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Synthesis, characterization, antioxidant and antimicrobial activities of some Metal(II) Complexes of the Mixed-Ligands, Vitamin B_2 and Benzoic acid

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ABSTRACT

Studies on synthesis, characterization, antimicrobial and antioxidant properties of some metal(II) complexes of the mixed ligands, Vitamins B_2 (Riboflavin, HL) and Benzoic acid (HL^2), where M = Mn, Fe, Co, Ni, Cu and Zn were carried out. The conductivity measurements and percentage metal analysis confirmed that the metal complexes were covalent in DMS with the formulations $[M(HL)(HL^1)Cl_2]$ and $[M(HL)(HL^1)SO_4]$. The room temperature magnetic moments and electronic spectra measurements were corroborative of 6-coordinate, octahedral geometry for all the metal complexes. In addition, the Fe(II), Co(II) and Ni(II) complexes exhibited spin-crossover, the Mn(II) and Cu(II) complexes were dimeric and the Zn(II) complex was mononuclear. The infrared spectra data showed that the coordination in the metal complexes occurred through the hydroxy oxygen atoms in Riboflavin, and the carboxylate oxygen atoms in Benzoic acid. The antimicrobial screening of the metal complexes against *Escherichia coli*, *Proteus spp*, *Streptococcus pyogenes*, *Candida albicans*, *Salmonella sp*, *Streptococcus sp*, *Bacillus spp*, *Staphylococcus sp* and *Pseudomonas spp* revealed that the Co(II) complex had the best activity with inhibitory zones range of 7.0-20.0 mm. The antioxidant screening of the metal complexes showed that $[Cu(HL)(HL^2)Cl_2]$ had the best activity with percentage inhibition of about 50.0 which was about twice that of the standards, Ascorbic acid and α-tocopherol, proving its potentials as an anticancer agent.

Introduction

Riboflavin is a form of flavin involved in oxidation-reduction processes and thus acts as an electrophile or nucleophile (McCormick, 1997). It is also a cofactor in catalytic enzyme and a chemically versatile vitamin which acts as polydentate ligand for metal ions (McCormick, 1994; Michael *et al*., 2004; Osowole *et al*., 2014a). Furthermore, Riboflavin is important in mammals for fetus development (Ramana and Adiga, 1982; White and Memil, 1988), while its deficiency result in pellagra, mouth ulcer, and scaly skin, bloodshot and itchy eyes (Brody, 1999; McCormick, 1997).

Benzoic acid is relatively non-toxic in nature and it is useful as an analgesic, topical antiseptic and inhalant decongestants (Bindu, 2001; Wilson *et al*., 2004). Furthermore, benzoic acid and its salts are used as a food preservatives (Warth, 1991). Thus, our aims are to synthesize, characterize and investigate the magnetic properties of these novel metal(II) complexes of Riboflavin and Benzoic acid for possible magnetic interactions such as antiferromagnetism and spin-crossover; their antimicrobial and antioxidant properties will also be investigated for their potentials as broad-spectrum antimicrobial and anticancer agents *in-vitro*. This is a continuation of the research activities of our group on metal-based therapeutic agents (Osowole *et al*., 2014a; 2014b; Osowole *et al*., 2013)

Experimental

Instrumentation

The infrared and electronic spectra of the ligands and the complexes were recorded as KBr disc on a Perkin-Elmer FT-IR spectrum BX in the range 4000-400 cm^{-1}, and UVD-2960 PC scanning spectrophotometers. The percentage metal analysis was determined by complexometric titration with EDTA, while melting point and decomposition temperatures of the ligands and metal complexes were determined using Gallenkamp melting point apparatus. Electrical conductivity measurements of the complexes in DMSO were done with electrochemical analyzer consort C933 and room temperature magnetic susceptibilities at 300K were measured using Sherwood susceptibility Balance MSB Mark 1 and diamagnetic corrections were calculated using Pascal's constants.

Materials

Riboflavin(Vitamin B_2), Benzoic acid, methanol, 1,10-phenathroline, manganese(II) chloride tetrahydrate, Iron(II) tetraoxosulphate(VI) heptahydrate, Cobalt(II) chloride hexahydrate, Nickel(II) chloride hexahydrate, Copper(II) chloride dihydrate and Zinc(II) tetraoxosulphate(VI) heptahydrate were obtained from Aldrich and BDH chemicals, and were used as received, and solvents were purified by distillation.

