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RESEARCH ARTICLE

THEORETICAL ELECTRONIC PROPERTIES, ADMET PREDICTION, and MOLECULAR DOCKING STUDIES of SOME IMIDAZOLE DERIVATIVES

Sevtap ÇAĞLAR YAVUZ[1*]

[1*]Erzincan Binali Yıldırım University, İliç Dursun Yıldırım Vocational School, Department of Medical Services and Technicians, sevtap.yavuz@erzincan.edu.tr, ORCID: 0000-0001-6497-2907

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ABSTRACT

Imidazole is a significant component of heterocyclic compounds and is employed in a wide range of practices. It is recognized that different imidazole-based constructions exhibit various biological activity features. Ten imidazole derivatives prepared from phenylglyoxal monohydrate and different guanylhydrazones were designed in our previous publication. This study was focused on the structural/electronic properties of these known imidazole derivatives. The molecular geometry of the compounds was calculated using Spartan 10 software and the structure was optimized using the DFT/B3LYP method with the 6-31G** basis set ground state. Also, *in silico* evaluation of imidazole derivatives was carried out using UCSF Chimera and AutoDock Vina software. The protein used in these calculations is the crystal structure of the 3SN6, beta2 adrenergic receptor-Gs protein complex, responsible for the hormonal regulation of adenylate cyclase.

Keyword: *Imidazole, DFT, Molecular docking, ADMET*

1. INTRODUCTION

Nitrogen-including heterocyclic compounds such as imidazole and benzimidazole display various biological activities. Imidazole and its derivatives are pharmacologically important scaffolds with a wide spectrum of activity, so they have attracted the attention of researchers in recent years. Imidazole-based structures indicate a wide range of biological activity features such as anticancer [1], anti-HIV [2], antitubercular [3], anti-hepatitis [4], antiinflammatory [5], antibacterial [6], antihypertensive [7], antioxidants [8], antiprotozoal [9] antimicrobial [10], antiviral [11], antifungal [12], and diverse enzyme inhibitors [13]. In the medical area, many imidazole-based compounds such as dacarbazine, temozolomide, mercaptopurine, nilotinib, and tipifarnib as clinical drugs have been commonly used to cure diverse types of cancers [14].

Relative to some heterocyclic molecules, imidazoles readily connect to protein molecules, and some imidazole drugs directly obstruct the synthesis of essential cell membrane components in high concentrations [15,16].

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Physicochemical features, over the few decades, have emerged as one of the important stages in drug discovery. The pharmaceutical descriptors provide a variety of suitable "drug-like" traits that can be advanced into structure-property collaboration [17]. Owing to imidazole compounds' unique optical, structural, and electronic properties, their applications have gradually attracted interest in recent years [18-20]. In here, the theoretical evaluation of synthesized imidazole compounds was made in the previous study [21]. The geometry of the molecules was determined theoretically by using the DFT method with the Spartan 10 package program. For the chemical stability of the structure, various parameters were calculated in the gas phase such as the highest occupied (E_{HOMO}) and lowest unoccupied molecular orbital (E_{LUMO}) energies, ovality, dipole moment (μ), electronegativity (χ) and chemical hardness (η) values. *In silico* studies such as DFT (Density Functional Theory) calculations, molecular modeling, and ADME predictions have been accomplished and debated to achieve more comprehensions into the structure-activity relationship of the imidazole derivative compounds. In this context, the physico-chemical and ADMET features were predicted. It was done molecular docking analysis of the imidazole derivative compounds using G protein-coupled receptors (GPCRs) as responsible for the majority of cellular responses.

2. MATERIALS AND METHODS

2.1. Theoretical Studies

All quantum chemical calculations were accomplished using the Spartan 10 program. Compounds (**1-10**) were computed by using the DFT method with B3LYP/6-31G** basic set. The molecular structures were visualized depending on the output data of the DFT computations again using the identical program. The general chemical structure and structural features of the studied compounds are given in Figure 1 and Table 1.

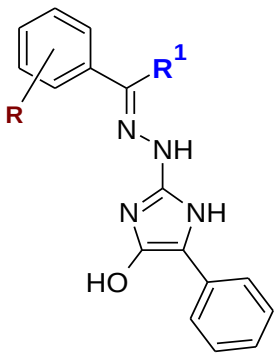

Figure 1. The chemical structure of studied compounds **(1-10)**.

Table 1. Structural features of studied compounds **(1-10)**.

Compounds	**R**	**R^1**
1	4-CH_3	H
2	H	H

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3	4-NO_2	H
4	2,4-*di*CH_3O	H
5	2-Cl-6-F	H
6	2-Cl	H
7	4-CH_3CH_2O	H
8	2,4-*di*Cl	H
9	4-Cl	H
10	H	CH_3

2.2. Docking and *In Silico* ADMET Studies

The inhibitory effect of the imidazole derivatives on the human beta2 adrenergic receptor-Gs protein was studied. Docking analyzes were performed using AutoDock Vina software and UCSF Chimera. The 3D structure of the beta2 adrenergic receptor (PDB code: 3SN6) in PDB format at 3.20 Å resolution was downloaded from the RSCB PDB website. The 2D structures of the ligands were drawn on ChemDraw Ultra 12.0 and optimized with Spartan 10 software [22]. The optimized structures were loaded into the UCSF Chimera tool. The docking analyzes of related compounds were operated utilizing the confirmed procedure present in the literature [23]. Interactions were visualized owing to Biovia Discovery Studio Visualizer [24]. The predicted ADMET properties were researched by way of the SwissADME website (http://www.swissadme.ch/). In addition, the estimated toxicity features of the compounds were studied by OSIRIS property Explorer (https://www.organic-chemistry.org/prog/peo/).

