



## Research Article

## SYNTHESIS AND ANTIFUNGAL ACTIVITY OF 6-BROMO-2[(4-PHENYL)-1-YL] METHYL]-3-[8-HYDROXY QUINOLINE -5-YL]-3-QUINAZOLIN -4-ONE LIGAND AND ITS METAL CHELATES

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## ABSTRACT

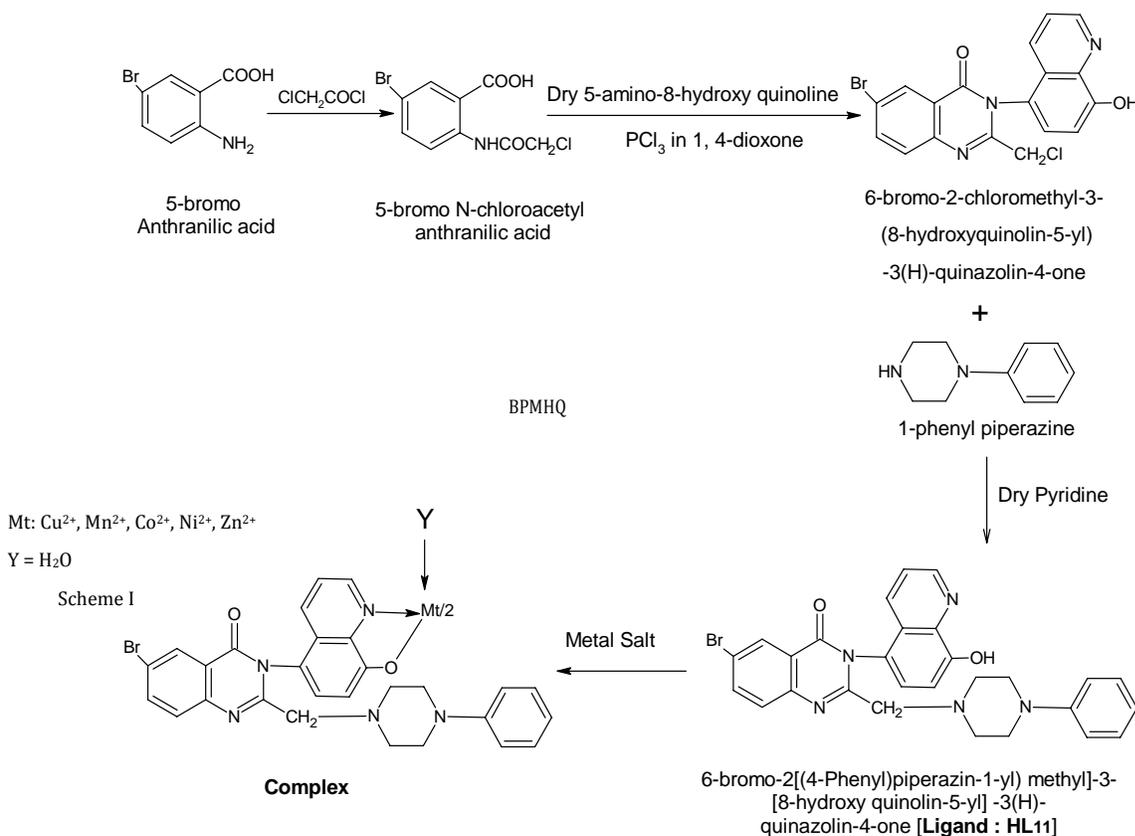
The novel ligand HL<sub>11</sub> was synthesized using anthranilic acid and it was undergo the chelating reaction with Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) to prepare transition metal chelates. These chelates were characterized by physicochemical methods such as elemental analysis, conductometric studies, magnetic susceptibility, FT-IR, NMR and electronic spectral data. The stoichiometry of the complex has been found to be 1: 2 (Metal: ligand). An octahedral geometry around Co(II), Ni(II) and Mn(II), distorted octahedral geometry around Cu(II) and tetra hedral geometry around Zn(II) have been proposed. The antifungal activity of ligand and its metal chelates was conducted against various fungi.

