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Synthesis, Physico-chemical and Spectral Studies of Mercury Complex of Glimepiride, An Oral Antidiabetic Drug

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ABSTRACT

Glimepiride is a current, potent hypoglycemic agent used in NIDDM (Non-Insulin Dependent Diabetes Mellitus). Metal complex of glimepiride has been synthesized by reaction with mercury (II) in the form of its chloride. The conductometric titration using mono variation method indicates that complex is non-ionic and ML_2 type with was further confirmed by Job's method of continuous variation as modified by Turner and Anderson. Analytical data agrees with the molecular formula $(C_{24}H_{34}N_4O_5S)_2Hg$. Structure of the complex was assigned as tetrahedral in which ligand molecules lies horizontally joining the central mercury atom. Infrared spectral and molar conductance data confirm the co-ordination of sulphonyl oxygen on one side and enolic oxygen attached from other side with the metal ion. Structure assigned to the complex is supported by analytical data and IR and NMR spectral data.

Key words: Synthesis; antidiabetics; glibenclamide; IR spectra, NMR spectra

INTRODUCTION

The study of chemistry and chemical reaction of co-ordination compound help in establishing structure activities relationship. It has been reported that in biological activity metal complex is more potent and less toxic as compared to the free ligand[1-6]. Inorganic chemistry and the use of metals in therapeutic drugs have become increasingly important over the last couple of decades resulting in a variety of exciting and valuable drugs such as cis-platin for cancer.

Recently metals in medicine has been recognized internationally as an important area for research. In this account the role of rare earth's metal neodymium has been undertaken for study[7-10].

In recent years, much attention is given to the use of sulphonyl ureas because their high complexing nature with essential metals. Sulphonyl ureas are effective for non-insulin dependent *diabetes mellitus*[11-13].

These compounds are completely absorbed on oral administration. They are metabolized by liver and are excreted predominantly through urine. Complexation of sulphonyl ureas with rare earth's metals have been studied in detail by several workers[14-16]. A persual of available literatures shows that systemic study on complexation neodyamium with various hypoglycemic drugs is relatively more important[17-19].

Here in the synthesis and characterization of mercuric chloride complex with glimepiride have been described[20-22].

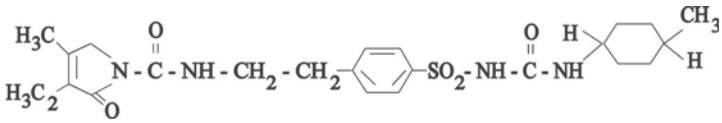

Fig 1: Structure of Glimepiride

EXPERIMENTAL

Pure sample of G.P (trade name amaryl) with m.f. ($C_{24}H_{34}N_4O_5S$) was received from Ipca laboratories ltd., Ratlam. Solvents and metal salts used were of the analytical grade. Melting point was determined by Perkin Elmer melting point apparatus and are uncorrected, pH values determined on Lab. India pH analyser. IR spectra of ligand and complex were recorded with Perkin Elemer spectrometer in the range of 4000-450cm^{-1} (CDRI Lucknow). The ^{1}HNMR spectra of the ligand and isolated complex was reported on a Bruker Avance II 400 NMR spectrometer (SAIF, Panjab University, Chandigarh). The DMSO was used as a solvent.

Ligand-metal ratio

For determining the ligand-metal ratio molar solutions were prepared of metal salt and ligand in 1:2 ratio and conductometric titrations were carried out by using mono variation method (Fig II). The ligand-metal ratio (1:2) was also confirmed by the way of doing the jobs method[23] of continuous variation as modified by Turner and Anderson[24] using conductance as index property. The indexed values were indicates 1:2 metal ligand ratio (Fig III).

