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*Full Length Research Paper*

# Cu(II) and Fe(III) complexes of sulphadoxine mixed with pyramethamine: Synthesis, characterization, antimicrobial and toxicology study

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**Two new mixed ligands metal complexes of sulphadoxine and pyramethamine were prepared by using $CuCl_2.6H_2O$ and $FeCl_3.6H_2O$. The complexes were characterized by elemental analysis, melting point determination, molar conductivity, metal content analysis (AAS), IR, magnetic susceptibility measurements and UV-Visible spectroscopy. Based on the analytical and spectroscopic data, the complexes were proposed to have the formulae $[M_1L_1L_2(Cl)_2]$ and $[M_2L_1L_2(Cl)_3]$ (where $M_1$ = Cu(II), $M_2$ = Fe(III)), $L_1$ = sulphadoxine, $L_2$ = pyramethamine). The spectroscopic data proposed $L_1$ to be a monodentate ligand and coordinated through N atom of the $NH_2$ group in both complexes. Also, $L_2$ was proposed to be tridentate ligand and coordinated through N atom of the $NH_2$ groups and through N atom of imine group. However, $[M_1L_1L_2(Cl)_2]$ and $[M_2L_1L_2(Cl)_3]$ were proposed to possess distorted octahedral geometry. Conductivity measurement values supported the non-electrolytic nature of the complexes. The complexes have been tested *in vitro* against a number of pathogenic bacteria [g(+) *Escherichia coli,* g(+) *Proteus species,* g(+) *Pseudomonas aeruginosa* and g(+) *Salmonella typhi*] by using disc diffusion method. Obtained results indicated that the metal complexes exhibited better antibacterial activities as compared to the ligands. Toxicology tests against some tissues of albino rat (*Rattus novergicuss*) revealed toxicity of the complexes in the kidney as compared to the parent drugs. $[M_1L_1L_2(Cl)_2]$ was found to be toxic to the sera, livers and kidneys of the rats used, while $[M_2L_1L_2(Cl)_3]$ was found to be non-toxic to the sera, livers and kidneys of the rats as their alkaline phosphatase (ALP) values showed non-significant difference to the control values.**

**Key words:** Metal complexes, complexation, antibiotics, antimicrobial properties, alkaline phosphatase.

## INTRODUCTION

Malaria remains the major killer disease in the developing countries that affects lives of more than 500 million people and kills about two million of them annually (Snow et al., 2005). Most of the drugs that are used to treat malaria can be broadly grouped into 4-aminoquinolines, 8-aminoquinolines, anti-folates, artemisinin derivatives and certain class of antibiotics, such as doxycycline and clindamycin. 4-aminoquiniline derivatives, such as chloroquine and amodiaquine, have been the first-line drugs against malaria for past several decades. Development of resistance against these drugs in several parts of world necessitated the use of other drugs along with it for efficient treatment. Malaria treatment guidelines issued by World Health Organisation (WHO) also recommends the use of amodiaquine along with sulphadoxine-pyramethamine combinations for the treatment of chloroquine-resistant malaria (Mishra et al., 2011). With the evolution of chloroquine resistance to malaria parasites in Africa and South-east Asia, the combination of the antifolate drugs pyrimethamine (PYR) and sulphadoxine (SDX), was one of the mainstays of anti-malarial drug therapy. Although, the resistance is now widespread, it is

