

## SOLVENT FREE SYNTHESIS OF HYDRAZINE CARBOTHIOAMIDE DERIVATIVES AS A PRECURSOR IN THE PREPARATION OF NEW MONONUCLEAR Mn(II), Cu(II), AND Zn(II) COMPLEXES: SPECTROSCOPIC CHARACTERIZATIONS

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**ABSTRACT.** Over the last few years considerable attention has been devoted to the study of Schiff base complexes of metal(II) containing nitrogen, oxygen and sulfur donor ligands due to their diverse biological activities. Therefore, the Schiff base thiosemicarbazone derivatives of 2-(2-hydroxy-3-methoxybenzylidene) hydrazine carbothioamide (HL<sub>1</sub>) and 2-(4-bromo-2-hydroxy-3-methoxybenzylidene) hydrazine carbothioamide (HL<sub>2</sub>) were synthesized with solvent free technique using silica gel as material support for the reaction. The structures of the precursor's organic products confirmed with their <sup>1</sup>H, <sup>13</sup>C NMR, IR and microanalysis data. Six new manganese(II), copper(II), and zinc(II) complexes of HL<sub>1</sub> and HL<sub>2</sub> 2-(2-hydroxy-3-methoxybenzylidene) hydrazinecarbothioamide derivatives with the general formulation [ML<sub>1</sub>Cl] and [ML<sub>2</sub>Cl], where M = Mn<sup>2+</sup>, Cu<sup>2+</sup>, and Zn<sup>2+</sup> were prepared and well discussed by using elemental analyses, magnetic moments, molar conductance, infrared and electronic spectral techniques. The assignments data of spectroscopic analysis confirm that the synthesized thiosemicarbazone Schiff bases of acts as a tridentate ligand as sulfur-oxygen-nitrogen donating atoms. The values of magnetic moments agreed with the data of electronic spectra which both suggested a four-coordination geometry of the synthesized complexes.

**KEY WORDS:** Schiff base, Thiosemicarbazone, Manganese(II) complex, Copper(II) complex, Zinc(II) complex

### INTRODUCTION

The use of cisplatin in treatment over the past 50 years [1, 2] demonstrates that mineral complexes can have significant antitumor activity, particularly the copper compounds that attract attention as an example of cancer, complexes, where the copper ion concentration in the tumor cells is higher than that in the healthy cells [3-5]. Salicylaldehyde thiosemicarbazone ligand complex with copper have showed good resistant, in vitro, against colon carcinoma, melanoma, pancreatic adenocarcinoma, thyroid carcinoma, and ovarian carcinoma [6]. Some benzaldehyde thiosemicarbazone derivatives demonstrate antimycobacterial activity, under hypoxia, against *M. tuberculosis* [7]. Palladium (II) salicylaldiminato thiosemicarbazone complexes showed an amazing antiprotozoal activity on metronidazole resistant *Trichomonas vaginalis* [8]. The organometallic complexes of osmium(II) and ruthenium(II) thiosemicarbazone derivatives have an antiproliferative efficiency [9]. In literature, the synthesized palladium(II) 3-methoxysalicylaldehyde thiosemicarbazone complexes gave a biological potential with calf thymus DNA, bovine serum albumin, and also in *vitro* the complexes showed a cytotoxicity towards human breast cancer cells (MCF-7) [10]. The chemistry of Schiff base transition metal complexes has become highly attractive due to their wide pharmacokinetic profile providing a variety of compounds with different activities [11-15]. In recent years, the distinguish ligands containing sulfur atom such as thiosemicarbazones derivatives and their complexes with some of transition metal ions have a great attention in the

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field of medicinal chemistry according to their therapeutic importance, such as anti-bacterial, anti-fungal, anti-viral, anti-allergic, anti-tumor, anticancer, and anti-HIV activities [16-28]. Based on these vital items, herein we reported the synthesis and spectroscopic characterization of two new Schiff base complexes of 2-(2-hydroxy-3-methoxybenzylidene) hydrazinecarbothioamide derivatives ligands with manganese(II), copper(II), and zinc(II) metal ions.

## EXPERIMENTAL

### *Reagents and chemicals*

The chemical used in this study were of fine grade chemical. The manganese(II), copper(II), and zinc(II) metal salts were used as a chloride. The solvents (methanol, diethyl ether, and dimethyl sulfoxide) were used without further purification.

