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COPPER COMPLEXES OF AMINOTHIOPHENE SCHIFF BASES AS ANTIMICROBIAL AGENTS: SYNTHESIS, STRUCTURAL CHARACTERIZATION, ANTIMICROBIAL AND ANTITUBERCULAR ACTIVITY EVALUATION

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ABSTRACT
Series of potentially tridentate Schiff bases (3a-d) were derived from condensation of ethyl 2-amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carboxylate (I) with o-hydroxyl aldehyde derivative (2a-d) which formed Cu(II) complexes in 1:1 molar ratio. All the complexes were characterized by elemental analysis, FTIR, UV-Visible and ESR spectroscopy, XRD, magnetic susceptibility and molar conductance technique. According to spectroscopic and magnetic moment data, the monobasic tridentate ligand forms square planar complexes with Cu(II) metal ions. Metal complexes exhibited pronounced activity against gram-negative ESBL and MBL bacterial strains compared to the ligands. In addition, metal complexes displayed good antitubercular activity against *M. tuberculosis* (H37Rv strain).

KEYWORDS
Copper complex; Uropathogens; Multidrug-resistant, Schiff bases; H37Rv

INTRODUCTION
Recently much attention has been devoted by researchers in the field of vastly growing coordination chemistry of Schiff base ligand and its metal complexes. Schiff base metal complexes cover very wide and diversified area of organometallic compounds, comprising applications from medicinal chemistry to dye and polymer industry [i]. Medicinal applications are more emphasized based on their broad spectrum biological properties, such as antifungal, antiviral, antiproliferative, antibacterial, antipyretic, anti-inflammatory, antioxidant and antimalarial properties [ii-iii]. Due to the ace of preparation and usefulness as precursors of molecules with pharmacological properties, Schiff bases derived from 2-aminothiophene scaffolds are gaining prime importance among heterocyclic compounds [iv-v]. Copper is one of the essential minerals and is involved in a variety of biological processes such as a myriad cellular activity, biosynthesis of neurotransmitter, cellular respiration, iron metabolism and free radical detoxification [vi]. Interest in the study of copper complexes has been increasing

because of their potential antimicrobial, antiviral, anti-inflammatory and antitumor properties along with enzyme inhibitor actions [vii].

Tuberculosis (TB) is also called a disease of urban poor, easily being one of the mega killers of the human race. TB claims over two million deaths every year and as many as one-third of world's population under the threat of infection. Battelle against TB control is aggravated by the rise of drug resistance strains, co-infection with HIV and nonavailability of new drugs. WHO published figures speak for themselves, an estimated 10.4 million new TB cases were reported worldwide in 2015, of which 4.8 million were multidrug-resistant TB (MDR-TB) cases, accounting for 1.8 million deaths including co-infection from HIV. India is among the top six highest TB burden countries, accounting for more than one quarter (22.7%) of the world's TB cases and deaths [viii]. To combat multidrug-resistant bacterial strains, there is an imperative need to develop new drugs with the novel mechanism with reduced duration of therapy.

In a previous paper, we reported synthesis, characterization and biological activity studies of novel Schiff bases derived from 2-aminothiophenes and their cobalt, nickel, and zinc complexes [ix-xi]. The current paper deals with the synthesis and characterization of Cu(II) complexes of Schiff bases and their antimicrobial and antitubercular studies.

EXPERIMENTAL

Materials and methods

All chemical used were of AR grade and the solvents were purified and distilled before use. The carbon, nitrogen, hydrogen and sulfur analysis was carried out on Thermo Finnigan CHNS(O) Analyzer, while the metal content was determined by ARCOS, ICP-Atomic Emission Spectrometer. Molar conductance was measured in DMF (10^{-3} M solution) using ELICO Digital conductivity meter Model CM-180 at room temperature. The IR spectra were recorded in KBr disc on a Perkin Elmer Model 1600 FTIR Spectrophotometer. Powder XRD diffractogram was collected on PAN analytical X-ray diffractometer. Electronic spectra were recorded on a UV-Vis Jasco Spectrophotometer Model V-630. Magnetic susceptibility measurements were carried out using $Hg[Co(SCN)_4]$ as calibrant by Gouy balance. The EPR spectrums of the copper complex were recorded using a JEOL model JES FA200 ESR spectrometer.

