

Article

Synthesis, Spectroscopic, and Antimicrobial Study of Binary and Ternary Ruthenium(III) Complexes of Ofloxacin Drug and Amino Acids as Secondary Ligands

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Abstract: This article aimed to synthesis, spectroscopic, physicochemical characterizations, and catalytic studies on some ofloxacin (OFL) complexes with ruthenium(III) [Ru(III)] metal ions. The Ru(III)-OFL complex, [Ru(OFL)₂(Cl)₂]Cl and two mixed-ligand complexes, [Ru(OFL)(AA)(H₂O)₂]Cl₂ derived from OFL as the primary ligand and amino acids [AA; either glycine (Gly) or alanine (Ala)] as the secondary ligands, were synthesized and characterized using microanalytical, spectroscopic, and physical techniques including element composition, molar conductivity, infrared, electronic spectra, thermal, X-ray powder diffraction (XRD), Energy dispersive X-ray spectroscopy (EDX), Scanning electron microscopy (SEM), and Transmittance electron microscopy (TEM) analyses. The element analysis data describe the formation of 1:2 [Ru(III):OFL] and 1:1:1 [Ru(III):OFL:AA] complexes. The octahedral geometry of the complexes was confirmed by their magnetic moment and diffused reflectance. Fourier Transform Infrared spectroscopic (FTIR) measurements suggested that the ligands chelated with Ru(III) ions through the nitrogen atoms of the piperazine ring. In vitro antibacterial efficiency of the OFL compounds was evaluated by paper disc diffusion method. Significant antimicrobial activities were observed for some compounds of the series.

Keywords: ofloxacin; mixed ligand; complexes; grain size; ruthenium; antimicrobial activity

1. Introduction

Fluoroquinolones are broad-spectrum antibiotics particularly effective against gram-negative organisms, notably *Pseudomonas aeruginosa*. Moreover, they are often used to treat infections like pneumonia [1–3]. Generally, these antibiotics are well tolerated and confer very few side effects [4]. Second-generation quinolones, e.g., ciprofloxacin, enoxacin, lomefloxacin, norfloxacin, and ofloxacin



(OFL; Figure 1), have greater systemic activity, potency against gram-negative strains, and atypical pathogen coverage. Therefore, compared to the first-generation drugs, the second-generation quinolones have broader clinical applications, including the treatment of skin infections, selected types of pneumonia, sexually transmitted diseases, pyelonephritis, and complicated urinary tract infections [5].



Figure 1. Structure of ofloxacin (OFL) drug.

The complexation of quinolones with metal ions has attracted recent attention due to their enhanced fluorescence properties, improved solubility in water [6–12], and more potent biological activity [13–16]. Drug complexation is a vital topic in the field of inorganic chemistry and biology [17,18] and in several cases, the addition of a metal atom provides beneficial attributes that enhance the activity of the compound [19–23]. Four chelation modes have been reported for quinolones regarding metal ions, as described in Figure 2 [24–28]. Electrostatic interactions between quinolones and metal ions were only observed in acidic media because, under this condition, singly and/or doubly protonated quinolones can bind to the metal ions [24–26]. Neutral quinolones in zwitterionic form can form simple complexes through bidentate chelation [27–29]. Also, quinolones can act as unidentate ligands by forming metal complexes using the terminal piperazinyl nitrogen [30–32].



Figure 2. (a–d) Four chelation modes of quinolones with metal ions.

In this work, we prepared three complexes of ruthenium(III) [Ru(III)] ions and OFL. **Complex 1** was directly synthesized from the reaction of Ru(III) ions and OFL ligand. **Complex 2** and **Complex 3** were mixed-ligand complexes containing the amino acids glycine (Gly) and alanine (Ala), respectively. The three complexes, formulated as $[Ru(OFL)_2(Cl)_2]Cl$, $[Ru(OFL)(Gly)(H_2O)_2]Cl_2$, and $[Ru(OFL)(Ala)(H_2O)_2]Cl_2$, respectively, were fully characterized. These complexes were characterized

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structurally using FTIR, XRD, SEM, and EDX, and analyzed to determine their antibacterial efficiency against two of Gram (+) and Gram (–) species.

