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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDIES OF SOME METAL (II) COMPLEXES OF TRIDENTATE LIGAND DERIVED FROM ETHYLENEDIAMINE, NITROBENZALDEHYDE AND AMINOBENZOPHENONE.

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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDIES OF SOME METAL (II) COMPLEXES OF TRIDENTATE LIGAND DERIVED FROM ETHYLENEDIAMINE, NITROBENZALDEHYDE AND AMINOBENZOPHENONE.

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ABSTRACT

The Schiff base ligand and its metal complexes derived from ethylenediamine, nitrobenzaldehyde and aminobenzophenone were prepared using hydrated metal salts of Ni(II), Co(II), Mn(II) and characterized by molar conductivity, magnetic susceptibility measurement, elemental analysis, FTIR, GC-MS, UV-Vis spectroscopy and (^{1}H, ^{13}C) NMR spectra. Some physical parameters were obtained using molar conductance measurement and melting point determination. From the analytical and spectroscopic data, N donor atoms of the Schiff base ligand and N of NH_2 group participated in coordination with metal (II) ions, proposed to be a tridentate ligand. Octahedral geometry was proposed for the complexes of Co, Ni while tetrahedral geometry proposed for Mn respectively. The antimicrobial activity of the ligand and its metal complexes were compared with the standard drugs Amoxicillin and Nystatin by screening them against isolates of two Gram-positive, three Gram-negative and two fungal strain, using agar well diffusion method for bacteria while the fungal cultures were maintained on Sabouraud liquid medium. The results obtained showed that the metal complexes were more potent against Gram-positive bacterial and fungi than the free ligand, while the ligand showed greater activity against Gram-negative bacterial than the metal complexes.

Keywords: *Tridentate ligand, ethylenediamine, 2-aminobenzophenone, antibacterial, metal (II) complex.*

1. INTRODUCTION

Imines were first prepared and reported in the 19th century by Hugo Schiff [1–3]. A Schiff base is a nitrogen analog of an aldehyde or ketone in which the C = O group is replaced by C=N–R group. In azomethine derivatives, the C=N linkage is essential for biological activity, several of it were reported to possess remarkable antibacterial, antiviral, antifungal, anticancer activities [4 – 11]. Schiff bases derived from an amino and carbonyl compound are important class of ligands that coordinate to metal, metal ions play many important functions in humans. The ability to understand at the molecular level and to treat diseases caused by inadequate metal-ion function constitutes an important aspect of medicinal bioinorganic chemistry. Transition metals exhibit different oxidation states and can interact with a few negative charged molecules, this properties led to the development of metal–based drugs with promising pharmacological application and unique therapeutic opportunities. In this article, we report the synthesis and biological studies of new tridentate Schiff base derived from ethylenedianine, nitrobenzaldehyde, aminobenzophenone and its metal (II) complexes.

2. EXPERIMENTAL

2.1. Materials and Method

All reagents were purchased from Sigma-Aldrich, Germany and used without further purification. FT-IR spectra of synthesized compounds (in a KBr) were recorded in 4000 – 500 / 400cm^{-1} region on infrared spectrometer Virian 660 MidIR Dual / MCT / DTGS bundle with ATR. The ^{1}H and ^{13}C NMR spectra of the Schiff base ligand were recorded in deuterated DMSO (Internal standard TMS) on Bruker spectrometer. The electronics spectra of the synthesized compounds were recorded on a Spectrum lab7525 spectrophotometer in the 0–400, 400–900 range for ligand and complexes. Magnetic susceptibility measurements of the metal complexes were determined on Gouy balance at room temperature using Swissmake -H-1640 with maximum capacity 80g and precision ± 0.01mg. Melting point were recorded on a gallenkamp apparatus and are uncorrected. MS analysis of prepared ligand and metal complexes were performed on GC–MSQP–2010 (Shimazu), Elemental analysis were determ ined using micro analyser, Perkin Elmer U.S.A 2400 Series II. Conductivity measurements were recorded at (R.T)^{O}C for solution of samples in DMSO/water using Conductivity Metre DDS - 307.