Anti-microbial activity analysis

Well-known agar well-diffusion method was employed for the antimicrobial activity evaluation of all synthesized compounds against ESBL and MBL producing bacterial strains as given in Table-4. All the bacterial cultures were acquired from nearby hospitals and pathological laboratories located in Mumbai to study the MBL and ESBL characteristics. The metal complex concentration of 25µg/mL for antimicrobial studies was prepared using DMSO solvent. Inoculation of bacterial culture was carried out using Brain Heart Infusion broth (10 ml) and incubated for one day at 37°C. Molten Mueller and Hinton agar butt (20 ml) containing 0.4 ml test culture (0.1 O.D. at 540 nm) was prepared and uniformly distributed in Petri plate of dia. 9 cm. Petri plate was bored to prepare wells of dia. 8 mm after solidification. Each well was added with 50 µL of the test sample. All plates were kept in an incubator at 37°C for one day. The zones of inhibition around the wells were measured after the incubation period in comparison with control wells containing 50µl of DMSO solvent. The experiment was carried out in three sets and the results were reported as mean ± SD [xii].

Anti-tuberculosis activity analysis

Nontoxic microplate Alamar Blue assay method was employed for the assessment of the antimycobacterial activity of synthesized compounds against *M. tuberculosis* (ATCC No-27294) [xiii]. Test compounds were prepared in the concentration range of 0.2μg/mL to 100μg/mL. In the 96 well plate, Middlebrook 7H9 broth (100μL) with test compound in series of dilution was taken. De-ionized water is used in the outer perimeter wells so as to minimize the evaporation of medium throughout the incubation period. Paraffin is used to seal the plate and incubated at 37ºC for five days. After this time, the equimolar mixture (25μL) of freshly prepared Tween 10% and 80% and Almar blue reagent was poured into each well and incubated for another one day. A blue color in the well was interpreted as no bacterial growth and pink color was scored as growth giving minimum inhibitory concentration.

Synthesis of ligand

The Schiff base ligands HL_1, HL_2, HL_3, and HL_4 were prepared (Figure-1) according to the literature method [ix].

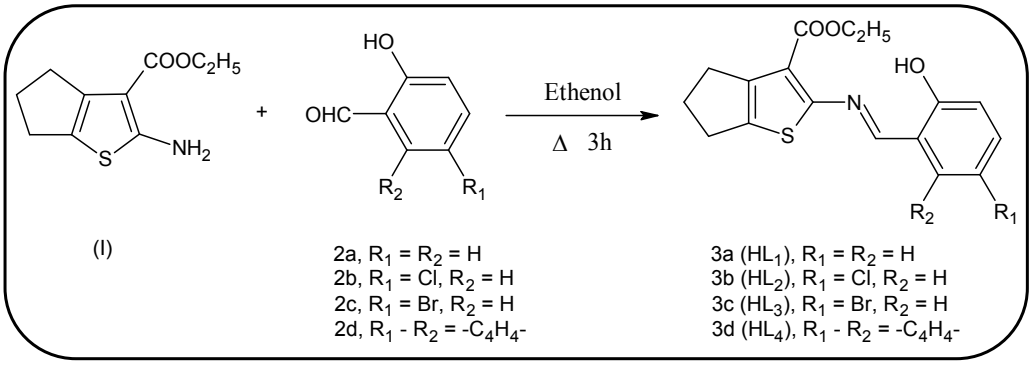

Figure 1: Reaction Scheme

Synthesis of metal complexes

Copper chloride (0.01 mol) dissolved in ethanol was added to a magnetically stirred solution of the Schiff base dissolved in ethanol (0.01 mol) in small parts. The pH was adjusted to 6-7 and the mixture was stirred in a water bath for about five hours. The reaction mixture was concentrated and cooled. The formed precipitate was filtered from the solution by suction filtration, purified by washing several times with aqueous ethanol and ether, and dried in vacuum.

RESULTS AND DISCUSSION

Analytical data indicated formulation of the well-defined Cu(II) complexes with Schiff bases. All the complexes are colored, and non-hygroscopic. The complexes are insoluble in common organic solvents except for dimethylformamide and dimethyl sulphoxide. The molar conductance values support the non-electrolyte nature of the complexes. The elemental data (Table-1) exhibited that the complexes have 1:1 (metal: ligand) stoichiometry of the type $[M(L_{1-4})Cl]$ where L stands for the singly deprotonated ligand. The purity of the ligand and its complexes has been checked by TLC.

