A Novel 2-Aminobenzoylthiosemicarbazide Metal Complexes and their Biological Activities.

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ABSTRACT

A new Mannich base, 2-aminobenzoylthiosemicarbazide (ABT), was synthesized and characterized by spectral studies. Chelates of ABT with cobalt(II), nickel(II) and copper(II) ions were prepared and characterized by Ultraviolet/Visible, Atomic Absorption and Infrared spectroscopes. ABT was tentatively found to act as a tridentate ligand, bonding through the carbonyl oxygen of the cyclic group, sulphur and hydrazinic nitrogen of the thiosemicarbazide in all the complexes. Based on the above using the spectroscopic data, octahedral geometry were proposed for all the complexes.

The antimicrobial studies show that the complexes are more active against some molds of microorganism used. The anti-plasmodial studies using *Plasmodium berghei* as test organism showed that the parent ligand and the metal complexes showed anti-malaria activity with Ni(II) complex showed high percentage clearance of 80% as compared to a standard reference drug Chloroquine. *In vitro* evaluation of anti-tubercular activity showed that the complexes possess Antitubercular activity. *In vivo* toxicological activities reveals that the complexes were non-toxic at the dosage level orally administered.

(Keywords: chelates, Mannich base, anti-plasmodial, anti-microbial, anti-tubercular, toxicological activities)

INTRODUCTION

Metal chelates of Mannich bases form an interesting class of compounds, which find extensive applications in various fields (Mohd et al.; 2014. Gandhi and Kulkarani,1999). Among the very few number and variety of transition, inner transition and main group metal complexes of Mannich bases, those formed from bivalent transition metals are of particular interest, because of their synthetic flexibility, structural diversities, bonding interactions, biological significance, and other multiple applications. (Raman and Ravichandran, 2003, Pelczar et al., 1998, and Muruganandam et al., 2013).

Thiosemicarbazide and their metal complexes present a wide range of applications that stretch from their use in analytical chemistry, through pharmacology to nuclear medicine. The presence of amide, imine, and thione groups makes them potential polydentate ligands and it is not surprising that numerous thiosemicarbazone complexes have been prepared and characterized (Adediji et al., 2012, 2013, 2014). In addition, in the last few years there has been a growing attention towards thiosemicarbazones related to their range of biological properties, specifically as antifungal, antiviral, antibacterial and anticancer agents (Adediji et al., 2011).

Thiosemicarbazones are compounds that have been studied for a considerable period of time for their biological properties. Traces of interest date back to the beginning of the 20th century but the first reports on their medical applications began to appear in the Fifties as drugs against tuberculosis and leprosy *(*Bavin et al., 1990). In the Sixties their antiviral properties were discovered and a huge amount of research was carried out that eventually led to the commercialization of methisazone and Marboran to treat smallpox.

In this period one of the first antitumor activity results was published. Recently, Triapine (3-aminopyridine-2-carboxaldehyde thiosemi-carbazone) has been developed as an anticancer drug and has reached clinical phase II on several

cancer types. Presently, the areas in which thiosemicarbazones are receiving more attention can be broadly classified according to their antitumor, antiprotozoal, antibacterial or antiviral activities and in all cases their action has been shown to involve interaction with metal ions. (Sartorelli and Booth, 1967).

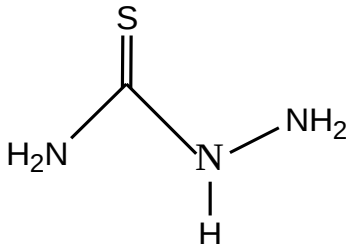
One of the most promising areas in which thiosemicarbazone compounds are being developed is their use against cancer. Their antitumor activity is extremely differentiated and it is very much dependent on the typology of tumor cells (French and Blanz,1965). This characteristic renders the whole class of compounds very interesting because it implies selectivity. At the same time it makes difficult to extract from the literature general information valid for the whole class of compounds since their activity is certainly due to more than one target in the cell machinery. Nevertheless, the presence of a metal ion almost systematically increases the activity or contributes to mitigate the side effects of the organic parent compounds.

Presently, the main known effects related to their anticancer activity are, in order of discovery, ribonucleotide reductase (RR) inhibition reactive oxygen species (ROS) production, topoisomerase II inhibition, mitochondria disruption, and, more recently, a multidrug resistance protein (MDR1) inhibition. (Koch and Stuttgen, 1950).

