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Antibacterial Studies of Transition Metal Complexes of Tetradentate Thiazole Based Schiff Base

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ABSTRACT

A novel Schiff base ligand and its metal complexes of Co(II), Ni(II), Cu(II) and Zn(II) were synthesized and characterized. The characterization was done by using elemental analyses, molar conductivity, magnetic susceptibility, Mass, ^{1}H NMR, ^{13}C NMR, UV-Vis and IR spectroscopy. The experimental data predict that all the complexes are mononuclear with M(II) being coordinated by a tetradentate Schiff base ligand through the deprotonated oxygen atom, nitrogen atom in thiazole ring and two azomethine nitrogen atoms. The data confirm that the complexes have the composition of [ML] Cl type. The electronic absorption spectral data of the complexes propose a square planar geometry around the central metal ion. The biological activities of the synthesized compounds were tested against bacteria by *well-diffusion* method.

Keywords: 2-Aminothiazole, 4-aminoantipyrine, transition metal complexes, antibacterial activity

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INTRODUCTION

Schiff bases are a significant group of organic compounds that have biological activities and diverse applications because of their antibacterial, antivirus activities, metal complexation and other pharmacological effects. The Schiff bases having sulphur and nitrogen donor atoms act as good chelating agents for the transition and non-transition metal ions[1-4].There is highly enhanced activities[5] for coordination compounds with metal ions such as copper, nickel and iron as it has been an account for pathogenic fungi. Azomethine linkage is vital for biological activity; several azomethines were reported to possess important antibacterial[6-9], antifungal[10-11], anticancer[12] and diuretic activities[13]. In recent years, Schiff bases and their complexes were established to have significant antitumor and biological activity[14-15]. Antipyrine derivatives of Schiff bases are reported to exhibit analgesic and anti-inflammatory effects[16], antiviral[17], antibacterial[18], anticonvulsant[19] and herbicidal[20] activities. Transition metal complexes with ligands derived from 4-aminoantipyrine have important biological activity[21-24]. In this article, we report the synthesis and structural characterization of 4-aminoantipyrine based tetradentate heterocyclic Schiff base derived from 4-aminoantipyrine, salicylaldehyde and 2-aminothiazole and its complexes with Cu(II), Co(II), Ni(II), Zn(II) metal ions.

MATERIAL AND METHODS

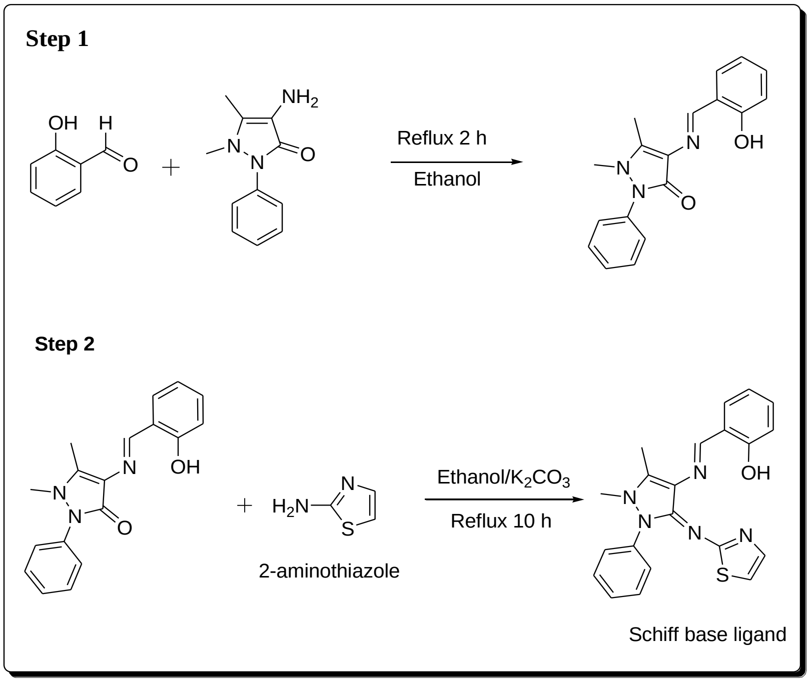
Salicylaldehyde, 4-aminoantipyrine, 2-aminothiazole and metal chlorides were obtained from Merck. All the chemicals used were of AR grade. Solvents were purified and distilled before use. ^{1}H NMR spectra were recorded on Bruker 300 MHz instrument. IR spectra were recorded on a Perkin Elmer 783 instrument in anhydrous KBr pellets. UV-Visible spectra of the complexes were recorded on Perkin Elmer Lambda EZ201 spectrophotometer in DMSO solution. Molar conductivity was determined using Systronic Conductivity Bridge with a dip type cell using 10^{-3} M solution of complexes in DMSO. Magnetic susceptibility was measured with a Guoy balance.

