Nigerian Research Journal of Chemical Sciences **(ISSN: 2682-6054)**
Volume 9, Issue 1, 2021

SYNTHESIS, CHARACTERISATION AND ANTIMICROBIAL STUDIES OF METAL(II) COMPLEXES OF TRIMETHOPRIM AND 2,2' BIPYRIDINE HETEROCYCLE

[*1]Tunmise T. Eugene-Osoikhia, [1]Sodeeq A. Ojeyemi, [1]Raymond A. Akong,
[2]Temidayo Oyetunde, [3]Emmanuel U. Onche, [4]Funmilola Ayeni
[1]Department of Chemistry, University of Ibadan, Ibadan, Nigeria
[2] Department of Chemical Sciences, Redeemer's University, Ede, Nigeria
[3]School of Chemistry, University of Manchester, Manchester, United Kingdom
[4]Department of Pharmaceutical Microbiology, University of Ibadan, Ibadan, Nigeria
* Corresponding Author: kemitunmise@yahoo.co.uk

ABSTRACT

Mixed-ligand complexes of trimethoprim (TMP) with 2,2′-bipyridine (bipy) with the formular $[M(TMP)(bipy)X].nH_2O$, where M = Mn(II), Co(II), Ni(II), Cu(II), Fe(II), Zn(II) and X= Cl/SO_4, were synthesized and characterized by percentage metal, infrared, electronic spectroscopies, room temperature magnetic moments, melting points, conductance measurements and elemental analysis. From the infrared spectral data, TMP behaves as a bidentate ligand bonding to the metals via the N atom of the pyrimidine amino group (3412-3300 cm^{-1}) and nitrogen atom of the azomethine moiety (1666-1639 cm^{-1}) while the bipy coordinated through the diimine nitrogen atoms (1593-1404 cm^{-1}). The room temperature magnetic moment and electronic spectra indicated that the metal(II) complexes were monomeric and octahedral. The molar conductance of the synthesised complexes in the range 24-40 $\Omega^{-1}cm^2$ mol^{-1} confirmed their non-electrolytic and covalent nature. The antimicrobial studies showed that the complexes were inactive towards the tested fungus but possessed good antibacterial activities. The observed trend for the antibacterial activities demonstrated by the mixed metal complexes was in the order Mn >Zn > Cu > Fe > Co ~ Ni thus making $[Mn(TMP)(bipy)Cl_2].2H_2O$ the most biologically active among them. It was also observed that antibacterial activities exhibited varied directly with concentration as the highest activities were observed at the highest concentration of 40 mg/mL.

Keywords: Antimicrobial, 2,2'-bipyridine, Complexes, Heterocycle, Trimethoprim, Mixed-ligands.

INTRODUCTION

Development of antimicrobial drugs was one of the great medical accomplishments of the twentieth century [1]. The present resistance against antimicrobial agents has become public health problem worldwide [2–8]. In the search for novel drugs against drug resistant diseases, the use of metal complexes has received tremendous awareness and had resulted in a variety of exciting and important drugs such as *cis*-platin [9-17]. Trimethoprim (TMP) (Fig. 1), chemically known as 5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine is a broad-spectrum antimicrobial agent used in prophylaxis treatment and urinary tract infections [18]. It is a structural analoque of pteridine fraction of dihydrofolic acid which competitively inhibits dihydrofolatereductase [19-20]. As a pyrimidine inhibitor of bacterial dihydrofolatereductase, it binds tightly to the bacterial enzyme, blocking the production of tetrahydrofolic acid from dihydrofolic acid [21].

