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SYNTHESIS, CHARACTERISATION AND ANTIMICROBIAL STUDIES OF MIXED LIGANDS METAL (II) COMPLEXES OF SULFAMETHOXAZOLE AND N,N- DONORS HETEROCYCLES

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ABSTRACT
Two mixed ligands of sulfamethoxazole (SMX) with N,N donor heterocycles: 1,10-phenanthroline (phen) and 2,2′-bipyridine (bipy) metal complexes having the composition [M(SMX)(phen)X].nH_2O and [M(SMX)(bipy)X].nH_2O (where M = Zn(II) , Co(II) , Fe (II), Mn (II),Cu(II) ; X = SO_4/Cl_2) have been synthesised and characterised by physicochemical methods based on their solubility , metal analysis, infrared and UV-Visible techniques. Infrared spectra data showed SMX as a bidentate ligand coordinating to the metals through the N atom of the sulfonamide group ((3195-3030cm^{-1}) and oxygen atom of the sulfonyl moiety (1158-1103 cm^{-1}) while the heterocycles also bonded as bidentate ligands through their diimine nitrogen atoms (1606-1423 cm^{-1}). The electronic spectra data indicated that all the metal (II) complexes were monomeric and octahedral. The *in-vitro* antimicrobial studies of these complexes and their ligands against environmental strains of microorganisms: *Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Aspergillus niger* and *Candida albicans* showed that SMX-phen metal complexes [M(SMX)(phen)X].nH_2O are better heterocycle with zone of inhibition in the range 28-10mm to combine with SMX for the enhancement of its antimicrobial spectrum this may be due to their more extensive aromatic ring system which gave better lipophilicity, hence aided cell membrane penetration and promoted hostile intracellular interactions leading to death of microoganisms.

Keywords: Sulfamethoxazole, 1,10-phenanthroline, mixed ligands, 2,2′-Bipyridine, antimicrobial, heterocycles

INTRODUCTION

Sulfamethoxazole (SMX) (Fig.1), a sulfonamide drug is a structural analoque of p-aminobenzoic acid that inhibits the synthesis of intermediary dihydrofolic acid from its precursors (Masters *et al*., 2003). It is a bacteriostatic antibiotic, used in synergistic combination therapy with Trimethoprim for the treatment of urinary tract infections, respiratory tract pathogens, skin pathogens, certain enteric pathogens (Silver, 2011); and as an substitute to amoxicillin-based antibiotics in treating sinusitis and prophylaxis of pneumonia in patients living with AIDS (Sayar *et al*., 2008). The clinical importance of sulfamethoxazole and trimethoprim-sulfamethoxazole combination has slowly declined in the most recent decades, largely as a result of the development and rapid spread of resistance to these agents among all major bacterial pathogens (Huovinen, 2001). Hence, the need to seek for an alternative combination for sulfamethoxazole which will also offer expanded spectrum of action against disease pathogens.

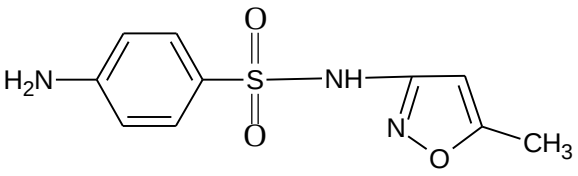
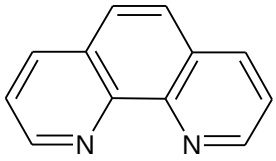


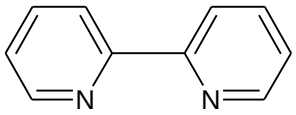
Figure 1: Structure of Sulfamethoxazole

Reported literatures have suggested that heterocycles and their derivatives have excellent broad spectrum of biological activities (Helio *et al*., 2006; Taghreed *et al*., 2015), so a search for a new drug from heterocycles is believed to support the chance of success (Tirkeso *et al*., 2019). Among the heterocycles, 1,10-Phenanthroline (phen) and 2,2′ bipyridine (bipy) have extended planar π systems and can be used in model compounds to copy the non covalent interactions in biological processes (Armani *et al*., 2007). Since its discovery at the end of nineteenth century (Shubert and Eschbaumer, 2002), the 2,2′-bipyridine (bipy) (Fig. 2) ligand has been used extensively as a metal chelating ligand due to its robust redox stability and ease of functionalization (Kaes *et al*., 2000) . 1,10-Phenanthrolines (phen) (Fig.2) is a classic nitrogen heterocycle present in sterols, sex hormones, cardiac glycosides, bile acids and morphine

alkaloids (Liscombe *et al*., 2005). It is chelating bidentate ligand for metal ions, which have played a vital role in the progress of coordination chemistry (Kitagawa *et al*., 2004; Kitagawa *et al*.,2006; Bencini and Lippolis, 2010), and still it continues to be of considerable interest as versatile starting material for organic, inorganic and supramolecular chemistry. 1,10-Phenanthrolines is a rigid planar, hydrophobic, electron-poor heteroaromatic system whose nitrogen atoms are beautifully placed to act cooperatively in cation binding. These structural features determine its coordination ability towards metal ions (Selvaganapathy and Raman, 2016). Due to its excellent ability to coordinate with many metal ions, 1,10-phenanthrolines and its derivatives are often used in many processes involving metal complexes, for example, as ligands for catalysis (Schoffers, 2003), stabilizing agents for nanoparticle synthesis(Toshima *et al*., 2001), electroluminescent materials (Yang *et al*., 2012; Starosta *et al*., 2012; Yan and Gu, 2013), organic light-emitting devices (OLED) (Zhang *et al*.,2011),organic semiconductors (Zhao *et al*., 2011), antimicrobial agents (McCann *et al*., 2012; Santos *et al*., 2012; Raman *et al*., 2014) or as chemical nucleases and therapeutic agents, owing to their ability to bind or interact with the DNA biomacromolecule (Villar-Garcia *et al*., 2012; Li *et al*., 2012; Kellett *et al*., 2012).



