

Synthesis, Characterization, Cytotoxicity and Antimicrobial Studies of Schiff Base Derived From 2-Benzoylbenzoic Acid And 4-Nitro Aniline and Its Metal (Ii) Complexes

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Abstract

Schiff base derived from 4-nitro aniline and 2-benzoylbenzoic acid, and its Mn(II), Co(II) and Ni(II) complexes have been synthesized and characterized based on their melting/decomposition temperature, solubility, magnetic and infrared analysis. Gravimetric analysis and Job's method of continuous variation reveal that all metal complexes are in 1:2 metal-ligand ratios. All complexes have low conductance value ($13.6\text{--}20.6\text{ ohm}^{-1}\text{cm}^{-1}\text{mol}^{-1}$), indicating that they are non-electrolyte. However the cytotoxic analysis indicates that Co(II) complex was more toxic with the LC_{50} value of 181.72 $\mu\text{g/ml}$ than the other complexes. The Schiff base and its respective metal complexes were screened for their antimicrobial activities and the results revealed that the compounds showed significant activity against all isolates

Nomenclature and units

k	Kurtosis
γ	Skewness
τ_{MED}	Mean Excess Delay
τ_{RDS}	Root Mean Squared Delay Spread
μ	Mean

1.0 Introduction

Schiff bases are important class of organic compound, which were discovered by Hugo Schiff in 1864 (Hussain *et al.*, 2014), Schiff base is also a type chemical compounds containing carbon-nitrogen double bond as functional group, where the nitrogen atom connected to aryl group or alkyl group (R) but not hydrogen. Since then Scientist shows great interest in the field of transition metal complexes, it also represent one of the most employed class of ligands in coordination chemistry due convenient synthetic preparation and high versatility. These aspects influence their ability to form stable complexes with the large majority of transition metal ions. Significant number of Schiff bases and their complexes has been well studied due to their interesting properties which include; ability to reversibly bind oxygen (Cotton 2006), catalytic activity in hydrogenation of Olefins, transfer of an amino group, photochromatic properties and complexing ability toward some toxic metals (Chandra 2006). The high affinity for the chelation of the Schiff bases towards the transition metal ions is utilized in preparing the solid complex. Schiff base complexes have been a subject of interest due to growing applications in the field of catalysis. In case of transition metals, they have characteristics properties like variable in oxidation states, metals offer a wide range of oxidation state and reactivity of the metal complexes depend upon the stability and inter convertibility of these oxidation states.

Schiff bases are of some most widely used organic compounds. They are used as pigments and dyes, catalyst, intermediate in organic synthesis and as polymer stabilizers. Schiff bases have shown a broad range of biological activities, which include antifungal, antibacterial, antimalarial, antiviral and antipyretic properties (Da Silva *et al.*, 2011). Tetradentate Schiff base ligands are well known to form stable complexes, where the coordination takes place through Nitrogen or Oxygen donor atoms (Akila *et al.*, 2013).

Azomethine or imines are present in various natural, naturally derived, and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities. Schiff base are important compounds. The imine group present in such compounds has been shown to be critical to their

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biological activities. Schiff bases are important compounds due to their wide range of industrial applications (Hussain *et al.*, 2014). Schiff bases have been playing an important part in the development of coordination chemistry. Schiff base metal complexes have been studied extensively because of their attractive chemical and physical properties and their wide range of applications in numerous scientific areas. They play an important role in both synthetic and structural research, because of their preparative accessibility and structural diversity (Nagajothi *et al.*, 2012).

In the research work presented, a new Schiff base ligand was synthesized by condensation of 2-benzoylbenzoic acid with 4-nitro aniline. The synthesized ligand was complexed with Mn(II), Co(II) and Ni(II) respectively. The cytotoxicity and antimicrobial activities of all synthesized compounds was also screened. The aim of the research work was to synthesize Schiff base derived from 2-benzoylbenzoic acid and 4-nitroaniline and its metal (II) complexes.

