

## Investigation of anti-cancer properties of derivatives of 2-benzimidazole

Burak TÜZÜN<sup>1\*</sup>, Sultan ERKAN<sup>1</sup>

<sup>1</sup>Sivas Cumhuriyet University, Faculty of Science, Chemistry department, SİVAS

\*Corresponding author: btuzun@cumhuriyet.edu.tr

+Speaker: btuzun@cumhuriyet.edu.tr

Presentation/Paper Type: Oral/Full Text

**Abstract-** Transition metal complexes are playing an important role in the field of bioorganic chemistry. It has been attempted to investigate the anti-cancer properties of complexes of 2-benzimidazole derivatives formed with various metal atoms [1-2]. In these examinations, biological agents of these derivatives will be compared [3]. The most active ligand will examine the complexes that this ligand creates with its metal atoms. Metal complexes are useful in the development of effective drugs for various diseases like cancer. The ability of transition metal ions to exhibit variable oxidation states has made them to be potential molecules in the biological system. Many of the coordination complexes with copper and zinc have been established to be effective antibacterial, cytotoxic, anti-inflammatory and antiviral agents. Optimized structures are calculated in B3lyp, HF and m062x, method 3-21g, 6-31g, sdd basis set.

The <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, UV-VIS and IR spectra of these ligands will be examined by looking at their spectroscopic properties. At the same time, Molecular docking calculations are carried out between studied ligand and the 2ING is well known like the breast and ovarian cancer proteins at DockingServer. Anti-cancer properties will be examined by the most optimized structures of ligands.

**Keywords-** 2-benzimidazole, Molecular docking, DFT, spectroscopy

### 1. Introduction

Medical organic chemistry can use the unique properties of metal ions for the design of new drugs. This review discusses recent trends in the field. Metal-based compounds have been widely used in the treatment of disease conditions, but there is no clear separation between therapeutic and toxic doses. In 1960, by the discovery of cisplatin by Barnett Rosenberg, he witnessed a milestone in the history of the metal-based compounds used in the treatment of cancers. This is the basis of the modern era of metal-based anticancer drugs. In parallel, more metal-based compounds have been synthesized by redesigning the existing chemical structure through ligand substitution or by constructing the whole new compound with improved safety and cytotoxic profile. However, due to an increasing emphasis on the clinical significance of metal-based complexes, several of these drugs are currently in the clinical trial and many more await ethical approval to participate in the trial.

### 2. Computational details

DFT calculation is the most popular method for the activity of molecules. In this study, we prepared the input files of the molecules studied by gaussian view 5.08 programs [5].

Calculations of studied molecules were performed with Gaussian IA32W-G09RevA.02 and Gaussian AS64L-G09RevD.01 programs [6-7]. Studied molecules were performed using the Hartree-Fock (HF) [8] and Becke, 3-parameter, Lee-Yang-Parr (B3LYP) [9-11] method with sdd, cep-4g, 3-21G, 6-31G, 6-31++G, lanl2dz basis set in gas and an aqueous phase. HOMO and LUMO are given information about activity of molecules. Chemical reactivity parameter of molecules is given to found a good corrosion inhibitor such as  $E_{HOMO}$ ,  $E_{LUMO}$ ,  $\Delta E$  (HOMO-LUMO energy gap), electronegativity ( $\chi$ ), chemical potential ( $\mu$ ), chemical hardness ( $\eta$ ), electrophilicity ( $\omega$ ), nucleophilicity ( $\varepsilon$ ), global softness ( $\sigma$ ) and proton affinity (PA) [12-16].

$$\mu = -\chi = \left( \frac{\partial E}{\partial N} \right)_{v(r)} \quad (1)$$

$$\eta = \frac{1}{2} \left( \frac{\partial^2 E}{\partial N^2} \right)_{v(r)} = \frac{1}{2} \left( \frac{\partial \mu}{\partial N} \right) \quad (2)$$

