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Synthesis, Characterisation and Antimicrobial Studies of Metal(II) Complexes of Ofloxacin and Metronidazole

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ABSTRACT

Mixed ligands metal (II) complexes of Ofloxacin (OFL) and Metronidazole (MET) were synthesized and characterized by percentage metal analysis using complexometric titration method, infrared and electronic spectroscopies, magnetic susceptibility, melting points and conductance measurements. Infrared spectral data established that coordination was through OFL's carboxy group oxygen and the pyridone carbonyl oxygen and MET's imidazole nitrogen atom N and the hydroxyl oxygen atom of the terminal ethanol group. The magnetic susceptibility and electronic spectral data indicated that the metal (II) complexes have octahedral geometries while the low values of their molar conductance measurement suggest their non-electrolyte nature. The in-vitro antimicrobial studies were carried out against clinical strains of *Staphylococcus aureus, Enterotoxigenic Escherichia. coli, Enteropathogenic Escherichia. coli , Klebsiella pneumonia, Leclercia adecarboxylata, Morganella morganii, Salmonella typhi and* one fungus (*Trichophyton rubrum)* showed enhancement in antimicrobial activities of the free ligands through coordination to the metals as all the complexes exhibited better antimicrobial activities than the free ligands with the cobalt complex $[Co(OFL)(MET)(H_2O)_2]$ showing the best activity at the concentration of 100 µg/ml.

Keywords: Antibiotics, Metronidazole, Microorganisms, Mixed ligands, Ofloxacin

INTRODUCTION

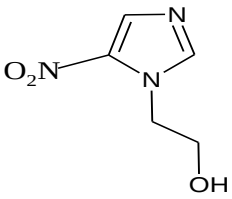
Combinations of antibiotics offer a helpful strategy to deal with the widespread emergence of antibiotic- resistant strains of microorganisms (Tyers and Wright, 2019). The recognition that no antibiotic compound is universally efficacious for all infections is an important driver in combining antibiotics in order to provide better effectiveness over individual compounds (Tyers and Wright, 2019). The fluoroquinolones are class of antimicrobial agents with a broad range of antibacterial activity against gram-negative species, but are less potent against some anaerobic pathogens and several gram-positive strains such as staphylococci and streptococci (Zhanel *et al*., 2002; Mitscher, 2005). Thus, there is a significant interest in combinations of other antimicrobial agents with fluoroquinolones to improve their antibacterial spectrum of activity in clinical situations (Acar, 2000). For example, in mixed aerobic-anaerobic infections such as aspiration pneumonia or intra-abdominal infections, in which initial therapy has to be empirical (Reller *et al.*, 2009). Metronidazole (MET) (Fig.1a) has an antibacterial spectrum that includes most anaerobes (Nguyen *et al.*, 2000). Therefore, metronidazole combination with ofloxacin (OFL) (Fig.1b) a fluoroquinolone will expand its antibacterial spectrum (Stein and Goldstein, 2006).

The complexes of antibiotics with metal ions offer great opportunities in medicine. This is probably because many drugs possess modified pharmacological and toxicological properties when they appear in the form of metal complexes (Guerra *et al*., 2016; Yu *et al*., 2016; Mohler *et al*., 2017; Nazir *et al*., 2018; Shahabadi *et al*., 2019). Thus, the use of metallo-antibiotics allows for reduction of dose introduced into the body, enhancement of bioavailability and benefiting from the pharmaceutical effects of both ligand antibiotics and metal ions (Ramotowska *et al*., 2020). Numerous studies regarding the interaction between quinolones with several metallic cations have been reported in the literature (Meggers, 2007; Gaber *et al*., 2012; Xiao *et al*., 2013). The chelation of certain metal ions through the carbonyl and carboxyl group of quinolones plays an important biological role (Park *et al.*, 2000). Ofloxacin (OFL) (Fig.1b) is a second-generation quinolone antibiotic which is currently among the most frequently used fluoroquinolone drugs (Abd-Allah *et al*., 2000; Dinakaran *et al*., 2008) with broad spectrum antibacterial activity, which acts as a specific inhibitor of bacterial DNA-gyrase, the enzyme responsible for converting double-stranded DNA into a negative super helical form (Sagdinc and Bayari, 2004). Studies of interaction between

