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Research article

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF SOME NEW THIOSEMICARBAZIDE DERIVATIVES AND THEIR TRANSITION METAL COMPLEXES

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ABSTRACT: Transition metal complexes of 3-Methyl butanalthiosemicarbazone (MBTSC) derived from the condensation of 3-Methylbutaraldehyde with thiosemicarbazide are reported and characterized. Antibacterial activity of the ligand and its complexes were studied against selected bacteria. And their metal complexes of Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) their characterization are done by different analytical techniques, such as elemental analysis NMR ,FT-IR, ES-Mass.

Key Words: Thiosemicarbazide, Metal Complexes, Spectral Characterization.

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INTRODUCTION

Thiosemicarbazones (hydrazine carbothioamides) are a family of compounds having high biological activity. They are very good ligands. The biological activity of these ligands is related to their ability to coordinate to metal centers in enzymes. An interesting feature of pharmaceutically promising thiosemicarbazone derivatives is that, these derivatives possess additional functional group that are not coordinated to their "primary" metal ion, there by suggesting that the biological activity may also depend on the non-coordinating groups(Alomar. et.al. 2009). This class of compounds is in general prepared by condensation of carbonyl group (ketone or aldehyde) with TSC or with N (4) substitution. Based upon the nature of the ketone or aldehyde the resulting thiosemicarbazone may differ. They defy the usual rules of valence at that time and hence called complexes (Chandra et.al. 2007). They play vital role in our lives. Transitions metal complexes with soft or hard donor groups have been used extensively in coordination and organo metallic chemistry (Bal et.al. 2008). In most complexes thiosemicarbazones behave as bidentate ligands because they can bond to metals through sulphur and the hydrazinic nitrogen atoms, although in a few cases they behave as unidentate ligands and bond through only sulphur atom (Chandra et.al. 2008). Thiosemicarbazones derivatives are of special importance because of their versatile biological and pharmacological activities. Thiosemicarbazone derivatives have found application in drug development for the treatment of central nervous system disorders, of bacterial infection, as well as analgesic and antiallergic agent (Chandra et.al. 2005). Thiosemicarbazones are potent intermediates for the synthesis of pharmaceutical and bioactive materials and thus, they are used extensively in the field of medicinal chemistry. Moreover, thiosemicarbazones have found their way into almost every branch of chemistry; commercially they are used as dyes, photographic films, plastic and in textile industry (Chandra et.al. 2009). Over the years, thiosemicarbazone derivatives have demonstrated wide range of biological activity *viz.* antimicrobial (Bhattacharya. et.al. 2012), antitumor, sodium channel blocker (Dakshayani et.al. 2012), anticancer, antitubercular, antiviral (Das et.al. 2008). Keeping mind various biomedical application of these class of compounds, we report the synthesis and characterization of Fe(III), Co(II) ,Ni(II), Cu(II), Zn(II), Cd (II) & Hg(II) complexes of thiosemicarbazones derivative.

Experimental section

All the chemicals were purchased from Sigma-Aldrich and were used as received. Melting point of ligand and metal complexes were taken in open capillary and was in corrected. FT-IR spectra was obtained in KBr pellet in the 4000-400 cm-1 region on a Fourier transform infrared spectrophotometer-Bruker- tesnsor 27 spectrometer (4000-400 cm^{-1}), Mass spectra were recorded on a GCMS-QP2010 Shimandzu & micro mass Q-T of Micro, elemental analysis was carried out on EURO EA Elemental Analyzer, EA-3000, RS-232.

