# Synthesis, *In Vivo* Evaluation of Antimalarial and Toxicological Screening of Mefloquine Metal Complexes.

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## ABSTRACT

Complexes of Ni(II) and Fe(III) with Mefloquine hydrochloride (Antimalarial drug) have been synthesized and characterized by elemental analysis, magnetic measurements, infrared, UV/visible, and conductance measurements. The Infrared revealed that the ligand acts as a tridentate donor N^N^O while the stoichiometry of the complexes has been found to be 1:2.

*In vivo* evaluation of antimicrobial studies of the complexes showed greater activities when compared with the free Mefloquine. The complexes were also screened against malarial parasites (*Plasmodium yoelii nigeriensis*): It was evident from the results obtained that Ni(II) and Fe(III) showed 75% and 62% parasitaemia reduction respectively compared to the free Mefloquine. Toxicological activities at the dose of 0.60mg/kg body weight on albino rats (Wistar strain) administered twice daily for seven days on the rat serum, liver and kidney revealed that both Mefloquine and its metal complexes gave mild toxicity particularly on the liver and kidney.

(Keywords: Mefloquine complexes, characterization, antimalarial activity, toxicological studies)

## INTRODUCTION

Recently, interest in the trend of metal drug complexes, has increased in order to achieve an enhanced therapeutic effect in combination with decreased toxicity (Peter and Zijian, 1998). Transition metal complexes with soft or hard donor groups have been used extensively in coordination and organometallic chemistry (Sakar and Mandal, 2000).

Various studies have been carried out on complexation of some common anti-malaria drugs with metals (Nadira and Singh, 1987; Adediji et al., 2009).

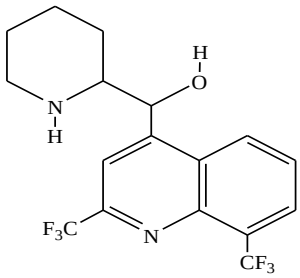
The basic aim of this study is to find molecules that would be more effective therapeutic substitutes for available anti-malaria drug that malaria parasites had developed resistance against (Adediji et al., 2009).

Mefloquine Hydrochloride (Ligand study) is (±)-erythro-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinoline methanol, and it is known for anti-malaria 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 anti-malaria activity during the Vietnam War at the Walter Reed Army Institute (WRAI) in the USA (WHO, 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. It shows polymorphism.

However, the emergence and increasing problem of drug resistant particularly to plasmodium falciparum have rekindled research interest in the development of new and more effective drugs, natural or synthetic, with novel actions as resurgence of interest in old drugs (Adediji et al., 2009).

In continuation of our work on antimalarial metal drug complexes, we report herein the synthesis, characterization, antimicrobial, anti-malaria and

toxicological properties of Ni(II) and Fe(III) Mefloquine complexes; with view to provide chemotherapeutic agents with greater biological activities in pharmacological research devoid of malaria parasites' ability to developing resistance against.



**Mefloquine Structure**

## EXPERIMENTAL SECTION

All chemicals used were of AR grade from BDH Chemicals and were used as received. Mefloquine hydrochloride was obtained from SWISS Pharmaceutical Limited, Lagos, Nigeria. Carbon, Hydrogen and Nitrogen contents were determined using a Perkin-Elmer CHN 2400. The metal estimation was done using an Alpha 4 Atomic Absorption Spectrophotometer with PM 8251 simple pen recorder. Infrared spectra were recorded on KBr disc in the range 40000-600cm$^{-1}$ on PUC scientific model 500 FTIR spectrometer. The UV/Visible spectra were on an Aquamate spectrophotometer model V4.60. Molar conductivities were carried out using a Jenway 4010 conductivity meter. The molar magnetic susceptibilities of the powdered samples were measured using a Faraday Balance model 7650 using $Hg[Co(SCN)_4]$ calibrant. Thin layer chromatography was carried out using TLC plates coated with silica gel.

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, Ilorin, Nigeria. *Plasmodium yoelii nigeriensis* used in this study were obtained Through University of Ibadan Teaching Hospital. Swiss mice, obtained from the Department of Biological sciences, University of Ilorin, Nigeria.