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still used in Africa, sometimes in combination with the artemisinin derivative, artesunate, to treat uncomplicated malaria (Nosten and White, 2007). PYR and SDX synergistically inhibit enzyme activities of the folate biosynthesis pathway, namely dihydrofolate reductase (DHFR) and dihydropteroate synthetase (DHPS). The action of antifolate drugs, the genetic basis of parasite resistance, and the complexities of the relationships between parasite genotype and *in vivo* and *in vitro* drug response phenotypes have been comprehensively investigated (Hyde, 2005; Nzila, 2006). Antimicrobial resistance is fast becoming a global concern. The emergence of resistance is an evolutionary process that is based on selection of organisms that have enhanced ability to survive dose that are considered to be lethal. Resistance results from a mutation in the parasite chromosome or the acquisition of extra-chromosomal DNA (Trampuz et al., 2003). The spread of resistant parasite strains to all kinds of drugs is growing high in tropical and sub-tropical regions, including Africa, Asia and part of America (Sachs and Malaney, 2002). The medicinal uses and applications of metals and metal complexes are of increasing clinical and commercial importance. The introduction of metal ions into chemotherapy agents with the aim of increasing their efficacy has been an extensive research area for more than three decades since the discovery of Cis-platin (Farrell, 2003; Fahmideh et al., 2010; Ajibade, 2008). The metallo-elements play vital roles at the molecular level in a living system. In the search for novel therapy against resistant organism, the modification of existing drug by combination to a metal centre has gained attention in recent years (Delhaes et al., 2001). The efficacies of some therapeutic agents are known to increase upon co-ordination, thus metal-based drug is seen as promising alternatives for possible replacement for some of the current drugs. Metal complexes as pharmaceuticals have received considerable attention in the development of anticancer agents using platinum, ruthenium and other metals, with greater efficacy and reduced toxic side effects (Timerbaev et al., 2006). Vanadium compounds, either alone or in combination with other agents, have the potential to serve as anti-diabetic agents (Roat-Malone, 2007; Ajibola et al., 1998). Despite the existence of various chemotherapeutic options available to man, malaria epidemic is still stronger than ever. Even though several agents are under clinical trials, the field of inorganic chemistry can still offer better hope for the future. Thus, the search for new anti-resistant therapies is of high priority. In continuation of our search for new chemotherapic agents, we synthesize novel metal complexes of pyramethamine mixed with sulphadoxine.

## EXPERIMENTAL

Sulphadoxine and pyramethamine (product of Sigma Chemical Co., USA) were obtained from Bond Chemical, Lagos, Nigeria. Other reagents are product of Aldrich & Sigma, Co., UK. They were used without further purification. The metal sources are $CuCl_2.6H_2O$ and $FeCl_3.6H_2O$. Melting points were determined using Gallenkamp melting point apparatus. The UV-Vis spectra measurements were obtained from solution of the compounds in dimethylformamide (DMF) on Thermo Genesys 10UV scanning UV-Vis spectrometer. Magnetic susceptibility measurements of the complexes in the solid state were determine by Gouy balance using $Hg[Co(NCS)_4]$ as a calibrant. Infrared (IR) spectra of the samples in KBr pellets were obtained in the ranges of 400 to 4000 $cm^{-1}$ using Thermo-Nicolet FT-IR Spectrometer (Covenant University, Nigeria). Conductivity measurement was carried out in DMF using Hand-held conductivity-TDS meter. Microanalyses for C, H, O and N were performed on Perkin Elmer 204C micro-analyser. Metal content was measured by Thermo S-Series Atomic Absorption Spectrometer (AAS). Isolates of g(-) *E. coli*, *P. aureginosa*, *S. typhi* and *Proteus spp.* were obtained from Microbiological Department, Covenant University, Nigeria. Albino rats (*Rattus novergicuss*) were obtained from Biochemistry Department, Covenant University (Nigeria).

### Synthesis of metal complexes

0.6206 g (2 mmol) of sulphadoxine and 0.500 g (2 mmol) of pyramethamine were dissolved separately in 20 ml of ethanol (Elzahany et al., 2008). The solutions were mixed thoroughly together in round bottom flask. The resulting mixture was stirred under reflux for 1 h at 60°C, after which 0.01 mol of each of the metal salt in 20 ml methanol was added. The reaction mixture was refluxed for 3 h, after which the solution was allowed to cool to room temperature and left on the bench for 2 weeks. The crystals formed were filtered under vacuum, washed twice with ethanol and dried in desiccator containing $CaCl_2$ as drying agent. The purity of the compounds was confirmed by using thin layer chromatography (TLC).

