SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL STUDIES OF Fe (II) and Cu(II) COMPLEXES OF ACETYLATED AND BENZOYLATED DERIVATIVES OF CIPROFLOXACIN

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ABSTRACT

Derivatization of ciprofloxacin is a promising alternative to the challenge of antibiotic resistance. Incorporation of substituents at the C-7 position (N-piperazine) moiety through acetylation and benzoylation of ciprofloxacin have resulted in its acetylated and benzoylated derivatives (CPCOR) and (CPCOPh) with enhanced biological activities. Copper and iron (II) complexes of the derivatives have been synthesized and characterised by percentage metal analysis, infrared and electronic spectroscopies, room temperature magnetic moments and melting points. The derivatised ligands (CPCOR) and (CPCOPh) act as bidentate ligands through the participation of the carboxy group oxygen and the pyridone carbonyl oxygen. The room temperature magnetic moment and electronic spectra data indicated that the complexes have octahedral geometries which is slightly distorted in the acetylated copper(II) complex.
The in-vitro antimicrobial studies were carried out on the derivatised ligands and their complexes against Bacillus subtilis (ATCC 39090), Escherichia.coli (ATCC 8739), Staphylococcus aureus (ATCC 6538), Pseudomonas aeruginosa (ATCC 7306), Klebsiella pneumonia (ATCC 4592), and Candida albicans (ATCC 10231). It was observed that the ligands as well as their complexes did not exhibit antifungal activity against the tested fungus Candida albicans.The acetylated derivative (CPCOR) showed better activity than the standard drug ciprofloxacin against Bacillus subtilis and Pseudomonas aeruginosa and Klebsiella pneumonia at all the concentrations used while the benzoylated derivative (CPCOPh) exhibited reduced activity in comparison to ciprofloxacin against all the tested organisms, this might be due to the bulkiness of phenyl moiety present in its structure. However, the metal (II) complexes of both the acetylated and benzoylated derivatives showed better activities than ciprofloxacin.

Keywords: Antimicrobial, Ciprofloxacin, Benzoylated, Acetylated, N-piperazine

INTRODUCTION

Ciprofloxacin (CP) (Fig. 1) is a synthetic, broad-spectrum fluoroquinolone antibacterial agent for oral administration[1]. It is active against a wide variety of aerobic gram-negative and gram-positive bacteria[2–4]. It has been principally approved for the treatment of intricate and basic urinary tract infections and pyelonephritis, lower respiratory tract infections, skin infections, urethral and cervical gonococcal infections, bone and joint infections, infectious diarrhea, typhoid fever and acute sinusitis[5]. The antibacterial mechanism of action of ciprofloxacin involves the destruction of the activities of two important enzymes, DNA

gyrase and topoisomerase IV that belong to the type II topoisomerase family by formation of a ternary drug-topoisomerase-DNA complex resulting in cell death[6-11].

The emergence of resistance strains of bacteria has led to further structural activity study of fluoroquinolones. Many advances have been already made for development of new fluoro quinolone antibiotics but derivatization of existing antibiotics is a promising alternative[12]. In recent times, ciprofloxacin have gained unusual consideration in finding new antibiotics for the treatment of drug-resistant bacteria infections[13-14]. Structure activity relationship (SAR) studies of fluoroquinolone antibacterial agents have been mostly reviewed and have been shown that substitution at the C-7 position is connected with their antibacterial properties, bioavailability and safety[15-17].

Therefore research concerning this moiety has been focused on the basic groups at the position of C-7 (piperazine) which is the most adaptable site for chemical change and an area that greatly influences their potency[18-21]. Earlier researches have proven that the large substituents placed in these positions do not have adverse effect on drug's permeability through bacterial membr-anes, and at the same time they significantly modify the strength of action [22-23].

The basic N-4 position of piperazine ring at C-7 position is an appropriate site for substitution with bulky groups, thus a number of N-substituted piperazinyl quinolones with different substituents have been described in the literature[24-28]. For instance, the acetylated and the benzoylated derivatives of ciprofloxacin by the modification of the piperazine N ring were reported [29].

Transition metals are essential elements widely distributed in biological systems, such as cells and body fluids and, many of their complexes bind to DNA through various modes[30-31]. Subsequently, it became apparent that antibacterial drugs become more effective against bacteria upon chelation/ coordination with the transition metal ions. The interactions of quinolones and metal ions have been thoroughly studied especially owing to their interesting biological and chemical properties. Ciprofloxacin generally act as a bidentate ligand through the pyridone oxygen and one carboxylate oxygen. In the literature, diverse transition metal complexes of ciprofloxacin have been structurally characterized and reported[32]. More specifically, metal (II) complexes of acetylated ciprofloxacin and their biological activities[33].

Complexes of coppe(II) ion has proved beneficial in many diseases such as tuberculosis, gastric ulcers, rheumatoid arthritis and cancers[34-37]. A metal ion such as iron (II) is necessary for a number of vital functions in life Sciences[38]. Iron is the central atom of the heme complex, which is made of photoporphyrin IX

and iron (II)[39]. Apart from the porphyrins, a number of iron complexing ligands are found in aerobic microbial cells[40-41]. Considering the vital functions of copper and iron in living system, we hereby report extension of coordination of Copper (II) and Iron (II) metals not only to the acetylated ciprofloxacin derivative earlier reported but also to the benzoylated ciprofloxacin derivatives, their characterization and their antimicrobial studies.

