Conductometric, Spectrophotometric, and Computational Investigation of Binary and Ternary Complexes of Co(II) and Cu(II) Bivalent Metal Ions with L-Valine Amino Acid and Paracetamol Drug

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Abstract: The conductivity and spectrophotometry techniques were employed to evaluate the binary and ternary complexes of the divalent metal ions Co(II) and Cu(II) with the physiologically relevant amino acid L-Valine (Val) and the analgesic paracetamol. The conductivity experiments were generated by direct conductivity equation from conductivity titration data, while the spectrophotometry experiments were performed using the continuous variations approach (Job's method). Both techniques were accomplished in an aqueous solution with a constant concentration of 0.004 M of divalent metal ions at (40.0 ± 0.1) °C. The binary complexes of Co(II) and Cu(II) have a 1:1 binding ratio of metal to paracetamol (M:para). However, the binary complexes of Co(II) and Cu(II) have metal: Val binding ratios of either 1:1 or 2:1. In addition, the Cu(II) binary complexes of both ligands have a higher stability constant than Co(II) binary complexes of paracetamol and Val ligands, which was in good agreement with the Rossotti-Willime order. The ternary complexes of Co(II) and Cu(II) have a 1:1:1 binding ratio of metal to paracetamol: L-valine, (M:para:Val). The stability constants were in order: The ternary metal complexes > The binary metal-L-Val complexes > The binary metal-para complexes. DFT (Density Functional Theory) simulations were used in order to gain a better understanding of the molecular interactions of Co(II) and Cu(II) divalent metal ions with L-Val and paracetamol. Calculations were made on the electronic structure, HOMOs and LUMOs, and molecular geometry of complexes and their corresponding ligands. The findings unequivocally demonstrate that the metal ion is bound to both the amide nitrogen in the paracetamol ligand and the oxygen atom of the carbonyl group. Moreover, the metal ion is bound to the nitrogen atom of the amine NH_2 group and the oxygen atom of the hydroxyl group for the L-Val ligand.

Keywords: Binary complexes, ternary complexes, Conductometry, Spectrophotometry, L-Valine, Paracetamol, Stability constant.

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1. INTRODUCTION

Metal ions are required for the survival of all living organisms, including humans, animals, and plants. Their lack can contribute to diseases, tumorigenesis, or death. They further play a crucial role in the effective functioning of muscles and nerve cells, the central nervous system, the heart, and a variety of natural processes. Because of their unique electronic and stereochemical characteristics, as well as their distinct molecular geometries (which organic molecules cannot easily access) and ligand transfer, oxidation/reduction, catalytic, and photochemical reactions, metal complexes are extensively utilized in the chemical and physical sciences. Such compounds can interact with biological macromolecules in different manners and therefore by different pathways of reactions (1). In addition, this field has important implications in many other sciences, ranging from medicine to the environment, where initial transition series play an important role in biological processes in many treatments related to humans, and the environment, for example, Ni(II), Cu(II) and Co(II) ions are important in the fields of drugs and clinical applications such as fungal (2), bacterial (3), and cancer inhibitors treatments (4). These transitional metals can form coordination compounds with ligands due to the presence of partially empty d orbital and ligands found either at the active sites or as structural components of several enzymes (5). Amino acids can be both free and bound, similar to a living creature. The bound amino acids are integrated into proteins or other molecular and cellular functional structures, and enzymes and polypeptide hormones direct and control metabolism in the body. The number and sequence of amino acids in a polypeptide chain or chains of a protein, starting with the free amino group and sustained by peptide bonds that link up each amino acid to the next, governs how many amino acids are prevalent in the chain or chains (6). However, some free amino acids bind to metallic materials in the human body as bidentate, in which they can bind via (S, N), (N, O), or (S, O) donor atoms due to the body's acid-basic behavior (7-10). One such example is L-Val Figure 1, which demonstrates that the positively charged NH_3^+ group or the negatively charged COO^- group can behave externally as an acid or a base (11, 12), and L-Val is one of the 20 amino acids that go into making proteins. It is also an essential amino acid and a glycogen amino acid for mammals (13).

Numerous investigations are being made to determine how metal binding affects the activities of human biological processes (14, 15). For example, Paracetamol has two functional groups (NH amide / OH phenol) as in Figure 1, B, thus acting as a ligand with metal ions after entering the human body. In addition, It is used as a treatment for headaches and toothache, an antipyretic (non-narcotic) and fever for children after vaccination for children, and treatment for migraine attacks to moderate strength, cases of arthritis, and pains (16). However, unlike other combinations, paracetamol is not considered carcinogenic at the therapeutic dose. Also, it is not generally classified as a Non-steroidal Anti-inflammatory drug (NSAID) because it exhibits only weak anti-inflammatory activity (17).

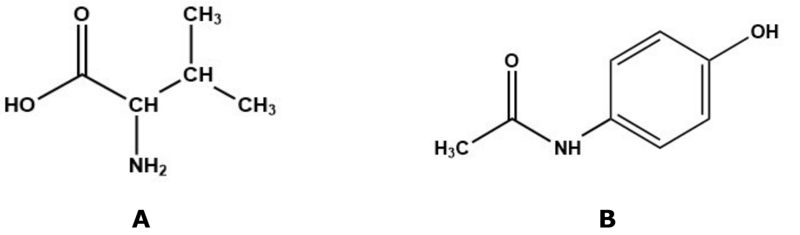


Figure 1: A. Structure of L-Val (chemically 2-amino-3-methyl butanoic acid). B. Structure of Para (chemically N-(4-Hydroxy phenyl) acetamide).

In a recently published paper by our group, the potentiometric method was used to determine the stability constant of Co(II) and Cu(II) binary and ternary complexes of L-Val ligands (18, 19). Thus, the present paper deals with the determination of the formation constants and the binding ratio of the binary and ternary complexes formed by Co(II) and Cu(II) with L-Val and Para using the conductometric and the spectrophotometric methods at (40 ± 0.1 °C) temperature. The method of conductometric (20, 21) as adopted by the direct conductivity method has been employed to determine K values, while the spectrophotometric using the continuous variation method has been employed to determine K values and binding ratio for the binary ligands-metal complexes (21-23).

2. EXPERIMENTAL SECTION

2.1. Materials and Methods

All the compounds used in this research were of the finest quality and analytical grade quality (AR). Valine (Fluka, >99%), paracetamol (CCM (Malaysia), 99.5%), metal salts including $CuCl_2.2H_2O$ (T-Baker lab chemicals, ≥99.99%), $CoCl_2.4H_2O$ (Surechem Products, 98%), sodium hydroxide (Shandong, 98.8%). The pH-conductivity meter (Thermo Electron/Orion4star /USA, with an accuracy of 0.002 and a cell constant equal to 0.55 cm^{-1}) was used to perform the conductometric procedure. before each titration, the conductivity meter was calibrated using a buffer solution containing NaCl at concentrations of 1413 S/cm and 12.9 mS/cm. A Grant Instruments (Cambridge) Ltd/SUB28 Thermostat Water Bath Apparatus maintained the temperature constant (± 0.1). Spectrophotometric methods were recorded on UV/Visible spectrophotometer in the range of 200 to 800 nm.

2.2. Solutions and Procedure

The stock solution of L-Val (0.02 M) was freshly made by accurately diluting 0.9372 g of solution with a small portion of deionized water. The precise quantity (0.3023 g) of Para was dissolved in deionized water to formulate a stock solution (0.02 M), The required amount of each metal salt of 0.4754 g Co(II) and 0.3409 g Cu(II) were solubilized in distilled deionized water to prepare the stock solution. EDTA titrations were employed to calibrate the metal's salt final concentration. The experiment involves titrating 40 ml of each metal ion (4×10^{-3} M) with (2×10^{-2} M) of Para and (4×10^{-3} M) with (2×10^{-2} M) of L-Val solution in 1 mL intervals utilizing the conductometric technique at 313.15 K temperature. By multiplying the specific conductance values by a factor of (40+V)/40, where V is the volume of titrating added. According to the requirements of Job's approach, stock solutions of the ligand (4×10^{-3} M) and metal (4×10^{-3} M) were made for use in spectrophotometric methods. The total number of moles of metal plus the total number of moles of ligand were held constant in a series of flasks. First, the absorbance values were recorded after filling one of the cells with water as a reference and the other with an experimental solution. All measurements were performed using the same cells.

