterization of compounds

3.1.1. IR spectra

Selected vibrational frequencies of the sulfonylhydrazone are shown in Supplementary Table 1 and FT-IR spectra are shown in Supplementary Figs. 1–3. The bands in the 3172, 3186, and 33,186 cm-1 region may be due to υ (NH) stretching vibrations in 4-Dea-Esh, 4-Dea-Psh, and 4-Dea-Bsh, respectively. The strong bands at 1628, 1625, and 1634 cm1 are assigned to the υ (C = N) stretching mode of the imine group in the compounds. The ligands also exhibit bands at 1237, 1241, and 1236 cm^{-1} assigned to υ (C–O) stretching vibrations at 4Dea-salesh, 4Dea-

Psh, and 4Dea-salbsh, respectively. υas(SO_2) and υs(SO_2) stretching vibrations are observed between 1312 and 1337 cm^{-1} and 1129–1134 cm^{-1} for the compounds, respectively.

3.1.2. NMR spectra

The ^{1H}NMR spectra of the 4Dea-salesh, 4Dea-salpsh, and 4Dea-salbsh series were recorded in DMSO and are given in Fig. 2. In this study, 4Dea-Esh, 4Dea-Psh, and 4Dea-Bsh show signals at 8.10–9.61 ppm attributable to the imine protons (–N—CH –). The HC—N proton signals show no splitting, and the positions of the ring proton signals are typical. In general, the multiple signals observed at 6.10–8.22 ppm, 6.09–7.25 ppm, and 6.12–7.45 ppm are assigned to the 4Dea-salesh, 4Dea-salpsh, and 4Dea-salbsh ring protons, respectively. Signals at 11.25 ppm,10.60 ppm; 10.60 ppm, and 10.76 ppm; 10.20 ppm, and 10.25 ppm are assigned to the NH and OH protons, for 4Dea-salesh, 4Dea-salpsh and 4Dea-salbsh, respectively. The high field shift of NH protons could be due to the involvement of this group with a hydrogen bond in DMSO-d6, which is known for its interaction with an amide proton.

The ^{13}CNMR spectra of the 4Dea-salesh, 4Dea-salpsh, and 4Dea-salbsh,series (Supplementary

Figs. 4–6) were recorded in DMSO. Imine (C = N) carbon atoms are observed in the 13C NMR spectra in the range of 132.99, 133.51, and 132.64 ppm for 4Dea-salesh, 4Dea-salpsh, and 4Dea-salbsh, respectively. The 13C—NMR spectral data of the sulfonylhydrazone derivatives confirm the results of the 1H NMR spectra. All spectroscopic data were presented in the experimental section

3.2. In vitro choline esterase activities of the synthesized compounds

AChE and BChE inhibitors are used clinically to prevent Alzheimer's

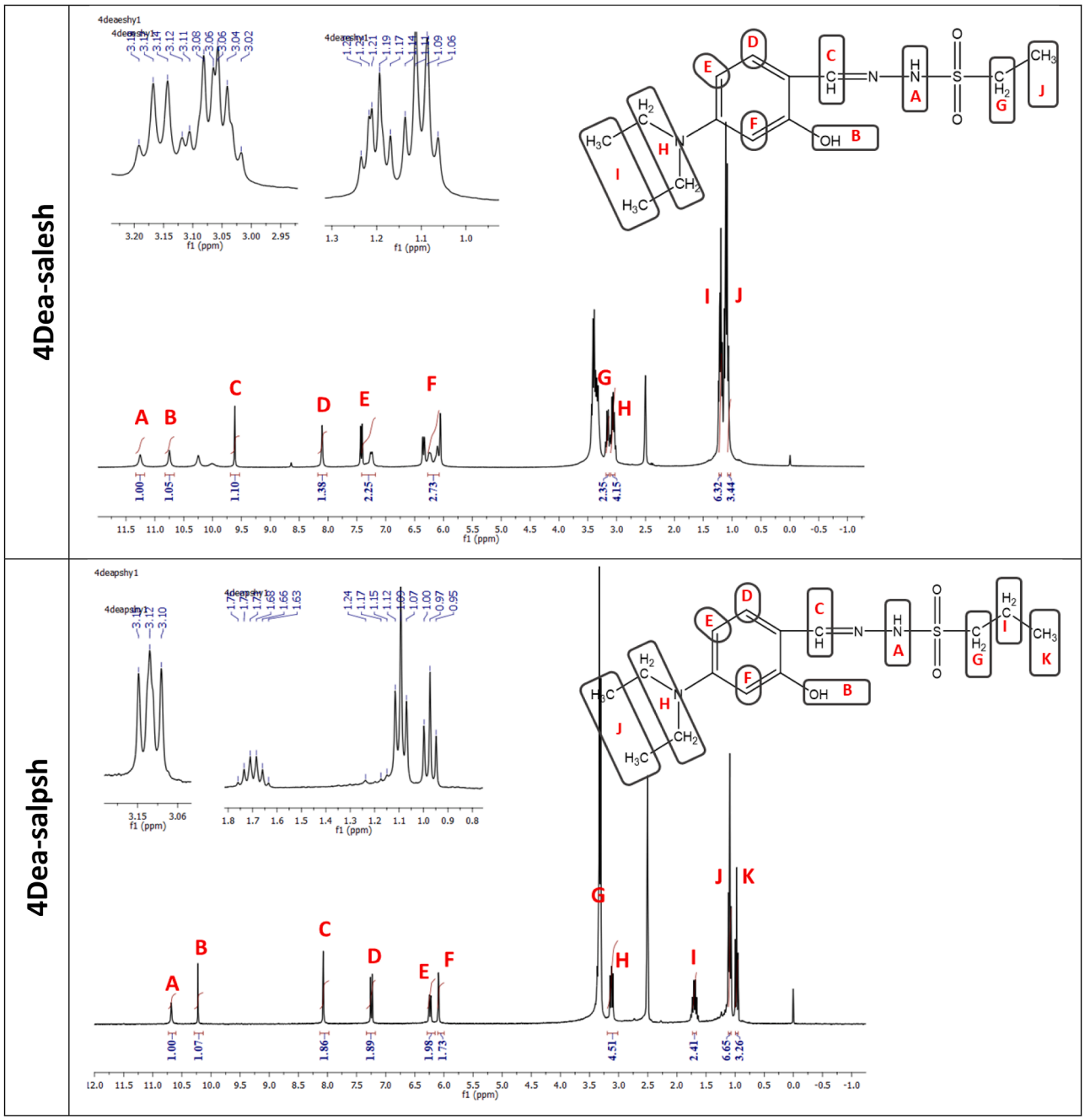


Fig. 2. ^{1H}NMR spectrum of 4Dea-sal series.