### Synthesis of The Metal Complexes

The complexes were prepared based on previous reported procedures with slight modifications (Nadira and Singh, 1987; Adediji et al., 2009). 0.01mol of ethanolic solutions of Ni(II) chloride ($NiCl_2.6H_2O$) were prepared in a round bottomed flask. 0.01mol (8.296g) of Mefloquine hydrochloride was dissolved in 20 cm$^3$ ethanol and added to the solution of the metal salt in 10 cm$^3$ ethanol in a round-bottomed flask fitted with a condenser and refluxed with constant stirring for 2 h. The product 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 desiccator. 10% methanolic ammonia (buffer) solution was used to maintain the pH of the reacting solution of metal salt and ligand under reflux. The same procedure were used for Fe(III) complex of Mefloquine hydrochloride.

**$M + 2L \rightarrow ML_2$**

Where M = $Ni^{2+}$ and $Fe^3$

**Table 1**: The Experimental Rsults and Physical Data of Ligand and its Metal Complexes.

| Compound | M.F. | M.W g/mole | Color | M.Pt. °C | Yield % | $\mu_{eff}$ (BM) | Conductivity $\Omega^{-1}cm^{-1}dm^{-1}$ | Elemental Analysis % Calculated(Found) C | H | N | M |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ligand (Mef) | $C_{18}H_{16}F_6N_2OCl$ | 425.5 | White | 260 | - | - | - | 50.73 (50.68) | 3.76 (3.77) | 6.58 (6.40) | - - |
| $Ni(Mef)_2$ | $Ni(C_{36}H_{32}F_{12}N_4O_2Cl_2)$ | 909.0 | White | 240 | 66.0 | 4.25 | $1.31x10^{-4}$ | 47.52 (47.64) | 3.52 (3.82) | 6.16 (6.30) | 6.38 (6.40) |
| $Fe(Mef)_2$ | $Fe(C_{36}H_{32}F_{12}N_4O_2Cl_2)$ | 907.0 | Light yellow | 221 | 70.2 | 5.80 | $1.62x10^{-4}$ | 47.63 (47.52) | 3.53 (3.72) | 6.17 (6.19) | 6.17 (6.21) |

## Antimicrobial Screening of the Ligand and Metal Complexes

The stimulatory or inhibitory activity of the ligand and the metal complexes synthesized were determined according to the procedure previously reported by (Obaleye and Famurewa, 1989) as modified by (Mohammed and Abdel-Wahab, 2005). 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; *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. They were kept in wire meshed cages and fed with commercial rat chow (Bendel Feeds Nigeria, Ltd.) and water *ad libitum*.

Twenty four rats were divided into four 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 $Ni(Mef)_2$ and the fourth group was treated with $Fe(Mef)_2$. The distilled water, ligand and solution of metal complexes were administered orally to the rats of various groups two times daily, morning and evening for seven days at the dose of 0.60 mg/Kg body weight. The animals were sacrificed 24 h after the last treatment.

## Preparation of Serum and Tissue Homogenate

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 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 AST, ALT, and ALP Activities

Serum and tissues AST, ALT, and ALP activities were determined using Randox diagnostic kits. Determination of AST and ALT activities were based on the principle described by (Reitman and Frankel, 1957). ALP activity determination was based on the method of (Wright et al.,1972). The yellow colored p-nitro phenol 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) and Malomo et al. (1993), 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.

## Antimalarial Activities

The method used by (Obaleye et al.,1999) was employed with slight modifications.

Sixteen Swiss mice were divided into four groups with four rats per group. They were inoculated with 0.2ml of $1x10^6$ parasitized erythrocytes suspended in buffered physiological saline (pH 7.4). After 96 hours of infection, the degree of parasitaemia was determined from Glemsa stained thin blood smears by examining 100 erythrocytes in 5 different fields. This was

expressed as a percentage of cell parasitized (Obaleye et al., 1999). On the same day, the drug was administered to the mice. A solution of ligand and metal complexes were prepared with a concentration of 1ppm each. 0.4ml of the solutions was injected into the mice in each group, while only physiological saline solution was given to the control animals. The mice were left for another 4 days after which a blood smear was prepared to check the level of parasitaemia.

## RESULTS AND DISCUSSION

The Mefloquine hydrochloride and it metal complexes were subjected to elemental analysis. The results of elemental analyses (C, H, N, and M) with molecular formula and melting points are presented in Table 1. The results obtained are in good agreement with those calculated for the suggested formula. Coordination by the ligand in the metal ion is confirmed by IR, UV/Vis, Magnetic and conductance measurements, which are discussed below.

