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Synthesis and Characterization of Complexes of Glipizide with Zirconium and Cobalt

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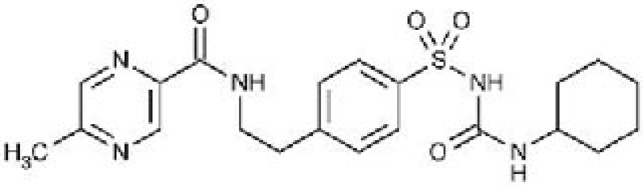
ABSTRACT

Glipizide1-[[p-[2-(3-ethyl4methyl2oxo3pyrroline1carboxamido)ethyl]phenyl]sulphonyl]-3-(trans-4-methylcyclohexayl)urea the recently used hypoglycaemic agent is active in NIDDM. Metal complexes of Glipizide have been synthesized by reaction with different metals such asZirconium and Cobalt in the form of their nitrate and chloride salts repectively. Thereafter these were characterized by their physical and analytical data, IR, NMR, electronic spectra, Mass spectrometry and X-Ray diffraction analysis.

Key words: Glipizide, Crystal , metal complex, IR, NMR, electronic spectra.

INTRODUCTION

Glipizide 1-[[p-[2-(3-ethyl4methyl2oxo3 pyrroline 1carboxamido)ethyl]phenyl]sulphonyl]-3-(trans-4-methylcyclohexayl)urea is a sulphonyl urea derivative. It is a white crystalline powder practically tasteless, insoluble in water, sparingly soluble in ethanol and insoluble in solvent ether. It dissolves in dilute solutions of alkali hydroxides as well as in DMF and DMSO.



Scheme 1: Structure of Glipizide

Glipizide has been in extensive use to treat NIDDM and acts by increasing the release of endogenous insulin as well as its peripheral effectiveness; but it has been associated with severe and sometimes fatal hypoglycaemia and gastric disturbances like nausea, vomiting, heartburn, anorexia and increased appetite after oral therapy in normal doses[1,2].

Glipizide is bisubstituted urea derivative which can exist in keto and enolic form when dissolved in an organic solvent and react with various metal ions to form intensely colored metal complexes that provide the basis for their use as a sensitive reagent. Many transition and inner transition metal complexes have been synthesized for analytical and commercial applications, many of medicinal use[3-5].

The synthesis and characterization of new Glipizide metal complexes is of great importance for understanding the drug–metal ion interaction and for their potential pharmacological use.The synthesis and characterization of the glipizide metal complexes is reported in this paper. Different spectroscopic techniques such as infrared spectroscopy, H^1-NMR, C, H, N elemental analysis, electronic spectra, mass spectrometry and X-Ray diffraction techniques have been used for their characterization.

Ligand-metal ratio.

Mono-Variation method

T he ligand-metal ratio of complex formation was determined by conductivity measurements. Conductivity water was obtained by distilling laboratory de-ionized water over potassium permanganate. Pure Glipizide m.p. 206°C, 0.005 M, was diluted to 100 ml as required and titrated conductometrically against metals at 30±1°C. Results were plotted in the form of a graph which indicate ligand metal ratio as 2:1 (L_2M).

Job's method of continuous variation as modified by Turner and Anderson

0.002M and 0.005 M solutions of ligand Glipizide and metal salt were prepared in DMF and alcohol respectively. The solution of metal salt and reagent were mixed in varying proportions and pH of the solution was adjusted to 6.5, the precipitated complex was filtered and dried. The absorbance was measured at 630 nm. The absorbance was recorded in table 1-4 and jobs plot is given as fig. 1a, 1b- 4a,4b. It is evident from the graph that absorbance increases up to molar composition of metal to the ligand and after that it decreases indicating 1:2 stoichiometry of the complex[6,7].