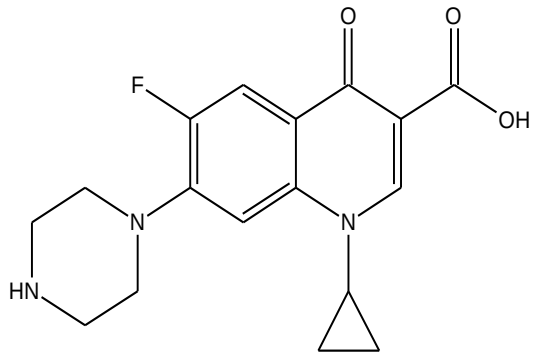


Figure 1: Structure of Neutral Ciprofloxacin

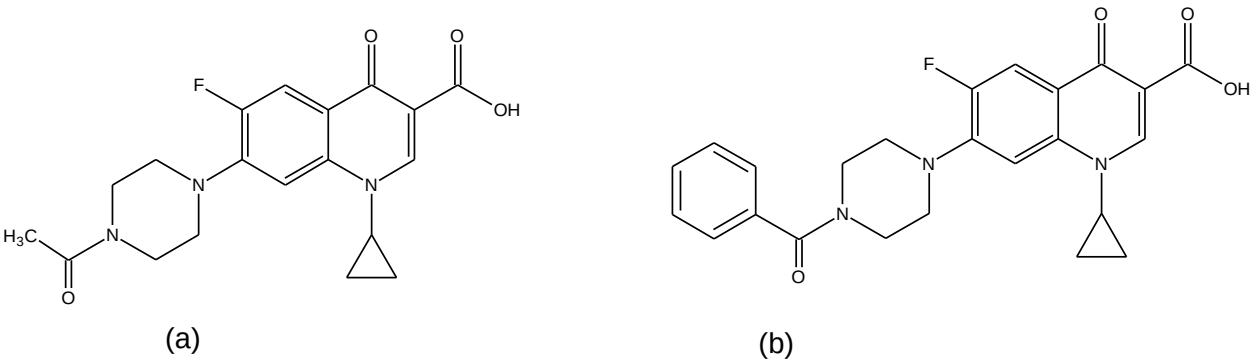


Figure 2: Structure of (a) Acetylated Ciprofloxacin (CPCOR) (b) Benzoylated Ciprofloxacin (CPCOPh)

MATERIALS AND METHODS

Materials and Reagents.

All reagents and solvents were of analytical grade and used without further purification. Ciprofloxacin hydrochloride was a gift from Bond Chemical Plc Awe, Oyo State and Unique Pharmaceutical Lagos. Sodium hydroxide pellet, acetic acid, acetic anhydride, tetrahydrofuran, triethylamine, benzoyl chloride, dichloromethane, brine, methanol, DMSO, nitromethane, N-hexane, acetone, ethanol, diethyl ether, copper(II) sulphate pentahydrate, iron(II) chloride tetrahydrate and sodium carbonate. They were all of analytical grade and were obtained from Sigma Aldrich.

Physical measurements

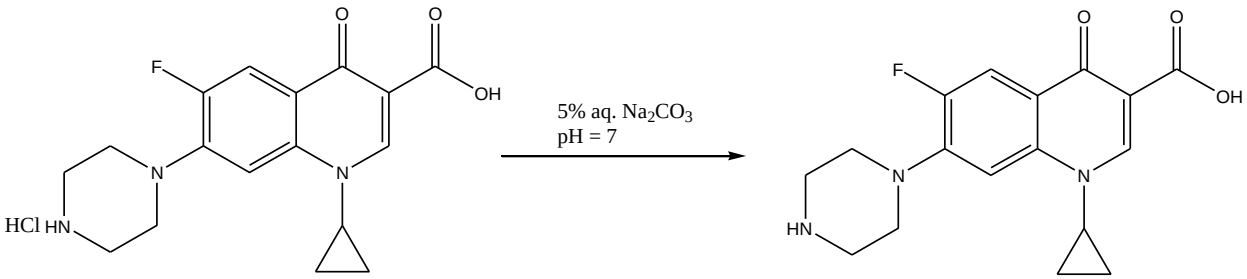
The electronic spectra of the complexes in distilled water were recorded on a Perkin-

Elmer Lambda 25 Spectrophotometer and infrared spectra were recorded using KBr discs on a Perkin-Elmer BX II FT-IR spectrometer 4000–370 cm^{-1}. The room temperature magnetic susceptibilities at 303K were measured on Sherwood Susceptibility Balance MSB Mark 1 and diamagnetic corrections were calculated using Pascal's constant, and melting points were determined with Stuart SMP10 Melting point apparatus.

Regeneration of free/Neutral Ciprofloxacin (Fig.1)

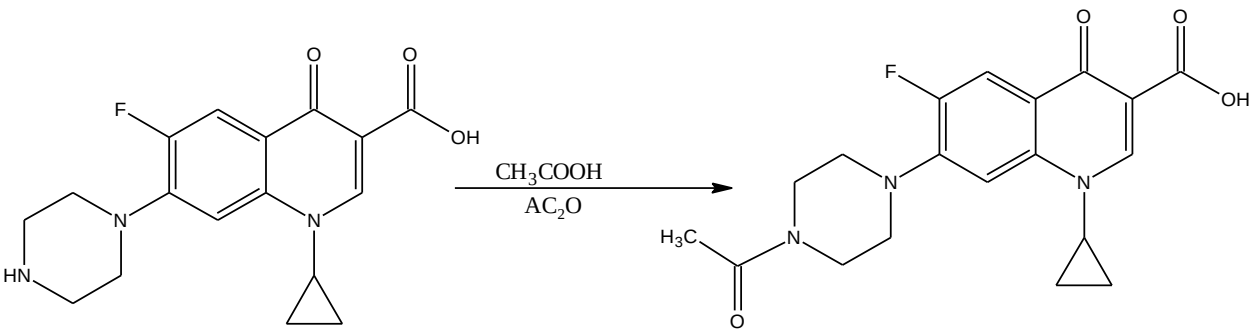
Neutral Ciprofloxacin was prepared from Ciprofolxacin hydrochloride according to published procedure [33] as given in the equation below.

