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Investigation of antimicrobial potencies of mixed-ligand complexes of divalent metal ions with Barbituric acid and 2,2-Bipyridine

Oluwabiyi J. Olaoye[1], Mary A. Oladipo[1], Kayode T. Ishola[2], Omobola A. Odedokun[2], Olayinka G. Ogunlade[1]

[1]*Pure & Applied Chemistry Department, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria.*

[2] *Chemistry Department, Federal College of Education (Special), Oyo, Oyo State, Nigeria.*

Corresponding author: *Isholatk@gmail.com*

ABSTRACT

The development of resistance by many pathogenic microorganisms towards many conventional antibiotic drugs has now become one of the major worldwide health challenges, which requires a search for more effective drugs to combat the growing threat of widespread antibiotic resistance. Therefore, in an attempt to search for new and effective antibiotic drugs, antimicrobial potencies of mixed ligand complexes of Cu (II), Co (II), Ni (II) involving barbituric acid and 2,2-bipyridine chelating agents were examined. The mixed-ligand complexes were synthesized and the formation of the complexes was established using elemental analysis, metal analysis, melting points, solubility test, infra-red and Uv-visible analysis. The complexes were investigated for their pharmaceutical exploits against bacteria (*Bacillus substilis and Staphylococcus aureus, Pseudomonas aeruginosa and Clostridium spp.*) and four fungi (*Aspergillus flavus, Aspergillus niger, Saccharomyces cerevisiae* and *Candida albican*). Three conventional antibiotic drugs were employed as reference drugs. The formation of the metal complexes in ratio 1:1:1 and molecular formulas were confirmed via elemental and metal analyses. The purity of the metal complexes was ascertained by the sharp melting points. Infrared spectroscopic analysis revealed the formation of coordination bonds between the ligands and the metal ions through nitrogen and oxygen donors. The formation of the metal complexes was substantiated by UV-visible electronic transitions. The diversity of antimicrobial activities was displayed by the metal complexes against the pathogenic organisms at inhibitory zones of 6 mm – 25 mm. The metal complexes produced more significant antimicrobial activity than the standard drugs and succeeded where the standard drugs failed. The complexes could be considered potential antimicrobial agents to replace the less effective conventional antibiotic drugs. The toxicity of the metal complexes should be evaluated to establish their suitability for replacement.

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INTRODUCTION

Many pathogenic microorganisms such as bacteria strains (*Staphylococcus aureus, Bacillus substilis, Clostridium spp and Pseudomonas aeruginosa)* and fungi strains (*Saccharomyces cerevisiae, Candida albican, Aspergillus flavus* and *Aspergillus niger)* have been observed to develop resistance to many available synthetic antibiotics such as ciprofloxacin, colistin, methicillin, sulphonamides, penicillins, tetracyclines, macrolides and fluoroquinolones (Rendrup & Patterson, 2017; Rhodes 2019; Vivas et al., 2019; Xinfu et al., 2021; Fisher, 2022). The problem of global drug resistance has characterized one of the major tasks for public health because the resistance to the available drugs has led to the proliferation of infections thereby increasing illness and mortality (*Yang et al.,* 2021*)*.

Currently, the multi-drug resistance developed by fungi and bacteria has become rampant and consequently many antimicrobial drugs have been rendered ineffective leading to progressive challenges in the treatment of infections (Li & Webster, 2018; World Health Organization, 2021). The ineffectiveness of antibiotics has been attributed to the low bioavailability of the drugs and inadequacy in their access to spots of infection (Canaparo et al., 2019). Therefore, to overcome the resistance posed by pathogenic microorganisms, there is a necessity for the development of antifungal and antibacterial drugs which are characterized by high bioavailability and access to spots of infection and are capable of functioning in alternative ways to the available conventional antibiotics (Francesca, 2011).

