

## SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITIES OF HETEROLEPTIC METAL CHELATES OF ISONIAZID AND 2,2'-BIPYRIDINE

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**ABSTRACT.** The Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes of isoniazid ( $L_1$ ) mixed with 2,2-bipyridine ( $L_2$ ) were synthesized and characterized by solubility studies, percentage metal analysis, UV-Vis spectroscopy, IR spectroscopy, conductivity measurements and magnetic moment measurements. The IR spectra revealed that the isoniazid coordinated as a bidentate ligand. In Co(II) and Ni(II) complex it coordinated via the carbonyl oxygen (C=O) and the amide nitrogen, while in the Cu(II), Mn(II) and Zn(II) complexes it coordinated using the amide and carbonyl oxygen via enolization. Bipyridine also bonded to the metals as a bidentate ligand through the pyridinic nitrogen atoms. The magnetic data showed that all the complexes were paramagnetic with values ranging from 1.70 to 5.0 B.M., except  $[Zn(Is)(Bipy)(H_2O)Cl_2]$  which was diamagnetic. The conductivity results revealed that the Cu(II), Mn(II), Zn(II) complexes were 1:1 electrolytes while Co(II) was 1:2 electrolyte and  $[Ni(Is)(Bipy)Cl_2]$  was non-electrolytic in nature. The antibacterial activities of the ligands and the complexes as evaluated via the agar diffusion method showed that the complexes displayed moderately high antimicrobial activity in comparison with the free ligands when tested against ten strains of bacteria.

**KEY WORDS:** Isoniazid, Electronic structure, Geometry, Antimicrobial activity, Electrolytic nature, Magnetic moment

### INTRODUCTION

Isoniazid also known as isonicotino-hydrazide is a widely known drug used in the treatment of tuberculosis. It is always administered in combination with other drugs such as ethambutol, and pyrazinamide. Isoniazid acts as an antituberculosis drug by inhibiting the production of mycolic acid [1]. Apart from its use in the treatment of tuberculosis, it is recommended as a prophylaxis therapy for HIV patients having a PPD reaction of 5 mm [2]. Due to its ability to form hydrazones with ketones, it is used in chromatography to show distinctions between the various degrees of conjugation in organic compounds that possess a ketone group [3].

Isoniazid has been widely reported to form metal complexes that are relatively stable [4-6]. Interestingly some of these complexes have been reported to exhibit significant activity against several stains of *M. tuberculosis* including the resistant strains [6-8].

Reports on the studies of the complexes of isoniazid have shown that Fe(II) and Cu(II) complexes of isoniazid possess significant potential for the treatment of tuberculosis than the drug [9]. The synthesized complexes of isoniazid have been characterized and reported to possess both octahedral and tetrahedral geometries [10, 11]. The synthesis and characterization of the mixed ligand complexes of isoniazid have been carried out [12], and their antimicrobial activity has been reported [13]. The studies have shown that the mixed ligand complexes had more activity on the micro-organisms than the free ligand.

However, reports on the synthesis, characterization and antibacterial activity of the Co(II), Ni(II), Cu(II), and Zn(II), Mn(II) mixed ligand complexes of isoniazid with 2,2-bipyridine has not been reported, the results of this study are herein reported.

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## EXPERIMENTAL

### *Reagents and solvents*

All the chemicals and solvents (isoniazid, 2,2-bipyridine, methanol, copper(II) chloride dihydrate, manganese(II) chloride tetrahydrate, cobalt(II) chloride hexahydrate, and nickel(II) chloride hexahydrate) used in the study were obtained from Bond Pharmaceutical and BDH and used without further purification. The percentage metal content was determined by complexometric titration using EDTA and atomic absorption spectroscopy (AAS). The infrared spectra were recorded in the 4000–400  $\text{cm}^{-1}$  region with a Shimadzu FT-IR 8000 spectrophotometer using KBr pellets. UV-Visible spectra of the samples were measured in the range 800–200 nm using a Shimadzu UV-Vis 1800 spectrophotometer. Magnetic susceptibility measurements were carried out at room temperature using a Sherwood Scientific MXI model Gouy magnetic balance. Melting points of the compounds were determined using a Gallenkamp melting point apparatus.

