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Original Research Article

SYNTHESIS, PHYSICO-CHEMICAL AND ANTIDIABETIC STUDIES OF ZINC COMPLEX OF GLIMEPIRIDE, AN ORAL HYPOGLYCEMIC AGENT

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ABSTRACT

The synthesis and characterization of Zinc complex with glimepiride (an oral antidiabetic drug) has been studied. The conductometric titration using monovariation method indicates that complex is non-ionic and of ML_2 type. Analytical data agrees with the molecular formula $(C_{24}H_{34}N_4O_5S)_2$ Zn. Structure of the complex was assigned as tetrahedral in which ligand molecules lies horizontally joining the central zinc atom. IR, NMR, Mass spectral and X-ray studies confirm the co-ordination of sulphonyloxygen on one side and enolic oxygen attached from other side with the metal ion. Tentative structure for complex was proposed on the basis of analytical data and Elemental analysis.

Key words: Synthesis; Characterization, Glimepiride-metal ion complex, Infrared spectroscopy.

INTRODUCTION:

Glimepiride 1-(p-(2-(3-ethyle-4-methyl-2-oxo-3-pyroline-1-carboxamido)ethyl)phenyl sulfonyl)-3-(trans-4-methylcyclohexyl) Urea is a third generation hypoglycemic sulfonylurea, which is useful in the treatment of non-insulin dependent *diabetesmellitus* (NIDDM) (Ammar, 2007, Massimo,2003) . Glimepiride is a white crystalline powder, relatively insoluble in water. It exhibits slow gastrointestinal absorption rate and inter individual variation of its bioavailability (Kouichi, 2005). The slow absorption rate of drug usually originates from

either poor dissolution of drug from the permeability of drug across gastrointestinal membrane. For poorly water soluble and highly permeable drugs the rate of oral absorption is often controlled by the dissolution rate in the gastrontestinal tract[4]. Complexation of sulfonylurea with lighter transition metal has been studied. (Yoshinaga and Yamamotto , 1966, Qureshi and Iqbal, 1985). A persual of available literature shows that systemic study on complexation of zinc with sulphonyl ureas is relatively scanty. Baliar et.al.2009, Montazeri et.al. 2012, Kelode and Nandlik. 2012, Ghashang and Orient. 2012). The study of chemistry and chemical reaction of structure co-ordination compound helps in establishing structure activity relationship. It has been reported that in biological activity metal complex is more potent and less toxic as compared to the free ligand (AL-Duby and AL-Jibori. 2012).

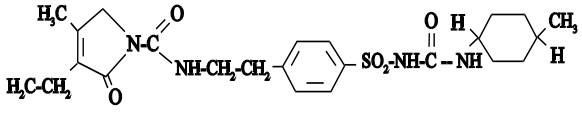


Fig 1 Structure of glimepirid

Ligand-metal ratio

To confirm the ligand metal ratio, conductometric titrations using monovariation method were carried out at 27 ± 1^0C 0.005M solution of glimepiride drug was prepared in and free energy changes were also calculated using Job's method[8] of continuous variation modified (Turner and Anderson. 1949). (Fig III).