Ionization energy (I) and electron affinity (A) [17] of studied molecules are calculated with HOMO and LUMO energy that are interested Electronegativity, global softness and chemical hardness obtaining the following equations.

$$\chi = -\mu = \left( \frac{I + A}{2} \right) \quad (3)$$

$$\eta = \frac{I - A}{2} \quad (4)$$

As it is well known that global softness is defined as the inverse of the chemical hardness [18].

$$\sigma = 1 / \eta \quad (5)$$

$$\chi = -\mu = \left( \frac{-E_{HOMO} - E_{LUMO}}{2} \right) \quad (6)$$

$$\eta = \left( \frac{E_{LUMO} - E_{HOMO}}{2} \right) \quad (7)$$

The global electrophilicity index ( $\omega$ ) that is investigated by Parr et al., is the inverse of nucleophilicity and are given in equality (8). Electrophilicity and nucleophilicity are used for the prediction organic and inorganic reaction mechanisms. Nucleophilicity ( $\varepsilon$ ) is defined as the inverse of the electrophilicity in equations (9).

$$\omega = \mu^2 / 2\eta = \chi^2 / 2\eta \quad (8)$$

$$\varepsilon = 1 / \omega \quad (9)$$

### 3. Result and discussion

2-benzimidazole is investigated by Gaussian software program. This molecule is calculated at different basis set. The results obtained from these calculations are given in table 1. In figure 1, the studied molecules are optimized by the gaussian software. The figural representation of HOMO, LUMO and ESP are calculated by optimized structure.

Table 1. The calculated quantum chemical parameters with B3LYP method in gas phase (eV)

	$E_{HOMO}$	$E_{LUMO}$	I	A	$\Delta E$	$\eta$	$\sigma$	$\chi$	PI	$\omega$	$\epsilon$	dipol	Energy
<b>2-(1H-indol-3-yl-diazenyl)-4,5,6,7-tetrahydro-1,3-benzimidazole</b>													
B3lyp/3-21g	-5,810	-1,004	5,810	1,004	4,807	2,403	0,416	3,407	-3,407	2,415	0,414	5,004	-22679,660
B3lyp/6-31g	-5,713	-0,996	5,713	0,996	4,717	2,358	0,424	3,354	-3,354	2,385	0,419	4,918	-22799,145
B3lyp/sdd	-5,871	-1,255	5,871	1,255	4,616	2,308	0,433	3,563	-3,563	2,750	0,364	5,202	-22801,589
Hf/3-21g	-8,096	2,868	8,096	-2,868	10,96	5,482	0,182	2,614	-2,614	0,623	1,604	5,313	-22532,530
HF/6-31g	-8,039	2,853	8,039	-2,853	10,89	5,446	0,184	2,593	-2,593	0,617	1,620	5,436	-22650,068
HF/sdd	-8,195	2,465	8,195	-2,465	10,65	5,330	0,188	2,865	-2,865	0,770	1,299	5,722	-22652,510
M062x/3-21g	-7,151	-0,011	7,151	0,011	7,141	3,570	0,280	3,581	-3,581	1,796	0,557	5,204	-22669,786
M062x/6-31g	-7,082	-0,123	7,082	0,123	6,960	3,480	0,287	3,603	-3,603	1,865	0,536	3,915	-22789,810
M062x/sdd	-7,255	-0,398	7,255	0,398	6,857	3,429	0,292	3,826	-3,826	2,135	0,468	4,242	-22792,653

