



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

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### ABSTRACT

Glibenclamide is a current, potent hypoglycemic agent used in NIDDM (non-insulin dependent *Diabetes mellitus*). Metal complexes of glibenclamide has been synthesised by reaction with mercury (II) in the form of its chloride. The conductometric titration using monovariation method indicates that complex is non-ionic and  $ML_2$  type which was further confirmed by Job's method of continuous variation as modified by Turner and Anderson. Analytical data agrees with the molecular formula  $(C_{23}H_{28}ClN_3O_5S)_2 Hg$  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, IR spectra and NMR spectra.

**Key words:** Synthesis; antidiabetics; glibenclamide; IR spectra, NMR Spectra.

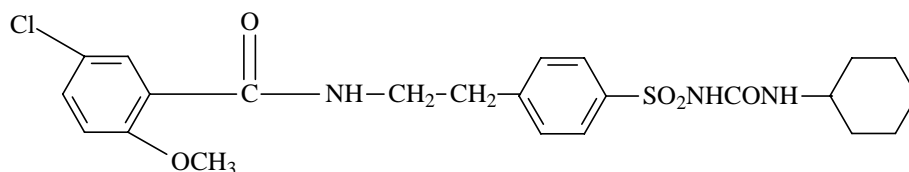
### INTRODUCTION

Man has been in continued search for chemotherapeutic agents right from the earliest times, about 2000 B.C. or even earlier. As a result of this research several naturally occurring substances, plant materials and minerals including Arsenic, Mercury, Bismuth, Gold and Silver as metals or as their salts have been used for several thousand years, especially in *Ayurveda* and *Unani* system of medicines. In the early part of the twentieth century, organo-metallic compounds emerged as important agents in the treatment of

syphilis, tropical diseases etc<sup>1-3</sup>. Chemically arsenic, antimony and bismuth belong to the same family and have some common pharmacological actions. Mercurials comparatively, still hold importance in medicine and organic mercurials are used as divretics<sup>4</sup>. The discovery of vitamin B<sub>12</sub> and copper phthalocyanine has given impetus to the development of metal complexes with organic ligands. A survey of literature reveals that metal complexes of some drugs have been found to be more potent than the drug alone therefore in continuation of our previous work<sup>5-10</sup> on metal complexes of oral antidiabetic agents of

hypoglycemic activity, the synthesis and structural studies of glibenclamide-Hg complex is described here. Glibenclamide (Euglucon, 1-(4-(2-chloro-2-methoxybenzamide<sup>o</sup>) ethyl) – benzene sulphonyl)-3-cyclo hexyl urea, is a sulphonyl urea derivative having melting point 169-174°C is a white or almost white crystalline orderless powder, practically without taste, insoluble in water and soluble in ethanol, methanol and in alkalisolution. It dissolves in diethyl ether also. Glibenclamide is a second

generation oral hypoglycemic agent which is more potent than those of first group<sup>11</sup> and is used to assist in the control of mild to moderately severe type (II) *Diabetes mellitus*. Complexation of sulphonyl urea with lighter transition metals has been studied in detail<sup>12-13</sup>. A perusal of available literature shows that many drugs possessed modified pharmacological and toxicological properties when administered in the form of metallic complexes.



**Fig. 1: Structure of Glibenclamide**

## EXPERIMENTAL

### Ligand-Metal ratio

#### Pure glibenclamide (1)

Trade name, Euglecon a sulphonyl urea derivative is supplied by Aventis pharma Ltd; Goa in powdered form. 0.005 M drug and mercuric (II) chloride (HgCl<sub>2</sub>) 0.01M (Analar grade) were prepared in purified 80% ethanol. Glibenclamide (20ml) was diluted to 200ml and titrated conductometrically against mercuric chloride at 27±1°C.

Formation of 2:1 (L<sub>2</sub>M) ratio was also confirmed by Job's method<sup>14</sup> of continuous variation as modified by Turner and Anderson<sup>15</sup> using Δconductance as index property. From these value, the stability constant (logk) and free energy change (-ΔF) were also calculated<sup>16-17</sup> (Fig. 2).