Synthesis of 3-Methylbutanalthiosemicarbazone

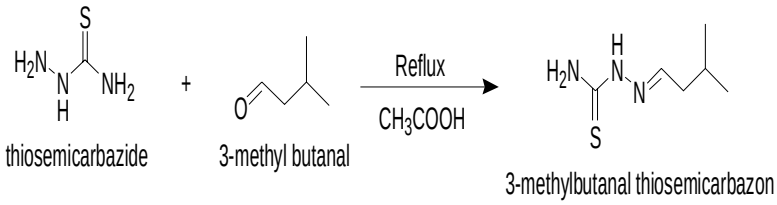
An equimolar amount of 3-Methylbutaraldehyde (0.01 M) and thiosemicarbazide (0.01 M) were dissolved in 20 ml aqueous methanol. The resulting mixture was reflux for 24 hours in the Presence of catalytic amount of glacial acetic acid. The progress of the reaction and purity of the products were monitored by TLC. After completion of the reaction, reaction mixture was poured into crushed ice (Agarwal.et.al. 2006). The separated product was filtered wash with cold water, several times and dried at room temperature. Physical data of ligand is shown in Table 1.

Synthesis of 3-Methylbutanal thiosemicarbazone metal complexes:

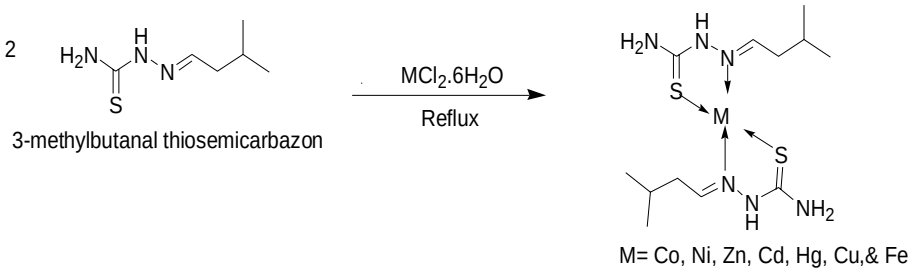
3-Methylbutnalthiosemicabazone (0.02M) was dissolved in methanol & aqueous solution of the appropriate salt $MCl_2.6H_2O$ (0.01M) (where M = Fe, Co, Ni, Cu, Zn, Cd, & Hg) was added to reaction mixture (Ferrari et.al. 2005). The resulting reaction mixture was refluxed for 24 hours in the presence catalytic amount of NH_3 with continues stirring (Kal et.al. 2007). After completion of the reaction the resulting solid was filtered and wash with cold Methanol and dried at room temperature. Physical data of complex is shown in table 1.

Reaction scheme

Step I: Synthesis of 3-Methylbutanalthiosemicarbazone



Step II: Synthesis of Co(II),Ni(II), Zn(II), Cd(II),Cu(II),Hg(II)&Fe(III) metal complexes of thiosemicarbazide derivative



RESULTS AND DISCUSSION

The 3-Methylbutanal thiosemicarbazone (L) and their metal complexes were subjected to elemental analyses. The results of elemental analyses (C, H, N, S and M) with and melting points are presented in table-**(1)**. The results obtained are in good agreement with those calculated for the suggested formula. The structures of the ligand and metal complexes are also confirmed by IR, MASS, which are discussed below.

The IR spectrum of the ligand showed (Fig. 4) a strong absorption band at 1590 cm^{-1} which was assigned to the azomethine group, ν(C=N). The strong band observed at 1170 & 830 cm^{-1} in the spectrum was due to the □(C=S) & □(C=S). The bands observed in ligand at 3400 cm^{-1} and 3100 cm^{-1} were assigned to □(NH_2) and □(N–H) vibrations respectively (Latheef et.al. 2008). This further indicates that the ligand remained in the thione form. In the spectra of all the complexes, the band due to the azomethine moiety (C=N) was shifted to higher frequency, indicating 1631cm^{-1} ,1621 cm^{-1} , 1630 cm^{-1}, 1620 cm^{-1}, 1625 cm^{-1},1623 cm^{-1},1620 cm^{-1} involvement in coordination with metal ion (Latheef et.al. 2008). The ν(C=S) & □(C=S) frequency was lowered in the spectra of the complexes, indicating the involvement of the thioketo sulphur in the coordination (Murthy et.al. 2002). The diagnostic IR spectral bands of the complexes (Fig.2, 3, 4, 5, 6, 7, & 8) are presented in table-**(2)**.