The metal chloride salts reacts with the ligand, L (L = Mefloquine) forming a compound [$ML_2$] using the proposed equation:

$$\mathbf{M + L_2 \rightarrow ML_2}$$

Where M = $Ni^{2+}$ and $Fe^{3+}$ metal salts. L = Mefloquine.

The complexes synthesized were found to be a non-hygroscopic solid with a white and light yellow color (Table1). The complexes are very soluble in ethanol, methanol and distilled water. It has a sharp melting point, and no decomposition observed. The average percentage yield was 66.0% for $Ni(Mef)_2$ and 70.2% for $Fe(Mef)_2$.The retention factor ($R_f$) values were calculated from the developed single spot for the complexes indicating the purity of the compound (Bakhtiar and Ochiai,1999). The $R_f$ of the metal complexes was found to be higher than the ligand. Comparing the conductivity of the ligand with that of the metal complexes at a room temperature suggests that it is non-electrolytic in nature. The analytical data of the anti-malarial metal complexes showed 1:2 stoichiometry.

**Table 2**: IR Spectra Data ($cm^{-1}$) of the Ligand and their Metal Complexes in KBr Pellets.

| Mefloquine ($cm^{-1}$) | $Ni(Mef)_2$ ($cm^{-1}$) | $Fe(Mef)_2$ ($cm^{-1}$) | Tentative Assignment |
|---|---|---|---|
| $3447.4_{w,b}$ | $3346.8_b$ | $3341.9_b$ | υ(OH), υ(N-H)strech |
| $2925.1_{s,b}$ | $2939.5_{w,b}$ | $2931.3_{w,b}$ | υ(C-H)stretch of $CH_3$ |
| 1586.2s | $1580.0_s$ | $1520.8_s$ | υ(C=N) |
| 1380.9s | $1340.2_s$ | $1380.2_s$ | υ(C-N) |

**Table 3**: UV/Visible Spectra Assignment of Mefloquine and its Metal Complexes (Wavelength, nm($cm^{-1}$)).

| Compound | Band 1 | Band 2 | Band 3 | Band 4 |
|---|---|---|---|---|
| Ligand (Mef) | 272.0 (36765) | 207.0 (48309) | — | — |
| $Ni(Mef)_2$ | 222.0 (45045) | 207.0 (48309) | — | — |
| $Fe(Mef)_2$ | 279.0 (35778) | 222.0 (45045) | — | — |

The UV-spectra of the ligand and its metal complexes have been interpreted in terms of charge transfer transitions from the metal to the anti-bonding orbital of the ligand and of the π → π* transitions of the ligand (William and Fleming, 1980). The ultraviolet spectrum of the free mefloquine HCl shows two absorption bands at 272.0 nm and 207.0 nm (Table 3). These transitions involve energies of 36765 $cm^{-1}$ and 48309 $cm^{-1}$. The bands have been assigned to the n→ π* and n → **σ*** transition, respectively.

These bands undergo hypsochromic effect (blue shift) in the metal complexes due to complexation. The infrared data (Table 2) showed the vibration frequency of the most informative functional group. The assignments have been interpreted based on literature values obtained for similar structural compounds (Micheal et al., 2004).

The change observed in the wave number between mefloquine and its metal complexes suggested that there is coordination. Metal-Ligand bands were observed in the ranges of 610 - 950 $cm^{-1}$ in the metal complexes. The Ni (II) complex shows a $\mu_{eff}$ value of 4.25 BM and Fe(III) complex $\mu_{eff}$ value of 5.80 BM , which corresponds to high spin (octahedral) stereochemistry ( Kamrudin and Roy, 2001). The proposed structure is as shown in Figure 7 below.

## BIOLOGICAL ACTIVITIES

### Antimicrobial Activity

Figures 1 and 2 show the results of antibacterial and antifungal activities of free mefloquine and the metal complexes. The studies of the ligand and its metal complexes gave the antimicrobial activity of the compounds.