**Key words:** 8-Hydroxy quinoline ligand, Complexes, Electronic, NMR spectral studies, Antifungal activity

## INTRODUCTION

The heterocyclic nitrogen compounds especially quinazolinone derivatives play a vital role in many biological processes and as synthetic drugs<sup>1</sup>. A Quinazolin-4-one derivative possesses biological activities such as antifungal<sup>2-4</sup>. The 8-hydroxyquinoline and quinazolin-4-one molecules

into one molecule have not received any attention in spite of well-defined applications of both the molecules. Hence it was thought to explore the study of quinazolin-4-one 8-hydroxyquinoline merged molecules as ligand HL<sub>11</sub> with their complexes with Cu (II), Ni (II), Co (II), Mn (II) and Zn (II) metal ion. Antifungal activity of the ligand and its metal chelates has also been studied.



Scheme I: General structure of formation of chelates

## EXPERIMENTAL

All the chemicals used were of pure grade (Merck and B.D.H). Double distilled water was used throughout the experiment. The melting point of ligand was determined by open capillary method and were found to be uncorrected.

**Synthesis of BPMHQ ligand (HL<sub>11</sub>):** The 5-bromo anthranilic acid was converted into 5-bromo N-chloroacetyl anthranilic acid by means of chloroacetyl chloride then it refluxed with 5-amino-8-hydroxy quinolin and phosphorous trichloride in dry 1, 4-dioxone under anhydrous condition for 4 hrs. The reaction mixture was allowed to cool and phosphorous trichloride was decomposed by titrating with cold water. Then, 1, 4-dioxone was distilled off to get the product, 6-bromo-2-chloromethyl-3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one. It was filtered and washed with small portion of sodium bicarbonate solution (10 %) after then extensively with cold water. The mixture of 6-bromo-2-chloromethyl-3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one and 1 - phenyl piperazine in dry pyridine was refluxed for 12 hrs. Pyridine was distilled off as much as possible and the residue was poured into little crushed ice with stirring. The product, HL<sub>11</sub> i.e. 6-bromo-2-[(4-Phenyl)-1-yl] methyl-3-[8-hydroxy quinoline -5-yl]-3-quinazolin-4-one ligand was separated out, filtered and washed with water and finally with ethanol. The air dried product was quantitative. Melting point for HL<sub>11</sub> > 230 °C.

**Synthesis of Chelates:** A dried ligand sample HL<sub>11</sub> (0.01 M) was stirred in 85 % (v/v) formic acid and then it was diluted by water until complete dissolution. The resultant solution was designated as reagent solution. This solution was used for preparation of chelates with particular ligand with transition metal ions. The formic acid solution of ligand was added dropwise to a solution of Cu(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O, Ni(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O, Co(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O, MnCl<sub>2</sub>.6H<sub>2</sub>O, Zn(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O (0.005 mole) in 100 ml of water with constant stirring. The resultant pH 4.5 [for Cu(II)], pH 6.0 [for Ni(II)] and Co(II)] and pH 5.6 [for Mn(II) and Zn(II)] were maintained by addition of sodium acetate. A dark colored solid precipitated out. It was allowed to settle and digested on water bath at 70 °C for about 2 h. The solid mass was filtered, washed with 1:1 mixture of water-ethanol and finally with acetone then dried. The percentage yield of chelates was in the range of 59-75 %. All the chelates were powdered well and dried at 70 °C over a period of 24 h.