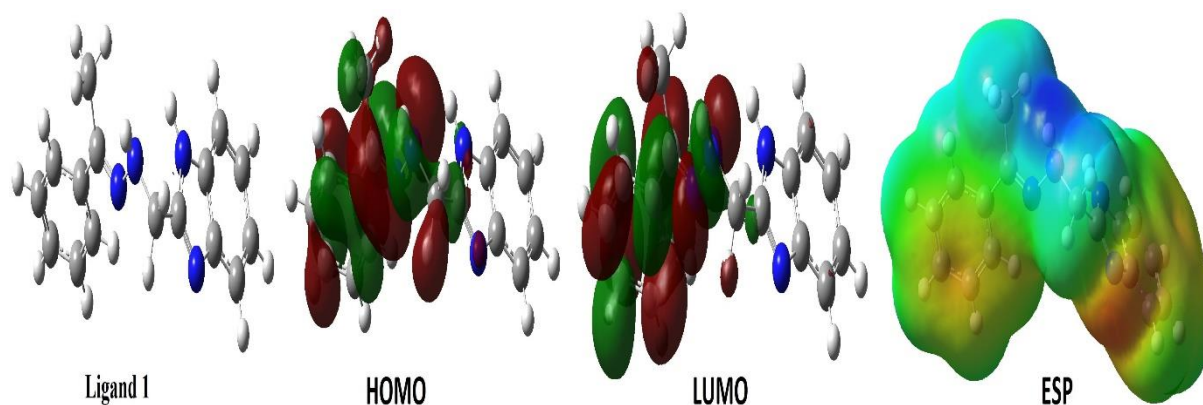


Figure 1. The structure and schematic representation of ligands

IR spectrum of studied molecule are calculated in gas phase at hf/6-31g basis set. IR spectrum of mentioned molecules is significant in determination of functional groups of molecules. These spectrums are represented in figure2.

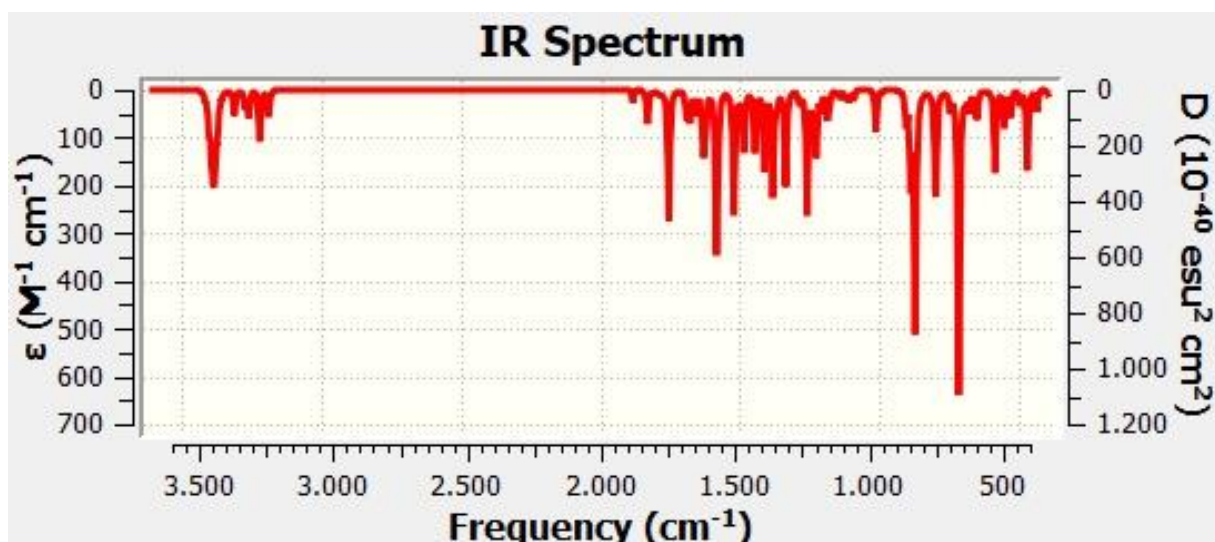


Figure 2. IR spectrum of this molecule

The <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts of the molecule studied is given in Figure 3. NMR spectrum of <sup>13</sup>C NMR chemical shifts in the upper figure and <sup>1</sup>H NMR chemical shifts in the below figure are given in figure 3.

