Metal-Bithiourea Complexes: Synthesis, Characterization, and Biological Studies.

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ABSTRACT

In the present study, bithiourea was synthesized from semicarbazide hydrochloride by condensation reaction with potassium thiocynate. The metal complexes were prepared using template method. The complexes formed are of the type ML_2 [Where M=Cu(II), Co(II), Ni(II) and L=Bithiourea (BTU)]. Chemical structures were confirmed by means of UV/Visible, infrared, magnetic moment and elemental analysis. The complexes are non-electrolyte in DMF. Bithiourea acts as a neutral bioactive potential ligand with S, N, S- donor sequence towards the metal ions. Cu(II), Co(II), and Ni(II) complexes were tentatively assigned octahedral geometry. The antimicrobial activities of ligand and its metal complexes were carried out. Ligand and metal complexes exhibited potent activity against microorganisms used. *In-vivo* toxicological activities were also carried out at the dose of 1.00 mg/kg body weight, twice daily for seven days on alkaline phosphatase (ALP), alanine aminotransferase (ALT), and Aspartate aminotransferase (AST) activities of the rat serum, liver and kidney. Overall, it was revealed that both ligand and its metal complexes were not toxic, particularly on the liver and kidney. The compounds might be useful in pharmacological research.

(Keywords: metal-bithiourea, condensation, antimicrobial, toxicological, pharmacological)

INTRODUCTION

A worldwide opinion had been expressed over the need to develop novel agents to treat bacterial infections that have become increasingly unresponsive to standard antibacterial therapy (Chu et al., 1996). Emergence of bacteria resistance to a number of antimicrobial agents such as β-Lactam antibiotics, quinolines, macrolide among others; it is becoming a major health problem. Chemical modifications of existing drugs in the market will give way in future to therapeutic agents that had been discovered. This approach produces incrementally improved compounds particularly with respect to pharmacokinetic properties (Slawinski and Gdaniek, 2005).

Many drugs possess modified pharmacological and toxicological properties when administered in the form of metallic complexes (Chen et al, 2005). It has been reported that some semicarbazide and thiosemicarbazide derivatives and their metal complexes exert biological activity against various microorganisms and have some positive effects in the treatment of certain diseases (Turel et al., 1999).

Since most living systems contain metal ions which are essential for proper functioning, it is important to know how bithiourea, a derivative of semicarbazide interact with the metal ions under different conditions. Studies have been reported on the interaction of metal ions and semicarbazide using various methods; however this work is aimed at synthesizing metal-bithiourea, using template methods, which will yield new compounds.

The composition and other physicochemical properties of these new compounds would be determined. The preparation of its metal complexes and the biological activities, carried out has not been reported elsewhere to the best of our knowledge.

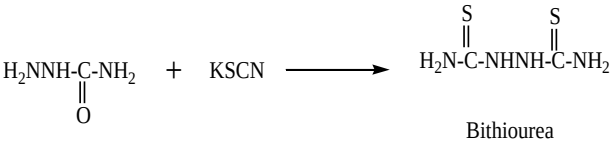
EXPERIMENTAL

All the chemicals are reagent grade. Solvents were dried and distilled before use according to

standard procedures (Nieto M.J et al, 2000). The metal salts used were in their hydrated form.

Synthesis of Bithiourea [Russo and Santagar, 1986; Russo, 1981; Charanjit et al., 1986]

25.4 g (0.22 mole) semicarbazide Hydrochloride and 21.4 g (0.22 mole) potassium thiocynate were introduced in to a round-bottomed flask. The mixture was dissolved in 60 mL water and refluxed for 3 hours. The solution was allowed to cool. White crystals separated out and the separated crystals was filtered and dried at 100°C in the oven for 2 hours. The product was thereafter recrystallized from boiling water.



