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# Cu(II) and Ni(II) Complexes of Sulfamethazine Mixed with Pyrimethamine: Synthesis, Characterization and Antimicrobial Study

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**ABSTRACT**
Two novel mixed ligand metal –drug complexes of sulfamethazine and pyrimethamine were prepared using $CuCl_2.2H_2O$ and $NiCl_2.6H_2O$.The complexes were characterized by elemental analysis, melting point determination, molar conductivity, FT-IR and Uv-Visible spectroscopy. Based on the analytical and spectra data the complexes were formulated as $[M(SUFPRM)Cl_2.XH_2O$,(SUFPRM)=Sulfamethazine+Pyrimethamine, M=Cu, Ni. And the complexes formed possessed octahedral geometry. In the complexes, sulfamethazine and pyrimethamine acted as bidentate ligand coordinating through the sulfonamide N-atom and the pyrimidinicN-atom. The complexes have been tested in vitro against a number of pathogenic bacteria[g+][Eschericha coli, Proteus specie, Klebsiella pneumonia, Salmonella typhi and Bacillus]by using paper disc method. Obtained results indicated that the metal complexes exhibited better antimicrobial activities as compared to the ligand.
**Keywords**: Sulfamethazine, Pyrimethamine, metal-drug complexes, ligands, antimicrobial properties.

## INTRODUCTION

There are three major infectious diseases ravaging the World, of which malaria is one of them, others are tuberculosis and AIDS [Robert et al., 2002].After the World War II due to easy access to cheap insecticides and readily available drugs like chloroquine, it was erroneously believed that malaria could be successfully reduced or possibly eradicated.

According to the World Health Organization [WHO] 300-500 million people become infected and close to a million die of malaria every year. Those particularly at risk include children (especially those less than five years), pregnant women and people living with HIV/AIDS (PLAWHA) others include children with sickle cell anaemia, glucose-6-phosphate dehydrogenase deficiency (National Malaria Policy, 1998).

The emergence spreading of parasites resistance to antimalaria drugs currently in use indicates that novel compounds need to be developed by identification of novel chemotherapeutical targets [Oldiaro et al., 1996]. Hence, the search for new antimalaria therapies is a high priority for the control of the disease.

The use of metal complexes as pharmaceuticals has shown promise in recent years particularly as anticancer agents [Lebwohl and Canreta, 1998, Mesori et al., 2000] as well as gadolinium complexes used as contrast agents for magnetic resonance imaging [Abrams and Murrer, 1993].

The introduction of metal ions into chemotherapy agents with the aim of increasing their efficacy has been an extensive research for more than three decades since the discovery of Cis-platin [Farrell, 2003, Ajibade, 2008, Fahmudeh et al., 2000].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, 2001]. 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].

Even with 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 synthesis novel metal complexes of sulfamethazine mixed with pyrimethamine.

## MATERIALS AND METHODS

Sulfamethazine and Pyrimethamine (product of Sigma Chemical Co.USA)were obtained from Bond Chemicals, Lagos, Nigeria. Other reagents are product of British Drug House (BDH)of analar grade and were use without further modification. The metal sources are $CuCl_2.2H_2O$ and $NiCl_2.6H_2O$.Melting points were determined using Optimelt AutomatedMelting Point System. The Uv-Visible Spectra measurement were obtained from solution of the compounds in Dimethylsulfoxide (DMSO) on Shimadzu 10UV scanning UV-

ViSspectrometer. Infrared (IR) spectra of the samples in KBr pellets SP3-30 Infrared Spectrometer FT_IR - 8400S (Fourier Transforms Infrared Spectrophotometer (Shimadzu) at Redeemer's University, Mowe, Ogun State, Nigeria. At the range of 4000-500cm$^{-1}$.Conductivity measurement was carried out in DMSO/Water using Hand –held conductivity TDS meter. Analysis of the chemical elements (CHN) was carried using elemental analyzer, Thermo Flash 1112 CHNSO Elemental Analyzer available at MEDAC Ltd, Surrey in United Kingdom. Isolates of E.Coli, Klebsiella, proteus, Salmonella and bacillus were obtained from Microbiology Department, Delta State University, Nigeria.