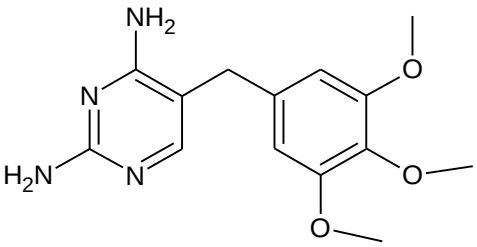


Figure 1: Structure of trimethoprim

Most gram-negative and gram-positive microorganisms are sensitive to trimethoprim, but resistance can develop when the drug is used as a single therapy [22]. Thus, it is normally used as combination therapy with sulfamethoxazole in 1 to 5 ratios [23] to give sequential and synergistic inhibition of bacterial folate metabolism [24]. As a fixed combination formulation it is applied in the treatment of respiratory tract infections such as bronchitis [25], *Pneumocystis carinii* pneumonia with AIDS [26-27], severe urinary tract infections [28] and enteric infections [29]. The combination of trimethoprim-sulfamethoxazole has been outstandingly successful [23]. However, it has been suggested that the clinical conquest of this combination is due mainly to the efficacy of TMP [23]. Therefore, the recent decline in the clinical importance of TMP-SMZ combination as a first line therapy for several infections due to the emergence of resistance disease pathogens and serious side effects of sulfamethoxazole (sulfonamides) [20, 30] requires modification of the combination by the search for an alternative to sulfamethoxazole.

Heterocycles and their derivatives have been reported to have remarkable broad spectrum of biological activities [31-32]. Nitrogen heterocycles are one of the most important classes of ligands in coordination chemistry [33-36]. Among the nitrogen heterocycles, 2,2′-bipyridine (bipy) (Fig. 2) have been widely used as a chelating donor site due to its robust redox stability and relative ease of functionalization [37]. It is an attractive core structure of a large class of chelating compounds that are able to form stable complexes with metal ions [38-39]. Numerous classes of biologically active natural products share this core structure such as caerulomycins [40-42], collismycins [43], orellanine [44], camptothecin [45] and streptonigrinoids [46].

Mixed-ligand complexes involving heterocyclic bases such as pyridine, 2,2′-bipyridine, o-phenanthroline, have been reported due to their bioinorganic applications, thermal stability [47-49], antineoplasticity, cytotoxicity, antitumor effect, genotoxicity, and bactericidal effect [50-51]. Few reports are available on the mixed metal complexes of trimethoprim [52]. Osowole *et al* reported mixed drug metal(II) complexes of trimethoprim and sulfamethoxazole [53], isoniazid and trimethoprim was synthesised by Bamgbose *et al* [54], but no report was available on mixed ligand of 2,2′-bipyridine and trimethoprim. Here, we report the mixed-ligand complexes of trimethoprim and 2,2′-bipyridine and their antimicrobial activities.

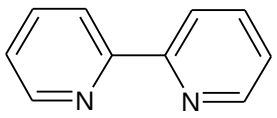


Figure 2: Structure of 2,2'-Bipyridine

EXPERIMENTAL

Materials and Reagents

All reagents and solvents were of analytical grade and used without further purification. Trimethoprim was gift from Bond Pharmaceutical company Plc, Oyo, Nigeria while 2,2′-bipyridine, cobalt(II) chloride hexahydrate, copper(II) chloride dihydrate, manganese(II) chloride tetrahydrate, iron(II) sulphate heptahydrate, nickel(II) chloride hexahydrate and zinc(II) sulphate heptahydrate, were obtained from Aldrich chemicals.

Physical measurements

The electronic spectra of the complexes in DMSO were recorded on a Perkin-Elmer Lambda 25 Spectrophotometer and infrared spectra were recorded as KBr disc on a Perkin-Elmer BX II FT-IR spectrometer 4000–370 cm^{-1}. The room temperature magnetic susceptibilities at 303K were measured on Sherwood Susceptibility Balance MSB Mark 1 and diamagnetic corrections were calculated using Pascal's constant, melting points were determined with Stuart SMP10 melting point apparatus and conductivity measurement was obtained using a Labtech Digital conductivity mechanical device in 1 x 10^{-3} M solutions of nitromethane. CHN elemental analysis was carried out at University of Manchester using Flash 2000 elemental Analyser.