2. Experimental

2.1. Chemicals and Reagents

Ofloxacin (OFL) was obtained from Jamjoom Pharmaceutical Company (Jeddah, Saudi Arabia). The Ru(III) chloride hydrate and RuCl₃.*x*H₂O from the Sigma-Aldrich Chemical Company (Saint Louis, MO, USA). All solvents were obtained from the Fluka Chemical Company (London, UK), Glycine from BDH Chemicals (London, UK), DL-alanine from the FARCO Chemical Company (Moscow, Russian Federation), and ammonia solution (3%) from the Panreac ITW Company (Barcelona, Spain).

2.2. Instrumental Analyses

A Perkin Elmer CHN 2400 (PerkinElmer Inc., Shelton, USA) was used to conduct the analysis of %C, %H and %N element content. Ru and H₂O content were determined gravimetrically. A Jenway 4010 conductivity meter (Jenway, Staffordshire, UK) was used for the molar conductivity measurements of the samples at 10^{-3} M in dimethylsulfoxide (DMSO). A UV2–Unicam UV/Vis spectrophotometer (METTLER TOLEDO, Columbus, OH, Country) was used to scan the UV–vis absorption spectra for samples dissolved in dimethylformamide (DMF) solvent within the 800–200 nm range. A Bruker FT–IR spectrophotometer (Bruker, Billerica, MA, USA) was used to collect the IR spectra for solid samples on KBr discs within the 4000–400 cm⁻¹ range. A Shimadzu TG/DTG–50H thermogravimetric analyzer (Shimadzu Scientific Instruments, Kyoto, Japan) was employed for the thermal analyses of solid samples under atmospheric nitrogen conditions. A X'Pert Philips X-ray diffractometer (Philips, Manchester, UK) was used to collect the XRD patterns for the solid samples using CuK_{α 1} radiation. SEM micrographs were obtained using a Jeol Jem–1200 EX II electron microscope (Jeol Ltd., Akishima, Japan) operated at an acceleration voltage of 25 kV. A Gouy magnetic balance (Sherwood Scientific Ltd., Cambridge, UK) was used to measure the mass susceptibility (X_g) of the complexes at room temperature. The melting point was determined using a STUART melting point device.

2.3. Complex Synthesis

2.3.1. [Ru(OFL)₂(Cl)₂]Cl Complex; Complex 1

A hot methanol-based solution (4 mmol, 40 mL) of OFL was added to an aqueous solution (2 mmol, 25 mL) of RuCl₃.*x*H₂O. This reaction mixture was neutralized to pH = 8–9 and then refluxed for 6–7 h at ~70–80 °C. The colored solution was filtered off and left to evaporate slowly. After being dried in an oven to remove any remaining solvent, the resulting dark-brown colored deposits were collected in a glass bottle for chemical analyses. The yield was obtained at about 75%.

2.3.2. [Ru(OFL)(Gly)(H₂O)₂]Cl₂Complex; Complex 2

A hot methanol-based solution (2 mmol, 40 mL) of OFL was added to an aqueous solution (2 mmol, 25 mL) of RuCl₃.*x*H₂O and (2 mmol, 5 mL) glycine. This reaction mixture was neutralized to pH = 8–9 and then refluxed for 6–7 h at ~70–80 °C. The colored solution was filtered and left to evaporate slowly. After being dried in an oven for 6–15 h to remove any remaining solvent, the resulting dark-brown colored deposits were collected in a glass bottle for chemical analyses. The yield was obtained at about 71%.

2.3.3. [Ru(OFL)(Ala)(H₂O)₂]Cl₂Complex; Complex 3

A hot methanol-based solution (2 mmol, 40 mL) of OFL was added to an aqueous solution (2 mmol, 25 mL) of RuCl₃.*x*H₂O and (2 mmol, 5 mL) alanine. This reaction mixture was neutralized to pH = 8-9 and then refluxed for 6–7 h at ~70–80 °C. The colored solution was filtered and left to evaporate slowly.

After being dried in an oven for 6–15 h to remove any remaining solvent, the resulting dark-brown colored deposits were collected in a glass bottle for chemical analyses. The yield was obtained at about 73%.