CONDUCTOMETRIC TITRATION MONOVARIATION METHOD

GLIMEPIRIDE WITH ZINC CHLORIDE

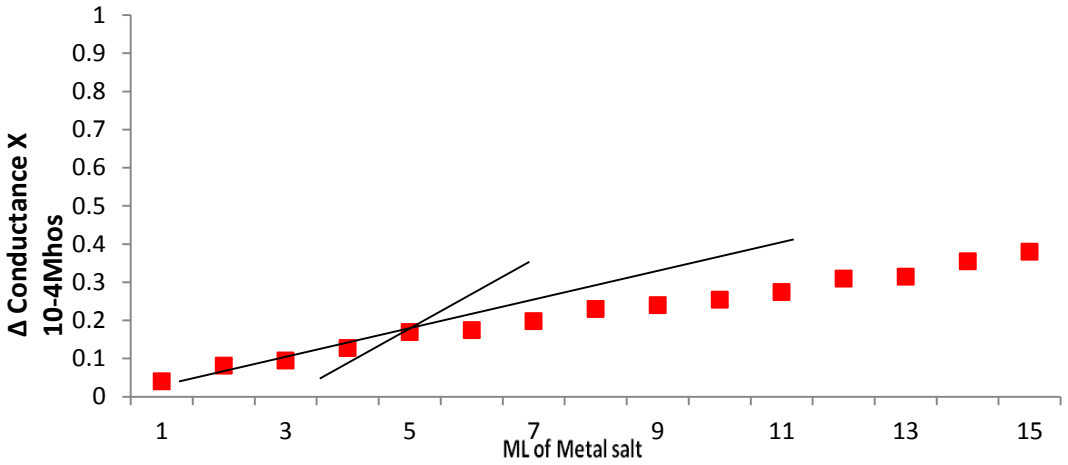
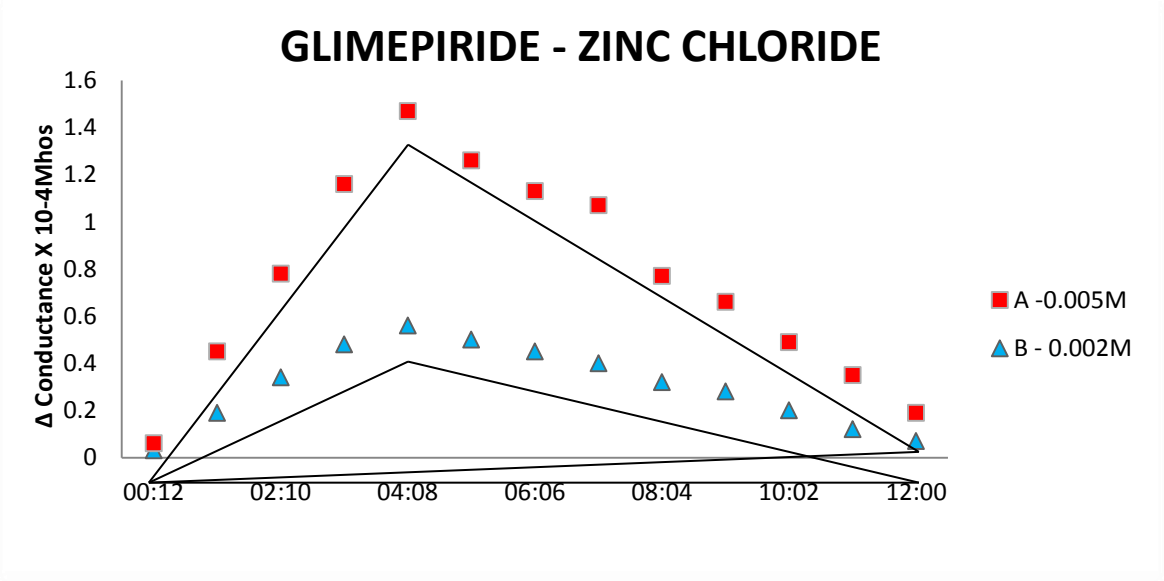
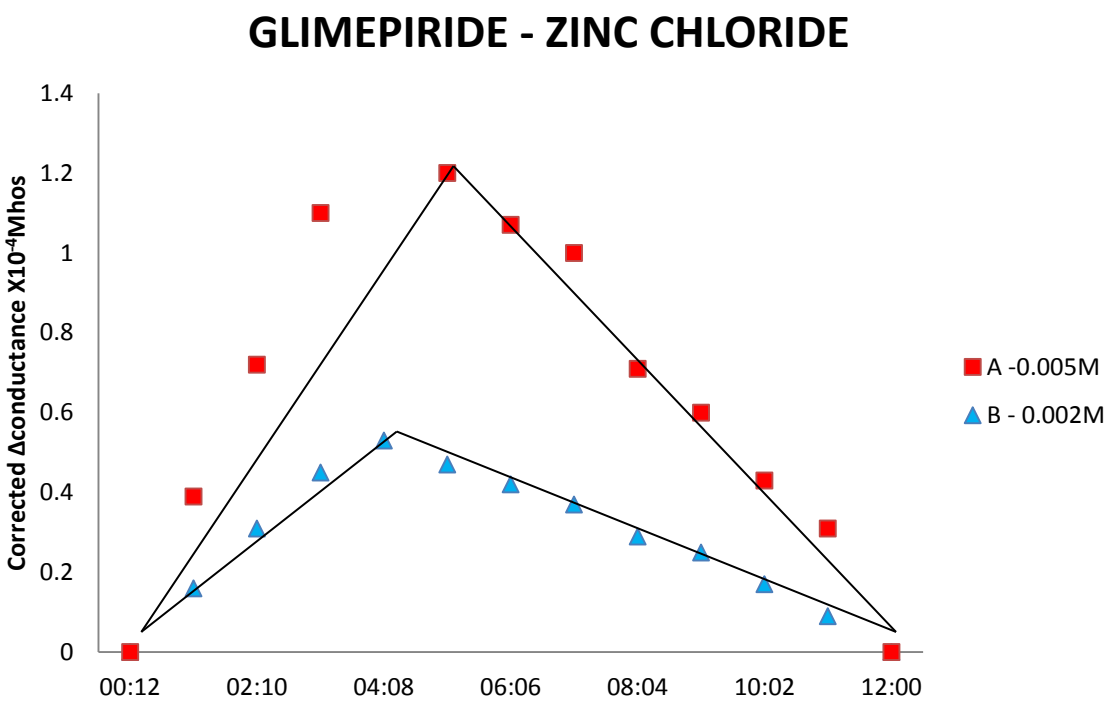


Fig. (II)



Mole Metal Ligand Ratio



Mole Metal Ligand Ratio

Modified Job's Curve or Turner Anderson method

Experimental:

All chemicals used were of analytical grade. Pure sample of Glimepiride (Molecular fornula $C_{24}H_{34}N_4O_5S$ and mol.wt 490.62) was obtained from Ipca laboratories Ltd, Ratlam in powdered form m.p 207^0C.

Metal salt $Zncl_2$ was of merck chemical. The solvent used were distilled water and DMF. Metal-ligand ratio was calculated using Systronics Digital Conductivity meter. Melting point was determined by Parkin Elmer melting point apparatus and are uncorrected pH values determined on LabIndia pH Analyser. IR spectra of ligand and complex were recorded with perkin Elmer spectrometer in the range of 4000-450cm^{-1} (CDRI Lucknow). The ^{1}HNMR spectrum of the ligand glimepiride and their isolated complex zinc-glimepiride, were scanned through Bruker DRX-300 NMR Spectrometer from CDRI Lucknow using deuterated acetone as a solvent. Mass spectral analysis of pure ligand as well as metal complex were obtained from CDRI, Lucknow. X-ray diffraction studies were carried out by X-ray Diffractometer model with 45kV rotating anode and Cukα (1W = 1.54060A^0) radiation (Panjab University).

Synthesis

Complex was synthesized by mixing the solution (80% DMF) metal salt solutions with that of ligand in 1:2 molar ratios; respectively at room temperature maintaining the pH between (6.5-8) by the addition of dilute NaOH solution. On refluxing the mixture content for 3hrs at 80^0C and on cooling the off white coloured crystals were obtained (Iqbal and Jacob. 2007, Iqbal et al. 2012, Nakamoto. 1963, Bellamy. 1956). The complex was washed with 80% DMF or alcohol and weighed (yield-52%).

