Synthesis and Antibacterial Studies of Fe(II), Co(II), Ni(II) and Cu(II) Complexes of Lumefantrine

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Abstract— *Effect of metal complexation on the spectra and bactericidal activity of lumefantrine was carried out. The synthetic technique was based on the modification of lumefantrine by the introduction of metal ions into the molecular structures of the drug. Four metal complexes derived from the ligand lumefrantine was synthesized using the following metal ions Fe(II), Ni(II), Cu(II) and Co(II). The melting point, solubility and colour of the complexes were determined. The complexes were characterized based on electronic and infrared spectroscopy. The infrared spectroscopy revealed significant shift in ν(O-H), ν(M-N) and ν(C-N) and were used to proposed the structures of the complexes. The UV-Visible spectra shows the π-π* absorptions due to the aromatic compound of lumefantrine and ligand to metal change transfer (LMCT) in the complexes. The results of the antibacterial activities of lumefantrine complexes against Streptococcus pneumonia and Shigella dysenteriae revealed that the zone of inhibition of lumefantrine at 500, 250 and 125 mg/ml were significantly lower ($P < 0.05$) than the complexes. Lumefantrine behaved as a bidentate ligand with Fe(II), Cu(II) and Ni(II) and behaved as a monodentate ligand with Co(II). The complexes exhibited higher antigrowth activity against the bacteria species than the free ligand. Thus it can be inferred that the lipophilic property of the complexes enhanced absorption of compounds to their target sites of action.*

Keywords— ligand, Lumefantrine, Shigella dysenteriae, spectroscopy, Streptococcus pneumonia.

I. INTRODUCTION

Complexation is simply the chemistry of coordination compounds containing a central atom or ion to which are attached molecules or ions whose number usually exceeds the number corresponding to the oxidation number or valence of the central atom or ion. They are of great theoretical importance and also of great practical utility[1]. Combat against bacterial infections has resulted in the development of a variety of antibiotics. After so many years of misuse and overuse of antibiotics, bacteria are becoming antibiotic resistant, resulting in a potential global health crisis. There is already evidence that antibacterial resistance is associated with an increase in mortality. The immune status of the individual and population plays most important role in the clinical response to infection and transmission. Maternally derived antibody offers limited and short duration protection to the new-born [2]. In heavily endemic areas, over 30% of children acquire parasites by 3 months of age.

Over the past three decades, intensive efforts have been made to design novel compounds to confront new strains of resistance micro-organisms [3]. The ongoing intense search for novel and innovative drug delivery systems is predominantly a consequence of the generally accepted fact that the conventional dosage forms are not sufficiently effective in conveying the drug compound to its site of action and this have necessitated the needs to search for more potent drugs. The use of metal complexes capable of enhancing biological activity has become a vibrant and growing area of research among inorganic chemists and biologists over the last few decades resulting in a variety of exciting and invaluable drugs such as cis-platin [4]. Dadachova [5] labelled gold chloroquine and explored the possibility of using radio-labelled metal complexes with therapeutic radioisotopes for treatment of chloroquine-resistant malaria. In 1999, Obaleye [6] studied the activity of Fe (II) and Ni(II) complexes of chloroquine against *P. yoeliinigeriensis.* Wasi and co-workers [7] reported the synthesis and *in vitro* evaluation of some metal complexes of amodiaquine and primaquine and concluded that the antiparasitic activity of the two drugs is independent of their coordination to any metal. The recognition of the potential employment of metal complexes and chelates in the therapeutic application provides useful outlet for basic research in transition metal chemistry [8, 9].

Lumefantrine (Ligand employed in this study) was introduced in Nigeria in 2005 as the first line antimalarial drug for the treatment of uncomplicated malaria. The drug is a fixed combination of artemether-lumefantrine in the ratio of 1(20 mg artemether):6(120 mg lumefantrine). Artemether is sequiterpene lactone derived from the

naturally occurring compound artemisinin (dehydroartemisinin methyl ether) while lumefantrine is a racemic mixture of the synthetic fluorine derivative of the aryl amino alcohol family. The structure of lumefantrine is shown in Figure 1.

