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SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF MIXED LIGAND COMPLEXES OF NICOTINAMIDE AND 2,2'-BIPYRIDINE

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ABSTRACT

Metal complexes of nicotinamide (L_1) mixed with 2,2'-bipyridine (L_2) were synthesized and characterized by solubility studies, magnetic susceptibility, percentage metal analysis, UV-Vis spectroscopy, IR spectroscopy and conductivity measurements. The observed metal analysis were in agreement with the theoretical values. The magnetic susceptibility data showed that all the complexes were paramagnetic with values ranging from 1.50 to 4.92 B.M, except [Zn(NA)(Bipy)Cl_2H_2O] which is diamagnetic. The conductivity values of 96.20, 123.20 and 130.80 $\Omega^{-1}cm^2mol^{-1}$ Cu(II), Co(II) and Mn(II) complexes respectively reveal their 1:1 electrolytic nature, while Fe(III) (175.20 $\Omega^{-1}cm^2mol^{-1}$) is a 1:2 electrolyte, .[Ni(NA)(Bipy)Cl_2] and [Zn(NA)(Bipy)(H_2O)Cl_2] with conductivity values of 55.70 and 74.40 $\Omega^{-1}cm^2mol^{-1}$ are non-electrolytes. The IR spectra showed that nicotinamide in the zinc(II), copper(II), iron(III) and manganese(II) complexes coordinated as an ambidentate ligand through the pyridinic nitrogen, while in the cobalt(II) and nickel(II) complexes, the nicotinamide coordinated through the carbonyl oxygen (C=O), while the bipyridine bonded to the metals as a bidentate ligand through the pyridinic nitrogen. The antibacterial activities of the ligands and the mixed ligand complexes were screened using the agar diffusion method. The results showed that the mixed ligand complexes displayed higher antimicrobial activity than the free ligands when tested against ten strains of bacteria.

Keyword: Nicotinamide, bipyridine, metal complexes, coordination compounds, antibacterial agents

INTRODUCTION

Nicotinamide also known as 3-pyridinecarboxamide has been known for a very long time, as it is an essential vitamin found in several food products. It is beneficial for several metabolic processes that take place in living organisms aside its status as a necessary dietary supplement. Besides these interesting properties, it has been reported to be used in the treatment of several ailments such as schizophrenia and chronic alcoholism). In fact, the deficiency of nicotinamide leads to a medical condition known as pellagra, which is characterized by dementia, diarrhoea and could result in death.

Metal complexes of several drugs and vitamins have been reported to possess antimicrobial activities, hence the increasing interest in the synthesis, characterization and antimicrobial activities of nicotinamide complexes (Allan *et al.*, 1979; Lawal *et al.*, 2001; Atac *et al.*, 2011; Sahin *et al.*, 2016). The syntheses and structural elucidations of several mixed ligand complexes of nicotinamide have also been reported (Sahin et al., 2016; Cakir *et al.*, 2001; Ucar *et al.*, 2007, Kose , 2007; Al-noor, 2007, Yurdakul *et al.*, 2014). Studies on the antimicrobial activities of the mixed ligand complexes of nicotinamide have shown that the complexes possess higher activity than the free ligands, which is in agreement with numerous reports that have shown that metal complexes of ligands or organic drugs are more active than the free ligands or drugs (Lawal *et al.*, 2015; Akinyele *et al.*, 2020). However, work on the synthesis, structural elucidation and antibacterial activity of Co(II), Ni(II), Cu(II), and Zn(II), Fe(III), Mn(II) mixed ligand complexes of nicotinamide with 2,2-bipyridine has not been reported, this is the essence of this study. The results of this study are herein reported.

EXPERIMENTAL

All the chemicals and solvents used in the study were obtained from Bond Pharmaceutical and BDH and were used without further purification. They are nicotinamide, 2,2'-bipyridine, methanol, copper(II) chloride dihydrate, manganese(II) chloride tetrahydrate, iron(III) chloride hexahydrate, cobalt(II) chloride hexahydrate, and nickel(II) chloride hexahydrate. 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 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. The Magnetic susceptibility measurements were carried out at room temperature using a Sherwood Scientific MXI model Gouy magnetic balance while the melting points of the compounds were determined using a Gallenkamp melting point apparatus, while the conductivity measurement was done by weighing appropriate quantity of the metal complexes on an analytical balance and dissolved in 10 ml of water to get 1×10^{-3} M at 28^0C solution using HANNA instrument (TDS Conductimeter).

