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Synthesis, Characterization and Antimicrobial Properties of Mixed Ligand of Sulphamethoxazole and Trimethoprim and Their Manganese (II) and Copper (II) Complexes

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Abstract:- Sulphamethoxazole and trimethoprim mixed ligand and their Mn(II) and Cu(II) metal complexes have been synthesized and characterized. The characterization of metal complexes is based on the results of the solubility, colour, melting points and spectroscopic studies. The UV-Visible spectra revealed characteristic wavelength maxima at 600 nm, 700 nm, 750 nm and 800 nm assigned to the d-d electronic transition of the metal complexes. The FTIR results confirmed that the manganese and copper ions coordinated through the nitrogen atom and oxygen atom (S=O) of sulphamethoxazole and through the nitrogen atoms in trimethoprim. The antimicrobial activities of the metal complexes synthesized indicated that the metal complexes were more potent against selected organisms than the free ligands.

Keywords:- *Sulphamethoxazole, Trimethoprim, Mixed ligands, Metal complexes, Antimicrobial activities, Spectra studies, Characterization.*

I. INTRODUCTION

The discovery of coordination compounds resulted in a synthetic revolution in Inorganic Chemistry which leads to formation of new products with effective applications in wide selection of areas including fungicides, paints, pigments, polymers, pharmaceuticals, catalysis and photoconductors (Gaikwad & Yadav, 2016). The effectiveness of a coordination compound can be enhanced by the nature of ligands coordinated. The nature of metal- ligand bonding range from covalent to ionic with bond order from one to three. Ligands are lewis bases but in rare cases occur as lewis acids.

Transition metals are a class of element with partially filled d sub-shell distinguished by characteristics such as formation of coloured compounds, having variable oxidation state and formation of complexes. Although, high level of heavy metals could relatively lead to increase serum liver enzymes, kidney function parameters and reduction in haemoglobin level packed cell volume and Red Blood Cells (Oguntuase *et al*., 2019), Cu and Mn are nutrient minerals which play major roles in metabolic processes such as muscular activity, endocrine function, reproduction, skeletal integrity and overall development (Adeyeye *et al*., 2021). They are essential micronutrients for plants and animals growth but when present in higher concentrations can cause health defects such as cardiovascular, nervous, kidney and bone diseases (Araromi *et al*., 2020). Copper is an example of transition metal, it plays a crucial role in human metabolism because it allows many critical enzymes to function properly. Copper is essential for maintaining the strength of the skin, blood vessels, epithelial and connective tissues throughout the body. It is highly important in the production of hemoglobin, myelin, melanin and it also keeps thyroid gland functioning normally. Copper can act as both an antioxidant and a pro-oxidant (Osredkar & Sustar, 2011).

Cu(II) Complexes are four-coordinate which are generally blue or green due to the maximum of four electronic transitions; d-d transitions; charge transfer transitions and internal ligand transitions. Electronic spectroscopy cannot be used in isolation as a tool for structural identification due to the large distortion associated with this compound (Gaikwad & Yadav, 2016). Cu is one of the various metals commonly used for metal based drugs because of its ability to form low molecular weight complexes which prove to be more potent against several diseases (Olagboye *et al*., 2018; Kozarich, 2005). Whereas, manganese is a hard but brittle metal which is difficult to fuse but easy to oxidize. Manganese have variable oxidation state from +2 to +7 but the +2 state is most prevalent in the biological system. Manganese (II) ions function as cofactors for a large variety of enzymes with many functions (Schmidt and Husted, 2019).

Metal complexes formed from most transition metal ions is an important class of coordination compounds which are studied extensively due to their enormous applicability in various fields of human interests (Ejelonu *et al*., 2018) ranging from biological, chemical, agricultural and industrial applications. Metal drug complexes are attracting research interests due to their increasing importance in the design of drugs (Lawal and Obaleye, 2007).

Antioxidant, water softening, ion exchange resin, photosynthesis in plants, removal of undesirable and harmful metals from living organisms, electroplating and dying are some of the diverse ways in which mixed ligand complexes are applied in medicine, chemical and biological systems (Taghreeed & Lekaa, 2016).