The C, H and N contents of metal chelates were determined on elemental analyzer Thermofinigan 1101 Flash EA. The metal contents were estimated using standard methods<sup>5</sup>. The molar conductance of the complexes in DMF (10<sup>-3</sup> M) solutions were measured at room temperature using Systronics model 305 direct reading conductivity bridge. <sup>1</sup>H NMR spectra of ligand was recorded on Bruner NMR spectrophotometer. PMR chemical shifts were recorded in δ - value using TMS as an internal standard in CDCl<sub>3</sub>/D<sub>6</sub>- DMSO. The IR spectra (KBr) were recorded in the range 4000-600 cm<sup>-1</sup> on a Nicolet -760 Spectrophotometer. Electronic spectra of the metal chelates were recorded on a Beckman -DK-2A spectrophotometer using MgO as reference. Magnetic susceptibility 'χ<sub>m</sub>' was measured by Gouy's

method<sup>6</sup> at room temperature (300 K) using Hg [Co(CNS)<sub>4</sub>] as calibrant<sup>7</sup>, and the effective magnetic moment from relation<sup>8</sup>, μ<sub>eff</sub> = 2.84 √ χ<sub>m</sub> × T, where T is the absolute temperature. Diamagnetic corrections were made by using Pascal's constants.

The ligand and its metal chelates were screen at 1000 ppm concentration in vitro for their antifungal activity against five fungi viz. *Botrydepladia thibromine*, *Nigrospora sp.*, *Rhizopus nigricans*, *Aspergillus fumigatus* and *Candida albicans*. The antifungal activity of the compounds was measured by plate method<sup>9</sup>. Five days old cultures were suspended in potato dextrose agar (PDA) medium and autoclaved at 1200 °C for 15 minutes at 15 atmospheric pressure. The percentage inhibition of fungi was calculated after 5 days using the formula given below:

$$\text{Percentage of inhibition} = 100 (X-Y) / X$$

Where X= area of colony in control plate (without sample) and Y = area of colony in test plate.

## RESULTS AND DISCUSSION

The complexes are microcrystalline colored powders having melting points higher than the ligand. They are stable in air at room temperature. All compounds gave satisfactory elemental analysis, suggesting 1:2 (metal: ligand) stoichiometry. Elemental and molar conductance data were shown in Table-1. The result indicates that they are less ionic in DMF. The molar conductance values found to be 21.68, 8.80, 8.12, 7.96 and 7.68 ohm<sup>-1</sup>cm<sup>2</sup>mol<sup>-1</sup> for Co (II), Ni (II), Zn (II), Cu (II) and Mn (II) respectively. So, the electrical conductivity of these chelates was found in the decreasing order: Co > Ni > Zn > Cu > Mn. The very low values of chelates indicates that they are non-electrolytic<sup>10</sup> and monomeric in nature. The low conductance values may be attributed to the large cations<sup>11</sup>.

**Infrared spectra:** FT-IR spectrum of ligand HL<sub>11</sub> show a broad band extended from 3400 to 2600 cm<sup>-1</sup> which might be responsible to phenolic group bonded to N atom of 8-hydroxy quinoline moiety<sup>12</sup>. The inflexions at 2923, 2852 and 1470 cm<sup>-1</sup> are due to aromatic CH and methylene group of bridge and piperazine ring<sup>13</sup>. The strong band at 1710 cm<sup>-1</sup> was attributed to C=O of quinazolin-4-one moiety. Several bands appeared between 1500-1600 cm<sup>-1</sup> region may arise from aromatic breathing. The IR band at ~ 1580 cm<sup>-1</sup> (C=N of 8-quinolinol system) of HL<sub>11</sub> ligand shifted to higher frequency side ~1600 in the spectra of the metal chelates indicating involvement of nitrogen in the chelate formation<sup>12,16</sup>. Most of bands appeared in the spectra of corresponding ligand were observed at their metal chelates. Only a new band at 1095 cm<sup>-1</sup> had appeared in the spectra of metal chelates. This may be assigned to ν c-o of C-O-M bond formation. All the complexes show additional bands at 840-830 cm<sup>-1</sup> indicating the presence of coordinated water<sup>15</sup>(Figure-1).

