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RESEARCH ARTICLE

Anti-Diabetic Activity of Chelating Bis N- Propylethylenediamine Zinc Complex

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ABSTRACT

Metals are an integral part of many structural and functional components in the body, and the critical role of metals in physiological and pathological processes has always been of interest to researchers. Metals have been used in the treatment of diseases of humans since ancient time. The primary objective of the study was to describe anti-diabetic activity by bis N-propylethylenediamine zinc (II) complex. The synthesised complex was characterised by elemental analysis, FTIR, powder X-ray diffraction and EDAX. Stability of the complex was determined by TGA & DTA. Anti-Diabetic activity was studied by invitro alpha glucosidase and alpha amylase assay.

Keywords: Chelate complex, Charge Transfer Transition, Thermal analysis, Co-ordination Compound, Alpha glucosidase and Alpha amylase

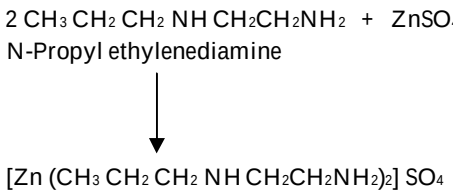
INTRODUCTION

It is also known as simply diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. This high blood sugar produces the symptoms of frequent urination, increased thirst, and increased hunger. The common symptom of diabetes includes poly urea (frequent urination), polydipsia (increased thirst) and poly phagia (increased appetite). [1] Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced. [2] Metal complexes are playing an

important role in pharmaceutical field, catalyst in chemical industries, material synthesis and photochemistry. Bioinorganic chemistry can exploit the unique properties of metal ions for the design of new drugs. Research has shown significant progress in utilization of transition metal complexes as drugs to treat several human diseases. Transition metals exhibit different oxidation states and can interact with a number of negatively charged molecules. This activity of transition metals has started the development of metal based drugs with promising pharmacological application and may offer unique therapeutic opportunities

MATERIALS AND METHODS

The chelating complex bis N-propylethylenediamine Zn (II) was prepared from zinc sulphate hepta hydrate and N-propylethylenediamine. 2 mM aqueous solution of metal salt was taken in a beaker and 6 mM of N-propylethylenediamine was added drop by drop. With order to get proper mixing continuous stirring for an hour, 2 ml of ethyl alcohol was added for complete precipitation then transferred into a Petri dish to remove solvent in hot air oven at 45°C. After 3 days, white-coloured bis N-propylethylenediamine Zn (II) complex was formed. [3]



ELEMENTAR Vario EL III is used as CHNS analyser. Precision >0.1%abs, Auto sampler, Ultra microbalance Analysis time is automatically optimized. FTIR spectrometer model Thermo Nicolet Avtar 370 DTGS, Range: 4000- 400 cm-1 Perkin Elmer STA 600 is used as thermo gravimetric analyzer. TG Sensitivity: 200 mg , DTA Sensitivity: +1000µV, temperature range: Ambient to 1200 °C. Model of X-ray diffraction is Bruker AXS D8 Advance, Maximum usable angular range:30 to 1350, using Diffraction plus software,Wavelength:1.5406A° EDAS allows the elemental composition of the specimen to be measured. Jeol 6390 LA / OXFORD XMXN is used as spectrometer, resolution 136 eV and acceleration voltage 0.5 to 30 kV. Alpha glucosidase activity was measured by the determination of reducing sugar arise from hydrolysis of sucrose by alpha glucosidase enzyme. Acarbose drug (10mg/mL DMSO) was used as reference. The reducing sugars produced by the action of α amylase react with dinitrosalicylic acid and reduce it to a brown coloured product, nitro amino salicylic acid. Acarbose drug (10mg/mL DMSO) was used as reference. All the characterizations were taken at SAIF Cochin.

