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New thiosemicarbazone derivatives and their Mn(II), Ni(II), Cu(II) and Zn(II) complexes: Synthesis, characterization and *in-vitro* biological screeningBansuri Nandaniya<sup>a</sup>, Siva Prasad Das<sup>a,b\*</sup> and Darshan Jani<sup>c</sup><sup>a</sup>Department of Chemistry, School of Science, RK University, Bhavnagar Highway, Kasturbadham, Rajkot-360020, Gujarat, India<sup>b</sup>Department of Chemistry, University Institute of Science, Chandigarh University, Mohali, Punjab 140413, India<sup>c</sup>Department of Chemistry, School of Science, Dr. Subhash University, Junagadh, 362001, Gujarat, India

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## ABSTRACT

In the present work, we synthesized new thiosemicarbazone based Schiff base ligands and their Mn(II), Ni(II), Cu(II) and Zn(II) complexes. The synthesized compounds were characterized and their antimicrobial activities were studied. Elemental analysis, IR, <sup>1</sup>H-NMR and mass spectrometry were done to fully characterize all the compounds. The ligands and their complexes were screened for *in-vitro* biological study against Gram positive (*Bacillus subtilis*) and Gram negative (*E. coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*) bacteria for the Zone of Inhibition method. The thiosemicarbazone based complexes showed better activity than the ligands.

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## 1. Introduction

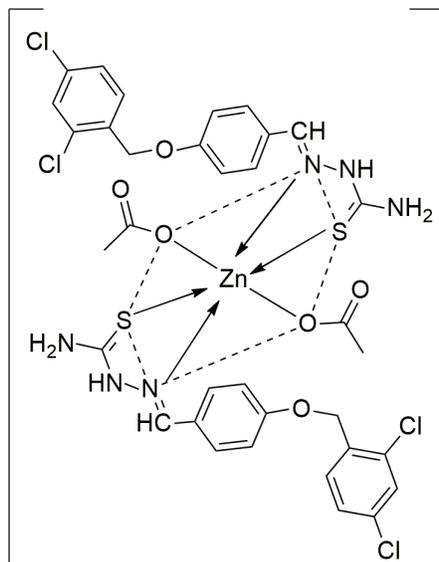
In recent years coordination chemistry of Schiff base with transition metals is an important class of study mainly because of their facile synthesis, easy availability and electronic properties. In recent times, coordination chemistry of Schiff base gain significance attention due to their broad range of applications such as thermal studies,<sup>1</sup> catalytic,<sup>2</sup> toxicity,<sup>3</sup> optically active material,<sup>4</sup> agriculture,<sup>5,6</sup> antibacterial activity,<sup>7-9</sup> antifungal,<sup>10</sup> antitumor activity,<sup>11</sup> antiviral<sup>12</sup> as well as DNA binding.<sup>13</sup> In such class of compounds, the C=N (Imine) moiety is important for biological activity. On the other hand, coordination compounds of thiosemicarbazone Schiff base ligands with transition metal have received considerable interest due to its ability to disrupt DNA synthesis by causing modification in the reductive conversion of ribonucleotides to deoxyribonucleotides.<sup>14</sup> Furthermore, introduction of aldehydes or ketones to thiosemicarbazone, the Schiff bases that are formed can interact with metal ions to form complexes that have stable four, five or six coordination numbers.<sup>15,16</sup> The thiosemicarbazone Schiff base ligands are known for their ability to make coordination compounds with transition metal ions.<sup>17</sup> Coordination compounds of different geometries and properties can be synthesized easily through nitrogen and sulphur of thiosemicarbazone Schiff base ligand to metal centre.<sup>18-22</sup> Studies also reported that the biological activity of the coordination compounds of thiosemicarbazone-derived Schiff bases often had higher and selective bioactivities as compared to the corresponding free thiosemicarbazones Schiff bases.<sup>23-25</sup>

In view on the importance of transition metal based coordination compounds and our curiosity in the science of coordination compounds of thiosemicarbazone based Schiff base ligands, here we are reporting the synthesis,

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characterization and *in-vitro* biological screening of new thiosemicarbazone based Schiff base ligands and their Mn(II), Ni(II), Cu(II) and Zn(II) complexes. The general structure of the coordination compound is shown in **Fig. 1**.