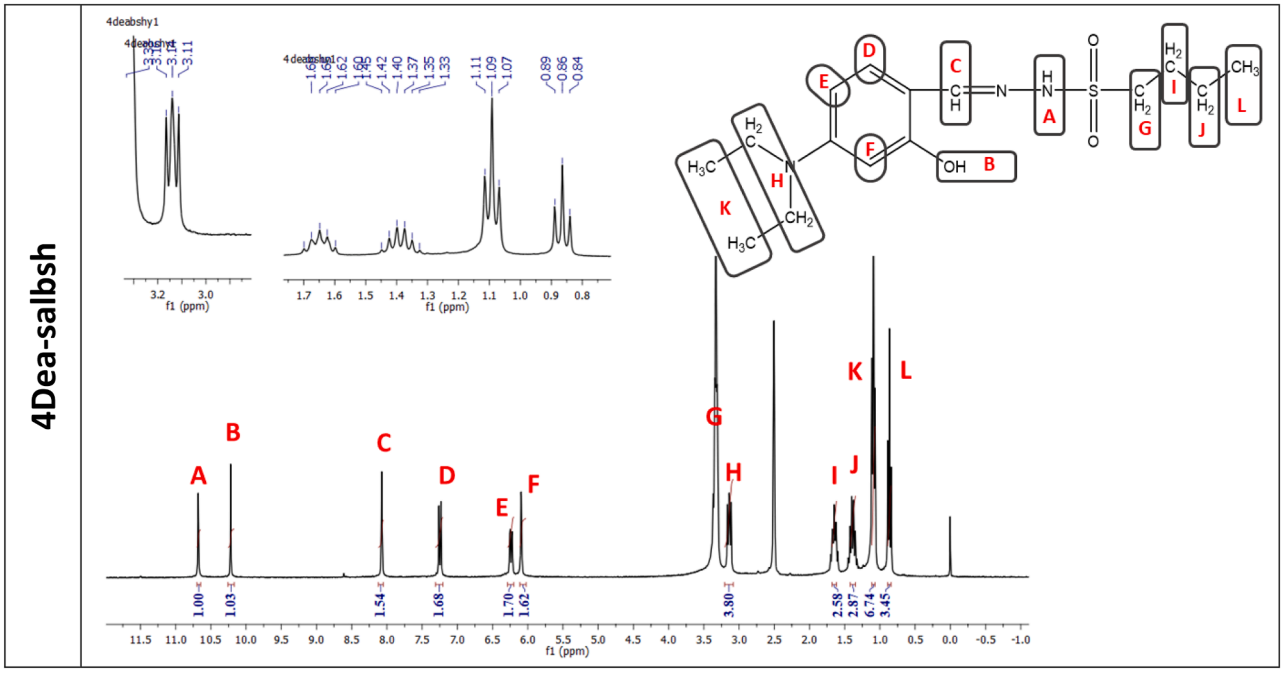
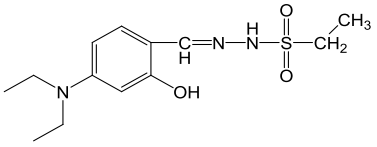
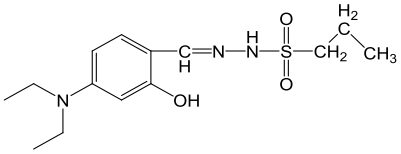
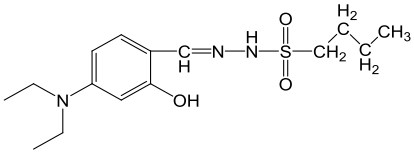
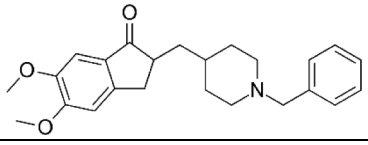


Fig. 2. (*continued*).

disease. Since only a limited number of drugs are available, there is a need to develop new cholinesterase inhibitors. To this end, the inhibitory effects of the newly synthesized sulfonylhydrazone series on two esterase enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) were investigated. The inhibitory effects of the new sulfonylhydrazone derivatives were evaluated using the IC_{50} value which is one of the most appropriate parameters for inhibitors and represents the 50% inhibitory molarity of the enzyme [34]. Donepezil was also investigated as a standard inhibitor, used clinically against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). The results are presented in Table 1 and Fig. 3 (IC50 values of the sulfonyl hydrazone series against AChE and BChE) and in Supplementary Figs. 7 and 8 (percent inhibition graph for the sulfonylhydrazone series against AChE and BChE) and are commented on below. According to the results:

- ➢ All sulfonylhydrazone compounds behave as inhibitors against AChE/BChE.
- ➢ When comparing the effects of the inhibitors on the enzymes, it was found that the inhibitory effects on the AChE enzyme were stronger than the inhibitory effects on the BChE enzyme. The anti-BChE

Table 1
The result of inhibition effect on choline esterase enzymes of the sulfonyl hydrazone compounds.

Structure	Molecular Structure of 4-Dea Derivatives and Donepezil	AChE IC_{50} (μM)	BChE IC_{50} (μM)	Selectivity index AChE[a]	BChE[b]
4-Dea-salesh		20.75±1.56	330.1 ± 6.12	15.9	0.063
4-Dea-salpsh		15.71±1.92	209.0 ± 11.53	13.3	0.075
4-Dea-salbsh		9.549±0.75	153.9 ± 5.79	16.1	0,062
Donepezil		0.0107±0.025	2.55±0.10	238.3	0.0042

[a] Selectivity for AChE = IC_{50} (BChE) / IC_{50} (AChE).
[b] Selectivity for BChE = IC_{50} (AChE) / IC_{50} (BChE).