Analysis of Complex

The resulting complex so formed was characterized by its elemental analysis, physical characteristics, IR, NMR Mass spectral and X-ray diffraction studies.

Table–1: Synthesis and Physicochemical characteristics of Glimepiride-Zinc complex.

Ligand/ Complex	Ligand Metal Ratio	Colour	% Yield	Stability Constant LogK (L/mole)	Free Energy Change (-ΔF) KCal/mole
Glimepiride	-	White		-	-
Glimepiride-Zinc Complex	2:1	Off white	52%	11.01	15.13

Table -2 : Analytical data of Complex

Ligand Complex	Elemental analysis Found (calc) m.p^{0}C					
	C	H	N	S	Metal	^{0}C
$C_{24}H_{34}N_4O_5S$	58.77 (58.50)	6.93 (6.95)	11.92 (11.94)	6.53 (6.57)	-	207
$(C_{24}H_{34}N_4O_5S)_2.Zn$	52.22 (52.42)	5.21 (5.31)	7.85 (7.97)	5.09 (6.07)	6.07 (6.17)	218

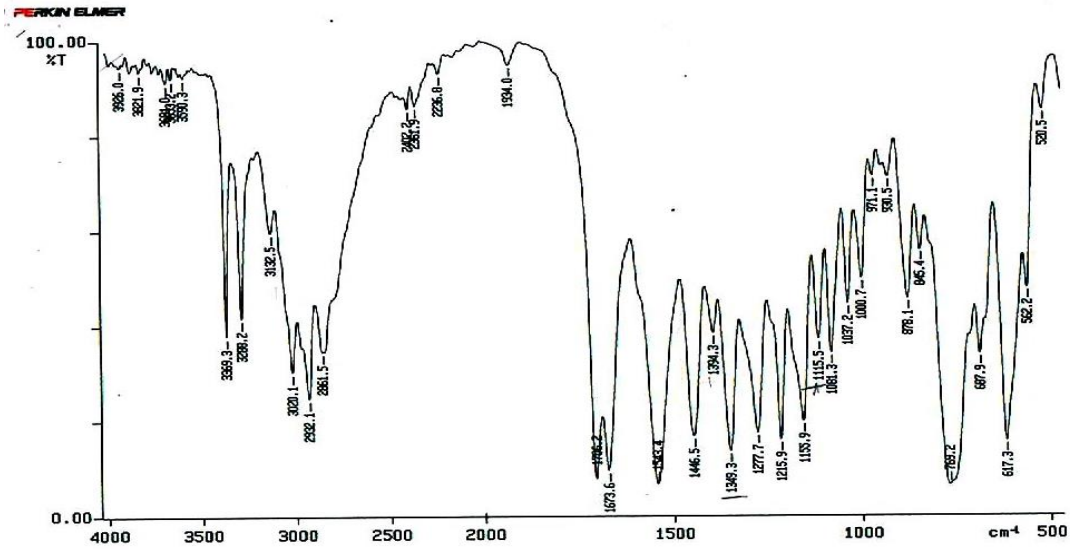
RESULTS AND DISCUSSION

The synthesized complex is offwhite and stable, being soluble in DMSO, acetone and insoluble in water, ethanol etc. Analytical data (table 2) and conductometric studies suggest 2:1 (L:M) ratio. Measured conductance values of these complex are too low to account for their electrolytic behaviour.

Structure Determination

(i) IR ABSORPTION STUDIES

The IR spectrum (Dyer. 1978, Rao. 1970, Chandran et.al. 2011, Tawkir et.al. 2011) of the ligand and the isolated complex were recorded in the range 4000-450 cm^{-1} and the probable assignments are given in (table 3). The proposed structure for the isolated complex is also supported by IR absorption bands and characterized by the absorption of carbonyl (C=O) and sulphonyl urea group at 1701 cm^{-1} and 1216 cm^{-1} respectively. The NH group observed at 3681 cm^{-1} in the ligand (glimepiride) was shifted to 3752 cm^{-1} in Zinc glimepiride complex. The next IR band of structural significance of the ligand appears at 1656 cm^{-1} which may be assigned to υ (C-O), which was absent in pure ligand and the considerable frequency of υ (C=N) was obtained at 1542 cm^{-1} in metal complex while absent in pure ligand were indicates that these specific IR absorptions are appeared due to complexation. The linkage through amide-O and sulphone –O- atom was further supported by the appearance of αband in the far IR region at 670cm^{-1} in the complex that may be assignable to M-O frequency (Fig IV a&b).