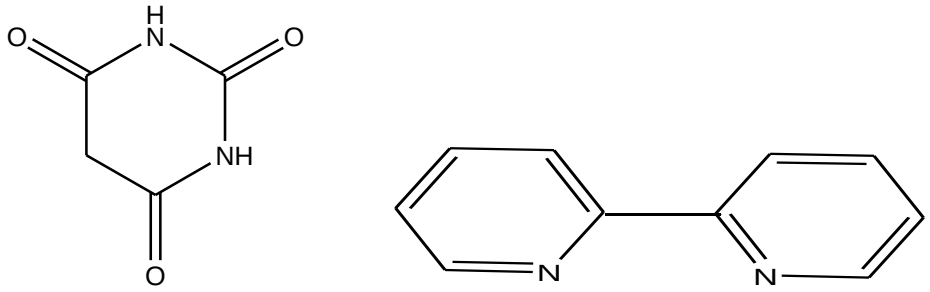
Complexes of transition metals with different biomolecular chelating agents have been considered as a potential replacement and evaluation of their antimicrobial properties has increased over the years. Transition metal complexes are known to display a great diversity of antimicrobial actions and the innovation in the discipline of inorganic chemistry has led to the discovery of diverse metal complexes as therapeutic agents (Hariprasath *et al.,* 2010). Transition metals are known to possess distinctive properties which have been considered in the development of new compounds having anti-diabetic, anti-cancer, anti-inflammatory, antifungal and antibacterial properties (Bruijnincx *et al.,* 2008). Different complexes of metal (II) of chelating agents containing donor atoms of nitrogen and oxygen have been reported to exhibit significant antimicrobial activities (Sigel *et al.,* 2006; Czakis-Sulikowska *et al.,* 2007; Warra, 2011).

Barbituric acids (Figure 1) is an organic chelating agent capable of exhibiting biological activities such as hypnotics, antihypertensives, anaesthetics, sedatives, anticonvulsants, antioxidants, anticancer, antifungal, antibacterial, and alpha-glycosidase enzyme inhibition (Francesca, 2011; Mathew et al., 2013; Humberto et al., 2016). 2,2′-bipyridine (Figure 2) is a chelating agent having nitrogen donors capable of forming chelates with different transition metals. The chelating agents with other biomolecular ligands have been extensively used in medicinal inorganic chemistry mainly in synthesizing different metal complexes. The metal complexes have been widely applied as cytotoxicity, antitumor, antifungal, antineoplastic, and bactericidal and genotoxicity agents (Selvaganapathy & Raman, 2016; Hayder & Nesser, 2018).

The development and widespread of drug-resistant pathogens continue to threaten every nation's ability to remedy common diseases and prevent mortality. Therefore, new antibiotics are exigently required to fight drug-resistant pathogens. Consequently, many chelating agents have been considered in the past as potential antibiotics. Biological applications of these ligands are known to associate with their ability to chelate metal ions in biological systems (McCann et al., 2012). Festus et al. (2019) synthesized and characterized transition metal ions complexes of 2-(4,6-dimethylpyrimidin-2-ylamino) naphthalene-1,4-dione (HL) and 2,2′-bipyridine. Biological properties of the metal complexes were evaluated on *P. aeruginosa, E. coli, B. cereus, S. aureus, P. mirabilis, A. niger, A. flevus, K. oxytoca* and *R. Stolonifer* strains. The mixed ligand complexes demonstrated moderate activity against the pathogenic strains. Kani et al. (2016) synthesized, characterized some Mn (II) complexes of 2,2'-bipyridine and investigated their biological against certain bacteria and fungi which include *S. aureus, K. pneumonie, P. aeroginosa, E. coli, Proteus vulgaris, E. feacalis, L. Monocytogenes* and C*andida tropicalis,* C*andida zeylanoides,* C*andida krusei, Candida parapsilosis,* C*andida globrata,* C*andida albicans,* respectively. The complexes were found to be more active against the tested bacteria than the employed reference drug.

Synthesis and characterization of Pt(II) and Pd(II) complexes of sodium barbitone ligand was carried out by Hassan et al. (2020). Antimicrobial efficacy of the metal complexes was determined on two bacterial strains (*Escherichia coli* and *Staphylococcus aureus*) and two fungal strains (*Candida albicans and Aspergillus flavus)*. Their antimicrobial efficacy was compared with that of amphotericin and ampicillin drugs. The metal complexes displayed better antimicrobial activity on the organisms than the parent ligand and the standard drugs. Mamdouh et al. (2020) prepared and elucidated the structures of Co (II), Cu (II) and Ni (II) complexes of thiobarbituric acid and barbituric. The ligands and the metal complexes were tested for their antimicrobial activities on bacterial strains (*Streptococcus Pyogenes, Staphylococcus Aureus, Micrococcus Luteus, Proteus Mirabilis, Pseudomonas aeruginosa, and Nisseria Saprophytica)* and fungal strain (*Helminthosporiumorezae*). The metal complexes showed different degrees of activity on the organisms while the parent ligands were reported to show excellent antifungal activity.