3. RESULTS AND DISCUSSION

3.1. Theoretical Studies

The visuals of the molecules obtained as a result of the calculations made with the Spartan 10 program are demonstrated in Figure 2. Frontier molecular orbital (FMO) analysis is extensively used to elucidate the optical and electronic features of organic compounds [25]. Notice of the HOMO and LUMO, and their properties is considerably helpful to evaluate the chemical reactivity of compounds [26]. A molecule with a high HOMO-LUMO energy gap has high kinetic stability and low chemical reactivity. In this way, it is distinctly from Table 2 that compound **2** (R and R'=H) is hard and more stable (less reactive), while compound **3** (R=4-NO_2 and R'=H) is soft and the least stable (more reactive). The calculation of HOMO displays that the surfaces are situated over imidazole and hydroxyl groups. The calculations of LUMO of the compound were seen on the aromatic ring attached to the Schiff base. Also, the electrostatic potential maps (EPM) with transparent shape are given in Figure 2. The electrostatic potentials at the surface are symbolized by diverse colors; red, blue, yellow, orange, and green. The fields with yellow, orange, and green are responsive to a low nucleophilic and electrophilic attack. It shows the high electron density (red in color) inside the aromatic ring attached to the imidazole ring. On the other hand, the electron density of the other aromatic ring in the compound varies according to the substituent attached to the ring (electron acceptor-electron donor). The dipole moment is an extensively utilized parameter to describe the chemical and physical properties of molecules associated with molecular stability [27,28]. In this work, the experimental dipole moment is not known. The computed dipole moments are demonstrated

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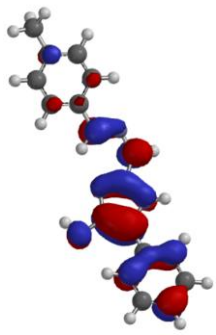
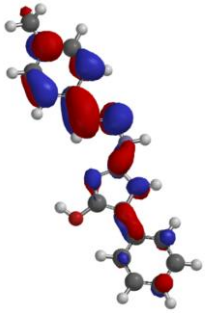
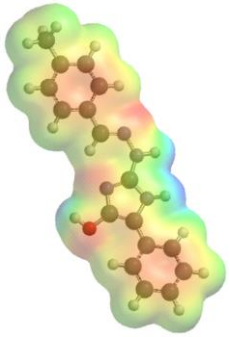
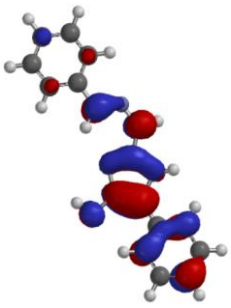
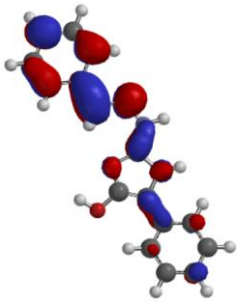
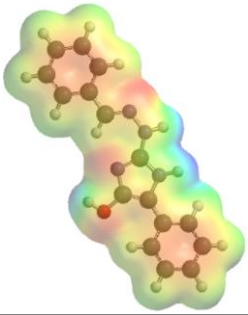
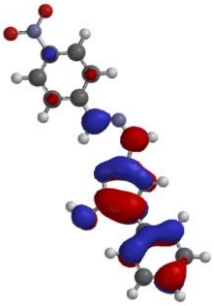
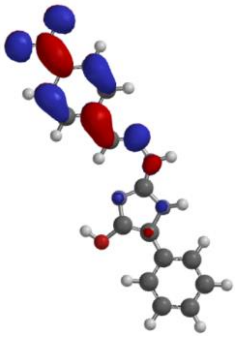
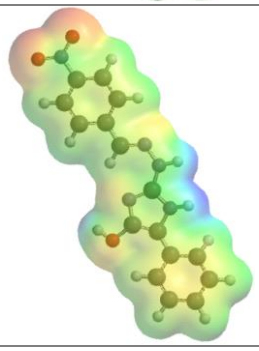
in Table 2. Among the calculated compounds **1–10**, compound **5** (R=2-Cl, 6-F, R'=H substituents) has the highest dipole moment.

