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Investigation of Some Novel Schiff Base Copper(II) Complexes of 2-aminophenol and ortho Substituted Benzaldehydes as Potential Antiseptic Agents

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Abstract: *The increasing microbial resistance to existing antiseptics and disinfectants has necessitated the search for new compounds with potential effects against pathogenic organisms. Schiff bases and their metal complexes are important class of compounds for the search of new antibacterial agents. In line with this, novel copper (II) complexes with Schiff bases derived from ortho substituted benzaldehydes and 2-aminophenol have been synthesized. The compounds were fully characterized using elemental analysis, atomic absorption spectroscopy, infrared spectroscopy, ^{1}H NMR, electronic absorption spectroscopy, magnetic susceptibility measurements and thermal gravimetry analysis. The Schiff bases and their metal complexes were screened for in-vitro antibacterial activities against 6 human pathogenic bacteria; Escheriachia coli (ATCC 8739), Staphylococcus aureus (ATCC 6538), Pseudomonas aeruginosa (ATCC 19582), Bacillus cereus (10702), Enterococcus faecalis (ATCC 29212) and Kribsella pneumonia (ATCC 10031). Ampicillin was used as a reference compound. The result showed that methoxy and chloro substituted Schiff base metal complexes exhibited higher antibacterial activity compared to ampicillin. Our results show that these complexes can be employed as active ingredients in development of broad-spectrum antiseptics agents. Further research on mechanism and cytotoxicity would provide understanding of key biological entities to identify drug targets.*

Keywords: *2-aminophenol, antibacterial, copper complexes, Schiff bases*

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1.0 Introduction

The problem of resistance of pathogenic microorganisms against antibiotics has resulted in the need for novel antibacterial agents. Both developed and resource-poor countries are faced with the burden of healthcare-associated infections (Tikhomirov, 1987). There is therefore a need to synthesize and investigate new antiseptics and disinfectants on a range of microorganisms. One important class of compounds that have drawn much attention as therapeutics are Schiff bases and their metal complexes. Schiff bases are organic compounds that contain the carbon-nitrogen double bonds. They play pivotal role in coordination chemistry on a range of metallic ions with varying geometries and oxidization states. A growing interest and research in the field of coordination chemistry, specifically in the study of Schiff base metal complexes lies in their potential applications in areas such as medicinal chemistry, materials science, and catalysis (Boulechfar et al., 2023).

Schiff bases have shown a wide range of biological activities such as antibacterial, antifungal, antituberculosis and analgesic (Mohamed et al., 2005, Khan et al., 2002, Sivakumar & Rajasekaran, 2013). Schiff bases also have great utility in important fields such as agriculture, industry and a wide variety of applications in inorganic and analytical chemistry (Wang et al., 2021, George et al., 1993, Singh & Quraishi, 2012, Mohamed & Salah, 2007). The use of Schiff bases in synthesizing metal complexes is based on the presence of more electronegative nitrogen which enhances the coordinating possibilities of these ligands; hence Schiff base metal complexes have gained a lot of attention due to diverse structural aspects and increased antibacterial activity.

Aminophenol has been proved to be a powerful antibacterial agent. Studies of the *in-vitro* activity of aminophenols and aminochlorophenols show that these compounds possess intrinsic biological properties such as inhibition of cellular function and lactase dehydrogenase (Valentovic et al., 1996). Based on these reports, Schiff base metal complexes containing aminophenol moeity have been synthesized and screened for use as active compounds in the formulation of antiseptics and disinfectants. The effect of substituent group have also been evaluated.

2.0 Materials and Methods

2.*1* *Materials*

All reagents and solvents were of analar / spectroscopic grades and used without further purification. Ethanol, chloroform, dimethyformamide, 2-aminophenol, 2-methoxybenzaldehyde, 2-chlorobenzaldehyde, 2-nitrobenzaldehyde, copper (II) chloride, were purchased from Aldrich-Sigma company.