### *Instrumentations*

Microanalytical analysis (%C, H and N) were performed using a Perkin Elmer CHN 2400 (USA). With  $10^{-3}$  M concentration the molar conductivities using dimethyl sulfoxide solvent were detected by Jenway 4010 conductivity meter. Electronic UV-Vis absorption spectra within 800-200 nm range were scanned in DMSO solvent using a UV2-Unicam UV/Vis Spectrophotometer fitted with a quartz cell of 1.0 cm path length. Infrared using discs of potassium bromide ( $4000-400\text{ cm}^{-1}$ ) were recorded on Perkin-Elmer 1650 spectrometer.  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra were determined using solutions of dimethyl sulfoxide on a Bruker AC-400 Hz instrument using an internal standard tetramethylsilane. The  $X_g$  mass susceptibility of complexity was determined using a Gouy magnetic balance at room temperature. The purity of organic ligand was analyzed using Shimadzu GC-MS-QP 1000 EX spectrometer. Melting points were estimated by Electrothermal IA 9100 series digital apparatus. The metal ion contents were calculated using gravimetrically method.

### *Synthesis of thiosemicarbazones 2a-b (general procedures)*

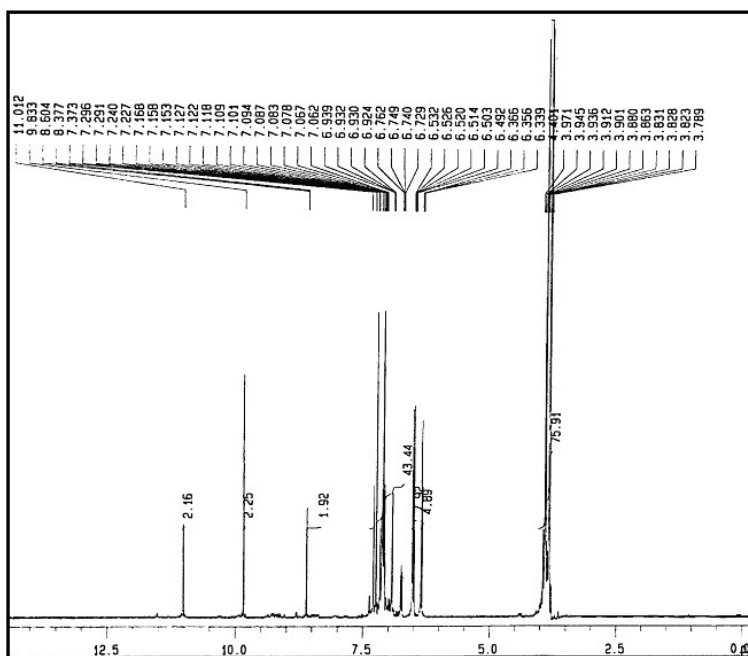
*Method A (traditional method).* The appropriate 3-methoxysalicylaldehyde derivative (0.01 mol) dissolved in 15 mL absolute ethanol, then thiosemicarbazide (0.091 g, 0.01 mol) was added to the hot stirred solution of salicylaldehyde. The reflux of the reaction mixture stopped after 6hr (the reaction monitored with TLC, ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  9:1 mixture),  $R_f = 0.56$ ). After solvent evaporation, the solid product formed washed with little amount of water then after drying crystallized with ethanol, yield: 75-81%, m.p.: 220-222 °C and 250-252 °C.

*Method B (solvent free method).* Compound **1a,b** (0.01 mol) and thiosemicarbazide (0.091 g, 0.01 mol) were mixed in a dry glass beaker and then added 0.5 g silica gel (200-400 mesh), methylene chloride 15 mL added and the mixture stirred with glass rod until the  $\text{CH}_2\text{Cl}_2$  evaporates on cold, the dry mixture irradiated for 2.0-3.0 min in a domestic microwave oven (2450 MHz, 800 W). After irradiation finished, the content dissolved in acetone and filtered off. The product formed after acetone evaporation crystallized from ethanol, yield: 82-89%, m.p.: 223-225 °C and 251-253 °C. The synthesis route of the Schiff base thiosemicarbazone derivatives of 2-(2-hydroxy-3-methoxybenzylidene) hydrazine carbothioamide ( $\text{HL}_1$ ) and 2-(4-bromo-2-hydroxy-3-methoxybenzylidene) hydrazine carbothioamide ( $\text{HL}_2$ ) is shown in Scheme 1.