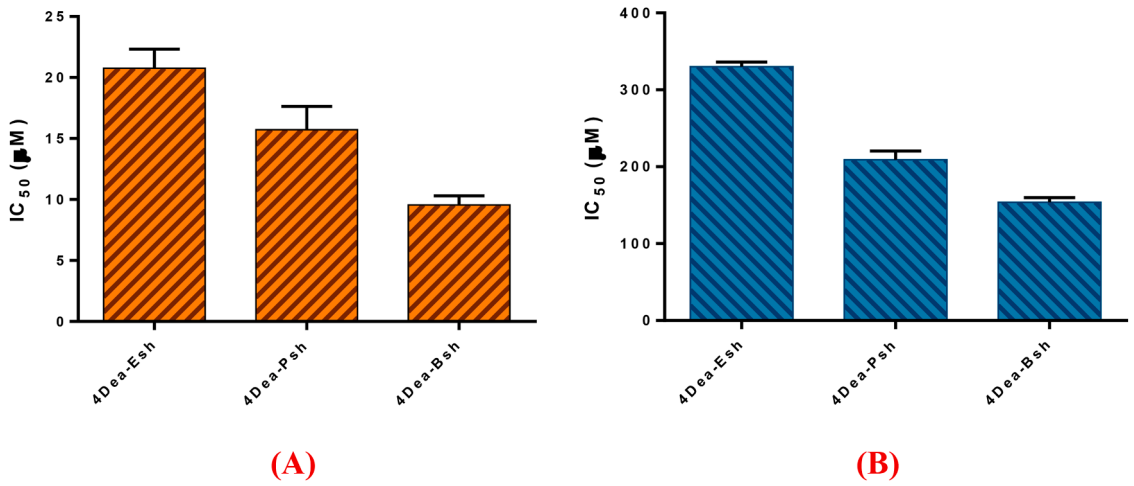


Fig. 3. IC_{50} values of sulfonylhydrazones against AChE (A) and BchE (B). Data represent means ± SE for three independent experiments.

activity of 4dea-Salbsh derivative was lower than AChE inhibition with 16.1-fold selectivity, the anti-BChE activity of 4dea-Salpsh derivative was lower than AChE inhibition with 13.3-fold selectivity, and the anti-BChE activity of 4dea-Salesh derivative was lower than AChE inhibition with 15.9-fold selectivity for AChE over BChE.

- ➢ When the inhibition activity of the compounds against the acetylcholine esterase enzyme was examined, the compound 4Dea-salbsh (IC_{50} = 9.549±0.75 μM) showed the best inhibitory activity compared with the other compounds ((IC_{50} = 15.71±1.92 μM for 4Dea-salpsh and IC_{50} = 20.75±1.56 μM for 4dea-salesh). This compound (4dea-salbsh) also shows similar properties to the best inhibitor of the butyrylcholineesterase enzyme.
- ➢ Considering the inhibition effects of the compounds on the two enzymes;

In the following order, butanesulfonylhydrazones are effective first, followed by propanesulfonylhydrazones, and finally ethanesulfonylhydrazone compounds

(4Dea-salbsh) 〉 (4Dea-salpsh) 〉 (4Dea-salesh)

All compounds have a diethylamine group (-N(C2H5)2) attached to the aromatic ring, Which is thought to play a role in the inhibition activity of both enzymes with its electron-donating property on the ring [20]. Moreover, the best inhibition in the synthesized sulfonylhydrazone series shows a butyl-containing compound (4Dea-salbsh). This shows that the inhibitors increase the enzyme inhibition by lengthening the aliphatic chain with the increase of alkyl group [20].

3.3. Theoretical calculations studies (DFT, ADME properties, and Molecular Docking)

Theoretical calculations provide important information about many chemical properties of molecules. Many chemical and biological properties of the synthesized compounds were studied using the parameters obtained as a result of the calculations. In the calculations, the optimized structures of the compounds were obtained using the B3LYP, HF, and M062X methods with basis sets of 6–31++*g*(d,p).

3.3.1. DFT properties of synthesized compounds

Many quantum chemical parameters of molecules are calculated using the Gaussian software program. Each quantum chemical parameter gives important information about a different property of molecules in Table 2. Among the many parameters calculated, two of the most important are HOMO and LUMO, which show the ability of molecules to donate and accept electrons [35]. However, the ΔE energy gap of molecules is another parameter used to explain the activity of molecules. This parameter is calculated from the difference between the HOMO and LUMO energy values of the molecule, which is the smallest when the activity of the molecule is highest.

Apart from these parameters, some parameters explain many chemical properties of molecules. One of them is electronegativity, which parameter indicates the strength of atoms in the molecule to attract bond electrons. If the electronegativity value of the molecules is high, the bond will attract more electrons and this will reduce the activity of the molecules. Another parameter is chemical hardness, which is an important parameter to compare the activities of molecules. Softness is the opposite of chemical hardness (1/ η). Both chemical hardness and softness are important properties that measure reactivity and

Table 2
The calculated quantum chemical parameters of molecules.

	E_{HOMO}	E_{LUMO}	I	A	ΔE	η	μ	χ	Pİ	ω	ε	dipol	Energy
B3LYP/6–31++*g*(d,p) LEVEL													
1	−5.5572	−1.6218	5.5572	1.6218	3.9353	1.9677	0.5082	3.5895	−3.5895	3.2740	0.3054	7.4389	−35,261.4611
2	−5.5471	−1.6090	5.5471	1.6090	3.9381	1.9690	0.5079	3.5781	−3.5781	3.2510	0.3076	7.3746	−36,330.5943
3	−5.3759	−1.3195	5.3759	1.3195	4.0564	2.0282	0.4930	3.3477	−3.3477	2.7628	0.3620	10.012	−37,399.8607
HF/6–31++*g*(d,p) LEVEL													
1	−7.8190	0.9581	7.8190	−0.9581	8.7771	4.3886	0.2279	3.4304	−3.4304	1.3407	0.7459	7.2831	−35,091.4804
2	−7.8122	0.9489	7.8122	−0.9489	8.7610	4.3805	0.2283	3.4317	−3.4317	1.3442	0.7440	7.1910	−36,152.9514
3	−8.8073	0.9304	8.8073	−0.9304	9.7377	4.8688	0.2054	3.9385	−3.9385	1.5929	0.6278	7.0035	−37,214.5428
M062X/6–31++*g*(d,p) LEVEL													
1	−6.6511	−0.6732	6.6511	0.6732	5.9778	2.9889	0.3346	3.6621	−3.6621	2.2435	0.4457	7.5786	−35,249.3533
2	−6.7172	−0.6338	6.7172	0.6338	6.0834	3.0417	0.3288	3.6755	−3.6755	2.2206	0.4503	6.8034	−36,317.9900
3	−6.5743	−0.4689	6.5743	0.4689	6.1055	3.0527	0.3276	3.5216	−3.5216	2.0312	0.4923	8.4241	−37,386.6383

stability. The softness value of the molecules is the numerical value of the polarization property of the molecules [36]. Soft molecules are more reactive because soft molecules are more reactive than hard molecules and can easily donate electrons to an acceptor [37].