2.5g (6.80mmol) of Ciprofloxacin hydrochloride in 12.5ml of distilled water was treated with excess 5% Na_2CO_3 solution dropwisely until pH of 7 was attained. The resulting white precipitate was filtered via a vacuum pump and allowed to dry to give 90% yield (2.02g).



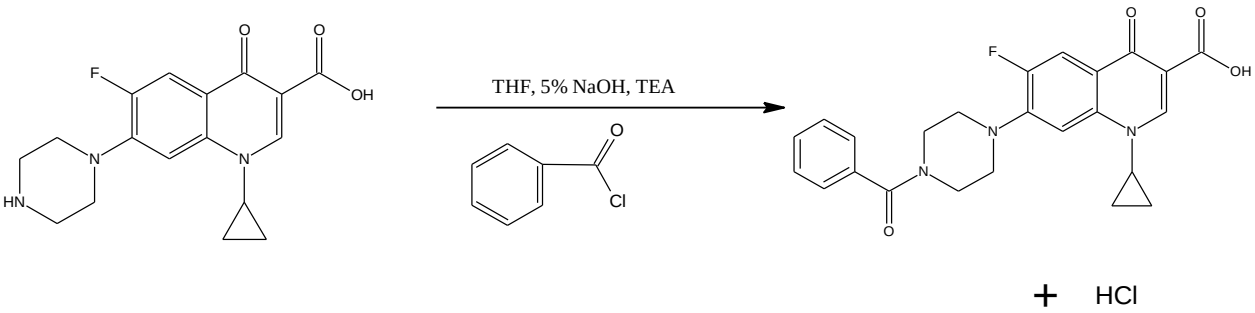
Synthesis of acetylated Ciprofloxacin (CPCOR) (Fig.2a)

The neutral ciprofloxacin synthesised was subsequently acetylated published method[29]. Neutral Ciprofloxacin (1 g) was dissolved in acetic acid (0.32 mL) and then the solution was treated with acetic anhydride (1.6 mL) in the presence of 20ml THF and 0.41ml triethylamine. The reaction mixture was warmed for an hour and allowed to cool for crystallization. The precipitate was filtered off, washed and dried under vacuum in a desiccator to give 80% yield (0.80g).



Synthesis of benzoylated Ciprofloxacin (CPCOPh)(Fig.2b)

Neutral ciprofloxacin (1.5g, 4.5mmol) was dissolved in 9.7ml (5%) NaOH, and treated with 0.6ml benzoylchloride in the presence of 10ml tetrahydrofuran and 0.42ml triethylamine. The solution was warmed for one hour with stirring and acidified with 5ml acetic acid resulting in formation of white precipitate. The precipitate was filtered, dried and recrystallized; percentage yield is 50% (0.75g).



Synthesis of complexes ***[Cu(CPCOR)$_2$(H$_2$O)$_2$].3H$_2$O*** ***and*** ***[Fe(CPCOR)$_2$(H$_2$O)$_2$]***

(0.373g, 1mmol) of the acetylated derivative (CPCOR) was dissolved in 5% aqeous NaOH solution. This was followed by the addition of the metals: (0.125g, 0.5mmol) of $CuSO_4$. $5H_2O$ to prepare $[Cu(CPCOR)_2(H_2O)_2].3H_2O$ and (0.099g, 0.5mmol) $FeCl_2.4H_2O$ to give $[Fe(CPCOR)_2(H_2O)_2]$ in 2:1 stoichiometric ratio. The pH of each of the reaction mixture was adjusted to 8. The solution was stirred continuously for 12hours resulting in green and orange precipitates for the copper and iron complexes respectively. These were filtered, washed and dried under vacuum.

Synthesis of complexes ***[Cu(CPCOPh)$_2$]*** ***and*** ***[Fe(CPCOPh)$_2$(H$_2$O)$_2$]***

(0.435g, 1mmol) of the benzoylated derivative (CPCOPh) was dissolved in 5% aqeous NaOH followed by the addition of the metals in 2: 1 stoichiometric ratio and similar work up as given above resulted in the benzoylated complexes of the copper and iron respectively.

Antimicrobial susceptibility test

Antibacterial and antifungal activities of the ligands and their complexes were tested in

vitro using Agar diffusion method at Department of Pharmaceutical Microbiology, University of Ibadan. The prepared culture plates were inoculated with different identified laboratory strains of bacteria and a fungus such as: *Bacillus subtilis* (ATCC 39090), *Escherichia.coli* (ATCC 8739), *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa (*ATCC 7306), *Klebsiella pneumonia* (ATCC 4592), and *Candida albicans* (ATCC 10231), using streak plate method. Wells were made on the agar surface with 6mm sterile cork borer. The prepared different gradient concentrations of the complexes and the ligand were poured into the well using sterile syringe. The plates were incubated at 37 ºC ± 2 ºC for 24 hours for bacterial and 25 ± 2 ºC for 48hours for fungal activity. The plates were observed for the zone clearance around the wells. The zone of inhibition was calculated by measuring the diameter of the inhibition zone around the well (in mm) including the well diameter. The experiments were conducted in triplicates with Gentamycin and Ketoconazole being used as the reference drug (positive control) for the bacteria and fungi acitvities respectively.