1			
2			
3			

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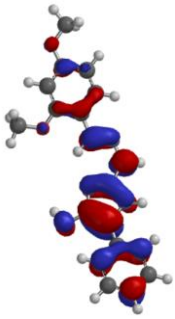
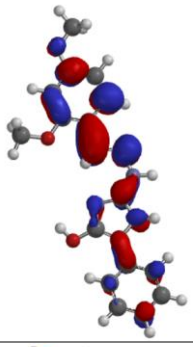
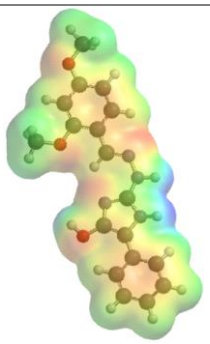
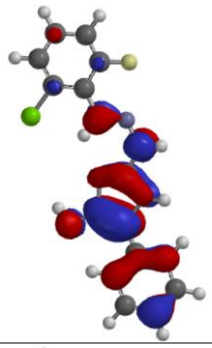
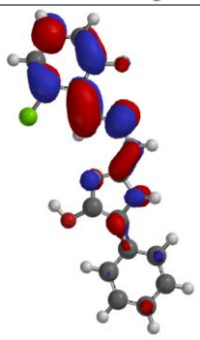
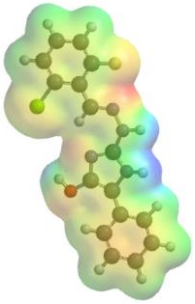
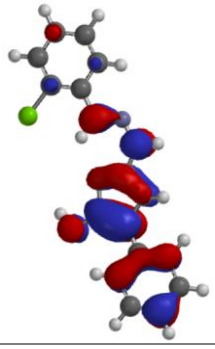
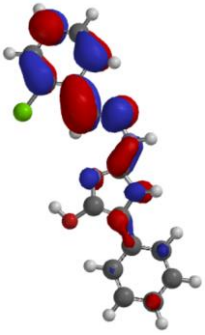
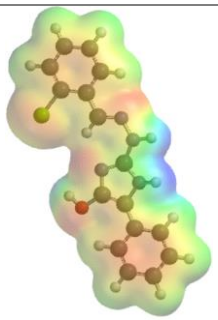
4			
5			
6			

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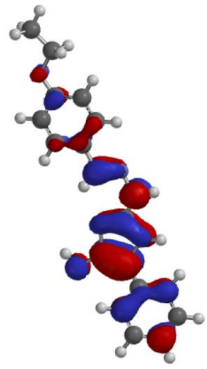
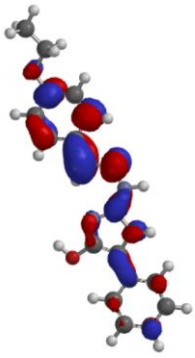
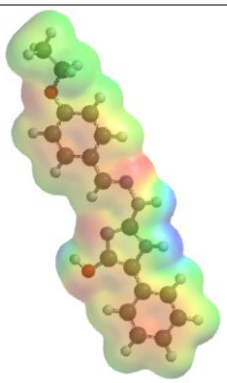
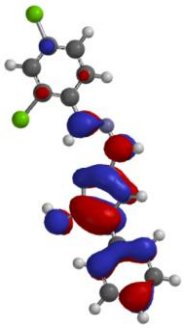
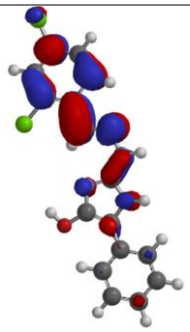
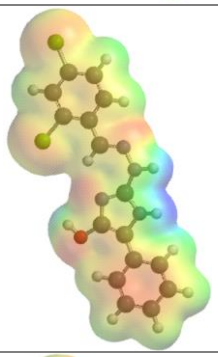
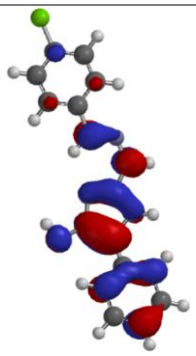
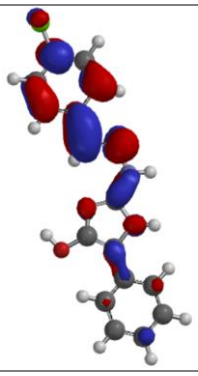
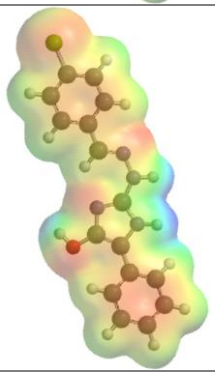
7			
8			
9			

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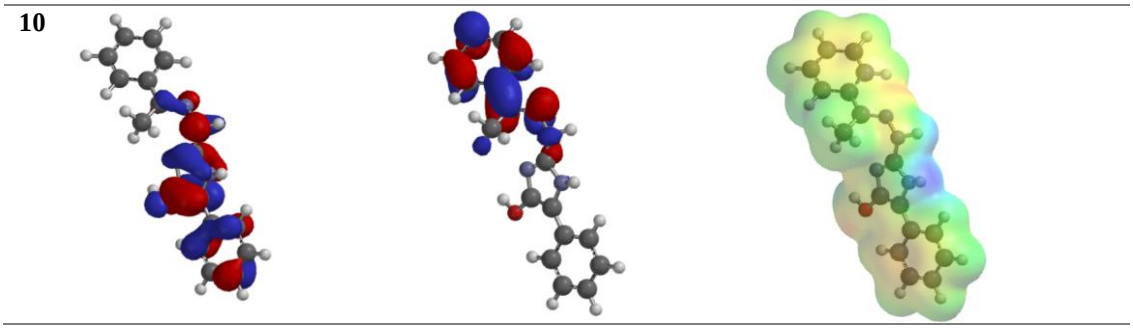

Figure 2. HOMO, LUMO and electrostatic potential maps as transparent for compounds (**1-10**).

