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Synthesis, Characterization and Biological Studies of Zn(II) Complex of Schiff Base Derived from 5-Acetazolamido-1,3,4 - Thiadiazole-2-Sulphonamide, A Diuretic Drug

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Abstract : 5-acetazolamido–1,3,4–thiadiazole–2–sulphonamide, trade name acetazolamide, is a diuretic drug (Diuretic drugs increase the output of urine through kidneys). In the present communication, the metal complex of Zn(II) with schiff base derived from salicyladehyde and 5-acetazolamide –1,3,4 – thiadiazole–2–sulphonamide have been synthesized keeping in view that some metal complexes are found to be more potent than their parent drugs. These complexes were characterized on the basis of elemental analysis, conductivity, IR and ^{1}H NMR spectral studies. The analytical data reflects the metal to ligand stoichiometry to be 1: 2. The ratio of complex formation with the above metal was further confirmed conductometrically using Job's method of continuous variation. The conductivity data of the complexes also suggests their non-electrolytic nature. The stability constants and free energy change for the complexes have been calculated. The diuretic activity of these complexes was checked on albino rats and the results have been found to be very encouraging.

Key words : Diuretic, acetazolamide, schiff base, stoichiometry.

Introduction

Schiff base metal chelates are widely applicable because of their industrial and biological importance and hence have well been studied in the past (Chouhan and Supuran, 2004; Orita *et al*., 1997). A detailed survey of literature revealed that very little work has been done on metal complexes of diuretic drugs. Zinc salts have been reported to have therapeutic value (Boukaiba, 1993; Pandley *et al*., 1985; Sigel and Sigel, 1997). Therefore, in present communication synthesis and characterization of metal complex of Zn (II) with 5-acetazolamide–1,3,4–thiadiazole–2–sulphonamide (acetazolamide) has been aimed.

Materials and Methods

All the chemicals used were of AR/GR grade. Pure sample of Acetazolamide (AZM), molecular formula $C_4H_6N_4O_3S_2$, molecular weight 222.24, was obtained from Shalak's pharmaceutical. Metal salt $ZnCl_2$ was used. Solvents used were methanol, acetone and deionized double distilled water.

Preparation of Schiff base

Schiff base of 5-acetazolamido–1,3,4–thiadiazole–2–sulphonamide (Acetazolamide) was prepared by reported methods (Ghosh *et al.*, 2008). Pale yellow crystals of acetazolamide schiff base was formed in the

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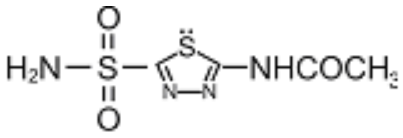
reaction mixture, which were filtered washed thoroughly with 50% methanol, dried over vacuum and weighed. Melting point was recorded

Synthesis of Complex

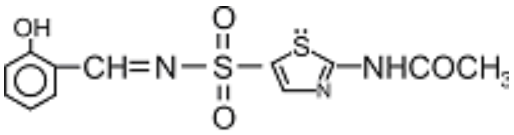
For the synthesis of complex ligand-metal ratio was confirmed by conductometric titration using monovariation method on systronics conductivity meter using dip type electrode. Conductometric titration supported 2:1 (L:M) ratio in the complex which was further supported by Job's method of continuous variation as modified by Turner & Anderson. The stability constant and free energy changes were also calculated.

Results and Discussion

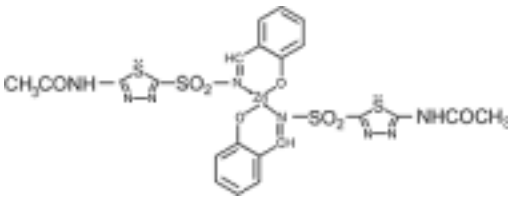
For the synthesis of complex of acetazolamide-Zn, 0.006M ligand solution (AZM- SA) was prepared in 60% acetone and refluxed for four hours with 0.003M solution of $ZnCl_2$. The refluxed solutions were kept for some days. Solid white crystalline compound appeared in the solution, was filtered, washed with 60% acetone, dried and weighed, Melting point was recorded.