Synthesis of metal complexes

Metal complexes were synthesized by adding metal salt solution in appropriate solvent to the solution of the ligand. The mixture was refluxed for 3-4 hours. Then the precipitate of metal complexes was obtained. It was filtered, washed and dried in vacuum desiccators. All selected metals form 1:2 complexes with glipizide, was confirmed by Jobs method of continuous variation[8] as modified by Turner and Anderson[9].

RESULTS AND DISCUSSION

The elemental analysis of the isolated complexes was carried out using Elementar Vario EL III analyzer at STIC Kerala, India.The IR spectrum of the ligand as well as of the complex was recorded on Perkin Elmer Spectrometer at CDRI Lucknow and ^{1}H-NMR spectra of the ligand and isolated complex was recorded on a Bruker DRX-300 Spectrometer at IISER Bhopal and $CdCl_3$ was used as a solvent and X-Ray diffraction analysis from Punjab University, Chandigarh.From stoichiometry and analytical data, the composition of the complex comes out to be $(C_{21}H_{25}N_5O_4S)_2$metal , which favours 2:1 (L_2M) ratio. The tentative structure (I) has been assigned to complex on the basis of analytical data and IR, NMR and X-ray.

Infrared spectral studies of the complex

The IR Spectrum of pure drug Glipizide[10-12] and the complexes of Zr, Cr, Mo and Co complexes of Glipizide were recorded in the range 4000cm^{-1}-450cm^{-1}. The IR data of the spectra of ligand Glipizide and its complexes are listed in table 7 The IR spectra of the complexes are compared with those of the free ligand Glipizide in order to determine the co-ordination sites that may be involved in chelation. The tautomeric equilibrium depends on the extent of conjugation, nature and position of the substituents, polarity of the solvent etc.

H^1-NMR Studies

We have observed imides (NH) proton around (d8.35) in the spectrum of the ligand that has disappeared in the spectra of the complexes molecule due to formation of M-O bond. This also confirms the de-protonation of imide NH group through enolisation.

Table 1: Glipizide with cobalt chloride

Glipizide-0.002M and 0.005M
Solvent: Ethyl alcohol
Wavelength: 630 nm

Cobalt chloride-0.002M.0.005M
Temperature: 30±1^{0}C
pH: 5.9

S.	Metal:	Absorbance		Corrected Absorbance	
No.	Ligand	.002M	.005M	.002M	.005M
1	0:12	0.006	0.014	0.00	0.00
2	1:11	0.048	0.075	0.042	0.061
3	2:10	0.085	0.114	0.079	0.1
4	3:9	0.109	0.167	0.103	0.153
5	4:8	0.152	0.207	0.146	0.193
6	5:7	0.136	0.186	0.13	0.172
7	6:6	0.109	0.166	0.103	0.152
8	7:5	0.082	0.136	0.076	0.122
9	8:4	0.068	0.107	0.062	0.093
10	9:3	0.047	0.085	0.041	0.071
11	10:2	0.033	0.058	0.027	0.044
12	11:1	0.018	0.033	0.012	0.019
13	12:0	0.011	0.025	0.00	0.00

Table 2: Glipizide with Xirconium nitrate

Glipizide-0.002M and 0.005M
Solvent: Ethyl alcohol
Wavelength: 630 nm

Cobalt chloride-0.002M.0.005M
Temperature: 30±1^{0}C
pH: 5.9

S.	Metal:	Absorbance		Corrected Absorbance	
No.	Ligand	.002M	.005M	.002M	.005M
1	0:12	0.019	0.027	0.00	0.00
2	1:11	0.042	0.079	0.03	0.055
3	2:10	0.081	0.092	0.069	0.068
4	3:9	0.093	0.122	0.071	0.098
5	4:8	0.114	0.171	0.102	0.147
6	5:7	0.106	0.151	0.094	0.127
7	6:6	0.083	0.146	0.071	0.122
8	7:5	0.066	0.127	0.054	0.103
9	8:4	0.048	0.093	0.036	0.069
10	9:3	0.037	0.069	0.025	0.045
11	10:2	0.025	0.041	0.013	0.017
12	11:1	0.018	0.036	0.006	0.012
13	12:0	0.014	0.025	0.002	0.001

