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RESEARCH ARTICLE

SYNTHESIS AND CHARACTERIZATION OF MOLYBDENUM COMPLEX OF GLIMEPIRIDE, AN ORAL ANTIDIABETIC DRUG.

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ABSTRACT

The synthesis and characterization of molybdenum 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 $(C_{24}H_{34}N_4O_5S)_2$ $Mo.2H_2O$. Structure of the complex was assigned as octahedral in which ligand molecules lies horizontally joining the central molybdenum atom and one water molecule, each attached vertically with the metal. Infrared, 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. The structure for complex was proposed on the basis of analytical data and Elemental analysis.

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

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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 diabetes mellitus (NIDDM)[1,2]. Glimepiride is a white crystalline powder, relatively insoluble in water. It exhibits slow gastrointestinal absorption rate and inter individual variation of its bioavailability.[3]

The slow absorption rate of drug usually originates from either poor dissolution of drug from the formulation or poor 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 in detail by Yoshinaga and Yamamotto (1966)[5], Qureshi and Iqbal (1985)[6]. A persual of available literature shows that systemic study on complexation of molybdenum with sulphonyl ureas is relatively scanty. 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[7]. In view of the above and in continuation of our work, It is interesting to have an insight into the synthesis of molybdenum complex with glimepiride and to diagnose various structural aspects of the isolated complex. Here the synthesis and characterization of molybdenum trioxide with glimepiride has been described.

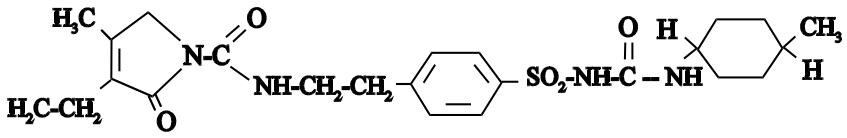


Fig 1 Structure of glimepiride

Ligand-metal ratio

To confirm the ligand metal ratio, conductometric titrations using monovariation method were carried out at 27±1^{0}c 0.005M solution of glimepiride drug was prepared in 80:20 mixture of DMF and water. Similarly solution of metal salt MoO_3 was prepared in the same solvent of 0.01M concentration. 20mL of ligand was diluted to 200ml with the same solvent. The ligand was titrated against metal salt solution using monovariation method. Conductance was recorded after each addition, Graph is plotted between corrected conductance and volume of metal salt added (Fig II). From the equivalence point in the graph it has been concluded that the complex formation has taken place in the ratio of 2:1 (L:M). Stability constant and free energy changes were also calculated using Job's method[8] of continuous variation modified by Turner and Anderson[9] (Fig III).