Antimicrobial assay

Antimicrobial susceptibility tests were performed using agar diffusion technique. The surface of Muller Hinton's agar in Petri-dish was uniformly inoculated with 0.3 mL of 18 hours old test *Escherichia coli(Typed strain), Proteus mirabilis, Streptococcus pyogenes, Candida albicans, Salmonella sp, Streptococcus sp(Blood), Bacillus sp(food strain), Staphylococcus sp, Pseudomonas sp (Clinical isolate),*

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Pseudomonas sp (environmental strain), Bacillus sp (environmental strain) and *Escherichia coli (clinical strain)* cultures. 1 mmol solution of each compound in 3 mL dimethyl sulphoxide (DMSO) was added to a 6 mm well-bored unto the agar. The plates were allowed to stand on the bench for 30 minutes before incubation at 37^0C for 24 hours after which inhibitory zones were observed in mm as a measure of antimicrobial activity. The experiments were conducted in duplicates and streptomycin sulphate was used as a reference drug.

Antioxidant Assay

Ferrous ion-chelating ability

The ferrous ion-chelating ability was determined by the standard colorimetric method. 1mL of 1,10-phenantroline (50 mg in 100 mL of methanol), 1mL $FeSO_4.7H_2O$ (400 µM) and 1mL of sample solution of the same concentration (1.0 mg/mL) were mixed together and stirred mechanically for five minutes, while 2 mL of methanol was added. The resulting homogeneous solution was then incubated at room temperature for 15 minutes, after which the absorbance of the sample was read at 510 nm spectrophotometrically. The blank contained 2 mL of methanol with 1mL of 1,10-phenantroline (50 mg in 100 mL of methanol) and 1 mL $FeSO_4.7H_2O$ (400 µM) solution respectively, while α-tocopherol and ascorbic acid were used as the standards. The tests were conducted in triplicate and percentage scavenging inhibition of ferrous ion-chelating ability was expressed as:

% scavenging inhibition = *(Ac – Ae/As)/Ac x 100*

where, Ac is the Absorbance of control reaction, Ae is the Absorbance of sample solution and As is the Absorbance of standard.

Preparation of Metal complexes

0.42-0.61g (2.12 $x10^{-3}$ moles) of the hydrated metal(II) chlorides/sulphates, were added neat to a stirring 15 mL70% methanolic solution of 0.80 g (2.12 $x10^{-3}$ moles) Riboflavin (HL) and 0.29 g (2.12 $x10^{-3}$ moles) of Benzoic acid (HL^2). The resulting homogeneous, coloured solutions were buffered with triethylamine to a pH of 9, and were then refluxed for 6 hours at 50^0C. The resulting precipitates formed were filtered, washed with methanol and dried over silica gel.

$MSO_4.nH_2O + HL + HL^2 \rightarrow [M(HL)(HL^2)SO_4].aH_2O + bH_2O$ ---------- (1)

(When M = Fe{a =1, b = 5, n = 6}; Zn{ a =1, b = 6, n = 7})

$MCl_2.nH_2O + HL + HL^2 \rightarrow [M(HL)(HL^1)Cl_2].aH_2O + bH_2O$ ----------(2)

(When M = Mn, n = 4, a = 2, b = 2; Co and Ni, n = 6, a = 2, b = 4; Cu, n = 4, a = 0, b = 4)

Results and Discussion

Analytical Data

The analytical data(Table 1) showed that the ligands, Riboflavin and Benzoic acid, decomposed at 280^oC and melted in the range 120-122^{o}C respectively, whereas their metal complexes decomposed in the range 246-250 ^{o}C confirming coordination. The complexes were of good yields (60-90%), and the experimental percentage metal analysis values were very close to theoretical values, thus corroborating formulated masses.

Solubility and Molar Conductance Measurements

The ligands and the complexes were slightly soluble in methanol, ethanol, nitromethane, methylene chloride and water but were soluble in DMSO. Consequently, their molar conductances were done in DMSO and values in the range of 8.89-12.52 $\Omega^{-1}cm^2mol^{-1}$ were obtained, indicating their covalent nature (Refat *et al*., 2013).