Mass spectral data confirm the structure of the ligand and their Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), & Hg(II) complexes as indicated by the molecular ion peaks corresponding to their molecular weight. The mass spectrum of ligand L gives a peak at 160 m/Z, which is assigned for [L+H] peak. Fe, Co, Ni, Cu, Zn, Cd & Hg, complexes gives molecular ion peak at 374, 377 [M+1], 375[M-1], 382 [M+1], 384, 430 respectively are presented in table-**(4)** (Nair et.al. 2008).

ESR Spectra confirms that $g_{\|}$ value is less than 0.08 for covalent character and is greater than 2.3 for ionic character of the metal – ligand bond in complexes. The trend $g\| > g_{ave} > g\perp > 2.0023$ observed for the complex indicates that the unpaired electron is localised in d_{x2-y2} or dz^2 orbital of the Cu (II) ions for the complex (Parekh et.al. 2006). The observed $K_{\|} < K_{\perp}$ indicates the presence of out of plane π bonding. The α^2 values for MBTSC complex is 0.551, it also indicates that the complexes show covalent character. ESR spectral data indicates an octahedral geometry for MBTSC-Cu, complex (Prasad. et. al. 2008). The spin Hamiltonian, orbital reduction and bonding parameters of MBTSC-Cu complex are shown in table-**(5)**.

Electronic absorption bands of the ligand and its complexes are given in table-(**6**). The magnetic moment values of all complexes are also presented in the table. There are two bands ~43227 and ~33960 cm^{-1} assigned to π→π* and n→π* transition of the ligand moiety. These bands are also presented in the spectra of the complexes with small shift. The shift of n→π* transition shows donation of lone pair of electron to the metal and hence the coordination of azomethine nitrogen (Vashi. et. al 2009).

The anti bacterial activity of the metal complexes studied against three bacterial strains one is a gram positive *pseudomonas* & two are gram negative *Escherichia coli, Klebsiella species.* All the complexes show good bacterial activity compared to ligand (Vashi. et. al 2010). The results are presented in table (7**) &** fig **(1).**

Table 1: The experimental result and physical data of ligand and its complexes

S. No	Compound	Colour	M.P	Elementary Analysis % calculated (found)					M. wt	Conductance Ohm^{-1}cm^{2}mole^{-1}
				C	H	N	**S**	Metal		
1	MBTSC	White	62^{O}C	45.21 (45.02)	8.12 (8.08)	26.42 (25.90)	20.15 (20.20)		159	
2	Co-MBTSC	Brown	202^{O}C	38.20 (39.10)	6.89 (7.90)	22.28 (23.01)	16.98 (16.80)	15.62 (16.01)	376	10
3	Ni-MBTSC	Green	200^{O}C	38.23 (39.05)	6.90 (7.03)	22.29 (23.02)	16.97 (17.03)	15.60 (16.05)	376	14
4	Zn-MBTSC	Pale yellow	198^{O}C	37.05 (38.01)	6.77 (7.90)	21.88 (22.01)	16.67 (17.01)	17.16 (18.10)	383	8
5	Cd-MBTSC	Yellow	204^{O}C	33.45 (34.05)	6.04 (7.06)	19.51 (19.80)	14.86 (15.10)	26.11 (27.10)	430	13
6	Hg-MBTSC	Black	192^{O}C	27.79 (28.06)	5.01 (5.09)	16.21 (17.02)	12.30 (13.00)	38.61 (38.90)	518	12
7	Cu-MBTSC	Brown	204^{O}C	37.74 (38.90)	6.81 (7.06)	22.01 (22.07)	16.77 (16.90)	16.44 (17.01)	318	9
8	Fe-MBTSC	Brick red	200^{O}C	38.52 (39.02)	6.95 (7.00)	20.46 (19.90)	13.11 (13.50)	30.06 (29.78)	373	65

