### MANGANESE (II) AND IRON (II) COMPLEXES OF CLOXACILLIN -SYNTHESIS, SPECTRAL STUDIES AND ANTIMICROBIAL ACTIVITIES

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#### ABSTRACT

Manganese (II) and iron (II) complexes of cloxacillin (clox) were synthesized by direct combination of the reactants in methanol and characterized using elemental analysis, conductivity measurement and spectroscopic techniques. The ligand was found to behave as a bidentate ligand coordinating the metal ions through the carbonyl oxygen atom of  $\beta$ -lactam ring and nitrogen atom of secondary amide forming compounds with molecular formulae [ $Mn(clox)_2Cl_2$ ]. $3H_2O$ , [ $Fe(clox)_2(H_2O)_2$ ] $SO_4$ . $2H_2O$ , and [ $Fe(clox)_2(H_2O)_2$ ]. Antimicrobial activities of the synthesized complexes investigated against important bacteria and fungi strains at a concentration of 1.6 mg/mL in DMSO indicated that [ $Fe(clox)_2(H_2O)_2$ ] $SO_4$ . $2H_2O$  displayed higher antibacterial activity than the parent antibiotic ligand while the remaining two complexes were inactive against the four bacterial and two fungal strains used.

Key words: Metal complexes; Antimicrobial; Spectral studies; Antibiotics; Cloxacillin

### **1.0 INTRODUCTION**

Development of penicillinase-resistant penicillins such as oxacillin, cloxacillin and methicillin came into focus because of early clinical success of benzylpenicillinase associated resistance to antibiotics. Nevertheless, a rising in the resistance to these drugs by bacterial species staphylococci and fungi makes much research work directed at preparing derivatives, which could combat this health challenge, a necessity. Particular interest was on getting rid of  $\beta$ lactamases produced by penicillinresistant strains of *Staphylococcus* 

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*aureus* (Rodica-Mariana, 2007; Ogunniran *et al.*, 2008; **Alekseev, 2012**). Cloxacillin {3-(2-chlorophenyl)-5methyl-4-isoxazolylpenicillin}is often used in the form of monohydrate sodium salt (Figure 1) to treat staphylococcal infections (**Masoud** *et al.*, **2015**) and remedy some clinical disorder such as septicaemia, meningitis and soft tissue infection.





[Cloxadillin Sodum]

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Manganese (ii) And Iron (ii) Complexes Of Cloxacillin - Synthesis, Spectral Studies And Antimicrobial Activities

### **Figure 1**. Structure of clox

Many antimicrobial drugs have donor atoms and are excellent ligands with their activities affected when coordinated while the metal complexes formed were very active against certain bacteria and fungi (Obaleye et al., 2001; Mishra and Thakur, 2014; Singhal et al., 2016). Limited works have been carried out on the interaction of isoxazolyl penicillins with transition metal ions and the activity of the complexes formed. For example the binding sites available in cloxacillin as proposed by previous workers (Aldea, 1993; Chohan and Supuran, 2006; Chao et al., 2007; Mishra and Thakur, 2014) are the secondary and tertiary amide oxygen atoms, the carboxylate oxygen, as well as the nitrogen atoms of  $\beta$ -lactam ring and of the secondary amide. Metal ions involved in their works are the divalent zinc, nickel, cobalt, and copper; and some trivalent lanthanide ions. It is of good interest, therefore, to probe the coordination behaviour of this semisynthetic antibiotics further especially when other metal ions are involved. The knowledge of the effect that this coordination may have on the drug's antibacterial and antifungal activities will be beneficial. This work, therefore, describes the results obtained from the interaction of Mn (II) and Fe (II) with cloxacillin sodium and the properties of the new complexes formed. Their activities against *Staphylococcus* aureus, Escherichia coli, Klebsiella pneumonia, Proteus vulgaris, Candida albican and Aspergillus niger are also discussed.