2.2. Synthesis of Schiff Base Ligand and metal complexes

2.2.1. Synthesis of Schiff Base Ligand (L)

The ligand (L) (Figure 1) was prepared according to the literature [12]. Ethylenediamine (0.01mol, 0.6g) with 2-aminobenzophenone (0.01mol, 1.97g) and 4-nitrobenzaldehyde (0.01mol, 1.51g) in a 50ml round bottom flask was stirred in 20ml ethanol at room temperature for 3 hours, two drops of Conc. H_2SO_4 was added to the mixture to adjust its pH to ~ 6. The resulting orange colour precipitate formed was separated by filtration and purified by recrystallization from ethanol and dried overnight in air.

2.2.2. Synthesis of Ni (II), Co (II) and Mn (II) complexes

Schiff base (0.0011mol, 0.4g) in 20ml of absolute ethanol were added to a solution containing metal salts (0.0011mol) in 20ml absolute ethanol. The mixture was reflux with stirring. The precipitate formed were filtered and washed with ethanol and dried overnight in a desiccator. Metal salts ($CoCl_2.6H_2O$, $NiSO_4.6H_2O$ and $MnSO_4.H_2O$) were used, the yield and melting points of each product were determined.

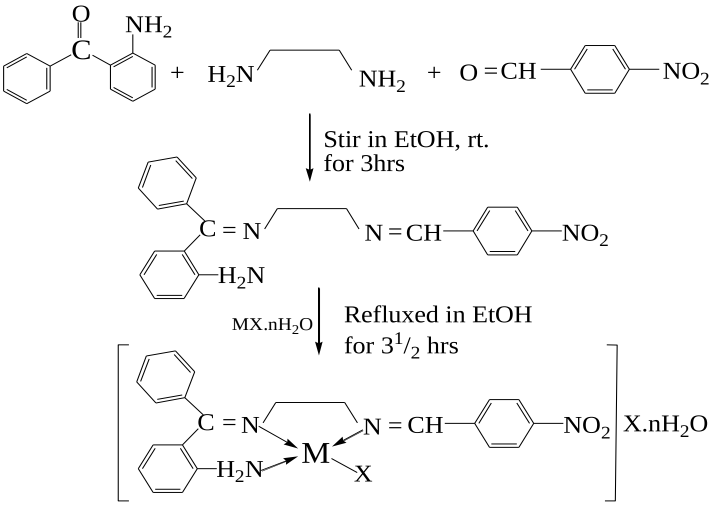

Fig 1: Synthesis of ligand (L) and its metal(II) complexes. M = Co(II), Ni(II) and Mn (II)

2.3. Biological Activity

Organisms used were isolates collected from out patients' ward of the Federal Medical Centre Owo. The bacterial cultures were maintained on nutrient broth while the fungal cultures were maintained on Sabouraud liquid medium. Seven organisms were used, two Gram-positive, three Gram-negative and two fungi. A sterile 6mm cork borer was used to make well on already solidified agar. The well were filled with the oil ensuring that there was no spill on the agar surface surrounding the well. The plates were allowed to stand for about 2 hours to allow absorption of the oil into the medium. Macrobroth dilution technique as modified by [13] was used in this research for MIC. Those recorded as MIC were the lowest concentration of the tested ligand and metal complexes that showed no visible growth of the tested isolate. Serial dilutions of the prepared ligands and complexes were carried out to give concentration of 50mg/ml, 25mg/ml, 12.5mg/ml, 6.25mg/ml and 3.125mg/ml. 2ml of each diluted concentration was added to 18ml of pre-sterilized molten Mueller – hinton and Sabouraud agar mixed properly and allowed to set after which the standardized inoculums were seeded on the plates. The bacterial plates were incubated at 37^0c for 24 hours, while the fungi at 25^0c for 7 days. The results were observed and recorded.