### *Synthesis of mixed ligand complexes*

Solutions of each of the metal salts (1 mmol of  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ ,  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ ,  $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ ,  $\text{ZnCl}_2$ ,  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ) in 5 mL of methanol was added into stirring homogenous solution of isoniazid (1 mmol) and 2,2'-bipyridine (1 mmol) in 10 mL methanol. The solution was stirred for one hour at room temperature, during which precipitate was formed. The product was filtered, washed with methanol and dried over anhydrous calcium chloride.

### *Antimicrobial study*

The biological activities of the synthesized ligands and their metal complexes have been studied for their antimicrobial activities. These microorganisms include typed cultures of National Collection of Industrial Bacteria (NCIB) and locally isolated organism (LIO). The bacterial strains were: Gram positive: *Bacillus cereus*, *Staphylococcus aureus*, *Proteus vulgaris*, *Vibrofuminisi*, *Clostridium sporogenes*. The Gram negative bacteria include, *Escherichia coli*, *Pseudomonas aeruginosa*, *Pseudomonas flourescens*, *Klebsiella pneumoniae*, *Microoccus luteus*. Nutrient broth (biomark) and nutrient agar (rapid lab) were used for sub-culturing the organisms while Mueller-Hinton agar (LAB M) was used for sensitivity testing. The media were sterilized using autoclave at 121 °C and 1.05  $\text{kg/cm}^3$  for 15 min.

The bacterial strains used in the experiment were sub-cultured into nutrient broth and incubated at 37 °C for 18 h. The organisms were stored on sterile nutrient agar slants in McCartney bottles and sub-cultured at three months' interval to maintain them for further use.

The sensitivity testing of the compounds were determined using agar-well diffusion method [14], with some modification. The bacterial strains were first grown in nutrient broth for 18 h before use. About 0.2 mL of the standardized test isolates (108 cfu/mL or 0.5 McFarland standard) was then sub-cultured into Mueller-Hinton agar (LAB M). Wells were then bored into the agar medium using a sterile 6mm cork borer. The wells were then filled up with prepared solutions of the complex. Care was taken not to allow solutions to spill on the surface of the medium. The plates were allowed to stand on the laboratory bench for about 1-2 h to allow for proper in flow of the solution into the medium before incubating the plate in an incubator at 37 °C for 24 h. The plates were later observed for zones of inhibition, and the effects of the extract on bacterial strains were compared with that of standard antibiotic, ampicillin.

## RESULTS AND DISCUSSION

*Physicochemical parameters*

The precursor  $MCl_2 \cdot xH_2O$  reacted with 2,2'-bipyridine (Bipy) and isoniazid (Is) in methanol to afford  $[M(\text{bipy})(\text{Is})(\text{H}_2\text{O})\text{Cl}]\text{Cl}$ . The six complexes presented here are in octahedral molecular geometry surrounding the metal center according to magnetic moment measurement and spectroscopic studies. A representation of the synthetic route employed is shown in Scheme 1. The synthesis was carried out at room temperature under constant magnetic stirring. The physicochemical properties of the synthesized complexes are shown in Table 1. The mixed ligand complexes showed high melting points and a variety of colors ranging from greenish yellow to light pink except for the zinc complex which was whitish in color. The complexes displayed high melting points and that suggests high thermal stability.

The theoretical %metal content in the mixed ligand complexes of isoniazid with 2,2'-bipyridine showed a good correlation with the experimental values. All the complexes synthesized are soluble in water, while they show varying degrees of solubility in the five common solvents. The solubility of all the complexes in water suggests that they are ionic in nature. The molar conductivity of Cu(II), Zn(II), Mn(II) complexes are within the range of 92.00 to 130.00  $\Omega^{-1}\text{cm}^2\text{mol}^{-1}$  depicting that they are 1:1 electrolytes while Co(II) complexes is a 1:2 electrolyte [15]. The molar conductivity of the Ni(II) complexes suggests that it is a non-electrolyte.

Table 1. Physical properties and analytical data for compounds.

