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Full Length Research Paper

Fe (III) complex of mefloquine hydrochloride: Synthesis, antimicrobial and toxicological activities

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As part of the ongoing research for more effective antimalarial drug, Fe (III) complex of mefloquine hydrochloride (antimalarial drug) was synthesized using template method. Mefloquine was tentatively found to have coordinated through the hydroxyl and the two nitrogen atoms in the quinoline and piperidine in the structure, respectively. Characterization has been done on the basis of analytical, conductance, atomic absorption, magnetic measurement, electronic and Infra-red spectrometry. From analytical data, the stoichiometry of the complex has been found to be 1:1. Infra-red spectral data also suggest that the ligand (mefloquine) behaves as a tridentate ligand with N:N:O donor sequence towards the metal ion. On the basis of the above physico-chemical data it is proposed that the complex is assigned octahedral geometry. The antimicrobial activities of mefloquine metal complex exhibited greater inhibition than the parent ligand. The ligand and metal complex were screened for their toxicological activities at the dose of 6.66 mg/kg body weight twice daily for seven days on the alkaline phosphatase (ALP), alanine aminotranferase (ALT) and aspartate aminotransferase (AST) activities of rat serum, liver and kidney. Overall, it was revealed that both mefloquine and its metal complex might show mild toxicity particularly on the liver and kidney.

Key words: Fe(III) complex, synthesis, anti-malarial drug, antimicrobial, toxicology.

INTRODUCTION

Malaria is a parasitic disease that has brought misery and death to many parts of the world. Despite the huge efforts being made to control the disease, malaria can be considered one of the worlds most wide spread devastating disease causing illness and death in the world, particularly in Africa (WHO, 1981).

Earlier hopes of eradicating malaria with drugs and insecticides in the late 1950s and early 1960s were dashed in 1966 by the development and spread of drug-resistant malaria parasites and of insecticide-resistant mosquitoes carrying the parasites (Audu, 1991). In the last 30 years the emergence and increasing problem of drug resistance particularly to *Plasmodium falciparum* have emphasized the limitations of these drugs and have rekindled research interest in the development of new and more effective drugs, natural or synthetic, with novel actions as well as a resurgence of interest in old drugs.

Various studies have been carried out on complexation of some common antimalarial drugs with metals (Obaleye et al., 1997). The basic aim of the studies is to find molecules that would be more effective therapeutic substitutes for available antimalarial drugs that the malaria parasites had developed resistance against (Obaleye et al., 1999).

Mefloquine hydrochloride (ligand employed in this study) is (±)-erythro-α-(2-piperidyl)-2,8-bis(trifluoromethyl) -4-quinoline methanol, are known for their antimalarial activity. The choice of quinoline moiety was as a result of the success with the case of chloroquine. Mefloquine was the only candidate drug that came off successfully during Vietnam War. Its total synthesis was first reported by Ohnmacht et al. (1971).

More than 10,000 synthesized compounds, most of which were based on the quinoline moiety, were screened for antimalarial activity during the Vietnam War at the Walter Reed Army Institute (WRAI) in U.S.A (WHO,

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Abbreviation: W, weak; **B,** broad; **S,** strong.

1987). Mefloquine is a white or slightly yellow, crystalline powder, very soluble in water, freely soluble in methanol and alcohol. It melts at about 260°C, with decomposition. Mefloquine shows polymorphism. Since the ligand (mefloquine) consists of potential binding sites such as oxygen and two nitrogen atoms, this work set out to study out the coordination tendencies, characterization after complexing with metal and the biological activities of mefloquine hydrochloride.

MATERIALS AND METHODS

Materials

Metal salts iron(III) chloride hexahydrate used for the complexation was obtained from British Drug Houses chemical limited, Poole, England and were used as supplied. The ligand (mefloquine hydrochloride) was obtained from SWISS pharmaceuticals Company Lagos, Nigeria. ALP, ALT and AST assay kits were obtained from Randox Laboratories Limited., Antrim, United Kingdom. Isolates of *Escherichia coli*, *Klebsiella pneumonia* and *Staphylococcus aureus* were obtained from the Department of Microbiology, University of Ilorin, Nigeria. Albino rats (Wistar strain) were obtained from the Department of Biochemistry, University of Ilorin, Nigeria. This study was carried out in the Department of Chemical Sciences Laboratory, Ajayi Crowther University, Oyo, Nigeria.