CONDUCTOMETRIC TITRATION MONOVARIATION METHOD

GLIMEPIRIDE WITH MOLYBDENUM TRIOXIDE

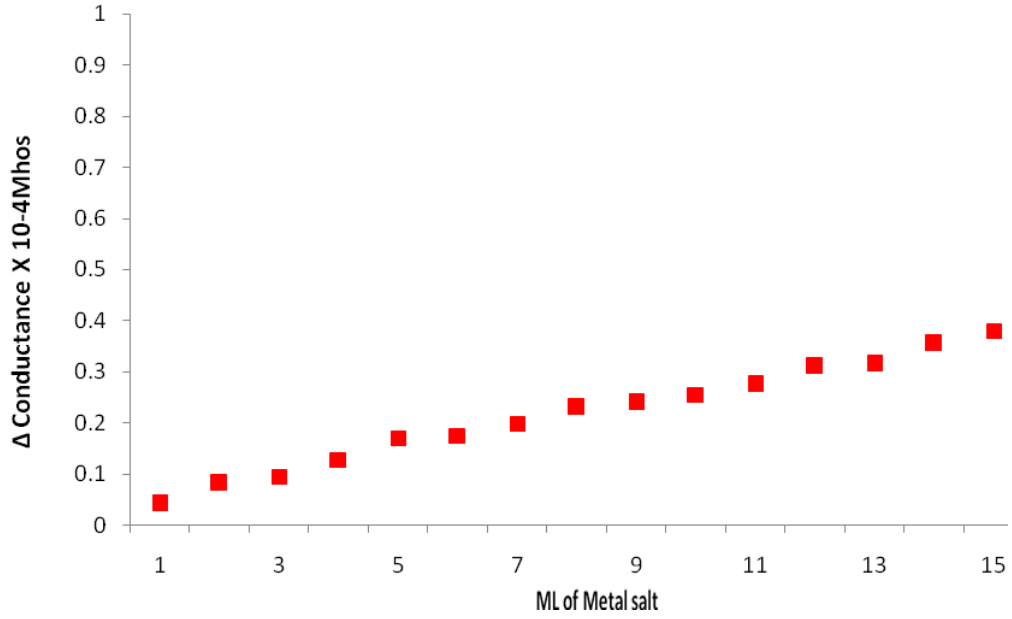
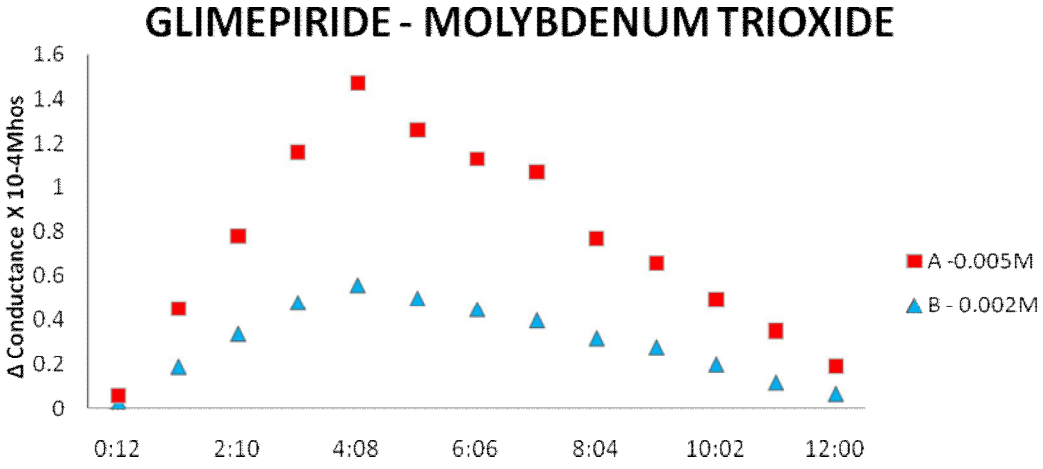
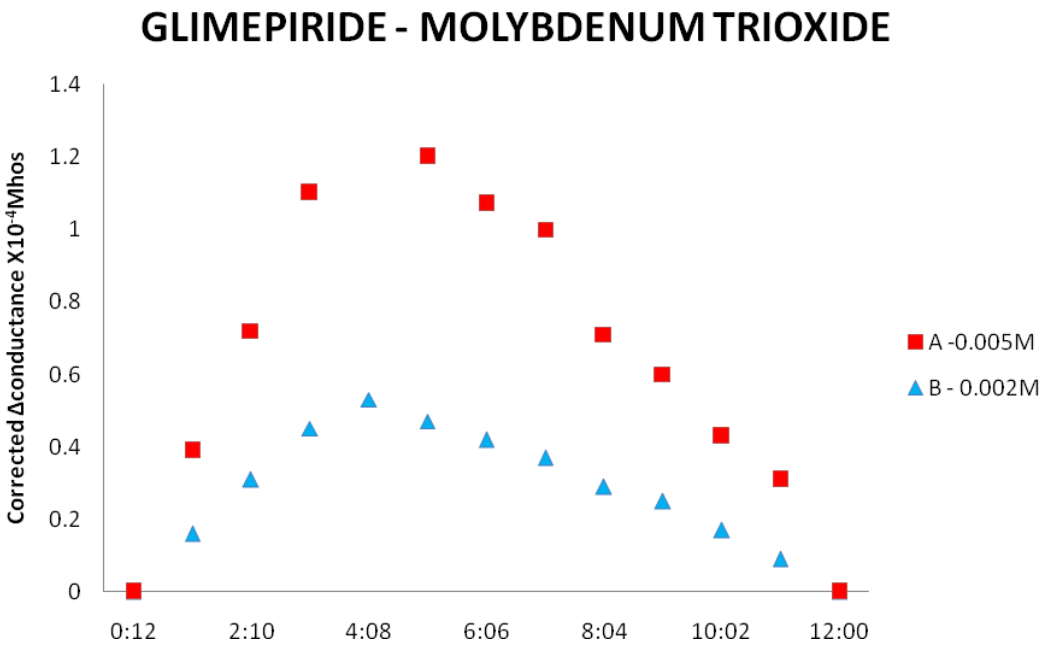


Fig. (II) Conductivity curve



Mole Metal Ligand Ratio

Fig (III) a – Job's Curve



Mole Metal Ligand Ratio

Fig (III) b - Modified Job's Curve

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^{0}C. Metal salt MoO_3 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 ligands and complexes were recorded with perkin Elmer spectrometer in the range of 4000-450cm^{-1} (CDRI Lucknow). Mass spectral analysis of pure ligand as well as metal complex were also 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 temprature maintaining the pH between (6.5-8) by the addition of dilute NaOH solution. On refluxing the mixture content for 3hrs at 80^{0}C and

on cooling the grey coloured crystals were obtained.[10-13] Thecomplex was washed with 80% DMF or alcohol and weighed (yield-54%).

