SYNTHESES, CHARACTERIZATION, AND BIOLOGICAL ACTIVITY OF MIXED ANTIMALARIA METAL COMPLEXES

ABSTRACT

This project deals with the synthesis, spectroscopic characterization and antimicrobial activity of metal complexes with Amodiaquine and pyrimethamine drugs. Five metal complexes derived from amodiaquine and pyrimethamine have been synthesized using the following metal ions: Co(Il), Cu(Il), Zn(Il), Ni(II) and Fe(III). The complexes were characterized by decomposition temperature, solubility, conductivity measurement, elemental analyses, UV-Vis and IR spectroscopy. According to the results of physiochemical and spectroscopic data, the metal complexes were proposed to have the formula: $[ML_1L_2].Y,xH_2O$ (where M = Cu(II), Ni(II), Zn(II) and Fe(III), Y = SO_4 or Cl_2.

The complexes have higher melting point than their free ligands and the lower value of conductivity test showed that the complexes are non-electrolytes. The spectroscopic data proposed that Amodiaquine coordinated through the oxygen atoms of hydroxyl group, and pyrimethamine coordinated through Nitrogen atom of primary amine group. The complexes showed octahedral geometry with the ligands acting as bidentate.

The complexes were evaluated for *in vitro* antibacterial and antifungal activity against four isolates of *Pseudomonas aeruginosa, E. coli, Klebsiella pneumonia, Staphylococcus aureus and Candida albicans spp*. The results show that the synthesized mixed ligands have higher antibacterial activities compared with the original ligands.

INTRODUCTION

In 2011, it was estimated that 3.3 billion people were at risk of malaria, with Africa bearing the brunt of the disease [1,2]. Approximately 80% of malaria cases and 90% of malaria-related deaths occur in Africa, disproportionately affecting children under five and pregnant women [3,4,5]. For decades, drug resistance in the malaria parasite Plasmodium falciparum has been a growing concern [6], with the potential for widespread resistance posing a significant public health risk [7], particularly given the lack of alternative antimalarial medicines expected to be available within the next five years [8,9,10]. “This underscores the urgent need for the continued search for more affordable and effective compounds against these disease-causing organisms.”

A major challenge in modern inorganic pharmaceutical chemistry is the development of safe and affordable drugs to combat malaria and antibiotic resistance [11]. While drug efficacy, pharmacology, and toxicity are crucial in selecting compounds for development, efforts to standardize antimalarial and antibiotic drug efficacy studies remain limited [12,13,14]. The

significance of metal complexes in medicine cannot be overstated; transition metals not only facilitate synthesis but also enhance drug delivery [15]. The unique properties of metal complexes offer distinct advantages in the discovery and development of new drugs.

Mechanism of Action of Amodiaquine

Its mechanism of action is thought to be similar to CQ [16], but this is very controversial. Amodiaquine is a relatively wide compound closely related to chloroquine. In any case, Amodiaquine is as viable as chloroquine and is powerful against some chloroquine-resistant strains, even though protection from amodiaquine has been accounted for [17,18]. The mode of action of amodiaquine has not been determined. The structure of amodiaquine is shown below.

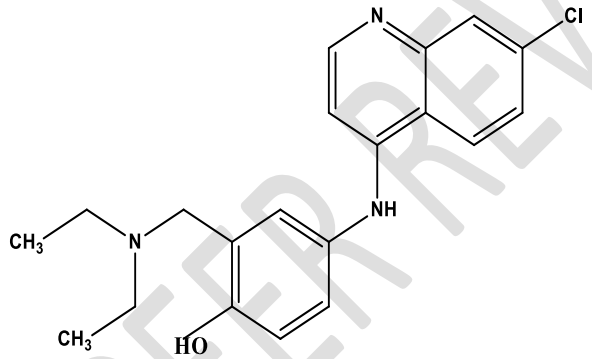


Fig 1: Chemical structure of amodiaquine

1.5.2 Pyrimethamine

Pharmacodynamics of Pyrimethamine.