Infrared Spectroscopy

The relevant infrared data are presented in Table 2. The band at 3496 cm^{-1} in Riboflavin(HL) was assigned as *ν*(N-H) band. On coordination, this band remained un-shifted in the spectra of the metal(II) complexes indicating non-coordination of the imine group's nitrogen to the metal ions. The broad bands at 3377 cm^{-1} and 3452 cm^{-1} in Riboflavin (HL) and Benzoic acid (HL^2) were assigned as *ν*(O-H) stretching vibration. On coordination, these bands shifted to 3370-3441 cm^{-1} in the spectra of the metal(II) complexes indicating the coordination of the hydroxy oxygen atoms to the metal(II) ions(Khan and Asnani,2011). The carbonyl (C=O) vibrations at 1733 cm^{-1} and 1687 cm^{-1} (Tharmaraj *et al*., 2009; Ispir *et al*., 2005) in Riboflavin (HL) and Benzoic acid (HL^2) remained un-shifted in Riboflavin(HL) showing non-coordination of the carbonyl oxygen atom of the Riboflavin (HL) to the metal ions. However, this band shifted to 1621-1622 cm^{-1} in Benzoic acid (HL^2) indicative of coordination of the carbonyl oxygen atom in Benzoic acid (HL^2) to the metal ions. The azomethine, *ν*(C=N) vibration at 1581, 1546 and 1649 cm^{-1} in Riboflavin (HL) remains un-shifted in the metal(II) complexes indicative of non-coordination of imine nitrogen atom to the metal(II) ions. The bands due to *ν*(M-Cl), *ν*(M-N) and *ν*(M-O) were observed in the range 361-328 cm^{-1}, 596-501 cm^{-1} and 486-409 cm^{-1} respectively. These bands were absent in the spectra of the Riboflavin (HL) and Benzoic acid (HL^2), because the ligands were free of metal ions (Gulcan *et al.*, 2012, PooNam *et al.*, 2010, Reddy and Reddy, 2000; Pessoa *et al*.,1999).

Electronic Spectra and Magnetic moments

The metal-free ligand bands were observed at 27.32- 29.41 kK and 30.68- 32.79 kK and were assigned to $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ transitions respectively (Table 2). The Mn(II) complexes showed two absorption bands at 17.33 kK and 25.32 kK typical of low spin octahedral geometry and were assigned to $^2T_{2g}\rightarrow{}^2A_{1g}$ and $^2T_{2g}\rightarrow{}^2B_{1g}$ transitions respectively. An observed room temperature moment of about 2.0 B.M was reported for low spin Mn(II) (Conplate and Kaya, 2004). However, the Mn(II) complex has a moment of 1.05 B.M which indicated antiferromagnetism operating through a M-M bond in a dimeric structure (Saha, 2000).

The Fe(II) complex had two absorption bands at 11.67 kK and 22.42 kK typical of a spin-cross over system, and were assigned as $^5T_{2g}\rightarrow{}^5E_g$ and $^1A_{1g}\rightarrow{}^1T_{1g}$ transitions. An observed moment of 3.61 B.M was complimentary of equilibrium between high spin ↔ low spin (spin-crossover) octahedral geometry (Salmon *et al*., 2009).

Similarly, the Co(II) complexes exhibited bands at 15.12 kK and 25.64 kK which was typical of a spin-cross over system and were assigned to $^4T_{1g}(F)\rightarrow{}^4A_{2g}(F)$ and $^1A_{1g}\rightarrow{}^1T_{2g}$ respectively. Moments in the range 2.2 -2.4 B.M are expected for low spin octahedral Co(II) complexes. However, a magnetic moment of 4.42 B.M was observed, which was corroborative of equilibrium between high spin and low spin octahedral geometry, *that is*, spin-cross over (Gasper *et al*., 2001).

The Ni(II) complexes showed two absorption bands at 17.33 kK and 25.38 kK typical a spin-cross over system and were assigned to $^3A_{2g}\rightarrow{}^3T_{1g}(F)$ and $^1A_{1g}\rightarrow{}^1B_{2g}$ transitions of 6-coordinate high spin and low spin octahedral geometry. Room temperature magnetic moments in the range 2.8-3.3 B.M were reported for high spin octahedral Ni(II) while low spin Ni(II) were diamagnetic. However, an observed moment of 0.51 B.M corroborated spin-crossover, *that is*, equilibrium between high spin and low spin octahedral geometry (Ma *et al*., 2011).