3. Results and Discussion

3.1. Results Interpretation of Ru(III)-OFL Complexes

3.1.1. Microanalytical Values

The microanalytical element analysis of the OFL complexes indicated 1:2 [Ru(III):OFL] and 1:1:1 [Ru(III):OFL:AA] stoichiometry for the Ru(III)-OFL complexes, as listed in Table 1. According to these results, proposed chemical structures for **Complex 1**; [Ru(OFL)₂(Cl)₂]Cl, **Complex 2**; [Ru(OFL)(Gly)(H₂O)₂]Cl₂, and **Complex 3**; [Ru(OFL)(Ala) (H₂O)₂]Cl₂ are provided in Figure 3.



Complex 1



Complex 2

Figure 3. Cont.



Complex 3

Figure 3. Proposed chemical structures of the Ru(III)-OFL complexes.

Compound	Calar	M.P.	М.Р. Л т		Elemental Results, % Found % (Calc				
Compound	Color	(°C)	(μS)	С	Η	Ν	Cl	Ru	
OFL	White	254	0.14	69.83	5.58	11.63	-	-	
Complex 1 Dark brown		> 250	1.40	46.39	4.22	9.01	11.18	10.65	
Complex 1	Dark brown	>200	1.40	(46.48)	(4.33)	(9.03)	(11.43)	(10.87)	
Complex 2	Dark brown	~250	2 59	37.20	4.28	8.65	10.95	15.54	
Complex 2	Dark Drown	~230	2.39	(37.33)	(4.39)	(8.71)	(11.02)	(15.71)	
Complay 2	Dark brown	>250	2 10	38.30	4.43	8.50	10.63	15.31	
Complex 5	Dark brown	~230	2.10	(38.36)	(4.60)	(8.52)	(10.78)	(15.37)	

lable 1.	Microanal	ytical and	d physica	il values of free	OFL and the	e Ru(III)	complexes

3.1.2. Melting Point Data

The isolated dark brown solid Ru(III) OFL complexes showed high melting points, all above 250 °C. The melting points for **Complex 1**, **Complex 2**, and **Complex 3** were 265–270 °C, 245–250 °C, and 257–260 °C, respectively.

3.1.3. Molar Conductivity

The three prepared Ru(III) complexes were only soluble in DMF and DMSO. Comparing the molar conductance values (1.40–2.59 μ S) of these complexes to the free OFL drug (0.14 μ S) revealed the difference in their electrolytic properties [33,34]. These values were suggestive of one or two chloride ions existing outside of the complexes' coordination spheres.

3.1.4. UV–Vis Electronic Spectra

The UV–vis electronic spectrum of free OFL had three absorption bands at 338, 353, and 370 nm. The band at 338 nm was attributed to the $\pi \rightarrow \pi^*$ electronic transition for the aromatic rings. The bands at 370 and 353 nm were due to the $n \rightarrow \pi^*$ transition for the carboxylic and ketonic groups, respectively [35,36].

 ${}^{2}T_{2g}$ is the ground state of Ru(III) and ${}^{2}A_{2g}$ and ${}^{2}T_{1g}$ are its first excited doublet levels [37]. The Ru(III) complexes showed three electronic transitions at 29069–27027, 16556–16286, and 12578–12468 cm⁻¹, which were assigned to ${}^{2}T_{2g} \rightarrow {}^{2}A_{2g}$ (v3), ${}^{2}T_{2g} \rightarrow {}^{4}T_{2g}$ (v2), and ${}^{2}T_{2g} \rightarrow {}^{4}T_{1g}$ (v1), respectively. The values of the spectroscopic parameters of the ligand field (10Dq) and interelectronic repulsion (B and C) were determined using the following equations [38,39], also listed in Table 2.