Table 2. Some calculated electronic parameters of the optimized structure of compounds **(1-10)**.

Compound	*Energy*	E_{HOMO}	E_{LUMO}	ΔE	*Chemical Hardness (η)*	*Electronegativity (χ)*	*Ovality*	*Dipole moment (μ)*
1	-951.675560	-0.1735	-0.0383	0.1352	0.07	0.11	1.499	1.72
2	-912.354634	-0.1786	-0.0407	*0.1379*	0.07	0.11	1.467	1.71
3	-1516.85641	-0.1881	-0.0897	*0.0984*	0.05	0.14	1.513	4.36
4	-1141.40444	-0.1662	-0.0309	0.1353	0.07	0.10	1.554	2.03
5	-1471.17287	-0.1775	-0.0515	0.1260	0.06	0.11	1.493	5.09
6	-1371.94708	-0.1770	-0.0491	0.1279	0.06	0.11	1.487	3.82
7	-1066.20235	-0.1696	-0.0334	0.1362	0.07	0.10	1.547	3.00
8	-1431.54060	-0.1808	-0.0568	0.1240	0.06	0.12	1.514	3.98
9	-1371.94963	-0.1789	-0.0490	0.1299	0.06	0.11	1.494	3.24
10	-951.669185	-0.1734	-0.0404	0.1330	0.07	0.11	1.479	3.35

3.2. Molecular Docking Studies and ADMET Properties

The one of the great membrane proteins, GPCRs are assigned in signal transduction.These receptors have an important role various physiological and pathological conditions [29]. As mentioned above, imidazole derivative compounds which excellent pharmacological properties against beta2 adrenergic receptor-Gs protein complex investigated the molecular docking behavior. Binding affinity values were calculated to determine the inhibitory effects of compounds (**1-10**) on the human beta2 adrenergic receptor-Gs protein. According to this, compounds showed pretty good binding affinities.

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The binding affinities of the imidazole derivatives (**1-10**) were calculated as -8.9, -9.5, -7.3, -9.3, -9.6, -9.4, -7.4, -9.1, -6.8 and -8.4 kcal/mol, respectively. Compound **5** gave the lowest binding energy value (Table 3). The best interaction of the compound **5** was displayed as π-cation interaction (PHE R:320), π- π T-shaped interaction (PHE R:392), π-alkyl interaction (ILE R:411 and VAL R:247), and hydrogen bond interactions (ASN R:395 and TYR R:410). The three-dimensional interaction, the 2D structure, and the best binding pose of all of the compounds are shown in Figure 3. In this pose, compound **5** occurs salt bridges among the NH of the hydrazone and the carbonyl groups of residues ASP R:243 and PHE R:320. TYR R:410 and ASN R:395 form two hydrogen bonds with the hydroxyl attached to the imidazole group. In addition, TRP R:239 and CYS R:318 residues with the chlorine group attached to the aromatic ring form two halogen interactions.

Table 3. The docking results of imidazole derivatives, **1-10**.

Compounds	**Docking Score (kcal/mol)**	**RMSD (Å)**
1	-8.9	1.073
2	-9.5	1.608
3	-7.3	0.79
4	-9.3	1.341
5	-9.6	1.562
6	-9.4	1.551
7	-7.4	1.205
8	-9.1	1.15
9	-6.8	1.212
10	-8.4	1.285

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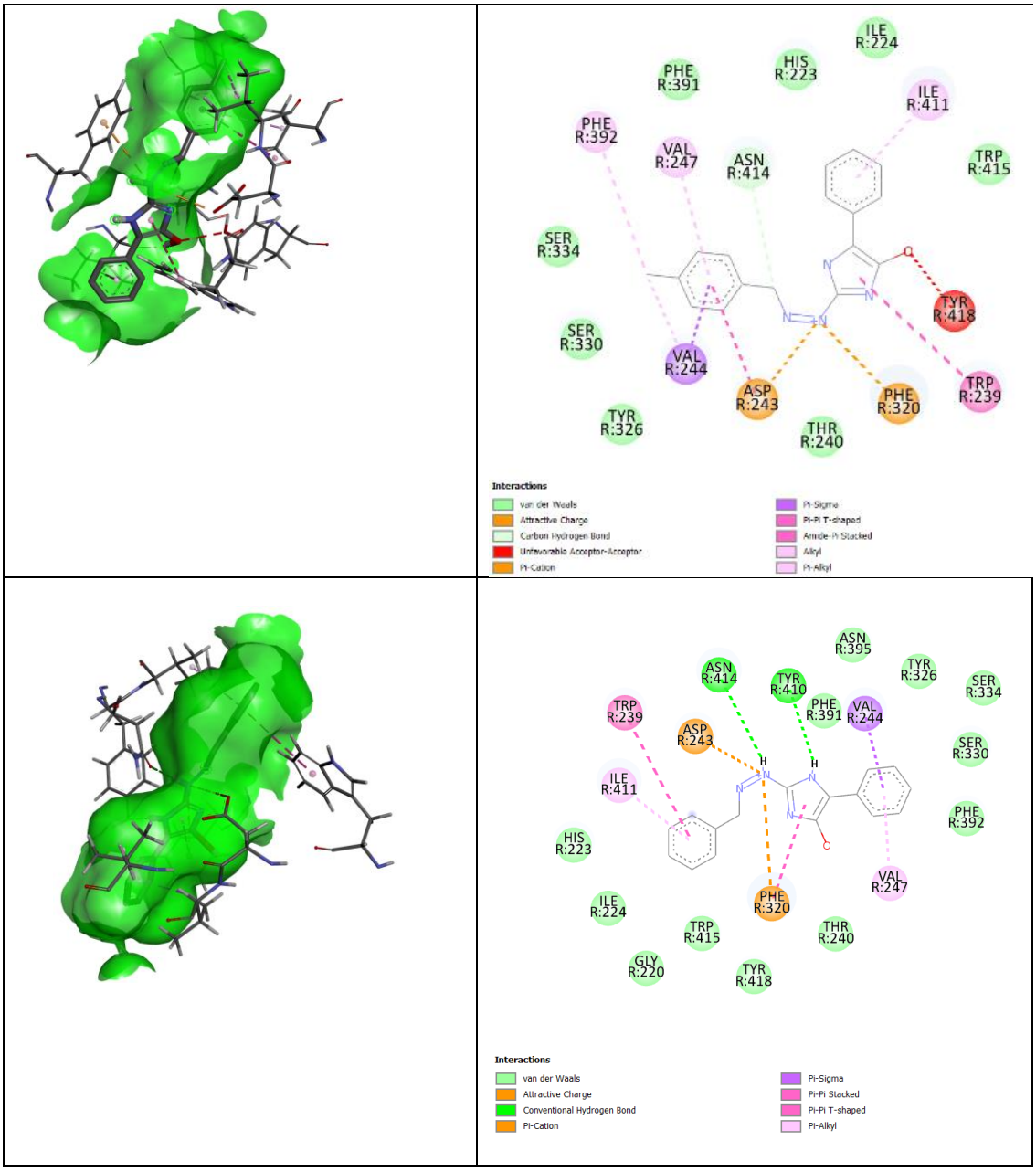