Microbial infections are a menace worldwide which does not subside despite active research devoted to the discovery and development of novel antimicrobial agents.

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Antibiotics are used to treat bacterial infections and its improper and unnecessary use has made antibiotic resistance a growing problem (Miniyar & Makhija, 2009).

Sulphamethoxazole is an antibacterial which has been utilized in combination with trimethoprim or pyrimethamine since the 1960s for the treatment of various systemic infections in humans and other species (IARC monographs Vol. 79). Urinary tract infection is one of the most common infectious diseases caused by *Escherichia coli* in many countries. *E. coli* have been found to be highly resistant to trimethoprim-sulphamethoxazole (Kurutepe *et al*., 2005), efforts are therefore progressively made to develop novel antibiotics.

Trimethoprim (TMP) is an antibiotic drug used mainly in the treatment of bladder infections, it is also used for middle ear infections and travellers'diarrhoea. It interferes with the production of tetrahydrofolic acid, a chemical that is necessary so as for bacteria and human cells to produce proteins (Akinyele *et al*., 2020). The pharmaceutical use of metal complexes has excellent potentials (Zhang & Lippard, 2003) which has gained tremendous attention overtime (Ejelonu *et al*., 2018; Allardyce *et al*., 2005).

Malaria, tuberculosis and AIDS are the three major infectious diseases grievously damaging the world. Efforts are being made to eradicate and control malaria for over a decade but the disease still remain a major threat to human health and economic development around the world. Sulfanilamides are used as antibacterial as well as antimalarial drugs (Ajibade *et al*., 2006). The continuous emergence of resistant parasites to available antimalarial drugs has made the development of novel antimalarials and modification of existing antimalarial drugs a necessity in order to eradicate or control the disease. This research work involved the synthesis, characterization and antimicrobial properties of sulphamethoxazole and trimethoprim mixed ligand metal complexes.

II. MATERIALS AND METHODS

Materials and Reagents; Trimethoprim Salt, Sulphamethoxazole Salt, Manganese(II)sulphate monohydrate ($MnSO_4.H_2O$), Copper(II)Chloride dihydrate ($CuCl_2.2H_2O$), Methanol, sodium hydroxide, hydrogen peroxide, n-Hexane, chloroform and ethanol used were obtained in analytical grade and used without further purification.

A. Physical measurement

The melting points of the complexes were determined using melting point apparatus. The solubility tests were carried using polar and non polar solvents. The FTIR spectra were recorded using FTIR 8300 shimadzu specterophotometer in the frequency range of 4000-400cm^{-1}. The UV-visible spectra were also recorded using shimadzu UV-VIS.16OA ultra-violet spectrophotometer in the range of 200-800nm.

III. EXPERIMENTAL

A. Synthesis of Sulphamethoxazole-metal complexes in ratios 1:1 and 1:2

The complexes were prepared by adding aqueous methanol solution of 0.01mol of the cu (1.7054g) & Mn (1.69g) metal salts to an aqueous methanol solution of 0.01 (2.5328g) and 0.02 (5.0656g) moles sulphamethoxazole respectively. The mixture was stirred for 2hrs 30mins on a magnetic stirrer. The complexes were recovered from solutions by filtration followed by washing with distilled water and methanol and then dried to a constant weight in a dessicator.

B. Synthesis of the mixed ligand-metal complexes

2.5328g (0.01mole) of sulphamethoxazole and 2.9032g(0.01mole) of trimethoprim were dissolved in 20ml aqueous methanol. 0.01mole (1.69g $MnSO_4.H_2O$ and 1.7054g $CuCl_2.2H_2O$) of the metal salts were added. The resulting solution was stirred for 2hrs 30mins on a magnetic stirrer. The product formed was filtered, washed with a mixture of methanol and water and then dried to a constant weight in a dessicator.

