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Investigation of Spectroscopic, Theoretical and Molecular Docking of methoxyphenyl derivatives

Burak TÜZÜN[1*+], Sultan ERKAN[1]

[1]*Sivas Cumhuriyet University, Faculty of Science, Chemistry department, SİVAS*
[*]*Corresponding author: btuzun@cumhuriyet.edu.tr*
[+]*Speaker: btuzun@cumhuriyet.edu.tr*
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Abstract- The metal ions accelerate drug action and efficiency of therapeutic compounds [1]. Metal complexes may inhibit the protein synthesis because of interference in the cellular respiration. Cancer is leading cause of fatality in recent years and remained as a challenge for the world [2-3]. It is known that The formation of transition metal complexes of 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (curcumin), such as Co(II), Cu(II) and Zn(II) ions, is another effective strategy for improvement of the bioavailability of curcumin and has become an attractive field of research for organic researchers. There are a large number of reported metal complexes of curcumin but the metal complexes of Cu(II) and Zn(II) ions have received more attention because of their immense and diverse biological or biomedical applications. Optimized structures are calculated in B3lyp, HF and m062x, method 3-21g, 6-31g, sdd basis set.

The ^{1}H-NMR, ^{12}C-NMR, UV-VİS 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 1JNX that is well known one of the breast cancer proteins at DockingServer. Anti-cancer properties will be examined by the most optimized structures of ligands.

Keywords- methoxyphenyl derivatives, Molecular docking, DFT, spectroscopy

1. Introduction

Metals are essential cellular components selected by nature to function in several indispensable biochemical processes for living organisms. Metals are endowed with unique characteristics that include redox activity, variable coordination modes, and reactivity towards organic substrates. Due to their reactivity, metals are tightly regulated under normal conditions and aberrant metal ion concentrations are associated with various pathological disorders, including cancer. For these reasons, coordination complexes, either as drugs or prodrugs, become very attractive probes as potential anticancer agents. Cells require tight regulation of the intracellular redox balance and consequently of reactive oxygen species for proper redox signaling and maintenance of metal (e.g., of zinc and copper) homeostasis. In several diseases, including cancer, this balance is disturbed. The redox properties of both metals and ligands in transition metal complexes offer unusual routes for new mechanisms of anticancer therapy. Metal complexes can introduce artificial reductive and oxidative stress into cancer cells, including behavior as photoactivatable agents and catalysts.

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}, ΔE (HOMO-LUMO energy gap), electronegativity (χ), chemical potential (μ), chemical hardness (η), electrophilicity (ω), nucleophilicity (ε), global softness (σ) and proton affinity (PA) [12-16].

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

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

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.

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

$$\eta = \frac{I - A}{2} \tag{4}$$

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

$$\sigma = 1/\eta \tag{5}$$

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

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

The global electrophilicity index (ω) 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 (ε) is defined as the inverse of the electrophilicity in equations (9).

$$\omega = \mu^2/2\eta = \chi^2/2\eta \tag{8}$$

$$\varepsilon = 1/\omega \tag{9}$$

3. Result and discussion

1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (curcumin) 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	ΔE	η	σ	χ	Pİ	ω	ε	dipol	Energy
2-(1H-indol-3-yldiazenyl)-4,5,6,7-tetrahydro-1,3benehiazole													
B3lyp/3-21g	-4,978	-1,618	4,978	1,618	3,360	1,680	0,595	3,298	-3,298	3,237	0,309	3,219	-42971,186
B3lyp/6-31g	-4,992	-2,046	4,992	2,046	2,946	1,473	0,679	3,519	-3,519	4,203	0,238	5,610	-43196,264
B3lyp/sdd	-5,164	-2,261	5,164	2,261	2,903	1,451	0,689	3,712	-3,712	4,748	0,211	5,939	-43202,173
Hf/3-21g	-8,259	2,483	8,259	-2,483	10,74	5,371	0,186	2,888	-2,888	0,776	1,288	2,785	-42703,045
HF/6-31g	-8,051	-2,301	8,051	2,301	5,750	2,875	0,348	5,176	-5,176	4,659	0,215	5,562	-42943,384
HF/sdd	-5,164	-2,261	5,164	2,261	2,903	1,451	0,689	3,712	-3,712	4,748	0,211	5,940	-43202,173
M062x/3-21g	-6,134	-0,060	6,134	0,060	6,074	3,037	0,329	3,097	-3,097	1,579	0,633	2,171	-42952,389
M062x/6-31g	-6,579	-0,286	6,579	0,286	6,293	3,147	0,318	3,433	-3,433	1,873	0,534	3,094	-43178,560
M062x/sdd	-5,164	-2,261	5,164	2,261	2,903	1,451	0,689	3,712	-3,712	4,748	0,211	5,940	-43202,173