$$^{2}T_{2g} \rightarrow ^{4}T_{1g} (\nu 1) = 10Dq - 5B - 4C$$

$${}^{2}T_{2g} \rightarrow {}^{4}T_{2g} (\nu 2) = 10Dq + 3B - 4C$$

 ${}^{2}T_{2g} \rightarrow {}^{2}A_{2g}, {}^{2}T_{1g} (\nu 3) = 10Dq - 2B - C$

Complex	λ_{max} (cm $^{-1}$)	Assignments	B (cm ⁻¹)	C (cm ⁻¹)	10Dq (cm ⁻¹)	$\nu 2/\nu 1$	β
1	12,578 16,556 27,027	27 47 (1)	497	1988	30,009	1.316	0.789
2	12,500 16,393 29,069	$^{2}T_{2g} \rightarrow ^{4}T_{1g}(\nu 1)$ $^{2}T_{2g} \rightarrow ^{4}T_{2g}(\nu 2)$ $^{2}T_{2g} \rightarrow ^{2}A_{2g}, ^{2}T_{1g}$	487	1948	31,991	1.311	0.773
3	12,468 16,286 27,777	(\v3)	477	1908	30,639	1.306	0.757

Table 2. Ligand field and interelectronic repulsion parameters of the synthesized complexes.

The value of B (Racahinterelectronic repulsion parameter) for the complexes was less than the Ru(III) ion alone (B' = 630 cm⁻¹) [39,40]. The nephelauxetic parameter (β = B/B') was ≤1.0, and the 10Dq value was high. These results were indicative of a strong covalent bond between the OFL ligand and Ru(III) ions [39].

3.1.5. Magnetic Susceptibility

The effective magnetic moment of the Ru(III) complexes existed within the 1.92–1.82 B.M range. These values were lower than the predicted value for the Ru(III) complex (2.10 B.M), this may be due to extensive electron delocalization or ligand fields with less symmetry [41]. These values also aligned with a single unpaired electron in a low spin 4d⁵ octahedral configuration for the Ru(III) ion [42] and confirmed that the Ru(III) complex existed in a (+3) oxidation state.

3.1.6. FTIR Spectroscopy

The IR spectra of free OFL, Gly, Ala, the Ru(III)-OFL complex, and the mixed ligand complexes are shown in Figure 4a–f, and their characteristic bands are listed in Table 3. Free OFL, as a bidentate ligand, has two coordination sites: the carboxylate and carbonyl oxygen atoms or the piperazinenitrogens [43]. The free OFL ligand exhibited a strong band at 1709 cm⁻¹ due to the carbonyl stretching vibrations of the carboxyl group. This band was observed at a higher frequency than the carbonyl group of the pyridine-4 with one moiety observed at 1617 cm⁻¹ [44]. The bands located in the 1200–1400 cm⁻¹ region in the IR spectrum of free OFL were due to coupling between the C–O and C–N stretching vibrations. Medium-to-strong bands observed in the 3040–2790 cm⁻¹ region were due to the asymmetric and symmetric stretching vibrations of the CH (aromatic), CH₂, and CH₃CH groups. The deformation vibrations of both the CH₂ and CH₃ groups generated medium-to-strong bands at 1399 and 1358 cm⁻¹ [45,46]. The bands that appeared at 1520 and 1452 cm⁻¹ were assigned to the ν (C=C) vibrations of the aromatic rings.



Figure 4. Cont.



Figure 4. Cont.



Figure 4. (a) FTIR spectrum of free OFL drug; (b) IR spectrum of free Gly amino acid; (c) IR spectrum of free Ala amino acid; (d) IR spectrum of complex 1; (e) IR spectrum of complex 2; (f) IR spectrum of complex 3.

IR spectra of **Complex 1**, **Complex 2**, and **Complex 3** are shown in Figure 4d–f. These IR spectra reflected the presence of stretching vibration motion from the ν (C=O)_{ketonic} of the carboxyl group. This band was observed in the 1702–1705 cm⁻¹ region and the other pyridine-4-one stretching vibration band ν (C=O) for the carbonyl group in the 1610–1615 cm⁻¹ region [44]. As no changes were observed for the stretching vibrations ν (C=O) of the carbonyl groups for both carboxylic and pyridine-4-one moieties, these groups likely didn't participate in the coordination step. New bands were observed at

 $480-485 \text{ cm}^{-1}$ due to v(Ru-N) stretching vibration motion [44]. The presence of these bands confirmed that the OFL ligand coordinated to the Ru(III) ions as a bidentate ligand via the nitrogen atoms of the piperazine ring.