Synthesis

A weighed quantity of glimepiride (2mol) was dissolved in minimum quantity of 80% DMF. The mercuric chloride solution was prepared by dissolving it separately in the same solvent. A few drops of alkali NaOH solution was added to metal solution to increase the solubility. Metallic solution was added slowly with stirring into the solution of ligand at room temperature maintaining the pH between 6 to 8 by adding dilute NaOH solution and refluxed for 2-4 hours at 80^{0}C. The solutions were left for crystallization at room temperature for 18-20 hours shiny grey coloured. crystals of complex were obtained which were filtered, washed, dried and then their melting points determined were recorded.[25]

Glimepiride with mercuric chloride

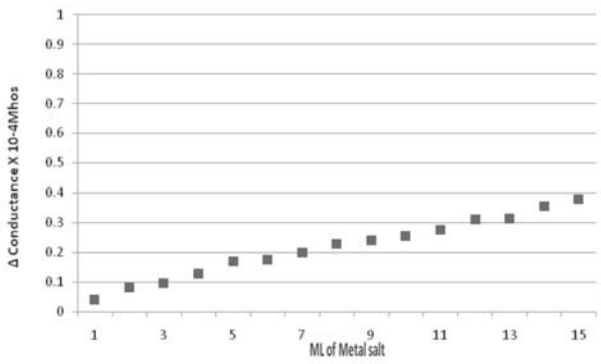

Fig. 2: Conductometeric titration onovariation method

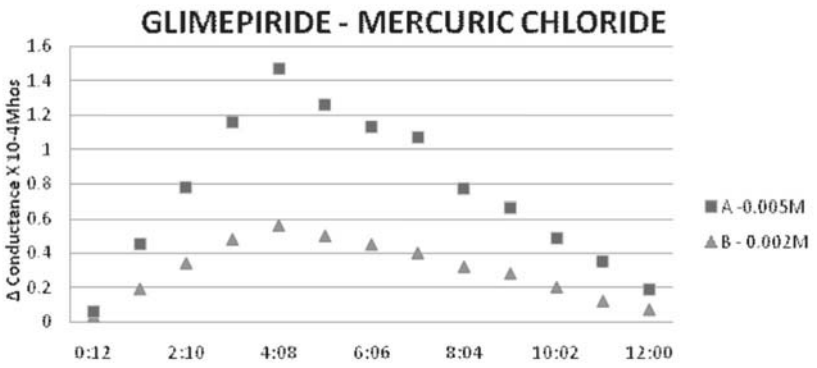

Fig. 3: Job's Curve

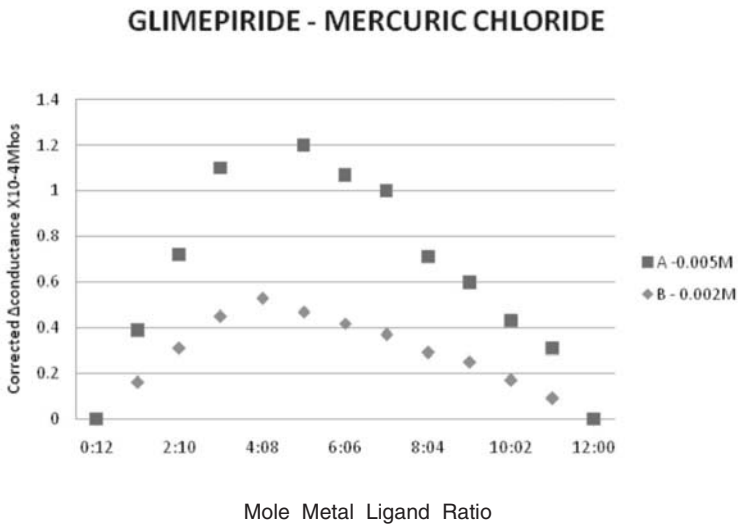

Fig. 4: Modified Job's Curv e

Table 1: Synthesis and physico chemical characteristes of Glimepiride-mercury Complex

Ligand/Complex	Ligend Metal Ratio	Colour	%yield	Stability constant Logk (L/mole)	Free energy change (-ΔF) Kcal/mole
Glimepiride (Ref)	-	White	-	-	-
Glimepiride-mercury Complex	2:1	Light Brown	78%	11.79	-16.21

Analysis of complex

The resulting complex so sormed was characterized by its elemental analysis through SEM-EDAX method and IR, NMR studies (table. 3 and 4). Metal was estimated as a sulphide.

