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Research Article

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Cu(II), Ni(II) and Co(II) Complexes of Malonic Acid Dihydrazide with Bis-Br-Salicylhydrazone

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Abstract

New complexes of Cu(II), Ni(II), and Co(II) with N1,N3-bis(5-bromo-2-hydroxybenzylidene)-malonohydrazide (LH4) have been synthesized. It was shown that, in the synthesized Cu(II) and Co(II) complexes with the LH4 ligand, coordination occurs according to the Schiff base type, while in the Ni(II) complex the oxygen atom of the amide (hydrazide) group in the enol form and the nitrogen atom of the azomethine group take part in the coordination groups. Based on the data of IR, electron spectroscopy, EPR, thermogravimetry and elemental analysis of the obtained complexes, the octahedral coordination of Cu(II) ions and the binuclear structure of the complexes are assumed. It was established that all obtained compounds have high bactericidal and fungicidal activity. After, the activities of the studied ligand and its metal complexes against various cancer proteins including breast, colon, and lung cancer were compared.

Keywords: Hydrazones, Malonic Acid Dihydrazides, Cu(II), Ni(II), and Co(II) Complexes, Thermal Analysis, Coordinated Ligands.

1. Introduction

The synthesis of complex compounds of hydrazone and its derivatives with transition metals, the study of their structure and properties has been one of the most intensively studied areas in the chemistry of coordination compounds in the last 20 years. Metal complexes with acid hydrazides and their derivatives are of interest from the point of view of their potential application in bioorganic chemistry, magnetochemistry, chemistry of materials, etc.[1-5]. Hydrazones have several coordination centers and can easily coordinate transition metal ions to form complexes, which exhibit biological activity [6].

Dihydrazones of dibasic acid hydrazides are polydentate ligands and form mono-, bi- and trinuclear complexes with transition metal ions [7]. The dihydrazones of malonic acid dihydrazides are more flexible than the dihydrazones of dihydrazides of other dibasic acids (for example, oxalic, phthalic, etc.) due to the possibility of rotation around the methylene group [8,9].

It is well known that the biological activity of organic molecules is lower than the activity of their metal complexes. Therefore, molecules with good activity interacted with various metal atoms to obtain metal complexes with higher activity [10,11].

In this study a synthesized organic molecule - N^1,N^3-bis(5-bromo-2-hydroxybenzylidene) - malonohydrazide was interacted with copper (II), cobalt (II), and nickel (II) transition metals. The activity values of the ligand LH4 molecule and its metal complex-

es against various cancer proteins that breast cancer (PDB ID: 1JNX), colon cancer protein (PDB ID: 4UYA) and lung cancer protein (PDB ID: 3WZE) were compared. Afterward, the molecules are examined by PLIP (protein-ligand interaction profiler) analysis to examine the chemical interactions that occur [12-14].

Here we report the new ligand - N^1,N^3-bis(5-bromo-2-hydroxybenzylidene)- malonohydrazide (LH4), synthesized by the reaction of malonic ester dihydrazide with 5-bromosalicylic aldehyde, its complexes with Cu(II), Ni(II), and Co(II) and their structure, antibacterial and fungicidal properties.

2. Experimental

2.1. Materials and measurements

All reagents and solvents were obtained from commercial sources and were used without further purification unless otherwise noted. IR spectra were recorded on a Specord-M40 infrared spectrophotometer (Charles Zeiss Jena) and Nicolet IS10 in the form of KBr tablets in the range of 4000-400 cm^{-1} and vaseline oil.

Electronic spectra were recorded on Evolution-60S spectrophotometers. The magnetic susceptibility was measured at room temperature in a Faraday setup using Hg[Co(SCN)4] as a standard. Thermogravimetric measurements were carried out on a NETZSCH STA 449F3 derivatograph, elemental analyzes were carried out at the Tubitak Analytical Laboratory (Ankara) on a LECOCHNS 932 analyzer.

2.2. Synthesis

2.2.1. Malonic acid dihydrazide: 2 g (0.02 mol of malonic acid diethyl ester was mixed with 4 g (a double portion of 50% hydrazine) of hydrazine hydrochloric acid and was refluxed for 5 hours and left overnight. The next day a white precipitate was separated, washed with distilled water, and dried. Yield: 80%. M.p.: 152-1530C. Elemental analysis (%) $C_3H_8N_4O_2$ Calculated %:
C 27.27; H 6.06 ; N 42.42 Found %: C 27.35; H 6.21; N 42.35.

2.2.3. N^1,N^3-bis(5-bromo-2-hydroxybenzylidene)- malonohydrazide (LH4): 1.32 g (10^{-2} mol) of malonic ester dihydrazide was dissolved in 20 ml of methanol and mixed with a solution of 4.02 g ($2 \cdot 10^{-2}$ mol) of Br-salicylic aldehyde in 30 ml of ethanol. The solution was stirred on a magnetic stirrer at a temperature of 30-40°C. After 20 minutes, light yellow crystals appeared, which were separated and dried in the air. Yield: 78%, M.p.>250°C. Elemental analysis (%): $C_{17}H_{14}N_4O_4Br_2$ Calculated %: C 40.98; H 2.81; N 11.25; Br 32.10. Found %: C 40.86; H 2.70; N 11.23; Br 32.15

2.2.4. Copper(II) complex with the LH_4 ligand $[Cu_2(L_2)]$: An ethanol solution of 0.498 g (10^{-3} mol) of the ligand was neutralized with 10 ml of an aqueous solution of 0.08 g ($2 \cdot 10^{-3}$) sodium hydroxide. Then this solution was mixed with an aqueous solution of 0.250 g ($1 \bullet 10^{-3}$ mol) of copper sulfate. The color immediately changed to bright green. After 10–15 minutes a finely crystalline green precipitate formed, which was washed with water and dried in air. The yield is almost quantitative. M.p. >250°C. Elemental analysis (%): C34H24N8O8Br4Cu2 Calculated %: C 36.47; H 2.15; N 10.01; Br 28.57; Cu11.35. Found %: C 36.45; H 2.12; N 10.00; Br 28.54; Cu11.30.

2.2.5. Nickel(II) complex with the LH_4 ligand $[Ni^2(L^2)]$: 0.498 g ($1 \bullet 10^{-3}$ mol) of the ligand in ethanol was neutralized with 10 ml of the aqueous solution of 0.08 g ($2 \cdot 10^{-3}$ mol) of sodium hydroxide. The resulting solution was mixed with 10 ml of the aqueous solution of 0.281 g (10^{-3} mol) of nickel sulfate. The solution is light brown. A precipitate appeared after 20 minutes, which was separated, washed with water, and dried in air. Yield 75%. M.p. >250°C. Elemental analysis (%): $C_{34}H_{20}N_8O_8Br_4Ni_2$ Calculated %: C 36.79; H 2.16; N 10.10; Br 28.82; Ni 10.59. Found %: C 36.80; H 2.13; N 10.08; Br 28.80; Ni 10.52.

