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Research Article

SYNTHESIS, CHARACTERIZATION, AND ANTIBACTERIAL ACTIVITY OF SCHIFF BASES DERIVED FROM THIOSEMICARBAZIDE, 2-ACETYL THIOPHENE AND THIOPHENE-2 ALDEHYDE

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ABSTRACT

Two Schiff bases 2-acetylthiophene thiosemicarbazone (L_1) and thiophene-2-aldehyde thiosemicarbazone (L_2) were prepared in excellent yield via the condensation of 2-acetyl thiophene/ thiophene-2-aldehyde and thiosemicarbazide. The lead (II) and nickel (II) metal complexes of the Schiff base ligands ($[Pb(L_1)_2]Cl_2$ and $[Ni(L_1)_2]Cl_2$ were also prepared. The ligands and complexes were tested against gram- negative [*E. Coli* (MTCC No: 452)] and gram- positive bacterial strains *Bacillus sp* [(MTCC No: 297)] by using Kirby-Bauer's method. The compound ($[Pb(L_1)_2]Cl_2$ was found out to be more active against both bacterial strain (*E. coli* & *Bacillus sp*) having zone of inhibition12.45 ± 1.2 and 11.27 ± 1.1 mm respectively.

Keywords: Antibacterial activity, Azomethine linkage, Schiff bases, Thiosemicarbazide

INTRODUCTION

Compound containing an azomethane group (-CH=N-) are known as Schiff bases. They are condensation products of ketones (or) aldehydes (aldehyde and ketones) with primary amines and were first reported by Hugo Schiff[1] in 1864. Schiff bases have wide applications in food industry, dye industry, analytical chemistry, catalysis, fungicidal, agrochemical and biological activities[2]. In recent years, the attention of Schiff bases and their metal complexes are increasing due to their remarkable biological and pharmacological applications[3].

Metal complexes of Schiff bases as ligand with transition metals have received attention because of their biological and electrochemical activity including antitumor, antibacterial, fungicidal and anticarcinogenic properties[4]. The high affinity of the Schiff bases towards chelation with metal ions makes it suitable to for solid metal complexes[5]. They serve as models for biologically important species.

Many biologically important Schiff bases have been reported which possess antibacterial[6-8], antifungal[9-10], antimicrobial[11-13] and anti-HIV[14, 15] activities. The Schiff bases show the highest degree of hydrolysis and solubility in water at pH 5. Antitumor activity of the Schiff bases towards acidic tumors also increases considerably with the slight increase in watersolubility[16]. Several studies have also revealed that by the condensation of aldehyde or ketone with different heterocyclic compound, Schiff bases with potent antibacterial and antifungal activity was obtained[17].

In the present work we have synthesized new Schiff bases, 2-acetylthiophene thiosemicarbazone (L_1) and thiophene-2-aldehyde thiosemicarbazone (L_2) and their Co(II), Cu(II), Zn(II) and Ni(II) complexes. The Schiff bases and their complexes were tested for antibacterial activity.

MATERIALS AND METHODS

All the chemicals used were of analytical grade (AR) and of the highest purity available. 2-acetyl thiophene, thiophene-2-aldehyde and thiosemicarbazide were procured from CDH and SRL. Metal salts were purchased from E. Merck and were used as received.
The C, H, N and S were analyzed on a Vario Micro Cube elemental analyzer, Model Vario-III. ^1H and ^{13}C NMR spectra were recorded on a Bruker, Model DPX-300 NMR spectrophotometer using DMSO as solvent. The IR spectra were recorded as KBr pellets on a Perkin Elmer FT-IR spectrophotometer, Model No. BX-2.

Preparation of Schiff base Complexes[18,19]

Synthesis of ligand (L_1)

Ethanolic solution of 2-acetyl thiophene (1.26g, 0.01 mol) was added in hot ethanolic solution (20 mL) of thiosemicarbazide (0.91g, 0.01 mol) with few drops of acetic acid with constant stirring. The mixture was refluxed at ~80 °C for 2 hours. On cooling, a light yellow coloured compound was separated out. It was then filtered, washed several times with 50% ethanol, dried and recrystallized from methanol (Fig. 1). Yield (88.0%), Melting Point: 140 °C.