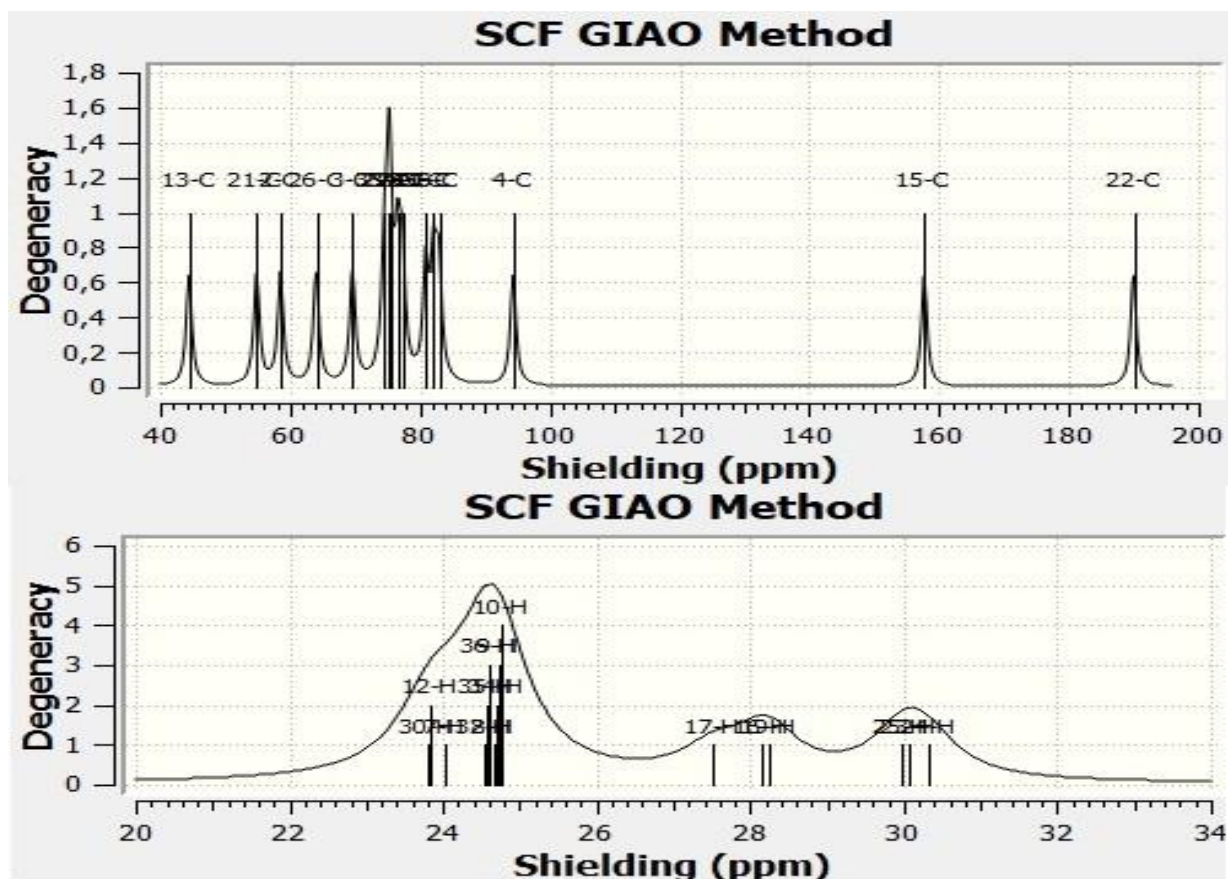


Figure 3. <sup>1</sup>H (below) and <sup>13</sup>C (upper) NMR chemical shifts of studied ligand

UV-VIS spectrum of studied molecules and complexes are calculated at same level basis set. UV-VIS spectrum of two ligands are very similar spectrums that have two main band. Each peak take place from many electronic transitions. Their wavelengths are 180 and 265 nm that have higher than 78000 Epsilon.