2.2.6. Cobalt(II) complex with the LH_4 ligand $[Co_2(L_2)]$: 0.498 g ($1 \bullet 10^{-3}$ mol) of the ligand in ethanol was neutralized with 10 ml of an aqueous solution of 0.08 g ($2 \cdot 10^{-3}$) of sodium hydroxide. Then this solution was mixed with 0.249 g ($1 \bullet 10^{-3}$ mol) methanolic solution of cobalt acetate. The color of the solution turned to red and after 30 minutes a precipitate appeared. The precipitate was washed with distilled water and dried in the air. Yield 87%, M.p.>2500C. Elemental analysis (%): $C_{34}H_{24}N_8O_8Br_4Co_2$ Calculated %: C 36.77; H 2.16; N 10.10; Br 28.81; Co10.62 Found %: C 36.75; H 2.12; N 10.05; Br 28.78; Co10.57.

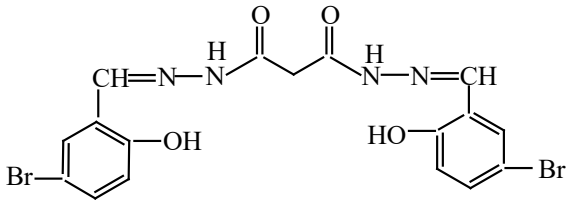
NMR spectra of the ligand LH_4:^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) - 3.75 (s, 2H methylene group), 6.42 (d, J=8.41, 2H), 7.21(d, J=8.41, 2H), 8.15(s, 2H azomethine group);
NMR spectrum of the ligand LH_4: ^{13}C (300 MHz, $(CD_3)^2SO$): δ 42.0 (1C,s), 116.4 (2C, s), 115.9 (2C,s), 119.9 (2C,s), 133.0 (2C,s), 131,5 (2C,s), 145,1(2C,s), 162,1(2C,s),165.1(2C,s).

3. Molecular Docking Calculation

Then, the biological activities of the ligand and its metal complexes against cancer proteins were compared. The proteins and metal complex files were studied at HEX 8.0.0 programs [15]. For molecular docking calculation purposes, X, Y, and Z proteins were used. The following parameters are used for docking: correlation type shape only, FFT mode: 3D, grid dimension: 0.6, receptor range: 180, ligand range: 180, twist range: 360, distance range: 40. Finally, Protein-Ligand Interaction Profiler (PLIP) server was used to examine the interaction between protein and the metal complex [16,17].

3. Results and Discussion

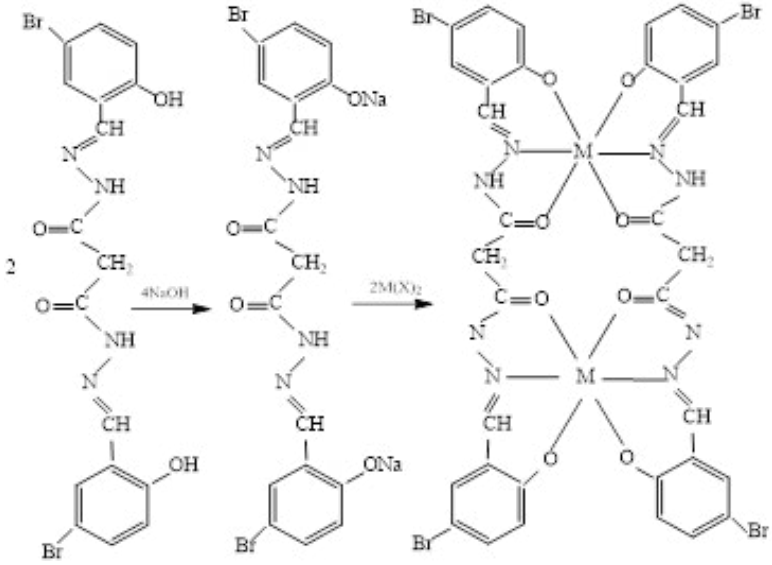
N^1,N^3-bis(5-bromo-2-hydroxybenzylidene)malonohydrazide (LH_4) was synthesized by the reaction of malonic acid dihydrazide and 5-bromo salicylaldehyde (Scheme 1).



Scheme 1: Molecular Structure of N^1,N^3-bis(5-bromo-2-hydroxybenzylidene)Malonohydrazide (LH_4)

Synthesis of complexes Cu(II) and Co(II) were carried out through the sodium salt of the ligand, which was obtained by adding sodium hydroxide to the ligand solution (Scheme 2).

IR spectroscopy data indicate that the ligand LH4 is predominantly in the ketone form. This is confirmed by the presence of absorption bands of the carbonyl group at 1697 cm^{-1} in the IR spectrum. The absorption band of the azomethine group is observed at 1610 cm^{-1} and the bands of the NH groups of the hydrazide fragment are observed at 3180 and 3281 cm^{-1}.

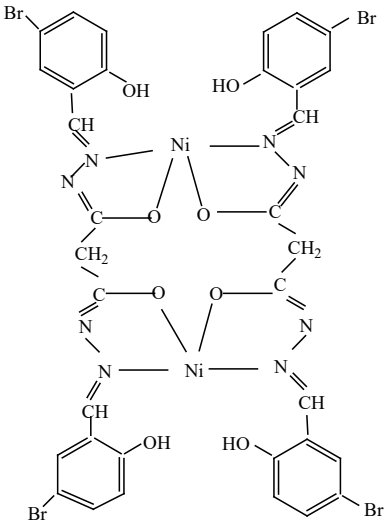


Scheme 2: The Preparation of Cu(II), Co(II) Complexes of LH_4 Ligand.

Upon coordination with the Cu(II) ion, the band of the carbonyl group shifts towards lower wavenumbers and is observed at 1650 cm^{-1} and decreases in intensity. The azomethine bond band present at 1610 cm^{-1} in the free ligand is located at 1620 cm-1 in the Cu(II) complex. The NH absorption bands of the amide group at 3180 and 3281 cm^{-1} also undergo changes and are observed at 3240 and 3400 cm-1 The obtained data indicate the coordination of the Cu(II) ion according to the "Schiff bases" type with the participation of phenolic oxygen and azomethine nitrogen in the coordination [18-21].

The magnetic moment of the Cu(II) complex measured at room temperature was 1.85 μB. Elemental analysis data indicated a metal:ligand ratio of 1:1. Considering the above, we can assume the following structure for Cu(II) complex with ligand in Scheme 2.

The Co(II) complex of LH_4 ligand, according to the IR study has a similar structure to that of the copper complex (Scheme 2).



Scheme 3: Structure of the Ni(II) Complex

Scheme 3 shows the predicted molecular structure of the Ni complex. The Ni(II) complex obtained in a similar way has a different Cu(II) and Co(II) structure. In this compound, according to IR spectrometry data, the oxygen atom of the amide (hydrazide) group in the enol form and the nitrogen atom of the azomethine group take part in coordination. Indeed, in the IR spectra, there is no absorption band of the amide CO-NH-N= group and an absorption band of NH and at the same time, an intense absorption band of the phenolic hydroxyl group at 3400 cm^{-1} is observed (Figure 1).

