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CHEMISTRY AND BIOLOGICAL IMPORTANCE OF COPPER SCHIFF BASE COMPLEXES

[1]ABIRAMI M, [2]NADARAJ V*

[1]Department of Chemistry, Sri Ramakrishna Engineering College, Coimbatore-22
[2]Department of Chemistry, Tamilnadu College of Engineering, Coimbatore-641659

***Corresponding author: E.Mail: vnraj303@gmail.com**

ABSTRACT

A series of Cu (II) complexes were prepared from salicyldimine with acetate of Copper in water medium at room temperature. The chemical structures of metal complexes were confirmed by spectroscopic analysis and all of the compounds were evaluated for their antimicrobial properties. The Schiff base Cu (II) complexes have good biological activity against all tested bacteria and fungi.

KEYWORD: complex, Schiff base, antimicrobial, copper

INTRODUCTION

The development of simple synthetic routes to widely used organic compounds using readily available reagents is one of the main objectives of organic synthesis. Schiff bases are known to possess variety of biological properties (Jarrhpour A A, 2004). They can be used for synthesis of bioactive molecules. Nowadays, the research field dealing with Schiff base coordination chemistry has expanded enormously. Schiff bases of hydroxy aldehydes and ketones were widely used in co-ordination chemistry for the preparation of metal complexes (Raman N, 2001 and Pawlica D, 2004). Schiff bases and their co-ordination compounds have been gained importance now-a-days as they are useful in biochemical (S. Sha, 1992), anti-cancer (Pandeya S N, 1999), anti-inflammatory (More P G, 2001) and antipyretic (Kuzmin V E, 2005), among others.

Here in this paper we report the synthesis of Cu (II) complexes of salicyldimine Schiff bases. All the synthesized metal complexes were screened for their antimicrobial activity. Further the structures of synthesized compounds were confirmed by elemental analysis and spectral studies.

MATERIALS AND METHOD

Melting points (mp) were determined using Boetieus micro heating table and are uncorrected. IR (KBr, cm^{-1}) spectra were obtained on Shimadzu-8201 spectrophotometer. ^1H NMR spectra were recorded on Bruker AMX-400 (400 MHz) spectrometer using TMS as an internal reference (Chemical shifts in δ, ppm). Elemental analyses were performed on Perkin Elmer CHN-analyzer. Mass spectra were recorded on Shimadzu GCMS-QP5050A (70 ev) mass spectrometer. For microwave irradiation a Kenstar (OM-20ESP, 2450 MHz) domestic microwave oven was used.

Synthesis of ligands: A mixture of respective anilines and salicylaldehyde was taken in a 50 mL beaker and mixed well. The mixture was irradiated in a microwave oven at power of 160 W for the specified time (Table 1). The reaction was monitored by thin layer chromatography (TLC) and spots were visualized in iodine chamber. After completion of the reaction, the reaction mixture was poured into ice water. The yellow solid obtained was filtered, washed, dried and recrystalised from ethanol.

Preparation of complexes: The salicylaldimine ligand (0.01 mole) and cupric acetate (0.01 mole) was dissolved in 50 ml ethanol. An immediate colour change was observed and then the solution stirred for 1 hr. After 1 hr, the reaction mixture was kept on undisturbed overnight. Solid complex thereafter separate out washed with distilled water to remove excess of metal and dried in vacuum. The structures of the ligands and metal complexes are shown in scheme-I.

Antimicrobial Bioassay: All the synthesized compounds were screened for their antibacterial and antifungal activities. For preliminary screening, the antimicrobial tests were carried out by disc-diffusion method (Karaman I, 2003). One hundred µl of suspension containing 10^8 CFU/ml of bacteria, 10^6 CFU/ml of fungi were spread on Mueller-Hinton agar medium (MHA) and Sabouraud's dextrose agar (SDA) medium respectively. The discs (6 mm in diameter), impregnated with 10 µl of the test compounds (500 µg/disc and 1000 µg/disc) at the concentration of 50 mg/ml and 100mg/ml were placed on the inoculated agar. Negative controls were prepared using the same solvent (Dimethyl sulphoxide) employed to dissolve the test compounds. Ofloxacin (5 µg/disc) and Clotrimazole (10 µg/disc) were used as positive reference standard to determine the sensitivity of each

microbial species tested. The inoculated plates were incubated at 37˚ C for 24 hr and 27˚ C for 72 hr for bacteria and fungi strains respectively. Antimicrobial activity was evaluated by measuring the diameter of zone of inhibition against test organisms.