Synthesis of the metal complex

The complex was prepared based on previous reported procedures with slight modifications (Nadira and Singh, 1987; Ogunniran et al., 2008). 0.01 mol of ethanolic solutions of Iron (III) chloride ($FeCl_3.6H_2O$) were prepared in a round bottomed flask. 0.01 mol (4.148 g) of Mefloquine Hydrochloride was dissolved in 20 ml ethanol and added to the solution of the metal salt in 10 ml ethanol in the round-bottomed flask fitted with a condenser and refluxed with constant stirring for 2 h. The chelate was separated out after leaving it for four days. The metal chelates thus separated were filtered and washed with methanol and then with distilled water to remove unreacted ligand and metal. Finally the solid complex was dried in a dessicator. 10% methanolic ammonia solution was used to maintain the pH of the reacting solution of metal salt and ligand under reflux.

Determination of physical properties of the complex

Infra-red spectral of the ligand and complex were recorded in KBr disc in the range (4000 - 6000 cm^{-1}) on PUC Scientific model 500 FTIR Spectrometer. Electronic spectra were on Aquamate Spectrophotometer Model V4.60. The metal estimation was done using an Alpha4 Atomic Absorption Spectrophotometer with PM 8251 simple-pen recorder. Conductivity measurements were carried out using WTW Conductometer Bridge. Thin layer Chromatography was carried out using TLC plate coated with silica gel.

Antimicrobial screening of the ligand and metal complex

The stimulatory or inhibitory activity of the ligand and the metal complex synthesized were determined according to the procedure previously reported by Obaleye and Famurewa (1989) as modified by Mohamed and Abdel-Wahab (2005). The bacteria species used for this test include clinical sample of *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella pneumonia*. The antibacterial activeties 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 (Wistar strain), weighing between 160 - 180 g were obtained from the Department of Biochemistry, University of Ilorin, Ilorin and housed in the animal house of the Department of Chemical Sciences, Ajayi Crowther University, Oyo, Nigeria for acclimatization. They were kept in wire meshed cages and fed with comercial rat chow (Bendel Feeds Nigeria Ltd) and supplied water ad libitum.

Eighteen 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 (mefloquine), while the third group was treated with metal complex ($Fe(Mef)Cl_3$). The distilled water, ligand and solution of metal complex were administered orally to the rats of various groups two times daily, morning and evening for seven days at the dose of 6.66 mg/kg body weight. The animals were sacrificed 24 h 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 stunning. Blood samples were collected by cardiac punctures into clean, dry centrifuge tubes 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 were rinsed in 1.15% KCl and homogenized in 4 volumes of ice-cold 0.01 M 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 coloured 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. P values less than 0.05 were considered statistically significant.

Table 1. Some physical properties of mefloquine and its metal complex.

Compounds	Melting point (°C)	Colour	Yield (%)	Metal content (%) theoretical (experimental)	Conductivity ($^{-1}$ cm^{-1} dm^{-3})
Mefloquine(Mef)	259 - 260	White	-	-	3.221×10^{-5}
$Fe(Mef)Cl_3.6H_2O$	220 - 222	Light Yellow	66.2	5.64 (5.88)	1.597×10^{-4}

Table 2. UU/Visible spectral assignment of mefloquine and its metal complex.

Compound	wavelength (nm)	cm^{-1}
Mefloquine(Mef)	272.00	36765
	207.00	48309
$Fe(Mef)Cl_3$	343.00	29155
	317.00	31546
	279.00	35778
	222.00	45045

Table 3. IR spectral assignment of mefloquine and its metal complex.

Mefloquine (cm^{-1})	$Fe(Mef)Cl_3$ (cm^{-1})	Tentative assignment
3447.4 w,b	3341.9 b	N(OH), v(N–H) stretch
2925.1 s,b	2931.3 w,b	N(C–H) stretch of CH_3
1586.2 s	1520.8 s	N(C=N)
1380.9 s	1380.2 s	N(C–N) stretch

RESULTS AND DISCUSSION

The metal chloride salt possibly reacts with the ligand L (L = Mefloquine) forming a compound with the proposed equation [M(III)LCl_3]:

$$MX_3 \cdot nH_2O + L \rightarrow ML \cdot X_3 + nH_2O$$

Where M = Fe^{3+} metal salt, L = Mefloquine and X = Chloride

The complex synthesized was found to be a non-hygroscopic solid with a light yellow colour (Table 1). The complex is very soluble in ethanol, methanol and distilled water. It has a sharp melting point and no decomposition observed. The average percentage yield was 66.2%. The retention factor (R_f) values were calculated from the developed single spot for the complex indicating the purity of the compound (Mohamed and Abdel-Wahab, 2005). The R_f of the metal complex was found to be higher than the ligand. Comparing the conductivity of the ligand with that of the metal complex, at a room temperature suggests that it is non-electrolytic in nature. The analytical data of the antimalarial metal complex showed 1:1 stoichiometry.