Regarding the coordination of the Gly and Ala as secondary ligands, the IR spectra exhibited prominent bands related to the v(COO⁻) and v(NH₂) frequencies. The v(NH₃) vibrations of free amino acids absorb in the ~3000–3100 cm⁻¹ range. In metal complexes, the NH₃ group is deprotonated and binds to metal ions via the neutral NH₂ group. The transformation of NH₃ to NH₂ results in an upward shift in v(NH₂) vibrations compared to free amino acids [47,48]. **Complex 2** and **Complex 3** showed characteristic bands in the 3300–3000 cm⁻¹ region due to the v(NH₂) vibrations, suggesting that the nitrogen of the amino group participated in the coordination with Ru(III) ions. The band shift Δv values (vCOO_{asym} – vCOO_{sym}) indicated that the carboxylate group in Gly and Ala were chelated in a monobasic bidentate (amino nitrogen and carboxylate oxygen) statement relative to the Ru(III) ions. The low-intensity bands observed in the IR spectra of the complexes within the 600–400 cm⁻¹ range were due to v(Ru–O) and v(Ru–N) stretching vibrations [44,45]. IR measurements suggested that the OFL ligand acted as a neutral bidentate ligand with NN coordination sites that coordinated to the Ru(III) ions via the piperazine nitrogen atoms. Gly and Ala acted as uninegativebidentate ligands with NO donor sites that coordinated to the Ru(III) ions via the piperazine nitrogen atoms. Gly and Ala acted as uninegativebidentate ligands with NO donor sites that coordinated to the Ru(III) ions via the piperazine nitrogen atoms. Gly and Ala acted as uninegativebidentate ligands with NO donor sites that coordinated to the Ru(III) ions via the riperazine nitrogen atoms. Gly and Ala acted as uninegativebidentate ligand amino group.

OFL	Gly	Ala	Complex 1	Complex 2	Complex 3	Assignments
			3367			
	2151	2071	3230	3121	3112	$v_{as}(NH)$; NH ₂ +
-	3151	3071	3132	3034	3036	$\nu(OH); H_2O$
			3037			
1709	1737	1710	1704	1705	1702	ν (C=O) _{COOH}
1617	-	-	1615	1614	1610	ν (C=O) _{pyridone}
-	1580	1580	-	1530	1522	$\delta(NH_2)$
-	1499	1451	-	1445	1447	$v_{as}(COO)$
-	1320	1349	-	1291	1259	$\nu_{s}(COO)$
1049	1029	1015	1046	1046	1045	ν (C-N) + ν (C-F)
-	-	-	528	530	534	$\nu(Ru-O)$
-	-	-	481	484	479	v(Ru–N)

Table 3. IR spectral bands (cm⁻¹) of free OFL, Gly, Ala, and the synthesized complexes.

3.1.7. SEM, EDX, and XRD Data

The morphological and structural properties of **Complex 1** and the mixed ligand **Complex 2** and **Complex 3** were characterized using SEM (Figure 5a–c). The structural morphology of **Complex 2** and Complex 3 was homogenous and their particle sizes were within the nanometer range. In contrast, the particles of **Complex 1** were irregularlyshaped and most were agglomerated. SEM analysis confirmed the nanostructure morphology of the synthesized complexes. The relative weights of the elements (ruthenium "Ru", oxygen "O", carbon "C", chlorine "Cl", and fluorine "F") present in the free OFL ligand and synthesized complexes were determined using EDX. Ru usually displays a strong peak within 2.558 keV. The EDX graph, shown in Figure 6a-c, contains a peak at 2.5 keV that confirms the presence of Ru in the three Ru(III)-OFL complexes. Peaks at 0.525, 0.277, 2.621, and 0.677 keV corresponding to O, C, Cl, and F were also observed and established these elements as essential components of the molecular formula of the synthesized complexes. Figure 7 contains the XRD patterns of **Complex 1**, Complex 2, and Complex 3. These data indicated that the complexes had different reflections with high phase purity, and the sharp peaks observed in these patterns were due to the nano-dimensional nature of the particles. The Debye–Scherrer equation [49] was used to calculate the particle sizes (D) of the complexes (Table 4). The particle sizes of **Complex 1**, **Complex 2**, and **Complex 3** were 41, 43, and 45 nm, respectively. The synthesized complexes generated smaller particles—perhapsdue to