2.3. Molecular Reactivity

The structure of the studied binary complexes, the molecular geometry, HOMO and LUMO orbitals, and the active sites in ligands which will coordinate to the metal ion, the electronic structures and binding energies were calculated at the DFT level with DMol^3 using the Materials Studio suite of programs (version 5.5). Structure optimization calculations were performed using a generalized gradient approximation (GGA) function (24, 25) and a hybrid exchange–correlation function (Becke-Lee-Yang-Parr) BLYP (26, 27) with a double numeric plus polarization (DNP) basis set to map the orbital structure of the compound. Frontier molecular orbitals (HOMO and LUMO and the energy gap between them (ΔE) are used to predict the bonding atoms of the ligands molecules.

3. RESULTS AND DISCUSSION

3.1. Conductometric Method

3.1.1. Conductometric method of binary complexes

The formation constants for each metal in the stoichiometric binary Para-metal or L-Val-metal complexes were calculated using the experimental data of (Λm). The formation constants for each metal in the stoichiometric binary Para-metal or L-Val-metal complexes were calculated using the experimental data of (Λm). By graphing the correlation between the molar ratio of ligand to metal (L/M) concentrations and the molar conductance (Λm), seen in Figure 2, different lines are established, with sharp breaks reflecting the formation of a 1:1 or 1:2 (L:M) stoichiometric ratio.

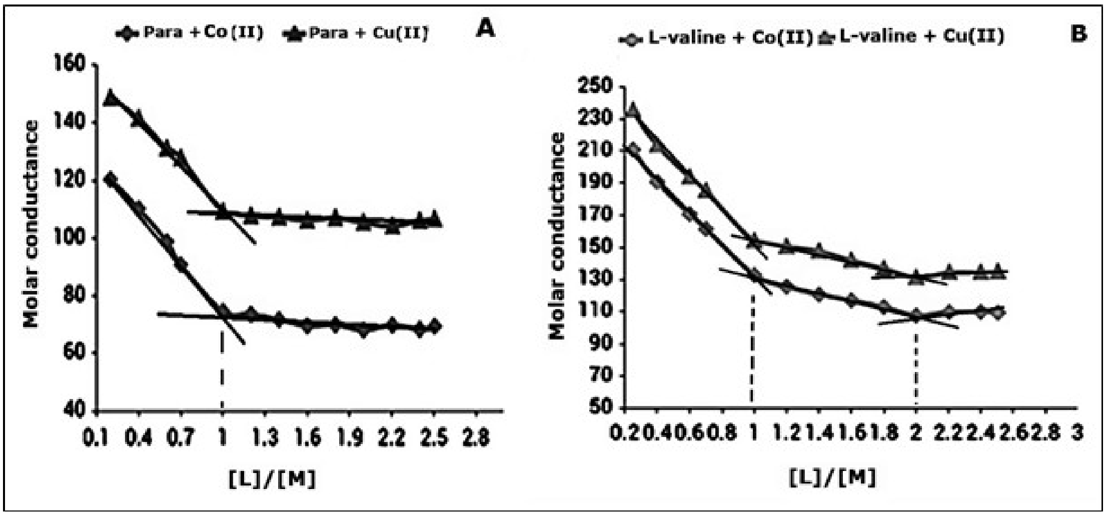


Figure 2. The relation between Λ_m and [L/M], A) Para-M(II) and B) L-Val-M(II) at 313.15 K.

The conductivity is decreased as concentration increased, and that, all solutions behave as Weak Electrolytes or natural. The formation constants (K_f) for binary Para + metal and L-Val + metal complexes were calculated for each metal of complexes (1:1) or (2:1) (L: M) by using the Eq. 1-3 (8, 20, 28):

For 1:1

$$K_f = \frac{[M\,L]}{[M][L]} = \frac{(\Lambda_M - \Lambda_{obs})}{(\Lambda_{obs} - \Lambda_{ML}) \times [L]} \qquad (1)$$

For 2:1

$$K_f = \frac{[M\,L]}{[M][L]^2} = \frac{(\Lambda_M - \Lambda_{obs})}{(\Lambda_{obs} - \Lambda_{ML}) \times [L]^2} \qquad (2)$$

In (1) and (2), the following equation will be used:

$$[L] = C_L - \left[C_M + \frac{(\Lambda_M - \Lambda_{obs})}{(\Lambda_M - \Lambda_{ML})} \right] \times [L] \qquad (3)$$

Where Λ_m is the limiting molar conductance of the metal salt alone, Λ_{obs} is the molar conductance of solution during titration, and Λ_{mL} is the molar conductance of the complex. The obtained values (K_f) for metal-ligand stoichiometric complexes are presented in (Table 1). The data show that binary Cu(II) complexes are more stable (favoured) than binary Co(II) complexes.

Table 1: Formation constants for 1:1 and 2:1 (L/M) (Para-Metal) and (L-Val-Metal) complexes in distilled water at 313.15 K.

Metal ion (M)	K_f (Para-M)(1:1)	K_f (L-Val-M)(1:1)	K_f (L-Val-M)(2:1)
Co(II)	3.717 ± 0.56	8.401 ± 0.49181	2.783 ± 0.6493
Cu(II)	4.09 ± 0.95	9.342± 0.49532	2.982 ± 0.4062

3.1.2. Conductometric method of ternary complexes

There were no derived lows to calculate the stability constant of the ternary complex by the conductivity method. Therefore, the electrolyte behavior of formed ternary metal complexes will be only disused here. The specific conductance values (K_s) of 0.004 M metal solution were measured experimentally in the presence of 0.004M ligand at 313.15 K. The molar conductance (Λ_m) values were calculated. The limiting molar conductance (Λ_o) at infinite dilutions were estimated for all solutions of ternary metal complexes by extrapolating the relation between Λ_m ($S.Cm^2.mol^{-1}$) and $C_m^{½}$ to zero concentration Figure 3. The conductivity decreases with increased concentration. Moreover, the conductivity values for Cu(II)-L-Val-Para complexes are greater than that for Co(II)-L-Val-Para.

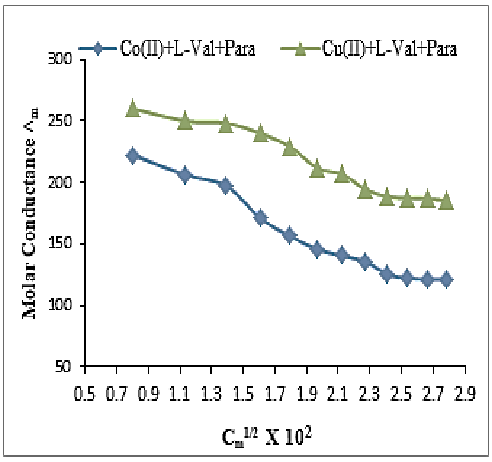


Figure 3: $C_m^{½}$ versus molar conductivity of metal- L-Val-Para complexes at 313.15 K.