UV-Visible spectroscopic studies

The electronic spectrum of the Co(II) complex with the formula (glipizide)2Co.2H2O gives three bands at 15360,16,980 and 23,250cm^{-1}. The bands observed are assigned to the transitions $^4T_1g(F) \rightarrow {}^4T_2g(F)$ and $^4T_1g(F) \rightarrow {}^4A_2$ g(F)f and $^4T_1g(F) \rightarrow f^4T_2g(P)$ respectively, suggesting the presence of Co(II) complex in octahedral geometry[13,14].

Mass spectral studies

Mass spectrophotometric studies gave useful information regarding the accurate determination of molecular weight and which provided information about the structure ofcompounds by examination of the fragmentation pattern[16,17]. Now a days, chemist haveen thusiastically embarrassed mass spectroscopy to identify and characterize molecule Mass spectrum of the compound is a plot which represents the intensities of the signals at various m/z value[18-20]. It is highly characteristic of the compound ,no two compounds can have similar mass spectra. It

Table 5:Physico-chemical and analytical data of Glipizide complexes

S.No.	Metal complex	Metal ligand ratio	colour	% yield	m.p.
1.	$(C_{21}H_{25}N_5O_4S)_2Zr$	1:2	white	52.14	234
2.	$(C_{21}H_{25}N_5O_4S)_2Co.2H_2O$	1:2	green	54.16	208

Table 6: Analytical data of Glipizide complexes

S. No.	% C	%H	%N	%S	Stability constant Log K lit/ mol	Free Energy(-ΔF)
1	45.14(48.7)	3.94(6.06)	10.02(9.23)	9.18(11.01)	10.52	-14.586
2	51.06(49.6)	4.49(6.01)	10.02(9.45)	7.21(9.56)	10.87	-15.071

*Values given outside the ( ) are observed values and those in the ( ) are required values

Table 7: IR Absorption bands of Glipizide Metal Complexes

Complexes	Main IR Absorption in cm^{-1}
Glipizide	538.26w 606.61vw 671.96w 770.48vs 837.84w 902.93w 1032.55s 1085.83w 1156.99s 1217.85s 1330.3s 1370.39m 1442.2s 1529.09vs 1646.48vs 1686.79vs 2855.77s 2939.57s 3023.85s 3247.81vs 3322.01vs
Glipizide-Zr Complex	668.19m 771.39vs 1094.07w 1217.75s 1387.93w 1410.22w 1437.7w 1670.37s 2143.48vw 3016.51m 3444.46s
Glipizide-Co Complex	459.63vw 672.66w 769.70vs 927.87vw 1043.37vw 1217.73m 2401.99vw 3021.64w 3445.19m

Table 8: Estimation of metals by AA spectroscopy

Compound	Metal calculated	Metal found
Glipizide – Zirconium complex	12.54	12.12±0.001
Glipizide – Cobalt complex	9.67	9.37±0.001