## SYNTHESIS OF THE METAL COMPLEXES

The Copper and Nickel complexes were made from $CuCl_2.2H_2O$ 0.170 g (1 mmol) and $NiCl_2.6H_2O$ 0.238 g(1mmol). The complexes were prepared by dissolving 0.278 g (1 mmol) Sulfamethazine in 30 mL methanol and followed by dropwise addition of 10 ml methanolic solution of each of the metal salts [Elzehany et al., 2008]. The solutions were mixed thoroughly together in round bottom flask. The resulting mixture was stirred continuously while the second ligand was added slowly after 30 mins. The army green and sea green solution obtained in each case was stirred constantly at room temperature for 2 h. the products were filtered, washed with methanol and the filtrate left to evaporate slowly at room temperature and precipitate formed was dried in a desiccators containing silica gel. The purity of the compounds was confirmed by Thin Layer Chromatography and their sharp melting point.

## ANTIMICROBIAL ACTIVITIES

The antimicrobial activities of the ligands and their metal complexes were carried out using 5 mm diameter paper disc (Whatman No 1) as described by previous workers [Collins, 1980].The compounds were dissolved in DMSO at 50 and 100 ppm concentrations. The filter paper disc were soaked in different solution of the compounds, dried and placed on the sterile petri dishes previously seeded with the test organisms (Escherichia Coli, Klebsiella pneumonia, Proteus spp, Salmonella and Bacillus). The plates were incubated for 24-30 h at 37$^{o}$C and the zone around each disc was measured in mm using meter rule. The average Zone of inhibition in millimeter was determined from the readings taken in triplicate. DMSO was used as control.

**Table 1: Analytical Data for Mixed–Ligand Complexes of Sulfamethazine (SUF)With Pyrimethamine (PRM)**

| Ligands/ Complexes | Appearance/ colour | Yield % | Molecular weight | Melting point $^{O}$C | Conductivity (µs/cm) | % Elemental Analysis found (calc) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| SUF ($L_1$) | Amorphous powder/white | - | 283.34 | 199 | | 24.69 (24.68) | 2.40 (2.38) | 9.60 (9.50) |
| PRM ($L_2$) | Amorphous Powder/white | - | 249 | 193 – 194 | | 57.89 (57.95) | 4.44 (4.46) | 22.50 (22.52) |
| [Cu(SUFPRM)$Cl_2$] | Powder/army green | 52 | 699.54 | 234.54 | 39.4 | 39.87 (41.21) | 3.72 (4.75) | 15.16 (16.02) |
| [Ni(SUFPRM)$Cl_2$] | Powder/green | 62 | 656.06 | 315DT | 23.9 | 43.76 (43.76) | 2.84 (4.44) | 16.89 (17.01) |

## RESULTS AND DISCUSSION

Physical characteristics and elemental analysis (CHN) of the ligands and Cu (11) and Ni (11) complexes prepared are presented in Table 1. The results of C, H and N percentages are in close agreement with the composition suggested for the two complexes. The solubility of the metal complexes was compared with the ligands by dissolving them in warm and cold medium of some polar solvents, such as water, methanol, ethanol, acetone, chloroform and non-polar solvents e.g. DMF and DMSO. However, they were found to be more soluble in DMF and DMSO. This is an indication that the complexes are non- polar in nature [Vogel, 1989]. The two complexes possess high decomposition temperature and were coloured. They are amorphous and stable in air. The proposed stoichiometric equation for the synthesized complexes could be represented as:

$MCl_n.xH_2O + L_1 + L_2 \rightarrow ML_1L_2Cl_n + xH_2O$

Where M=Cu(II) & Ni(II) n=2

$L_1$=Sulfamethazine, $L_2$=Pyrimethamine

## CONDUCTANCE MEASUREMENT

The conductivity of the complexes was measured in DMSO .The complexes showed molar conductance values ranging from 23.9µs $cm^{-1}$ indicating their non-electrolytic nature [Vogel, 1989].The values obtained indicate that no anion is present outside the coordination sphere.