(a) 1,10-phenanthroline



(b) 2,2'-bipyridine

Figure 2: Structures of the N,N-donors heterocycles used

In this report we present two different mixed ligands of sulfamethoxazole of 1,10-phenanthroline and 2,2′-bipyridine , their metal (II) complexes and their antimicrobial studies with the aim of comparing the extent to which each of these heterocycles can influence the antibacterial spectrum of sulfamethoxazole free drug.

EXPERIMENTAL

Materials and Reagents. All reagents and solvents were of analytical grade and used without further purification. Sulfamethoxazole was a gift from Unique pharmaceutical, Ogun State and Bond Pharmaceutical Company Plc, Awe, Oyo State, Nigeria. Cobalt (II) sulphate heptahydrate, Manganese (II) sulphate tetrahydrate, Zinc (II) sulphate heptahydrate, Iron (II) sulphate heptahydrate, Copper (II) chloride dihydrate, 1,10-phenanthroline and 2,2′-bipyridine were obtained from Aldrich chemicals and used as supplied.

Physical measurements

The electronic spectra of the complexes in ethanol were recorded on a Perkin-Elmer Lambda 25 Spectrophotometer and infrared spectra were recorded using KBr discs on Perkin-Elmer BX II FT-IR spectrometer. Melting points were determined with Stuart SMP10 melting point apparatus and percentage metal was obtained by complexometric titration using EDTA.

Synthesis of Metal Complexes of [M(SMX)(phen)X].nH2O, where M = Cu(II), Co(II), Mn(II), Fe(II) and Zn(II); X = SO_4 or Cl_2

The complexes of mixed sulfamethoxazole and 1,10-phenanthroline ligands were synthesised using previously reported procedures (Alias and AbdulHassan, 2015). 0.2533g (1mmole) of sulfamethoxazole (SMX) in 5ml ethanol was added slowly to warm ethanolic solution of equimolar amount (1mmole) of the respective metal (II) salt. To the resulting mixture was added 0.1802g (1mmole) of 1,10-phenanthroline (phen) in 5ml ethanol. The resulting homogeneous solution was refluxed for 3 hours with stirring and then cooled. Precipitates obtained were filtered, washed with ethanol and dried over silica gel.

Synthesis of Metal Complexes of [M(SMX)(bipy)X].nH2O, where M = Cu(II), Co(II), Mn(II), Fe(II) and Zn(II); X = SO_4 or Cl

The complexes of mixed sulfamethoxazole and 2,2′-bipyridine ligands were synthesised using previously reported procedures (Alias and AbdulHassan, 2015). 0.2533g (1mmole) of sulfamethoxazole (SMX) in 5ml ethanol was added slowly to warm ethanolic solution of equimolar amount (1mmole) of the respective metal (II) salt. To the resulting mixture was added 0.1562g (1mmole) of 2,2′-bipyridine (bipy) in 5ml ethanol. This was followed by the similar work up as indicated above.

Antimicrobial studies

Antibacterial screening of the free ligands and the synthesized complexes were tested *in vitro* using Agar diffusion method (Chaudhary *et al*., 2003; Shahzadi *et al*., 2006). Prepared culture plates were inoculated with different environmental strains of gram positive, gram negative bacteria and fungi: *Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Aspergillus niger* and *Candida albicans*.

The bacteria were cultured using the pour-plate method. From the diluted organisms (10^{-2}) 0-2ml was injected into the prepared sterile nutrient agar which was at 45ºC, then aseptically poured into sterile petri dishes, which were allowed to solidify for about 45-60minutes. Wells were made on the agar surface (Nutrient agar) with 6mm sterile cork borer. The prepared different graded (50µg/ml and 10µg/ml) concentrations of the complexes and ligands were poured into the well using sterile syringes. The plates were incubated at 37 ºC ± 2 ºC 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) (*Aspergillus niger* and *Candida albicans*) were spread to cover the surface of the agar. Wells were also made using sterile cork borer of 6mm 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 2hours to allow pre diffusion and then incubated at 25 ± 2 ºC for 48hours. Ketoconazole was used as the reference drug.

RESULTS AND DISCUSSION

The mixed ligands of sulfamethoxazole with N, N-donor heterocycles; 1,10 phenanthroline and 2,2′-bipyridine with metal(II) salts of Mn, Co, Zn, Fe and Cu gave varying shades of coloured complexes in low to moderate yields (17-60 %) as given in the Table 1 below. The ligands, sulfamethoxazole, 1,10 phenanthroline and 2,2′-bipyridine melted at 168-172°C, 117-118°C and 70-73°C respectively, whereas their metal complexes all decomposed on melting at temperature above 300°C. They were insoluble in most solvents but were soluble in water, ethanol and DMSO. The analytical data are summarized in Table1 below

Table 1: Analytical data for sulfamethoxazole, 1,10-pheanthroline, 2,2-bipyridine and their complexes

