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Article

Synthesis of Co(II) and Ru(III) Complexes with Benzoyl Thiourea Derivatives and study DFT and Anti-breast cancer activity

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Abstract

This study was conducted to prepare complexes of carbonyl thiourea derivatives with Cobalt(II) and Ruthenium(III). The geometries of these complexes were investigated using mass spectrometry, electrostatic spray ionization (ESI), and infrared (IR) spectroscopy, including molar conductivity, magnetic susceptibility, cyclic voltammetry (CV), and thermogravimetric analysis (TGA). The elemental ratios in the complexes were determined using inductively coupled plasma atomic emission spectroscopy (ICP-AES). Co(II) and Ru(III) complexes were prepared in different molar ratios: 1:1 (liquid –metal) and 2:1 (liquid –metal). The ligands were selected as (S,O) bistochondria . The metal is bonded to the ligand via oxygen and sulfur atoms. The geometry of the prepared Co(II) and Ru(III) complexes was octahedral. To support and justify the experimental results, a comprehensive theoretical study was conducted using density functional theory (DFT) with the functional basis set B3LYP\LANL2DZ. The computational study included determining the energies of the boundary molecular orbitals (HOMO and LUMO) and the atomic Molten charges. The structural parameters of the compounds, including bond length, triangular angle, and quadrantal angle, were analyzed and compared with experimental data. The cytotoxicity of the Co(II) and Ru(III) synthesized complexes was evaluated in vitro against human MCF-7 breast cancer cells using the MTT assay. The results showed that the compounds exhibited low cytotoxicity under the experimental conditions.

Keywords:ThioureaBenzamide,Cobalt,Ruthenium,DFT,CyclicVoltammetry,Breast cancer.

Introduction

Carbonyl thiourea compounds are important chemical compounds of organic chemistry and organic synthesis, as these compounds are the basis for the preparation of many pharmaceutical compounds and biological materials that have wide-ranging pharmacological and therapeutic properties. They are also used as raw materials for the synthesis of a large number of compounds that are characterized by their wide applications in the field of pharmaceutical industry due to their biological activity, including antiparasitic activity, anticancer, antioxidant, antibacterial, antifungal, antituberculosis, antispasmodic, anti-HIV, inflammation, malaria, microbes, and tumors, as well as their ability to combat insects [1,2]. The study of carbonylthiourea compounds dates back to the early 20th century, when chemists began exploring their reactions and properties. With the development of chemical analysis techniques, interest in their practical applications increased, leading to the development of numerous methods for their preparation and study. The simplest carbonylthiourea derivative (1-ecylthiourea $CH_3C(O)NHC(S)NH_2$) was first prepared by Noicki [3]. Carbonylthiourea compounds are characterized by the presence of two functional groups: carbonyl (C=O) and thiocarbonyl (C=S). The structural diagram shows that carbonylthiourea compounds consist of a hydrophilic central part and hydrophobic side parts. Carbonylthiourea compounds have received great attention from the scientific community and have been the focus of research and admiration for many years [4] . Carbonylthioureas are extremely versatile starting materials for the synthesis of a wide range of heterocyclic compounds due to the presence of two free hydrogen atoms, one at each nitrogen atom [5].Thus, the available information on the chemistry of substituted thiourea carbonyls and their potential applications has been updated. Furthermore, the presence of hard and soft donor sites in these compounds provides tremendous binding potential, as both carbonyl and thiocarbonyl groups can Coordinated With the metal ions in different ways [6]. The nitrogen, oxygen and sulfur donor atoms of thiourea carbonyl derivatives provide multiple binding potential, making them crucial for coordination with metal ions. The coordination process plays an important role in biological systems, which may lead to the development of new metal-based drugs [7]. Thiourea carbonyl compounds have several coordination modes, the most common of which is shown in Figure (1), where the ligand reacts with the metal in a molar ratio of 1:2 [metal:ligand] or 1:1 [metal:ligand] depending on the reaction conditions (a) The metal may bond with oxygen and sulfur as a chargeless ligand, (b) or the metal may bond with oxygen and sulfur as a negatively charged ligand, (c) or sulfur may bond with the metal as a chargeless ligand [8]. It is noted that the metal ion has an effect on determining the electron-donating atom. Studies indicate that there is a diversity in the geometric shapes of thiourea carbonyl complexes with transition elements, as these complexes can vary between tetrahedral and octahedral shapes, passing through tetragonal and square planar shapes, due to the variation in the degree of distortion. In the geometric shape of the complexes [9-11], as well as due to the symmetrical effect between C=O and C=S in the thiourea carbonyls, which have a high ability to bind to metal ions due to their proximity to each other [12-14]. These ligands usually form hexagonal ring systems by coordination between sulfur and oxygen; thanks to the additional coordination site of the carbon atom double bonded to oxygen [15,16]. Thiourea carbonyl derivatives are also used as good ligands due to their ease of preparation, as well as the properties of the C=S, C=O and N-H groups, which combine a combination of weak non-covalent interactions, such as van der Waals forces, π-bonding, and hydrogen bonding, as well as strong covalent bonds between molecules to form compounds with different properties and applications, as thiourea carbonyl molecules are characterized by great geometric flexibility when coordinating with metal ions [17-21].

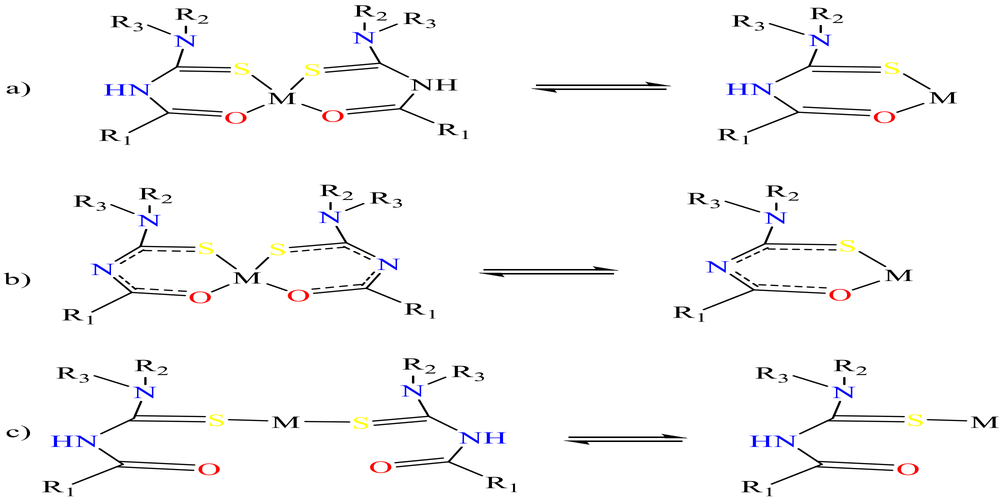


Figure (1): Carbonyl thiourea compounds with metal ions

Experimental

Materials and Methods

Cobalt chloride ($CoCl_2.2H_2O$),Ruthenium trichloride ($RuCl_3.nH_2O$), sodium carbonate(Na_2CO_3), acetone, ethanol, methanol, ethyl acetate, diethyl ether, chloroform, and hexane were purchased from Merck and Sigma-Aldrich. The purity level of the compounds was very high (around 97–99%).

Instrumentation

Melting Point was measure by equipment from Thermo Scientific. Using the KBr method, infrared spectra were collected in the 400–4000 cm^{-1} range using FT-IR 84005-SHIMADZU device. The ESI-MS spectrum of the complexes was recorded on a Shimadzu LCMS (2010A FT-IR 84005-SHIMADZU). Molar conductivity was measured using a Cond 3110 set1 instrument. The magnetic susceptibility of the complexes was recorded using a magnetoresistive balance. Thermogravimetric analysis TGA (Build 20 SDT Q600 V20.9) was performed, and The atomic emission spectroscopy technique was used to determine the metal content in complexe (ICP-AES). Cyclic voltammetry was also used for the ruthenium complexes.