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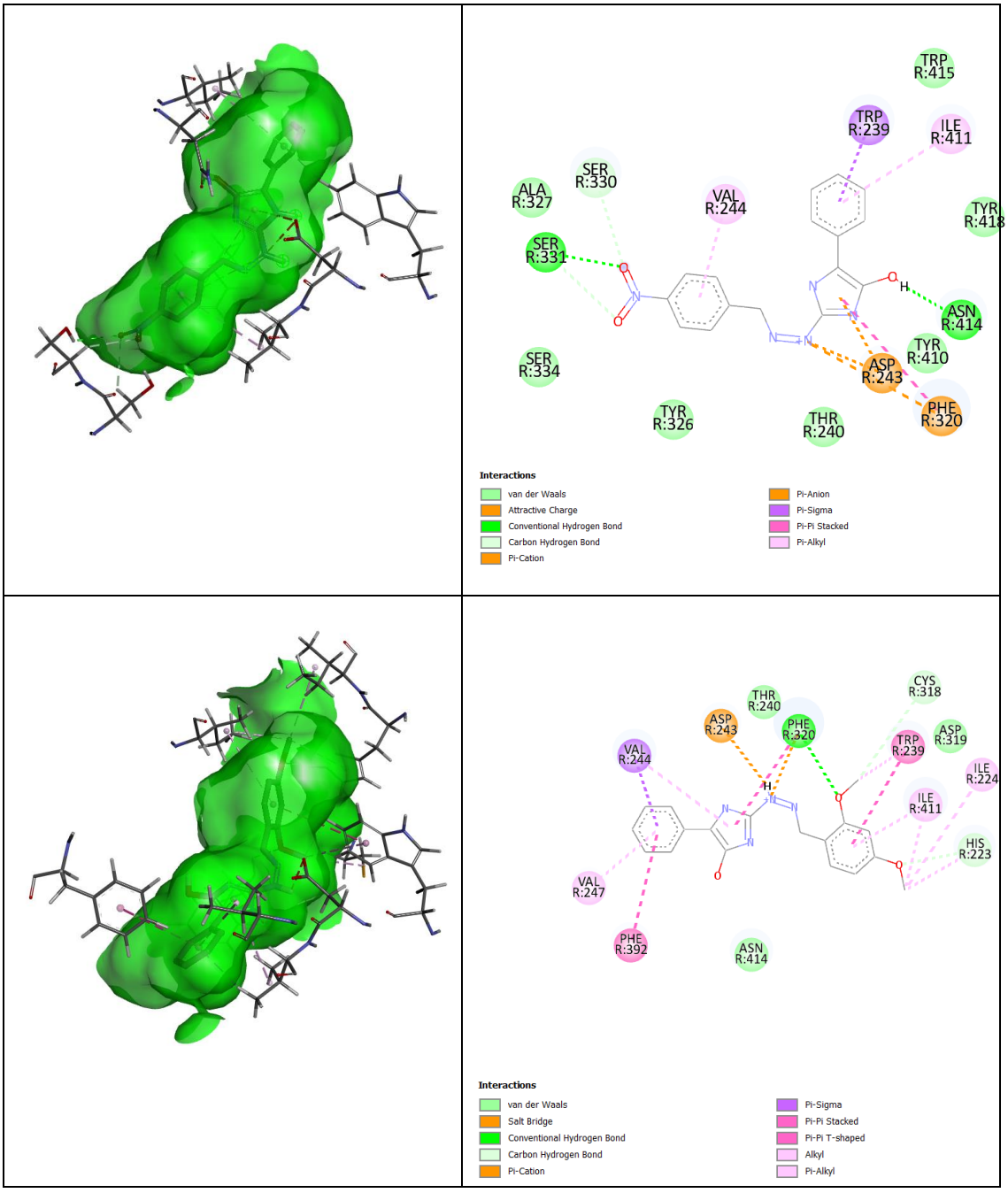