Compound	Mol.Wt (g/mol)	Colour	% Yield	M.Pt (^{0}C)	%Metal Exp (Calc)
Sulfamethoxazole (SMX)	253.28	White	_	168-172	_
1,10-phenanthroline (phen)	180.21	White	_	117-118	_
2,2′-bipyridine (bipy)	156.18	White	_	70-73	_
$[Zn(SMX)(bipy)SO_4].3H_2O$	626.87	White	28	300*	10.30 (10.43)
$[Co(SMX)(bipy)SO_4].H_2O$	584.39	Pale pink	18	300*	10.01(10.08)
$[Fe(SMX)(bipy)SO_4].2H_2O$	599.31	Deep red	42	300*	9.26 (9.31)
$[Mn(SMX)(bipy)SO_4].2H_2O$	598.41	Gold cream	60	300*	9.24 (9.18)
$[Cu(SMX)(bipy)Cl_2]$	543.91	Light green	17	300*	11.45 (11.68)
$[Zn(SMX)(phen)SO_4].2H_2O$	632.90	White	35	300*	10.28(10.33)
$[Co(SMX)(phen)SO_4].2H_2O$	626.42	Pale pink	50	300*	9.22 (9.41)
$[Fe(SMX)(phen)SO_4].2H_2O$	623.34	Brick red	38	300*	8.73 (8.95)
$[Mn(SMX)(phen)SO_4].2H_2O$	604.42	Gold cream	42	300*	9.00 (9.08)
$[Cu(SMX)(phen)Cl_2].2H_2O$	603.94	Green	52	300*	10.44 (10.52)

D = diamagnetic, *= decomposition temperature, Exp = experimental, M. Pt = melting point.

Infra red spectra studies of synthesized complexes

The assignments of the peaks for the principal ligand sulfamethoxazole (SMX), co-ligands: 2,2′-bipyridine (bipy), 1-10-phenanthroline (phen) and their metal complexes are presented in Tables 2 and 3 respectively. The bonding of the ligands to metal ions was investigated by comparing the FTIR spectra of the complexes with those of the free ligands.

SMX is a positional ligand which may act as a bidentate or tridentate as illustrated by its structure, so its IR measurements are very signifying with respect to the complexation behaviour

with various metal ions. Infrared spectrum of the free SMX ligand shows two strong bands at 3467 and 3377 cm^{-1} equivalent to the asymmetric and symmetric stretching vibrations of the aromatic amino group (Janiak, 2000). These aromatic amino ($\nu(NH_2)$) band did not show any appreciable changes (± 5 cm^{-1}) in all the complexes which demonstrated its non participation in the coordination with the metal centers (Rostamizadeh *et al*., 2019). The medium and strong signals of SMX at 3299 and 3240 cm^{-1} are due to the presence of asymmetric and symmetric frequency vibration of the sulfonamide -NH group. The multiband and shifting of sulfonamide –NH in the spectra of the prepared complexes, indicated the involvement of this group in chelation with central metal ion by nitrogen of this group (Mondelli *et al*., 2013). The SMX peak at 1621 cm^{-1} is connected to the methoxazole ring (ν (C=N)**)** stretching vibration, which showed a very slight shift in the range of $\pm 4 cm^{-1}$ in the spectra of the metal complexes indicating the non- participation of this moiety in coordination with metal ions (Silverstein *et al*., 2005).

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

Compounds	ν(OH)/H2O	ν (NH2)(Ar amino)	ν (N-H) (sulfonamide)	ν (C=N) (methoxazole)	ν (S=O) (sulfonyl)	ν (C=C/C=N) (diimine grp)	ν(M-N)	ν(M-O)	ν(M-Cl)
Sulfamethoxazole (SMX)	_	3467(asy) 3377(sym)	3299(asy) 3240(sym)	1621	1307(asy) 1188(sym)	_	_	_	_
2,2′-bipyridine (bipy)	_	_	_	_	_	1580,1557, 1453, 1415	_	_	_
[Zn(SMX)(bipy)SO_4].3H_2O	3490(b)	3465(asy) 3373(sym)	3106(asy) 3062(sym)	1617	1317(asy) 1118(sym)	1599, 1573. 1492, 1443	619	411	_
[Co(SMX)(bipy)SO_4].H_2O	3356 (b)	3469(asy) 3377(sym)	3152(asy) 3077(sym)	1615	1315(asy) 1113(sym)	1599, 1574, 1478, 1447	570	415	_
[Fe(SMX)(bipy)SO_4].2H_2O	3376 (b)	3466(asy) 3381(sym)	3170(asy) 3090(sym)	1620	1314(asy) 1104(sym)	1597, 1561, 1476, 1445	612	484	_
[Mn(SMX)(bipy)SO_4].2H_2O	3490 (b)	3467(asy) 3380(sym)	3095(asy) 3057(sym)	1625	1313(asy) 1118(sym)	1592, 1572, 1504, 1435	546	413	_
[Cu(SMX)(bipy)Cl_2]	_	3470(asy) 3383(sym)	3108(asy) 3090(sym)	1619	1318(asy) 1158(sym)	1596, 1567, 1522, 1444	546	418	392

b = broad, asy= asymmetric, sym= symmetric, Ar. Amino = aromatic amino

Table 3: Relevant IR data of sulfamethoxazole, 1,10-phenanthroline and their complexes in cm^{-1}