IR Spectra of Pure Drug Glimepiride

IR Spectra of Glimepiride-Zinc complex

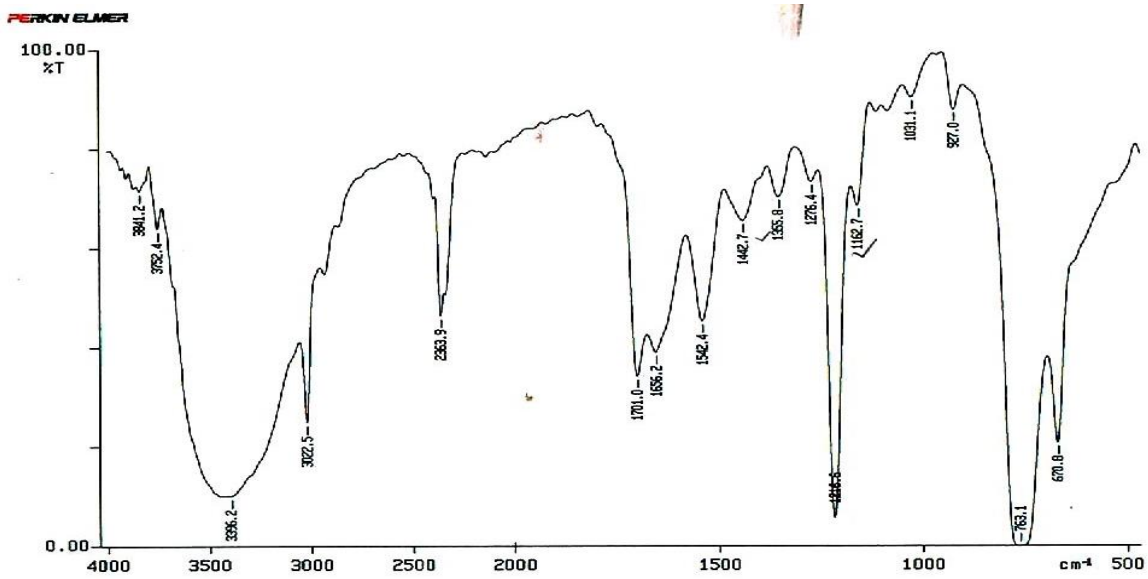


Table - 3 : IR Absorption data of the comple x in cm^{-1}

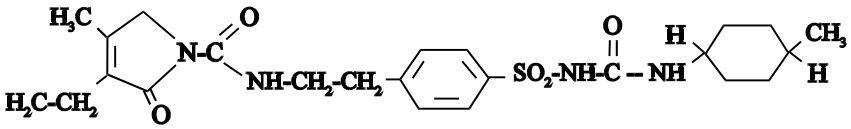
Ligand/Complex	v(NH)	v(C=O)	v(S=O)	v(C-O)	v(C=N)	v(SO_2N)	v(M-O
$C_{24}H_{34}N_4O_5S$	3681	3681	3681	-	-	3020	-
$(C_{24}H_{34}N_4O_5S)_2.Zn$	3752	1701	1216	1656	1542	3022	670

(ii) NMR SPECTRAL ANALYSIS

^{1}H NMR spectra of Glimepiride and its Zinc

For pure ligand Glimepiride.

(300 MH_Z, Acetone)