### 1.0 MATERIALS AND METHOD 2.1 Materials

Analytical grade reagents and solvents used were obtained from Aldrich, M&B Laboratory and BDH. Solvents were distilled before use. CHN elemental analysis was performed on Thermo Flash 1112 CHNSO elemental analyser (Medac Ltd., United Kingdom). Electronic spectra of the ligands and their complexes were recorded in acetone solution and on J e n w a y 6405 UV - V i s i b l e spectrophotometer in the range 200-800 nm. The IR spectra were recorded on S h i m a d z u 8400 S F T I R spectrophotometer as KBr pellets in the range 4000-400 cm<sup>-1</sup>.

## 2.2 Synthesis of the Metal Complexes

The metal complexes were synthesized by following the method earlier described by Singhal *et al.* (2016) with some modifications.

2.2.1 Preparation of Iron (II) Complexes:

Suspension of  $FeSO_4$ .  $7H_2O(0.6980 g, 2.5 mmol)$  in 25 mL of methanol was mixed with a solution of Naclox.  $H_2O(1.380 g, 5 mmol)$  in methanol (10 mL) and refluxed for 3 h with constant stirring. A brown solid precipitated and was filtered to obtain the residue,  $[Fe(clox)_2(H_2O)_2]$  (Equation 1). Slow evaporation of the filtrate gave a dark shiny solid,  $[Fe(clox)_2(H_2O)_2]SO_4.2H_2O$  (Equation 2). Both products were separately washed with distilled water and characterized.

[Fe(clox)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]: Yield = 53.60% (1.4650 g). Anal. Calcd. for FeC<sub>38</sub>H<sub>38</sub>N<sub>6</sub>O<sub>12</sub>S<sub>2</sub>Cl<sub>2</sub> (%): C, 47.46; H, 3.98; N, 8.74. Found (%) C, 47.27; H, 4.39; N, 8.21. UV-vis (acetone)  $\lambda_{max}$  (nm): 340, 360, 375, 400. IR (KBr, cm<sup>-1</sup>): 3404, 1742, 1663, 1603, 1437, 1414, 1132, 698, 577, 476.

[Fe(clox)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]SO<sub>4</sub>.2H<sub>2</sub>O: Yield = 44.96 % (1.2294 g). Anal. Calcd. for FeC<sub>38</sub>H<sub>42</sub>N<sub>6</sub>O<sub>18</sub>S<sub>3</sub>Cl<sub>2</sub> (%): C, 41.73; H, 3.39; N, 7.68. Found (%): C, 42.07; H, 3.92; N, 7.22. UV-vis. (acetone)  $\lambda_{max}$ (nm) 360, 385, 405. IR (KBr, cm<sup>-1</sup>): 3391, 1742, 1655, 1605, 1437, 1418, 1132, 698, 577, 461. 2.3 Antibacterial and Antifungal Activity Tests

The metal complexes were screened *in vitro* against a Gram positive (*S. aureus*) and three Gram negative bacteria, and two fungi species. Solutions containing 320  $\mu$ g of each test compound (0.2 mL) in DMSO were pipetted into the bored media wells and allowed to disperse evenly. The plates were incubated for 24 h at 37 °C in the case of bacteria and at room temperature (30 °C) for 72 hours for fungi. Zones of clearance were observed and diameter of these inhibition zones was measured using cloxacillin as the reference antibacterial drug (Obaleye *et al.*, 2016).

# 1.0**RESULTS AND DISCUSSION**3.1 Synthesis of Metal Complexes and<br/>Analytical Data

All the metal complexes prepared were of good yield; the combined yield of Fe (II) complexes was above 90%. Except that of Mn (II) complex which was lower. Unlike the parent drug they were nonhygroscopic and coloured (Table 1). They all melted with decomposition at temperatures significantly different from that of the ligand suggesting the formation of coordinate bonds which alter the bond energy in the new compounds. Results of elemental analysis of the complexes were in good agreement with calculated values and indicated 1:2 stoichiometry of metal ion to the ligand. The molecular weight of  $[Fe(clox)_2(H_2O)_2]SO_4.2H_2O$  obtained from filtrate of Fe (II) complex was higher than the other one separated from residue as indicated by the elemental analysis results presented in Table 1.