2-(2-Hydroxy-3-methoxybenzylidene)hydrazinecarbothioamide **2a** (*HL*<sub>1</sub>). IR,  $\nu$ ; 3448  $\text{cm}^{-1}$  (OH), 3351, 3330  $\text{cm}^{-1}$  ( $\text{NH}_2$ ), 3271  $\text{cm}^{-1}$  (NH), 1610 (C = N), 1235 (C = S);  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, 300 MHz):  $\delta$  = 3.72 (s, 3H, OCH<sub>3</sub>), 6.35 (s, 1H, CH=N), 6.38, 6.39 (2s, 2H, NH<sub>2</sub>), 7.10 (d, 1H, *J* = 4.4 Hz, aromatic C<sub>6</sub>H), 7.18 (dd, 1H, aromatic C<sub>5</sub>H), 7.24 (d, 1H, 4.4 Hz, aromatic C<sub>4</sub>H), 9.75 (s, 1H, OH), 11.12 (s, 1H, NH).  $^{13}\text{C}$  NMR (DMSO-*d*<sub>6</sub>, 100 MHz):  $\delta$  = 63.10 (OCH<sub>3</sub>), 117.7 (C1), 123.3 (C4), 125.3 (C5), 131.5 (C6), 151.2 (C-OCH<sub>3</sub>), 153.2 (C-OH), 171.6 (C=S). Calcd for C<sub>9</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>S (225.27): C, 47.99; H, 4.92; N, 18.65; S, 14.23; found: C, 48.07; H, 4.88; N, 18.31; S, 14.09.

2-(4-Bromo-2-hydroxy-3-methoxybenzylidene)hydrazinecarbothioamide **2b** (*HL*<sub>2</sub>). IR,  $\nu$ ; 3452  $\text{cm}^{-1}$  (OH), 3355, 3325  $\text{cm}^{-1}$  ( $\text{NH}_2$ ), 3259  $\text{cm}^{-1}$  (NH), 1616 (C = N), 1249 (C = S);  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, 400 MHz):  $\delta$  = 3.78 (s, 3H, OCH<sub>3</sub>), 6.33 (s, 1H, CH=N), 6.35, 6.36 (2s, 2H, NH<sub>2</sub>), 7.06 (d, 2H, *J* = 4.4 Hz, aromatic C<sub>6</sub>H), 7.15 (d, 2H, *J* = 4.0 Hz, aromatic C<sub>5</sub>H), 9.83 (s, 1H, OH), 11.01 (s, 1H, NH).  $^{13}\text{C}$  NMR (DMSO-*d*<sub>6</sub>, 100 Mz):  $\delta$  = 61.15 (OCH<sub>3</sub>), 117.3 (C1), 119.5 (C-Br), 124.1 (C5), 130.7 (C6), 149.9 (C-OCH<sub>3</sub>), 151.4 (C-OH), 170.7 (C=S). Calcd for C<sub>9</sub>H<sub>10</sub>BrN<sub>3</sub>O<sub>2</sub>S (304.16): C, 35.54; H, 3.31; Br, 26.27; N, 13.81; S, 10.54; found: C, 35.32; H, 3.25; Br, 26.11; N, 13.59; S, 10.44.