2.2 Physical Measurements

Infrared (IR) spectra of the compounds were recorded on a Bruker FT-IR (ATR) tensor 27 spectrophotometer directly on small samples of the compounds in the range 400 to 4000 cm^{-1}. ^{1}H-NMR spectra in DMSO-d_6 solution of the ligands were recorded on a Bruker Avance III 400 MHz. Chemical shifts were reported in ppm relative to TMS as an internal standard. Electronic absorption spectra of Schiff bases and metal complexes recorded from 200 to 1100 nm using freshly prepared chloroform ($CHCl_3$) and dimethylformamide (DMF) solutions were measured on a Cary Model 50 spectrophotometer. Thermogravimetric analysis (TGA) was carried out at 15 ^oC min^{-1} heating rate using a Perkin Elmer Pyris 6 TGA from 50 to 900 ^oC in a closed perforated aluminium pan. The differential scanning calorimetric (DSC) analysis was carried out at 20 ^oC min^{-1} heating rate from room temperature to 450 ^oC using a Perkin Elmer DSC 4000 series, calibrated with indium metal. Metal analysis was determined using Analyst 200 atomic absorption spectrophotometer (AAS) Perkin

Elmer. Melting points were determined on a Reichert Thermovar melting-point apparatus and were uncorrected. Magnetic susceptibility measurements were performed using a Sherwood Scientific magnetic susceptibility balance on powdered samples. $Hg[Co(SCN)_4]$ was used as the calibrant and corrections for diamagnetism calculated from Pascal's constants. Microanalytical data were obtained on a Perkin Elmer model 2400 series II CHNS/O elemental analyzer.

2.3 Synthesis of Schiff Bases

Equimolar quantities (10 mmol.) of 2-aminophenol and ortho substituted benzaldehydes were dissolved in ethanol (25 ml) and stirred under reflux at 70°C for 6 hours. The precipitate formed was separated by filtration, re-crystallized from ethanol, dried and stored in a desiccator.

2.4 Synthesis of Schiff Base Copper(II) Complexes

An ethanolic (40 ml) solution of Schiff base (4 mmol.) was mixed with Cu (II) chloride (2 mmol.) in ethanol (20 ml) solution keeping a ligand-metal ratio 2:1. The solution was made alkaline with triethylamine (TEA) and heated to reflux for 4 h. The solid product was collected by filtration, washed in ethanol, dried and stored in a desiccator.

2.5 Antibacterial Studies

The antibacterial sensitivity of ligands and metal complexes were individually tested against a panel of standard microorganisms namely *Escherichia coli* (ATCC 8739), *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa* (ATCC 19582), *Bacillus cereus* (10702), *Enterococcus faecalis* (ATCC 29212) *and Klebsiella pneumoniae* (ATCC 10031) using the paper disc diffusion method (Bauer et al., 1996).

The compounds were prepared in DMSO to obtain a final concentration of 10 mg/ml. The minimum inhibitory concentration (MIC) was determined using the 96-well microplate dilution method (Eloff, 1998).