Table 1: Physico-chemical data of metal complexes

Complex	(Colour) Mol. Formula	F.W.	Elemental analysis (%) found (calc.)						Molar conductance in DMF (Ω^{-1} cm^2 mol^{-1})
			C	H	N	S	Cl	M	
[Cu(L_1)Cl]	(Dim gray) $CuC_{17}H_{16}NO_3SCl$	413.38	49.78 (49.35)	3.71 (3.87)	3.60 (3.39)	7.01 (7.74)	8.92 (8.58)	15.55 (15.37)	7.10
[Cu(L_2)Cl]	(Dim gray) $CuC_{17}H_{15}NO_3SCl_2$	447.82	44.94 (45.55)	3.55 (3.35)	3.22 (3.13)	7.49 (7.15)	15.13 (15.84)	13.89 (14.19)	7.70
[Cu(L_3)Cl]	(Gray) $CuC_{17}H_{15}NO_3SBrCl$	492.24	41.09 (41.44)	3.01 (3.05)	2.69 (2.84)	6.79 (6.50)	7.11 (7.20)	12.15 (12.91)	13.20
[Cu(L_4)Cl]	(Black) $CuC_{21}H_{18}NO_3SCl$	463.44	54.23 (54.38)	3.97 (3.88)	3.02 (3.02)	6.46 (6.90)	7.23 (7.65)	13.27 (13.71)	17.20

IR spectral studies

Characteristics FTIR bands of the Schiff base ligands and its metal complexes were compared and are depicted in Table-2. The marginal red shift was observed in the complex spectra indicating that no change in the structural arrangement of ligand atoms on the coordination of metal ions. The stretching vibrations due to phenolic –OH at 3000-3200 cm^{-1} of the Schiff base ligand disappeared while ν(C-O) band in the region 1307-1311 cm^{-1} in Schiff base was shifted to higher wave number by 13-30 cm^{-1} in the Cu(II) complexes, suggesting complexation of Schiff base ligand with central metal atom through deprotonated phenolic -OH. Absorption band in the region 1682-1708 cm^{-1} is assigned to ester carbonyl frequency ν(C=O) which is shifted to lower wavenumber region by 30-56 cm^{-1} on chelation, indicating coordination of oxygen atom of ester carbonyl group in the metal complexes. The characteristic azomethine ν(C=N) peak at 1597-1598 cm^{-1} is shifted to lower frequency by 18-23 cm^{-1} in metal complexes confirming the involvement of azomethine nitrogen in coordination with a copper ion. The stretching vibrations of υ(C=S) have no significant change in the complex spectra, indicating non-involvement of thiophene sulfur in the coordination. The appearance of the non-ligand band around 510-515 cm^{-1} and 409-415 cm^{-1} can be assigned to ν(M-O) and to ν(M-N) stretching vibrations respectively which confirms the coordination of oxygen and nitrogen atoms with a copper ion. Further, the coordination of chlorine atoms was supported by the appearance non-ligand peak due to ν(M-Cl) at 376 cm^{-1} in the far IR spectra of [Cu(L_4)Cl] complex [ix-x].

Table 2: FTIR spectral data

Compound	υ(O-H) phenolic	υ(C=O) ester	υ(C=N) azomethine	υ(C-O) phenolic	υ(C=S) thiophene	υ(M←O)	υ(M←N)
HL_1	3200-3000	1682	1597	1310	616	-	-
HL_2	3200-3000	1704	1598	1311	619	-	-
HL_3	3200-3000	1708	1598	1311	626	-	-
HL_4	3200-	1704	1598	1307	617	-	-

	3000						
[Cu(L_1)Cl]	-	1652	1579	1340	622	510	415
[Cu(L_2)Cl]	-	1657	1577	1329	618	514	415
[Cu(L_3)Cl]	-	1652	1575	1324	625	515	409
[Cu(L_4)Cl]	-	1669	1575	1329	617	510	411

Electronic spectra and magnetic moment studies

The electronic absorption spectra of Cu(II) complexes were recorded in DMF at 300 K, (Table-3, Figure-2) were compared with those of the ligands. In the copper complexes, the $\pi\rightarrow\pi^*$ transitions were slightly red-shifted indicating the coordination of ligand to copper with no structural alteration of the ligand on chelation [xiv]. Two bands appeared in the region 39500-38400 cm^{-1} and 30400-29700 cm^{-1} in all the ligands, which were assigned to $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions respectively [xv]. All the Cu(II) complexes exhibited a broad band around 20000 cm^{-1} corresponding to d-d transitions of the metal ions ($^2B_{1g}\rightarrow{}^2A_{1g}$) which suggested square-planar geometry around the central metal ion. The absence of band below 10000 cm^{-1} excludes the possibility of tetrahedral geometry. Further, the magnetic moment values for all the complexes, in the range 1.83-1.86 BM which indicates the presence of one unpaired electron per Cu(II) ion and absence of any metal to metal interaction. This confirms the square-planar geometry [xvi-xvii].

