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SYNTHESIS, CHARACTERIZATION, CYTOTOXICITY AND ANTIMCIROBIAL STUDIES OF METAL(II) COMPLEXES OF SCHIFF BASE DERIVED FROM 2-BENZOYLBENZOIC ACID AND 1,3-DIAMINOPROPANE

UMAR SANI[1*], AISHA S. DAYYIB[1], SAMAILA ABUBAKAR[2] AND DAILAMI S. ADAM[3]

[1]Department of Pure and Industrial Chemistry, College of Physical Sciences, Bayero University, PMB 3011 Kano.

[2]Department of Chemistry, Gombe State University, PMB 127 Gombe, Gombe State

[3]Department of Chemistry, Federal University Lokoja, PMB 1154 Lokoja, Kogi State

Corresponding author email: sumar.chm@buk.edu.ng

ABSTRACT

Metal complexes of Ni(II), Cu(II) and Zn(II) with a Schiff base derived from 2-benzoylbenzoic acid and 1,3-diaminopropan have been prepared and characterized. Infrared spectral studies reveal that Schiff base behaves as a neutral tetradentate ligand and coordinates to the metal ions via the two azomethine nitrogen and carboxylate oxygen. Molar conductance measurement of (7.97 – 29.46) ohm^{-1} cm^2 mol^{-1} indicates a non-electrolytic nature of all the complexes. Solubility test showed that all complexes and Schiff base are soluble in DMSO and methanol. Magnetic susceptibility and IR studies suggests tetrahedral structure for the complexes while Job's method of continues variation establish 1:1 metal to ligand ratio, on which basis the coordination structures are proposed. The *in vitro* antibacterial and antifungal activity showed that the complexes are more active than the Schiff base. Moreover, the cytotoxicity analysis indicates that the tested compounds possess low toxicity.

Key words: Schiff base · Metal complexes · Spectroscopic study · Antimicrobial activity · Solubility · Cytotoxicity activity

INTRODUCTION

A Schiff base is a type of chemical compounds containing a carbon-nitrogen double bond as functional group, where the nitrogen atom connected to aryl group or alkyl group (R) but not hydrogen (Bader, 2010). These compounds were named after Hugo Schiff (Bader, 2010). Schiff-bases are considered as a very important class of organic compounds, having wide applications in many biological aspects, proteins, visual pigments, enzymic aldolization and decarboxylation reactions (Cakır and Bicer, 2010; Abbas *et al*., 2010).

Moreover, some Schiff bases and their metal complexes exhibit biological activities such as antiviral, antifungal, antibacterial and as antitumor agents,. They are also used as catalysts in polymer and dyes industry, beside some uses as antifertility and enzymatic agents (Kumar *et al*, 2009).

Tetradentate Schiff base ligands are well known to form stable complexes, where the coordination takes place through N or O type donor atoms (Akila *et al*., 2013). They possess many advantages such as facile approach, relative tolerance, readily adjusted auxiliary ligands, and tunable steric and electronic coordination environments on the metal center (Al-Shemary and Zaidan, 2016).

Schiff bases could form complexes with metals in terminal, bridging or chelation mode via nitrogen and other donor atoms such as oxygen, phosphorus and carbenes. Schiff base complexes have been reported to possess a wide range of biological activities against bacteria, fungi, and certain type of tumors (Zoubi, 2013).

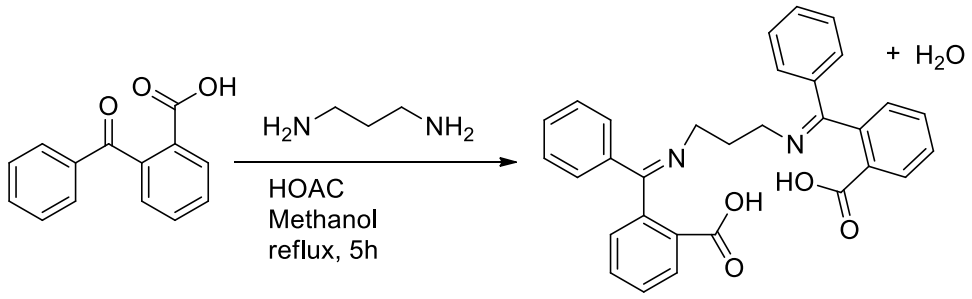
In the work presented here in, a new Schiff base ligand was synthesized by condensation of 1,3-diaminopropane with 2-benzoylbenzoic acid. The synthesized ligand was complexed to Ni(II), Cu(II) and Zn(II). They are inexpensive, environmentally benign earth abundance element of group II. The cytotoxicity and antimicrobial activities of all the synthesized compounds was also studied.