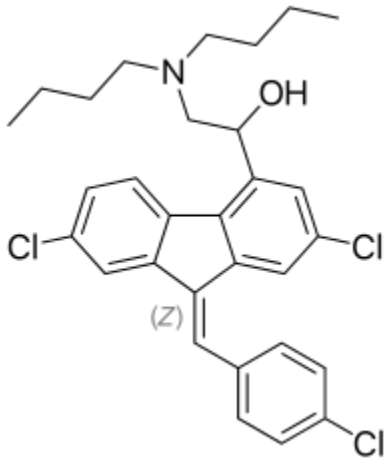

Fig. 1: Structure of lumefantrine

It is evident that lots of work has been done on synthesis of metal complexes and their biological screening has produced very encouraging results. The main objective of this study therefore is to contribute to efforts being made in search for novel chemotherapeutic drugs against the resistant strains of bacteria. We hereby present the effect of metal complexation on the spectra and bactericidal activity of lumefantrine

II. MATERIALS AND METHODS

Chemicals and solvents

The drug, chemicals and solvents used in this study were of analytical grade and were used as obtained. Lumefantrine was obtained from Strides Arcolab limited Anekal Taluk, Bangalore- India. Cobalt(II) nitrate, copper (II) sulphate, nickel(II)sulphate hexahydrate, Iron(II) sulphate, ethanol, methanol, chloroform and distilled water were obtained from Sigma-Aldrich Chemical Company.

UV-Visible spectroscopy

The electronic spectra of the complexes in solution were determined using Perkin Elmer UV-Visible spectrophotometer in the range of 190-750nm. The samples were dissolved in 5ml of chloroform then 1ml each of the solution was dissolved in another 5ml of chloroform. The solutions were then placed in quartz cuvette of 1cm path length.

Infrared spectroscopy

Infrared spectra were collected on a Perkin Elmer Spectrum BX 100 FTIR Spectrophotometer equipped with caesium iodide window (4000-250cm^{-1}) using KBr pellets.

Melting point

The melting point of lumefantrine and its complexes were measured using capillary tube method.

Solubility Test

The solubility test of lumefantrine and its complexes were carried out using solvent like; methanol, ethanol, chloroform and water.

Synthesis of lumefantrine complexes

The solution of lumefantrine was prepared by dissolving 26.45 g (0.05 mol) in 30 ml of methanol then a solution of metal salt obtained by dissolving 0.05 mol of the corresponding metal salt ($FeSO_4$, 7.6g; $Co(NO_3)_2$, 9.15g ; $NiSO_4.6H_2O$, 13.13g; $CuSO_4$, 7.98g) in 30 ml of methanol and 10ml of methanol was used in rinsing both beakers then the mixture was placed in the thermostatic water bath and continuously stirred at 40^0C for an hour. After an hour the solutions were allowed to cool for 24 hours for the reaction to go to completion. After which the crystals were filtered off and washed with methanol to remove any unreacted materials. The product was finally dried in a vacuum at room temperature.

Antibacterial test

Antibacterial activities of the parent drug and the complexes were tested against two different species of bacteria, namely: *Streptococcus pneumonia* and *Shigella dysenteriae*. Nutrient agar was used as the bacteriological growth media. The bacterial activities in the presence of both the parent drug and the complexes were determined by filter paper disc agar diffusion method [10]. The antibacterial activity of the compounds was estimated on the basis of the size of the inhibition zone formed around the wells on the seeded nutrient agar.

III. RESULTS AND DISCUSSION

Some physical properties of lumefantrine and its complexes are shown in Table 1. The solubility data of lumefantrine and its complexes are presented in Table 2. Infrared and electronic spectra of lumefantrine and its complexes are shown in Figures 2 – 11. The zone of inhibition of lumenfantrine and its complexes against *Streptococcus pneumonia* and *Shigella dysenteriae* are shown in Tables 3-5.