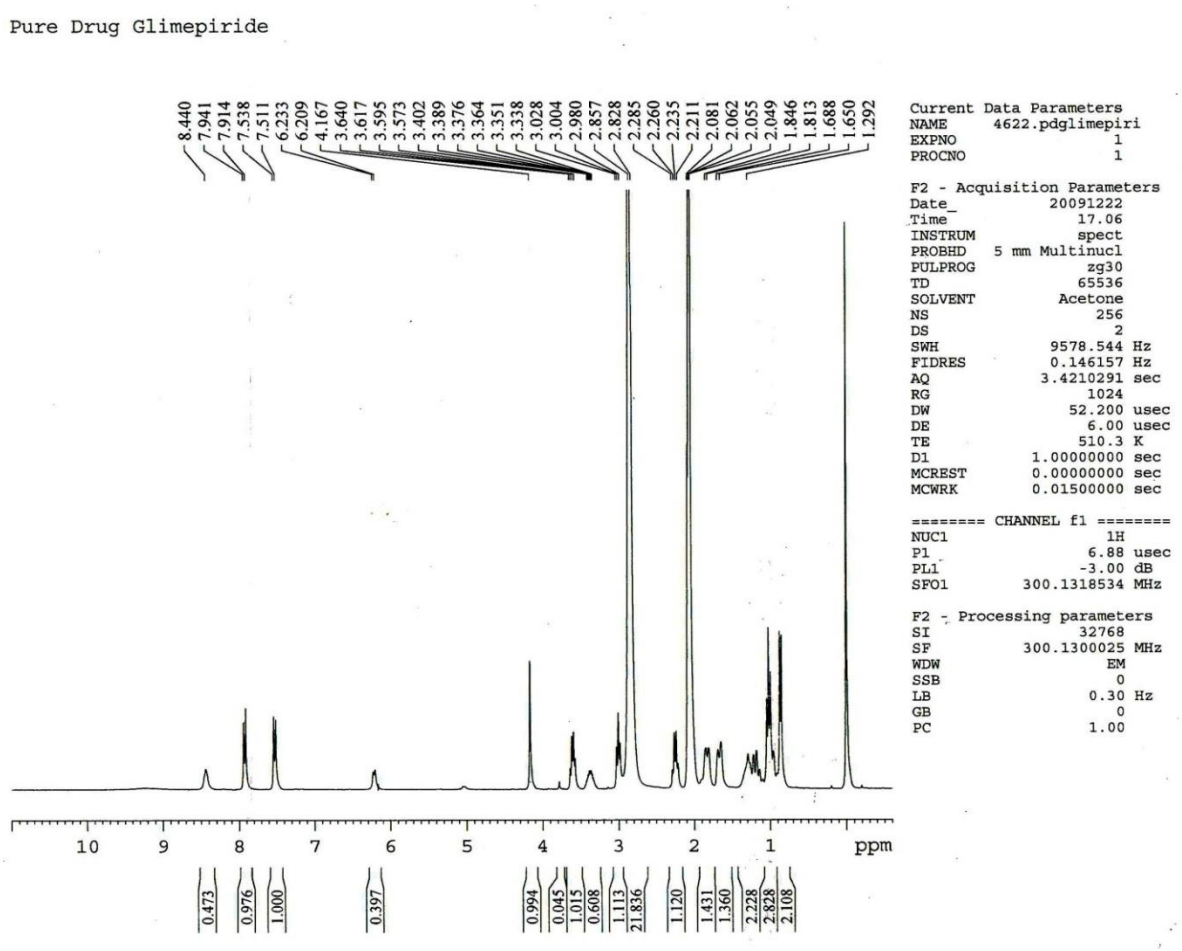


Table 6. [1]HNMR spectral data of pure drug

8.44 (S, 1H NHCO), 7.94 (d, benzene J = 0.97 H_Z), 7.53 (d, benzene J = 1H_Z), 6.23 (S, SO_2NH J = 0.39 H_Z), 4.1(Se, CH_2N J = 0.994), 3.61 (S, Pyrollidine), 3.33(t, CH_2 attached with benzene J = 0.60), 3.02 (q, CH_2 attached with carbonyl, J = 21.83), 2.21(p, CH_2 attached with methyl J = 1.43H_Z), 1.65 (t, CH_2 attached with cyclohexane J = 1.36 H_Z) 1.04(t, CH_3 group, J = 2.82 H_Z).

s = singlet , d = doublet, t = triplet, q = quatrate

(B) Glimepiride –Zinc Complex.

(300 MH_Z, Acetone)