Table 3: Electronic spectral assignments and magnetic values for the Copper(II) complexes

Complex	Absorption maxima (cm^{-1})	Tentative assignment	Magnetic moment (B.M.)
[Cu(L_1)Cl]	39526 29762 20000	$\pi\rightarrow\pi^*$ $n\rightarrow\pi^*$ $^2B_{1g}\rightarrow{}^2A_{1g}$	1.83
[Cu(L_2)Cl]	38610 30303 20000	$\pi\rightarrow\pi^*$ $n\rightarrow\pi^*$ $^2B_{1g}\rightarrow{}^2A_{1g}$	1.84
[Cu(L_3)Cl]	38610 30211 20000	$\pi\rightarrow\pi^*$ $n\rightarrow\pi^*$ $^2B_{1g}\rightarrow{}^2A_{1g}$	1.84
[Cu(L_4)Cl]	38462 30395 20121	$\pi\rightarrow\pi^*$ $n\rightarrow\pi^*$ $^2B_{1g}\rightarrow{}^2A_{1g}$	1.86

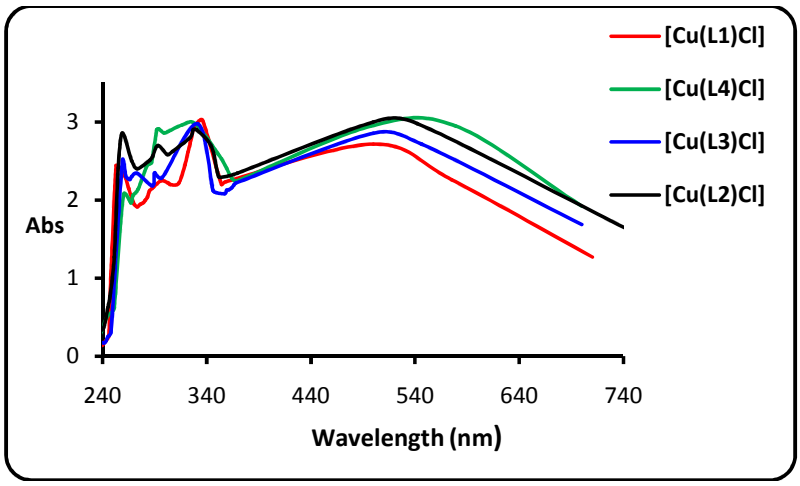

Figure 2: Electronic spectra of Cu(II) complexes

ESR spectral studies

The X-band ESR spectrum of [Cu(L_1)Cl] and [Cu(L_3)Cl] was recorded in a solid state at RT, while ESR of [Cu(L_1)Cl] was also recorded in DMSO at liquid nitrogen temperature (LNT). The EPR spectra possess resolved peaks originating from g∥ component and broadened peaks from the g⊥ component. The spin Hamiltonian parameters have been calculated and are depicted in Table-4. The [Cu(L_1)Cl] complex at LNT exhibits a typical four-line spectral pattern (Figure-3b), assignable to monomeric Cu(II) complexes while [Cu(L_1)Cl] (Figure-3a) and [Cu(L_3)Cl] (Figure-3c) complex at RT shows only two peak spectra (g∥ and g⊥).

The observed trending in g tensor ($2.3 > g\parallel > g_{av} > g\perp > 2.0023$) for both complex suggests that the unpaired electron is localized in the dx^2-y^2 orbital of Cu(II) ion with the considerable covalent character of the metal-ligand bond. The g∥/A∥ quotient is used to evaluate tetrahedral distortions in tetra-coordinated complexes. The ratio close to 100 indicates square planer geometry, while 105 to 135 denotes small to extreme distortion in square planar geometry [xviii]. Magnetic moment was calculated using equation $\mu_{eff} = g_{av} = [S(S+1)]^{1/2}$. The observed g∥/A∥ ratio is in the range of 130-133 with the observed μ_{eff} between 1.83-1.86 reflects square planer geometry of Cu(II) complexes. The axial symmetry parameter G was evaluated using the expression, $G = (g\parallel - 2/g\perp - 2)$ which is a measure of the exchange interactions between copper-copper centers. For the G value between 3 to 5, unit cell contains magnetically equivalent ions and if the $G < 4$, the ligand is regarded as a strong field with weak exchange coupling of the magnetically non-equivalent Cu(II) ions in the unit cell. If $G > 5$, a strong exchange coupling takes place among the magnetically non -equivalent Cu(II) ions in the unit cell [xix]. The observed G values in the range of 4.54-4.93, predicts the formation of monomeric complexes with negligible exchange interaction. In addition, inplane σ covalency parameter (α^2) was calculated according to Kivelson and Neiman equation, $\alpha^2_{Cu} = -(A\parallel/0.036) + (g\parallel - 2.002) + 3/7\ (g\perp - 2.002) + 0.04$. The molecular orbital coefficient (α^2) ranges from 0.70 to 0.78 which indicates a considerable covalent character in the metal-ligand bond [xx-xxi].