2.0 Experimental

2.1 Materials and Method

Materials: The glass wares used were washed with detergent and then rinsed with distilled water and dried in an oven at 110 °C. All weighing were carried out on electric Metler balance model B154. Infrared spectral analysis was carried out using Shimadzu FTIR-8400S spectrophotometer in the range of 650-4000 cm⁻¹, Melting point and decomposition temperatures were determined using SMP10 melting point machine. Electrical conductivity measurements were recorded using conductivity meter jenway 4010 model, Magnetic susceptibility of the complexes was determined using MBS MK1 Magnetic susceptibility balance at room temperature. UV-visible measurements were done on a PerkinElmer Lambda 35 UV-visible spectrophotometer. Bacterial and fungal isolates were obtained and identified at the Microbiology Department, Faculty of Life Sciences, Bayero University, Kano.

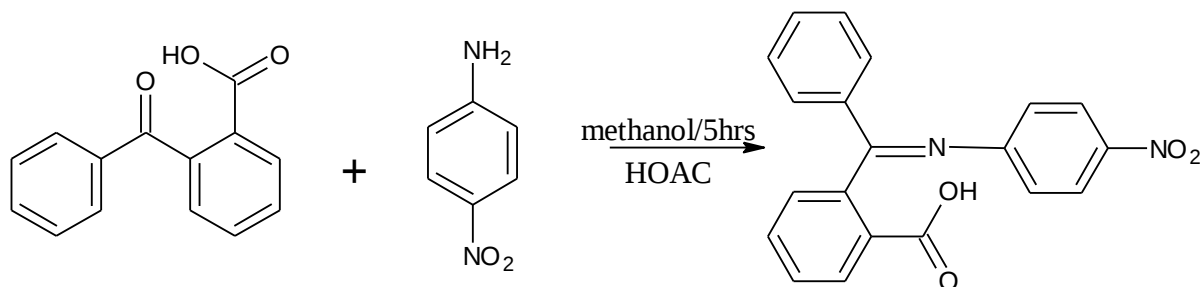
2.2 Synthesis of Ligand

The Schiff base was prepared by condensation of equal molar ratio of p-nitro aniline (0.414 g, 0.03 mol) with 2-benzoylbenzoic

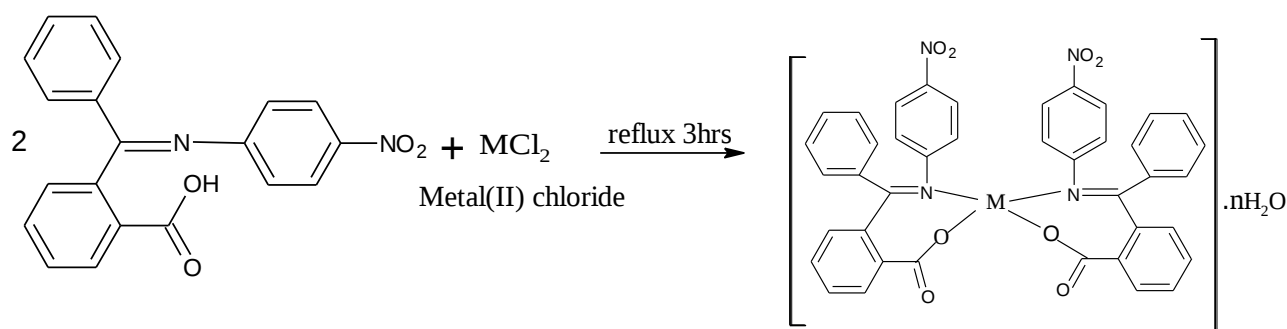
acid (0.679 g, 0.03 mol) dissolved in 50 cm³ methanol, and a few drops of glacial acetic acid was added. The resulting solution was stirred, refluxed for 5 hours and then allowed to cool overnight.

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The yellow crystalline precipitate obtained was filtered, washed with hot methanol and finally dried in a desiccator under phosphorous pentaoxide (Al-Shemary *et al.*, 2017).



