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Synthesis Characterzation and Biological Application of 2,3,4-Trimethoxy Benzaldehyde Semicarbazone Ni(II) Metal Ions

Vidhya R.S[1] and Rathika Nath.G[2]
[1]S.T.Hindu College Nagercoil,
[2]D.B.College Sasthamcotta, Kollam, Kerala.

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ABSTRACT
$[Ni(L_4)_2Cl_2]$,were prepared by reacting 2,3,4-trimethoxy benzaldehyde semicarbazone ligands with $NiCl_2.6H_2O$. The IR,UV, Mass and ^{1}H NMR spectra of the complexes have been assigned. Thermo gravimetric analysis were also carried out. The data agree quite well with the proposed structures and show that the complexes were finally decomposed to the corresponding ligands. Complexes were screened for antimicrobial activities by the disc diffusion technique using DMSO as solvent. The activity data show that the semicarbazone metal complexes are more potent antimicrobials metal complexes.

1. Introduction

The availability of different types of amines and carbonyl compounds enabled the synthesis of Schiff bases with diverse structural features. The bonding ability of the ligands depends on the nature of atoms that act as coordination site, their electro negativity and steric factors. By virtue of the presence of lone pair of electrons on the nitrogen atom, electron donating character of the double bond and low electro negativity of nitrogen, N of the azomethine group[(1)] (>C=N) act as good donor site and Schiff bases as active ligands[(2-3)].

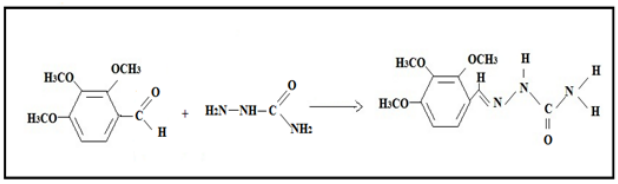
Coordination chemistry of semicarbazones appears to be very interesting from the point of view of both the number of metals forming complexes with them and the diversity of the ligand systems themselves which include macro cyclic systems. Many of these were prepared for physiological studies and their structures were not fully discussed[(4-6)]. The transition metal complexes of semicarbazones have been getting significant interest mostly because of their bioinorganic consequences. Condensation reaction between a ketone or aldehyde and semicarbazide, produces a semicarbazone[(7)] of the types R-CH=NNH-CO-NH_2 or R^1R^2C=N-NH-CO-NH_2.

2. Experimental details

All chemicals used were of analytical reagent grade (AR) and procured from Sigma-Aldrich and Flucka and the metal salts were purchased from E.Merck and used as received.

2.1. Synthesis of Ligand

0.01 mole of the corresponding aldehyde in ethanol (2,3,4-trimethoxy benzaldehyde in cold ethanol was added to a 250ml RB flask containing 0.01 mole of semicarbazide in hot water. The mixture was refluxed for about 4 to 5 hours at 80^{o}C, with continuous stirring, and then allowed to cool overnight at room temperature. The isolated yellow colored precipitate was filtered, washed with cold ethanol and dried under vacuum.



2.2. Synthesis of metal complexes

Aqueous solution of the corresponding metal salt (0.01 mole), (Nickel Chloride hexahydrate) was individually mixed with hot ethanolic solution of the corresponding ligand (0.02 mole). The mixture was refluxed for 4-5 hours at 70-80^{o}C with continous stirring, allowed to cool overnight at room temperature to yield light brown coloured metal complexes. The products were filtered, washed with 50% ethanol, and dried under vacuum.

3. Result and Discussion

3.1. Physical Parameters of Ligands and their metal complexes

Schiff bases were prepared in 1:1 ratio and the Schiff base metal complexes prepared by 1:2 ratio. All the metal complexes were found to be soluble in DMSO. Physical parameters of the resulting complexes are summarized below:

Table.1. Physical parameters of the ligand and its metal complex.

