

Synthesis, Spectral Antioxidant Study of Ni (II) Complexes Derived from Thiosemicarbazone and N (4) Thiosemicarbazone

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ABSTRACT: 5-chloro 2-hydroxy acetophenonethiosemicarbazone and N (4) thiosemicarbazone were synthesized by refluxing 5-chloro 2-hydroxy acetophenone and thiosemicarbazide in the mole ratio 1:1. The complexes of thiosemicarbazones with Ni (II) were synthesized by refluxing thiosemicarbazone and Ni (II) chloride in the mole ratio 1:2. The synthesized thiosemicarbazones and complexes were characterized by means of Elemental analysis, ESI-MS, FT-IR spectroscopy, UV-Visible, Nuclear Magnetic Resonance ($^1\text{H-NMR}$ and $^{13}\text{C-NMR}$) spectroscopy magnetism and conductivity measurement. The metal complexes and thiosemicarbazone were tested against bacterial parasites. The free radical scavenging activity of synthesized compounds was screened for antioxidant activity. It was found that the complexes are more biologically active than thiosemicarbazone.

KEYWORDS: Bioactive metal complexes, antimicrobial activity, antioxidant activity, 1:2 ratio

I. INTRODUCTION

The biological activity of thiosemicarbazones is also depended on parent aldehyde or ketone [1,2]. The presence of a bulky group at the terminal nitrogen raises the activity [3]. The presence of bulky groups at the N (4) position of the thiosemicarbazone moiety together with an additional binding site greatly affects biological activity [4-6]. In recent years the biological and medicinal properties of transition metal complexes of thiosemicarbazones, Pd (II) and Pt (II) complexes of 5-chloro semicarbazones, Pd (II) and Pt (II) complexes of 5-chloro 1-3-dihydro-3-[2-(phenyl)-ethylidene]-2H-indol-2-one-hydrazine carbothiomide have been studied, synthesized and tested for their antimicrobial activity. The results showed that the compounds exhibit antimicrobial properties and the metal chelates show better inhibitory effects than the parent ligands. The study suggests the increased lipophilic character of these complexes may be responsible for their enhanced biological potency [7]. The thiosemicarbazones molecules have ability to chelate with traces of metals in the biological system and this is a reason for their biological activity. A great clinical challenge in the treatment of cancer with anticancer drugs is that certain tumour cells develop a particular phenotype called multi drug resistance, which makes these cells resistant to other classes of anticancer agents [8]. The palladium complex of phenanthrenequinonethiosemicarbazone has been found potent neoplastic agent possessing selective activity against tumour cells. It is also found effective against drug resistant breast cancer cells [9]. The antitumour activities of Mn^{2+} , Co^{2+} , Ni^{2+} and Cu^{2+} chelates of anthracene-9-carboxaldehyde thiosemicarbazone and cytotoxic activity of phenyl glyoxalbis (thiosemicarbazone) against Ehrlich ascites carcinoma cells have been studied and reported [10].

II. LITERATURE SURVEY

Thiosemicarbazone of benzoylformic acid behaves as a monobasic acid under acidic conditions and as a dibasic acid under alkaline solutions. The Fe (II), Co (II), Ni (II), Cd (II) and Pb (II) complexes of the dibasic form have been reported [11]. The magnetic moment for the coordination compounds of Cu (II) with thiosemicarbazones of benzoylformic acid and adipic acid have been reported [12]. The structure of the two six coordinate paramagnetic complexes of Ni (II) with tridentate thiosemicarbazones of isoquinoline-1-carboxaldehyde and pyridine-2-aldehyde have been determined [13,14]. The metal complexes of resacetophenonethiosemicarbazone and also its mixed ligand products with DMG (M = Co (III), Cr (III), Fe (III), Cu (II), Ni (II)) have been reported [15]. Resacetophenonethiosemicarbazone acts as tridentate ligand using S and N atoms of hydrazone group and O atom of the phenol group in ortho position.

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Considering the above applications it is desirable to synthesize and characterize the Ni (II) complexes with Schiff base. The present research work reports the synthesis, spectral characterisation and biological evaluation of six coordinate complexes of Ni (II) with 5-dichloro 2-hydroxy acetophenonethiosemicarbazones.