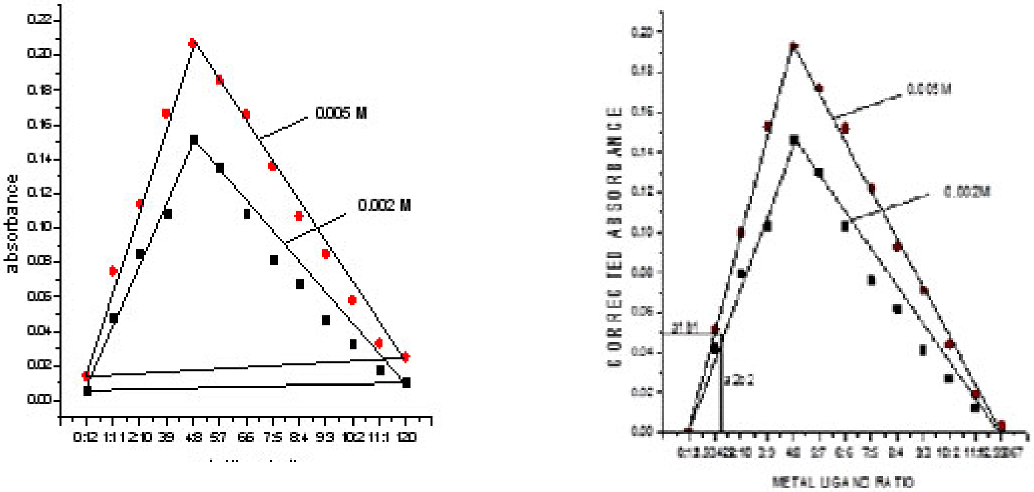


Fig: 1 (a-b)

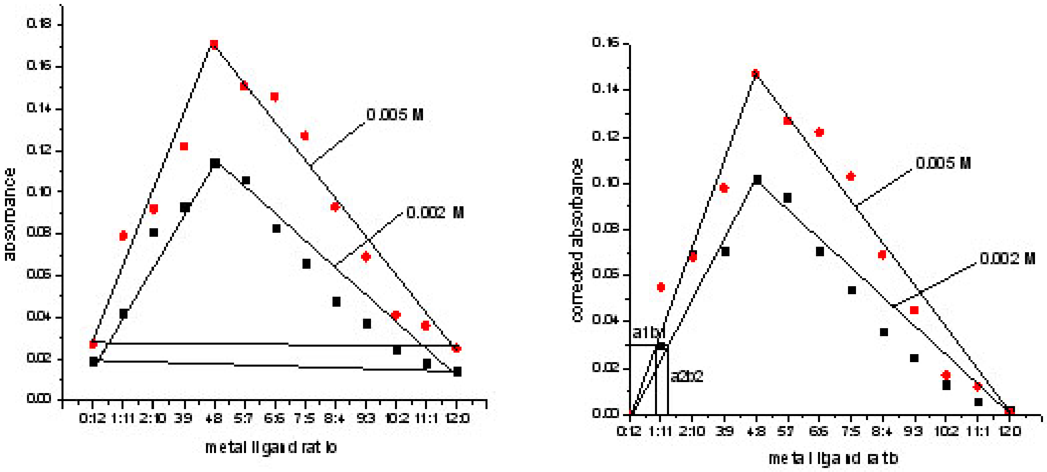


Fig: 2 (a-b)