Scheme 1: Synthesis of Schiff base



Metal(II) complexes

Scheme 2: Synthesis of metal complexes

2.3 Synthesis of Metal Complexes:

25 cm³ methanolic solution of the synthesized Schiff base (0.002 mol, 0.69 g) was added 25 cm³ methanolic solution of the appropriate metal(II) chloride (0.001 mol, 0.237 g). The mixtures were refluxed for 3 hours and the resulting products were separated by filtration, washed with diethyl ether and dried in a desiccator over phosphorous pentaoxide. (Al-Shemary *et al.*, 2017).

2.4 Antibacterial Test:

The *in-vitro* antibacterial activity of the Schiff base ligand and its metal complexes were assayed by using bacterial isolates of *Staphylococcus aureus*, *streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Escherichia coli*. The suspension of each microorganism was smeared on the surface of the solidified Muller-Hinton Agar (MHA) already poured into petri dishes. The

Schiff base and the metal Complexes were separately dissolved in DMSO so as to have three distinct concentrations (60 µg/ml, 30 µg/ml and 15 µg/ml) through serial dilution and placed on the surface of the culture media, incubated at 37 °C for 24 hours. Activities were determined by measuring (mm) the diameter of the zone of inhibition and compared with a standard drug (Sharma *et al.*, 2009).

2.5 Antifungal Test:

The *in-vitro* antifungal activity of the Schiff base ligand and that of its metal complexes were tested against three pathogenic fungi; *Aspergillus flavus*, *Candida albicans* and *Aspergillus fumigatus*, using disc diffusion method. Ketoconazole was used as standard fungicide and DMSO was used as a negative control (Khan *et al.*, 2014). The fungal suspension was smeared on the solidified Potato Dextrose Agar (PDA) already poured into petri dishes. The Schiff base and the metal Complexes were separately dissolved in

DMSO to have three different concentrations (60 µg/ml, 30 µg/ml and 15 µg/ml) per well. They were placed on the surface of the culture media and allowed to stand at room temperature for good 48 hours. Activities were determined by measuring (mm) the diameter of the zone of inhibition and compared with the standard (Sharma *et al.*, 2009).

2.6 Cytotoxicity assay (Brine Shrimp lethality test):

Brine shrimp eggs were hatched for 48 hours. The stock solutions were prepared by dissolving 20 mg of each of the Schiff base ligand and metal complexes in 2 ml of methanol. From the stock solution, aliquots of 500 µl, 50 µl and 5 µl were pipette and added into separate vials and allowed to dry overnight. Usually three (3) vials for each concentration (1000, 100, 10) were prepared making a total of nine (9) vials per sample. Ten (10) shrimps were transferred to each vial using a Pasteur pipette and the volume of the liquid in each vial was adjusted to 5 ml using sea water. After 24 hours, the numbers of surviving shrimps were counted and the LC₅₀ was determined at 95% confidence interval using regression analysis (Rahamatullah *et al.*, 2010).

2.7 Determination of Number of Coordinated Ligand:

The number of the ligands to coordinated to the metal ion was determined using Job's method of continuous variation (Angelici, 1971).

3 mmol aqueous solution and the metal chlorides were prepared. The following Ligand to Metal salt ratio (ml): 1:15, 3:13, 5:11, 7:9, 9:7, 11:5, 13:3 and 15:1 respectively was taken from the ligand solution and each of the metal Chloride solution respectively. A total volume of 16ml was maintained (in that order) throughout the process and the mole fraction of the ligand was calculated in each mixture. The solutions of the metal chlorides were scanned (as blank) to find the wavelength of maximum absorption for the particular metal ion (Angelici,

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1971). The machine was fixed at $\lambda_{\max}$ (in each case) before taking the absorbance values.