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

Ligand/ Complex	Ligand Metal Ratio	Colour	% Yield	Stability Constant LogK (L/mole)	Free Energy Change (-ΔF) kcal/mole
Glimepiride	-	White		-	-
Glimepiride-Molybdenum Complex	2:1	Grey	54%	11.93	16.40

Analysis of Complex

The resulting complex so formed was characterized by its elemental analysis, physical characteristics, IR Mass spectral and X-ray diffraction studies (Table 2, 3, 4 and 5).

Table -2 : Analytical data of Complex

Ligand Complex	Elemental analysis Found (calc) m.p ^{0}C						
	C	H	N	S	Metal	Water	^{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
$(C_{24}H_{34}N_4O_5S)_2$. Mo.$2H_2O$	50.98 (51.75)	6.03 (6.10)	9.98 (10.06)	5.03 (5.75)	7.98 (8.53)	3.34 (3.23)	217

RESULT AND DISCUSSION

The synthesized complex is greyish 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[14-17] of the ligand and the isolated complex were scanned 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 1700 cm^{-1} and 1216 cm^{-1} respectively. The NH group observed at 3681 cm^{-1} in the ligand (glimepiride) was shifted to 3750 cm^{-1} in molybdenum 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 1595 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 671cm^{-1} in the complex that may be assignable to M-O frequency (Fig IV a&b).