Table 4: ESR parameters of Cu(II) complexes

Complex	Magnetic moment $\mu_{eff\,(BM)}$		Solid/ Solution	Temp.	g∥	g⊥	g_{av}	A∥	α^2_{Cu}	g∥/A∥	G
	observed	calculated									
$[Cu(L_1)Cl]$	1.83	1.86	DMSO	LNT	2.30	2.07	2.14	120.0	0.70	-	4.55
	1.83	1.83	Powder	RT	2.25	2.05	2.12	169.0	0.78	133.02	4.88
$[Cu(L_3)Cl]$	1.85	1.83	Powder	RT	2.23	2.05	2.11	171.0	0.76	130.41	4.93

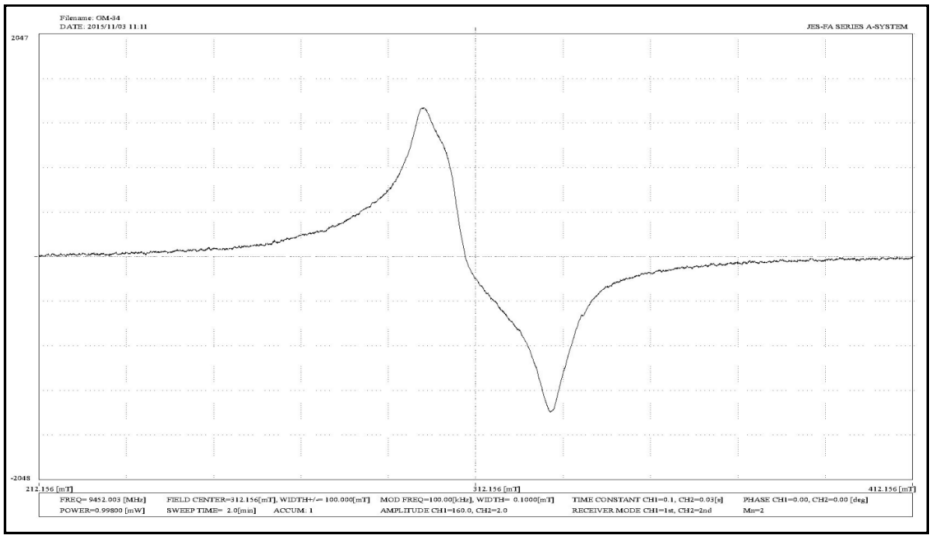

Figure 3a: ESR of $[Cu(L_1)Cl]$ at RT

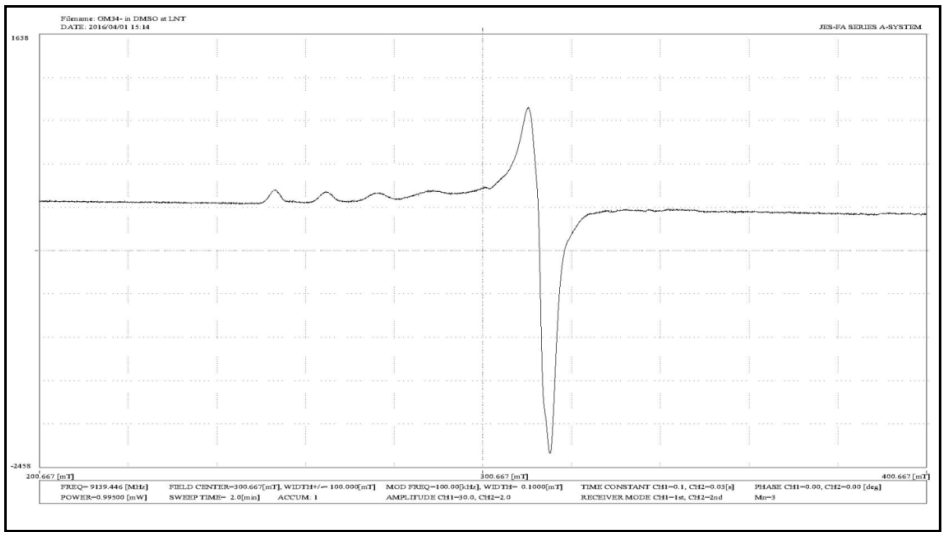

Figure 3b: ESR of $[Cu(L_1)Cl]$ at LNT

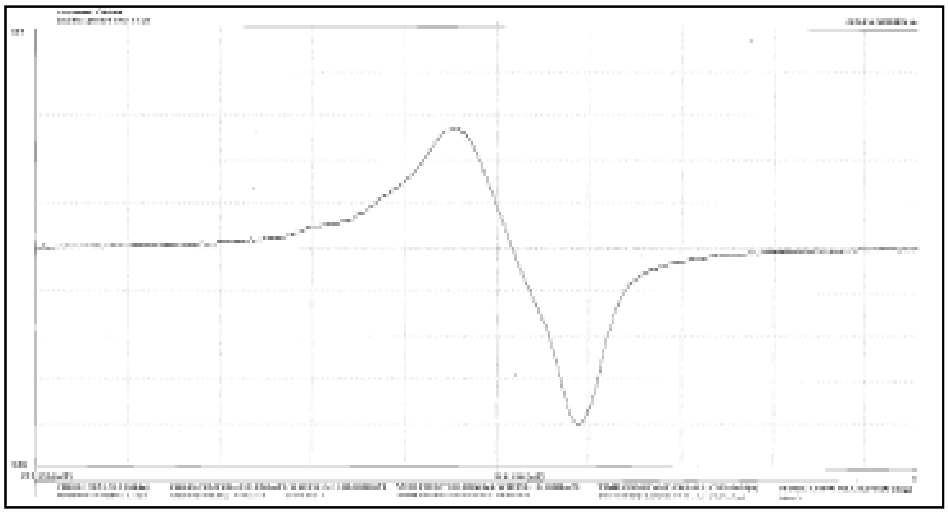

Figure 3c: ESR of [Cu(L_3)Cl] at RT

Powder XRD studies

The powder X-ray diffractogram of [Cu(L_1)Cl] complex was obtained as a single crystal of sufficient size and quality could not be prepared (Figure-4). The complex exhibited crystalline peaks. The X-ray pattern was scanned between 2θ ranging from 10° to 