**NMR spectra:** <sup>1</sup>H NMR spectra of ligand was depicted in figure -2, which shows results in δ ppm as follows: 3.47 (CH<sub>2</sub> bridge) 3.44 to 3.52 (triplet -CH<sub>2</sub> of piperazine), 3.47 (-CH<sub>2</sub> bridge), 4.82 (singlet of phenolic -OH), and 7.1 to 8.84 (multiplet, quinazolin).

**Table 1: Analytical and physical data of ligand and its metal chelates**

Ligand / Mol. Formula	M. W. (g/mole)	Yield (%)	Elemental Analysis (%)					Observed μ <sub>eff</sub> (B.M) (Expected)	Λ <sub>M</sub> (Ohm <sup>-1</sup> cm <sup>2</sup> mol <sup>-1</sup> )
			Found	Calcd.)	C	H	N		
HL <sub>11</sub>	542.00	59	62.30	4.40	13.01	14.70	-	-	-
C <sub>28</sub> H <sub>24</sub> N <sub>5</sub> O <sub>2</sub> Br			(62.45)	(4.46)	(12.90)	(14.86)			
(HL <sub>11</sub> ) <sub>2</sub> Cu <sup>2+</sup>	1181.54	69	56.80	4.20	11.80	13.30	5.30	1.88	7.96
C <sub>56</sub> H <sub>50</sub> N <sub>10</sub> O <sub>6</sub> Cu <sup>2+</sup> Br <sub>2</sub>			(56.87)	(4.23)	(11.84)	(13.37)	(5.37)	(1.7-2.2)	
(HL <sub>11</sub> ) <sub>2</sub> Ni <sup>2+</sup>	1176.69	69	56.90	4.10	11.70	13.40	4.80	3.32	8.80
C <sub>56</sub> H <sub>50</sub> N <sub>10</sub> O <sub>6</sub> Ni <sup>2+</sup> Br <sub>2</sub>			(57.10)	(4.24)	(11.89)	(13.42)	(4.98)	(2.9-3.4)	
(HL <sub>11</sub> ) <sub>2</sub> Co <sup>2+</sup>	1176.90	72	57.00	4.10	11.80	13.30	4.90	3.94	21.68
C <sub>56</sub> H <sub>50</sub> N <sub>10</sub> O <sub>6</sub> Co <sup>2+</sup> Br <sub>2</sub>			(57.09)	(4.24)	(11.89)	(13.42)	(5.00)	(4.4-5.2)	
(HL <sub>11</sub> ) <sub>2</sub> Mn <sup>2+</sup>	1172.90	59	57.20	4.20	11.90	13.40	4.60	5.55	7.68
C <sub>56</sub> H <sub>50</sub> N <sub>10</sub> O <sub>6</sub> Mn <sup>2+</sup> Br <sub>2</sub>			(57.29)	(4.26)	(11.93)	(13.47)	(4.63)	(5.2-6.0)	
(HL <sub>11</sub> ) <sub>2</sub> Zn <sup>2+</sup>	1183.39	75	56.70	4.20	11.80	13.30	5.50	-	8.12
C <sub>56</sub> H <sub>50</sub> N <sub>10</sub> O <sub>6</sub> Zn <sup>2+</sup> Br <sub>2</sub>			(56.78)	(4.22)	(11.83)	(13.35)	(5.52)		