3.0. Result and Discussion

The Schiff base ligand (L) is soluble in DMSO. The metal complexes are coloured solid which are stable in air, soluble in DMSO and water. The melting points of the complexes were higher than that of the Schiff base ligand indicating that the complexes are more stable than the ligand. The chemical equation showing the preparation of the ligand and its metal(II) complexes are presented in Figure 1.The molar conductance at room temperature and 10^{-3}M dilution in water were fund in the range of 66 –77 Ohm^{-1} mol^{-1}cm^2 for Ni (II) and Mn (II) indicating the non-ionic nature of these complexes while, 220 Ohm^{-1} Mol^{-1}cm^2 for Co (II) indicate electrolytic nature [13]. It suggested that there were anions present outside the coordination sphere of Co (II) complex. The results of analytical data (Table 1) revealed that the complexes and the ligand were of good purity.

3.1. FTIR Spectra

The significant infrared bands of the Schiff base and their metal complexes are given in Table 2.The free ligand showed a strong band at 1641cm^{-1} which is characteristic of the azomethine

(HC=N) group[16]. The HC=N stretching frequencies in metal comp lexes were observed at 1594, 1590, 1589cm^{-1} for Co(II), Ni(II) and Mn(II), respectively, shift to lower wave numbers indicating coordination of the azomethine nitrogen to metal ion[14, 15]. The stretching vibration v(NH_2) which appeared at 3446cm^{-1} in the spectrum of free ligand (L) shifted in the spectra of its complexes, which indicate coordination of NH_2 group in the formation of respective complexes [16–19]. The appearance of new bands in the region 517-578cm^{1} is attributed to v(M-N) which confirmed the coordination of metal ions via nitrogen atom The FTIR Spectra data confirmed the coordination of imino nitrogen atom to the Co, Ni and Mn ions. The complexes also showed bands in the 3426–3635cm^{1} region, suggesting the presence of coordinated/ lattice water in the complexes [20, 21].

Table 1: Physical and Analytical Data of Schiff Base Ligand and its Complexes

Compound	Empirical Formula	M.wt (g)	M.P (^{0}c)	Colour	Yield (%)	Molar cond. Ohm^{-1}mol^{-1}cm^2	Elemental analysis (found/calc.)			
							C	H	N	M
L	$C_{22}H_{20}N_4O_2$	372	222	Orange	61	——	70.97 (70.95)	5.38 (5.27)	15.05 (15.08)	___
[Ni(L)]	$[NiLSO_4(H_2O)_2](H_2O)$	581	264	Yellow	76	66	44.75 (44.68)	4.57 (4.55)	9.49 (9.53)	10.00 (9.96)
[Co(L)]	$[CoL(H_2O)_3]Cl_2.H_2O$	583	245	Green	55	220	45.75 (45.34)	4.97 (5.01)	9.61 (9.64)	10.12 (10.13)
Mn(L)	$[MnL(SO_4)].H_2O$	574	310	Brown	80	77	48.79 (48.82)	4.07 (4.06)	10.35 (10.38)	10.17 (10.18)

Table 2: FTIR Spectral data of the Schiff base ligand and its metal complexes

Compound	v(C = N)	v(NH_2)	v(M – N)	v(H_2O)
L	1641	3446	______	______
$[CoL(CH_2O)]Cl_2.H_2O$	1594	3573	5.78	3635
$[NiLSO_4(H_2O)].H_2O$	1590	3299	529	3426
$[MnLSO_4].H_2O$	1589	3572	517	3591

