SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF TRANSITION METAL COMPLEXES OF THIOSEMICARBAZONE BEARING VANILLIN MOIETY

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ABSTRACT
The synthesis and spectral analysis of Cu(II), Ni(II), Co(II) and Zn(II) complexes of 3-Chloro Vanillin Thiosemicarbazone (3-CVTSC) is reported. Their characterization using mass spectroscopy, elemental analysis, $^1$H NMR, $^{13}$C NMR, infrared spectroscopy, UV spectroscopy and Thermal Gravimetric Analysis as well as their antimicrobial properties were evaluated. In the formation of metal complexation, the metal is coordinated through the azomethine nitrogen and covalently to the sulfur atom.

Keywords: Synthesis, Thiosemicarbazone, Metal Complexes, Antimicrobial Activity.

INTRODUCTION
Thiosemicarbazones are unique type of ligand among all ligands, because they possess a variety of flexible donor sets as well as they exhibit diverse biological, structural and electrochemical properties. These compounds present a wide variety of biological activities such as antitumor, antiviral, antifungal and antibacterial. They have been used for metal analysis, for device applications relative to telecommunications, optical computing, information processing and storage. It is now well established that transition metal complexes of thiosemicarbazones are biologically more potent than its parent thiosemicarbazones.

Our research group works in the field of metal complexes of thiosemicarbazones containing various heterocycles. In this work, we have synthesized a new series of transition metal complexes...
complexes obtained from 3-Chloro Vanillin Thiosemicarbazide (3-CVTSC) (Fig. 1) as a ligand. All structures were determined on the basis of elemental analysis and various spectroscopic techniques.

**MATERIALS AND METHODS**

The room temperature magnetic moments for the copper(II), nickel(II), cobalt(II) and zinc(II) complexes correspond to the values observed of compounds (where $\mu_{\text{eff}}$ is the effective magnetic moment). The molar conductivities of the complexes were measured using an ELICO CM-180 conductivity meter in dimethyl formamide solutions (10-3 M). Molar conductivity and magnetic moments were shown in Table 1.

**Synthesis and analysis of 1-(3-chloro-4-hydroxy-5-methoxybenzylidene) thiosemicarbazide**

The 1-(3-chloro-4-hydroxy-5-methoxybenzylidene)thiosemicarbazide was synthesized by refluxing 3-chloro-4-hydroxy-5-methoxybenzaldehyde and thiosemicarbazide (1:1 molar ratio) in absolute ethanol in the presence of glacial acetic acid. The mixture was refluxed and monitored by TLC. After completion of the reaction, the solvent was evaporated and the residue was washed with cold ethanol and recrystallized from a mixture of ethanol (75% V/V) and water. The white microcrystalline product was obtained.

Elemental Analytical Calculation for $\text{C}_9\text{H}_{10}\text{ClN}_3\text{O}_2\text{S}$ (259.71 g/mol): C, 41.62%; H, 3.88%; Cl, 13.65%; N, 16.18%; S, 12.35%. Found: C, 41.54%; H, 3.79%; Cl, 13.59%; N, 16.10%; S, 12.26%; MS (m/z):260 (M+1); IR (KBr, cm$^{-1}$): $\nu$(OH) 3470; $\nu$(NH) 3354; $\nu$(NH$_2$) 3254; $\nu$(C=N) 1678; $\nu$(N-N) 1047; $\nu$(C=S) 1280; $\delta$(C=S) 837; $\nu$(Ar–C–H) 3136-3010; $\nu$(Ar–C=C) 1498; $\nu$(C-Cl) 1489; $^1$H-NMR (DMSO-$d_6$): $\delta$ppm 3.87 (s, 3H, OMe); 7.41, (d, 1H, $J = 1.6$ Hz, Ar-H); 7.47, (d, 1H, $J = 1.6$ Hz, Ar-H); 8.05, 8.12 (d, 2H, NH$_2$); 8.43 (s, 1H, HC=N); 9.98 (s, Cl, 1H, OH); 11.32 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ppm 56.40 (O-CH$_3$); 109.0, 109.29, 124.26, 126.49, 145.44, 148.52 (Ph); 141.25 (HC=N); 177.64 (C=S); UV-Vis:(DMF) ($\lambda_{\text{max}}$/ nm): 268, 338.
Figure 1. Scheme of synthesis