Experimental

Materials: All chemical used were of analytical grade and of high purity. 2-benzoylbenzoic acid and 1,3-diaminopropane were obtained from Sigma-aldrich. Metal (II) chloride salts were obtained from Bayero University Kano store. Solvents were used without further purification. All weighing were carried out on an electronic Metler balance model H3OAR, melting point/decomposition temperatures were determined using Stuart SMP10 melting point apparatus. Molar conductance measurements were carried out in DMSO using Jenway conductivity meter 4010 model. Magnetic susceptibility measurement was conducted using magnetic susceptibility Balance MK1 model, infrared spectral analyses were recorded using FTIR Cary 630 (Agilent Technology) model in the range of 4000 - 400cm^{-1}. Absorbance measurements were carried out on UV spectrophotometer PerkinElmer lambda 35. Microbial activity studies were carried out at the Microbiology Department, Bayero University Kano, Nigeria.

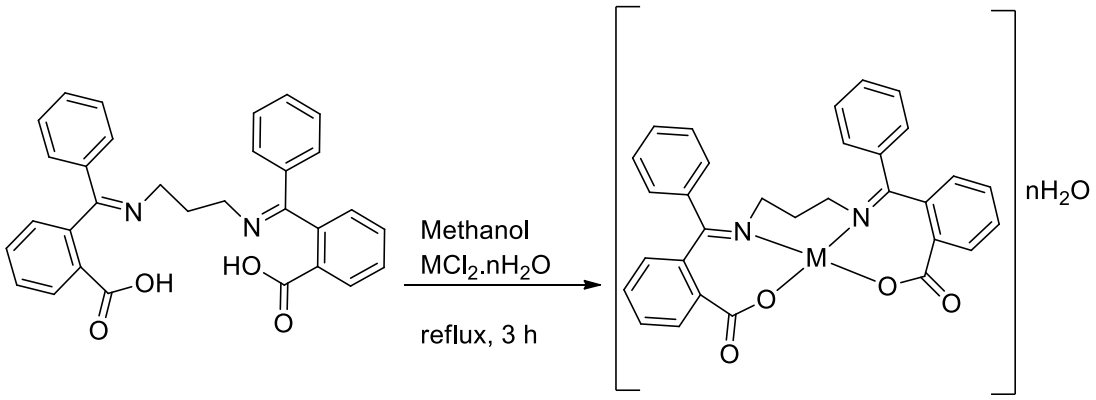
Synthesis of Schiff Base Ligand: The Schiff base ligand was prepared according to the adopted method of (Al-Shemary and Zaidan, 2016). Benzophenone-2-carboxylic acid (0.03mole; 6.78g) was placed in a round bottom flask and was added to it, 1,3-daiminoproane (0.015mole; 1.11g). Methanol 40 ml was then added to the mixture and a few drops of glacial acetic acid was also added the mixture was refluxed for 5hrs with constant stirring. The resulting reaction mixture was concentrated to one third of its total volume and the precipitated product obtained on cooling was collected by filtration, washed and dried in a desiccator

over phosphorus pentaoxide. The ligand is soluble in methanol and DMSO. Scheme 1



Scheme 1: Synthesis of Schiff base

Synthesis of Metal Complexes: In each case the ligand precursor (0.003moles) was placed into a round bottom flask and mixed with equimolar amount of the metal(II) chloride salts (0.003moles) in 20 ml of methanol and the mixture was stirred and refluxed for 3 hours. The resulting reaction mixture was concentrated to one third of the original volume and the precipitates obtained on cooling was filtered, washed twice with diethylether and dried in a dessicator over phosphorus pentaoxide. (Al-Shemary and Zaidan, 2016). Scheme 2



Scheme 2: Synthesis of metal complexes

Antibacterial Test:

Standard inoculums of the isolates were swabbed on to the surface of prepared and solidified Muller Hinton Agar (MHA) in separate petri-dishes. The wells (6 mm in diameter) were dug in the agar media with the help of a sterile metallic borer. Three concentrations (15, 30 and 60 µg/ml) of the ligand and the metal (II)

complexes in DMSO were prepared through serial dilution and placed on the nutrient agar before incubation at 37 ℃ for 24 hours. The antibacterial activity was assayed by measuring the diameter of the inhibition zone formed around the well (Yusha'u *et al*, 2011). The results were compared with standard drug, Ciprofloxacin.

