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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF METAL COMPLEXES OF 2- AMINO ACETATE – 6 – BROMO BENZOTHIAZOLE.

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Abstract

Five new metal complexes of the ligand 2-amino acetate - 6 - bromo benzothiazole with some metal ions Ni(II), Cu(II), Sn(II) Zn(II), and Cd(II) were synthesized and evaluated for their anti-bacterial activity. The prepared complexes were characterized by ^{1}H, Fourier transform infrared spectra, UV-Visible spectroscopy, magnetic moment, and conductivity measurement. The spectral study showed that all the complexes obtained as monomeric structures and central metal moieties are four–coordinated, with tetrahedral geometry, except for the copper complex, which had square planar geometry. All the complexes showed moderate activity against Gram-positive and Gram-negative pathogenic bacteria using disc diffusion method.

Keywords: *amino acetate benzothiazole, Transition metal complexes, Antibacterial activity*

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INTRODUCTION:

Benzothiazole nucleus is found to possess a number of biological activities such as anticancer, antidiabetic, antimicrobial, anti-inflammatory, antiviral, antileishmanial antifungal etc. These activities are probably due to presence of the –N=C-S group. [1] A large number of therapeutic agents are synthesized with help of benzothiazole nucleus. A substituted benzothiazole can also acts as ligand, in particular halo group (Cl,Br,F) attached to benzothiazole, increasing biological activity by complexation. [2] The complexes of substituted beznzothiazole have been reported to have antimicrobial activity [4]. It was decided to synthesize some new metal complexes of 2- amino acetate - 6 - bromo benzothiazole and study the antimicrobial activity.

MATERIALS AND METHOD:

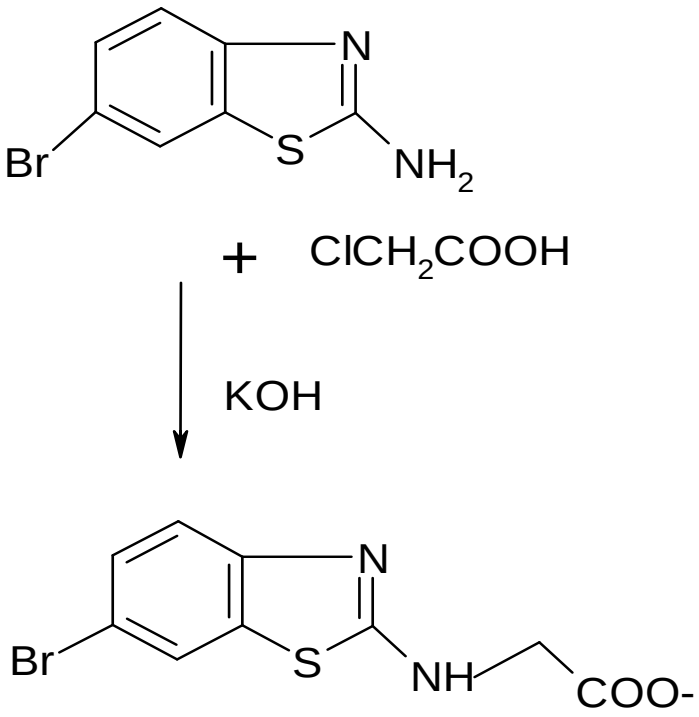
All the reagents, starting material and solvents were purchased commercially and used without further purification. The melting point were measured on hot –stage Gallen kamp meltig point apparatus. The Fourier transform infrared spectra recorded on FTIR 8300 Shimadzu spectrometer in frequency range 4000-200 cm-1. [5] The ultra-violet –visible (UV-VIS) spectra were recorded by using shimadzu UV-VIS 1800. An ultra violet spectrometer in the range of 200-1100 nm. The magnetic susceptibility was measured at room temperature on magnetic susceptibility balance Bruke Magnet B.M.6 .The spectra of 1H was measured on Jeol 400 MHZ spectrometer. Conductivity was measured on conductivity meter.

Part 1:- Preparation of 2-amino - 6- bromo benzothiazole

A mixture of 4-bromo aniline (0.1 mol) and potassium thiocynate (0.1 mol) were dissolved in ethanol containing 6 ml of conc. hydrochloric acid, to this 20 ml of bromine in glacial acetic acid was added and the mixture and heating under reflux for 1 hours. Then, it was cooled in ice –water mixture. The precipitate obtained. Strained well, filtered, washed with cold water and dried. The crude product was recrystallised from rectified spirit.

Part 2:- Preparation of 2-amino acetate - 6 -bromo benzothiazole

A mixture of 2- amino - 6 - bromo benzothiazole (0.01 Mol) and α- chloroacetic acid (0.01 Mol) in presence of KOH to make the slightly alkaline as refluxed for 3 hours to give 2-amino acetate - 6 - bromo benzothiazole. The yellow precipitate which formed was filtered and recrystallised from ethanol to give the final product.