Table 2: IR spectral data (cm^{-1}) of the ligand and their metal complex in KBr pellets

	Frequency in cm^{-1}							
Compound	**νNH_2**	**νN-H**	**ν C-H**	**$\nu C=N_{azo}$**	**ν(N-N)**	**ν (CS)**	**δ (CS)**	**ν(M-S)**
MBTSC	3385	3168	2953	1590	1140	1170	830	
Fe-MBTSC	3410	3120	2980	1631	1020	1156	710	600
Co-MBTSC	3451	3163	2953	1621	1036	1141	750	600
Ni-MBTSC	3410	3152	2955	1630	1020	1141	760	640
Cu-MBTSC	3410	3180	2957	1620	1105	1156	783	650
Zn-MBTSC	3434	3148	2956	1625	1026	1153	815	590
Cd-MBTSC	3424	3171	2958	1623	1037	1152	812	620
Hg-MBTSC	3410	3168	2955	1620	1020	1156	783	650

Table 3: ^{1}H NMR spectral data of ligand MBTSC

Signal No.	Signal Position (ppm)	Relative No of Protons	Multiplicity	Inference
1	10.29	1H	Singlet	-NH
2	7.75	2H	Singlet	$-NH_2$
3	6.97	1H	Triplet	-CH
4	2.05	2H	Quartet	$-CH_2$
5	1.17	1H	Multiplet	-CH
6	0.94	6H	Doublet	$-CH_3$, $-CH_3$,

Table 4: Mass spectra of the ligand and their complexes

	Calculated mass m/Z	Obtained mass m/Z
MBTSC	159	160
Fe- MBTSC	374	374
Co- MBTSC	376	377
Ni- MBTSC	376	375
Cu- MBTSC	381	382
Zn- MBTSC	384	384
Cd- MBTSC	430	430
Hg- MBTSC	518	518

Table 5: Spin Hamiltonian and orbital reduction parameters

S. No	Parameters	MBTSC-Cu
1	$g_{\|\|}$	2.1698
2	g⊥	2.0297
3	g_{ave}	2.0797
4	G	4.754
5	$A^*_{\|\|}$	0.01870
6	A^*⊥	0.00519
7	A^*_{ave}	0.0071
8	d-d	16435
9	$K_{\|\|}$	0.6170
10	K⊥	0.760
11	P^*	0.0152
12	α^2	0.551

Table – 6: Electronic spectral data of the ligand and complexes

Compound	Magnetic moment(B.M)	Electronic Bands (cm^{-1})	Possible Assignments	Proposed Geometry
HL^2 = MBTSC	-	43227 33960	π→π* n→π*	
$[Fe(MBTSC)_2Cl_2]Cl$	5.61	43060 35700 29480 17360	π→π* n→π* LMCT $^6A_{1g}\rightarrow{}^4T_{2g}$	Octahedral
$[Co(MBTSC)_2Cl_2]Cl$	4.94	42300 29400 27400 16670	π→π* n→π* LMCT $^4T_{1g}\rightarrow{}^4T_{2g}$	Octahedral
$[Ni(MBTSC)_2Cl_2]Cl$	3.07	40125 32550 25400 16450	π→π* n→π* LMCT $^3A_{2g}\rightarrow{}^3T_{2g}$	Octahedral
$[Cu(MBTSC)_2Cl_2]Cl$	1.82	40125 32790 25225 17300 14200	π→π* n→π* LMCT $^2B_{1g}\rightarrow{}^2B_{2g}$ $^2B_{1g}\rightarrow{}^2A_{1g}$	Distorted Octahedral
$[Zn(MBTSC)_2Cl_2]Cl$	Diamagnetic	42250 33750 24940	π→π* n→π* LMCT	Octahedral
$[Cd(MBTSC)_2Cl_2]Cl$	Diamagnetic	41350 32350 25725	π→π* n→π* LMCT	Octahedral
$[Hg(MBTSC)_2Cl_2]Cl$	Diamagnetic	42030 32280 25150	π→π* n→π* LMCT	Octahedral