The previously prepared compounds(L1,L2,L3and L4)[22], and their reaction with metal ions were used to prepare coordination complexes.

L1) 3-(3,4-dimethylphenyl)-1-(4-nitrobenzoyl)thiourea
L2) 1-(3,4-dimethylphenyl)-3-(4-methoxybenzoyl)thiourea
L3) 1-(4-nitrobenzoyl)-3-[2-({[(4-nitrophenyl)formamido]methanethioyl}amino)phenyl]thiourea
L4) 3-(4-methoxybenzoyl)-1-[2-({[(4-methoxyphenyl)formamido]methanethioyl}amino)phenyl]thiourea

Synthesis of the Complexes cobalt (II) and ruthenium (III).

The preparation methods were followed according to the literature with some modifications [11].

Synthesis of Cobalt (II) complexes

Complexe C1: The produced ligand (0.64 g, 2 mmol, L1) was added to a heated mixture of $CoCl_2.2H_2O$ (0.23 g, 1 mmol) in 20 mL of mixed solvent (1:1, MeOH:acetone). Then, add drops of sodium carbonate (Na_2CO_3) solution until the acidic function reaches pH = 8. The mixture was allowed to reflux with stirring for 6 hours. Finally, the result was precipitated by filtering the cooled mixture and repeatedly washing it with distilled water, ethanol, and diethyl ether. The resulting product was dried under a vacuum to obtain the final colour solids.

$[Co(L1)_2(H_2O)_2].5/2H_2O$: lead colour. Yield: 45 %, M.P: 240-242°C. IR spectrum (KBr, cm^{-1}): 3554 (O– H), 3408(N–H), 3153 (Ar–CH), 2968 (Al-CH), 1612 (C=C), 1289 C-N, 1164 (C=S) and 1511-1391(NO_2). μeff (B.M): 1.80. Molar conductivity (DMSO,$Ohm^{-1}.cm^{-2}mol$): 17.6. MS (ESI, m/z):796 [M+,5], Base Peak $(C_{16}H_{14}CoN_4O_2S_2)^+$,417. Complexe C2 : The Co-based complex (C2) was synthesised using the same process as the complex (C1), but with The produced ligand (0.62 g, 2 mmol, L2). [Co(L2)$_2$(H$_2$O)$_2$]: lead colour. Yield: 62 %, M.P: 180-182°C. IR spectrum (KBr, cm^{-1}): 3410 (O– H), 3251(N–H), 3155 (Ar–CH), 2977 (Al-CH), 1613 (C=C), 1289 C-N, 1167 (C=S) .μeff (B.M): 1.95. Molar conductivity (DMSO,Ohm^{-1}.cm^{-2}mol): 14.9. MS (ESI, m/z):721 [M+,5], Base Peak $(C_{29}H_{24}CoN_4O_2S_2)^+$,583. Complexe C3: The Co-based complex (C3) was synthesised using the same process as the complex (C1), but with The produced ligand (0.52 g, 1 mmol, L3) .Na[Co(L3)Cl(H$_2$O)].3H$_2$O: lead colour. Yield: 59 %, M.P: 160-162°C. IR spectrum (KBr, cm^{-1}): 3400 (O– H), 3309 (N–H), 3188 (Ar–CH), 2886 (Al–CH), 1607 (C=C), 1277 (C-N), 1150 (C=S) and1513-1339 (NO$_2$). . μeff (B.M): 2.07. Molar conductivity (DMSO, Ohm^{-1}cm^{-2}/M): 83.5. MS (ESI, m/z): 712 [M+, 5], Base Peak $(C_2H_2CoN_2O_2)^+$, 145.

Synthesis of ruthenium (III) complexes

The Ru-based complex (C4) was synthesised using the same process as the Co-based complex (C1), but with 1mmol and 0.20g of RuCl$_3$.nH$_2$ O replaced. Walnut colour: Na[Ru(L1)$_2$Cl(H$_2$O)]. Yield: 51%, M.P: above 300°C, IR spectrum (KBr, cm^{-1}): 3370 (O– H), 3245 (N–H), 3100 (Ar–CH), 2970 (Al–CH), 1717 (C=O), 1600(C=C), 1280 (C-N) , 1176 (C=S) and 1498-1339 (NO$_2$). μeff (B.M): 0.00Di. Molar conductivity (DMSO, Ohm^{-1}.cm^{-2}mol): 17.16. MS (ESI, m/z): 834 [M+, 4], Base Peak $(C_{14}H_{11}NO_2Ru)^+$, 326. Complexe C5:The Ru-based complex C5 was synthesized following the procedure for Co based complexes number C3, with(1mmol, 0.20g of RuCl$_3$·nH$_2$ O) substituted . Na$_2$[Ru(L3)Cl$_2$].2H$_2$O: black colour. Yield: 56 %, M.P:>300°C. IR spectrum (KBr, cm^{-1}): 3550 (O– H), 3282-3177 (N–H), 3100(Ar–CH), 2995 (Al–CH), 1614 (C=C), 1294 C-N and 1158(C=S) and 1521-1345 (NO$_2$). μeff (B.M): 0.00Di.Molar conductivity (DMSO, Ohm^{-1}cm^{-2}/M): 182.2. MS (ESI m/z):776 ,Base Peak (CH$_3$O$_2$Ru), 148. Complex C6: The Ru-based complex C6 was synthesized following the procedure for Co based complexes number C1, with The produced ligand (0.44g, 1 mmol, L4) and RuCl$_3$•nH$_2$ O (1mmol, 0.20g) substituted.Na$_2$[Ru(L4)Cl$_2$].2H$_2$O: dark green colour. Yield: 53 %, M.P:>300°C. IR spectrum (KBr, cm^{-1}): 3500 (O– H), 3293- (N–H), 3100(Ar–CH), 2896 (Al–CH), 1601 (C=C), 1257 C-N and 1172(C=S). μeff (B.M): 0.00Di .Molar conductivity (DMSO, Ohm^{-1}cm^{-2}/M): 128. MS (ESI m/z):746 ,Base Peak (C$_4$H$_6$NO$_2$RuS$_2$), 265.

Anti breast -cancer activity

The cytotoxicity of Co(II) and Ru(III) complexes produced in vitro was determined using the MTT assay. The MCF-7 human breast cancer cell line was obtained from Iran's National Cell Bank (Pasteur Institute). Cells were grown in RPMI-1640 (Gibco) and DMEM (Gibco) media, supplemented with 10% FBS (Gibco) and the antibiotics penicillin (100 U/ml) and streptomycin (100 μg/ml).

Cells were incubated at 37°C in humidified air with 5% CO_2 and then passed through trypsin/EDTA (Gibco) and phosphate-buffered saline (PBS). The fluids and conditions utilised for cell culture in three-dimensional colonies were comparable to those used in monolayer cell culture[22].

Computational study on the test complexes Co(II) and Ru(III)

The geometry optimization of the complexes was performed using density functional theory (DFT) and the GENECP hybrid basis set method which involves combining two different basis functions for both the metal and ligand atoms. The (B3LYP/LANL2DZ) basis set was used for Co(II) and Ru(III) , using the Gaussian 09 program[23].

Results and Discussion

Co(II) and Ru(III) complexes were prepared with ligands L1 and L2 in a 1:2 metal:ligand molar ratio (as shown in the Figure:2) and ligands L3 and L4 in a 1:1 metal:ligand molar ratio (as shown in the Figure:3) [21].

