



Spectroscopic and biological studies of mixed ligand complexes of transition metal (II) ions with chloroquine and ketoprofen

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ABSTRACT

To create fresh transition metal complexes of chloroquine and ketoprofen, we combined Ni(II), Co(II), Cu(II), and Zn(II). Metal analysis, IR, UV-vis, and X-ray diffraction (XRD) spectrum analyzes of the complexes were utilized to characterize them. The octahedral geometry was proposed for all compounds on the basis of the UV-vis and magnetic susceptibility data. The practical size of the ligands and complexes with crystallinity structure was in the nano range according to the XRD data. The antibacterial and antifungal activities of the ligands and their metal complexes have been examined.

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1. Introduction

Mixed-ligand complexes are distinct from typical complexes in that they have a minimum of two different types of ligands linked to the same metal ion. The potential of a complex's predicted features to change increases when multiple ligand types are present [1]. In biological and chemical processes including antioxidants [2], water smoothing [3], ion exchange resin [4] and photosynthesis in metals from the electrical components of living organisms [5,6], mixed ligand complexes are crucial. In our daily lives, fields such as bioinorganic, medicine, chemistry, photochemistry, and molecular biology all depend on mixed ligand-metal complexes [7,8]. One of the main goals of modern inorganic coordination chemists and pharmaceutical

research is the discovery and development of better drugs to treat diseases, and this has led to innumerable investigations on drug-metal complexes [9].

The antimalarial drug chloroquine (CQ) was first created in the 1930s. It is made through a convergent synthesis in which the final step of the aromatic nucleophilic displacement combines aliphatic (novaldiamine, 2-amino-5-dimethylami nopentane) and quinoline (4,7-dichloroquinoline) components. Chloroquine is inexpensive and widely accessible; however, due to *P. falciparum*'s drug resistance, the most deadly variant of the malaria parasite, it is no longer very effective against it [10,11]. The synthesis, characterization, and biological activity of several chloroquine metal complexes have been studied, according to a review of the

literature [12-19]. In this study, the biological actions of these compounds are examined together with the production and characterization of complexes from chloroquine phosphate and ketoprofen with transition-metal ions.

2. Materials and methods

2.1 Materials

High-purity chemicals were used from numerous companies. Shaphaco Pharmaceutical Company was used to purchase ketoprofen and chloroquine phosphate. The other chemicals, solvents, indicators, and metal (II) chlorides from BDH (nicke, cobalt, copper, and zinc chloride) were used without any extra purification.

2.2 Preparation of metal complexes

In general, aqueous solutions of 0.01mmol hydrated metal chlorides (2.376g, 2.379g, 1.704g and 2.442g for nicke, cobalt, copper, and zinc chloride, respectively), chloroquine phosphate (0.01mmole, 5.158g) and 10% ammonia solution of ketoprofen (0.01mmole, 2.542g) to create solid mixed complexes. The combination of each was refluxed on a hot plate for three hours at 60-80°C with constant stirring to get colored precipitates. Filters were used to remove solid precipitates, which were then carefully cleaned in hot water and dried by air [20].

2.3 Physical measurements

The study of elements C, H, N, and S was carried out by the Central Laboratory, Faculty of Science, Cairo University, Giza, Egypt, using a Vario EL Fab. CHNS Nr. Using an atomic absorption spectrophotometer, the metal content was evaluated at the Global Pharmaceutical Company. The Global Pharmaceutical Company measured the molar conductance of 10^{-3} M solutions of metal complexes in 10% DMSO solvent using a Sartorius conductivity meter model pp20. All measurements of the recently created solutions were carried out at room temperature. The infrared properties of the complexes. The magnetic susceptibilities were measured by Gouy's method using a magnetic

susceptibility balance from the Johnson-Metthey and Sherwood model. The melting point of every compound is specified in degrees Celsius and is determined using glass capillary tubes. A gravimetric approach was employed to quantify chloride using silver nitrate [21]. The quantity of coordinated and uncoordinated water molecules was calculated gravimetrically using the weight-loss method. TLC was carried out on Silica Gel GF254 plates (mn-kieselgel G., 0.2 mm thickness) with acetone solution serving as the mobile eluent. The plates were scanned at Alrazy University using an ultraviolet 254 nm lamp. XRD patterns were acquired at the Yemen Geological Survey and Mineral Resources Board using a powder X-ray diffractometer XD-2 (Shimadzu ED-720) at a voltage of 35 kV and a current of mA utilizing CuK(α) radiation in the range of $5^\circ < 2\theta < 70^\circ$ at a scan rate of 1° and a wavelength of 1.54056 \AA .