Minimum inhibitory concentration (MIC) of the compounds was also estimated by broth dilution assay for the microorganisms, which were determined as sensitive to the compounds in disc-diffusion assay (Mishra D, 2002). Nutrient broth (NB) and Sabouraud's dextrose broth (SDB) were used to estimate the MIC values of the test compounds against bacteria and fungi respectively. A twofold serial dilution of test compounds were followed with 1ml of sterile broth in test tubes to provide various concentration ranges from 3.9-1000 µg/ml of the test compounds. Ten µl of the test organism was added to each tube and incubated at 37˚ C for 24 hours and 27˚ C for 72 hours for bacteria and fungi strains respectively. The highest dilution of the test compound completely inhibiting the test organism was considered as MIC value of the test compound respectively.

RESULTS AND DISCUSSION

The synthetic procedure of ligand salicylaldimine and its metal complexes are presented in Scheme 1. Schiff base salicylaldimine was synthesized by the condensation of substituted aryl amine with salicylaldehyde. The reactions of divalent transition metal ions Cu (II) with the ligand salicylaldimine in 1:1 molar ratio in methanol, yielded the corresponding metal chelates. An immediate colour change obtained, it confirm the formation of metal complex. All the synthesized compounds are colored and stable to air and moisture. The yields of the complexes are about 85-92%. The ligand is soluble in common organic solvents, but its metal complexes are generally only soluble in DMF and DMSO.

The IR spectra of the free ligands and complexes were compared to determine the coordination sites that may be involved in coordination. Based on the comparison it was determined that the *v*(C=N) stretching vibration is found in the Schiff base at 1600 to 1615 cm^{-1}. This band shifted to lower wave numbers in the complexes indicating the participation of nitrogen in coordination. The new bands at *v* M-N stretching vibrations were appeared at 540-525 cm^{-1} in the spectra of metal complexes.

^{1}H NMR spectra of the Schiff base and transition complexes were compared. The signal for the azomethine proton appearing as a singlet at δ8.59-9.92 ppm in the spectra of ligands was downfield shifted in the spectra of Cu (II) complexes at δ10.05-10.22 ppm. This deshielding was attributed to the donation of the lone pair of electrons on the azomethine nitrogen to the copper ion, resulting in the formation of a coordinate bond. ^{1}H NMR spectra of ligands exhibited a multiplet between the region δ6.47-8.30 ppm for aromatic hydrogens. In the spectra of Cu (II) complexes, these peaks have downfield shifts which can be attributed to the increased conjugation upon complex formation. The intensity of the signal observed at δ12.23-13.00 ppm due to OH in spectra of Ligands disappeared in the spectra of Cu (II) complexes 3a-e. It refers to the complex formation occurring *via* the deprotonation of the OH group. The changes and downfield shifts in the spectra of copper complexes are good indications for participation of these groups in the coordination with the metal ions, and give further support for the presence of the metal ions. All the compounds have elemental analysis consistent with their formulations. The elemental analytical data of the complexes reveal a metal to ligand ratio is 1:1. The physical and analytical data of salicylaldimine and its metal complexes are given in Table 1, Table 2, Table 3 and Table 4.

All the Cu (II) complexes synthesized in the present study were tested for antibacterial activity against seven bacteria and five fungi stains (Table 5 & Table 6). The Cu (II) complexes exhibited good antibacterial activity against *Bacillus subtilis* and *Pseudomonas aeruginosa* whereas *Escherichia coli* and *Staphylococcus aureus* have shown moderate activity. Excellent activity against *Pseudomonas aeruginosa* was also shown by 3d followed by good inhibition against most of the strain. In the case of antifungal activity all the tested complexes have shown good activity against both *Aspergillus flavus* and *Trichoderma viridie, Rhodotorula rubra* fungi. The 3b complexes have shown higher activity against both the bacterial and fungal strains. The ligands with nitrogen and oxygen donor atoms inhibit enzyme activity, since the enzymes which require these groups for their activity appear to be especially more susceptible to deactivation by metal ions on coordination.