## INFRARED SPECTRA

The informative infrared band of the complexes are presented in Table 2. The IR spectra of the free ligands and their metal complexes were compared and assigned on the basis of careful comparison. The bands in the region 3468 $Cm^{-1}$-3313 $Cm^{-1}$ in the ligands showed appreciable changes in the spectra of the complexes. These differences may be due to the interaction between the free $NH_2$ group on sulfamethazine and pyrimethamine and the stretching, wagging and rocking vibrations of the coordinated and /orlattice water or due to intermolecular hydrogen bonding. The shifting of this group to lower frequency when compared with the two free ligands suggesting a coordination of Cu(II) and Ni(II) ion ,respectively through the nitrogen atom of the sulfonamide group.[Farrell, 2003]

Also, the infrared spectra display strong band at 594 $cm^{-1}$[Cu (SUFPRM)$Cl_2$]and 597 $cm^{-1}$ [Ni(SUFPRM)$Cl_2$] attributed to M-N vibration.[Mc. Claverty 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.

**Table 2: IR Spectra 4000 – 400cm-1 of the Ligands and their Metal Complexes**

| Compound | ν($NH_2$)$cm^{-1}$ | ν(C-N) | ν(N-H) | ν(S=0) | M – N |
|---|---|---|---|---|---|
| SUF ($L_1$) | 3443(s) | 1477(s) | 3343(s) | 1147(s) | - |
| PRM ($L_2$) | 3468(s) | 1437(w) | 3313(s) | - | - |
| Cu($L_1L_2$)$Cl_2$ | 3462(b) | 1460(m) | 3232(s) | 1138(m) | 594(s) |
| Ni($L_1L_2$)$Cl_2$ | 3462(b) | 1437(s) | 3333(b) | 1143(m) | 597(s) |

w – weak, s – strong, m – medium, b - broad

**Table 3: Uv-Visible Spectra Assignment of Sulfamethazine with Pyrimethamine and Their Metal Complexes**

| Compound | Wavelength (nm) | ($cm^{-1}$) | Tentative assignment |
|---|---|---|---|
| $L_1$ | 268<br>306 | 37313<br>32679 | n - $\pi^*$<br>$\pi$ - $\pi^*$ |
| $L_2$ | 230<br>326 | 43478<br>30674 | n - $\pi^*$<br>$\pi$ - $\pi^*$ |
| Cu($L_1L_2$)$Cl_2$ | 223<br>343<br>486 | 44843<br>29154<br>20576 | n - $\pi^*$<br>$\pi$ - $\pi^*$<br>$^2Eg(D) – 2T_2g(D)$ |
| Ni($L_1L_2$)$Cl_2$ | 229<br>332<br>678 | 43668<br>30120<br>14749 | n – $\pi^*$<br>$\pi$ - $\pi^*$<br>$^3Ag – 3T_1g$ |

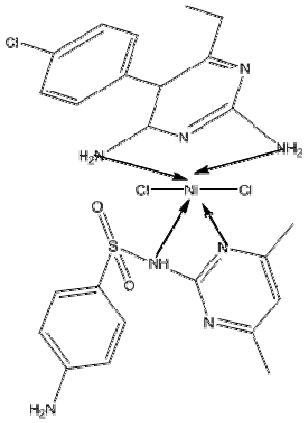
## ELECTRONIC SPECTRA OF THE MIXED LIGANDS AND THEIR METAL COMPLEXES

The Cu (II) complex of the ligands showed a broad asymmetric band in the region 20576 cm-1 expected for a d-d transition of an octahedral Cu(II) complex [Greenwood and Earnshaw, 1984].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 [Kopel et al., 2001]

The Ni (11) complex gave two bands, Table 3 corresponding to the UV-region, which is assignable to n-π and π-π respectively and one allowed transition with a broad band which peaked at 14749 $cm^{-1}$ is assigned to $^3Ag$-$^3T_{1g}$.