**Fig. 1.** The suggested structure of metal complexes

## 2. Results and Discussion

The structure of all the prepared Schiff base ligands and coordination compounds were carried out using elemental analysis, IR, <sup>1</sup>H-NMR and FAB-Mass spectra. The <sup>1</sup>H-NMR data of Schiff base ligands are given in the experimental section. The analytical and physical data of coordination compounds are given in **Table 1**. Heterochelates were sparingly soluble in methanol and completely soluble in DMF and DMSO. All the complexes were found to be stable at room temperature.

**Table 1.** Analytical and physical data of metal complexes

Compounds Chemical Formula	Formula Weight	Colour	(%Yield)	Analysis (%) Found (Cal)						
				C	H	Cl	N	O	S	M
[Mn(L <sub>1</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub> ]	940	White	(75)	46.02 (46.00)	3.65 (3.56)	15.09 (14.98)	8.94 (8.85)	13.62 (13.55)	6.83 (6.76)	5.85 (5.77)
[Ni(L <sub>1</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub> ]	943	Yellow	(79)	45.84 (45.76)	3.63 (3.55)	15.03 (14.98)	8.91 (8.87)	13.57 (13.48)	6.80 (6.74)	6.22 (6.18)
[Cu(L <sub>1</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub> ]	948	Dark	(66)	45.60 (45.53)	3.61 (3.58)	14.96 (14.88)	8.86 (8.81)	13.50 (13.42)	6.76 (6.71)	6.70 (6.63)
[Zn(L <sub>1</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub> ]	950	White	(74)	45.51 (45.47)	3.61 (3.55)	14.93 (14.87)	8.85 (8.79)	13.47 (13.36)	6.75 (6.69)	6.88 (6.81)
[Mn(L <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub> ]	880	Dull	(64)	46.43 (46.39)	3.44 (3.38)	16.12 (16.05)	9.56 (9.46)	10.91 (10.86)	7.29 (7.22)	6.25 (6.19)
[Ni(L <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub> ]	883	Greenish	(81)	46.23 (46.15)	3.42 (3.36)	16.06 (16.00)	9.51 (9.45)	10.87 (10.78)	7.26 (7.21)	6.64 (6.57)
[Cu(L <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub> ]	888	Brown	(77)	45.98 (45.96)	3.40 (3.37)	15.97 (15.91)	9.46 (9.39)	10.81 (10.79)	7.22 (7.17)	7.16 (7.11)
[Zn(L <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub> ]	891	Yellow	(71)	45.89 (45.86)	3.40 (3.39)	15.93 (15.88)	9.44 (9.42)	10.79 (10.75)	7.21 (7.15)	7.35 (7.32)

### 2.1 <sup>1</sup>H-NMR spectra of ligands and their metal complexes

The <sup>1</sup>H-NMR data for L<sub>1</sub> and L<sub>2</sub> are given in the experimental section and a spectrum for the ligand L<sub>2</sub> is shown in **Fig. 2**. From the spectra it is observed that the peak for benzylic -CH<sub>2</sub> is obtained as singlet at 5.2 δ, while the singlet for -CH proton is obtained at 11.3 δ and the Ar-H are obtained as a complex peak in aromatic region in range of 7.0-8.1 δ. Here, the peaks for -NH and -NH<sub>2</sub> protons are merged in the aromatic region so it is difficult to separate it out. However, the numbers of protons are exactly matched with the molecular formula of the compound which was also confirmed with mass spectra. As the <sup>1</sup>H-NMR spectrum of coordination compound [Zn(L<sub>2</sub>)<sub>2</sub>(CH<sub>3</sub>COO)<sub>2</sub>] is shown in **Fig. 3**. When we compare the spectra of ligands with coordination compounds, it is observed that the resonances belonging to ligands were seen in the spectra of coordination compounds. The most substantial change upon coordination of ligand to Zn(II) ion is observed for Ar-H which is located closest to the metal ion. Its resonance is shifted up field by 0.2 δ.<sup>26</sup> Two extra signals are located at 2.74 and 2.89

$\delta$  which are ascribed to the two methyl groups of the bridging acetates.<sup>27</sup> This NMR spectrum agrees with the existence of the zinc cluster  $[\text{Zn}(\text{L}_2)_2(\text{CH}_3\text{COO})_2]$  in solution which is confirmed by mass spectra.