Antibacterial activity

Test organisms and culture condition

A collection of three organisms including Gram-positive and Gram-negative organisms were used for this study of clinical isolates such as *Escherichia coli*, *psedomoas, Klebsiella species* were obtained from Microbiology laboratory of Global Hospital, Hyderabad. All strains were tested for purity by standard microbiological methods. The bacterial stock cultures were maintained on Mueller Hinton Agar (MHA) slants and stored at 4°C.

Determination of antibacterial activity

An agar-well diffusion method was employed for evaluation of antibacterial activity. The bacterial strains were reactivated from stock cultures by transferring into Mueller Hinton Broth (MHB) and incubating at 37°C for 18 h. A final inoculum containing 10^6 colony forming units (1 x 10^6 CFU/ml) was added aseptically to MHA medium and poured into sterile Petri dishes. Different test compounds at a concentration of 0.2mg/50µL were added to wells (8 mm in diameter) punched on agar surface. Plates were incubated overnight at 37°C and diameter of inhibition zone (DIZ) around each well was measured in mm. Experiments were performed in triplicates. Antibiotic such as ciprofloxacin at a concentration of 0.4mg/50µL were used as positive reference to determine sensitivity of microorganisms tested. DMSO was used as a negative control (Yidliz. et. al 2004).

Table 7: Antibacterial activity of ligand & their metal complexes

S.No	Name of Compounds	Diameter of inhibitation Zone (mm)					
		1mg/250 uL			2mg/250 uL		
		Escherichia coli	*Klebsiella pneumoniae*	*Pseudomonas*	*Escherichia coli*	*Klebsiella pneumoniae*	*Pseudomonas*
1	MBTSC	-	-	-	-	-	-
2	Fe-MBTSC	14	20	25	-	-	13
3	Co-MBTSC	-	-	13	13	-	15
4	Ni-MBTSC	15	-	11	10	-	14
5	Cu-MBTSC	10	25	27	15	30	31
6	Zn-MBTSC	10		14	16		12
7	Cd-MBTSC	18		14	17	20	22
8	Hg-MBTSC	13	19	21	16	24	28
9	Ciprofloxacin	46	55	45	47	55	53