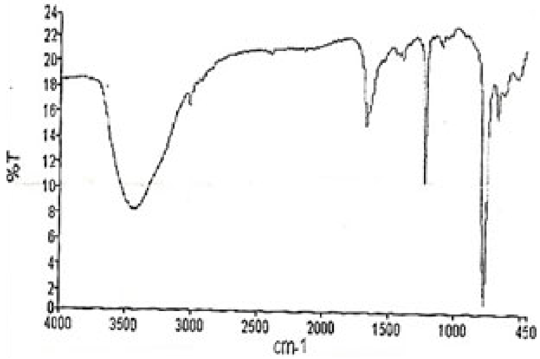


Fig. 5: IR spectra of glipizide-Zr complex

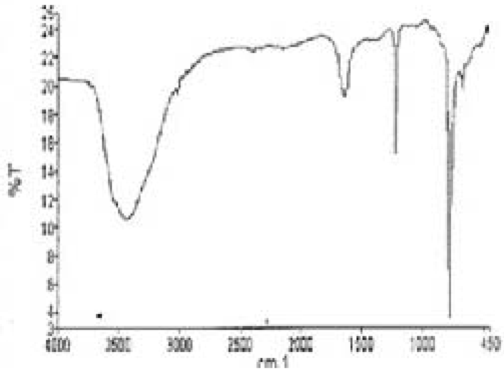


Fig. 6: IR spectra of glipizide-Co complex

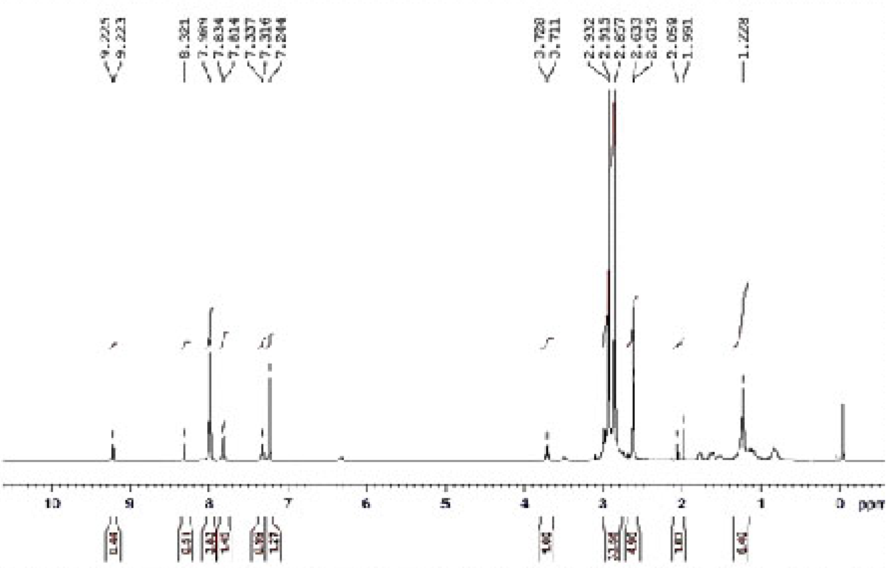


Fig. 10: H¹ NMR spectra of Glipizide-Zr complex

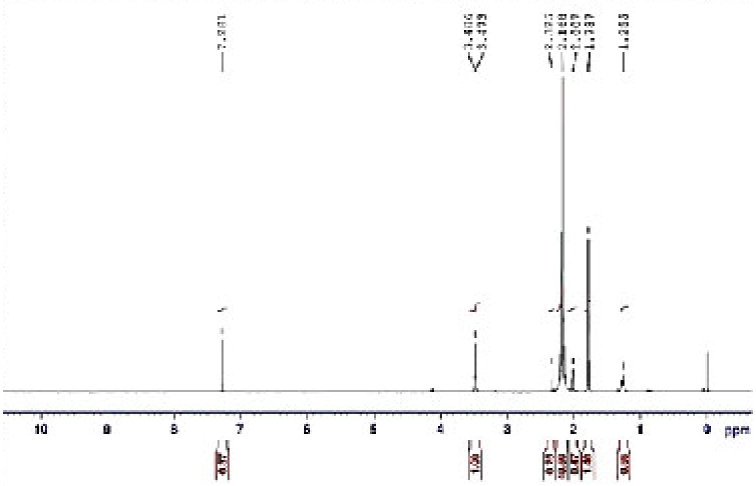


Fig. 11: H¹ NMR spectra of Glipizide-Co complex

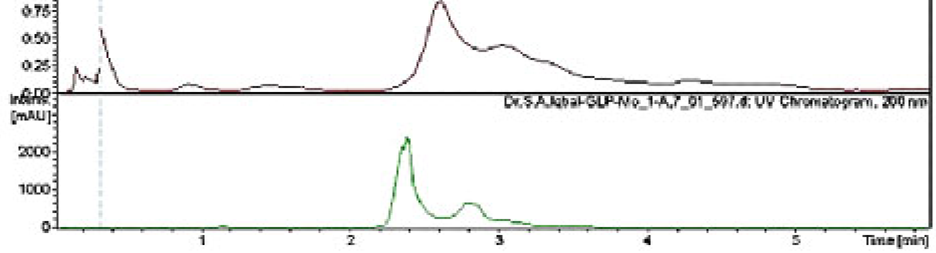


Fig. 13: Mass spectra of glipizide- Mo complex

provides information regarding the molecular structure of organic and inorganic compounds. We have studied complexes of the drug glipizide with Zr and Co. One representative spectra is given below.