Compound	Formula (FW)	Colour	Melting point ( $^{\circ}\text{C}$ )	% metal found (calc)	$\Lambda_m \Omega^{-1}\text{cm}^2\text{mol}^{-1}$
Isoniazid	$\text{C}_7\text{H}_9\text{ON}_2$ (138.167)	White	171	-	-
2,2'-Bipyridine	$\text{C}_{10}\text{H}_8\text{N}_2$ (156.184)	White	70 – 72	-	-
$[\text{Mn}(\text{Is})(\text{Bipy})(\text{H}_2\text{O})\text{Cl}]\text{Cl}$	$\text{MnC}_{17}\text{H}_{20}\text{ON}_4\text{O}_2\text{Cl}_2$ (438.210)	Yellow	>350	12.60 (12.54)	133.90
$[\text{Co}(\text{Is})(\text{Bipy})_2]\text{Cl}_2 \cdot \text{H}_2\text{O}$	$\text{CoC}_{27}\text{H}_{26}\text{N}_6\text{OCl}_2$ (580.374)	Reddish Brown	226-234	9.94 (9.85)	147.90
$[\text{Ni}(\text{Is})(\text{Bipy})\text{Cl}_2] \cdot \text{H}_2\text{O}$	$\text{NiC}_{17}\text{H}_{20}\text{ON}_4\text{O}_2\text{Cl}_2$ (441.966)	Green	>350	13.52 (13.28)	64.10
$[\text{Cu}(\text{Is})(\text{Bipy})(\text{H}_2\text{O})\text{Cl}]\text{Cl}$	$\text{CuC}_{17}\text{H}_{20}\text{N}_4\text{O}_2\text{Cl}_2$ (446.818)	Greenish Yellow	298-301	14.50 (14.22)	97.80
$[\text{Zn}(\text{Is})(\text{Bipy})(\text{H}_2\text{O})\text{Cl}]\text{Cl}$	$\text{ZnC}_{17}\text{H}_{20}\text{N}_4\text{O}_2\text{Cl}_2$ (448.652)	White	>350	14.70 (14.57)	92.00

*Infrared spectroscopy*

Infrared spectra of the complexes are shown in Figure 1. Table 2 shows the significant absorption bands for the free ligands; isoniazid and 2,2'-bipyridine and their Cu(II), Mn(II), Co(II), Zn(II), and Ni(II) complexes. Comparison of the infrared spectra of the free ligands with that of the metal complexes provided an evidence of coordination.

The bands due to the amino group in the isoniazid ( $3340\text{ cm}^{-1}$ ,  $3214\text{ cm}^{-1}$ ), carbonyl group ( $1669\text{ cm}^{-1}$ ) and N-H bend ( $1493\text{ cm}^{-1}$ ) are displayed. The data from the infrared spectra of the ligand and the complexes depicts that isoniazid acted as a bidentate ligand, which is in agreement with earlier reports [8]. In amides, coordination through the carbonyl oxygen results in a negative shift of the C=O stretching frequency [7, 14]. This was observed in the Co and Ni complexes which showed C=O stretching frequencies at  $1649$  and  $1651\text{ cm}^{-1}$  as against the C=O stretching vibration.

The disappearance of the C=O band at  $1669\text{ cm}^{-1}$  and subsequent appearance of the enolic C-O stretching band at  $1055$ ,  $1059$ ,  $1063\text{ cm}^{-1}$  for the Mn(II), Cu(II) and Zn(II), respectively, indicates enolization thus isoniazid coordinated to the metals via the enol oxygen [16]. There was an appearance of new bands at  $627$ - $637$  and  $415$ - $419\text{ cm}^{-1}$  which are due to M-O and M-N bands, respectively [10]. The appearance of a broad O-H band at wave numbers from  $3403\text{ cm}^{-1}$  to  $3460\text{ cm}^{-1}$ , depicts the presence of water molecule in the complexes.

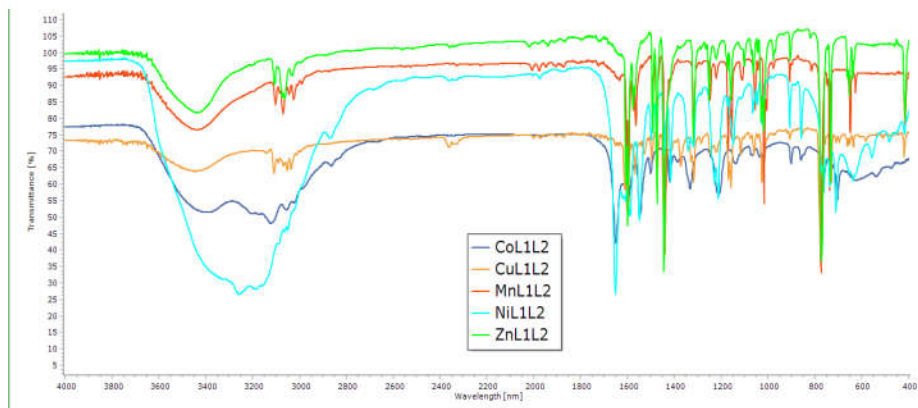


Figure 1. Infrared spectra of the complexes:  $\text{CoL}_1\text{L}_2$ ,  $\text{CuL}_1\text{L}_2$ ,  $\text{MnL}_1\text{L}_2$ ,  $\text{NiL}_1\text{L}_2$ ,  $\text{ZnL}_1\text{L}_2$ .