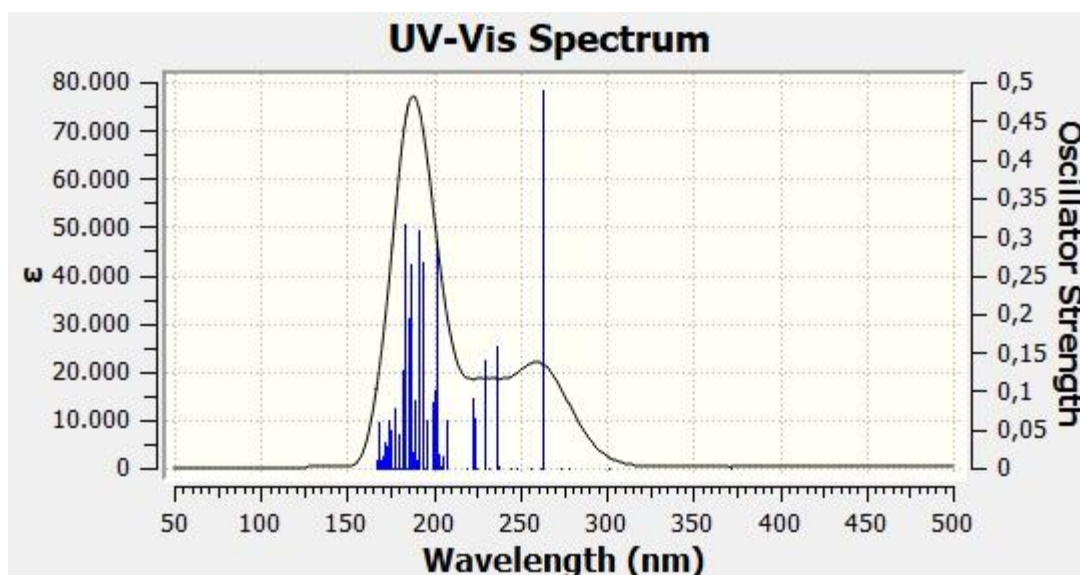


Figure 4. calculated UV-VIS spectra of ligand



Figure 5. optimized structure of metal complexes

In this work, ligands were interacted with zinc, nickel and copper atoms. thermodynamic energy values of the complexes of ligands formed with zinc, nickel and copper atoms are given in table 2. As a result of these interactions, the resulting complexes are distorted triangular planar. When these complexes are observed, the Gibbs Free Energy values of these complexes appear to be formed spontaneously in table 2.

Table 2.  $\Delta G$  of the complexes formed with metal atoms of ligands

$\Delta G_{\text{Cu-complexe}}$	-12524,500
$\Delta G_{\text{Zn-complexe}}$	-12525,203
$\Delta G_{\text{Ni-complexe}}$	-12526,421

Studied molecule are calculated at DockingServer. Numerical values of studied molecule are given table 6. The protein is obtained from Protein Data Bank by ID 2ING, the molecular docking calculations are performed on DockingServer for virtual placement of small molecules into macromolecular receptors and developed for making related accounts.