Pyrimethamine is one of the folic acid antagonist that is used as an antimalarial or with a sulfonamide to treat toxoplasmosis [19,20]. It is used for the treatment of taxoplasmosis and acute malaria; For the prevention of malaria in areas non-resistant to pyrimenthamine [21]. It has molecular formular $C_{12}H_{13}N_{14}$ with IUPAC name 5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediam. It is an antiparasitic compound used as an adjunct in the treatment of uncomplicated, chloroquine resistant P. *falciparum* malaria. Being a folic acid antagonist its rationale for therapeutic action is based on the differential requirement between hots and parasite for nucleic acid precursor involved in growth [22,23,24], hence it becomes highly selective against plasmodia and toxoplasma gondii. Pyrimethamine posseses tissue schizonticidal and blood

schizonticidal activity against malaria parasites of humans [25]. The action of pyrimethamine against toxoplasma gondii is greatly enganced when combined with sulfonamides [26,27].

It is primarily active against Plasmodium *falciparum,* but also against *Plasmodium Vivax.* Due to the emergence of pyrimethamine-resistant strains of P. *falciparum,* pyrimethamine alone is seldome used now [28,29].

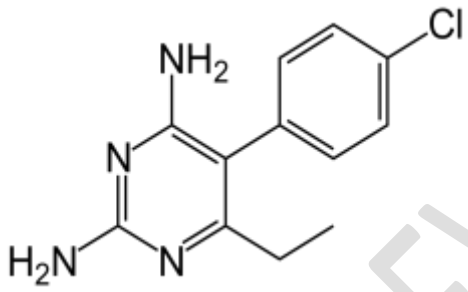


Fig 2. **Structure of Pyrimethamine**

This study focuses on the synthesis and characterization of mixed antimalarial metal complexes, contributing to the ongoing efforts to discover novel antimalarial drugs that can effectively address the problem of drug resistance. The objectives of this research work are to;

i) Synthesize mixed transition metal complex of Amodiaquine, and pyrimethamine (an antimalarial drug) (ii) Characterize the resultant compounds using both the physical and spectroscopic properties such as solubility, melting point, conductivity, Ultraviolet-Visible and infrared spectroscopy, magnetic susceptibility and elemental analysis. (iii) Evaluate their biological potency by determining the antimicrobial properties of the complexes against some organisms such as Pseudomonas aeruginosa, Bacillus subtilis, Escherichia coli, Salmonella typhi, Shigella spp, Aspergillus niger and Candida alicans

2. Experimental

All solvents and chemicals used in this research work are of quality analytical grade obtained from commercial dealers in Ilorin. The solvents used are Methanol, Ethanol, Chloroform, Ethyl Acetate. The metal salts are obtained from the Chemistry Department, University of Ilorin and they are; Cobalt (II) chloride hexahydrate [CoCl2.6H2O], Copper nitrate trihydrate [Cu(NO3)2.3H2O], Manganese Chloride tetrahydrate [MnCl2.H2O], Cadmium chloride monohydrate [CdCl2.H2O], Iron (III) chloride [FeCl3], Nickel Nitrate hexahydrate [Ni(NO3)2.6H2O], and Zinc nitrate hexahydrate [Zn(NO3)2.6H2O].

The drugs used for this research work are obtained from May, Joy, Tuyill and Baker Pharmaceutical Industries Nigeria Plc. They are: L1 Amodiaquine and L2 Pyrimethamine

2.1 General procedure to synthesized the Metal Complex

Using the procedure carried out by Obaleye et al., [30]. A metal salt (1 mmol) was dissolved in 10 mL of ethanol in a round bottom flask. 1mmol of the L1 was mixed with 1mol of L2 in a beaker. The mixed ligand was dissolved in 5ml Acetone and 5ml ethanol and added to the solution of the corresponding metal salt previously dissolved in 10ml ethanol in a round bottom flask. The solution was allowed to reflux with constant stirring for about 5 hours. The complexes thus formed were filtered, washed with ethanol to remove unreacted ligands, and then dried. The precipitate formed was filtered, washed, and dried in a vacuum. The mixed ligand metal complexes were prepared according to Equation 1.