Many researchers have also investigated the antimicrobial activities of several metal complexes including binary metal complexes of barbituric acid and 2,2′-bipyridine and their mixed ligand with other ligands (Yilmaza et al., 2008; Ikotun et al., 2011; Ismail et al., 2014; Osowole et al., 2014; Palmucci et al., 2016; Akinyele et al., 2020; Andrejevi et al., 2022). The researchers failed to test the complexes for their antimicrobial activity on the organisms at different concentrations and the antimicrobial consequence of the complexes on the organisms is discovered to be limited. However, no researcher has ever investigated the antimicrobial activities of mixed ligand complexes of barbituric acid and 2, 2-bipyridine with different metal ions at different concentrations. Therefore, an attempt has been made in this study for the first time to synthesize three mixed ligand complexes containing transition metal ion, barbituric acid, 2,2-bipyridine and investigate their antimicrobial activities at different concentrations.



Barbituric acid 2, 2-bipyridine

Fig. 1. Structures of the ligands.

OBJECTIVES OF THE STUDY

This study is aimed at synthesizing three new mixed ligand complexes of metal (II) ions involving barbituric acid and 2,2-bipyridine, and investigating their antimicrobial activities at different concentrations to establish their antimicrobial potencies which could be useful in determining their effectiveness as potential antimicrobial drugs.

MATERIALS

The chemicals and reagents were obtained from J.T Baker and they were used without further purification. They include copper (II) sulphate pentahydrate, Cobalt(II) acetate, Nickel (II) sulphate hexahydrate, concentrated nitric acid, perchloric acid, solochrome black T, disodium- ethylenediamine tetraacetic acid, concentrated ammonia, ammonium chloride, sodium hydroxide, methanol, distilled water, murexide dye, dimethyl suphoxide, ethanol, dichloromethane, chloroform, propan – 2 – ol ,acetone, diethyl ether, ethylacetate, n – hexane, butan – 1 – ol, petroleum ether, sodium chloride, 2,2-bipyridine, Barbituric acid. The standard drus used include gentamicin (Gen), ampiclox (Amp) and cotrimoxazole (Cot).

Four bacterial pathogens (*Bacillus substilis, Pseudomonas aeruginosa, Clostridium spp. and Staphytococcus aureus* and four fungi (*Aspergillus flavus*, *Saccharomyces cerevisiae*, *Aspergillus niger* and *Candida albican*) pathogenic fungi were employed for this study.

METHODS

Characterization

The percentage metal ion composition of the metal complexes was estimated using complexometric titration. Infrared of the chelating agents and the metal complexes were examined through Perkin Elmer FT-IR Spectrum Bx spectrophotometer with KBr disc in the range 400-4500 cm-1. The electronic transitions occurring in the ligands and the metal complexes in the range of 190 nm-900 nm were studied using Spectro UV–Visible double beam pc scanning spectrophotometer UVD 2960. Elemental (CHN) analysis was carried out at Atlantic Microlab Inc. Norcross, Georgia,USA. Melting point apparatus was employed in measuring the melting points of the metal complexes and solubility tests were carried out in different solvents.

Synthesis of Mixed-ligand Metal Complexes

Solutions of 0.256 g (0.002 mol) of barbituric acid in 15 ml of 50% ethanol and 0.397 g (0.002 mol) of 2,2-bipyridine in 15 ml of 50% ethanol were prepared in separate beakers. The two solutions were added simultaneously and dropped wisely to a stirring solution of 0.499 g (0.002 mol) copper (II) acetate salt on a magnetic stirrer at 60 ℃. The metal complex precipitated out of the solution after 2 hours of stirring and was filtered by suction filtration. The filtered precipitate was thoroughly washed with ethanol and dried over silica gel in a desiccator. Other metal complexes were synthesized using the same method.

