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Jisha Joseph [a] , N. L. Mary [a] & Raja Sidambaram [b]

[a] Department of Chemistry , Stella Maris College , Chennai, India

[b] Centre for Research in Science and Technology, Stella Maris College , Chennai, India

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Synthesis, Characterization, and Antibacterial Activity of the Schiff Bases Derived from Thiosemicarbazide, Salicylaldehyde, 5-bromosalicylaldehyde and their Copper(II) and Nickel(II) Complexes

Jisha Joseph,[1] N. L. Mary,[1] and Raja Sidambaram[2]
[1]*Department of Chemistry, Stella Maris College, Chennai, India*
[2]*Centre for Research in Science and Technology, Stella Maris College, Chennai, India*

Two Schiff bases salicylidene thiosemicarbazone (SALTSC) and 5-bromosalicylidene thiosemicarbazone (5-BrSALTSC) were prepared in excellent yield via the condensation of salicylaldehyde/5-bromosalicylaldehyde and thiosemicarbazide. The copper (II) and nickel (II) complexes of the Schiff base ligands (CuSALTSC, 5-BrCuSALTSC, NiSALTSC, and 5-BrNiSALTSC) were also prepared. The complexes were tested against *Staphylococcus aureus* (gram-positive) and *Escherichia coli* (gram-negative) using Disc diffusion method. Among these complexes, 5BrCuSALTSC was found to be highly active against *S. aureus* at a concentration of 100 μg/disc and against *E. coli* at a concentration of 150 μg/disc. 5BrNiSALTSC was found to be highly active against *E. coli* at a concentration of 150 μg.

Keywords antibacterial activity, azomethine linkage, Schiff bases

INTRODUCTION

Many biologically important Schiff bases have been reported possessing antibacterial,[1–7] antifungal,[8–10] antimicrobial,[11–13] and anti-HIV[14,15] activities. Also, certain polymeric Schiff bases have been found to possess antitumor activity. The Schiff bases have the highest degree of hydrolysis at pH 5, and the solubility in water is also high at this pH. Antitumor activity of the Schiff bases towards acidic tumors increases considerably with the slight increase in water solubility.[16]

Schiff bases are important intermediates for the synthesis of some bioactive compounds such as beta-lactams. The base catalyzed condensation of acetyl chlorides with N-arylaldimines occurs by initial acylation at the nitrogen atom and leads to β-lactams of interest in penicillin chemistry.[17] It has been suggested that the azomethine linkage might be responsible for the biological activities displayed by Schiff bases.[18] The compounds having antimicrobial activity may act either by killing the microbe or by inhibiting multiplication of the microbe by blocking their active sites.[19] Schiff bases derived from salicylaldehydes are well known as polydentate ligands, coordinating as deprotonated or neutral forms.[20]

In the present study we synthesized Salicylidenethiosemicarbazone (SALTSC) and 5-Bromosalicylidene thiosemicarbazone (5-BrSALTSC) and their Cu (II) and Ni (II) complexes. The complexes were tested for their antibacterial activity.

EXPERIMENTAL

Preparation of Schiff base Complexes[21,22]

A mixture of 0.735 ml of salicylaldehyde (0.01 M) dissolved and 0.0919 g of thiosemicarbazide (0.01 M) dissolved in ethanol refluxed for two hours on a water bath till a clear solution was obtained. It was allowed to cool and the Schiff base separated out was filtered and recrystallized from hot ethanolic solution. The melting point of this base was 203°C.

5-bromosalicylaldene thiosemicarbazone was prepared by using brominated salicylaldehyde (1.99 g; 0.01 M) and thiosemicarbazide (0.01 M).

Salicylaldene thiosemicarbazone/ 5-bromosalicylaldene thiosemicarbazone (0.01 M) dissolved in ethanol was mixed with corresponding metal ion (0.01 M) in ethanol. The resulting solution was refluxed for two hours. If necessary, sodium acetate was added to control the pH at 8.2. The refluxed solution was cooled and the precipitated complex was filtered. The filtered complex was washed with ethanol and dried over anhydrous calcium chloride.

CHARACTERIZATION STUDIES

The complexes were characterized using FT IR spectra, mass spectra, and NMR spectra.

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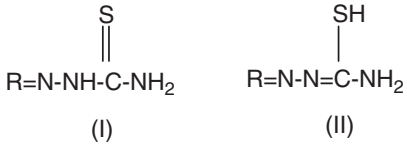
Address correspondence to Raja Sidambaram, Technical Director, Centre for Research in Science and Technology, Stella Maris College, Chennai, India. E-mail: rajasidambaram@gmail.com

Infrared Spectra

SALTSC and 5-BrSALTSC exhibit a sharp band at 1610 cm^{-1} due to azomethine linkage. In all the complexes, this band appears at a frequency lower (approximately 20cm^{-1}) than that on the free ligand. This clearly indicates the involvement of nitrogen atom in coordination due to a reduction in the electron density in the azomethine linkage. Keto-enol tautomerism is possible for thiosemicarbazone, and the ligand can exist as keto (I) or enol (II) or as a mixture of both.