90° at the wavelength of 1.5406 Å. Rietveld refinement technique [xxii] is used to evaluate crystal lattice parameters. The unit cell parameters were tabulated in Table-5. The complex crystallized in monoclinic system with space group $P12_1/c1$ [xxiii]. The average grain size was calculated using Scherer's formula $D = 0.9\lambda/\beta\cos\theta$ [xxiv].

Table 5: Crystal lattice parameters of [Cu(L_1)Cl] complex

Complex	**[Cu(L_1)Cl]**
Molecular formula	$CuC_{17}H_{16}NO_3SCl$
Molecular weight	413.38
Crystal system	monoclinic
Space group	$P12_1/c1$
a (Å)	8.1235
b (Å)	14.9124
c (Å)	15.5084
β (Å)	100.571
V (Å^3)	1846.82
Z	4
Density (g/cc)	1.876
Crystal size (nm)	31

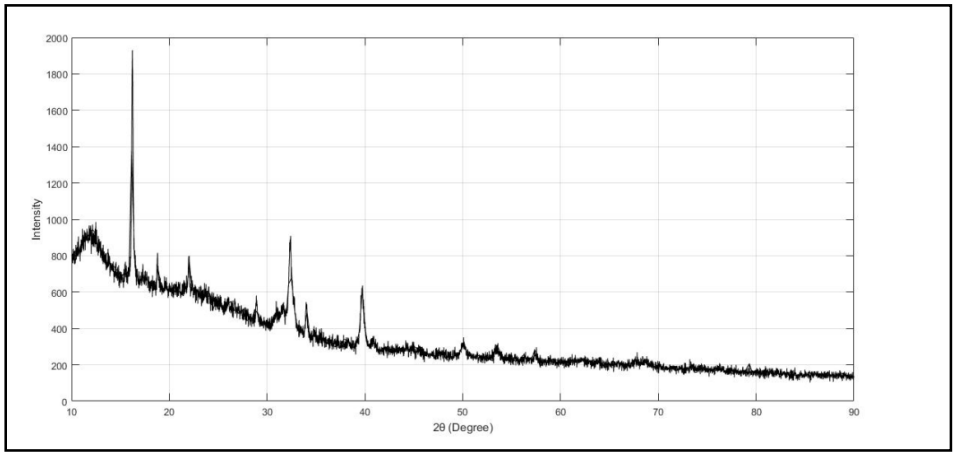

Figure 4: XRD of [Cu(L_1)Cl]

From the spectral and physiochemical data interpretation probable structures can be assigned to copper complexes as given in Figure 5.