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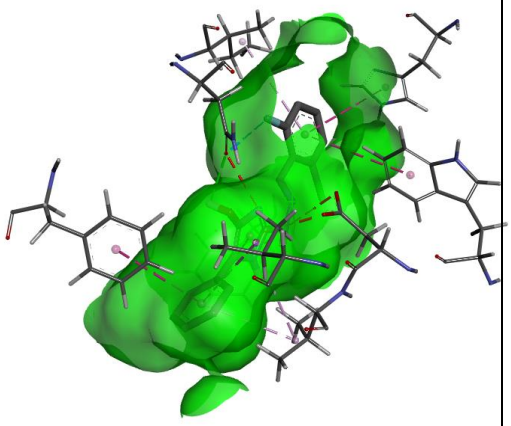	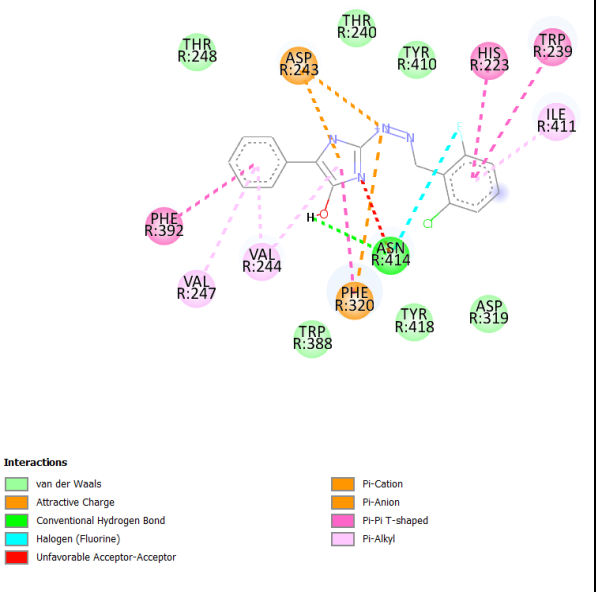
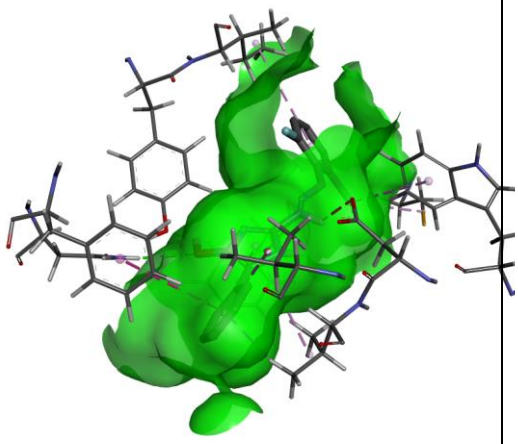	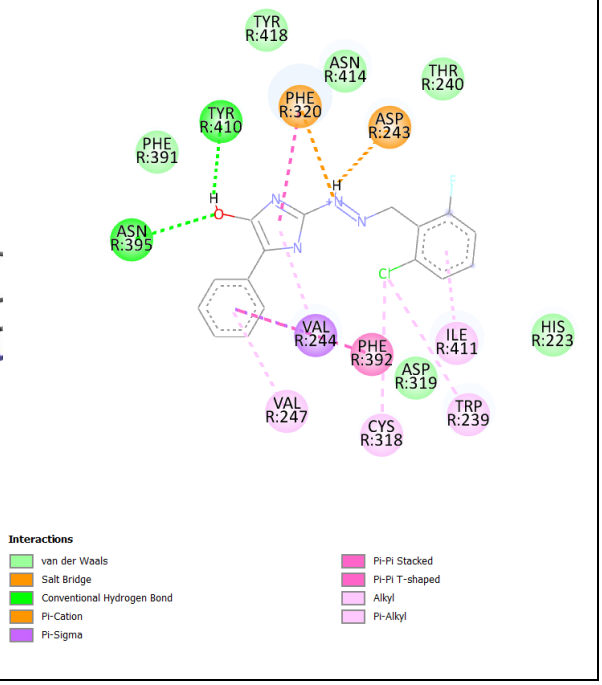