C. Antimicrobial studies of the metal complexes

Ten (10) different bacteria and four fungi were collected from University of ife Teaching Hospital, Ile ife osun state Nigeria. They were sub-cultured on nutrient agar for bacteria and potato dextrose agar for fungi. Both media were prepared according to manufacturer's specifications. True representatives of each of the different organisms were sub-cultured, their identification and taxonomic studies were carried out to confirm each organism. The confirmed organisms were then prepared for use as test organisms for the antibiotic susceptibility test. Each of the test organisms was transferred to a liquid medium nutrient both for bacteria and enriched peptone both for fungi. They were inoculated for 18h after which they were used for the test. Mueller-Hinton agar was prepared according to manufacturer's specification, poured into petri dishes and allowed to set. Sterile swab were then used to seed the set agar plates with each test organism, then an 8mm diameter cork-borer was used to bore wells in the plates, after which each wells was filled with the solution of each test compound. The plates were incubated for 24h at 37^0c.

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IV. RESULTS AND DISCUSSIONS

TABLE 1; PHYSICAL AND ANALYTICAL DATA OF THE COMPLEXES

COMPLEXES	MOLECULAR WEIGTH	COLOUR	YIELD (%)	MELTING POINT (°C)
SMT $C_{10}H_{11}N_3O_3S$	253.28	White	-	165-167
TMP $C_{14}H_{18}N_4O_3$	290.32	White	-	190-192
$[Cu(SMT)Cl_2]H_2O$	405.55	Green	51	148-150
$[Cu(SMT)_2Cl_2]H_2O$	658.55	Light green	53	152-154
$[Cu(SMT\text{-}TMP)Cl_2]H_2O$	695.55	Light green	65	138-140
$Mn(SMT)SO_4$	403.94	White	48	166-168
$Mn(SMT)_2SO_4$	656.94	White	75	166-168
$Mn(SMT\text{-}TMP)SO_4$	693.94	693.94	90	172-174

LEGEND; SMT= SULPHAMETHOXAZOLE ($C_{10}H_{11}N_3O_3S$) TMP= TRIMETHOPRIM ($C_{14}H_{18}N_4O_3$)

The results of the physical measurements are presented in Table 1. All the complexes were stable and obtained in moderate to high yield 48% - 90%. The mixed ligand-manganese complex has the highest yield of 90% while the least yield was recorded from the 1:1 sulphamethoxazole-manganese complex. The copper complexes generally have less yield compared to their analogous manganese complexes which could be linked to the reactivity of the metals. Sharp melting points were observed in all the complexes with melting temperature ranging from 138°C in copper mixed ligand complex to 174°C in manganese mixed ligand complex suggesting the formation of pure metal complexes. The melting point is generally higher in the manganese complexes than their corresponding copper complexes.

TABLE 2; SOLUBILITY OF THE COMPLEXES

COMPLEXES	Chloroform	Ethanol	n-Hexane	Ethyl acetate
$[Cu(SMT)Cl_2]H_2O$	Very soluble	Very soluble	Slightly soluble	Very soluble
$[Cu(SMT)_2Cl_2]H_2O$	Very soluble	Very soluble	Slightly soluble	Very soluble
$[Cu(SMT\text{-}TMP)Cl_2]H_2O$	Very soluble	Very soluble	Slightly soluble	Very soluble
$Mn(SMT)SO_4$	Very soluble	Very soluble	Slightly soluble	Very soluble
$Mn(SMT)_2SO_4$	Very soluble	Very soluble	Slightly soluble	Very soluble
$Mn(SMT\text{-}TMP)SO_4$	Very soluble	Very soluble	Slightly soluble	Very soluble

The solubility test of the complexes were also done using different solvents, they were soluble in chloroform, ethyl acetate and ethanol but insoluble in n-hexane.