Table 1. Analytical data of ligands and their metal(II) complexes

Complexes	Formula Mass	Colour	μ_{eff} (B.M)	M.pt(^oC)	%Yield	%M(Exp)
HL	376.36	Orange	D	280(D)	-	-
HL^2	122.12	white	D	120-122	-	-
$[\{Mn(HL)(HL^2)\}_2Cl_2].2H_2O$	1213.82	Orange	1.05	250(D)	60	8.32 (8.18)
$[Fe(HL)(HL^2)SO_4].H_2O$	668.33	Yellow	3.61	250(D)	80	8.36 (8.31)
$[Co(HL)(HL^2)Cl_2].2H_2O$	664.41	Yellow	4.42	246 (D)	80	8.87 (8.76)
$[Ni(HL)(HL^2)Cl_2].2H_2O$	664.17	Orange	0.51	250(D)	60	8.84 (8.73)
$[\{Cu(HL)(HL^2)\}_2Cl_2]$	1194.96	Orange	3.42	250(D)	90	9.49 (9.46)
$[Zn(HL)(HL^2)SO_4].H_2O$	677.85	Yellow	0.15	250(D)	70	9.64 (9.73)

M = Metal; Exp = Experimental; HL = Riboflavin; HL^2 = Benzoic acid; M.pt = Melting point; D = Decomposition temperature

Table 2. Electronic and infrared spectral data of the ligands and their metal complexes

Compound	*v*N-H	*v*OH	*v*C=O	*v*C=N	*v*M-N	*v*M-O	*v*M-Cl	Absorption Bands (kK)
HL	3496(w)	3377(b)	1733(s)	1581(s) 1546(s) 1649(s)	-	-	-	29.41 32.79
HL^2	-	3452(b)	1687(s)	-	-	-	-	27.32 27.86 29.24 30.68
$[\{Mn(HL)(HL^2)\}_2Cl_2].2H_2O$	3497(w)	3370(b)	1621(s) 1733(s)	1546(s) 1581(s) 1649(s)	502(m) 571(m) 596(w)	410(m) 448(s) 486(m)	373(s)	17.33 25.32 27.40
$[Fe(HL)(HL^2)SO_4].H_2O$	3496(w)	3402(b)	1621(s) 1732(s)	1547(s) 1580(s) 1649(s)	501(s) 572(s) 596(s)	409(s) 449(s) 485(m)	377(m) 361(m)	11.67 22.42 29.76
$[Co(HL)(HL^2)Cl_2].2H_2O$	3497(w)	3393(b)	1622(s) 1733(s)	1546(s) 1580(s) 1648(s)	502(m) 571(m) 596(w)	409(m) 448(s) 486(m)	377(m) 361(m)	15.12 25.64 29.33
$[Ni(HL)(HL^2)Cl_2].2H_2O$	3496(w)	3382(b)	1732(s) 1622(s)	1648(s) 1581(s) 1546(s)	501(s) 571(s) 595(s)	409(s) 448(s) 486(m)	374(m)	17.33 25.38 29.67
$[\{Cu(HL)(HL^2)\}_2Cl_2]$	3495(w)	3441(b)	1621(s) 1732(s)	1594(m) 1581(s) 1649(s)	502(m) 571(m) 596(w)	409(m) 448(s) 486(m)	376(m) 361(m)	18.80 25.13 29.41
$[Zn(HL)(HL^2)SO_4].H_2O$	3498(w)	3386(b)	1622(s) 1733(s)	1649(s) 1581(s) 1546(s)	596(m) 572(s) 502(m)	486(m) 448(s) 409(m)	376(s)	25.64 29.67

b = broad, s = strong, w =weak, m = medium, HL = riboflavin, HL^2 = benzoic acid, 1kK = 1000 cm^{-1}

Table 3. Antimicrobial activities of the ligands and their metal complexes (mm)