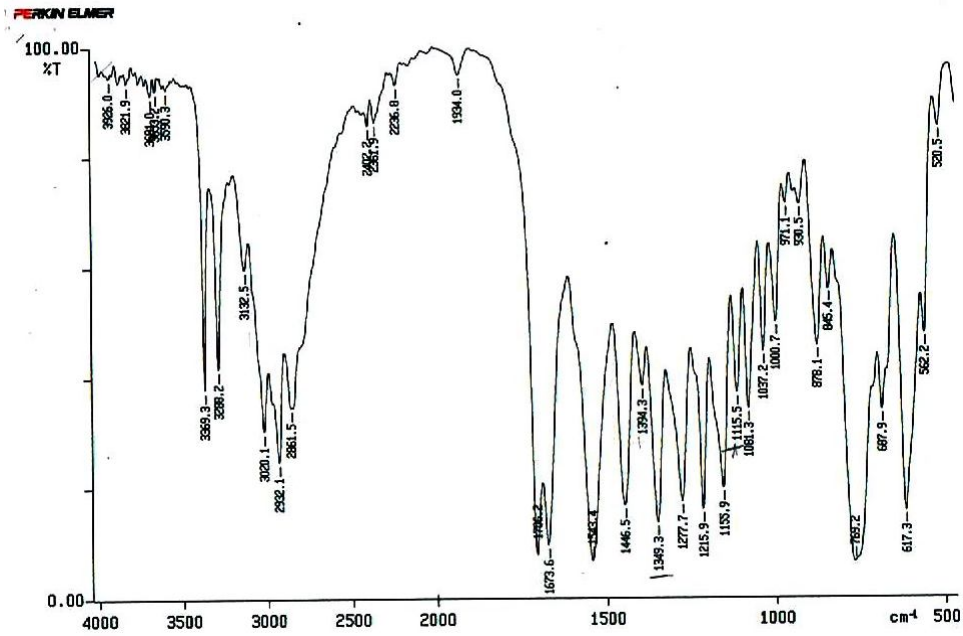


Fig. (IV a) : IR Spectra of Pure Drug Glimepiride

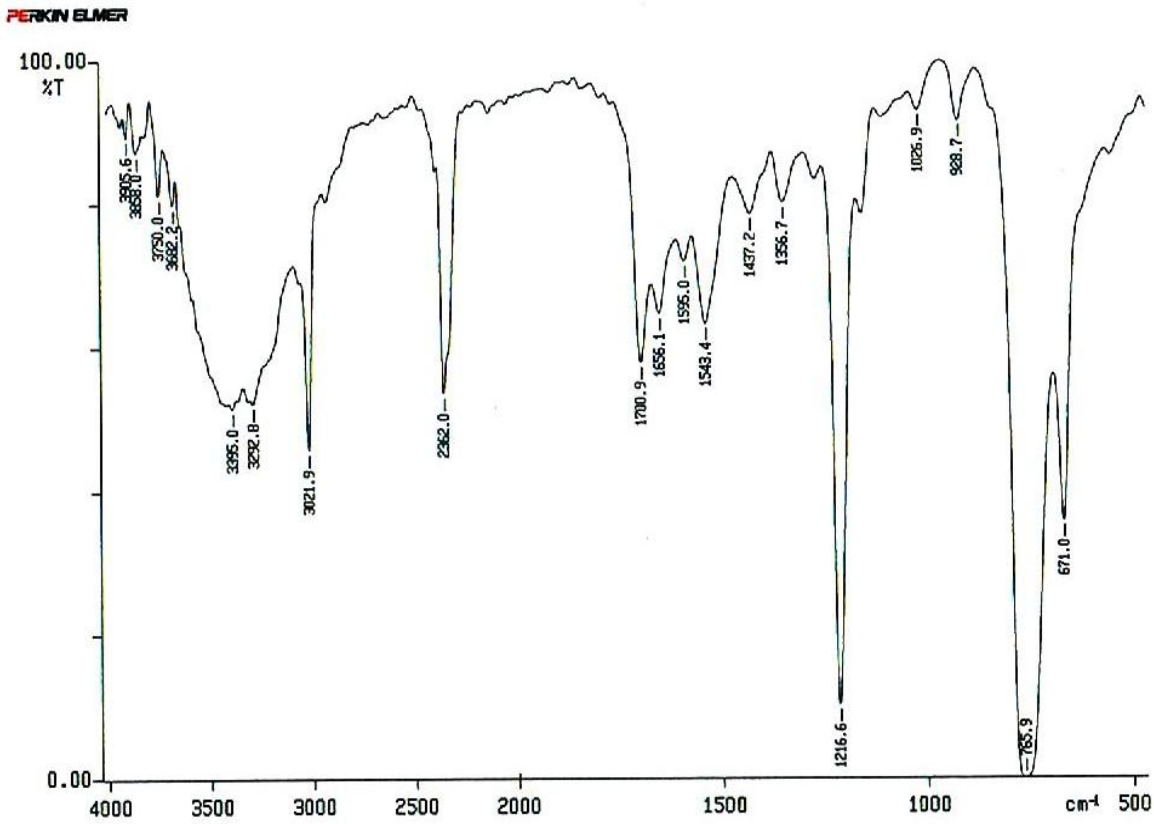
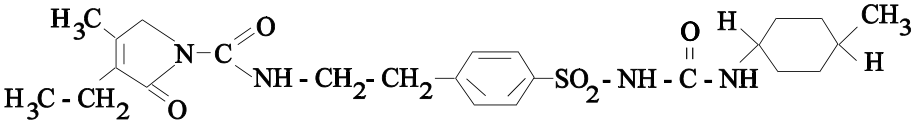


Fig. (IV b) : IR Spectra of Glimepiride-Molybdenum complex

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

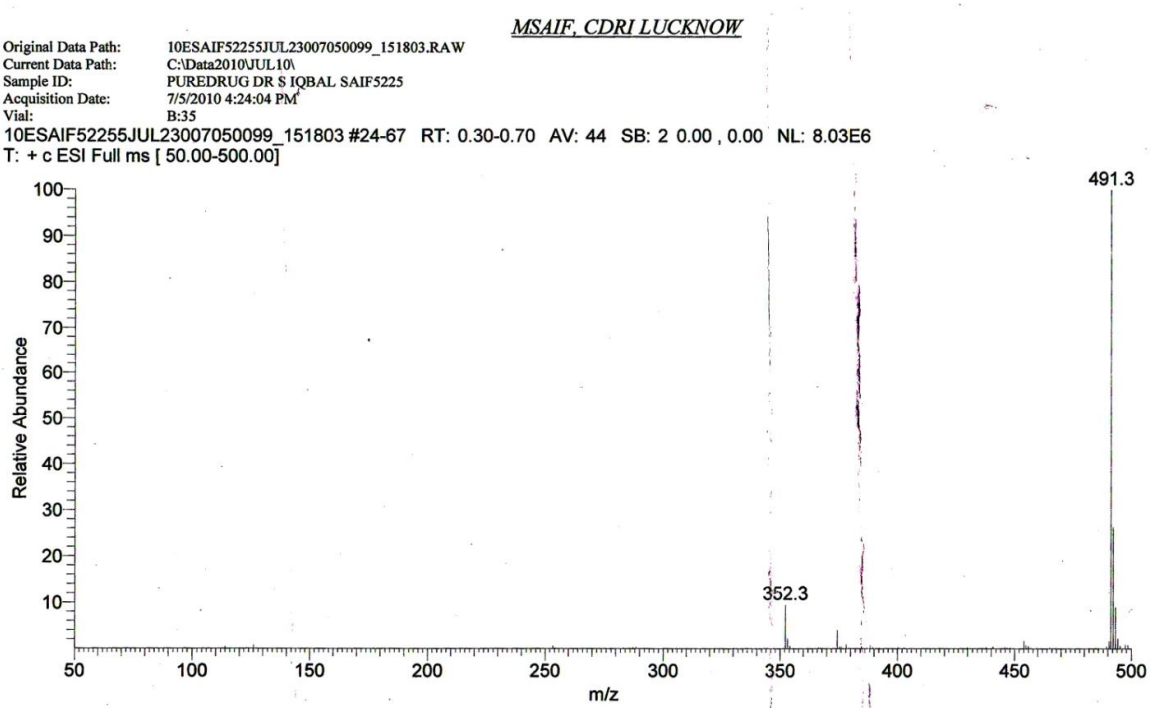
Ligand/Complex	v(NH)	v(C=O)	v(S=O)	v(C-O)	v(C=N)	$v(SO_2N)$	v(M-O
$C_{24}H_{34}N_4O_5S$	3681	1706	1215	-	-	3020	-
$(C_{24}H_{34}N_4O_5S)_2.Mo.2H_2O$	3750	1700	1216	1656	1595	3021	671