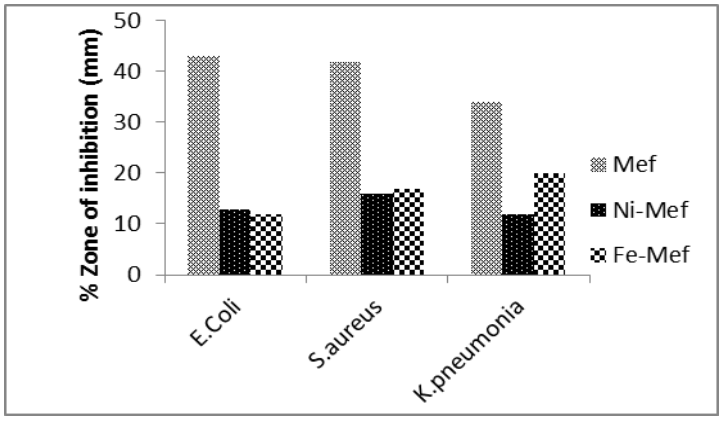



**Figure 1:** Inhibitory Activity of the Ligand and Metal Complexes against *E. coli*, *S. aureus*, and *K. pneumonia*.

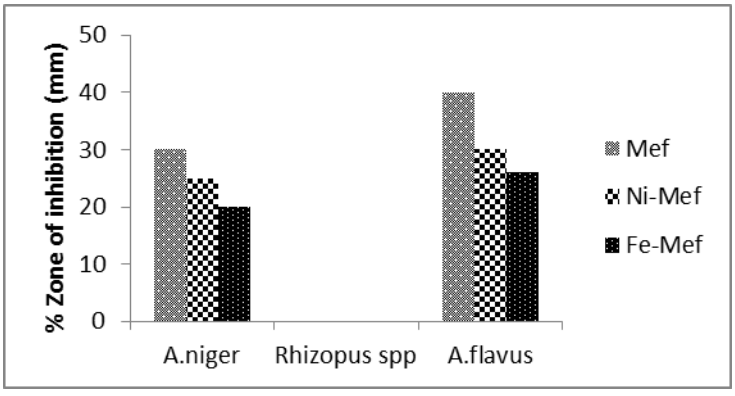



**Figure 2:** Inhibitory Activity of the Ligand and Metal Complexes against *A. niger*, *Rhizopus species,* and *A. flavus.*

The Metal complexes were found to be more active at higher (1.0 g/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 $NiCl_2.6H_2O$ and $FeCl_3.6H_2O$ has no inhibitory activity on bacteria and fungi species (Obaleye et al., 1999; Dorman and Deans. 2000).

Figures 3 - 5 show the results of ALP, ALT and AST activities of the serum, kidney and liver of rat. There was a significant increase ($p<0.05$) in serum ALT, AST, and ALP activities of Mefloquine and its metal complexes treated rats compared with the control, with the Mefloquine group higher than the metal complexes. The data also indicate that there was a significant reduction ($p<0.05$) in the liver and kidney. The observed significant increase in the serum ALT, AST, and ALP activities with a concomitant significant reduction in the same enzymes activities in the liver and kidney of rats administered with Mefloquine and the metal complexes 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 (Malomo et al., 1993). 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 AST, ALT and ALP as recorded in these studies are indications of derangement in cellular activities and hence no toxicity in metal complexes group and the Mefloquine group.

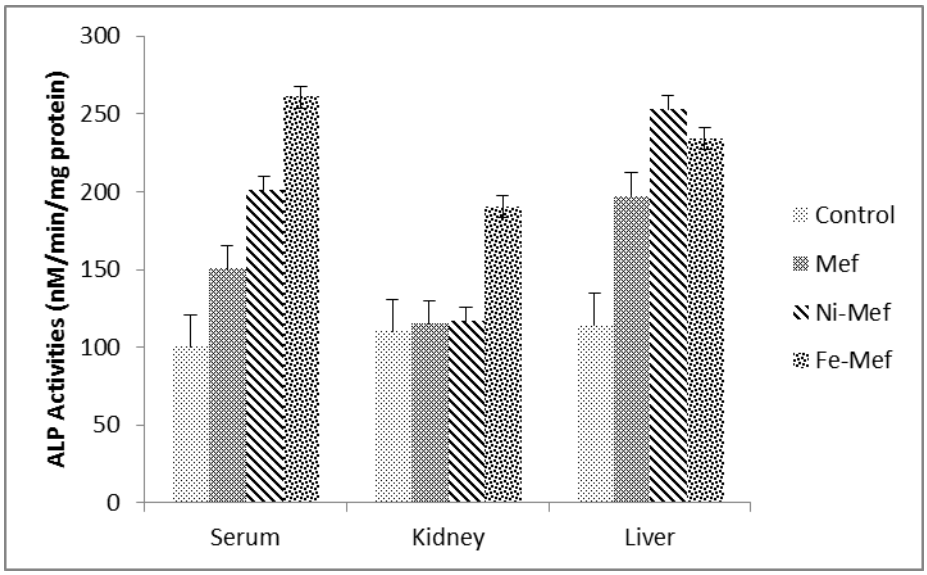



**Figure 3:** Effect of Administration of Ligand and Metal Complexes on the Activities of Alkaline Phosphatase of Rat Serum, Kidney, and Liver. *Significantly different from the control ($p<0.05$).