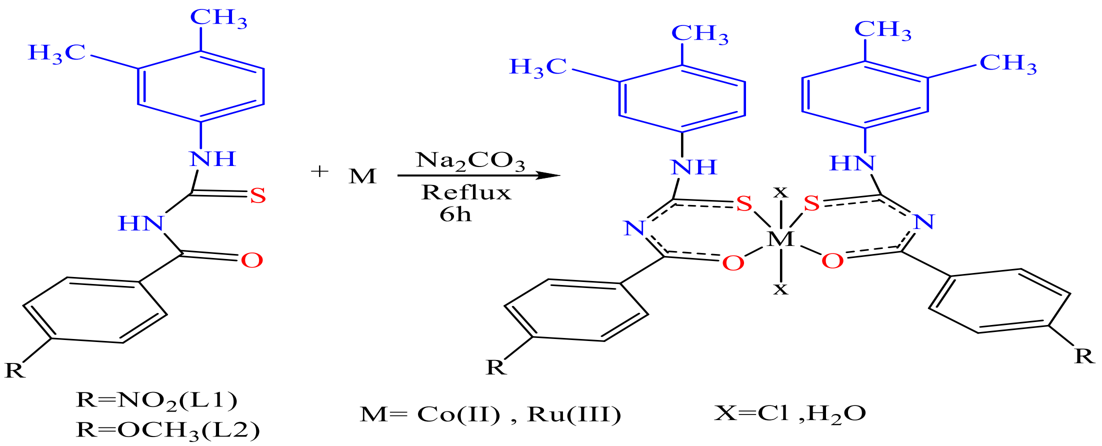
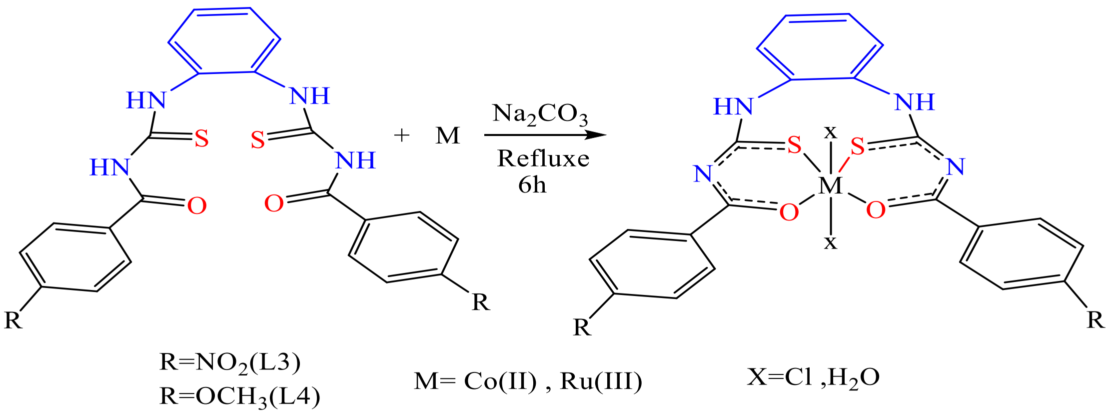


Figure (2): Synthesis complexes $[Co(L1)_2(H_2O)_2].5/2H_2O$(C1), $Na[Ru(L1)_2Cl(H_2O)]$ (C4),$[Co(L2)_2(H_2O)_2]$ (C2)in a molar ratio of 1:2 metal ligands



Figure(3): Synthesis complexes Na[Co(L3)Cl(H_2O)].3H_2O (C3) , Na_2[Ru(L3)Cl_2].2H_2O (C5), Na_2[Ru(L4)Cl_2].2H_2O(C6) in a molar ratio of 1:1 metal ligands

Characteristics of the metal complexes

Characterization methods

Figure:(4). The infrared spectra of the prepared complexes were characterized and the band positions were interpreted based on the scientific literature[24,25]. The synthesized compounds' infrared spectra displayed bands with varying ranges of medium and strong intensity. A weak peaks at (3408,3251,3309,3245,3282-3177,3293) cm^{-1} were due to the stretching vibrations of the (N-H) group. for complexes (C1–C6), respectively. Additionally, (it was observed that for C-H) aromatic compounds formed as a result of the existence of both symmetrical and asymmetric stretching vibrations, occurred at (3153,3155,3188,3100,3100,3100) cm^{-1} complexes (C1–C6) respectively Also. bands assign to stretching vibration of aliphatic C-H appeared at(2968,2977,2886,2970,2995,2896) cm^{-1} in spectrum of complexes (C1–C6) respectively. strong bands appear at (1717) cm^{-1} related to the vibration of amide (C=O) for complex C4, while the (C=C) group of aromatic structure has an average intensity band appeared at(1612,1613,1607,1600,1614,1601) cm^{-1} for complexes (C1–C6), respectively. strong bands appear in the range (C-N) group at (1289,1257,1277,1280,1294,1257) cm^{-1} . for complexes (C1–C6) respectively,it was observed that for (NO_2) strong bands appear in the range (1511-1391) ,(1513-1339) ,(1498-1339),(1521-1345)cm^{-1} for complexes C1,C3,C4and C5 respectively. strong bands appear in the range (C=S) group at(1164,1167,1150,1176,1158,1172)cm^{-1}.for complexes (C1–C6) respectively. The spectra of the complexes showed the disappearance of the C=O group, and in some cases, a shift in the position of the C=O group bands, resulting from binding to the metal. Similarly, the absorption bands of the C=S group in the complexes appeared in different positions and with different intensities than the ligand spectra [22], which confirms the binding of all cobalt and rithenium metal ions via the (S, O) atoms.