Compounds	**ν (OH)/H2O**	**ν (NH2)(Ar amino)**	**ν (N-H) (sulfonamide)**	**ν (C=N) (methoxazole)**	**ν (S=O) (sulfonyl)**	**ν (C=C/C=N) (diimine grp)**	**ν(M-N)**	**ν(M-O)**	**ν(M-Cl)**
Sulfamethoxazole (SMX)	_	3468(asy)(s) 3377(sym)(s)	3299(asy) 3240(sym)	1621	1307(asy) 1188(sym)	_	_	_	_
1,10-phenanthroline (phen)	_	_	_	_	_	1561,1503, 1492, 1422	_	_	_
[Zn(SMX)(phen)SO_4].2H_2O	3420(b)	3461(asy) 3383(sym)	3081(asy) 3049(sym)	1621	1308(asy) 1103(sym)	1602,1521, 1462,1438	506	426	_
[Co(SMX)(phen)SO_4].2H_2O	3500 (b)	3463(asy) 3376(sym)	3195(asy) 3060(sym)	1621	1306(asy) 1146(sym	1581, 1516, 1495,1425	504	411	_
[Fe(SMX)(phen)SO_4].2H_2O	3352 (b)	3466(asy) 3380(sym)	3100(asy) 3070(sym)	1624	1305(asy) 1111(sym	1576, 1517 1496, 1428	603	424	_
[Mn(SMX)(phen)SO_4].2H_2O	3465 (b)	3464(asy) 3381(sym)	3110(asy) 3030(sym)	1623	1306(asy) 1147(sym)	1591, 1577, 1517, 1450	553	474	_
[Cu(SMX)(phen)Cl_2].2H_2O	3490 (b)	3470(asy) 3374(sym)	3080(asy) 3044(sym)	1625	1309(asy) 1146(sym)	1606, 1514, 1495, 1423	508	428	364

b = broad, asy= asymmetric, sym= symmetric, Ar. Amino = aromatic amino

The asymmetric and symmetric stretching frequencies of the sulfonyl group (O=S=O) in SMX were observed at 1307 and 1188 cm^{-1} respectively. The asymmetric sulfone band at 1307cm^{-1} slightly shifted in the complexes which was indicative of non-coordination of one of the sulphone oxygen atoms, whereas the second sulphone band at 1188 cm^{-1} shifted to 1158 - 1104 cm^{-1} in [M(SMX)(bipy)X].nH_2O and 1147-1103cm^{-1} in [M(SMX)(bipy)X].nH2O metal complexes confirming coordination to the metal atom through the second sulfone oxygen atom
(Bamigboye *et al*., 2012). Based on these, the coordination mode of SMX with metal ions is predicted as a bidentate through the N atom of sulfonamide group and oxygen atom of the sulfonyl moiety for all the complexes.

The binding of the co-ligands phen and bipy was shown by the shift of the diimine ((C=C), (C=N)) ring stretching vibration to higher frequencies in the spectra of all the complexes and confirming the coordination nature of co-ligands (Soliman and Mohamed, 2004; Anupama and Kumari, 2013; Abu-Hussen, 2006; Mukherjee, 2000). Also, new bands appeared in the range (484-411) cm^{-1} and (619- 504) cm^{-1} due to the stretching frequencies of (M-O) and (M-N) bonds respectively. Another new bands at 364 and 392 cm^{-1} assigned to M–Cl stretching vibrations appeared in the spectrum of [Cu(SMX)(phen)Cl_2].2H_2O and [Cu(SMX)(bipy)Cl_2] complexes respectively. In all the complexes except [Cu(SMX)(bipy)Cl_2] the presence of lattice/coordinated water molecules were indicated by the appearance of broad bands in the region 3352–3500 cm^{-1}(Rîmbu *et al*., 2014).

Electronic Spectra of the synthesised complexes

The electronic spectral absorptions of the ligands and complexes are presented in Table 4. The electronic spectrum of sulfamethoxazole (SMX) exhibited two absorption bands in the ultraviolet region, the band at 47169 cm^{-1} (212nm) assigned to the $\pi \rightarrow \pi^*$ transition for the intra ligand aromatic system (C=C) and the signal at 37037 cm^{-1} (270nm) to $n \rightarrow \pi^*$ transition for oxygen atom of S=O group or nitrogen atom of amine moiety and imine –N=C– group, respectively (Zahid *et al*., 2009). In the electronic spectra of the heterocycles co-ligands: phen and bipy,the bands at 44247cm^{-1}(226nm) and 43103cm^{-1}(232nm) were assigned to $\pi \rightarrow \pi^*$ transition due to C=C group while the signals at 37735cm-^{1}(265nm), 35842cm^{-1}(279nm) and 34482cm^{-1}(290nm) were attributed to $n \rightarrow \pi^*$ transition due to the nitrogen atom of the –N=C– group (Wojciechowska *et al*., 2001; Scarborough and Wieghardt, 2011; Imam *et al*., 2011). In the metal complexes, these bands shifted to lower wave number due to coordination as presented in Table 4.