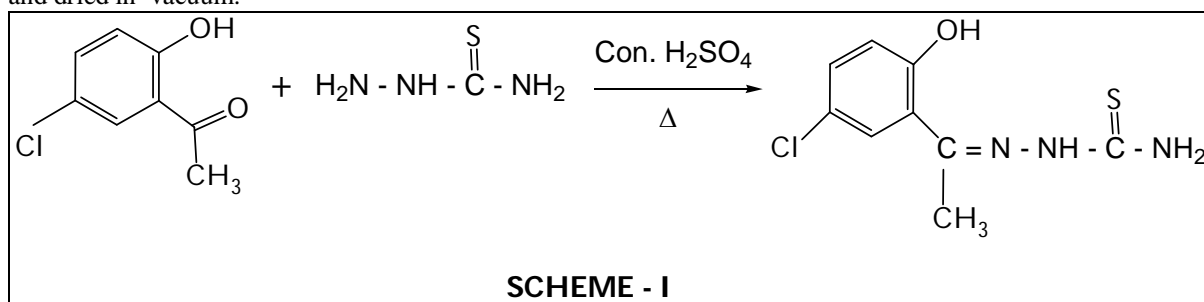
III. MATERIALS AND METHODS

All chemicals used were of A.R. grade for the synthesis. Magnetic moment was measured at room temperature by Faraday method. IR spectra were recorded in the range 4000-200 cm^{-1} range. NMR spectra were recorded in the mixture of CDCl_3 and DMSO-d_6 (1:1 v/v) with a Bruker AC-300F 300MHz spectrometer. Thermal stability was determined by carrying out thermogravimetric analysis. Metal in the complexes was estimated by standardized E.D.T.A.

IV. EXPERIMENTAL

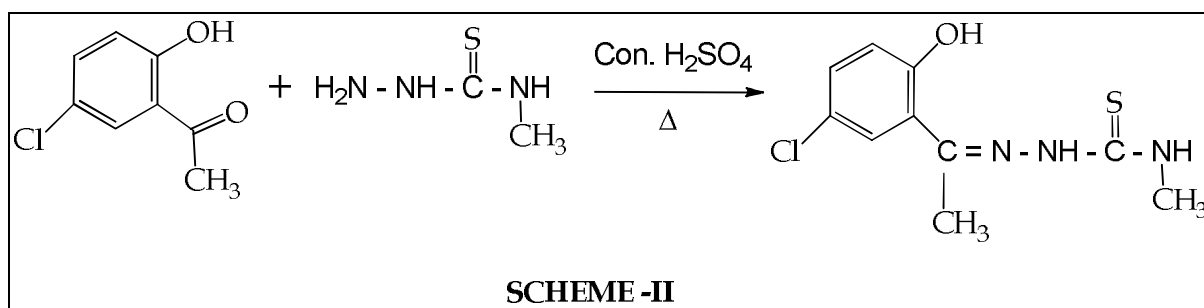
Synthesis of thiosemicarbazone L_1

Ethanol solutions of 5-chloro 2-hydroxy acetophenone was added to ethanol solution of thiosemicarbazide in the mole ratio 1:1. The reaction mixture was refluxed for three hours. The pale yellow product obtained on cooling was filtered and washed with hot water then cold ethanol and finally with ether. The compound was then purified in ethanol and dried in vacuum.



Synthesis of thiosemicarbazone L_2

Ethanol solutions of 5-chloro 2-hydroxy acetophenone was added to ethanol solution of N(4) methyl thiosemicarbazide in the mole ratio 1:1. The reaction mixture was refluxed for three hours. The pale yellow product obtained on cooling was filtered and washed with hot water then cold ethanol and finally with ether. The compound was then purified in ethanol and dried in vacuum.



