Synthesis and Characterization of Glimepiride Yttrium Complex

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Abstract*—Glimepiride is a sulphonylurea drug that is active in the management of non-insulin dependent diabetes mellitus (NIDDM). It stimulates the release of insulin by inhibiting the efflux of K^+ (K^+ channel blockers) from pancreatic ß-cells. Glimepiride yttrium complex was synthesized by reaction of glimepiride with yttrium nitrate pentahydrate ($Y(NO_3)_3.6H_2O$). The metal complex was characterized based on elemental analysis, UV, IR and ^{13}C NMR spectroscopy. The result of the elemental analysis was found to be in agreement with the calculated values. The ligand's electronic spectrum showed intra ligand charge transfer (ILCT), resulting from the presence of the chromophores present in the ligand. The electronic spectrum of the complex formed suggested intra ligand charge transfer (ILCT), ligand to metal charge transfer (LMCT), and d-d transition. IR spectrum of the yttrium complex showed the complexation of the metal ion to two carbonyls and one amino group. This further showed that the glimepiride acted as bidentate ligand. In the ^{13}C NMR spectrum, it is evident that the pyrrole ring was involved in coordination to the metal ion. Tetrahedral geometry was proposed for the complex.*

Keywords— Glimepiride, metal complex, spectrum, synthesis.

I. INTRODUCTION

Insufficiency of some metals in the body can cause disease. Iron deficiency causes anemia, copper deficiency causes heart disease in children, while zinc deficiency causes retardation of growth [1].

Therefore, iron, copper, and zinc are needed to support biological life [2].The unique characteristics of harmful metals like arsenic, platinum, technetium, and gadolinium are being harnessed by scientists to develop complexes that can be used as diagnostic agents [3]. Biochemistry has been recently considered as the coordination chemistry of living system, this is because one third of all enzymes in the human body contain a metal ion as essential component [4]. Interests in complexes have broadened over the years due to their roles in various biochemical, pharmaceutical, chemical and industrial processes [5]. Using ion specific chelating agents to remove metal overloads in the body is a new evolving science of bioinorganic chemistry [1]. The unique properties of some metals is harnessed in medicinal inorganic chemistry for the design of new drugs [6]. Exposure to toxic heavy metals can occur as a result of metal overload or heavy metal exposure which alter the functions of some body organs like the kidney and liver [7]. Recently, the use of sulphonylureas has been given much attention due to their high complexation ability with metals. Sulphonylureas are used in the management of type 2 diabetes. They enhance insulin secretion from the beta-cells [8].Studies on complexation of glimepiride with yttrium is relatively unavailable. It is therefore important to know the synthesis and complexation of yttrium with glimepiride, and also the structure of the complex formed. This present work focuses on the synthesis and characterization of yttrium with glimepiride. The structure of glimepiride is shown in Figure 1.

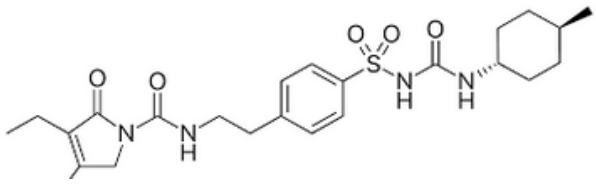

Fig.1: Structure of Glimepiride

II. EXPERIMENTAL

2.1 Chemicals and solvents

All chemicals and reagent used in this experimental work were of analytical grade and were imported from E. Merck Co Germany without further purification. The chemicals include pure glimepiride drug and yttrium nitrate pentahydrate($Y(NO_3)_3.6H_2O$).

2.2 Physical Measurements

The melting points were determined by MPA 160 melting point apparatus. The elemental analysis were carried out following a reported procedure [9]. The molar conductance of the complex was determined in DMSO using MRC

conductivity meter, with cell constant of 1.05. Atomic Absorption Spectroscopy was done using Duck-2010 Spectrophotometer (Duck instrumental company). About 0.5 g of the sample was digested using mixed acids of nitric acid (5 ml) and perchloric acid (2 ml) for 3 h at temperature of 150-250°C, the digest was allowed to cool, filtered, and made up to the mark using deionized water. The concentration of the analytes were further determined using AAS. The IR spectra of the complex and ligand were recorded using Perkin Elmer Paragon 1000 FT-IR Spectrophotometer (spectrum BX) equipped with cesium iodide window in the range of 4000-350 cm^{-1}. The electronic spectra of both the ligand and complex were recorded with Perkin Elmer (lambda 25) spectrometer in the range of 200-800 nm and DMSO as solvent. The mass spectra of the ligand and isolated complex were obtained using GCMS-QP 2010 plus Shimadzu, Japan. The ^{13}C Nuclear Magnetic Resonance (NMR) spectra of the ligand and metal complex were recorded with Varian 400 MHz Unity INOVA, using DMSO as solvent.