Although many parameters are calculated as a result of the calculations, only a few parameters are visualized. these images are given in Fig. 4. in this way, the optimized structures of the molecules include HOMO, LUMO, and the representation of the electrostatic potentials of the molecules. Electrostatic potentials of molecules give information about electron density. Although the red-colored regions are high in electron density, the blue-colored regions are electron poor [37]. As a result of the Gaussian calculations, it was seen that 4Dea-Salbsh molecule among the 3 studied molecules had higher activity than the other molecule in all methods.

3.3.2. *Molecular docking calculations of synthesized compounds*

After examining the DFT properties of molecules, it is important to compare the activity against biological materials to achieve better and more reliable results. In the study, the most important of many factors affecting the results obtained against proteins to compare the activities of molecules is the chemical interaction that occurs between proteins and molecules. These chemical interactions that occur are shown in Fig. 5 (interactions 4Dea-Salbsh with AChE and BchE enzyme) and Supplementary Figs. 9–12 (interactions of 4Dea-Salesh and 4Dea-Salpsh compounds with AChE and BchE enzyme). As a result of molecular docking calculations, many parameters are calculated, which are made to compare the molecule's activities and examine the chemical interactions that occur. Many parameters are calculated in these calculations and are given in Table 3. In this table, some of the given parameters are the parameters used to compare the activities of the molecules, and some of them give the numerical value of the interactions between molecules and proteins (Glide hbond, Glide evdw, and Glide ecoul), while the remaining parameters are related to the exposure that occurs as a result of chemical interactions between molecules and proteins. parameters (Glide emodel, Glide energy, Glide einternal, and Glide posenum) [38].

In the molecular docking calculations in the study, when the interactions of molecules with various enzyme proteins are examined, in Supplementary Fig. 9 when we examine the interaction between the molecule 4Dea-salesh and the AChE enzyme, it is seen that Pi-Pi stacking interaction occurs between the benzene ring in the center of the molecule and the TYR 341 protein. however, the hydroxy group attached to the benzene ring in the same center appears to form hydrogen bonds with the ASP 74 protein. at the same time, one of the interconnected nitrogen atoms appears to form hydrogen bonds with the ASP 74 protein. In Supplementary Fig.10 in the interaction of the molecule 4Dea-salpsh with the AChE enzyme, it is seen that the benzene haka in the center of the molecule creates a Pi-Pi stacking interaction with the TYR 341 and TRP 286 proteins. It is seen that one of the two nitrogen atoms bonded to each other in the molecule forms a hydrogen bond with the TYR 124 protein. In Fig. 5(A), it is seen that the interaction between the molecule 4Dea-salbsh and the AChE enzyme creates a Pi-Pi stacking interaction with the benzene ring TRP 286 and TYR 341 in the center of the molecule. however, one of the nitrogen atoms bonded to each other in the molecule makes a hydrogen bond with TYR 124. In Supplementary Fig. 11, in the interaction between the molecule 4Dea-salesh and the BChE enzyme, hydrogen bonding occurs between the hydroxy group attached to the benzene ring in the center of the molecule and the SER 287 protein. In Supplementary Fig. 12, it is seen that hydrophobic and polar interactions occur in the interaction between the molecule 4Dea-salpsh and the BChE enzyme. In Fig. 5(B), in the interaction between the molecule 4Dea-salbsh and the BChE enzyme, it is seen that Pi-Pi stacking interaction occurs with the benzene ring PHE 329 protein located in the center of the molecule. however, it is seen that the molecule generally has a hydrophobic and charged (negative) interaction. According to Docking results, it has been observed that docking score and hydrogen bonds play an important role in the interaction between molecules and the active site of the enzyme. The interaction of