### Antibacterial screening

The antibacterial activities of the ligands and the metal complexes were studied against four human pathogenic bacterial, namely: g(-) *E. coli* g(+) *S. aureus*, *P. aureginosa* and *S. typhi* (Collins and Lyne, 1980; Watson, 2000; Garba and Salihu, 2011). The filter disc diffusion method was adopted. Both sulphadoxine and pyramethamine were used separately as standard. Nutrient agar (5 g nutrient broth; 3.1 g of nutrient agar in 200 ml of sterile water for 8 plates) was prepared and used as basal medium for the cultured bacterial and were autoclaved. The paper discs impregnated with the test compounds were placed on the solidified medium. The plates were pre-incubated for 1 h at room temperature and incubated at 37°C for 24 h. The observed zone of inhibition in percentage was determined according to the Equation that follows:

% Inhibition = (Average diameter of bacterial colony on the test plate (mm)) / (Average diameter of growth of bacterial colony on the control plate (mm)) × 100

### Toxicology study

A total of twenty-five albino rats of Wistar strain weighing between 150 to 180 g housed in clean metabolic cages, were used for toxicology study (Yakubu et al., 2005; Tella and Obaleye, 2010; Ogunniran et al., 2007). They were well feed with rat pellets and tap water. They were grouped into five groups consisting of five animals in each group. Group A (control) administered with methanol, Group B, C, D and E were administered accordingly with sulphadoxine ($L_1$), pyramethamine ($L_2$), $Cu(L_1)(L_2)Cl_2$ and

**Table 1.** Colour, decomposition temperature, conductivities and analytical data of the ligands $L_1$ and $L_2$ and their mixed ligands metal complexes.

| Compound | Carbon found (Calc.) | Hydrogen found (Calc.) | Oxygen found (Calc.) | Nitrogen found (Calc.) | Metal found (Calc) | Conductivity ($\Omega^{-1}cm^2mol^{-1}$) | Melting point (°C) | Colour state | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| Sulphadoxine ($L_1$) | 46.17 (46.44) | 4.01 (4.22) | 20.32 (20.62) | 18.03 (18.06) | - | 4.55 | 191-192 | - | - |
| Pyramethamine ($L_2$) | 57.89 (57.95) | 4.44 (4.46) | - | 22.50 (22.52) | - | 3.37 | 193-194 | - | - |
| $Cu(L_1L_2)Cl_2$ | 41.25 (41.62) | 3.21 (3.49) | 9.10 (9.22) | 16.00 (16.15) | 9.02 (9.16) | 2.63 | 199 | White crystal | 53 |
| $Fe(L_1L_2)Cl_3$ | 39.89 (39.96) | 3.32 (3.35) | 8.81 (8.87) | 15.39 (15.53) | 7.29 (7.74) | 2.37 | 216 | Brown crystal | 46 |

$Fe(L_1)(L_2)Cl_3$. They were administered intravenously two times daily for 5 days at the dose level of 3.33 mg/kg body. All the rats were sacrificed 24 h after the last day of administration. Their kidneys and livers were harvested and kept inside sucrose solution separately and were stored in iced cold 0.25 M sucrose solution. The blood samples were collected into clean centrifuge tubes.

### Preparation of serum and tissue homogenate

The method described by Tella and Obaleye (2010) was adopted. The blood samples in the centrifuge tubes were then centrifuged for 15 min using Uniscope Laboratory Centrifuge (model SM 800B, England). The sera were then aspirated using Pasteur pipette into clean dried sample bottles after which they were stored for further analysis. The kidneys and livers were decapulated, blotted in tissue paper and were weighed. They were homogenized and stored in the freezer for further use. The alkaline phosphatase (ALP) activity was determined (Yakubu et al., 2005) and statistical significance was determined using Duncan multiple range test and values were considered statistically significant at $P < 0.05$.

## RESULTS AND DISCUSSION

Physical characteristics and elemental analysis (CHN) of the ligands and Cu(II) and Fe(III) complexes prepared are presented in Table 1. The results of C, H and N percentages are in accordance with the composition suggested for the two complexes. The solubility of the metal complexes was compared with the ligands by dissolving them in some polar solvents, such as water, methanol, ethanol, acetone and non-polar solvents, e.g. n-hexane, benzene and DMF. The two complexes were found to be non-soluble in distilled water, methane, ethanol and n-hexane. However, they were found to be soluble in acetone, benzene and DMF. This is an indication that the complexes are non-polar in nature (Vogel, 1989). The two complexes were coloured and possess high melting points. They are amorphous and stable in air. Hence, the proposed stoichiometric equation for the synthesized complexes could be represented as:

$$MCl_n.6H_2O + L_1 + L_2 \rightarrow ML_1L_2Cl_n + 6H_2O$$

where M = Cu(II) for n= 2 and Fe(III) for n=3, $L_1$ = Sulphadoxine and $L_2$ = pyramethamine.