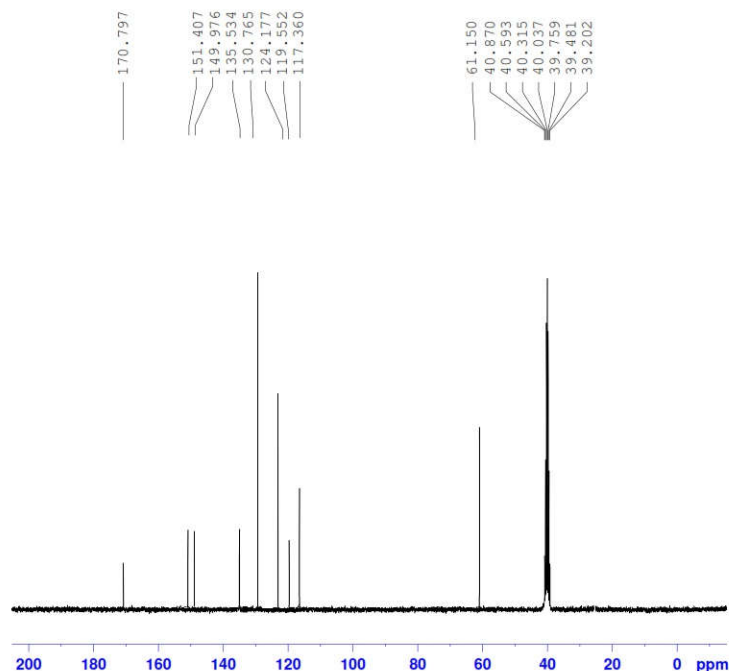


Figure 1.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of compound **2a**.

#### *Electronic and magnetic properties*

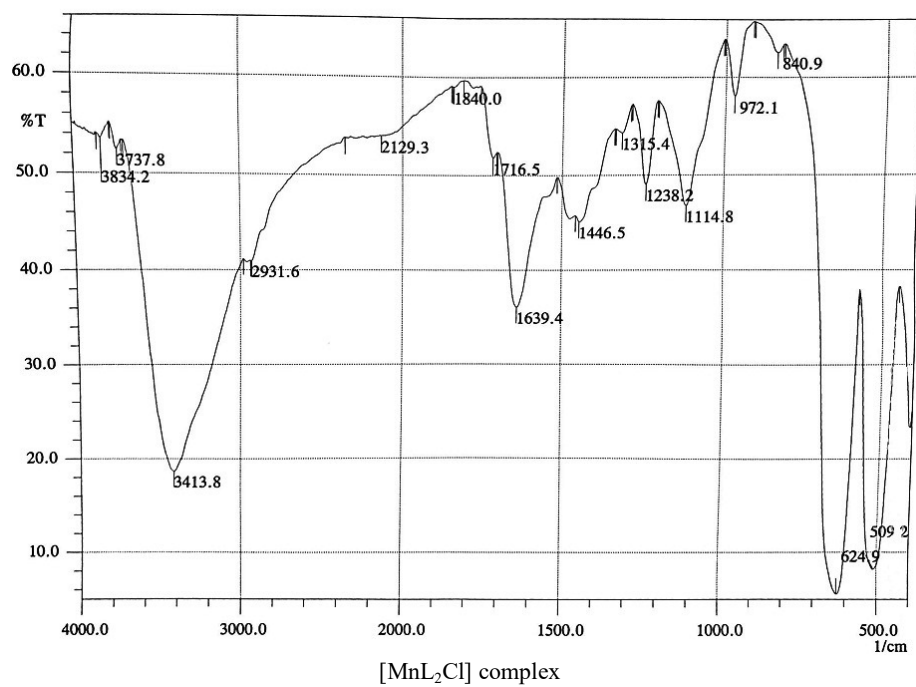
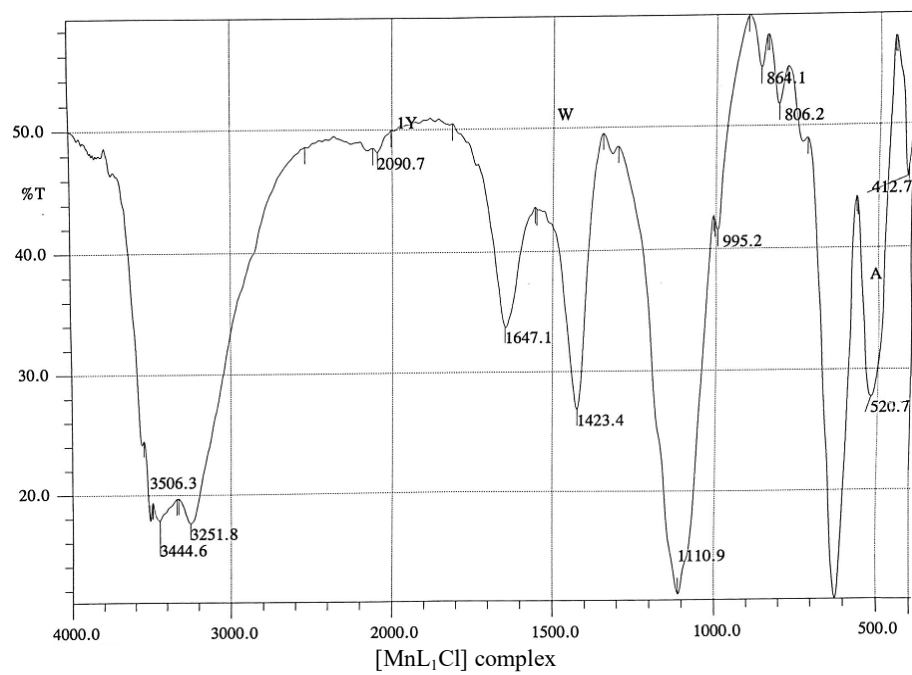
The manganese(II), copper(II) and zinc(II) complexes display an intense charge transfer (CT) band in the range 217–266 nm, which can be attributed to the  $\pi \rightarrow \pi^*$  transition of the coordinated Schiff bases  $\text{HL}_1$  and  $\text{HL}_2$ . The band around 318 and 372 nm in all the complexes is attributed to the OH phenolic,  $\text{NH}_2$ , imine ( $-\text{HC}=\text{N}-$ ) and  $\text{C}=\text{S}$  groups. The Cu(II) complexes show three transition bands at  $13513\text{--}13423\text{ cm}^{-1}$ ,  $24752\text{--}25316\text{ cm}^{-1}$  and  $37735\text{--}37736\text{ cm}^{-1}$  due to the electronic transition bands  ${}^2\text{B}_{1g} \rightarrow {}^2\text{A}_{1g}$  and two intra ligand charge transfer bands. These electronic transitions and observed magnetic moment value (1.80–1.83 B.M.) suggests square-planar geometry around Cu(II) [30, 31]. The electronic spectra of the Mn(II) complexes display three absorption bands at  $13459\text{ cm}^{-1}$ ,  $26882\text{ cm}^{-1}$  and  $31446\text{ cm}^{-1}$ , due to  ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{1g}$ ,  ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{2g}(\text{G})$  and  ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{2g}(\text{D})$  transitions, respectively [32]. The manganese(II) complexes gave 5.85–5.91 B.M. values, indicating a high spin complex and suggesting tetrahedral geometry [33, 34]. In the case of Zn(II) complexes, no significant absorption bands in their electronic spectra were obtained due to diamagnetic nature of zinc metal ion.