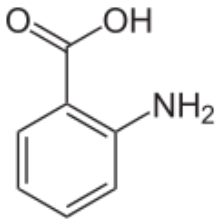
Metal complexes of thiosemicarbazides are found to possess antifungal activity, which is effected by a substituent group at N (1) and N (4) positions of Thiosemicarbazide moiety. Thiosemicarbazide inactivates the non-heme subunit and this inhibitory action is due to the coordination of iron *via* their tridentate ligating system, either by a preformed iron complex binding to the enzyme. Studies have shown that iron and copper complexes are more active in cell destruction as well as in the inhibition DNA synthesis than the un-complexed thiosemicarbazide. These observations provide an impetus to the synthesis of a large number of 2-heterocyclic thiosemicarbazides. Copper (II) complexes of heterocyclic thiosemicarbazides have shown more fungal growth inhibition property. (Jeragh and El-Dissouky, 2005).

2-amino benzoic acid is otherwise known as Anthranilic acid; it is an organic compound with molecular formula $C_7H_7NO_2$. The molecule consists of a benzene ring, hence is classified as aromatic with two adjacent or ortho-functional groups; a carboxylic acid and an amine. The compound is consequently amphoteric, although it is not usually referred to as an amino-acid as it has more than one carbon separating it two functional groups. In appearance, anthranilic acid is a white solid when pure, although commercially samples may appear yellow or grey. It may be sensitive to prolonged exposure to air and light. It is flammable and will produce nitrogen oxide fumes when burning. It's sometimes referred to as Vitamin L_1 and has a sweet taste (Sandra et al., 2007).

Anthranilic acid is biosynthesized from chromic acid. It is the precursor to the amino acid tryptophan via the attachment of phosphoribosyl pyrophosphate to the amine group. The result antimicrobial studies indicated that, in general, the synthesized compounds were found to be bacteriostatic and fungistatic in action.



Thiosemicarbazide



2-aminobenzoic acid

In continuation of our effort to find novel molecule effective against diseases that resist most available drugs especially in malaria and tuberculosis chemotherapy. We report here the synthesis, characterization and biological activities of 2-aminobenzoylthiosemicarbazide Metal Complexes.

MATERIALS AND METHODS

All reagents and chemicals were used as obtained from Aldrich. IR spectra were obtained

as KBr disc on a Perkin-Elmer FTIR spectrophotometer. UV-Visible spectra were obtained on an Aquamate v4.60 spectrophotometer. The molar conductance measurements of the complexes were carried out in DMF using a GenWay 4200 conductivity meter. Metal contents of the complexes were determined using an Alpha-4 Atomic Absorption Spectrophotometer with PM8251 simple-pen recorder. Thin layer chromatography was carried out using TLC plate coated with silica gel.

ALP, ALT, and AST assay kits were obtained from Randox Laboratories Limited, Antrim, UK. Clinical cultures of the microorganism 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.

The Antimicrobial Studies

The stimulatory or inhibitory activity of the ligand and the metal complex synthesized were determined according to the procedure previously reported (Adediji, 2011). The bacteria species used for this test include clinical sample of *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella pneumonia*. The antibacterial activities of the compounds were estimated on the basis of the size of the inhibition zone formed around the wells on sensitivity media.

Antifungal activity of each compound was determined using culture of three fungi species; they are *Aspergillus niger*, *Aspergillus flavus* and *Rhizopus* species. They were cultured on potato dextrose agar. The plates were incubated aerobically at 28 ±2°C for 96 h.

Treatment of Animals

Male albino rats (Wister strain), weighing between 160 and 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 rats were divided into five 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 (ABT), while the third group was subdivided into three groups treated with metal complexes $Co(ABT)_2$, $Ni(ABT)_2$ and $Cu(ABT)_2$. The distilled water and 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 0.80mg/Kg body weight. The animals were sacrificed 24 hrs. after the last treatment.

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.

Anti-malaria Studies

Albino Swiss mice (NK-65) were obtained from the animal house of Nigeria Institute of Medical Research, Yaba, Lagos. *Plasmodium berghei* used in this study were obtained through the same source.