# **Table 1**. Analytical data and conductivity<br/>of cloxacillin and its metal

Compound Mol. Formulae (Colour)	Colour	Decom. point (°C)	Conduct. at 26°C (μScm <sup>-1</sup> ) in DMSO
Naclox.H <sub>2</sub> O	White	170	64.86
[Fe(clox) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]SO <sub>4</sub> .2H <sub>2</sub> O	Dark brown	140	41.01
$[Fe(clox)_2 (H_2O)_2]$	Light Brown	201	5.80
[Mn(clox) <sub>2</sub> Cl <sub>2</sub> ].3H <sub>2</sub> O	Creamy Yellow	215	-

 $clox = C_{19}H_{16}N_{3}O_{5}SCl$ 

The two Fe (II) complexes prepared were insoluble in water and methanol but soluble in acetone and DMSO while the Mn (II) complex was practically insoluble in all the solvents used. These changes may be due to new compound formed which affects the chemical environments of the antibiotic. The compound containing complex cation,  $[Fe(clox)_2(H_2O)_2]SO_4.2H_2O$ , is of a much higher conductivity than the neutral complex,  $[Fe(clox)_2(H_2O)_2]$ , as expected of their electrolytic strengths (Geary, 1971).

# 3.2 Electronic Spectra

The electronic absorption spectra of the complexes have been interpreted in terms of *d-d* transitions and charge transfer from metal to the  $\pi$  antibonding orbitals of the ligand (Table 2). The ligand and its metal complexes showed several absorption maxima in the UV and visible regions. Absorption bands at 285 and 340 nm involving the energies 35 088 and 29 412 cm<sup>-1</sup> were observed in the spectrum of

Naclox and attributed to  $n \rightarrow \pi^*$  and  $\pi \rightarrow \pi^*$ transitions respectively of the isoxazolyl ring and ethylenic double bond in benzene. The spectra of the complexes show shifts in energy of absorption due to complex formation (Osowole and Odutemu, 2016).

Table 2. UV-vis spectral bandassignment for cloxacillin metalcomplexes

Compound	UV-Vis peaks		
	(nm)		
Naclox. H <sub>2</sub> O	285, 340		
$[Fe(clox)_2$	360, 385, 405		
$(H_2O)_2]SO_4.2H_2O$			
$[Fe(clox)_2(H_2O)_2]$	360, 375, 400		
$[Mn(clox)_2 Cl_2].3H_2O$	326, 349, 412, 497		

 $[Fe(clox)_2(H_2O)_2]SO_4.2H_2O$  and  $[Fe(clox)_{2}(H_{2}O)_{2}]$  have a common UV band at 360 nm  $(27778 \text{ cm}^{-1})$  but different peaks in the visible region. The visible peaks at 400 and 405 nm are assigned to  ${}^{5}E_{g} \rightarrow {}^{5}T_{2g}$  for octahedral complexes (Cotton et al., 2004). Their bands in the UV region are assigned to  $\pi \rightarrow \pi^*$ transition of the ligand and found to shift bathochromically suggesting coordination. Manganese (II) complex similarly showed several *d*-*d* transitions in the visible region at 412 and 497 nm and are assigned to  ${}^{6}A_{lg} \rightarrow {}^{4}T_{2g}(D)$  and  ${}^{6}A_{lg}$  $\rightarrow {}^{4}E_{a}(D)$  transitions respectively. There were shift to higher wavelength in the UV region (349 and 326 nm) of the Mn (II) complex compared with the ligand  $\pi \rightarrow \pi^*$ transitions. Marked spectral changes when compared to the spectrum of cloxacillin are indicative of complex formation (Cotton and Wilkinson, 1972). **3.3 Infrared Spectra** 

Important infrared absorption frequencies and their assignment are presented in Table 3. According to Kupka (1997) characteristic infrared features of cloxacillin include strong bands due to the  $\beta$ -lactam carbonyl vibration at about 1770 cm<sup>-1</sup> and the side amide link at about 1660 cm<sup>-1</sup> which partly overlap with the ionized carboxylate group. The spectrum of the ligand showed a strong band attributed to  $\beta$ -lactam carbonyl of tertiary amide at 1769 cm<sup>-1</sup> due to  $\beta$ -lactam ring strain (Chao *et al.* (2007).