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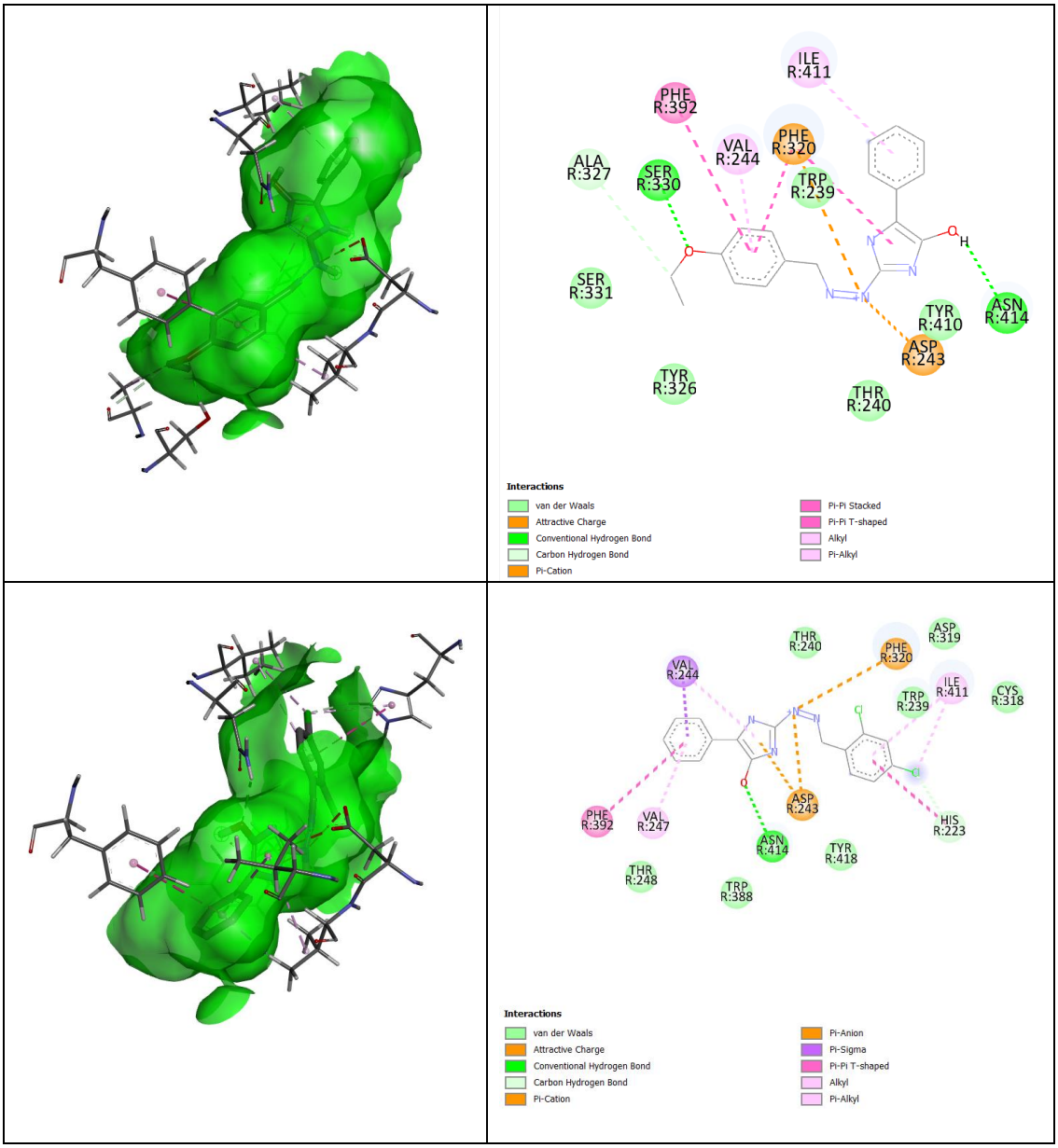

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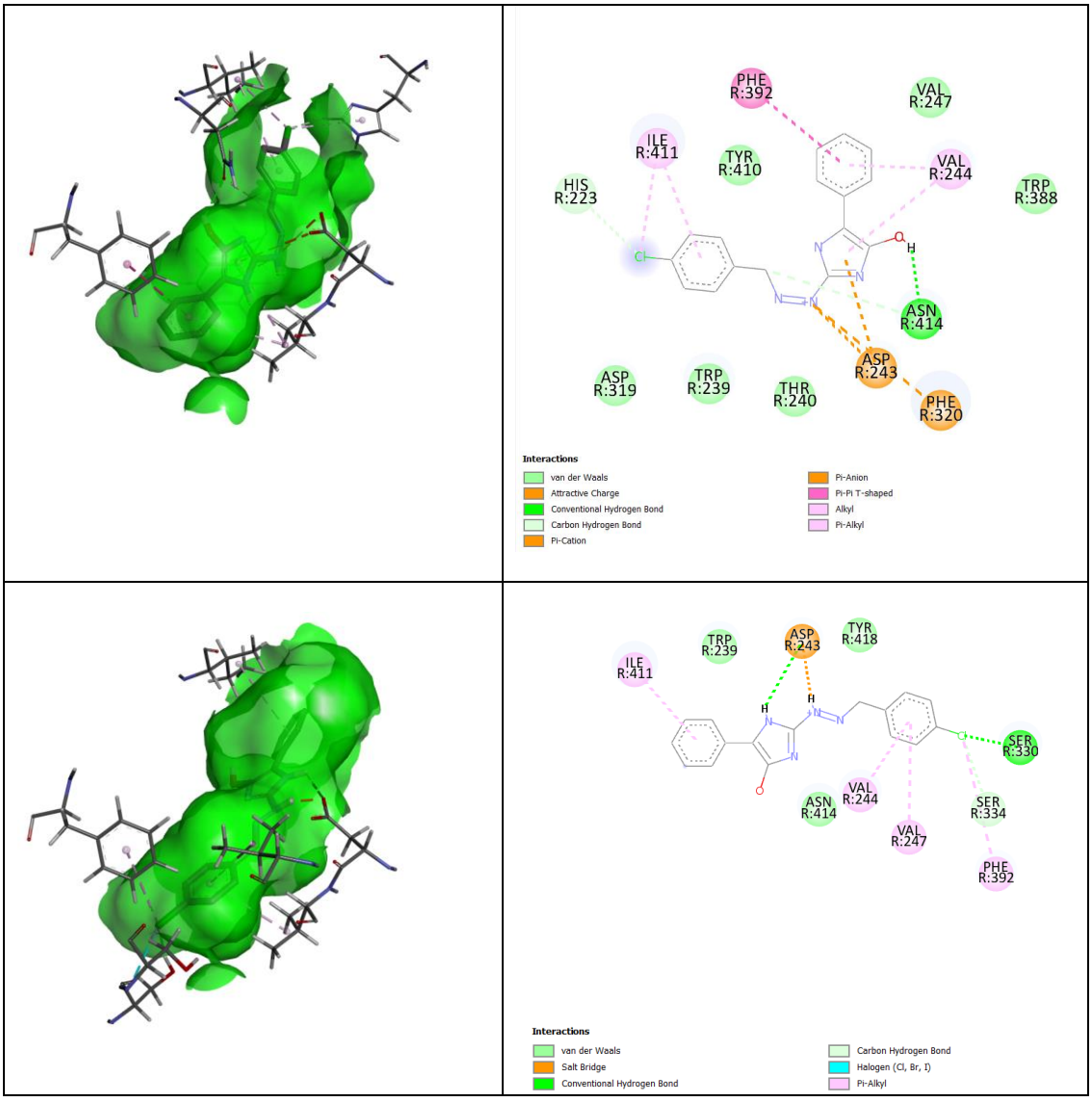