Antibacterial Test

The biological actions of the metal complexes against the bacterial strains were evaluated using filter paper. Petri dishes were used to prepare Mueller Hinton Agar base plates. The agar was inoculated at a temperature of 48 ℃ with MH broth culture of each bacterium strain and poured unto the base plates. The paper was subjected to heating at 85 ℃ for 60 mins in an oven and then cut into discs using 5.0 mm cork borer and sterile blade. The dried sterilized paper discs were inserted into 4 ml of the various samples, placed upon cultured plates and kept in the fridge for 24 h. The incubation of the plates was carried out at 37 ℃ for 24 h and the zones of inhibition were subsequently discovered and determined. The samples were prepared in DMSO at different concentrations of 5 mg/l, 20 mg/l, 50 mg/l, 100 mg/ml and 250 mg/l (Jonathan & Fasidi, 2003; Buwa & Staden, 2005). Antibiotic drugs such as gentamicin and ampiclox were employed as standard drugs.

Antifungal Test

Antifungi efficacy of the metal complexes was investigated by using Whatman filter papers No. 1 and the papers were carved into discs using 5.0 mm cork borer and sterile blade. The sterilization of the papers was carried out by heating them at 85 ℃ for 60 mins in an oven. The Saboraud dextrose agar method was employed for the cultivation of fungi and the cultivated fungi were transferred into the sterilized Petri dishes. Then, the Petri dish plates containing *Aspergillus flavus*, *Aspergillus niger*, *Saccharomyces cerevisiae,* and *Candida albican* pathogenic organisms were cultured for 24 h. The filter papers covered with the samples were placed upon the cultured plates and kept in the fridge for suitable distribution of the samples within the papers and then incubated at 30 ℃ for 72 h (Jonathan & Fasidi, 2003). Thereafter, the zones of inhibition were measured. DMSO solvent was used to prepare the solutions of the metal complexes. The experiments were replicated and cotrimoxazole drug was used as a reference drug.

RESULTS

Tables 1 and 2 show physical properties, analytical measurements and different solubility properties of the metal complexes, respectively.

Table 1. Physical and Analytical Measurement

Complex	Molecular Formula	Yield %	Melting Point (°C)	Colour	Elemental analysis C Calc. (Found)	H Calc. (Found)	N Calc. (Found)	(%) Metal Calc.	Found
L1	$C_4H_4N_2O_2$		245	Cream					
L2	$C_{10}H_8N_2$		69-73	Colourless					
01	$NiC_{14}H_{30}N_4O_{12}$	12.43	275	Pale blue	33.30 (33.23)	5.99 (4.95)	11.09 (14.65)	11.62	11.57
02	$CuC_{14}H_{20}N_4O_1S$	10.43	270	Green	32.60 (33.11)	3.91 (3.34)	10.86 (7.68)	12.32	13.78
03	$CoC_{14}H_{26}N_4O_{10}$	49.72	260	Pink	35.83 (35.08)	5.58 (4.62)	11.94 (11.94)	12.32	13.78

L1= Barbituric acid (Barb), L2= 2, 2-bipyridine(bpy), 01 = [Ni(Barb)(bpy) $(H_2O)_2$].7H_2O, 02 = [Cu(barb)(bpy)(H_2O)(SO_4)].3H_2O, 03= [Co(barb)(bpy)$(H_2O)_2$].5H_2O

Table 2. Solubility Test

Complex	Ac	EtOH	MeOH	$CHCl_3$	EtOAc	DH_2O	Hex	DCM	DMSO	DEE
01	IN	SSH	IN	IN	IN	SSH	IN	IN	S	II
02	IN	SH	SH	IN	IN	SH	IN	IN	S	IN
03	IN	SH	SH	IN	IN	IN	IN	IN	S	IN

Key : S = Soluble, SH = Soluble when heated, SSH = Slightly soluble when heated, IN = Insoluble, Ac= Acetone, EtOH= ethanol, MeOH =Methanol, $CHCl_3$=Chloroform, EtOAc=Ethylacetate, DH_2O=Distilled water, Hex= n-hexane, DCM=dichloromethane DMSO=dimethysuphoxide, DEE= Diethyl ether.