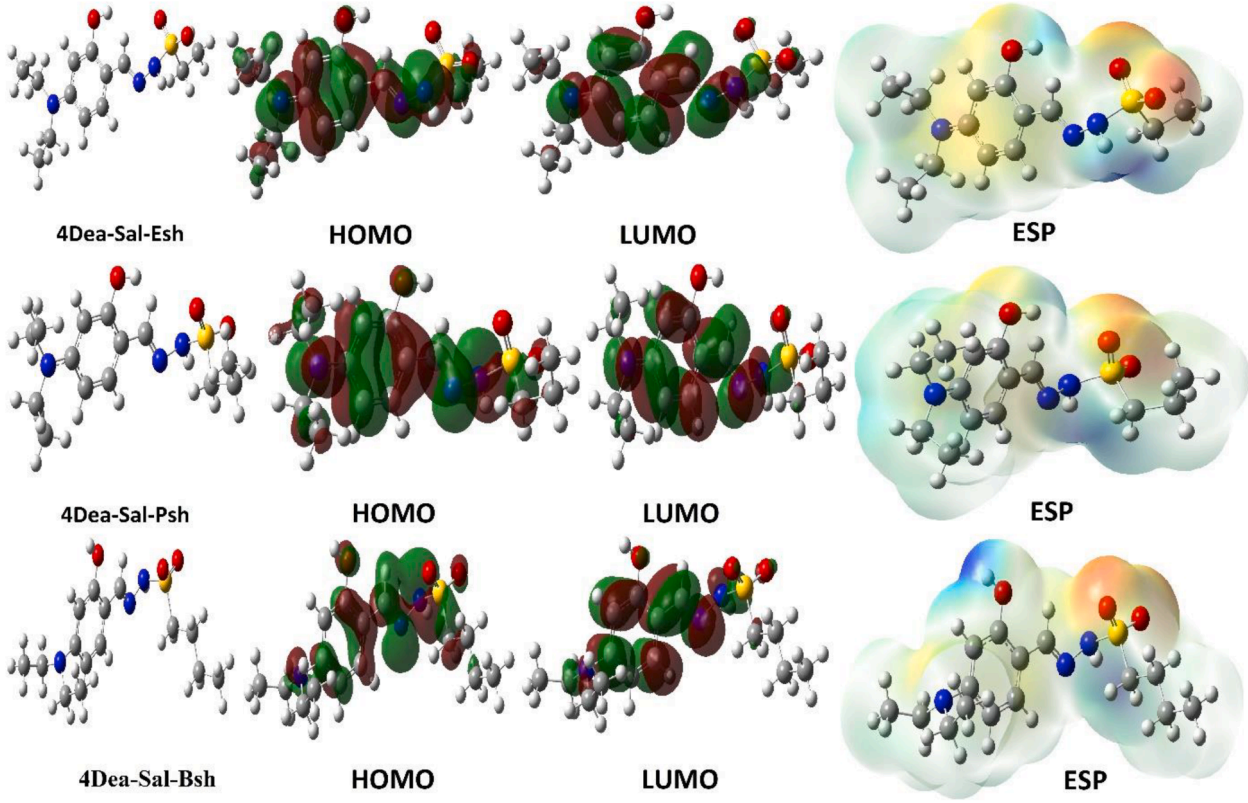


Fig. 4. Representations of optimized structures, HOMO, LUMO, and ESP.

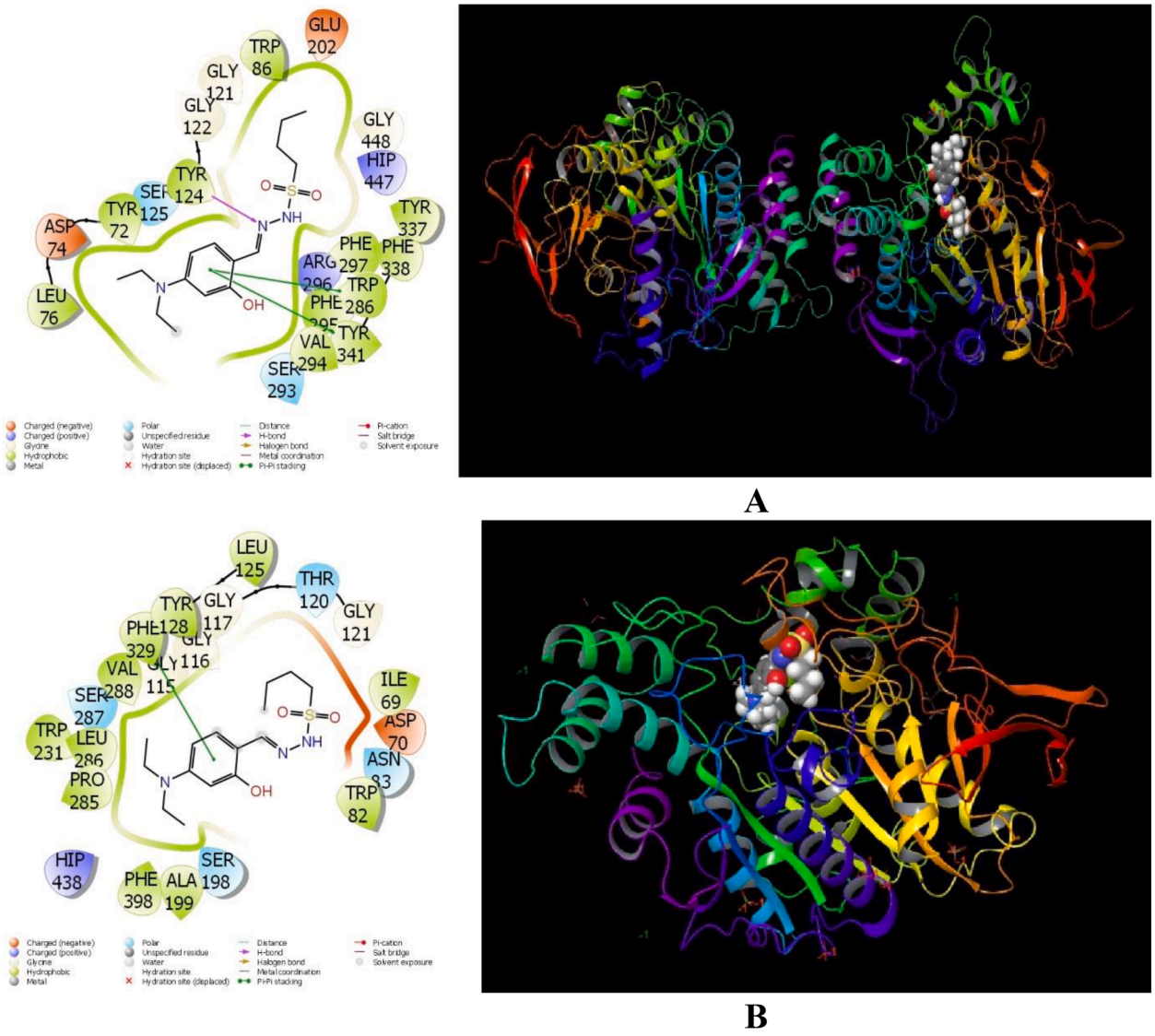


Fig. 5. Presentation interactions of 4Dea-Salbsh with AChE enzyme (A) and BChE(B).

Table 3
Numerical values of the docking parameters of molecule against enzymes.

4M0E	Docking Score	Glide ligand efficiency	Glide hbond	Glide evdw	Glide ecoul	Glide emodel	Glide energy	Glide einternal	Glide posenum
1	−6.33	−0.32	−0.32	−31.24	−5.84	−47.73	−37.09	6.47	361
2	−6.78	−0.32	−0.32	−36.54	−7.18	−56.86	−43.73	5.18	379
3	−6.84	−0.28	−0.32	−38.27	−9.11	−59.22	−47.38	7.83	168
1OCE	Docking Score	Glide ligand efficiency	Glide hbond	Glide evdw	Glide ecoul	Glide emodel	Glide energy	Glide einternal	Glide posenum
1	−5.67	−0.28	0.00	−34.65	−4.76	−49.48	−39.41	6.29	8
2	−5.52	−0.26	0.00	−38.90	−2.90	−51.98	−41.80	8.17	377
3	−5.69	−0.21	0.00	−37.16	−8.13	−61.51	−45.30	13.52	161
5NN0	Docking Score	Glide ligand efficiency	Glide hbond	Glide evdw	Glide ecoul	Glide emodel	Glide energy	Glide einternal	Glide posenum
1	−4.51	−0.23	−0.32	−30.45	−4.79	−43.87	−35.23	3.68	167
2	−4.85	−0.23	0.00	−30.48	−1.54	−32.31	−32.02	7.74	374
3	−6.34	−0.29	0.00	−40.91	−0.87	−51.44	−41.78	11.52	320
6R6V	Docking Score	Glide ligand efficiency	Glide hbond	Glide evdw	Glide ecoul	Glide emodel	Glide energy	Glide einternal	Glide posenum
1	−6.34	−0.32	−0.38	−40.57	−5.28	−54.46	−45.84	9.75	176
2	−5.91	−0.27	−0.41	−40.00	−4.63	−56.10	−44.62	3.26	287
3	−6.64	−0.28	−0.30	−31.10	−8.14	−49.08	−39.25	5.71	296

the molecules with the choline esterase enzyme was compared with theoretical calculations. As a result of this comparison, it was seen that 4-Dea-salbsh molecule had higher activity than other molecules.