Synthesis of Metal Complexes of [M(TMP)(bipy)X].nH O, where X= Cl /SO4]

A previously reported procedure by Osowole *et al* was employed with slight modification in the synthesis of the metal(II) complexes of trimethoprim and 2,2′-bipyridine [53]. Trimethoprim 0.5 g (1.72 mmole) and 2,2′-bipyridine 0.2690 g (1.72 mmole) were dissolved in 30 ml of methanol. To the resulting homogenous solution, equimolar amount (1.72 mmole) of the respective metal(II) salt in 1:1:1 stochiometric was added dry in bits with continuous stirring at 60 ˚C. The resulting solution was then refluxed for 6 hours to give the product. This was then kept and left undisturbed for about 4 – 6 days to aid the complex precipitation. The resulting complexes were dried over silica gel. The preparation is given by equations (I) and (II) respectively:

Equation of the reaction

$$MCl_2.xH_2O + TMP + bipy \longrightarrow [M(TMP)(bipy)Cl_2].nH_2O + yH_2O \quad .....(I)$$

(where M = Ni, x= 6, n= 0, y= 6; M= Mn, x= 4, n=2, y=2; M= Cu, x=2, n=2, y=0; M= Co, x=6, n=0, y=6)

$$MSO_4.xH_2O + TMP + bipy \longrightarrow [M(TMP)(bipy)SO_4].nH_2O + yH_2O \quad .....(II)$$

(where M = Fe, x=7, n=3, y=4; M= Zn, x=7, n=3, y=4)

Antimicrobial Studies

Antimicrobial screening of the free ligands and the synthesized complexes were tested in vitro using Agar diffusion method [54-56]. The prepared culture plates were innoculated with different identified clinical strains of gram positive, gram negative bacteria and a fungus: *Staphylococcus aureus, Enterotoxigenic E. coli, Enteropathogenic E. coli, Klebsiella pneumonia,*

Leclercia adecarboxylata, *Morganella morganii*, *Salmonella typhi* and a fungus *Candida albicans.* The bacteria were cultured using the pour-plate method. From the diluted organisms (10^{-2}), 0.2 ml was injected into the prepared sterile nutrient agar which was at 45 ^{o}C, then aseptically poured into sterile petri dishes, which were allowed to solidify for about 45-60 minutes. Wells were made on the agar surface with 6 mm sterile cork borer. The prepared different graded concentrations of the complexes and the ligand were poured into the well using sterile syringes. The plates were incubated at 37 ^{o}C ± 2 ^{o}C for 24 hours. The plates were observed for the zone clearance around the wells. The zone of inhibition was calculated by measuring the diameter of the inhibition zone around the well (in mm) including the well diameter. The experiments were conducted in triplicates with gentamycin used as positive control.

Sterile Sabourad Dextrose Agar was prepared for fungus culture. The prepared agar was poured into sterile plates in triplicates allowed to set properly. The organisms (0.2ml) (*Candida albicans*) were spread to cover the surface of the agar. Wells were also made using sterile cork borer of 6 mm in diameter this was followed by the introduction of the prepared concentrations of the ligands and their complexes. The plates were left on the bench for 2 hours to allow pre diffusion and then incubated at 25 ± 2 ^{o}C for 48 hours. Ketoconazole was used as reference drug.

RESULTS AND DISCUSSION

The complexes Figures 3 and 4 exhibit variety of colours with their percentage yields ranging from 36 – 98% as shown in Table 1. The resultant complexes are soluble mainly in DMF and DMSO and are non-electrolytes. The low values of the molar conductivity of the compounds in the range 24-38 $\Omega^{-1}cm^{2}mol^{-1}$ indicate that they are non-electrolyte in solution [57]. The analytical data, melting point/decomposition temperatures and room temperature magnetic moments of the complexes are presented in Table 1

