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Synthesis, Physico-chemical, Spectral and Hypoglycemic Activity of Samarium Complex of Glimepiride, An Oral Antidiabetic Drug

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ABSTRACT

This paper deals with the synthesis and characterization of a glimepiride-samarium complex a rare earth's metal. Glimepiride is an oral hypoglycemic agent. The conductometric titrations were conducted using monovariation method which shows the ligand metal ratio as 2:1. Molar conductance value indicate that complex is non-ionic in nature. Analytical results agree to the molecular formula $(C_{24}H_{34}N_4O_5S)_2$ Sm.$4H_2O$. Rare earth's element Sm shows the high coordination sites. The structure of the complex was assigned as hexagonal in which ligand moleculas joining the central Sm(III) atom with nH_2O molecules. Infrared spectral studies have supported coordination of sulphonyl oxygen on one side and enolic oxygen attached from other side and four water molecule attached by four co-ordination sides with the samarium ion. Mass spectral and nuclear magnetic resonance studies of the complex proposed structure of the complex on the basis of analytical data.

Key words: Synthesis; Characterization; Samarium Glimepiride complex, Infrared and NMR spectroscopy.

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 two of decades resulting in a variety of exciting and valuable drugs such as cis-platin for cancer.

Recently metals in medicine has been recognised 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 suphonyl 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 samarium with variours hypoglycemic drugs is relatively more important[17-19].

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

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 monovariation method (Fig 2). The ligand-metal ratio (1:2) was also confirmed by the way of doing the jobs method[23] of continuous variation using " conductance. The indexed values were indicates 1:2 metal ligand ratio (Fig 3).

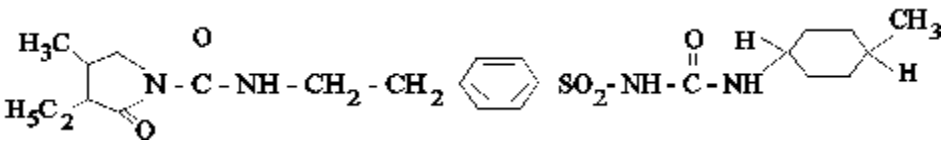


Fig. 1: Structure of Glimepiride

EXPERIMENTAL

Pure sample of glimepiride (trade name, amaryl) with m.f. ($C_{24}H_{34}N_4O_5S$) was received from Ipca laboratories Limited, Ratlam. Solvents and metal salts used were of the analytical grade. Melting point was determined by Parkin Elmer model 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 4000-450 cm^{-1} (CDRI Lucknow). Nuclear magnetic spectral studies of ligand and complex were obtained from CDRI Lucknow (India).

Conductometric titration monovariation method

Table 1: Glimepiride with samarium trioxide (Job's Method)

Glimepride – 0.005 M — Sm_2O_3– 0.005 M
Solvent – 90% Ethanol — Temperature 31±1°C

Mole metal ligand ratio	Conductance X10^{-4}Mhos M:S C_1	S:L C_2	M:L C_3	Conductance X10^{-4}Mhos $C_1+C_2-C_3$	Corrected-conductance X10^{-4}Mhos
0:12	0.94	1.62	2.52	0.04	0.00
1:11	1.57	1.55	2.96	0.16	0.12
2:10	2.20	1.48	3.34	0.34	0.30
3:9	2.80	1.46	3.73	0.53	0.49
4:8	3.45	1.36	4.16	0.65	0.61
5:7	3.95	1.15	4.66	0.44	0.40
6:6	4.47	1.06	5.07	0.46	0.42
7:5	4.58	0.89	5.29	0.28	0.24
8:4	5.14	0.75	5.68	0.21	0.18
9:3	5.13	0.71	5.69	0.15	0.11
10:2	5.62	0.42	5.19	0.13	0.09
11:1	6.21	0.32	6.45	0.08	0.04
12:0	6.69	0.22	6.87	0.04	0.00

Table 2: Glimepiride with samarium trioxide (Job's Method)

Glimepride – 0.002 M — Sm_2O_3 – 0.002 M
Solvent – 90% Ethanol — Temperature 31±1°C