Infrared and Uv-visible Measurement

Tables 3 and 4 show the infrared bands and electronic transitions data, respectively obtained from the ligands and the ternary complexes.

Table 3. Infrared Data (cm^{-1}) for the Chelating agents and their Metal Complexes

Compound	$\nu_{C=C}$ (m-w)	$\nu_{C=N}$ (w-s)	ν_{C-N} (m-s)	$\nu_{C=O}$ (m-s)	ν_{N-H} (br)	ν_{O-H} (br)	ν_{SO4} (w)	ν_{M-S} (s)	ν_{M-N} (s)	ν_{M-O} (m-s)
L1	-	-	1409	1719	3477	-		-	-	-
L2	1502 1641	1587	1344	-	3410	-		-	-	-
01	1450 1691	1500	1294	1691	3450	-		-	530	422
02	1452	1550	1384	1689	3400	3500	1074	754	551	478
03	1452	1598	1390	-	3400	3450		-	545	459

Key: br = broad, s = strong, m = medium, w = weak

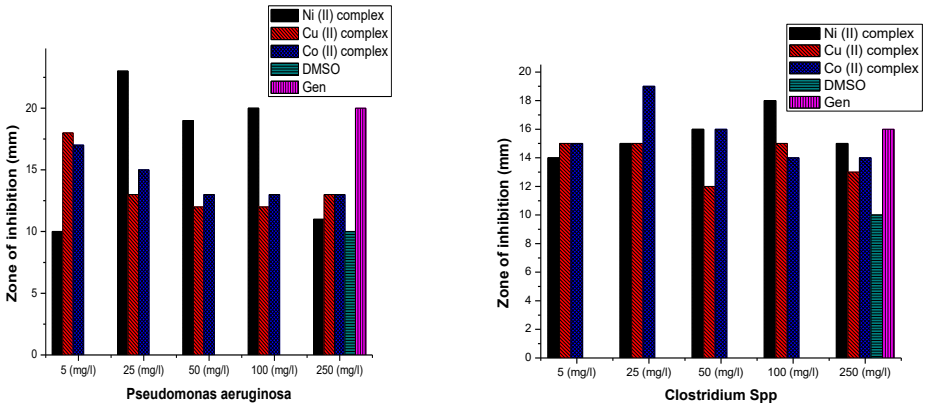
Table 4. Electronic Transitions for the Chelating agents and their Metal complexes

Complex	Band/nm(kk)	Assignment of Transitions
L1	264 (37.89) 246 (40.65) 228 (43.86)	$\pi - \pi^*$ $\pi - \pi^*$ $\pi - \pi^*$
L2	280 (35.71) 236(42.37) 214(46.72) 198(50.50)	$\pi - \pi^*$ $\pi - \pi^*$ $n - \pi^*$ $n - \pi^*$
01	596(16.77) 575(17.39) 538 (18.58)	d-d
02	774(12.92) 600(16.66) 550(18.18)	d-d
03	462(21.64) 430(23.25)	d-d

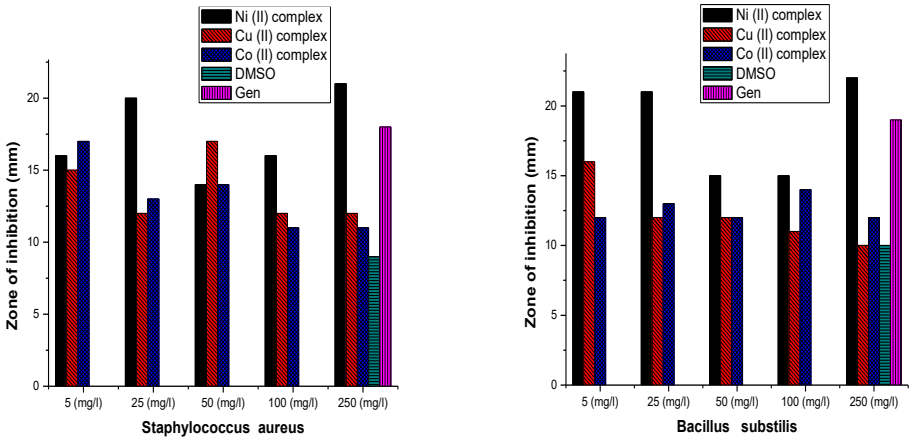
Antimicrobial Activity

The zones of inhibition as shown in Figure 2 are measured while Figures 3 and 4 show antimicrobial exploits of the metal complexes against the bacteria and fungi, respectively.