$MCl_2.H_2O+AMD+PRY \rightarrow [M(AMD)(PRY)(H_2O)_2]Cl_2$

where M is the metal ions, AMD is Amodiaquine and PRY and Pyrimethamine

2.2 Antimicrobial Studies

The antibacterial activities of the ligands and the metal complexes were carried out using a well diffusion method described in the literature by Lautre *et al.,* The nutrient agar medium and 5mm diameter Whatman No1 paper disc were used. The compounds were dissolved in DMSO at 50 and 100ppm concentrations. The filter paper was soaked in different compounds solutions, allowed to dry and then placed in petri dishes previously seeded with the test organisms. The plates were incubated for 24-30 hours at 37^{o}C and the inhibition zone around each disc was measured in mm using zone reader. Using DMSO as control the average zone of inhibition was determined from the readings that will be taken in duplicate.

The bacteria species that was used in the test include standard strain of Esherichia *Coli,* Staphylococcus *aureus* and Klebsiella *Pneumoniae.* The antibacterial activity of the compounds was estimated based on the size of the inhibition zone formed around the wells on the seeded nutrient agar.

The antifungal activity of the ligands and the metal complexes was determined using the culture of three fungi species. They are Aspergillus *Niger,* Aspergillus *flavus* and Rhizopus *species.* They will be cultured on potato dextrose agar. The fungal culture will be incubated at 37^{o}C for 38 hours before use.

3.0 RESULT AND DISCUSSION

In the present study shows the feasibility and justification for the synthesis of mixed antimicrobial metal complexes using amodiaquine and pyrimethamine as ligands. Five metal complexes of

Cu(II), Fe(III), Ni(II), Co(II) and Zn(II) ion have been successfully synthesized and characterized by spectral and analytical data.

Solubility of the Ligand and Complexes

Table 1: Result of Solubility of the ligand and Drug-metal complexes

Complexes/Ligand	**Distilled H_2O**		**Methanol**		**Ethanol**		**Acetone**	
	C	H	C	H	C	H	C	H
Amodiaquine	NS	NS	NS	S	NS	S	NS	S
Pyrimethamine	NS	NS	NS	S	NS	S	SS	S
$Cu(Amd)(Pry)Cl_2.6H_2O$	NS	NS	NS	NS	NS	S	S	SS
$Co(Amd)(Pry)Cl_2.6H_2O$	NS	NS	NS	SS	NS	SS	S	S
$Zn(Amd)(Pry)(NO_3)_2.7H_2O$	NS	NS	NS	SS	NS	SS	S	SS
$Ni(Amd)(Pry)(NO_3)_2.6H_2O$	NS	NS	NS	S	NS	S	S	S
$Fe(Amd)(Pry)SO_4.7H_2O$	NS	NS	NS	SS	NS	SS	S	S

Key: C-Cold, H-Hot, NS-Not soluble, SS-Sparingly Soluble and S-Soluble

Melting point and Conductivity of the Ligand and Complexes

Table 2: Result of physical properties, melting point, conductivity

COMPOUND	**Colour**	**Melting point (^{o} c)**	**Conductivity**
Amodiaquine	Yellow	176.7	0.56
Pyrimethamine	White	240.8	0.04
$Cu(Amd)(Pry)Cl_2.6H_2O$	Blue	201.7	0.01
$Co(Amd)(Pry)Cl_2.6H_2O$	Brown	249.5	0.11
$Zn(Amd)(Pry)(NO_3)_2.7H_2O$	Cream	279.9	0.03
$Ni(Amd)(Pry)(NO_3)_2.6H_2O$	Green	191.2	0.32
$Fe(Amd)(Pry)SO_4.7H_2O$	Brown	105.7	0.41

The colour of the complexes varied ranging from yellowish to green and brown, from white to cream. The complexes also showed variable solubility in different solvents used, but they were generally soluble in Dimethylsulfoxide (DMSO). Some melting points of the mixed complexes were found to be higher compared to the free ligands.