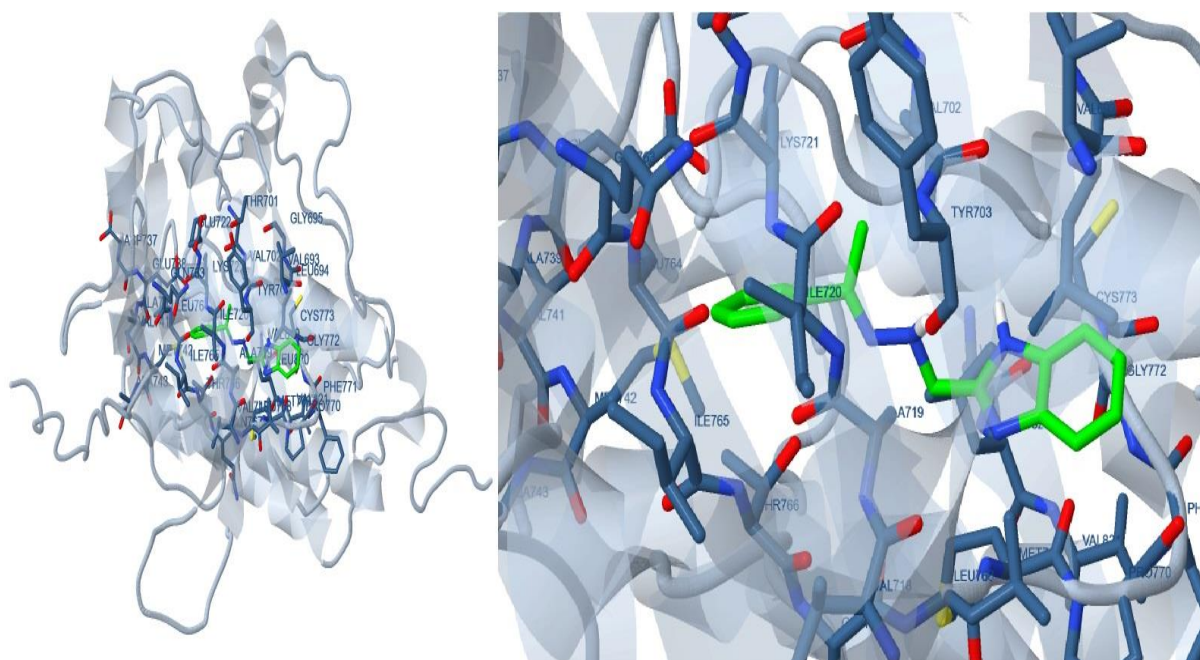


Figure 6. studied molecule interaction with protein 2ING

Table 4. Molecular Docking energy data for studied molecule

	Ligand
Est. Free Energy of Binding, kcal/mol	-6.81
Est. Inhibition Constant, Ki, uM	10.16
vdW + Hbond + desolv Energy, kcal/mol	-7.98
Electrostatic Energy, kcal/mol	-0.03
Total Intermolec. Energy, kcal/mol	-8.00
Frequency	% 30
Interact. Surface	728.193