### Synthesis of Complex

The chemicals used in this synthesis were all of analytical grade. A weighed quantity of glibenclamide (2 mol) was dissolved in minimum quantity of 80% ethanol. The mercuric (II) chloride solution was prepared by dissolving it separately in the same solvent. Lignd solution was added slowly

with constant stirring into the solution of metallic salt at room temperature maintaining the pH between 6.2 to 6.9 by adding dilute NaOH solution. On refluxing the mixture for 3h at 80°C on cooling, the complex separated out which was filtered off, washed well with ethanol (80%) and finally dried in vacuum and weighed. The elemental analysis of the isolated complex was carried out using the reported methods<sup>18-19</sup>. In the complex, mercury was estimated gravimetrically as sulphide, nitrogen by Kjeldhal method and sulphur by massenger's method, using modified digestion mixture<sup>20-21</sup>. The IR spectrum of the ligand as well as of the complex was recorded on Perkin Elmer Spectrophotometer RX1 (4000-450 cm<sup>-1</sup>) CDRI, Lucknow.

The <sup>1</sup>H-NMR spectra of the ligand and isolated complex was reported on a Bruker DRX-300 spectrometer (CDRI Lucknow). Deuterated Acetone was used as a solvent the other features of NMR spectrum were the aromatic proton resonances located and the presence of unresolved multiplet is suggestive of excessive deshielding of aromatic protons. The NMR signal of enolic OH group is observed in the ligand while absent in the complex indicates the involvement of enolic OH group in complexation<sup>25-27</sup>.

**Job's Method as modified by Turner & Anderson:  
GLIBENCLAMIDE - MERCURIC CHLORIDE**

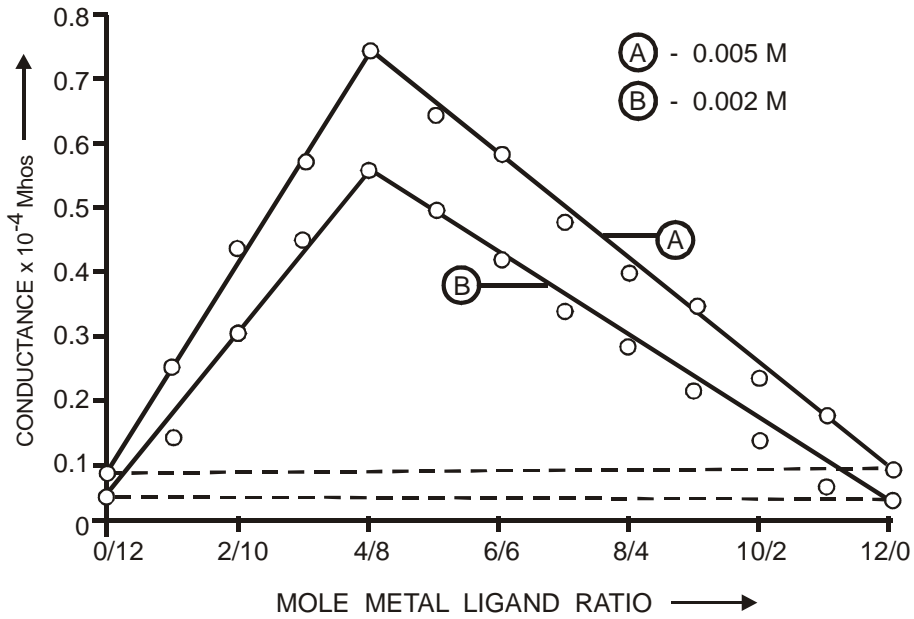


Fig. 1:

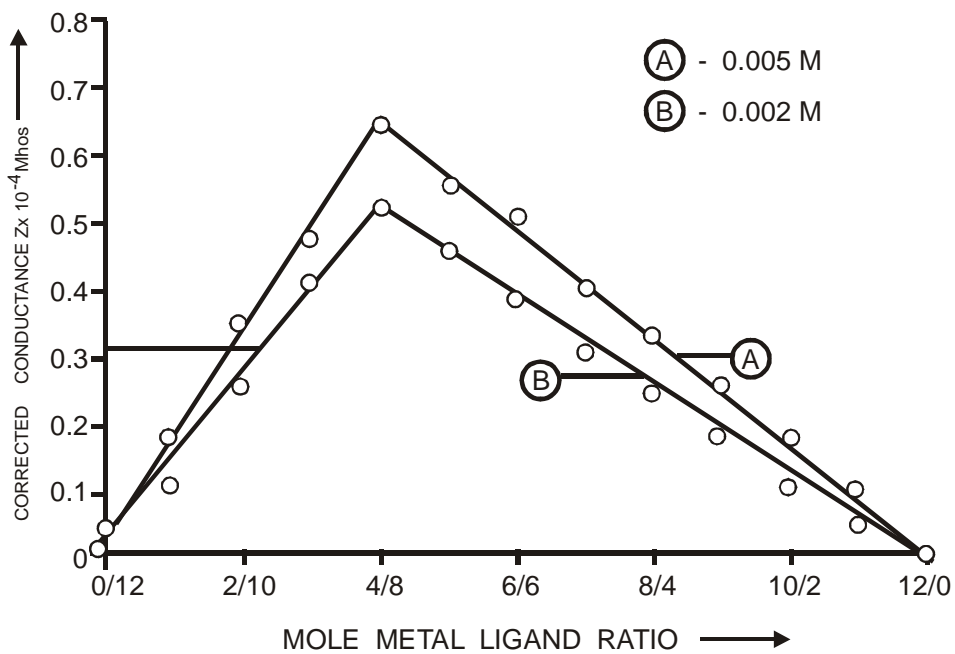


Fig. 2:

**Table 1: Physico-chemical and Analytical data of Glibenclamide-Mercury Complex**

Composition of Complex	(C <sub>23</sub> H <sub>28</sub> ClN <sub>3</sub> O <sub>5</sub> S) <sub>2</sub> Hg
Ligand metal ratio	2:1
Yield (%)	65%
Colour	greyish
Geometry	Tetrahedral
Melting point (°C)	178°C
% of metal observed (required)	15.20 (16.76)
% of carbon observed (required)	46.36 (46.50)
% of hydrogen observed (required)	7.35 (4.71)
% of nitrogen observed (required)	7.05 (7.07)
% of sulphur observed (required)	5.38 (5.39)
% of Chlorine observed (required)	5.96 (5.98)
Stability constant (logk) lit./mole	11.59 lit./mole
Free energy change (ΔF k.Cal./mole)	-15.95 k.Cal./mole

**Table 2: Specific IR assignments of Glibenclamide and its mercury complex**

IR Frequencies (cm <sup>-1</sup> )	Assignments
670±5	Metal oxygen bond
764	-CH stretching frequencies
929	Aromatic ring vibrations
1030	S=O stretch similar to sulphoxides (B/359)
11625	-SO <sub>2</sub> absorption band (JD/38)
12165	-SO <sub>2</sub> N frequency band
1280	-C=N stretch similar to secondary amides
13555	six membered enolic ring structure modified in complex
1702	-C=O stretching frequency
3373	Urea NH stretching
5415	vCl frequency