Equation of the reaction

Properties: % yield=95.1, M.pt; 207-208^{o}C; Color; white; Appearance: crystalline powder, Solubility: Found soluble in (a) hot water (b) Aqueous ethanol

Preparation of Complexes

Warm ethanolic solution of metal(II)chloride (0.01 M) were added to ethanolic solution of ligand (0.02 M) in about 30 mL of ethanol. The resulting solutions were refluxed for about 2 hrs. The complexes thus formed was filtered and washed with alcohol and dried in vacuum over fused $CaCl_2$. The metal estimation was carried out using Alpha4 Atomic Absorption Spectrophotometer with PM8251 simple-pen recorder. Elemental analyses (C, H, N and S) were carried out using micro-analytical techniques on Heraens-CHN rapid analyzer. The conductance was measured in DMF solvent on an Elico CM-82 conductivity bridge. The magnetic susceptibility measurements were made on Gouy balance at room temperature using $HgCo(NCS)_4$ as calibrant. The IR spectra of ligand and its metal complexes were recorded on a Perkin-Elmer instrument in KBr pellets in the range of 4000-350cm^{-1}. UV/Visible spectra were recorded on Elico SL 164 double beam UV/Visible spectrometer in the range 190-1000 nm.

ALP, ALT, and AST assay kits were obtained from Randox Laboratories Limited, Antrim, United Kingdom. Clinical cultures of the micro-organism used were obtained from the University Teaching Hospital and Department of Microbiology, University of Ilorin, Ilorin, Nigeria. Albino rats (*Wistar Strain*) were obtained from the Department of Biochemistry, University of Ilorin, Ilorin. Nigeria.

Antimicrobial Screening

The stimulatory or inhibitory activity of the ligand and the metal complexes synthesized were determined according to the procedure previously reported with slight modification (Mohammed and Abdel-Wahab, 2005; Adediji et al., 2009).

The bacteria species used for this test include clinical cultures of *Escherichia coli, Staphylococcus aureus, Klebsiella species, Niesseria gonorrhoea, Salmonella typhi, Shigella species, Penicillium species, Pseudomonas aeruginosa and Aspergillus species*. The antibacterial activities of the compounds were determined using sensitivity test, minimum inhibitory concentration and minimum bacterial concentration.

Treatment of Animals

Male albino rats (Wister strain), weighing between 160 - 180 g were obtained commercially from Ilorin, Kwara state. Nigeria. They were kept in wire meshed cages and fed with commercial rat chow (Bendel Feeds Nigeria, Ltd.) and supplied water *ad libitum*.

Thirty six rats were divided into three groups of 6 rats per group. The first group was used as control and received distilled water. The second group of rats was treated with free ligand (Bithiourea) while the third group were subdivided into three groups treated with metal complexes $[Cu(BTU)_2]$, $[Co(BTU)_2]$ and $[Ni(BTU)_2]$. The distilled water, ligand and solution of metal complexes were administered orally to the rats of various groups two times daily for seven days at the dose of 1.00 mg/Kg body weight. The animals were sacrificed 24 hrs. after the last treatment.

Preparation of Serum and Tissue Homogenates

The method described by (Yakubu *et al., 2005)* was used to prepare the serum. The rats were sacrificed by cervical dislocation. Blood samples were collected by cardiac punctures into clean, dry centrifuge tube after which they were left for 10 min at room temperature. The tubes were then centrifuged for 10 min at 3000 x g in an MSC (Essex, UK) bench centrifuge. The clear supernatant (serum) was aspirated using a Pasteur pipette into clean, dry sample bottles and then frozen overnight before use.

The liver and kidney excised from rat, blotted of blood stains was rinsed in 1.15% KCl and homogenized in 4 volumes of ice-cold 0.01 mol dm^{-3} potassium phosphate buffer (pH 7.4). The homogenates were centrifuged at 12,500 x g for 15 min at 4°C and the supernatants, termed the post-mitochondrial fractions (PMF) were aliquoted and used for enzyme assays.

Determination of Serum and Tissue ALP, AST, and ALT Activities

Serum and tissue's ALP, AST and ALT activities were determined using Randox diagnostic kits. Determination of AST and ALT activities were based on the principle described by (Relitman and Frankel, 1957). ALP activity determination was based on the method of (Wright *et al.*, 1972). The yellow color p-nitrophenol formed was monitored at 405 nm. Protein determination of serum and all fractions was estimated by the method of (Lowry *et al.,* 1951) as modified by (Yakubu *et al.,* 2005) using bovine serum albumin as standard.

Statistical Analysis

The data were analyzed using one way ANOVA followed by Duncan multivariable post-hoc test for comparison between control and treated rats in all groups. Values of *P less* than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

The elemental analysis shown in Table 2 indicates that, all the metal complexes have 1:2 stoichiometry and are dark, peach and green colored, respectively. They are amorphous substances, soluble in DMF and DMSO.