RESULTS AND DISCUSSION

Complexes of Cu(II) and Fe(II) (Fig.6 &7) obtained from the reaction of the metals salts with acetylated (CPCOR)) and benzoylated (CPCOPh) ciprofloxacin derivatives (Fig.2) are stable at room temperature exhibiting variety of colours with good yields ranging from 50-91% as presented in Table1. The ciprofloxacin derivatives (CPCOR)) and (CPCOPh) decomposed at 256 ^{o}C and 273^{o}C respectively while the complexes melted in the range 257-293^{o}C above that of the derivatized ligands. They are insoluble in most solvents and but are soluble in DMSO and slightly soluble in water. The analytical data are summarized in Table1 below.

Table 1:- Analytical data for the complexes

Compound	Mol.Wt (g/mol)	Colour	% Yield	M.Pt (^{0}C)	%Metal Exp (Calc)	μ_{eff} (BM)
CPCOR	373.4	White	80	256(D)	_	_
CPCOPh	435.5	Creamy white	50	273-275(D)	_	_
$[Cu(CPCOR)_2(H_2O)_2].3H_2O$	898.3	Dark green	80	259-262	6.6 (7.0)	1.80
$[Fe(CPCOR)_2(H_2O)_2]$	836.7	Orange	91	257-260	6.2 (6.7)	4.50
$[Cu(CPCOPh)_2(H_2O)_2]$	967.4	Dark green	72	290-293	6.5 (6.6)	2.05
$[Fe(CPCOPh)_2(H_2O)_2]$	960.9	Orange	69	285-286	5.4 (5.8)	4.80

D= Decompose, CPCOR= Acetylated ciprofloxacin, CPCOPh= Benzoylated ciprofloxacin

Infra red spectra studies of synthesized compounds

The analysis of the FT-IR spectra of the acetylated **(CPCOR)** and benzoylated **(CPCOPh)** derivatives of ciprofloxacin and their complexes provided information on the coordination mode between the ligands and the metal ion. The IR data for the ligands and the complexes are given in Table 2 below while the IR spectra for neutral ciprofloxacin, the acetylated and benzoylated are as shown in Figures 3-5. The absence of bands at 1580cm^{-1} due to ν_{COO}^{-} in **(CPCOR)** acetylated and **(CPCOPh)** benzoylated ciprofloxacin derivatives (Fig.4&5) showed the destruction of the zwitterion ion character of ciprofloxacin due to the acetylation and benzoylation of secondary amine of the piperazine moiety[42]. The O-H streching bands due to hydroxyl was observed at 3540cm^{-1} and 3391cm^{-1} in (CPCOR) and (CPCOPh) respectively. All the complexes exhibit broad bands in the range of 3444–3460 cm^{-1}, which can be attributed to the presence of coordinated water molecules[43].

A strong band at 1700 cm^{-1} in (CPCOR) and 1721 cm^{-1} in (CPCOPh) due to the stretching vibrations of carboxy carbonyls ($\sqrt{}_{C=O}$ in COOH) was shifted to a lower wave number (1632-1627 cm^{-1}) in the metal complexes showing the participation of the carboxy groups in complex formation[42] . Similarly, a bathochromic shifts of the acetyl carbonyl in the form of an amide which possibly overlapped with the absorption for conjugated keto carbonyl [40] that is √(C=O) (pyridone) from 1626 cm^{-1} (CPCOR) and 1629cm^{-1}(CPCOPh) to 1591-1571 cm^{-1} upon bonding suggest coordination to the metals through the pyridone carbonyl oxygen[42,44].

The presence of new bands at about 600-589cm^{-1} assigned to M-O vibrations in the spectra of the metal complexes not observable in the ligands support the involvement of O atom in complexation of the metal ions under investigation[45].

Table 2: IR data of acetylated and bezoylated ciprofloxacin ligands and the complexes

Compounds	$\sqrt{}$ **(O-H)/H2O**	$\sqrt{}$**C-H(aliphatic)**	$\sqrt{}$**C=O (COOH)**	$\sqrt{}$**C=O (pyridone, conjugated keto)**	$\sqrt{}$**C-O**	$\sqrt{}$**C-N**	$\sqrt{}$**C-F**	$\sqrt{}$**M-O**
(CPCOR)	3593	2923,2853	1700	1626	1377	1463	1251	_
(CPCOPh)	3391	2923, 2853	1721	1629	1385	1467	1257	_
$[Cu(CPCOR)_2(H_2O)_2].3H_2O$	3444	2925,2851	1632	1574	1257	1470	1210	599
$[Fe(CPCOR)_2(H_2O)_2]$	3452	2929,2851	1631	1571	1284	1458	1253	597
$[Cu(CPCOPh)_2(H_2O)_2]$	3454	2933,2851	1629	1591	1299	1436	1257	600
$[Fe(CPCOPh)_2(H_2O)_2]$	3461	2923, 2853	1627	1586	1299	1441	1258	589