2.4 Crystallinity and particle size from XRD

The integrated peak sizes of the major peaks were used to calculate the percentage of crystallinity, XC (%) [22]. As a ratio, the crystallinity of the complexes is determined in relation to that of the ligands:

$$XC (\%) = (A_{\text{complex}}) / (A_{\text{ligand}}) \times 10$$

where A_{complex} and A_{ligand} are the areas under the principal peaks of the complex and ligand sample, respectively.

The estimated average particle size of the Scherrer equation (D), which was also determined by X-ray diffraction [23,24]:

$$D = K \lambda / \beta \cos\theta$$

where K is Scherrer constant and equals 0.94, λ is the X-ray wavelength of Cu-K α radiations (1.5405 \AA), β is the full width at half maximum (FWHM), and θ is the Bragg diffraction angle in degrees.

2.5 Biological screening

The filter paper disc method was used to test the ligands and their metal complexes for their antibacterial activity against four species of bacteria (*Staphylococcus aureus*, *Bacillus*, *Escherichia coli*, and *Pseudomonas aeruginosa*),

as well as their antifungal activity against *Candida albicans* fungus. Each of the screened metal complexes was separately diluted in 10% DMSO (dimethyl sulfoxide) to create a solution with a concentration of 1000 $\mu\text{g/ml}$. The solution of these compounds was applied evenly on 5 mm diameter Whatman No. 1 filter paper discs. The discs were placed on top of Mollar Henton agar dishes that had been hardened and seeded with the test bacteria. After a 24-hour incubation period at 37°C, the widths of the inhibitory zones (mm) were measured. Ofloxacin 5 micrograms/disc was used as a reference substance for these bacteria, while Ketoconazole 10 micrograms/disc was used as a reference substance for these fungi. Discs saturated with 10% DMSO were used as a solvent control [25,26].

3. Results and discussion

The created Ni(II), The melting values of the Co(II), Cu(II), and Zn(II) complexes with the ligands were collected and then washed with hot water. As a result, the complexes on their thin-layer chromatography showed single spots with respectable R_f values, demonstrating their purity. All of the complexes were colored and stable in the presence of air, but were insoluble in water, ethanol, methanol, acetone, CHCl_3 , 0.1N NaOH, and DMF. However, they were all soluble in 10% DMSO and 0.1M HCl. The melting points of the novel complexes are greater than those of the pure ligands. The melting values of the Co(II), Cu(II), and Zn(II) complexes were ($> 350^\circ \text{C}$). The molar conductance values of the complexes of Ni (II), Co (II), Cu (II) and Zn(II) ranged between 8 and 12 $\Omega^{-1} \text{mol}^{-1} \text{cm}^2$, confirming the non-electrolytic character of these complexes [27]. Tables 1 and 2 contain a list of some of the physical characteristics of these complexes and analytical information.

3.1 Infrared Spectra

The infrared spectra of chloroquine and those of the metal complex were compared. According to reports [28], the N-H and C=N stretching vibration frequencies are 3260 cm^{-1}

and 1580 cm^{-1} , respectively. Because of the nitrogen atom in the quinoline ring, chloroquine in these compounds behaves as a neutral monodentate molecule. Through the oxygen atoms in the carboxyl group, ketoprofen in these compounds functions as a bidentate molecule. Thus, in these complexes (Figures 1-4), a single metal ion is coordinated with the two ligands, the ketoprofen and chloroquine molecules. Based on the following evidence, Table 3 summarizes the assignments of bonding sites:

- 1- Ketonic carbonyl bands with a center at 1697 cm^{-1} were the bands identified for the ketoprofen ligand, as opposed to carboxyl carbonyl bands with a center at 1654 cm^{-1} [29] and $\nu(\text{OH})$ bands with a center at 3429 cm^{-1} . FTIR spectroscopy proved that the metal ions were coordinated. While for ketoprofen it was at 1697 cm^{-1} in all spectra, the absorption bands of the complexes ascribed to the stretching vibration of the OCO group occurred at 1718-1720 cm^{-1} [30].
- 2- Compared to free ketoprofen, the vibrational frequencies of the ketonic carbonyl stretches of the complexes remained unchanged, indicating that these functionalities were not involved in the interaction with the metal centers [31]. Due to coordination through the functional group C = N, the band of C=N extending at 1580 cm^{-1} for chloroquine [32] is moved to 1457–1465 cm^{-1} . The length of the C=N bond increases as the electron density decreases, slowing the vibration frequency cm^{-1} in the process. This modification implies that the location of the quinoline ring in chloroquine plays a role in the coordination.
- 3- N-H stretching vibrations have been attributed to the free chloroquine's absorption band at 3260 cm^{-1} [33]. Due to coordination, this band has been displaced by 40–55 cm^{-1} in the spectra of metal complexes [34]. If we compare our results for the produced complexes with the pure ligand, carbonyl appears at 1654 cm^{-1} but is

moved to 1718–1720 cm^{-1} through complexation.