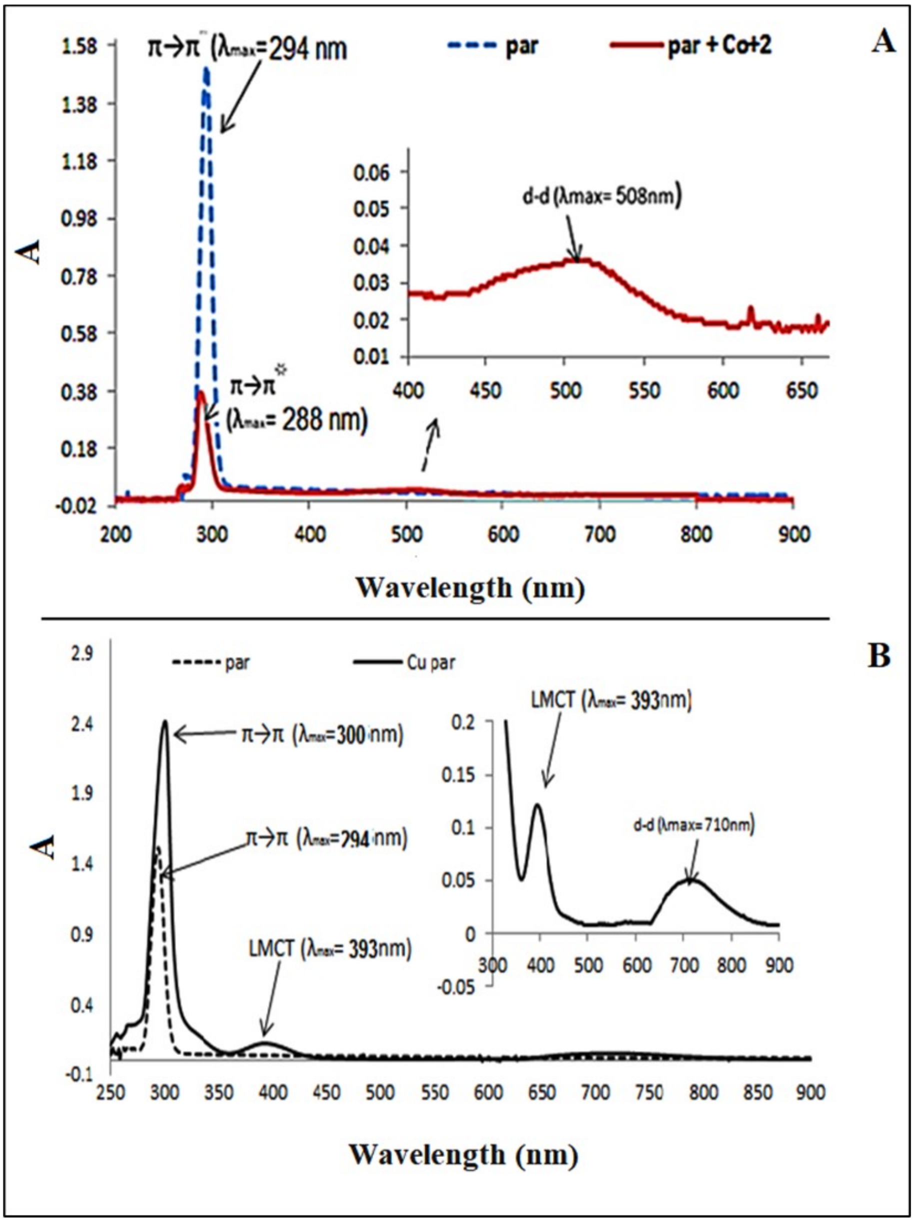


Figure 4: UV-Vis spectrum of A) Para+Co(II) and B) Para+Cu(II) complexes.

3.2. Spectrophotometric Measurements

This method is based on the absorption of visible and ultraviolet light by the molecules of the substance in the solution. The absorption of visible and ultraviolet radiation by chemical systems leads to the transition of one or more electrons in low-energy orbits (stability level) to high energy levels (the level of irritability). It should be noted that the nature of the electrons in the molecule is responsible for the extent to which the molecule can be absorbed in the visual and violet fields (29).

3.2.1. Para-Metal complexes

The UV spectra of Paracetamol demonstrated an absorption peak of the complex at the site (294 nm), which resulted from the electronic (п→п*) type excitation of it extended the п-conjugation system. Upon light absorption, an п electron is excited from the ground state to the first excited state, and new absorption peaks of the formed complex (Para-M(II)) ions have been attributed to the d→d transition (17), as shown in (Table 2 and Figure 4).

The free ligand has an absorption maximum (λ_{max}) wavelength of around 294 nm depending on the solvent. Upon chelating with Co(II) ions, the absorption maxima (λ_{max}) were shifted to 288 nm and 510 nm, while chelating with Cu(II) ions, the absorption maxima (λ_{max}) were shifted to 300 nm, 393 nm, and 710 nm (20).

Job's method of continuous variation (20, 21), which is straightforward, quick, measurable, and valid, was employed to ascertain the stoichiometry and formation constants of Para-metal(II) complexes by spectrophotometry. Metals and Para were mixed in various ratios ranging from 0.188:1 to 1:0.188, and the absorbance of each mixture was measured at the complexes' maxima (17, 21). The maximum absorbance was obtained at XL= 0.5-0.55, demonstrating that the stoichiometric ratio for the complexation of metals and Para is 1:1 as depicted in Figure 5. The graph of absorbance against molar ratios displays inflections correlating to different stoichiometries of the complexes.

Table 2: Electronic spectral data of Para ligand and its complexes formed at (0.004 M) and 313.15 K.

Assignment	(λ_{max})nm	Complex
*π→π**	294	Para ligand
*π→π**	288	(Para+Co(II))
d→d	510	
*π→π**	300	(Para+Cu(II))
lmct	393	
d→d	710	

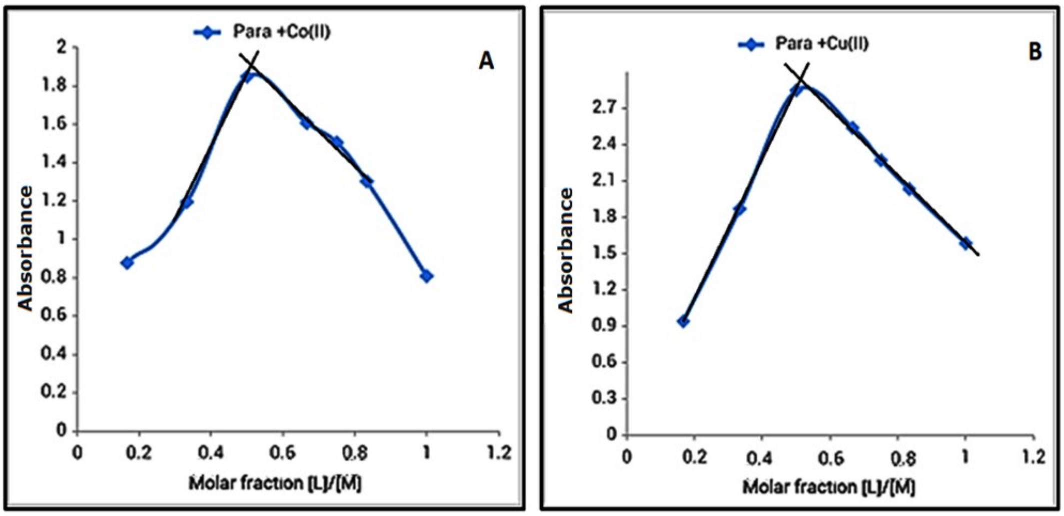


Figure 5. The Job's plot of absorbance at λ_{max} versus the molar fraction of metal ions with Para A) Para+Co(II), B) Para+Cu(II).

$$M+nL \rightleftarrows ML_n \quad (4)$$

$$K=frac\left(1-\alpha\right)C\left(\alpha C\right)\left(\alpha C\right)\rightarrow K=frac\,1-\alpha\alpha^2C \quad (5)$$

The formation constants are measured spectrophotometrically by measuring the absorbance of several sets of solutions of the metal salts Co(II) and Cu(II) and the ligands (Para and L-Val). The correlation seen in Eqs. 4 and 5 was employed to determine the amount of production of each complex, where K_f = formation constant. The dissociation degree is given in α and C is the concentration, α = A_m - A_s/A_m, the absorbance of a solution containing an excess and a stoichiometric quantity of reagent is represented by A_m and A_s, respectively. Calculated K_f values for the prepared complexes are recorded below in (Table 3).

Table 3: Formation constants for 1:1 (L/M) Para-metal complexes in distilled water at 313.15 K.

Metal complexes	α	K_f
(Para+Co(II))	0.209	3.654
(Para+Cu(II))	0.145	4.007

3.2.2. L-Val-Metal complexes

The UV spectra of L-Val showed an absorption peak at the site (229 nm) which was due to (п→п*) transition, and an absorption peak at (250 nm) which was due to (n→п*) transition (11). The occurrence of displacement at the site of this summit was found in the composition of the complex consisting of (L-Val+M(II)), which confirms the consistency between L-Val and M(II). As well as the emergence of new absorption peaks of the formed complex (L-Val+M(II)) due to the d → d transition as shown in (Table 4) and Figure 6.

Table 4: Electronic spectral data of L-Val ligand and its complexes formed at (0.004 M).

Assignment	(λ)nm	Complex
п→п*	229	L-Val ligand
n→п*	250	
п→п*	219	(L-Val+Co(II))
n→п*	228	
d→d	510	
п→п*	229	(L-Val+Cu(II))
n→п*	245	
d→d	700	

The determination of stoichiometry and formation constants of L-Val-Metal complexes by spectrophotometry was based on Job's method of continuous variation (21-23). The maximum absorbance was observed at XL=0.66–0.7, confirming that the stoichiometric ratio for the complexation of metals and Val is 1:2 as shown in Figure 7. The plot of absorbance against molar ratios reveals inflections corresponding to different stoichiometries of the complex.