CPCOR= Acetylated ciprofloxacin, CPCOPh= Benzoylated ciprofloxacin

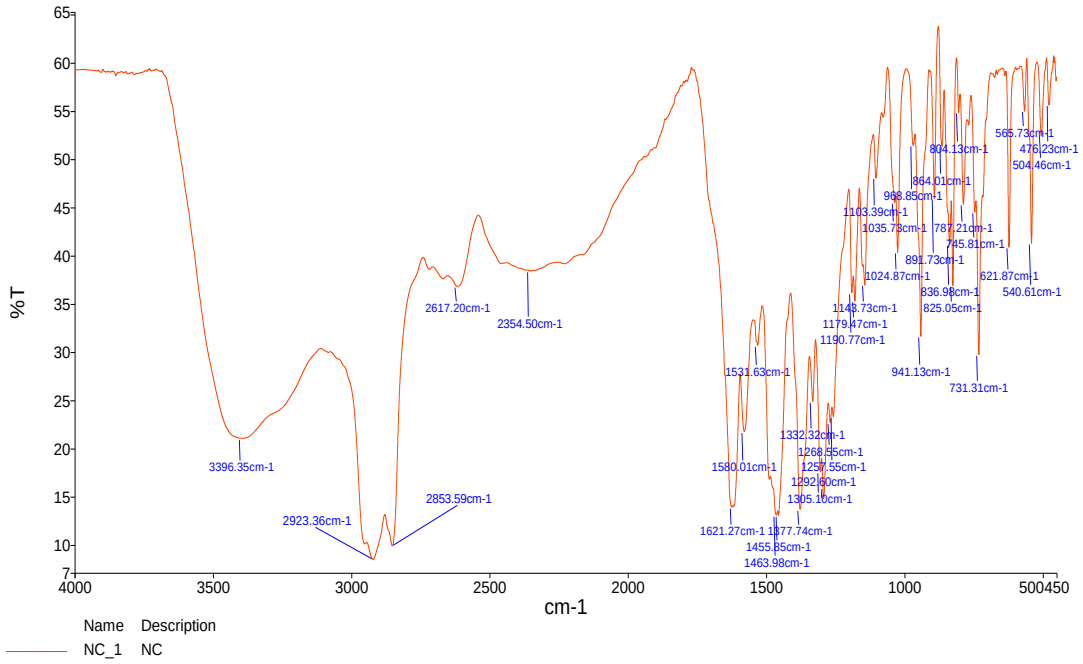


Figure 3: Infra red spectrum of neutral ciprofloxacin

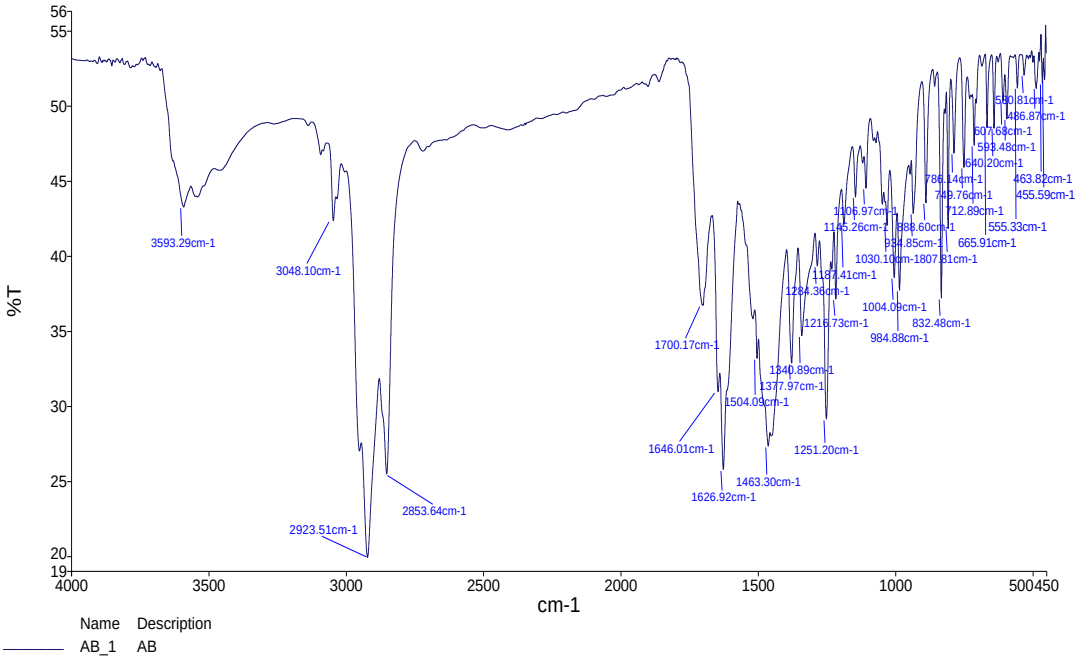


Figure 4: Infra red spectrum of acetylated ciprofloxacin (CPCOR)