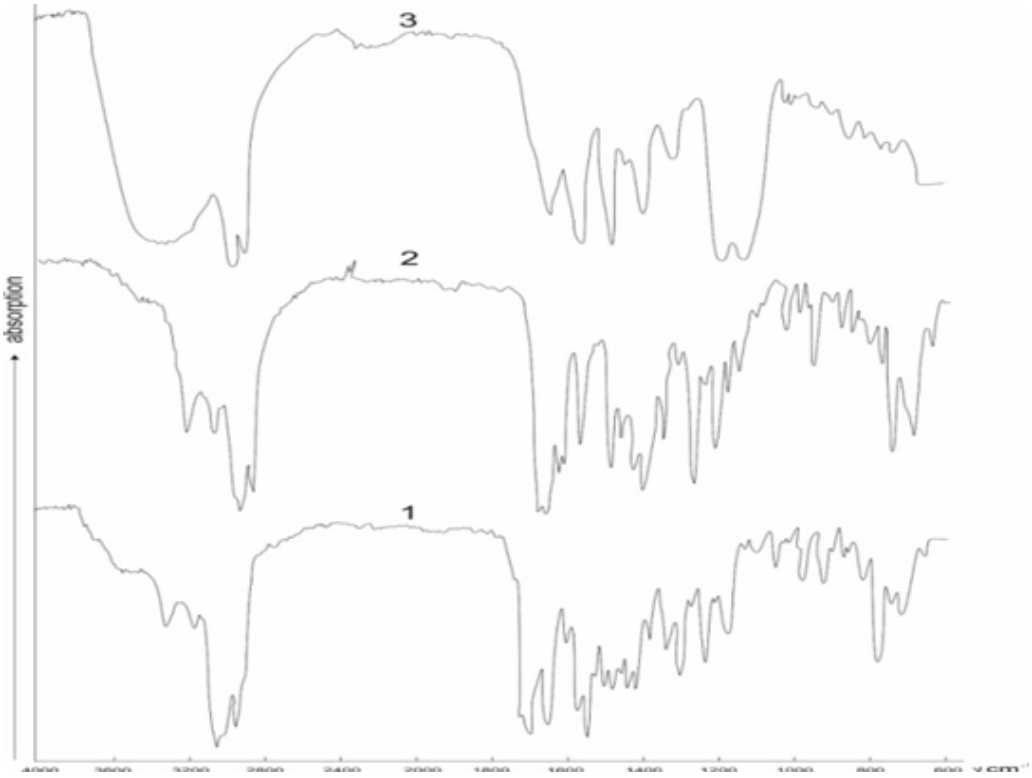


Figure 1: IR Spectra of the Complexes. 1- IR spectrum of the $[Cu_2(L)_2]$ Complex, 2- IR Spectrum of the $[Co_2(L)_2]$ Complex, 3- IR Spectrum of the $[Ni_2(L)_2]$ Complex in Vaseline Oil.

The electronic absorption spectra Co(II), Ni(II), and Cu(II) complexes of LH_4 ligand in addition to the ligand absorption bands in the visible region, there are also two new absorption bands at 420 and 557 nm, referred to the charge transfer band and d-d transition (Figure 2).

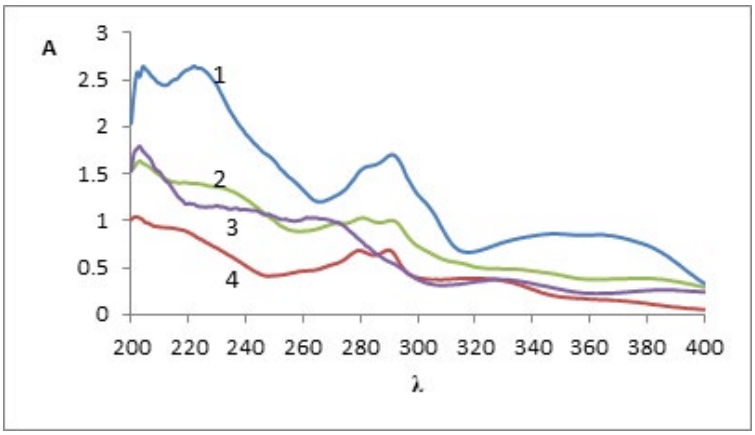
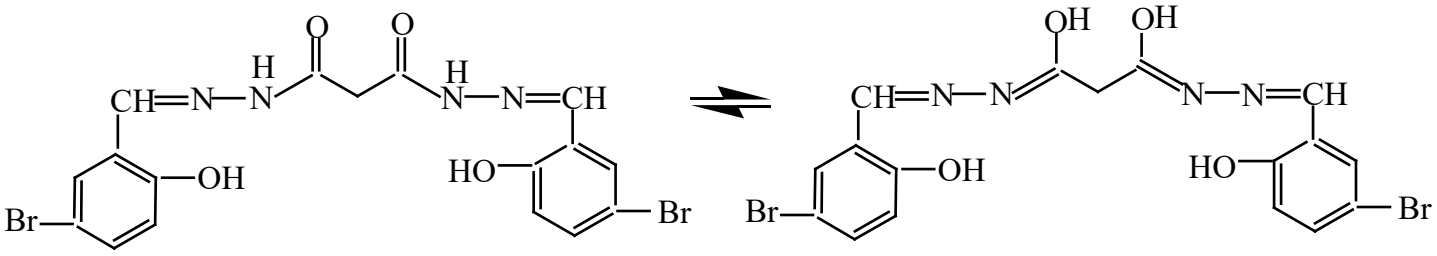


Figure 2: Electron Absorbtion Spectras 1-of the H_4L ligand, 2- of the $[Co_2(L)_2]$ Complex, 3- of the $[Ni_2(L)_2]$ Complex, 4- of the $[Cu_2(L)_2]$ in the UV Region in Ethanol.

The spectrum of the ligand contains four absorption bands at 220, 290, 340, and 380 nm. The two former bands are related to aromatic ring absorption. The latter can be attributed to the absorption of the azomethine group conjugated to the benzene ring (band at 340 nm) and to the absorption of the -CH=N-N=COH- group conjugated to the phenol ring, which is formed due to the keto-enol equilibrium (Scheme 4).



Scheme 4: Keto-Enol Equilibrium in the N^1,N^3-bis(5-bromo-2-hydroxybenzylidene)- Malonohydrazide

Upon complex formation, the band at 340 nm undergoes a hypsochromic shift and is observed at 320 nm, while the band at 380 nm strongly decreases in intensity. In the visible region, there are d-d transitions, for example, for the cobalt (II) complex at 520 and 640 nm. Due to the low solubility of the Cu(II) and Ni(II) complexes, we failed to observe absorption in the visible region.