- 4- For the complexes, the $\nu_{\text{asym}}(\text{COO}^-)$ occurs at 1560 cm^{-1} and that $\nu_{\text{sym}}(\text{COO}^-)$ at 1384 cm^{-1} , whereas the calculated value of $\nu_{\text{asym}}(\text{COO}^-)$ (asymmetrical, symmetrical carboxylate vibrations) shows the smaller value at 182 cm^{-1} - 144 cm^{-1} in comparison with the calculated value for the ketoprofen (182 cm^{-1} , Table 3). This finding points to the bidentate chelate coordination mode, in which a metallic ion is coordinated with one carboxylate group oxygen atom [35].

- 5- The appearance of a single new strong absorption band at 423–439 cm^{-1} in the spectra of the Nickel(II), Cobalt(II), Copper(II), and zinc (II) complexes also supports the creation of the metal complexes. This novel band, which lacks a match in the spectra of the unbound ligand, can be attributed to the vibration of metal-ligand bands, specifically $\nu(\text{M-O})$. Additionally, there are some novel bands that occur for these complexes at (403–422 cm^{-1}) that are associated with the vibration of metal ligand bands, specifically (M-N) [36].

Table 1: Some physical properties of the complexes

Compound	Color (Yield%)	M.P. ($^{\circ}\text{C}$)	$\Delta m(\Omega^{-1} \text{cm}^2 \text{mol}^{-1})$	F.Wt (g/mole)	TLC	
					No. of Spots	R_f^*
[Ni(CQ)(Keto)(H ₂ O) ₂ Cl]	Light yellow(25)	270	11	703.343	One	0.76
[Co(CQ)(Keto)(H ₂ O) ₂ Cl]	Light purple(31)	>350	9	703.583	One	0.68
[Cu(CQ)(Keto)(H ₂ O) ₂ Cl]	Light blue(22)	>350	12	708.199	One	0.46
[Zn(CQ)(Keto)(H ₂ O) ₂ Cl]	White(17)	>350	8	710.033	One	0.56

* R_f = retention factor in thin layer chromatography

Table 2: Elemental Analysis of the complexes

Complex (Molecular formula)	Element Analysis, Found Calculated%				
	C	H	N	M	Cl
[Ni(CQ)(Keto)(H ₂ O) ₂ Cl] (C ₃₄ H ₄₃ Cl ₂ NiN ₃ O ₅)	58.10 (58.06)	6.14 (6.16)	5.99 (5.97)	8.33 (8.34)	10.11 (10.08)
[Co(CQ)(Keto)(H ₂ O) ₂ Cl] (C ₃₄ H ₄₃ Cl ₂ CoN ₃ O ₅)	58.08 (58.04)	6.15 (6.16)	5.99 (5.97)	8.36 (8.38)	10.07 (10.08)
[Cu(CQ)(Keto)(H ₂ O) ₂ Cl] (C ₃₄ H ₄₃ Cl ₂ CuN ₃ O ₅)	57.62 (57.66)	6.15 (6.12)	5.94 (5.93)	8.96 (8.97)	10.05 (10.01)
[Zn(CQ)(Keto)(H ₂ O) ₂ Cl] (C ₃₄ H ₄₃ Cl ₂ ZnN ₃ O ₅)	57.54 (57.51)	6.15 (6.10)	5.93 (5.92)	9.26 (9.21)	9.95 (9.99)

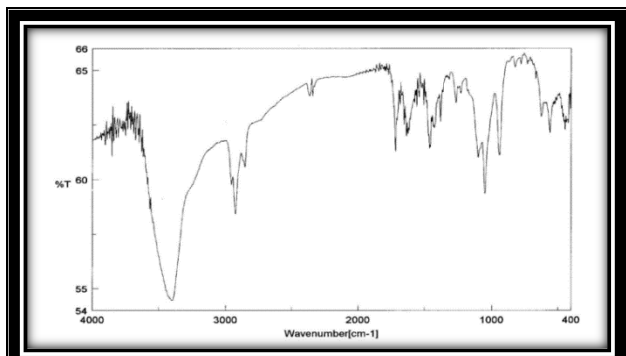


Figure. 1: Infrared Spectrum of [Ni(CQ)(Keto)(H₂O)₂Cl]