The result of the UV-visible analysis of the compounds prepared is presented in Table 3. The results indicated that the metal complexes are coloured because of the d-d electronic transition within the metal atoms and charge transfer between the metal and the ligands. The colour of metal ion solution is strongly affected by the presence of other species such as anions and ligands, therefore, the colour of the metal complex solution changes as well as the wavelength of maximum absorption. The wavelength of maximum absorption was observed at 700 nm for the metal complexes. Higher absorbances (23.86, 23.54 and 23.67) were observed for the Copper (II) complexes as compared to the manganese (II) complexes (23.06, 23.56 and 23.75).

TABLE 3: UV RESULT OF THE COMPLEXES

Wavelengths (nm)	200	300	400	500	600	700	800	900
SMT	0.09	0.09	0.59	10.10	17.75	23.24	13.16	13.99
$[Cu(SMT)Cl_2]H_2O$	0.09	0.10	0.57	10.08	17.89	23.86	13.12	13.95
$[Cu(SMT)_2Cl_2]H_2O$	0.09	0.10	0.59	10.07	17.75	23.54	13.11	13.93
$[Cu(SMT\text{-}TMP)Cl_2]H_2O$	0.09	0.10	0.57	10.13	17.83	23.67	13.98	14.02
$Mn(SMT)SO_4$	0.09	0.10	0.57	10.07	17.75	23.06	13.11	13.94
$Mn(SMT)_2SO_4$	0.09	0.10	0.58	10.26	18.02	23.56	13.79	14.18
$Mn(SMT\text{-}TMP)SO_4$	0.09	0.10	0.59	10.16	17.92	23.75	13.59	14.07

The prominent IR bands of the ligands and metal complexes are represented with table 4. The stretching modes of the ligands are expected to change upon complexation due to either weakening or strengthening of the bonds involved in the bond formation (Olagboye *et al*., 2018) the absorption bands due to metal- ligand coordination are observed in the far IR region (400 - 600cm^{-1}) while the bands due to structural changes of the ligands appear in the finger print region of the spectra (1500-750cm^{-1}) (Saha *et al*., 2002; Nakamoto, 1986). Assignments of bands are done based on comparison with the spectra data of similar compounds (Lawal and Obaleye, 2007). The bonding of the ligands to metal ions was

investigated by comparing the FTIR spectra of the complexes with those of the free ligands (Eugene-Osoikhia *et al*., 2020).

IR spectrum of the free ligand shows two strong bands at 3465 and 3374 cm^{-1} equivalent to the asymmetric and symmetric stretching vibrations of the aromatic amino group (NH_2). This band did not show any appreciable changes in all the complexes which demonstrates its non participation in the coordination (Eugene-Osoikhia *et al*., 2020 ; Rostamizadeh *et al*., 2019). The medium and strong signals at 3140 and 3296 cm^{-1} are due to the presence of asymmetric and symmetric frequency vibration of the sulfonamide -NH group. The shifting of the band in the spectra of the complexes indicated its involvement in the coordination or chelation with central metal ion through the N atom of this group (Eugene-Osoikhia *et al*., 2020 ; Mondelli *et al*., 2013). The peak at 1613 is assigned to the C=N stretching vibration. Based on the IR result, the coordination mode of sulphamethoxazole with metal ion is predicted as a bidentate through the N atom of sulfonamide group and one of the oxygen atom of the sulfonyl. The absence of broad bands in the region 3300-3500 in all the spectra of the complexes indicates that there is no coordinated H_2O molecule. The metal-nitrogen and metal-oxygen stretching frequency were observed at 682-685 and 559-562 cm^{-1} respectively for all the metal complexes.

Generally, mixed ligand complexes demonstrate better activities because chelation reduces the polarity of the metal ion by partial sharing of its positive charge with the donor groups and also due to pi -electron delocalization on the whole chelating ring, increased lipophilicity enhances the penetration of the complexes into lipid membrane and blocking off all of the metal binding sites in the enzymes of microorganisms. These complexes also disturb the respiration process and thus block the synthesis of the protein which restricts further growth of the organisms (Eugene-Osoikhia *et al*., 2020 ; Raman *et al*., 2009).