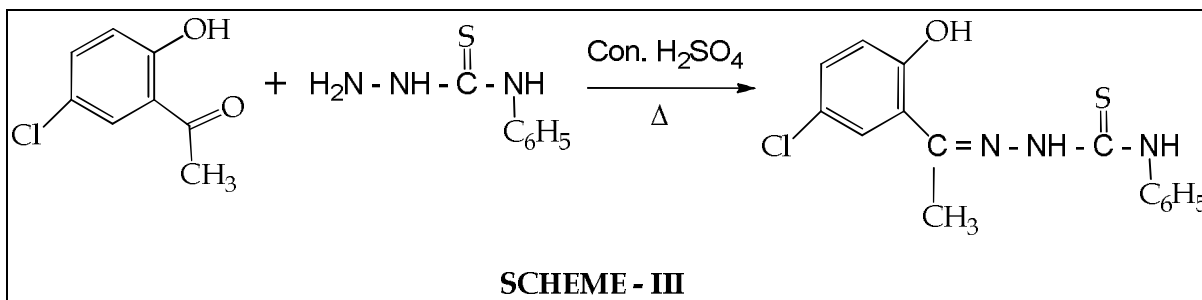
Synthesis of thiosemicarbazone L_3

Ethanol solutions of 5-chloro 2-hydroxy acetophenone was added to ethanol solution of N(4) phenyl thiosemicarbazide in the mole ratio 1:1. The reaction mixture was refluxed for three hours. The pale yellow product obtained on cooling was filtered and washed with hot water then cold ethanol and finally with ether. The compound was then purified in ethanol and dried in vacuum.

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Synthesis of complex ML₂

The complex of the type ML₂ was synthesized by refluxing ethanolic solutions of thiosemicarbazones (0.01mole), NiCl₂.6H₂O in the mole ratio 1:2 for one hour. The reaction mixture was then concentrated to about 20% of the original volume. The green product obtained was filtered and washed with hot water, cold absolute ethanol and then ether and dried in vacuum.

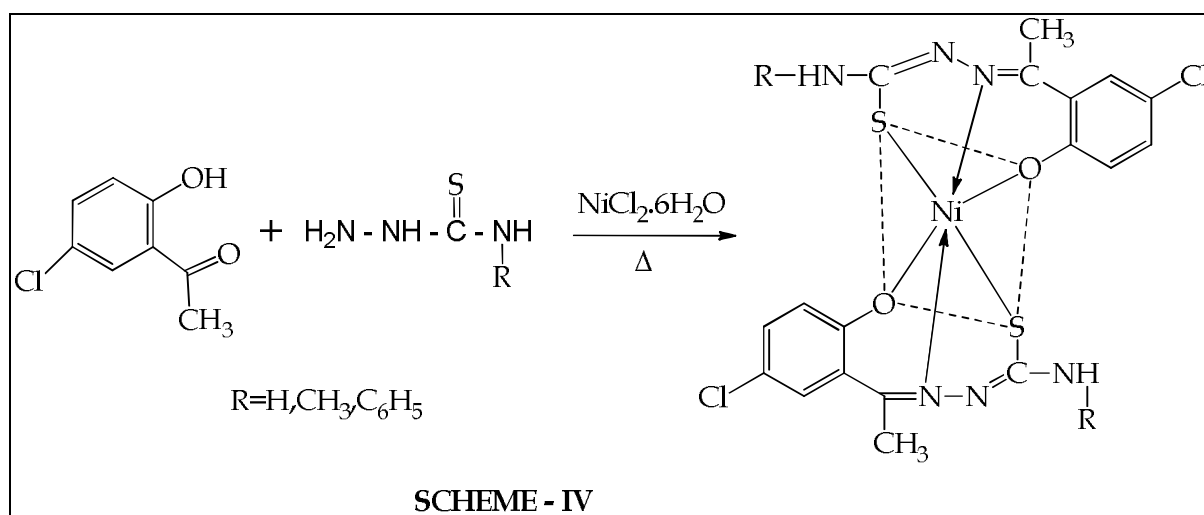


TABLE 1 PHYSICAL PROPERTIES:

Compounds	Colour	Empirical Formula	Molar conductance Ohm ⁻¹ cm ² mole ⁻¹	Magnetic Moment B.M.
L ₁	Yellow	C ₉ H ₁₀ N ₃ O ₂ Cl	-	-
L ₂	Yellow	C ₁₀ H ₁₂ N ₃ O ₂ Cl	-	-
L ₃	Yellow	C ₁₅ H ₁₄ N ₃ O ₂ Cl	-	-
Ni L ₁	Green	C ₁₈ H ₁₆ N ₆ O ₂ S ₂ Cl ₂ Ni	47	2.82
Ni L ₂	Green	C ₂₀ H ₂₀ N ₆ O ₂ S ₂ Cl ₂ Ni	43	2.88
Ni L ₃	Green	C ₃₀ H ₂₄ N ₆ O ₂ S ₂ Cl ₂ Ni	50	2.94