3.3.3. ADME/T analysis of synthesized compounds

Although the molecular docking calculations made allow us to comment on the activities of the molecules, they do not provide sufficient data for the molecules to be taken into human metabolism as drugs. For this, it is important to examine the molecules by making ADME/T analysis. Many parameters calculated as a result of this analysis are useful to collect the necessary information in Table 4. The parameter obtained as a result of the calculations examines both its chemical properties and biological properties. Some of the investigated chemical properties of molecules are molar mass (mol MW), dipole moment (dipole), Total solvent accessible surface area (SASA), volume (volume), number of hydrogens (donorHB and accptHB), Globularity descriptor (glob), Predicted polarizability (QPpolrz) values. In addition, some of the examined biological properties of molecules are predicted IC_{50} value for blockage of HERG $K+$ channels (QPlogHERG), Predicted apparent Caco-2 cell permeability (QPPCaco), predicted brain/blood partition coefficient (QPlogBB) [39].

But among the calculated parameters, two parameters decide whether the molecules can be drugs. These are RuleOfFive, which is the number of violations of Lipinski's rule of five, and RuleOfThree, which is the number of violations of Jorgensen's rule of three [40]. The numerical value of these parameters is desired to be zero for a good drug molecule.

This is the first report to our knowledge that sulfonyl hydrazone derivatives (4Dea-salesh, 4Dea-salpsh, 4Dea-salbsh) have a significant inhibition effect over Acetyl and butyryl choline enzymes. The limitations of our study are that we did not evaluate the cytotoxicity tests of sulfonylhydrazone compounds on cell culture and antimicrobial activity in vitro assay.

Table 4
ADME properties of molecules.

	4Dea-Salesh	4Dea-Salpsh	4Dea-Salbsh	Referance Range
mol_MW	299	313	327	130–725
dipole (D)	8.2	8.0	7.9	1.0–12.5
SASA	589	612	644	300–1000
FOSA	331	365	397	0–750
FISA	153	143	143	7–330
PISA	103	103	103	0–450
WPSA	1	1	1	0–175
volume (A^3)	999	1047	1107	500–2000
donorHB	2	2	2	0–6
accptHB	6.3	6.3	6.3	2.0–20.0
glob (Sphere =1)	0.8	0.8	0.8	0.75–0.95
QPpolrz (A^3)	29.0	30.3	32.1	13.0–70.0
QPlogPC16	9.7	10.1	10.7	4.0–18.0
QPlogPoct	16.2	16.5	17.0	8.0–35.0
QPlogPw	10.0	9.7	9.6	4.0–45.0
QPlogPo/w	1.9	1.6	2.6	−2.0–6.5
QPlogS	−3.3	−3.6	−3.9	−6.5–0.5
CIQPlogS	−3.2	−3.5	−3.7	−6.5–0.5
QPlogHERG	−4.9	−5.0	−5.2	*
QPPCaco (nm/*sec*)	351	438	438	**
QPlogBB	−1.5	−1.5	−1.6	−3.0–1.2
QPPMDCK (nm/*sec*)	162	206	206	**
QPlogKp	−3.1	−2.8	−2.7	Kp in cm/hr
IP (ev)	8.0	8.0	8.0	7.9–10.5
EA (eV)	0.7	0.7	0.7	−0.9–1.7
#metab	2	2	2	1–8
QPlogKhsa	−0.3	−0.2	−0.1	−1.5–1.5
Human Oral Absorption	3	3	3	–
Percent Human Oral Absorption	84	84	90	***
PSA	88	84	84	7–200
RuleOfFive	0	0	0	Maximum is 4
RuleOfThree	0	0	0	Maximum is 3
Jm	0.1	0.1	0.1	–

* corcern below −5.
** <25 is poor and >500 is great.
*** <25% is poor and >80% is high.

4. Conclusions

In the present study, sulfonyl hydrazone derivatives (4Dea-salesh, 4Dea-salpsh, and 4Dea-salbsh) were synthesized and characterized by using elemental analyses and spectroscopic methods (FT-IR, ^1H, and ^{13}C NMR). This synthetic method has advantages such as room temperature, short time, and good selectivity to the development trend of green chemistry.

According to biological activity results, the three compounds against the AChE enzyme and the BChE enzyme showed inhibitory properties, especially 4Dea-salbsh exhibited the best activity with IC_{50} value of 9.549±0.75 μM on AChE and can be used as a potential inhibitor for the treatment of Alzheimer's disease. The interaction of the molecules with the choline esterase enzyme was compared with theoretical calculations. As a result of this comparison, it was seen that 4-Dea-salbsh molecule had higher activity than other molecules. The remarkable activity of compound the 4dea-salbsh may be arising from increasing methyl units, which may play an important role in biological activities. Changing the alkyl chain increases lipophilicity and easily passes the cell membrane. Physicochemical properties, lipophilicity, water-solubility, pharmacokinetics, drug-likeness, and medicinal chemistry properties were calculated for the synthesized molecules. Analysis of the ADME parameters for compounds showed their optimal oral drug-like traits in most compounds and the potential for development as candidates for oral drugs. To evaluate the binding interactions between the compounds and enzymes molecular docking studies were performed. According to Docking results, it has been observed that docking score and hydrogen bonds play an important role in the interaction between molecules and the active site of the enzyme.

As a result of the theoretical calculations, the activities of the molecules were examined by both gaussian calculations and molecular docking calculations. show the results obtained. indicates that the molecules will be good drug molecules for further studies.