Synthesis of mixed ligand complexes

Solutions of each of the metal salts (1.0 mmol of $CoCl_2.6H_2O$, $CuCl_2.2H_2O$, $MnCl_2.4H_2O$, $ZnCl_2$, $NiCl_2.6H_2O$, $FeCl_2.4H_2O$) in 5 ml of methanol was added into stirring homogenous solution of nicotinamide (0.02 mmol) and 2,2'-bipyridine (0.01 mmol) in 10 ml methanol. The solution was stirred for one hour, during which precipitate was formed. The product was filtered, washed with methanol and dried over anhydrous calcium chloride.

Antibacterial Study

The biological activities of the synthesized ligands and their metal complexes were studied for their antimicrobial activities. Microorganisms used in this study were obtained from culture collections of the Department of Microbiology, Obafemi Awolowo University, Ile-Ife, Osun state, Nigeria. These organisms include typed cultures of National Collection of Industrial Bacteria (NCIB) and locally isolated organism (LIO). The bacterial strains were *Bacillus cereus, Staphylococcus aureus, Proteus vulgaris, Vibro fuminisi Clostridium sporogenes, Escherichia coli, Pseudomonas aeruginosa, Pseudomonas flourescens, Klebsiella pneumoniae, Microccus 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 kg/cm^3 for 15 minutes. The bacterial strains used in the experiment were sub-cultured into nutrient broth and incubated at 37 ºC for 18 hours. The organisms were stored on sterile nutrient agar slants in McCatney 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. The bacterial strains were first grown in nutrient broth for 18 hours 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 6m 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 hours to allow for proper in flow of the solution into the medium before incubating the plate in an incubator at 37 °C for 24 hours. The plates were later observed for zones of inhibition, and the effects of the extract on bacterial strains were compared with that of standard antibiotics, ampicillin.

RESULTS AND DISCUSSION

The properties of the synthesized compounds including the percentage yields are shown in Table 1. The mixed ligand complexes displayed high melting points and a variety of colours ranging from yellow to lilac except for the zinc complex which was white. The melting point of nicotinamide is 127 – 129 ºC, while the complexes have their melting points above 300 ºC, thus the relatively high melting point of the metal complexes suggests high thermal stability.

The theoretical %metal in the mixed ligand complexes showed good correlation with the experimental values as shown in Table 1. All the complexes synthesized are soluble in water, while they show varying degrees of solubility in the six common solvents. The solubility of all the complexes in water suggests that they are ionic in nature.

Table 1: Physical properties and analytical data for compounds

Compound	Formula (formula weight)	Colour	Melting point (°C)	%metal found (calc)	Yield (%)
Nicotinamide	$C_6H_6N_2O$(122.125)	White	127- 129	-	-
2,2'- bipyridine	$C_{10}H_8N_2$(156.184)	White	70 - 72	-	-
[Mn(NA)(bipy)(H_2O)$_2$Cl]Cl	$MnC_{16}H_{18}N_4O_3Cl_2$ (440.183)	Yellow	>350	12.62(12.48)	31.80
[Fe(NA)(bipy)$_2$Cl]$Cl_2 \cdot H_2O$	$FeC_{26}H_{24}N_6O_2Cl_3$ (614,712)	Deep Yellow	306 - 308	9.15(9.08)	60.00
[Co(NA)(bipy)(H_2O)$_2$Cl]Cl	$CoC_{16}H_{18}N_4OCl_2$ (444.2740)	Lilac	316 - 318	12.90(13.26)	63.07
[Ni(NA)(Bipy)(H_2O)Cl_2]	$NiC_{16}H_{16}N_4O_2Cl_2$ (425.923)	Green	>350	14.12(13.78)	62.30
[Cu(NA)(bipy)(Cl]Cl	$CuC_{16}H_{14}N_4OCl_2$ (412.761)	Blue	300 - 302	15.59 (15.40)	64.54
[Zn(NA)(Bipy)(H_2O)Cl_2]	$ZnC_{16}H_{16}N_4O_2Cl_2$ (432.610)	White	>350	15.30(15.11)	78.99