Synthesis of the Ligand

2-aminobenzoylthiosemicarbazide (ABT) was synthesized by employing the Mannich synthetic route (Raman and Ravichandran, 2003). Thiosemicarbazide (9.29g, 0.1mol) was dissolved in minimum quantity of distilled water. To this solution, 2-aminobenzoic acid that has been dissolved in 40mL ethanol (13.97g, 0.1mole) was added to the solution with continuous stirring. A mixture of thiosemicarbazide and 2-aminobenzoic acid in 1:1 molar ratio was heated for 15mins on a water bath. The shiny white plates of product separated out on cooling was recrystallized from water. The compound was dried in air and then at 60^0C in an air oven and recrystallized from ethanol.

Color: brown
Nature: crystalline
Yield:81.4%
Melting Point: 162^0C
Conductivity: 3.0 x10^{-6} µs/cm^3
IR (KBr, cm^{-1}): 3474.19, 3175.73, 1666.00, 1304.22, 791.70
UV-Vis(DMF): λ, nm: 245, 266, 274, 323, 386.

General Procedure of Synthesis of Metal Complexes of ABT

0.01mole of each ($CoCl_2.6H_2O$, $NiCl_2.6H_2O$ and $CuCl_2.2H_2O$) in 20mL distilled water was added to a stirred solution of 0.02mole (4.58g) of ABT in 60mL of ethanol. The mixture was refluxed for 2hrs. The pH of the solution for complexation was maintained by adding few drops of dilute ethanolic ammonium hydroxide solution. The metal- ligand is in ratio 1:2. The insoluble complexes formed, were filtered, washed with methanol and ethanol to remove the unreacted metal and ligand, dried in air and then in an air oven at 80^0C.

$Co(ABT)_2$
Color: pinkish solid
Nature: Powder
Yield: 54.24%
M.Wt: 286.9g/mol
Melting Point: 186^0C
IR (KBr, cm^{-1}): 3306.31, 3141.60, 1602.53, 1327.93, 709.0
UV-Vis(DMF): λ, nm: 256, 267, 275, 503, 562.
Conductivity: 1.6×10^{-6} µs/cm^3

$Ni(ABT)_2$
Color: green solid
Nature: Powder
Yield: 56.64%
M.Wt: ?g/mol
Melting Point: 176^0C
IR (KBr, cm^{-1}): 3302.85, 3125.71, 1660.36, 1310.36, 753.90
UV-Vis (DMF): λ, nm: 253, 296, 275, 400, 602.
Conductivity: 1.2×10^{-6} µs/cm^3

$Cu(ABT)_2$
Color: blue solid
Nature: Powder
Yield: 83.64%
M.Wt: 291.5g/mol
Melting Point: 190^0C
IR (KBr, cm^{-1}): 3268.57, 3119.00, 1617.00, 1382.65, 753.94
UV-Vis(DMF): λ, nm: 252, 258, 267, 401, 860.
Conductivity: 1.3×10^{-6} µs/cm^3

Anti-parasitic Screening

Plasmodium berghei and mice were collected from NIMR, Yaba Lagos.Nigeria. Mice for the experiment were infected as described by previous worker (Malomo et al., 1995 and Adediji et al., 2013). Thirty six Swiss mice (male) were divided into groups of six animals each and kept in cages fed with mice cubes and water ad *libitum*. Group 1: control, group 2: chloroquine, group 3: 2-aminobenzoylthiosemicarbazide (ABT), group 4: $Co(ABT)_2$, group 5: $Ni(ABT)_2$, group 6: $Cu(ABT)_2$.

The mice in each group were marked for easy identification. The mice received 0.2 mL of 1 x 10^6 parasitized erythrocytes suspended in buffered physiological saline (pH 7.4) inoculated intravenously. The mice were left for 4 days; their levels of parasitaemias were monitored daily by counting parasites in blood smear, fixed with 70% methanol and giemsa stained. The slides were then rinsed and allowed to dry.

The slides were viewed under the microscope with magnification of 100. The level of parasitaemia was then determined by counting the number of infected erythrocytes/1000 erythrocyctes on tail blood smears stained with giemsa. 1 µg/mL solution of each of the ligands and complexes was prepared. 0.4 mL of each of the solution prepared with dimethylsulphoxide was injected daily into the mice in each group from day 0 to day 3 of infection. Levels of parasitaemia were determined on day 4. Only physiological saline solution was given to the control animals. The results were expressed as the percentage of infected cells or inhibition of parasitaemia calculated from the equation.

$$\textbf{\% Inhibition} = 100 - \frac{\text{Estimated no of infected parasitaemia treated with compound}}{\text{Estimated no of infected parasitaemia treated with no compound}}$$

In vitro Antitubercular screening

Determination of minimal inhibitory concentration: The activity of the complexes against M. tuberculosis virulent strain H_{37}Rv was determined *in vitro* as described below:

Antitubercular activity was evaluated against *Mycobacterium tuberculosis* H_{37} Rv using Microplate alamar blue assay (MABA) method (Collins *et al.*, 1997; Enayat and Ashraf, 2004).