**Table 3.** Important IR spectral bandassignment for cloxacillin metalcomplexes

Compoun		Infra red bands				
d	N- H <sub>str</sub>	C=O <sub>str</sub> (β-	C=O <sub>s</sub>	C=O <sub>str</sub> (carbox	Δν	
	(sec. amid e)	)	(sec. amid e)	y-late)		
Naclox. H <sub>2</sub> O	3516 w, 3384 m	1769s	1661 s	1603s, 1412s	191	
[Fc(clox) 2(H <sub>2</sub> O) <sub>2</sub> ] SO <sub>4</sub> . 2H <sub>2</sub> O	3391 s, br	1742s	1655 s	1605s, 1418s	187	
[Fe(clox) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	3404 m, br	1742 m	1663 s	1603s, 1414s	189	
$[Mn(clox)_2Cl_2].3H_2O$	3385 s, br	1734 w	1645 s	1603s, 1412s	191	

br=broad; m=medium; s=strong; w =weak

In the spectra of the complexes this band shifts to lower frequencies and there are remarkable changes in their intensities compared to the spectrum of the ligand. This is in agreement with the results reported by Anacona and Figueroa, (1999) on Zn (II), Cd (II) and Ni (II)

complexes of penicillin. The result, however, is in sharp contrast with the findings of other previous workers (Kupka, 1997; Chohan and Supuran, 2006; and Chao, 2007) on zinc (II), cobalt (II) complexes of cloxacillin and with Anacona and Figueroa, (1999) on Fe (III) complexes where such change was rather insignificant compared to the band in the free drugs. Different metal ions or oxidation state might be responsible for these disparity observed. The blue shift of the C=O bands can be attributed to the coordination of the metal ions by the ligand. The metals possess empty orbital into which they can accept the lone pair of electrons on the oxygen atom of the carbonyl group. This results in the lengthening of C=O bond and reduced bond order. The bond is weakened and a shift to lower frequency of the band is observed. According to Nakamoto (1970), there is a direct relationship between IR stretching frequency and change in bond length upon coordination. The sharp bands at 3516 and 3384  $\text{cm}^{-1}$ are assigned to N-H stretching frequencies. Oku et al. (1997) assigned a strong band at 3428 cm<sup>-1</sup> to stretching frequency of N-H of amide while other workers (Kupka, 1997; Chao, 2007) found the same absorption band at 3514 and 3363 cm<sup>-1</sup>. In the complexes the band shifted to lower frequencies with some broadening observed and increased intensity. These changes can be attributed to coordination of the antibiotic to the metals through N-H of secondary amide. The presence of coordinated water molecules is responsible for the broadening of these bands (Mishra and Thakur, 2014) in the complexes which supports the results obtained from elemental analysis. The vN-H band of  $[Fe(clox)_{2}(H_{2}O)_{2}]SO_{4}.2H_{2}O at 3391 cm^{-1}$ 

displayed a reduced intensity compared to the same band observed at  $3404 \text{ cm}^{-1}$  in the spectrum of [Fe(clox)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] which suggests that the complexes were of different composition.