Synthesis of ligand (L_2)

Thiophene-2-aldehyde thiosemicarbazone was synthesized by adding ethanolic solution of thiophene-2-aldehyde (1.12g, 0.01 mol) in hot ethanolic solution (20 mL) of thiosemicarbazide (0.91g, 0.01 mol) with few drops of acetic acid with constant stirring. The mixture was refluxed at ~80 °C for 3 hrs. On cooling, off-white coloured compound was separated out. It was filtered,

washed several times with 50% ethanol, dried and recrystallized from methanol (Fig. 2). Yield (75.0%), Melting Point: 160 ºC.

Synthesis of metal complex

A general method was used for the synthesis of the complexes. The metal complexes of the Schiff bases, L_1 and L_2, were prepared by adding a hot aqueous solution (20 mL) of corresponding metal ion (0.01M) dropwise with constant stirring to the hot ethanolic solution (0.02 M) of 2-acetylthiophene thiosemicarbazone/ thiophene-2-aldehyde thiosemicarbazone. The mixture was refluxed for 4-5 hours at 70 to 75 ºC for complete complexation. On cooling a metal complex precipitate was separated out. The same was filtered, washed with 50% ethanol, dried over anhydrous calcium chloride and recrystallized from methanol (Fig. 3).

Biological Activity

The synthesized Schiff bases were screened for antibacterial activity.

Antibacterial Screening

All compounds including Schiff bases (L_1 & L_2) and synthesized metal complexes of ligands L_1 i.e. $([Pb(L_1)_2]Cl_2$ and $[Ni(L_1)_2]Cl_2$ were analyzed against gram negative [*E. Coli* (MTCC No: 452)] and gram positive bacterial strains *Bacillus sp* [(MTCC No: 297)] through Kirby-Bauer's method[20]. Bacterial strains were cultivated and maintained by using Luria Bertani agar media (Hi-media laboratory, India). All compounds were tested at the concentration of 50 µg/ml against positive control (Ampicillin, 10 µg/ml) (Fig. 4 & 5).

Statistical Analysis

Values of antimicrobial assay were expressed as mean ± standard deviation (SD) and analyzed by using one-way analysis of variance (ANOVA) followed by Tukey's test. The value of $p<$ 0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

The Schiff base ligands and their metal complexes were characterized by modern spectroscopic methods such as FT-IR, UV-Vis., NMR and C, H, N, S elemental studies. Pre-confirmatory test for the synthesis of ligand was done through UV-Vis. and IR spectra. The composition of compound was confirmed by ^{1}H NMR, and CHN analysis.

Characterization of Schiff bases[21]

2-acetylthiophene thiosemicarbazone (L_1)- Analytical calculation (%) for = $C_7H_9N_3S_2$: C, 42.18%; H, 4.55%; N, 21.09%; and Observed values: C, 40.66%; H, 3.49%; N, 22.15%.

The UV spectra of the ligand L_1 shows 3 bands (λ_{max}) at 210, 256 and 326 nm. The first two bands at 210 and 256 nm are attributed to $\pi\rightarrow\pi^*$ transitions of the aromatic ring, and thioketonic moieties, respectively[22]. The other band at 326 nm due to $n\rightarrow\pi^*$ is associated with the azomethine linkage[23,24]. FT-IR spectra for the ligand L_1 is given in Figure 6. Infrared spectra of the ligands show strong bands at 3407 cm^{-1} and 3146 cm^{-1} were assigned to symmetric or asymmetric $\nu(NH_2)$ stretching and ν(N–H) vibration of free NH_2 groups[25,26]. The spectrum also shows bands at 1588, 1294 and 838 cm^{-1} due to the ν(C=N), ν (C=S) & δ(C=S) groups respectively[27,28].

The ^{1}H NMR spectra of the ligand exhibits signals are given as (ppm) δ10.35 (H,s,- NH); δ7.43-7.58 (m,Ar-H); 8.3 (H,s,-N=CH); 3.39 (2H,s,-NH_2); δ2.28 (s, H_3C-C)[29].

thiophene-2-aldehyde thiosemicarbazone (L_2)- Analytical calculation (%) for = $C_6H_7N_3S_2$: C, 38.89%; H, 3.81%; N, 22.68%; and Observed values: C, 41.35%; H, 3.68%; N, 24.05%.