Antitubercular susceptibility test was performed in black, clear-bottomed, 96-well microplates (Packard Instrument Company, Meriden, Conn., USA) in order to minimize background fluorescence. Initial drug dilutions were prepared

in dimethylsulfoxide and subsequent two-fold dilutions were performed in 0.1 ml of 7H9GC media in the microplates. An aliquot (100 µl) of 2000CFU/ml of *M. tuberculosis* H_{37} Rv were added to each well of 96-well microtitre plate containing test compounds.

Three control well plates containing drug and medium, bacteria and medium, and medium only were also prepared. All microtitre plates were incubated at 37 °C for seven days. At day 7 of incubation, Alamar Blue dye solution (20 µl Alamar Blue solution and 12.5 ml of 20% Tween 80) was added to all the wells and the plates re-incubated at 37 °C for 24 h.

Fluorescence was measured in a Victor II multilabel fluorometer (Perkin Elmer Life Sciences Inc., Boston, MA, USA) and MIC was determined. The minimum inhibitory concentration (MIC), concentration that inhibits the colony forming ability of M. tuberculosis was determined by incorporating decreasing concentrations of the test compounds dissolved in dimethylsulfoxide in Middlebrook 7H9GC agar medium. MIC values represent mean of three separate experiments.

RESULTS AND DISCUSSION

The metal complexes of 2-aminobenzoylthiosemicarbazide are generally soluble in DMSO and DMF and are sparingly soluble in methanol. The metal halide salts react with the 2-aminobenzoylthiosemicarbazide according to the general equation:

$$M_nX_2 \,.\, nH_2O + 2ABT \longrightarrow M(ABT)_2 + H_2O$$

The metal-ligand stoichiometry is ratio 1:2 corresponding to the formula $[M(ABT)_2]$ (where M = Co(II), Ni(II) and Cu(II) and ABT = 2-aminobenzoylthiosemicarbazide).

The analytical and spectroscopic analyses are in good agreement with the proposed stoichiometry of the complexes. The molar conductance of the solid complexes (λm, µs/cm^3) was calculated. The DMF solubility of the above complexes made calculations of the molar conductivity (λm) of 10^{-3} mol dm^{-3} solution at 25 °C possible.

The analytical data showed that the molar conductance values of the Co(II), Ni(II), and Cu(II) complexes were relatively low, indicating the non-electrolytic nature of these complexes. The complexes were characterized by UV-Visible, Infrared, and Atomic Absorption spectroscopes. From spectroscopic studies and analytical data, suggested structures of the complexes are shown in the tables below.

The assignments of infrared spectra of ABT and its complexes are given in Table 1. The infrared spectrum of the complexes was recorded down to the far IR region of 400cm^{-1} and compared with that of ABT ligand.

Table 1: FT**-** IR of the ABT and its Metal Complexes.

ABT	$Cu(ABT)_2$	$Co(ABT)_2$	$Ni(ABT)_2$	Tentative Assignment
3474.19	3268.57	3306.31	3302.85	N-Hstr of NH_2
3175.73	3119.00	3141.60	3125.71	N-Hstr
1666.00	1617.00	1602.53	1660.36	C=O
1304.22	1382.65	1327.93	1310.36	C=S
791.70	753.94	709.0	753.90	M-L or M-Cl

Table 2: UV-VIS of the Ligand and its Metal Complexes.

Compound	Band 1(nm)	Band 2(nm)	Band 3(nm)	Band 4(nm)	Band 5(nm)
ABT	245	266	274	323	386
$Cu(ABT)_2$	252	267	274	401	860
$Co(ABT)_2$	256	267	275	503	562
$Ni(ABT)_2$	253	296	323	400	602

FT-IR Spectral

The assignments of infrared spectral of ABT and its complexes are given in Table 1. The infrared spectrum of the complexes was recorded down to the far IR region of 400cm^{-1} and compared with that of the ligand.