RESULT AND DISCUSSION

Elemental Analysis

The empirical formula and possible geometry of the complex is confirmed by elemental analysis. The analytical data (Table.1) suggest that the chelating complex is mono nuclear with the ligand coordinated to the central metal atom. The metal to ligand ratio of N-propylethylenediamine zinc (II) complex is 1:2 with empirical formula $ZnN_4C_{10}H_{28}SO_4$. The N-propyl ethylenediamine Zn (II) complex exhibits as square planar complex. The observed and calculated values of the percentage of elements are well agreed with each other. [4]

FT-IR SPECTROSCOPY

In order to study the bonding of the ligand to the metal, the infrared spectrum of the ligands compared with spectra of the corresponding metal chelates. The infrared spectra provide valuable information regarding the nature of the bonding attached to the metal ion. [6] . The ligand N-propylethylenediamine (Fig.3 & 4) exhibits N-H stretching frequency at 3287 cm^{-1}, the aliphatic amine of C-H stretching frequency at 2953 cm^{-1} and C-N stretching frequency at 1377 cm^{-1}. The chelating bis N-propylethylenediamine Zn (II) complex shows that, (Table 3) the N-H stretching frequency at 3308 cm^{-1}, the aliphatic amine of C-H stretching frequency at 2932 cm^{-1} and C-N stretching frequency at 1357 cm^{-1} and M-N stretching frequency at 510 cm^{-1}. The free ligand with stretching frequency is greater than the corresponding metal complex. It is due to the electron flow from the ligand to the metal (CTT). The stretching frequency $\nu_{C\text{-}N}$ constantly decreases in the metal complex compared with free N-propylethylenediamine. It is evident that the ligand surely co-ordinated with the ligand. [5]

THERMAL ANALYSIS

The thermal behaviour of the synthesised chelating complexes are studied to establish different decomposition pattern and to confirm the proposed stoichiometry. The results are summarised in **(Table 4)** The chelating bis N-Propylethylenediamine zinc complex **(Fig.5)** exhibits four endothermic peaks. The complex is stable up to 218.13 °C. The ligand N-methyl ethylenediamine liberates at this temperature, by the loss of 30% weight. Upon increasing the temperature the two methylamine gets liberates at 338.87 °C and 394.86 °C, by the loss of 10% weight respectively. At 660.25°C zinc sulphate dissociate into SO_3 and ZnO. Above the temperature stable metal oxide is appeared. The decomposition pattern of the chelating complex confirms the proposed stoichiometry and geometry. [7]

POWDER X-RAY DIFFRACTION STUDY

The X-Ray diffraction method is the most powerful technique available for the examination of complex in the solid state. X-Ray diffraction is used to obtain information about the structure and composition. Average crystalline sizes of the complex and hkl planes are given in the (Table 5). The XRD patterns of chelating bis N-propylethylenediamine Zn (II) complex is shown in (Fig.6). The chelating Zn (II) complex shows that the sharp peak at 8.433°, 15.307° and 17.016°. Which indicates the complex is high quality and polycrystalline in nature. It exhibits 100% intensity peak at 8.433°. The hkl plane of the complex is calculated by $\sin^2\theta$ method. The high intense peak with hkl planes are 8.433° (110), 15.307° (211) and 17.016° (111). The crystalline sizes are predicted for prominent peaks for the synthesised chelating complexes by using Debye-Scherrer's formula. The complex with average crystalline size is 80. [8]

ENERGY DISPERSIVE X-RAY ANALYSIS

EDX Spectroscopy used for elemental identification by measuring the number and energy of x-rays emitted from a specimen after excitation with an electron beam. The elemental percentage is shown in (Table. 6). Metal complex with their elements are shown in (Fig.7). Bis N-propylethylenediamine zinc complex exhibits the weight percentage of carbon is 33.26%. This is well agreed the percentage of carbon obtained from CHNS analyser 32.80%. The weight percentage of nitrogen is 15.45%, which is well agreed with the percentage of nitrogen observed from CHNS analyser 15.35%. The weight percentage of sulphur is 8.78%, which is agreed with the percentage of sulphur observed from CHNS analyser 9.78%. The weight percentage of zinc is 18.92%, which is well agreed with the percentage of zinc obtained from calculated 17.87%. All these data further prove the square planar geometry of this complex. [9]

***In-vitro* ANTI-DIABETIC ACTIVITY OF METAL COMPLEXES**

Diabetes is characterized by hyperglycemia, altered lipids, carbohydrates, and proteins metabolism which affect the patient quality of life in terms of social, psychological well- being as well as physical ill health [10]. Two forms of diabetes (Types 1 and 2) differ in their pathogenesis, but both have hyperglycemia as a common hall mark. In type 2

diabetes, hyperglycemia caused due to impairment in insulin secretion combined with or without impairment of insulin action [11].