3.0 Results and Discussion

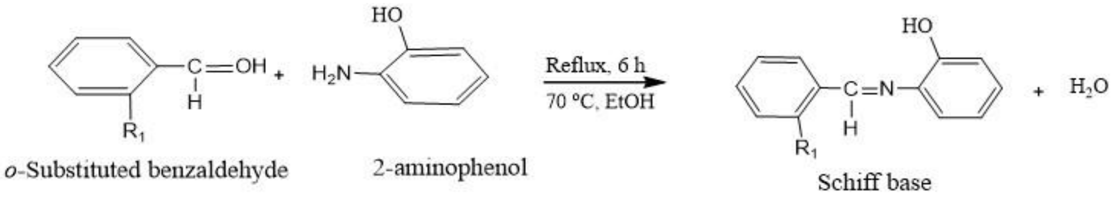
3.1 Synthesis

The Schiff base (SB) ligands were obtained in good yields from the reactions of 2-aminophenol with 2-substituted-benzaldehydes namely; 2-methoxybenzaldehyde (S1), 2-chlorobenzaldehyde (S2), 2-nitrobenzaldehyde (S3) in a 1:1 stoichiometric ratio Scheme 1. The formation of the desired ligands was confirmed by ^1H NMR and microanalysis Table 1. The Schiff bases showed the diagnostic ^1H NMR singlet in the range 8.17-8.26 ppm. Treatment of the ligands with Cu(II) chloride afforded metal complexes corresponding to the general formula $[Cu_nS_2(H_2O)_n]$ where n = 0-2 Scheme 2. The complexes were soluble in common organic solvents such as DMF and DMSO. The metal content analysis of the complexes revealed the percentage of metal ions per mole of the complex. Copper (II) complexes with OMe and Cl substituents at *o*-positions exhibited two moles of copper per mole of the complex while nitro complexes showed one mole of metal ion per mole of the complex. Complexes of the form $Cu_2Cl_2(L)_2$ containing 2 moles of copper per mole of the complex has been reported from 2-acetylpyridine and s-benzyldithiocarbazate (Beshir et al., 2008).

3.2 Infrared Spectroscopy

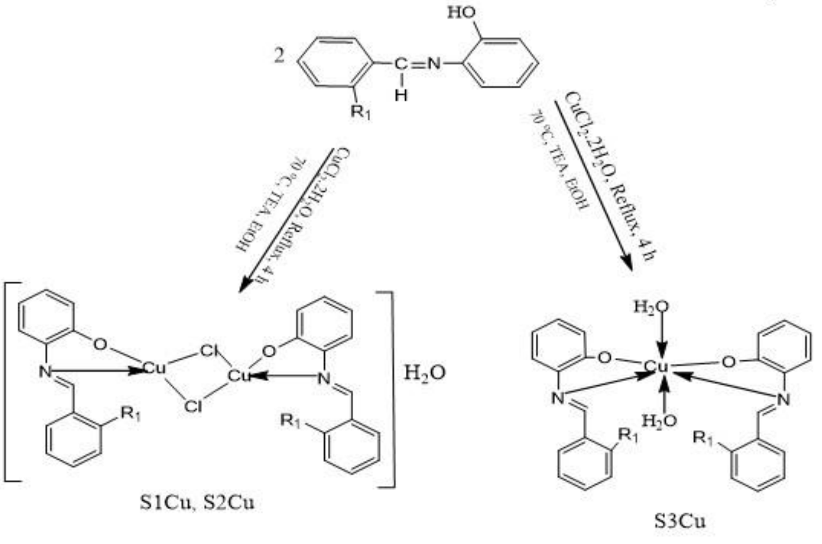
The IR spectra of Schiff bases in Table 2 reveal bands in the region 1626-1616 cm^{-1} attributed to the C=N bond. To determine the bonding mode of the Schiff base to the metal ion, the IR spectra of the Schiff bases were compared with those of the corresponding metal complex. The hetero atoms, nitrogen and oxygen due to the presence of lone pairs of electrons are expected to be involved in complexation and therefore the position of bands for these functional groups will vary in metal and ligand. In the spectra of the Schiff base and Schiff base metal complex, a shift in IR band (1625-1618 cm^{-1}) methoxy-substituted compounds, (1616-1570 cm^{-1}) chloro-substituted compounds, (1626-1556 cm^{-1}) nitro-substituted compounds indicate coordination of azomethine nitrogen to metal ion (Nishat et al., 2010). The presence of methoxy and nitro groups increased the IR stretching frequency for (C=N) while Cl group decreased the IR stretching frequency. These may be attributed to electronic effects (resonance effects in methoxy, nitro and inductive effects in chloro). A comparison between spectra of Schiff base and Schiff base metal complex also shows a band characteristic of ν(C-O) 1284-1271 cm^{-1}, 1270 -1277 cm^{-1}, 1269-1256 cm^{-1} for methoxy, chloro and nitro substituted compounds respectively. New broad band in **S1Cu** and **S2Cu** in the region 3312-3441 cm^{-1} could assign to ν(H_2O) (Howsaui et al., 2021). The presence of coordinated water in **S3Cu** is indicated by a broad band at 3307 cm^{-1} (Patil et al., 2011). New bands in the spectra of metal complexes 418-447 cm^{-1} and 578-581 cm^{-1} are assigned to stretching frequencies of ν(M-N) and ν(M-O) bond formation (Jouad et al., 2001).