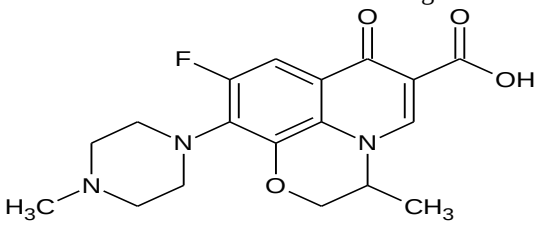
ofloxacin and several metal cations commonly found in several drugs used as antacids have been reported (Park *et al*., 2000; Macias *et al*., 2001; Macias *et al*., 2002; Turel, 2002; Serafin and Stańczak, 2009).

Similarly, metronidazole (Fig.1a) is an antibiotic from the group of nitroimidazole derivatives which is effective in the treatment of diseases caused by anaerobic bacteria (Kalinowska-Lis *et al*., 2015). It was reported that complexation of metronidazole with metals often protects it against enzymatic degradation (Athar *et al*., 2005). Also, the increase efficacy of anti-amoebic activity of metronidazole was enhanced by metal complexation with Pd(II), Pt(II), and Cu(II) (Bharti *et al*., 2002)

In a bid to expand the antibacterial spectrum of ofloxacin against anaerobic bacteria in aerobic/anaerobic clinical condition, we hereby report the synthesis, characterization, and the antimicrobial properties of metal (II) complexes of ofloxacin –metronidazole mixed ligands.



a) Metronidazole



b) Ofloxacin

Figure 1: Structure of Ligands

MATERIALS AND METHODS

Materials and reagents.

All reagents and solvents were of analytical grade and used without further purification. Ofloxacin and Metronidazole were obtained from Unique pharmaceutical, Ogun State, Nigeria and Bond Pharmaceutical Company Plc, Awe, Oyo State, Nigeria. Cobalt (II) Chloride hexahydrate, Copper (II) Sulphate pentahydrate, Manganese (II) Chloride tetrahydrate, Nickel (II) Chloride hexahydrate and Zinc (II) sulphate heptahydrate, were obtained from Aldrich chemicals.

Physical measurements

The electronic spectra of the complexes in ethanol were recorded on a Perkin-Elmer Lambda 25 Spectrophotometer and infrared spectra were recorded as nujol mull on a Perkin-Elmer BX II FT-IR spectrometer 4000–400 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, melting points were determined with Stuart SMP10 Melting point apparatus and conductivity measurement was obtained using a Labtech Digital ST3100C-F bench top conductivity meter in 1 x 10^{-3}M solutions of nitromethane. Metal analysis was determined by complexometric titration using EDTA solution, murexide indicator and ammonia/ammonium chloride buffer.

Synthesis of Metal Complexes of [M(OFL)(MET).2H2O], where M = Cu(II), Co(II), Mn(II),Ni(II) and Zn(II):

Previously reported procedures were employed with slight modification (Ogunniran *et al*., 2008; Osowole *et al*., 2015). 0.3610g (1mmole) of Ofloxacin (OFL) and 0.1711g (1mmole) of Metronidazole (MET) were dissolved in 10mL ethanol. To the mixed antibiotics solution was added (1mmole) equimolar amount of the respective metal (II) salt in 10mL ethanol. The resulting homogeneous solution was refluxed for 3 hrs and then cooled in ice. The resulting precipitate was filtered, washed with ethanol and dried over silica gel.

Antimicrobial Studies.

Antibacterial screening of the free ligands and the synthesized complexes were tested in vitro using Agar diffusion method (Chaudhary *et al*., 2003; Shahzadi *et al*., 2006). The prepared culture plates were inoculated with different identified clinical strains of gram positive and gram negative bacteria: *Staphylococcus aureus, Enterotoxigenic E. coli, Enteropathogenic E. coli, Klebsiella pneumonia, Leclercia adecarboxylata, Morganella morganii, Salmonella typhi and* one fungus (*Trichophyton rubrum).* The bacteria were cultured using the pour-plate method. From the diluted organisms (10^{-2}) 0-2ml was injected into the prepared sterile nutrient agar which was at 45ºC, then aseptically poured into sterile petri dishes, which were allowed to solidify for about 45-60minutes.