Table.1: Some physical properties of the lumefantrine and its complexes

Compounds	Melting point (°C)	Yield (%)	Colour
LUM	125 - 130	-	Yellow
$[FeLUM]_x$	215 - 220	80	Yellowish brown
$[CoLUM]_x$	218 - 227	73	Brown
$[NiLUM]_x$	221 - 228	83	Grey
$[CuLUM]_x$	216 - 222	82	Pale yellow

LUM = lumefantrine

Table.2: Solubility of the lumefantrine and its complexes

Sample	Methanol	Ethanol	Chloroform	Distilled Water
LUM	S	NS	S	SS
$[FeLUM]_x$	NS	NS	SS	NS
$[CoLUM]_x$	SS	SS	SS	NS
$[NiLUM]_x$	SS	SS	SS	NS
$[CuLUM]_x$	SS	SS	SS	NS

Where S = Soluble, NS = Not soluble, SS = Slightly Soluble, LUM = Lumefantrine

Table.3: Zone of inhibition lumenfantrine and its complexes against steptococcus puenomia and shigella dysenteriae at 500 mg/ml

Bacteria	[CuLUM]	[FeLUM]	[NiLUM]	[LUM]
Steptococcus puenomia	35.6 ± 0-6[a]	22.5 ± 0.5[b]	15.1 ± 0.96[c]	9.3 ± 0.6[d]
Shigella dysenteriae	27.5 ± 0.9[a]	18.7 ± 1.3[b]	16-5 ± 1.4[c]	8.3± 0.3[d]

Values are means ± standard deviation of triplicate determination. Means bearing different superscripts in the same column are significantly different ($P < 0.05$) while means with the same superscript shows no significant difference ($P > 0.05$).

Table.4: Zone of inhibition lumenfantrine and its complexes against steptococcus puenomia and shigella dysenteriae at 250 mg/ml

Bacteria	[CuLUM]	[FeLUM]	[NiLUM]	[LUM]
Steptococcus puenomia	17.38 ± 0.6[a]	10.7 ± 0.4[b]	7.0 ± 0.9[c]	5.0 ± 0.23[d]
Shigella dysenteriae	13.0 ± 0.9[a]	9.3 ± 0.5[b]	7.6 ± 0.5[c]	3.8 ± 0.3[d]

Values are means ± standard deviation of triplicate determination. Means bearing different superscripts in the same column are significantly different ($P < 0.05$) while means with the same superscript shows no significant difference ($P > 0.05$).

Table.5: Zone of inhibition lumenfantrine and its complexes against steptococcus puenomia and shigella dysenteriae at 125 mg/ml

Bacteria	[CuLUM]	[FeLUM]	[NiLUM]	[LUM]
Steptococcus puenomia	8.7± 0.4[a]	4.7 ± 0.5[b]	1.9 ± 0.2[c]	1.6 ± 0.3[d]
Shigella dysenteriae	6.9 ± 0.9[a]	40 ± 0.2[b]	3.0 ± 0.2[c]	0.5 ± 0.6[d]

Values are means ± standard deviation of triplicate determination. Means bearing different superscripts in the same column are significantly different ($P < 0.05$) while means with the same superscript shows no significant difference ($P > 0.05$).