Scheme 1: Synthesis of Schiff bases



Scheme 1: Synthesis of Schiff bases

compounds	R1
S1, S1Cu	OMe
S2, S2Cu	Cl
S3, S3Cu	NO_2



Scheme 2: Synthesis of Schiff base copper (II) complexes

Table 1: Physical and analytical data of substituted 2-aminophenol Schiff bases and Metal complexes

Compound	R_1	R_2	Empirical Formula (M.wt)	Yield (%)	Colour	M.pt (°C)	% Found (cacld) C	H	N	Metal (%)
S1	OMe	H	$C_{14}H_{13}NO_2$ (227)	71.74	Yellow	70-71	73.30 (73.77)	5.77(5.77)	6.05 (6.16)	-
S1Cu	OMe	H	$C_{28}H_{24}Cl_2Cu_2N_2O_4$ (685)	51.83	Brown	>250	48.84 (49.03)	2.78 (3.53)	7.74 (6.08)	21.20
S2	Cl	H	$C_{13}H_{10}NOCl$ (231)	58.16	Yellow	58-59	67.38(67.39)	4.24(4.35)	6.03 (6.05)	-
S2Cu	Cl	H	$C_{26}H_{18}Cl_4Cu_2N_2O_2$ (659)	43.76	Brown	>250	47.91(47.36)	2.68(2.75)	7.98 (7.25)	18.17
S3	NO_2	H	$C_{13}H_{10}N_2O_3$ (242)	65.48	Yellow	64-65	64.62 (64.46)	4.07(4.16)	11.60 (11.56)	-
S3Cu	NO_2	H	$C_{26}H_{22}CuN_4O_8$ (582)	40.00	Brown	>250	52.80(52.65)	2.90(3.81)	9.82 (9.63)	10.13

3.3 ^{1}H NMR

The ^{1}H NMR of all Schiff bases exhibits a singlet in the region 8.17-8.26 δ attributed to the imine proton. Schiff bases with electron-donating groups appeared upfield due to an increase in the electron density in the vicinity of the proton which causes shielding from the magnetic field while Schiff bases with electron-withdrawing groups appear at a lower field as a result of low electron density in the vicinity of the proton. These effects and trends were also exhibited in the phenolic protons. The three protons of $-OCH_3$ group resonated in the region 3.93 δ as expected.

Table 2: Spectroscopic data of substituted 2-aminophenol Schiff bases and metal complexes

Compound	R_1	R_2	ν(O-H)	ν(C=N)	ν(C-O)	ν (H_2O)	ν(C-Cl)	ν(M-O)	ν(M-N)	HC=N (s,1H)	OH (s, 1H)	OCH_3 (s, 3H)
S1	OMe	H	3438	1625	1284	-	-	-	-	8.17	9.17	3.93
S1Cu	OMe	H	-	1618	1271	3441, 3312	-	581	441	-	-	-
S2	Cl	H	3414	1616	1270	-	349	-	-	8.26	9.21	-
S2Cu	Cl	H	-	1570	1277	3431, 3312	349	578	447	-	-	-
S3	NO_2	H	3360	1626	1269	-	-	-	-	8.25	9.15	-
S3Cu	NO_2	H	3307	1556	1256	-	-	581	418	-	-	-