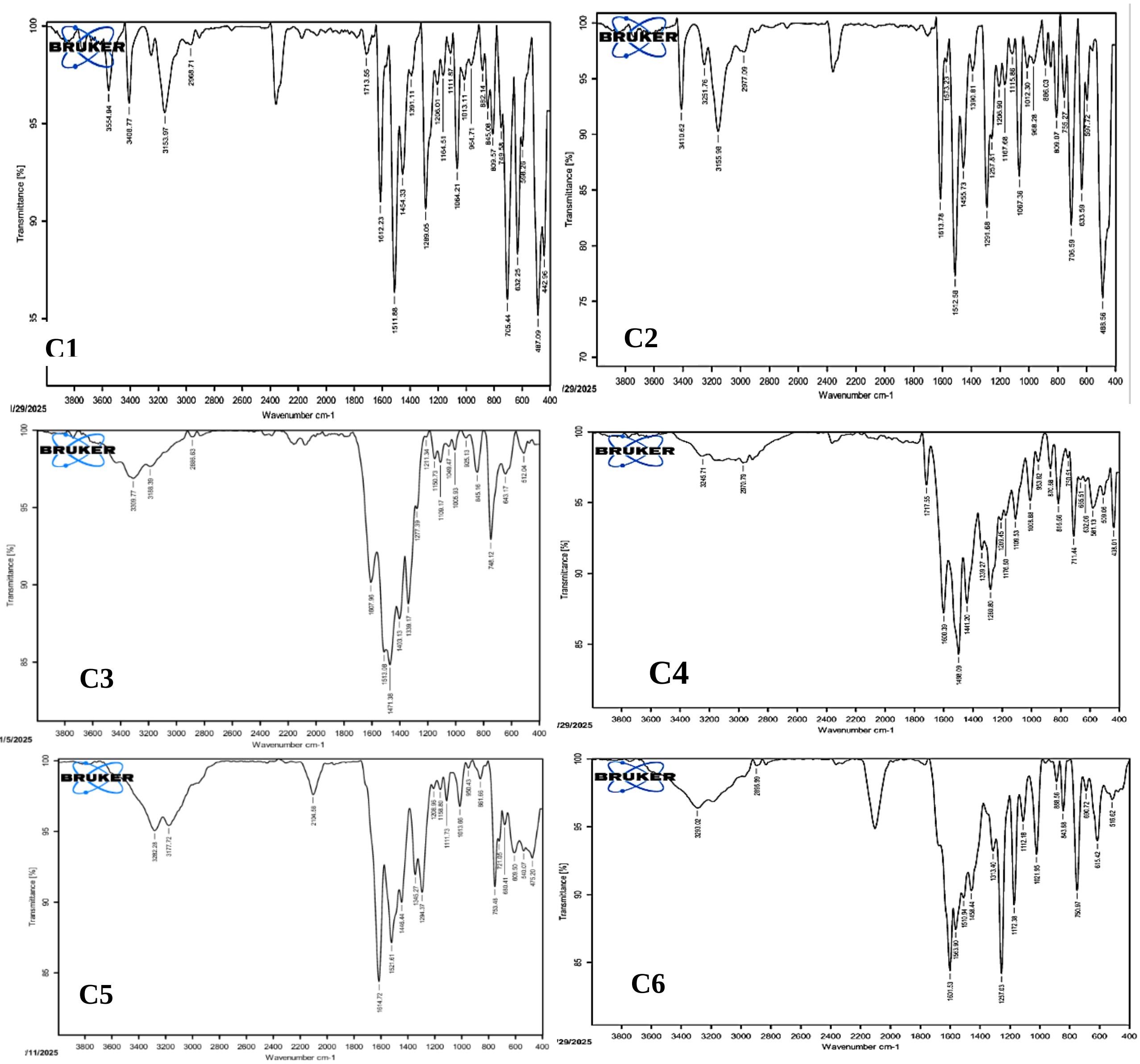


Figure (4): FT-IR spectra of complexes(C1-C6)

Properties of metal complexes ESI-MS

Figure(5): Spectra of complexes revealed molecular ion peaks at m/z 796(C1), 721(C2), 712(C3), 834(C4), 776(C5), 746(C6)respectively. In some compounds, the molecular ion portion appeared in relatively small amounts, while in others it did not appear. This indicates the instability of the molecular ion in these compounds. The base ion peak of the complexes(C1-C6)g/mol(417,583,145,326,148,256) is shown. Which goes back to the ions $[C_{16}H_{14}CoN_4O_2S_2]^+$, $[C_{29}H_{24}CoN_4O_2S_2]^+$, $[C_2H_2CoN_2O_2]^+$, $[C_{14}H_{11}NO_2Ru]^+$, $[CH_3O_2Ru]^+$, $[C_4H_6NO_2RuS_2]^+$respectively, This indicates the stability of these fragments in all mass spectra of the prepared complexes[11].

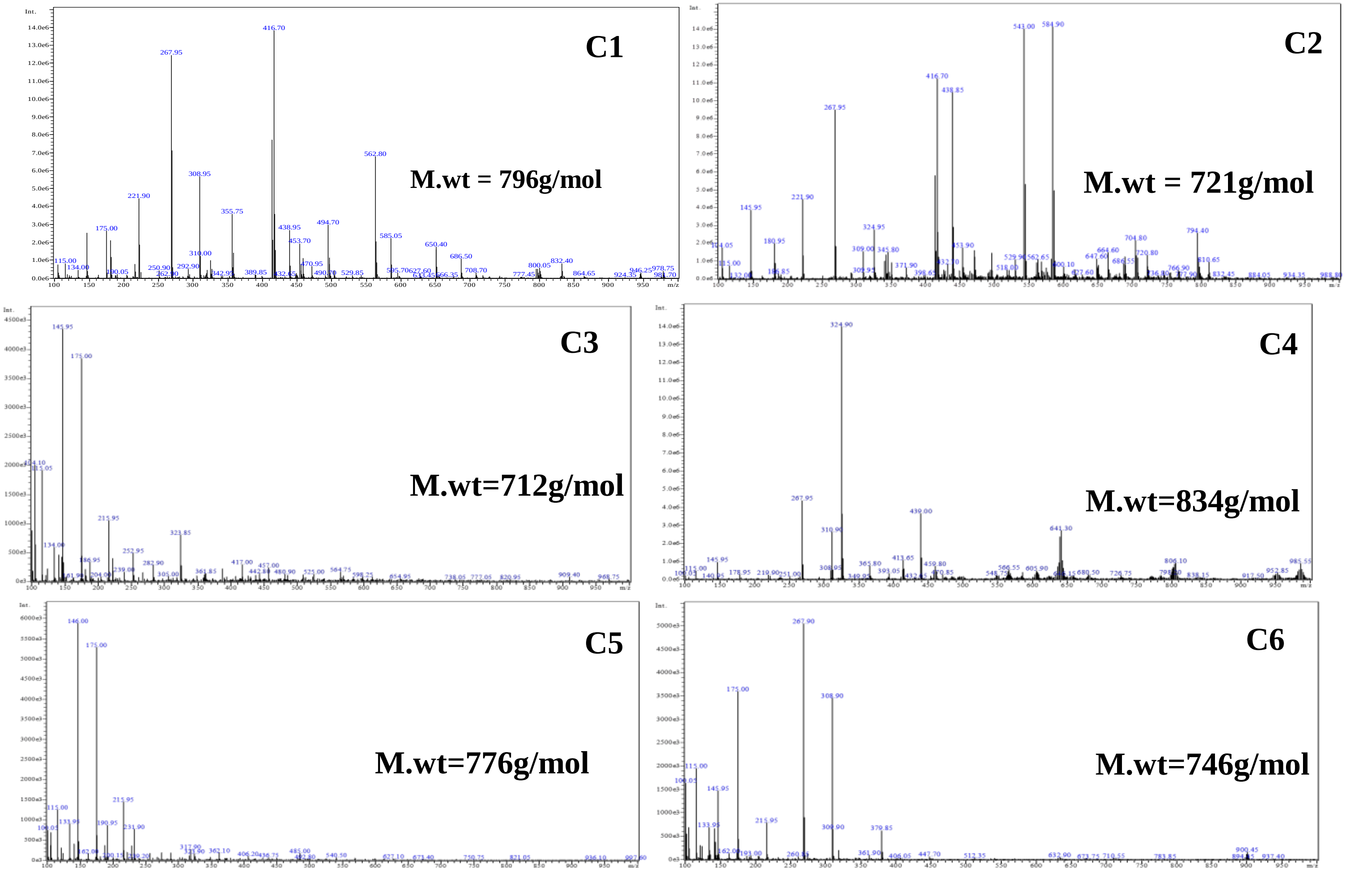


Figure (5): EsI-MS spectra of complexes (C1-C6)

CyclicVoltammetry

Cyclic scanning potential studies were performed on ruthenium complexes at a 2:1 ligand-metal molar ratio for the complex $Na[Ru(L1)_2Cl(H_2O)]$ and at a 1:1 ligand-metal molar ratio for the complexes $Na_2[Ru(L3)Cl_2].2H_2O$ and $Na_2[Ru(L4)Cl_2].2H_2O$ in DMSO solvent in the range of (-2.0 to +1.0) V at room temperature using the supporting electrolyte [Bu4N][PF6] at a concentration of 0.001 M and a scanning rate of 50 MeV s^{-1}. The reason for choosing ruthenium complexes for this study was to determine the oxidation state of ruthenium [26]. Cyclic voltammetry surveys of the prepared ruthenium complexes shown in Table (1) and Figure (6) indicate that this process is a quasi-reversible oxidation of one electron (-0.847, -0.697, -0.636) V for complexes (C4-C6)respectively, as shown in