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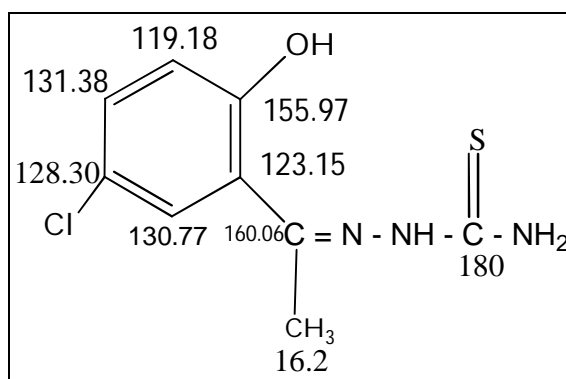
Physical data of ligand and its complexes is presented in Table 1. The complex and all adducts are in soluble in ethanol and soluble in DMF. Molar conductance measured in DMF solution of these complexes indicates non electrolyte. The regular octahedral Ni (II) complexes are always paramagnetic having $^3A_{2g}$ ground state. The deviation from the spin only value of 2.83 B.M. i.e. the orbital contributions to the magnetic moment, depends very much on the stereochemistry so in suitable cases the magnetic moment gives a good indication of the structure of the complex. The temperature independent magnetic moments are found in the range 2.9-3.3 B.M.

$^1\text{H-NMR } L_1$

Signals at 13, 3.40 ppm are assigned to -OH, -CH₃ protons respectively. Thiosemicarbazone does not show any peak corresponds to S-H proton, indicating it exists in thioketo form. Absence of ^2NH proton signal suggests enolisation of $^2\text{NH} - \text{C} = \text{S}$ group to $^2\text{N} = \text{C} - \text{SH}$. Little low field position of ^4NH (7.8 ppm) could be attributable to the deshielding caused by -N=C\ of the system N=C(SH)=NH. Aromatic protons show multiples at 7.00, 7.25 and 7.50 ppm range.

$^{13}\text{C-NMR } L_1$

119.18 (C=C), 131.38 (C=C), 128.27 (C=C-Cl), 130.77 (C=C), 123.15 (C=C), 155.97 (C=C-OH), 160.06 (C=N), 180.0 (C=S), 16.2 (C-CH₃).

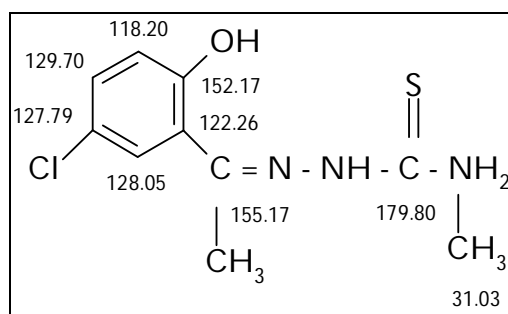


$^1\text{H-NMR } L_2$

NMR signals at 13.00 and 3.00 ppm are assigned to -OH and -CH₃ protons respectively. The signals at 2.19, 2.25 correspond to ^4NH and $\text{H}^4\text{N-CH}_3$ respectively. Absence of ^2NH proton signals suggests enolisation of $^2\text{NN} - \text{C} = \text{S}$ group to $^2\text{N} = \text{C} - \text{SH}$. Aromatic protons show multiplet at 6.9, 7.255, 7.45, ppm range.

$^{13}\text{C-NMR } L_2$

118.20 (C=C), 129.70 (C=C), 127.79 (C=C-Cl), 128.05 (C=C), 122.26 (C=C), 152.17 (C=C-OH), 155.39 (C=N), 179.80 (C=S), 31.03 (NH-CH₃)



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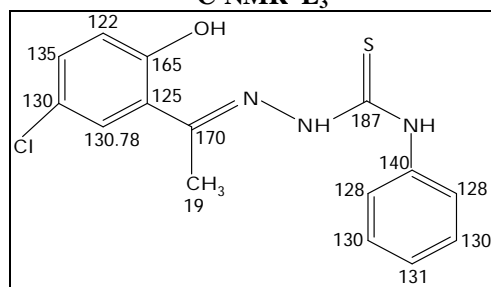
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¹H-NMR L₃

122 (C=C), 135 (C=C), 130 (C=C-Cl), 130.78 (C=C), 125(C=C),165 (C=C-OH),170 (C=N),19 (=C-CH₃),187 (C=S),140 (NH-C=C),128 (C=C),130 (C=C),131 (C=C),130 (C=C),128 (C=C).