CRediT authorship contribution statement

Ummuhan Ozdemir Ozmen: Project administration, Conceptualization, Methodology, Visualization, Writing – original draft, Funding acquisition, Supervision. **Burak Tuzun:** Project administration, Software, Validation, Writing – review & editing, Formal analysis, Data curation. **Esra Bilen Ayan:** Investigation, Methodology, Resources, Writing – review & editing. **Bekir Sıtkı Cevrimli:** Resources, Writing – review & editing.

Declaration of Competing Interest

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

Data availability

Data will be made available on request.

Acknowledgments

This research was supported by Gazi University Research Fund under Project No 05/2019–01. The numerical calculations reported in this paper were fully/partially performed at TUBITAK ULAKBIM, High Performance and Grid Computing Center (TRUBA resources). This work

was supported by the Scientific Research Project Fund of Sivas Cumhuriyet Uniney (CUBAP) under project number RGD-020.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2023.135514.

References

[1] H. Göçer, A. Akıncıoğlu, N. Öztaşkın, S. Göksu, İ. Gülçin, Synthesis, antioxidant, and antiacetylcholinesterase activities of sulfonamide derivatives of dopamine-related compounds, Arch. Pharm. (Weinheim) 346 (2013) 783–792.

[2] D. Nachmansohhn, Modern Trens in Physiology. Biochemistry, Academic Pres, New York, 1952.

[3] A.N. Çokuğraş, Butyrylcholinesterase: structure and physiological importance, Turkish J. Biochem. 28 (2003) 54–61.

[4] A.R. Allam, G.R. Sridhar, U.N. Das, Elevated butrylcholinesterase and acetylcholinesterase may predict the development of type 2 diabetes mellitus and Alzheimer's disease, Med. Hypothesis Discov. Innov. Ophthalmol. 69 (6) (2007) 1272–1276.

[5] G. David, P.T. Wilkinson, E. Schwam, J.P. Parrish, Cholinesterase inhibitors used in the treatment of alzheimer's disease. the relationship between pharmacological effects and clinical efficacy, Drugs Aging 21 (7) (2004) 453–478.

[6] D. Grisaru, M. Sternfeld, A. Eldor, D. Glick, H. Soreq, Structural roles of acetylcholinesterase variants in biology and pathology, Eur. J. Biochem. 264 (1999) 672–686.

[7] G. David, P.T. Wilkinson, E. Schwam, J.P. Parrish, Cholinesterase inhibitors used in the treatment of alzheimer's disease. the relationship between pharmacological effects and clinical efficacy, Drugs Aging 21 (2004) 453–478.

[8] J. Moeker, T. Peat, L. Bornaghi, D. Vullo, C. Supuran, S. Poulsen, Cyclic secondary sulfonamides: unusually good inhibitors of cancer-related carbonic anhydrase enzymes, J. Med. Chem. 57 (8) (2014) 3522–3531.

[9] S. Monti, C. Supuran, G. De Simone, Anticancer carbonic anhydrase inhibitors: a patent review, Expert Opin. Ther. Pat. 23 (6) (2013) 737–749.

[10] M. Kaya, E. Demir, H. Bekci, Synthesis, characterization and antimicrobial activity of novel xanthene sulfonamide and carboxamide derivatives, J. Enzyme Inhib. Med. Chem. 28 (5) (2012) 885–893.

[11] R. Ulus, İ. Yeşildağ, M. Tanç, M. Bülbül, M. Kaya, C. Supuran, Synthesis of novel acridine and bis acridine sulfonamides with effective inhibitory activity against the cytosolic carbonic anhydrase isoforms II and VII, Bioorg. Med. Chem. 21 (18) (2013) 5799–5805.

[12] H. Girisha, J.Narendra Sharath Chandra, S. Boppana, M. Malviya, C. Sadashiva, K. Rangappa, Active site-directed docking studies: synthesis and pharmacological evaluation of cis-2,6-dimethyl piperidine sulfonamides as inhibitors of acetylcholinesterase, Eur. J. Med. Chem. 44 (10) (2009) 4057–4062.

[13] E.Kocaman Akıncıoğlu, H. Akıncıoğlu, R. Ekhteiari Salmas, S. Durdagi, I. Gülçin, C. T. Supuran, S. Göksu, The synthesis of novel sulfamides derived from β-benzylphenethylamines as acetylcholinesterase, butyrylcholinesterase and carbonic anhydrase enzymes inhibitors, Bioorg. Chem. 74 (2017) 238–250.

[14] M. Prinz, S. Parlar, G. Bayraktar, V. Alptüzün, E. Erciyas, A. Fallarero, D. Karlsson, P. Vuorela, M. Burek, C. Förster, E. Turunc, G. Armagan, A. Yalcin, C. Schiller, K. Leuner, M. Krug, C. Sotriffer, U. Holzgrabe, 1,4-Substituted 4-(1H)-pyridylene-hydrazone-type inhibitors of AChE, BuChE, and amyloid-β aggregation crossing the blood–brain barrier, Eur. J. Pharm. Sci. 49 (4) (2013) 603–613.

[15] V. Alptüzün, M. Prinz, V. Hörr, J. Scheiber, K. Radacki, A. Fallarero, P. Vuorela, B. Engels, H. Braunschweig, E. Erciyas, U. Holzgrabe, Interaction of (benzylidene-hydrazono)-1,4-dihydropyridines with β-amyloid, acetylcholine, and butyrylcholine esterases, Bioorg. Med. Chem. 18 (5) (2010) 2049–2059.

[16] U. Ozdemir, O.S. Senturk, S. Sert, N. Karacan, F. Ugur, Reaction of metal carbonyls with 2-hydroxy-1-naphthaldeyde methanesulfonylhydrazone and characterization of the substitution products, J. Coord. Chem. 59 (17) (2006) 1905–1911.

[17] U. Ozdemir, N. Karacan, O.S. Senturk, S. Sert, F. Ugur, Synthesis and characterization of metal carbonyl complexes of M(CO)(6)(M = Cr, Mo, and W), *Re*(CO)(5)Br, and Mn(CO)(3)CP with - acetonemethanesulfonylhydrazone (amsh) and methanesulfonylhydrazone (msh) synthesis and reactivity in inorganic and metal-organic chemıstry. 34(6) (2004) 1057–1067.