By measuring the absorbance of two sets of solutions at λ_{max} (30), it could spectrophotometrically estimate the formation constants. The relationship seen in Equations 4 and 5 (21) was employed to determine the amount of formation of each complex (31). The prepared complexes' estimated K_f values are presented in Table 5 below.

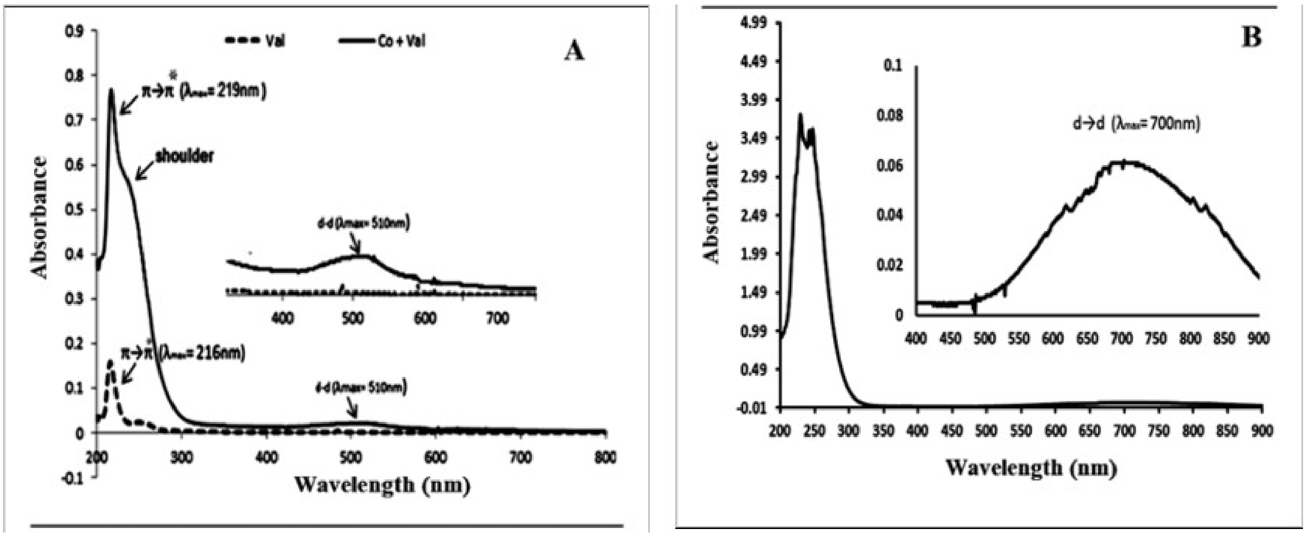


Figure 6: UV-Vis spectrum of A) Val+Co(II) and B) Val+Cu(II) complexes.

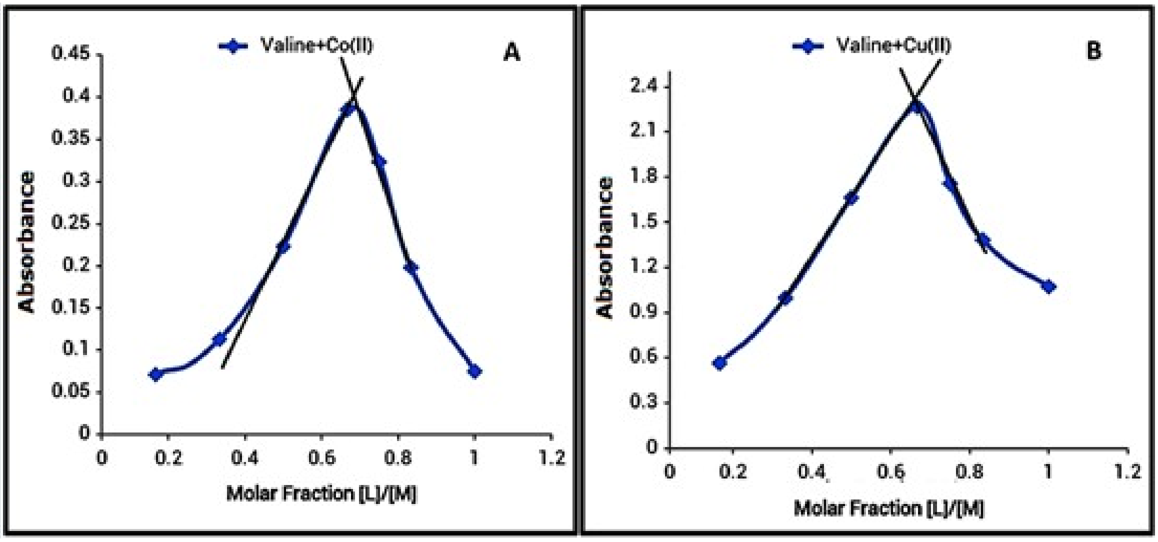


Figure 7: The Job's plot of absorbance at λ_{max} versus the molar fraction of metal ions with A) L-Val+Co(II), B) L-Val+Cu(II).

The data show that binary Cu(II) complexes are more stable than binary Co(II) complexes, these results were noted great with data of the conductometric method.

Table 5: Formation constants for 1:2 (M/L) L-Val complexes in distilled water at 313.15 K.

Metal complexes	α	K_f
(L-Val+Co(II))	0.476	2.763
(L-Val+Cu(II))	0.392	2.996

3.2.3. Spectrophotometric measurements of M-L-Val-Para complexes

There were no derived lows to calculate the stability constant of the ternary complex by the spectrophotometry method. Therefore, the electronic spectra of formed ternary metal complexes will be only discussed here. The UV–Vis absorption spectra of [Co(L-Val)(Para)] and [Cu(L-Val)(Para)] show a $d\to d$ maximum at 678 and 747 nm, respectively, in the visible range of the spectrum (see Figure 8). However, The maximum absorption in the UV range was 308, 308, 316 for [Co(Para)(L-Val)], [Ni(Para)(L-Val)] and [Cu(Para)(L-Val)], respectively. These transitions were assigned to a $\pi\to\pi$ mixed with $n\to\pi$ transitions from the coordinate ligands, which red-shifted upon coordination as shown in Table 6.

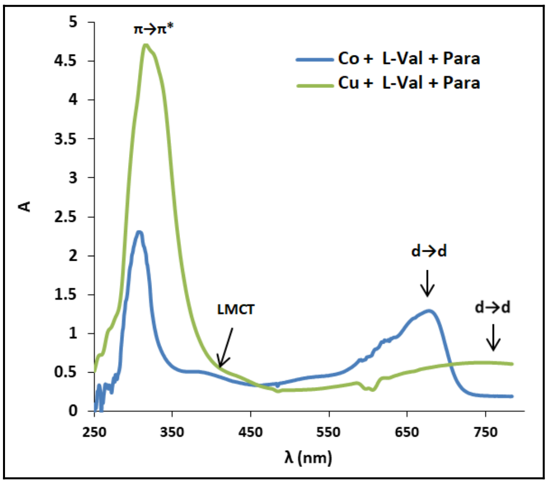


Figure 8: The spectrum of the maximum wavelength of M-L-Val-Para complexes.

Table 6: Results of measurements of the electronic spectra of ligands and M-L-Val-Para complexes formed at (0.004 M) and 313.15 K.