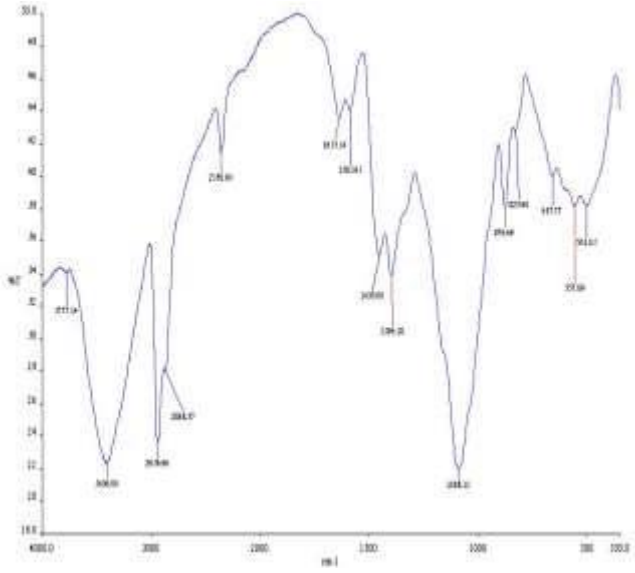

Fig. 2: Infrared spectrum of lumefantrine

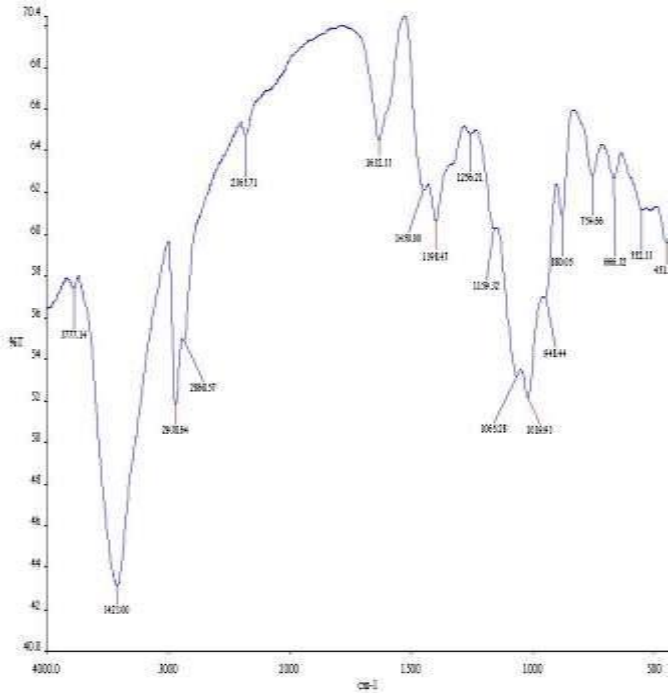

Fig.3: Infrared spectrum of [FeLUM]

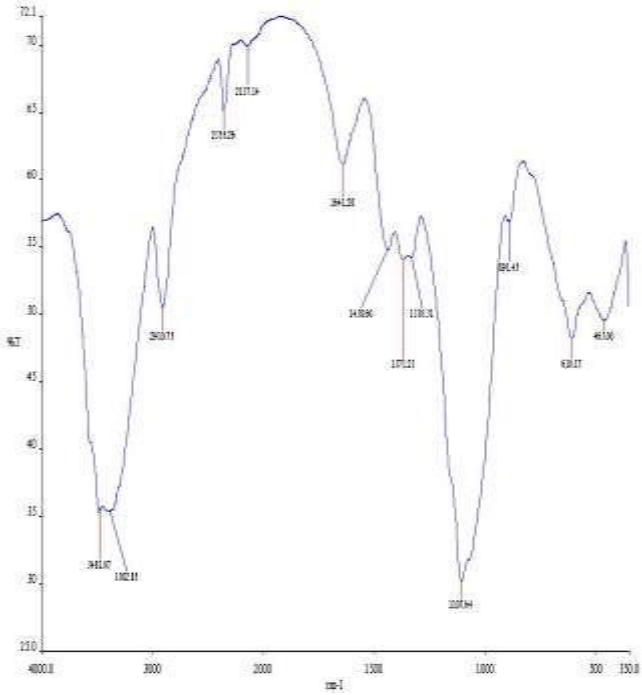

Fig. 5: Infrared spectrum of [NiLUM]