¹³C-NMR L₃



(Calcd) found ESI-MS

L₁:C₉H₁₀ N₃OSCl(243.70) 243.11,**L₂**:C₁₀H₁₂ N₃OSCl(257.72) 257.15,**L₃**:C₁₅H₁₄ N₃OSCl(319.79) 319.41,**Ni.L₁**:C₁₈H₁₆N₆O₂S₂Cl₂Ni(542.06) 542.86,**Ni.L₂** :C₂₀H₂₀N₆O₂S₂Cl₂Ni(570.11) 570.87,**Ni.L₃**:C₃₀H₂₄N₆O₂S₂Cl₂Ni(694.24) 694.72.

Mass spectral data confirmed the structure of the thiosemicarbazones and complexes as indicated by molecular ion peak (M + 1) corresponding to their molecular weights.

V. ANALYTICAL DATA

- L₁**:% C 44.91 (44.35),% H 4.88 (4.14),% N 17.92 (17.24), %O 6.06 (6.57) % S 13.71 (13.16)
- L₂**% C 46.02 (46.60),% H 4.04 (4.69),% N 16.91 (16.30),%O 6.78 (6.21)% S 12.87 (12.44)
- L₃** :% C 56.81 (56.33),% H 4.92 (4.41),% N 13.82 (13.14),%O 5.81 (5.00)% S 10.54 (10.03)
- Ni.L₁**: % Ni 10.16 (10.83), %C 39.12 (39.88), %H 2.12 (2.98), %N 15.08 (15.50)%O 5.14 (5.90) , %S 11.22 (11.83).
- Ni.L₂**: % Ni 10.74 (10.29), %C 42.70 (42.13), %H 4.05 (3.54), %N 14.09 (14.74), %O 5.05 (5.61) %S 11.76 (11.25).
- Ni.L₃**: % Ni 8.94 (8.45), %C 51.14 (51.90), %H 3.01 (3.48), %N 12.79(12.11), %O 4.98 (4.61) %S 9.88 (9.24).

On the basis of elemental analysis data,the complexes were found to have 1:2composition.The calculated and theoretical values are matched.

VI.INFRARED SPECTROSCOPIC DATA(cm⁻¹)

- L₁**:: ν (- OH) 3147; ν (C = N) 1624; ν (- C - S) 758 (s), 1374 ; ν (²N-H) 3252, ν (N - N) 1049; ν (²N-H) 2943; ν (C - O) 1281.
- L₂**:ν (- OH) 3225; ν (C = N) 1638; ν (- C - S) 795 , 1358 ; ν (²N-H) 3255,ν (N - N) 1049; ν (²N-H) 2925; ν (C - O) 1388.
- L₃**:ν (- OH) 3340; ν (C = N) 1678; ν (- C = S) 790, 1375 ;ν (²N-H) 3260, ν (N - N) 1075; ν (²N-H) 3240; ν (C - O) 1285.
- 4Ni.L₁**:ν (C = N) 1556ν (C = N - N = C) 1560,ν (C-S) 710, 1314,ν (N-N) 1132,ν(M - N) 425, ν (M-O) 520, ν (M-S) 320, ν (C - O) 1215.
- 5 Ni.L₂**:ν (C = N) 1560,ν (C = N - N = C) 1565,ν (C-S) 715, 1320,ν (N-N) 1140, ν (M - N) 430, ν (M - O) 525, ν (M-S) 325, ν (C - O) 1220.
- 6. Ni.L₃**: ν (C = N) 1565,ν (C = N - N = C) 1568,ν (C-S) 720, 1325,ν (N-N) 1145,ν (M - N) 435, ν (M - O) 530, ν (M-S) 330, ν (C - O) 1230.

The band in the range 3252-3260 cm⁻¹ in the free ligands due to the ν(²NH) disappeared in the spectra of complexes.This indicates the coordination of the ligand around the Ni(II) ion in its deprotonated form.It is confirmed by decrease in ν(CO) frequency appearance of a band in the range 520-530cm⁻¹ due to a ν (Ni-O) in the spectra of

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complexes [16]. It indicates coordination through phenolic oxygen. $\nu(\text{C}=\text{N})$ shifts to lower side on complexation. The coordination of azomethine nitrogen is confirmed with the presence of new band in the range $425\text{-}435\text{cm}^{-1}$ due to $\nu(\text{Ni}-\text{N})$ in the complexes [17, 18]. The $\nu(\text{N}-\text{N})$ of the thiosemicarbazones is found in the range $1049\text{-}1075\text{cm}^{-1}$. It is shifted to higher side in the spectra of the complexes, due to the increase in the bond strength. It confirms the coordination via the azomethine nitrogen. The bands in the ranges $1358\text{-}1375$ and $758\text{-}790\text{cm}^{-1}$ due to thioamid stretching and bending vibrations, respectively in thiosemicarbazones are shifted to lower side, indicating coordination of the thiolate sulfur to the Ni(II) ion. This decrease in frequency can be due to a change of bond order and strong electron delocalization upon chelation [19]. This negative shift of $\nu(\text{C}-\text{S})$ in the complexes is reported by Campbell [20]. It is again confirmed with the presence of new band in the range $320\text{-}330\text{cm}^{-1}$, assignable to $\nu(\text{Ni}-\text{S})$ in the complexes [21, 22].