Wells were made on the agar surface (Nutrient agar) with 6mm sterile cork borer. The prepared different graded concentrations of the complexes and the ligands were poured into the well using sterile syringes. The plates were incubated at 37 ºC ± 2 ºC for 24 hours. 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 used as positive control.

Sterile Sabourad Dextrose Agar was prepared for Fungus culture, the prepared agar was poured into sterile plates in triplicates allowed to set properly. 0.2 ml of the organism ((*Trichophyton rubrum)* was spread to cover the surface of the agar. Wells were also made using sterile cork borer of 6mm in diameter, followed by the introduction of the prepared concentrations of the ligands and their complexes. The plates were left on the bench for 2hours to allow pre diffusion and then incubated at 25 ± 2 ºC for 48hours. Tioconazole was used as the reference drug.

RESULTS AND DISCUSSION

The reaction of the Ofloxacin (OFL), Metronidazole (MET) with the metal (II) salts of Mn, Ni, Co, Zn, and Cu gave varying shades of coloured complexes in low to moderate yields (20.24-95.32%) as given in the Table 1 below. The ligands, Ofloxacin (OFL) and Metronidazole (MET) melted at 250-252°C and 160-162°C respectively, whereas their metal complexes all decomposed in the range 182- 232 °C. They are insoluble in most solvents and but are soluble in DMSO and slightly soluble in ethanol. The low values of the molar conductivity of the compounds in the range 10-18 $\Omega^{-1}cm^2\ mol^{-1}$ indicate that they are non-electrolyte in solution (Golcu *et al*., 2005). The analytical data are summarized in Table1.

Table 1: Analytical data for the complexes

Compound	Mol.Wt (g/mol)	Colour	% Yield	M.Pt (^{0}C)	%Metal Exp (Calc)	μ_{eff} (BM)	^m (ohm^{-1}cm^2 mol^{-1})
Ofloxacin (OFL)	361.37	Off White	_	250-252	_	_	_
Metronidazole (MET)	171.15	Light Yellow	_	160-162	_	_	_
[Cu(OFL)(MET)(H_2O)$_2$]	630.06	Green	68.23	232*	10.02(10.07)	1.83	18
[Ni(OFL)(MET)(H_2O)$_2$]	625.21	Light Green	35.08	202*	9.42 (9.39)	2.92	17
[Co(OFL)(MET)(H_2O)$_2$]	625.45	Pink	95.32	192*	9.37 (9.42)	4.52	14
[Mn(OFL)(MET)(H_2O)$_2$]. H_2O	639.45	Yellow	87.98	182*	8.45 (8.59)	5.70	10
[Zn(OFL)(MET)(H_2O)$_2$]	631.93	White	16.24	200*	10.41(10.35)	D	13

D = diamagnetic, *= decomposition temperature, Molar conductance (^m) = ohm^{-1} cm^2 mol^{-1}, Exp = experimental, μ_{eff} = effective magnetic moments, M. Pt = melting point.