Scheme 1

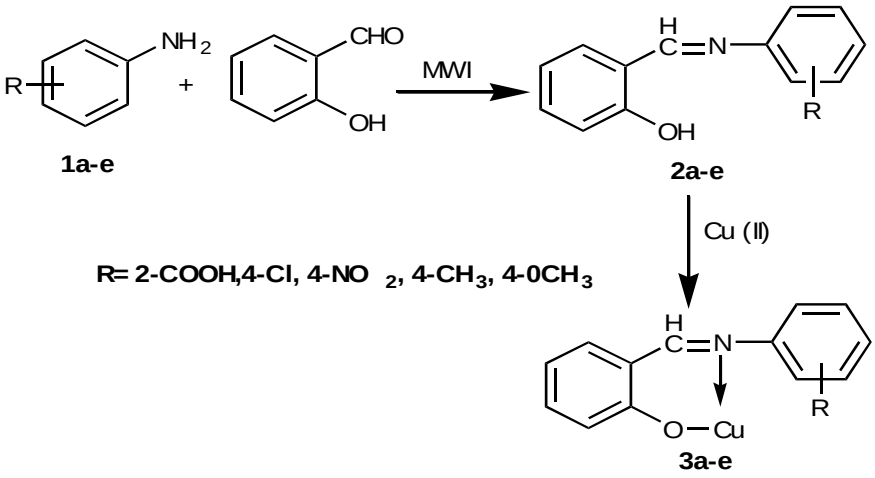


Table.1. Analytical and IR Spectral data of Schiff bases 2a-e

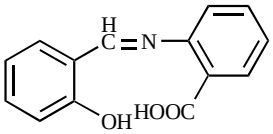
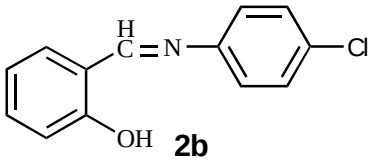
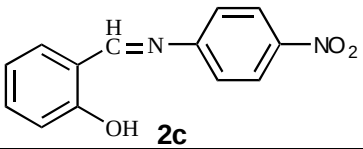
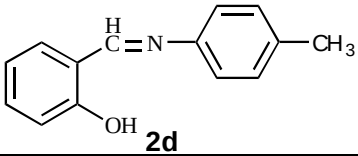
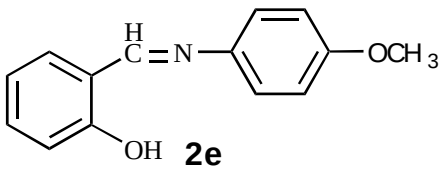
Compound	Physical Data			IR Spectrum (KBr,cm^{-1})		
	Reaction Time (min)	**Yield (%)**	**mp° C**	**$\nu_{C=N}$**	**ν_{C-O}**	**ν_{C-C} (aromatic stretching)**
 **2a**	4	92	120	1615	1230	1507 1454 1373
 **2b**	3	97	105	1614	1280	1588 1571 1498 1457
 **2c**	3	97	130	1600	1272	1565 1508 1484 1459
 **2d**	4	95	125	1615	1278	1560 1510 1482 1459
 **2e**	5	95	185	1612	1280	1575 1518 1464 1462