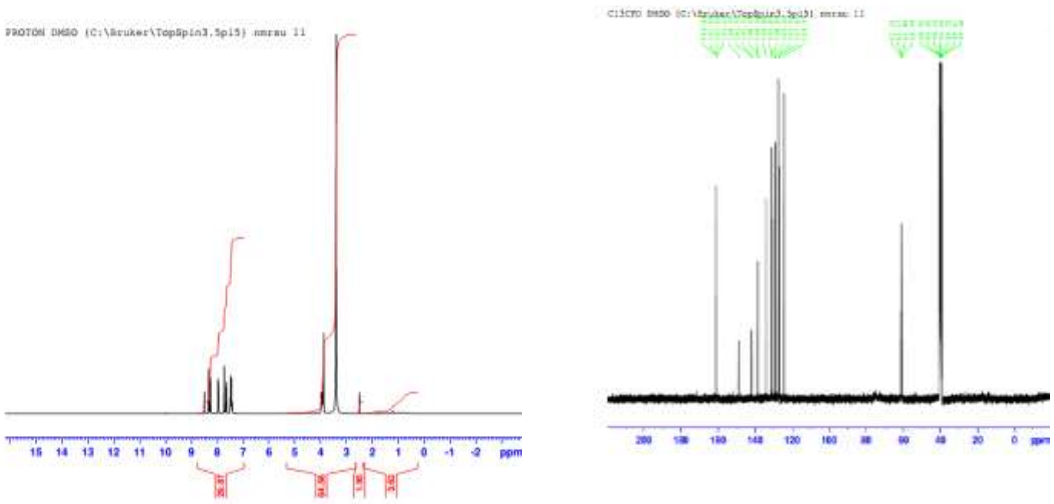

Figure 2: (a) ^{1}HNMR spectrum of ligand (L) (b) ^{13}CNMR Spectrum of ligand (L)

3.2 NMR Spectral Analysis.

The ^{1}H and ^{13}C NMR spectral of the Schiff base and its metal (II) complexes were recorded in DMSO-d_6 as shown in Figure 2 (a) and (b): The ^{1}H NMR spectrum shows a signal peak at 8.7 ppm corresponding to azomethine proton(HC=N) confirmed the formation of Schiff base during condensation reaction (21 – 22)

Table 3: Spectroscopic Data of Ligand (L)

Compound	^{1}HNMR, δ(ppm)	^{13}C NMR, δ(ppm)
L	8.7 (CH = N)	161.33 (HC = N)
	2.5 (N – H)	124.39 – 148.99 (Ar – C)
	7.4 – 8.5 (Ar – H)	61.17 (C – N)

The observed peak (7.4–8.5) ppm corresponded to aromatic protons while the observed signal at 2.5ppm is assigned to NH_2 group. The observed peak of δ = 161.33 in the ^{13}C NMR spectrum corresponding to (HC=N) was a further confirmation that the ligand was successfully synthesized [24, 25].

Table 4: Electronic spectra data of ligand (L) and its complexes

Compound	λ_{max} nm	Assignment	μ_{eff} (B.M)	Molar cond. ($\Omega^{-1}mol^{-1}cm^2$)	Geometry
L = $C_{22}H_{20}N_4O_2$	315, 350	$n \rightarrow \pi^*, \pi \rightarrow \pi^*$	——	——	——
$[NiLSO_4(H_2O)_2.H_2O]$	680 699 768	$^3A_{2(g)} \rightarrow {}^3T_{2(g)}v_1$ $^3A_{2(g)} \rightarrow {}^3T_{1(g)}(F)v_2$ $^3A_{2(g)} \rightarrow {}^3T_{1(g)}(P)v_3$	2.85	66	O.h
$[CoL(H_2O)_2]Cl_2.H_2O$	680 522	$^4T_{1(g)}(F) \rightarrow {}^4T_{2(g)}(F)$ $^4T_{1(g)}(F) \rightarrow {}^4A_{2(g)}(F)$	4.3	220	O.h
$[MnLSO_4].H_2O$	866 880 896	$^6A_1 \rightarrow {}^4T_1$ $^6A_1 \rightarrow {}^4T_2(G)$ $^6A_1 \rightarrow {}^4T_2(D)$	5.98	77	T.h