Infrared Spectra Studies of Synthesized Complexes

The relevant infrared data are presented in Table 2. IR spectra of Ofloxacin (OFL), Metronidazole (MET) and their metal complexes were studied and assigned based on careful comparison of their spectra. A strong band at 1713 cm^{-1} due to the stretching vibrations of carboxy carbonyls ($\sqrt{}_{C=O}$ in COOH) in OFL was shifted to a lower wave number (1631-1573 cm^{-1}) in the metal complexes showing the participation of the carboxy groups in complex formation (Dorofeev, 2004). Similarly, a bathochromic shift of the conjugated keto carbonyl that is √(C=O) (pyridone) from 1621 cm^{-1} in free ofloxacin to 1580-1549 cm^{-1} upon bonding suggest coordination to the metals through the pyridone carbonyl oxygen (Dorofeev, 2004; Psomas, 2008). Likewise, on comparison of the spectrum of free MET and the spectra of the complexes, the strong bands at 3215cm^{-1} attributed to O-H str vibration of the terminal ethanol group of MET disappeared in the spectra of the complexes which suggest that this group was involved in coordination (Masciocchi *et al*., 2001; Berg, 2007; Al-Khodir and Refat, 2017). The bathochromic shift of √(C=N) band of the imidazole group at 1535cm^{-1} of free metronidazole ligand to lower wave numbers (1533–1523 cm^{-1}) in the spectra of the complexes also indicate coordination through the imidazole nitrogen atom with the metal ions.

All the complexes exhibit broad bands in the range of 3300–3389 cm^{-1}, which can be attributed to the presence of coordinated water molecules (Rîmbu *et al*., 2014). The appearance of new bands at about 557-503cm^{-1} and 499-420 cm^{-1} are assigned to M-N and M-O vibrations, respectively which support the involvement of N and O atoms in complexation with metal ions under investigation (Sujarani, S and Ramu, 2015; Osowole *et al*., 2015).

Table 2: Relevant IR data of Ofloxacin and Metronidazole ligands and their complexes in cm^{-1}

Compounds	**√ (OH)/H2O**	**√C-H(aliphatic)**	**√C=O (COOH)**	**√C=O (pyridone, conjugated keto)**	**√C=N**	**√C-F**	**√M-N**	**√M-O**
Ofloxacin(OFL)	_	2923,2853(s)	1713(s)	1621(s)	_	1287(m)	_	_
Metronidazole(MET)	3215(s)	2923, 2853(s)	_	_	1535(s)	_	_	_
[Cu(OFL)(MET)$(H_2O)_2$]	3371(b)	2924,2854(s)	1622(s)	1580(s)	1523(s)	1274(m)	513(s)	476(s)
[Ni(OFL)(MET)$(H_2O)_2$]	3373 (b)	2924,2854(s)	1573(s)	1549(s)	1526(s)	1281(m)	507(s)	460(m)
[Co(OFL)(MET)$(H_2O)_2$]	3300 (b)	2923,2853(s)	1625(s)	1573(s)	1533(s)	1277(m)	557(s)	499(m)
[Mn(OFL)(MET)$(H_2O)_2$]. H_2O	3389 (b)	2924, 2854(s)	1622(s)	1579(s)	1524(s)	1278(m)	505(s)	420(s)
[Zn(OFL)(MET)$(H_2O)_2$]	3348 (b)	2923,2854(s)	1631(s)	1574(s)	1531(s)	1232(m)	503(s)	465(s)

b = broad, s = strong, m= medium

Electronic Spectra and Magnetic Moments of the Synthesised Complexes

The ultraviolet spectra of Ofloxacin (OFL) and Metronidazole (MET) were characterized by strong absorption maxima at 33670, 32258 and 30303 cm^{-1} assigned to $\pi\rightarrow \pi^*$ and $n\rightarrow \pi^*$ transitions respectively. In the metal complexes, these bands shifted to lower wave number due to coordination as presented in Table 3. The electronic absorption spectra of manganese-complex $[Mn(OFL)(MET)(H_2O)_2].H_2O$ presents three major absorptions maxima at 28571, 20000, 13123cm^{-1} which were assigned to $^6A_{1g}\rightarrow{}^4A_{1g}$, $^6A_{1g}\rightarrow{}^4T_{2g}$ and $^6A_{1g}\rightarrow{}^4T_{1g}$ transitions (Singh and Chaudhary 2004; Sreekanth, *et al*., 2006), Its room temperature magnetic moment value of 5.70 B.M in the expected range of octahedral geometry around the central metal ions (Patel *et al*., 2005; Kurmoo, 2009) further typified the existence of octahedral configuration.