Table 2. Spectral data of Schiff bases 2a-e

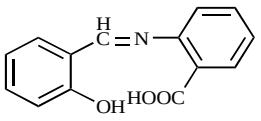
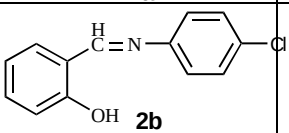
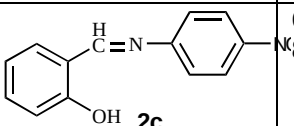
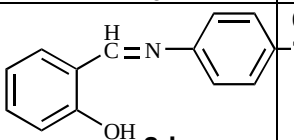
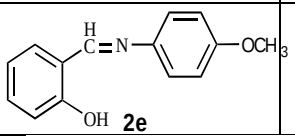
Compound	^{1}HNMR Spectrum (ppm)					^{13}CNMR Spectrum (ppm)					Mass Spectrum (70 eV, *m/e*)
	δ_{C-H}	δ_{OH}	$\delta_{CH=N}$	δ_{COOH}	δ_{CH3}	δ_{C}(Ar)	δ_{CN}	δ_{COOH}	δ_{CH3}	Molecular Formula	(M^{+})
 **2a**	6.6-7.4	12.94	8.59	11.06	-	117.3-163.7	76.7-77.4	196.59	-	$C_{14}H_{11}NO_3$	241
 **2b**	6.47-7.75	13.00	9.92	-	-	109.9-174.9	82.8-82.9	-	-	$C_{13}H_{10}NOCl$	231
 **2c**	6.98-8.30	12.58	9.65	-	-	117.5-165.3	76.7-77.3	-	-	$C_{13}H_{10}N_2O_3$	242
 **2d**	6.62-7.92	12.23	9.62	-	2.45	119.4-162.3	77.4-78.4	-	29.03	$C_{14}H_{13}NO$	211
 **2e**	6.78-8.02	12.52	9.78	-	3.97	111.5-172.5	82.4-82.8	-	35.66	$C_{14}H_{13}NO_2$	227

Table.3.Analytical and IR Spectral data of Cu (II) complexes 3a-e

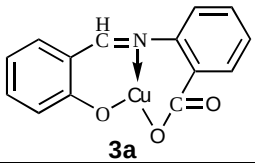
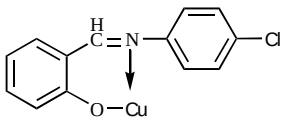
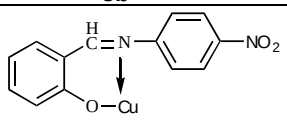
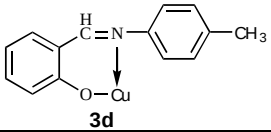
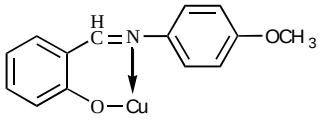
Compound	Physical Data		IR Spectrum (KBr,cm^{-1})		
	Yield (%)	mp° C	$\nu_{C=N}$	ν_{C-O}	ν_{C-C} (aromatic stretching)
 **3a**	89	166	1585	1151	1535 1444 1388
 **3b**	86	205	1585	1180	1585 1537 1446 1377
 **3c**	92	190	1581	1147	1512 1446 1377
 **3d**	85	185	1586	1208	1550 1500 1444 1434
 **3e**	85	215	1580	1125	1546 1508 1458 1452

Table.4.Spectral data of Schiff bases 3a-e

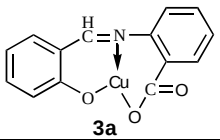
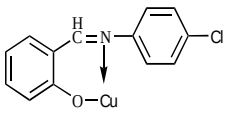
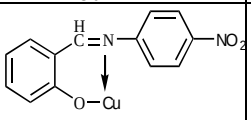
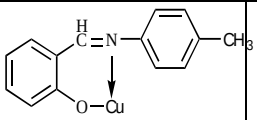
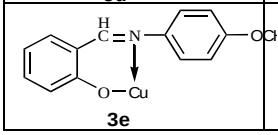
Compound	^{1}HNMR Spectrum (ppm)					^{13}CNMR Spectrum (ppm)				Mass Spectrum (70 eV, *m/e*)	
	δ_{C-H}	δ_{OH}	$\delta_{CH=N}$	δ_{COOH}	δ_{CH3}	δ_{C}(Ar)	δ_{CN}	δ_{COOH}	δ_{CH3}	Molecular Formula	(M^{+})
 **3a**	7.33-8.92	Disappeared	10.15	Disappeared	-	119.4-167.3	76.7-77.4	197.55	-	$C_{14}H_{9}NO_{3}Cu$	302
 **3b**	7.28-8.68	-	10.05	-	-	1109-179	85.2-86.9	-	-	$C_{13}H_{9}NOClCu$	293
 **3c**	7.56-9.20	-	10.18	-	-	117.5-165.3	78.5-80.6	-	-	$C_{13}H_{9}N_{2}O_{3}Cu$	304
 **3d**	7.95-9.25	-	10.22	-	2.52	122.6-170.4	77.4-78.4	-	31.05	$C_{14}H_{12}NOCu$	273
 **3e**	8.10-9.00	-	10.10	-	3.99	120.0-177.6	83.7-85.0	-	39.44	$C_{14}H_{12}NO_{2}Cu$	289