Table 1: Physical and analytical data for the complexes

Complexes	Empirical Formula	Formular mass (g/mol)	M.pt (°C)	μ_{eff} (B.M)	^M $\Omega^{-1}cm^2mol^{-1}$	% Yield	Elemental Analysis(Found)			
							C	H	N	M
Trimethoprim (TMP)		290.32	228-239	-	-	-	---			
2,2′-bipyridine (bipy)		156.19	72-75	-	-	-	---			
[Co(TMP)(bipy)Cl_2]	[$CoC_{24}H_{26}N_6O_3Cl_2$]	575.93	196	3.3	40	42.49	50.01 (51.03)	4.55 (5.00)	14.58 (14.62)	10.22 (10.39)
[Cu(TMP)(bipy)Cl_2].2H_2O	[$CuC_{24}H_{26}N_6O_3Cl_2$].2H_2O	616.55	230	1.8	38	79.77	46.71 (46.68)	4.25 (4.29)	13.62 (13.59)	10.94 (10.64)
[Fe(TMP)(bipy)SO_4].3H_2O	[$FeC_{24}H_{26}N_6O_3SO_4$].3H_2O	651.85	245*	3.1	24	48.83	44.18 (44. 25)	3.99 (3.87)	12.89 (12.93)	9.33 (9.37)
[Mn(TMP)(bipy)Cl_2].2H_2O	[$MnC_{24}H_{26}N_6O_3Cl_2$].2H_2O	607.93	250*	2	35	88.72	47.37 (48.01)	4.27 (4.30)	13.82 (13.84)	8.77 (8.73)
[Ni(TMP)(bipy)Cl_2]	[$NiC_{24}H_{26}N_6O_3Cl_2$]	575.69	242*	2.2	38	36.07	50.02 (50.00)	4.51 (4.86)	14.59 (14.62)	10.19 (10.21)
[Zn(TMP)(bipy)SO_4].2H_2O	[$FeC_{24}H_{26}N_6O_3SO_4$].3H_2O	643.41	253*	D	24	98.02	44.76 (44.63)	4.04 (4.07)	13.05 (13.09)	10.76 (10.74)

D = diamagnetic, *= decomposition temperature, Molar conductance (^M) =$\Omega^{-1}cm^2$ mol^{-1}, Exp =experimental, μeff = effective magnetic moments, M. pt = melting point

Infrared Spectra Studies of Synthesized Complexes

The relevant infrared data are presented in Table 2. IR spectra of trimethoprim, 2,2′ bipyridine and their metal complexes were studied and assigned based on careful assessment of their spectra. The characteristics asymmetric $\nu(NH)_{asy}$ and symmetric $\nu(NH)_{sym}$ stretching vibrations of pyrimidine amino group (NH_2) of free TMP at 3466 and 3313 cm^{-1} [58] were shifted in all the complexes in the region 3412- 3300 cm^{-1} showing the bonding of the amino group's nitrogen to the metal(II) ions without deprotonation [59]. The azomethine $\nu(C=N)$, band at 1641 cm^{-1}in TMP shifted in the range 1666 - 1639 cm^{-1} in the metal complexes confirming the participation of the azomethine nitrogen atom in bonding to the metal(II) ions [60-61].

The binding of the bipy was indicated by the shift of the diimine ((C=C), (C=N)) ring stretching vibration to higher frequencies in the spectra of the complexes [62-65]. Appearance of new bands in the range (626-510) cm^{-1} and (508-474) cm-1 were attributed to the stretching frequencies of (M-N) and (M-O) bonds respectively. Again, new bands in the range 381-370 cm^{-1}were assigned to M–Cl stretching vibrations in the complexes. In all the complexes except $[Co(TMP)(bipy)Cl_2]$ and $[Ni(TMP)(bipy)Cl_2]$ the existence of lattice/coordinated water molecules were shown by the appearance of broad bands in the region 3480–3550 cm^{-1} [66].

Table 2: Relevant IR data of trimethoprim, 2,2′-bipyridine and their metal complexes in cm^{-1}

Compounds	$\nu_{(OH)/H2O}$	$\nu_{(NH2)}$ **(amino)**	$\nu_{(C=N)}$ **(pyrimidine)**	$\nu_{(C=C/C=N)}$ **(diiminegrp)**	$\nu_{(M-N)}$	$\nu_{(M-O)}$	$\nu_{(M-Cl)}$
Trimethoprim (TMP)	_	3466(asy) 3313(sym)	1641	_	_	_	_
2,2′-bipyridine (bipy)	_	_	_	1566,1557, 1443, 1404	_	_	_
$[Co(TMP)(bipy)Cl_2]$	_	3412(asy) 3319(sym)	1646	1589, 1563. 1458, 1413	510	_	377
$[Cu(TMP)(bipy)Cl_2].2H_2O$	3486 (b)	3404(asy) 3300(sym)	1649	1590, 1574, 1445, 1422	626	_	370
$[Fe(TMP)(bipy)SO_4].3H_2O$	3550 (b)	3406(asy) 3321(sym)	1666	1591, 1560, 1508, 1420	614	474	_
$[Mn(TMP)(bipy)Cl_2].2H_2O$	3490 (b)	3404(asy) 3320(sym)	1646	1589, 1562, 1457, 1430	514	_	381
$[Ni(TMP)(bipy)Cl_2]$	_	3403(asy) 3322(sym)	1651	1589, 1565, 1500, 1459	510	_	379
$[Zn(TMP)(bipy)SO_4].2H_2O$	3480(b)	3406(asy) 3315(sym)	1639	1593, 1560, 1455, 1419	616	508	_