Structure of Acetazolamide



Structure of Schiff base



Structure of Complex

Proposed structure was further confirmed by IR (Rao, 1963; Nakamoto,1956) spectral data. Bands observed at 1164.5 cm^{-1} are characteristics of SO_2-N linkage. Absorption bands at 1440 cm^{-1} show the presence of chelate ring. The appearance of the M-O bands at 680 cm^{-1} and M-N bands at 600-550 cm^{-1}

Table 1 : Synthesis and physicochemical characteristics of complex

	Ligand-metal ratio	Colour	Yield	Stability constant log K (Lit/mole)	Free energy Change, Δ F
AZM-SA	—	Pale yellow	54.50%	—	—
$(AZM)_2$ Zn	2:01	Off white	41.50%	8.56	-11.58

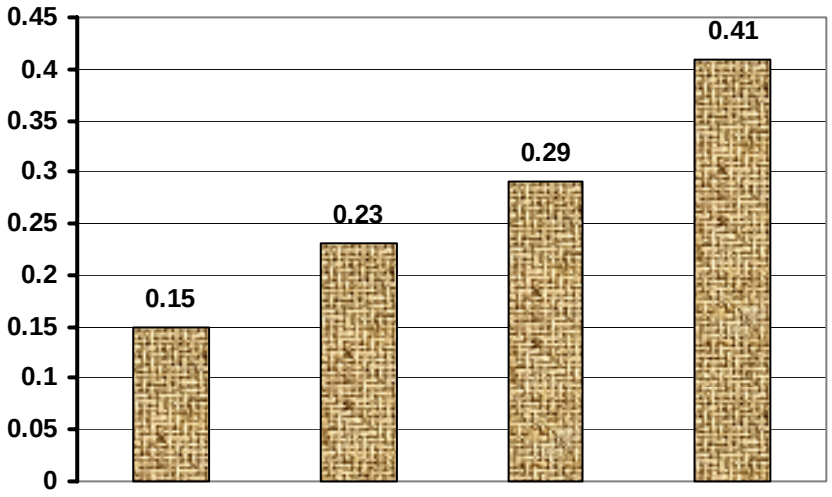
Table 2 : Analytical data & IR study of complex

Complex	Elemental analysis % Found (Calculated)						Melting Point ºC
	C	H	N	S	O	Metal	
$(AZM)_2$ Zn	35.8	2.53	15.53	17.18	17.15	9.01	150 ºC
$(C_{11}H_9N_4O_4S_2)_2Zn$	-36.5	-2.34	-16.6	-17.5	-17.5	-9.7	

Table 3 : Diuretic activity of different drugs

Sr. No.	Drug Code	Volume of Urine in mμ lit			Average Value (in mμ lit)
		11:00 AM	3:00 PM	7:00 PM	
1	C	0.14	0.15	0.17	0.15
2	AP	0.44	0.23	0.2	0.23
3	AS	0.13	0.45	0.31	0.29
4	Azn	0.15	0.18	0.9	0.41

C = Controlled rat; AP = Acetazolamide pure drug; AS = Acetazolamide schiff base; Azn = Acetazolamide schiff base zinc complex



in the complex indicates that AZM-SA is coordinated through O & N atom. Absorption band at 3303 cm^{-1} shows the presence of water of coordination in complexes. Bands appearing at 710.22 cm^{-1} shows the presence of S in the heterocyclic ring. Frequency at 840.49 cm^{-1} indicates the S-N linkage. The disappearance of phenolic-OH group in complex supports its involvement in complexation.

Diuretic activity

The diuretic activity of this complex was checked on albino rats and the effects have been compared with that of parent drug. The results have been found to be encouraging with metal chelates as compared to parent drug. After the administration about 90% of the dose gets excreted within 24 hours (Dollery, 1991).

The above result confirms that Zinc complex of Acetazolamide schiff base shows better diuretic activity than the parent drug.

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