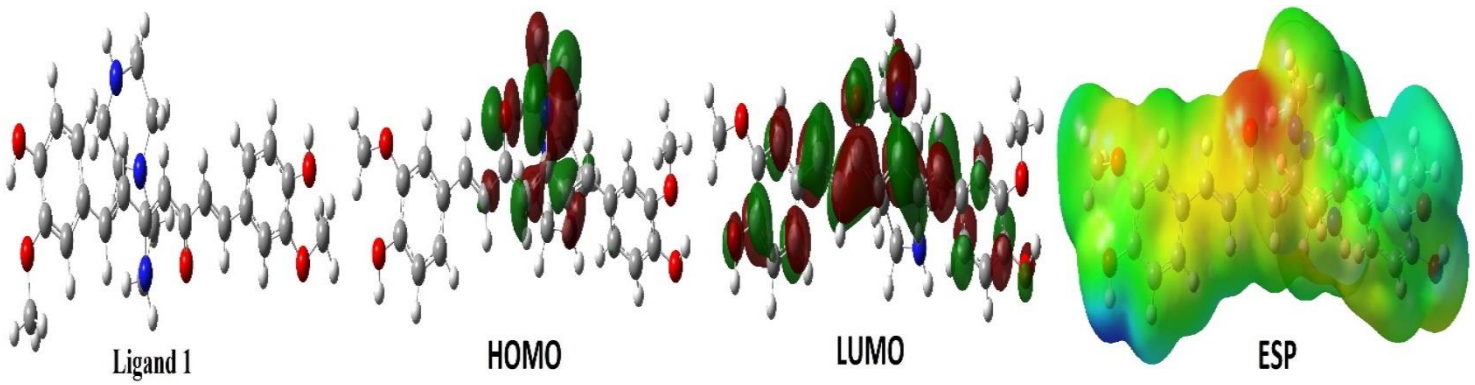

Figure 1. The structure and schematic representation of ligands

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.