The SH stretching vibrations are absent in the expected region. 2650–2500 cm^{-1} indicate that the free ligand exists in this keto form in the solid state. However, during the complex formation, it might exist in the enol form. This is indicated by the absence of the band due to νC-S of the ligand in the complexes. In the free ligand, the band appears at 754 cm^{-1}. A new band arises on complexation at 704 cm^{-1}, which can be attributed to νC-S. In all these studies, the clear indication is of the participation of sulphur atom in coordination.

The free hydroxyl group in a compound has stretching mode at 3700–3450cm^{-1}. The –OH band is weakened, if the group is hydrogen bonded, and in such cases the band is broadened with a shift to lower frequency. In salicylidene thiosemicarbazone and 5 Bromosalicylidene thiosemicarbazone, this band occurs at 3439 cm^{-1}, which excludes the possibility of hydrogen bonding. It also shows two N-H stretching bands, one at 3317cm^{-1} and the other at 3171cm^{-1}. These two bands also appear as sharp bands indicating the absence of hydrogen bonding.

The bands due to νNH and νOH are retained almost at the same position in the case of complexes. This excludes any possible participation of the oxygen of the phenol group or nitrogen of the NH_2 group in coordination (Table 1).

TABLE 1
The characteristic FT IR frequencies of the ligand and complexes

Name of the compound	$\nu_{HC=N}$ cm^{-1}	ν_{OH} cm^{-1}	ν_{C-S} cm^{-1}	ν_{NH} cm^{-1}
SALTSC	1610	3439	754	3171
CuSALTSC	1612	3447	789	3250
5BrCuSALTSC	1612	3445	766	3259
NiSALTSC	1622	3445	752	–
5BrNiSALTSC	1610	3483	762	2980

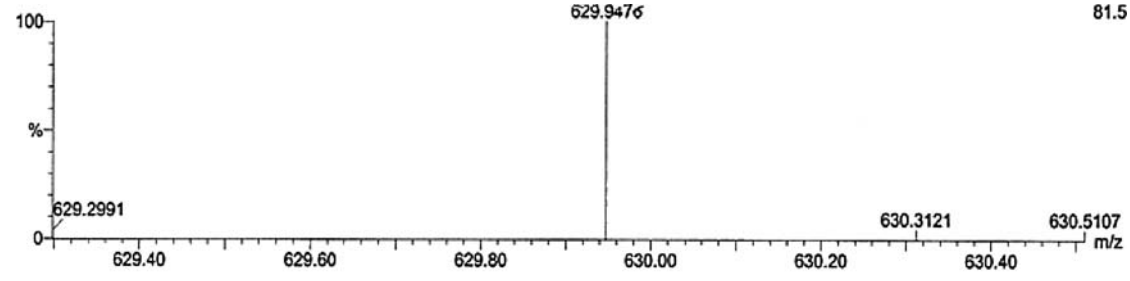
Mass Spectra

In the mass spectra of the CuSALTSC complex, the molecular ion peak is observed at 630 m/z. Since the compound contains six nitrogen atoms (even number), it gives a molecular ion peak with an even mass number (nitrogen rule). Isotopic peaks of 13C, 15N, 33S (M + 1 peak), and 18O, 34S (M + 2 peak) are also observed. Since the compound is a dimer, it shows m/2 peak at m/z = 315 and corresponding isotopic peak at m/z = 316.

The mass of the same compound has been determined with considerable accuracy with the help of high resolution mass spectra. The experimental mass and the calculated mass are in good agreement in both cases. For CuSALTSC, the mass is 629.9476 and the calculated mass is 629.9478 (Figure 1).

NMR Spectra

1H NMR spectra of SALTSC, BrSALTSC have been characterized by using DMSO-d6 as the solvent. The peaks between δ 6.71 and 6.95 showed the presence of azomethine (HC=N) protons. Singlet peaks between δ 9.3–10.1 indicated NH proton and the phenolic protons have shown peak at δ 7.1 to 7.8 ranges. 13C spectra of SALTSC and CuSALTSC have also been taken. The spectra showed bands attributed to C-N at δ 156.9 and 160.3, respectively, aromatic carbon between δ 139 and 120, carbonyl



Minimum:				-1.5		
Maximum:		200.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
629.9476	629.9478	-0.2	-0.3	14.0	1	C20 H20 N6 O6 S2 Cu2

FIG. 1. High resolution mass spectra of CuSALTSC.