Synthesis of Schiff base (HL)

Salicylidine-4-aminoantipyrine was prepared by the condensation of salicylaldehyde and 4-aminoantipyrine as reported earlier[25]. Salicylidine-4-aminoantipyrine (2 mmol) and 2-aminothiazole (2 mmol) were taken in ethanol (50 ml) solvent. To this mixture, 1 g of anhydrous potassium carbonate was added and then refluxed for 10 h. The resulting solution was concentrated on a water bath and allowed to cool at 0°C for ~24 h. The solid product formed was separated by filtration and washed thoroughly with ethanol and then dried in vacuum. (Yield: 68 %) (Scheme 1).

Synthesis of metal (II) complexes

A solution of metal (II) chloride (2 mmol) in ethanol (25 mL) was stirred with an ethanolic solution (25 mL) of the Schiff base (2 mmol). The above mixture was magnetically stirred and refluxed for 4 h. Then the solution was reduced to one-third on a water bath. The solid complex precipitated was filtered off and washed thoroughly with ethanol and dried in *vacuo*.



Scheme 1. Synthetic route of Schiff base ligand

Antibacterial activity

The synthesized compounds were tested for their antibacterial activity by *well diffusion* method using Mueller-Hinton Agar (MHA). The antibacterial activities were done at 60 µg/mL concentrations in DMSO solvent using bacteria *(Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis* and *Staphylococcus aureus) at* the minimum inhibitory concentration (MIC). The stock solutions were prepared to 3 mg of Compound / 2 mL of DMSO concentration. From the stock solution, different diluted measurements such as 20 µL, 40 µL, 60 µL (20 µL diluted sample contain 30 µg of the test compound) were immediately dispensed into agar wells of culture inoculated plates (MHA) using sterilized microtips. The plates were incubated at 37°C overnight. The antibacterial activity was measured by the diameter of the inhibition zone including the diameter of the well.

RESULTS AND DISCUSSION

Elemental analysis and molar conductivity measurements

The analytical data for the ligand and the complexes together with some physical properties are summarized in Table 1. The analytical data of the complexes correspond to the general formula MLCl, where M = Cu(II), Co(II), Ni(II) and Zn(II); L = $C_{21}H_{19}N_5OS$. The magnetic susceptibilities of the complexes at RT are consistent with square-planar geometry around the central metal ion.

The formation of these complexes may proceed according to the equation given below:

$$MCl_2.nH_2O + L \rightarrow MLCl + HCl + nH_2O$$

Where, M = Cu(II), Co(II), Ni(II) and Zn(II)

The metal(II) complexes were dissolved in DMSO and the molar conductivities of 10^{-3}M solutions at RT were measured. The higher conductance values (120–144 Ω^{-1} cm^2 mol^{-1}) of the complexes indicate their electrolytic nature[26].

Table 1 Physical and analytical data of the synthesized Schiff base and its complexes

Compound	**Empirical Formula**	**Yield (%)**	**Colour**	**Found (Calculated) (%)**				**Formula weight**	**(Λ_M)Ω^{-1}cm^2 mol^{-1}**	**μ_{eff} (B.M.)**
				M	C	H	N			
HL	$C_{21}H_{19}N_5OS$	66	Brown	-	64.26 (64.76)	4.24 (4.92)	17.25 (17.98)	389.4	-	-
[CuL] Cl	$[CuC_{21}H_{18}N_5OS]Cl$	56	Black	12.66 (13.04)	51.89 (51.74)	3.14 (3.72)	14.17 (14.37)	487.4	132	1.71
[CoL] Cl	$[CoC_{21}H_{18}N_5OS]Cl$	52	Red	12.22 (12.21)	52.42 (52.24)	3.37 (3.76)	14.34 (14.50)	482.8	120	3.52
[NiL] Cl	$[NiC_{21}H_{18}N_5OS]Cl$	62	Green	12.14 (12.16)	52.35 (52.26)	3.25 (3.76)	14.05 (14.51)	482.6	138	Diamagnetic
[ZnL] Cl	$[ZnC_{21}H_{18}N_5OS]Cl$	46	Brown	13.17 (13.36)	51.20 (51.55)	3.59 (3.71)	14.17 (14.31)	489.3	144	Diamagnetic