Table 2. Some relevant infrared spectra data ( $\text{cm}^{-1}$ ) of mixed ligand complexes of isoniazid.

Frequency/ Compound	$\nu(\text{OH})$	$\nu(\text{NH}_2)_{(a)}$ $\nu(\text{NH}_2)_{(s)}$	$\nu(\text{NH})$	$\nu(\text{C}=\text{O})$	$\nu(\text{C}-\text{O})$	$\nu(\text{NH})_{(b)}$	$\nu(\text{M}-\text{O})$	$\nu(\text{M}-\text{N})$
Is	3431	3304 3214	3113	1669		1493	-	-
Bipy	-	-	-	-		-	-	-
$\text{MnL}_1\text{L}_2$	3441	-	3100	-	1055	1490	627	415
$\text{CoL}_1\text{L}_2$		3385 3202	3121	1649		1501	637	434
$\text{NiL}_1\text{L}_2$		3258 3187	-	1651		1497	637	417
$\text{CuL}_1\text{L}_2$	3447	-	3109	-	1059	1497	634	419
$\text{ZnL}_1\text{L}_2$	3441	-	3063	-	1063	1490	652	415

#### Electronic spectroscopy and magnetic susceptibility

Electronic spectral data measured in water as well as the magnetic measurements for the synthesized complexes are shown in Table 3. From the ultraviolet spectra, it can be observed that there are electronic transitions. These transitions are primarily intra-ligand in nature and since the ligands (isoniazid and 2,2-bipyridine) contains aromatic groups as well as atoms with nonbonding electrons,  $n-\pi^*$  and  $\pi-\pi^*$  transitions are expected. However, the electronic transitions of the complexes exhibited a shift towards longer wavelength, with values that range from  $220$ - $321\text{ nm}$  which are also assigned to  $n-\pi^*$  and  $\pi-\pi^*$  transitions [17]. This is an evidence of strong interaction between the ligand and the metallic ion. The extensive conjugation of the ligands gives rise to the several peaks as seen in ultraviolet spectra shown in Figure 2a. The visible spectra of the complexes are shown in Figure 2b.

The visible spectrum of the Co(II) complex showed two bands at 509 and 664 nm which were assigned to  ${}^4T_{1g} \rightarrow {}^4A_{2g}$  and  ${}^4T_{1g} \rightarrow {}^4T_{2g}$ . The visible spectrum of the Cu(II) complex displayed one band at 715 nm which was assigned to  ${}^2E_g \rightarrow {}^2T_{2g}$  transition that is expected for Cu(II) in an octahedral environment [18], while the nickel complex displayed two bands at 636 nm, and 708 nm, attributed which to  ${}^3A_{2g} \rightarrow {}^3T_{1g}(P)$ ,  ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$  [19-20, 22].

All the bands shown by the manganese complex in the visible region had very low intensities suggesting high spin octahedral geometry of the complex, since the transitions in a  $d^5$  ( $Mn^{2+}$ ) high spin complex are all spin forbidden transitions, they give rise to very weak bands [19].

The zinc complex only displayed bands within 258–309 nm in the ultraviolet region, bands were absent in the visible region as zinc complex cannot produce d-d spectra [19]. The values reveals that all the complexes are paramagnetic, except the Zn(II) complex which is diamagnetic as expected for metals that possess a  $d^{10}$  configuration [14]. The magnetic moment value for Cu(II), Ni(II), Co(II), and Mn(II) which were 1.70, 2.55, 4.10 and 6.8 BM suggests an octahedral geometry for the complexes [19, 23]. The predicted structures are shown in Figure 3.

Table 3. Electronic spectra and magnetic moments of mixed ligand complexes of isoniazid and 2,2'-bipyridine.