3.4 Electronic absorption data and magnetic susceptibility measurements

The electronic absorption spectra of Schiff bases and their metal complexes were recorded at room temperature using chloroform and DMF as solvents Table 3. The Schiff bases exhibited two absorption bands; a high energy band attributed to π→π* transitions of the aromatic ring and a lower energy band due to n→π* transition of the non-bonding electrons present on the nitrogen of the azomethine group (Issa et al., 2005). The absorption spectra of Schiff bases feature an intense band system with maxima at 35,842, 36,1011, 36,630 cm^{-1} and 27,777, 28,571, 28,100 cm^{-1} attributed to π→π* and n→π* for methoxy, chloro and nitro substituted compounds respectively. In the metal complexes, imine transitions shifted to longer wavelengths due to *d-d* transitions and charge transfer transitions confirming the coordination of Schiff base to metal ion (Abd El-Wahab et al., 2007). The metal complexes exhibited different absorption bands in solvents of different polarities. A pronounced change in the position of a UV-vis absorption band is associated with increasing solvent polarity, which usually leads to a red shift while the corresponding is a blue shift. The effects of solvents on the Schiff base metal complexes lead to bands of different wavelengths and intensities. Electronic absorption spectra of Schiff base metal complexes in chloroform show hypsochromic shift (blue shift), while in DMF bathochromic shift (red shift) was observed. The spectra of Cu(II) complexes in DMF for methoxy and chloro substituted complexes (**S1Cu, S2Cu**) showed broad bands centered at 22,988 cm^{-1}, 22,799 cm^{-1} which could be attributed to the $^2A_{Ig}(F) \rightarrow {}^2B_{1g}(P)$ transitions characterized Cu(II) ion in a square-planar geometry.

The room temperature magnetic moment values of 1.52 and 1.60 B.M for the complexes, indicate that, as expected, magnetic exchange occurs between the two copper ions which may have led to lower values than expected (1.7-2.2 B.M).

Table 3: Electronic absorption data and magnetic susceptibility measurements of substituted 2-aminophenol Schiff bases and metal complexes

Compound	R_1	R_2	$CHCl_3$ ($\bar{\nu}$/ cm^{-1})(logε)	Assignment	DMF ($\bar{\nu}$/ cm^{-1})((logε)	Assignment	Magnetic Moments μ_{eff}	Geometry
S1	OMe	H	35,842(4.00) 27,777(4.40)	$\pi\rightarrow\pi^*$ $n\rightarrow\pi^*$	- -	- -	-	-
S1Cu	OMe	H	30,120(3.56) 23,041(3.81)	CT d-d	30,581(4.43) 22,988(4.20)	CT d-d	1.52	Square-planar
S2	Cl	H	36,101(4.78) 28,571(4.75)	$\pi\rightarrow\pi^*$ $n\rightarrow\pi^*$	- -	- -	-	-
S2Cu	Cl	H	31,847(3.93) 23,255(4.22)	CT d-d	22,799(4.39)	d-d	1.60	Square-planar
S3	NO_2	H	36,630(4.90) 28,100(4.80)	$\pi\rightarrow\pi^*$ $n\rightarrow\pi^*$	- -	- -	-	-
S3Cu	NO_2	H	32,154(3.81) 23,255(3.95)	CT d-d	31,250(3.89) 22,727(4.35)	CT d-d	1.72	Tetrahedral

Based on the magnetic data, the copper (II) complexes probably have a binuclear structure (Karabocek et al., 2007). The nitro-substituted copper(II) complex **S3Cu** exhibited two absorption bands. The bands around 31,250 and 22,727 cm^{-1} are due to charge transfer and $^2B_{1g}\rightarrow$ $^2B_{2g}$ transitions in a tetrahedral field (Lakshmi et al., 2011).