2.3 Synthesis

The preparation of the complex was carried out as reported in a previous publication [10]. 12.25 g (0.025 mol) of glimepiride was weighed and dissolved in 20 ml of ethanol (80%). The yttrium nitrate salt was prepared by dissolving 9.125 g (0.025 mol) of the salt separately in 25 ml ethanol. The glimepiride solution was added slowly into the salt solution with stirring, maintaining the pH between 6.0-6.5 by adding dilute solution of NaOH and refluxing for 3 hours. On cooling, the complex separated out, and was further washed with ethanol, recrystallized, filtered and dried in vacuum [11, 12]. The melting point and yield were recorded [13].

III. RESULTS AND DISCUSSION

3.1 Physical Properties

The physical properties of the ligand and metal complex are summarized in Table 1. Differences in melting points of the ligand as compared to the metal complex suggests the formation of new product. The molar conductivity of the metal complex was observed to be less than 30 $Ohm^{-1}cm^2mole^{-1}$, showing that the complex is a non-electrolytic solution [14, 15, 16].

3.2 Elemental Analysis

The % composition of C, H, N, O, S and the metal in the complex , are summarized in Table 2. This also suggested the formation of new product. The elemental analysis of glimepiride and its complex shows that the experimental values are in agreement with the calculated values. It also suggests the mole ratio of the ligand to the metal to be 2:1.

3.3 IR Absorption Analysis

The IR spectra [17, 18] of both the ligand and complex formed were recorded using Perkin Elmer Paragon 100 FT-IR Spectrophotometer, ranging 4000-350 cm^{-1}, and the probable assignment given in Table 3. In the ligand, the vibration frequency at 3468.57 cm^{-1} has been assigned to ν(NH), while in the complex, the NH stretch was seen at 3468.00 cm^{-1}. This suggests that coordination did occur at this site. The C=O band was observed at 1640.41 cm^{-1} in the ligand, but shifted to 1694 cm^{-1} in the complex. This shift in the stretching frequency indicates the involvement of the C=O group in complexation. The C-O stretch was absent in the ligand, but was present in the complex, this suggests conversion of C=O group to C-O during complexation.

Table.1: Physical properties of Glimepiride and its metal complex

Ligand/Metal Complex	Color	Yield	Melting point (°C)	Molar conductance $Ohm^{-1}cm^2mole^{-1}$
Glimepiride	White	------	207	25.7
Y complex	White	69.71	260	27.18

Table.2: Elemental analysis of Glimepiride and its metal complex.

Ligand/Metal Complex	% C	% H	% N found (calculated)	% O	% S	% Metal
Glimepiride	58.77	6.95	11.92	16.10	5.22	-----
Y complex	52.21 (53.92)	6.42 (6.32)	10.43 (10.48)	14.95 (14.96)	5.95 (6.00)	8.28 (8.32)

Table.3: IR Spectral data of Glimepiride and its metal complex.

Ligand/Metal Complex	ν(NH)	ν(C=O) (RCONH)	ν(S=O) (sulfone)	ν(C-O)	ν(C-H) (aromatic)	ν(C-H) (aliphatic)
Glimepiride	3468.57	1640.41	1316	----	3062.91	2937.14
Y complex	3468.00	1674.00	1310.36	1193.52	3068.57	2941.93

3.4 Electronic spectral analysis

In the spectrum of the ligand, absorption band was observed at 200 nm which have been assigned n-π^* transition. This is as a result of the chromophores that are present in the ligand that includes C=O, S=O, C=C respectively. This transition is also called intra-ligand charge transfer (ILCT). Absorption bands in the spectrum of the metal complex was observed at 250 nm, 450 nm, and 600 nm which have been assigned n-π^* (ILCT), LMCT, and d-d transition respectively [19].

Table.4: Electronic spectral data of glimepiride and its metal complex.

Ligand/ Metal Complex	λmax (nm)	Assignment
Glimepiride	200	n-π^* (ILCT)
Y Complex	250	n-π^* (ILCT)
	400	LMCT
	600	d-d transition

3.5 Mass Absorption Analysis

The mass spectral data as summarized in Table 5, gave useful information in determining the molecular weight of the componds [20]. In the mass spectrum of the ligand, prominent peak was observed at m/z 491 due to $[C_{24}H_{34}N_4O_5S]^{+\cdot}$molecular ion [21] peak which is in agreement with the structure of the ligand. Another appreciable peak was observed at m/z 352, which corresponds to $[C_{16}H_{20}N_3O_4S]^{+\cdot}$due to loss of $C_8H_{14}NO\cdot$m/z 140. Y complex showed molecular ion peak at m/z 1069 $[C_{48}H_{67}YN_8O_{10}S_2]^{+\cdot}$which corresponds to the molecular weight of the complex with base peak at m/z 591$[C_{29}H_{35}YN_4O_4]^{+\cdot}$. Other peaks of appreciable intensity were observed at m/z 971, 791, 631, 619, 479, 451, 413, 351, 283, 237, 199, 112 and 74.