[18] O.S. Senturk, U. Ozdemir, S. Sert, N. Karacan, F. Ugur, Photochemical reactions of metal carbonyls [M(CO)(6) (M = Cr, Mo, W), *Re*(CO)(5)Br, Mn(CO)(3)Cp] with salicylaldehyde ethanesulfonylhydrazone (Hsalesh), J. Coord. Chem. 60 (2) (2007) 229–235.

[19] U.O. Ozdemir, F. Ilbiz, A.Balaban Gunduzalp, N. Ozbek, Z. Karagoz Genç, F. Hamurcu, S. Tekin, Alkyl sulfonic acid hydrazides: synthesis, characterization, computational studies and anticancer, antibacterial, anticarbonic anhydrase II(hCA II) activities, J. Mol. Struct. 1100 (2015) 464–474.

[20] E. Bilen, U.O. Ozmen, S. Cete, S. Alyar, A. Yasar, Bioactive sulfonyl hydrazones with alkyl derivative: characterization, ADME properties, molecular docking studies and investigation of inhibition on choline esterase enzymes for the diagnosis of Alzheimer's disease, Chem. Biol. Interact. 360 (2022).

[21] D. Becke, Density-functional thermochemistry. I. The effect of the exchange-only gradient correction, J. Chem. Phys. 96 (3) (1992) 2155–2160.

[22] E.G. Hohenstein, S.T. Chill, C.D. Sherrill, Assessment of the performance of the M05− 2X and M06− 2X exchange-correlation functionals for noncovalent interactions in biomolecules, J. Chem. Theory Comput. 4 (12) (2008) 1996–2000.

[23] J. Cheung, E.N. Gary, K. Shiomi, T.L. Rosenberry, Structures of human acetylcholinesterase bound to dihydrotanshinone I and territrem B show peripheral site flexibility, ACS Med. Chem. Lett. 4 (11) (2013) 1091–1096.

[24] S. Pajk, D. Knez, U. Košak, M. Zorović, X. Brazzolotto, N. Coquelle, S. Gobec, Development of potent reversible selective inhibitors of butyrylcholinesterase as fluorescent probes, J. Enzyme Inhib. Med. Chem. 35 (1) (2020) 498–505.

[25] G.L. Ellman, K.D. Courtney, V.J.R. Andres, R.M. Featherstone, A new and rapidcolorimetric determination of acetylcholinesterase activity, Biochem. Pharmacol. 7 (2) (1961) 88–95.

[26] R. Dennington, T.A. Keith, J.M. Millam, GaussView 6.0. 16, Semichem Inc., Shawnee Mission, KS, USA, 2016.

[27] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishi7V87621da, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A. D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 09, Revision C.01, Gaussian Inc., Wallingford CT, 2009.

[28] E.H. Alici, A.T. Bilgiçli, B. Tüzün, A. Günsel, G. Arabaci, M.N. Yarasir, Alkyl chain modified metalophthalocyanines with enhanced antioxidant-antimicrobial properties by doping Ag+ and Pd2+ ions, J. Mol. Struct. 1257 (2022), 132634.

[29] Schrödinger Release 2021-3, Maestro, Schrödinger, LLC, New York, NY, 2021.

[30] Schrödinger Release 2019-4: Protein Preparation Wizard, Epik, Schrödinger, LLC, New York, NY, 2016.Impact, Schrödinger, LLC, New York, NY, 2016; Prime, Schrödinger, LLC, New York, NY, 2019.

[31] Schrödinger Release 2021-3: LigPrep, Schrödinger, LLC, New York, NY, 2021.

[32] M. Rbaa, S. Haida, B. Tuzun, A. El Hassane, A. Kribii, Y. Lakhrissi, E. Berdimurodov, Synthesis, characterization and bioactivity of novel 8-hydroxy-quinoline derivatives: experimental, molecular docking, DFT and POM analyses, J. Mol. Struct. 1258 (2022), 132688.

[33] Schrödinger Release 2021-3: QikProp, Schrödinger, LLC, New York, NY, 2021.

[34] U. Ozmen Ozdemir, A. Altuntas, A. Balaban Gündüzalp, F. Arslan, F. Hamurcu, New aromatic/heteroaromatic propanesulfonylhydrazone compounds: synthesis, physical properties and inhibition studies against carbonic anhydrase II (CAII) enzyme, Spectrochim. Acta, Part A 128 (2014) 452–460.

[35] H. Yalazan, B. Tüzün, D. Akkaya, B. Barut, H. Kantekin, S. Yıldırmış, Quinoline-fused both non-peripheral and peripheral ZnII and MgII phthalocyanines: anti-cholinesterase, anti-α-glucosidase, DNA nuclease, antioxidant activities and in silico studies, Appl. Organomet. Chem. (2022) e6696.

[36] D. Majumdar, B. Tüzün, T.K. Pal, S. Das, K. Bankura, Architectural view of flexible aliphatic–OH group coordinated hemi-directed Pb (II)-salen coordination polymer: synthesis, crystal structure, spectroscopic insights, supramolecular topographies, and DFT perspective, J. Inorg. Organomet. Polym. Mater. (2022) 1–18.

[37] M. Rezaeivala, S. Karimi, B. Tuzun, K. Sayin, Anti-corrosion behavior of 2-((3-(2-morpholino ethylamino)-N3-((pyridine-2-yl) methyl) propylimino) methyl) pyridine and its reduced form on carbon steel in hydrochloric acid solution: experimental and theoretical studies, Thin. Solid. Films 741 (2022), 139036.

[38] M. El Faydy, N. Dahaieh, K. Ounine, B. Lakhrissi, I. Warad, B. Tüzün, A. Zarrouk, Synthesis, identification, antibacterial activity, ADME/T and 1BNA-docking investigations of 8-quinolinol analogs bearing a benzimidazole moiety, Arab. J. Sci. Eng. 47 (1) (2022) 497–510.

[39] S.Faramarz Poustforoosh, M.H. Nematollahi, H. Hashemipour, B. Tüzün, A. Pardakhty, M. Mehrabani, 3D-QSAR, molecular docking, molecular dynamics, and ADME/T analysis of marketed and newly designed flavonoids as inhibitors of Bcl-2 family proteins for targeting U-87 glioblastoma, J. Cell. Biochem. 123 (2) (2022) 390–405.

[40] W.J. Jorgensen, E.M. Duffy, Prediction of drug solubility from the structure, Adv. Drug. Deliv. Rev. 54 (3) (2002) 355–366.