3.5 Thermogravimetric Analysis

Thermal analysis plays an important role in studying the thermal stability and decomposition pathway of compounds. The thermal decomposition of 2-aminophenol Schiff base copper complexes was studied using thermal analytical techniques (TGA and DSC) under nitrogen. Analysis of the obtained TG-curves is given in Table 4 and the correlationship between the different decomposition steps of the complexes with the corresponding weight losses are discussed in terms of the proposed formulae of the complexes.

All the complexes lost adsorbed water at an equivalent range before the final decomposition. The data from the thermogravimetric analysis indicates that the decomposition of the complexes proceeds in four steps. The final decomposition products were metal oxides formed above 700 ºC. The thermogram of **S1Cu** Fig. 1 shows four decomposition steps within the temperature range 71-786 ºC. The first step of decomposition within the temperature range 71-227 ºC corresponds to the loss of water molecules with a mass loss of 2.83 % (calcd. 3.12 %). The onset of decomposition of the complex occurs at 295-343 ºC due to the initial loss of an organic moiety ($C_{13}H_9NCl$) from the aromatic ring with a mass loss 34.68 % (calcd. 34.98 %). Before the process of losing is completed, a second moiety $C_{15}H_{13}NCl$ starts to dissociate at 361-504 ºC with a mass loss of 25.64 % (calcd. 26.06 %). The complete decomposition occurred at 504 ºC and the observed residue corresponds to the copper oxide. These steps are accompanied by an endothermic peak at 320 ºC and an exothermic peak at 340 ºC in the DSC graph Fig. 2. A similar trend was observed for **S2Cu** and **S3Cu**. The effect of substituent was not affected in the decomposition steps.

3.6 Antibacterial Activity

The antibacterial activity of synthesized Schiff bases and their metal complexes are related to the nature of substituent groups. Structure activity-relationship of Schiff bases of 2-aminophenol derivatives were studied considering the nature of substituent groups.

The Schiff bases **S1-S3** and their copper (II) complexes **S1Cu-S3Cu** were tested against six human pathogenic bacteria; *Escherichia coli (ATCC 8739), Staphylococcus aureus (ATCC 6538), Pseudomonas aeruginosa (ATCC 19582), Bacillus cereus (10702), Enterococcus faecalis (ATCC 29212)* and *Klebsiella pneumoniae (ATCC 10031).*

Table 4: Thermoanalytical data (TGA and DSC) of substituted 2-aminophenol Schiff base metal complexes

Compound (M.Wt)	R_1	R_2	Endothermic t_{min} (°C)	Exothermic t_{max} (°C)	Temp range in TGA[a]	Weight loss[a] %Found(calcd)	Decomposition assignment
S1Cu	OMe	H	320	340	71-227	2.83(3.12)	H_2O
$C_{28}H_{24}Cl_2Cu_2NO_4$					295-343	34.68(34.98)	$C_{13}H_9NCl$
(685)					361-504	25.64(26.06)	$C_{15}H_{13}NCl$
					538-786	12.20(11.67)	CuO
S2Cu	Cl	H	354	370	70-220	2.73(3.12)	H_2O
$C_{26}H_{18}Cl_4Cu_2N_2O_2$					280-338	9.38(10.01)	Cl_2
(659)					370-740	56.64(56.06)	$C_{26}H_{16}N_2Cl_2$
					760-870	12.65(12.13)	CuO
S3Cu	NO_2	H	254	270	72-167	2.91(3.09)	H_2O
$C_{26}H_{22}CuN_4O_8$					205-316	12.79(13.05)	$C_6H_4N_2$
(582)					409-798	31.11(30.75)	$C_{19}H_{18}N_2$
					825-900	13.70(13.01)	CuO

*****TGA [a]: data obtained from thermal gravimetry analysis, DSC[b]:data obtained from differential scanning calorimetry***