The molar conductance values obtained for these complexes at the concentration of 10^{-3}m. The values are too low to account for any dissociation of the complexes in DMF. Hence these complexes can be regarded as non-electrolytes.

Table 1: Physicochemical Data of Ligand and its Metal Complexes.

Compounds	Melting point (°C)	Color	% Yield	Conductivity (Ω^{-1} cm^{-1} dm^{-3})
BTU	208	White	95.1	–
$Cu(BTU)_2$	140	Dark	85.5	1.2×10^{-5}
$Co(BTU)_2$	180	Peach	75.2	1.5×10^{-2}
$Ni(BTU)_2$	200	Light green	65.2	1.0×10^{-4}

Table 2: Magnetic Moment and Elemental Data of Ligand and their Metal Complexes.

Compound	Empirical formula	Formula weight	μ_{eff} (BM)	Elemental Analysis Calculated (Found)				
				C	H	N	S	M
BTU	$C_2H_6N_4S_2$	150.00	-	16.00 (16.30)	4.00 (4.02)	37.33 (37.42)	42.67 (42.40)	-
Cu(BTU)$_2$	$CuC_4H_{12}N_8S_4$	213.50	1.90	22.48 (22.50)	5.62 (5.60)	52.46 (52.47)	59.95 (59.88)	29.74 (29.60)
Co(BTU)$_2$	$CoC_4H_{12}N_8S_4$	208.93	5.10	22.97 (22.96)	5.74 (5.77)	53.61 (53.60)	61.26 (61.39)	28.33 (28.41)
Ni(BTU)$_2$	$NiC_4H_{12}N_8S_4$	208.70	2.80	22.91 (22.90)	5.75 (5.72)	53.67 (53.62)	61.33 (61.30)	28.13 (28.21)

Table 3: Ultraviolet/visible spectral assignment of L and its metal complexes (wavelength, nm (cm^{-1}))

Compound	Band 1	Band 2	Band 3	Band 4
BTU	196(51020)	241(41494)	-	-
Cu(BTU)$_2$	208(48077)	274(36496)	493(20284)	538(18587)
Co(BTU)$_2$	244(40984)	616(16234)	655(15267)	817(12240)
Ni(BTU)$_2$	223(44843)	259(38610)	427(23419)	655(15267)

Magnetic Moment

The magnetic moment values for Cu(II), Co(II), and Ni(II) complexes of the ligand are shown in Table 2. Co(II) complex is in the range of 5.05-5.14 BM indicating that the Co(II) complex are typically high spin complex and having octahedral structure. The Ni(II) complex exhibit the magnetic moment values in the range of 2.8-3.2 BM, indicating octahedral co-ordination of the ligand around Ni(II) ion. The Cu(II) complex exhibit magnetic moment in the range of 1.61-1.85 BM suggestive of distorted octahedral nature for these complex. (Obaleye *et al*., 2009).

Electronic Spectra

The electronic spectral data of Cu(II), Co(II) and Ni(II) complexes and the ligand were recorded in DMF as shown in Table 3.

For Co(II) complex with ligand (BTU) the UV/visible spectra showed three bands at visible region at 16234 cm^{-1}, 15267 cm^{-1} and 12240 cm^{-1} which were assigned to $^4T_{1g}$ (F) → $^4T_{2g}$ (F) and $^4T_{1g}$ (F) → $^4E_{2g}$ (F) and $^4T_{1g}$ (F) → $^4T_{2g}$ (P) transitions, respectively, which assume an octahedral geometry for Co(II) complex (Cotton *et al*., 1999; Reddy and Reddy, 2000).

The electronic spectra of the Ni(II) complex of Bithiourea ligand displays three bands in the visible region at 38610 cm^{-1} , 23419 cm^{-1} and 15267cm^{-1}which is assigned to $^3A_{2g}$ → $^3T_{2g}$, $^3A_{2g}$ → $^3T_{1g}$ (F) and $^3A_{2g}$ → $^3T_{1g}$ (P) The one band at 44843 cm^{-1} refers to LMCT (Macfarlane *et al*., 2000). This indicates octahedral geometry of the Ni(II) complex (Moustafa, 1997).