Ternary Complexes 1:1:1	λ_{max}	Assignment
Co + L-Val + Para	308	π→π*
	377	LMCT
	678	d→d
Cu + L-Val +Para	316	*π→π
	747	d→d

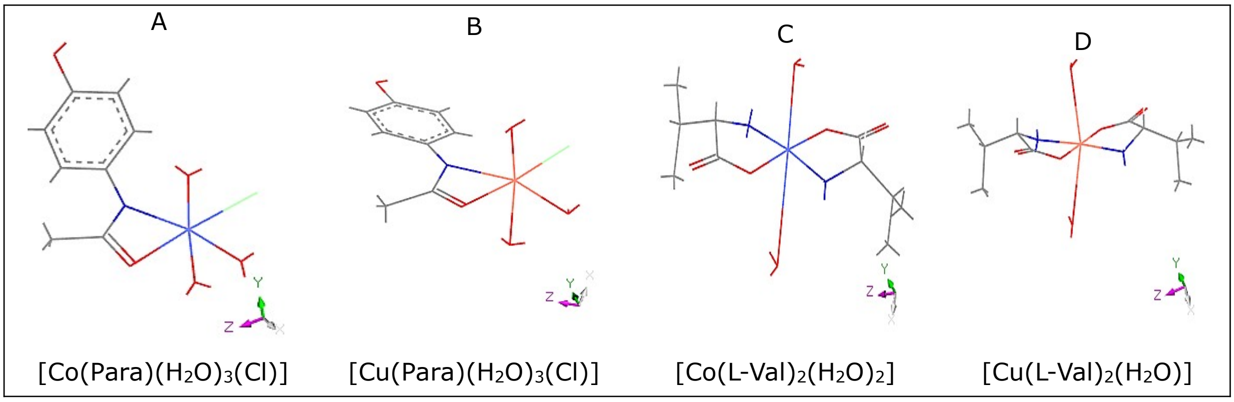
3.3. The Role of the Structure of the Binary and Ternary Complexes

Coordination substances have certain bond types and structures. A large number of compounds found in nature are categorised as coordination substances due to their structure, characteristics, and biological action. As a lot of distinct ligands are anticipated to compete for metal ions in vivo, binary and ternary complexes (Mixed ligand complexes) play a significant role in biological chemistry. This is because mixed chelation is common in biological fluids. Coordination compounds with biological activity include haemoglobin, myoglobin, and vitamin B_{12} as well as enzymes that contain metals. It is common practise to dissolve renal and the gallbladder stones in the bladder utilising a particular class of chemicals that have the capacity to form complexes with several cations. Because they bind the metal ions that catalyse oxidation reactions, they are utilised as stabilisers in blood conservation. They operate as stabilisers in the maintenance of blood because they bind the metal ions that catalyse oxidation reactions. Additionally, they are utilised to cleanse the body of radioactive isotopes and harmful metal ions. The largest stability constant, which is the strongest and most stable, is typically what determines whether a binary or ternary complex forms. And they depend on the geometry and configuration of the metal and the ligand. The distinctive properties of metal ions, such as their tiny size, positive charge, and electron spin configuration, enable them to carry out a wide range of biofunctions (32, 33). However, the ligand's nature, the chelating activity, and the macrocyclic effect The stability of binary and ternary complexes is also impacted by steric or steric hindrance effects.

Amino acids, Paracetamol, and its derivatives are some of these ligands. Leach and Angelici (34) described a Cu(II) combination with a wide range of L-amino acid affinities. According to a set of stability constants calculated by potentiometry, Cu(II) forms stronger complexes with L-leucine, L-phenylalanine, alanine, L-serine, and valine than with the respective antipodes. Complexes of Mn(II), Fe(II), Co(II), Ni(II), Cu(II), and Cd(II) ions with L-valine as a main ligand and 1,10-phenanthroline as a secondary ligand had been created by Noori et al. (35). According to the research, Co(II) has an octahedral geometry. Six unique mixed ligand complexes of metals(II) were synthesised by Fayad et al. (36) employing saccharin and l-valine as primary and secondary ligands, respectively. In the other hand, paracetamol complexes with Mn(II), Co(II), Fe(III), Zn(II), and Cu(II) were created by Refat et al. (37, 38). In these complexes, paracetamol behaves as a monobasic bidentate ligand, and elemental analysis, FT-IR spectroscopy, and thermal analysis have all been used to confirm the structures of those complexes. Complexes of Co(II), Ni(II), and Fe(III) with paracetamol were produced and studied by Obaleye et al. (39, 40). The oxygen of the hydroxyl and amide groups are coordinated by the paracetamol ligand, which, according to studies, functions as a bidentate chelating agent (Fig. 11). Aspirin and ascorbic acid mixed metal complexes with the ions Fe(II), Co(II), Ni(II), Cu(II), and Zn(II) were created by Babamale et al. (41).

3.4. Computational Study

According to the literature review and the conductivity and spectrophotometry results of this study, it is possible to give the general formula of prepared metal complexes of Para and L-Val ligands depending on I) the most commonly the coordination bonding of amino acids with metal ions by N, O atoms of the amine and carboxylate groups respectively, in which forms a five chelated ring (42-45). Thus, simple mixing of Co(II) and Cu(II) metal salts with solutions of L-Val amino acids often provides neutral binary complexes that favor octahedral coordination. II) paracetamol ligand tends to behave like a mono-negative ion (-1) by deprotonation of the NH amidic group. Thus paracetamol is attached to Co(II) and Cu(II) metal ions by N, O atoms of the amidic group, which forms a four-chelated ring (18, 23, 40, 41, 46). III) The conductivity of all formed complexes indicates that all complexes are neutral complexes which support 1:2 metal to L-Val complex by replacement of both chloride ions in the starting metal complex salts of $CuCl_2$ and $CoCl_2$, and 1:1 metal to paracetamol by replacement of one chloride ion in the starting metal salts to form a neutral metal complex. By taking all of these notes, the general structure of metal complexes is shown in Figure 9 (A to D).



[Co(Para)$(H_2O)_3$(Cl)] [Cu(Para)$(H_2O)_3$(Cl)] [Co(L-Val)$_2(H_2O)_2$] [Cu(L-Val)$_2(H_2O)$]

Figure 9: Different geometric shapes of complexes according to DFT.

It can be ascertained where the metal ion is bonded to paracetamol and L-Val using the DFT. Geometric factors and the energy difference between HOMO-LUMO confirmed the donor atom sites in Figures 10 and 11.

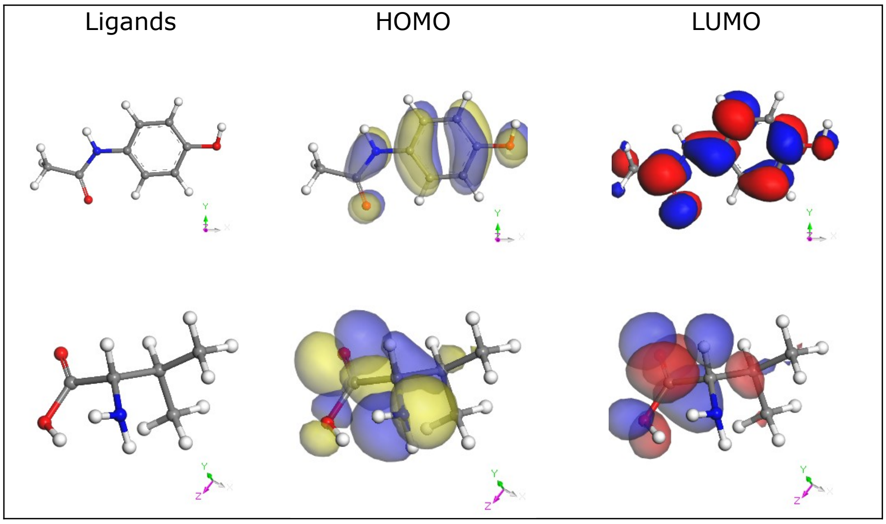


Figure 10: The obtained optimized structures, HOMO and LUMO of the neutral para and L-Val ligands molecules.

The molecular reactivity of the studied drug was investigated via analysis of frontier molecular orbitals of HOMO and LUMO. The energy of HOMO is associated with the electron-donating ability of a ligand to donate electrons to the metal atom with an empty molecular orbital. On the other hand, the energy of LUMO is associated with the electron-accepting ability of ligands (47-49). The presence of nitrogen and oxygen atoms together with several p-electrons on the entire paracetamol and L-Val molecules enhances the ability of ligands to react with metal ions.

The optimized structures and frontier molecule orbital density distributions of HOMO & LUMOs of the investigated ligands and their metal complexes were presented in Figures 10 and 11. As seen from the Figure, the HOMO and LUMO are distributed around the whole ligands molecules. This indicates the high reactivity of these ligands to bond to metal ions. The DFT results of the calculations of binary metal complexes are proposed in Figure 10 and Table 7, which clearly show the metal ions of Co(II) and Cu(II) to bond to the oxygen atom of the carbonyl group and the amide nitrogen in paracetamol ligand. In addition, the oxygen atom of the hydroxyl group and the nitrogen atom of the amine NH_2 group for the L-Val ligand. From Figure 11, it's clear that the HOMOs and LUMOs of binary meta L-Val complexes are metal based, however, the HOMOs and LUMOs of binary metal-paracetamol complexes are ligand-based. As a consequence, the binding energies for metal-L-Val complexes are higher than the metal-paracetamol complexes (see Table 7). In addition, the DFT results of the calculations of ternary metal complexes are proposed in Figure 11 and Table 7, which clearly show the HOMOs and LUMOs are metal-based.