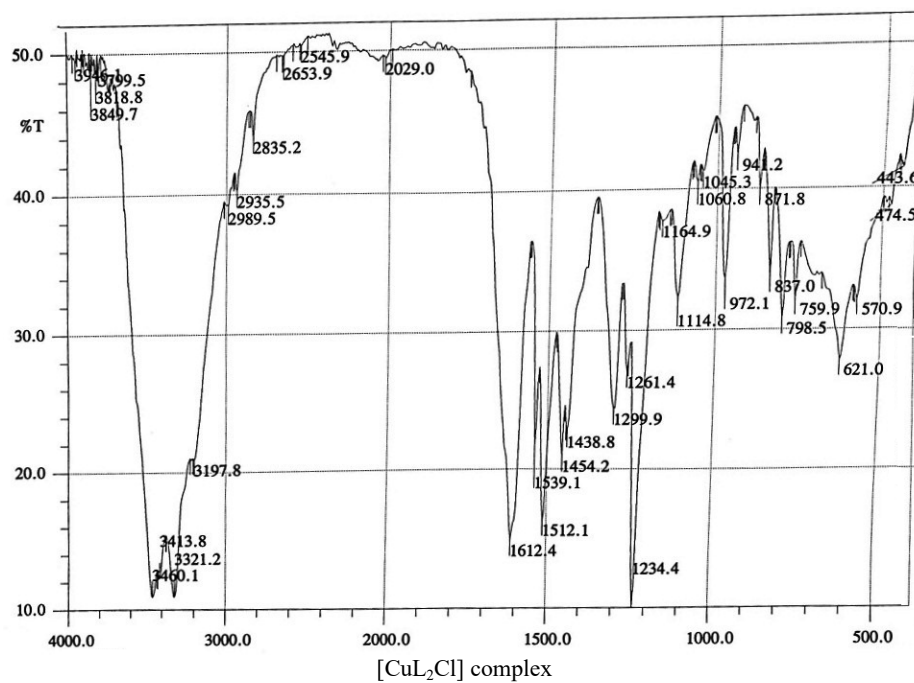
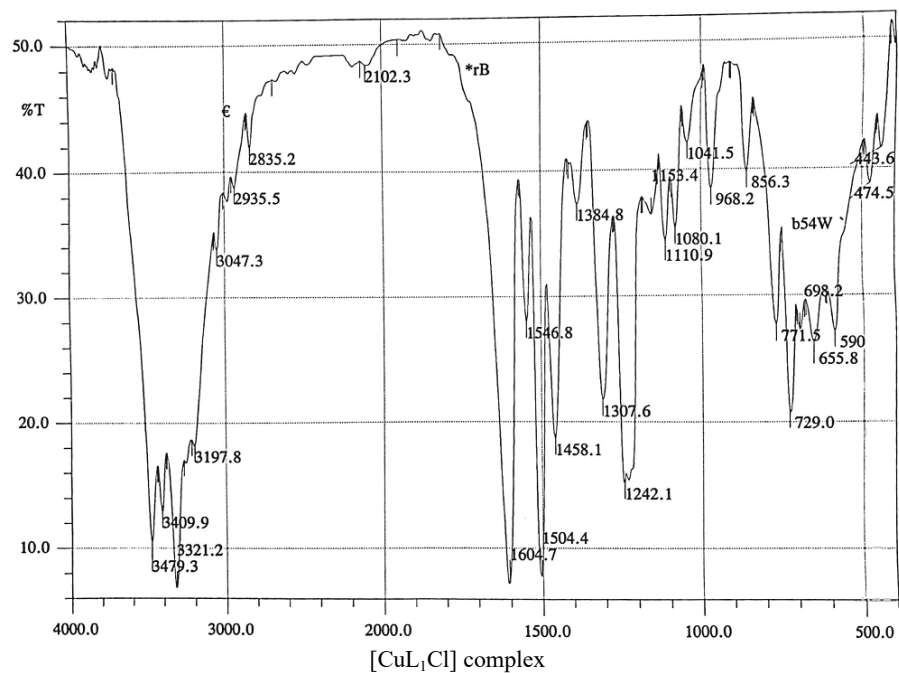
Table 1. Characterization of manganese(II), copper(II) and zinc(II) complexes.