Table 2: Antifungal activity of ligand HL<sub>11</sub> and its metal chelates

Samples	Zone of inhibition at 1000 pm (%)				
	<i>Candida Albicans</i>	<i>Botrydepladia Thibromine</i>	<i>Nigrospora Sp.</i>	<i>Aspergillus Fumigatus</i>	<i>Rhizopur Nigrlicums</i>
HL <sub>11</sub>	59	69	68	87	70
(HL <sub>11</sub> ) <sub>2</sub> Cu <sup>2+</sup>	80	82	80	88	79
(HL <sub>11</sub> ) <sub>2</sub> Ni <sup>2+</sup>	59	52	56	69	54
(HL <sub>11</sub> ) <sub>2</sub> Co <sup>2+</sup>	68	62	63	66	67
(HL <sub>11</sub> ) <sub>2</sub> Mn <sup>2+</sup>	70	75	71	72	73
(HL <sub>11</sub> ) <sub>2</sub> Zn <sup>2+</sup>	77	69	68	65	63

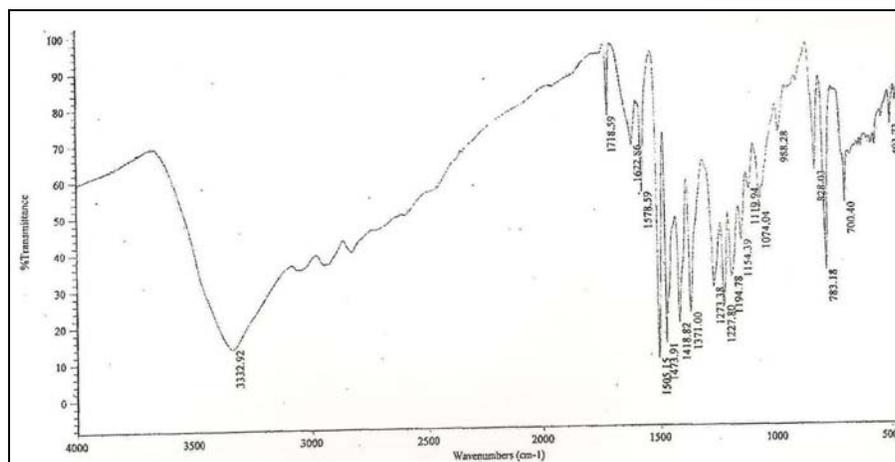


Fig. 1: IR spectra of ligand HL<sub>11</sub>

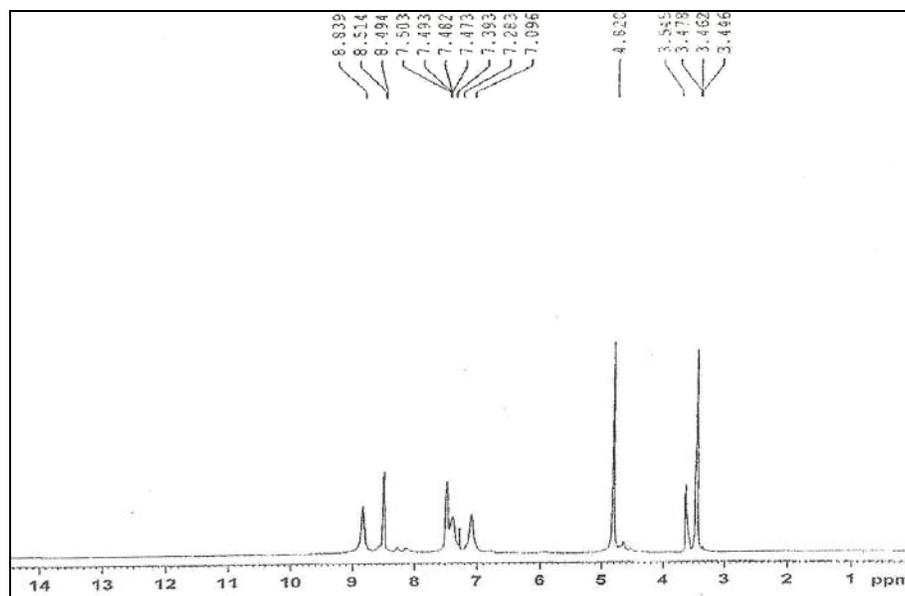


Fig. 2: <sup>1</sup>H-NMR spectra of ligand HL<sub>11</sub>

**Magnetic moment and Electronic spectra:** At room temperature the magnetic moment ' $\mu_{\text{eff}}$ ' values for the Co (II) complex is 3.94 B.M (Table-1) suggest high spin octahedral geometry, which is further supported by the electronic spectral data. The electronic spectra of the Co (II) complex display three absorption bands in the range 8542, 19586 and 22489  $\text{cm}^{-1}$ , assigned to the transitions  ${}^4T_{1g}(\text{F}) \rightarrow {}^4T_{2g}(\text{F})$  ( $\nu_1$ ),  ${}^4T_{1g}(\text{F}) \rightarrow {}^4A_{2g}(\text{F})$  ( $\nu_2$ ) and  ${}^4T_{1g}(\text{F}) \rightarrow {}^4T_{1g}(\text{P})$  ( $\nu_3$ ) respectively<sup>16</sup>. The values of transition ratio  $\nu_2 / \nu_1$  was 2.29

providing further evidences for octahedral geometry for the Co (II) complexes.

In the Ni (II) complex,  $\mu_{\text{eff}}$  value at room temperature is observed to be 3.32 B.M. as expected for six coordinated spin free Ni (II) species. The reflectance spectra of the Ni (II) complex, exhibit two strong bands at 14896 and 22800  $\text{cm}^{-1}$ , assignable to  ${}^3A_{2g}(\text{F}) \rightarrow {}^3T_{1g}(\text{F})$  and  ${}^3A_{2g}(\text{F}) \rightarrow {}^3T_{1g}(\text{P})$  respectively. The  $\nu_2/\nu_1$  ratio for the chelate is 1.53 occurs in the usual range (1.6 -1.82) for octahedral Ni (II)