***In- vitro* Alpha Glucosidase Inhibition Assay**

Alpha glucosidase activity was measured by the determination of reducing sugar arise from hydrolysis of sucrose by alpha glucosidase enzyme. The effects of samples were assayed according to the method Matsui et al., with slight modifications. Acarbose drug (10mg/mL DMSO) was used as reference.

Procedure

Different volumes of sample such as 12.5µL-100µLfrom the stock solution given were taken and was incubated for five minutes before initiating the reaction with substrates sucrose(37mM), in a final reaction mixture of 1mL of 0.1 M phosphate buffer (pH 7.2). The reaction mixture was incubated for 20 and 30 min at 37^{0}C and the reaction was stopped incubating in a boiling water bath for 2 minutes. A tube with phosphate buffer and enzyme was maintained as control. The tubes were added with 250µL of glucose reagent and incubated for 10 minutes followed by measuring absorbance at 510nm using a micro plate reader.

Calculation

$$\% \text{ inhibition} = \frac{\text{control} - \text{test}}{\text{control}} \times 100$$

***In vitro* Alpha Amylase Inhibitory Assay**

The reducing sugars produced by the action of α amylase react with dinitrosalicylic acid and reduce it to a brown coloured product, nitro amino salicylic acid. Acarbose drug (10mg/mL DMSO) was used as reference.

Procedure

Different volumes of sample such as 12.5µL - 100µL from the stock solution given and make up to 1000µl using 25mM phosphate buffer pH 6.9, containing 25µl of porcine α amylase at a concentration of 0.5 mg/ml were incubated at 25°c for 10 min. After pre incubation, 25µl of 0.5% starch solution in 25mM phosphate buffer pH 6.9 was added. The reaction mixtures were then incubated at 25°c for 10 min. The reaction was stopped with 50µl of 96mM 3, 5 dinitro salicylic acid colour reagent. The micro plate was then incubated in a boiling water bath for 5 min and cooled to room temperature. Absorbance was measured at 540nm using a microplate reader.

Calculation

$$\% \text{ inhibition} = \frac{\text{control} - \text{test}}{\text{control}} \times 100$$

The In vitro anti-diabetic study of metal complex is carried out by alpha glucosidase inhibition assay and alpha amylase inhibition assay. Chelating zinc complex exhibits greater anti- diabetic activity in both these assays than standard Acarbose. Zinc is a natural component of insulin, a substance crucial to the regulation of carbohydrate metabolism.

CONCLUSION

The synthesised Chelating complex bis N-propylethylenediamine Zn (II) complex exhibits as square planar geometry. The stretching frequency $\nu_{C\text{-}N}$ constantly decreases in the metal complex compared with free N-propylethylenediamine. It is evident that the ligand surely co-ordinated with the ligand. The complex is stable up to 218.13 °C. The decomposition pattern of the chelating complex confirms the proposed stoichiometry and geometry. The complex exhibits sharp peaks. It indicates the complex is high quality and polycrystalline in nature. It exhibits 100% intensity peak at 8.433°. The complex exhibits greater anti- diabetic activity in both alpha glucosidase and alpha amylase assays than standard Acarbose.

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Table.1 Elemental Analysis and physical parameters

Complex	Molecular Weight	Colour	pH	Molar Conductance	C % Obs. (Cal)	H % Obs. (Cal)	N % Obs. (Cal)	S % Obs. (Cal)
$ZnN_4C_{10}H_{28}SO_4$	365.85	White	8.43	1.347	32.80 (32.83)	7.68 (7.73)	15.31 (15.35)	9.78 (8.76)

Table 2 Vibrational Frequencies of Ligand (pren) and Complexes

Ligand & Compound	Stretching ν_{C-H}	Stretching ν_{N-H}	Stretching ν_{C-N}	Stretching ν_{M-N}
$CH_3CH_2CH_2NHCH_2CH_2NH_2$	2953	3287	1377	-
$[Zn\ (pren)_2]^{2+}$	2932	3357	1308	510