Complexes	Color	Elemental analysis, found (calcd.)					$\Lambda_m$ $\Omega^{-1}\cdot\text{cm}^2\cdot\text{mol}^{-1}$	$\mu_{\text{eff}}$ (B.M.)
		C%	H%	N%	S%	M%		
H L <sub>1</sub>	Yellow	48.07 (47.99)	4.88 (4.92)	18.31 (18.65)	14.09 (14.23)	-	7	-
H L <sub>2</sub>	Orange	35.32 (35.54)	3.25 (3.31)	13.59 (13.81)	10.44 (10.54)	-	9	-
[MnL <sub>1</sub> Cl]	Yellow	34.21 (34.36)	3.12 (3.20)	13.34 (13.36)	10.15 (10.19)	17.11 (17.46)	20	5.85
[CuL <sub>1</sub> Cl]	Green	33.21 (33.44)	3.10 (3.12)	12.89 (13.00)	9.89 (9.92)	19.43 (19.66)	15	1.83
[ZnL <sub>1</sub> Cl]	Yellow	33.09 (33.25)	3.08 (3.10)	12.90 (12.93)	9.82 (9.86)	20.05 (20.11)	18	Diamagnetic
[MnL <sub>2</sub> Cl]	Brown	27.40 (27.47)	2.28 (2.31)	10.65 (10.68)	8.14 (8.15)	13.90 (13.96)	14	5.91
[CuL <sub>2</sub> Cl]	Green	26.75 (26.88)	2.24 (2.26)	10.43 (10.45)	7.95 (7.97)	15.77 (15.80)	12	1.80
[ZnL <sub>2</sub> Cl]	Yellow	26.60 (26.76)	2.24 (2.25)	10.38 (10.40)	7.91 (7.94)	16.09 (16.18)	17	Diamagnetic