Antifungal Test:

Standard inoculums of the isolates were swabbed on to the surface of prepared and solidified Potato Dextrose Agar (PDA) in separate petri-dishes. The wells (6 mm in diameter) were dug in the agar media with the help of a sterile metallic borer and 10 uL of the solutions (15, 30 and 60 µg/ml) were added in each well. The plates were then incubated at 25 ^{0}C for 48hrs. The antifungal activity was assayed by measuring the diameter of the inhibition zone formed around the well (Yusha'u *et al*, 2011). The results were compared with standard drug, Ketoconazole.

Cytotoxicity assay (brine shrimp lethality test)

A sample of the test compounds were prepared by dissolving 0.02g (20 mg) of each compound in 2ml of methanol from which an aliquot of 500, 50, 5µL was transferred into a glass vials (three for each dilutions were used for each test sample) and allowed to dry overnight. Two drops of DMSO was used in each vial to moisten the compounds followed by addition of 2ml of sea water.10 shrimps lava were fed into the vile using pasture pipette and made to 5ml using labeled negative control (containing 2 drops of DMSO and 5ml of sea water only). This gives concentration of 1000, 100, and 10 µg/ml for each fraction. The number of mortality (death) was recorded after 24 hours in each vile and LC_{50} (lethal concentration at 50%) was estimated using a probit regression analysis (Olowa and Nuneza, 2013).

Determination of Number of Coordinated Ligand

The ligand to metal ratio in the complexes was determined using continuous variations method (Job's method) (Agelici, 1971). 0.003moldm^{-3} solution of the ligand and that of the metal(II) salt was prepared. A solution mixture having total volume of 16cm^3 in which the mole fraction of the ligand, x_i is $0.06 \leq x_i \geq 0.9$ were also prepared. The absorbance of each solution mixture was measured at the wavelength of maximum absorbance of the metal (II) chloride solutions. 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.

$$n = \frac{xi}{1} - xi$$

Where n = the number of coordinated ligand

x_i = corresponding mole fraction of the ligand at maximum absorbance

Determination of the percentage of metal content:

The metal contents were determined gravimetrically by digestion with nitric acid. The percentages of each of the metal ion were obtained from their gravimetric factor.

RESULTS AND DISCUSSIONS

The ligand precursor **1** was synthesized by the reaction of 2-benzoylbenzoic acid with 1,3-diaminopropane in methanol. Confirmation for the formation of the ligand was supported by its analytical and spectral data. The subsequent reaction of the ligand precursor with the selected metal salts ($NiCl_2.4H_2O$, $ZnCl_2.2H_2O$, and $CuCl_2.2H_2O$ in methanol gives the corresponding complexes. The physical characteristics and analytical data of ligands and metal complexes are presented in Tables 1-5. All the complexes are colored solid, air stable, non-hygroscopic and insoluble in non-polar solvents but sparingly soluble in methanol and DMSO. The job's analysis support 1:1 metal to ligand stoichiometry for all the complexes.