Some of the complexes are powdery while some are crystalline. The result of the conductivity test of the complexes showed that they were non-electrolytes. Some of the complexes have a high percentage yield.

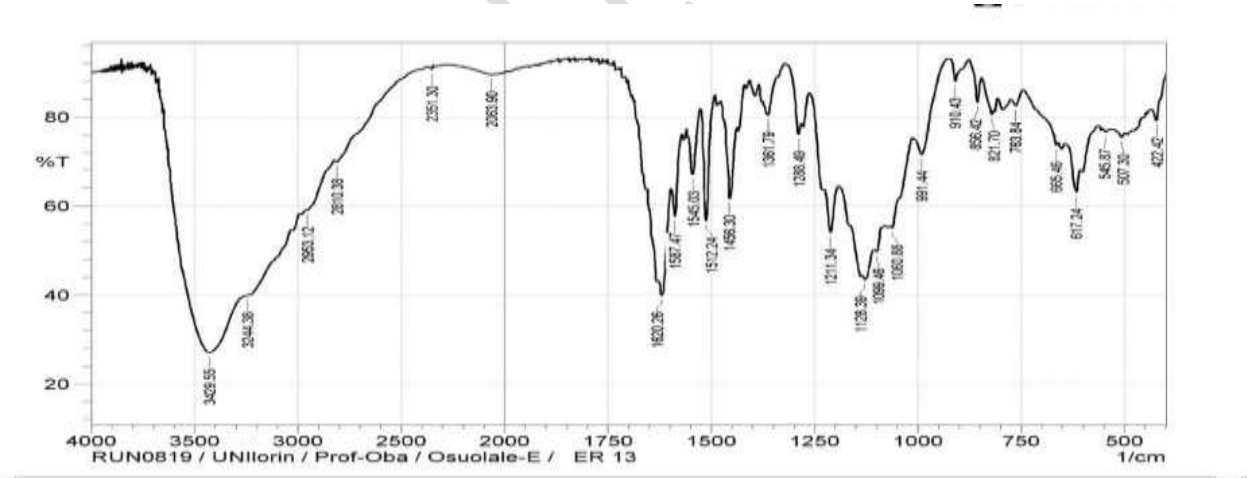
3.1 IR Spectral Studies

The infrared spectra of the complexes in the far IR region 4,000 – 500 cm^{-1} were compared with those of the ligands as shown in Table above. The infra-red spectra of the complexes were found to be different from those of the ligand and showed either a shift or disappearance of some characteristic frequencies and the appearance of some new band. The band of OH in the region 3418.94 cm^{-1} in the ligand was conspicuously absent in the complexes which suggest they are coordinating at the region.