Electronic spectra and magnetic moments of the synthesised complexes

The electronic spectral absorptions of the ligands and complexes are presented in Table 3. The electronic spectrum of trimethoprim (TMP) showed two major bands the first at 47847 cm^{-1} (209 nm) due to intra ligand $\pi \rightarrow \pi^*$ transition of the aromatic (C=C) group. The second band at 36764 cm^{-1} (272 nm) arose from $n \rightarrow \pi^*$ transition due to the nitrogen atom of imine (-N=C-) group (Table 3) [67]. The co ligand (bipy) exhibited bands at 42553 cm^{-1}(235 nm) attributed to $\pi \rightarrow \pi^*$ transition due to C=C group and 35587 cm^{-1} (281 nm) attributed to $n \rightarrow \pi^*$ transition owing to the nitrogen atom of the –N=C– group [68-70]. These transitions undergo a shift in the metal complexes due to metal–ligand interaction which obviously indicated the coordination of the ligand to the metal ion [71].

The electronic spectrum of the Co(II) complex gives three bands at 14,599 cm-^{1} (685 nm), 19,342 cm-^{1} (517 nm) and 23,419 cm^{-1} (427 nm). The bands observed were assigned to the transitions , $^4T_{1g(F)} \rightarrow {}^4T_{2g(F)}(\nu 1)$, $^4T_{1g(F)} \rightarrow {}^4A_{2g(F)}(\nu 2)$and $^4T_{1g(F)} \rightarrow {}^4T_{1g(P)}(\nu 3)$, respectively, suggestive of an octahedral geometry around Co(II) ion [72-73]. The magnetic susceptibility value of 3.3 B.M was lower than the value expected for high spin three unpaired electrons (3.87 BM) and abnormally high for value of one unpaired, thus falls within the anomalous range. The observed moments of 3.3 BM can be explained by assuming an equilibrium mixture of the spin-paired (inner orbital) and spin-free (outer orbital) states in each case. Therefore, it can be 0inferred that the metal-ligand bonds must be quite strong, involving appreciable pi-bonding and that the energy difference between the two electronic states (spin-paired and spin-free) is of the order of kT [74].

The copper complex $[Cu(TMP)(bipy)Cl_2].2H_2O$ exhibited two unsymmetrical absorption bands at 13369 cm^{-1} and 23810 cm^{-1} assigned to $^2B_{1g} \rightarrow {}^2B_{2g}$ and $^2B_{1g} \rightarrow {}^2E_{1g}$ transitions of a tetragonal octahedral geometry in consistent with distorted octahedral geometry [61]. A magnetic moment of 1.8 BM confirmed the monomeric nature of the copper (II) complex [75].

The Fe(II) complex had two bands at 18692 cm^{-1} (535 nm) and 21598 cm^{-1} (463 nm) typical of 6-coordinate, high spin and low spin octahedral geometry and were assigned to $^5T_{2g} \rightarrow {}^5E_g$ and $^1A_{1g} \rightarrow {}^1T_{2g}$ transitions and a magnetic moment of 3.10 B.M observed for this complex was indicative of spin equilibrium between the high spin and low spin octahedral geometry [76-77]. The electronic absorption spectra of manganese-complex

$[Mn(TMP)(bipy)Cl_2].2H_2O$ gave two absorptions at 13123 cm^{-1} (762 nm) and 15038 cm^{-1} (665 nm) characteristic of low spin octahedral geometry assigned to $^2T_{2g}\rightarrow{}^2A_{1g}$ and $^2T_{2g}\rightarrow{}^2B_{1g}$ transitions respectively. The effective magnetic moments 2.0 of this complex was consistent of a low spin octahedral geometry [78].