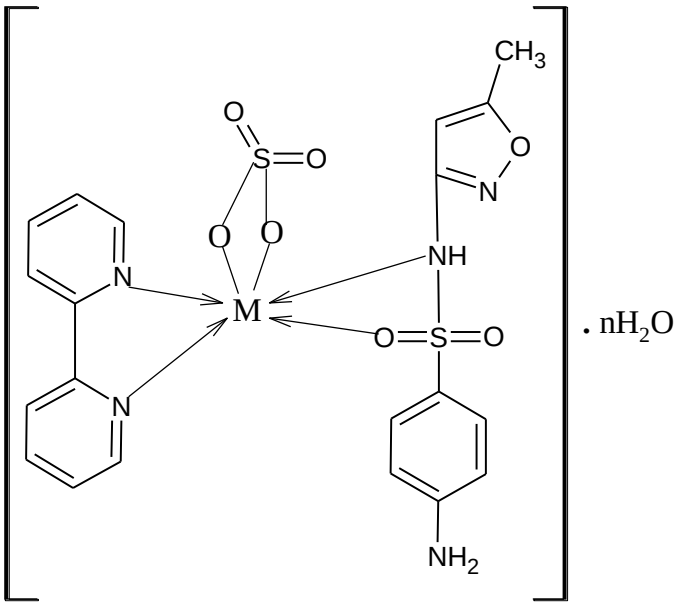
The two zinc complexes Zn(SMX)(bipy)SO_4].3H_2O and [Zn(SMX)(phen)SO_4].2H_2O showed only the charge transfer transitions from metal to ligand, as no d-d transition was expected due to their d^{10} configurations. These complexes assumed a 6-coordinate octahedral geometry (Raman *et al*., 2001; Onah *et al*., 2011). In the visible region, three bands were exhibited by [Co(SMX)(bipy)SO_4].H_2O at 16474cm^{-1}(607nm), 19762cm^{-1}(506) and 23752cm^{-1}(421nm) and [Co(SMX)(phen)SO_4].2H_2O complex at 19762cm^{-1}(506nm), 20920cm^{-1}(478nm) and 23640cm^{-1}(423nm), these signals were assigned to, $^4T_{1g(F)} \rightarrow {}^4T_{2g(F)}$, $^4T_{1g(F)} \rightarrow {}^4A_{2g(F)}$ and $^4T_{1g(F)} \rightarrow {}^4T_{1g(P)}$ transitions predicting octahedral geometry (Sarhan *et al.,* 2011; Osowole *et al*., 2015).

A single absorption band at 16474cm-1(607nm) and 15576cm-1(642nm) typical of 6-coordinate, high spin octahedral geometry and assigned to $^5T_{2g} \rightarrow {}^5E_g$ were exhibited by [Fe(SMX)(bipy)SO_4].2H_2O and [Fe(SMX)(phen)SO_4].2H_2O complexes respectively (Osowole *et al*., 2015). The electronic spectral of [Cu(SMZ)(bipy)]Cl_2] and [Cu(SMZ)(phen)Cl_2]. 2H_2O showed single broad band at 14771 cm^{-1} (677nm) and 14306 cm^{-1}(699nm) respectively assigned to $^2Eg \rightarrow {}^2T_{2g}$ transition was an indication of octahedral geometry as reported in literature (Sudhamani *et al*., 2009; Agwara *et al*., 2010; Scotti *et al*., 2015). The electronic absorption spectra of manganese-complex [Mn(SMX)(bipy)SO_4].2H_2O presents three major absorptions maxima at 24330, 15384, 13175cm^{-1} and [Mn(SMX)(phen)SO_4].2H_2O at 23419, 20703, 15313cm^{-1} which were assigned to $^6A_{1g} \rightarrow {}^4A_{1g}$, $^6A_{1g} \rightarrow {}^4T_{2g}$ and $^6A_{1g} \rightarrow {}^4T_{1g}$transitions typical of octahedral geometry(Singh and Chaudhary 2004; Sreekanth, *et al*., 2006),

Table 4: Electronic spectra data of sulfamethoxazole, 1,10-phenanthroline, 2,2′ -bipyridine and their metal complexes

compounds	UV bands (cm^{-1})	Probable transitions
Sulfamethoxazole (SMX)	47169	$\pi \rightarrow \pi^*$
	37037	$n \rightarrow \pi^*$
1,10-phenanthroline (phen)	44247	$\pi \rightarrow \pi^*$
	37735	$n \rightarrow \pi^*$
	34482	$n \rightarrow \pi^*$
2,2′-bipyridine (bipy)	43103	$\pi \rightarrow \pi^*$
	35842	$n \rightarrow \pi^*$
$[Zn(SMX)(bipy)SO_4].3H_2O$	42100	CT
	40983	$\pi \rightarrow \pi^*$
	34129	$n \rightarrow \pi^*$
$[Co(SMX)(bipy)SO_4].H_2O$	40983	CT
	33783	$\pi \rightarrow \pi^*$
	23752	$^4T_{1g(F)} \rightarrow {}^4T_{1g(P)}$
	19762	$^4T_{1g(F)} \rightarrow {}^4A_{2g(F)}$
	16474	$^4T_{1g(F)} \rightarrow {}^4T_{2g(F)}$
$[Fe(SMX)(bipy)SO_4].2H_2O$	40650	CT
	33783	$\pi \rightarrow \pi^*$
	29761	$n \rightarrow \pi^*$
	16474	$^5T_{2g} \rightarrow {}^5E_g$
$[Mn(SMX)(bipy)SO_4].2H_2O$	36630	$\pi \rightarrow \pi^*$
	29411	$n \rightarrow \pi^*$
	24330	$^6A_{1g} \rightarrow {}^4A_{1g}$
	15384	$^6A_{1g} \rightarrow {}^4T_{2g}$
	13175	$^6A_{1g} \rightarrow {}^4T_{1g}$
$[Cu(SMX)(bipy)Cl_2]$	40322	CT
	34346	$\pi \rightarrow \pi^*$
	29411	$n \rightarrow \pi^*$
	14771	$^2E_g \rightarrow {}^2T_{2g}$
$[Zn(SMX)(phen)SO_4].2H_2O$	43100	CT
	39370	$\pi \rightarrow \pi^*$
$[Co(SMX)(phen)SO_4].2H_2O$	42735	CT
	39062	$\pi \rightarrow \pi^*$
	23640	$^4T_{1g(F)} \rightarrow {}^4T_{1g(P)}$
	20920	$^4T_{1g(F)} \rightarrow {}^4A_{2g(F)}$
	19762	$^4T_{1g(F)} \rightarrow {}^4T_{2g(F)}$
$[Fe(SMX)(phen)SO_4].2H_2O$	40816	CT
	34129	$\pi \rightarrow \pi^*$
	30864	$n \rightarrow \pi^*$
	15576	$^5T_{2g} \rightarrow {}^5E_g$
$[Mn(SMX)(phen)SO_4].2H_2O$	34129	$\pi \rightarrow \pi^*$
	27624	$n \rightarrow \pi^*$
	23419	$^6A_{1g} \rightarrow {}^4A_{1g}$
	20703	$^6A_{1g} \rightarrow {}^4T_{2g}$
	15313	$^6A_{1g} \rightarrow {}^4T_{1g}$
$[Cu(SMX)(phen)Cl_2].2H_2O$	42194	CT
	39525	$\pi \rightarrow \pi^*$
	28901	$n \rightarrow \pi^*$
	14306	$^2E_g \rightarrow {}^2T_{2g}$