The electronic spectra of the Cu(II) complexes (Table 3) showed low energy bands at 18050cm^{-1} attributed to $^2Eg \rightarrow {}^2T_{2g}$ transition(Scotti *et al*., 2015). The low-energy band in this position is expected for an octahedral configuration and strong high energy band at 42100cm^{-1} to metal to ligand charge transfer transitions (Prasad and Agarwal, 2007). Also, the magnetic moment values 1.83 BM are indicative of octhahedral configuration. Hence, the Cu (II) complexes appear to be in the octahedral geometry (Bagihalli *et al*., 2008).

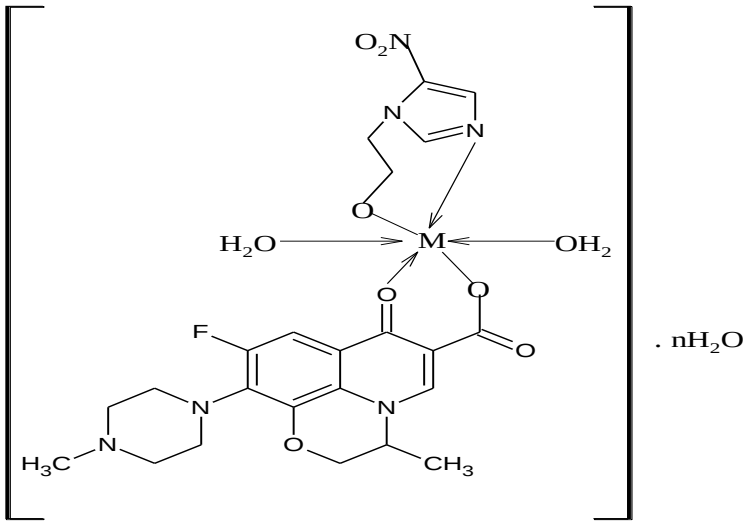
The Co(II) complex exhibited three bands at 12690, 19920 and 20661cm^{-1}, assigned to, $^4T_{1g(F)}\rightarrow {}^4T_{2g(F)}$, $^4T_{1g(F)}\rightarrow {}^4A_{2g(F)}$ and $^4T_{1g(F)}\rightarrow {}^4T_{1g(P)}$ transitions of an octahedral geometry (Osowole *et al*., 2015). An observed moment of 4.52 B.M was complimentary of this geometry. The Nickel complex $[Ni(OFL)(MET)(H_2O)_2]$ displayed two absorption bands typical of an octahedral geometry at 15151and 29411cm^{-1} which were assigned to $^3A_{2g(F)}\rightarrow{}^3T_{1g(F)}$ and $^3A_{2g(F)}\rightarrow{}^3T_{1g(P)}$ transitions respectively. Usually, square planar Ni(II) complexes are diamagnetic while octahedral and tetrahedral complexes are paramagnetic with moments in the range 2.90- 3.40 B.M and 3.50-4.10 B.M respectively. The Ni(II) complex studied in this work had a moment of 2.92 B.M. and hence have octahedral geometry (Masoud *et al*., 2008; Khann and Asnani, 2011).

The Zn(II) complex showed only the Charge transfer transitions from Metal to ligand, as no d-d transition is expected owing to its d^{10} configuration. This complex was expectedly diamagnetic and assumed a 6-coordinate octahedral geometry (Raman *et al*., 2001; Onah *et al*., 2011).

Table 3: Electronic spectra data of Ofloxacin, Metronidazole and their complexes

compound	UV bands (cm^{-1})	Probable transitions
Ofloxacin (OFL)	33670	$\pi\rightarrow \pi^*$
	30303	$n\rightarrow \pi^*$
Metronidazole (MET)	32258	$\pi\rightarrow \pi^*$
	30303	$n\rightarrow \pi^*$
$[Cu(OFL)(MET)(H_2O)_2]$	42100	CT
	31746	$\pi\rightarrow \pi^*$
	27173	$n\rightarrow \pi^*$
	18050	$^2E_g \rightarrow {}^2T_{2g}$
$[Ni(OFL)(MET)(H_2O)_2]$	32154	$\pi\rightarrow \pi^*$
	26041	$n\rightarrow \pi^*$
	15151	$^3A_{2g(F)}\rightarrow{}^3T_{1g(F)}$
	29411	$^3A_{2g(F)}\rightarrow{}^3T_{1g(P)}$
$[Co(OFL)(MET)(H_2O)_2]$	44123	CT
	31112	$\pi\rightarrow \pi^*$
	20661	$^4T_{1g(F)}\rightarrow {}^4T_{1g(P)}$
	19920	$^4T_{1g(F)}\rightarrow {}^4A_{2g(F)}$
	12690	$^4T_{1g(F)}\rightarrow {}^4T_{2g(F)}$