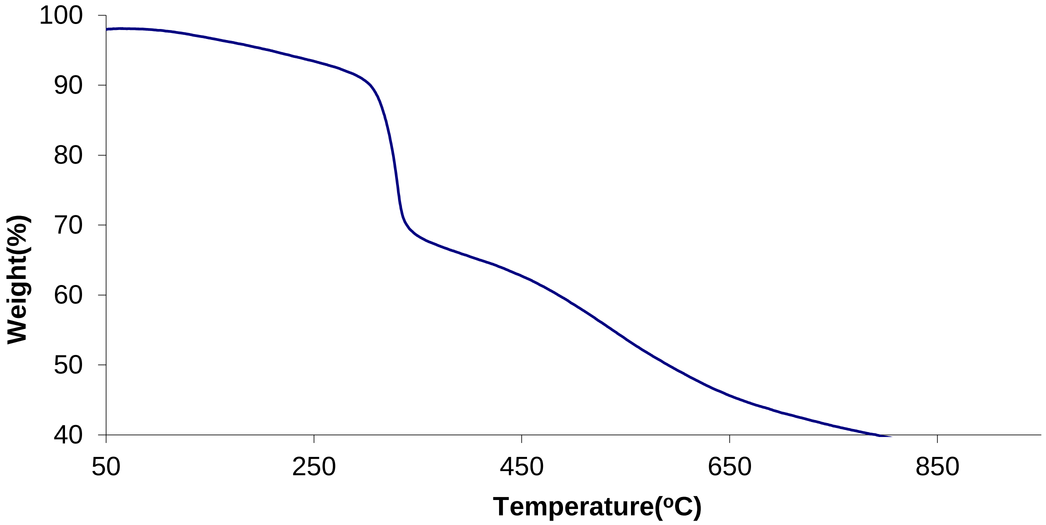


Fig. 1: TGA spectrum of S1Cu

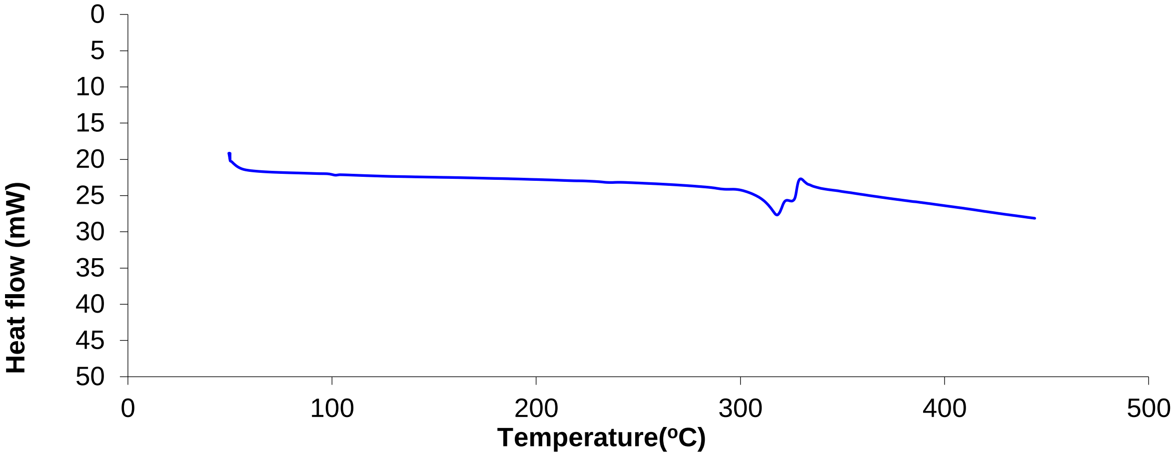


Fig. 2: DSC spectrum of S1Cu

Ampicillin was used as a reference compound. The *in-vitro* antibacterial activity of synthesized compounds presented in Table 5 show that Schiff base ligands **S1** and **S2** exhibited moderate activity against the tested organisms when compared with **S3** ligands, with low activity. The activities may have arisen from the substituents (methoxy and chloro) which play an important role in antibacterial activity, in addition to the presence of imine groups which is involved in transamination reactions in biological systems (Zhang et al., 2006, Mohamed, 2006). The high activity of **S1** ligand (methoxy substituent) from the MICs may be due to the presence of an electron-donating group (Liew et al., 2020). Methoxy group substitution has been reported to contribute greatly to inhibit metastasis (Sari et al., 2003).