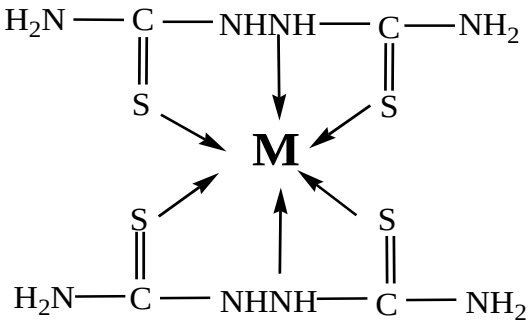
The UV/visible of the Cu(II) complex consists of a broad and low intensity shoulder band at 48077-18587 cm^{-1} that forms part of the charge transfer band. The ^2E_g and $^2T_{2g}$ states of the octahedral Cu(II) ion (d^9) split under the influence of the

tetragonal distortion to three transitions; to remain unresolved in the spectra. It is concluded that all three transitions lie within the single broad envelope centered at the same range previously mentioned. This assignment is in agreement with the general observation that Cu(II) d-d transitions are normally close in energy.

Infrared Spectra and Mode of Bonding

The IR spectra of the free ligand and their metal complexes were carried out in the range of 4000 – 400 cm^{-1} and listed in Table 4. The assignments have been carried out based on literature values obtained for similar structural compounds (Obaleye *et al.*,1999).

The important IR frequencies of the ligand, L and the metal complexes (in KBr) with their tentative assignments are given. Both the free ligand and the metal complexes are characterized by υ(N−H), δ(NH_2), υ(C=S) bands (Obaleye, 1997). The absorption patterns look quite similar to that of the free ligand which is in agreement with coordination through nitrogen atom. The band around 3400 – 3100 cm^{-1} is assigned to υ(NH) and is supported by the presence of δ(NH_2) deformation bands around 1600-1500 cm^{-1}. A blue shift was observed in the υ(C=S) frequency of the complexes, in comparison to the free ligand, which indicates coordination through the sulphur atom. Bands between 400 – 420 cm^{-1} which were absent in the free ligand are assigned to M-L that is the metal-ligand coordination. Using, the IR spectra, it is concluded that the ligand L behaves as a neutral tridentate ligand. It coordinated to the metal ions via the nitrogen of the hydrazine and sulphur atom.



Proposed structure (Where M=Cu, Co and Ni)

Biological Activities: The antimicrobial potency of the ligand and the coordination compounds has been established.

Figures 1 - 3 reported the result of antimicrobial activities. The *in-vitro* studies of the ligand and its metal complexes gave the antimicrobial activity of the compounds. Generally, the ligand and metal complexes showed antimicrobial effect against the tested organism species as presented in the figures above. *Niesseria gonorrhoea* was the most sensitive organism to the bithiourea and its metal complexes. Metal complexes showed comparable activity or greater activity against some of the micro-organisms in comparison to the parent compounds.

Table 4: IR spectral assignment of Land its metal complexes

Ligand/Complexes	υ(NH_2)	υ(NH)	υ(C=S) cm^{-1}	υ(M-S)
BTU	3431.31,b	2974.10str	780.12, str.	-
Cu(BTU)$_2$	3374.06,b	2956.89s	760.98,s	420.92,s
Co(BTU)$_2$	3265.48,b	2814.00s	740.82,s	410.62,s
Ni(BTU)$_2$	3215.82, b	2810.68s	710.37,s	400.12s