Atomic Absorption Studies

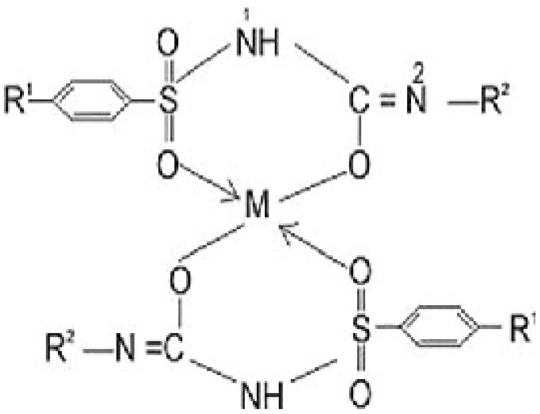
This analysis was carried out by direct method, which gave total metal content. Reference standard solutions for each metal were prepared having various concentration ranges. Absorbance of these solutions was measured at the specific wavelength of each metal. A graph was plotted between absorbance and concentration of each metal solution, which show a straight line in each case. The concentrations of unknown solutions were calculated from the absorbance of unknown solutions by using the standard values. Results of analysis are given in table 8.

X-Ray Diffraction Studies

X-ray diffraction studies also confirm the complexes and formation of new bonds.In the X-ray diffractrogram of pure glipizide, a sharp peak is presented at a diffraction angle (2¸), and it confirms that the drug is in the crystalline form. Glipizide diffractrogram shows sharp peaks at 7.49, 11.08, 15.67, 18.67 and 21.86 2¸. While no. of peaks in all the three complexes vary. Thus indicating that complexes formed are a well kit one, moreover in theX-ray pattern of complexes of glipizide all the reflections present are new ones and the patterns are fairly strong. On comparing the pattern obtained with available Literature. It is evident that its pattern is not in good agreement with available information and thus confirms the formation of totally new complexes.

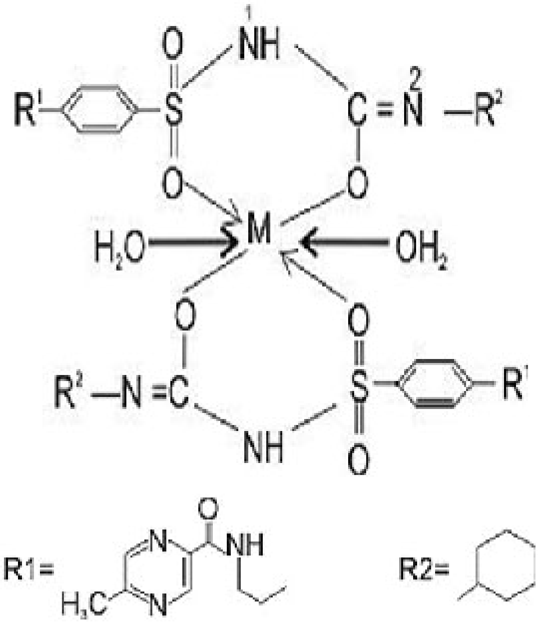
DISCUSSION

For supporting the proposed structure of Zr(II) and Co(II) complexes of glipizide, initially Job's method of continuous variation as modified by Turner and Anderson was conducted which indicates 2:1 ligand metal ratio of the complexes. Moreover, stability constant and free energy change was also calculated. Analytical data agrees to the molecular formula $(C_{21}H_{25}N_5O_4S)_2$Zr sand $(C_{24}H_{31}N_4O_6S)_2$Co.2H_2O. The differences in melting point of all these complexes as compared to pure drug glipizide suggested that a new product has been formed. For determining the proposed structure I and II on the basis of stoichiometry and analyzing the complexes, advanced spectrophotometric methods like elemental analysis, IR, NMR, UV-Visible and AA spectroscopy were conducted which suggest the co-ordination of the metal atom with enolic oxygen of the carbonyl group on one side and oxygen of the sulphonyl group from the other side. The shift of peaks in IR