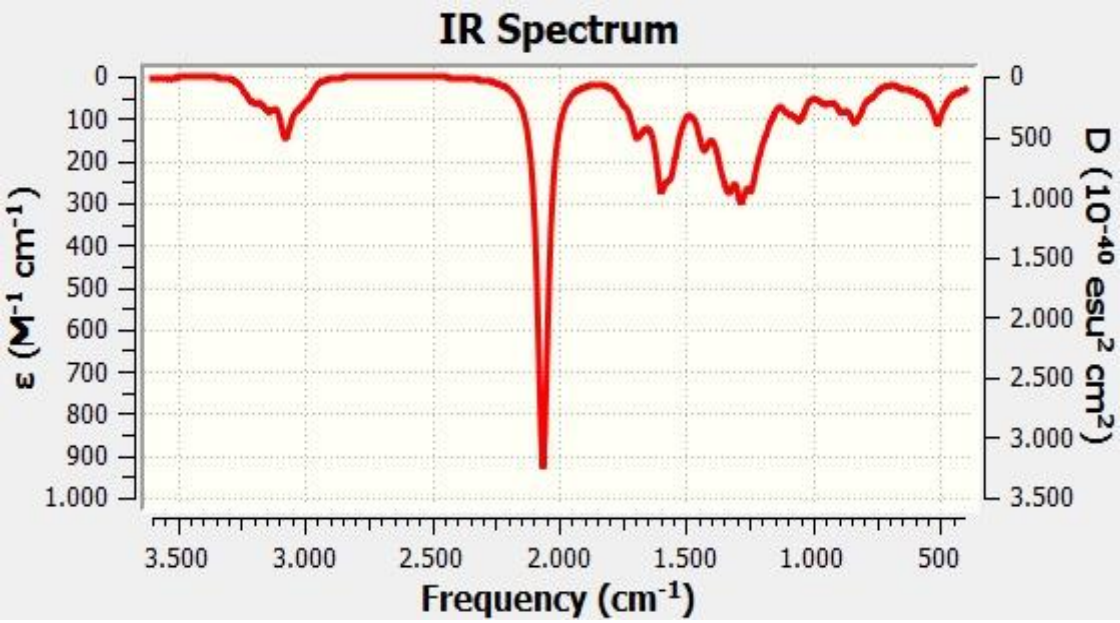

Figure 2. IR spectrum of this molecule

The ^{1}H and ^{13}C NMR chemical shifts of the molecule studied is given in Figure 3. NMR spectrum of ^{13}C NMR chemical shifts in the upper figure and ^{1}H NMR chemical shifts in the below figure are given in figure 3.

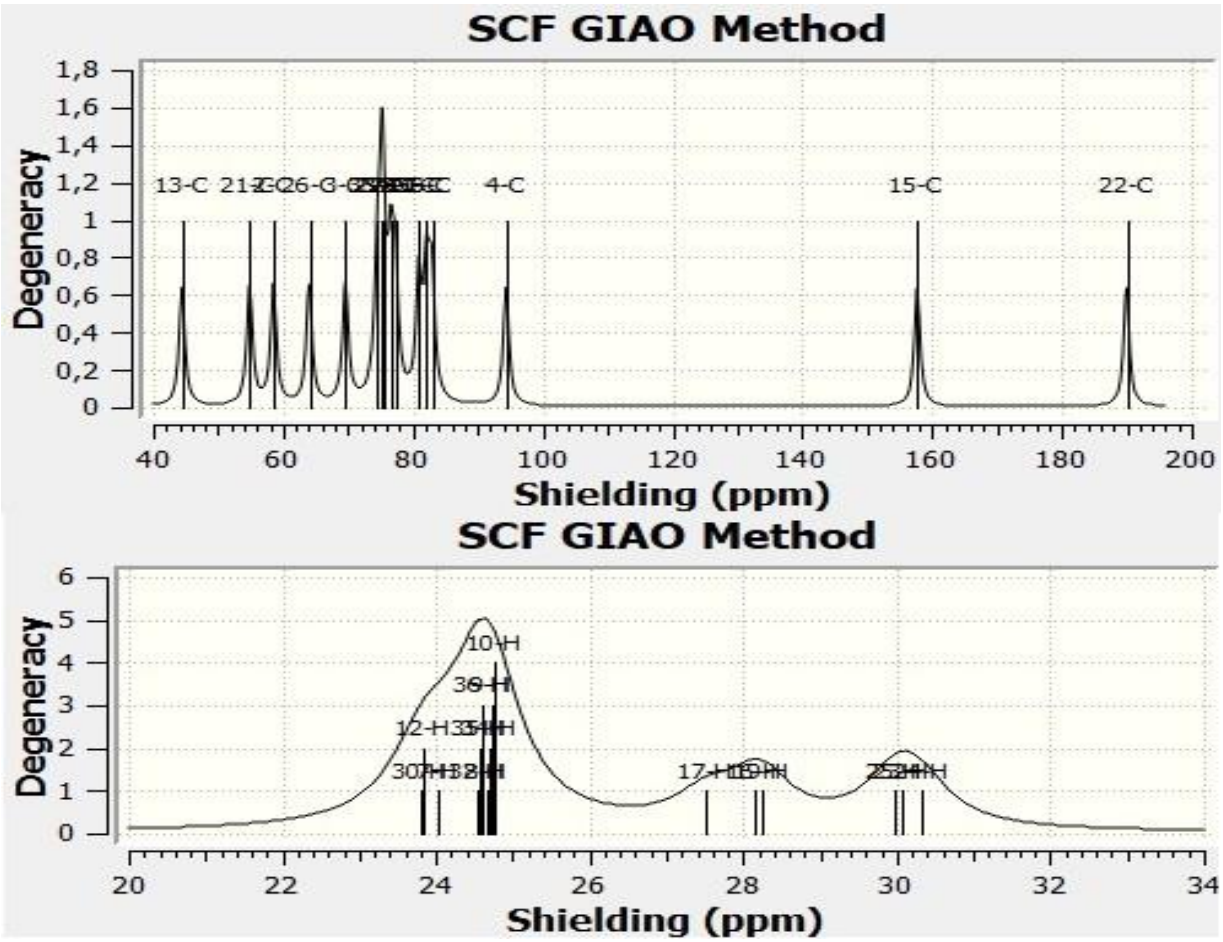

Figure 3. ^{1}H (below) and ^{13}C (upper) NMR chemical shifts of studied ligand

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 172 and 201 nm that have higher than 44000 Epsilon.