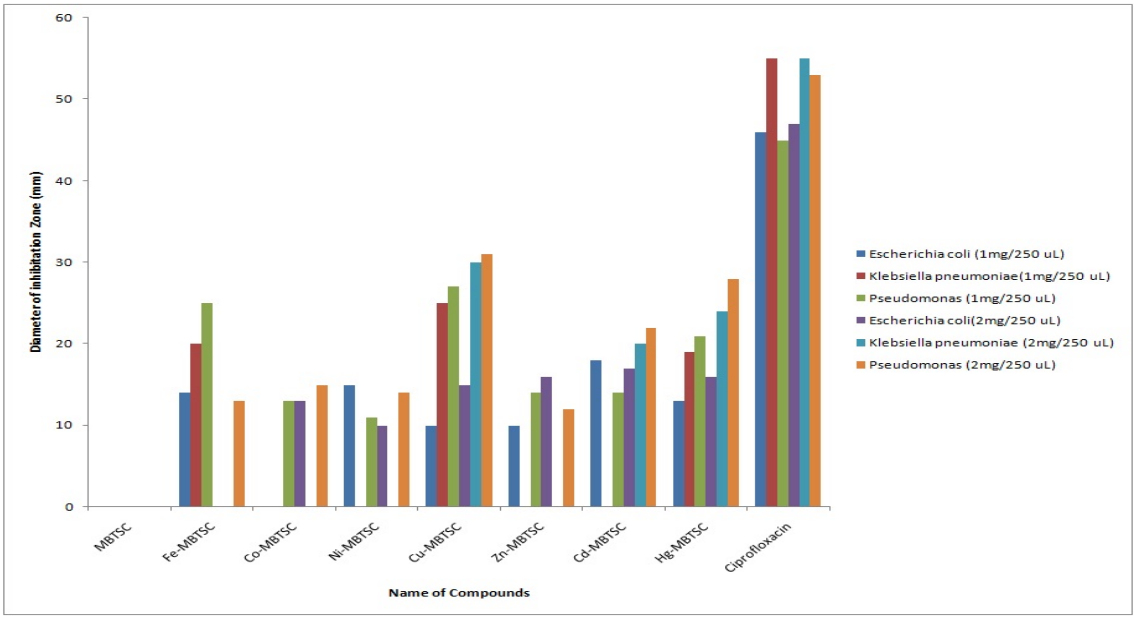


Figure-1: Antibacterial activity of the Schiff base complexes against bacterial organisms