In the spectrum of ABT there was a disappearance of the hydroxyl group bands as expected due to replacement by the in-coming thiosemicarbazide group into the carboxylic group to form coordination compound ABT. A sharp peak at 3175cm^{-1}, in the ABT was also observed which may be assigned to the V_{NH} of the hydrazinic nitrogen in the ligand; this undergoes hypsochromic shifts in all the complexes. The bands near 3474cm^{-1} in the ABT and 3268, 3306 and 3302cm^{-1} for the complexes the bands assigned to Vasy and Vsy(N-H) vibrations of the NH_2 group are not significantly shifted with respect to those of the free ligand 3474cm^{-1}.

The slight modification may be as a result of increased acidity of the NH_2 group derives mainly from polarization effect which arises in the complexes, rather than from direct coordination to the metal ion. It could even be due to hydrogen bonds involving the amino groups. This is an indication that the NH_2 group in the free ligand is affected by coordination to the metal ion.(Garcia-Raso; 1997 and Adediji et al 2012).

The strong bands appearing at 1666cm^{-1} in the ligand and at 1617, 1602 and 1660cm^{-1} in the complexes are assigned to $\upsilon_{C=O}$ stretching mode, slightly down shifts experience in the metal complexes are due to coordination to the metal ions.

The strong band related to the symmetrical and asymmetrical stretching of the $\upsilon_{(C=S)}$ moiety at 1304cm^{-1} in the carbazide show important changes upon complexation. The shifts experience in the complexes is at higher frequencies. These changes suggest coordination of the metal on to the sulphur of the (C=S) moiety (Sanchez –Delgado et al 1996). The appearances of bands around 753-709cm^{-1} in the complexes have been assigned to M-L.

Electronic Spectra of ABT and its Complexes

The electronic spectra of ABT and its metal complexes are shown in Table 2. The electronic spectrum in DMF of ABT gave absorption bands in the range of 245-386nm, these bands are assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions.

$Cu(ABT)_2$ complex showed abroad band at 401nm and 860nm as expected. This is in the d-d region and has been attributed to $^2E_g \rightarrow {}^2T_{2g}$.

$Co(ABT)_2$ is d^7 with spectroscopic ground term ^4F. The complex showed two bands in the visible region. The absorption band at 503nm is assigned to $^4T_{1g} \rightarrow {}^4A_{2g}$ and the second band at 562nm is attributed to $^4T_{1g} \rightarrow {}^4T_{2g}$.

$Ni(ABT)_2$ is d8 and a spectroscopic ground term is ^3F. The absorption band at 400nm is assigned to $^3A_{2g} \rightarrow {}^3T_{1g}(P)$, a second band at 602nm is assigned to $^3A_{2g} \rightarrow {}^3T_{1g}$. The assignments are in good agreement with the proposed octahedral geometry for the complex (Tella et al., 2011).

The melting points and color of the complexes are quite distinct from that of the corresponding mixed ligands which is an evidence of formation of the complex. Based on the above spectroscopic studies and in conjunction with analytical data, the proposed structures for the metal complexes are octahedral. In all the complexes the metal ions coordinated through oxygen of the carbonyl, nitrogen of the hydrazine and sulphur atom of the ABT.

BIOLOGICAL STUDIES

Antimicrobial Study

The studies of the ligand and its metal complexes gave the antimicrobial activity of the compounds. The metal complexes were found to be more active at higher (1.0g/dm^3) concentration than its corresponding ligand. The synthesized complexes were active against the three bacteria used, while they were found to be active against only two of the fungi used, *Aspergillus niger* and *Aspergillus flavus*. Reports have shown that metal salts ($CoCl_2.6H_2O$, $NiCl_2.6H_2O$ and $CuCl_2.4H_2O$) has no inhibitory activity on bacteria and fungi species (Obaleye et al., 1999).

Toxicological Activities

Figures 2-4 show the results of ALP, ALT and AST activities of the serum, kidney and liver. There was a significant reduction ($p < 0.05$) in

serum ALP activities of mefloquine and its metal complex treated rats compared with the control.

The observed significant increase in the ALP activities in the liver and kidney of the rats administered with mefloquine and the metal complex 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. ALP is a membranebound enzyme often used to assess the integrity of the plasma membrane and endoplasmic reticulum (Akanji et al., 1993).

In a bid to offset this stress, the tissue may increase the de novo synthesis of the enzyme, thus accounting for the increase in ALP activities in these tissues (Malomo et al., 1993).