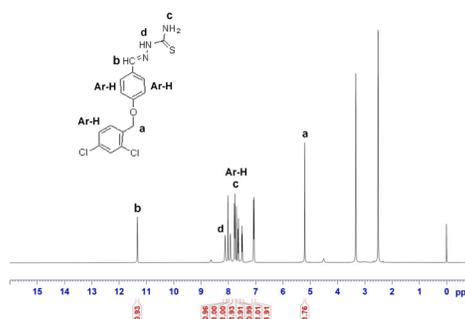


Fig. 2.  $^1\text{H}$  NMR Spectrum of Ligand  $\text{L}_2$

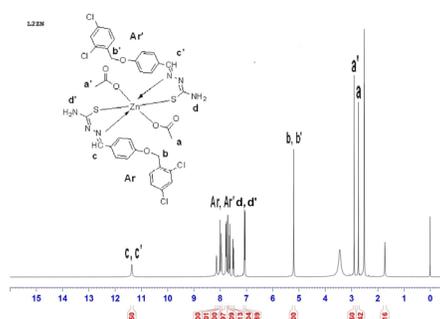


Fig. 3.  $^1\text{H}$  NMR Spectrum of  $[\text{Zn}(\text{L}_2)_2(\text{CH}_3\text{COO})_2]$

## 2.2 Infrared Spectra

In order to study the binding mode of Schiff base ( $\text{L}_1$  &  $\text{L}_2$ ) to the transition metal, Mn(II), Cu(II), Ni(II) and Zn(II) ion in the heterochelates, the IR spectra of Schiff base were compared with spectra of corresponding heterochelates. The IR data of ligands and coordination compounds are given in **Table 2**. The Schiff base ligands viz.,  $\text{L}_1$  &  $\text{L}_2$ , showed a sharp and strong peak of a  $\nu(\text{C}=\text{N})$  of the acyclic azomethine group at 1598 and 1597  $\text{cm}^{-1}$ , respectively. The observed low energy shift of this band in the heterochelates and appearing at 1531 to 1577  $\text{cm}^{-1}$  suggest the co-ordination of azomethine nitrogen.<sup>28,29</sup> The  $\nu(\text{N}-\text{H})$  bands are visible in the spectra of ligands in the range 3379–3452  $\text{cm}^{-1}$ . However, they do not show an (S-H) band at  $\sim 2570$   $\text{cm}^{-1}$ , but only strong bands for  $\nu(\text{N}-\text{H})$ , indicating that in the solid state Schiff bases ligands are mainly in the tautomeric thione form. In all spectra of organic ligands there are several bands ascribed to  $\nu(\text{C}=\text{S})$ . Due to the coordination of the sulphur atom with the metal ion, the spectra in this range become less crowded. The disappearance of most of these bands in all complexes indicates formation of metal-sulphur bonds.<sup>30</sup>

**Table 2.** IR data of ligands and its metal complexes

Compounds	$\nu(\text{N}-\text{H})$ ( $\text{cm}^{-1}$ )	$\nu(\text{C}=\text{N})$ ( $\text{cm}^{-1}$ )	$\nu(\text{C}=\text{S})$ ( $\text{cm}^{-1}$ )	$\nu(\text{M}-\text{OOCCH}_3)$ ( $\text{cm}^{-1}$ )
$\text{L}_1$	3452	1598	1174	-
$\text{Mn}(\text{L}_1)_2(\text{CH}_3\text{COO})_2$	3452	1573	1139	1510
$\text{Ni}(\text{L}_1)_2(\text{CH}_3\text{COO})_2$	3466	1564	1147	1519
$\text{Cu}(\text{L}_1)_2(\text{CH}_3\text{COO})_2$	3417	1564	1139	1512
$\text{Zn}(\text{L}_1)_2(\text{CH}_3\text{COO})_2$	3419	1541	1141	1512
$\text{L}_2$	3379	1597	1111	-
$\text{Mn}(\text{L}_2)_2(\text{CH}_3\text{COO})_2$	3352	1566	1103	1512
$\text{Ni}(\text{L}_2)_2(\text{CH}_3\text{COO})_2$	3342	1531	1101	1504
$\text{Cu}(\text{L}_2)_2(\text{CH}_3\text{COO})_2$	3410	1566	1102	1510
$\text{Zn}(\text{L}_2)_2(\text{CH}_3\text{COO})_2$	3383	1577	1095	1510