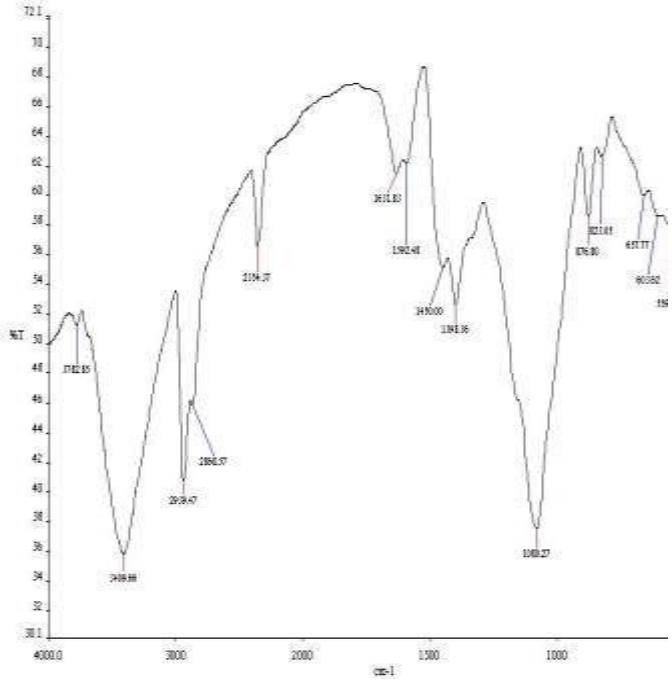

Fig. 4: Infrared spectrum of $[CoLUM]_x$

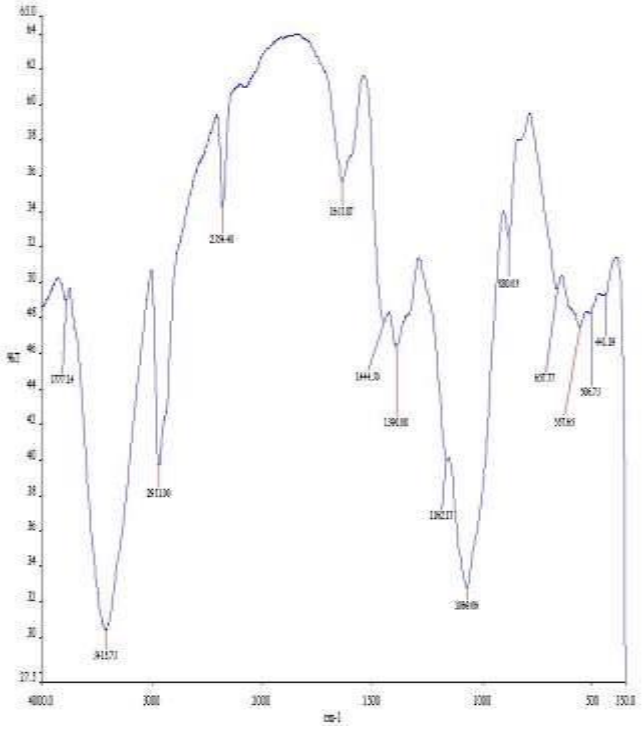

Fig.6: infrared spectrum of $[CuLUM]_x$

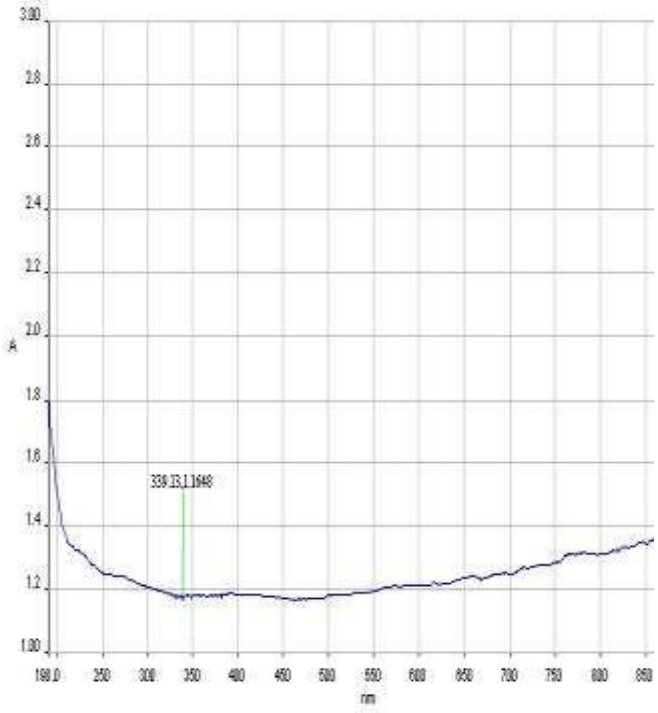

Fig.7: Electronic spectrum of lumefantrine

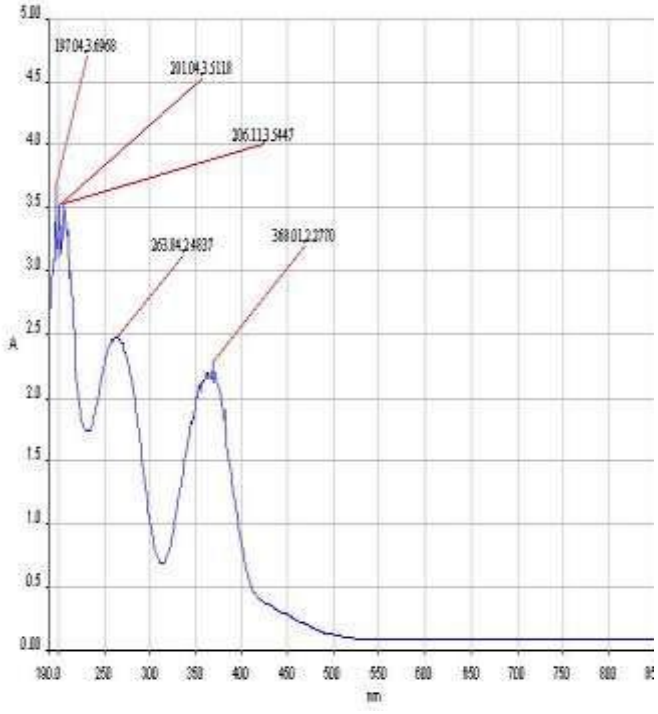

Fig. 8: Electronic spectrum of $[FeLUM]_x$

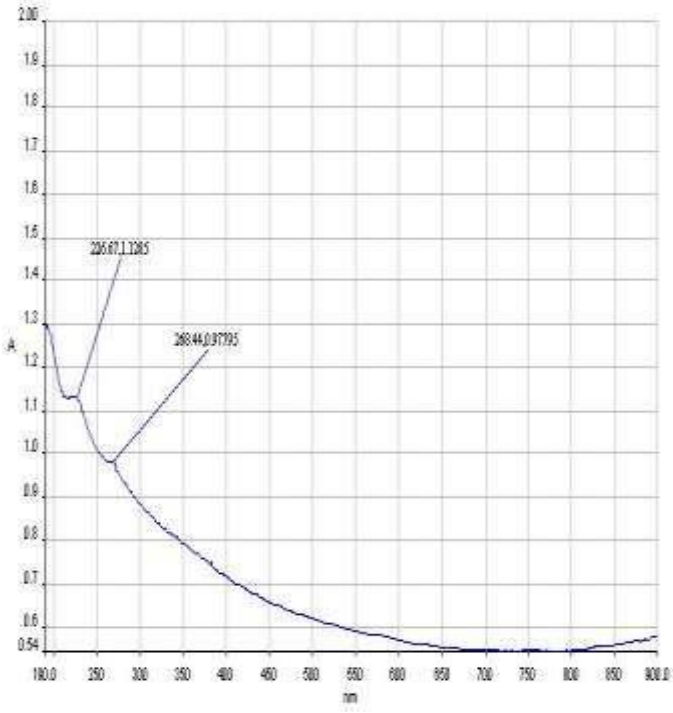

Fig. 9: Electronic spectrum of $[CoLUM]_x$

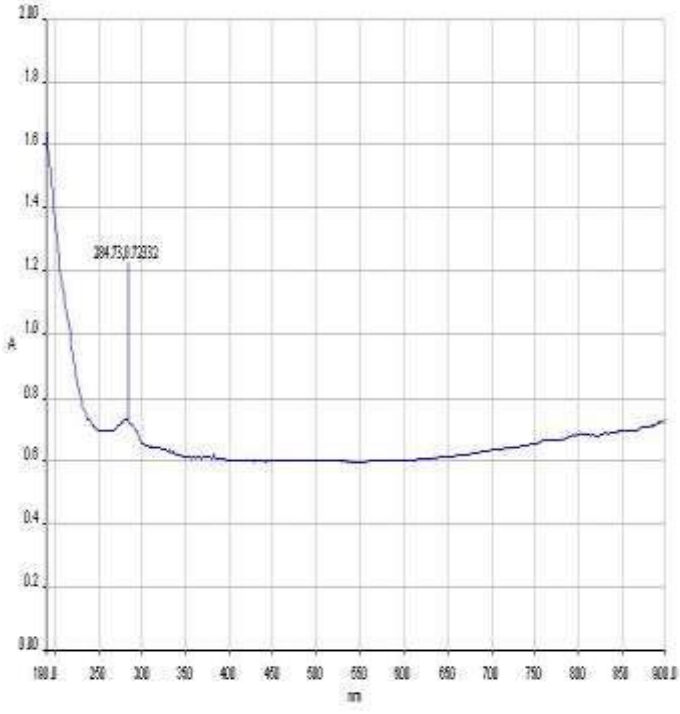

Fig. 10: Electronic spectrum of $[NiLUM]_x$

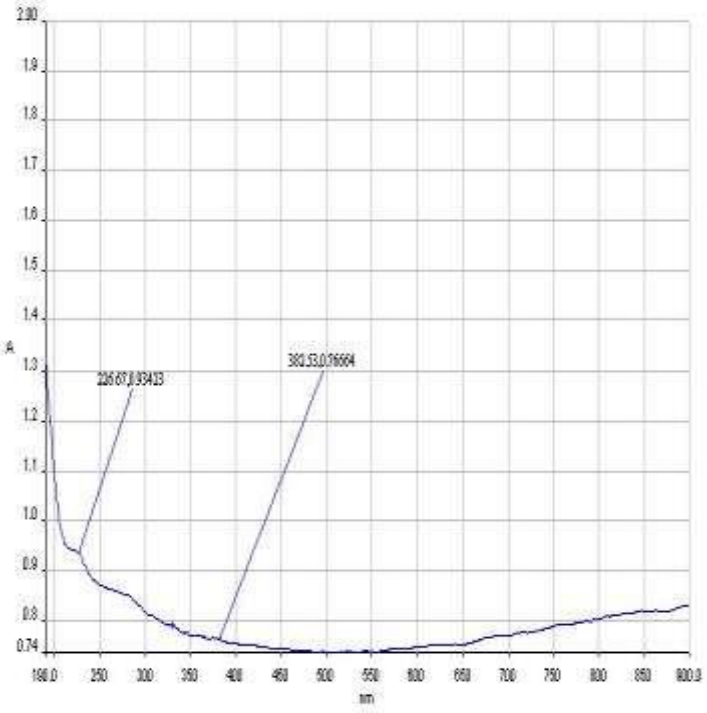

Fig. 11: Electronic spectrum of $[CuLUM]_x$

The melting point of the lumefantrine was observed in the range 125 – 130 ^oC. The melting points of the complexes were higher than the ligand (Table 1). This suggests that coordination occurred. It was observed that the complexes are insoluble in water and other polar solvents used in the test (Table 2). The insolubility is attributed to the coordination with the metal. The ligand was soluble in chloroform; this shows the presence of polar materials.