Fig. 2. Inhibitory Zones displayed by the Metal Complexes on the Organisms

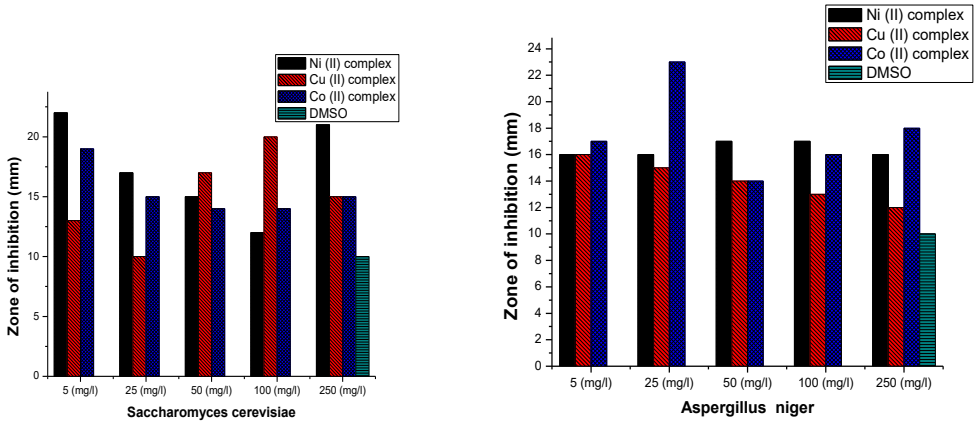


a. (Gram Negative)



(b) Gram positive

Fig. 3. Histogram Representation of Antibacterial Activity of the Metal Complexes



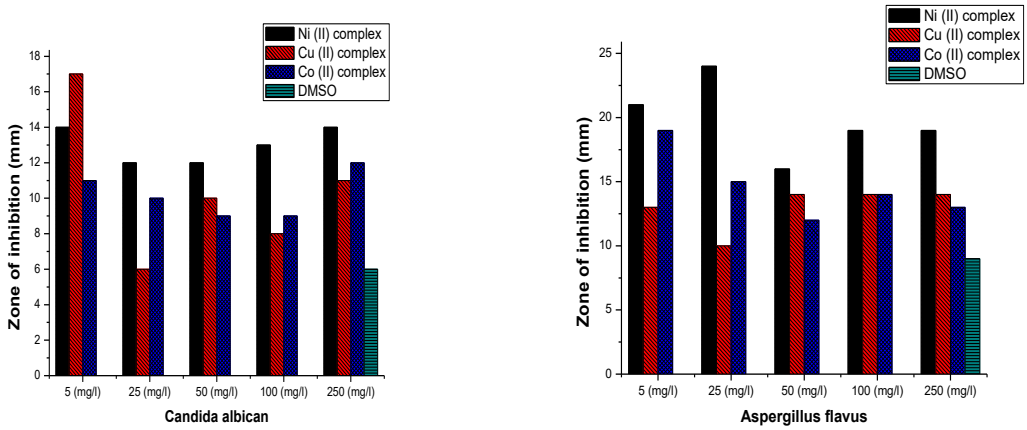


Fig. 4. Histogram Representation of Antifungal activity of the Metal Complexes

DISCUSSION

The microanalytical information and physical properties of the metal complexes of barbituric acid and 2,2-bipyridine ligands are shown in the Table 1. The mixed ligand complexes of Co (II), Cu (II) and Ni (II) of the chelating agents are pale blue, green and pink in colours, respectively as shown in the Table. The percentage composition of carbon, hydrogen, and oxygen and the number of metal ions in the complexes are also displayed in the Table. The total number of constituent atoms in the complexes was in close agreement with the theoretical values thereby the proposed molecular formulas for the complexes and formation of 1:1:1 (ML1 L2) are established. Barbituric acid and 2,2-bipyridine are observed to melt at temperatures of 100-240 °C and 69-73 °C, respectively. The metal complexes melted between 260-300 ºC (Table 1). The greater melting points displayed by the metal complexes than the chelating agents confirmed the formation of new bonds in the chelates. The observed sharp melting points also established the purity of the metal complexes. The complexes are observed to soluble in DMSO but show different degrees of solubility in other solvents as shown in the Table 2.