The UV spectra of the ligand L_2 shows 3 bands (λ_{max}) at 208, 262 and 329 nm. The first two bands at 208 and 262 nm are attributed to $\pi\rightarrow\pi^*$ transitions of the aromatic ring, and thioketonic moieties, respectively[22]. The other band at 329 nm due to $n\rightarrow\pi^*$ is associated with the azomethine linkage[23,24]. IR spectra for the ligand L2 is given in Figure 7. Infrared spectra of the ligands show strong bands at 3413 cm^{-1} and 3135 cm^{-1} were assigned to symmetric or asymmetric $\nu(NH_2)$ stretching and ν(N–H) vibration of free NH_2 groups[25,26]. The spectrum also shows bands at 1579, 1279 and 837 cm^{-1} due to the ν(C=N), ν (C=S) & δ(C=S) groups respectively[27,28].

The ^{1}H NMR spectra of the ligand exhibits signals are given as (ppm) – δ11.33 (H,s,- NH); 6.94-7.41 (Ar-H); 8.14 (H,s,- N=CH); 2.92 (2H,s,-NH_2)[29].

Metal Complexes of ligand L_1

In FT-IR spectra of metal complex (Fig. 8 & 9), the position of ligand band due to azomethene moiety (>C=N) at 1588 cm^{-1} shifted towards lower side i.e. 1492 cm^{-1} compared to the uncoordinated ligand, indicating its involvement in coordination with metal ion. The (>C=S) stretching frequency observed at 1294 cm^{-1} in ligand was shifted in the spectra of the complex at 1328cm^{-1}, indicating the involvement of the sulphur in the coordination[24, 28]. This indicates, that the coordination take place through the nitrogen atom of the imine groups and sulphur atom of the thioketonic group (>C=S). In the ^{1}H NMR spectrum, signals due to -NH- in ligand undergoes downfield shift on complexation with metal. This indicates participation of nitrogen and thioketonic sulphur in bonding.

Assessment of Antibacterial assay

All compounds showed significant antibacterial activity at the concentration of 50 µg/ml (Table 1) assured by Kirby-Bauer's method. The inhibition potential of bacterial growth exhibited by all compounds has shown in Figure 4 & 5, observation revealed that synthesized lead complex of L_1 ligand, $([Pb(L1)_2]Cl_2$ has much stronger anti-bacterial effect against all compounds. Thus, the synthesized metal complex of ligand L_1 acts as excellent anti-bacterial activity against both gram positive and gram-negative bacteria with zone of inhibition12.45 ± 1.2 and 11.27 ± 1.1 mm respectively.

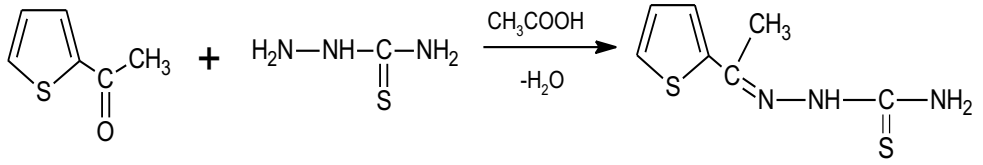
CONCLUSION

In the present work we successfully synthesized 2-acetylthiophene thiosemicarbazone and thiophene-2-aldehyde thiosemicarbazone ligands and their metal complexes. These ligands and metal complexes have been characterized by various analytical and spectral techniques. The results of antibacterial activity revels that these compounds exhibited significant activity against *E. Coli* and gram-positive bacterial strains *Bacillus sp.*

Table 1: Antibacterial activity (% inhibition) of ligands complexes against *E. coli*. and *Bacillus sp* at various concentrations