### Conductance measurements

The conductivity of the complexes was measured in DMF. The complexes showed molar conductance values ranging from 2.37 $\Omega cm^2mol^{-1}$ indicating their non-electrolytic nature (Vogel, 1989). The obtained values suggested that no anion is present outside the coordination sphere.

### Infrared spectra

The infrared spectra of the ligands were compared with those of metal complexes (Table 2). The infrared spectra data of the ligands and their metal complexes are in agreement with the expected range. The strong band in the range of 3410 to 3682 $cm^{-1}$ was attributed to (N-H) stretching vibration (Fessenden and Fessenden, 1990; Fahmideh et al., 2010). The same band was observed in the metal complexes spectra at lower wavelength $[Cu(L_1L_2)Cl_2]$ (3598 $cm^{-1}$) and in $[Fe(L_1L_2)Cl_3]$ (3600 $cm^{-1}$). The shifting of this group to lower frequency when compared with the two free ligands suggesting a coordination of Cu(II) and Fe(III) ion, respectively through nitrogen atom of the respective amine group (Farrell, 2003; Elzahany et al., 2008). However, this observation was confirmed by C-N bending vibration which appeared as medium band at 1170 $cm^{-1}$ in $L_1$ and at 1080 $cm^{-1}$ in $L_2$. The band was observed to have shifted to lower frequency (1050 $cm^{-1}$) in both complexes coupled with reduction in intensity. The appearance of C-N bending at this position further supports the involvement of nitrogen atoms in complexation with metal ions under investigation (Fahmideh et al., 2010). Also, the infrared spectra display strong band at 500 $cm^{-1}$ $[Cu(L_1L_2)Cl_2]$ and at 730 $cm^{-1}$ $[Fe(L_1L_2)Cl_3]$ attributed to M-N vibration (McCleverty

**Table 2.** IR Spectra (4000-400 $cm^{-1}$) of the ligands $L_1$ and $L_2$ and their mixed metal complexes.

| Compound | Ѵ(N-H) $cm^{-1}$ | Ѵ(C-H) $cm^{-1}$ | Ѵ(C=C) $cm^{-1}$ | Ѵ(C-N) $cm^{-1}$ | Ѵ(C-O) $cm^{-1}$ | Ѵ(S=O) $cm^{-1}$ | L-M |
|---|---|---|---|---|---|---|---|
| $L_1$ | 3682.01$^{s}$<br>3600.10$^{s}$ | 3010$^{s,b}$ | 1580.07$^{s}$ | 1170.03$^{m}$ | 1210.01$^{s,b}$ | 1190.27s | - |
| $L_2$ | 3605.07$^{s}$<br>3410.01$^{s}$ | 3010$^{s,b}$ | 1600.01$^{s}$<br>1510.07$^{s}$ | 1080.12$^{vw}$ | 1220.03$^{s,b}$ | - | - |
| $Cu(L_1L_2)Cl_2$ | 3598.02$^{s}$ | 3005.10$^{s,b}$ | 1525.17$^{s}$<br>1420.01$^{s}$ | 1078.11$^{m}$<br>1050.32$^{m}$ | 1200.03$^{s,b}$ | 1185.26$^{m}$ | 504.17$^{s}$ |
| $Fe(L_1L_2)Cl_3$ | 3600.01$^{m}$ | 3005.21$^{s}$ | 1520.07$^{m}$<br>1420.12$^{m}$ | 1050.02$^{w}$ | 1310.22$^{vw}$ | 1200.20$^{s,b}$ | 730.34$^{s}$ |

w- weak, s-strong, m-medium, vw- very weak, vs-very strong, m,b- medium and broad, s,b- strong and broad.