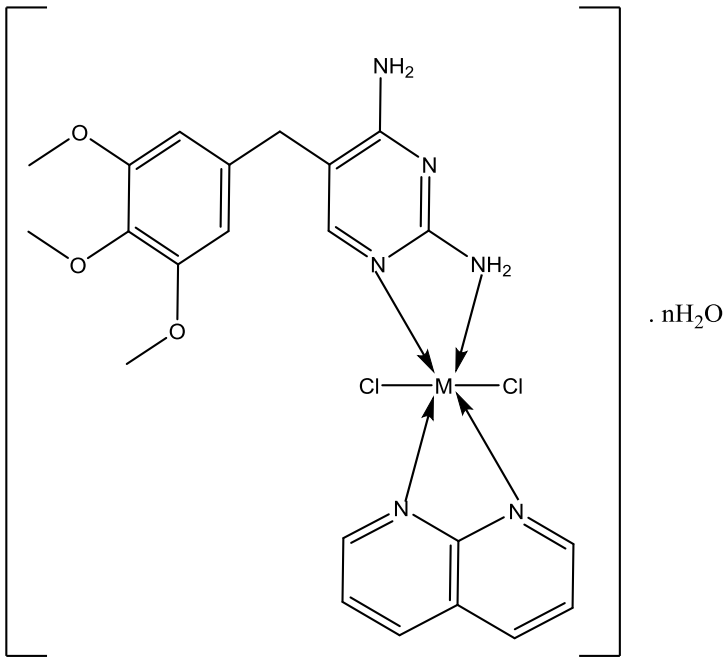
The electronic spectrum of $[Ni(TMP)(bipy)Cl_2]$ exhibited two d-d transitions at 12594cm^{-1} (794 nm) and 14368 cm^{-1} (696 nm) assigned to $^3A_{2g}\rightarrow{}^3T_{2g}$ and $^3A_{2g}\rightarrow{}^3T_{1g}$ (F) respectively. Generally, square planar Ni(II) complexes are diamagnetic while octahedral and tetrahedral complexes are paramagnetic with moments in the range 2.90 – 3.40 B.M and 3.50 – 4.10 B.M respectively [79]. In this study, magnetic moment of 2.2 B.M observed for the Ni complex, showed equilibrium between the high spin octahedral and low spin octahedral geometry [80-81]. The zinc complexes $[Zn(TMP)(bipy)SO_4].2H_2O$ showed only the charge transfer transitions from metal to ligand, as no d-d transition was expected due to their d^{10} configurations. These complexes assumed a 6-coordinate octahedral geometry [82-83].

Table 3: Electronic spectra data of trimethoprim, 2,2′-bipyridine and their metal complexes

Compounds	UV bands (cm^{-1})	Probable transitions
Trimethoprim (TMP)	47847	$\pi\rightarrow\pi^*$
	36764	$n\rightarrow\pi^*$
2,2′-bipyridine (bipy)	42553	$\pi\rightarrow\pi^*$
	35587	$n\rightarrow\pi^*$
$[Co(TMP)(bipy)Cl_2]$	48309	CT
	36232	$n\rightarrow\pi^*$
	23419	$^4T_{1g(F)}\rightarrow{}^4T_{1g(P)}$
	19342	$^4T_{1g(F)}\rightarrow{}^4A_{2g(F)}$
	14599	$^4T_{1g(F)}\rightarrow{}^4T_{2g(F)}$
$[Cu(TMP)(bipy)Cl_2].2H_2O$	48780	CT
	35088	$n\rightarrow\pi^*$
	23810	$^2B_{1g}\rightarrow{}^2E_{1g}$
	13369	$^2B_{1g}\rightarrow{}^2B_{2g}$