(ii) MASS SPECTRAL ANALYSIS



Molecular formula :- $C_{24}H_{34}N_4O_5S$

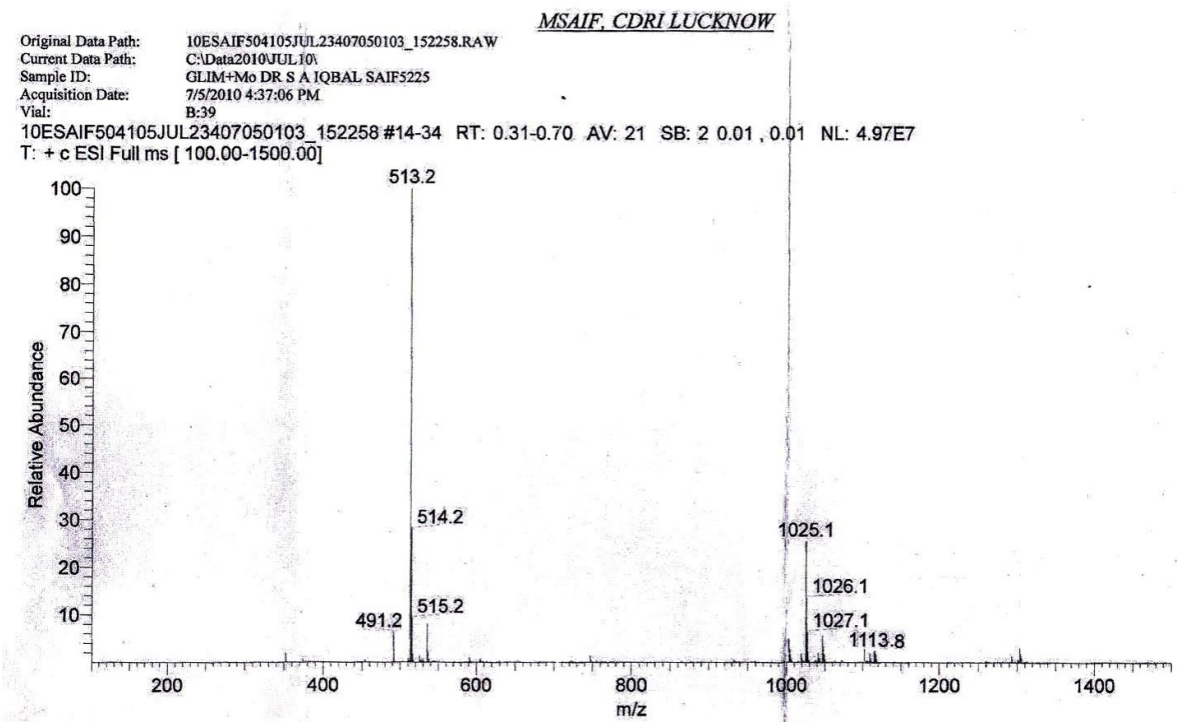
Molecular mass : - 490 g/mol



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 $(C_{17}H_{16}N_3O_4S)^{\bullet+}$

Molecular formula :- $(C_{24}H_{34}N_4O_5S)_2.Mo.2H_2O$

Molecular mass : - 1113 g/mol



m/z 1113 due to $[M(L_2)(H_2O)_2]^{\bullet+}$ or $[Mo(C_{24}H_{34}N_4O_5S)_2(H_2O)_2]^{\bullet+}$ molecular ion peak or parent ion peak; m/z 1025 due to $[Mo(C_{22}H_{33}N_4O_5S)_2]^{\bullet+}$ fragment ion; at m/z 1026 and 1027 isotopic abundant ion peak and m/z 513 due to $(C_{26}H_{33}N_4O_5S)^{\bullet+}$ base peak ion.

The mass spectrum of the pure ligand shows a molecular ion peak $m^{\bullet+}$ at m/z 491 due to $(C_{24}H_{34}N_4O_5S)^{\bullet+}$ parent ion peak[18] 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 $(C_{17}H_{16}N_3O_4S)^{\bullet+}$ due to loss of $(C_7H_{18}NO)^{\bullet+}$ fragment radieal cation having a molecular mass 132. While the mass spectrum of $[Mo(C_{24}H_{34}N_4O_5S)_2(H_2O)_2]$ shows a molecular ion peak $m^{\bullet+}$ at 1113 which corresponds to molecular weight of complex supported for the dimeric structure[19]. Beside this peak the complex showed the fragment ion peak at m/z 1025 due to $[Mo(C_{24}H_{34}N_4O_5S)_2]^{\bullet+}$ radical cation, it is also corresponds to loss of co-ordinated water. The peak of appreciable intensity have been observed at m/z values 491, 513, 514, 515, 1025, 1026 1027 and 1113.