The UV-spectra of the ligand and its metal complex have been interpreted in terms of charge transfer transitions from the metal to the anti-bonding orbital of the ligand and of the $\pi \rightarrow \pi^*$ transitions of the ligand (William et al., 1980). The ultraviolet spectrum of the free mefloquine HCl shows two absorption bands at 272.0 nm and 207.0 nm (Table 2). These transitions involve energies of 36765 and 48309 cm^{-1}. The bands have been assigned to the $n \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ transition, respectively. These bands undergo hypsochromic shifts in the metal complex due to complexation. The infrared data (Table 3) showed the results of most informative and indicative region. The assignments have been interpreted based on literature values obtained for similar structural compounds (Obaleye et al., 1999). The shifts observed in the absorption bands between mefloquine and its metal complex show that there is coordination. Metal-Ligand bands were observed in the ranges of 610-950 cm^{-1} in the metal complex. As shown in Table 4, the Fe(III) complex shows a μ_{eff} value of 6.00 BM, which corresponds to high spin (octahedral) stereo-chemistry (Kamaruddin and Roy, 2001)

Figures 1 and 2 show the results of antibacterial and antifungal activities of free mefloquine and metal complexes. The studies of the ligand and its metal complex gave the antimicrobial activity of the compounds. The Metal complex was found to be more active at higher (1.0 g/dm^3) concentration than its corresponding ligand. The synthesized complex was 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 $FeCl_3.6H_2O$ has no inhibitory activity on bacteria and fungi species (Obaleye et al., 1999).

Figures 3-5 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 membrane-bound 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

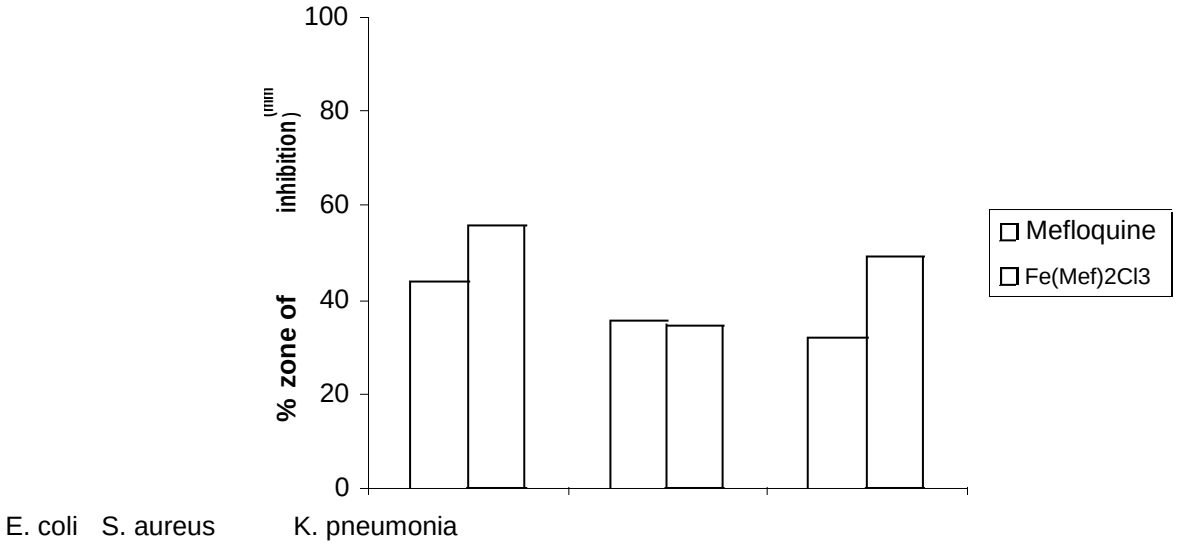

Figure 1. Inhibitory activity of the ligands and metal complexes against E. coli, S. aureus and K. pneumonia.