VII. ELECTRONIC SPECTRA IN Cm^{-1}

Compound	State	d-d	LMCT	$n \rightarrow \pi^*$	$\pi \rightarrow \pi^*$
L_1	DMF	-	-	28750	35205
L_2	DMF	-	-	29610	36402
L_3	DMF	-	-	30110	37503
Ni. L_1	DMF	17550	26802	29500	36202
Ni. L_2	DMF	17690	26405	30750	37530
Ni. L_3	DMF	17850	26308	31440	37900

Each thiosemicarbazone and its Ni (II) complex shows a ring $\pi \rightarrow \pi^*$ band in the range $35000\text{-}38000\text{cm}^{-1}$ and an $n \rightarrow \pi^*$ band in the range $28000\text{-}32000\text{cm}^{-1}$, involving transitions within the thiosemicarbazone moiety [23]. These bands are slightly shifted to higher side upon complexation. The shift of the $\pi \rightarrow \pi^*$ bands to longer wavelength region in complexes is due to weakening of the $\text{C}=\text{S}$ bond and the conjugation system enhanced on complexation [24, 25]. The $n \rightarrow \pi^*$ bands in the complex shows a blue shift. This is due to donation of lone pair of electrons to the metal and hence the coordination of azomethine with a reduction of intensity [24]. In the case of complexes having ONS donor ligands, the shift of two ligand to metal charge transfer bands are observed in the $26000\text{-}27000\text{cm}^{-1}$. Each complex has a broad d-d combination bands on the intraligand and charge-transfer bands in the range $17000\text{-}18000\text{cm}^{-1}$. The nickel complexes show a trend of increasing size of the N(4) substituent and lower energy of the d-d band maximum, due to weakening of the coordinate bonding with increased bulkiness of the ligands.

VIII. TGA ANALYSIS DATA

1. **Ni-L₁**: First step, $145\text{ }^\circ\text{C}$, Mass loss 18 % second step, $210\text{ }^\circ\text{C}$, Mass loss, 32 % Third Step $355\text{ }^\circ\text{C}$, Mass loss, 45 % Fourth Step, $660\text{ }^\circ\text{C}$, Mass loss 65 %, Residue $790\text{ }^\circ\text{C}$, % of NiO, 13.22 (13.78).
2. **Ni-L₂**: First step, $147\text{ }^\circ\text{C}$, Mass loss 20 % second step, $210\text{ }^\circ\text{C}$, Mass loss, 34 % Third Step $357\text{ }^\circ\text{C}$, Mass loss, 50 % Fourth Step, $665\text{ }^\circ\text{C}$, Mass loss, 68%, Residue, $790\text{ }^\circ\text{C}$, % of NiO, 13.74 (13.10).
3. **Ni-L₃**: First step, $150\text{ }^\circ\text{C}$, Mass loss 22% second step, $215\text{ }^\circ\text{C}$, Mass loss, 37 % Third Step $360\text{ }^\circ\text{C}$, Mass loss, 52 % Fourth Step, $667\text{ }^\circ\text{C}$, Mass loss 70 %, Residue $790\text{ }^\circ\text{C}$, % of NiO, 10.13 (10.76).

The hydrated layer in the complexes was removed below $100\text{ }^\circ\text{C}$. The above data indicated that the decomposition of the complexes proceeded in four steps. The complexes are stable up to about $360\text{ }^\circ\text{C}$. In the second step the loss in mass is upto 37%. The organic molecule was lost upto $670\text{ }^\circ\text{C}$. The mass lost corresponding to this step is about 65-70%. The decomposition was complete and metal oxide was formed at a temperature about $790\text{ }^\circ\text{C}$. No coordinated water molecule was found in the analysis. The thermal stability is related to the coordination of metal in the complexes.