The peaks of appreciable intensity observed at m/z values 514, 515, 1026 and 1027 due to isotopic abundances and m/z 513 value correspond to base peak intensity. The relative intensities of the various peaks give an idea about the stabilities of the above fragments.[20-21]

Some important mass spectral intensities of metal complex of Glimepiride are summarised in table(4).

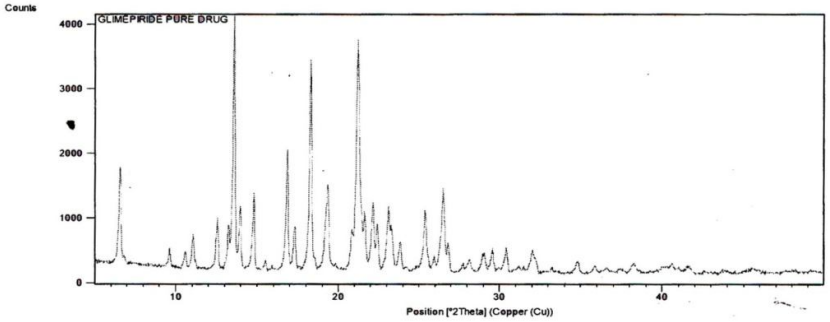
Table-4 : Mass spectral Intensities of Metal Complexes of Glimepiride

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-Molybdenum Complex	m/z 1113 ($m^{\bullet+}$) $[Mo(C_{24}H_{34}N_4O_5S)_2(H_2O)_2]^{\bullet+}$	Molecular ion peak.
		m/z 1025 $[Mo(C_{24}H_{34}N_4O_5S)_2]^{\bullet+}$	due to loss of co-ordinated water.
		m/z 513	base peak.

(iii) X-RAY DIFFRACTION STUDIES :-

X-ray diffractometer model 00011023505 with 45kV rotating anode X-ray generator was used for scanning the ligand and respective complex. Radiation used was Cuα (1W = 1.54060A^0). The samples were scanned in the range 25^0C. Powder data were indexed using computer software (Panjab University). X-ray diffraction studies also confirm the complexation and formation of new bands.

XRD DATA OF PURE LIGAND GLIMEPIRIDE



Dataset Name	GLIMEPIRIDE PURE DRUG
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Comment	Configuration=Flat Sample Stage, Owner=jagtar, Creation date=6/11/2007 3:57:00 PM Goniometer=PW3050/60 (Theta/Theta); Minimum step size 2Theta:0.001; Minimum step size Omega:0.001 Sample stage=PW3071/xx Bracket Diffractometer system=XPERT-PRO Measurement program=PU, Owner=jagtar, Creation date=4/15/2008 1:52:59 PM
Measurement Date / Time	2/28/2011 10:10:23 AM
Operator	Panjab University
Raw Data Origin	XRD measurement (*.XRDML)
Scan Axis	Gonio
Start Position [°2Th.]	5.0084
End Position [°2Th.]	49.9904
Step Size [°2Th.]	0.0170
Scan Step Time [s]	25.1954
Scan Type	Continuous
PSD Mode	Scanning
PSD Length [°2Th.]	2.12
Offset [°2Th.]	0.0000
Divergence Slit Type	Fixed
Divergence Slit Size [°]	0.9570
Specimen Length [mm]	10.00
Measurement Temperature [°C]	25.00
Anode Material	Cu
K-Alpha1 [Å]	1.54060
K-Alpha2 [Å]	1.54443
K-Beta [Å]	1.39225
K-A2 / K-A1 Ratio	0.50000
Generator Settings	40 mA, 45 kV
Diffractometer Type	0000000011023505
Diffractometer Number	0
Goniometer Radius [mm]	240.00
Dist. Focus-Diverg. Slit [mm]	91.00
Incident Beam Monochromator	No
Spinning	No