The serum ALT activity in rats administered with mefloquine did not show significant difference compared with control. However, the Mefloquine and its metal complex caused an increase in serum AST activity compared with control with a concomitant significant reduction in kidney AST activity. AST and ALT are enzymes associated with liver parenchymal cells. They are raised in acute liver damage. They are also present in red blood cells, heart cells, muscle tissue, pancreas and kidneys.

When body tissue or an organ such as the heart or liver is diseased or damaged, additional AST and ALT are released into the bloodstream. Both ALT and AST levels are reliable indicators of liver damage. In short, 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).

Alteration in serum/tissue levels of ALP, AST and ALT as recorded in this studies are indications of derangement in cellular activities.

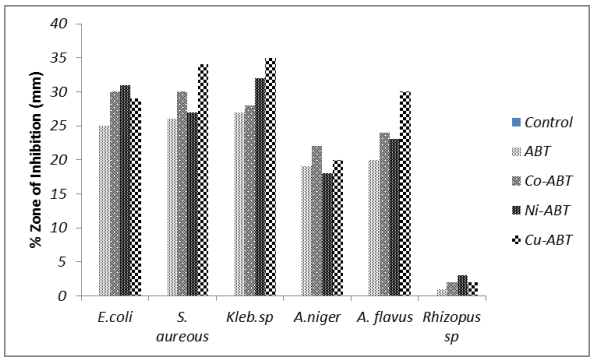


Figure 1: The Results of Antibacterial and Antifungal Activities of ABT and its Metal Complexes.

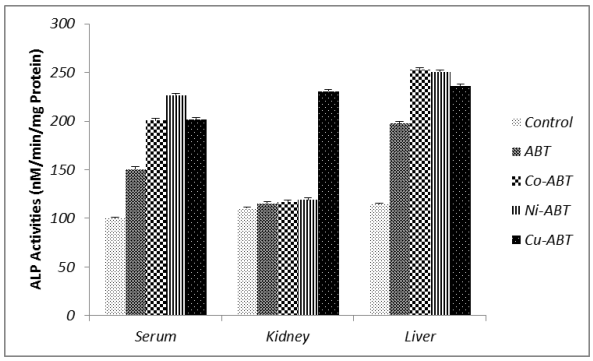


Figure 2: Effect of Administration of Ligands and Metal Complexes on the Activities of Alkaline Phosphatase of Rat Serum, Kidney and Liver. *Significantly different from the control ($p < 0.05$).

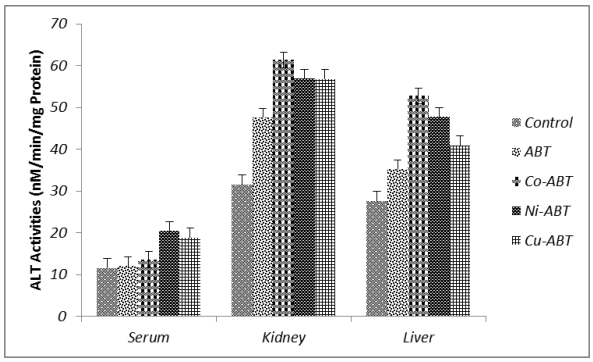


Figure 3: Effect of Administration of Ligands and Metal Complexes on the Activities of Alanine Amino Transferase (ALT) of Rat Serum, Kidney and Liver. *Significantly different from the control ($p < 0.05$).

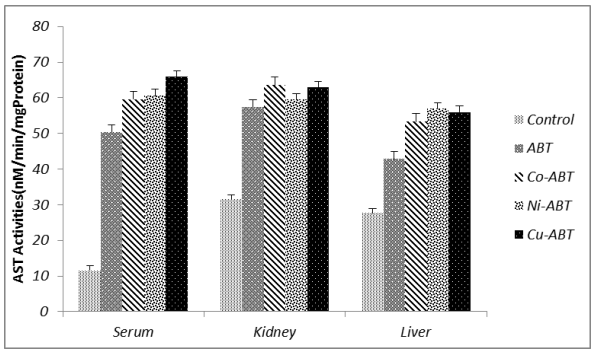


Figure 4: Effect of Administration of Ligands and Metal Complexes on the Activities of Aspartate Amino Transferase (AST) of Rat Serum, Kidney and Liver. *Significantly different from the control ($p < 0.05$).

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