Table 2: Analytical Data of complex

Complex	Elemental analysis found (calculated)						m.p.
	C	H	N	S	Metal	Water	^{0}C
$C_{24}H_{34}N_4O_5S$	58.77 (58.80)	6.93 (6.95)	11.92 (11.94)	6.53 (6.57)	-	-	207
$(C_{24}H_{34}N_4O_5S)_2.Hg$	48.07 (48.80)	5.64 (5.76)	8.93 (9.48)	5.39 (5.42)	15.75 (16.86)	-	218

Structure determination

IR Absorption Studies

The infrared spectrum of glimepiride and metal complex were recorded on Perkin Elemer Spectrometer RX1 (4000-450cm^{-1}). The major absorption bands for the infrared frequencies and the correspondign assignments are listed in Table 3.

The Glimepiride metal complex showed a prominent IR absorption band in the region 1701

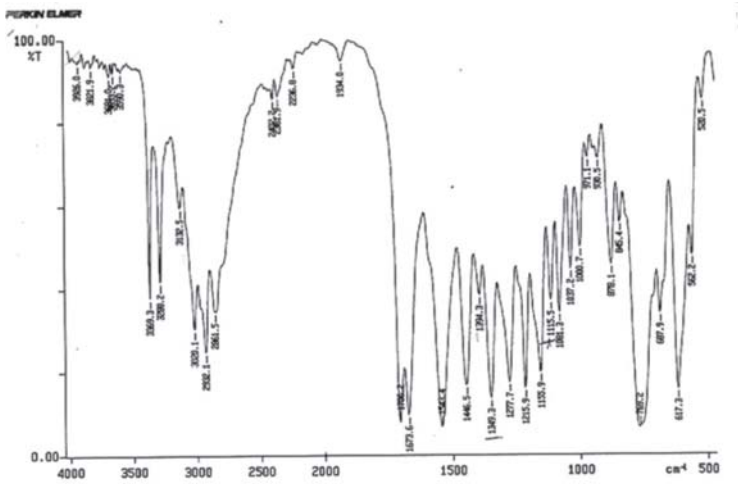

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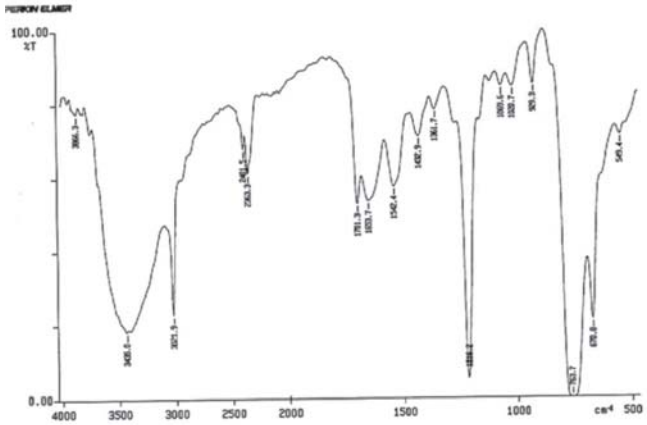
Fig. 4: IR Spectra of pure drug Glimepiride



SAIF No. : 4526

Fig. 5: IR Spectra of Glimepiride-Mercury complex

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

Ligand/Complex	υ (NH)	υ (C=O)	υ (C=N)	υ (C-O)	υ (M-O)
$C_{24}H_{34}N_4O_5S$	3681	1706	-	-	-
$(C_{24}H_{34}N_4O_5S)_2$.Hg	3680	1701	1542	1653	670