**Table 3.** UV-Vis spectra assignments of sulphadoxine, pyramethamine and their mixed metal complexes.

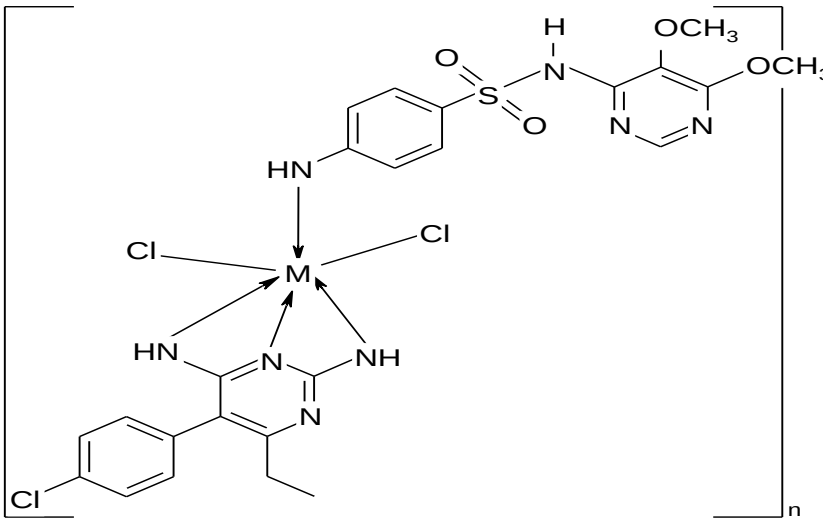
| Compound | Wavelength (nm) | ($cm^{-1}$) | Tentative assignment | $\mu_{eff}$ B.M. |
|---|---|---|---|---|
| $L_1$ | 202 | 49504 | π- π* | - |
| | 271 | 36900 | n- π* | |
| $L_2$ | 202 | 49504 | π- π* | - |
| | 286 | 34965 | n- π* | |
| $Cu(L_1L_2)Cl_2$ | 486 | 20576 | $^{2}Eg_{(D)} \rightarrow {}^{2}T_2g_{(D)}$ | 1.5 |
| | 347 | 26041 | π- π* | |
| | 230 | 43478 | n- π* | |
| $Fe(L_1L_2)Cl_3$ | 495 | 27624 | $^{6}A_1g \rightarrow {}^{4}T_2g(G)$ | 5.4 |
| | 362 | 39682 | $^{6}A_1g \rightarrow {}^{4}T_1g(G)$ | |

g-gerade

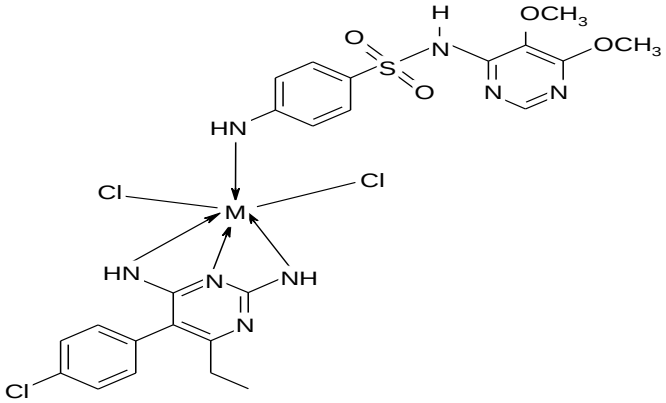
and Meyer, 2003). The band was conspicuously absent in the spectra of the ligands. The appearance of M-N vibration further supports the involvement of nitrogen in the complexation. Other bands observed in the spectra of the ligands were also observed in the metal complexes with shifting in their position due to the effect of complexation.