3.3 Electronic Spectral and Magnetic Studies

The electronic spectral of the synthesized ligand and metal complexes are given in (Table 4). The ligand showed two absorption bands at 315 and 350 cm^{-1}. The bands were assigned to $n \rightarrow \pi^*$, $\pi^* \rightarrow \pi^*$. These bands were observed in the metal complexes at higher wavelength due to complexation [25]. Bands observed in Ni(II), Co(II) and Mn (II) complexes were attributed to d-d transition. In Ni(II), three band were observed at 680, 699 and 768cm^{-1} due to splitting of ^3F (ground term). The bands were attributed to $^3A_{2(g)} \rightarrow {}^3T_{2(g)}v_1$, $^3A_{2(g)} \rightarrow {}^3T_{1(g)}(F)v_2$ and $^3A_{2(g)} \rightarrow {}^3T_{1(g)}(P)v_3$ respectively. The magnetic moment value of 2.85BM obtained for the complex is within the octahedral environment range of 2.8–3.5BM [13]. The electronic spectral of Co(II) complex displayed two absorption bands assigned to $^4T_1g(F) \rightarrow {}^4T_2g(v_1)$ and $^4T_1(g)(F) \rightarrow {}^4A_2(g)(v_2)$ transitions respectively. These bands are characteristics of high spin octahedral Co(II) complex. The magnetic measurement of Co(II) complex of 4.3BM is within the octahedral range of 4.3–5.2BM. In Mn(II), three bands were observed at 866, 880, 896cm^{-1}. The bands were assigned to $^6A_1 \rightarrow {}^4T_1v_1$, $^6A_1 \rightarrow {}^4T_2(G)v_2$ and $^6A_1 \rightarrow {}^4T_2(D)v_3$ transitions respectively. The complex exhibit magnetic moment of 5.96BM, which supported tetrahedral geometry around Mn(II) ion [26, 27].

3.4 Conductivity Measurement

The molar conductivity values (Table 1) for complexes were measure at room temperature in 10^{-3}M water. The values of molar conductivity of the synthesized compounds range between 66–220 $Ohm^1cm^2.mol^{-1}$. The conductivity values for Ni(II) and Mn(II) indicating their non electrolytic nature while for Co(II) indicating electrolytic nature [13].Conductivity measurement provide the method of testing the degree of ionization of the complexes, the higher the number of molecular ions that a complex liberates in solution (increase presence of anions outside the coordination sphere), the higher will be its molar conductivity and vice versa [21].