Complexes / Organisms	$[\{Mn(HL)(HL^2)\}_2Cl_2].2H_2O$	$[Fe(HL)(HL^2)SO_4].H_2O$	$[Co(HL)(HL^2)Cl_2].2H_2O$	$Ni(HL)(HL^2)Cl_2].2H_2O$	$[\{Cu(HL)(HL^2)\}_2Cl_2]$	$[Zn(HL)(HL^2)SO_4].H_2O$	HL	HL^2	Streptomycin Sulphate
E.coli ^{T}	R	R	R	5.0±0	5.0±0	7.0±0	R	5.0±0	9.0±0
S. pyogenes	11.0±0	10.0±0	7.0±0	R	5.0±0	R	R	R	17.0±0
Proteus sp	15.0±0	10.0±0	8.0±0	R	5.0±0	7.0±0	9.0±0	7.0±0	11.0±0
C. albicans	R	R	R	7.0±0	9.0±0	7.0±0	13.0±0	9.0±0	11.0±0
Salmonella sp	10.0±0	R	7.0±0	R	7.0±0	7.0±0	7.0±0	5.0±0	8.0±0
Streptococcus sp ^{B}	17.0±0	15.0±0	11.0±0	R	R	R	7.0±0	7.0±0	R
Bacillus sp ^{F}	3.0±0	6.0±0	7.0±0	R	8.0±0	5.0±0	R	6.0±0	8.0±0
Staphylococcus sp	R	R	20.0±0	R	10.0±0	11.0±0	R	R	19.0±0
Pseudomonas sp ^{C}	9.0±0	9.0±0	9.0±0	10.0±0	7.0±0	R	9.0±0	7.0±0	21.0±0
Pseudomonas sp ^{E}	R	R	R	R	R	10.0±0	R	R	R
Bacillus sp ^{E}	7.0±0	9.0±0	9.0±0	6.0±0	R	6.0±0	R	7.0±0	27.0±0
E.coli ^{C}	R	11.0±0	15.0±0	R	R	R	R	15.0±0	20.0±0

HL = Riboflavin, HL^2 = Benzoic acid, T= typed strain, C= Clinical, F = Food, E = Environmental, R= Resistant

Table 4. Antioxidant data of ligands and their metal(II) complexes

Complex	Absorbance(error) nm	% Inhibition(error)
$[\{Mn(HL)(HL^2)\}_2Cl_2].2H_2O$	0.29(0.007)	24.43(0.47)
$[Fe(HL)(HL^2)SO_4].H_2O$	0.50(0.004)	40.06(0.30)
$[Co(HL)(HL^2)Cl_2].2H_2O$	0.48(0.003)	38.64(0.18)
$[Ni(HL)(HL^2)Cl_2].2H_2O$	0.39(0.003)	31.32(0.22)
$[\{Cu(HL)(HL^2)\}_2Cl_2]$	0.67(0.000)	54.20(0.28)
$[Zn(HL)(HL^2)SO_4].H_2O$	0.38(0.002)	30.72(0.13)
A_1	0.41(0.001)	33.36(0.05)
α_I	0.41(0.002)	33.19(0.17)

HL=Riboflavin; HL^2= Benzoic acid; A_1= ascorbic acid; α_I-tocopherol

The Zn(II) complex had only charge transfer transition from metal to ligand at 25.64 kK as no d-d transition is expected. The complex was essentially diamagnetic with a moment of 0.15 B.M (Nagagbu *et al*., 2006).

The Cu(II) complex exhibited two transition at 17.33 kK and 25.38 kK, typical of a 6-coordinate, trigonal (octahedral) geometry and were assigned to $^2B_{1g} \rightarrow {}^2B_{2g}$ and $^2B_{1g} \rightarrow {}^2E_g$ transitions (Osanai *et al*., 2006). An observed moment of 3.42 B.M was indicative of a dimeric structure with bridging Chloride(Figure 1) since moments in the range 1.7-2.2 B. M were reported for mononuclear Cu(II) complexes regardless of geometry (Gulcan *et al*., 2012).