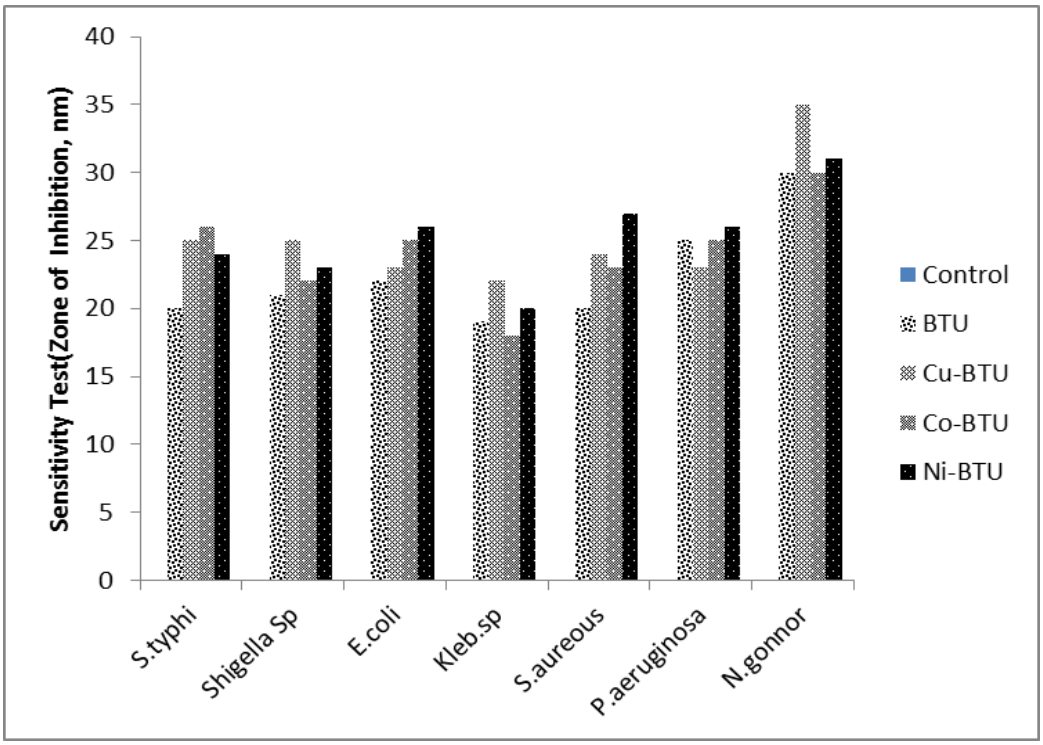


Figure 1: Sensitivity Test of the Ligand and Metal Complexes against some Micro-Organisms.
Key: *S.typhi=Salmonella typhi, S.sp=Shigella species, E.coli=Echerichia coli, K.sp=Klebsiella species, S.aureus=Staphylococcus aureus, P.aeru=Pseudomonas aeruginosa, N.gonnorrhoea=Niesseria gonorrhoea.*

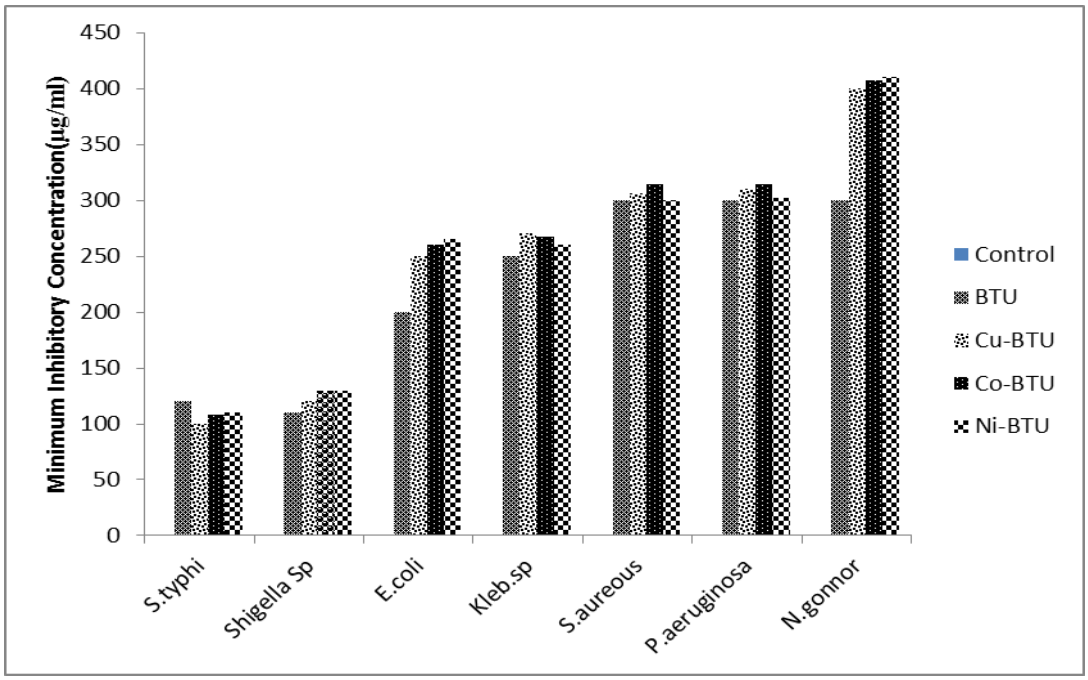


Figure 2: Minimum Inhibition Concentration of the Ligand and Metal Complexes against some Micro-Organisms.