$2H_2O$

**Fig. 1: Ni(SUFPRM)$Cl_2$**

**$C_{24}H_{29}Cl_3N_8NiO_2S$**

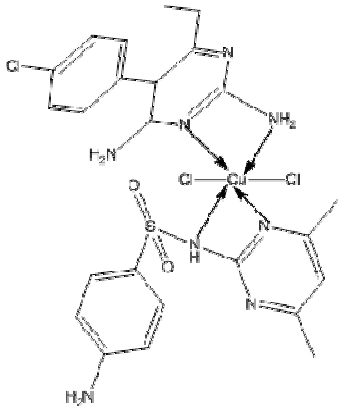


Fig. 2: **Cu(SUFPRM)$Cl_2$**

**$C_{24}H_{29}Cl_3CuN_8O_4S$**

## RESULTS OF ANTIMICROBIAL STUDY

The results of biological activity of the ligands and the metal complexes against some strains of microorganisms are as shown in Fig. 3. The diameters of zone of inhibition (mm) for the ligands (Sulfamethazine + Primethamine) were found to be in the range of 6.67 to 15.67 for the five bacteria used. They were found to be moderately active. The overall results for metal complexes, however, showed that the two complexes better activity against the microorganisms used under the same experimental conditions than their parent ligands.

Their results suggest, therefore, that upon chelation, it facilitates 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.

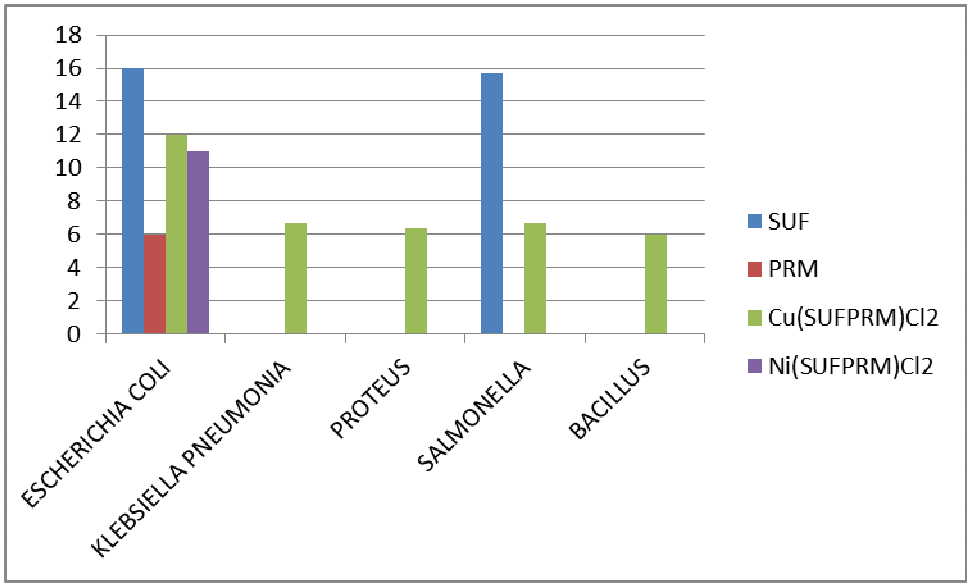



Fig. 3: Zones of inhibition

## CONCLUSION

Cu (II) and Ni (II) complexes of Sulfamethazine mixed with Pyrimethamine have been synthesized and characterized by elemental analysis, electronic and IR Spectra. The two novel complexes are insoluble in the original solvents used for the synthesis and common polar solvents, but were soluble in DMF and DMSO. They are air stable.

Based on these data, distorted octahedral geometry has been assigned to the complexes. In the complexes, Sulfamethazine was proposed to coordinate through N-atom of the Sulfonamide group and the N-atom of the pyridinyl group while Pyrimethamine was to coordinate through an N-atom of imine and N-atom of the two amine groups. They both act as bidentate ligands. The antimicrobial results clearly indicate that the complexes are much more effective as chemotherapy agents than their parent drugs.

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