## Electronic absorption spectra and magnetic moment

The electronic absorption data of the ligands and the metal complexes are as shown in Table 3. $L_1$ showed two absorption bands at 202 and 271 nm, while $L_2$ showed similar bands at 202 and 286 nm. The bands were assigned to π- π* transition of C=C of the phenyl rings and n-π* transitions of C-N and C-O groups (Obaleye et al., 2001; Vogel, 1989). However, the bands were observed to have undergone bathochromic shift in the metal complexes due to complexation. The electronic transition of $[Cu(L_1L_2)Cl_2]$ complex shows two weak bands at 230, 347 and a broad band at 486 nm corresponding to n- π*, π- π* and $^{2}Eg_{(D)} \rightarrow {}^{2}T_2g_{(D)}$ transition, respectively. The band at 486 nm is expected for d-d transition of Cu(II) complex (McCleverty and Meyer, 2003; Heslop and Jones, 1986). The broadness of the band could be attributed to the overlapping of several bands as a result of strong Jahn-Teller distortion expected in a $d^9$ ion (Ajibade et al., 2006). However, molar conductance value for the complex in DMF (14.63 $\Omega^{-1}cm^{2}mol^{-1}$) shows that the chloride ions are coordinated to the Cu(II) ion (Douglas et al., 1999). Thus, the electronic absorbance data supports a distorted octahedral geometry (Youssef and Hegab, 2005). The Cu(II) complex showed $\mu_{eff}$ value of 1.5 B.M., indicative of one unpaired electron per Cu(II) ion. This suggests that




Where M= Fe(III) ion and n=Cl




Where M= Cu(II) ion

**Scheme 1.** Proposed structure of (Fe(III) and Cu(II) complexes of sulphadoxine mixed with pyramethamine.

the complex has structure within the range consistent to spin-free distorted octahedral geometry. The electronic transition of $[Fe(L_1L_2)Cl_3]$ showed two weak and broad absorption bands at 362 and 495 nm corresponding to $^6A_1g \rightarrow {}^4T_1g(G)$ and $^6A_1g \rightarrow {}^4T_2g(G)$ transitions, respectively. The transitions are consequence of very weak forbidden transitions to excited states of spin multiplicity other than 6, and thus favour distorted octahedral geometry around metal ions with the apical positions occupied by two coordinated chloride atom. The third chloride atom was proposed to be outside the coordination sphere. This was confirmed by the precipitation of white precipitate when the solution of the complex was treated with $AgNO_3$ solution. However, the magnetic moment of Fe(III) complex was found to be 5.4 B.M. indicating high spin state of the complex (Tella and Obaleye, 2010; Cotton and Wilkinson, 1981).

Combining spectral data, elemental analyses and analytical data were used to arrive at the proposed structure as shown in Scheme 1.

## Results of antimicrobial study

The results of biological activity of the ligands and the metal complexes against some strains of micro-organisms are as shown in Figures 1 to 3. The diameters of zone of inhibition (mm) for the ligands were found to be in the range of 37.12 to 48.12 mm for the four bacteria used. They were found to be averagely active. However, the overall results for metal complexes indicate that the two complexes show better activity than the ligands against all the organisms used under the same experi-mental conditions. This suggests that the chelation could