M=Zr

Proposed structure I



M=Co

Proposed structure 2

region as well as in H^1 NMR further confirmed the drug metal complexation. These observations were further supported from the IR and NMR values of M-O and the appearance of N-H linkage in NMR. Moreover looking to the higher electronegativity of the oxygen as compared to nitrogen, N^2 enolisation is strongly supported. The final proof of metal incorporation in glipizide was confirmed by the estimation of the metals from these complexes by atomic absorption spectroscopy which again suggested that new compounds were 2:1 species containing metal oxygen bond.

Hypoglycemic activity

The isolated glipizide-metal complexes were found to be more potent than the parent drug. Hence as compared to standard synthetic drug, the glipizide- metal complexes are having more hypoglycemic activity.

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REFERENCES

1 Wilson and Gisvolds, Text book of organic medicinal and pharmaceutical chemistry, Eleventh edition, edited by John H. Block, John M. Beale, Jr. Lippincott William's and Wilkins , Wolters Kluwer, London UK: 2004; p 670.

2 Goodman and Gilman's, The pharmacological basis of therapeutics,11th edition, Edited by Laurence L. Brunton, John S. Lazo, Keith L. Parkar, McGraw-Hill, Medical Publishing division,2006; p 1635-1638.

3 R.N.Pandey,D.P.Singh, Priya and R.K.Singh, .*Orient.J.Chem.*,**26**(4): 1513-1516 (2 010)

4 K.Jamuna, D. Harikishore, B.N.Kumar and D.K.Ramana., *Orient.J.Chem.*,.**27**(3): 1141-1147 (2011)

5 Gehad G. Mohd et al., *Arabian J. of Chem.*,**2,** 109-117 (2009).

6 Sharma, R.N.,Sharma, K.P and DixitN.,*Orient.J.Chem.*, **26**(1):283-86(2010).

7 Iqbal S. A., Sibi Jose and Ishaq Zaafarany., *Orient.J.Chem.*, **28**(1): 613-618 (2012).

8 Job, P., Ann. Chim, 113, 10 (1928).

9 Turner, S.E. and Anderson, R.C., *J. Am. Chem. Soc.,*912, 71 (1949).

10 Mohd. Tawkir., S.A. Iqbal., Bal Krishan and Ishaq Zaafarany.,*Orient.J.Chem,***27** (2): 603-609 (2011).

11 Bal Krishan., Om Prakash and E. H. EL-Mossalamy.,*Orient.J.Chem,***29** (1):381-388 (2013).

12 Mohd. Tawkir., Khalid Khairou and Ishaq Zaafarany.,*Orient.J.Chem,***28**(4):1697-1710(2012).

13 R.K. Agrawal, I. Chakraborti and N.K. Sharma, *Orient. J. Chem.,* 19, 95 (2003).

14 Bal Krishan and Iqbal, S.A, *Orient.J.Chem,* 28(4) (2012), 1883-1888

15 Cotton, F.A., Wilkinson, G., Murillo, C.A and Bochmann, M., Advanced Inorganic Chemistry, sixth ed. Wiley, New York,(1999).

16 F. Afridi, S.A. Iqbal and G. Jacob*, Orient. J.Chem.* 20: 413 (2004).

17 Mohammad Azim and Shamim Ahmad, *Orient. J. of Chem,* 27(2): 673-677(2011).

18 Mc Lafferty and Turecek: *Interpretation of mass spectra*,4th Ed. (1993)

19 Sorrell: *Interpreting spectra of organic molecules* (1988).

20 Arpino,P., *Mass spectrum review*, 8:35 (1989).

21 Suresh, G.P., Prakasha, K.C., Wethroe,Kapfo and Channe, Gowada D., *E. Journal of Chem.,* **7**(2): 449-546 (2010).