A plot of absorbance against mole fractions was made and by extrapolation, mole fraction (x_i) at maximum absorbance was recorded, which was the point where the metal ion and the ligand are in stoichiometric ratio. The number of coordinated Schiff base ligand to metal ion was calculated using the relation;

$$\bar{n} = \frac{x_i}{1 - x_i}$$

where $\bar{n}$ = the number of coordinated ligand

X_i = corresponding mole fraction of the ligand at maximum absorbance

2.8 Determination Empirical Formula:

The composition of each complex was determined from the known percentage of the metal ion and water content in the complex. The percentage composition of the ligand was obtained by adding percentage composition of the metal and water in the complex and subtracted from 100 to get that of ligand. The empirical formula of each of the complex was calculated using the percentage composition of the species involved.

3.0 Results And Discussion

The ligand was synthesized by condensation by condensation reaction if 2-benzoylbenzoic acid with 4-nitro aniline in methanol. The ligand formed was observed to be yellow crystal formed with good yield of 69.5% and melting point of 120°C. The metal complexes were achieved by the interaction between Schiff base and metal salts solutions. The Mn(II), Co(II) and Ni(II) complexes were synthesized and found to be of different colors with percentage yield of 75.3%, 70.6% and 66.0% respectively. The decomposition temperature of metal complexes ranges from 165-187°C, which was in agreement with respective similar metal (II) complexes observed in literature adopted (Al-Shemary *et al.*, 2017). The result obtained are presented in table 1, below

Table 1: physical properties of ligand and its corresponding metal (II) complexes

Compound	Colour	% yield	Decomposition Temp (°C)	Melting point Temp. (°C)
Ligand	Yellow	69.5		120
[MnL ₂].2H ₂ O	Dark Yellow	75.3	165	
[CoL ₂].5H ₂ O	Brown	70.6	171	
[NiL ₂].4H ₂ O	Green	66.0	187	

L=C₂₀H₁₄N₂O₄

Solubility test was carried out on Schiff base and metal complexes and it has shown that the compound were soluble in methanol, DMF, DMSO, but insoluble in distilled water, N-hexane and Chloroform. However, in ligand its soluble in

Methanol, ethanol, DMSO, DMF, but insoluble in distilled water, N-hexane, Chloroform and slightly soluble in carbon tetrachloride, acetone and petroleum ether. As shown in table 2 below:

Table 2: Solubility test of the Schiff base and its Metal (II) Complexes

Solvents	Ligand	[MnL ₂].2H ₂ O	[CoL ₂].5H ₂ O	[NiL ₂].4H ₂ O
Water (H ₂ O)	IS	IS	IS	IS
Methanol	S	S	S	S
Ethanol	S	S	SS	S
N-hexane	IS	IS	IS	IS
Carbon Tetrachloride	SS	SS	IS	SS
Acetone	SS	SS	SS	IS
Chloroform	IS	SS	IS	SS
Petroleum ether	SS	IS	SS	SS
DMF	S	S	S	S
DMSO	S	S	S	S

KEY: IS=Insoluble, S=soluble and SS=slightly soluble. Ligand, L=C₂₀H₁₄N₂O₄

DMF=Dimethylformamide and DMSO=Dimethylsulphoxide

The FTIR spectra data of Schiff base ligand and its metal complexes was studied by comparing the FTIR spectra of free

ligand with that of complexes. IR spectra of free ligand shows a band of 334 6cm⁻¹ assigned to ν(OH) stretching vibrations. A

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 strong peak at 1607 cm^{-1} region were attributed to the azomethine $\nu(\text{C}=\text{N})$ group. (Mahmoud *et al.*, 2016). These relative shifts observed for $\nu(\text{C}=\text{N})$ band in complexes showed the participation of azomethine nitrogen in coordination to the metal ions (Gehad *et al.*, 2016). Two bands at absorptions $717\text{--}769\text{ cm}^{-1}$ and that of

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 $441\text{--}518\text{ cm}^{-1}$ support the formation of M-N and M-O bands. (Ali, 2014). These data suggest that the azomethine -N, carboxylate-O and enolic -O are involved in coordination with metal (II) ion in the complexes. As shown in table 3:-