Infrared Spectra

Table 2 shows the significant absorption bands for both ligands; nicotinamide and 2,2-bipyridine and their Cu(II), Fe(III), Mn(II), Co(II), Zn(II), and Ni(II) mixed ligand complexes. Bands due to the amido group in the nicotinamide (3368 cm^{-1}, 3361 cm^{-1}), Carbonyl group (1679 cm^{-1}) and C-N (1395 cm^{-1}) are displayed in amide complexes, coordination via the amido group and the carbonyl group leads to a negative shift in the frequency of absorption due to a decrease in bond strength of the groups. However , the results showed that there was no coordination via the amido group as the frequency of absorption in all the complexes remained unchanged or showed positive shifts which could be as a result of intramolecular hydrogen bonding and other factors. The inability of the ligand to coordinate to nicotinamide via the amido nitrogen is due to the resonance stabilized nature of amides which accounts for their decreased basicity (Lawal *et al.*, 2015). In the same manner, the absorption bands of the C-N remained relatively unchanged.

The absorption bands for the C=O showed a negative shift for the cobalt and nickel complexes depicting coordination, however, in the copper complex, there was a positive shift which suggests that no coordination took place via the carbonyl group. The positive shift could be due to combined factors such as intermolecular interactions, the degree of conjugation with the pyridinic nitrogen (Ucar *et al.*, 2007, Lawal *et al.*, 2014). In the remaining complexes, there was a disappearance of the carbonyl group and appearance of a broad O-H group at the high-frequency region, this could be due to the amide-amidol tautomerism.

The infrared spectra of the complexes also show positive shifts in the pyridine ring vibration of nicotinamide (1592, 1573, 1484 and 995 cm^{-1}) for the Mn(II), Cu(II), Ni(II), Zn(II) complexes. Positive shifts in the ring vibration of nicotinamide have been reportedly shown to be an evidence of coordination through the pyridine nitrogen of the nicotinamide moiety (Ucar *et al.*, 2007, Lawal *et al.*, 2014). The positive shifts observed for the pyridine ring vibrations arise due to the formation of the M-N (pyridine) bond and changes in the force field (Atac *et al.*, 2011). The positive shifts also served as evidence of coordination of the metal to the two pyridinic nitrogen that occurs in 2,2'-bipyridine although the differences in the shifts were larger.

The appearance of low-intensity bands 415 – 428 cm^{-1} and 576, 583 cm^{-1} in the low-frequency region of the spectra strongly suggests coordination, and these bands are attributed to M-O and M-N vibrations. The IR spectra are shown in Figure 1.

Table 2: Some relevant Infrared spectra data (cm^{1}) of mixed ligand complexes of nicotinamide

Frequency(ν) Compound	ν_{N-H}	ν_{N-H}	$\nu_{C=O}$	$\nu_{py(ring)}$	$\nu_{C=N}$	ν_{M-O}	ν_{M-N}
Nicotinamide (NA)	3368	3361	1679	1592, 995	1395	-	-
Bipyridine (bpy)	-	-	-	1579, 991	-	-	_
$[Mn(NA)(bpy)(H_2O)_2Cl]Cl$	3440	-	-	1574, 1017	-	-	415
$[Fe(NA)(bpy)_2Cl]Cl_2 \cdot H_2O$	3437	-	-	1563, 1026	-	-	422
$[Co(NA)(bpy)(H_2O)_2Cl]Cl$	3405	3322	1667	1481, 1049	1395	583	421
$[Ni(NA)(bpy)(H_2O)Cl_2]$	3408	3322	1670	1579, 939	1397	576	428
$[Cu(NA)(bpy)(Cl]Cl$	3406	3163	1707	1568, 1026	1379	-	-
$[Zn(NA)(bpy)(H_2O)Cl_2]$	3439	-	-	1599, 1018	-	-	415