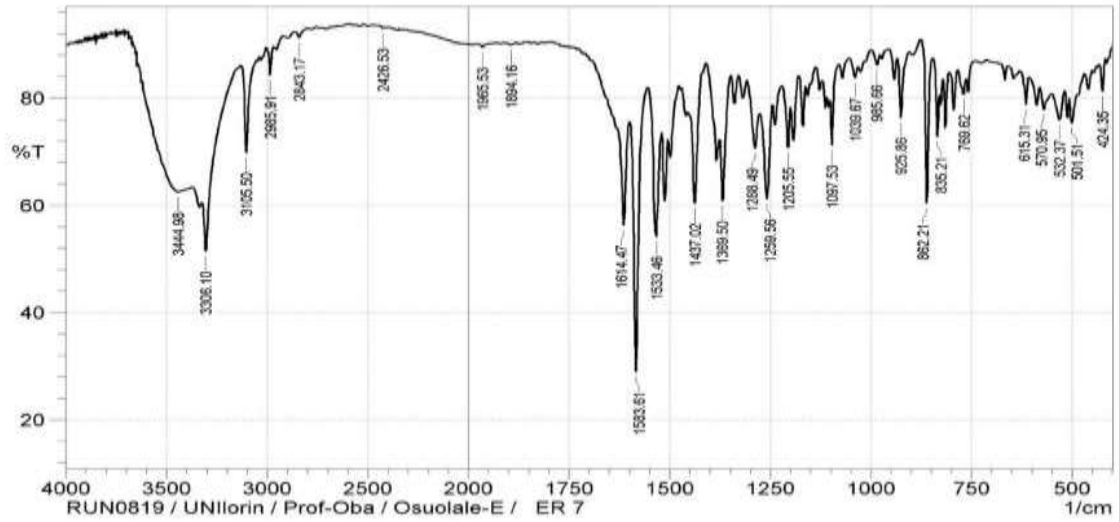
The assignments were carried out by comparison of the IR spectra of the ligands with their complexes. The absorption region at 3468.13 cm^{-1} assigned to broad N-H in the free ligand has been shifted to a higher frequency in regions of 3358 cm^{-1},3306 cm^{-1}, 3306 cm^{-1}, 3431 cm^{-1} and 3429 cm^{-1} coupled with a reduction in intensity ranging from medium to broadband.

However, the strong band at 1627 cm^{-1} has been shifted to the most intense band at 1641 cm^{-1}, 1639 cm^{-1}, 1614 cm^{-1} and 1620 cm^{-1}, which is assigned to the stretching frequency, ν (-C=N), of the azomethine (-CH=N) group of Amodiaquine and pyrimethamine respectively.

Also, the infrared spectra display medium bands at 653.89 cm^{-1}, 532.37 cm^{-1}, 601.81 $cm^{-1,}$ and 665.46 cm^{-1} attributed to M-L vibration. The water molecules present were confirmed to be coordinated through the metal ion.



$FeSO_4$+Amd+Pry



$Zn(NO_3)_2$+Amd+Pry

Co+Amd+Pry

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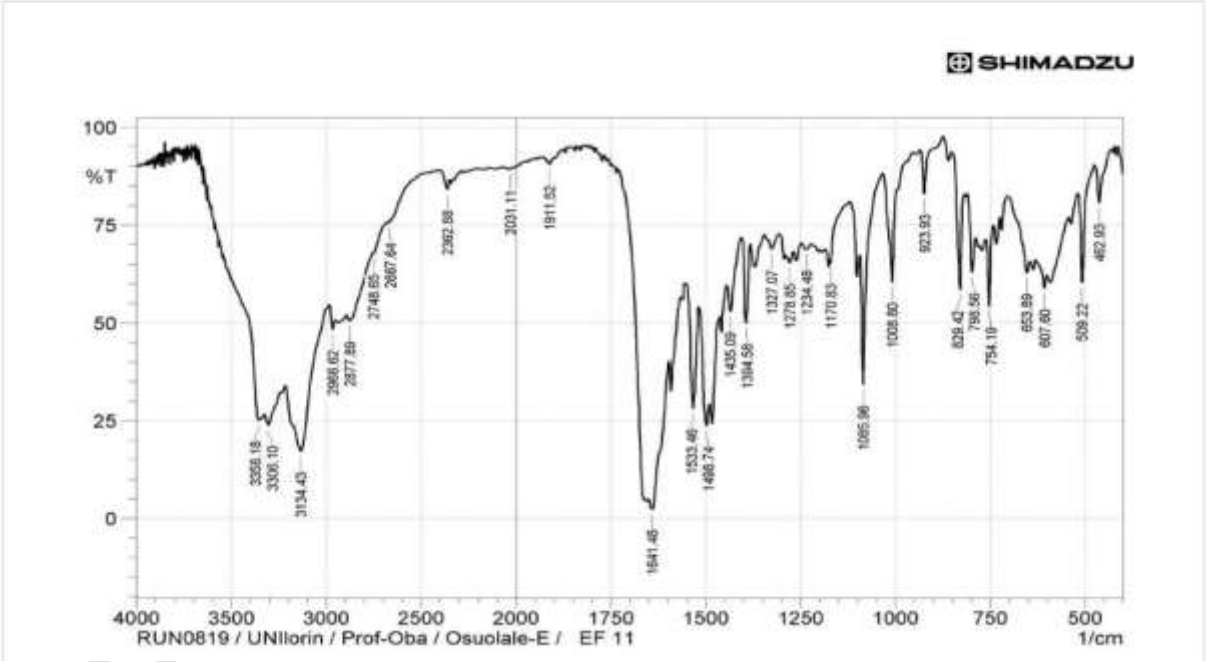