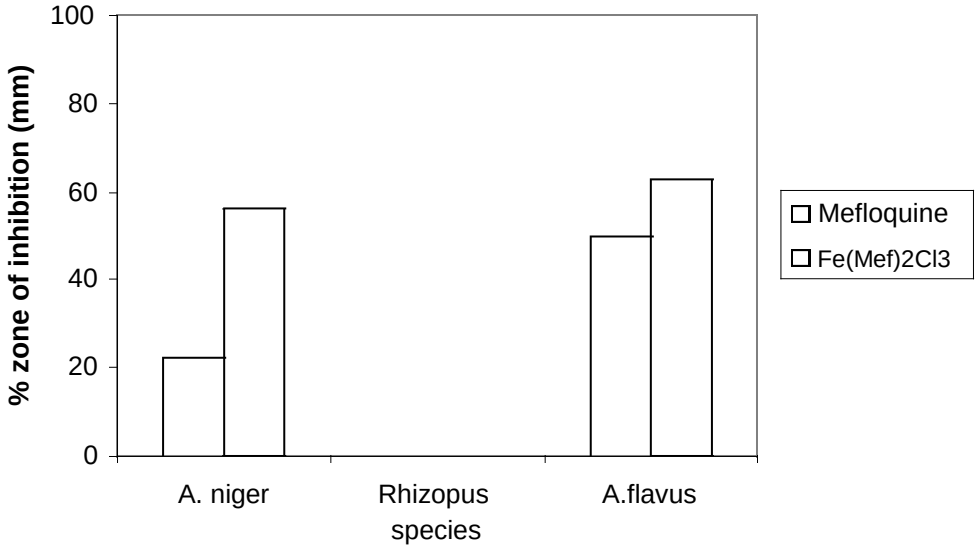

Figure 2. Inhibitory activity of the ligands and metal complexes against A. niger, Rhizopus species and A. flavus.

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.

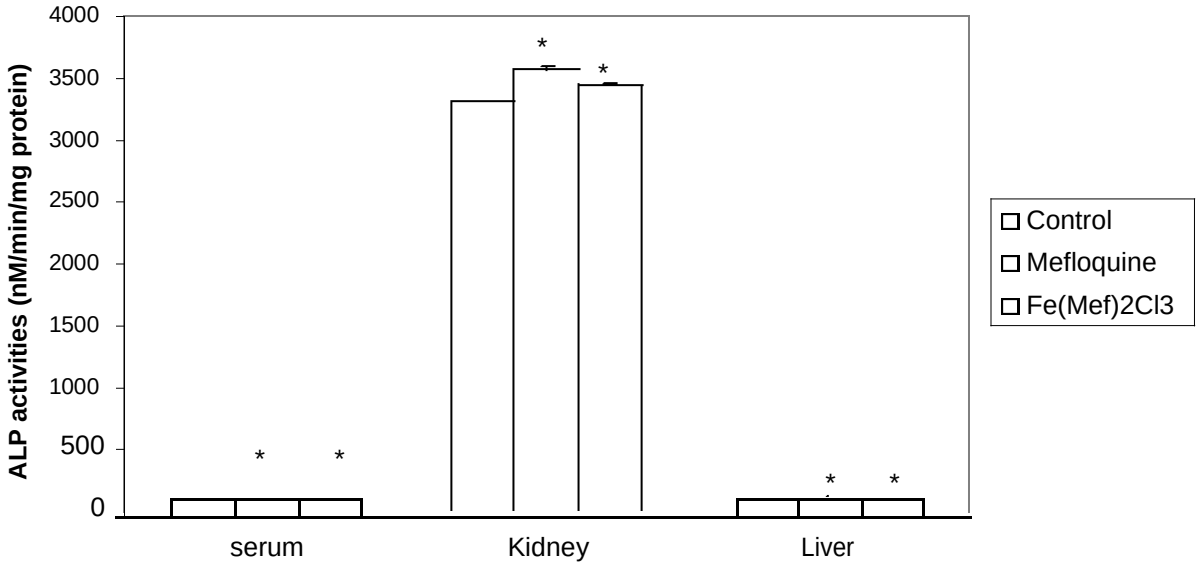

Figure 3. Effect of administration of ligands and metal complexes on the activities of alkaline phosphatase of rat serum, kidney and liver. *Significantly different from the control ($p < 0.05$).