Table 7: Comparison between binary M-(Para) and (L-Val) complexes and ternary M-L-Val-Para complexes.

Type	Complexes	HOMO (eV)	LUMO (eV)	$\Delta E_{LUMO-HOMO}$ (eV)	Binding Energy (kcal/mol)
Binary Para complexes	[Cu(Para)(H_2O)$_3$(Cl)]	-4.458	-4.025	0.433	-3024.44
	[Co(Para)(H_2O)$_3$(Cl)]	-4.448	-3.607	0.841	-3187.95
Binary L-Val complexes	[Cu(L-Val)$_2$(H_2O)$_2$]	-4.465	-3.59	0.875	-4181.39
	[Co(L-Val)$_2$(H_2O)$_2$]	-4.354	-3.482	0.872	-4212.6
Ternary (Mixed) complexes	[Cu(L-Val)(Para)(H_2O)$_2$]	-3.998	-1.598	2.4	-4545.66
	[Co(L-Val)(Para)(H_2O)$_2$]	-4.938	-3.003	1.935	-4764.733

The sites of the donor atoms were confirmed by the geometric variables and the energy difference between HOMO-LUMO extracted from the calculations. Consequently, the value of the ΔE gap provides a measure of the strength of the crystal field of formed complexes, where the higher value of ΔE; the higher the crystal field is. The decrease in band gap is due to the decrease in strength of the crystal field, which is inversely proportional to the metal–ligands bond length. The strong-field ligands produced large electrostatic repulsion between the HOMO and the LUMO orbitals, which lead to a large band gap. Table 7 and Figure 12 depicted that the band gap order is: The ternary metal complexes > The binary metal-L-Val complexes > The binary metal-Para complexes. This consequence is in good agreement with the stability constant those calculated from the conductivity and spectrophotometry methods, in which, ternary M-L-Val-Para complexes are more stable than the binary complexes of M-para or complexes of M-L-Val. Moreover, the binary M-L-Val complexes are more stable than binary M-Para complexes.

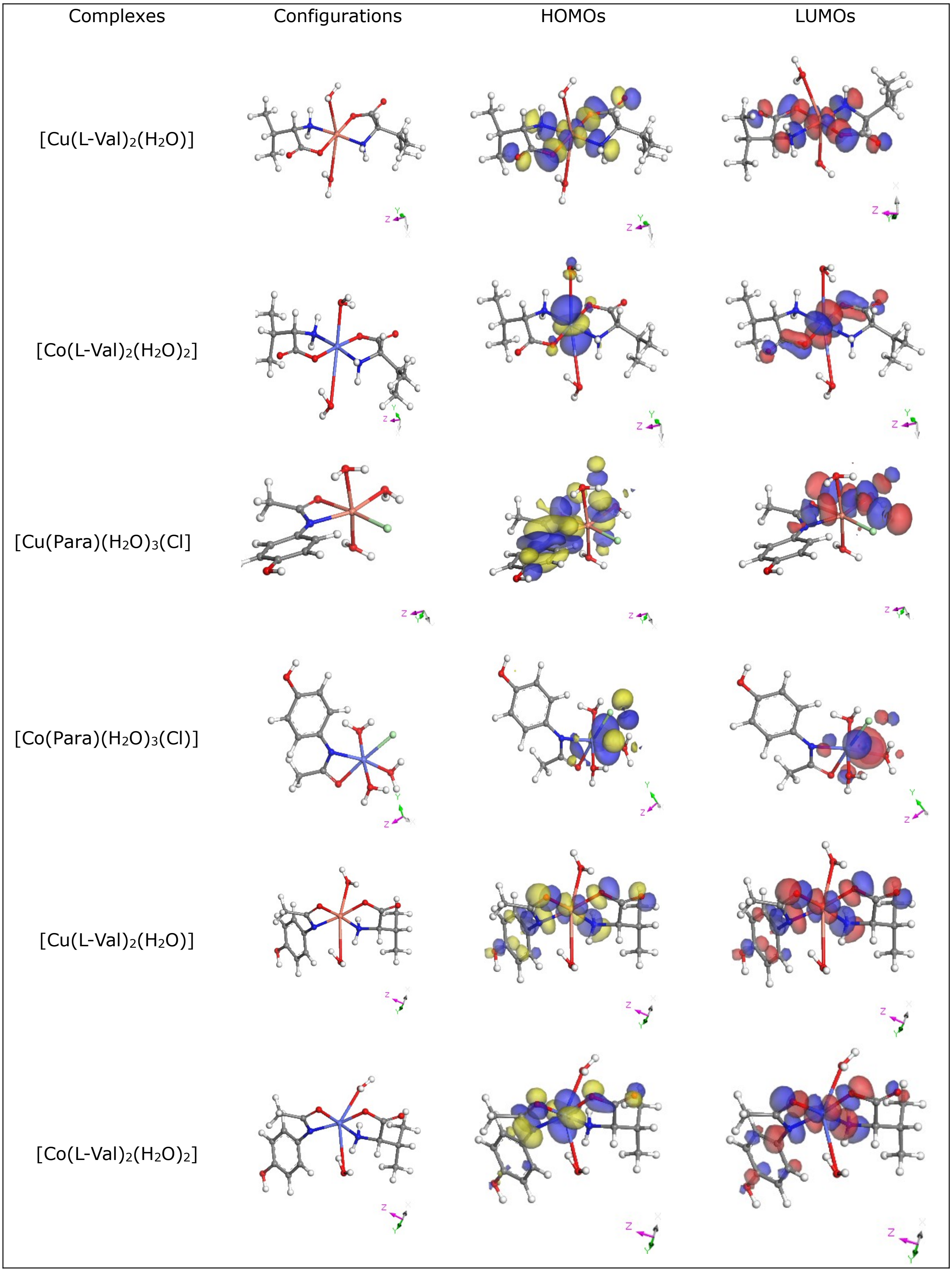


Figure 11: The obtained optimized structures, HOMO and LUMO of the binary and ternary metal complexes of para and L-Val ligands.