chelates<sup>17</sup>. The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier<sup>18</sup>.

The Cu(II) complex exhibit normal magnetic moments (1.88 B.M.) indicating the distorted octahedral geometry, which is in agreement with data reported by several research workers<sup>19</sup>. These complex show broad asymmetric bands in the region at 13999 and 25896 cm<sup>-1</sup> assignable to <sup>2</sup>B<sub>1g</sub> ----> <sup>2</sup>A<sub>1g</sub> and charge transfer transition respectively<sup>20</sup>. These results reveal the distorted octahedral geometry for these complexes. The former band may be due to <sup>2</sup>E<sub>g</sub> ---> <sup>2</sup>T<sub>2g</sub> accounted due to Jahn Teller effect suggesting thereby a distorted octahedral geometry for these complexes<sup>21</sup>. The value of transition ratio  $\nu_2/\nu_1$  was 1.85.

Zn(II) complexes are diamagnetic as expected for d<sup>10</sup> systems and may have tetrahedral geometry<sup>23</sup>.

The electronic spectra of the Mn(II) exhibited three spin allowed bands in the region 16458, 18965 and 25489 cm<sup>-1</sup> assigned to the transitions <sup>6</sup>A<sub>1g</sub> ----> <sup>4</sup>T<sub>1g</sub> (<sup>4</sup>G), <sup>6</sup>A<sub>1g</sub>----> <sup>4</sup>T<sub>2g</sub> (<sup>4</sup>G) and <sup>6</sup>A<sub>1g</sub> ----> <sup>4</sup>E<sub>g</sub>, <sup>4</sup>T<sub>1g</sub> (<sup>4</sup>G) respectively, indicating octahedral geometry <sup>29</sup>. The observed magnetic moment ( 5.55 B.M.) of the complexes indicates high spin octahedral environment<sup>24</sup>.

**Antifungal activity:** The ligand and chelates were used for their antimicrobial studies by means of fungi, such as *Candida Albicans*, *Botrydepladia Thibromine*, *Nigrospora Sp*, *Aspergillus Fumigatus* and *Rhizopur Nigrificums*. Antifungal activity of ligand and its metal chelates shown in Table-2 inhibition of fungal in following decreasing order:

Cu (II) > Mn (II) > Zn (II) > Co (II) > Ni (II).