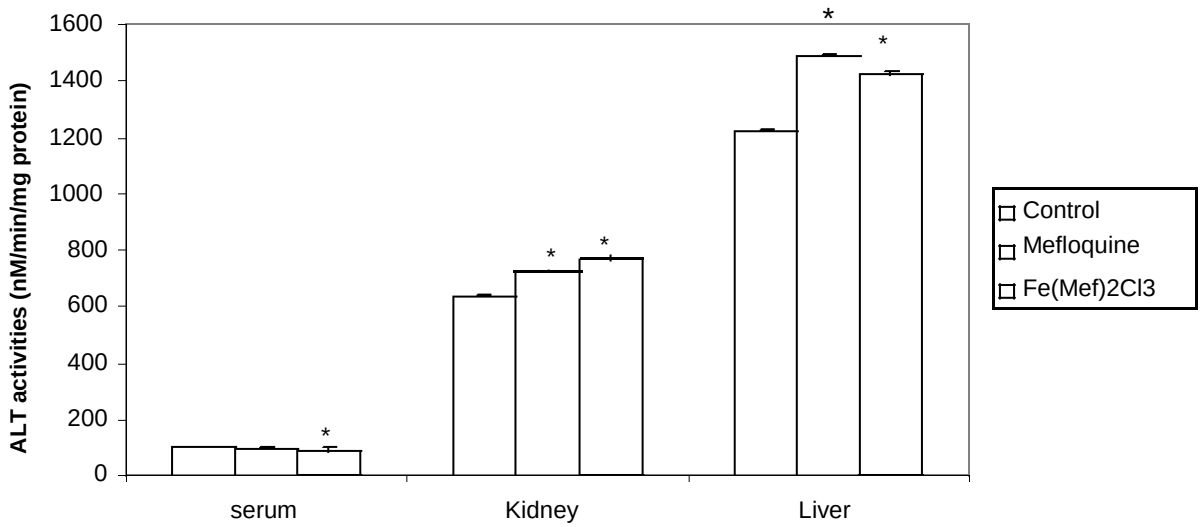

Figure 4. Effect of administration of ligands and metal complexes on the activities of alanine amino transferase (ALT) of rat serum, kidney and liver. *Significantly different from the control ($p < 0.05$).

Table 4. Magnetic moment of the ligands and metal complexes.

Compound	Empirical formula	Formular weight	$\propto_{eff}$ (BM)	% Metal content found (calculated)
Mefloquine	$C_{17}H_{16}F_6N_20$	414.80	-	-
$Fe(Mef)_2Cl_3$	$Fe(C_{17}H_{16}F_6N_2O)Cl_3.6H_2O$	685.3	6.00	7.69(8.17)

Conclusion

The results of the chemical and physical analysis from this study show that the ligand (mefloquine) employed in this work coordinated with Fe(III). The metal complex possesses better physical properties than the parent

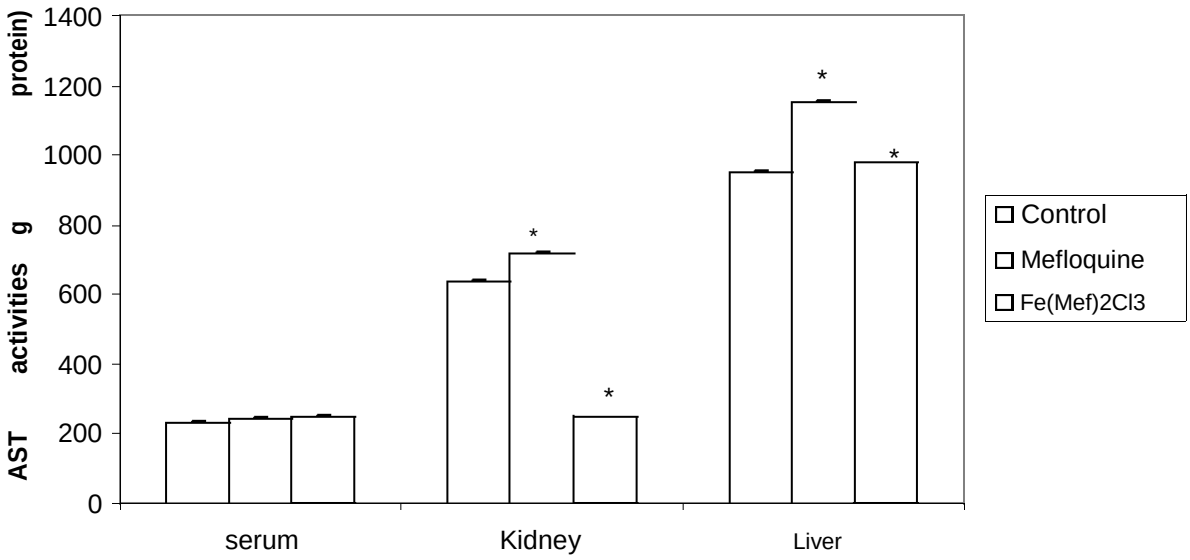

Figure 5. Effect of administration of ligands and metal complexes on the activities of aspartate amino transferase (AST) of rat serum, kidney and liver. *Significantly different from the control ($p < 0.05$).

compound. The toxicological studies revealed that both mefloquine and its metal complex might show mild toxicity particularly on the liver and kidney.

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