Figure 2. Mass spectrum of JGM-1

Figure 3. IR spectrum of JGM-1
Synthesis of copper(II), nickel(II) cobalt(II) and zinc(II) complexes of 1-(3-chloro-4-hydroxy-5-methoxybenzylidene) thiosemicarbazide

The metal acetate (0.01 mole) was dissolved in a minimum quantity of water and then added to the hot solution of ligand (0.02 mole) in ethanol (50-60 ml). The reaction mixture was heated to 80-90 °C for 1 hour with constant stirring and then it was stirred for 3 days, until a colored solid mass separated out. The precipitate was filtered, washed with ethanol and finally with diethyl ether and dried in the vacuum.

TABLE - I

<table>
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<tr>
<th>Comp. Code</th>
<th>M</th>
<th>Yield %</th>
<th>M. P.  °C</th>
<th>$\Lambda_m$ (Ω⁻¹ cm² mol⁻¹)</th>
<th>$\mu_{eff}$ B. M.</th>
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<td>MJG -2</td>
<td>Ni(II)</td>
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<td>MJG -3</td>
<td>Co(II)</td>
<td>75</td>
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<td>4.24</td>
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<tr>
<td>MJG -4</td>
<td>Zn(II)</td>
<td>79</td>
<td>274</td>
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[1] Copper(II) complex of 1-(3-chloro-4-hydroxy-5-methoxybenzylidene) thiosemicarbazide (MJG-1).

Color: Cream, Anal. Calcd. For C_{18}H_{18}Cl_{2}CuN_{6}O_{5}S_{2} (580.96 g/mol): C, 37.21%; H, 3.12%; N, 12.21%; S, 11.04%; Cu, 10.94%. Found: C, 37.34%; H, 3.01%; N, 12.10%; S, 10.96%; Cu, 11.07%; ESIMS (m/z): 582.1 (CuL₂)+; IR (KBr, cm⁻¹): $\nu$(OH) 3471; $\nu$(NH₂) 3246; $\nu$(C=N) 1577; $\nu$(N-N) 1045; $\nu$(C=S) 1267; $\delta$(C=S) 846; $\nu$(Ar–C-H) 3136-3009; $\nu$(Ar–C=C) 1460; $\nu$(C-Br) 607; $\nu$(Cu-N) 505; $\nu$(Cu-S) 426; $^1$H-NMR (DMSO-d₆): $\delta$ ppm 3.81 (s, 3H, OMe); 6.65, (d, 2H, Ar-H); 7.40 (s, 2H, NH₂); 8.26 (s, 1H, HC=N); 9.66 (s, 1H, OH); UV-
Vis:(DMF) ($\lambda_{max}$ nm): 290, 348, 748; TGA wt. loss in %(temp.): 5.77 (100°C); 11.07 (200°C); 35.56 (300°C); 47.28 (400°C); 52.21 (500°C); 57.67 (600°C); 66.91 (700°C); 75.09 (800°C).


**Color:** Gray, Anal. Calcd. For C$_{14}$H$_{18}$Cl$_{2}$N$_{6}$NiO$_{3}$S$_{2}$ (576.1 g/mol): C, 37.53%; H, 3.15%; N, 14.59%; S, 11.13%; Ni, 10.19%. **Found:** C, 37.44%; H, 3.02%; N, 14.70%; S, 11.08%; Ni, 10.32%; ESIMS (m/z): 576.0 (NiL$_{2}$)+; IR (KBr, cm$^{-1}$): $\nu$(OH) 3444; $\nu$(NH$_{2}$) 3252; $\nu$(C=N) 1578; $\nu$(N-N) 1042; $\nu$(C=S) 1286; $\delta$(C=S) 873; $\nu$(Ar–C–H) 3099-3014; $\nu$(Ar–C=C) 1433; $\nu$(C-Br) 610; $\nu$(Ni-N) 538; $\nu$(Ni-S) 416; $^1$H-NMR (DMSO-d$_{6}$): $\delta$ ppm 3.86 (s, 3H, OMe); 7.33, (d, 2H, Ar-H); 7.91 (s, 2H, NH$_{2}$); 8.02 (s, 1H, HC=N); 9.64 (s, br, 1H, OH); UV-Vis:(DMF) ($\lambda_{max}$/ nm): 266, 332, 740; TGA wt. loss in %(temp.): 0.00 (100°C); 4.83 (200°C); 37.65 (300°C); 56.54 (400°C); 71.89 (490°C).