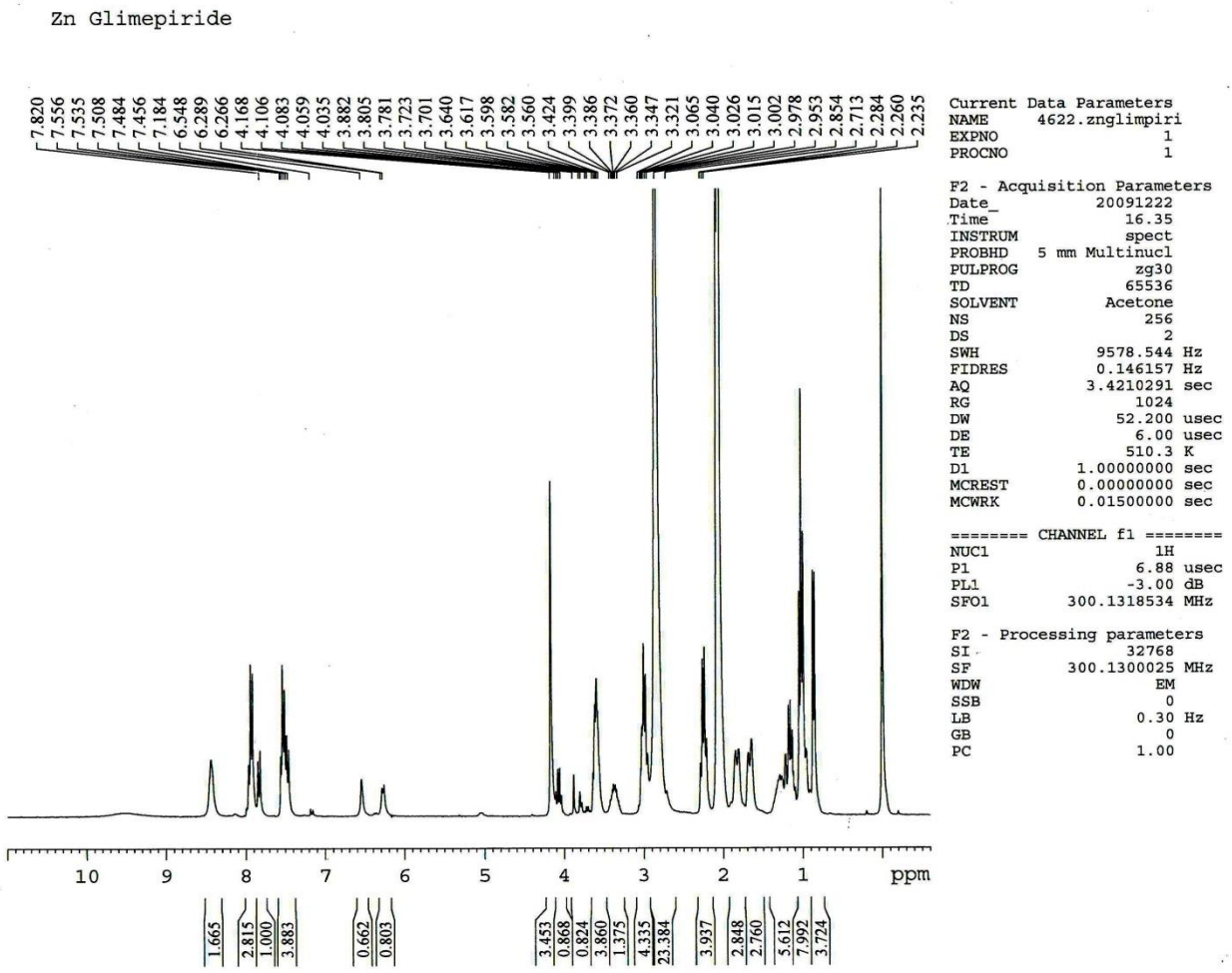


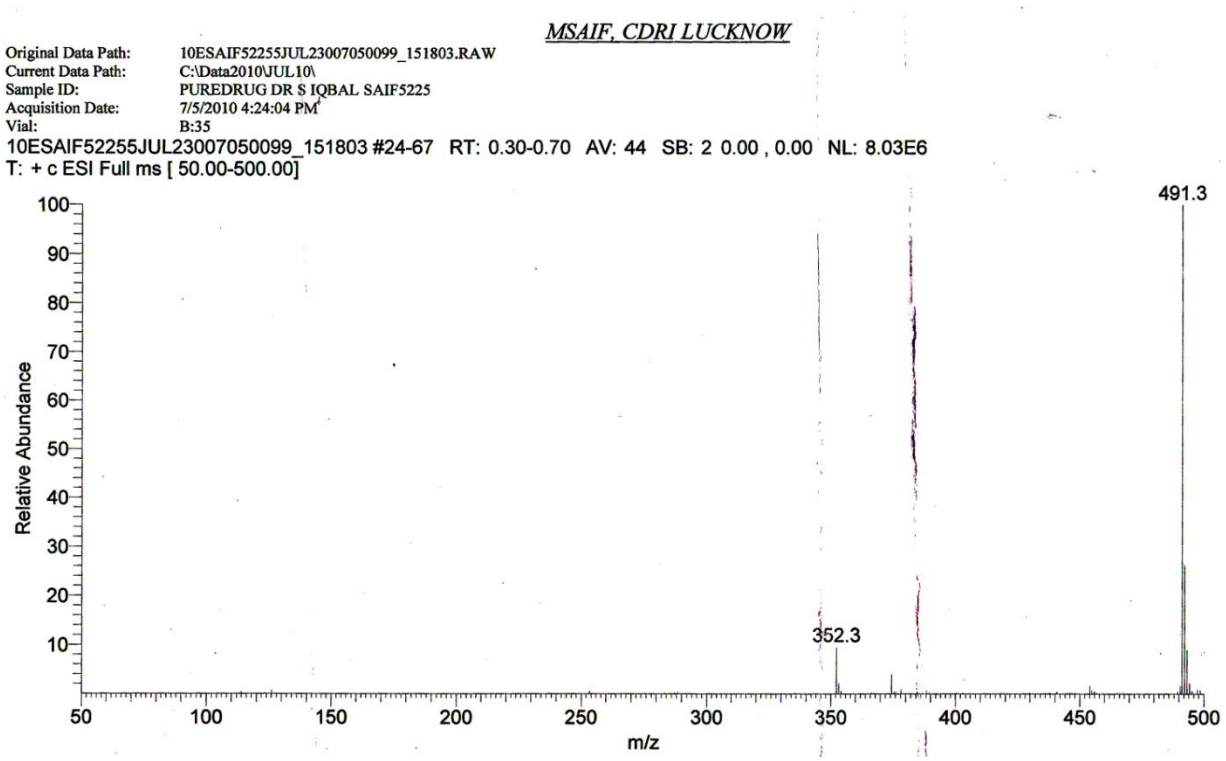
Table 7. : ^{1}HNMR spectral data of Glimepiride-Zn complex.

8.43 (S, 1H NHCO), 7.94 (t, benzene J = 2.81 H_Z), 7.45 (q, benzene, J = 3.88 H_Z), 6.28 (S, SO_2NH, J = 0.80 H_Z), 4.1 (Se, CH_2N. J = 3.45 H_Z), 3.72 (S, NHCO-Zn, J = 0.82 H_Z), 3.61 (S,pyrollidine), 3.32(m, CH_2 attached with benzene, J = 1.37H_Z), 3.06 (q, CH_2 attached carbonyl J = 4.33 H_Z), 2.21 (p, CH_2 attached with methyl J = 3.93 H_Z), 1.64 (S, CH_2 attached with cyclohexane, J = 2.76 H_Z) 1.04 (t, CH_3 group j = 7.99 H_Z).

s = singlet d = doublet t = triplet q = quatrate

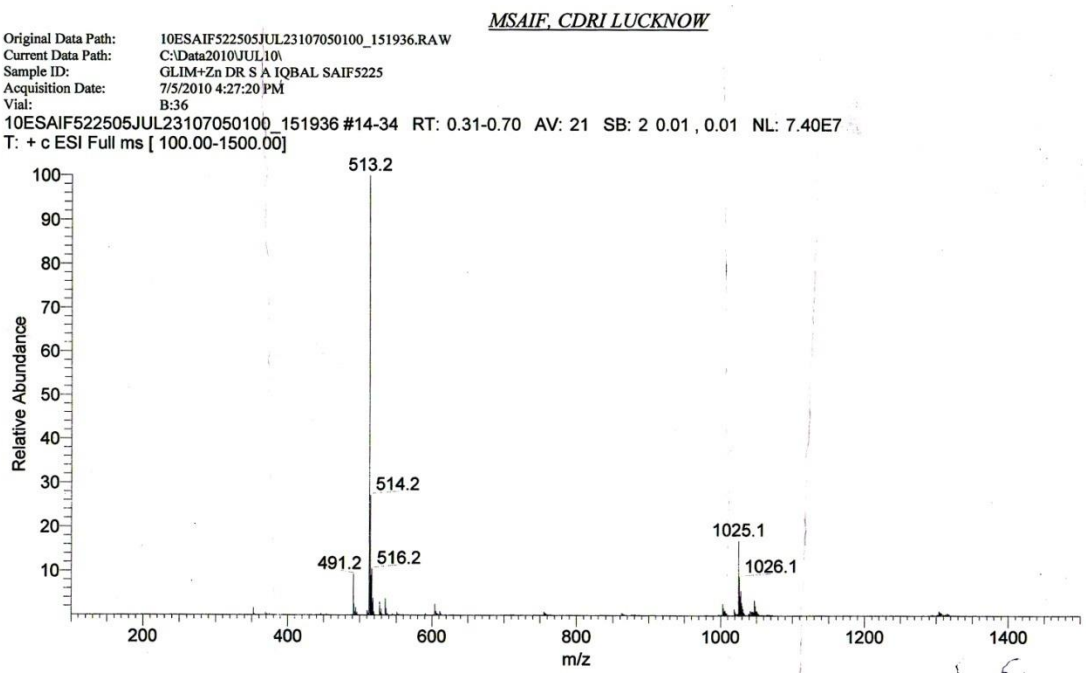
The $^{-1}$HNMR spectrum of the ligands Glimepiride and its isolated complex zinc were scanned through bruker DRX-300 NMR spectrometer from DCRI Lucknow using deuterated acetone as a solvent (table 4). In the spectra of glimepiride-zinc complex (table 5) exhibit a broad singlet signal at 8043 ppm, shows a down field shift, Δδ for NH in NHCO group (8.44 ppm) in pure ligand (Iqbal et.al 2005, Khan and Sahdev. 2011, Santhi and Namboori. 2011).