Table 3 TGA and DTA of chelating N-propyl ethylenediamine complexes

Compound	Number of Endo peaks	T (°C)	Temp: Range (°C)	Wt. Loss % (Cal %)	Removed Fragments	Residue
$[Zn(pren)_2]\ SO_4$	I	219.30	200-260	28(27.89)	Pren	ZnO
	II	340.03	260-380	15(16.3)	$CH_3CH_2CH_2NH_2$	
	III	394.86	380-450	8(8.47)	CH_3NH_2	
	IV	661.41	450-700	16(15.69)	SO_3	

Table 4 XRD data of bis N-propylethylenediamine zinc complex

Complex	2θ Angle (degree)	θ Radian	Sin θ	$Sin^2\theta$	Ratio 1	Ratio 2	M	hkl	Average particle size D
$[Zn\ (pren)_2]^{2+}$	8.433	0.07357	0.07350	0.005402	1	2	2	110	80
	15.307	0.1335	0.1313	0.01723	3.1895	6.379	6	211	
	17.016	0.1484	0.1478	0.02184	1.2675	2.535	3	111	

Table 5 EDAX Data

Complex	Element	Weight %	Atomic %
$[Zn\ (CH_3CH_2CH_2\ NHCH_2CH_2NH_2)_2]\ SO_4$	C	33.26	48.17
	N	15.45	18.28
	O	23.59	24.22
	S	8.78	4.53
	Zn	18.92	4.8

Table.6 Anti–Diabetic Data (Alpha Glucosidase Inhibition Assay)

Sample concentration(µg/mL)	**OD at 540nm**	**Percentage inhibition**
Control	0.8714	0
Sample code: Acarbose Drug		
125	0.5124	42.51
250	0.4228	52.32
500	0.3442	61.20
1000	0.1956	72.86
Concentration(µL)	**OD at 540nm**	**Percentage inhibition**
Control	0.2519	0
Sample code: $Zn(pren)_2$		
12.5	0.1933	23.63
25	0.1652	37.24
50	0.1143	51.45
100	0.0894	63.57

IC50 Value- Acarbose- 269.77µg/mL(Calculated using ED50 PLUS V1.0 Software)

Zn- 43.3948µL(Calculated using ED50 PLUS V1.0 Software)

Table 7 Anti–Diabetic Data (Alpha Amylase Inhibition Assay)

Concentration(µg/mL)	**OD at 540nm**	**Percentage of inhibition**
Control	**0.1150**	
Standard: Acarbose Drug		
125	0.0513	58.48
250	0.0519	60.56
500	0.0462	63.37
1000	0.0302	75.94
Concentration(µL)	**OD at 540nm**	**Percentage inhibition**
Control	0.7916	0
Sample code: Zn		
12.5	0.5172	36.83
25	0.4256	47.62
50	0.2734	65.54
100	0.1262	84.79

IC50 Value: Acarbose- 111.907µg/mL(Calculated using ED50 PLUS V 1.0 Software)
Zn- 38.2118µL(Calculated using ED50 PLUS V 1.0 Software)

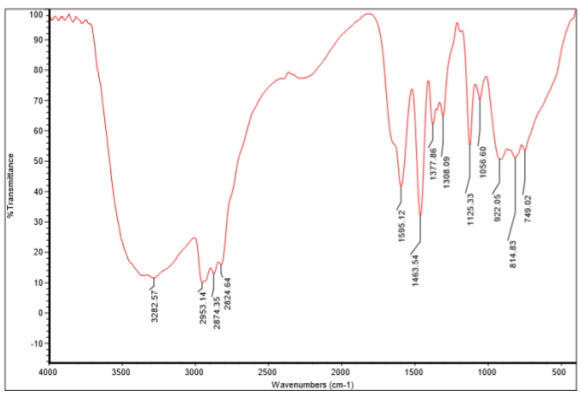

Fig.1.FT-IR Spectrum of N-propyl ethylenediamine (Ligand)