Infrared Spectra

The IR spectra provide valuable information regarding the nature of the functional group attached to the metal ion. The IR spectral data of the Schiff base and its complexes are given in Table 2**.** The IR spectrum of the ligand shows a broad band in the region 3200-3600 cm-1, assignable to $\upsilon_{(OH)}$ group. The disappearance of this peak in all the spectra of the complexes indicates that the –OH group is indeed involved in complexation. The spectrum of the ligand shows two different $\upsilon_{(C=N)}$ bands in the region 1615-1690 cm^{-1}, which are shifted to lower frequencies in the spectra of all the complexes (1600-1650 cm^{-1}) indicating the involvement of –C=N nitrogen in coordination to the metal ion[27-28]. Also the ligand shows a band at 1608 cm^{-1} which is attributed to $\upsilon_{(CH=N)}$ of thiazole ring and $\upsilon_{(C=C)}$ at 1550 cm^{-1}. The stretching vibration appearing at 780 cm^{-1} is due to $\upsilon_{(C-S)}$ of thiazole ring[29]. A shift in the band at 1608 cm^{-1} of the thiazole ring (1600–1580 cm^{-1}) in complexes suggest the coordination via thiazole nitrogen (N → M)[30]. In all the complexes the $\upsilon_{(C-S)}$ remains unchanged indicating that sulphur is not involved in coordination. IR spectra of complexes show new bands at 440–484 cm^{-1} and 526–560 cm^{-1}

assignable to υ(M–N) and υ(M–O) modes respectively[31].

Table 2 The IR spectral data of Schiff base and its complexes (cm^{-1})

Compound	$\upsilon_{(OH)}$	$\upsilon_{(C-S)}$	$\upsilon_{(C=N)}$	$\upsilon_{(M-N)}$	$\upsilon_{(M-O)}$
SAAPAT (HL)	3430	780	1643, 1685	-	-
[CuL] Cl	-	788	1620, 1636	484	526
[CoL] Cl	-	777	1616, 1643	440	530
[NiL] Cl	-	781	1612, 1624	485	533
[ZnL] Cl	-	776	1625, 1641	472	560

^{1}H-NMR spectra

^{1}H NMR spectra of the Schiff base ligand and its zinc complex were recorded at RT in $CDCl_3$. Schiff base ligand (HL) exhibited the following signals: aromatic protons at 7.26-7.49 δ (10H, m), -CH=N at 9.66 δ (1H, s), -N-CH_3 at 3.11 δ (3H, s), C-CH_3 at 2.46 δ (3H, s) and S-CH=CH- of thiazole ring at 6.25 δ (1H, d). N-CH=CH of thiazole proton of free ligand at 6.90 δ (1H, d) also showed a downfield shift in the complex providing an evidence for coordination of thiazole nitrogen to the metal. The peak at 10.48 δ is attributable to –OH of salicylaldehyde moiety observed in Schiff base. The absence of this peak noted for zinc complex indicates the loss of the OH proton due to chelation. The azomethine proton signals in the spectra of zinc complex was moved downfield compared to the Schiff base ligand, suggesting deshielding of azomethine group due to coordination with metal atom. There is no significant change in all other signals of the ligand.

Electronic absorption spectroscopy

The electronic absorption spectra were recorded at 300 K. The various absorptions, band assignments and the proposed geometry of the complexes are given in **Table 3.** The electronic spectra of copper complex displays two bands, which are assigned as an intra-ligand charge transfer band (31,645 cm^{-1}) and d-d band (19,607 cm^{-1}) which is due to $^2B_{1g}\rightarrow{}^2A_{1g}$ transition. This d-d band strongly favors square-planar geometry for the copper complex[32-33]. It is further supported by its magnetic susceptibility value (1.71 B.M). The UV-visible spectrum of Cobalt(II) complex shows two peaks at 28,571 cm^{-1} and 22,471 cm^{-1}. The first peak is due to intraligand charge transfer band and the band at 22,471 cm^{-1} is due to the $^1A_{1g}\rightarrow{}^1B_{1g}$ transition. This is true of square-planar geometry. This is further confirmed by its magnetic susceptibility value (3.52 B.M). Ni(II) has a (d^8) configuration giving peaks at 28,089 cm^{-1} and 23,148 cm^{-1}. The first peak is assigned to the intraligand charge transfer band and the second peak is for $^1A_{1g}$ $^1B_{1g}$ to square planar geometry. No transitions were observed in the visible region for Zn(II) complex consistent with the d^{10} configuration of Zn(II) ion. This complex is found to be diamagnetic as expected for d^{10} configuration. According to stoichiometry of these complexes and elemental analyses they are four coordinated, which could be a square-planar geometry. Based on the above spectral and analytical data, the proposed geometry of the metal(II) complexes is given in **Figure 1**.