### Infrared spectroscopy

Infrared spectra of the complexes are shown in Figure 2. The FTIR data of ligands HL<sub>1</sub> and HL<sub>2</sub>, and its metal complexes are listed in Table 2. In general, the HL<sub>1</sub> and HL<sub>2</sub> both ligands can exhibit thione↔thiol tautomerism since it contains a thioamide –NH–C=S characteristic group. The  $\nu(\text{S–H})$  band at  $2560\text{ cm}^{-1}$  is absent in the FTIR spectra of the two ligands, but  $\nu(\text{N–H})$  band at  $3259\text{--}3271\text{ cm}^{-1}$  is present, indicating that in the solid state two ligands remain as the thione form. The frequency of  $\nu(\text{C=N})$  band of the thiosemicarbazone moiety appeared at  $1610\text{--}1616\text{ cm}^{-1}$  is shifted towards lower or higher wavenumbers in the synthetic complexes indicating coordination *via* the azomethine nitrogen. This is also confirmed by the appearance of band in complexes in the range of  $412\text{--}514\text{ cm}^{-1}$ , which has been assigned to the  $\nu(\text{M–N})$  [35]. A medium to weak band presence at around  $\sim 1000\text{ cm}^{-1}$  is due to the  $\nu(\text{N–N})$  group of the thiosemicarbazone moiety. The frequency of this band is shifted towards higher wave number in the spectra of complexes. It is due to the increase in the bond strength, which again confirms the coordination *via* the azomethine nitrogen. The band appearing at  $\sim 1235\text{--}1249$  and  $820\text{--}830\text{ cm}^{-1}$  corresponding to  $\nu(\text{C=S})$  in the FTIR spectra of two ligands are shifted towards lower wavenumbers. It indicates that thione sulfur coordinates to the metal ion [36]. During complexation, the band  $3448\text{--}3452\text{ cm}^{-1}$  for  $\nu(\text{O–H})$  is absent evident that oxygen of deprotonated phenolic group was coordinated to metal atoms. In addition, the shifted of  $\nu(\text{C–O})$  phenolic group to lower wavenumbers also indicated the coordination to the metal ion. Thus, it may be concluded that both ligands behave as tridentate chelating agent coordinating through azomethine nitrogen, phenolic oxygen and thione sulfur. The C–H aromatic stretching and bending vibrations appear at  $2900\text{--}2800\text{ cm}^{-1}$  and  $1450\text{--}1400\text{ cm}^{-1}$ , respectively