The substitutions of phenyl rings by chlorine have much more effect on the fungicidal activity. The results suggest that variation in structure on coordination affects the growth of micro organisms and may result in to inhibitory or reduction in toxicology of metal ions towards some organisms<sup>25</sup>.

## CONCLUSION

The ligand molecule acts as a hexadentate ligand in all the studied cases of complex. Bonding either among N (4) depending upon the nature of the metal ions. Octahedral structures for Ni (II), Co(II) and Mn(II) complexes, tetrahedral polymeric structure for Zn(II), and distorted octahedral for Cu(II) complex have been tentatively proposed. Present work will contribute in the field of new antifungal for some plant pathogenic organisms.

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## REFERENCES

1. Patel N B & Chaudhari R C, *J Indian Chem Soc*, 83 (2006) 838.
2. Vashi R T, Patel S B & Kadiya H K, *Der Pharma Chemica*, 2(1), (2010) 109-116.
3. Vashi R T & Patel S B, *E-J Chem*, 6 (S1) (2009) S445-S451.
4. Vashi R T & Shelat C D, *Asian J Chem.*, 22(3) (2010) 1745-1750.
5. Vogel A I, *A Text book of Quantitative Inorganic Analysis*, 3<sup>rd</sup> Ed, ELBS, London 1978.
6. Lewis J & Wilkins R G, *Modern Coordination Chemistry*, Newscience, New York, 1964.
7. Figgis B N & Lewis J, *The Magneto Chemistry of Chelates in Modern Coordination Chemistry*, Interscience, New York, 1960.
8. Williams J O, *Adv Phys Org Chem*, 16 (1979) 159.
9. Barry A L, *Antibiotics in Laboratory Medicine*, Williams & Wilkins, Baltimore, 3<sup>rd</sup> Ed 1996.
10. Geary W J, *Coord Chem Rev*, 81 (1971).
11. Upadhyay R K, *J Indian Chem Soc*, 74 (1977) 535-537.
12. Bellamy L J, *Infrared spectra of complexes molecules*, Chapman & Hall, London 1957.
13. Silvestein R M, *Spectrometric identification of organic compounds*, 5<sup>th</sup> Ed, John Wiley, 123, 1991,
14. Nakamoto K, *Infrared spectra of Inorganic & Coordination Compounds*, Wiley- Interscience, New York 1975.
15. Nakamoto K, *Infrared & Raman Spectroscopy of Inorganic & coordination Compounds*, 3<sup>rd</sup> Ed, Wiley, Inter Science, New York 1978.
16. Lever A B P, *Inorganic Electronic Spectroscopy*, Elsevier, New York, 1968.
17. Syamal A & Maurya M R, *Synth React Inorg Metal-Org Chem*, 16 (1986) 39.
18. Singh D P, Shishodia N, Yadav B P & Rana V B, *Polyhedron*, 16 (1997) 2229.
19. Reddy S N & Agarwal B V, *Syn React Inorg Chem*, 17 (1987) 10.
20. Chaudhary G L, Prasad S R & Rahman A, *J Indian Chem Soc*, 4 (1997) 683-685.
21. Satapathy K C, Dash D C, Pradhan G C & Naik A, *J Indian Chem Soc*, 66 (1989) 292
22. Yidliz M, Dulger B, Yancu S Y K & Yanpici B M, *J Indian Chem Soc*, 81 (2004) 7.
23. Aswar A S & Bhava N S, *J Indian Chem Soc*, 4 (1997) 75.
24. Sahu B K & Mahapatra B K, *J Indian Chem Soc*, 56 (1979) 825.
25. Patel M M & Patel H R, *J Indian Chem Soc*, 73 (1996) 313- 317.