## 2.3 FAB Mass Study of metal complexes

The recorded mass spectrum **Fig. 4** and the molecular ion peak for the heterochelate  $[\text{Zn}(\text{L}_2)_2(\text{CH}_3\text{COO})_2]$  were used to confirm the molecular formula. The proposed fragmentation pattern is shown in **Scheme 1**. The first peak at  $m/z=891$  represents the molecular ion peak of heterochelates. Scheme (1) demonstrates the possible degradation path for the investigated heterochelates. The primary fragmentation of the heterochelate takes place due to the loss of a coordinated  $\text{CH}_3\text{COO}$  molecule from the species (a) to give species (b) with peak at  $m/z=828$ . Further degradation yields species (c) with loss of remaining molecules of  $\text{CH}_3\text{COO}$ . Species (c) further degrade to species (d) with loss of  $\text{C}_7\text{H}_5\text{Cl}_2$ . Further degradation of species (d) yields species (e) with loss of remaining part  $\text{C}_7\text{H}_5\text{Cl}_2$ . The measured molecular weight for all the suggested degradation steps was exactly matched with the expected values.<sup>31</sup>

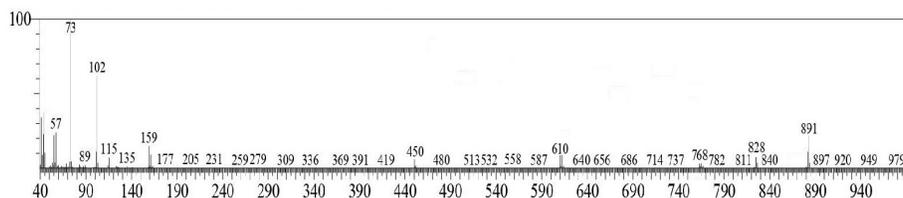
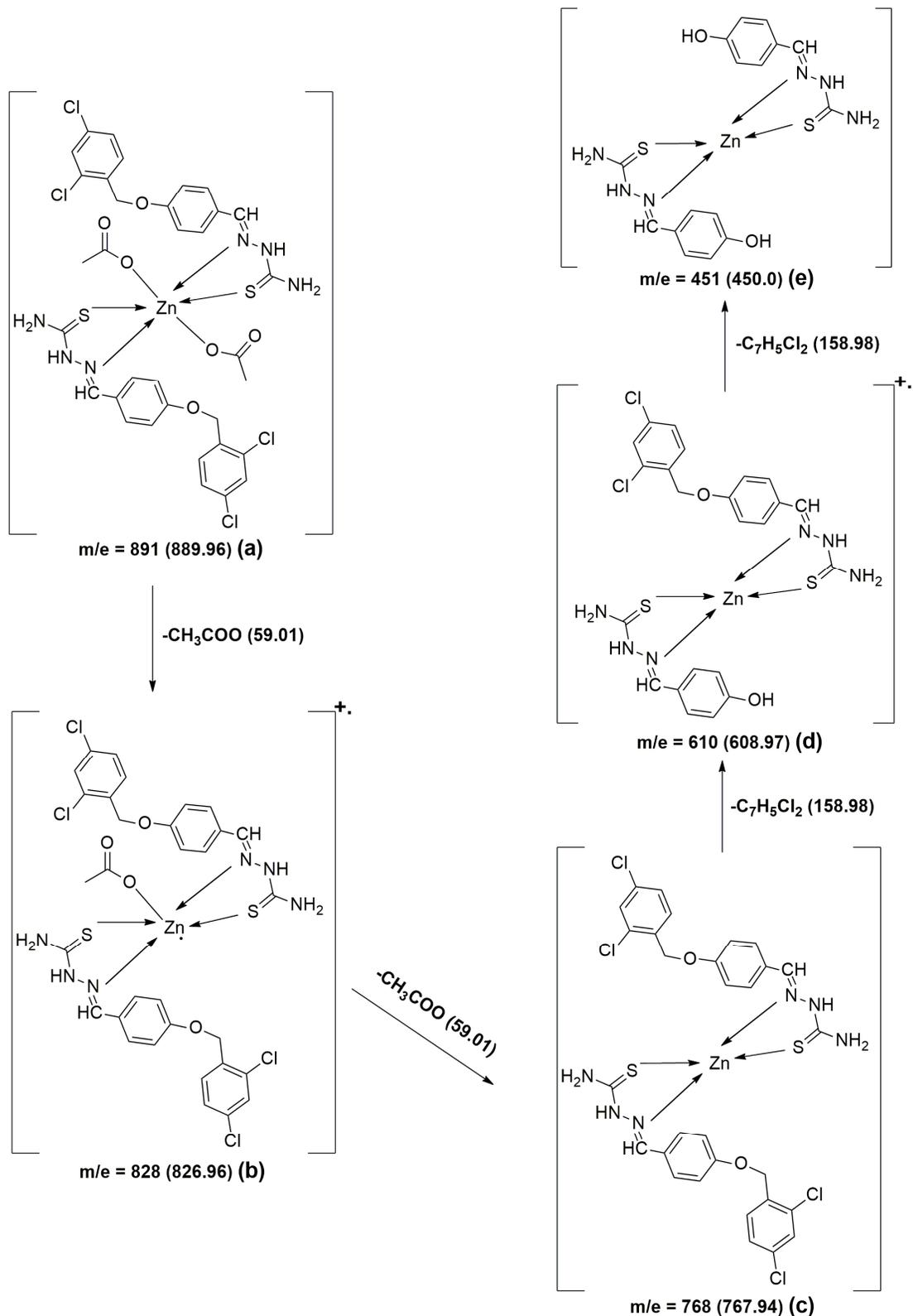