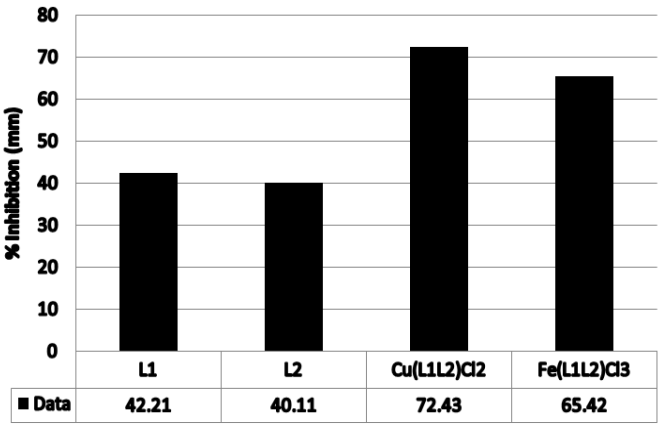



**Figure 1.** Zone of inhibition (%) of the ligands and metal complexes against *E. coli*.

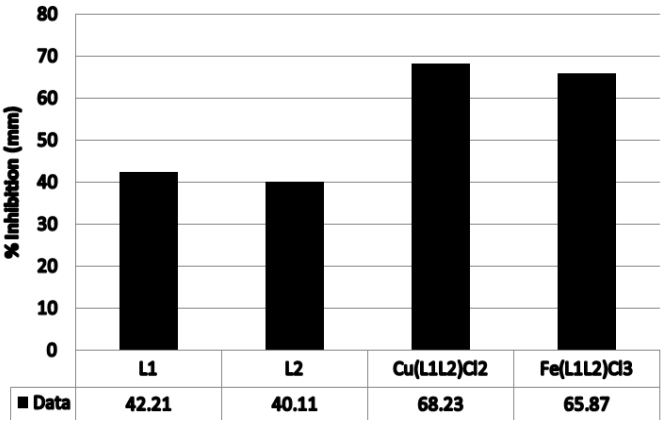



**Figure 2.** Zone of inhibition (%) of the ligands and metal complexes against *Proteus* spp.

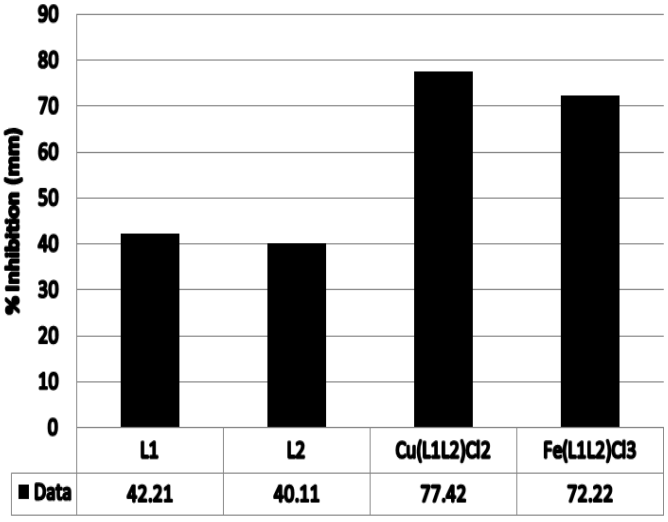



**Figure 3.** Zone of inhibition (%) of the ligands and metal complexes against *P. aureginose.* L1=Sulphadoxine, L2=Pyramethamine.

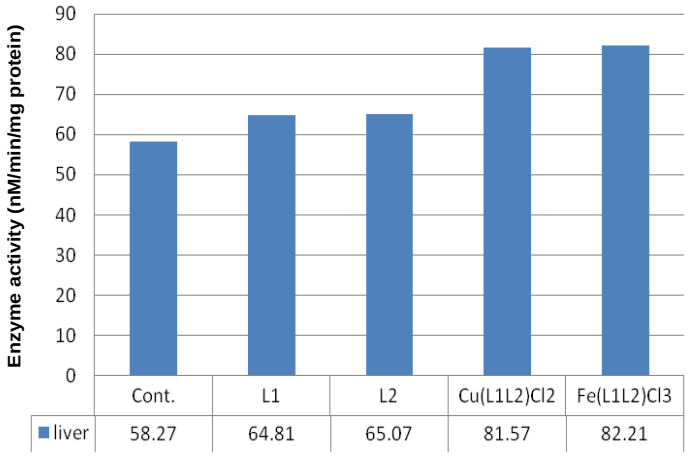



**Figure 4.** Results of toxicology test of the ligands and the metal complexes against liver homogenate.

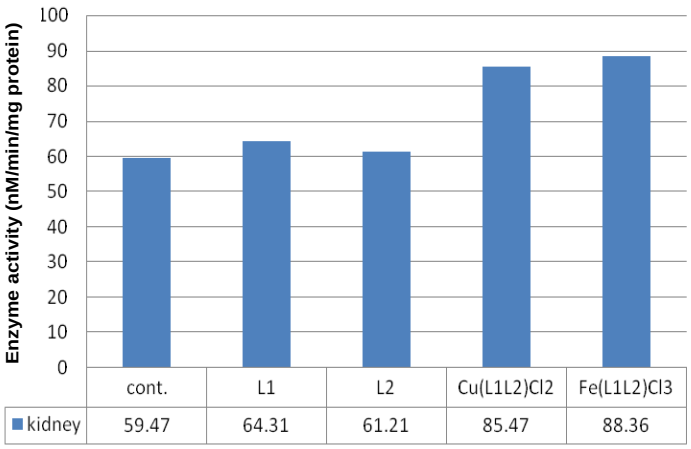



**Figure 5.** Results of toxicology test of the ligands and the metal complexes against kidney homogenate.

facilitate the ability of a complex to cross a cell membrane. Also, chelation could moderately enhance the lipophilic character of the compounds and thus subsequently favour its permeability through the cell membrane. The passage of molecules across cellular barriers increases with lipophilicity and that the most lipophilic compounds will have the highest intestinal absorption (Garba and Salihu, 2011).