$[Mn(OFL)(MET)(H_2O)_2].H_2O$	30959	$\pi \rightarrow \pi^*$
	29500	$n \rightarrow \pi^*$
	28571	$^6A_{1g} \rightarrow {}^4A_{1g}$
	20000	$^6A_{1g} \rightarrow {}^4T_{2g}$
	13123	$^6A_{1g} \rightarrow {}^4T_{1g}$
$[Zn(OFL)(MET)(H_2O)_2]$	35500	CT
	31545	$\pi \rightarrow \pi^*$
	28248	$n \rightarrow \pi^*$



where M= Cu, Co, Mn, Ni, Zn and n= 0 or 1

Figure 2: Proposed Structure of Metal (II) Complexes of Mixed Ligands of Ofloxacin and Metronidazole

Antimicrobial Studies

The Ofloxacin (OFL), Metronidazole (MET) and their metal complexes were screened for their antimicrobial activities against clinical strains of *Staphylococcus aureus, Enterotoxigenic Escherichia. coli, Enteropathogenic Escherichia. coli, Klebsiella pneumonia, Leclercia adecarboxylata, Morganella morganii, Salmonella typhi and* one fungus (*Trichophyton rubrum)* The antimicrobial activities of the ligands and their metal complexes are presented in Table 4.

Generally, all the metal complexes of mixed ofloxacin- metronidazole ligands showed better activities against the tested microrganisms than the free antibiotics used. The better activity of the metal complexes was due to chelation, which reduces the polarity of the metal atom and increases lipophilic character, favoring its permeation through lipid layers of the organism membrane (Matangi *et al*., 2012). The cobalt and the manganese complexes $[Co(OFL)(MET)(H_2O)_2]$ and $[Mn(OFL)(MET)(H_2O)_2]$. H_2O exhibited the best activities at the concentrations of 100µg/ml. However, the cobalt complexes still showed appreciable activity at a lower concentration of 1µg/ml against *Staphylococcus aureus and Salmonella typhi.*

It was observed that free metronidazole did not show antibacterial activity against the tested clinical strains of microorganisms used this might be attributed to the nature of the strain and the belief that, pathogens transmitted from the hospital environment are often resistant to commonly-used antibiotics (Urszula et al., 2015). Nevertheless, it showed good activity against the fungus used *Trichophyton rubrum at 28 mm zone of inhibition*.

Table 4: Antimicrobial activities of Ofloxacin,Metronidazole ligands and their metal (II) complexes