the increase in OFL chelates around the Ru(III) ions [50]. The strain (ε) and dislocation density (δ) values for the synthesized complexes were determined [51] and these are also listed in Table 4. The synthesized complexes showed three XRD patterns at ~ 52°, 46°, and 32° due to the (101), (100), and (002) planes of Ru, respectively [52].



Figure 5. Cont.



Figure 5. (a) SEM micrograph of **Complex 1**; (b) SEM micrograph of **Complex 2**; (c) SEM micrograph of **Complex 3**.



(a)

Figure 6. Cont.





Figure 6. (a) EDX spectrum of Complex 1; (b) EDX spectrum of Complex 2; (c) EDX spectrum of Complex 3.







Figure 7. Cont.



(c)

Figure 7. (a) XRD diagram of Complex 1; (b) XRD diagram of Complex 2; (c) XRD diagram of Complex 3.

Table 4. XRD spectral data for the synthesized complexes.

Complex	20	Intensity	D (nm)	δ (10 ¹² .lin.m ⁻²)	ε (10 ⁻⁴)
Complex 1	32.53	6770	41	$5.95 imes 10^{-4}$	0.5173
Complex 2	32.77	7110	43	1.41×10^{-4}	0.5525
Complex 3	32.77	9025	45	1.11×10^{-4}	0.5922

3.1.8. Thermal Analysis (TGA and DTG)

Figure 8a–c presents the TGA and DTG thermograms for free OFL and synthesized complexes and the thermal decomposition steps are listed in Table 5. The TG analyses of free OFL was performed from 25 to 1000 °C. The thermogram showed that, from 271 to 375 °C (DTG_{max} = 350°C), the weight loss was 31.50%, corresponding to the release of 1-methyl piperazine and a terminal methyl group. From 375 to 465 °C (DTG_{max} = 414°C), OFL lost its carboxylic group, with a total weight loss of 13.18% (calculated value: 12.45%). The third and final decomposition step occurred within the 465 to 1000 °C range (DTG_{max} = 603 °C); the total weight loss from this step was 55.32% (calculated value: 56.05%), which corresponded to the decomposition of OFL and release of the 8-fluoro-2,3-dihydro-1-oxa-3a-aza-phenalene-6-one organic moiety.



(a)



(**b**)

Figure 8. Cont.



(c)



(**u**)

Figure 8. (a) TGA and DTA curves of free OFL drug; (b) TGA and DTA curves of **Complex1**; (c)TGA and DTA curves of **Complex 2**; (d)TGA and DTA curves of **Complex 3**.

Complex 1 was thermally decomposed in three main degradation steps. The first step occurred at a maximum temperature of 115 °C with a weight loss of 16.12% (theoretical 15.99%) due to the loss of two terminal methyl groups, two fluorine atoms, and two carboxyl groups (2CH₃, 2F, 2COOH);as such, this result confirmed that the carboxyl group was far removed from the coordination of the Ru(III) metal ion. The DTG_{max} of the second and third steps occurred at 328 and 420 °C, respectively. The

weight loss corresponding to these steps was 74.52% due to the loss of two OFL molecules and three chlorine atoms, leaving Ru as the final product. **Complex 2** was thermally degraded in four steps. The weight loss corresponding to the first step was 7.16% due to the removal of two coordinated water molecules and one terminal methyl group. The total weight loss from the second to fourth steps was 77.30% due to the removal of one OFL and Gly molecule and two chlorine atoms. Ru was the final residue (theoretical: 15.71%; found: 15.54%). The thermal decomposition of **Complex 3** took place in four degradation steps. Coordinated water molecules and one terminal methyl group were lost in the first step with a total mass loss of 7.16%. The second to fourth steps represented a total weight loss of 78.05% with a DTG_{max} at 220 °C, corresponding to the loss of one OFL and Ala molecule and two chlorine atoms. Ru was the final residue (theoretical: 15.37%; found: 14.79%). From Figure 8a–c, the strong endothermic peaks in the 808–885 °C range with no associated weight loss were attributed to the formation of Ru nanostructures with changed physicochemical transformation states.