Preparation of complexes:
An ethanol solution of the suitable metal salt (Nickel acetate tetra hydrate, Copper acetate, Cadmium acetate dihydrate, Stannous chloride and Zinc acetate dihydrate) was added to an ethanol solution of 2-amino acetate, 6-bromo benzothiazole in 2:1(ligand: metal) [3] molar ratio. The mixture was heated under reflux for 30 min and coloured precipitates were obtained. Washed with distilled water and finally recrystallized.

RESULT AND DISCUSSION:

Melting points of all complexes studied are tabulated in Table 1.

Table 1: Melting point of ligand and metal complexes

Compound	Melting point ^{0}C
L	180-183
Ni(L)$_2$	179-181
Cu(L)$_2$	212-216
Sn(L)$_2$	200-205
Zn(L)$_2$	192-195
Cd(L)$_2$	172-177

L - 2-amino acetate - 6 - bromo benzothiazole

Infra- red spectroscopy

The FTIR spectrum of the ligand showed a characteristics stretching band at 3454, 1720, 1570, 682 and 514.9 cm^{-1} assigned to secondary amine, carbonyl, aromatic C-O stretch, stretching of C-S group and C- Br respectively.[11] The reaction between this ligand and Ni(II), Cu(II), Sn(II), Zn(II) and Cd(II) gives different types of complexes. In the free ligand, the band at 1720 and 1050 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.[12] 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 cm^{-1}, but other bands such C=C , C-H aromatic were didn't show any shifting because they are not participate in the complexation. **Table 2**

Table 2:_Infrared data of L and Complexes

Compound	ν (C=N)	ν(C=O) cm^{-1}	ν (C-O) cm^{-1}	ν (M-O) cm^{-1}
L	1638	1710	1050	
Ni(L)$_2$	1605	1560	1005	450
Cu(L)$_2$	1600	1670	988	410
Sn(L)$_2$	1600	1645	990	415
Zn(L)$_2$	1610	1575	996	440
Cd(L)$_2$	1611	1580	965	435

L - 2-amino acetate - 6-bromo benzothiazole.

Ultraviolet-visible spectroscopy

The absorption spectra of the ligand (L) and their complexes were recorded in DMSO solvent in the range 200-1100 nm. The electronic spectra of this ligand shows three bands 215, 256, 350 nm attributed to π ⟶ π* , π ⟶ π*, n π*[6,7,8] electron transition respectively. The complexes with Cd(II), Sn(II) and Ni(II) had similar electron transition with ligand, but in the complexes of Cu(II) and Zn(II) d-d electron transition of metal d orbital has been observed form the study.

1H NMR Spectroscopy

The 1H NMR spectra of the complexes provide support for the complexation. The ligand show a sharp peak δ (OH) at 9.90 ppm which was absent in spectra of the complexes indicating the complexation of ligand anion to metal ions. The aromatic proton signals for ligand at δ 7.45 ppm and 7.03 - 8.06 respectively. [9,10] But for the complexes the values of δ lies up-field region .The ^{1}H spectral data for the ligand and the complexes are shown **Table 3**

Table 3: ^{1}H NMR data for ligand and complexes

Symbol	-CH$_2$ aliphatic	Aromatic
L	4.17	7.03-8.06
Ni(L)$_2$	4.13	6.59-7.90
Cu(L)$_2$	4.07	6.40-7.99
Sn(L)$_2$	4.10	6.76-7.85
Zn(L)$_2$	4.12	6.79-7.95
Cd(L$_H$)$_2$	4.15	6.87-7.82

Magnetic Susceptibility and conductivity measurement:

Magnetic moment measurements are commonly used to study transition metal complexes in **Table 4**. The magnetic properties are due to presence of unpaired electrons in d orbital of metal. The magnetic measurements give the electron state of the metal ions in the complexes. The magnetic moment for Ni (II) complexes is approximately 1.07 B.M. this value refers as paramagnetic with high spin tetrahedral structure, while the value of Cu (II) is approximately 0.8 refers to paramagnetic the square planar structure. Other complexes have no magnetic moment because it is diamagnetic.

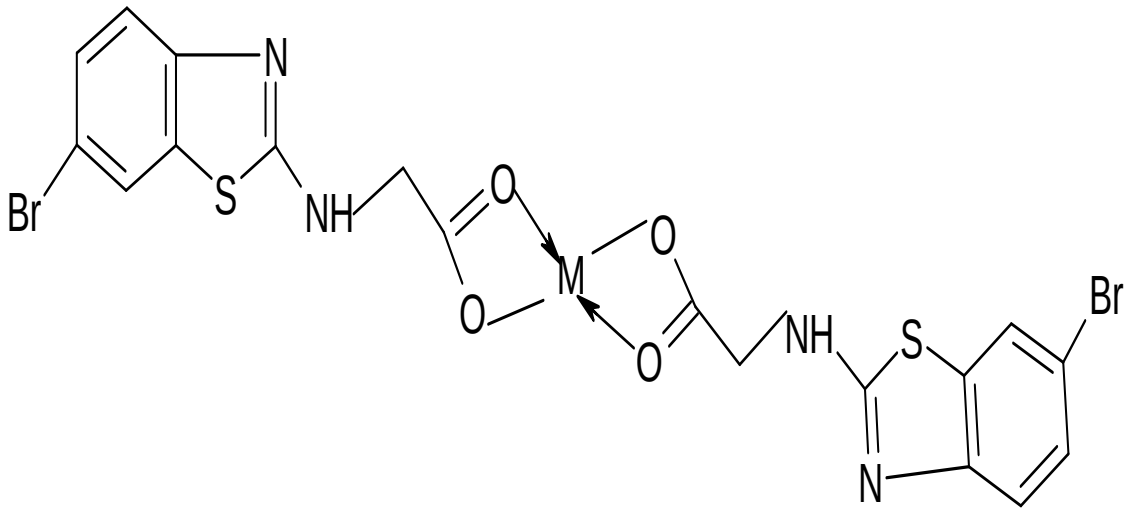
Molar conductivity measurement (**Table 4**) of these complexes was recorded as a solution in ethanol solvent. This measurement gives an idea about solution is electrolyte or non electrolyte.