**Color:** Pink, Anal. Calcd. For C$_{14}$H$_{18}$Cl$_{2}$CoN$_{6}$O$_{3}$S$_{2}$ (576.34 g/mol): C, 37.51%; H, 3.15%; N, 14.58%; S, 11.13%; Co, 10.23%. **Found:** C, 37.73%; H, 3.03%; N, 14.46%; S, 11.22%; Co, 10.14%; ESIMS (m/z): 576.1(CoL$_{2}$)+; IR (KBr, cm$^{-1}$): $\nu$(OH) 3450; $\nu$(NH$_{2}$) 3252; $\nu$(C=N) 1581; $\nu$(N-N) 1024; $\nu$(C=S) 1257; $\delta$(C=S) 829; $\nu$(Ar–C–H) 3117-3009; $\nu$(Ar–C=C) 1492; $\nu$(C-Br) 617; $\nu$(Co-N) 505; $\nu$(Co-S) 416; $^1$H-NMR (DMSO-d$_{6}$): $\delta$ ppm 3.92 (s, 3H, OMe); 7.39, (d, 2H, Ar-H); 7.91 (s, 2H, NH$_{2}$); 8.14 (s, 1H, HC=N); 9.64 (s, 1H, OH); UV-Vis:(DMF) ($\lambda_{max}$/ nm): 288, 332, 744; TGA wt. loss in %(temp.): 1.20 (100°C); 5.90 (200°C); 31.44 (300°C); 42.91 (400°C); 48.21 (490°C).


**Color:** White, Anal. Calcd. For C$_{14}$H$_{18}$Cl$_{2}$ZnN$_{6}$O$_{3}$S$_{2}$ (582.8 g/mol): C, 37.10%; H, 3.11%; N, 14.42%; S, 11.00%; Zn, 11.22%. **Found:** C, 37.32%; H, 3.00%; N, 14.30%; S, 11.09%; Zn, 11.13%; ESIMS (m/z): 582 (ZnL$_{2}$)+; IR (KBr, cm$^{-1}$): $\nu$(OH) 3457; $\nu$(NH$_{2}$) 3259; $\nu$(C=N) 1573; $\nu$(N-N) 1028; $\nu$(C=S) 1253; $\delta$(C=S) 845; $\nu$(Ar–C–H) 3076-3013; $\nu$(Ar–C=C) 1481; $\nu$(C-Br) 622; $\nu$(Zn-N) 511; $\nu$(Zn-S) 420; $^1$H-NMR (DMSO-d$_{6}$): $\delta$ ppm 3.35 (s, 3H, OMe); 7.36, (d, 2H, Ar-H); 7.89 (s, 2H, NH$_{2}$); 8.18 (s, 1H, HC=N); 9.69 (s, 1H, OH); UV-
Vis:(DMF) ($\lambda_{\text{max}}$ nm): 274, 337; TGA wt. loss in % (temp.): 1.32 (100°C); 5.73 (200°C); 34.94 (300°C); 44.71 (400°C); 58.74 (490°C).

![Suggested structure of metal complexes](image)