The formation of coordination bonds by the chelating agents with the metal ions is established by comparing IR spectra of the chelating agents with those of the metal complexes (Table 3). The relevant bands at 3477 cm^{-1}, 1719 cm^{-1} and 1409 cm^{-1} present in the barbituric acid spectrum are ascribed to υ(N-H), υ(C=O) and υ(C-N) stretching vibrations, respectively. The bands at 1641 cm^{-1}, 1587 cm-1 and 1344 cm^{-1} observed in the 2,2-bipyridine spectrum are ascribed to υC=C, υC=N and υC-N, vibrations, respectively. The υC=N, υC-N, υ(C=O) and υ(N-H) bands were observed to undergo a hypsochromic shift to 1500 cm^{-1}, 1294 cm^{-1}, 1691 cm^{-1} and 3450 cm^{-1}, respectively in the metal complexes. The shifts suggest the participation of nitrogen and oxygen donor atoms in the complex formation. Also, the occurrence of the broad band at 3000-3550 cm^{-1} in the spectra of the metal complexes establishes the attachment of water molecules to the metal complex while the existence of a band at 1074 cm^{-1} in the Cu (II) complex confirms the formation of a new coordination bond with the metal ion by sulphate ion. The participation of nitrogen, oxygen and sulphur atoms in the complex formation is correspondingly confirmed by the occurrence of M-N, M-O, and M-S bands at 422 cm^{-1}, 530 cm^{-1} and 754 cm^{-1} (Coates, 2000; Hasnain et al., 2009; Singh et al., 2011).

Different electronic transitions are observed in the chelating agents and the metal complexes as shown in Table 3. The three bands observed in barbituric acid at 37.89 kk, 40.65 kk and 43.86 kk are attributed to $\pi - \pi^*$ electronic transition. The bands at 35.71 kk, 42.37 kk and 46.72 kk 50.50 kk in the spectrum of 2, 2-bipyridine are ascribed to $\pi - \pi^*$ electronic transition. Bands at 16.77 kk, 17.39kk and 18.58 kk are observed for the Co (II) complex. These bands are attributed to the d-d transition (Cotton et al., 1999; Ekennia et al., 2015). In the Cu (II) metal complex, electronic bands at 18.18kk, 16.66kk and 12.92kk are observed as a result of d-d electronic transitions of distorted octahedral geometry (Cotton *et al*., 1999). The bands observed in Co (II) complex at 21.64 kk and 23.25 kk are attributed to d-d electronic transitions of tetrahedral geometry (Singh & Kaushik, 2008).

The antimicrobial potencies of the chelating agents and the metal complexes were examined on different bacterial strains at concentrations of 5 mg/l, 25 mg/l, 50 mg/l, 100 mg/l and 250 mg/l and zones of inhibition are measured (Figure 2). The ligands and the reference drug (ampiclox) were found to be inactive against the bacteria while gentamicin and the metal complexes exhibit different activities against the bacteria at the concentrations. The antimicrobial activities corresponding to the measured zones of inhibition were presented using two histograms (Figure 3). The inhibitory effects of the metal complexes on the growing gram-negative bacterial strains (*Pseudomonas aeruginosa* and *Clostridium spp.*) are measured and shown in Figure 3 (a). The metal complexes display a varying degree of activity against *Pseudomonas aeruginosa.* At the concentration of 25 mg/l, the Ni (II) complex displays the highest activity while other metal complexes exhibit moderate activities on the bacterium. However, gentamicine drug at 250 mg/l shows to be more active against the bacteria than all the complexes except Ni (II) complex. Ni (II) complex is also found to be more active than other metal complexes on *Clostridium spp* strain at a concentration of 100 mg/l while Co (II) complex shows more activity than Cu (II) complex and gentamicine against *Clostridium spp* at 25 mg/l. The metal complexes show outstanding antimicrobial effects on *Pseudomonas aeruginosa* than *Clostridium spp.*