CT = charge transfer



where M = Zn, Co, Fe, Mn and n = 1,2 3

Figure 3: Proposed structure of [M(SMX)(bipy)SO_4].nH2O

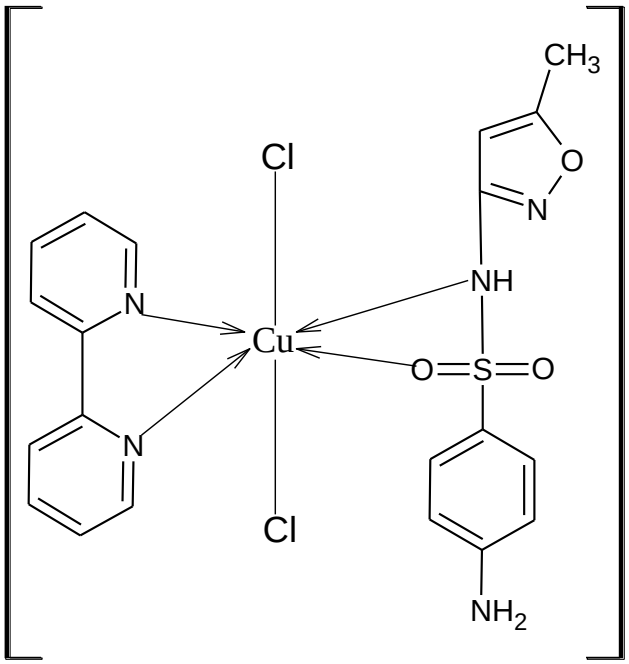
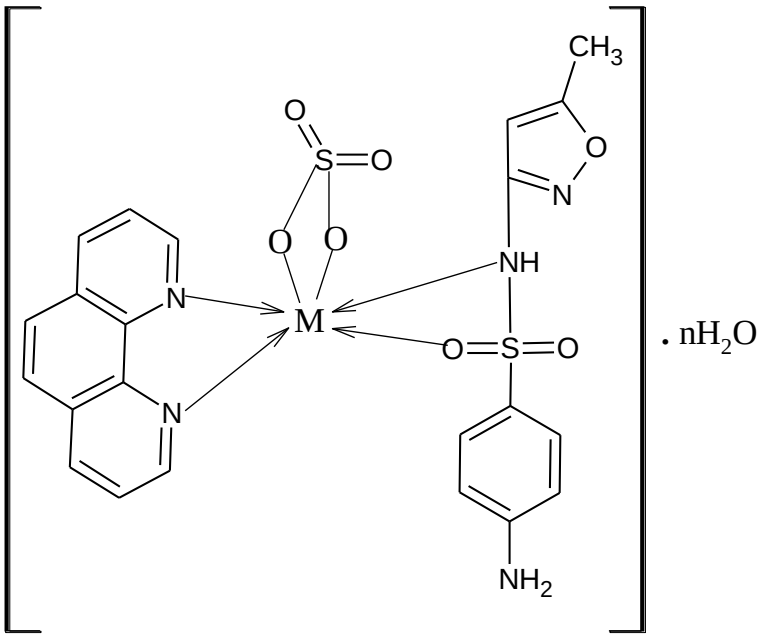