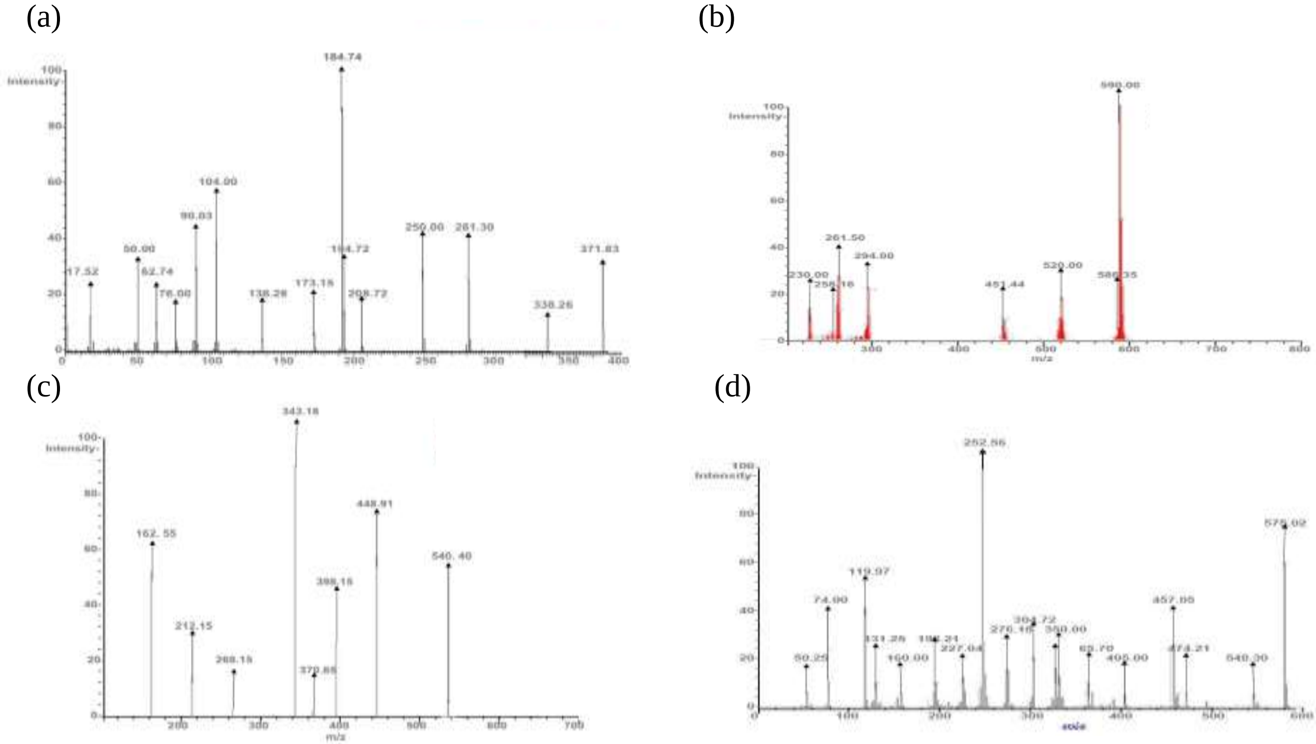

Fig 3: (a) Mass spectrum of ligand (L), (b) Mass spectrum of complex Ni(L), (c) Mass spectrum of complex Mn(L) (d) Mass spectrum of complex Co(L)

3.5 Mass Spectra

The recorded mass spectra of ligand and its metal (II) complexes with the molecular ion peaks have been used to confirm the proposed structures.

3.6 Antimicrobial Activity

The antimicrobial activity tests were conducted according to standard procedures using two Gram-positive, three Gram-negative and two fungi strains. The results were recorded in Tables 5 – 7.

Table 5: Antibacterial Activity

Concentration (mg/mL) / zone of inhibition (mm)					
	Gram - negative			Gram - positive	
Compound	*Escherichia coli*	*Klebsiella pneumonia*	*Shigella flexneri*	*Staphylococcus aureus*	*Bacillus subtilis*
L	27.00 ± 2.00	23.67 ± 0.58	23.67 ± 0.58	22.67 ± 0.58	21.33 ± 2.08
NiL	20.00 ± 3.00	21.67 ± 1.15	22.00 ± 0.00	24.00 ± 2.00	25.00 ± 1.00
MnL	19.33 ± 0.58	14.67 ± 2.00	17.33 ± 3.00	24.00 ± 0.00	24.00 ± 1.00
CoL	22.00 ± 2.00	22.00 ± 1.00	21.00 ± 1.00	26.00 ± 1.00	22.00 ± 1.00
Amoxicillin	33.33 ± 0.58	29.00 ± 1.00	29.00 ± 1.00	31.67 ± 3.51	33.33 ± 3.06

Values are mean ± standard deviation of three replicates.

Table 6: Antifungal Activity

Concentration (mg/mL) / zone of inhibition (mm)		
Compound	*Candida albicans*	*Aspergillus fumigatus*
L	25.67 ± 0.57	13.00 ± 0.00
NiL	26.33 ± 0.58	25.00 ± 1.00
MnL	27.00 ± 1.00	26.00 ± 0.00
CoL	26.67 ± 0.57	25.00 ± 1.00
Nystatin	32.33 ± 7.23	34.00 ± 2.00

Values are mean ± standard deviation of three replicates.