Sl. No	Compound	Molecular weight	Melting point (^{o}C)	Colour	Molecular Formula
1	L_4	253.29	230	Yellow	$C_{11}H_{15}N_3O_4$
2	$[Ni(L_4)_2]$	565.27	210	Light brown	$[Ni(C_{11}H_{15}N_3O_4)_2]$

Tele:
E-mail address: vvidhya276@gmail.com

3.2. Elemental analysis

Elemental analysis of ligand L_4 ($C_{11}H_{15}N_3O_4$) found (calc.) (%), C, 52.14 (52.16); **H**, 5.95 (5.98); **N**, 16.60 (16.59); **O**, 25.31 (25.27).

Metal complexes like $[Ni(C_{11}H_{15}N_3O_4)_2]$: **C ,** 46.77 (46.74); **H**, 5.34 (5.36) ; **N,** 14.86 (14.87); **O,** 22.67 (22.64); **M,** 10.35 (10.38).

Table 2. CHNS data table of L_4 and its complexes

Compound	% Observed (Calculated)				
	C	H	N	O	M
$C_{11}H_{15}N_3O_4$	52.14 (52.16)	5.95 (5.98)	16.60 (16.59)	25.31 (25.27)	-
$[Ni(C_{11}H_{15}N_3O_4)_2]$	46.77 (46.74)	5.34 (5.36)	14.86 (14.87)	22.67 (22.64)	10.35 (10.38)

3.3. Spectral and thermal characterization data

IR spectral analysis

L_4 and its metal complexes

The IR spectra of L_4 and its metal complexes are provided below.

Figure 1.IR spectra of L_4

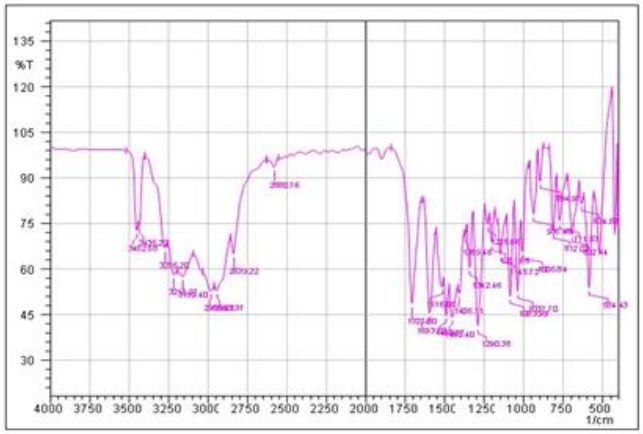
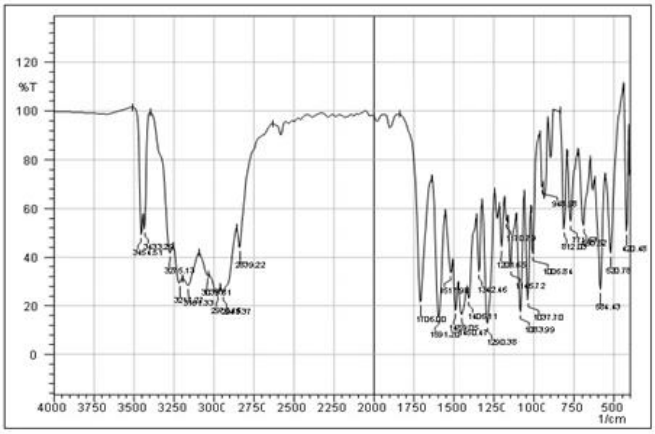


Figure 2. IR spectra of $[Ni(L_4)_2]$



IR absorption band in the region 1707.00 cm^{-1} can be attributed to the C=O stetching vibration of L_4, while its transition metal show absorption shifted to values 1706.00cm^{-1}, in $NiCl_2$. 1593.20cm^{-1} in the spectrum assigned to the azomethine (C=N) vibration. This is seen to suffer lower shift to values around 1591.20cm^{-1} in the complexes of $NiCl_2$.