Pos. [°2Th.]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]	Area [cts*°2Th.]
6.5769	0.1171	13.43963	36.96	165.77
9.6248	0.0836	9.18947	7.42	23.77
10.5561	0.1171	8.38075	5.61	25.15
11.0783	0.0836	7.98682	11.03	35.33
12.5609	0.0836	7.04728	19.86	63.64
13.2334	0.0836	6.69059	17.45	55.90
13.5966	0.1171	6.51272	100.00	448.51
13.9677	0.1004	6.34050	23.61	90.77
14.8031	0.1171	5.98450	30.37	136.22
15.5129	0.1004	5.71222	3.31	12.73
16.8615	0.1004	5.25829	47.20	181.44
17.3321	0.1171	5.11656	16.19	72.60
18.3051	0.1338	4.84673	83.27	426.83
19.3576	0.0836	4.58550	33.15	106.21
20.8063	0.0836	4.26938	13.41	42.95
21.2003	0.1506	4.19093	90.48	521.73
21.6577	0.0836	4.10344	20.80	66.65
22.1546	0.1171	4.01252	27.82	124.76
22.4490	0.1004	3.96056	17.81	68.47
23.1159	0.1338	3.84778	25.39	130.14
23.3171	0.1004	3.81504	16.36	62.91
23.8470	0.1506	3.73144	11.45	66.05
25.3875	0.1004	3.50840	23.47	90.24
25.9445	0.1004	3.43433	5.43	20.89
26.5144	0.1171	3.36180	29.99	134.53
26.7990	0.1004	3.32674	11.34	43.60
27.7402	0.1004	3.21597	2.84	10.91
28.1590	0.1673	3.16909	4.71	30.17
29.0505	0.2342	3.07383	7.10	63.71
29.5916	0.1171	3.01884	9.27	41.57
30.4222	0.0669	2.93829	9.83	25.19
32.0273	0.1338	2.79460	8.49	43.52
33.2354	0.1004	2.69573	1.85	7.10
34.8346	0.1673	2.57555	4.23	27.13
35.9001	0.1673	2.50152	2.54	16.26
36.6025	0.2007	2.45511	1.81	13.93
37.4142	0.3346	2.40369	1.56	20.01
38.2693	0.3011	2.35193	3.86	44.56
40.5891	0.2007	2.22271	3.54	27.24
41.6287	0.2676	2.16957	2.33	23.86
43.8666	0.4015	2.06394	0.88	13.53
45.6466	0.6528	1.98587	1.39	46.95

Table - 5(a) XRD DATA OF GLIMEPIRIDE-MOLYBDENUM COMPLEX

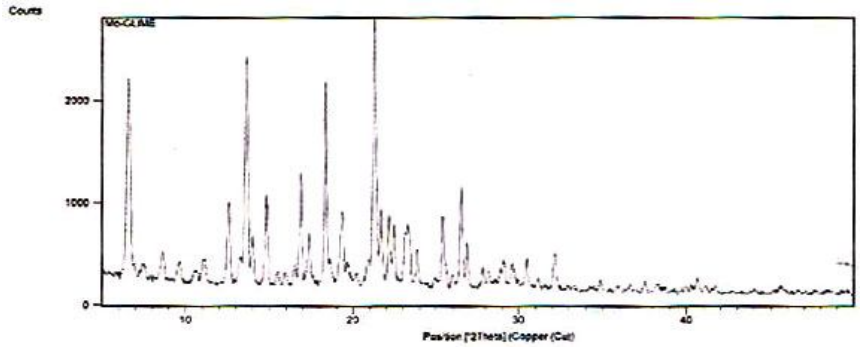

Fig. – (V b)

Table - 5(b):

Pos. [°2Th.]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]	Area [cts*°2Th.]
6.5695	0.1004	13.45470	73.97	191.20
6.6960	0.0669	13.20084	52.66	90.74
7.5559	0.2007	11.70043	4.73	24.46
8.6504	0.2342	10.22233	10.26	61.88
9.6664	0.2342	9.14999	6.35	38.27
10.5763	0.2007	8.36477	3.68	19.04
11.0986	0.2342	7.97231	8.99	54.24
12.5834	0.1673	7.03471	29.99	129.19
13.2173	0.1673	6.69873	9.43	40.63
13.6174	0.2175	6.50280	83.48	467.52
14.0033	0.1506	6.32443	17.65	68.43
14.7988	0.1840	5.98621	32.57	154.34
15.4873	0.1673	5.72160	5.21	22.46
15.9500	0.2007	5.55666	4.43	22.91
16.4911	0.1171	5.37554	7.85	23.68
16.8722	0.1673	5.25498	39.88	171.81
17.4095	0.1338	5.09397	17.38	59.89
18.3158	0.1506	4.84391	75.43	292.46
19.4009	0.1338	4.57538	24.21	83.43
19.6448	0.1338	4.51912	8.66	29.84
20.2547	0.2007	4.38439	4.31	22.27
20.8737	0.1338	4.25575	10.34	35.62
21.2414	0.1840	4.18292	100.00	473.87
21.6823	0.1338	4.09885	28.43	97.96
22.1340	0.1338	4.01619	27.34	94.21
22.4401	0.1171	3.96210	23.07	69.56
23.1080	0.1338	3.84907	18.83	64.89
23.4226	0.2342	3.79809	16.92	102.07
23.8608	0.1171	3.72931	14.32	43.17
25.3862	0.1338	3.50859	26.85	92.54
25.9796	0.1338	3.42978	5.10	17.58
26.5258	0.1506	3.36039	36.40	141.11
26.8568	0.1171	3.31972	17.43	52.55
27.8277	0.1338	3.20605	7.58	26.13
28.1891	0.1673	3.16577	6.32	27.24
29.1111	0.1338	3.06757	10.33	35.61
29.5900	0.2342	3.01900	9.28	55.94
30.4961	0.1506	2.93134	10.85	42.06
31.1695	0.1338	2.86953	4.49	15.47
32.1532	0.2007	2.78394	13.45	69.51
33.1206	0.4015	2.70481	1.06	10.93
34.8675	0.1673	2.57319	3.76	16.19
35.9038	0.2007	2.50127	1.76	9.08
37.5376	0.1338	2.39607	3.77	12.98
38.2722	0.2676	2.35176	2.60	17.94
40.5974	0.1171	2.22227	4.91	14.80
41.1227	0.2007	2.19509	2.25	11.62
41.7073	0.2007	2.16566	2.39	12.36
43.9523	0.4015	2.06012	0.84	8.71
45.5758	0.2856	1.98879	2.38	23.62