$[Fe(TMP)(bipy)SO_4].3H_2O$	48544	CT
	36363	$\pi \rightarrow \pi^*$
	24330	$n \rightarrow \pi^*$
	21598	$^1A_{1g} \rightarrow {}^1T_{2g}$
	18692	$^5T_{2g} \rightarrow {}^5E_g$
$[Mn(TMP)(bipy)Cl_2].2H_2O$	47847	CT
	36232	$\pi \rightarrow \pi^*$
	15038	$^2T_{2g} \rightarrow {}^2B_{1g}$
	13123	$^2T_{2g} \rightarrow {}^2A_{1g}$
$[Ni(TMP)(bipy)Cl_2]$	48544	CT
	37037	$\pi \rightarrow \pi^*$
	14368	$^3A_{2g} \rightarrow {}^3T_{1g(F)}$
	12594	$^3A_{2g} \rightarrow {}^3T_{2g}$
$[Zn(TMP)(bipy)SO_4].2H_2O$	48543	CT
	35971	$\pi \rightarrow \pi^*$

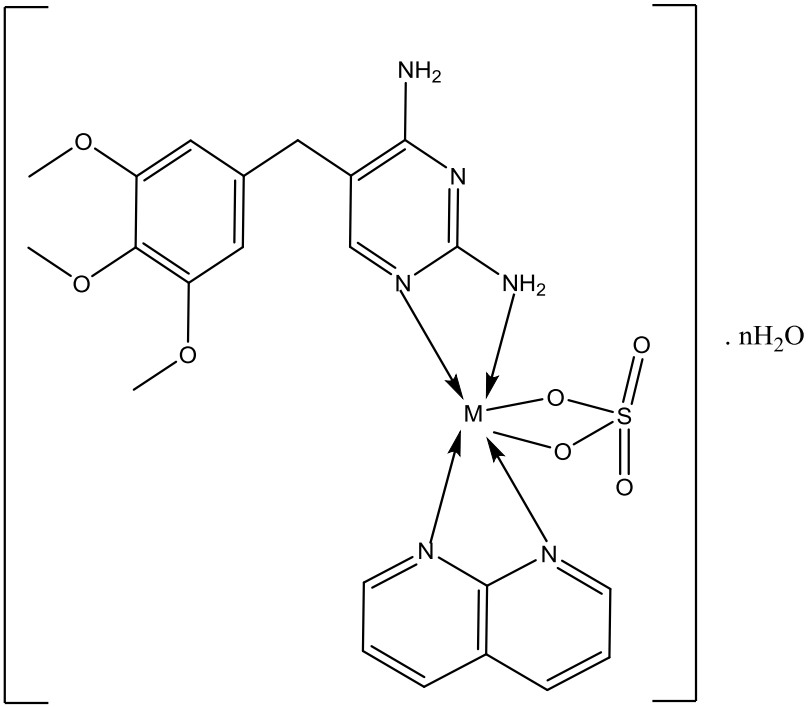
CT = Charge transfer



. nH_2O

Where M = Co, Cu, Mn, Ni and n = 0, 2,

Figure 3: Proposed structure of [M (TMP)(bipy)Cl_2].n$H_2$0



Where M = Zn, Fe and n = 2, 3

Figure 4: Proposed structure of [M (TMP)(bipy)SO_4].n$H_2$0

Antimicrobial studies

The antimicrobial activities of the ligands, Trimethoprim, 2,2′-bipyridine and their metal complexes are presented in Table 4. The ligand 2,2'-bipyridine showed better activity against all the tested bacteria with inhibitory zone range of 22.0 to 38.0 mm in comparison with trimethoprim and the standard drug gentamycin. The greater activity exhibited by 2,2′-bipyridine might be attributed to point mutation, which caused alteration of the DNA due to the transformation of the bases in a pair of nucleotides during DNA replication, leading to oxidative damages in DNA [84].

All the metal complexes showed greater activities against gram negative *Enteropathogenic E. coli* at all concentrations compared to Trimethoprim, 2,2′-bipyridine and the reference drug gentamycin. The better activities demonstrated by all the mixed ligand complexes against *Enteropathogenic E. coli* can be explained on the basis of the Overtone's concept [85] and Tweedy'schelation theory [86], where chelation caused reduction in the polarity of the metal ion due to the partial sharing of its positive charge with the donor groups which led to increase in the delocalization of the pi-electron resulting in increased lipophilicity and so favors

permeation into the bacterial membrane to cause the death of the organisms [87-88]. The observed trend for the activities demonstrated by the mixed metal complexes was Mn >Zn > Cu > Fe > Co ~ Ni thus making $[Mn(TMP)(bipy)Cl_2].2H_2O$ the most biologically active among them.