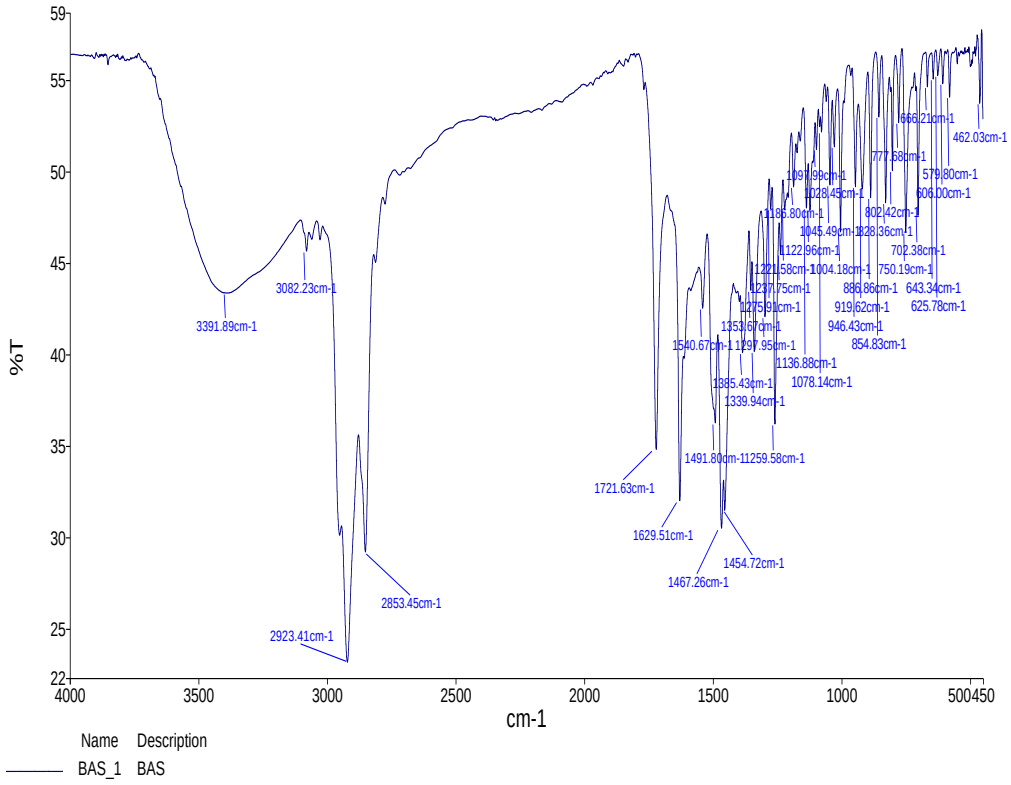


Figure 5: Infra red spectrum of benzoylated ciprofloxacin (CPCOPh)

Electronic spectra and Magnetic moments of acetylated and bezoylated ciprofloxacin ligands and the complexes

The electronic spectral absorptions of the ligand and complexes are presented in Table 3. The Intraligand absorptions of the acetylated (CPCOR) and benzoylated (CPCOPh) ciprofloxacin derivatives from 21178 -33333 cm^{-1} were assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ respectively. The iron complexes $[Fe(CPCOR)_2(H_2O)_2]$ and $[Fe(CPCOPh)_2(H_2O)_2]$ showed a single d-d electronic absorption band in the visible region expectedly at 16778cm^{-1} and 17301cm^{-1} which are typical of 6-coordinate, high spin octahedral geometry and was assigned to $^5T_{2g}$ ^5E_g. The corresponding magnetic moments of 4.5 and 4.8 observed for these complexes were complimentary of high spin octahedral geometry.

The $[Cu(CPCOR)_2(H_2O)_2].3H_2O$ complex displayed low intensity broad band in the region 16,290 - 17,200 cm^{-1} assigned as d-d bands corresponding to $^2Eg \rightarrow {}^2T_{2g}$ transition[47]. Added to this was a high intensity band in the region 26178 - 30,395 cm^{-1}. This band is due to symmetry forbidden ligand → metal charge transfer transition[48]; while the band at 45045cm^{-1}

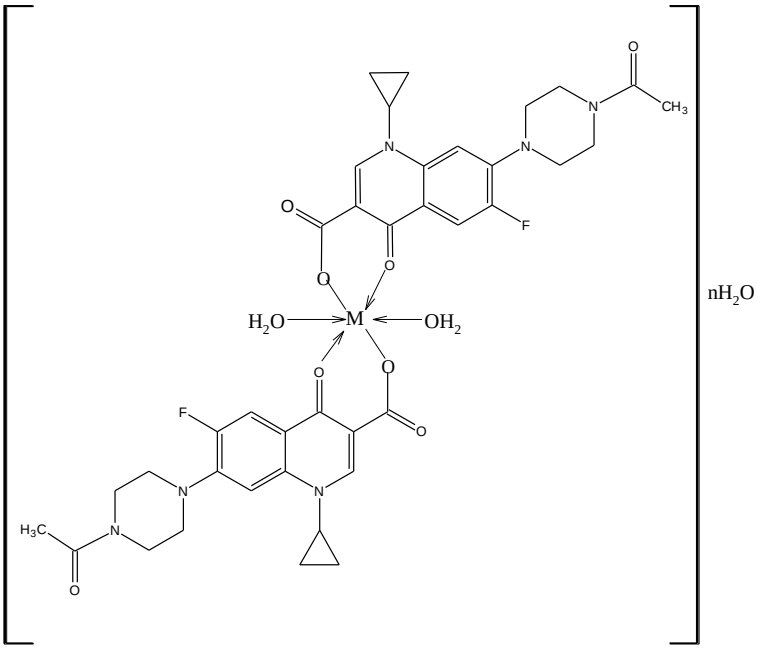
was assigned as charge transfer band. Therefore distorted octahedral geometry around was suggested on the basis of electronic spectra[49]. A moment of 1.9- 2.2 B.M. is usually observed for mononuclear copper(II) complexes regardless of stereochemistry[50]; thus, a magnetic moment of 1.8 BM of $[Cu(CPCOR)_2(H_2O)_2].3H_2O$ is complimentary of octahedral complexes.