Table 3: IR Spectral data of the Schiff base and its metal (II) complexes

Compound	$\nu(\text{C} = \text{N})\text{ cm}^{-1}$	$\nu(\text{M} - \text{N})\text{ cm}^{-1}$	$\nu(\text{M-O})\text{ cm}^{-1}$	$\nu(\text{OH})\text{ cm}^{-1}$
Ligand	1607	-	-	3346
$[\text{MnL}_2] \cdot 2\text{H}_2\text{O}$	1633	769	504	3476
$[\text{CoL}_2] \cdot 5\text{H}_2\text{O}$	1629	717	444	3357
$[\text{NiL}_2] \cdot 4\text{H}_2\text{O}$	1577	765	518	3391
$\text{L} = \text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_4$				

The molar conductance of each metal complex was observed in 10^{-3}M DMSO solution at room temperature using procedure reported by Geary 1971. The conductance value observed to be relatively low within the range of $13.6\text{--}20.6\text{ }\Omega^{-1}\text{ cm}^{-1}\text{ mol}^{-1}$ which

shows that all metal (II) complexes prepared were non-electrolyte in nature which is in agreement in literature reported by Gupta, 2012. As shown in the table 4:- below

Table 4: Molar conductance of Metal (II) complexes in 10^{-3}M DMSO solution

Compounds	Electrical conductance ($\text{Ohm}^{-1}\text{ cm}^{-1}$)	Molar Conductivity ($\text{Ohm}^{-1}\text{ cm}^{-1}\text{ mol}^{-1}$)
$[\text{MnL}_2] \cdot 2\text{H}_2\text{O}$	61.8	20.6
$[\text{CoL}_2] \cdot 5\text{H}_2\text{O}$	46.0	15.3
$[\text{NiL}_2] \cdot 4\text{H}_2\text{O}$	40.9	13.6
$\text{L} = \text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_4$		

The magnetic susceptibility of Mn(II), Co(II) and Ni(II) complexes were measured. The respective values were given in table 5 and indicated that they are all paramagnetic in nature, these finding was in good agreement with previous report on transition

metal complexes of Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) synthesized with Schiff base derived from saccharine (Taghreed, 2016).

Table 5: Magnetic susceptibility values of the metal (II) complexes

Compound	Mass Susceptibility, X_g (erg. G ⁻² g ⁻¹)	Molar Susceptibility, X_m (erg. G ⁻² mol ⁻¹)	μ_{eff} (B.M)	Property
[MnL ₂].2H ₂ O	1.986x10 ⁻⁵	1.48x10 ⁻²	5.9	Paramagnetic
[CoL ₂].5H ₂ O	1.15x10 ⁻⁵	8.62x10 ⁻³	4.53	Paramagnetic
[NiL ₂].4H ₂ O	4.7x10 ⁻⁶	3.55x10 ⁻³	2.91	Paramagnetic

$L = C_{20}H_{14}N_2O_4$

The metal- ligand ratio determination was done by using Job's method of continuous variation (UV-Visible) and the results were given in table 6. The result reveals that the metal-ligand ratio was

1:2. Gravimetric analysis was used for the determination of percentage of metal (II) ion in complexes as shown in the table 6 below:-

Table 6: Empirical formula of the metal complexes

compound	% metal	% ligand	% water	metal:ligand:water	Empirical formula
Manganese complex	9.0	86.5	4.5	1:2:2	[MnL ₂].2H ₂ O
Cobalt complex	6.5	84.6	9.0	1:2:5	[CoL ₂].5H ₂ O
Nickel complex	8.5	82.0	9.5	1:2:4	[NiL ₂].4H ₂ O

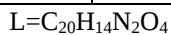
$L = C_{20}H_{14}N_2O_4$

The *in-vitro* antibacterial activity of Schiff base ligand and its respective metal (II) complexes was carried out against four bacterial isolates (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*), using well diffusion method and DMSO as solvent. The results indicated that the ligand shows high activity at high concentration and minimal activity at low concentration against *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Escherichia coli* except *Streptococcus pneumoniae* which shows no activity at both high

and low concentration. In addition to that the metal (II) complexes exhibit different concentration, showing higher activity against *Klebsiella pneumoniae* than the other isolates, *Staphylococcus aureus*, and *Escherichia coli* shows moderate activity while the other one shows low activity in all complexes, antimicrobial data reveals that the activity of ligand and their respective metal (II) complexes were found to be lower than the control used *ciprofloxacin* as shown in table 7 below:-