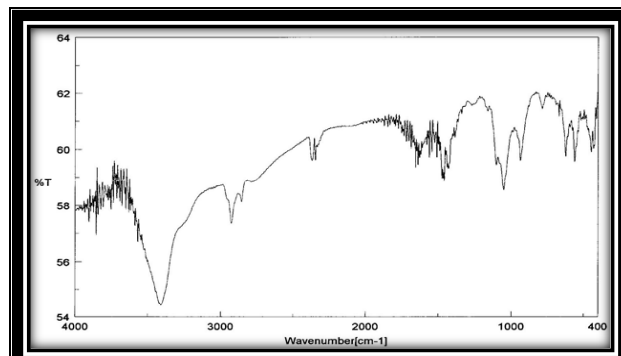
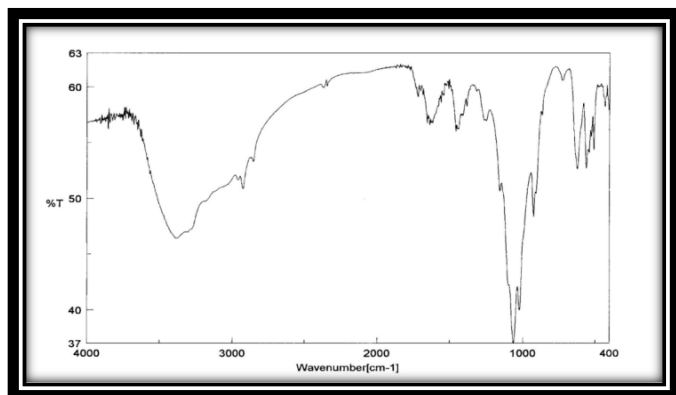
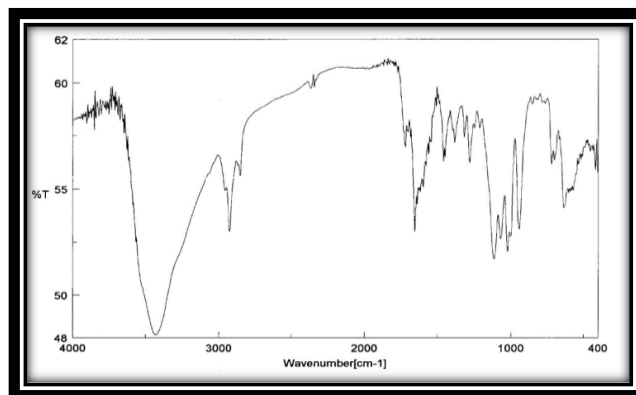


Figure. 2: Infrared Spectrum of [Co(CQ)(Keto)(H₂O)₂Cl]

Table 3: Significant IR spectral bands (cm^{-1}) of complexes with Chloroquine and ketoprofen

[Ni(CQ)(Keto)(H ₂ O) ₂ Cl]	[Co(CQ)(Keto)(H ₂ O) ₂ Cl]	[Cu(CQ)(Keto)(H ₂ O) ₂ Cl]	[Zn(CQ)(Keto)(H ₂ O) ₂ Cl]	Assignment
32201 br &w	3205 br &w	3210 br&w	3217 br &w	v(NH)
3567 sh&w	3442 br &s	3404 br &s	3422 br &s	v(OH) of H ₂ O
1636sh&w	1634sh&w	1638 sh&w	1637sh&w	Benzene ring +pyridine ring stretch
2955sh&w	2923sh&w	2959sh&w	2959sh&w	vCH-arom
2854sh&w	2854sh&w	2855br&w	2854sh&w	vCH-aliph
1050sh&m	1051 sh&m	1023sh&s	1024sh&m	v(C-N)
1719sh&m	1718 sh&w	1720 sh&w	1719 sh&m	v(C=O)
1577 sh& w	1577 sh& w	1560 sh&w	1560 sh& w	v(C -O)asym
1420 sh& w &1370 sh& w $\Delta v=182$	1429 sh& w &1386 sh& w $\Delta v=170$	1420 sh&w &1384 sh& w $\Delta v=158$	1448 sh& w &1384 sh& w $\Delta v=144$	v(C -O)sym
1465 sh&w	1465 sh&w	1457 sh&w	1458 sh&w	v(C=N)
423sh&w	431sh&w	432sh&w	439sh&w	v(M-O)
406 sh&w	411sh&w	403sh&w	422 sh&w	v(M-N)

**Figure 3:** Infrared Spectrum of [Cu(CQ)(Keto)(H₂O)₂Cl]**Figure 4:** Infrared Spectrum of [Zn(CQ)(Keto)(H₂O)₂Cl]

3.2 Magnetic and Electronic Spectral Studies

The absorption spectra of the metal complexes in DMSO were read between 200 and 800 nm (Table 4).