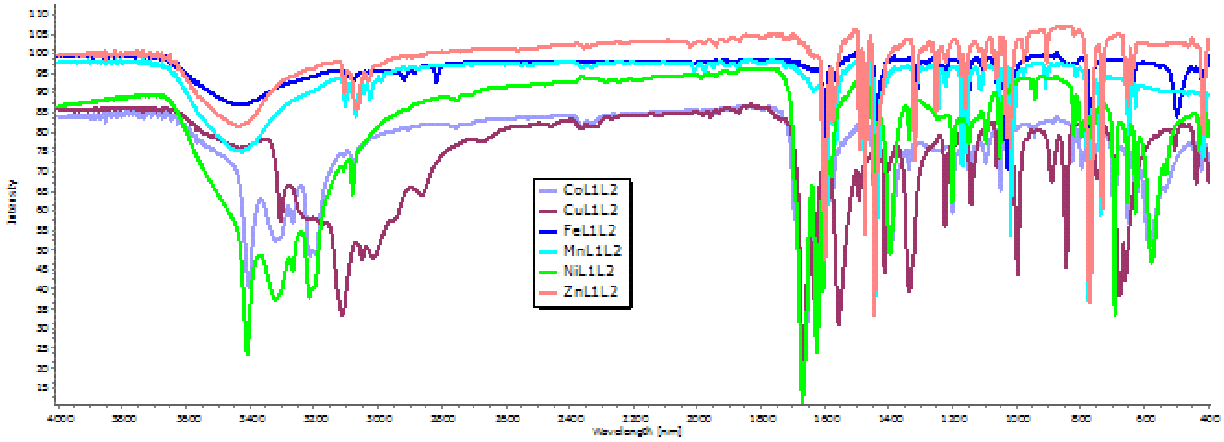

Fig 1: IR spectra of CoL_1L_2, CuL_1L_2, FeL_1L_2, MnL_1L_2, NiL_1L_2, ZnL_1L_2

Electronic spectra

The electronic spectral data measured in water for the synthesized mixed ligand complexes are shown in Table 3.

Upon coordination, the electronic transitions of the complexes exhibited a positive shift toward longer wavelength with values ranging from 264-312 nm which were due to π-π* and n-π* transitions (Cakir *et al.*, 2001; Akinyele *et al.*, 2020), which implies a strong interaction between the ligand and the metallic ion. The visible spectra of the Co(II) complex of nicotinamide mixed with 2,2'-bipyridine showed two distinct bands at 509 nm and 666 nm which is attributed to $^4T_1g \rightarrow {}^4A_1g$ (P) and $^4T_1g \rightarrow {}^4T_2g$ in an octahedral environment (Cakir *et al.*, 2001; Kose, 2007). Likewise, the visible spectra of the Cu(II) complexes showed one band at 737 nm due to $^2T_2g \rightarrow {}^2Eg$, no distortion was observed in the electronic spectra of Cu(II) which is consistent for Cu(II) in a tetrahedral environment (Lee, 1996). The visible spectra of the nickel complexes of nicotinamide with 2,2'-bipyridine showed three bands at 497, 568, 677 nm due to $^3A_2g \rightarrow {}^3T_1g$ (p), $^3A_2g \rightarrow {}^3T_1g$ and $^3A_2g \rightarrow {}^3T_2g$, as expected for Ni(II) in an octahedral environment (lee, 1997; Cakir *et al.*, 2001) , while the iron (III) complex displayed one band at 480 nm in the visible region of the spectrum, this is attributed to MLCT since the metal d-orbitals are relatively close in energy to the ligand π* orbital in an octahedral field. The Mn(II) complex displayed a weak band at 668 nm which is attributed to charge transfer transitions in an octahedral environment (Lee, 1996) and these are responsible for their yellowish colour. The zinc complexes of all the complexes only displayed bands within 287 – 312 nm, in the ultraviolet region, there were no bands in the visible region as zinc complexes do not produce d-d spectra (Lee, 1996). The electronic spectral data with the assigned transitions are shown in Table 4 while the ultraviolet and the visible spectra of copper, cobalt and manganese mixed nicotinamide and 2,2'-bipyridine complex are displayed in Figures 2a and 2b respectively.