Generally, the synthesised complexes demonstrated better activities the than the standard drugs gentamycin as evidenced by their activities against *Morganella morganii* as indicated by zones of inhibition in the range 10 to 30 mm which the standard drug gentamycin has no activity. However, it was observed that the activities shown by the mixed metal complexes varies with the concentrations as the highest activities were observed at the highest concentration of 40mg/mL but as the concentration decreases the activities decreases as evidenced by the reduction in the zone of inhibitions.

In contrast, the ligands and their complexes did not exhibit antifungal activities against the tested fungus *Candida albicans* at all concentrations showing them to be potential antibacterial agents rather than as antifungal agents.

Table 4: Antimicrobial activity of ligands and its metal(II) complexes in mg/ml

Complexes	TMP		bipy				$[Co(TMP)(bipy)]Cl_2$			$[Cu(TMP)(bipy)Cl_2].2H_2O$			$[Fe(TMP)(bipy)SO_4].3H_2O$			$[Mn(TMP)(bipy)Cl_2].2H_2O$			$[Ni(TMP)(bipy)Cl_2]$			$[Zn(TMP)(bipy)SO_4].2H_2O$		(+) Gentamycin	
	40	20	10	40	20	10	40	20	10	40	20	10	40	20	10	40	20	10	40	20	10	40	20	10	10
	(mg/ml)		(mg/ml)				(mg/ml)			(mg/ml)			(mg/ml)			(mg/ml)			(mg/ml)			(mg/ml)		(μg/ml)	
Candida Albicans	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$	$R^{\neq}$
Enteropathogenic E. coli	32	28	20	30	28	24	38	36	30	34	32	30	40	34	32	30	26	24	36	34	14	36	34	30	24
Enterotoxigenic E.coli	22	18	16	30	28	24	18	16	14	20	17	14	20	14	13	26	25	20	20	15	12	25	18	15	30
Klebsiella pneumonia	28	26	22	34	32	28	15	10	R	20	18	16	25	20	14	30	30	20	18	16	R	16	14	12	16
Leclerciaadecar Boxylata	28	22	18	30	24	22	16	14	R	18	16	R	14	12	R	36	30	24	16	14	12	40	34	30	26
Morganella morganii	22	16	14	38	32	30	19	14	12	25	20	12	22	20	12	30	25	20	20	10	10	20	18	15	R
Salmonella typhi	20	18	16	36	30	26	20	18	12	20	16	12	24	20	18	26	24	20	18	16	14	20	18	14	16
Staphylococcus aureus	18	16	14	38	34	30	16	14	R	30	28	24	20	18	16	30	26	20	16	14	12	36	34	30	20

TMP = Trimethoprim, bipy = 2,2′ bipyridine, R = Resistance, $R^{\neq}$ = No growth, (+) = positive control

CONCLUSION

Mixed-ligands complexes of trimethoprim (TMP) and 2,2′-bipyridine (bipy) with Co(II), Cu(II), Fe(II), Mn(II), Ni(II) and Zn(II) were synthesised and characterised spectroscopically. From the infrared spectra data, TMP behaves as a bidentate ligand bonding to the metals via the N atom of the pyrimidine amino group and nitrogen atom of the azomethine moiety while the bipy coordinated through the diimine nitrogen atoms. The electronic spectra data showed that all the metal(II) complexes were monomeric and octahedral. From the antimicrobial studies, the complexes and their ligands did not show antifungal activity, however, the observed trend for the antibacterial activities demonstrated by the mixed metal complexes was Mn >Zn > Cu > Fe > Co ~ Ni thus making $[Mn(TMP)(bipy)Cl_2].2H_2O$ the most biologically active among them. It was also observed that antibacterial activities exhibited varied directly with concentration as the highest activities were observed at the highest concentration of 40mg/mL.

Acknowledgement

The authors thank Bond Chemical Plc Awe, Oyo State, Nigeria and Unique Pharmaceutical Lagos State, Nigeria for the gift of Trimethoprim. Mr. Sunday of Pharmaceutical Microbiology Department, University of Ibadan, Oyo State, Nigeria, is also appreciated for his technical assistance.

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