Infrared Spectroscopy: The FT-IR spectrum of 1,3-diaminopropane shows peaks at 3279 cm^{-1} and 3357 cm^{-1} due to stretching frequencies of free $-NH_2$, these bands are absent in the spectrum of the Schiff base. Also, no strong band was observed at 1715 cm^{-1} indicating the absence of v(C=O) group of 2-benzoylbenzoic acid, and this indicates the formation of the Schiff base between the carbonyl group and the amino group of 1,3-diaminopropane has taken place. Furthermore, the IR spectrum of the ligand showed an absorption band at 1633cm^{-1}, which is assigned to v(C=N) stretching vibration. However, as expected this band was observed to have shifted to a lower frequency within the range of (1626-1614) cm^{-1} in the metal complexes., these shift of wave numbers was an indication of formation of –C=N-M bonding (Mahmoud *et al*., 2015). The spectra of the ligand also showed a broad band near 3286 - 2344 cm^{-1} due to v(OH) stretching frequency of 2-benzoylbenzoic acid (Al-Shemary, 2015). Absence of this band in the spectra of the complexes indicated deprotonation and involvement of the oxygen of carboxylate in chelation (Al-Shemary, 2015). Furthermore, the free ligand exhibits strong absorption band at (1666)cm^{-1} due to the stretching vibration of v(C=O) of carboxylic group (Abdallah *et al*., 2010; Mahmoud *et al*., 2015) and this band disappeared in the spectra of the metal complexes accompanied by the appearance of new absorption bands at around (1562-1596) cm^{-1} and (1380 - 1398) which were assigned to υ_{asymm} (COO^-) and to υ_{symm} (COO^-) for all the complexes, ($\Delta\upsilon_{asym.} - \Delta\upsilon_{sym}$) = (167 -198) cm^{-1}, supporting the idea that the ligand coordinate through deprotonated oxygen of carboxylate (Al-Shemary and Zaidan, 2016). Furthermore, the spectra of the complexes revealed the presence of a bands in the range 3327 - 3506cm^{-1} due to the v(OH) of the water molecules associated with the complexes (Ejidike and Ajibade, 2017, Aliyu and Ado, 2011). In all the complexes additional band was also noeted in the region of (676-736) cm^{-1} and (478 - 489) cm^{1}. These vibrations has been ascribed to v(M-N) and v(M-O) respectively indicating coordination

of the Schiff base to the respective metal ion. The FTIR results are presented in Table 3

Molar Conductance:

The molar conductance measurement in DMSO carried out on the metal (II) complexes were found to be 7.97- 29.46 ohm^{-1} cm^{-1} mol^{-1}, these lower values suggested that, the complexes are non-electrolytes (Geary, 1971). Results are presented in table 4.

Magnetic Susceptibility:

Magnetic susceptibility measurement carried out at room temperature showed that the metal (II) complexes are all found to be paramagnetic in nature with the exception of zinc complex. The diamagnetism of Zn complex can be attributed to the d^{10} configuration of the metal. All the magnetic moment values of the metal (II) complexes prepared were found within the range of tetrahedral complexes according to the Figgis and Lewis assertion ((Figgis *et al*., 1960). Results are presented in Table 5.

Antibacterial activity:

The *in vitro* antibacterial assay of the Schiff base and its metal(II) complexes were carried out on four bacterial isolates; *Staphylococcus aureus, Streptococcus pneumoniae, Klebsiella pneumonia* and *Escherichia coli.* The results were interpreted by measuring the zones of inhibition of growth of the bacterial culture. The Schiff base ligand shows activity only at higher concentrations in all the isolates. However, the metal complexes exhibit moderate activity in all the bacterial strains used. The activity of the complexes increases with increase in concentration and the activity follows the order Ni (II) > Cu(II) > Zn(II). All the complexes showed potential activity toward *Staphylococcus aureus* and *Klebsiella pneumonia* than other bacterial isolates used. Furthermore, a comparative study of the ligand and its metal (II) complexes indicates that the metal chelates exhibit higher antibacterial activity than the free ligand but lower antibacterial activity compared with the standard Ciprofloxacin as recorded. Table 7

Antifungal activity:

The Schiff base and its metal(II) complexes were also evaluated for antifungal activity on *Aspergillus flavous, Aspergillus fumigatus* and *Candida albicans* respectively. The result revealed that the Schiff base possessed no antifungal activity even at higher concentration while the complexes exhibits moderate activity in all the used isolates. Moreover, the activity of the complexes increases with increase in concentration and showed activity against the isolates in the order; *Aspergillus fumigatus*> *Candida albicans*> *Aspergillus flavous*. Though the complexes showed higher activity than the Schiff base they were found to be lower than that of the control Ketoconazole. Table 8

Generally, all the synthesized complexes were found to be more potent in inhibiting the growth of microorganisms than the Schiff base ligand under similar experimental conditions; this might be due to chelation or complexation (pethe *et al*., 2015). Chelation reduces the polarity of central metal atom because of partial sharing of its positive charge with the donor group within the whole

chelate ring system and thus increases the lipophilic nature of the central atom, which favour the permeation of the complexes through the lipid layer of the cell membrane and result in enhancement of activity (pethe *et al*., 2015).