Table 3 Electronic spectral data of Schiff base and its complexes

Compound	Absorption nm(cm^{-1})	Band assignments	Geometry
SAAPAT (HL)	360 (27,777)	INCT	-
[CuL] Cl	316 (31,645)	INCT	Square planar
	510 (19,607)	$^2B_{1g}\rightarrow{}^2A_{1g}$ transition	
[CoL] Cl	350 (28,571)	INCT	Square planar
	445 (22,471)	$^1A_{1g} \rightarrow {}^1B_{1g}$ transition	
[NiL] Cl	356 (28,089)	INCT	Square planar
	432 (23,148)	$^1A_{1g} \rightarrow {}^1B_{1g}$ transition	

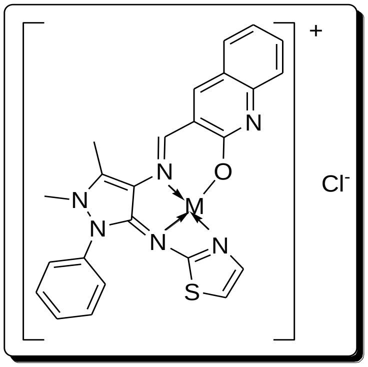


Figure 1. Square planar geometry of metal complexes

Where M = Cu(II), Co(II), Ni(II) and Zn(II)

Antibacterial activity

The Schiff base ligand and its complexes have been screened for their antibacterial activity against various pathogenic bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Staphylococcus aureus*. *Tetracycline* was used as the standard for bacterial studies.

The data regarding the zone of inhibition are given in Table 4. It has been observed that the metal complexes have a higher activity than the free ligand. Probably this may be due to the greater lipophilic nature of the complexes. The increase in antibacterial activity is due to faster diffusion of metal complexes as a whole through the cell membrane or due to the combined activity effect of the metal and ligand. Such increased activity of the metal complexes can be explained on the basis of Overtone's concept[34] and Tweedy's chelation theory[35]. According to Overtone's concept of cell permeability the lipid membrane that surrounds the cell favors the passage of only lipid soluble materials due to which liposolubility is an important factor which controls the antimicrobial activity. On chelation, the polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of positive charge of metal ion with donor groups. Further, it increases the delocalization of π-electrons over the whole chelate ring and enhances the lipophilicity of the complex. The increased lipophilicity leads to break-down of the permeability barrier of the cell and thus retards the normal cell processes.

Table 4 Antibacterial activity data for the Schiff base and its complexes

Compound	***E. coli***			***P. aeruginosa***			***B. subtilis***			***S. aureus***		
	30µg	**60µg**	**90µL**	**30µg**	**60µg**	**90µg**	**30µg**	**60µg**	**90µg**	**30µg**	**60µg**	**90µg**
SAAPAT (HL)	11	12	14	-	-	-	10	11	12	-	14	15
[CoL]	11	15	16	14	18	18	11	12	14	-	12	13
[CuL]	16	18	22	-	13	14	10	15	20	15	17	20
[NiL]	11	14	18	14	19	19	-	12	13	-	-	10
[ZnL]	12	14	16	14	19	19	10	12	14	-	12	14

Zone of Inhibition (mm)

CONCLUSION

A Schiff base ligand was obtained from the reaction of 4-aminoantipyrine, salicylaldehyde and 2-aminothiazole. Cu(II), Co(II), Ni(II) and Zn(II) complexes were synthesized using the above Schiff base ligand and characterized on the basis of elemental analyses, molar conductivities, IR spectra, NMR, mass spectra and UV–vis spectra. Based on these data, a square-planar geometry has been assigned to the complexes. Evaluation of antibacterial activity of the complexes against *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis* and *Staphylococcus aureus* exhibited that the complexes have more potent biocidal activity than the free ligand.

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