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Synthesis and antibacterial activity of new complexes of benzothiazole derivatives

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ABSTRACT

In present study, five new metal complexes of the ligand 2- amino acetate, 6-chloro benzothiazole with some metal ions Ni(II), Cu(II), Zn(II), Cd(II) and Sn(II) were synthesized and evaluated for their anti-bacterial activity. The prepared complexes were characterized by elemental analysis, magnetic moment, electronic spectra, infrared spectra, conductivity measurement. From spectral measurement, monomer structures for the complexes were proposed. Square planar geometry was proposed for copper complex. The other complexes were proposed to be tetrahedral. The anti-bacterial activities against Gram-positive and Gram-negative pathogenic bacteria were investigated using disc diffusion method. and appreciate activity were observed.

Keywords: Amino acetate benzothiazole, metal complexes, anti-bacterial activity

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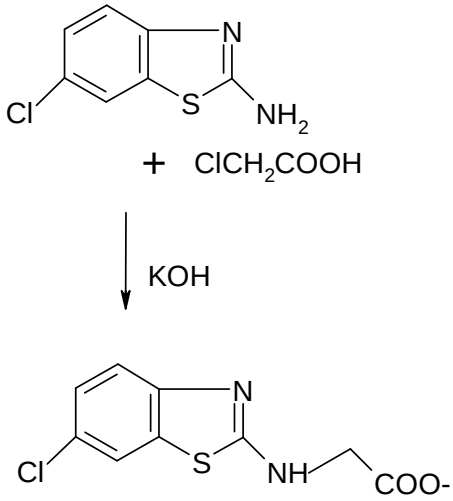
INTRODUCTION

Benzothiazoles are bicyclic ring system with multiple applications. In particular 2-amino benzothiazole were intensively studied as central muscle relaxants. Biologist's attention was drawn to this series when pharmacological profile was discovered. The aromatic benzothiazole[15] nucleus is associated with variety of antihistamine activity, pharmacological activities,[9,10] such as fungicidal, anti-inflammatory, anti-microbial, and anti-convulsant.[2] These activities are probably due to presence of the –N=C-S group.[13]Substituted benzothiazole have been reported to show diverse application as metal complexing agents. [1-5] and photostabliser. The wide range of application of the ligand and its complexes aroused our interest for assaying their antimicrobial activity against gram positive and gram negative micro-organism

MATERIALS AND METHODS

Synthesis of 2-amino acetate, 6-chloro benzothiazole:
A solution of p-chloro aniline (0.085 mol) in 95% acetic acid (50 ml) was added to a solution of KSCN (0.308 mol) in 95% acetic acid (100ml). The mixture was cooled to 0^0C & a solution of Br_2 (7.5 ml) in acetic acid (30ml) was added slowly with stirring so that temperature between 0 &10^0C. After addition was complete, the stirring was continued for 1hr. at 5^0C and then mixture was poured into water. The solid was collected & re-crystallized from ethanol. The product (0.036mol), conc. HCl (27ml) and water (50 ml) were refluxed for 2 hr. The solution was cooled and the product was filtered off, washed with water & re-crystallized from ethanol.

The steps of synthesis of 2-amino acetate, 6-chloro benzothiazole can be shown below:



Preparation of complexes:
Addition of ethanol solution of the suitable metal salt (Nickel acetate tetrahydrate, Copper acetate, Cadmium acetate dihydrate, Stannous chloride and Zinc acetate dihydrate) to an ethanol solution of 2-amino acetate, 6-chloro benzothiazole in 2:1(ligand: metal [3, 4] molar ratio was carried out. After refluxing for half an hour, crystalline colored precipitates formed at room temperature. Washed with distilled water, dried and recrystallized from ethanol and dried at $48^{0}{}_{C.}$ Table 1: Shows the melting point of the prepared compounds

Instrumentation:
The FTIR spectra in the range (4000-200) cm^{-1} were recorded as CsI disc on FTIR and the magnetic susceptibility values of prepared complexes were obtained at room temperature using Magnetic Susceptibility Balance of Bruke Magnet B.M. 6. The 1H nuclear magnetic resonance spectra were recorded on a Jeol 400 MHz spectrometer with tetra methyl silane (TMS) as internal standard. Melting points were recorded on a hot stage Gallen Kamp melting point apparatus.