The ${}^3A_{2g} \rightarrow {}^3T_{1g}(P)$ and ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$ transitions were attributed to the absorption bands at 15131 and 13889 cm^{-1} , respectively, in the [Ni(CQ)(Keto)(H₂O)₂Cl] complex electronic spectrum of the complex [Ni (CQ) (Keto) (H₂O) 2Cl] (Figure 5). The octahedral structure 2.99B.M. of the complexes is evident [37,38].

The Co^{2+} complex bands at 19607, 20833, and 21505 cm^{-1} were each ascribed to the ${}^4T_{1g} \rightarrow {}^4T_{1g}(P)$ (3), ${}^4T_{1g} \rightarrow {}^4A_{2g}$ (2), and ${}^4T_{1g} \rightarrow {}^4T_{2g}(F)$ (1) transitions, respectively (Figure 6). The compound's octahedral shape matches the effective magnetic moment of 4.64B.M [37,38].

The ${}^2E_g \rightarrow {}^2T_{2g}$ transition is responsible for the new broad band at 12346 cm^{-1} in [Cu(CQ)(Keto)(H₂O)₂Cl] (Figure 7). The broadness of the band might have resulted from the considerable Jahn-Teller distortion that is

predicted in a d^9 ion, which magnifies the distortion of the octahedral geometry. It is found that the magnetic moment of these complexes (1.88 B.M.) is within the permissible range for the d^9 -system with a single unpaired electron [38,39].

For Zn (II) complexes, there was no discernible peak, and there were no ligand field absorption bands in Figure 8. Figure 9 shows the structure of the complexes.

3.3 X-ray diffraction

Figures 10-15 show the XRD patterns of chloroquine, ketoprofen, and their complexes. The decrease in crystallinities brought on by complexation can be linked to the increase in X-

ray diffraction (XRD) peak intensities in complexes. This is in line with the calculated decrease in relative crystallinity for these compounds. Based on the integrated area of the main peaks of the complex relative to those of the ligands Chloroquine and Ketoprofen, the relative crystallinity is calculated in Table 5 [40]. The predicted particle size of chloroquine and ketoprofen (7.056-3.179 nm) falls within the range of nanoparticles; the literature reports that these particles have a size range of 1-100 nm [41]. Complexes' particles were discovered to be in the nano range (4.614, 3.326, 2.366 and 3.389 nm).

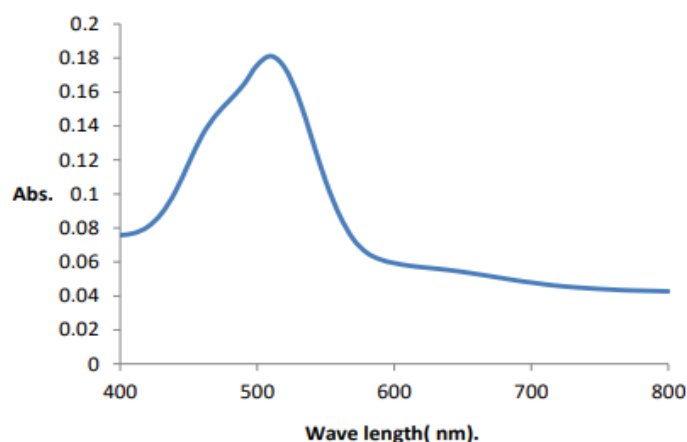
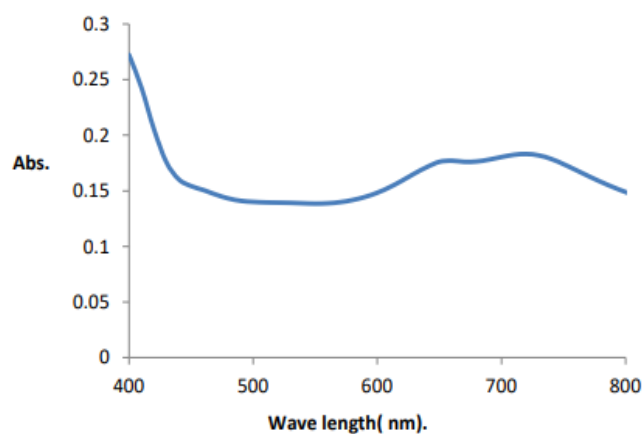


Figure. 5: UV-Visible Spectrum of $[\text{Ni}(\text{CQ})(\text{Keto})(\text{H}_2\text{O})_2\text{Cl}]$

Figure. 6: UV-Visible Spectrum of $[\text{Co}(\text{CQ})(\text{Keto})(\text{H}_2\text{O})_2\text{Cl}]$