Commound	Decomposition Stage	Decomposition Stage $T \sqrt{C}$		% Weig	ht Loss
Compound	Decomposition Stage	I _{max} / C	Lost Species	Found	Calc.
			1-methyl		
OFI	1st	350	piperazine + CH ₃	31.50	31.50
OFL	2nd	414	COOH	13.18	12.45
	3rd	603	OFL	55.32	56.05
	Residue	1000	-	-	-
Complex 1	1st	115	2CH ₃ + 2F + 2COOH	16.12	15.99
	2nd–3rd	328 420	20FL + 3Cl	74.52	73.14
	Residue	1000	Ru metal	9.36	10.87
	1st	70	$2H_2O + CH_3$	7.16	7.93
Complex 2	2nd-4 th	253 316 453	OFL + Gly + 2Cl	77.30	76.36
	Residue	1000	Ru metal	15.54	15.71
	1st	95	$2H_2O + CH_3$	7.16	7.76
Complex 3	2nd-4 th	220 306 429	OFL + Ala + 2Cl	78.05	76.87
	Residue	1000	Ru metal	14.79	15.37

Table 5. The maximum temperatures and corresponding weight losses for the decomposition steps of free OFL and the synthesized complexes.

3.1.9. Kinetic Thermodynamics Data

The Horowitz and Metzger (HM) [53] and Coats and Redfern (CR) [54] methods were used to evaluate the kinetic parameters (E, ΔH^* , ΔS^* , and ΔG^*) of the free OFL ligand and synthesized complexes. The HM and CR diagrams for the free OFL ligand and each complex are given in Figure 9a–d and the kinetic data are listed in Table 6. The high ΔG values of the synthesized complexes could be due to the structural rigidity of the remaining complex after the expulsion of one or more ligand [55]. The positive values for ΔH indicated that the decomposition process was endothermic, whereas the negative values for ΔS indicated that the reactions were slow and that the activated complex was more ordered than the reactants alone [56].



(a)

Figure 9. Cont.



(**b**)

Figure 9. Cont.



(c)

Figure 9. Cont.



(**d**)

Figure 9. (a) HM and CR curves of free OFL drug; (b) HM and CR curves of **Complex 1**; (c) HM and CR curves of **Complex 2**; (d) HM and CR curves of **Complex 3**.

Table 6. Thermodynamic parameters of the thermal decomposition of free OFL and the synthesized complexes.

		Parameter						
Compound	Stage	Method	E (J mol ⁻¹)	A (s ⁻¹)	ΔS (J mol ⁻¹ K ⁻¹)	ΔH (J mol ⁻¹)	ΔG (J mol ⁻¹)	r
OFL	3rd	CR HM	$\begin{array}{c} 1.19 \times 10^{5} \\ 1.32 \times 10^{5} \end{array}$	$\begin{array}{c} 2.68 \times 10^4 \\ 3.28 \times 10^5 \end{array}$	-1.69×10^{2} -1.48×10^{2}	$\begin{array}{c} 1.11\times10^5\\ 1.24\times10^5\end{array}$	2.60×10^5 2.55×10^5	0.99235 0.99411
Complex 1	3rd	CR HM	1.55×10^5 1.60×10^5	1.09×10^9 4.74×10^9	-79.2 - 67.0	$\begin{array}{c} 1.49 \times 10^{5} \\ 1.54 \times 10^{5} \end{array}$	2.05×10^5 2.02×10^5	0.99017 0.98764
Complex 2	3rd	CR HM	$\begin{array}{c} 1.25 \times 10^{5} \\ 1.38 \times 10^{5} \end{array}$	$\begin{array}{c} 1.87 \times 10^{6} \\ 1.95 \times 10^{7} \end{array}$	-1.33×10^{2} -1.13×10^{2}	$\begin{array}{c} 1.18 \times 10^{5} \\ 1.31 \times 10^{5} \end{array}$	2.19×10^5 2.18×10^5	0.99257 0.99204
Complex 3	3rd	CR HM	1.20×10^5 1.27×10^5	3.45×10^{6} 2.21×10^{7}	-1.27×10^{2} -1.11×10^{2}	$\begin{array}{c} 1.14\times10^5\\ 1.21\times10^5\end{array}$	2.03×10^5 1.99×10^5	0.98338 0.98635