Table 1. Physical data for ligand and metal complexes (melting point)

Compound	Melting point ^{0}C
L_H	180-185
$Ni(L_H)_2$	180
$Cu(L_H)_2$	210
$Sn(L_H)_2$	Above 300
$Zn(L_H)_2$	250
$Cd(L_H)_2$	256

L_H *- 2-amino acetate, 6-chloro benzothiazole*

RESULTS AND DISCUSSION

Infra- red spectroscopy: The ligand was prepared by the reaction of one mole of 2-amino, 6-chloro benzothiazole with one mole of chloroacetic acid in presence of KOH.

Table 1 shows the physical data (m.p.) for the ligand and the prepared complexes

The FTIR spectrum of the ligand shows a characteristics stretching absorption band at 3100, 1710, 1560, and 690 cm^{-1} assigned to secondary amine, carbonyl, C=N of the thiazole ring and stretching of C-S group respectively.[11]

The reaction between this ligand with Ni(II), Cu(II), Sn(II), Zn(II) and Cd(II)

Give different types of complexes. In the free ligand, the band at 1710 and 1033 cm^{-1} were assigned to the stretching of C=O and C-O of the carboxylate group. On complexation these bands were shifted to a lower frequency region.

The shift is probably due to the complexation of the metal to the ligand through oxygen of the carbonyl group.

Stretching of metal –oxygen bands of the complexes appeared in low frequency region (408-430) cm^{-1}. [12] The IR data of the complexes are shown in **table 2**

The table lists of stretching frequency (**ν**) for some the group exhibited by ligand and complexes.

Table 2: Characteristics absorption band of 2-amino acetate, 6-chloro benzothiazole and its complexes.

Compound	ν(C=O) cm^{-1}	ν (C-O) cm^{-1}	ν (M-O) cm^{-1}
L_H	1700	1020	
$Ni(L_H)_2$	1580	1000	430
$Cu(L_H)_2$	1665	980	410
$Sn(L_H)_2$	1630	975	408
$Zn(L_H)_2$	1550	990	425
$Cd(L_H)_2$	1565	970	428

L_H - 2-amino acetate, 6-chloro benzothiazole

Magnetic Susceptibility and conductivity measurement:
The experimentally determined value of magnetic moment for each complexes is listed in **Table 3**. Magnetic measurements are widely used in studying transition metal complexes. The magnetic properties are due to the presence of unpaired electrons in partially filled d-orbital in outer shell of the metal ion in the complex.

The magnetic moment for Ni (II) complexes is approximately 3.16 B.M. this value refers to high spin tetrahedral structure, while the value of Cu (II) is approximately 1.60 led to suggest the square planar structure. Other complexes have no magnetic moment because it's diamagnetic. Molar conductivity measurement in DMF solvent at 25 ^{0}C showed that complexes were non –electrolyte.

Table 3: Magnetic moment, conductivity measurement in DMF solvent

Symbol	Name	Conductivity ($ohm^{-1}cm^2\ mol^{-1}$)	μ_m (B.M.)	Suggested Structure
L_H	2-amino acetate, 6-chloro benzothiazole			
$Ni(L_H)_2$	Bis(2-amino acetate, 6-chloro benzothiazole) nickel(II)	13	3.16	Tetrahedral
$Cu(L_H)_2$	Bis(2-amino acetate, 6-chloro benzothiazole) copper(II)	20	1.60	Square planar
$Sn(L_H)_2$	Bis(2-amino acetate, 6-chloro benzothiazole) tin(II)	09	0.00	Tetrahedral
$Zn(L_H)_2$	Bis(2-amino acetate, 6-chloro benzothiazole) zinc(II)	11	0.00	Tetrahedral
$Cd(L_H)_2$	Bis(2-amino acetate, 6-chloro benzothiazole) cadmium(II)	16	0.00	Tetrahedral

NMR Spectroscopy: The data of 1H NMR of the 2-amino, 6-chloro benzothiazole and its complexes shows good solubility in DMSO. The proton nuclear magnetic resonance spectral data gave additional support for the composition of the complexes. [7] **Table 4**

The δ 7.35-8.14 ppm resonance signal protons of the aromatic ring shifted to higher field upon complexation. While proton of the CH_2 aliphatic group shifted to higher field also.