(iii) MASS SPECTRAL ANALYSIS



m/z 491 due to $(C_{24}H_{34}N_4O_5S)^{\bullet+}$ parent ion peak or $(m^{\bullet+})$ and m/z 352 due to $(C_{17}H_{16}N_3O_4S)^{\bullet+}$

Mass Spectra of Glimepiride-Zinc Complex.



m/z 1026 $[Zn(C_{24}H_{34}N_4O_4S)_2]^{\cdot+}$ molecular ion peak or $m^{\cdot+}$; m/z 1025 $[Zn(C_{24}H_{32}N_4O_4S)_2]^{\cdot+}$ at m/z 513 due to $(C_{26}H_{33}N_4O_5S)^{\cdot+}$ base peak ion; m/z 514 $(C_{26}H_{34}N_4O_5S)^{\cdot+}$ isotopic fragment ion and m/z 491 due to $(C_{24}H_{34}N_4O_5S)^{\cdot+}$ fragment ion.

The mass spectrum of the pure ligand shows a molecular ion peak $m^{\cdot+}$ at m/z 491 due to $(C_{24}H_{34}N_4O_5S)^{\cdot+}$ parent ion peak (Verma et.al. 2011) which is in accordance with the proposed formula of the ligand. The other peak of appreciable intensity has been observed at m/z value 352 correspond to species $(C_{17}H_{16}N_3O_4S)^{\cdot+}$ due to loss of $(C_7H_{18}NO)^{\cdot+}$ fragment radical cation having a molecular mass 132. While the mass spectrum of $[Zn(C_{24}H_{34}N_4O_5S)_2]$ shows a molecular ion peak $m^{\cdot+}$ at 1026 which corresponds to molecular weight of complex supported for the monomeric structure (Cullity. 1978). Beside this peak the complex showed the fragment ion peak at m/z 513 indicating base peak intensity. Other important peaks were observed at m/z values 514 and 516 which shows the relative abundances of Isotopes.

Some important mass spectral intensities of metal complex of Glimepiride are summarised in table(6).

Table-4 : Mass spectral Intensities of Metal Complexes of Glimepiride

S.No.	Ligand/Metal Complexes	Ms (ESI) m/z values	Assignment
1.	Pure ligand Glimepiride	491($m^{\bullet+}$)($C_{24}H_{34}N_4O_5S$)	molecular ion peak or parent ion.
		m/z 352 ($C_{17}H_{16}N_3O_4S$) $^{\bullet+}$	fragment ion or major product ion.
2.	Glimepiride-Zinc Complex	m/z 1026 ($m^{\bullet+}$)	Molecular ion peak.
		m/z 513	Base peak.
		m/z 491 (L) $^{\bullet+}$	Molecular weight of ligand.

(iv) ANTIDIABETIC ACTIVITY OF GLIMEPIRIDE ZINC COMPLEX

This isolated glimepiride-metal complex were found to be more potent as compared th the parent drug. Hence as compare to standard synthetic drug the glimepiride-zinc complex (Zaitoon et.al. 2011) was having more hypoglycemic activity. The hypoglycemic effect of glimepiride as well as metal complex were investigated on the blood sugar levels of male wistar rats by alloxan induced antidiabetic test (Seshadri et.al. 2011) (PBRI, Lab Bhopal). Analysis of data presented in table (7) reveals that the drug caused a marked decrease in blood sugar level. On comparing the hypoglycemic effect of zinc comple with parent drug it was revealed that in case of Zn-glimepiride treated male wistar rats blood sugar falls to 90.8± 1.9235 mg/dl while in glimepiride treated rate blood sugar falls to .96±1.5811 mg/dl. These results clearly indicate a better hypoglycemic activity of Zn-glimepiride complex over its parent drug.(Geinier. 1963, Soleymani et.al. 2012).

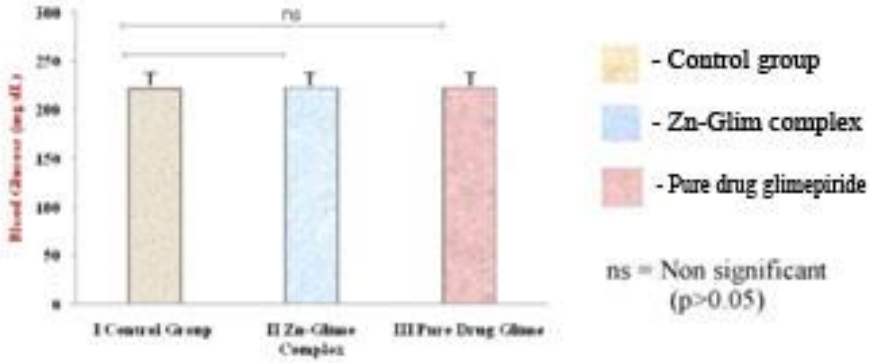
Table 7 : Antidiabletic Activity Analysis by Allozan Induced Antidiabetic Test.