Cytotoxicity analysis: Cytotoxicity (brine shrimp bioassay) was determined for the Schiff base ligand and its metal (II) complexes. The cytotoxicity is expressed as LC_{50} that is concentration, at which 50% of the larva cells were killed under the assay conditions. From the data recorded (Table 6) indicates that the Schiff base ligand shows the highest brine shrimp toxicity with LC_{50} of 771.495 µg/ml while Nickel (II) complex has the least cytotoxic power with LC_{50} 1101.110 µg/ml. However, the result showed that the activities in each viles are according to concentration that is more death at higher and less death at lower concentration. Furthermore, the toxicity was compared with highly toxic substance (potassium dichromate) used as positive control with LC_{50} of 13.371 µg/ml and this suggest the low cytotoxic activity of the synthesized compounds. According to Clarkson's assertion of toxicity index LC_{50} of 0-100 are considered highly toxic, 100-500 medium toxic, 500-1000 low toxic and above 1000 non- toxic (Hamidi *et al.*, 2014). Based on this protocol, the Schiff base, Cu(II), and Zn(II) complexes are low toxic while Ni(II) complexes is non-toxic.

Table 1: Physical Properties of the Schiff base and its Metal (II) Complexes

Compound	Colour	Melting point ^oC	Decomposition temp ^oC	Percentage yield (%)	% of metal Calculated (Found)
Schiff base (L)	White	150	-	84	-
[NiL].4H_2O	Light green		187	86	9.50 (10.20)
[CuL].2H_2O	Greenish blue		195	79	10.80 (9.60)
[ZnL].2H_2O	Off-white		180	87	11.01 (11.52)

L = Ligand = Schiff base ($C_{31}H_{26}O_4N_2$)

Table 2: Solubility of the Schiff base and its Complexes in some common Solvents

Compounds	D.water	MeOH	EtOH	$CHCl_3$	Acetone	CCl_4	n.hexane	p.ether	DMF	DMSO
Schiff base (L)	IS	S	SS	SS	IS	IS	IS	IS	SS	S
[NiL].$4H_2O$	IS	S	SS	SS	SS	IS	IS	IS	SS	S
[CuL].$2H_2O$	IS	S	SS	SS	S	IS	IS	IS	SS	S
[ZnL].$2H_2O$	IS	S	SS	SS	SS	IS	IS	IS	SS	S

Key: S - Soluble, SS - Slightly Soluble, IS - Insoluble. L = Ligand = Schiff base ($C_{31}H_{26}O_4N_2$)
$CHCl_3$ – Chloroform, CCl_4 – Carbon tetrachloride, MeOH- Methanol, EtOH – Ethanol

Table 3: Infrared Spectral data of the Schiff base and its Complexes

L = Ligand = Schiff base ($C_{31}H_{26}O_4N_2$)

Compound	υ(OH) cm^{-1}	ν(C=O) cm^{-1}	υ(C=N) cm^{-1}	$\nu(COO)_{asym}$ cm^{-1}	$\nu(COO)_{sym}$ cm^{-1}	υ(M-N) cm^{-1}	υ(M-O) cm^{-1}
Schiff base (L)	3286	1666	1633	--	--	--	--
[NiL].$4H_2O$	3327	--	1614	1562	1395	676	478
[CuL].$2H_2O$	3506	--	1626	1596	1398	721	481
[ZnL].$2H_2O$	3484	--	1622	1577	1380	736	489

Table 4: Molar Conductivity of Metal Complexes in 0.003mole/dm^3 DMSO solution

Compound	Specific conductance ($ohm^{-1}cm^{-1}$) × 10^{-6}	Molar conductance ($ohm^{-1}cm^{-1}mol$)
[NiL].$4H_2O$	88.40	29.46
[CuL].$2H_2O$	77.30	25.76
[ZnL].$2H_2O$	23.90	7.97

L = Ligand ($C_{31}H_{26}O_4N_2$)

Table 5: Magnetic Susceptibility of the Complexes

Compound	Gram magnetic susceptibility(X_g) (g^{-1})	Molar Magnetic Susceptibility (X_g) (mol^{-1})	μeff (B.M)	Magnetic property
$[NiL].4H_2O$	9.12×10^{-6}	4.99×10^{-3}	3.44	Paramagnetic
$[CuL].2H_2O$	1.05×10^{-6}	5.79×10^{-4}	1.17	Paramagnetic
$[ZnL].2H_2O$	-1.0×10^{-6}	-	-	Diamagnetic

L = Ligand ($C_{31}H_{26}O_4N_2$)