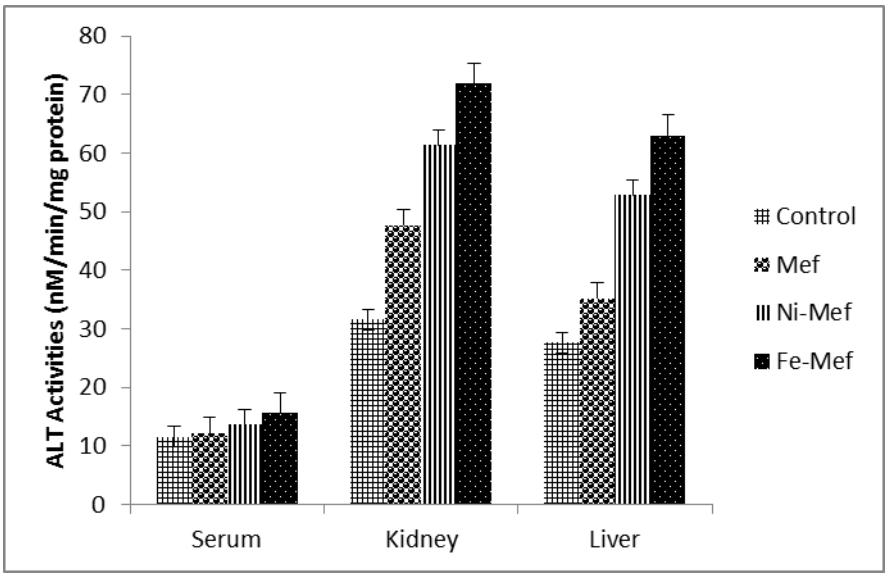



**Figure 4:** Effect of Administration of Ligand and Metal Complexes on the Activities of Alanine Amino Transferase of Rat Serum, Kidney, and Liver. *Significantly different from the control ($p<0.05$).

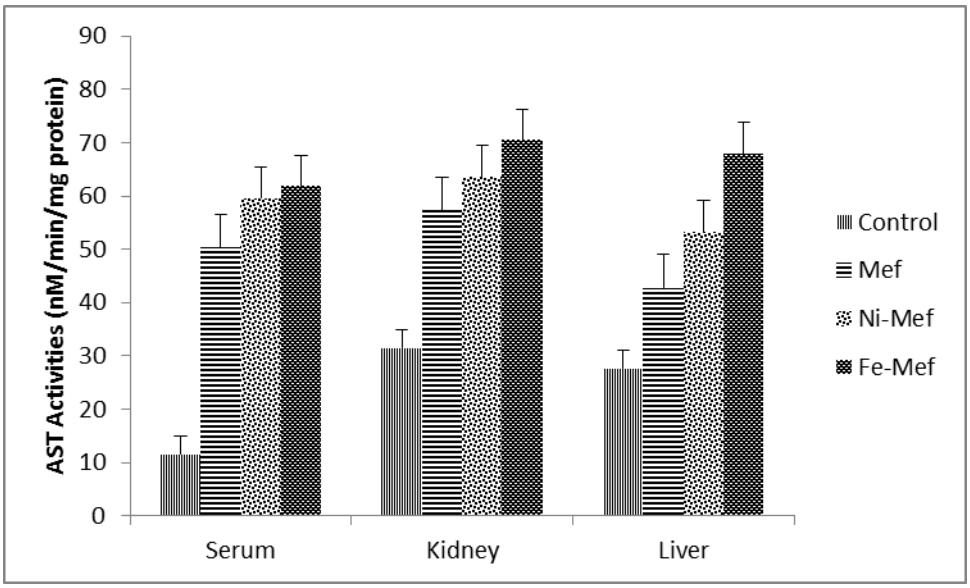



**Figure 5**: Effect of Administration of Ligand and Metal Complexes on the Activities of Aspartate Amino Transferase of Rat Serum, Kidney, and Liver. *Significantly different from the control ($p<0.05$).