## Results of toxicology assay

The values of ALP activities in the kidney, liver and serum following the administration of ligands and their mixed metal complexes as compared to the control are as shown in Figures 4 to 6. The results indicated that sera, livers and kidneys of the rats administered with $[Cu(L_1L_2)Cl_2]$ produced significant increase ($P < 0.05$) in ALP activities, while the ALP activities values for sera,

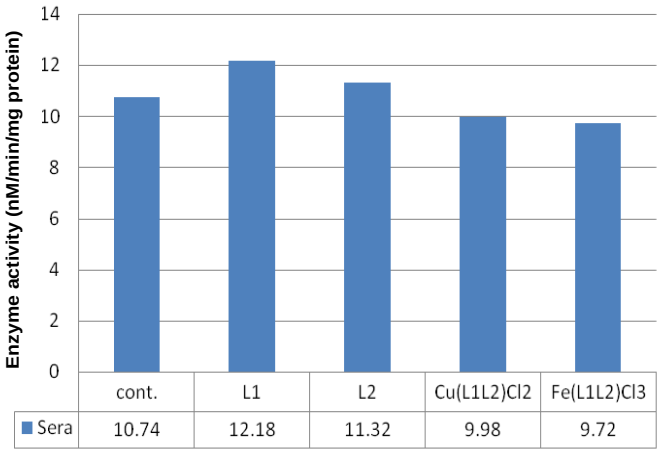



**Figure 6.** Results of toxicology test of the ligands and the metal complexes against sera.

livers and kidneys of the rats administered with $[Fe(L_1L_2)Cl_3]$ were found to be non-significantly ($P < 0.05$) different from the control values. The trend confirmed alteration in the enzymes activity of the kidneys, livers and sera due to the presence of $[Cu(L_1L_2)Cl_2]$. The alteration may likely be damage to their plasma membrane thus leading to leakages of membrane components into the extracellular fluid (Yakubu et al., 2005; Tella and Obaleye, 2010; Ogunniran et al., 2008) and therefore increased their enzymes activity abnormally. However, the non-significant changes observed in ALP activities of the livers, kidneys and sera against $[Fe(L_1L_2)Cl_3]$ suggested partial non-damage effect of the metal complex to them. It can therefore be concluded that $[Cu(L_1L_2)Cl_2]$ is toxic as compared to control at the dosage level used, while $[Fe(L_1L_2)Cl_3]$ is non-toxic.

## Conclusion

Reviews on anti-malarial drugs have shown that there are three consistent ways in which we believe antimalarial drug resistance emerges (Ian, 2004). Spontaneous drug-resistant mutations have affected the effectiveness of direct drug treatment. Therefore it is important to recognize the possibility of considering metal drugs as potential therapeutic agent. The present study shows the feasibility and justification for synthesis of mixed antibiotics metal complexes using sulphadoxine and pyramethamine as ligands. Cu(II) and Fe(III) complexes of pyramethamine mixed with sulphadoxine have been successfully synthesized and characterized by spectral and analytical data. Based on these data, distorted octa-hedral geometry has been assigned to the complexes. In the complexes, sulphadoxine was pro-posed to co-ordinate through N atom of the amine group while pyramethamine was to coordinate through an N atom of imine and N atom of the two amine groups. Thus, sulphadoxine has been proposed to be a monodentate ligand, while pyramethamine was proposed to be tridentate ligands. However, from the analytical data obtained, the complexes possessed better physical properties as compared to the parent drugs. The antimicrobial results clearly indicate that the complexes are much more effective as chemotherapy agents than their parent drugs. Therefore, they could be more effective against *Plasmodium faciparum* than the parent drugs. However, the complexes are toxic at the dose level used to the kidneys, but not to livers and sera of the rat administered with the complexes. Thus, the present study concluded that complexes could be used as potential drug of choice to manage the bacterial diseases after critical evaluation of the *in vivo* effect of the metal complexes experimentally on higher animals and are subjected to clinical trials.

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