Fig. 4. FAB Mass Spectrum of  $[\text{Zn}(\text{L}_2)_2(\text{CH}_3\text{COO})_2]$



**Scheme 1.** The Suggested Fragmentation pattern of  $[\text{Zn}(\text{L}_2)_2(\text{CH}_3\text{COO})_2]$

#### 2.4 Antimicrobial activity

All the synthesized Schiff base ligands namely  $\text{L}_1$ - $\text{L}_2$  and their transition metal (Mn, Ni, Cu, Zn) based coordination compounds were screened against the bacterial strains. The enhanced in antimicrobial activity of coordination compounds

may be considered with regards to Overtone's concept<sup>32</sup> and Tweedy's chelation theory.<sup>33</sup> In accordance with Overtone's concept of cell permeability, solubility is an important factor controlling the antimicrobial activity, higher the lipophilicity better is the activity. Besides, as per the Tweedy's chelation theory, by making the complex the polarity of metal ion is reduced to a greater extent. Thus, it may be presumed that in the coordination compounds the lipophilicity is increase by delocalization of  $\pi$ -electrons which leads to easy entry of the compounds to the cell to control the growth of microorganisms.<sup>34</sup>

**Table 3.** Antimicrobial effects of the ligands and their metal complexes

Sr.No.	Compounds	Gram +Ve (mm)		Gram -Ve (mm)	
		<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Klebsiella pneumonia</i>	<i>Pseudomonas aeruginosa</i>
1	L <sub>1</sub>	6	9	7	5
2	Mn(L <sub>1</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub>	11	14	15	13
3	Ni(L <sub>1</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub>	13	17	13	15
4	Cu(L <sub>1</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub>	17	19	14	12
5	Zn(L <sub>1</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub>	18	16	15	11
6	L <sub>2</sub>	8	7	5	4
7	Mn(L <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub>	13	15	14	13
8	Ni(L <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub>	19	17	14	12
9	Cu(L <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub>	17	19	18	16
10	Zn(L <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub>	18	16	15	13

The antimicrobial screening data, **Table 3**, shows that coordination compounds exhibit more inhibitory effects towards gram +ve and gram -ve bacteria then the parent Schiff base ligands. Among the coordination complexes of L<sub>1</sub>, Cu(L<sub>1</sub>)<sub>2</sub>(CH<sub>3</sub>COO)<sub>2</sub> was found to be much powerful bactericides against *E. coli*. In case of ligand L<sub>2</sub>, the coordination compounds Ni(L<sub>2</sub>)<sub>2</sub>(CH<sub>3</sub>COO)<sub>2</sub> and Cu(L<sub>2</sub>)<sub>2</sub>(CH<sub>3</sub>COO)<sub>2</sub> were found to be very active against *Bacillus subtilis* and *E. coli* bacteria, respectively. The properties of coordination compounds rely upon the metal ion, electron donating atoms, structure of the ligand and the binding mode of ligand with metal ion. Metal ion plays a significant job in various diverse biological procedures through co-enzymatic frameworks is a subject of excellence. It suggests that some kind of bimolecular binding to the metal ions and electrostatic interactions cause the prevention of biological procedures and inhibit reproduction of organisms.