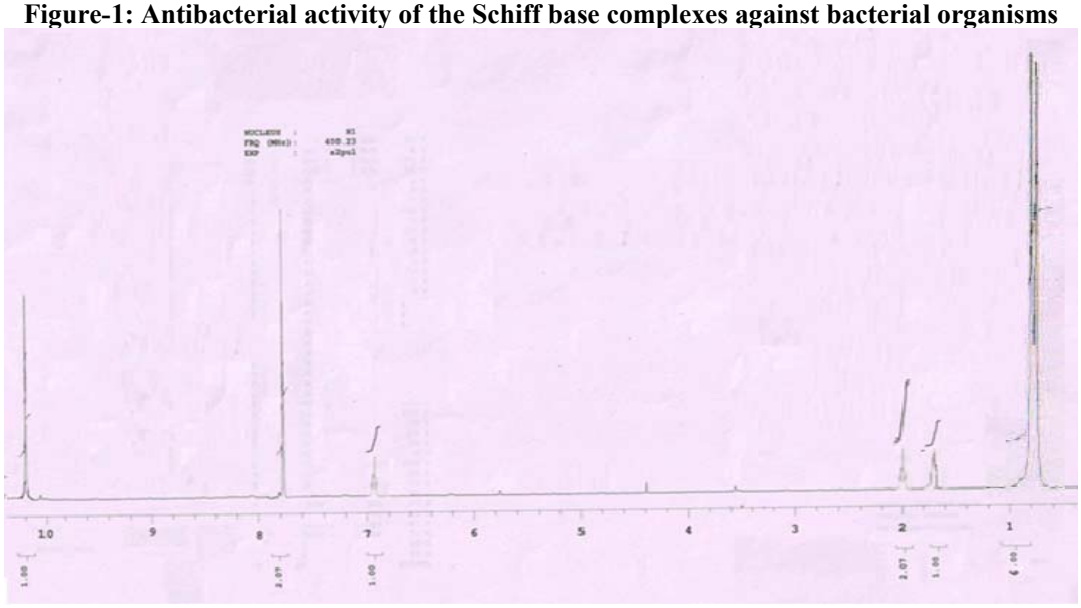


Figure-2: ^{1}H NMR Spectra of MBTSC ligand

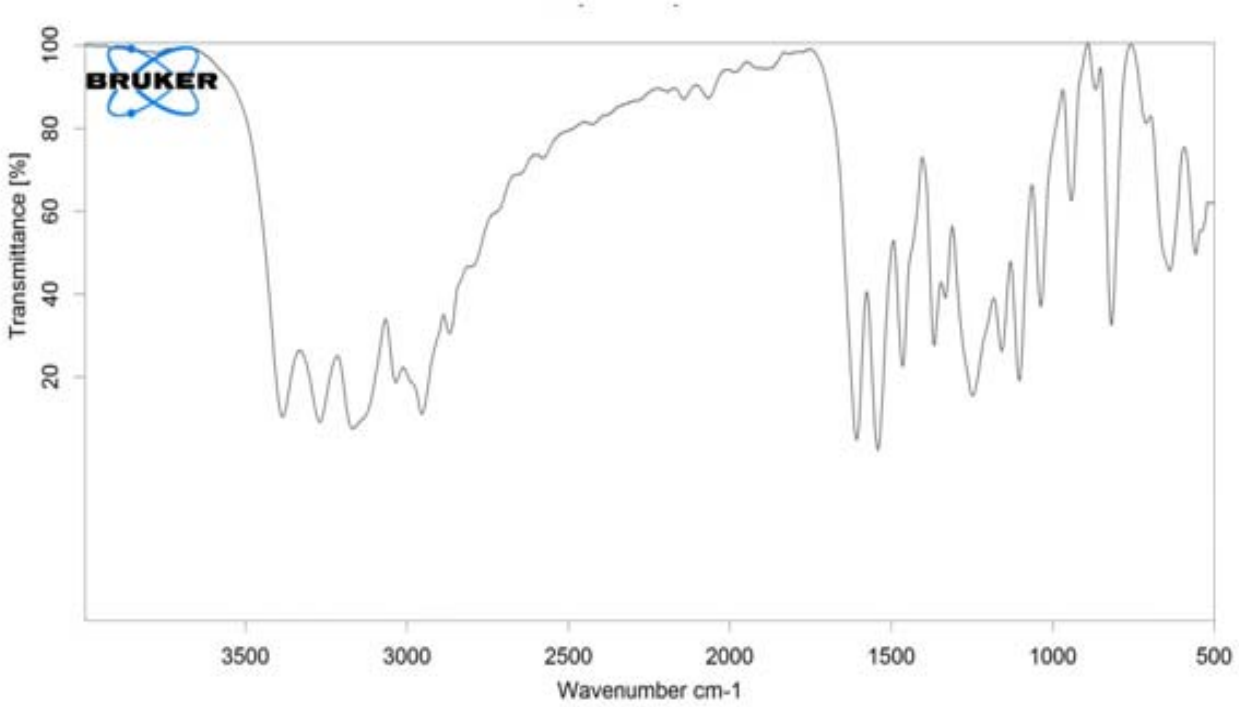


Figure-3: FT-IR Spectra of MBTSC ligand

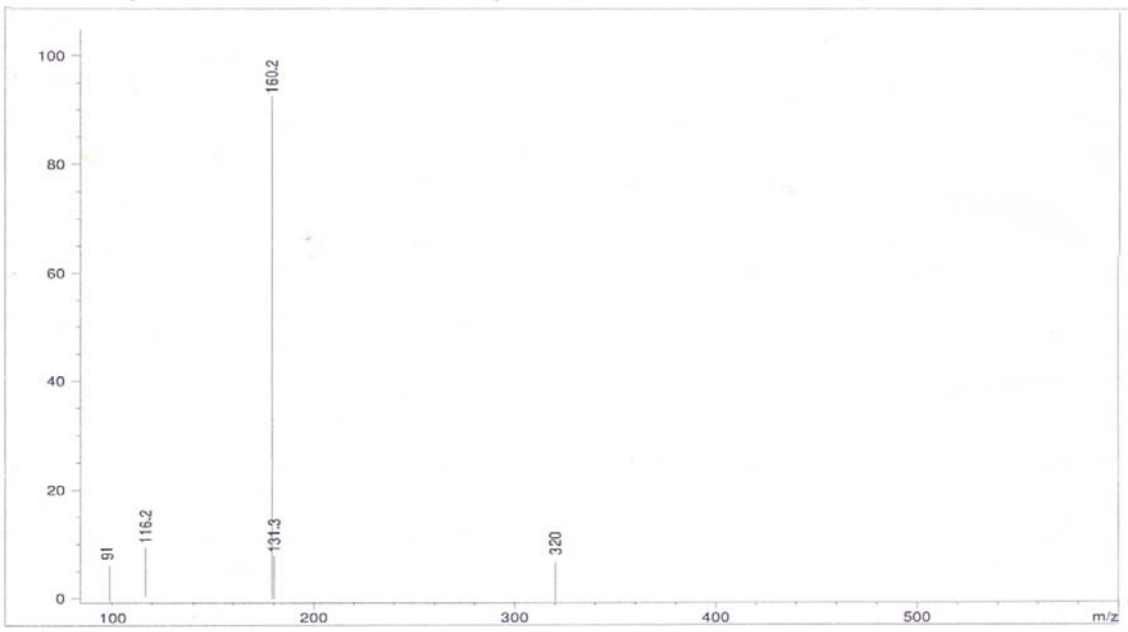


Figure-4: ES-Mass Spectra of MBTSC ligand

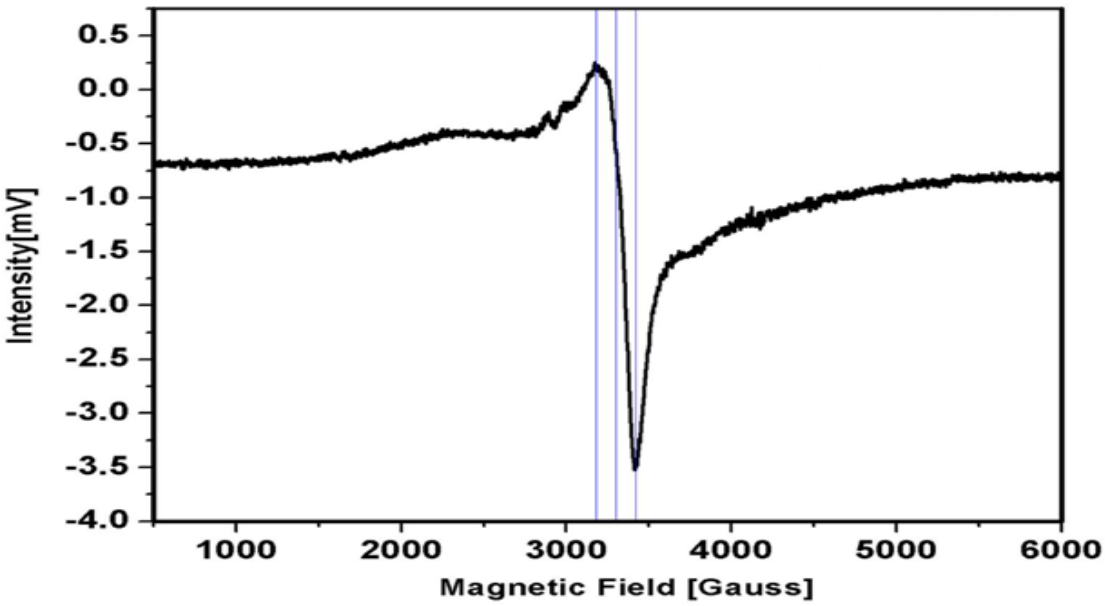


Figure-5: ESR Spectra of MBTSC-Cu complex

CONCLUSION

In this paper we have reported the synthesis of 3-Metylbuanal thiosemicarbazone (MBTSC) ligand derived from thiosemicarbazide with 3-Methylbutanal & metal complexes has been synthesized using the MBTSC ligand. The ligand and complexes were characterized by spectral and analytical data. Based on studies the complexes of Fe, Co, Ni, Cu, Zn, Cd, & Hg, has been found to be octahedral geometry. The anti bacterial studies carried out with the complexes confirm that they are good antibacterial agents.

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