TABLE 4; IR RESULTS OF THE LIGAND AND COMPLEXES

COMPLEXES	ν(NH)	ν(S=O)	ν(C=N)	νNH2	ν(C=C)	C=N	M-N	M-O	M-Cl
SMT	3296 3140	1309 1147	-	3465 3374	1476	-	-	-	-
TMP	3314	-	1639	3464	1456	1456	-	-	-
$[Cu(SMT)Cl_2]H_2O$	3394 3210	1311 1148	1613	3463	1500	1395	685	562	381
$[Cu(SMT)_2Cl_2]H_2O$	3391 3207	1309 1146	1613	3391	1499	1404	684	559	375
[Cu(SMT-TMP)Cl_2]H_2O	3356 3209	1310 1146	1613	3391	1497	1403	683	560	381
$Mn(SMT)SO_4$	3207	1145	1614	3393	1500	1405	683	559	---
$Mn(SMT)_2SO_4$	3206	1146	1614	3393	1501	1405	682	559	---
Mn(SMT-TMP)SO_4	3209	1146	1613	3393	1500	1405	684	560	---

TABLE 5; ANTIFUNGAL ACTIVITY OF THE COMPLEXES IN PERCENTAGE (%)

COMPLEXES	*Collectotrichum gloeosporioides*	*Rhizoctonia solani*	*Fusurium oxysporum*	*Verticillium albo-atrum*
SMT	**16.60**	**15.00**	**11.00**	**13.00**
TMP	**10.00**	**12.00**	**10.00**	**12.00**
$[Cu(SMT)Cl_2]H_2O$	**29.40**	**45.05**	**33.33**	**13.04**
$[Cu(SMT)_2Cl_2]H_2O$	**62.35**	**59.34**	**36.36**	**43.48**
[Cu(SMT-TMP)Cl_2]H_2O	**72.34**	**71.87**	**54.24**	**57.39**
$Mn(SMT)SO_4$	**27.05**	**30.77**	**22.73**	**26.09**
$Mn(SMT)_2SO_4$	**59.41**	**67.03**	**36.36**	**60.87**
Mn(SMT-TMP)SO_4	**28.24**	**34.07**	**27.27**	**17.39**
MANCOZEB	**100.00**	**90.00**	**69.00**	**69.00**

The antimicrobial screening of the synthesized complexes were carried out using agar well diffusion method. Table 5 presents the antifungal activity of the complexes against four different fungi including *Collectotrichum gloeosporioides*, *Rhizoctonia solani*, *Fusurium oxysporum* and *Verticillium albo-atrum*. All the complexes shows appreciable antifungal activity in the order $Mn(SMT)SO_4$ < Mn(SMT-TMP)SO_4 < $[Cu(SMT)Cl_2]H_2O$ < $[Cu(SMT)_2Cl_2]H_2O$ < $Mn(SMT)_2SO_4$ < [Cu(SMT-TMP)Cl_2]H_2O. From this trend of activity, it was observed that the activity increases with increasing concentrations of the sulphamethoxazole ligand. SMT complexes can also be said to have higher antifungal activity than the co- ligand TMP. Also, Cu (II) complexes show higher antifungal activity than the corresponding Mn (II) complexes. *Rhizoctonia solani* was observed to show highest susceptibility to the tested compounds and *Fusarium oxysporum* was least. Generally, the activity of the compounds against the tested organisms increases in the

order ; *Fusurium oxysporum* < *Verticillium albo-atrum* < *Collectotrichum gleosporoides* < *Rhizoctonia solani*.

All the ligands and their metal complexes synthesized are sensitive to the selected organisms. The combined dual properties of both the ligands and metal ions interacted with different steps of fungal life cycle (Iornumbe *et al*., 2018). There is also an evidence that the control antifungal commercial agent proved to be more active than both the ligands and metal complexes.