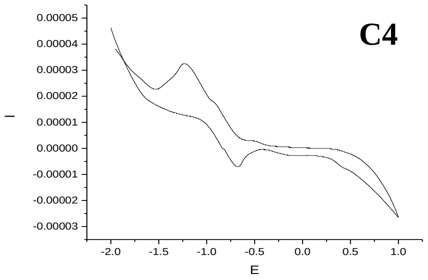
Table (1). The (Epcathodic and Epanodic) potential difference ΔEp, calculated from Equation.. (1)

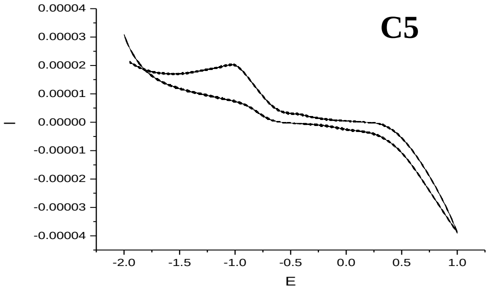
ΔEp=Epanodic - Epcathodic Mv .. (1)

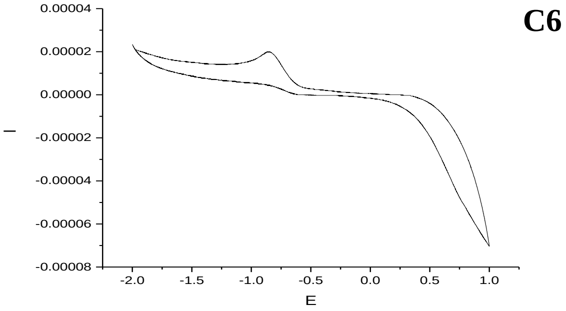
, is 387, 326, and 218 V for complexes (C4-C6) respectively, which is significantly higher than in standard reversible processes, indicating that the process is quasi-reversible.Furthermore, the ratio of complexes between the forward and reverse peak currents (ipcathodic/ipanodic) is less than one, as shown in Table (1), which also supports the quasi-reversible nature of the Ru(III) to Ru(II) band. This reaction is most likely attributed to a structural rearrangement during the transition from the Ru(III) to Ru(II) oxidation state. From the electrochemical data, we conclude that the current rithenium regime is ideally suited for stabilizing the Ru(II) oxidation state[27,28].

Table: (1) Cyclic voltammetry data for Ruthenium complexes(C4-C6)

No.	Complex	Epa V	Epc V	ΔEp Mv	Ipa μA	Ipc Ma	Ipc/Ipa
C4	Na[Ru(L1)$_2$Cl(H$_2$O)]	-0.847	-1.234	387	4.244	3.230	0.761
C5	Na$_2$[Ru(L3)Cl$_2$].2H$_2$O	-0.697	-1.023	326	5.786	2.020	0.349
C6	Na$_2$[Ru(L4)Cl$_2$].2H$_2$O	-0.636	-0.854	218	5.093	1.955	0.383







Figure(6):Cyclic voltammetry of the complexes ruthenium (C4-C6) quasi-reversible process in DMSO solution at a scan speed of 50 Mv.Sec^{-1}

Values of effective magnetic moment (μeff) complexes Co(II) and Ru(III)

The magnetic susceptibility results in Table (2) show that Co(II) complexes possess paramagnetic properties due to the presence of a single unpaired electron, as the effective magnetic moment values were (1.80-2.07 B.M). The presence of a single unpaired electron in the d orbitals confirms that the system is low spin (a strong ligand), and thus we can conclude that the geometry of the Co(II) complexes is a distorted octahedron with sp^3d^2 hybridization (outer orbital complexes). The cobalt(II) ion represents the d^7 system and has the electronic configuration $[Ar]3d^7 4s^0$ [29]. The magnetic susceptibility results show that the Ru(III) complexes possess diamagnetic properties (μeff = 0.0 B.M) as shown in Table (2). This confirms the reduction of the ruthenium ion from the oxidation state of Ru^{+3} to Ru^{+2} during the reaction. Thus, we conclude that the electronic configuration of the ruthenium ion is $[Kr\ 4d^6 5s^0]$, with a low spin. The geometry of the ruthenium complexes is octahedral with d^2sp^3 hybridization (inner orbital complexes)[30].

Table (2) Magnetic susceptibility values of the prepared complexes(C1-C6)

Complex symbol	Chemical Fotmula	-D x10^{-6}	X_g x10^{-6}	X_M x10^{-3}	X_A x10^{-3}	μ_{eff} B.M	hybridization type	shape geometry
C1	$[Co(L1)_2(H_2O)_2].5\backslash 2H_2O$	211	5.5	4.37	4.58	1.80	sp^3d^2	octahedral
C2	$[Co(L2)_2(H_2O)_2]$	248	6.9	4.97	5.22	1.95	sp^3d^2	octahedral
C3	$Na[Co(L3)Cl(H_2O)].3H_2O$	150.5	8.3	5.90	6.06	2.07	sp^3d^2	octahedral
C4	$Na[Ru(L1)_2CI(H_2O)]$	0.00	0.00	0.00	00.0	0.00	d^2sp^3	octahedral
C5	$Na_2[Ru(L3)Cl_2].2H_2O$	0.00	000.	0.00	0.00	0.00	d^2sp^3	octahedral
C6	$Na_2[Ru(L4)Cl_2].2H_2O$	0.00	00.0	000.	0.00	0.00	d^2sp^3	octahedral

The molar conductivity values of complexes

The study revealed that the molar conductivity measurements of Co(II) and Ru(III) complexes show variations in molar conductivity, with values ranging from (14.9-182.2 Ohm^{-1}.cm^{-2}/M) as shown in Table (3). This indicates a difference in the degree of ionization or dissociation of the compounds dissolved in DMSO. This indicates that all Co(II) complexes are electrolytic except for the two complexes $[Co(L1)_2(H_2O)_2].5/2H_2O$ and $[Co(L2)_2(H_2O)_2]$, which are non-electrolytic. As for the Ru(III) complexes, all molar conductivity values indicate electrolyticness [31].

Table (3) :of molar conductivity values of the prepared complexes(C1-C6)

No.	Chemical Fotmula	Electrical conductivity (Ohm^{-1})	Molar conductivity (Ohm^{-1}.cm^{-2} /M)	Electrical Type
C1	$[Co(L1)_2(H_2O)_2].5\backslash 2H_2O$	$17.6*10^{-6}$	17.6	Non-electrolytic
C2	$[Co(L2)_2(H_2O)_2]$	$14.9*10^{-6}$	14.9	Non-electrolytic
C3	$Na[Co(L3)Cl(H_2O)].3H_2O$	$83.5*10^{-6}$	83.5	electrolytic
C4	$Na[Ru(L1)_2CI(H_2O)]$	$66.6*10^{-6}$	66.6	electrolytic
C5	$Na_2[Ru(L3)Cl_2].2H_2O$	$182.2*10^{-6}$	182.2	electrolytic
C6	$Na_2[Ru(L4)Cl_2].2H_2O$	$128*10^{-6}$	128	electrolytic