All the complexes were studied to determine their metal: ligand ratio by Job' method [14]. A Solution of complexes was prepared with constant concentration (10^{-3} M) of the metal ion and the ligand. The ratio was determined from the relation of absorption of light and the molar ratio. The metal: ligand ratio was 1:2 for all the complexes as similar to that in solid state.

Table 4: Magnetic moment, conductivity measurement in DMF solvent

Compound	Conductivity (µS/cm)	Magnetic moment (B.M.)	proposed Structure
L			
$Ni(L)_2$	15	1.07	Tetrahedral
$Cu(L)_2$	25	0.8	Square planar
$Sn(L)_2$	32	0	Tetrahedral
$Zn(L)_2$	16	0	Tetrahedral
$Cd(L)_2$	14	0	Tetrahedral

On the basis of preceding discussion, the structure of the complexes suggested as follows,



ANTIBACTERIAL ACTIVITY

Antibacterial activity of the synthesized compounds (R1a-e) were assessed by using disc diffusion method.[17] The bacterial strains *Staphylococcus aureus* (MTCC 740), *Escherichia coli* (MTCC443) *Streptococcus pyogens* (MTCC 442) *Salmonella para typhi A* (MTCC735), *Salmonella typhi* (MTCC 734) *and Micrococcus luteus* (MTCC 106)were obtained from microbial type Culture Collection(MTCC) IMTECH, Chandigarh, India. Cultures were maintained on nutrient Agar Slopes and also checked for viability and purity before use.

For susceptibility testing, the standardized inoculums with cell density approximately 10^6 CFU/ml were streaked onto Mueller Hinton agar surface. A sterile disc of 6 mm diameter (SD067, Hi-media, Mumbai) was impregnated with 20µl of title compound solution (1000 µg/ml) in DMF. And then placed on the Mueller –Hinton agar, incubated at 37^0 C for 24 hours and growth inhibition zone formed around disc was measured.[9,10] Test was done in triplicate and means value was considered as inhibition zone.DMF was used as control and showed no inhibition in preliminary studies. All the synthesized complexes exhibited moderate to good activity against test organisms. These results are in agreement with the reports of previous study for 2-amino acetate-6-chloro- benzothiazole [16]. The Preliminary screening of synthesized compound exhibited variable inhibitory activity towards pathogenic micro-organism. The zone of inhibition was ranged between 10 to 22 mm. The Bis (2-amino acetate-6- bromo) copper (II) complex shows maximum inhibitory activity against *Salmonella Typhi, Escherichia coli, Salmonella para typhi A.* on the other hand Nickel, Zinc and Cadmium Complexes did not show any effect towards *Escherichia coli.* From the result it can be concluded that complexes of 2-amino acetate – 6 - bromo benzothiazole possess good to excellent antibacterial activity and may be used in future for the control of infections caused by multidrug resistance organism.

Table 5: antibacterial activity of complexes of 2-amino acetate-6-bromo benzothiazole

	Zone of Inhibition (mm)					
Complex	**Gram negative bacteria**			**Gram positive bacteria**		
	Salmonella typhi	*Salmonella para typhi* A	*E. coli*	*Streptococcus pyogenes*	*Micrococcus Luteus*	*S. aureus*
$Ni(L)_2$	**8**	**9**	**—**	**15**	**8**	**—**
$Cu(L)_2$	**20**	**14**	**21**	**16**	**17**	**22**
$Sn(L)_2$	**16**	**8**	**11**	**—**	**17**	**18**
$Zn(L)_2$	**15**	**18**	**—**	**—**	**19**	**20**
$Cd(L)_2$	**12**	**17**	**—**	**17**	**18**	**19**

CONCLUSIONS:

The complexes were successfully synthesized with ligand 2-amino acetate - 6 - bromo benzothiazole by condensation method. [13] The ligand was treated with different transition metal salts to formed corresponding complexes. It concluded that the ligand coordinated through carbonyl and oxygen group to the metal atom leading to formation of four member ring chelate.[15] All the complexes had tetrahedral geometry, except for the complex of Cu (II) had square planar geometry. An antibacterial study indicated that the complexes had significant activity against the bacterial strains.

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