The antibacterial screening of the complexes against ten bacteria strains *Agrobacterium tumefaciens, Xanthomonas phaseoli, Pseudomonas glycinea, Erwinia carotovora, Clavibacter michiganensis, Pseudoman solanacearium, Xanthomonas campestris, Corynebacterium sepedonicum, Agrobacterium rhizogenes* and *Corynebacterium flaccumfaciens* was carried out and the diameter of zone of inhibition of the antibacterial activities of the complexes against the standard bacteria strains were measured in mm as a mean of triplicates and the results are presented in Table 6.

The activity of the metal complexes and the mixed ligand complexes increase as the concentration of ligand increases, the increase in activity is attributed to chelation. The polarity of metal atom is reduced as a result of sharing of its positive charge with donor group of the ligand and the delocalization of the pi electrons on the aromatic rings. The cell membrane of the bacteria is permeated due to the increase in lipophilicity thereby resulting in the death of the bacteria (Khameneh *et al*., 2019).

The highest zone of inhibition was recorded in the Mn (II) mixed ligand complex with a value of 31mm which is higher compared to 25mm reported for the standard drug. The compounds of Mn has shown outstanding activity against *Pseudoman solanacearium* as compared to the inactivity of the Cu (II) complexes in inhibiting the growth of this organism. Of all the tested bacteria strain, *Agrobacterium rhizogenes* showed high susceptibility to all the chemical compounds screened with the complexes showing higher activity than their ligands. Also, the zones of inhibition observed for this organism is comparable to that of the standard drug streptomycin.

Generally, reduced activity was observed for *Xanthomonas campestris* and *Clavibacter michiganensis* as against the high zone of inhibition observed with the standard drug, the reduced activity might be associated to the inability of these compounds to permeate the membrane of these organisms (Ramzan *et al*., 2017). The Cu (II) complexes have highest activity recorded against *Agrobacterium rhizogenes* which may be due to the ability of the complex to permeate the cell membrane of the organism. The mixed ligand Cu(II) complex shows higher activity than the Mn (II) complex in the organisms; A, B, C, E and F while Mn complex have higher zones of inhibition in the organisms D, G, H, I and J.

TABLE 6; ANTIBACTERIAL ACTIVITY OF THE COMPLEXES

DIAMETER OF ZONE OF INHIBITION (mm)										
COMPLEXES	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**
SMT	05	02	02	---	---	0.1	01	05	06	02
TMP	03	01	0.15	0.1	15	---	15	0.3	04	01
Cu(SMT)Cl_2	11	05	10	04	03	---	03	16	17	11
$Cu(SMT)_2Cl_2$	10	05	04	04	04	---	08	09	20	06
Cu(SMT-TMP)Cl_2	08	09	07	03	04	---	03	07	15	06
Mn(SMT)SO_4	06	09	05	03	02	---	05	10	16	06
Mn(SMT)$_2SO_4$	07	08	03	09	03	25	03	21	17	17
Mn(SMT-TMP)SO_4	07	04	02	04	03	31	04	20	18	22
SOLVENT	---	---	---	---	---	---	---	---	---	---
STREP. (std.drug)	20	12	22	27	21	25	30	40	25	25

LEGEND; Diameter of cork-borer= 8mm, STREP= streptomycin, --- = not susceptible
A= *Agrobacterium tumefaciens* B= *Xanthomonas phaseoli* C= *Pseudomonas glycinea* D= *Erwiniacarotovora* E= *Clavibacter michiganensis* F= *Pseudoman solanacearium* G= *Xanthomonas campestris* H= *Corynebacterium sepedonicum* I= *Agrobacterium rhizogenes* J= *Corynebacterium flaccumfaciens.*

V. CONCLUSION

Sulphamethoxazole and Trimethoprim mixed ligand complexes with manganese (II) and copper (II) were synthesized and characterized. The complexes were polar with sharp melting points which confirm the formation of pure complexes. The formation of the complexes was indicated by the appearance and disappearance of bands in their FTIR spectra which confirmed that the complexes coordinated through the nitrogen atoms of trimethoprim and through S=O and –NH group in sulphamethoxazole. The antimicrobial activities of the metal complexes synthesized indicated that the metal complexes were comparatively potent against selected organisms with respect to the standard drug streptomycin.

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