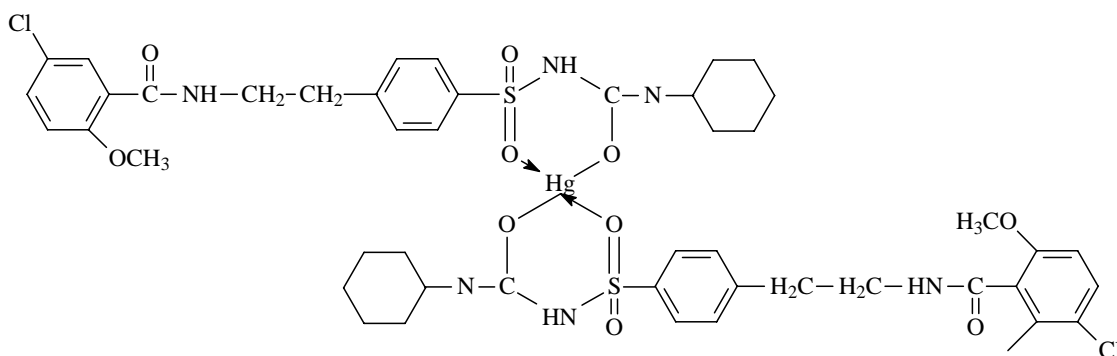
**Table 3**

Glibenclamide	Glibenclamide - Mercury Complex
Mercury Complex	
<sup>1</sup> HNMR (300 MH2, Acetone):	<sup>1</sup> HNMR (300 MH2,
8.14 (bs1H,-SO <sub>2</sub> NH), 7.99 (d2H,	<sup>1</sup> D Acetone); 8.00 (bs.H-SO <sub>2</sub> NH)
J=8Hz); 7.56 (d,2H J=8Hz)	7.97 (d, 24-NH-CH <sub>2</sub> );
6.29 (Urea NH) 6.26	7.18 (d, 2H J = 8Hz)
(t, <sup>1</sup> H-NH-CH <sub>2</sub> , J=6Hz); 2.86	3.70 (NHC-O-Hg),
Cq, 2H, J=6Hz), 1.74 (M4H),	3.01-3.03 (Urea'NH) 3.78
δ 8.14 (due to OH proton)	O-CH <sub>3</sub> , 1.77 (M.4H)

## RESULTS AND DISCUSSION

The synthesized complex is greyish, powdered and stable. It is soluble in acetone, DMF and DMSO etc. Infrared spectral studies :- The IR spectrum of the ligand and the isolated complex was scanned in the range 4000-400  $\text{cm}^{-1}$  and the probable assignments are given in tables. The proposed structure for the isolated complex is also supported by IR absorption bands and characterized by the prominent band in the region of 3302-3373  $\text{cm}^{-1}$  due to urea NH stretching, a very sharp peak observed at 764  $\text{cm}^{-1}$  due to -CH stretching. At 1702  $\text{cm}^{-1}$  the absorption was due to C=O, a strong absorption band at 11612  $\text{cm}^{-1}$  due to  $\text{SO}_2$  frequency<sup>22-23</sup>. The absorption peak of chlorine occurred at 541  $\text{cm}^{-1}$ . The carbonyl band was observed at 1713  $\text{cm}^{-1}$  in reference standard; but in transition metal complex this stretching frequency; which got shifted downward at 1702  $\text{cm}^{-1}$  region.

Also the absorption peak of  $\nu\text{S}=\text{O}$  group is observed at 1156  $\text{cm}^{-1}$  in reference standard. While at 1162  $\text{cm}^{-1}$  in the complex. The shift of the  $\nu\text{C}=\text{O}$  and  $\nu\text{S}=\text{O}$  group by changing frequency in the complex indicate that these group are involved in the complexation. 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  $\text{cm}^{-1}$  in the complex that may be assignable to M-O frequency<sup>24</sup>. The tentative structure of the complex is further supported from the values of <sup>1</sup>HNMR as well as from the IR frequencies.  $\nu(\text{C}=\text{N})$  1280 and 2362 indicate the enolization through nitrogen. NMR signal at  $\delta$  8.14 in the ligand while absent in the complex indicate the involvement of enolic OH group in complexation. Moreover, the enolization of  $\text{N}_1$  hydrogen is not possible because it is simultaneously attracted from the groups  $\text{SO}_2$  from one side and C=O on the other side<sup>25-28</sup>.



**Fig. Structure of Glibenclamide - Mercury Complex**

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.

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