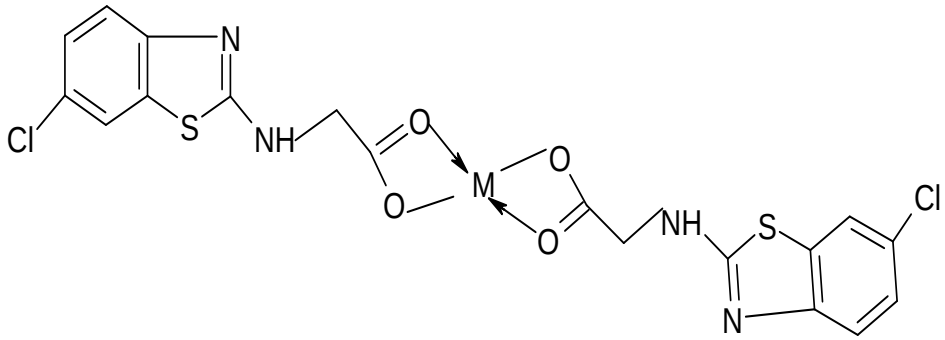
Table 4 ^{1H}NMR spectral data (δ ppm) of the ligand and complexes

Symbol	-CH_2 aliphatic	Aromatic
L_H	4.14	7.35-8.14
$Ni(L_H)_2$	4.12	6.40-7.12
$Cu(L_H)_2$	4.20	6.43-7.89
$Sn(L_H)_2$	4.16	6.65-7.83
$Zn(L_H)_2$	4.22	6.30-7.93
$Cd(L_H)_2$	4.21	6.60-7.80

Study of Complex formation in solution:
Mole ratio [M/L] in the complex was determined using **Mole ratio method**. [8] The complexes of L_H with metal ions were studied in solution using ethanol as a solvent.

The [M/L] ratio was determined from absorbed light [A]for metal salt and ligand.

The result of complexes in ethanol, Suggestion that metal to ligand ratio was [1/2] for all complexes. On the basis of preceding discussion, the structure of the complexes suggested as follows,



Pharmacology

Antibacterial activity

The title compounds (R1a-e) were screened for their antibacterial activity using disc diffusion method.[17] The bacterial organisms used included both gram positive and gram negative strains like *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pyogens*, *Salmonella enteric Ser para typhi*, *S.entrica ser typhi* and *Micrococcus luteus.*

For antibacterial susceptibility testing of title compounds (R1a-e), the sterile disc of 6 mm diameter (SD067, Hi-Media, Mumbai) was loaded with 20µl of title compound solution (1000 µg/ml) in DMF. The discs were then placed at centre on the Mueller-Hinton agar seeded with bacterial inoculums approximately 10^6 CFU/ ml, incubated at 37° C for 24 hrs and growth inhibition zone formed around disc was measured. Test was done in triplicate and mean value was considered as inhibition zone. Solvents were used as controls and showed no inhibitions in preliminary studies. All the synthesized complexes (R1 a-f) exhibited moderate to good activity against the test organisms. [16] The activity of complexes **R1c** showed excellent activity against all organisms.

Table 5: antimicrobial activity

Compound	Gram negative bacteria			Gram positive bacteria		
	S. enterica Ser typhi	*Salmonella enterica Ser para typhi*	*E.Coli*	*Streptococcus pyrogens*	*Micrococcus luteus*	*S.aureus*
R1 a	—	—	—	—	—	—
R1 b	+	+	+	—	—	+
R1 c	+++	+++	+	—	+++	++
R1 d	++	++	—	—	++	+
R1 e	+	+	—	++	++	+

*R1a=**Ni(L$_H$)$_2$**, R1b= **Sn(L$_H$)$_2$**, R1c= **Cu(L$_H$)$_2$** , R1d= **Zn(L$_H$)$_2$**, R1e= **Cd(L$_H$)$_2$***

+++ = Zone size 16-22 mm. ++ = Zone size 9-15 mm.; + = Zone size 6-8 mm.; — = No inhibition.

CONCLUSION

The complexes were successfully synthesized with ligand 2-amino acetate, 6-chloro benzothiazole by condensation method. The ligand was treated with different metal salt to formed corresponding complexes. Square planar geometry was for the copper complexes. The other complexes were proposed to be tetrahedral. significant anti-bacterial activity was observed with complex **R1c.**

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