Table 3. IR spectral values of L_4 and its metal complexes

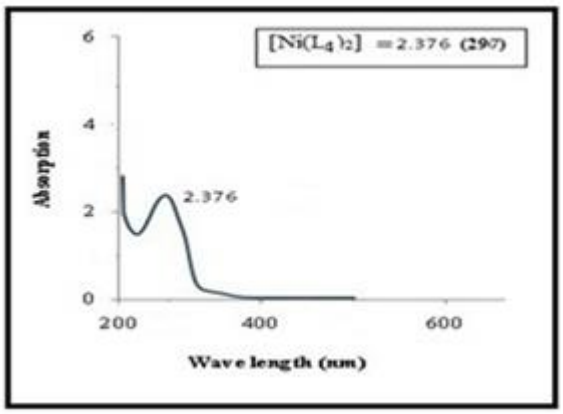
Compounds	ν (C=N)	ν (N-H)	ν (C=O)	ν (M-O)	ν (M-N)
L_4	1593.20	3275.20	1707.00	-	-
$[Ni(L_4)_2]$	1591.20	3275.13	1706.00	420.48	520.78

In the case of metal complexes, the appearance of bands (M-N) in the region of 520.78 cm^{-1} in $NiCl_2$, and (M-O) show a absorption band at 420.48cm^{-1}, in $NiCl_2$.

3.4. UV spectral analysis

The bands in the range 200–700 nm can be assigned to π-π* and/or n-π* transitions. In the absorption spectrum of $[Ni(L_4)_2]$ a band at 297nm is attributed to π-π * transition. The bands corresponding to three spin-allowed transitions viz. ^3T_1g (P) → ^3A_2g(P) were observed.

Figure 3. UV spectra of $[Ni(L_4)_2]$.

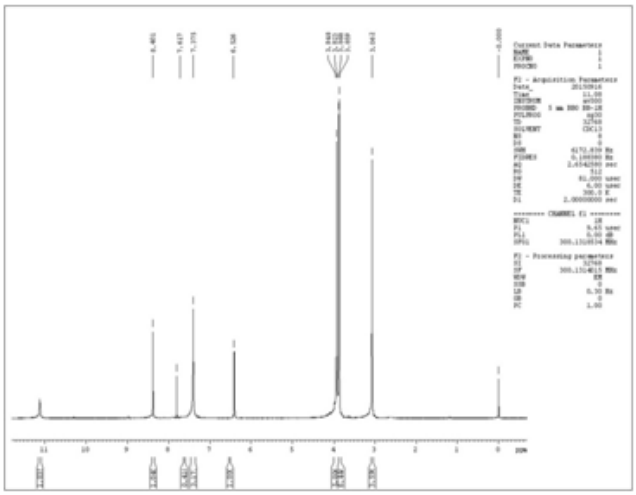


3.5. NMR spectral analysis

^1H NMR Spectra of L_4

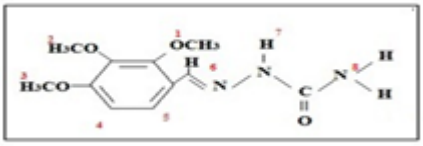
The 1H NMR spectrum of L_4 in DMSO is shown in Figure: 4. and peak assignments are given in the given Table 4.

Figure 4. 1H NMR spectrum of L_4.



Chemical Shifts of methoxy protons were observed as a single peak at δ 3.923 (ppm). Chemical shift of aromatic proton were observed as a multiplet at δ 7.375 ppm . The azomethine proton appeared at δ 6.526 (ppm) . The signals of the N-NH proton were observed as singlet at δ 8.401 (ppm) and -NH_2 proton signals observed as singlet at δ 7.617 (ppm).

Table 4. ^1H NMR spectra table of L_4.