NMR Spectral Studies

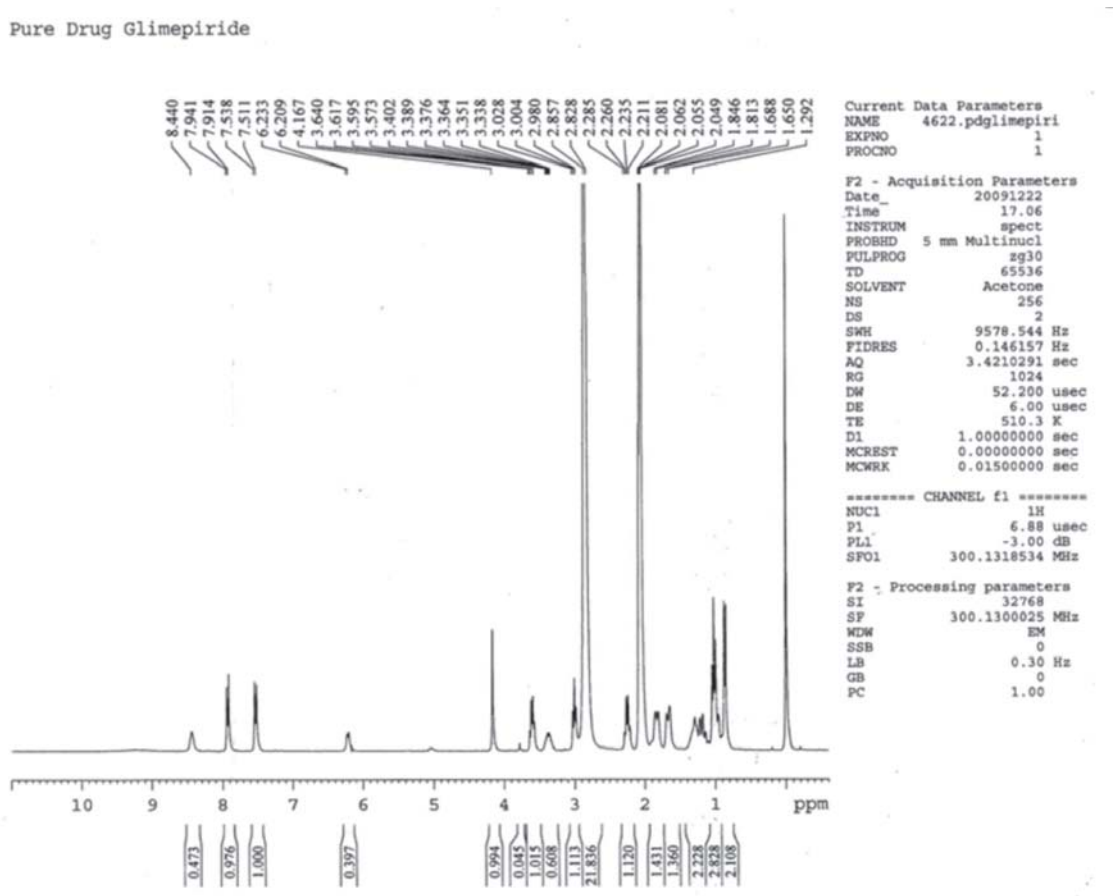


Fig. 6:

Table 4:

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

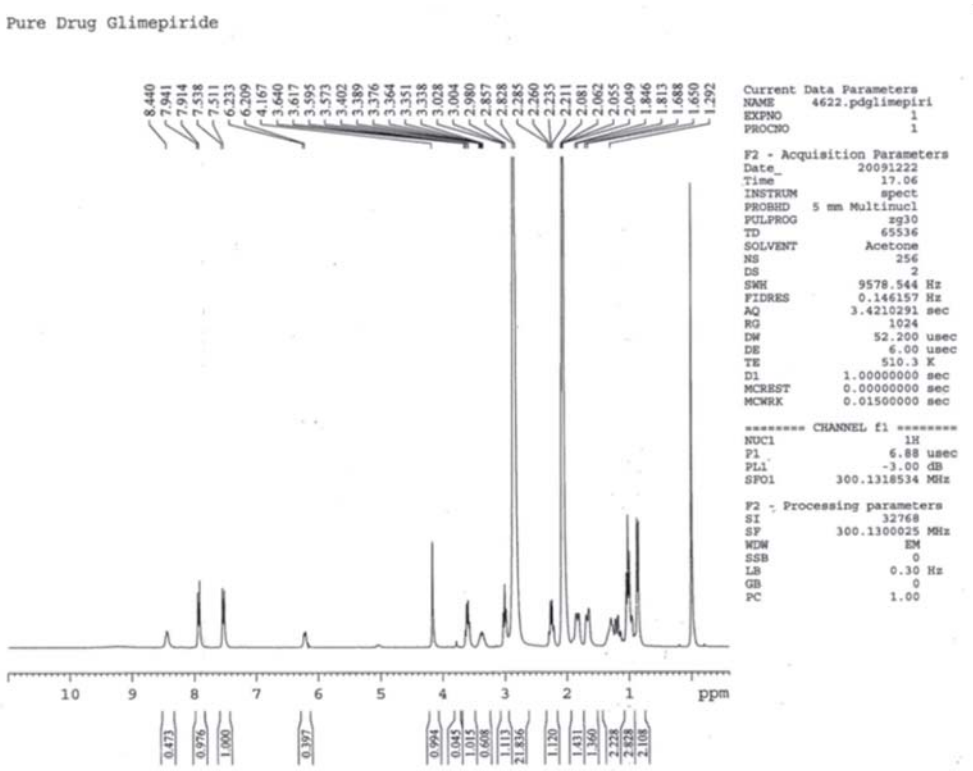


Fig. 7:

Table 5:

8.22 (S, 1H NHCO), 7.93 (d, benzene J = 1.42 H_z), 7.58 (d, benzene J = 1.45H_z), 6.95 (S, SO_2NH), 4.8 (Se, CH_2N J = 0.44 H_z), 3.65 (NHCO-Hg), 3.63 (d, pyrollidine J = 0.76 H_z) 3.05(t,CH_2 attached with carbonyl, J = 1.14 H_z), 2.12 (p, CH_2 attached with methyl J = 1.13 H_z), 1.56 (t, CH_2 attached with cyclohexane J = 0.64 H_z), 0.98 (t, CH_3 group j = 3.89 H_z).

s = singlet d = doublet t = triplet

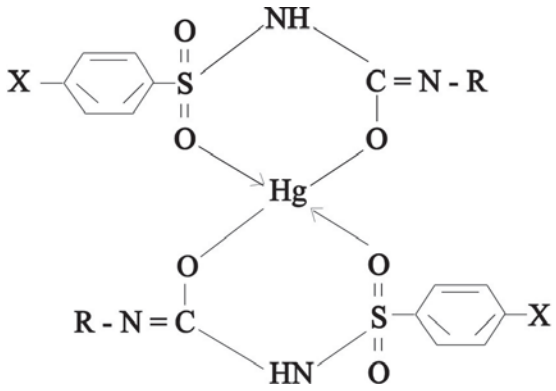
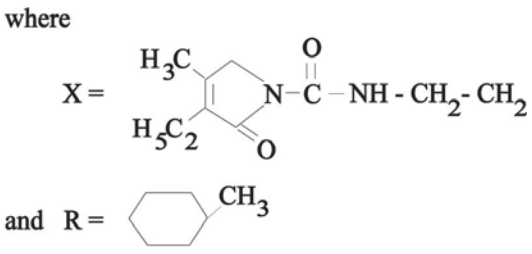


Fig . 8:



Scheme 1: Structure of Glimepiride-Mercury complex

cm^{-1} due to υ (C=O) carbonyl group[26-27]. The next IR band of structure significance of the ligand appears at 1215cm^{-1} which may be assigned to υ (S=O) which got shifted at 1216 cm^{-1} in the complex. The NH group observed at 3681 cm^{-1} in the ligand (glimepiride) shifted to 3680 cm^{-1} the mercury glimepiride comlex. The IR frequencies of υ (C=N) group was appeared at 1542 cm^{-1} in the complex while absent in ligand. The linkage through amide-O and sulphone-O- atom was further supported by the appearance of a band in the far IR region at 670 cm^{-1} in the complex that may be assignable to M-O frequency which was absent in ligand. In pure ligand there is no absorption band detected for u (C-O) and υ (C=N) due to enolisation are further supporting the structure of glimepiride mercury complex.

The mercury complex of glimepiride (table 4) the chemical shift Dd value for NH in NHCo was observed at 8.22 ppm while the same Δδ value in pure ligand glimepiride was observed at 8.44 ppm [28] showing a (0.22 ppm) down field shifting. The sulphonyl group in the complex is deshielded to a greater extent. This may be due to the sulphonyl group being adjacent to the bonding site and hence greater deshielding occurs in it.[29]

CONCLUSION

From the present study it can be concluded that the study of chemistry and chemical reaction of coordination compounds help in establishing structure activity relationship and it was also been observed that in biological activity metal complex is more potent and less toxic as compared to the free ligand.[30]

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