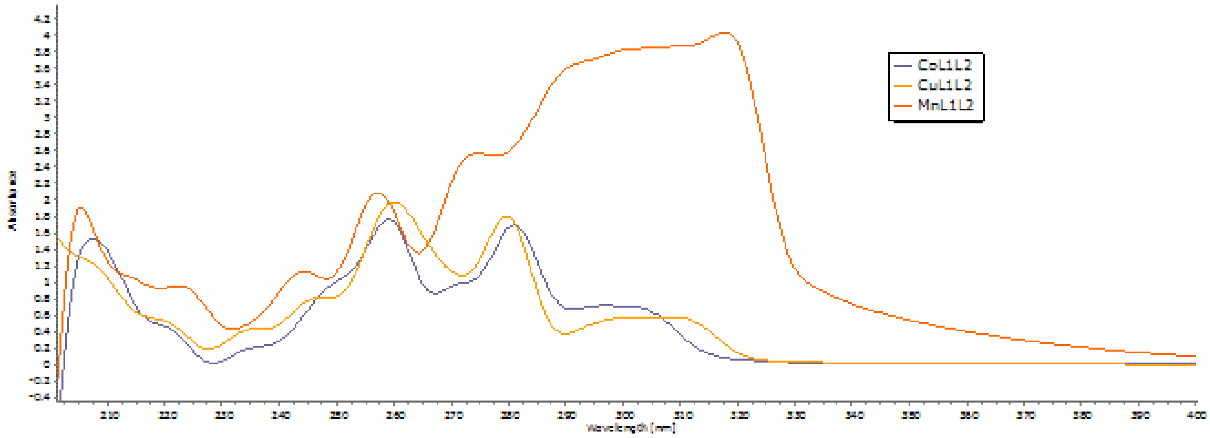

Fig 2a: UV spectra of CoL_1L_2, CuL_1L_2, MnL_1L_2

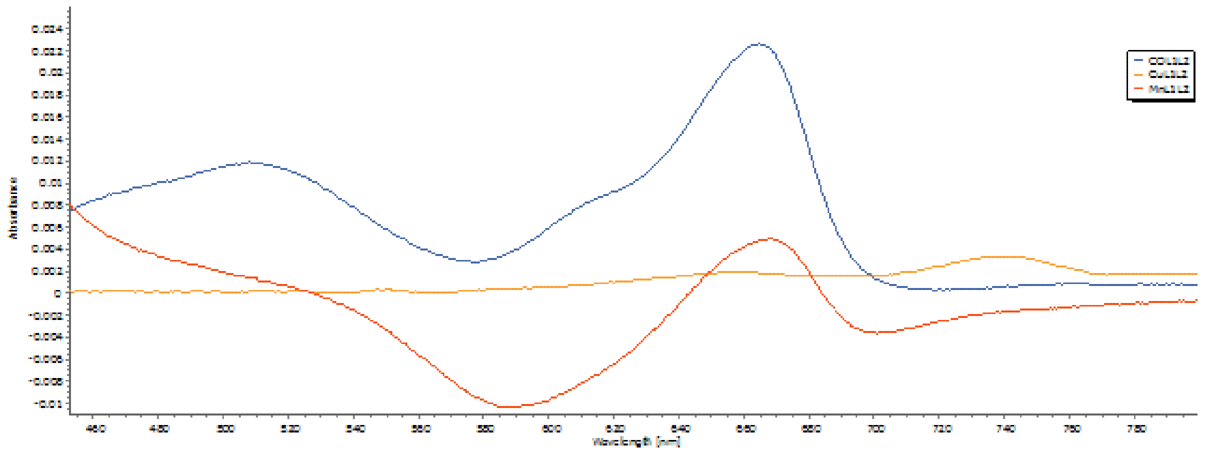

Fig 2b: Visible spectra of CoL_1L_2, CuL_1L_2, MnL_1L_2

Table 3: Electronic spectra of mixed ligand complexes of nicotinamide and 2,2'-bipyridine

Compounds	Intraligand transitions (nm)	Ligand field transitions	Assignments
Nicotinamide	215 262	-	π-π* n-π*
2,2'-Bipyridine	240 306	-	π-π* n-π*
$[Mn(NA)(Bipy)(H_2O)_2Cl]Cl$	257, 318	668	LMCT
$[Fe(NA)(bipy)_2Cl]Cl_2 \cdot H_2O$	233, 281	480	MLCT
$[Co(Bipy)(NA)(H_2O)_2Cl] \cdot Cl$	251, 281	509 666	$^4T_1g \rightarrow ^4A_2g$ $^4T_1g \rightarrow ^4T_2g$
$[Ni(NA)(Bipy)(H_2O)Cl_2]$	312	497 568 677	$^3A_2g \rightarrow ^3T_1g$ (P) $^3A_2g \rightarrow ^3T_1g$(F) $^3A_2g \rightarrow ^3T_2g$
$[Cu(NA)(Bipy)Cl]Cl$	260, 297, 307	737	$^2T_{2g} \rightarrow ^2E_g$
$[Zn(NA)(Bipy)(H_2O)Cl_2]$	308	-	-