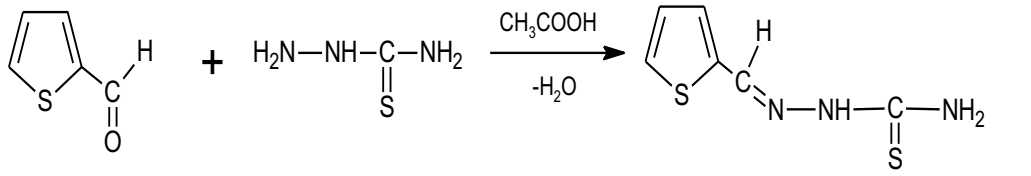
S. No.	Zone of Inhibition (Diameter in mm)			
1	**Treatment**	**Concentration (in µg)**	***Escherichia coli***	***Bacillus sp***
2	Normal control	-	1.2 ± 0.2	1.1 ± 0.2
3	Ampicillin	10	14.55 ± 0.9 [a]	15.23 ± 0.7 [a]
4	L_1	50	9.67 ± 0.8 [a]	11.33 ± 0.8 [a]
5	L_2	50	9.3 ± 0.8 [a]	9.6 ± 0.8 [a]
6	$([Pb(L_1)_2]Cl_2$	50	12.45 ± 1.2 [a]	11.27 ± 1.1 [a]
7	$[Ni(L_1)_2]Cl_2$	50	9.1 ± 0.9 [a]	11.2 ± 0.8 [a]

All data has represented in mean ± SD. a = $p < 0.05$ vs normal control, b = $p < 0.05$ vs standard concentration (10 µg) of ampicillin in respective bacterial strain



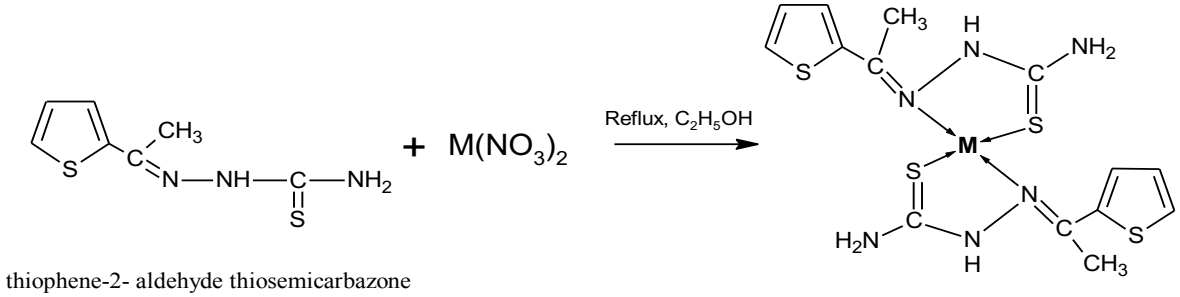
2-acetyl thiophene Thiosemicarbazide 2-acetyl thiophene thiosemicarbazone

Figure 1: Scheme for the synthesis of 2-acetylthiophene thiosemicarbazone (L1)



thiophene -2- aldehyde Thiosemicarbazide thiophene-2- aldehyde thiosemicarbazone

Figure 2: Scheme for the synthesis of thiophene-2-aldehyde thiosemicarbazone (L2)