Alloxan Induced Antidiabetic Model

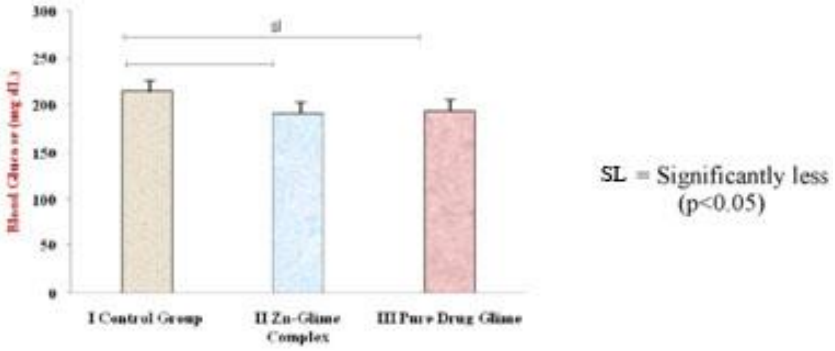
Group	Treatment Group	Dose mg/kg	Blood Glucose level (mg/dL)			
			Initial	**1 h**	**3 hrs**	**6 hrs**
I	Control group + Glucose (2g) + Vehicle	2 g	222.6± 1.1401	216.2± 1.3038	217.8± 1.7888	223± 1.5811
II	Zinc complex of Glimepiride (2mg) + Glucose + Vehicle	2 mg	223±1.5811	191.2± 1.9235	116.6± 2.0736	90.8± 1.9235
III	Pure drug Glimepiride (2mg) + Glucose +Vehicle	2 mg	223.4± 1.8165	193.6± 2.0736	115.2± 1.9235	96±1.5811

P>0.05 when compared to vehicle treated control group but P<0.05 ± & ** when compared to vehicle control group after 30 min. (*) & after 90 min (**).

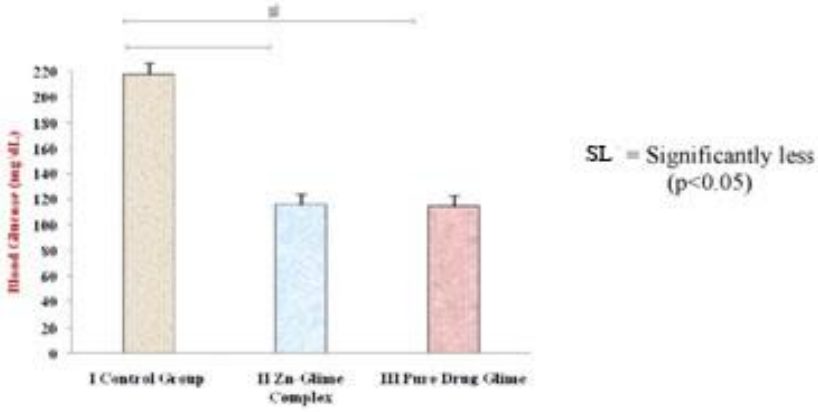
Blood-sugar level (Zero hour)



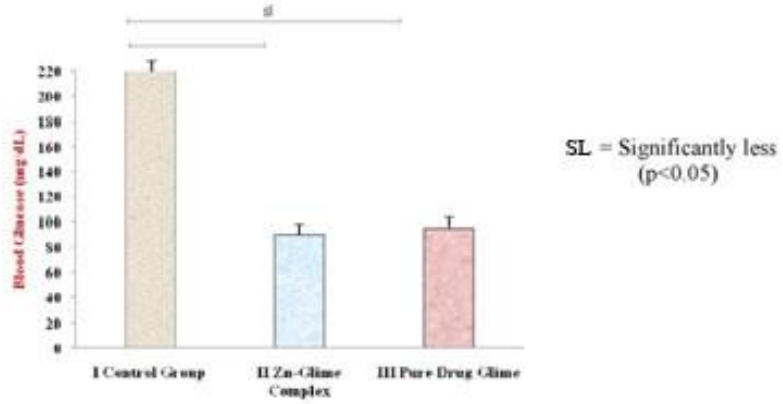
Blood-sugar level after 1 haur



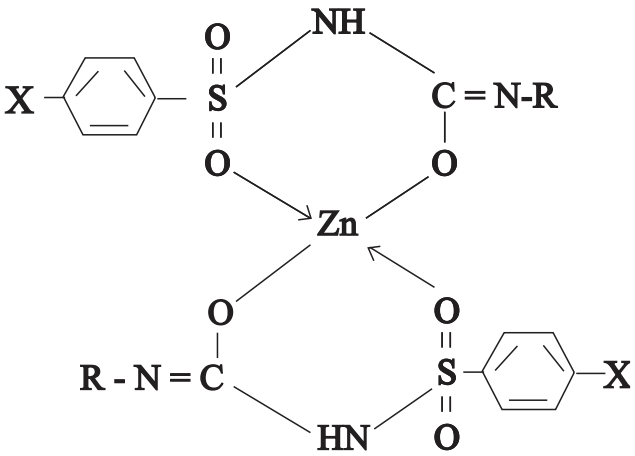
Blood-sugar level after 3 hrs.



Blood-sugar level after 6 hrs.



Alloxan Induced Antidibetic Activity Model



Structure of glimepiride zinc complex.

CONCLUSION

The differences in melting point of metal-ligand complex as compared to Glimepiride suggested that a new product was formed. The shifts of peaks in IR region as well as new signals around at X-ray diffractogram in X-ray studies further confirmed the drug metal complexation. The tentative structure of the complex are further supported by Mass spectral analysis. The overall studies indicate the glimepiride metal complex is non-ionic and have tetrahedral geometry.[31-33]

ACKNOWLEDGEMENTS

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