X-ray pattern of the complex glimepiride molybdenum trioxide shows a fairly strong pattern of the complex. In the case of glimepiride (Fig V a) 42 peaks can be onserved and the diffractogram of the

resultent complex shows (Fig V b) higher number of peaks i.e 50 which indicate that the pattern is fairly strong and the reflections clearly shows a complete conversion of the reactants to complex[22-24] against lack of periodicity in the diffractogram indicate the amorphous nature of the complex.[25] Important characteristic and comparable diffractograms of pure ligand and metal complex are given in table-6.

Table-6 : X-Ray Diffraction Data of Glimepiride with Metal Complexes

S.No.	Ligand/Complex	No. of peaks	Assignment
1.	Pure ligand-glimepiride	42	Amorphous in nature
2.	Molybdenum-glimepiride complex	50	Very strong pattern

Antidiabetic activity

The isolated glimepiride-metal complex were found to be more potent as compared to the parent drug. Hence as compare to standard synthetic drug the glimepiride-molybdenum[26] complex is 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 Oral glucose tolerance testr[27]. (PBRI, lab Bhopal). Analysis of data presented in table (6) reveals that the drug caused a marked decrease in blood sugar level. On comparing the hypoglycemic effect of molybdenum complex with parent drug it was revealed that in case of Mo - glimepiride treated male wistar rats blood sugar falls to 84.8+ 3.4928 mg/dl while in glimepiride treated rats blood sugar level falls to 90.2 +2.5884 mg/dl. These results clearly indicate a better hypoglycemic activity of Mo-glimepiride complex over its parent drug.

Table-7 : Antidiabetic Activity Analysis by Oral Glucose Tolerance Test

Oral Glucose Tolerance Test

Group	Treatment (mg/kg body weight)	Blood Glucose (mg/dL) Fasting	30 min.	90 min.
I	Control group + Glucose (2g) + Vehicle	73.8 ± 2.5884	142.8 ± 2.8635	120.6 ± 2.4083
II	Molybdenum complex of Glimepiride (2mg) + Glucose + Vehicle	72.6 ± 2.0736	103.8 ± 2.3874*	84.8 ± 3.4928**
III	Pure drug Glimepiride (2mg) + Glucose + Vehicle	74.4 ± 2.8809	100.6 ± 2.7018*	90.2 ± 2.5884**

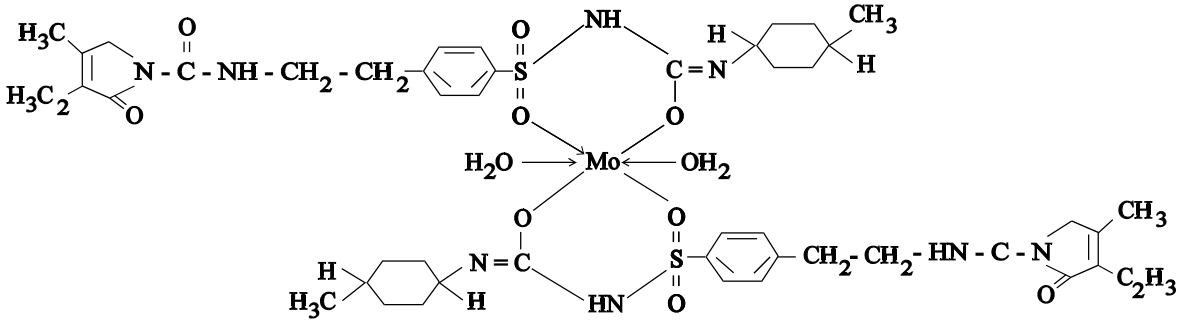

Fig (VI) Structure of Glimepiride-Molybdenum Complex

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 octahedral geometry.[28]

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