Compound	Intraligand transitions (nm)	Ligand field transitions	Assignments	$\mu_{eff}$ (BM)
Isoniazid	263	-	$n \rightarrow \pi^*$	-
2,2'-Bipyridine	240, 306	-	$\pi \rightarrow \pi^*$ , $n \rightarrow \pi^*$	-
[Mn(Is)(Bipy)(H <sub>2</sub> O)Cl]Cl	253,306	645(w)	Forbidden transitions	6.80
[Co(Is)(Bipy) <sub>2</sub> ]Cl <sub>2</sub> .H <sub>2</sub> O	255, 274 298	508 668	${}^4T_{1g} \rightarrow {}^4A_{2g}$ , ${}^4T_{1g} \rightarrow {}^4T_{2g}$	4.10
[Ni(Is)(Bipy)Cl <sub>2</sub> ].H <sub>2</sub> O	244,304	636, 708	${}^3A_{2g} \rightarrow {}^3T_{1g}(P)$ , ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$	2.55
[Cu(Is)(Bipy)(H <sub>2</sub> O)Cl]Cl	247, 266, 315, 321	715	${}^2E_g \rightarrow {}^2T_{2g}$	1.70
[Zn(Is)(Bipy)(H <sub>2</sub> O)Cl <sub>2</sub> ]	258,309	-	-	0.20

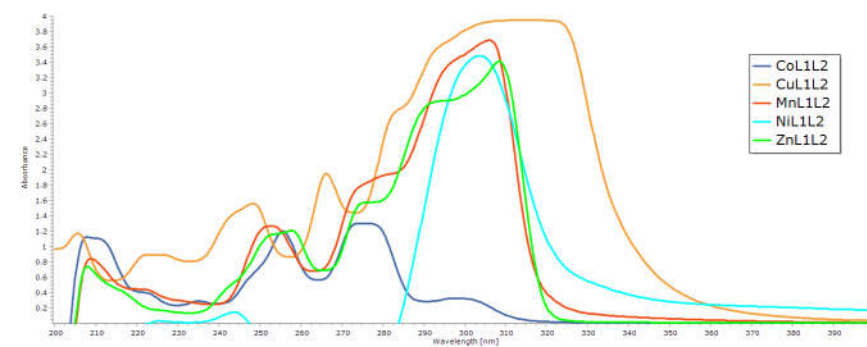


Figure 2a. UV spectra of the complexes:  $CoL_1L_2$ ,  $CuL_1L_2$ ,  $MnL_1L_2$ ,  $NiL_1L_2$ ,  $ZnL_1L_2$ .

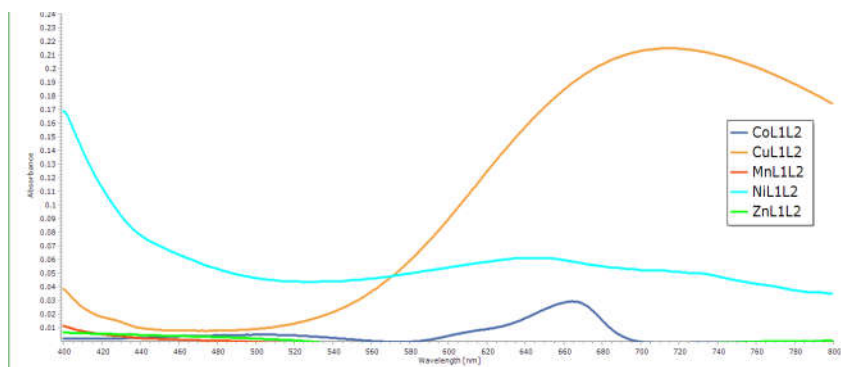


Figure 2b. Visible spectra of the complexes: CoL<sub>1</sub>L<sub>2</sub>, CuL<sub>1</sub>L<sub>2</sub>, MnL<sub>1</sub>L<sub>2</sub>, NiL<sub>1</sub>L<sub>2</sub>, ZnL<sub>1</sub>L<sub>2</sub>.