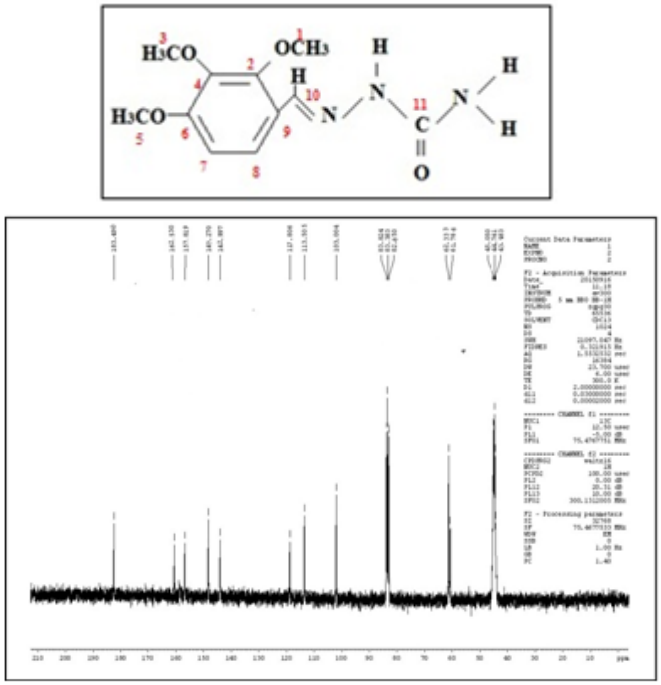


Chemical Shift (ppm)	Mark	Assignments in DMSO
3.923, 9h, t	1,2,3	OCH_3 Protons
7.375, 2h, d	4, 5	Aromatic proton
6.526, 1H, s	6	Azomethine proton (CH=N)
8.401, 1H, s ; 7.617, 1H, s	7, 8	Proton of NH & NH_2

^{13}C NMR Spectra of L_4

The ^{13}C NMR spectrum of 2,3,4-trimethoxy benzaldehyde semicarbazone compounds (L_4) in DMSO is shown in Figure. 7 and peak assignment are given in Table. 5

Figure 5. ^{13}C NMR spectra of L_4.



The spectrum showed a signal at 82.850-83.824 ppm which was assigned to methoxy carbon. The presence of carbonyl (ketone group) was found at around 206.194 ppm and aromatic carbons within the range 103.004-117.806 ppm. The azomethine carbon atom exhibited a peak at 162.530 ppm. The peak observed at 45.050-43.483 ppm may be due to methylene carbon (benzyl group.

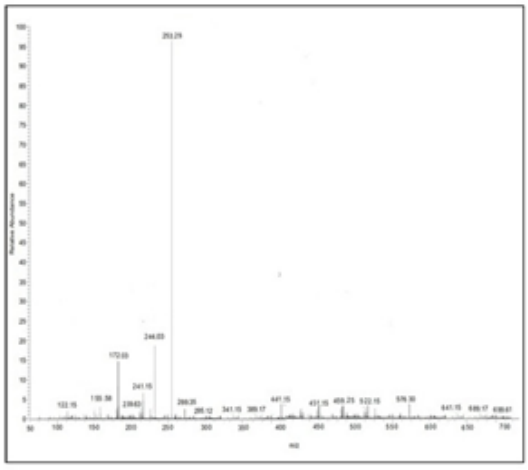
Table 5. ^{13}C NMR spectra table of L_4.

Chemical Shift (ppm)	Mark	Assignments in DMSO
82.850-83.824	2, 4, 6	Methoxy carbon
103.004-117.806	7,8	Aromatic Carbon
45.050-43.483	1,3,5	Methylene Carbon (Benzyl Group)
162.530	10	Azomethine Carbon (CH=N)
206.194	11	Carbonyl (ketone) (C=O)

3.6. Mass spectral analysis

The Electron impact mass spectrum of the ligand (L_4) figure: 6 shows a molecular ion (M^+) peak at m/z= 253.29amu corresponding to species $C_{11}H_{15}N_3O_4$.