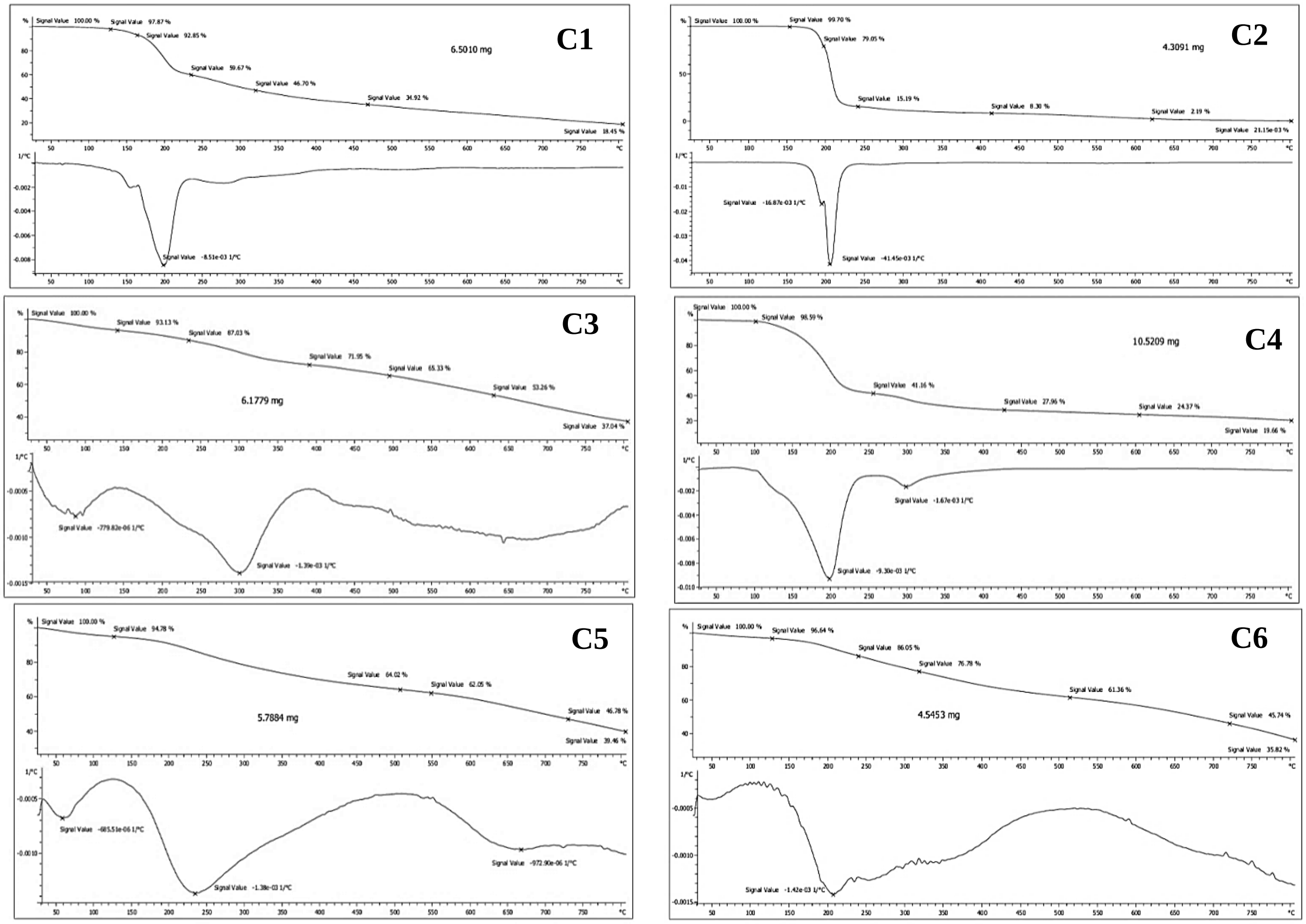
Thermogravimetric analyses of the complexes(TGA)

Figure (7) and Table (4) show the thermal breakdown stages of Cobalt(II) and Ruthenium(III) complexes. The decomposition stages and heat maps reveal the existence of water of crystallisation, water of coordination, and two chlorine atoms in complex molecules. This decomposition occurs in the early phases of decomposition, between 25 to 800°C, while later stages result in the loss of certain bonds[32,33].

Table (4): Thermogravimetric analysis(TGA) data of the complexes (C1-C6)

weight loss %		Decomposition part	Temp. range (℃)	Stage	Complex /M.Wt.	No.
Calculated	Observed					
5.65	2.13	$5/2H_2O$	25-130	1	$[Co(L1)_2(H_2O)_2].5/2H_2O$ 796 g/mol	C1
4.52	5.02	$2H_2O$	130-170	2		
32.41	33.18	$C_8H_{10}+NO_2$	170-240	3		
14.07	12.97	$C_6H_6+2NH_3$	240-320	4		
30.40	28.25	$CH_3S+C_8H_7N_2O_2S$	320-800	5		
21.19	20.95	$2(OCH_3)+4(CH_3)+2H_2O$	25-200	1	$[Co(L2)_2(H_2O)_2]$ 721g/mol	C2
61.0	63.86	$2(C_{14}H_{13}N_2)$	200-240	2		
7.58	6.87	$3H_2O$	25-150	1	$Na[Co(L3)Cl(H_2O)].3H_2O$ 712 g/mol	C3
5.75	6.1	$Na+H_2O$	150-240	2		
12.92	15.08	$-Cl+2NO_2$	240-390	3		
18.82	18.69	$C_8H_{10}N_2$	390-630	4		
14.74	16.22	C_7H_7N	630-800	5		
2.75	1.41	Na	25-100	1	$Na[Ru(L1)_2CI(H_2O)]$ 834 g/mol	C4
55.63	57.43	$H_2O+Cl+2(C_8H_{11}N)+C_6H_5NO_2+NO_2$	100-250	2		

12.58	13.2	C7H7N	250-430	3		
8.83	8.3	$C_2H_4N+CH_3$	430-800	4		
4.63	5.22	$2H_2O$	25-130	1	$Na_2[Ru(L3)Cl_2]$ .2H_2O 776 g/mol	C5
27.00	30.76	$2Na+2Cl+2NO_2$	130-510	2		
17.52	17.24	$C_8H_{12}N_2$	510-730	3		
8.24	7.32	2S	730-800	4		
4.82	3.36	$2H_2O$	25-130	1	$Na_2[Ru(L4)Cl_2]$. 2H_2O 746 g/mol	C6
10.92	10.59	2Na+Cl	130-240	2		
8.91	9.27	OCH_3+Cl	240-320	3		
14.74	15.42	$C_6H_6+OCH_3$	320-510	4		
14.74	15.62	$2NH_3+C_6H_6$	510-720	5		
10.45	9.92	C_6H_6	720-800	6		



Figure(7): Thermogravimetric analyses(TGA) of the complexes (C1-C6)

Determining the metal content in complexes using the inductively coupled plasma atomic emission spectroscopy technique(ICP-AES)

ICP is a spectroscopic analytical technique used to analyze elements (metals). Inductively coupled plasma is used to produce excited atoms and ions, which emit electromagnetic radiation at wavelengths characteristic of each element. The plasma acts as a high-temperature source of ionizing gas, usually argon. The temperature of the generated plasma ranges between 10000 and 6000 Kelvin. The intensity of the light emission at different wavelengths is proportional to the concentrations of the elements present in the sample being analyzed. The high-temperature plasma, 10,000 Kelvin, is used to break down the organic compounds present in the sample. This technique minimizes interference compared to other techniques, and the accuracy of the analysis is usually high for most elements, exceeding 2%. The concentration of 1mg/L, which is the digestion process of the complexes by dissolving approximately 0.001 g of the complexes in 5 mL of concentrated nitric acid, then heating the solution until it becomes clear, through which the solution is then diluted with distilled water free of ions. It is clear from the theoretical and practical values and calculations shown in Table (5) that there is a convergence with the theoretical values and calculations for the metals (Ru^{+3}, Co^{+2}) used in the synthesis of the complexes, and this convergence confirms that the metal-ligand binding ratios in the prepared complexes (C1, C2, C4,) were in a ratio of 1:2 [metal:ligand] and the complexes (C3, C5, C6) had binding ratios of 1:1 [metal:ligand] [34,35].