The EPR spectrum of the polycrystalline complex $[Cu_2(L_2)]$ recorded at 298 K is a symmetrical singlet with a line width between the points of maximum slope ΔH = 180 G and a g factor of 2.12 (Figure 3). The symmetrical singlet signal EPR suggested the octahedral structure of the complex.

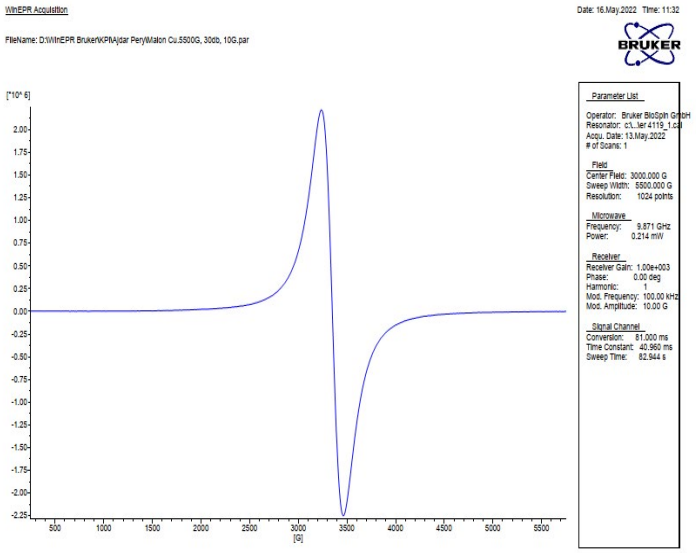


Figure 3: EPR Spectrum of the Polycrystalline Complex $[Cu_2(L_2)]$ at 298K.

Thus, the IR spectrometry data indicate that the synthesized Cu(II) and Co(II) complexes with the LH_4 ligand have a similar structure. The coordination geometry of metal atoms Cu(II) and Co(II) is octahedral and is carried out according to the type of Schiff bases, presumably with a binuclear structure. While in the Ni(II) complex, according to the IR spectrometry data Ni(II) atom is coordinated with the oxygen atom of the amide (hydrazide) group in the enol form and the nitrogen atom of the azomethine group.

The bactericidal and fungicidal activity of the obtained complexes has been studied. The antimicrobial activity of the test compound was studied by the zonal diffusion method. We used the following pure cultures of microorganisms Mycobacterium lacticolium - VKMV - 365, Pseudomonas aeruginosa VKMV - 588, and Staphylococcus aureus, which are widely distributed in petroleum products.To test the fungicidal activity, pure cultures of fungi were used: Aspergillus niger VKM-1119, Penicillium cyclonum-VKM-109; Cladosporium-Gesminoe-VKM-1701. Candida tropicalis was used as yeast.

The tests were carried out as follows. 20-25 ml of nutrient medium is poured into a Petri dish and cooled. Microorganisms are cultivated on the surface of the nutrient medium (for bacteria, MPA-meat-peptone agar, and for fungi, WA-wrot-agar). To determine the zone of destruction of microorganisms on the surface of a sterilized glass medium stick make 4-5 holes with a diameter of 10 mm and a depth of 4-5 mm in these holes is added 0.3-0.5 ml of biologically active solution (with biocide and without biocide).

The effectiveness of the antimicrobial properties of the studied additive in ethanol was determined by the diameter of the destroyed microorganisms (without additive and with additive) zones. The larger the zone, the greater the antimicrobial activity of the additive.

The antimicrobial activity of the complexes Cu(II) and Co(II) of N^1,N^3-bis(5-bromo-2-hydroxybenzylidene)malonohydrazide ligand in ethyl alcohol are shown in Table 1.

Name of connections	Concen-tration.%	Diameter of the destruction zone of microorganisms, cm	
		Bacteria: in MPA medium (meat peptone agar)	Mushrooms:in CA medium (wort agar)
$[Cu_2(L)_2]$	1	1.9-2.5	2.5-2.9
	0.5	1.6-1.8	2.2-2.4
	0.25	1.4-1.5	1.9-2.0
$[Co_2(L)_2]$	1	1,6-1,8	2,4-2,6
	0,5	1,4-1,4	1,8-1,8
	0,25	1,2-1,2	1,4-1,7

8-hydroxyquinoline (reference)	1	+	2,0-2,2
	0,5	+	1,1-1,1
Ethyl alcohol without biocide	5%	++	++
	10%	++	++

Table 1: Results of Studying the Antimicrobial Activity of the Complexes Of (Cu(Ii) and Co(Ii) of Malonic Acid Dihydrazide With Bis-Br-Salicylhydrazones

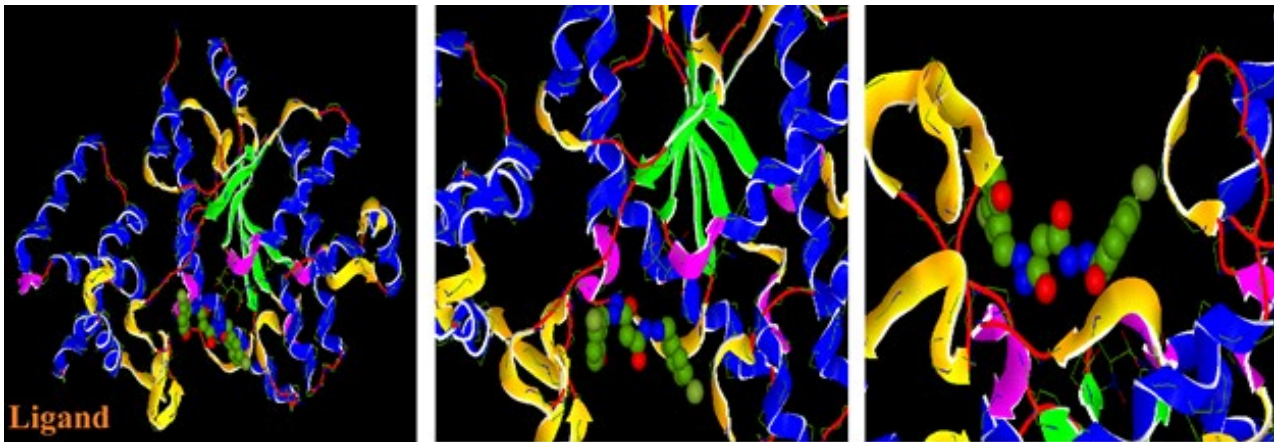
The Cu(II) complex of LH_4 at a concentration of 0.25 to 1% acts as an antimicrobial agent that protects against biological damage. The effectiveness of the studied compounds is higher than that of 8-hydroxyquinoline [22,23]. At the same time, the Co(II) complex of LH4 showed the highest fungicidal and bactericidal activity. It can be used as an antimicrobial additive for cutting fluids [23,24].