Figure 6. Mass spectra of L_4.



The intensities of the peaks give the idea of the strength of the fragments. The mass spectrum of the Ni(II) complex showed a molecular ion peak at m/z = 565.27 which was found to coincide with that of the molecular weight of the complex.

Figure 7. Mass spectra of $[Ni(L_4)_2]$.

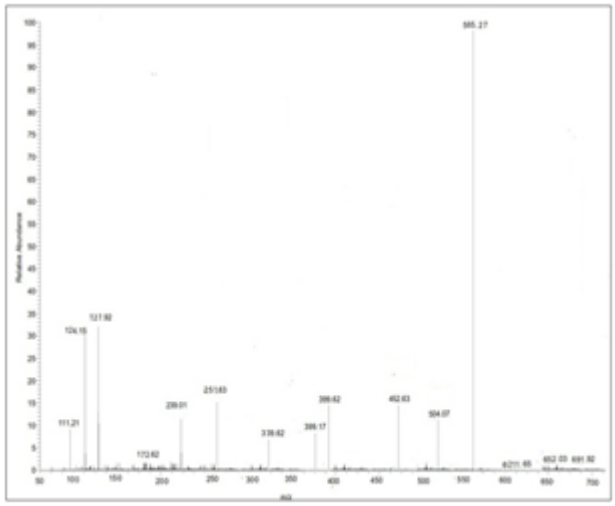


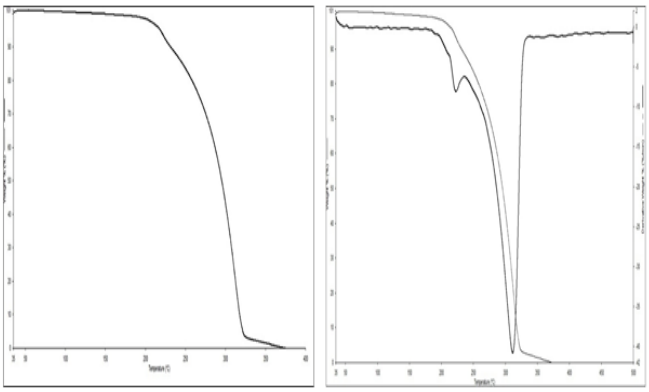
Table 6. Molecular weights of $L_4$and its metal complexes (by Rast's method).

Sl.No	Compound	Molecular weight
1	L_4	253.29
2	$[Ni(L_4)_2]$	565.27

3.7.TG analysis

Thermogram of the solid ligand shows that there is no weight loss up to 310^{o}C (Figure: 8)

Figure 8. Thermo gram of L_4.



The horizontal portion of the curve indicate there is no change in weight (0-200^{o}C & 310- 360^{o}C) and the vertical potion indicate that there is weight change (200-310^{o}C) . Thermogram of the solid complexes shows that there is no weight loss up to 339^{o}C signifying the lack of lattice as well as coordinated water molecule in complexes. Thermogram indicates incomplete decay of ligand moiety. The residual part of the ligand split at 300-500^{o}C. The straight curve indicates no change in weight (0-229^{o}C & 339- 500^{o}C) and the perpendicular potion indicate that there is weight change (229-339^{o}C) . The total weight loss up to 229^{o}C corresponds to two moles of ligand representing 1:2 composition of the complex.