Infrared Spectroscopy

The strong bands at 3406 cm^{-1} in lumefantrine were assigned to ν(O-H). On coordination, these bands shifted to 3423 cm^{-1} in [FeLUM] complex, 3481cm^{-1} in $[NiLUM]_x$ complex and 3415 cm^{-1} in $[CuLUM]_x$ complex. There was no coordination through OH in $[CoLUM]_x$ complex. The ν(M-N) band were observed in the complexes indicating bonding of the metal to the nitrogen bond.[11] This band was absent in the spectrum of lumefantrine. The functionality (C-N) was also observed to have shifted from 1088 cm^{-1} in lumefantrine to 1065 cm^{-1} in $[FeLUM]_x$ complex, 1080.26 cm^{-1} in $[CoLUM]_x$, 1107.6 cm^{-1} in $[NiLUM]_x$, and 1069.0 cm^{-1} in $[CuLUM]_x$. These shifts in ν(C-N) suggested complexation through this functionality.

Ultra-Violet/Visible Spectroscopy

The UV-Visible spectra of the lumefantrine and its complexes (Figures 7 – 11) have been interpreted in terms of the metal to ligand charge transfer and in terms of the π-π* transitions due to the aromatic compounds of the ligand.[12] The UV-Visible spectrum of the ligand shows bands which suggests that the ligand has a polycyclic aromatic chromophore which was assigned π-π* transitions. The spectra of the complexes indicated ligand to metal charge transfer and π-π* transitions of the aromatic compounds of the ligand lumefantrine.

Antibacterial Activity

The results of the antibacterial activities of lumefantrine complexes against *Streptococcus pneumonia* and *Shigella dysenteriae* revealed that the zone of inhibition of lumefantrine at 500, 250 and 125 mg/ml were significantly lower ($P < 0.05$) than the complexes. This implies that the complexes exhibited higher antigrowth activity against the bacteria species than the free ligand. Thus it can be inferred that the lipophilic property of the complexes enhanced absorption of compounds to their target sites of action.

Based on electronic and infrared spectra, tentative structures Figures 12 – 15 has been proposed for the complexes.