The molecular docking method was used to compare the biological activities of the organic molecule (LH_4 ligand) and its metal complexes against different proteins, such as breast-, colon-, and lung cancer proteins [25,26]. One of the most important things in this comparison that determine the activities of molecules is the chemical interactions that occur between molecules and proteins. Hydrogen bonds, polar and hydrophobic interactions, π–π stacking, water bridges, and halogen bonds are some of these kinds of interactions It is seen in many studies that as these interactions increase, the activities of the molecules increase [27,28]. Although there are many parameters in the molecular docking calculations, the E total energy value of the molecules is the most important among these parameters [26]. The most important factor affecting the numerical value of this parameter is the interactions between molecules and proteins, as mentioned above. The E total energy values of the molecules are given in Table 2.

	1JIJ	4UYA	3WZE
Ligand	-301.69	-300.21	-293.16
Cu-complex	-399.98	-400.97	-394.24
Co-complex	-399.84	-400.60	-394.01
Ni-complex	-414.42	-406.94	-367.70

Table 2: E Total Energy Parameter

As a result of the calculations made, it was seen that the ligand molecule had the highest value according to the E total energy value from the calculated parameters of the molecules [29]. Recent studies have shown that metal complexes had better biological activity than their ligand molecules. The E total energy values in Table 2 also support this situation. The interactions obtained in the study are given in Figure 4-6.



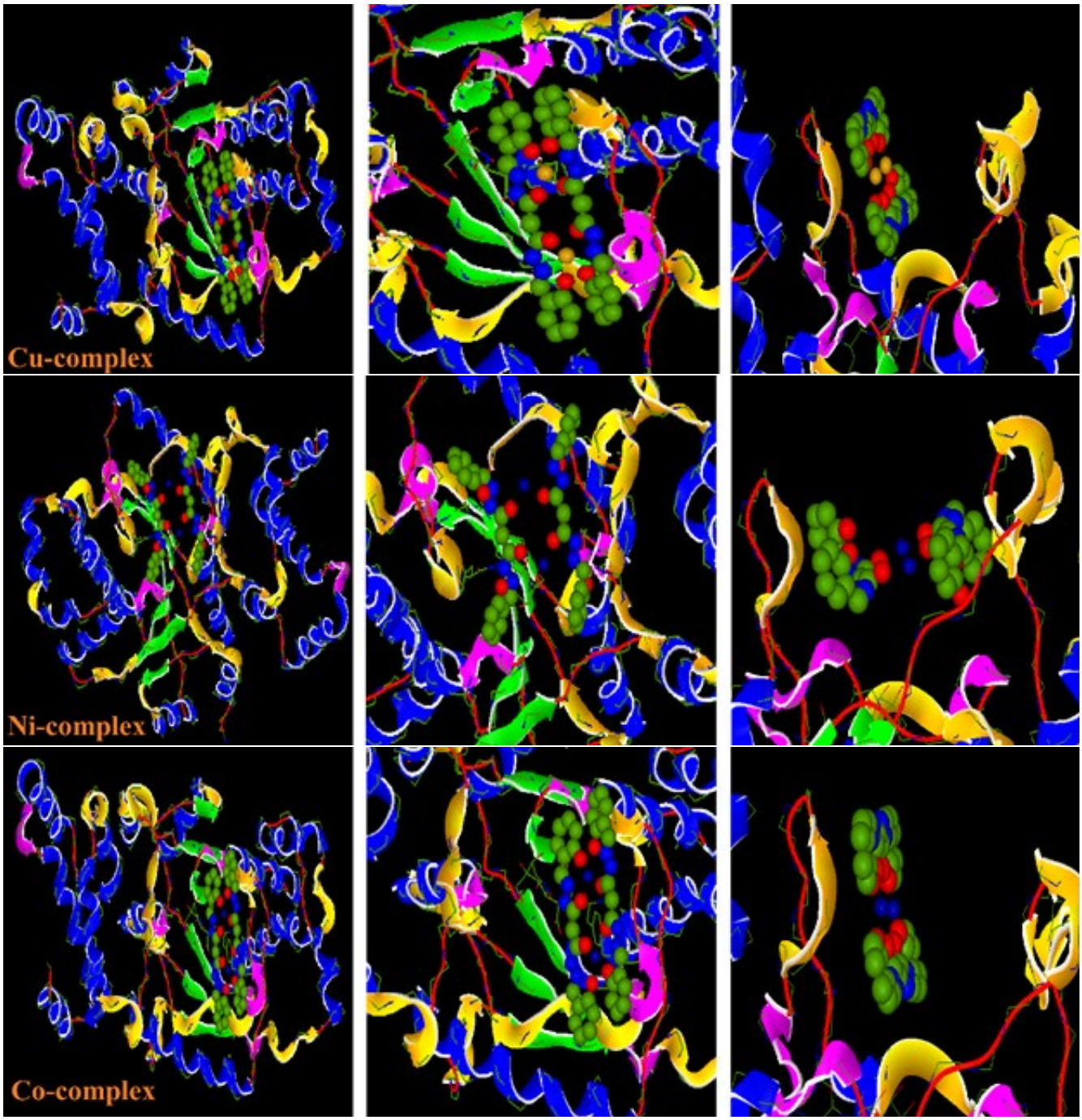
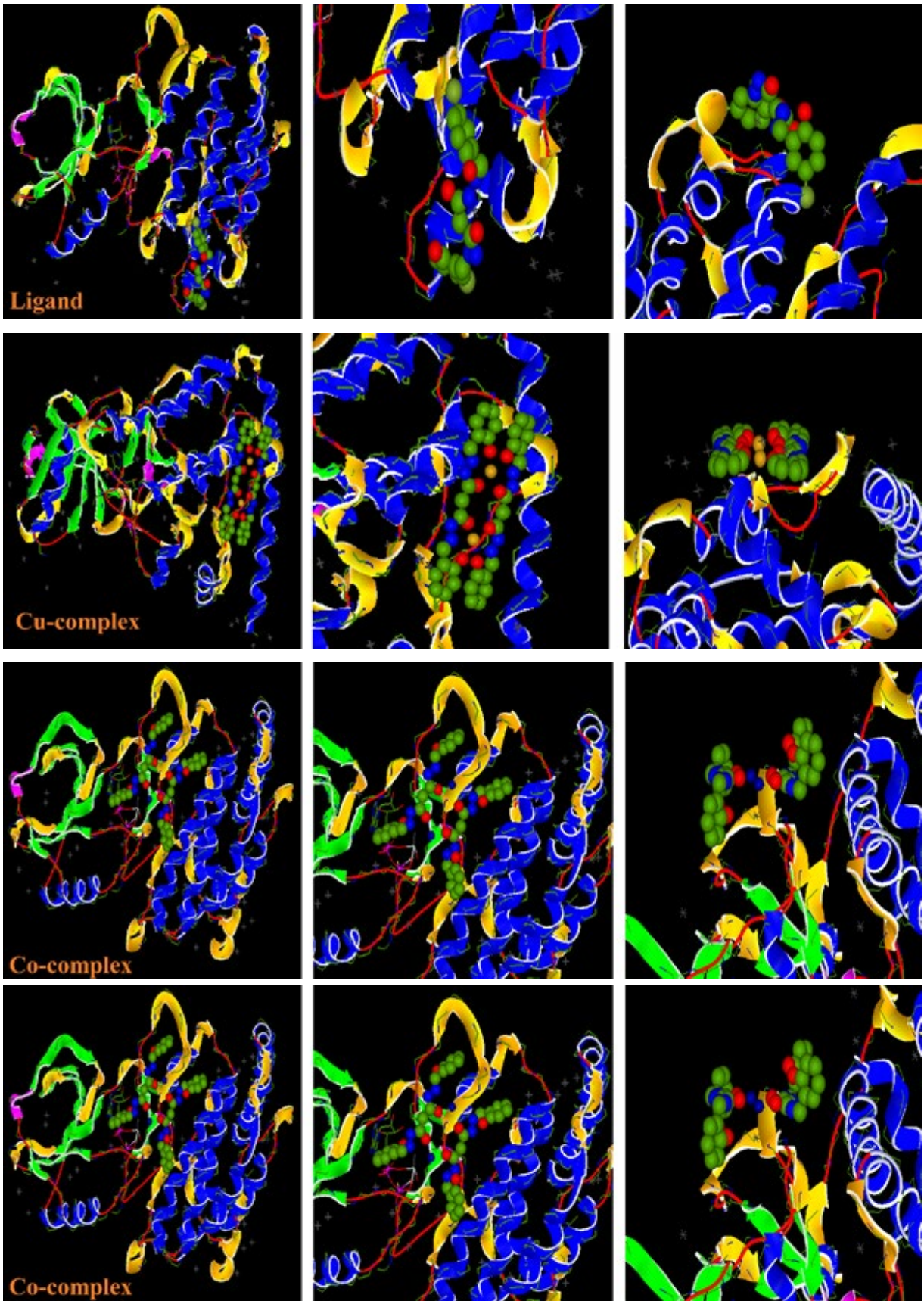