### 3. Conclusions

In present work, some novel thiocarbazine based Schiff base ligands have been successfully synthesized and confirmed with <sup>1</sup>H-NMR, IR and Mass Spectral studies. We have synthesized a series of some new transition metal-based coordination compounds and characterize their properties. All the synthesized compounds were screened for their bioassay. The coordination compounds exhibit strong activities against Gram positive (*Bacillus subtilis*) and Gram negative (*E. coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*) microorganisms in comparison with ligands. The coordination compounds were found more active against one or more bacterial strains introducing a new class of metal based bactericidal agents for further research.

### 4. Experimental

#### 4.1 Materials and Methods

All the chemicals were used of analytical grade and used without further purification. The thiosemicarbazones were purchased from Sigma Ltd (India). Acylchlorides were purchased from Qualigens Fine Chemicals, India and used without further purification. Elemental analysis (C, H, N) was performed on a model 2400 Perkin-Elmer elemental analyzer. FT-IR spectra were recorded as KBr pallets on the Nicolet-400D spectrophotometer. <sup>1</sup>H-NMR spectra were recorded on the Advance 400 Bruker FT-NMR instrument in DMSO-*d*<sub>6</sub> solvent. The FAB-mass spectrum of heterochelate was recorded with JEOL SX-102/DA-6000 mass spectrometer.

#### 4.2 General procedure for the synthesis of ligands (L<sub>1</sub> & L<sub>2</sub>)

The solution of vaniline and 4-hydroxybenzaldehyde (0.01 mol) in DMF (6 mL) stirred at 60°C in water bath with 2,4-dichlorobenzyl chloride (0.01 mol) and anhydrous K<sub>2</sub>CO<sub>3(s)</sub> (0.02 mol) for 4 h, after 4 h check reaction completion by TLC. Cooled the reaction mass up to room temperature and precipitated by addition of water, filtered the white solid mass and crystallized from methanol as intermediate. A 1:1 molar methanolic solution of intermediate (0.001 mol) taken in two necked round bottom flasks and stirred for several minutes. A methanolic solution of thiosemicarbazone (0.001 mol) added drop wise to an above solution and refluxed for 4 h at 60°C with constant stirring and check the reaction completion by TLC. After completion, the product is allowed to stand overnight at room temperature. Subsequently, methanol was added to the reaction mixture to precipitate the product. The solid product was washed twice with diethyl ether and dried in air.

#### Analysis for $L_1$

M.F- $C_{16}H_{15}Cl_2N_3O_2S$  Yield 79%; M.P. 218°C; Cream white powder; FT-IR (KBr, $cm^{-1}$ ): 3452  $\nu(N-H)$ , 1174  $\nu(C=S)$ , 1598  $\nu(C=N)$ ;  $^1H-NMR$  (400 MHz,DMSO- $d_6$ ):  $\delta$  (ppm) = 3.85 (3H,s,-OCH<sub>3</sub>); 5.17 (2H,s,-CH<sub>2</sub>); 11.33 (1H,s,-CH) 8.16 (1H,s,-NH); 8.02 (2H,s,-NH<sub>2</sub>); 7.05-7.98 (6H,c,Ar-H), Elemental analysis found (%) C, 50.21; H, 3.99; Cl, 18.57; N, 10.98; O, 8.45; S, 8.56 calculated for  $C_{16}H_{15}Cl_2N_3O_2S$ : C, 50.01; H, 3.93; Cl, 18.45; N, 10.93; O, 8.33; S, 8.34.