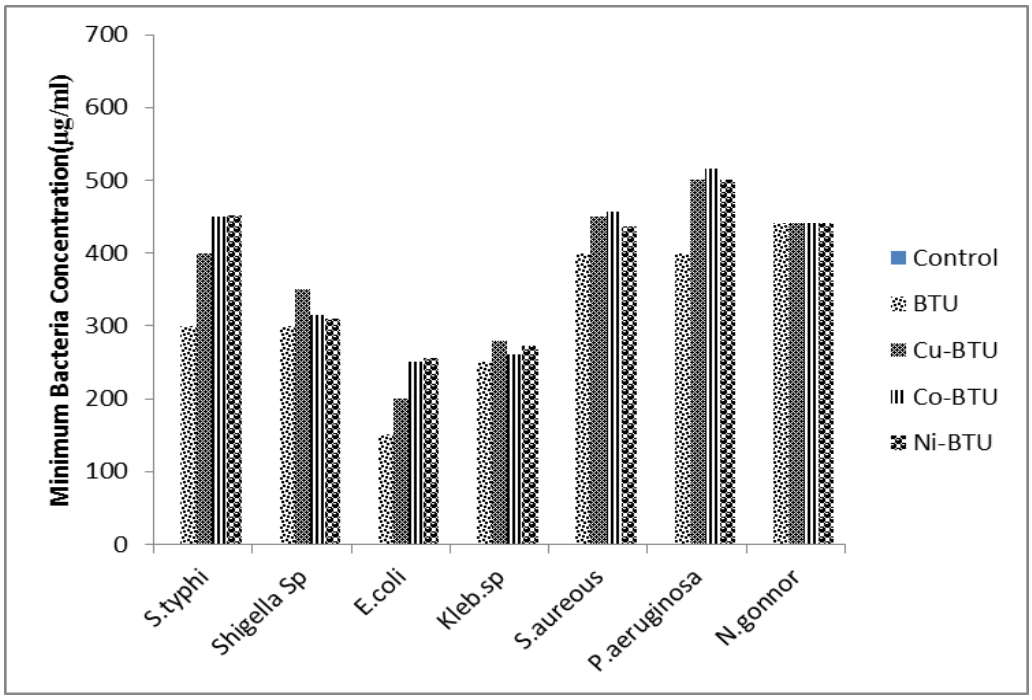


Figure 3: Minimum Bactericidal Concentration of the Ligand and Metal Complexes against some Micro-Organisms.

The MIC of the samples against the various isolates ranged from 15 µg/ml to 700 µg/ml. These concentrations in comparison to reported MIC_{90} of the ligand elsewhere are very high. This could be due to the different conditions under which the studies were carried out. These are reflections of the fact of possible interference from the media broth and some other materials and chemicals used during the test, which are not absolutely compatible with condition present in the cells (Reese and Belts, 1993).

For a particular antimicrobial, the organism involved is an important factor; *Salmonella typhi, Shigella species, Pseudomonas aeruginosa* sensitive to the metal complexes than *Klebsiella species, Escherichia coli* and *Staphylococcus aureus*. Reports have shown that $CuCl_2.2H_2O$, $CoCl_2.6H_2O$ and $NiCl_2.6H_2O$ have no inhibitory activity on bacteria and fungi species (Obaleye *et al*., 1999).

Figures 4 – 6 show the results of ALP, ALT, and AST activities on the serum, kidney and liver. There was no significant reduction ($p<0.05$) in serum ALP activities of bithiourea and its metal complexes compared with control, this suggests that the integrity of the plasma membrane of the cells in the various tissues might have not been adversely affected. This is because ALP is a membrane-bond enzyme often used to assess the integrity of the plasma membrane and endoplasmic reticulum (Malomo *et al*., 1993).

The observed significant increase in the ALP activities in the liver and kidney of the rat administered with metal complexes suggests an enhancement of the activities of the existing enzymes by the drugs and their metabolites. The increase may be as a result of stress imposed on the tissue by the drug, which may lead to loss of the enzyme molecule through leakage into extra-cellular fluid, which has been significantly noticed in the serum.