thiophene-2- aldehyde thiosemicarbazone

Metal complexes of thiosemicarbazide derivative

$M = Ni^{+2}, Pb^{+2}$

Figure 3: Synthesis of metal complexes $[M(L)_2]CL_2$

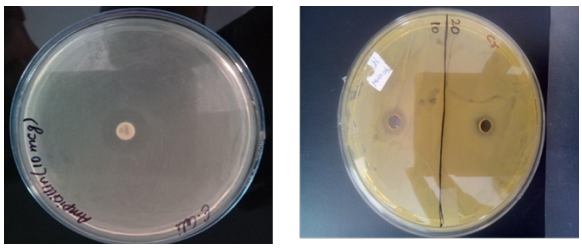


Figure 4: Zone of inhabitation against *Escherichia coli*

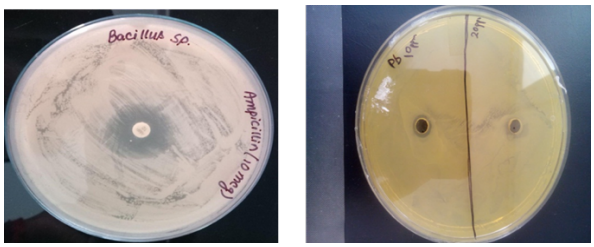


Figure 5: Zone of inhabitation against *Bacillus sp*

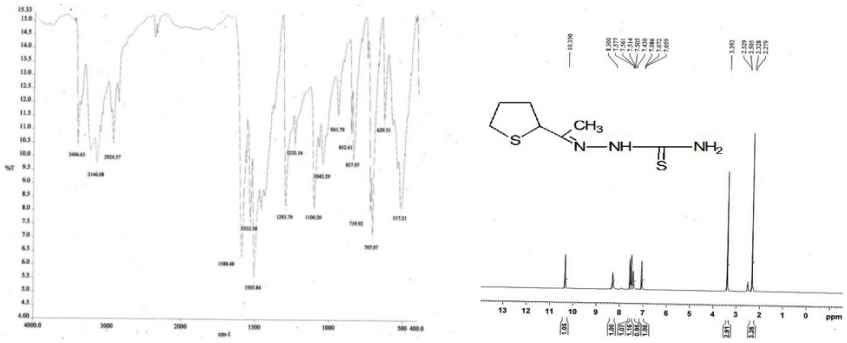


Figure 6: FT-IR and ^{1}H NMR spectrum of 2-acetylthiophene thiosemicarbazone (L1)

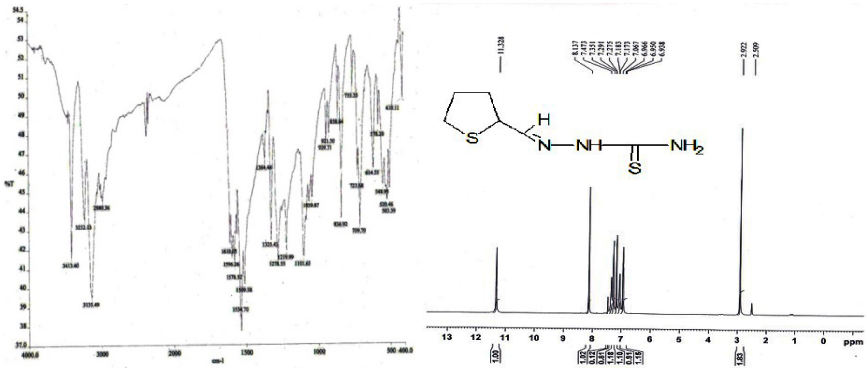


Figure 7: FT-IR and 1H NMR spectrum of thiophene-2-aldehyde thiosemicarbazone (L2)

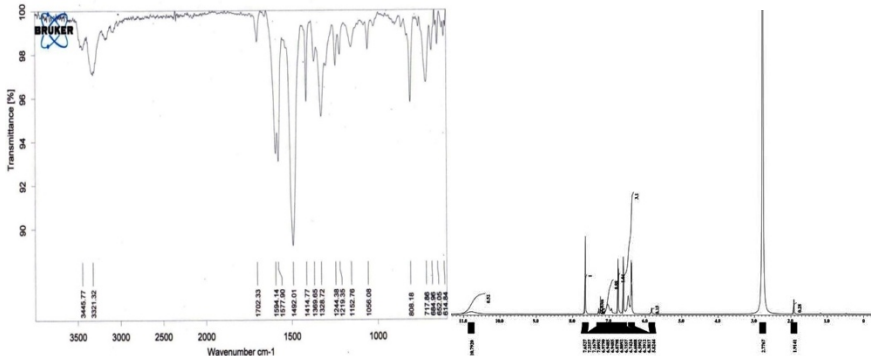


Figure 8: FT-IR and ^{1}H NMR spectrum of lead(II) complex with ligand L1

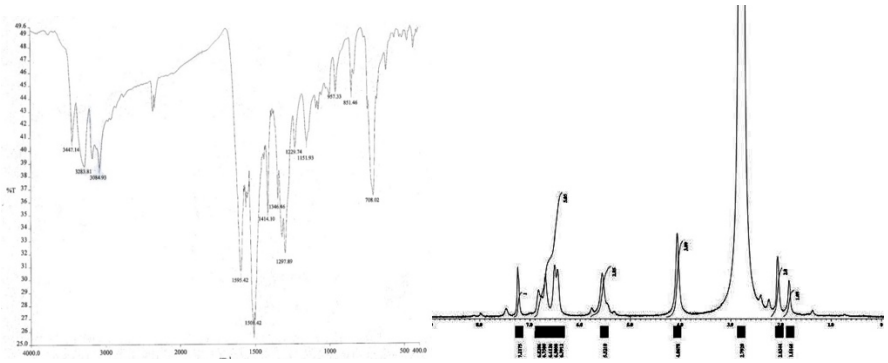


Figure 9: FT-IR and ^{1}H NMR spectrum of Nickel(II) complex with ligand L1

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