#### Analysis for $L_2$

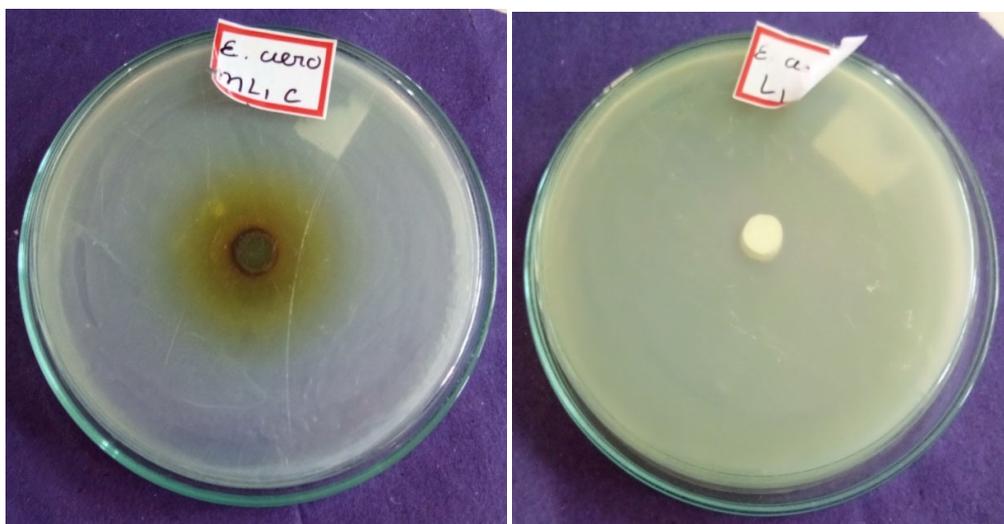
M.F- $C_{15}H_{13}Cl_2N_3OS$  Yield 77%; M.P. 215°C; Cream white powder; FT-IR (KBr, $cm^{-1}$ ): 3379  $\nu(N-H)$ , 1111  $\nu(C=S)$ , 1598  $\nu(C=N)$ ;  $^1H-NMR$  (400 MHz,DMSO- $d_6$ ):  $\delta$  (ppm) = 5.20 (2H,s,-CH<sub>2</sub>); 11.33 (1H,s,-CH) 8.11 (1H,s,-NH); 7.78 (2H,s,-NH<sub>2</sub>); 7.05-8.00 (6H,c,Ar-H), Elemental analysis found (%) C, 50.93; H, 3.82; Cl, 20.15; N, 11.98; O, 4.64; S, 9.33 calculated for  $C_{15}H_{13}Cl_2N_3OS$ : C, 50.86; H, 3.70; Cl, 20.02; N, 11.86; O, 4.52; S, 9.05.

#### 4.3 General procedure for the synthesis of metal complexes

A general process has been adopted for the preparation and isolation of all the coordination compounds. A hot methanolic solution of metal (II) acetate salt (0.001 mol) was added drop wise to the solution of the respective ligands (0.001 mol), by maintaining molar ratio of M:L = 1:2, with continuous stirring. The mixture was heated for 4 h at 70 °C and subsequently left overnight at room temperature. The obtained solid products were washed with water, methanol and finally dried in desiccators.

#### 4.4 Antimicrobial activity

A stock solution of 10 mg mL<sup>-1</sup> was made by dissolving compounds in a minimum amount of DMSO and making it up to the mark with double distilled water. The medium was made up by dissolving bacteriological agar (20 g) and Luria broth (20 g; SRL, India) in 1-liter distilled water. The mixture was autoclaved for 15 min at 120°C and then dispensed into sterilized Petri dishes, allowed to solidify and then used for inoculation. The target microorganism cultures were prepared separately in 15 mL of liquid Luria broth medium for activation. Inoculation was done with the help of a micropipette with sterilized tips; 100  $\mu$ L of activated strain was placed onto the surface of an agar plate and spread evenly over the surface by means of a sterile, bent glass rod. Then two wells having a diameter of 10 mm were made using a sterilized borer in each plate. Application of disks Sterilized stock solutions (10 mg mL<sup>-1</sup>) were used for the application in the well of earlier inoculated agar plates. When the disks were applied, they were incubated at 30°C (Gram +ve) and 37°C (Gram -ve) for 24 h. The zone of inhibition was then measured (in mm) around the disk shown in **Fig. 5**. The control experiments were performed with only the equivalent volume of solvents without added test compounds and the zone of inhibitions was measured (in mm) shown in **Table 3**.



**Fig. 5.** Zone of inhibition (mm) of Ligand and its metal complexes

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## Conflict of Interest

The authors announce that they don't have any conflict of interest regarding publication of the work.

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