Figure 4: Demonstration of the Interaction of the Ligand and Its Metal Complexes With the Breast Cancer Protein


Ligand
Cu-complex
Co-complex
Co-complex

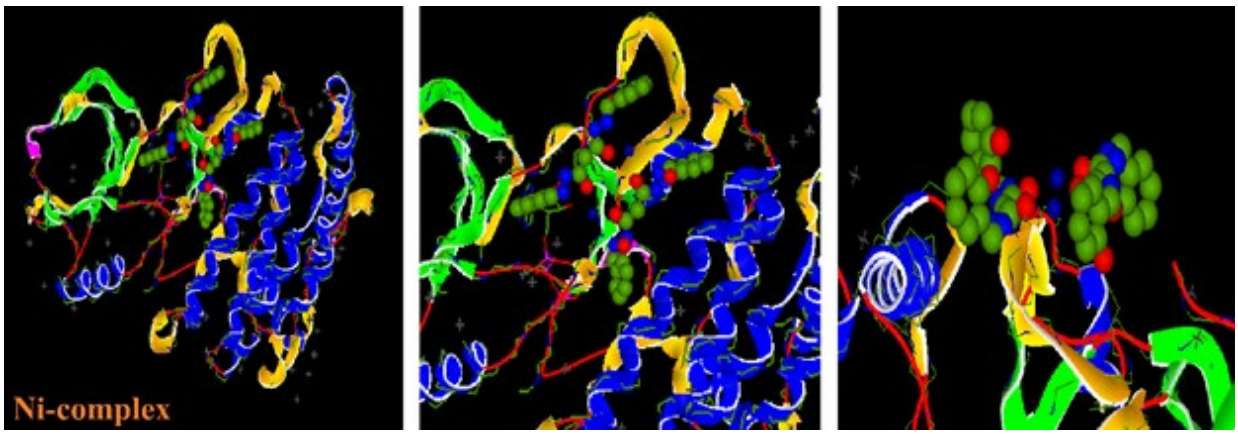
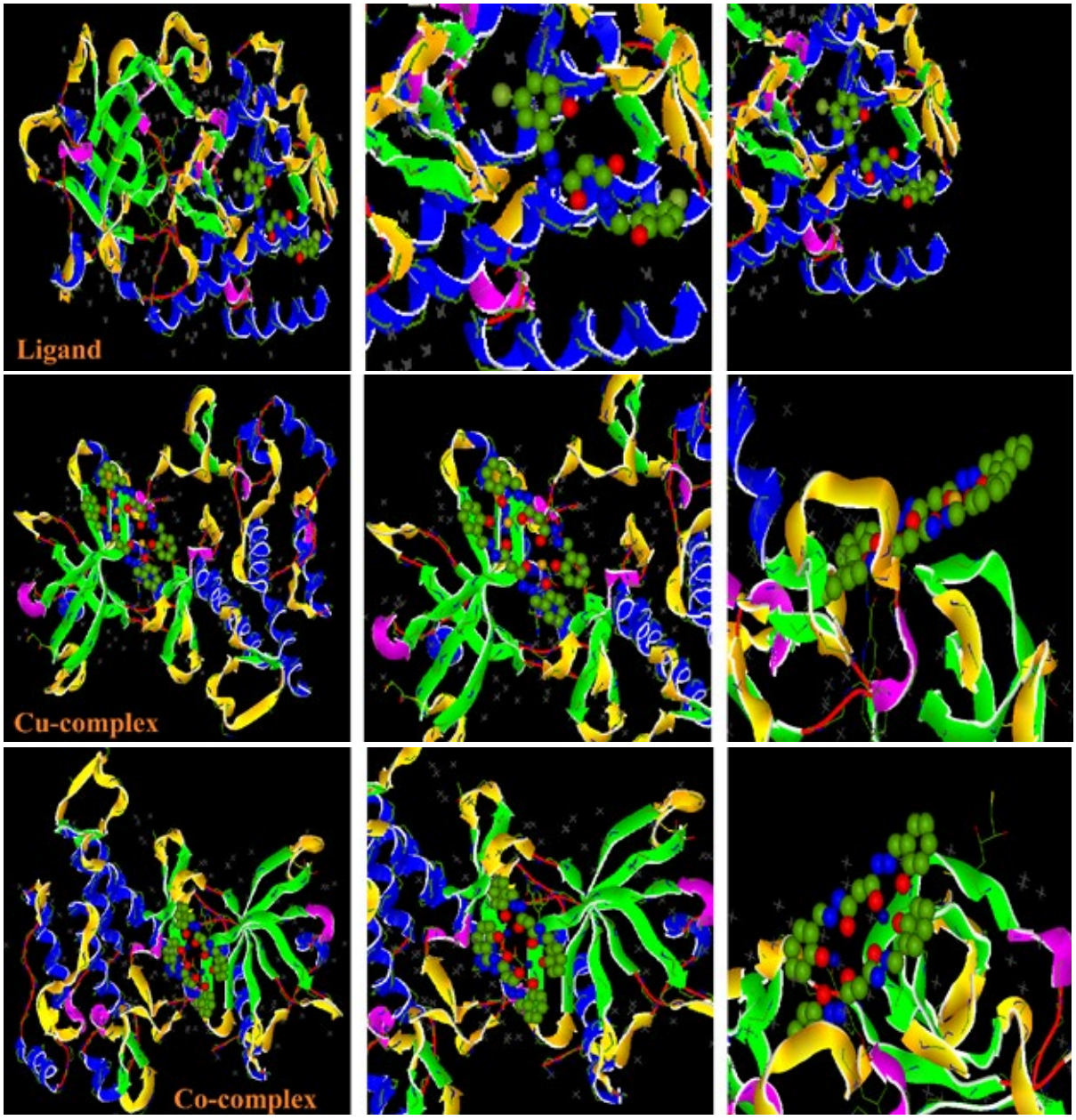