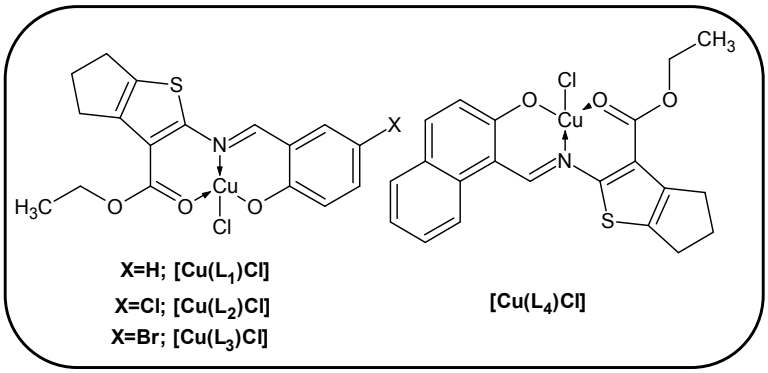

Figure 5: Probable structures of copper complexes

ANTIMICROBIAL ACTIVITY

Antimicrobial activity testing of all synthesized compounds was carried out using Kirby Bauer method against MBL and ESBL producing gram negative uropathogens. Multidrug resistance profile of these uropathogens against mainline drugs is given in Table-6 while the effect of synthesized compounds on these test isolates (zone of inhibition in mm) is presented in Table-7. DMSO is used as a solvent which did not yield any zone of inhibition against these uropathogens. All Schiff bases were found to be sensitive against ESBL producing *Escherichia coli-10* (Ec-10) and *Klebsiella pneumoniae-7* (Kp-7) and MBL producing *Pseudomonas aeruginosa* (isolate-85) and *Citrobacter amalonaticus* (isolate-135) uropathogens, while all copper complexes were sensitive against all the test isolates. Schiff bases HL_2 and HL_3 were also sensitive against ESBL producer *Escherichia coli* (isolate-220) and HL_3 against ESBL producer *Klebsiella pneumoniae* (isolate-618) uropathogen. Rests of the microbial strains were resistant to Schiff bases but their metal complexes displayed enhanced activity (10-17 mm). Schiff base HL_3 was found to be more active ligand followed by HL_2 and *Citrobacter amalonaticus* (isolate-135) was the most sensitive (14-17 mm) test isolate among the tested uropathogen.

Heavy metals can be potentially toxic to microorganism mainly due to damaging the cell membrane and DNA structure. They can also alter the conformational structure of nucleic acid and proteins and may interfere with the oxidative phosphorylation and osmotic balance resulting in more cell toxicity [xxv]. Antimicrobial activity of Schiff base ligands may be linked to the presence of active pharmacophores like azomethine bridging with substituted aromatic aldehydes and heterocyclic ring with thiophene moiety among the structural scaffold. The augmented antimicrobial activity of metal chelates can be explained on the basis of Overtone's concept of cell permeability and Tweedy's chelation theory. With the chelation, the overlap of ligand orbital and the charge sharing between metal ions and the donor groups is reduced resulting in the delocalization of π electrons over the whole ring. This phenomenon is responsible for enhancing the lipophilicity of complexes which allows deeper penetration of complexes in lipid membranes resulting in the growth inhibition or cell death [xxvi].

Table 6: Antibiotic resistance profile of ESBL and MBL producers

Cultures code name	Full form	Antibiotic sensitivity test		
		Sensitive	Intermediate	Resistant
ESBL PRODUCERS				
Citro-2	*Citrobacter diversus-2*	AS, BA, CH, RC, TE	CI, CF	CF, PC, ZN, GM, AK, GF, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
Ec- 10	*Escherichia coli-10*	CH, GM, AK, GF	PB, AS	BA, CF, PC, RC, CI, TE, ZN, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG
Kp	*Klebsiella pneumoniae*	GM, AK	-	AS, BA, CF, PC, CH,RC, CI, TE, ZN, GF, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
Kp-7	*Klebsiella pneumoniae- 7*	-	OX, TE	AS, BA, CF, PC, CH,RC, CI, ZN, GM, AK, GF, TT, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
Pro- 7	*Proteus mirabilis- 7*	CP, AS, PC, AK	RP, NA, CF, RC, GM, GF	BA, CH, CI, TE, ZN, TT, OX, ZX, CB, NX, AG, CU, FG, PB
MBL PRODUCERS				
85	*Pseudomonas aeruginosa*	AK, GF, PB	RC, CF, PC	AS, CI, TE, ZN, GM, TT, OX, RP, ZX, CB, BA, CH, NA, NX, AG, CU, CP, FG,
135	*Citrobacter amalonaticus*	CH, PB	AK	AS, BA, CF, PC, RC, CI, TE, ZN, GM, GF, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, CB, AS
220	*Escherichia coli*	CH, AK, GF	AS, ZN	BA, CF, PC, RC, CI, TE, GM, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
607	*Proteus mirabilis*	-	CH, GM	AS, BA, CF, PC, RC, CI, TE, ZN, AK, GF, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
618	*Klebsiella pneumoniae*	-	-	AS, BA, CF, PC, CH,RC, CI, TE, ZN, GM, AK, GF, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB

Key:
TT -Ticarcillin/clavulanic acid, OX- Oxytetracycline, RP – Ceftriaxone, ZX – Cefepime, CB – Cefuroxime, NA - Naladixic acid, NX- Norfloxacin, AG - Amoxycillin/clavulanic acid, CU – Cefadroxil,CP - Cefoperazone, FG- Ceftazidime, PB - Polymixin B, AS – Ampicillin, BA - Co-trimaxazole, CF – Cefotaxime, PC- Pipperacillin, CH – Chloramphenicol, RC – Ciprofloxacin, CI – Ceftizoxime, TE – Tetracycline, ZN – Ofloxacin, GM – Gentamicin, AK –Amikacin, GF – Gatifoxacin

Table 7: Antimicrobial activity

Sr. No.	Cultures used		Zone of Inhibition (mm) of Cu(II) complex								
			DMSO	HL_1	$[Cu(L_1)Cl]$	HL_2	$[Cu(L_2)Cl]$	HL_3	$[Cu(L_3)Cl]$	HL_4	$[Cu(L_4)Cl]$
1	**Citro-2**	**ESBL**	0	0	10	0	15	0	11	0	12
2	**Ec- 10**		0	11	11	11	11	10	10	10	10
3	**Kp**		0	0	10	0	11	0	11	0	10
4	**Kp-7**		0	11	12	12	12	10	11	12	13
5	**Pro- 7**		0	0	11	0	13	0	15	0	13
6	**85**	**MBL**	0	12	13	15	16	15	15	15	16
7	**135**		0	16	15	17	16	15	14	15	16
8	**220**		0	0	10	11	11	11	11	0	14
9	**607**		0	0	10	0	11	0	11	0	10
10	**618**		0	0	11	0	12	10	12	0	10

ANTITUBERCULOSIS ACTIVITY

Schiff bases and their metal complexes were assessed for antitubercular activity against *M. Tuberculosis* (H37Rv) employing Microplate Alamar Blue Assay (MABA) method with reference to Pyrazinamide, Ciprofloxacin, and Streptomycin standard drugs (Table-8). The MICs (Minimum Inhibitory Concentration) were defined as the lowest concentration affecting a pink coloration to blue coloration. All Schiff bases were found to effectively inhibit the growth of *M. tuberculosis* at MIC of 25.0 µg/mL. It has been found that all Cu(II) complexes have displayed enhanced anti-tubercular activity (MIC = 12.5 µg/mL). For any drug to exhibit potential antitubercular activity, must have a reasonable permeability in order to penetrate the thick waxy cell wall of MTB. The better activity of copper complexes compared to Schiff bases may be due to the coordination of metal atom to form a chelate with enhanced amphiphilic properties and increased solubility suitable for easier penetration of metal complex into the microorganism leading to growth inhibition [xxvii].

Table 8: Antitubercular activity

Compound	Test compound	MIC (µg/mL)
Standard	Pyrazinamide	3.125
	Ciprofloxacin	3.125
	Streptomycin	6.250
Ligand	HL_1	25.0
	HL_2	25.0
	HL_3	25.0
	HL_4	25.0
Copper	$[Cu(L_1)Cl]$	12.5

complex	$[Cu(L_2)Cl]$	12.5
	$[Cu(L_3)Cl]$	12.5
	$[Cu(L_4)Cl]$	12.5

CONCLUSION

Copper complexes of the form $[M(L_{1-4})Cl]$ were derived from Schiff bases and characterized by spectroscopic methods. Monobasic trident nature of ligand with coordination from carboxylic O, azomethine N and phenolic O towards central atom was observed. The structural investigation revealed square planer geometry for Cu(II) complexes. Antibacterial and antitubercular activities of ligands were found to increase upon coordination with the copper ion. The observed activity of the test compounds indicates the future potential for the development of more potent metal chelates derived from the aminothiophene scaffold.

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