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IXANTIBACTERIAL ACTIVITY(WELL DIFFUSION METHOD)
Table.2 Zone of inhibition in mm L₁,L₂,L₃ , Ni (II) complexes and standered

Compound	<i>Staphylococcus aureu</i>		<i>Bacilussubtilis</i>		<i>AspergillusNigara</i>		<i>Candida Albicans</i>	
	Gram positive bacteria				Fungi			
	10 ⁻³ M	10 ⁻⁴ M	10 ⁻³ M	10 ⁻⁴ M	10 ⁻³ M	10 ⁻⁴ M	10 ⁻³ M	10 ⁻⁴ M
L ₁	11	9	11	10	11	10	12	9
L ₂	12	10	11	9	12	8	11	10
L ₃	11	10	12	10	12	10	10	9
Ni.L ₁	15	14	13	12	13	11	12	10
Ni.L ₂	16	13	14	13	14	12	13	10
Ni.L ₃	15	13	14	12	15	13	14	11
NiCl ₂ .6H ₂ O	22	21	23	21	23	21	21	20
Standard	32	30	31	29	33	28	31	29

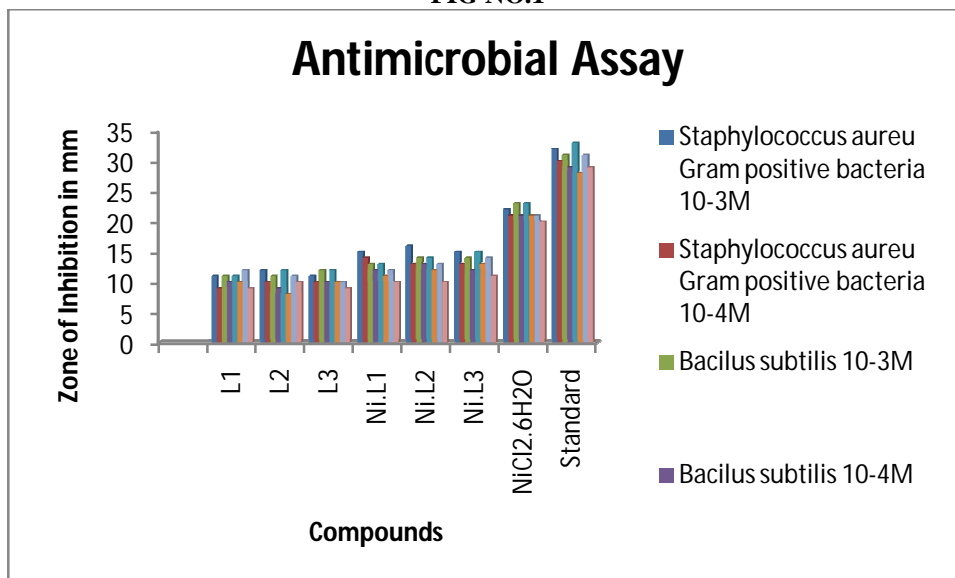
(Std-Amphiciline,Fluconazole)

The microbial activity was determined using the well diffusion method. Activity was measured in two different molar concentrations, 10⁻³M, 10⁻⁴ M. The zone of inhibition was measured in mm. The results indicated that the synthesized compounds exhibited antibacterial activity at low and high concentrations. The complexes showed maximum activity against bacterial species than free ligand. The increased activity of the synthesized compounds may be due to electron delocalization over the whole molecule. This increases the lipophilic character of the molecule and favors its permeation through the lipid layer of the bacterial membranes. The increased lipophilic character of this molecule may be responsible for its enhanced potent antibacterial activity. The thiosemicarbazones were found less active than their complexes. The delocalization of π-electrons increases lipophilicity and this facilitates the penetration into lipid membranes, further restricting proliferation of the microorganisms [26]. In complexes coordination number increases which increases antimicrobial activity. *Staphylococcus aureu* and *Bacilussubtilis* are gram +ve bacterial species and *AspergillusNigar*, *Candida Albicans* are fungal species. The nickel chloride salts were found more growth inhibitory than complexes. The Ni⁺² ions have small size having d⁸ configuration. This increases the permeability to cell membrane. But use of metal ion solution to treat bacterial diseases is toxic, so it can be used in coordination with ligand. The general sequence of inhibitory activity can be represented as -

Metal salt > Standard > complexes > ligand.

The growth inhibition decreases on dilution i.e. it is more in concentrated solution.

FIG NO.1



The above bar graph indicates maximum activity at higher concentration than at lower concentration. More activity was observed in case of Gram (+) bacteria than fungi.