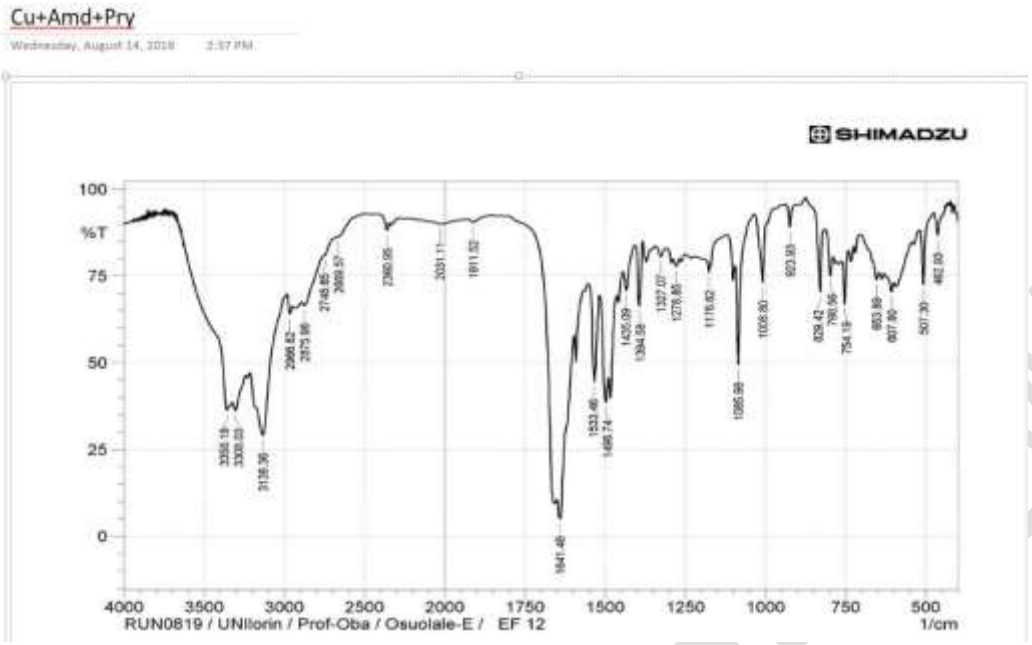

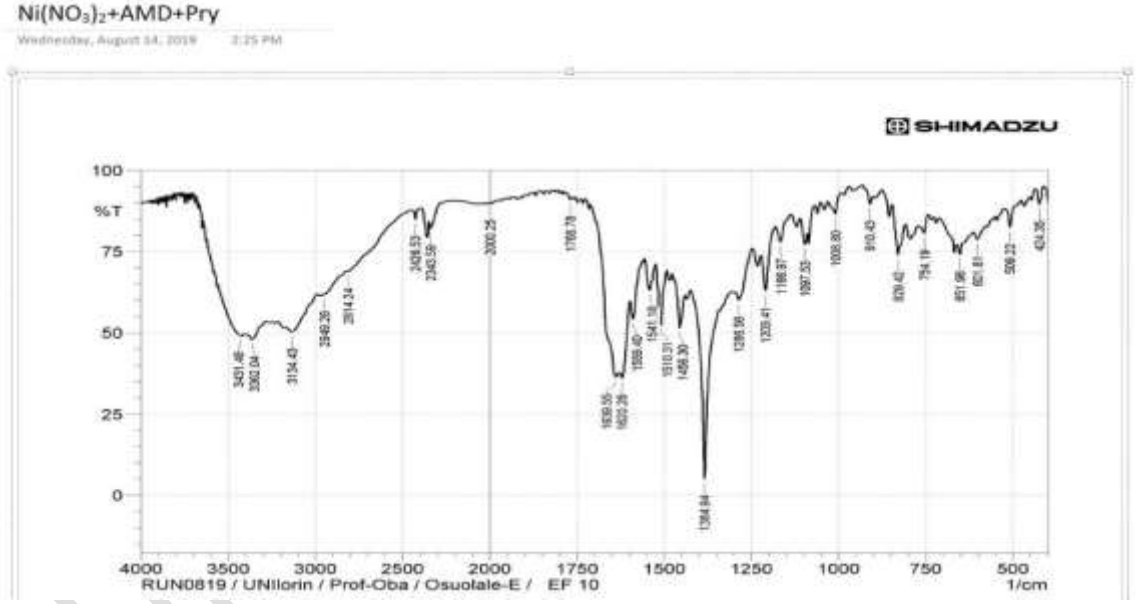

$Ni(NO_3)_2$+Amd+Pry

Fig 3. IR Spectra of the Ligand and Metal complexes

3.2 UV- Visible Spectra

Table 3: UV-Visible Spectra of mixed metal complexes of Amodiaquine and Pyrimethamine

COMPOUND	Wavelength (nm)	Energies cm^{-1}	Assignment
Amodiaquine	205	48973	π- π*
	325	30890	n - π*
	364	27497	n - π*
Pyrimethamine	272	36798	π- π*
$Cu(Amd)(Pry)Cl_2.6H_2O$	205	48973	π- π*
	328	30515	n - π*
$Co(Amd)(Pry)Cl_2.6H_2O$	280	35747	π- π*
	415	24118	$^4T_{1g} \rightarrow {}^4A_{2g}$
	529	18921	$^4T_{1g} \rightarrow {}^4A_{2g}$
$Zn(Amd)(Pry)(NO_3)_2.7H_2O$	276	36265	π- π*
	363	27573	n - π*
$Ni(Amd)(Pry)(NO_3)_2.6H_2O$	408	24532	$^3A_{2g}(F) \rightarrow {}^3T_{1g}$ (P)
	684	14633	$^3A_{2g}(F) \rightarrow {}^3T_{1g}$ (F)
$Fe(Amd)(Pry)SO_4.7H_2O$	446	22442	$^6A_{1g} \rightarrow 4T_{1g}(G)$
	781	12816	$^6A_{1g} \rightarrow 4T_{2g}(G)$

The electronic absorption data of the ligands and the metal complexes are as shown in Table 3 above. Copper complexes showed two absorption bands at 205 and 328 nm. However, the bands were observed to have undergone a bathochromic shift in the metal complexes due to complexation. The electronic transition of Cobalt complex shows the bands at 280, 415 and a broad band at 529 nm corresponding to π- π*, $4T_{1g} \rightarrow {}^4A_{2g}$, $^4T_{1g} \rightarrow {}^4A_{2g}$ transition, respectively. The band at 486 nm is expected for d-d transition of Co(II) complex [32]. The broadness of the band could be attributed to the overlapping of several bands as a result of the strong Jahn-Teller distortion expected in a d9 ion [31].