Mole metal ligand ratio	Conductance X10^{-4}Mhos			Conductance X10^{-4}Mhos	Corrected-conductance X10^{-4}Mhos
	M:S C_1	S:L C_2	M:L C_3	$C_1+C_2-C_3$	
0:12	0.93	1.66	2.51	0.08	0.00
1:11	1.58	1.54	2.93	0.19	0.08
2:10	2.21	1.44	3.32	0.33	0.27
3:9	2.84	1.36	3.70	0.50	0.42
4:8	3.47	1.25	4.18	0.54	0.48
5:7	3.96	1.14	4.64	0.46	0.38
6:6	4.48	1.06	5.12	0.42	0.34
7:5	4.61	0.92	5.14	0.39	0.31
8:4	5.02	0.79	5.44	0.37	0.29
9:3	5.14	0.60	5.45	0.29	0.21
10:2	5.62	0.46	5.89	0.19	0.09
11:1	6.21	0.34	6.42	0.13	0.07
12:0	6.69	0.21	6.84	0.06	0.00

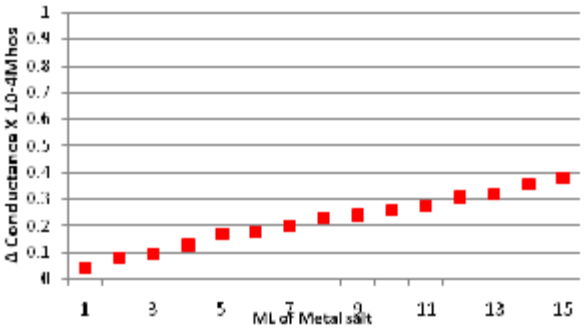


Fig. 2: Conductometric Titration graph of Samarium-Glimepiride Complex

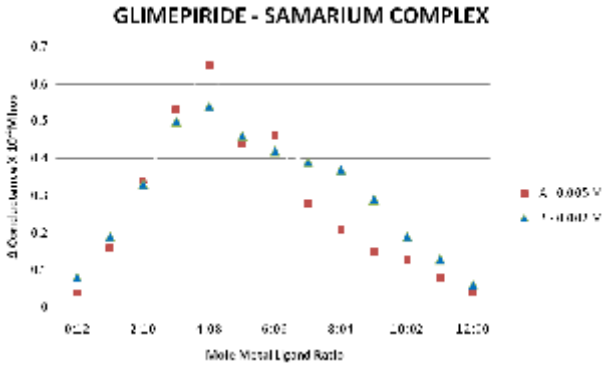


Fig. 3: Job's Method graph

Synthesis

A weighed quantity of glimepiride (2mol.) was dissolved in minimum quatity of 80% DMF. The samarium trioxide 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[24-27] at 80°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.

Table 3: Synthesis and physico chemical characteristics of Glimepiride-Samarium Complex

Ligand/Complex	Ligand Metal Ratio	Colour	%yield	Stability constant Logk (L/mole)	Free energy change (-ΔF) KCal/mole
Glimepiride (Ref)	-	White	-	-	-
Glimepiride-samarium Complex	2:1	Shiny Greyish Crystal	58	11.83	-16.26

Analysis of complex

The resulting complex so formed was characterized by its elemental analysis through SEM-EDAX method and IR, NMR studies (table 5 and 6) and metal was estimated by EDTA method.

Table 4: Analytical data of complex

Drug/Complex	Elemental analysis found (calculated)						M.P.
	C	H	N	S	Metal	Water	°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
$(C_{24}H_{34}N_4O_5S)_2.Sm(OH_2)_4$	49.93 (50.90)	5.93 (6.01)	9.09 (9.89)	5.18 (5.65)	12.98 (13.25)	4.98 (3.21)	212

RESULTS AND DISCUSSION

structure determination

IR Absorption Studies

The infrared spectrum of glimepiride and metal complex were recorded on Perkin Elemer Spectrometer RX1 (4000-450 cm^{-1}). The major absorption bands for the infrared frequencies and the corresponding assignments are listed in Table 5.

The Glimepiride metal complex showed a prominent IR absorption band in the region 1706 cm^{-1} and 1702 cm^{-1} due to (C=O) carbonyl group[28-29]. The next IR band of structure significance of the ligand appears at 1215 cm^{-1} which may be assigned to (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} in samarium glimepiride complex. The IR frequencies of (C=N) group was appeared at 2365 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. The IR frequency region at 3429 cm^{-1} was assigned to nH_2O molecule that may be not found in ligand frequency region. In pure ligand there is no absorption band detected for C-O and C=N due to enolisation are further supporting the structure for glimepiride samarium complex.