Figure 5: Demonstration of the Interaction of the Ligand and Its Metal Complexes with the Colon Cancer Protein



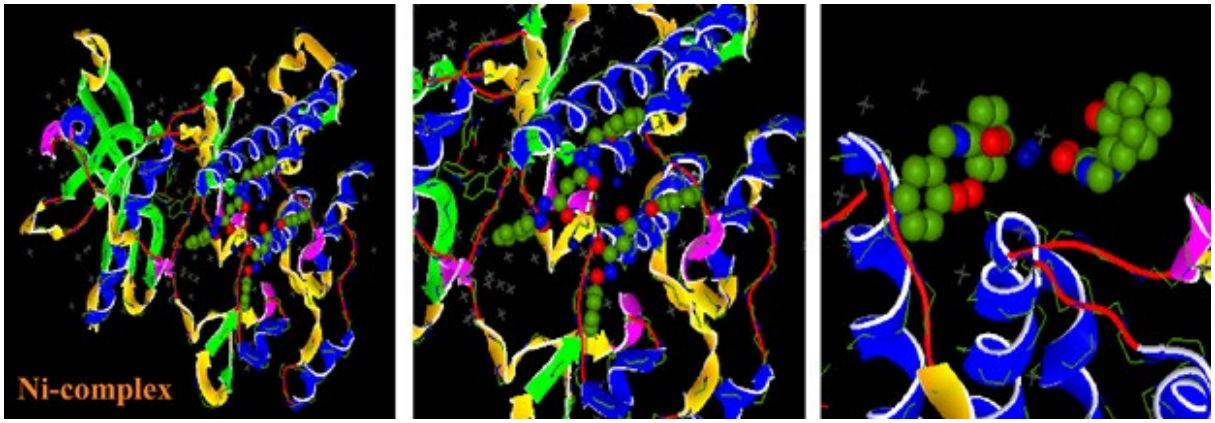


Figure 6: Demonstration of the Interaction of the Ligand and Its Metal Complexes With the Lung Cancer Protein

As a result of these molecular docking calculations, the activity of the ligand and its metal complexes was compared. The chemical interactions occurring in this comparison cannot be seen in detail. PLIP analysis of it was performed, and the interactions of ligand and its metal complexes with this analysis are given in Table 3-5 and Figure 7-9.

Index	**Residue**	**AA**	**Distance**	**Ligand atom**	**Protein atom**
Breast cancer protein- Cu metal complex					
1	1750X	LYS	2.71	2033	922
2	1751X	ARG	2.50	2042	928
3	1754X	GLU	3.00	1995	957
4	1754X	GLU	3.07	2034	957
5	1844X	LEU	3.64	2005	1708
6	1844X	LEU	3.36	2003	1709
7	1846X	GLN	2.39	2043	1729
8	1848X	GLN	3.58	1967	1743
9	1849X	GLU	3.70	1968	1754
Colon cancer -metal complex					
1	360A	LYS	2.62	2547	1775
2	361A	LEU	3.69	2506	1783
3	365A	ILE	2.91	2492	1815
4	371A	GLU	3.73	2516	1859
5	375A	LYS	2.85	2518	1890
6	383A	GLN	3.35	2545	1962
lung cancer -metal complex					
1	842A	ARG	3.81	3197	288
2	923A	ASN	2.35	3122	1047
3	1047A	PHE	3.00	3121	1782
4	1047A	PHE	3.40	3124	1778
5	1047A	PHE	2.87	3122	1780

In table: LYS: Lysine, ARG: Arginine, GLU: Glutamate, LEU: Leucine, ILE: Isoleucine, ASN: Asparagine, PHE: Phenyl alanine

Table 3: Hydrophobic Interactions of Protein and Metal Complex

Index	Residue	AA	Distance H-A	Distance D-A	Donor angel	Protein donor?	Side chain	Donor Atom	Acceptor Atom
Breast cancer - Cu metal complex									
1	1747X	GLN	2.88	3.44	115.95	√	X	900 [Nam]	2026 [Nam]
2	1751X	ARG	3.04	3.77	130.47	√	X	924 [Nam]	2026 [Nam]
3	1755X	SER	2.75	3.18	108.39	√	√	964 [O3]	1989 [N2]
Colon cancer - metal complex									
1	365A	ILE	2.23	3.18	158.46	√	X	1811 [Nam]	2497 [Nam]
2	378A	LYS	2.44	3.30	144.48	X	X	2536 [Nam]	1913 [O2]
lung cancer - metal complex									
1	842A	ARG	1.59	2.20	114.20	X	X	3142 [Nam]	286 [O2]
2	842A	ARG	2.46	3.32	143.87	√	X	283 [Nam]	3136 [O2]
3	1050A	ALA	2.99	3.77	135.41	X	X	3133 [Nam]	1801 [O2]
4	1052A	ASP	3.01	3.92	164.06	√	√	1828 [O3]	3144 [N2]

In table: ARG: Arginine, GLN: Glutamine, SER: Serine, ILE: Isoleucine, LYS: Lysine, ARG: Arginine, ALA: Alanine, ASP: Aspartate

Table 4: Hydrogen Bonds of Protein and Metal Complex

Index	Residue	AA	Dist. H-A	Dist. D-A	Donor angle	Water angle	Protein donor?	Donor atom	Acceptor atom	Water atom
Colon cancer - metal complex										
1	362A	THR	3.44	3.17	130.14	110.52		1791 [O3]	2551 [O2]	2461
2	362A	THR	3.65	3.17	130.14	86.43		1791 [O3]	2538 [N2]	2461
Lung cancer - metal complex										
1	923A	ASN	3.75	2.80	172.52	91.10		1050 [Nam]	3129 [O2]	3057
2	1052A	ASP	3.74	3.11	153.80	106.93		1821 [Nam]	3142 [Nam]	3074