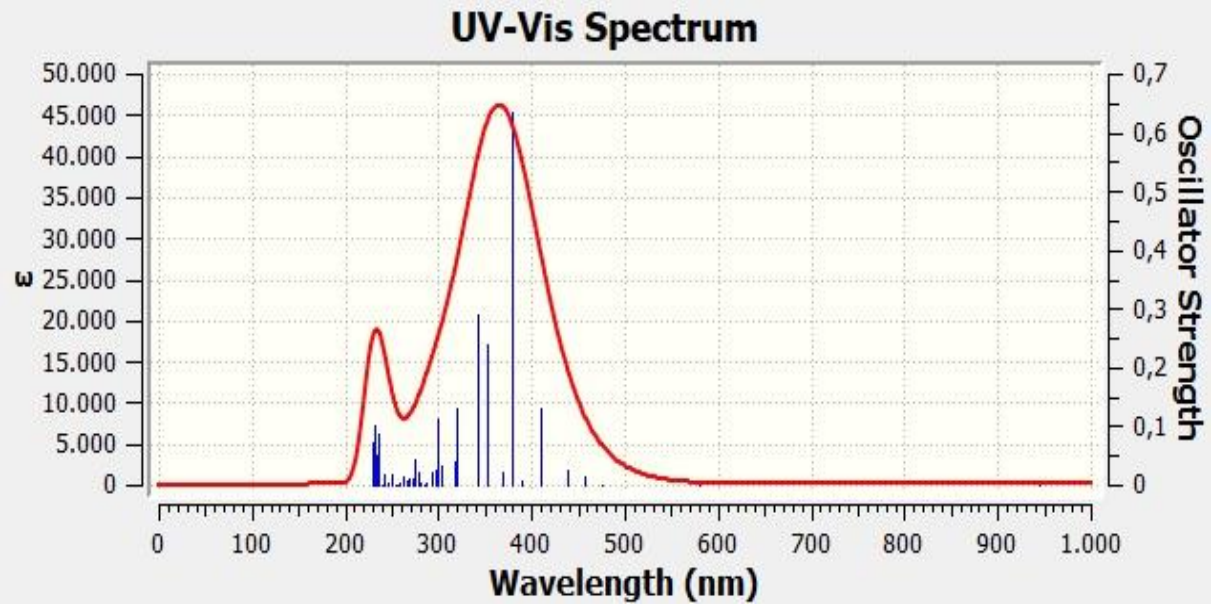

Figure 4. calculated UV-VIS spectra of ligand

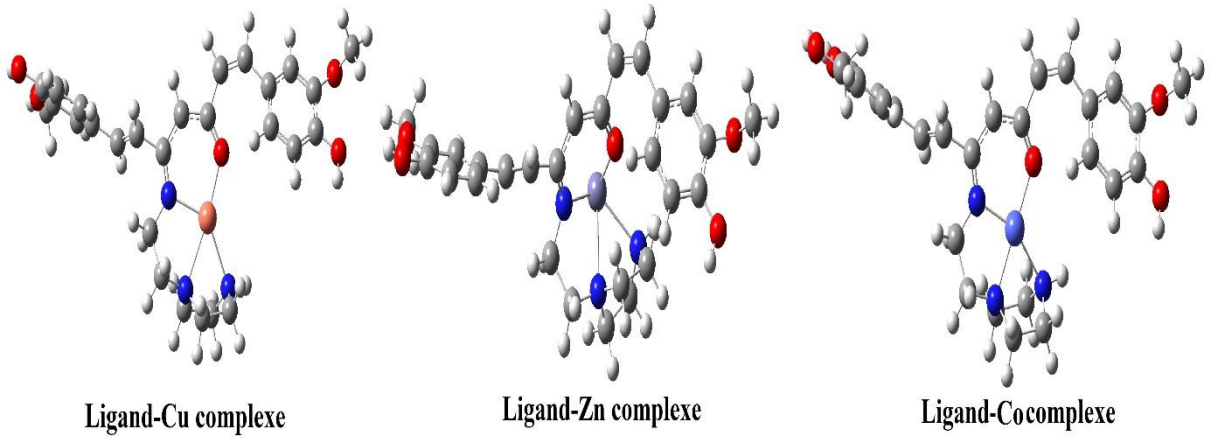

Figure 5. optimized structure of metal complexe

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

Table 2. ΔG of the complexes formed with metal atoms of ligands

$\Delta G_{Cu\text{-}complexe}$	-8,109
$\Delta G_{Zn\text{-}complexe}$	-8,377
$\Delta G_{Co\text{-}complexe}$	-9,522

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 1JNX, the molecular docking calculations are performed on DockingServer for virtual