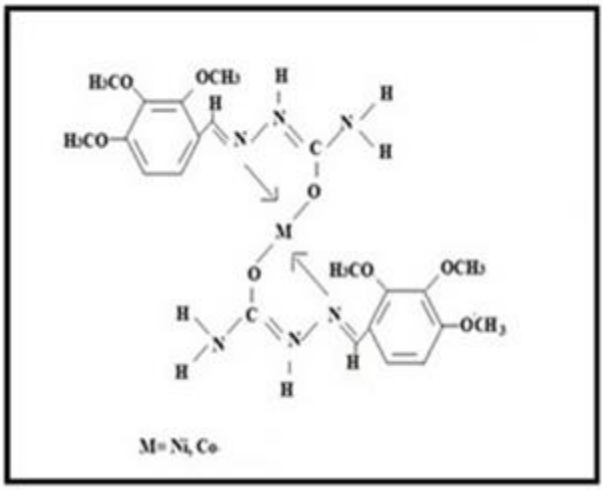
3.8. Magnetic moment

The magnetic moment of the complexes was determined using Guoy balance. Magnetic moment the value of magnetic moment of Nickel(II) was around 3.15 B.M.

Proposed structure of metal complexes.

From the above characterization details, the following structures are proposed for the complexes.

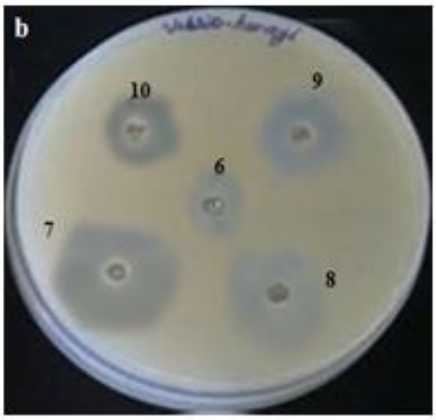
Fig 9. Proposed structure of $M(L_4)_2$.



3.9. Anti-bacterial Activity

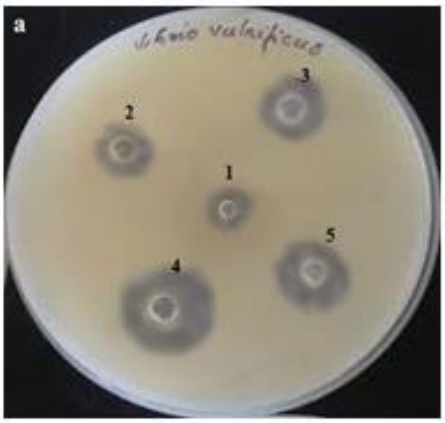
The antibacterial activities[8-11] of ligand and its metal complexes were screened against bacteria *Vibrio harveyi* (plate. 1), *Vibrio vulnificus* (plate. 2), *Escherichia Coli* (plate. 3), *Bacillus pumilus*, (plate. 4), by disc plate method.

Plate1. Antibacterial activity against *Vibrio Harvey.*



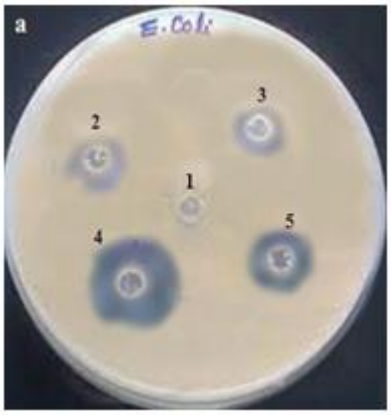
Antibacterial activity tested against *Vibrio harvey* exhibiting different size zones for ligand and its metal complexes. 2,3,4-trimethoxy benzaldehyde semicarbazone (L_4) Zone no: 6, [Ni $(L_4)_2$] Zone no: 10.

Plate 2. Antibacterial activity against *Vibrio vulnificus.*



Antibacterial activity tested against *Vibrio vulnificus*. 2,3,4-trimethoxy benzaldehyde semicarbazone (L_4) Zone no: 1, $[Ni(L_4)_2]$ Zone no: 5.

Plate 3. Antibacterial activity against *Escherichia Coli.*



Antibacterial activity tested against *Escherichia Coli*. 2,3,4,-trimethoxy benzaldehyde semicarbazone (L_4) Zone no: 1, $[Ni(L_4)_2]$ Zone no: 5.