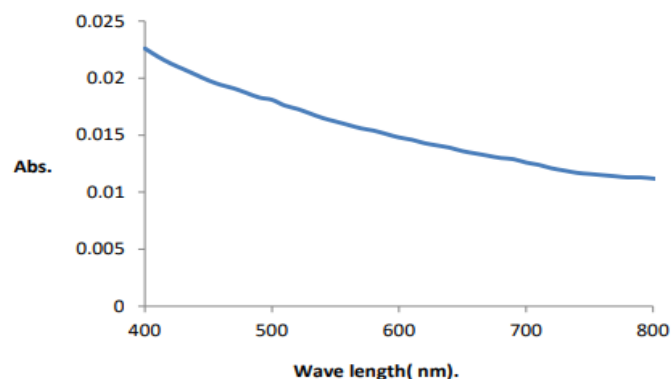
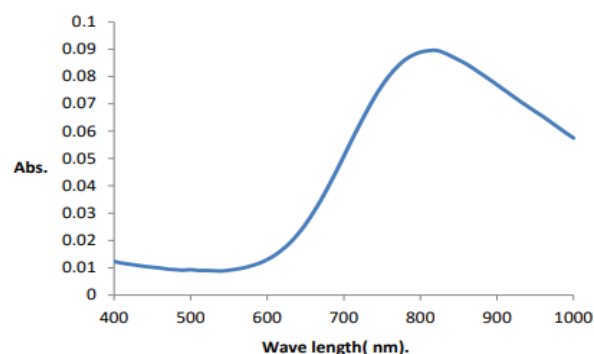


Figure. 7: UV-Visible Spectrum of $[\text{Cu}(\text{CQ})(\text{Keto})(\text{H}_2\text{O})_2\text{Cl}]$

Figure. 8: UV-Visible Spectrum of $[\text{Zn}(\text{CQ})(\text{Keto})(\text{H}_2\text{O})_2\text{Cl}]$

Table 4: Electronic spectral and magnetic moment data of the complexes

Compound	μ_{eff} (B.M.)	d-d transition band (cm-1)	Assignments	Supposed structure
[Ni(CQ)(Keto)(H ₂ O) ₂ Cl]	2.99	15131 13889	${}^3A_{2g} \rightarrow {}^3T_{1g}(P)$ ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$	Octahedral
[Co(CQ)(Keto)(H ₂ O) ₂ Cl]	4.64	19607 20833 21505	${}^4T_{1g} \rightarrow {}^4T_{1g}(P)$ ${}^4T_{1g} \rightarrow {}^4A_{2g}$ ${}^4T_{1g} \rightarrow {}^4T_{2g}(F)$	Octahedral
[Cu(CQ)(Keto)(H ₂ O) ₂ Cl]	1.88	12346	${}^2E_g \rightarrow {}^2T_{2g}$	Distorted Octahedral