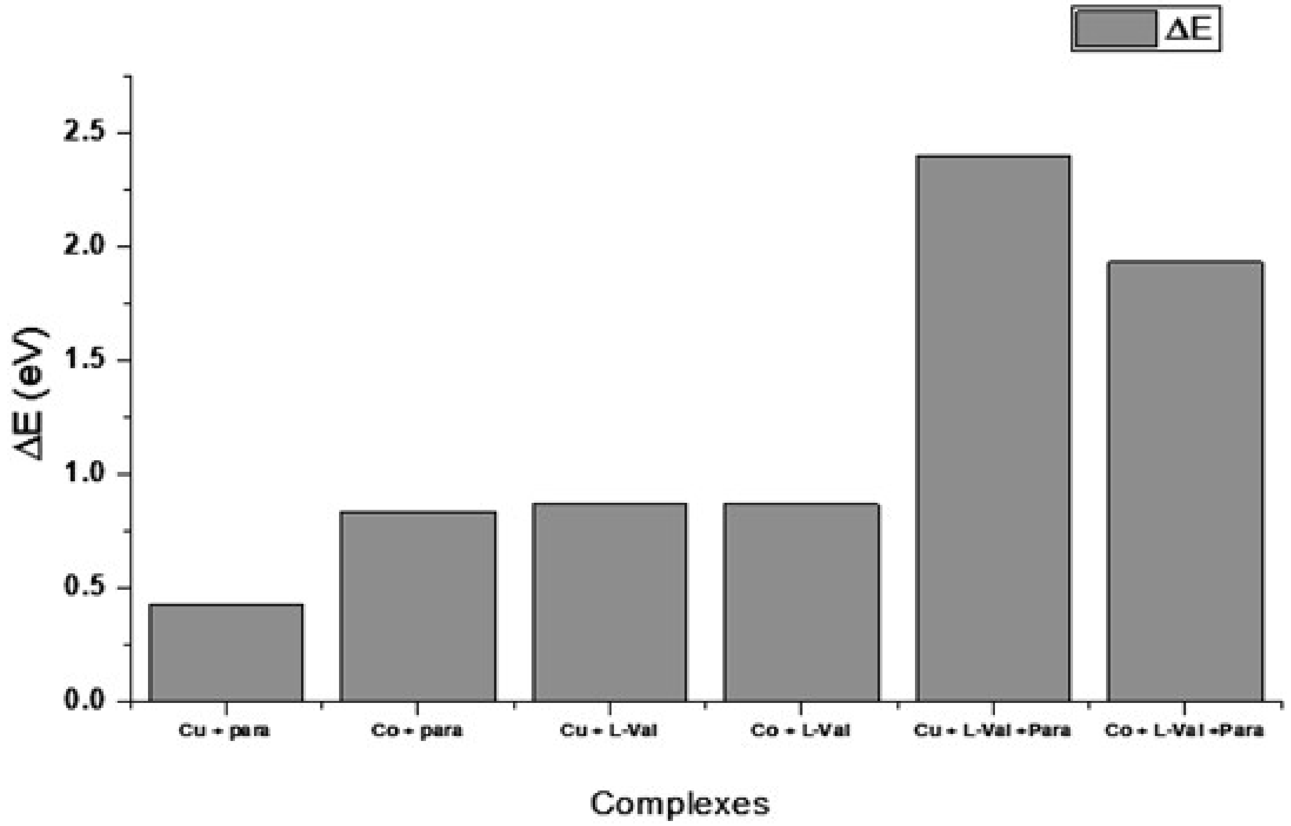


Figure 12: The band gap of binary M-(Para) and (L-Val) complexes and ternary M-L-Val-Para complexes.

4. CONCLUSION

The binary complexes of L-Val and Para with Co(II) and Cu(II) were investigated by conductometric and spectrophotometric methods based on formation constants (K_f) and stoichiometric (L:M): The formation constants for the binary-metal complexes were computed from conductivity titrations in the constant concentrations of (0.004 M) of metal ions, which Para-M(ll) and L-Val-M(ll) complexes were kept in a range 3.7 to 4.08 for Para-M(ll) (1:1) complexes and a range 11.18 to 12.32 for L-Val-M(ll) complexes (2:1), where these complexes were formed from the L-Val as primary ligand and the Para as a secondary ligand with metal ions. The values of formation constants of binary Cu(ll) complexes bigger than the values of stability constants of binary Co(ll) complexes, where these values great with the order is following Irving-Williams order of stability, indicating that the order of stability is Cu(II) > Co(II). While Stoichiometry and formation constants of binary-Metal complexes by spectrophotometry were based on Job's method of continuous variation, where the result was a maximum absorbance at XL= 0.66-0.7, confirming that the stoichiometric ratio for the complexation of metals and L-Val is 1:2, while the result was a maximum absorbance at XL= 0.5-0.55, confirming that the stoichiometric ratio for the complexation of metals and para is 1:1. The formation constants are obtained spectrophotometrically by measuring the absorbance of two sets of solutions at λ_{max}.

5. LIST OF ABBREVIATIONS

λ_{max}	Absorption maximum
A_m	Absorbance of a solution containing an excess of reagent
A_s	Absorbance of a solution containing a stoichiometric quantity
BLYP	Becke-Lee-Yang-Parr
α	Degree of dissociation
DFT	Density Functional Theory
Cu(II)	Divalent copper

Co(II)	Divalent cobalt
DNP	Double numeric plus polarization
ΔE	Energy gap
K_f	Formation constants
GGA	Generalized gradient approximation
HOMOs	High occupied molecular orbital
LUMOs	Lower unoccupied molecular orbital
L-Val	L-Valine amino acid
Λ_o	Limiting molar conductance at infinite dilutions
Λ_m	Molar conductance
Λ_{mL}	Molar conductance of the complex
Λ_{obs}	Molar conductance of solution
NSAID	Non-steroidal anti-inflammatory drug
Para	Paracetamol
K_s	Specific conductance values

5. CONFLICT OF INTEREST

The authors declare no conflict of interest.

7. ACKNOWLEDGMENTS

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8. REFERENCES

1. Karges J, Stokes R, Cohen S. Metal complexes for therapeutic applications. Trends Chem. 2021;3(7):523-34. Available from: <URL>.

2. Yin X, Ma K, Wang Y, Sun Y, Shang X, Zhao Z, et al. Design, synthesis, and antifungal evaluation of 8-hydroxyquinoline metal complexes against phytopathogenic fungi. J Agric. Food Chem. 2020;68(40):11096-104. Available from: <URL>.

3. Shi J, Shu R, Shi X, Li Y, Li J, Deng Y, et al. Multi-activity cobalt ferrite/MXene nanoenzymes for drug-free phototherapy in bacterial infection treatment. RSC Adv. 2022;12(18):11090-9. Available from: <URL>.

4. Li Y, Liu B, Shi H, Wang Y, Sun Q, Zhang Q. Metal complexes against breast cancer stem cells. Dalton Trans. 2021;50(41):14498-512.

5. Nelson J, Schelter E. Sustainable inorganic chemistry: metal separations for recycling. Inorg. Chem. 2019;58(2):979-90. Available from: <URL>.

6. Bhattacharya P, Samnani P. Metal ions in biochemistry: CRC Press; 2020. ISBN: 9781000292640.

7. Ahmed N, Al-Omar M, A. A, Obaidullah A, Bhat M, Kalmouch A, et al. Synthesis, characterization, and anti-diabetic activity of some novel vanadium-folate-amino acid materials. Biomolecules. 2020;10(5):781. Available from: <URL>.

8. Suhud K, Heng L, Rezayi M, Al-abbasi A, Hasbullah S, Ahmad M, et al. Conductometric Studies of the Thermodynamics for Complexation of 1,1-Diethyl-3-(4-methoxybenzoyl)thiourea and Cobalt(II) Cation in Aqueous Binary Mixtures of Polar Organic Solvents. Journal of Solution Chemistry. 2015;44(2):181-92. Available from: <URL>.

9. Al-abbasi A, Mohamed T., Kassim M. N-(Pyrrolidin-1-ylcarbothioyl)benzamide. Acta Crystallographica Section E. 2012;68(1):o201. Available from: <URL>.

10. Al-abbasi A, Mohamed Tahir M, Kassim M. 1,1-Diethyl-3-(4-methoxybenzoyl)thiourea. Acta Crystallographica Section E. 2011;67(12):o3414. Available from: <URL>.

11. Su J, Suo B, Cassam-Chenaï P. Theoretical Study of the Anisotropy Spectra of the Valine Zwitterion and Glyceraldehyde. J Phys. Chem. A. 2020;124(34):6824-33. Available from: <URL>.

12. Kamatchi K, Umarani P, Radhakrishnan T, Raja C. Investigation on organic-inorganic hybrid NLO crystal L-Valine Potassium Penta Borate octa hydrate (LVPPB) for NLO applications. Optik. 2018;172:674-9. Available from: <URL>.

13. Afzal Siddiqui H, Nadeem M, Azeem M, Arshad M, Haider A, Malik M. Topological properties of supramolecular chain of different complexes of N-Salicylidene-L-Valine. Polycycl. Aromat. Compd. 2022;42(9):6185-98. Available from: <URL>.

14. Martín J, Alés M, Asuero A. An overview on ligands of therapeutically interest. Pharm. Pharmacol. Int. J. 2018;6(3):198-214.

15. Chen A, Adamek R, Dick B, Credille C, Morrison C, Cohen S. Correction to Targeting Metalloenzymes for Therapeutic Intervention. Chem. Rev.. 2019;119(12):7719-.

16. Hejaz H, Kanan A, Al Mohtaseb M, Ja’bari A. Development and characterization of paracetamol medicated lollipops. Pharm. Technol. Hosp. Pharm. 2020;5(1). Available from: <URL>.

17. Alsamarrai K, Ameen S. Simultaneous Ratio Derivative Spectrophotometric Determination of Paracetamol, Caffeine and Ibuprofen in Their Ternary Form. Baghd. Sci J. 2022:1276-. Available from: <URL>.

18. Belkher N, Al-abbas A, Zidan M. Potentiometric Studies on Stability Constant of the Complexes of Some Essential Transition Metal Ions with L-Valine. Journal of Pure & Applied Sciences. 2019;18(3):59-63.