Table.5: Mass spectral data of glimepiride and its metal complex.

Ligand/Metal Complex	Ms (m/z) Values	Assignment
Glimepiride	m/z 491 $[C_{24}H_{34}N_4O_5S]^{+\cdot}$	Molecular ion peak
	m/z 352 $[C_{16}H_{20}N_3O_4S]^{+\cdot}$	Base peak
Y Complex	m/z 1069 $[C_{48}H_{67}YN_8O_{10}S_2]^{+\cdot}$	Molecular ion peak
	m/z 971 $[C_{32}H_{41}YN_6O_8S_2]^{+\cdot}$	Loss of C_7H_{13}
	m/z 791 $[C_{32}H_{40}YN_6O_8S_2]^{+\cdot}$	Loss of $C_{16}H_{26}N_2O_2$
	m/z 631 $[C_{32}H_{41}YN_4O_4S_2]^{+\cdot}$	Loss of $C_{16}H_{30}N_4O_6S_2$
	m/z 591 $[C_{29}H_{35}YN_4O_4]^{+\cdot}$	Base peak

3.6 ^{13}C-NMR spectral Analysis

As shown in Table 6, C=O (pyrrole ring) resonated at 174 ppm in the sectrum of the ligand, but shifted downfield in the Y complex (186 ppm). This downfield shift as observed in the complex indicates the complexation to the metal ion through the C=O group. The signal due to C=O (RCONH) was observed at 153 ppm in the ligand, but shifted downfield in the Y complex to 164 ppm as a result of complexation occurring through the group.Peaks observed at 154-159 ppm and 134-137 ppm indicates C=C carbons of the pyrrole ring.

Table.6: ^{13}C-NMR spectral data of glimepiride and its metal complex.

Ligand/ Complex	C=O (pyrrole ring)	C=O (RCONH)	C=O (NHCONH) (δ ppm)	4 C (aromatic)	C-CH_3 (pyrrole ring)	C-CH_2CH_3 (pyrrole ring)
Glimepiride	174	153	152	127	154	134
Y Complex	186	163	152	127	159	137

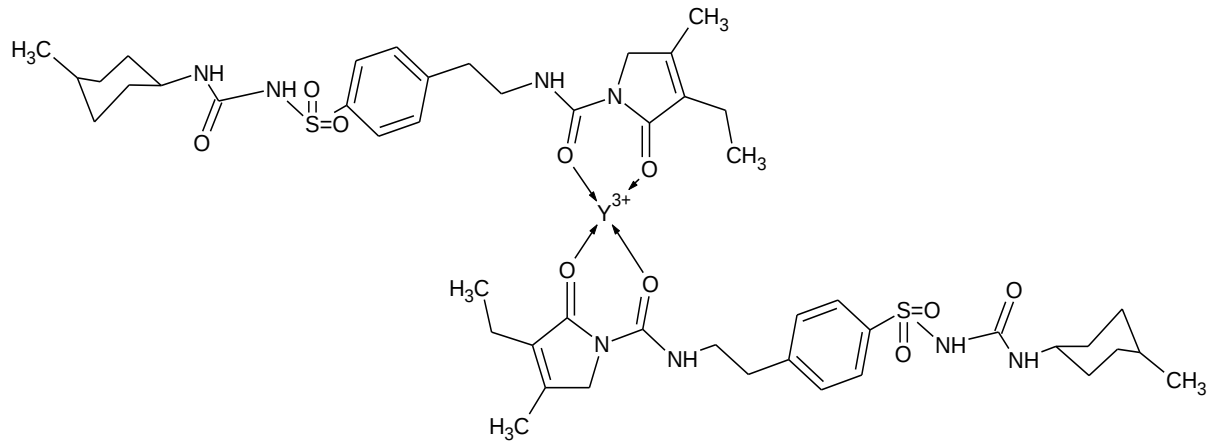

Fig.2: Proposed structure for Y (III) glimepiride complex.

From the elemental analysis, electronic, IR and ^{13}C NMR spectra of the metal complex, the structure of the metal complex have been proposed in Fig. 2 above.

IV. CONCLUSION

Y(III) complex was successfully synthesized. The melting point, conductivity, color, IR spectrum, UV spectrum, mass spectrum, ^{13}C NMR spectrum and elemental analysis all supported the proposed structure of the metal complex. Glimepiride can be successfully used to eliminate toxic metals from biological systems.

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