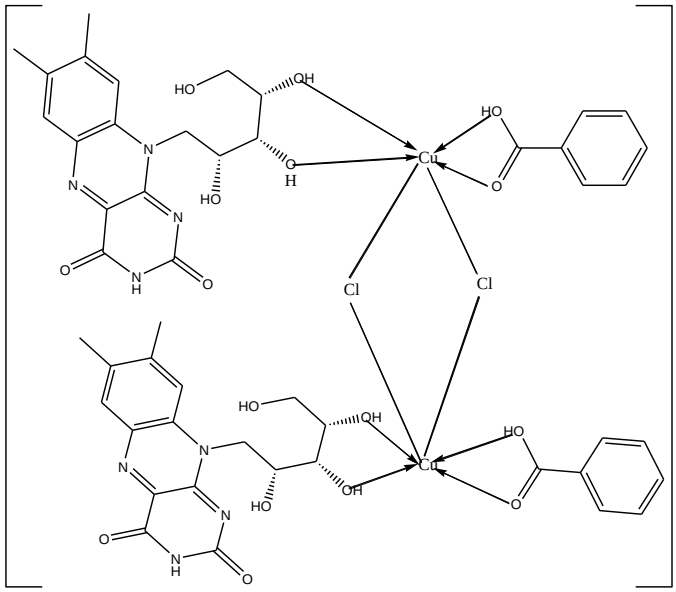

Figure 1: Proposed structure for the Cu(II) Complex

Antimicrobial activities

The antimicrobial activities of the metal(II) complexes of Riboflavin (HL) and Benzoic acid (HL^2) against different clinical, food and environmental isolates are presented in Table 3. Benzoic acid (HL^2), Ni(II), Cu(II), Zn(II) complexes, and Streptomycin (positive control) were active against *E. coli (Typed strain)* with inhibitory zone range of 5.0-9.0 mm. *Streptococcus pyogenes* was inhibited by Streptomycin (positive control), Mn(II), Fe(II), Co(II), Cu(II) complexes with inhibitory zones range of 5.0-17.0 mm. Interestingly, all the metal complexes, Riboflavin and Benzoic acid were active against *Proteus sp* with the exception of Ni(II) complex with the inhibitory zones range of 5.0-15.0 mm. Riboflavin (HL), Benzoic acid (HL^2), Ni(II), Cu(II), Zn(II) complexes and Streptomycin (positive control) were active against *Candida albicans* with an inhibitory zones range of 7.0-13.0 mm. It is noteworthy that all the complexes were active against *Salmonella sp* with inhibitory zones range of 5.0-10.0 mm with the exception of Fe(II) and Ni(II) complexes. The *Streptococcus sp* (blood) was inhibited by all the metal complexes with the exceptions of Ni(II), Cu(II), Zn(II) complexes and Streptomycin with inhibitory zones range 7.0-17.0 mm. Furthermore, Riboflavin (HL) and Ni(II) complex were inactive against *Bacillus sp(food)* but the remaining metal complexes had activity with inhibitory zones range of 3.0-8.0 mm. Co(II), Cu(II), Zn(II) complexes and Streptomycin (positive control)) were active against *Staphylococcus sp* with inhibitory zones range of 10.0-20.0 mm. Interestingly, only Zn(II) complex was active against the *Pseudomonas sp* (environmental) with an inhibitory zone of 10.0 mm. In contrast, all the metal(II) complexes were active against *Pseudomonas sp(clinical)* with the exception of Zn(II) complex with inhibitory zones range of 6.0-21.0 mm. The environmental strain of *Bacillus sp* was inhibited by virtually all the metal complexes with the exceptions of Cu(II) complex and Riboflavin (HL) with inhibitory zones range of 6.0-27.0 mm. Furthermore, the clinical strain of *E. coli* was inhibited by Benzoic acid, Streptomycin(positive control), Fe(II) and Co(II) complexes, with inhibitory zones range of 11.0-20.0 mm.

Generally, the inhibition of some of the microorganisms by the metal complexes may be due to their lipophilic nature which facilitates easy penetration into membrane of the organisms. Thus, stopping protein production by blocking the active sites of enzymes which in turn interfere with respiratory process of the cell (Carman *et al*., 2009; Padmaja *et al*., 2011).

Ferrous ion chelating activity

The antioxidant activities of metal(II) complexes are presented in Table 4. The ferrous ion chelating ability of the compounds showed that the Cu(II) complex had the best inhibitory activity of 54.20 percent which was better than the standard antioxidants, ascorbic acid and α-tocopherol, with percentage inhibitions of 33.36 and 33.19 respectively. Thus, proving it's potentials as an anticancer agent. The decreasing order of antioxidant potentials of the metal complexes was Cu(II)>>>Fe(II)~Co(II)>Ni(II)~Zn(II)>>Mn(II).

Conclusion

The ligands, Riboflavin and Benzoic acid, coordinated to the metal(II) ions (Mn, Fe, Co, Ni, Cu and Zn) using the hydroxy oxygen and carboxylate oxygen atoms respectively. The complexes assumed 6-coordinate octahedral geometry as supported by the room temperature magnetic moments and solid reflectance spectra. Furthermore, the antimicrobial studies showed that the metal(II) complexes had lower activity in comparison to the standard(streptomycin) against almost all the organisms with the exception of *Streptococcus sp and Pseudomonas sp(environmental*. The antioxidant activity of the metal(II) complexes showed that the Cu(II) complex had the best activity being about twice that of the standards – ascorbic acid and α-tocopherol.

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