In a bid to offset this stress, the tissue may increase the *de novo* synthesis of the enzyme, thus accounting for the increase in activities in these tissues (Macfarlane I et al, 2000). However metal complex of Cu(II) caused significant increase in serum ALT activity compared with control. There was a significant increase in liver and kidney ALT and AST activities compare with control. Elevation in serum ALT and AST activity is a pointer to leakage from a damaged tissue.

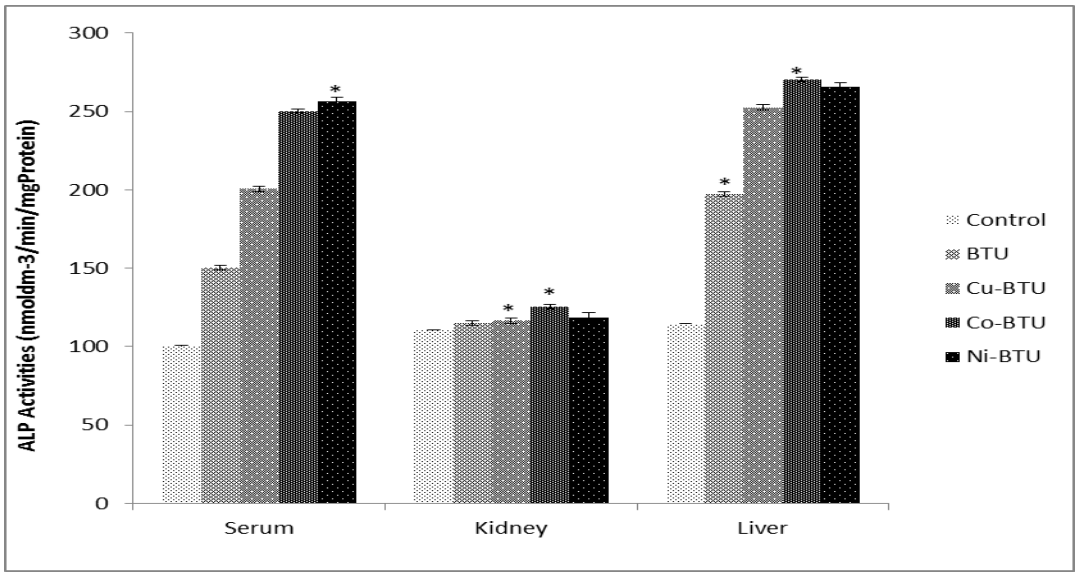


Figure 4: Effect of Administration of Ligand and the Metal Complexes on the Activities of Alkaline Phosphatase (ALP) of Rat Serum, Kidney, and Liver.
* Significantly different from the control ($p<0.05$)