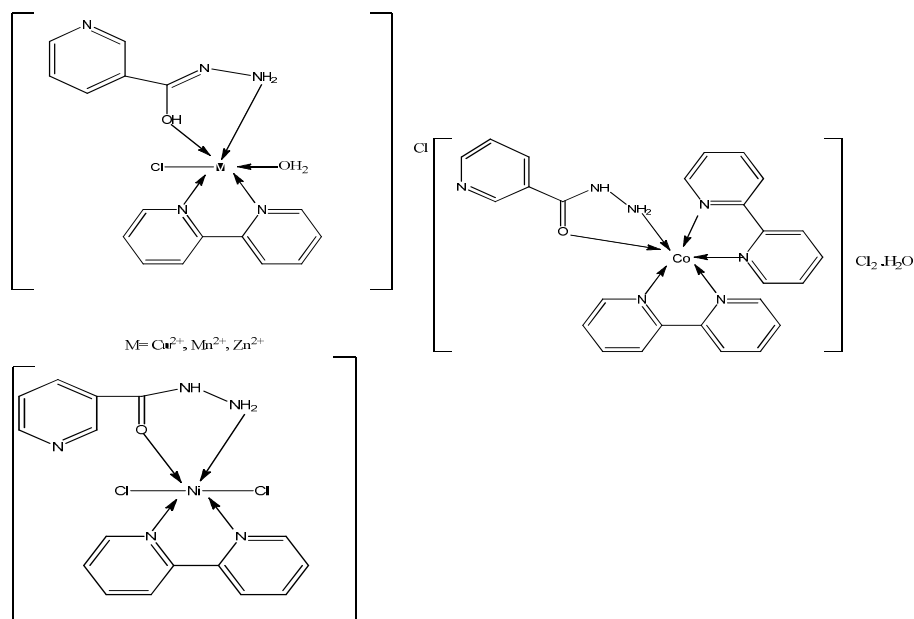


Figure 3. Predicted structures of complexes.

#### *Antibacterial activity*

The Cu(II), Co(II) mixed ligand complexes were tested against ten strains of bacteria consisting of five gram-negative and five gram-positive bacteria. The antibacterial activity was determined using 10 mg/mL of the synthesized complexes while 1 mg/mL ampicillin antibiotic was used as the standard. The zone of inhibition of the ligands and mixed ligand complexes are given in Table 4. The ligands and their mixed ligand complexes exhibited different ranges of antibacterial activity against the tested bacteria strains. The results showed that the ligands exhibited low antibacterial activity except for 2,2-bipyridine. The increased activity of the metal complexes may be attributed to an increase in their lipophilicity, which facilitates their

absorption through the lipid bilayer of the microorganism [24, 25]. The metal complexes undertake their action on the micro-organisms through several ways, but particularly earlier reports on isoniazid have revealed that the complexes undergo dissociation once inside the cell thus releasing the cytotoxic ligands [26]. [Cu(Is)(Bipy)(H<sub>2</sub>O)Cl]Cl displayed the highest activity on the microorganisms in term that are comparable to the standard (ampicillin), but it was found to have no activity on some of the microorganism.

Table 4. Zone of inhibition of the ligands and mixed ligand complexes.

Bacteria/ Compound	<i>E. coli</i>	<i>C. sporogenes</i>	<i>B. cereus</i>	<i>M. luteus</i>	<i>S. aureus</i>	<i>V. fuminisi</i>	<i>K. pnueomiae</i>	<i>P. fluoresens</i>	<i>P. ulgaris</i>	<i>P. aeriginus</i>
Is (L <sub>1</sub> )	0	0	0	10	0	0	12	0	0	0
Bipy (L <sub>2</sub> )	14	20	18	18	20	0	22	20	0	16
CoL <sub>1</sub> L <sub>2</sub>	10	12	10	12	0	0	14	14	16	0
CuL <sub>1</sub> L <sub>2</sub>	18	20	24	24	20	0	0	20	0	0
Standard ampicillin	22	0	20	18	28	0	22	24	22	18

### CONCLUSION

In conclusion, the synthesis of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes of isoniazid mixed with 2,2-bipyridine was carried out and characterized using UV spectroscopy, infrared spectroscopy, metal analysis, conductivity and magnetic measurements. The mixed ligand complexes displayed colours ranging from greenish yellow to light pink. The compounds were soluble in water, possessed high melting points which suggest thermal stability. Infrared spectra data revealed that the isoniazid and Bipyridine acted as bidentate ligands. The UV-Visible spectra in conjunction with the magnetic moments suggested an octahedral geometry for all the mixed ligand complexes. These observations were also supported by the conductivity measurement. The mixed ligand complexes showed moderate activity against the tested bacteria, with [Cu(Is)(Bipy)(H<sub>2</sub>O)Cl]Cl having the highest antimicrobial activity which was comparable to that of the standard drug, ampicillin. This could be attributed to increased lipophilicity of the metal complexes.

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