Table 7: Antibacterial activity of the Schiff base and its metal (II) complexes

Isolates	Compounds	Zone of inhibition (µg/ml)			Ciprofloxacin 500mg as standard
		60	30	15	
<i>Staphylococcus aureus</i>	Ligand	10	7	6	31
	[MnL ₂].2H ₂ O	12	10	7	
	[CoL ₂].5H ₂ O	15	9	8	
	[NiL ₂].4H ₂ O	13	7	6	
<i>Streptococcus pneumoniae</i>	Ligand	6	6	6	28
	[MnL ₂].2H ₂ O	7	6	6	
	[CoL ₂].5H ₂ O	20	16	11	
	[NiL ₂].4H ₂ O	12	9	6	
<i>Eschericia coli</i>	Ligand	15	10	8	22
	[MnL ₂].2H ₂ O	10	7	6 17	
	[CoL ₂].5H ₂ O	12	10		
	[NiL ₂].4H ₂ O	9	6	6	
<i>Klebsiella pnemoniae</i>	Ligand	14	10	6	26
	[MnL ₂].2H ₂ O	17	16	11	
	[CoL ₂].5H ₂ O	20	13	10	
	[NiL ₂].4H ₂ O	15	12	7	



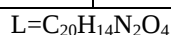
The in-vitro antifungal activity shows that the ligand exhibits moderate activity against all the fungal isolates tested. Moreover,

Co(II), Ni(II) complexes shows moderate activities against all isolates at high concentrations while Mn(II) complexes showed

low activities against tested microbes. However, all the activities were found to be lower than the control ketoconazole as shown in the table 8:-

Table 8: Antifungal activity of the Schiff base and its metal (II) complexes

Isolates	Compounds	Zone of inhibition (µg/ml)			Ketoconazole Standard
		60	30	15	
<i>Aspergillus fumigatus</i>	Ligand	18	15	11	33
	[MnL ₂].2H ₂ O	17	15	9	
	[CoL ₂].5H ₂ O	22	18	15	
	[NiL ₂].4H ₂ O	20	19	14	
<i>Aspergillus flavus</i>	Ligand	15	12	6	29
	[MnL ₂].2H ₂ O	12	10	6	
	[CoL ₂].5H ₂ O	21	16	12	
	[NiL ₂].4H ₂ O	20	18	10	
<i>Candida albicans</i>	Ligand	18	12	6	30
	[MnL ₂].2H ₂ O	18	13	6	
	[CoL ₂].5H ₂ O	17	13	12	
	[NiL ₂].4H ₂ O	23	19	13	



The cytotoxicity of the Schiff base and that of metal (II) complexes was conducted against brine shrimps larvae and the result are presented in table 9. The LC₅₀ value estimated for the ligand was found to be 147.718µg/ml and that of complexes was to range from 141.932-181.173µg/ml. by applying Clarkson toxicity criterion they were found to be toxic (Clarkson *et al.*, 2004).

4.0 Conclusion

The schiff base derived by condensation of 2-benzoylbenzoic acid and 4-nitro aniline and its metal (II) complexes has been synthesized, characterized and screened for their antimicrobial

activity as well as cytotoxicity, Job's method of continuous variation shows that metal-ligand ratio in all complexes is 2:1. Molar conductance value of the complexes were low which indicates the non-electrolyte nature of the complexes, the magnetic susceptibility measurement values of the complexes are paramagnetic in nature, all the respective metal complexes were evaluated in-vitro against four bacterial isolates and three fungal isolates indication that all compounds showed significant antibacterial, antifungal strength at high concentration moreover, cytotoxicity tests shows that the schiff base and corresponding metal complexes were toxic in nature.

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