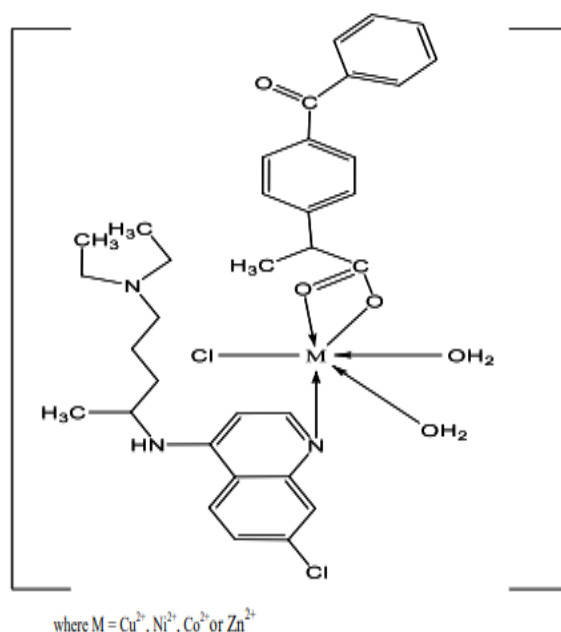


Figure. 9: Proposed structure of complexes

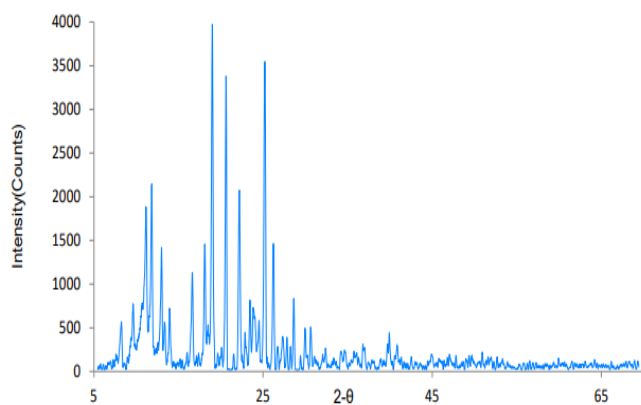


Figure. 10: XRD pattern for Chloroquinone

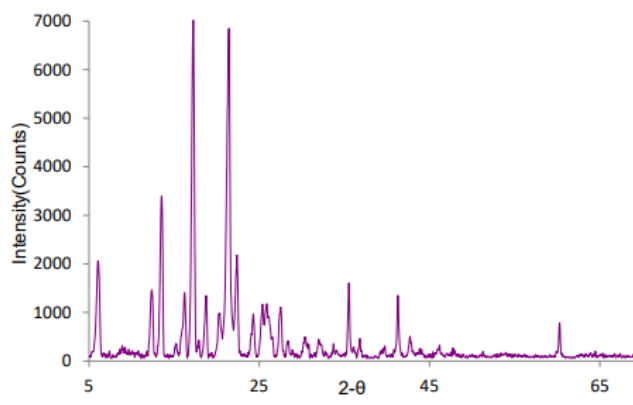


Figure. 11: XRD pattern for Ketoprofen

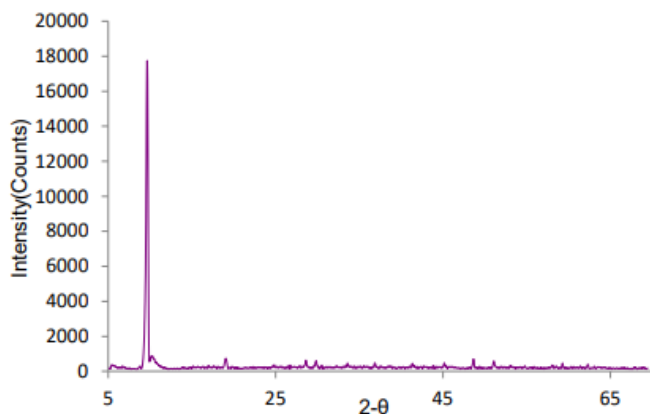


Figure. 12: XRD pattern for [Ni(CQ)(Keto)(H₂O)₂Cl]

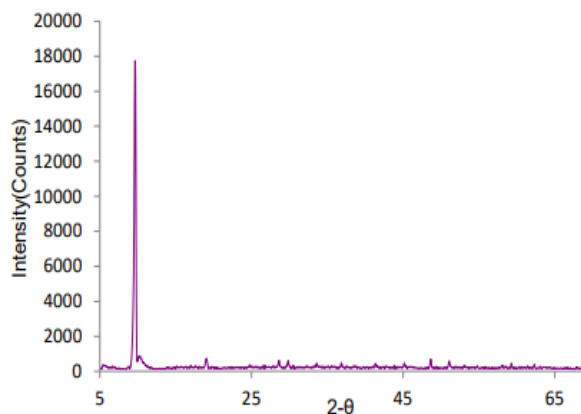


Figure. 13: XRD pattern for [Co(CQ)(Keto)(H₂O)₂Cl]

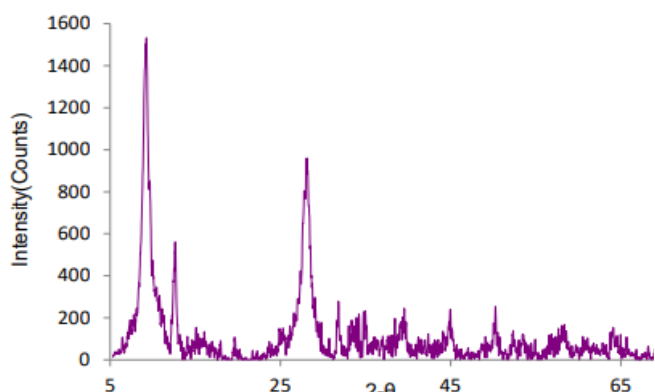


Figure. 14: XRD pattern for [Cu(CQ)(Keto)(H₂O)₂Cl]