X. ANTIOXIDANT STUDY

Antioxidant studies on the thiosemicarbazone metal complexes have been analysed by DPPH assay. DPPH is stable free nitrogen radical and the assay determines the ability of the compound to reduce DPPH radical. The antioxidants can act by converting the unpaired electrons to paired ones. The decrease in absorbance at 517 nm is the measure of test compound to reduce DPPH radical that acts as an antioxidant which is indicated by the formation of yellow colour.

Each extract or standard (from 21 mg/ml to 21 g/ml) was added to 2 ml of DPPH in methanol solution in a test tube. After incubation at 37°C for 30 min, the absorbance of each solution was determined at 517 nm using spectrophotometer. The corresponding blank readings were also taken and the remaining DPPH was calculated. IC₅₀ value is the concentration of the sample required to scavenge 50 % DPPH free radical lower the absorbance of the reaction mixture indicated higher free radical scavenging activity [27]. The results of antioxidant activity are presented in Table No. 3

Table.2 % RADICAL SCAVENGING EXHIBITED BY L₁,L₂,L₃Ni (II) COMPLEXES

Compound	20 µg/ml	40 µg/ml	60 µg/ml	80 µg/ml	3100 µg/ml	IC ₅₀ value
L ₁	69.76	76.74	79.06	79.06	81.39	14.33
L ₂	72.09	74.41	76.74	76.74	79.06	13.87
L ₃	72.09	74.41	76.74	76.74	79.06	13.87
Ni.L ₁	32.00	47.00	48.00	58.00	60.50	73.72
Ni.L ₂	5.33	6.50	18.50	16.30	37.00	146.85
Ni.L ₃	12.00	14.20	22.00	33.00	38.50	135.33
Vit. C	39.53	46.51	58.13	60.46	65.11	51.00

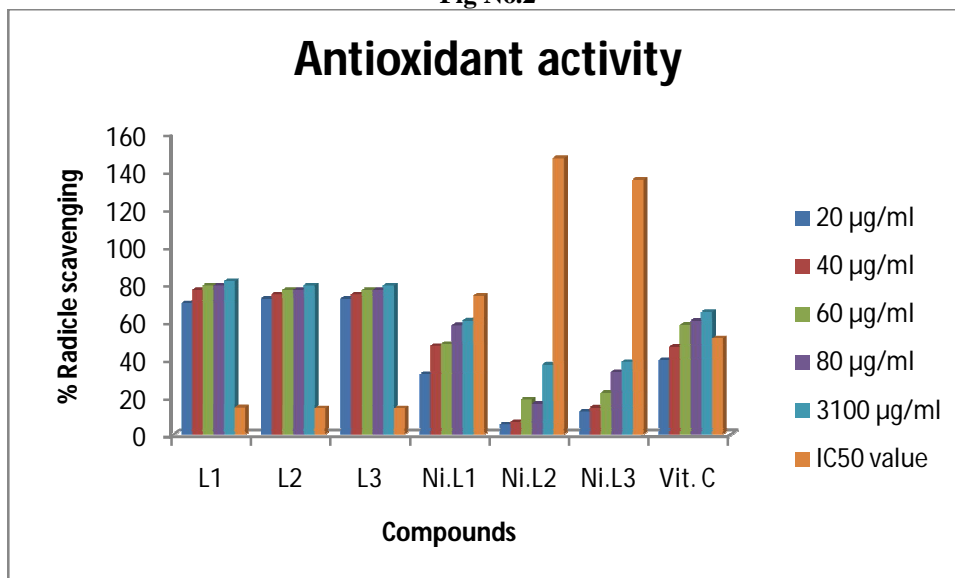
Lower the absorbance of the reaction mixture indicated higher free radical scavenging activity [28]. Complexes showed better % scavenging activity at higher concentration.

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Fig No.2



The above bar graph indicates % radical scavenging activity. More activity was observed in the complexes

XII CONCLUSION

The thiosemicabazones synthesized are tridentate ONS donors. The spectral data indicates octahedral geometry for complexes. The complexes are paramagnetic. Thermo gravimetric analysis indicates thermal stability of the complexes. The compounds are thermally stable upto 360°C. The decomposition took place in four steps. The complexes showed growth inhibitory activity against gram +ve bacterial and fungal species. The activity is more at 10⁻³M concentration. The metal salts showed more growth inhibition at higher concentration. The complexes showed radical scavenging.

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