Mixed metal complexes Amodiaquine and Pyrimethamine

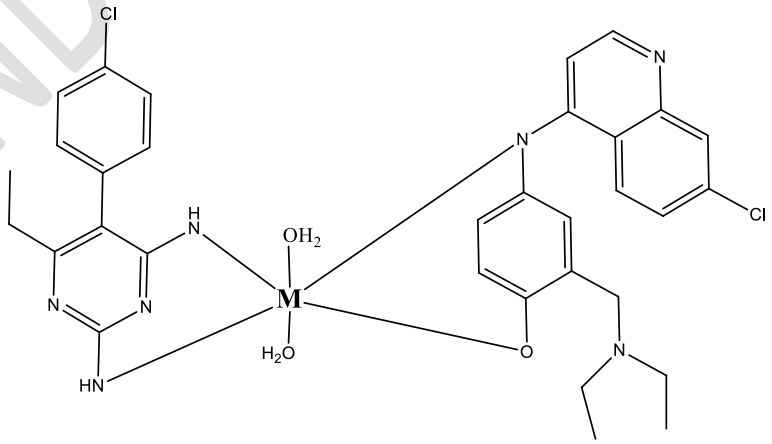

Fig 4: Proposed Structure of metal complexes of Amodiaquine and Pyrimethamine

Where M= Ni, Cu, Zn, Co and Fe

3.3 Antibacterial and Antifungal metal complexes of mixed Amodiaquine and pyrimethamine

Both antibacterial and antifungal were carried out on metal complexes of Amodiaquine and pyrimethamine. The result shows a remarkable contribution by the increase in the inhibition against some strains of bacterial and fungi.

Table 4: Antimicrobial result for metal complexes of amodiaquine and pyrimethamine

COMPLEXES	***Streptococus fecalis***	***Escherichia Coli***	***Klebsiella pneumoniae***	***Staphylococcus aureas***
Amodiaquine	09	10	20	15
Pyrimethamine	15	10	-	13
$Cu(Amd)(Pry)Cl_2.6H_2O$	30	20	11	25
$Co\ (Amd)(Pry)Cl_2.6H_2O$	14	15	-	13
$Zn(Amd)(Pry)(NO_3)_2.7H_2O$	11	16	16	10
$Ni(Amd)(Pry)(NO_3)_2.6H_2O$	25	17	-	-
$Fe(Amd)(Pry)SO_4.7H_2O$	-	15	-	-

Table 5: Anti-Fungi result for metal complexes of amodiaquine and pyrimethamine

Compound	Aspergillus niger	Candida albican
Amodiaquine	15	13
Pyrimethamine	16	-
$Cu(Amd)(Pry)Cl_2.6H_2O$	25	12
$Co(Amd)(Pry)Cl_2.6H_2O$	09	-
$Zn(Amd)(Pry)(NO_3)_2.7H_2O$	-	11
$Ni(Amd)(Pry)(NO_3)_2.6H_2O$	10	-
$Fe(Amd)(Pry)SO_4.7H_2O$	13	-

3.4 CONCLUSION

Reviews on anti-malarial drugs have shown that there are three consistent ways in which we believe antimalarial drug resistance emerges. Spontaneous drug-resistant mutations have affected the effectiveness of direct drug treatment [33,34]. Therefore, it is important to recognize the possibility of considering metal drugs as potential therapeutic agents. The present study shows the

feasibility and justification for the synthesis of mixed antimicrobial metal complexes using amodiaquine and pyrimethamine as ligands. The metal complexes of Cu(II), Fe(III), Ni(II), Co(II) and Zn(II) ion have been successfully synthesized and characterized by spectral and analytical data.

Based on these data, octahedral geometry has been assigned to the complexes. In the complexes, pyrimethamine was proposed to coordinate through N atom of the primary amine group, amodiaquine coordinated through the O atom of the hydroxyl group. However, from the analytical data obtained, the complexes possessed better physical properties as compared to the free ligands.

The antimicrobial results indicate that the complexes showed milder effects as chemotherapy agents than their parent drugs. Therefore, they could be more effective against *Plasmodium falciparum* than the parent drugs.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of manuscripts.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

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