Table (5) Metal binding ratio data(ICP-AES) for complexes(C1-C6)

No.	Chemical Fotmula	Molecular weight of the complex	Element concentration ppm	Practical ratio of the element%	Theoretical ratio of the element%	Correlation ratios [metal:ligand]
C1	$[Co(L1)_2(H_2O)_2].5\backslash 2H_2O$	796	263.459	9.41	7.40	1:2
C2	$[Co(L2)_2(H_2O)_2]$	721	47.961	6.85	8.17	1:2
C3	$Na[Co(L3)Cl(H_2O)].3H_2O$	712	2284.627	8.16	8.27	1:1
C4	$Na[Ru(L1)_2CI(H_2O)]$	834	459.196	9.38	12.11	1:2
C5	$Na_2[Ru(L3)Cl_2].2H_2O$	776	1240.704	13.64	13.02	1:1
C6	$Na_2[Ru(L4)Cl_2].2H_2O$	746	1389.960	14.19	13.54	1:1

(At.wt Co:58.9332 g/mol) (At.wt Ru:101.07 g/mol)

Anticancer Efficacy Study

The toxicity of complexes C1, C2, C3, C4, C5, and C6 against MCF-7 breast cancer cells was studied in vitro. The study was conducted using five different concentrations: 7.4, 22.2, 66.6, 200, and 600 µg/mL for each complexes respectively. The inhibitory activity was calculated at each concentration, along with the IC_{50} values. The results showed that the Co(II) and Ru(III) complexes were biologically inactive against the breast cancer cell line, meaning they had low cancer-killing activity [10], as shown in the values in Table (6).

Table (6): Inhibition potential of studied againt MCF-7 cell line complexes(C1-C6)

No.	concentration(μg/ml)					IC_{50}(μg/mL)
	7.4	22.22	66.66	200	600	
	Cells inhibition(%)					
C1	2.97	16.32	3.14	40.5	53.82	415.54
C2	3.51	14.36	29.24	45.25	64.36	255.03
C3	8.99	21.49	44.32	69.73	71.69	102.29
C4	98.1	11.98	24.28	37.6	40.91	1135.76
C5	5.27	10.54	15.91	18.8	34.81	14365.54
C6	5.5	32.0	45.05	50.79	58.41	186.33

Computational study of complexes

When performing geometric optimization of complexes, we use a mixture of basis sets because regular basis sets cannot be used for heavy metals. There is a set of basis sets called Effective Core Potential (ECP) Basis Sets that are used for heavy elements. However, there is an important point regarding these sets: when they are used, they will be applied to all atoms in the complex, not just the heavy atoms. That is, we will use a huge basis set for all atoms, and this requires a very long time in addition to the use of advanced computers with huge processors. Therefore, the basis sets can be separated, that is, we use more than one different basis set, some specific to the metal and others specific to the rest of the elements. This is done by using the (GENECP) option. The geometric optimization of the complexes was performed using density functional theory (DFT) and the hybrid GENECP method, which involves combining two different basis functions for both the metal atoms and the ligand atoms. The B3LYP/LANL2DZ basis set was used for complexes. Co(II) and Ru(III), the results were extracted using GaussView5.0 [36–38].

Energy calculations for cobalt-ruthenium complexes

The total energy, HOMO and LUMO energies, and the energy gap ΔE=LUMO-HOMO were calculated for the prepared complexes using the same method as the geometric optimization, and their values are shown in Table (7). When comparing the cobalt complex and the ruthenium complex, we note from the calculated total energy values that the stability of the ruthenium complex is more stable than the cobalt complex, as the complex with the lower energy is more stable [39] . By looking at the energy difference values between the HOMO and LUMO orbitals shown in Table (7), we find that the cobalt complex has the lowest value of ΔE=3.83920705(eV), which reflects its relative chemical reactivity compared to the ruthenium complex ΔE=8.02782335(eV), as the lower the value of ΔE for the molecule, the more chemically and biologically active it is. We also note that the cobalt and ruthenium complexes have the highest energy gap values, which indicates that these complexes have little chemical and biological activity [40].

Table (7) Values of the quantitative chemical data of the prepared complexes

Complexes	Total energy(a.u)	LUMO(eV)	HOMO(eV)	ΔE(ev)
Na[Co(L3)Cl(H_2O)].3H_2O	-3104.021	-5.842	-9.681	3.839
Na_2[Ru(L3)Cl_2].2H_2O	-3436.595	-8.038	-0.010	8.027

Quantum Chemical Parameters

The frontier molecular orbital theory, which includes higher-order (HOMO) and lower-order (LUMO) orbitals, is an effective theory for analyzing the stability of complexes. The HOMO orbitals of complexes are centered on the (S ,O and N) atoms, while the LUMO orbitals are located primarily on the aromatic rings of the ligand and the central metal ion [41]. Figure (8), which includes the shapes of some prepared complexes, shows that the HOMO and LUMO orbitals are hybrid orbitals containing the d orbitals of the metal atom. Since the HOMO and LUMO orbitals determine the stability of a molecule, they also determine its susceptibility to attack by nucleophiles and electrophiles.

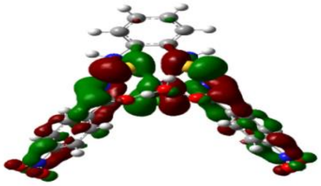
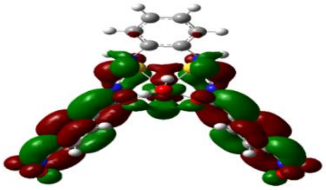
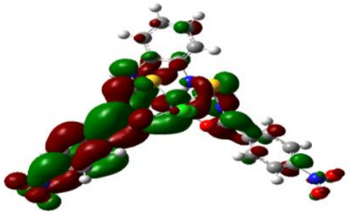
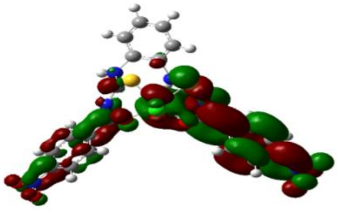
Complexes	HOMO	LUMO
Na[Co(L3)Cl(H_2O)].3H_2O		
Na_2[Ru(L3)Cl_2].2H_2O		

Figure (8) HOMO and LUMO orbitals of the complexes

Structural parameters of the molecular structure of the complexes

A comprehensive study of the basic structural parameters of the complex Na[Co(L3)Cl(H_2O)].3H_2O and Na_2[Ru(L3)Cl_2].2H_2O, including bond lengths and triple and quadruple bond angles, was conducted to describe the structural properties of these complexes. This analysis reflects the properties of bond lengths and angles after complex formation. The theoretical values were compared with those calculated experimentally for a similar complex. The results showed remarkable agreement with the values derived from X-ray diffraction analysis of single crystals, which was confirmed by previous studies [14,42- 49]. The bond length and angle values are also consistent with the proposed geometries shown in the tables.