A comparative study of the minimum inhibitory concentration of Schiff bases and its metal complexes indicates that metal complexes exhibited higher antibacterial activity than the free ligands. This is probably due to the greater lipophilic nature of the complexes. Such increased activity of the metal complexes can be explained based on overtone's concept and Tweedy's chelation (Mounika et al., 2010). Overtone concept of cell permeability, shows that lipid membrane surrounding the cell favors the passage of only lipid-soluble materials, which means that liposolubility is an important factor controlling antimicrobial activity. This increased lipophilicity enhances the penetration of the complexes into the lipid membrane and thus blocks the metal binding sites on enzymes of microorganisms. Schiff base metal complexes containing 2 moles of copper per mole of complex **S1Cu, S2Cu,** exhibited a higher antibacterial activity. This result corroborates Al-Sha'alan, 2007 report that the lipophilicity of Schiff base complexes leads to inhibition of metabolic pathway by deactivation of various cellular enzymes (Al-Sha'alan et al., 2007). In addition, Schiff base metal complexes with methoxy and chloro substituent's **S1Cu and S2Cu** can be attributed with extremely strong activity based on MIC values in the range of 0.62-1.25 mg/ml.

Table 5: Minimum inhibitory concentration (MIC) of substituted 2-aminophenol Schiff bases and metal complexes

	MIC (mg/mL)					
Compound	***S.aureus***	***E.feacalis***	***B.cereus***	***E.coli***	***P.aeruginosa***	***K.pneumonia***

	(ATCC 6538)	(ATCC 29212)	(ATCC 10702)	(ATCC 8739)	(ATCC 19582)	(ATCC 10031)
S1	*2.50*	*2.50*	*2.50*	*1.25*	*1.25*	*1.25*
S1Cu	0.62	1.25	0.62	1.25	1.25	0.62
S2	2.50	2.50	5.00	2.50	2.50	2.50
S2Cu	0.62	0.62	2.50	1.25	0.62	0.62
S3	>5.00	>5.00	>5.00	>5.00	>5.00	>5.00
S3Cu	>5.00	>5.00	>5.00	>5.00	>5.00	>5.00
Ampicillin	2.50	5.00	5.00	1.25	5.00	2.50

A minimum inhibitory concentration value of 0.28-1.27 mg/ml has been attributed with extremely strong activity while MIC values of 1.81-8.85 mg/ml are attributed with weak activities (Aligiannis et al., 2001). These results are in agreement with Xia et al., 2007 and Fang et al., 2019 which reports that methoxy and chloro groups significantly increase activity. Having identified lead complexes with potential antibacterial activity, we would investigate the mode of action and cytotoxicity to establish drug candidacy.

4.0 Conclusion

This study successfully synthesized and characterized a series of Schiff base copper complexes. The investigation into their antibacterial activity revealed promising results, particularly for complexes containing methoxy and chloro substituents **S1Cu** and **S2Cu**, demonstrating their potential as novel antibacterial agents. However, further research is necessary to address the limitations of this study. Future studies should explore a wider range of Schiff base metal complexes and evaluate their activity against a more diverse panel of bacterial strains. Additionally, investigating the mechanism of action of these complexes and assessing their cytotoxicity towards human cells is crucial for their development as safe and effective antibacterial agents. Finally, considerations of scalability and potential environmental impact should be addressed for real-world applications. The present study contributes valuable insights into the potential of Schiff base metal complexes as antibacterial agents, paving the way for further exploration and development of these promising candidates in the fight against bacterial infections.

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