Figure 4: Proposed structure of [Cu(SMX)(bipy)Cl_2]



where M = Zn, Co, Fe, Mn and n = 2

Figure 5: Proposed structure of [M(SMX)(phen)SO_4].nH2O

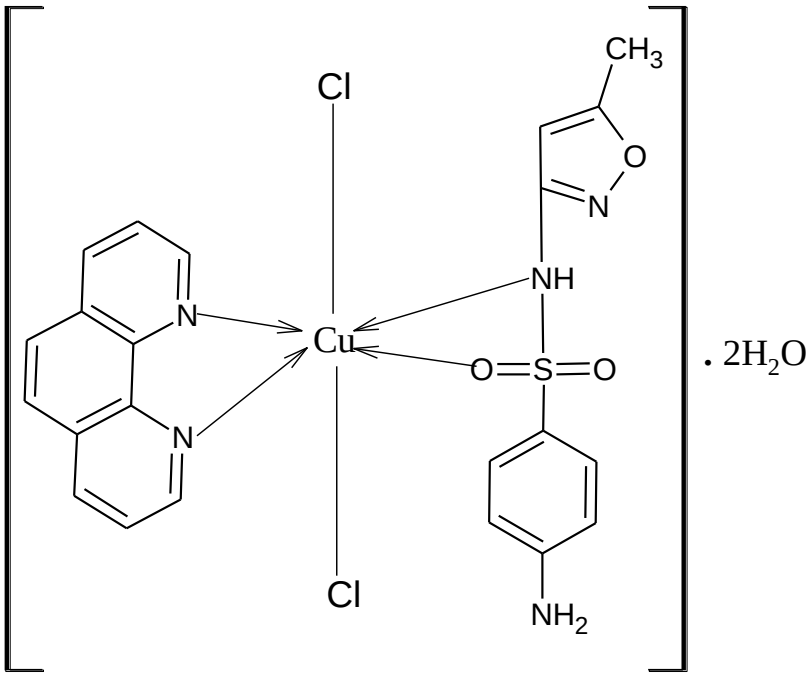


Figure 6: Proposed structure of [Cu(SMX)(phen)Cl_2].nH2O

Antimicrobial studies

The antimicrobial activities of the ligands Sulfamethoxazole (SMX), 1,10-phenanthroline (phen), 2,2′-bipyridine (bipy) and their metal complexes are presented in Table 5. The ligand phen exhibited the highest antimicrobial activities with zones of inhibition ranging from 24 mm to 30mm at 50µg/ml and 12-18mm at 10µg/ml. This was followed by SMX and lastly by bipy which exhibited selective antimicrobial activities against *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli and Aspergillus niger at* 50µg/ml with zones of inhibition

between 12-18mm, however, it showed no activity against all the tested microorganisms at 10µg/ml. The better antimicrobial activities exhibited by phen compare to bipy in this work might be attributed to the more extensive aromatic ring system of the phen molecule, which might confer on it greater lipophilicity and facilitate it to penetrate the cell membrane and promote adverse intracellular interactions (McCann *et al*., 2012) as well as the ability of phen to sequester essential trace metals (transition metals) from biological environments which has also been demonstrated to seriously impede the survival of microbial pathogens (Sevlever *et al*., 2001).

Generally, all the mixed ligand metal complexes were active against all tested microorganisms at 10µg/ml except $[Fe(SMX)(bipy)(SO_4)].2H_2O$ and $[Mn(SMX)(bipy)(SO_4)].2H_2O$ exhibiting inactivities against *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli and Aspergillus nigerat that concentrations.* It was observed that the SMX-bipy metal complexes showed better activities than free bipy ligands but lower than the free SMX ligand. The observed trend for the SMX-bipy metal complexes was Cu >Zn > Co > Fe > Mn making $[Cu(SMX)(bipy)Cl_2]$ the most biologically active among them.

On the other hand, SMX-phen metal complexes show greater antimicrobial activities at both 50µg/ml and 10µg/ml than their SMX-bipy metal complexes counterparts. This observation was attributed to the more extensive aromatic ring system of the phen molecule included in their composition as earlier stated which gave the complexes better lipophilicity and aid their cell membrane penetration and promote adverse intracellular interactions (McCann *et al*., 2012). Among the SMX-phen metal complexes, $[Mn(SMX)(phen)(SO_4)].2H_2O$ demonstrated the highest activity overall. Thus it can be inferred that phen N, N donor heterocycle was better combination for SMX for enhancement of its antimicrobial spectrum.

Generally, the better activities demonstrated by all the mixed ligand complexes can be explained on the basis of the Overtone's concept (Joseyphus and Nair, 2008**)** and Tweedy's chelation theory (Raman, *et al*., 2009). Chelation reduces the polarity of the metal ion considerably because of the partial sharing of its positive charge with the donor groups and also due to p-electron delocalization on the whole chelating ring increased lipophilicity enhances the penetration of the complexes into lipid membrane and blocking of 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 proteins which restricts further growth of the organisms.

Table 5: Antimicrobial activities of Sulfamethoxazole, 1,10-phenanthroline, 2,2′-bipyridine ligands and their metal (II) complexes in mm

Compound/Conc	B.S	S.A	P.A	E.C	A.N	C.A
SMX						
50µg/ml	20±0.11	17±0.32	20±0.22	27±0.00	22±0.00	23±0.88
10µg/ml	15±0.67	12±0.21	15±0.21	17±0.33	11±0.33	10±0.00
+C	28±0.00	28±0.00	18±0.00	20±0.00	26±0.00	26±0.00
-C	-	-	-	-	-	-
Phen						
50µg/ml	30±0.27	28±0.14	29±0.11	26±0.14	24±0.10	25±0.04
10µg/ml	18±0.42	17±0.32	14±0.33	16±0.23	12±1.54	13±0.88
+C	28±0.00	28±0.00	18±0.00	20±0.00	26±0.00	26±0.00
-C	-	-	-	-	-	-
Bipy						
50µg/ml	-	11±1.13	10±0.33	15±1.15	10±1.23	-
10µg/ml	-	-	-	-	-	-
+C	28±0.00	28±0.00	18±0.00	20±0.00	26±0.00	26±0.00
-C	-	-	-	-	-	-
$[Zn(SMX)(bipy)SO_4].3H_2O$						
50µg/ml	20±0.33	12±0.55	17±0.31	19±0.67	20±0.37	18±0.32
10µg/ml	10±0.24	6±1.13	-	-	12±1.23	-
+C	28±0.00	28±0.00	18±0.00	20±0.00	26±0.00	26±0.00
-C	-	-	-	-	-	-