## References

- 1) T. Manjuraj, G. Krishnamurthy, Yadav D. Bodke, H.S. Bodjya Naik, H.S. Anil Kumar, Synthesis, XRD, thermal, spectroscopic studies and biological evaluation of Co (II), Ni (II) and Cu (II) metal complexes derived from 2-benzimidazole Sarigül M., Deveci P., Köse M., Arslan U., Dagi H.T., Kurtoglu M., *Journal of molecular structure* 2015, 1096, 64-73
- 2) Williams N.H., Takasaki B., Wall M., *J. Chin. Acc. Chem. Res.* 1999, 32, 485-493
- 3) Surendra M.S., Umamaheswara B., Krishna V., *J. Saudi Chem. Soc.* 2017, 21, 291-299
- 4) Dennington R.D., Keith T.A., Millam J.M., *GaussView 5.0*, 2009. Wallingford CT.
- 5) Frisch M.J., Trucks G.W., Schlegel H.B., Scuseria G.E., Robb M.A., Cheseman J.R., Scalmani G., Barone V., Mennucci B., Petersson G.A., Nakatsuji H., Caricato H., Li X., Hratchian H.P., Izmaylov A.F., Bloino J., Zheng G., Sonnerberg J.L., Hada M., Ehara M., Toyota K., Fukuda R., Hasegawa J., Ishida M., Nakajima T., Honda Y., Kitao O., Nakai H., Vreven T., Montgomery J.A., Peralta J.E., Ogliaro F., Bearpark M., Heyd J.J., Brothers E., Kudin K.N., Staroverov V.N., Kobayashi R., Normand J., Raghavachari K., Rendell A., Burant J.C., Iyengar S.S., Tomasi J., Cossi M., Nega R., Millam J.M., Klene M., Knox J.E., Cross J.B., Bakken V., Adamo C., Jaramillo J., Gomperts R., Stratmann R.E., Yazyev O., Austin A.J., Cammi R., Pomelli C., Ochterski J.W., Martin R.L., Morokuma K., Zakrzewski V.G., Voth G.A., Salvador P., Dannenberg J.J., Daprigh S., Daniels A.D., Farkas A., Foreaman J.B., Ortiz JV, Cioslowski J, Fox DJ. *Gaussian 09, Revision D.01*, Gaussian, Inc., Wallingford CT, 2009.
- 6) Frisch M.J., Trucks G.W., Schlegel H.B., Scuseria G.E., Robb M.A., Cheseman J.R., Scalmani G., Barone V., Mennucci B., Petersson G.A., Nakatsuji H., Caricato H., Li X., Hratchian H.P., Izmaylov A.F., Bloino J., Zheng G., Sonnerberg J.L., Hada M., Ehara M., Toyota K., Fukuda R., Hasegawa J., Ishida M., Nakajima T., Honda Y., Kitao O., Nakai H., Vreven T., Montgomery J.A., Peralta J.E., Ogliaro F., Bearpark M., Heyd J.J., Brothers E., Kudin K.N., Staroverov V.N., Kobayashi R., Normand J., Raghavachari K., Rendell A., Burant J.C., Iyengar S.S., Tomasi J., Cossi M., Nega R., Millam J.M., Klene M., Knox J.E., Cross J.B., Bakken V., Adamo C., Jaramillo J., Gomperts R., Stratmann R.E., Yazyev O., Austin A.J., Cammi R., Pomelli C., Ochterski J.W., Martin R.L., Morokuma K., Zakrzewski V.G., Voth G.A., Salvador P., Dannenberg J.J., Daprigh S., Daniels A.D., Farkas A., Foreaman J.B., Ortiz JV, Cioslowski J, Fox DJ., *Gaussian 09, Revision A.02*, Gaussian, Inc., Wallingford CT, 2009
- 7) Becke A.D., A new mixing of Hatree-Fock and local density-functional theories, *J.Chem. Phys.* 98 (1993) 1372- 1377.
- 8) Wiberg K.B.. Basis set effects on calculated geometries: 6-311++G\*\* vs. aug-cc-pVDZ. *J. Comput. Chem.* 25 (2004) 1342–1346.
- 9) Beck A.D., Density-functional thermochemistry III. the role of exact, Exchange the *Journal of chemical physics* 98 (1993) 5648-5652.
- 10) Lee C., Yang W., Parr R.G., Development of the Colle-Savletti correlation-energy formula into a functional of the electron density, *Physical Review* 37 (1988) 785-789.
- 11) Tüzün B., Selectivity of Salicylaldehyde and its Derivatives, *Journal of New Results in Science* 3-5 (2014) 67-85

- 12) Tüzün B., Theoretical evaluation of six indazole derivatives as corrosion inhibitors based on dft, Turkish computational and theoretical chemistry, 2-1 (2018) 12-22
- 13) Kaya S., Tüzün B., Kaya C., Conceptual Density Functional Theoretical Investigation of the Corrosion Inhibition Efficiencies of Some Molecules Containing Mercapto (-SH) Group. Current Physical Chemistry 7-2 (2017) 147-153
- 14) Hepokur C., Günsel A., Yarasir M.N., Bilgiçli A.T., Tüzün B., Tüzün G., Yaylim I., Novel type ketone-substituted metallophthalocyanines: synthesis, spectral, structural, computational and anticancer studies, RSC Advances 89 (2017) 56296-56305
- 15) Kaya S., Tüzün B., Kaya C. Conceptual Density Functional Theoretical Investigation of the Corrosion Inhibition Efficiencies of Some Molecules Containing Mercapto (-SH) Group. Current Physical Chemistry, 7(2) (2017) 147-153.
- 16) Madkour L.H., Elshamy I.H. Experimental and computational studies on the inhibition performances of benzimidazole and its derivatives for the corrosion of copper in nitric acid. Int. J. Ind. Chem. 7 (2016) 195–221.
- 17) Pearson RG. Chemical hardness: applications from molecules to solids. Germany: Wiley-VCH: Weinheim; 1997.