TABLE 2
The antibacterial activity of the compounds

Compound	Concentration of compound-50 μg/disc		Concentration of compound-100 μg/disc		Concentration of compound-150 μg/disc	
	S. aureus	*E. coli*	*S. aureus*	*E. coli*	*S. aureus*	*E. coli*
SALTSC	+	++	+	−	+	−
CuSALTSC	+	++	++	++	+	++
5BrCuSALTSC	++	+	+++	++	+++	+++
NiSALTSC	+	−	+	−	+	+
5BrNiSALTSC	+	+	++	++	+++	−

Highly active = +++ (inhibition zone >12 mm)
Moderately active = ++ (inhibition zone 9–12 mm)
Slightly active = + (inhibition zone 6–9 mm)
Inactive = − (inhibition zone <6 mm)

carbon attached to N at δ 131.6, CH ranging from δ 40.1 and 39.9 and CH2 at δ 39.

Antibacterial Studies

The Schiff base ligand and selected four Schiff base complexes were screened *in vitro* for their antibacterial activity against one gram-positive (*Staphylococcus aureus)* and two gram-negative (*Escherichia coli* and *Klebsiella pneumoniae)* bacterial strains by disc diffusion method and tube dilution method.

Stock culture of bacteria was purchased from Science House, Chennai. A sub-culture was prepared from the stock culture.

Disc diffusion method[23]

When an antibiotic-impregnated disc is placed on agar previously inoculated with the test bacterium, the disc picks up moisture and the antibiotic diffuses radially outward through the agar, producing an antibiotic concentration gradient. The antibiotic is present at high concentrations near the disc and affects even minimally susceptible microorganisms (resistant organism will grow up to the disc). As the distance from the disc increases, the antibiotic concentration drops and only more susceptible pathogens are harmed. A clear zone or ring is present around an antibiotic disc after incubation if the agent inhibits bacterial growth.

An inoculating loop is touched to four or five isolated colonies of the pathogen grown on nutrient agar medium and then used to inoculate a tube of culture broth. The culture is incubated for a few hours at 37°C until it becomes slightly turbid. A sterile cotton swab is dipped into the standardized bacterial test suspension and used to evenly inoculate the entire surface of a Mueller-Hinton agar plate. After the agar surface has dried for about 5 minutes, the appropriate antibiotic test discs are placed on it with sterilized forceps or a needle. The plate is immediately placed in a 37°C incubator. After 24 hours of incubation, the diameter of the zones of inhibition measured to the nearest mm.

The concentration of the prepared compound was taken as 50 μg/disc, 100 μg/disc, and 150 μg/disc.

Tube dilution method

In broth dilution test, a series of broth tubes containing antibiotic concentrations in the range of 10 to 100μg/tube is prepared and inoculated with standard numbers of test organism. The lowest concentration of the antibiotic resulting in no growth after 16 to 20 hours of incubation is the MIC. Tryptone soya broth and sterile saline were used in this test.

TABLE 3
The MIC of the bacterial strains

Schiff base/complex	MIC for *S. aureus*	MIC For *E. coli*	MIC For *K. pneumoniae*
SALTSC	>100 μg	>100 μg	60 μg
CuSALTSC	>100 μg	>100 μg	60 μg
5-BrCuSALTSC	>100 μg	>100 μg	60 μg
NiSALTSC	>100 μg	>100 μg	60 μg
5-BrNiSALTSC	>100 μg	>100 μg	>100 μg

RESULTS AND DISCUSSION

To determine the antibacterial activity of these compounds, the disc-diffusion (Kirby-Bauer) method[10] was carried out using DMSO as control. The prepared compounds were examined against a gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli*) bacterial strains. The test results are given in Table 2.

Minimal inhibitory concentration (MIC)

The broth tube dilution method was used to determine the minimal inhibitory concentration (MIC). The MIC is determined

for the growth of one gram-positive (*Staphylococcus aureus*) and two gram-negative (*Escherichia coli* and *Klebsiella pneumoniae*) bacterial strains. The culture that shows no growth in the presence of the lowest concentration of the complex represents the MIC of the complex against those particular bacteria. The findings are given in Table 3.

From the data, it was observed that the antibacterial activity of these compounds showed significant increase on coordination. This enhancement in the antibacterial activity may be due to the possession of an additional azomethine bond. It has been suggested that the ligands with nitrogen and oxygen donor systems inhibit enzyme activity. Coordination reduces the polarity of the metal ion mainly because of the partial sharing of its positive charge with the donor groups within the chelate ring system. This process, in turn, increases the lipophilic nature of the central metal atom. This favors its permeation more efficiently through the lipid layer of the microorganism thus making the chelate compounds bacteriostatic.[24]

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