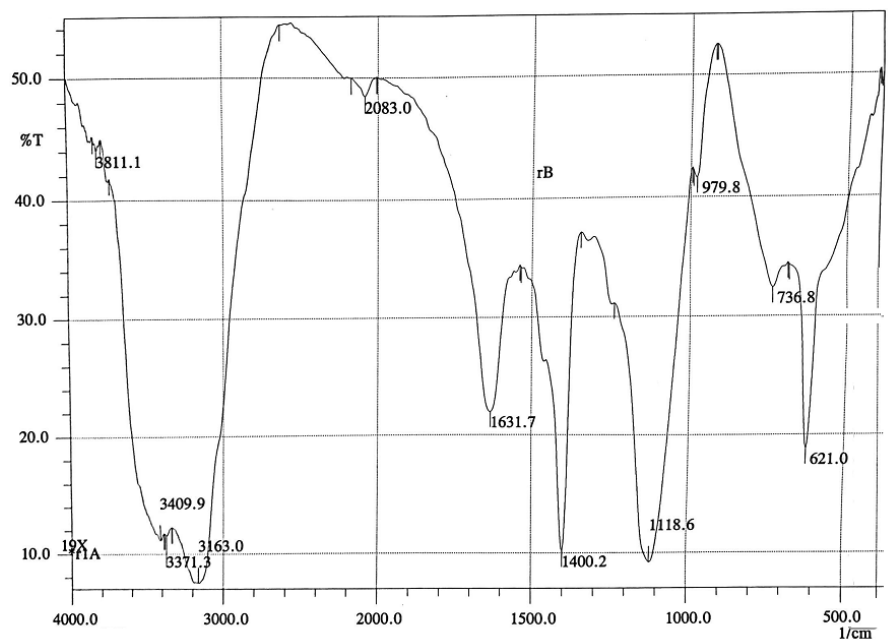
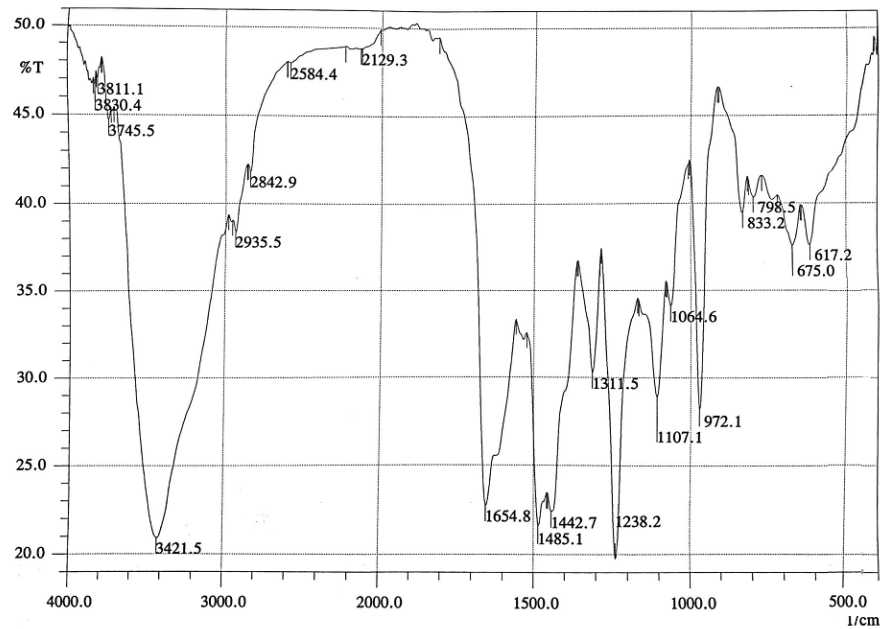
 $[ZnL_1Cl]$  complex $[ZnL_2Cl]$  complex

Figure 2. FTIR spectra of Mn(II), Cu(II), and Zn(II) complexes.

Table 2. Infrared spectral assignments of HL<sub>1</sub>, HL<sub>2</sub>, Mn(II), Cu(II), and Zn(II) complexes.

Assignments	Compounds							
	HL <sub>1</sub>	HL <sub>2</sub>	MnL1Cl	MnL2Cl	CuL1Cl	CuL2Cl	ZnL1Cl	ZnL2Cl
v(OH)	3448	3452	-	-	-	-	-	-
v(NH <sub>2</sub> )	3351 3330	3355 3325	3445	3414	3409	3460	3409	3421
v(NH)	3271	3259	3252	3250	3321	3321	3371	3350
v(C=N) azomethine	1610	1616	1647	1639	1605	1539	1631	1655
v(C=S)	1235 820	1249 830	- 806	-	- 771	1234 798	- 737	1238 798
v(C-O) phenolic	1211 1056	1225 1060	1110 995	1115 972	1111 1041	1115 972	1118 979	1107 972
v(M-O)	-	-	521	624	590	570	621	617
v(M-N)	-	-	412	509	474	474	510	514

### CONCLUSION

Six new Mn(II), Cu(II), and Zn(II) complexes have been prepared using the tridentate SON symmetrical Schiff base 2-(2-hydroxy-3-methoxybenzylidene) hydrazine carbothioamide derivatives and employing different manganese(II), copper(II) and zinc(II) starting chloride salts. These complexes were thoroughly characterized by elemental analysis, ES mass spectrometry, infrared and <sup>1</sup>H NMR spectroscopies, magnetic susceptibility measurements and molar conductivities. Electronic and magnetic susceptibility studies were also performed. All complexes obtained are four coordination compounds, with empirical formulae [ML<sub>1</sub>Cl] and [ML<sub>2</sub>Cl], where M = Mn<sup>2+</sup>, Cu<sup>2+</sup>, and Zn<sup>2+</sup>.

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