Also, the antibacterial behaviour of the metal complexes against growing *Bacillus substilis* and *Staphylococcus aureus* strains (gram-positive) is presented in Figure 3b. Ni (II) complex at 25 and 250 mg/l concentrations displayed high activity on *Staphylococcus aureus* strain than gentamicin. The standard drug shows more activity on the bacterium than other metal complexes. Biological activities of the metal complexes on *Bacillus substilis* strain show that Cu (II) complex is highly effective at concentrations of 5 and 25 mg/l than other metal complexes and gentamicin. The metal complexes show diverse actions against the bacteria. Ni (II) complex was found to display more effectiveness against the bacteria than the standard drug and most especially against *Pseudomonas aeruginosa* and *bacillus substilis* strains.

The effectiveness of the metal complexes and a standard drug (cotrimoxazole) is evaluated on the fungi at 5 mg/l, 25 mg/l, 50 mg/l, 100 mg/l and 250 mg/l concentrations, and inhibitory zones at the different concentrations are represented as measured using a histogram (Figure 4). The standard drug, cotrimoxazole, is inactive against the fungi. The tested Ni (II) compound displays higher antifungal activity against *Aspergillus flavus* than the complexes of Co (II) and Cu (II). The best activity is displayed by Ni (II) at 25 mg/l. Different antifungal activities are displayed by the metal complexes against *Saccharomyces Cerevisiae.* Ni (II) complex is observed to display the best antimicrobial activity against *Saccharomyces Cerevisiae* at 2 mg/l and 250 mg/l *while* Cu (II) complex exhibits better activity at 50 mg/l and 100 mg/l. Cu (II) complex showed high activity against *Candida albican* at a concentration of 5 mg/l while Ni (II) exhibited moderate activity against the fungus at 25 mg/l, 50 mg/l, 100 mg/l and 250 mg/l. However, the best activity is displayed by Co (II) against *Aspergillus niger* at concentrations of 25 mg/l and 250 mg/l.

The ternary metal complexes are observed to be effective against the pathogenic microorganisms and succeeded while the parent ligands and the employed standard drugs failed. The activity of the ternary metal complexes could be ascribed to chelation theory. The polarity of the metal atom reduces on chelation on account of the fractional distribution of positive charge with donors of the chelating agents and π-electron delocalization over the aromatic ring. Sequentially, the lipophilicity of the metal complexes is enhanced hence antimicrobial properties of the metal complexes increased. The enhanced lipophilicity is attributed to the diffusion of the metal complexes through the lipid membranes of the organisms thereby obstructing the metal binding sites in the microorganisms' enzymes. Also, the antimicrobial effectiveness of the metal complexes could be associated with the geometry of the complexes and the type of metal ions (Anacona & Lopez, 2012; Teleb et al., 2019). Additionally, the medicinal potency displayed by the metal complexes on the pathogens might be ascribed to the likelihood of the ligands and metal ions interacting with the pathogens at different stages of their life cycles (Dinah, 2013). The less antimicrobial activity of the standard drugs might be due to their inability to reach spots of infections as a result of less penetration of the organisms' lipid membranes by the drugs.

CONCLUSION AND RECOMMENDATIONS

The new metal complexes of Co (II), Cu (II) and Ni (II) ions involving barbituric acid and 2,2-bipyridine ligands are prepared. The formation of the metal complexes was established through infrared and UV-visible spectroscopy, elemental analysis, metal analysis, melting points and solubility test. The metal complexes exhibited, at varying degrees, in-vivo antimicrobial actions against the tested micro-organisms. The metal complexes displayed more medicinal activity than the employed standard drugs and succeeded where the standard drugs failed. Therefore, metal complexes are recommended as materials for the production of effective antibiotic drugs to replace the less effective conventional antibiotic drugs in combating multi-drug resistant pathogenic organisms.

Further analytical studies such as (13C, 1H) NMR, mass Spectroscopy and X-ray measurement are recommended to be performed to ascertain the actual structures of the mixed ligand complexes. Toxicology studies on the metal complexes should be carried out to establish their suitability for antibiotic drugs. Biochemists, microbiologists, physiologists and pharmacists should be collaborated to encourage the possibility of transforming these compounds into readily available drugs in the market.

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