[Co(SMX)(bipy)(SO_4)].H_2O						
50µg/ml	18±1.18	15±1.19	15±1.54	20±1.13	22±0.67	23±0.33
10µg/ml	-	-	-	-	11±0.37	-
+C	28±0.00	28±0.00	18±0.00	20±0.00	26±0.00	26±0.00
-C	-	-	-	-	-	-
[Fe(SMX)(bipy)(SO_4)].2H_2O						
50µg/ml	18±0.57	20±0.26	-	20±0.27	21±0.54	20±0.20
10µg/ml	-	-	-	-	-	-
+C	28±0.00	28±0.00	18±0.00	20±0.00	26±0.00	26±0.00
-C	-	-	-	-	-	-
[Mn(SMX)(bipy)(SO_4)].2H_2O						
50µg/ml	16±0.54	-	-	12±0.45	-	-
10µg/ml	-	-	-	-	-	-
+C	28±0.00	28±0.00	18±0.00	20±0.00	26±0.00	26±0.00
-C	-	-	-	-	-	-
[Cu(SMX)(bipy)Cl_2]						
50µg/ml	20±0.22	16±0.13	22±0.23	19±0.17	24±0.57	22±0.37
10µg/ml	18±1.28	-	16±1.44	13±0.13	10±0.26	20±1.10
+C	28±0.00	28±0.00	18±0.00	20±0.00	26±0.00	26±0.00
-C	-	-	-	-	-	-
[Zn(SMX)(phen)SO_4].2H_2O						
50µg/ml	25±0.33	22±0.78	24±1.13	26±0.67	20±1.13	22±0.67
10µg/ml	16±0.54	16±0.56	18±1.11	12±0.45	10±0.21	12±0.45
+C	28±0.00	28±0.00	18±0.00	20±0.00	26±0.00	26±0.00
-C	-	-	-	-	-	-
[Co(SMX)(phen)(SO_4)].2H_2O						
50µg/ml	23±0.20	24±0.23	23±0.33	22±0.71	24±0.27	21±0.21
10µg/ml	14±0.32	14±0.03	12±0.13	16±0.51	-	-
+C	28±0.00	28±0.00	18±0.00	20±0.00	26±0.00	26±0.00
-C	-	-	-	-	-	-
[Fe(SMX)(phen)(SO_4)].2H_2O						
50µg/ml	23±0.33	21±0.55	24±0.27	25±0.77	26±0.27	22±0.27
10µg/ml	16±0.45	110±0.25	-	12±0.65	10±0.34	-
+C	28±0.00	28±0.00	18±0.00	20±0.00	26±0.00	26±0.00
-C	-	-	-	-	-	-
[Mn(SMX)(phen)(SO_4)].2H_2O						
50µg/ml	28±0.37	28±2.07	28±1.17	26±0.29	22±0.65	21±0.27
10µg/ml	18±0.12	13±0.16	16±0.21	14±0.22	10±0.46	10±0.20
+C	28±0.00	28±0.00	18±0.00	20±0.00	26±0.00	26±0.00
-C	-	-	-	-	-	-
[Cu(SMX)(phen)Cl_2].2H_2O						
50µg/ml	23±0.30	21±0.13	22±0.23	23±0.61	26±0.27	20±0.70

10µg/ml	10±0.18	12±0.26	11±0.75	15±0.12	14±0.20	13±0.10
+C	28±0.00	28±0.00	18±0.00	20±0.00	26±0.00	26±0.00
-C	-	-	-	-	-	-

Data are mean of three replicates (n = 3) ± standard error; *-C= DMSO, +C(for bacteria) = Gentamycin,* +C for fungi = Ketoconazole, *B.S = Bacillus subtilis, S.A = Staphylococcus aureus, P.A = Pseudomonas aeruginosa E.C = Escherichia coli,* A.N = *Aspergillus niger, C.A = Candida albicans*

CONCLUSION

Mixed ligands of sulfamethoxazole (SMX) with N,N donor heterocycles: 1,10-phenanthroline (phen) and 2,2-bipyridine (bipy) metal complexes having the composition [M(SMX)(phen)X].nH2O and [M(SMX)(bipy)X].nH_2O (where M = Zn(II) , Co(II) , Fe (II), Mn (II),Cu(II) ; X = SO_4/Cl_2) have been synthesised and characterised by physicochemical methods based on their solubility , metal analysis, infrared and UV-Visible techniques. From the infrared spectra data, SMX behaves as a bidentate ligand bonding to the metals via the N atom of the sulfonamide group and oxygen atom of the sulfonyl moiety while the heterocycles (phen and bipy) coordinated through their diimine nitrogen atoms. The electronic spectra data showed that all the metal(II) complexes were monomeric and octahedral. The antimicrobial studies showed
that [M(SMX)(phen)X].nH_2O exhibited greater antimicrobial activities at both 50µg/ml and 10µg/ml than their SMX-bipy metal complexes counterparts this might be due to the more extensive aromatic ring system of the phen molecule included in their composition which gave the complexes better lipophilicity and aided their cell membrane penetration and promoted adverse intracellular interactions.

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