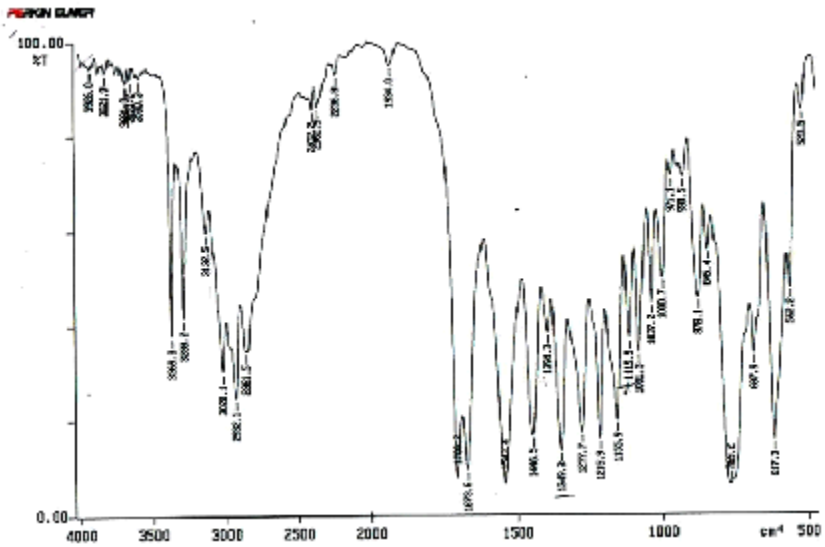


Fig. 4(a) : IR Spectra of pure drug Glimepiride

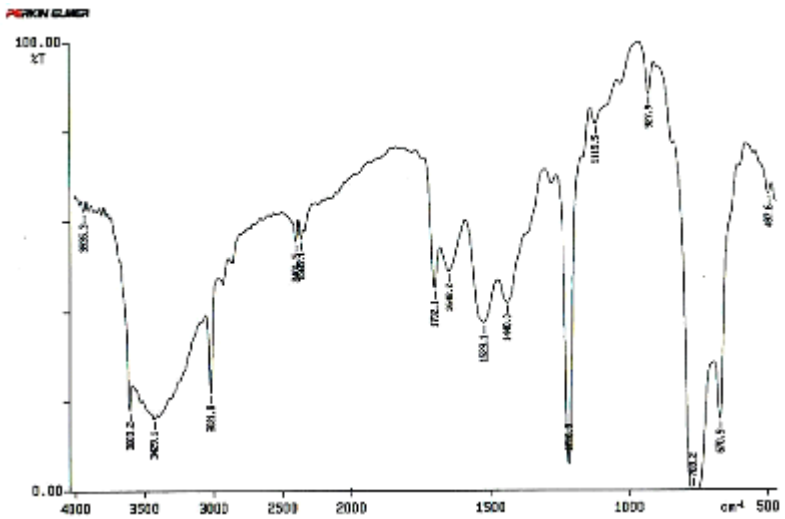


Fig. 4(b): IR Spectra of Glimepiride-Samarium complex

Table 5: IR Absorption data of the complex in cm^{-1}

Ligand/Complex	υ (NH)	υ (C=O)	υ (S=O)	υ (C-O)	υ (C=N)	υ (SO_2N	υ (M-O)	υ (H_2O)
$C_{24}H_{34}N_4O_5S$	3681	1706	1215	-	-	3020	-	-
$(C_{24}H_{34}N_4O_5S)_2.Sm.4H_2O$	3680	1702	1216	1648	2365	3021	670	3429

NMR Spectral Analysis

The samarium complex of glimepiride [Fig V (b)] the chemical shift ”δ value for NH in NHCO was observed at 7.94 ppm while the same -δ value in pure ligand glimepiride was observed at 8.44 ppm[30] showing a (0.50 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[31-35].