Similarly, $[Cu(CPCOPh)_2(H_2O)_2]$ showed low energy bands at 17212cm^{-1} attributed to $^2Eg \rightarrow {}^2T_{2g}$ transition[51] expected for an octahedral configuration[52] and strong high energy bands at 39115cm^{-1} and 45120 cm^{-1} assigned to $\pi \rightarrow \pi^*$ and metal to ligand charge transfer transitions. Also, the magnetic moment value of 2.05 BM was indicative of antiferromagnetic spin-spin interaction through molecular association. Hence, the Cu (II) complexes appear to be in the octahedral geometry[53].

Table 3: Electronic spectra data of acetylated and bezoylated ciprofloxacin ligands and the complexes

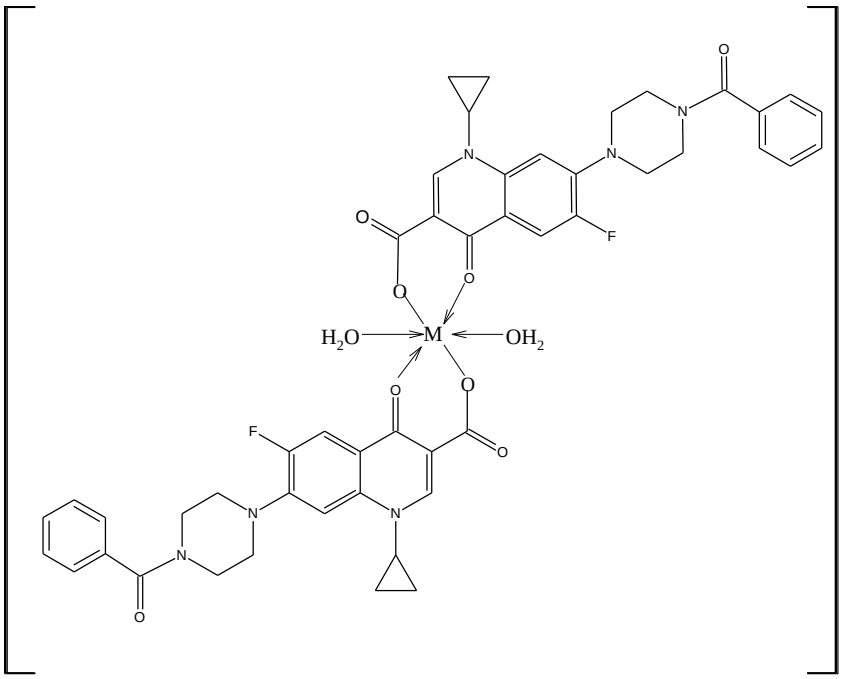
compound	UV bands (cm^{-1})	Probable transitions
(CPCOR)	33333	$\pi \rightarrow \pi^*$
	30303	$n \rightarrow \pi^*$
(CPCOPh)	31055	$\pi \rightarrow \pi^*$
	26178	$n \rightarrow \pi^*$
$[Cu(CPCOR)_2(H_2O)_2].3H_2O$	45045	CT
	30395	$\pi \rightarrow \pi^*$
	26178	$n \rightarrow \pi^*$
	17200	$^2E_g \rightarrow {}^2T_{2g}$
	17152	
	16920	
$[Fe(CPCOR)_2(H_2O)_2]$	36232	CT
	26041	$n \rightarrow \pi^*$.
	16778	$^5T_{2g} \rightarrow {}^5E_g$
$[Cu(CPCOPh)_2(H_2O)_2]$	45120	CT
	39115	$\pi \rightarrow \pi^*$
	17212	$^2E_g \rightarrow {}^2T_{2g}$
$[Fe(CPCOPh)_2(H_2O)_2]$	29525	CT
	26200	$n \rightarrow \pi^*$
	17301	$^5T_{2g} \rightarrow {}^5E_g$

CPCOR= Acetylated ciprofloxacin, CPCOPh= Benzoylated ciprofloxacin, CT= Charge Transfer



where M= Cu of Fe, n = 0 or 3

Figure 6: Proposed structure of Cu(II) and Fe(II) complexes of acetylated ciprofloxacin derivative



where M= Cu of Fe

Figure 7: Proposed structure of Cu(II) and Fe(II) complexes of benzoylated ciprofloxacin derivative

Antimicrobial studies

The derivatised ligands and their metal complexes were screened for their antimicrobial activities against *Bacillus subtilis* (ATCC 39090), *Escherichia.coli* (ATCC 8739), *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa (*ATCC 7306), *Klebsiella pneumonia* (ATCC 4592), and *Candida albicans* (ATCC 10231). The ligands as well as their complexes did not exhibit

antifungal activity against the tested fungus *Candida albicans.* Therefore only the antibacterial result is given in Table 4.

The acetylated derivative (CPCOR) showed better activity than the standard drug ciprofloxacin against *Bacillus subtilis and Pseudomonas aeruginosa; also* slightly better activity against *Klebsiella pneumonia* at all the concentrations used. In contrast the benzoylated derivative (CPCOPh) exhibited reduced activity in comparison to ciprofloxacin against all the organisms tested, this partly might be due bulkiness of phenyl moiety present in its structure compare to the less bulky methyl group in the acetylated derivative which might make it more lipophobic in character rather than lipophilic.

Generally, the metal complexes of both acetylated and benzoylated derivatives showed better activities than ciprofloxacin. The better activity of the metal complexes was due to chelation, which reduces the polarity of the metal atom and increases lipophilic character, favouring its permeation through lipid layers of the organism membrane[54]. However, the metal complexes formed from the acetylated derivative have better activities than their benzoylated counterparts.