Compound/Conc	K.P	S.A	ETEC	M.M	S.T	L.A	EPEC	T.R
Ofloxacin 100µg/ml	23±0.11	-	16±0.00	25±0.22	30±0.00	20±0.00	30±0.00	-
1µg/ml	-	-	-	-	-	-	-	-
0.01µg/ml	-	-	-	-	-	-	-	-
+C	20±0.00	14±0.00	24±0.00	10±0.00	16±0.00	26±0.00	24±0.00	28±0.00
-C	-	-	-	-	-	-	-	-
Metronidazole								
100µg/ml	-	-	-	-	-	-	-	24±0.67
1µg/ml	-	-	-	-	-	-	-	-
0.01µg/ml	-	-	-	-	-	-	-	-
+C	20±0.00	14±0.00	24±0.00	10±0.00	16±0.00	26±0.00	24±0.00	28±0.00
-C	-	-	-	-	-	-	-	-
[Cu(OFL)(MET)(H_2O)$_2$]								
100µg/ml	26±0.00	11±0.33	-	26±0.33	32±1.54	23±0.88	30±0.93	38±0.77
1µg/ml	-	-	-	-	-	-	-	-
25µg/ml	-	-	-	-	-	-	-	-
+C	20±0.00	14±0.00	24±0.00	10±0.00	16±0.00	26±0.00	24±0.00	28±0.00
-C	-	-	-	-	-	-	-	-
[Ni(OFL)(MET)(H_2O)$_2$]								
100µg/ml	24±0.67	-	-	23±0.67	-	16±0.32	30±0.23	40±0.02
1µg/ml	-	-	-	-	-	-	-	-
0.01µg/ml	-	-	-	-	-	-	-	-
+C	20±0.00	14±0.00	24±0.00	10±0.00	16±0.00	26±0.00	24±0.00	28±0.00
-C	-	-	-	-	-	-	-	-
[Co(OFL)(MET)(H_2O)$_2$]								
100µg/ml	22±0.24	30±1.13	26±0.33	25±1.15	34±1.23	23±0.33	26±0.78	34±0.42
1µg/ml	-	25±0.55	-	-	25±0.37	-	-	-
0.01µg/ml	-	-	-	-	-	-	-	-
+C	20±0.00	14±0.00	24±0.00	10±0.00	16±0.00	26±0.00	24±0.00	28±0.00
-C	-	-	-	-	-	-	-	-
[Mn(OFL)(MET)(H_2O)$_2$]. H_2O								
100µg/ml	25±0.37	12±2.07	24±1.17	28±0.29	30±0.65	26±0.22	32±0.66	20±0.66
1µg/ml	-	-	-	-	-	-	-	18±0.54
0.01µg/ml	-	-	-	-	-	-	-	-
+C	20±0.00	14±0.00	24±0.00	10±0.00	16±0.00	26±0.00	24±0.00	28±0.00
-C	-	-	-	-	-	-	-	-
[Zn(OFL)(MET)(H_2O)$_2$]								
100µg/ml	26±1.45	-	30±0.67	-	32±0.55	-	30±0.19	40±0.33
1µg/ml	-	-	-	-	-	-	-	-
0.01µg/ml	-	-	-	-	-	-	-	-
+C	20±0.00	14±0.00	24±0.00	10±0.00	16±0.00	26±0.00	24±0.00	28±0.00
-C	-	-	-	-	-	-	-	-

Data are mean of three replicates (n = 3) ± standard error; *-C= DMSO, +C(for bacteria) = Gentamycin,* +C for fungus = Tioconazole, *K.P = Klebsiella pneumonae, S.A = Staphylococcus aureus, ETEC = Enterotoxigenic Escherichia coli, M.M = Morganella morganii, S.T = Salmonella typhi, L.A = Leclercia adecarboxylata, EPEC = Enteropathogenic Escherichia coli, T.R = Trichophyton rubrum*

The inactivity of metronidazole against the bacteria was complemented by its combination with ofloxacin which exhibited good antibacterial activity but show inactivity against the fungus. The antimicrobial activities of the mixed ofloxacin-metronidazole antibiotics were certainly enhanced by coordination with metals as evidenced by the better zone of inhibitions of the complexes of 11-34mm against the bacteria and 20-40mm against the fungus which is higher than 28mm exhibited by metronidazole against the fungus *Trichophyton rubrum.*

CONCLUSION

The mixed ligands of ofloxacin and metronidazole metal (II) complexes of Copper, Cobalt, Nickel, Manganese and Zinc have been prepared and characterized by the spectroscopic methods. From the analytical and spectral data, the ligands coordinated in bidentate form to the metal ions; ofloxacin through the carboxy group oxygen and the pyridone carbonyl oxygen and metronidazole via the imidazole nitrogen atom and the hydroxyl oxygen atom of the terminal ethanol group to give octahedral geometries. Antimicrobial screening showed that coordination of the mixed antibiotic ligands to the metals leads to enhancement of their antimicrobial activities with the cobalt complex $[Co(OFL)(MET)(H_2O)_2]$ showing the best activity at the concentration of 100 µg/ml.

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