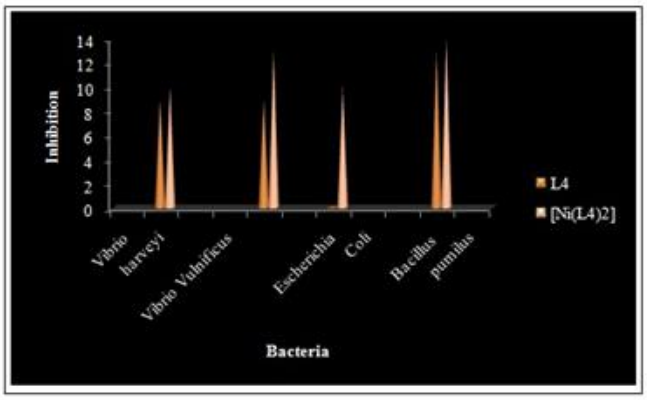
Plate 4. Antibacterial activity against *Bacillus Pumilus*

Antibacterial activity tested against *Bacillus Pumilus*. , 2,3,4-trimethoxy benzaldehyde semicarbazone (L_4) Zone no: 2, $[Ni(L_4)_2]$ Zone no: 4,. The measured activity values of L_4 and its metal complexe a graphical representation of the same is presented in fig: 10.

Table 7. Anti-bacterial activity of L_4 and its metal complexes.

Compounds	Gram-negative			Gram-positive
	Vibrio harveyi	*Vibrio Vulnificus*	*Escherichia Coli*	*Bacillus Pumilus*
L_4	9mm	9mm	Nil	13mm
$[Ni(L_4)_2]$	10mm	13mm	10mm	14mm

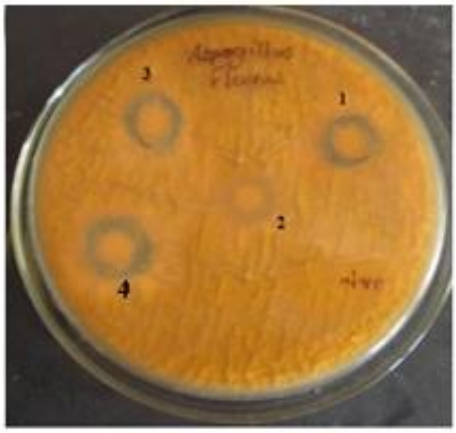
Figure 10. Anti-bacterial activity graph of L_4 and its metal complexes.



3.10.Anti-fungal Activity

The antifungal activity[12] of ligands and their metal complexes were tested against *Aspergillus flavus* (plate. 5) and *Aspergillus niger* (plate. 6).

Plate 5. Antifungal activity against *Aspergillus Flavus.*



Antifungal activity tested against *Aspergillus Flavus*. 2,3,4-trimethoxy benzaldehyde semicarbazone (L_4) Zone no : 1, [Ni(L_4)$_2$] Zone no : 4.

Plate 6. Antifungal activity against *Aspergillus Niger.*

Antifungal activity tested against *Aspergillus Niger* , 2,3,4-trimethoxy benzaldehyde semicarbazone (L_4) Zone no: 1, [Ni(L_4)$_2$] Zone no: 3.

Table 8. Anti-fungal activity of L_4 and its metal complexes.

Compounds	*Aspergillus flavus*	*Aspergillus niger*
L_4	11mm	8mm
[Ni(L_4)$_2$]	12mm	13mm

3.11. Anti-oxidant activity

The antioxidant assay study was carried out using different concentrations of the Schiff base and Ni(II), metal complexe.