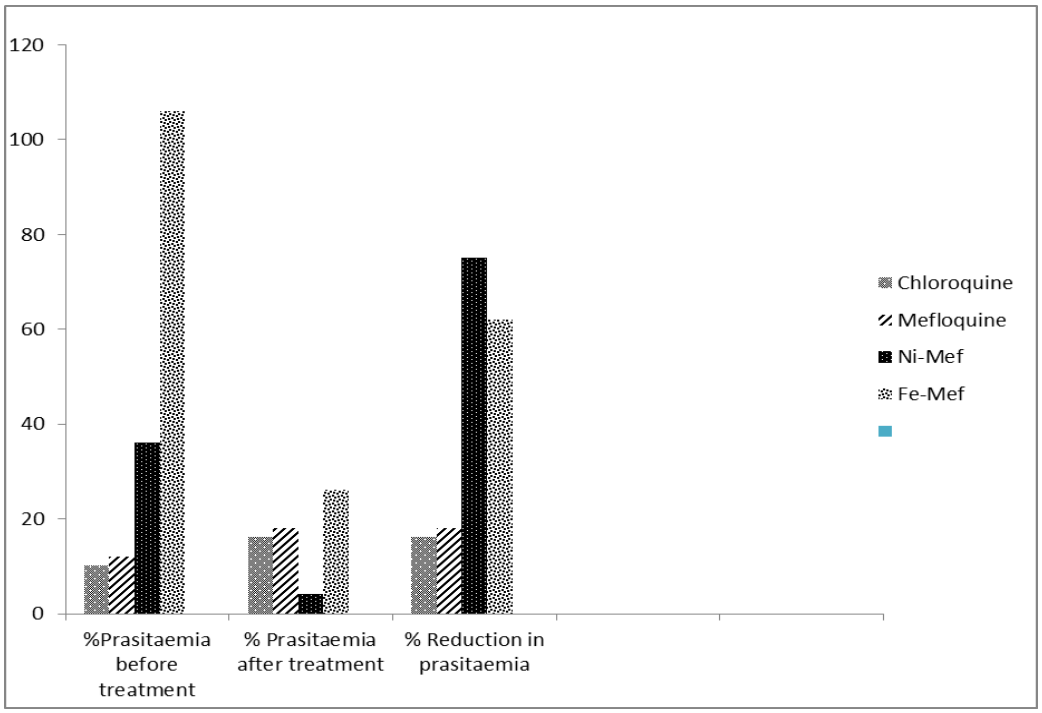



**Figure 6:** Percentage *Prasitaemia* of Ligand and Metal Complexes using Mice Infected with *Plasmodium yoelii nigeriensis.*

Figure 6 shows the anti-malaria activities of the metal complexes. Ni (II) complex has the best clearance with 75% reduction in parasitaemia while that of Fe(III) complex is 62%.

## CONCLUSION

The Mefloqine (Mef) coordinates to the Ni(II) and Fe(III) ions using the N^N^O donor atoms in the compound, resulting to octahedral geometry proposed by the information obtained from infrared measurements and elemental analysis. The metal complexes possess greater physical and biological properties compare to their parent compound. The metal complexes possess antimalaria properties with best clearance of 75% and 62% which make the complexes better antimalarial agents with no toxicity.

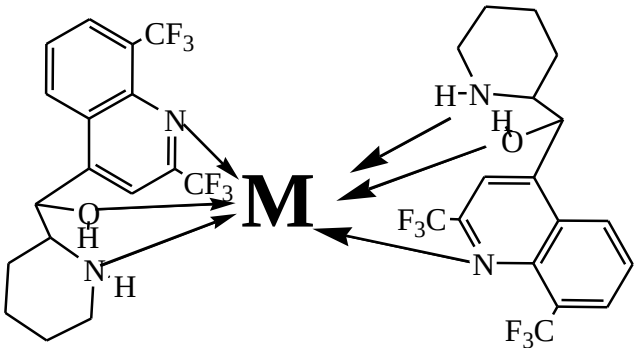



**Figure 7:** Proposed structure of Mefloquine.

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## SUGGESTED CITATION

Adediji, J.F., S.A. Amolegbe, S. Adewuyi, C.A. Akinremi, and Y.C Oyeniran. Synthesis, *In-Vivo* Evaluation of Antimalarial and Toxicological Screening of Mefloquine Metal Complexes". *Pacific Journal of Science and Technology*. 14(1):259-268.

Pacific Journal of Science and Technology