placement of small molecules into macromolecular receptors and developed for making related accounts.

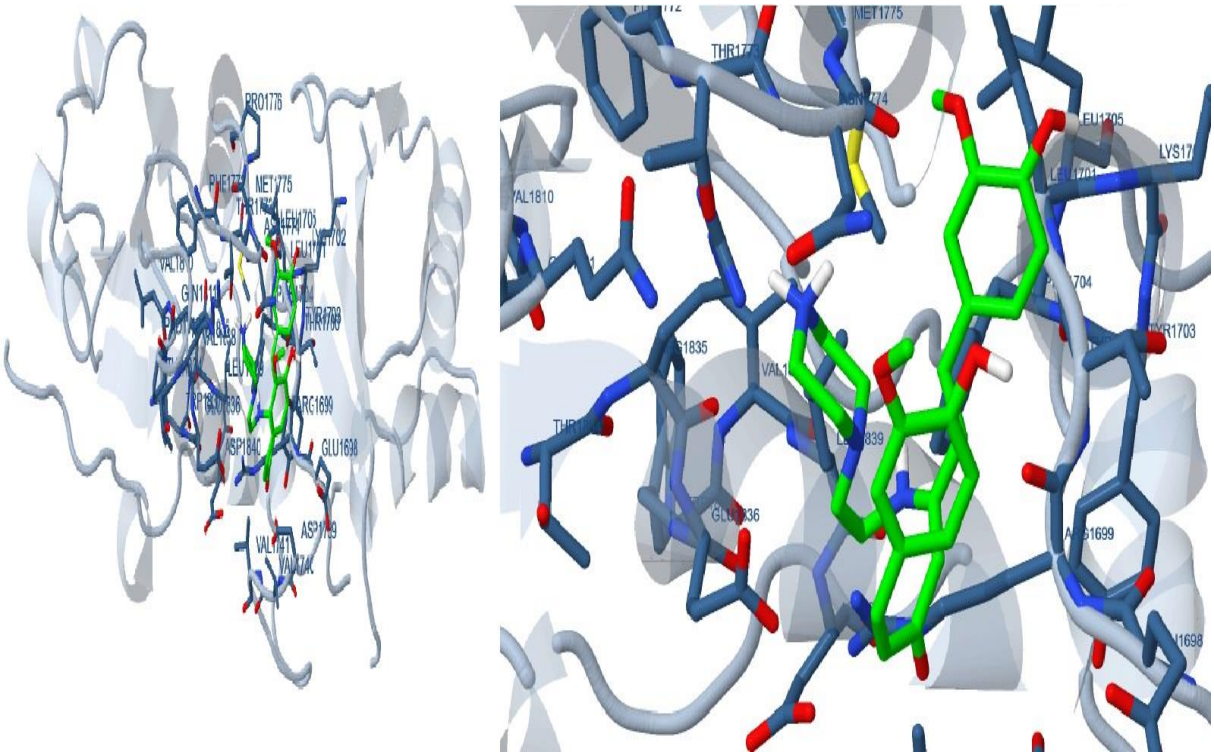

Figure 6. studied molecule interaction with protein 1JNX

Table 4. Molecular Docking energy data for studied molecule

	Ligand
Est. Free Energy of Binding, kcal/mol	64,54
Est. Inhibition Constant, Ki, uM	-
vdW + Hbond + desolv Energy, kcal/mol	20,12
Electrostatic Energy, kcal/mol	0,88
Total Intermolec. Energy, kcal/mol	21,00
Frequency	%10
Interact. Surface	702.114

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