Table 6: Cytotoxic Activity of the Schiff base and its Metal (II) Complexes

Compound	Concentration (μg/ml)	Replica	Brine shrimps lava	Survivors after 24hrs	Total death	%Mortality	LC_{50} (μg/ml)
Schiff base	1000	3	10	4, 5,5	16	53.3	771.495
	100	3	10	8, 6, 8	08	26.7	
	10	3	10	9, 8, 10	03	10.0	
$[NiL].4H_2O$	1000	3	10	6, 5, 5	14	46.7	1101.110
	100	3	10	8, 7, 8	07	23.3	
	10	3	10	10, 10, 9	01	3.3	
$[CuL].2H_2O$	1000	3	10	4, 5, 6	15	50.0	802.715
	100	3	10	7, 6, 7	10	33.3	
	10	3	10	8, 9, 10	03	10.0	
$[ZnL].2H_2O$	1000	3	10	4, 5, 5	16	53.3	909.064
	100	3	10	7, 8, 8	07	23.3	
	10	3	10	9, 9, 8	04	13.3	
Positive control (potassium dichromate)	1000	3	10	0,0,0	30	100.0	13.371
	100	3	10	2,2,2	24	80.0	
	10	3	10	6,4,6	14	46.7	

L = Ligand = Schiff base ($C_{31}H_{26}O_4N_2$)

Table 7: Antibacterial Activity of the Schiff Base and its Complexes

Isolates	Compounds	Zone of Inhibition (mm)/Concentration ($\mu g/cm^3$)			Control(mm) Ciprofloxacin ($30\mu g/cm^3$)
		60	30	15	
Staphylococcus aureus	Schiff base (L)	12	06	06	
	$[NiL].4H_2O$	15	12	09	31
	$[CuL].2H_2O$	16	10	06	
	$[ZnL].2H_2O$	14	09	06	
Streptococcus pneumoniae	Schiff base (L)	10	06	06	
	$[NiL].4H_2O$	14	06	06	
	$[CuL].2H_2O$	12	11	10	33
	$[ZnL].2H_2O$	11	08	06	
Escherichia coli	Schiff base (L)	08	06	06	
	$[NiL].4H_2O$	12	10	08	
	$[CuL].2H_2O$	11	10	09	26
	$[ZnL].2H_2O$	10	08	06	
Klebsiella pneumoniae	Schiff base (L)	09	08	06	
	$[NiL].4H_2O$	17	15	13	
	$[CuL].2H_2O$	11	10	07	29
	$[ZnL].2H_2O$	10	08	06	

Table 8: Antifungal Activity of the Schiff Base and its Complexes

Isolates	Compounds	Zone of Inhibition (mm)/Concentration ($\mu g/cm^3$)			Control (mm) Ketoconazole ($30\mu g/cm^{3)}$
		60	30	15	
Candida albicans	Schiff base (L)	06	06	06	
	$[NiL].4H_2O$	20	14	12	
	$[CuL].2H_2O$	13	10	08	30
	$[ZnL].2H_2O$	13	11	06	
Aspergillus flavous	Schiff base (L)	06	06	06	
	$[NiL].4H_2O$	20	16	09	
	$[CuL].2H_2O$	14	11	09	37
	$[ZnL].2H_2O$	09	07	06	
Aspergillus fumigatus	Schiff base (L)	06	06	06	
	$[NiL].4H_2O$	27	19	13	
	$[CuL].2H_2O$	18	13	09	40
	$[ZnL].2H_2O$	14	11	08	

L = Ligand = Schiff base ($C_{31}H_{26}O_4N_2$)

CONCLUSION

The Schiff base derived by the condensation of 2-benzoylbenzoic acid with 1,3-diaminopropane and its metal(II) complexes has been synthesized, characterized and screened for their antimicrobial and cytotoxicity activity. The FTIR analysis revealed that the Schiff base act as tetradentate ligand

coordinating to the metals through the azomethine nitrogen, and carboxylate oxygen. Molar conductance values of the complexes were low which indicate the non-electrolytic nature of the complexes. Both the Schiff base and its metal complexes are stable at room temperature. Job's method of continues variation establish 1:1 metal to ligand ratio and gravimetric method of analysis confirmed the empirical formula of the complexes. The magnetic susceptibility measurement values of the complexes revealed that all the complexes are paramagnetic with the exception of zinc complex. The result of the antimicrobial test revealed that the biological activity of the Schiff base is enhanced when it's presented in the form of metal (II) complexes. Cytotoxicity analysis indicates the low cytotoxicity activity of the synthesized compounds.

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