The iron complex from the acetylated derivative $[Fe(CPCOR)_2(H_2O)_2]$ exhibited better activity than the copper complex $[Cu(CPCOR)_2(H_2O)_2].3H_2O$ from the same ligands which showed comparable activities with the acetylated ligands against *Bacillus subtilis and Staphylococcus aureus* which the iron complex$[Fe(CPCOR)_2(H_2O)_2]$ was resistant towards . On the other hand, the copper complex $[Cu(CPCOPh)_2(H_2O)_2]$ obtained from the benzoylated derivatives displayed better activity than the iron counterpart. It was observed that the iron complexes from both the acetylated and the benzoylated derivatives showed no activity against *Staphylococcus aureus;* their inactivities might be attributed probably to the nature of the microbe strain.

Table 4: Antibacterial screening of ciprofloxacin, acetylated and bezoylated ciprofloxacin ligands and their complexes

Compound/Conc	B.S	E.C	S.A	P.A	K.P
CP 100µg/ml	22±0.23	32±0.33	28±0.33	26±0.22	24± 0.25
50µg/ml	20±0.17	30±0.33	26±0.52	24±0.53	22±0.13
25µg/ml	18±0.45	22±0.66	22±0.54	22±0.33	20±0.45
+C	16±0.00	14±0.00	16±0.00	20±0.00	20±0.00
-C	-	-	-	-	-
(CPCOR)					
100µg/ml	26±1.52	28±1.73	26±0.17	30±0.33	26±0.23
50µg/ml	24±0.67	26±1.12	24±0.67	26±1.15	24±0.67
25µg/ml	16±0.22	20±0.33	22±0.67	18±0.88	22±1.13
+C	16±0.00	14±0.00	16±0.00	20±0.00	20±0.00
-C	-	-	-	-	-
(CPCOPh)					
100µg/ml	18±2.30	22±0.33	10±1.12	17±0.33	18±1.54
50µg/ml	16±0.67	18±0.88	11±0.33	13±0.93	14±0.77
25µg/ml	7±1.18	12±0.23	10±1.75	9±1.12	13±0.33
+C	16±0.00	14±0.00	16±0.00	20±0.00	20±0.00
-C	-	-	-	-	-
$[Cu(CPCOR)_2(H_2O)_2].3H_2O$					
100µg/ml	26±0.67	25±1.45	26±1.76	26±0.67	30±0.67
50µg/ml	22±0.32	16±0.23	24±0.33	24±0.67	24±0.67
25µg/ml	18±1.18	15±1.19	22±1.54	20±1.13	22±0.67
+C	16±0.00	14±0.00	16±0.00	20±0.00	20±0.00
-C	-	-	-	-	-
$[Fe(CPCOR)_2(H_2O)_2]$					
100µg/ml	30±0.24	26±1.13	-	30±1.15	32±1.23
50µg/ml	24±0.33	24±0.55	-	25±0.67	24±0.37
25µg/ml	20±0.33	24±0.78	-	24±0.33	22±0.42
+C	16±0.00	14±0.00	16±0.00	20±0.00	20±0.00
-C	-	-	-	-	-
$[Cu(CPCOPh)_2(H_2O)_2]$					
100µg/ml	26±0.37	26±2.07	26±1.17	16±0.29	25±0.65
50µg/ml	18±1.17	24±1.27	24±0.22	14±0.66	24±0.66
25µg/ml	16±0.54	16±0.56	20±1.11	12±0.45	22±0.21
+C	16±0.00	14±0.00	16±0.00	20±0.00	20±0.00
-C	-	-	-	-	-
$[Fe(CPCOPh)_2(H_2O)_2]$					
100µg/ml	20±1.45	24±0.67	-	24±0.19	28±0.33
50µg/ml	18±0.67	20±0.36	-	22±0.67	22±0.55
25µg/ml	16±0.45	20±0.25	-	22±0.65	20±0.34
+C	16±0.00	14±0.00	16±0.00	20±0.00	20±0.00
-C	-	-	-	-	-

Data are mean of three replicates (n = 3) ± standard error; *-C= DMSO, +C = Gentamycin, B.S = Bacillus subtilis, E.C = Escherichia coli, S.A = Staphylococcus aureus, P.A = Pseudomonas aeruginosa, , K.P = Klebsiella pneumonae,* CP = Ciprofloxacin, CPCOR= acetylated ciprofloxacin, CPCOPh = benzoylated ciprofloxacin.

CONCLUSION

Ciprofloxacin has been derivatised through acetylation and benzoylation at the C-7 position (N-piperazine) moiety to give (CPCOR) and (CPCOPh) the acetylated and benzoylated derivatives with enhanced biological activities. Copper and iron (II) complexes of the derivatives have been synthesized and characterised by spectroscopic methods. From the analytical and spectral data, the derivatised ligands (CPCOR) and (CPCOPh) act as bidentate ligands through the carboxy group oxygen and the pyridone carbonyl oxygen to give octahedral geometries which is slightly distorted in the acetylated copper(II) complex.

From the in-vitro antimicrobial studies. It was observed that the ligands as well as their complexes did not exhibit antifungal activity.The acetylated derivative showed better activity than ciprofloxacin while the benzoylated derivative exhibited reduced activity. However, the metal (II) complexes of both the acetylated and benzoylated derivatives showed better activities than Ciprofloxacin.

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