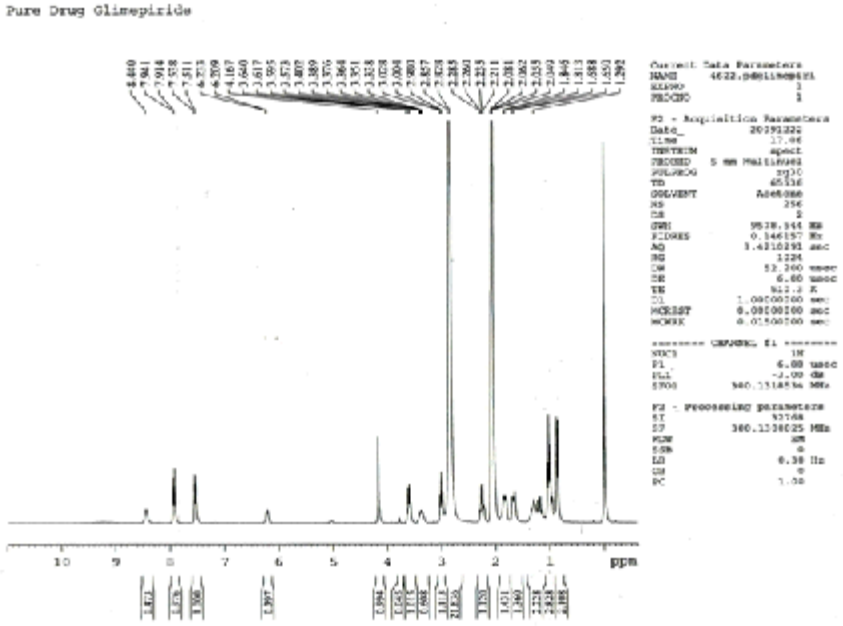


Fig. 5(a)

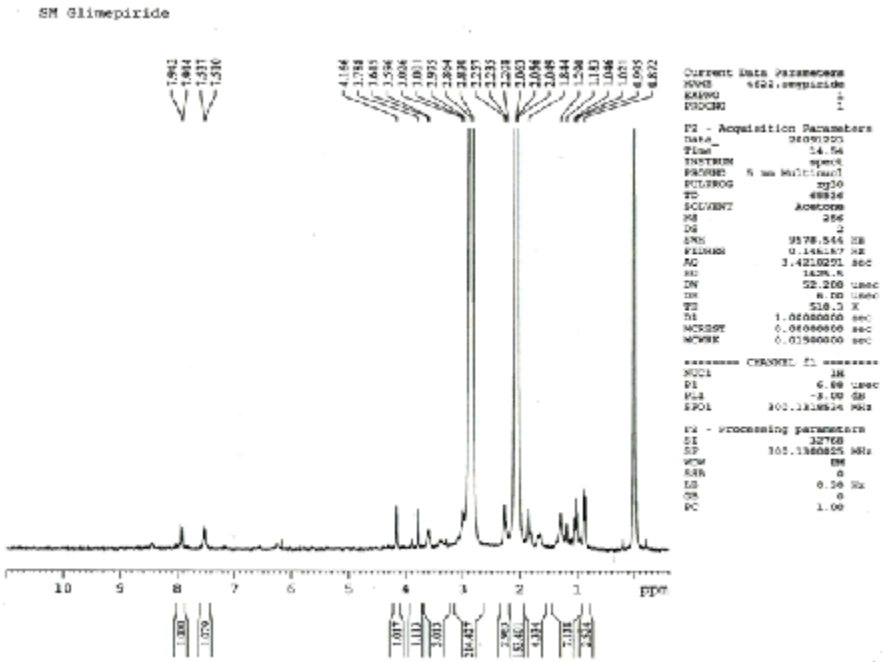
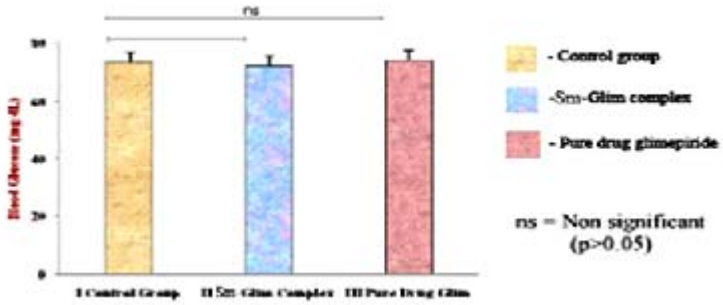
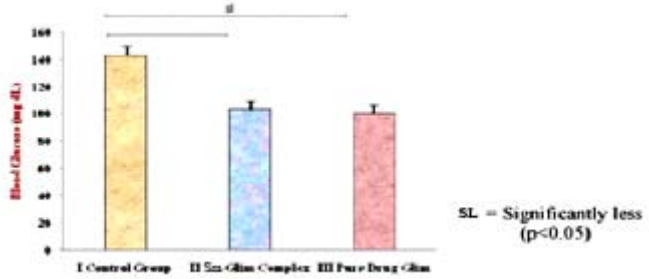