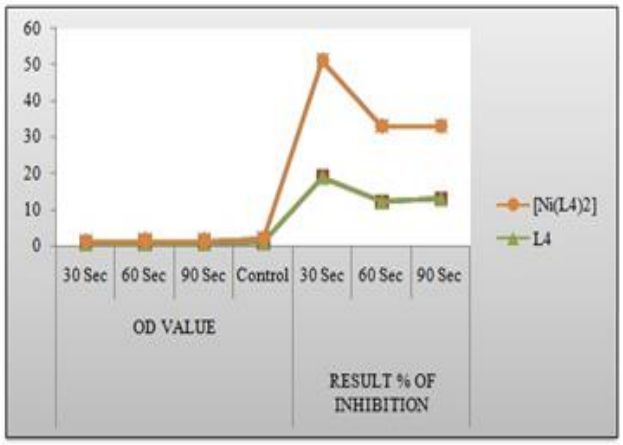
Catalase assay

The antioxidant activity using catalase assay were tested using ligand L_4 and its metal complexe. They were found to have different OD values at different time intervals (30 sec, 60 sec and 90 sec). The antioxidant activities of Schiff base (L_4,) and their Ni(II) metal complexe were assessed in Table 9.

Table 9. Anti-oxidant activity of L_4 and its metal complexes.

Catalase assay							
Sample	OD value				Result % of Inhibition		
	30 Sec	60 Sec	90 Sec	Control	30 Sec	60 Sec	90 Sec
L_4	0.517	0.601	0.598	0.775	19	12.1	13
[Ni(L_4)$_2$]	0.657	0.703	0.727	1.112	32	20.9	20.0

Figure 11. Anti-oxidant activity graph of L_4 and its metal complexe.



Catalase activity of Schiff base metal complexes was found significantly higher than that of free ligands (L_4), indicating that this complex is a much better catalase and antioxidant than the ligand. Antioxidant ability of Schiff base increased significantly after chelation of transition metal ions. The Ni(II) complexes posses higher antioxidant potential than ligand.

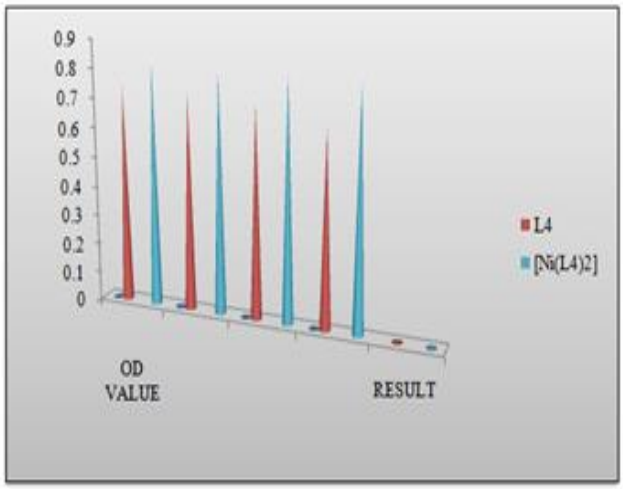
Peroxides assay

In the present work the antioxidant activity using peroxides assay were also tested using the ligands (L_4), and their metal complexe. They were found to have different OD values at different time intervals (30 sec, 60 sec, 90 sec, and 120 sec). The activity of Schiff bases and the metal complexe were presented in table :10.

Table 10. Anti-oxidant activity of L_4 and its metal complexes.

Peroxidase assay					
Sample	OD value				Result Units/ml
	30 Sec	60 Sec	90 Sec	120 Sec	
L_4	0.741	0.731	0.724	0.672	0.001423
[Ni(L_4)$_2$]	0.825	0.822	0.831	0.827	0.001614

Figure 12.Anti oxidant activity graph of L_4 and its metal complexe.



Ni(II) complexes were found to possess moderate to high activities relative to ligand.

Conclusion

The Ni(II) complex was found to exhibit good antibacterial ,antifungal, anti-oxidant activity than 2,3,4-trimethoxybenzaldehyde semicarbazone. Thus, is a good candidate for use in further clinical trials.

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