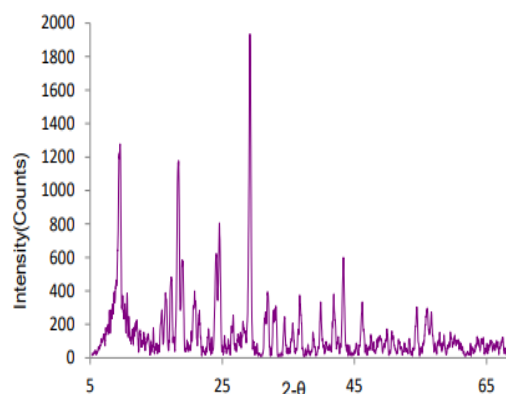


Figure. 15: XRD pattern for [Zn(CQ)(Keto)(H₂O)₂Cl]
[Zn(CQ)(Keto)(H₂O)₂Cl]

Table 5: XRD spectra data of the principal intensity values of the ligands chloroquine, ktoprofen and their complexes with (Ni,Co,Cu, and Zn)

Compound	2θ	β	D (nm)	Mean D	XC (%)
Chloroquine	19.581	0.223	6.5895	7.056	100
	26.259	0.231	6.4369		
	21.321	0.181	8.1409		
ketoprofen	6.14	0.435	3.3334	3.179	100
	14.26	0.339	4.3047		
	18.3	0.36 0.401	4.0742		
	22.84	0.555	3.6841		
	27.12	0.859	2.6840		
	27.66	0.612	1.7361		
	27.959		2.43835		
[Ni(CQ)(Keto)(H ₂ O) ₂ Cl]	10.06	0.388	3.7466	4.614	12.417
	32.20	0.275	5.4811		

[Co(CQ)(Keto)(H ₂ O) ₂ Cl]	10.04 10.64 10.959	0.287 0.569 0.617	5.0652 2.5559 2.3578	3.326	24.549
[Cu(CQ)(Keto)(H ₂ O) ₂ Cl]	9.301 9.739 12.96 29.302 29.699 29.999	0.697 0.508 0.46 0.654 0.741 0.845	2.0845 2.8611 3.1682 2.2886 2.0217 1.7742	2.366	46.583
[Zn(CQ)(Keto)(H ₂ O) ₂ Cl]	9.78 19.56 25.86 26.38 31.48	0.470 0.452 0.517 0.422 0.358	3.0921 3.2508 2.8739 3.5244 4.2047	3.389	47.797

3.4 Antibacterial and antifungal screening:

Using the well diffusion method [25,26], the ligands and their metal complexes were tested against four different bacterial species (*Staphylococcus aureus*, *Bacillus subtilis*,

Escherichia coli and *Pseudomonas aeruginosa*), as well as a fungus (*Candida albicans*), on solid Mollar Henton agar medium. The results are displayed in Table 6. These results led to the following conclusions:

Table 6: Effect of the ligands and complexes on the growth

Compound (1000 µg/ml)	Bacteria				Fungi
	gram-positive		gram-negative		<i>Candida albicans</i>
	<i>Staphylococcus aureus</i>	<i>Bacillus</i>	<i>Pseudomonas Aeruginosa</i>	<i>E. coli</i>	
Chloroquine Phosphate	-	-	-	-	-
Ketoprofen	++	+	-	-	-
[Ni(CQ)(Keto)(H ₂ O) ₂ Cl]	-	-	-	-	-
[Co (CQ)(Keto)(H ₂ O) ₂ Cl]	-	-	-	-	-
[Cu(CQ)(Keto)(H ₂ O) ₂ Cl]	-	-	-	-	-
[Zn(CQ)(Keto)(H ₂ O) ₂ Cl]	-	-	-	-	-
Placebo10%DMSO	-	-	-	-	-
Ofloxacin 5 micro grame/disc	++	+	++	+	
KetoConazole10 micro grame/disc					+

(-) No zone of inhibition were observed.

Moderately sensitive, (+) inhibition zone of 2-10.

Sensitive, (++) Inhibition zone of 10-20.

- 1- No inhibition zone was observed for the ligands and their metal complexes against *Pseudomonas Aeruginosa*, *Escherichia coli*, and *Candida albicans*.
- 2- Ketoprofen exhibited antibacterial activity against bacteria
- 3- No inhibition zone was observed for chloroquine phosphorus metal complexes

against *Staphylococcus aureus* and *Bacillus subtilis*.

4. Conclusions

In this latest study, we describe the preparation of four complexes using chloroquine phosphate and ketoprofen ligands with Ni(II), Co(II), Cu(II), and Zn (II). Many physicochemical techniques were used to

describe these compounds. The results of the magnetic susceptibility and UV-vis measurements suggested that the metal complexes had octahedral geometry. The nature of crystallization was investigated using ligands and complexes, and interesting modifications in XRD patterns of the free ligands and their complexes were observed. The ligands and their metal complexes have been tested for their ability to inhibit bacterial and fungal growth.

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