Table.5. *In vitro* antimicrobial activity of 3a-e (µg/disc) by disc diffusion assay

Microorganisms	Diameter of zone of inhibition in mm											
	3a µg/disc		**3b** µg/disc		**3c** µg/disc		**3d** µg/disc		**3e** µg/disc		**A** µg/disc	**B** µg/disc
	500	1000	500	1000	500	1000	500	1000	500	1000	5	10
Bacillus subtilis (NCIM 2063) [a]	-	11	9	10	7	8	10	11	-	11	23	NT
Bacillus cereus (NCIM 2155) [a]	7	9	7	12	-	-	7	10	7	10	22	NT
Escherichia coli (NCIM 2065) [a]	-	-	9	13	7	10	7	10	-	-	24	NT
Salmonella typhimurium (NCIM 2501) [a]	-	-	10	12	-	-	7	8	-	-	21	NT
Klebsiella aerogenes (NCIM 2239) [a]	-	8	9	11	-	10	-	-	7	9	24	NT
Pseudomonas aeruginosa (NCIM 2200) [a]	9	10	8	10	-	8	10	13	-	-	19	NT
Staphylococcus albus (NCIM 2178) [a]	-	-	7	10	-	-	7	10	-	9	21	NT
Aspergillus niger (NCIM 1196) [b]	-	-	8	10	7	10	-	-	-	-	NT	16
Trichoderma viridie (NCIM 1195) [b]	10	13	9	11	7	9	-	10	9	13	NT	16
Rhodotorula rubra (NCIM 3174) [b]	9	12	7	10	7	11	-	8	8	10	NT	17
Lipomyces lipofera (NCIM 3252) [b]	-	-	8	11	-	-	-	-	-	-	NT	18
Aspergillus flavus (NCIM 535) [b]	9	10	9	10	7	9	8	10	9	11	NT	19

[a] bacteria [b] fungi ; **A** = Ofloxacin, **B** = Clotrimazole, - No inhibition, NT- Not Tested

Table.6. Minimum Inhibitory Concentration values of 3a-e (μg/ml) against the microorganisms tested in broth dilution assay

Microorganisms	3a	3b	3c	3d	3e
Bacillus subtilis (NCIM 2063) [a]	62.5	62.5	125	125	62.5
Bacillus cereus (NCIM 2155) [a]	62.5	125	-	31.2	62.5
Escherichia coli (NCIM 2065) [a]	-	62.5	15.6	62.5	-
Salmonella typhimurium (NCIM 2501) [a]	-	125	-	7.8	-
Klebsiella aerogenes (NCIM 2239) [a]	125	62.5	125	-	125
Pseudomonas aeruginosa (NCIM 2200) [a]	62.5	62.5	31.2	7.8	-
Staphylococcus albus (NCIM 2178) [a]	-	62.5	-	-	62.5
Aspergillus niger (NCIM 1196) [b]	-	31.2	15.6	-	-
Trichoderma viridie (NCIM 1195) [b]	7.8	31.2	62.5	62.5	15.6
Rhodotorula rubra (NCIM 3174) [b]	62.5	7.8	31.2	125	62.5
Lipomyces lipofera (NCIM 3252) [b]	-	62.5	-	-	-
Aspergillus flavus (NCIM 535) [b]	31.2	7.8	15.6	7.8	15.6

[a] bacteria [b] fungi; - Not Tested

CONCLUSION

In this paper, we have synthesized a series of salicyaldimine Schiff base and its metal complexes. The formation of the compounds has been confirmed by the analytical data, IR, ^{1}H NMR and mass spectral studies. The above studies reveals that the Schiff base acts as neutral bidentate coordinating through azomethine nitrogen and phenolic oxygen atoms to the metal ions. The metal: ligand stochiometry in all the complexes is 1:1. All Cu(II) complexes tested by *in vitro* antimicrobial, activity which shows fine results with an enhancement of activity on complexation with metal ions. This enhancement in the activity may be due to increased lipophilicity of the complexes.

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