Table 7: Minimum concentration (MIC) of ligand and its metal complexes

L	*Escherichia coli*	*Klebsiella pneumonia*	*Shigella flexneri*	*Staphylococcus aureus*	*Bacillus subtilis*	*Candida albicans*	*Aspergillus fumigatus*
50	+	+	+	+	+	+	+
25	+	+	-	+	+	+	+
12.5	-	-	-	-	-	-	-
6.5	-	-	-	-	-	-	-
3.2	-	-	-	-	-	-	-
NiL							
50	+	+	+	+	+	+	+
25	+	+	+	+	+	+	+
12.5	+	+	+	+	-	+	+
6.5	-	-	-	-	-	-	-
3.2	-	-	-	-	-	-	-
MnL							
50	+	+	+	+	+	+	+
25	+	+	+	+	+	+	+
12.5	+	+	+	-	-	+	+
6.5	-	-	-	-	-	-	-
3.2	-	-	-	-	-	-	-
CoL							
50	+	+	+	+	+	+	+
25	+	+	+	+	-	+	+
12.5	+	-	-	-	-	-	-
6.5	-	-	-	-	-	-	-
3.2	-	-	-	-	-	-	-
Amoxicillin							
50	+	+	+	+	+		
25	+	+	+	+	+		
12.5	+	+	+	+	+		
6.5	+	+	+	-	-		
3.2	-	-	-	-	-		
Nystatn							
50						+	+
25						+	+
12.5						+	+
6.5						+	+
3.2						+	-

The ability of the Schiff base ligand and its metal complexes to inhibit the growth of the selected organisms was compared to that of the known standard antimicrobial drugs, Amoxicillin and Nystatin. All the tested organisms showed an intermediate to sensitive reaction to all the metal complexes and the ligand when compared with the standard drugs. Ligand (L) showed greater activity with 27.00, 23.67 and 23.67mm inhibitory zones against Gram-negative bacterial. This was contrary to what have been usually reported in the literatures that metal complexation enhances the bioactivity [28-31], in this case, the formation of the complexes induce a loss of antibacterial potency for Gram-negative bacterial of the complexes. Similar losses in activity have been previously reported with Pd (II), Pt (II) complexes with acetone Schiff bases [32] and Cu (II) complexed with tetradentate ligand [34]. It may also be due to the presence of nitro group in the ligand structure. It has been established that nitro group in aromatic compounds exhibit antimicrobial activity against Gram-negative microorganisms such as *Escherichia coli, Klebsiella pneumonia and Shigella flexneri* [35].

Mn(II) complex has the lowest antibacterial activity against all the Gram-negative bacterial when compared with other complexes. This observation could be as a result of ability of the bacterial to develop efflux mechanism against the complexes [31]. All the complexes showed greater activity against Gram–positive bacterial and fungi when compared with the free ligand. It was observed that the complexes have better antimicrobial and antifungal activity than ligand. The enhanced activity of the complexes can be determined based on chelation theory [22]. Chelation processes help decrease the polarity of central metal ions as a result of partial sharing of positive charge of cation with the donor groups. The minimum inhibitory concentration (MI C) was conducted at five different concentrations as shown in Table 7, the result shows that the compounds possess good activity against the organisms.In general, the complexes are more acti ve than the free ligand, chelation makes metal complex acts as more powerful and potent agent because of coordination which enhances the bacterial activity of the metal complexes thus killing more bacterial and fungal than the free ligand [22].

Conclusion

New tridentate Schiff base ligand derived from ethylenediamine, benzaldehyde and aminobenzophenone with its metal(II) complexes have been synthesized and characterized. The ligand coordinated to the metal(II) ion via azomethine nitrogen and amine to form stable complexes. Octahedral geometry has been proposed for Ni(II), and Co(II) while tetrahedral was proposed for Mn(II). All the tested compounds (ligand and the complexes) showed significant activity against the tested organisms. Thus, they could be used in designing more potent antimicrobial and antifungal agents for the treatment of some common diseases caused by the tested organisms. It can be deduced from this study that the inhibitory ability of the synthesized compounds possess good activity at higher concentrations.

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