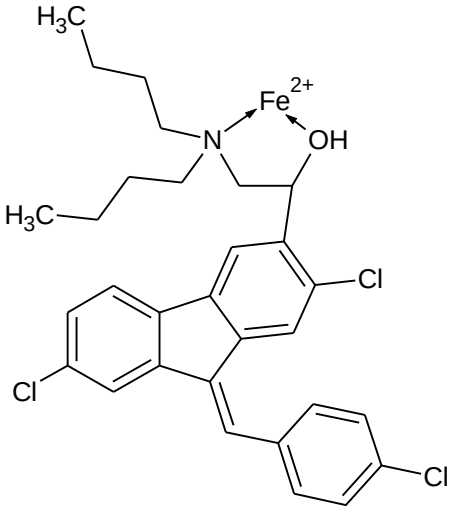

Fig. 12: Suggested structure for $[FeLUM]_x$

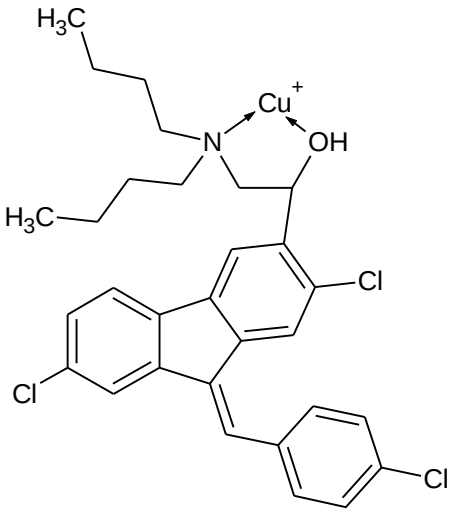

Fig. 13: Suggested structure for $[CuLUM]_x$

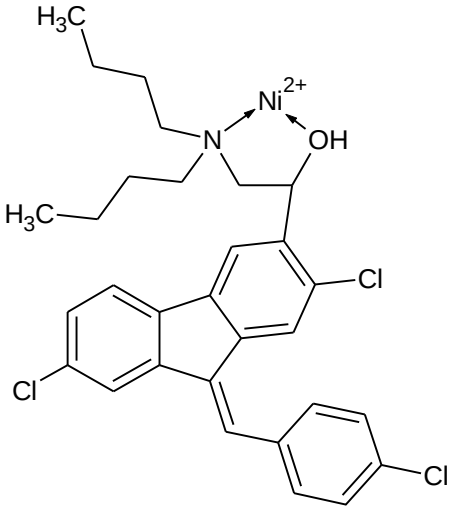

Fig. 14: Suggested structure for [NiLUM]$_x$

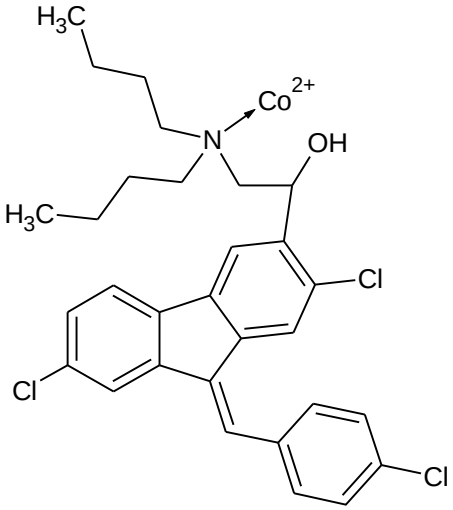

Fig. 15: Suggested structure for [CoLUM]$_x$

IV. CONCLUSION

The rapid spread of drug-resistant bacteria's worldwide has stimulated the search for new drugs to treat millions of people infected with bacteria. There is an urgent need for antibacterial with novel structures, modes of action, or both, to deal with the development of resistance to the drugs in current use. Previous research has shown that attaching organic drugs to metal-containing fragments could enhance their activity. Although metals have been used in medicine for centuries, the success of cisplatin, and related compounds as anticancer drugs has stimulated renewed interest in metal based chemotherapies.

This research discussed the effect of metal complexation on the spectra and bactericidal activity of lumefantrine. The synthetic technique was based on the modification of lumefantrine by the introduction of metal ions into the molecular structures of the drug. The complexes were characterized based on electronic and infrared spectroscopy. Lumefantrine behaved as a bidentate ligand with Fe(II), Cu(II) and Ni(II) and behaved as a monodentate ligand with Co(II).

The complexes were more potent that the parent drug against the bacterial strains used.

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