Magnetic Moment

The magnetic moment values as displayed in Table 4, shows that all the complexes are paramagnetic, except the Zn(II) complex which was diamagnetic. The copper(II) complex gave a value of 1.5 BM which indicates the presence of antiferromagnetism (Akinyele *et al.*, 2019, Akinyele, 2020). The magnetic susceptibility values for cobalt(II) and Ni(II) complexes supports an octahedral geometry (Cotton and Wilkinson, 1966; Lee, 1996). The low magnetic moment values displayed by the Mn(II) complexes is due to antiferromagnetism, which has been reported to be common in their complexes (Lee, 1996). The unusual sub-normal magnetic moment of 3.60 BM observed for Fe(III) complex is as a result of low spin-high spin equilibrium (Garg *et al.,* 1998), hence possesses an ion pair geometry.

The molar conductivity in water of Cu(II), Mn(II), Co(II) complexes are within the range of 96.20, 130.80, 123.20 $\Omega^{-1}cm^2mol^{-1}$ respectively depicting that they are 1:1 electrolytes while the Fe(III) complex is a 1:2 electrolyte (Geary, 1971). The molar conductivity of the Ni(II) and Zn(II) complexes with values of 55.70 and 74.40 $\Omega^{-1}cm^2mol^{-1}$ strongly suggests that they are non-electrolytes indicating that the two chlorides ions are present the coordination sphere. The molar conductivity measurements are presented in Table 4.

Table 4: Magnetic moment and Conductivity measurements of the complexes at 25°C (298 K)

Compounds	Molecular weight (g/mol)	μeff (BM) Experimental	Λm $\Omega^{-1}cm^{2}mol^{-1}$	Electrolyte
$[Mn(NA)(Bipy)(H_2O)Cl]Cl$	440.183	4.92	130.80	1:1
$[Fe(NA)(bipy)_2Cl]Cl_2{\cdot}H_2O$	614.712	3.60	175.20	1:2
$[Co(Bipy)(NA)(H_2O)Cl]Cl$	444.178	4.0	123.20	1:1
$[Ni(NA)(Bipy)(H_2O)Cl_2]$	425.923	2.48	55.70	Non-electrolyte
$[Cu(NA)(Bipy)Cl]Cl$	412.761	1.50	96.20	1:1
$[Zn(NA)(Bipy)(H_2O)Cl_2]$	432.610	0.30	74.40	Non electrolyte

Antibacterial activity

The 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 1mg/ml ampicillin antibiotic was used as the standard. The ligands and their mixed ligand complexes displayed variable ranges of antibacterial activity against the tested bacteria strains. The results revealed that the ligands had low antibacterial activity except for 2,2'-bipyridine which showed relatively good antibacterial activity against the bacterial strains, which could also have accounted for the high activity of the metal complexes.

Generally, the results from the zone of inhibition showed that the metal chelates are more active than the free ligands; this can be attributed to the reduction in the polarity of the metal ion which is a consequence of the partial sharing of its positive charge with the donor groups in the complexes. This results in an increased lipophilicity of the metal complexes which aid their absorption through the lipid bilayer of the selected microorganism (Farrel, 2003; Ali *et al.*, 2012). $[Fe(NA)(bipy)_2Cl]Cl_2H_2O$ had the highest activity against the selected microorganisms some of which were comparable to the activity of the standard drug used i.e. ampicillin except *Vibro Fuminisi*. This activity could be attributed to the increased lipophilicity of the metal complexes as well as the presence of heterocyclic compounds (Farrel, 2003, Ajayeoba *et al.*, 2017). Table 5 shows the zone of inhibition of the ligand and the mixed ligand complexes.