19. Al-abbasi A. BN, Ahmida K., Zidan M. . Potentiometric Studies on Binary and Ternary Complexes of Ni(II) and Cu(II) Ions with L-Valine and Paracetamol. Journal of the Turkish Chemical Society Section A: Chemistry. 2023;10(2):325-38. Available from: <URL>.

20. Yang L, He X, Dincă M. Triphenylene-bridged trinuclear complexes of Cu: Models for spin interactions in two-dimensional electrically conductive metal–organic frameworks. J Am. Chem. Soc. 2019;141(26):10475-80. Available from: <URL>.

21. Upadhyay S, Hari O. Spectrophotometric and conductometric study of the interaction of saponin with chromium (VI) and lead (II). International Journal of Environmental Science and Technology. 2019;16(12):7997-8004. Available from: <URL>.

22. Helmy E, Gomaa E, Elleef EA, Negm A. Conductometric, Spectrophotometric and In vivo Investigation of the Interaction of Ca (II) Ion with Oxytetracycline Hydrochloride. International Journal of Pharma Medicine and Biological Sciences. 2015;4(3):197. Available from: <URL>.

23. Chandrathilaka A, Ileperuma, O. Hettiarachchi, C. Spectrophotometric and pH-metric studies on Pb(II), Cd(II), Al(III) and Cu(II) complexes of paracetamol and ascorbic acid. Journal of the National Science Foundation of Sri Lanka. 2013;41(4):337–44. Available from: <URL>.

24. Perdew J, Burke K, Wang Y. Generalized gradient approximation for the exchange-correlation hole of a many-electron system. Physical Review B. 1996;54(23):16533. Available from: <URL>.

25. Baker J, Kessi A, Delley B. The generation and use of delocalized internal coordinates in geometry optimization: The Journal of Chemical Physics. 1996; 192-212 p. Available from: <URL>.

26. Becke A. Density-functional exchange-energy approximation with correct asymptotic behavior. Physical Review A. 1988;38(6):3098. Available from: <URL>.

27. Lee C, Yang W, Parr R. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. Physical Review B. 1988;37(2):785. Available from: <URL>.

28. Fouad R, Shaaban I, Ali T, Assiri M, Shenouda S. Co (ii), Ni (ii), Cu (ii) and Cd (ii)-thiocarbonohydrazone complexes: spectroscopic, DFT, thermal, and electrical conductivity studies. RSC. Adv. 2021;11(60):37726-43. Available from: <URL>.

29. Al-Abachi M, Abed S. Spectrophotometric determination of phenylephrine hydrochloride and salbutamol sulphate drugs in pharmaceutical preparations using diazotized metoclopramide hydrochloride. Baghd. Sci. J. 2015;12(1):167-77. Available from: <URL>.

30. Abdel-Rahman L, Ismail N, Ismael M, Abu-Dief A, Ahmed E, Abdel-Hameed. Synthesis, characterization, DFT calculations and biological studies of Mn (II), Fe (II), Co (II) and Cd (II) complexes based on a tetradentate ONNO donor Schiff base ligand. J Mol. Struct. 2017;1134:851-62. Available from: <URL>.

31. Stauffer M, Weller W, Kubas K, Casoni K. Limiting reactants in chemical analysis: influences of metals and ligands on calibration curves and formation constants for selected iron-ligand chelates. Stoichiometry and Research–The Impotance of Quantity in Biomedicine. 2012. p. 311-34. ISBN: 9789535101987.

32. Mandal S, Das G, Askari H. Physicochemical investigations of the metal complexes of l-valine with doubly charged ions of nickel, copper and zinc: a combined experimental and computational approach. RSC Adv. 2014;4(47):24796-809. Available from: <URL>.

33. Dudev T, Lim C. Metal Binding Affinity and Selectivity in Metalloproteins: Insights from Computational Studies. Annual Review of Biophysics. 2008;37(1):97-116. Available from: <URL>.

34. Leach B, Angelici R. Stereoselective interaction of optically active amino acids and esters with (L; valine-N-monoacetato) copper (II). Journal of the American Chemical Society. 1969;91(23):6296-300. Available from: <URL>.

35. Fayad N, Al-Noor T, Mahmood A, Malih I. Synthesis, Characterization, and Antibacterial Studies of Mn (II), Fe (II), Co (II), Ni (II), Cu (II) and Cd (II) Mixed-Ligand Complexes Containing Amino Acid (L-Valine) And (1, 10-phenanthroline). Synthesis. 2013;3(5).

36. Fayad N, Al-Noor T, Ghanim F. Synthesis, characterization, and antibacterial activities of manganese (II), cobalt (II), iron (II), nickel (II), zinc (II) and cadmium (II) mixed-ligand complexes containing amino acid (L-Valine) and saccharin. Advances in Physics Theories and Applications. 2013;9:1-13.

37. Refat M, El-Korashy S, Hussien M. Ligational, Spectroscopic (Infrared and Electronic) and Thermal Studies on the Mn (II), Co (II), Fe (II) and Cu (II) Complexes with Analgesic Drugs. Canadian Chemical Transactions. 2014;2(1):24-35. Available from: <URL>.

38. Refat M, Mohamed G, El-Sayed M, Killa H, Fetooh H. Spectroscopic and thermal degradation behavior of Mg (II), Ca (II), Ba (II) and Sr (II) complexes with paracetamol drug. Arabian Journal of Chemistry. 2017;10:S2376-S87. Available from: <URL>.

39. Amolegbe S, Adewuyi S, Akinremi C, Adediji J, Lawal A, Atayese A, et al. Iron(III) and copper(II) complexes bearing 8-quinolinol with amino-acids mixed ligands: Synthesis, characterization and antibacterial investigation. Arabian Journal of Chemistry. 2014;24. Available from: <URL>.

40. Lawal A, Obaleye J. Synthesis, characterization and antibacterial activity of aspirin and paracetamolmetal complexes. Biokemistri. 2007;19(1). Available from: <URL>.

41. Babamale H, Lawal A, Rajee O, Oloyede E. Synthesis, characterization and biological activity studies of mixed paracetamol-ascorbic acid metal complexes. Journal of Applied Sciences and Environmental Management. 2016;20(4):1157-61. Available from: <URL>.

42. Neeraja R, Hima Bindu G. Speciation study involving mononuclear binary transition metal (CoII, NiII and CuII) complexes of L-methionine in non-ionic micellar medium. Heliyon. 2021;7(4):e06729. Available from: <URL>.

43. Zheng C, Shi R, Jin X, Qiu Q, Li H. Three complexes with helical frameworks based on l-glutamine and l-asparagine: Crystal structures and circular dichroism properties. Inorganic Chemistry Communications. 2016;65:16-20. Available from: <URL>.

44. Doğan A, Kiliç E. Potentiometric studies on the stability constants of some α-amino acid-copper(II) and nickel(II) systems in ethanol-water mixture. Indian Journal of Chemistry - Section A Inorganic, Physical, Theoretical and Analytical Chemistry. 2003;42:1632-5. Available from: <URL>.

45. Wu Y, Koch W, Berezansky P, Holland L. The dissociation constant of amino acids by the conductimetric method: I. pK1 of MOPSO-HCl at 25°C. Journal of Solution Chemistry. 1992;21(6):597-605. Available from: <URL>.

46. Sandhu RS, Kalia RK. Complexation reaction of metal ions with peptide systems. VII. Equilibrium studies of N-benzoyl-L-valine, N-benzoyl-glycyl-L-valine and isovaleric acid with metal(II) ion systems. Thermochimica Acta. 1980;40(2):305-9. Available from: <URL>.

47. Madkour L, Elshamy I. Experimental and computational studies on the inhibition performances of benzimidazole and its derivatives for the corrosion of copper in nitric acid. International Journal of Industrial Chemistry. 2016;7(2):195-221. Available from: <URL>.

48. Al-abbasi A, Kassim M. 1-Ethyl-1-methyl-3-(2-nitrobenzoyl)thiourea. Acta Crystallographica Section E. 2011;67(7):o1840.

49. Al-abbasi A, Tan S, Kassim M. 1-Benzoyl-3-(4-hydroxyphenyl)thiourea. Acta Crystallographica Section E. 2010;66(12):o3181. Available from: <URL>.