3.1.10. Molecular Modeling

Molecular modeling and quantum chemical studies of the free OFL ligand were helpful in confirming the proposed chemical structures of the synthesized metal complexes [57,58]. Conformational analyses and geometric optimizations were conducted at the semi-empirical PM3 level using the HyperChem 7.5 software [59] (Figure 10 and Table 7). The quantum chemical parameters of Mulliken electronegativity; χ , global softness; S, global hardness; η , global electrophilicity; ω , chemical potential; P_i, electronic charge; ΔN_{max} , absolute softness; σ , the lowest unoccupied molecular orbital energy; E_{LUMO}, highest occupied molecular orbital energy; E_{HOMO}, the difference between HOMO and LUMO energy levels; and ΔE were obtained using equations described in the literature [60–64] and are listed in Table 7. The high E_{HOMO} value indicated that the OFL ligand behaved as a strong donator and its high ω value likely resulted from its high capacity to accept electrons. The negative values for both E_{HOMO} and E_{LUMO} were attributed to the stability of the synthesized complexes.



Figure 10. HOMO and LUMO structure of free OFL ligand.

Parameter	Value
Total energy (kcal/mol)	120,549
Binding energy (kcal/mol)	214,404
Heat formation (kcal/mol)	218,076
Electronic energy (kcal/mol)	-787,413
Dipole moment/Debye	730
E _{HOMO} (eV)	-8.6133
E _{LUMO} (eV)	2.4663
$\Delta E(eV)$	11.0796
χ (eV)	3.0735
η (eV)	5.5398
σ (eV)	0.180512
P _i (eV)	-3.0735
S (eV)	0.090256
ω (eV)	0.852594
ΔN_{max} (eV)	0.554803

Table 7. The quantum chemical parameters of free OFL ligand.

3.1.11. Antibacterial Activity

Herein, the antibacterial activity data are summarized in Table 8, a screening test for possible antibacterial activity was applied on the three synthesized compounds against four bacterial strains *Klebsiella, Escherichia coli, Staphylococcus aureus*, and *Staphylococcus epidermidis*. Using disc diffusion method [65] to test the antimicrobial effect. Inhibition zones diameters around the disc were determined. The increase of the zone of inhibition for metal complexes when compared with corresponding standard drugs (ceftriaxone and gentamycin) as shown in Table 8 is an indication that the metal complexes are able to decrease the population of bacterial species. It also an indication that the metal complexes are more effective than their corresponding ligand. The chelation increases the lipophilic nature of the central atom which subsequently favor its permeation through the lipid layer of the cell membrane [66]. The chelation theory account for the increased activities of the metal complexes. The chelation reduces considerably the polarity of the metal atom mainly because of the partial sharing of its positive charge with the donor group and possible p electron delocalisation within the whole chelating ring [67]. The result shows that the three complexes possess higher inhibitory activity against the bacterial species regarding *Klebsiella* and *Escherichia coli*.

Table 8.	Inhibition	zone diameter	of Ru(III) OFL co	mplexes	I–III a	against f	four	bacterial	strains
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Ç.			Inhibition Zone Diameter (mm/mg Sample)					
Sample		Klebsiella	Escherichia coli	Staphylococcus epidermidis	Staphylococcus aureus			
Contro	ol: DMSO	0.0	0.0	0.0	0.0			
Ct. 1.1	Ceftriaxone	0.0	0.0	1.6	1.9			
Standard	Gentamycin	0.3	0.0	1.8	1.5			
	Ι	0.4	0.3	0.1	0.0			
	II	0.5	0.3	0.0	0.1			
	III	0.6	0.4	0.1	0.0			

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