Table 5: Zone of inhibition of the ligands and mixed ligand complexes

Compounds Bacteria	NA	bpy	MnL_1L_2	FeL_1L_2	CoL_1L_2	NiL_1L_2	CuL_1L_2	ZnL_1L_2	Ampicillin
E. Coli	0	14	10	12	20	09	10	10	22
C. Sporogenes	0	20	12	20	16	18	22	16	0
B. cereus	0	18	12	20	12	19	20	18	20
M. Luteus	0	18	14	10	16	14	20	16	18
S. aureus	0	20	16	26	20	18	20	19	28
V. Fuminisi	0	0	0	0	10	0	0	0	0
K. Pnueomiae	0	22	16	20	18	08	0	08	22
P. Fluoresens	0	20	10	12	14	10	0	10	24
P. Vulgaris	0	0	10	12	12	10	0	08	22
P. aeriginus	0	16	12	14	0	12	0	12	18

CONCLUSION

The synthesis Cu(II), Ni(II), Fe(II), Co(II), Mn(II) and Zn(II) complexes of nicotinamide mixed with 2,2'-bipyridine and their characterization were carried out via UV-visible, infrared spectroscopy, metal analysis, conductivity and magnetic measurements. The mixed ligand complexes displayed colours ranging from yellow to lilac. The compounds are soluble in water, possess high melting points which depict thermal stability. Infrared spectra show that the nicotinamide acted as an ambidentate ligand bonding via the pyridinic nitrogen in Mn, Zn, Cu and Fe and and the carbonyl oxygen (C=O) in nickel and cobalt, while the bipyridine acted as a bidentate ligand. The UV-Visible spectra in conjunction with the magnetic moments suggested an octahedral geometry for the mixed ligand complexes except for [Cu(NA)(bipy)(Cl]Cl which possessed a tetrahedral geometry. These observations were also supported by the conductivity measurement values. The mixed ligand complexes showed moderate activity against the tested bacteria, with [Fe(NA)(bipy)$_2$Cl]Cl$_2$H$_2$O 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 and the presence of heterocyclic compounds.

Proposed Structures

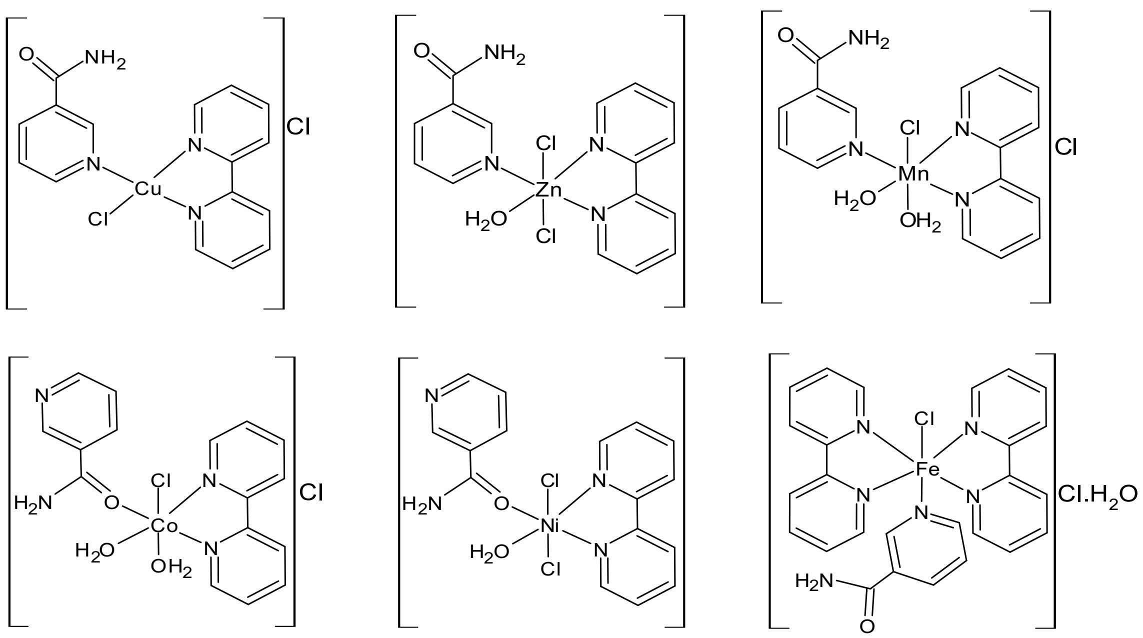

Fig. 3: Proposed Structure for mixed ligand complexes of Nicotinamide and 2,2'-bipyridine

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