Figure 3. The three-dimensional interaction, the 2D structure, and the best binding pose of all of the compounds.

Some ADME properties were given in Table 4. According to the SwissADME website, the target compounds are appropriate with regards to bioavailability and drug-likeness. The bioavailability scores of the compounds were 0.55. Log S (ESOL) values of the compounds range from -5.37 to -

4.20. All compounds are moderately soluble. According to the OSIRIS, the compounds are predicted to be safe in terms of mutagenic, tumorigenic, irritant, and reproductive. Also, topological polar surface area (TPSA) values of the imidazole derivatives were calculated at lower than 140 Å (Angstrom). When the TPSA values of the compounds are investigated, it can be deduced that they demonstrate drug-likeness properties.

Table 4. Some in silico ADME properties predicted by way of the SwissADME website of compounds **(1-10)**.

Some ADME properties	**Compounds**									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Molecular weight (g/mol)	292.34	278.31	323.31	338.36	330.74	312.75	322.36	347.20	312.75	292.34
Rotable bonds	4	4	5	6	4	4	6	4	4	4
H-bond acceptors	3	3	5	5	4	3	4	3	3	3
H-bond donors	3	3	3	3	3	3	3	3	3	3
TPSA (Å^2)	73.30	73.30	119.12	91.76	73.30	73.30	82.53	73.30	73.30	73.30
Log $P_{o/w}$ (XLOGP3)	4.02	3.65	3.48	3.59	4.38	4.28	3.99	4.91	4.28	3.87
Log K_p	-5.23	-5.41	-5.80	-5.82	-5.21	-5.17	-5.43	-4.93	-5.17	-5.34
Log *S* (ESOL)	-4.49	-4.20	-4.23	-4.31	-4.93	-4.78	-4.48	-5.37	-4.78	-4.40
Drug likeness (Lipinski)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

4. CONCLUSIONS

In this study, the electronic and molecular properties of synthesized ten heterocyclic compounds were theoretically assigned and discussed. Also, it was focused on the analysis of molecular docking on main the β-adrenergic receptors utilized for the treatment of asthma, cardiovascular and more many diseases. For this purpose, the previously designed and synthesized imidazole ring containing ligands were investigated for their molecular docking behaviors against on beta2 adrenergic receptor-Gs protein complex. According to obtained results, especially, compound 5 containing having chloro (2-) and fluoro (6-) at orto positions on phenyl ring functioned as the electron-withdrawing groups had lowest binding energy value (-9.6 kcal/mol). In silico ADMET analysis of the compounds was accomplished to assign drug-likeness, physicochemical, water-solubility, lipophilicity and toxicity properties. Log S (ESOL) values of the compounds were ranged between -5.37 to -4.20. All compounds were moderately soluble. Owing to toxicity calculations, the compounds were estimated to be safe in the way of mutagenic, tumorigenic, irritant, and reproductive. The predicted results proposed suitable ADMET values for the studied compounds. As a result of ADMET calculations, it was seen that molecules could theoretically be drugs. In addition, the docking conclusions showed

that these compounds inhibited through interactions including H-bonds, salt bridge, p-p stacking, halogen bond, and hydrophobic interaction. The theoretical consequences will be an major lead for designing drugs as anticancer agents and future in vivo experiments. Imidazole derivative compounds provide encouraging starting points for the improvement of new biologically active compounds.

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