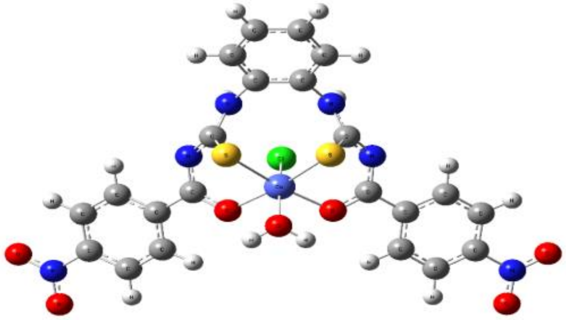


Table (8) values of bond lengths for the cobalt complex

bond lengths(Å)	Co-O	Co–S	Co-Cl	Co-H_2O	O=C_1	S=C_2	N_1-C_1	N_1-C_2
Na[Co(L3)Cl(H_2O)].3H_2O	1.980	2.41	2.43	1.96	1.31	1.80	1.33	1.33
X-ray analysis*	2.89	2.26	2.15	1.98	1.27	1.74	1.31	1.33

*[14,42-44]

Table (9) Trigonal angle values of the cobalt complex

Complex	O- Co –S	O- Co–O	S- Co –S	Co -O-C	C1-N1-C2	S-Co-Cl	N1-C2-S
Na[Co(L3)Cl(H_2O)].3H_2O	85.99	106.39	81.09	121.41	123.00	108.53	119.65
X-ray analysis*	100.58	93.342	81.28	126.98	122.8	108.92	120.88

*[42,43,45,46]

Table (10) values of the quadrilateral angles of the cobalt complex

Complex	O-C-N-C	S-C-N-C	Co-O-C-N	Co -S-C-N	Co -S-C-N_2	Co -O-C-R
Na[Co(L3)Cl(H_2O)].3H_2O	-20.02	-36.66	-0.21	77.68	-99.00	176.97

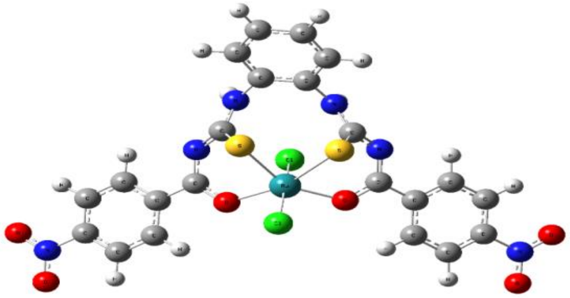


Table (11) values of bond lengths(Å) for the ruthenium complex

Comp	Ru-O	Ru –S	Ru –Cl	O-C_1	S-C_2	N_1-C_1	N_1-C_2
Na_2[Ru(L3)Cl_2].2H_2O	2.06	2.36	2.59	1.31	1.82	1.34	1.32
X-ray analysis*	2.11	2.41	2.42	1.22	1.70	1.36	1.38

[47,48.49]*

Table (12) of the values of the trigonal angles of the ruthenium complex

Comp	O-Ru-S	Ru -O-C	Ru -S-C	S-Ru-Cl	N-C-N	S-Ru-Cl	C1-N1-C2	N-C-S
$Na_2[Ru(L3)Cl_2]$ $.2H_2O$	83.95	125.66	89.14	91.30	122.64	100.03	122.34	119.95
X-ray analysis*	88.69	126.90	107.25	90.86	118.8	92.18	122.8	120.88

[47,48.49]*

Table (13) values of the quadrilateral angles of the ruthenium complex

Comp	O-C-N-C	S-C-N-C	Ru-O-C-N	Ru-S-C-N	Ru -S-C-N_2	Ru-O-C-R
$Na_2[Ru(L3)Cl_2].2H_2O$	-18.21	-28.90	-2.17	70.09	-110.76	176.85

Mullican Charge Analysis and Coordination of Metal Complexes

The Mullican charges of the prepared complexes, derived from Table (14) and Figure (9) showed that the most negative active sites were arranged as follows: The oxygen atom had the largest negative potential (highest basicity) equal to -(0.593,0.509), followed by the nitrogen atoms N1 and N2 equal to -(0.369,0.626), followed by the sulfur atom equal to (0.222,0.406) in all molecules. Therefore, it is expected that the bonding in this type of ligand occurs between the oxygen, nitrogen, and sulfur atoms due to the high electron density. These results indicate that the metal ions prefer to coordinate through oxygen, nitrogen, and sulfur, leading to the formation of closed hexagonal rings[50,51].

Table (14) Molecular charge values for the studied complexes

Atoms	O	S	N1	N2	Co	Ru	Cl	H_2O
$Na[Co(L3)Cl(H_2O)].3H_2O$	-0.593	0.222	-0.374	-0.623	-0.104	……	-0.329	-0.644
$Na_2[Ru(L3)Cl_2].2H_2O$	-0.509	0.406	-0.369	-0.626	…..	-0.122	-0.367	…….

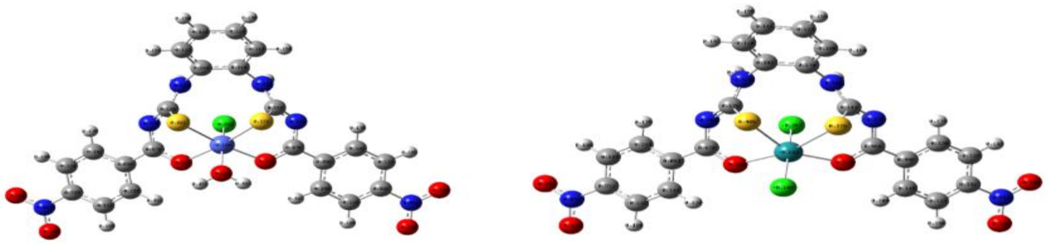


Figure (9) Charge of the molecules indicated on the atoms of the complexes

CONCLUSIONS

In this study, a series of Cobalt and Ruthenium complexes were successfully prepared from benzoylthiourea derivatives at different molar ratios: 1:1 (metal:ligand) and 1:2 (metal:ligand). The chemical structure was confirmed using a range of spectroscopic techniques. After the complexes were prepared, characterized, and studied both biologically and theoretically, we conclude that carbonylthiourea complexes are easy to synthesize. The ligands exhibited bidental (S,O)-type behavior, where the ligand is bonded to the metal via oxygen and sulfur atoms, forming a hexagonal ring. The magnetic susceptibility results for the Co(II) complexes showed paramagnetic properties. This is attributed to the presence of one unpaired electron, with the Cobalt ion exhibiting a d^7 system, an octahedral geometry, and an sp^3d^2 coordination type for all cobalt complexes. For the Ruthenium complexes, the Ruthenium ion exhibits a d^6 system. Due to the absence of unpaired electrons, the magnetic moment values indicate that these complexes are diamagnetic. This indicates that the Ruthenium complexes have undergone a reduction from the Ru(III) to the Ru(II) oxidation state. Therefore, we conclude that the octahedral shape and d^2sp^3 hybridization, along with cyclic voltammetry measurements of the Ruthenium complexes, show a quasi-reversible bandwidth, the ratio of the forward and reverse peak currents, Ipa/Ipc, is less than one, confirming the transition of the Ruthenium ion from the Ru(III) to the Ru(II) oxidation state. Computational studies have shown weak biological activity against breast cancer, as indicated by the energy gap (ΔE) values. The prepared complexes exhibit chemical stability based on LUOM and HOMO values, with electron density concentrated on oxygen, sulfur, and nitrogen atoms, supporting the results confirming metal binding via donor atoms (S, O, N). The calculated total energy values indicate that the Ruthenium complex is more stable than the Cobalt complex, with the lower-energy complex being more stable. The cytotoxic potential of in vitro-synthesized Cobalt-Ruthenium complexes against the human breast cancer cell line MCF-7 was evaluated using the MTT assay. The results showed reduced cytotoxic activity of the compounds under the in vitro conditions.

Conflict of Interest

The authors declare no conflict of interest authors’ declaration.

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