In table: THR: Threonine, ASN: Asparagine, ASP: Aspartate

Table 5: Water Bridges of Protein and Metal Complex

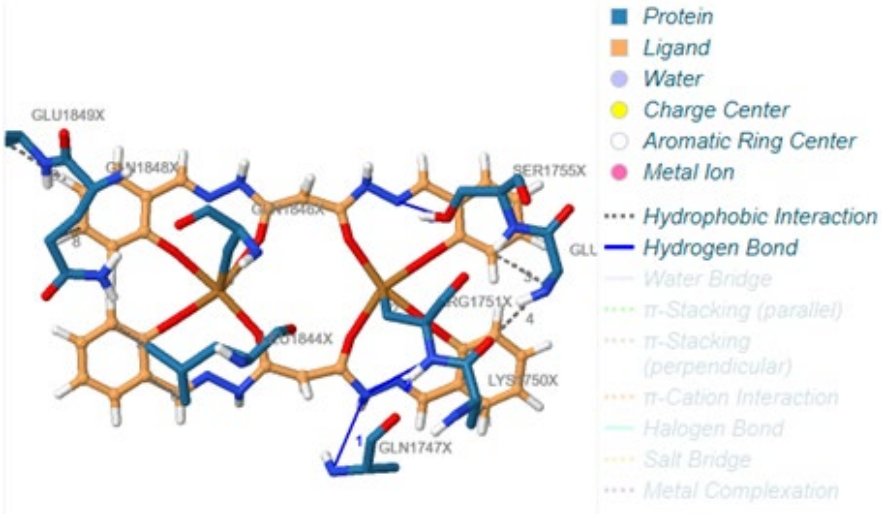


Figure 7: Representation of the Interaction of Cu Metal Complex with Breast Cancer

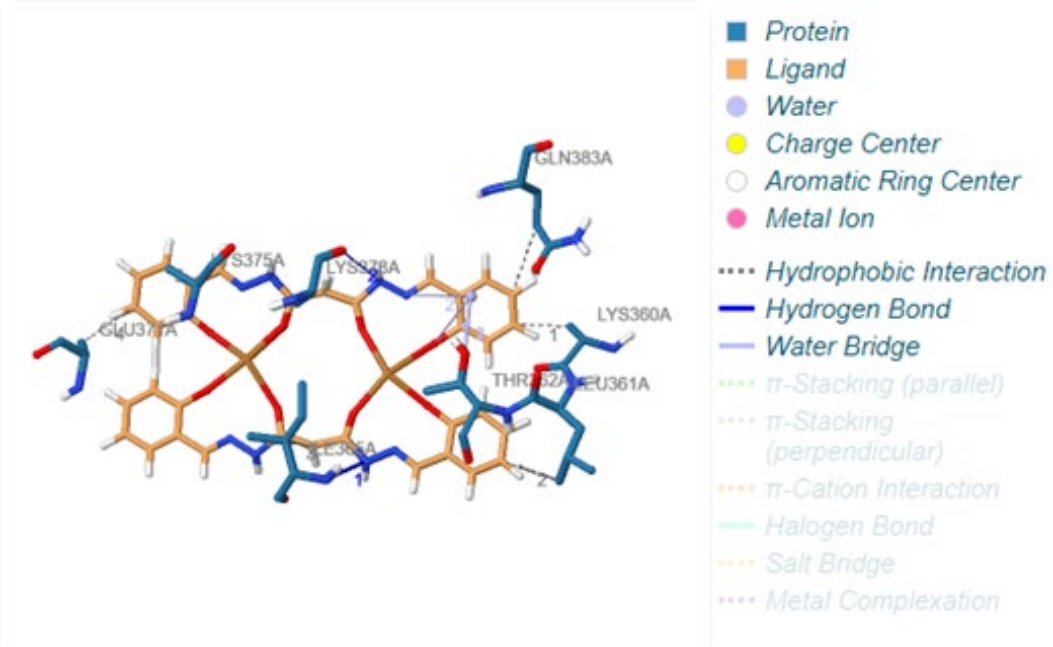


Figure 8: Representation of the Interaction of Cu Metal Complex with Colon Cancer

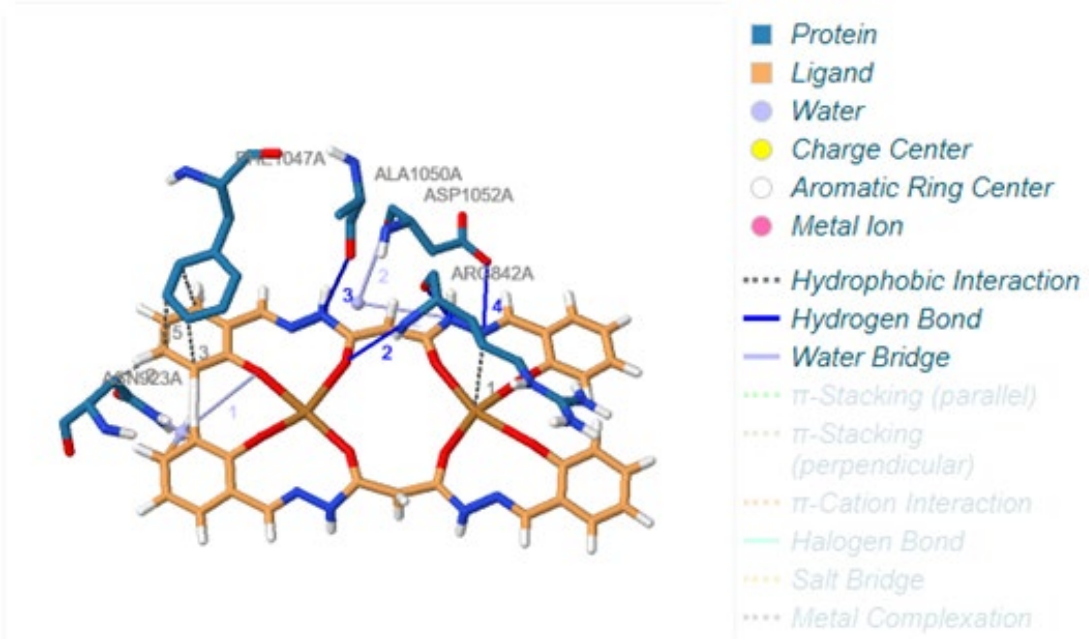


Figure 9: Representation of the Interaction of Cu Metal Complex with Lung Cancer

ructural, electronic and optical properties of 2,5-dichloro-p-xylene: experimental and theoretical calculations using DFT method

Conclusions

As a result of theoretical calculations, the activities of the ligand and its metal complexes were compared. The results of the calculations showed that when the activities of the ligand and its metal complexes against cancer proteins were compared, the activity of the Cu-complex was higher than the others. Afterwards, PLIP analysis was performed to examine the interaction of the Cu-complex in more detail. The interactions of this complex with cancer proteins were researched.

Disclosure Statement

No potensial conflict of interest was reported by the authors

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