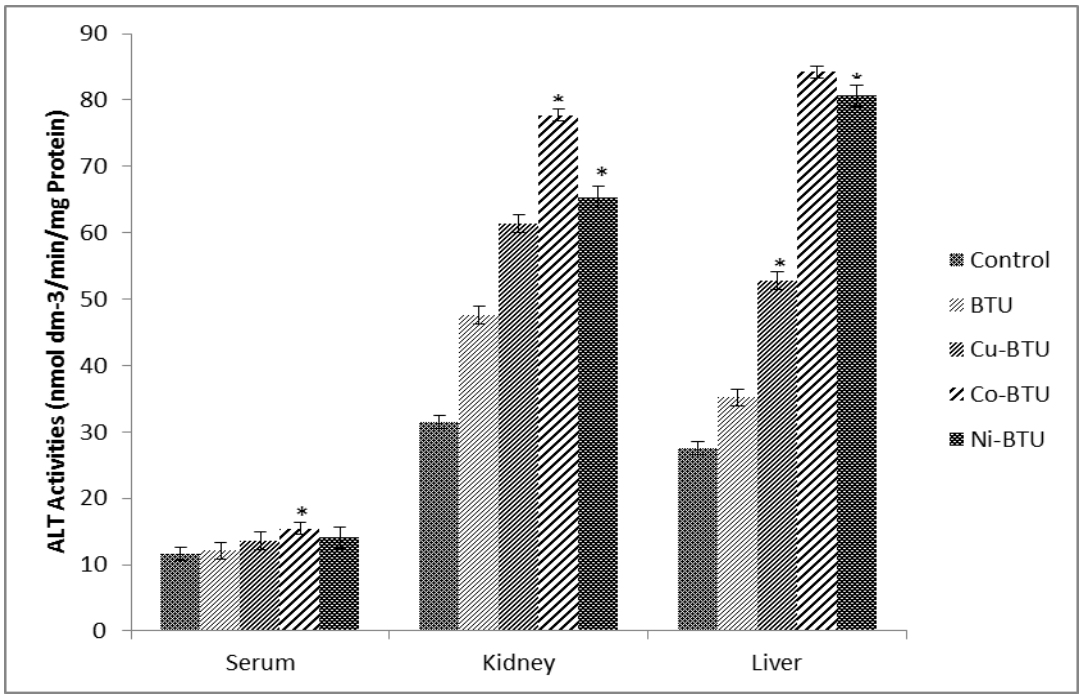


Figure 5: Effect of Administration of Ligand and the Metal Complex on the Activities of Alanine Amino Transferase (ALT) of Rat Serum, Kidney, and Liver.
* Significantly different from the control ($p<0.05$)

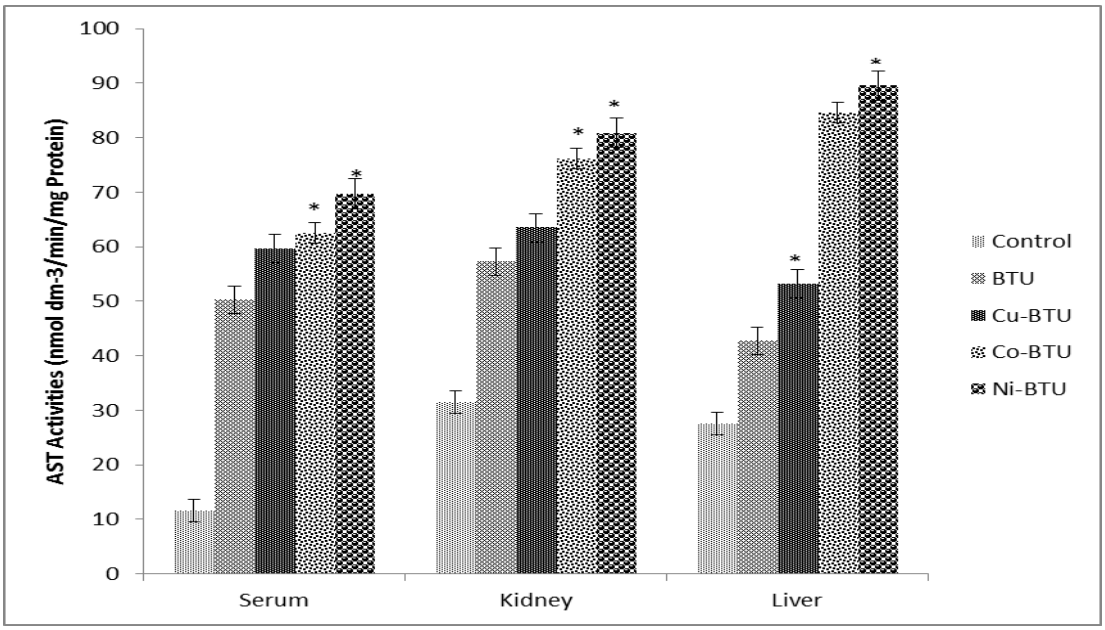


Figure 6: Effect of Administration of Ligand and the Metal Complex on the Activities of Aspartate Amino Transferase (AST) of Rat Serum, Kidney, and Liver.
* Significantly different from the control ($p<0.05$).

Increase in serum ALT and AST has been reported in conditions involving necrosis of hepatocytes (Macfarlane et al., 2000), myocardial cells, erythrocyte, and skeletal muscle cells (Halworth and Capps, 1993). Overall, the integrity of the cell membranes of the various tissues (especially kidney and liver) was not adversely affected by the metal complexes.

CONCLUSION

It is established from combined results of the chemical and physical analysis and from previous reports that the ligand (Bithiourea) employed in this work coordinated with Co(II), Ni(II), and Cu(II). The metal complexes possess enhanced physical properties than the parent compound (semicarbazide), with tentative octahedral geometry assigned. The toxicological studies revealed that the metal complexes are not toxic at the dosage level administered. Based on various activities observed, metal complexes of bithiourea would be a better therapeutic drug for antibacterial treatment.

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