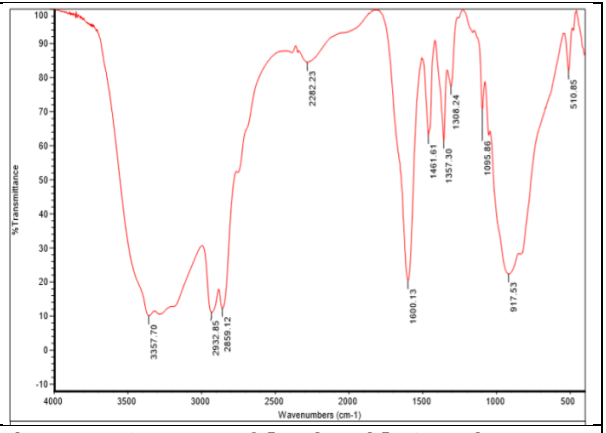

Fig.2.FT-IR Spectrum of $[Zn(pren)_2]^{2+}$ Complex

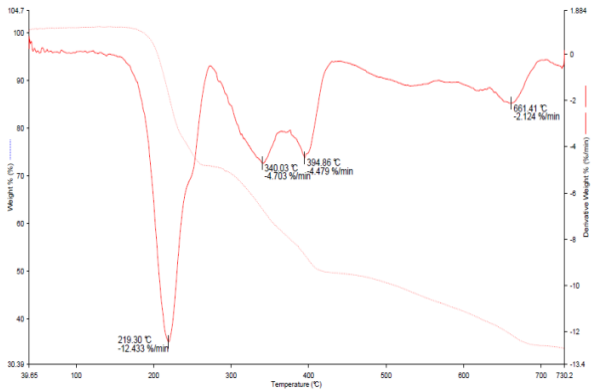

Fig.3. TGA & DTA Spectrum of $[Zn(pren)_2]^{2+}$ Complex

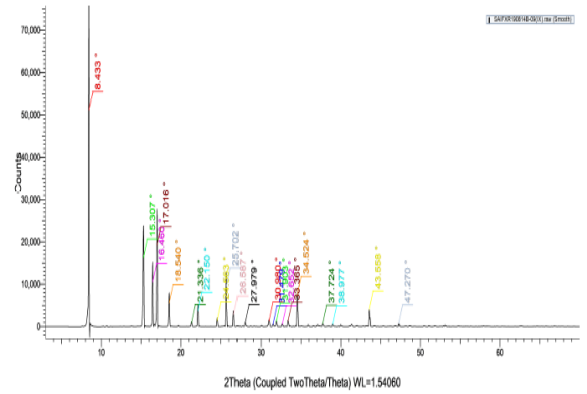

Fig.4. XRD Spectrum of $[Zn(pren)_2]^{2+}$ Complex

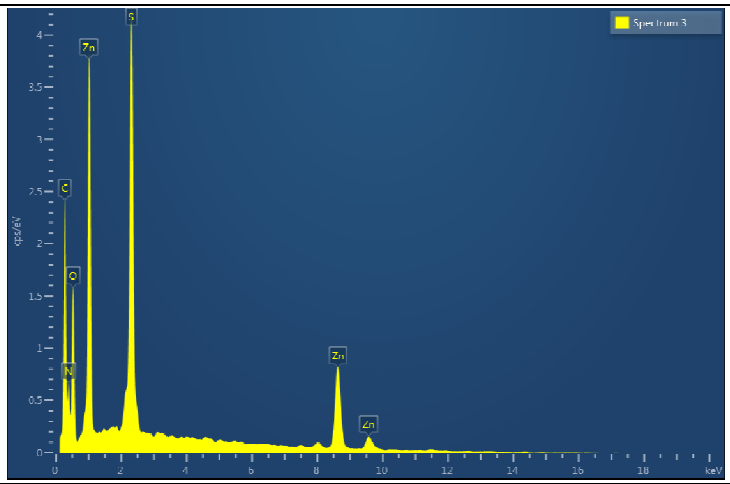

Fig.5. EDAX Spectrum of $[Zn\ (pren)_2]^{2+}$ Complex