**Fig. 1. Suggested structure of metal complexes**

**RESULTS AND DISCUSSION**

The elemental analysis of the 1-(3-chloro-4-hydroxy-5-methoxybenzylidene) thiosemicarbazide and its four metal complexes of Copper, Nickel, Cobalt and Zinc were shown by found percentages and were matched with calculated. The IR spectra of ligand shows some significant stretching bands due to -N-H, -N-N- and -C=S at 3354 cm$^{-1}$, 1047 cm$^{-1}$ and 1280 cm$^{-1}$ respectively. The band of an imine group in thiosemicarbazone (-CH=N-) was observed at 1678 cm$^{-1}$. The aromatic -C-H and -C=C bands were observed at 3136-3010 cm$^{-1}$ and 1498 cm$^{-1}$ respectively. We have shown the specific bands in the infrared spectra of the metal (II) complex of the ligand are along within their tentative assignment. Furthermore, in the spectra of ligand, the strong band observed at 837 cm$^{-1}$ was shifted to lower wavenumber by ca 10-25 cm$^{-1}$ in all four metal complexes, indicating that thiol sulphur participated as a coordinating site. This prediction was confirmed by the presence of a new band between 426-416 cm$^{-1}$, which was due to $\nu$(M-S). Thus from the IR data, it can be predicted that the ligand involved in the complexation as a bidentate ligand which was coordinated with metal ions through their thiol sulphur and azomethine N atom.

The $^1$H NMR spectra of ligand shows singlet due to (-CH=N-) proton appearing at 8.43 ppm. The -OH and -N-NH protons were observed at 9.98 and 11.32 ppm as a singlet, respectively. All the aromatic protons were observed in their expected regions in the spectrum. In the $^{13}$C NMR spectra of ligand the signal due to (-CH=N-) carbon, appeared near at 141 ppm and
C=S carbon appeared near at 178 ppm and all the aromatic carbons were observed in their expected regions in the spectrum.

The electronic spectra of complexes show bands, respectively at 266-290 and 332-348 nm due to $\pi \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions. All four complexes have bands at 410-445 nm due to ligand metal charge transfer transition and very weak and broad bands at 740-748 nm showed d-d transitions. The Zn(II) complex has no band near 700-800 nm, confirms that there were no d-d transitions. The entire complexes show the band near 748 nm according to $^2B_1g \rightarrow^2B_2g$, $^2B_g \rightarrow^2E_g$ and $^2B_1g \rightarrow^2A_1g$ transitions suggesting the square planar geometry for them$^{16}$.

**Antimicrobial activity**

Antibacterial and antifungal activity of all the synthesized compounds was tested. Minimum Inhibitory concentration of compounds was studied *in vitro* by broth dilution method$^{17}$. Three bacterial and four fungal strains were compared with standard drugs.

Antibacterial study shows that metal complexes MJG-2 and MJG-4 show better activity compared to its original ligand JGM-1 and moderate activity against bacteria compared to standard drugs (table-2). Similarly, metal complexes MJG-1 and MJG-4 show better activity against fungi compared to ligand JGM-1 and almost similar activities against fungi compared to standard drugs (table-3).

**Table 2.** MIC against different bacteria (in $\mu$g/ml)

<table>
<thead>
<tr>
<th>Code</th>
<th><em>E. Coli</em> MTCC 443</th>
<th><em>S. Epidermidis</em> MTCC 442</th>
<th><em>S. Aureus</em> MTCC 96</th>
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<tr>
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<td>MJG-1</td>
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<td>Ciprofloxacin</td>
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**Table 3.** MIC against different Fungi (in $\mu$g/ml)

<table>
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<tr>
<th>Code</th>
<th><em>C. Albicans</em> MTCC 227</th>
<th><em>A. Niger</em> MTCC 282</th>
<th><em>S. Cerevisiae</em> MTCC 170</th>
<th><em>E. Floccosum</em> MTCC 7880</th>
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<td>JGM-1</td>
<td>1000</td>
<td>250</td>
<td>500</td>
<td>200</td>
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<td>MJG-1</td>
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<td>MJG-3</td>
<td>MJG-4</td>
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**Figure 5. Zone inhibition of ligands and metal complexes**

**CONCLUSION**

In this paper, 1-(3-chloro-4-hydroxy-5-methoxybenzylidene) thiosemicarbazide was synthesized and structure was investigated. The Cu(II), Co(II), Ni(II) and Zn(II) complexes were synthesized and characterized by spectral techniques. The electronic spectral studies of the four complexes indicate the square planar geometry for the metal ions. The ligand exhibits moderate antimicrobial activity, but its complexes give considerable activity against microbes.

**ACKNOWLEDGMENT**

We are very grateful to Department of Chemistry, Saurashtra University, Rajkot for providing facilities and NFDD Center (National Facilities for Drugs Discovery) Rajkot for NMR analysis.

**REFERENCES**


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