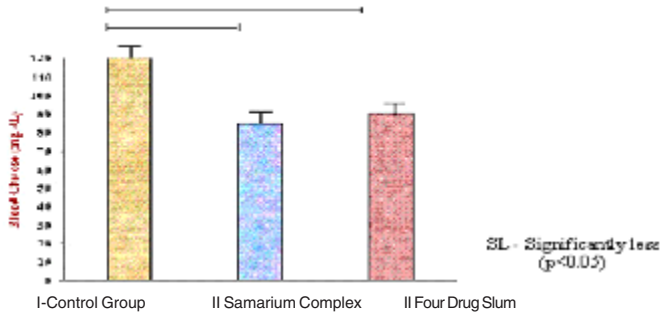
Fig. 5(b)



Fasting blood sugar level



(Blood sugar level) After 30 minutes



(Blood sugar level) After 90 minutes

Fig. 6: Graphical Representation of Comparative Antidiabetic Activity Analysis of Glimepiride-Samarium Complex by Oral Glucose Tolerance Test

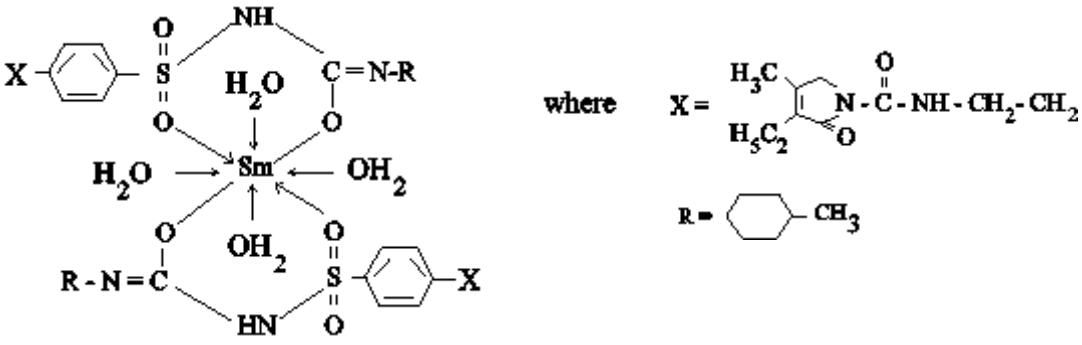


Fig. 7: Structure of Glimepiride-Samarium Complex

Table 6: Some Important characteristics ^{1}HNMR signals for glimepiride and its samarium complex

Glimepiride Pure	δValue (ppm)	Assignment
Ligand	Glimepiride-Samarium Complex	
8.44(0.47 Hz)	7.94(1 Hz)	^{1}HNMR signal for –NHCO group and for Aronatic proton)
6.23(0.39 Hz)	-	NH proton signal for $–SO_2NH$ group
1.65(1.36 Hz)	1.56(0.64 Hz)	$-CH_2$ proton signal
1.04(2.82 Hz)	1.04(7.1 Hz)	Methyl ($-CH_3$) proton signal
-	3.78(1.11 Hz)	NHCO-M signal (M= metal)

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-samarium complex[36-37] 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 test[38]. (PBRI, lab. Bhopal, M.P., India). Analysis of data presented in table (7) reveals that the drug caused a marked decrease in blood sugar level. On comparing the hypoglycemic effect of samarium complex with parent drug it was revealed that in case of Sm- 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 Sm-glimepiride complex over its parent drug.[39-40]

Table 7: Hypoglycemic Activity by 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	Samarium 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**

CONCLUSION

From the monovariation studies conducted by conductivity method and further confirmsed by Job's method of continuous variation suggest the ligand-metal ratio as L_2M. Analytical data agrees to the molecular formula $(C_{24}H_{34}N_4O_5S)_2.Sm.4H_2O$. The structure of the complex proposed on the basis of analytical data and stoichiometry was further supported by IR and NMR spectral studies which suggest the linking of sulphonyl and enolic oxygen to the metal atom. The disappearance of enolic hydrogen in complex as indicated by IR values. The results of NMR spectra are well in agreement with the mol.wt of the complex. Hypoglycemic activities of the complex shows more blood sugar lowering effect as compared to parent ligand. Calculating the toxicity in the complexes and on many trials on monkey's and men the complex may be introduced as medicine in future.

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