The sharp absorption at 1661 cm<sup>-1</sup> is assigned to C=O stretching frequency of secondary amide present in cloxacillin. When compared with the results presented by Chao et al. (2007) and Kupka (1997) on cobalt (II) and zinc (II) complexes of the penicillin, this band did not change significantly in intensity and position in the metal complexes. This may be due to non-involvement of the C=O oxygen in coordination with the metals (Anacona and Figueroa, 1999). Kupka (1997) reported a broadening and eventual overlapping of two bands belonging to carboxylate and secondary amide between 1660  $\text{cm}^{-1}$  and 1618  $\text{cm}^{-1}$ when  $ZnSO_4$  was used as the metal salt. Strong band observed for  $[Fe(clox)_{2}(H_{2}O)_{2}]SO_{4}.2H_{2}O$  at  $1655cm^{-1}$ showed up at 1663 cm<sup>-1</sup> for  $[Fe(clox)_{2}(H_{2}O)_{2}]$  complex. Asymmetric and symmetric stretching frequencies of carboxylate were found at 1603 and 1412 cm<sup>-1</sup> in the spectrum of cloxacillin respectively with asymmetric band overlapping with one of the aromatic ring  $C=C_{str}$  frequency around 1605 cm<sup>-1</sup>. According to previous workers (Rau et al., 1997), C=O<sub>str</sub> band of carboxylic acid around 1720 cm<sup>-1</sup> disappeared and was replaced by these two bands when the acid was deprotonated. Nakamoto (1970) stated that the separation  $\Delta v$  between the two modes of vibration could be used to predict coordination mode of the metals to the ligand through the carboxylate group. In the complexes the  $\Delta v$  calculated showed insignificantly changes which suggests that the carboxylate group was not involved in complex formation with

these metals. The study of IR spectra of cloxacillin sodium and its Fe (II) and Mn (II) complexes showed that the penicillin coordinates the metal ions via C=O group of  $\beta$ -lactam ring, and the N-H of secondary amide leaving unbound the carboxylate group of thiazolidine ring system.

### 3.4 Antimicrobial Activity Test

The inhibition zones developed at the concentration of 1.6 mgmL<sup>-1</sup> are shown in Table 4.  $[Fe(clox)_2(H_2O)_2]$  and  $[Mn(clox), Cl_2].3H_2O$  were found to be inactive against all the bacteria and fungi species tested. Loss of antimicrobial activity may be due to involvement of donor atom of  $\beta$ -lactam ring (responsible for antimicrobial activity) in coordination leading to drug inactivation (Martin, 1998). Eze et al. (2014) similarly ascribed reduced activity of Fe (III) complex of cloxacillin to pharmacophoric changes during metal ion dative bonding which make antibiotic binding sites unavailable for interaction or chelation with biological receptors in the fungi or bacteria. However,  $[Fe(clox)_2(H_2O)_2]SO_4.2H_2O$  displayed higher antibacterial activity than the free antibiotic against S. aureus and E. coli. As expected, cloxacillin was only active against S. aureus, a Gram positive bacteria but inactive toward all the three Gram negative bacteria. The increased activity as a result of metal coordination was explained by Tweedy's chelation theory (Raman et al., 2008; Tweedy, 1964). The polarity of the metal ion is reduced to a large extent on coordination. This is as a result of overlap with the ligand orbital and partial sharing of the positive charge on the metal ion with donor groups. Delocalization of  $\pi$ electrons further increases over the chelate ring which enhances the

penetration of the complexes into the lipid membranes and blocking of metal sites in the enzymes of the organism. Active complexes also disturb the respiration process in the cells and block the synthesis of proteins which restricts their growth (Tumer *et al.*, 2007). In the penicillin family of antibiotics potency is directly related to lipophilic character, particularly when Gram-positive organisms are involved (Chao *et al.*, 2007).

**Table 4.** Zones of inhibition of bacteriaand fungi by cloxacillin and its metalcomplexes at 1.6mg/ml (DMSO)

Organis	Clox	[Fe(clox)	[Fe(c	[Mn(clo
m/	acilli	2	$lox)_2$	$x)_2Cl_2].$
Compo	n	$H_2O)_2]S$	$(H_2O)$	$3H_2O$
unds		$O_4.2H_2O$	$)_{2}]$	
S.	15.0	25.0	0.0	0.0
aureus				
К.	0.0	0.0	0.0	0.0
pneumo				
niae				
E. coli	0.0	27.0	0.0	0.0
Р.	0.0	0.0	0.0	0.0
vulgari				
S				
С.	17.0	0.0	0.0	0.0
albican				
A. niger	0.0	0.0	0.0	0.0

### 1.0 CONCLUSION

Divalent manganese and iron complexes

of an isoxazolyl penicillin (cloxacillin) were synthesized and characterized by elemental analysis, conductivity measurement, UV-visible, and infrared spectroscopic studies. The antibiotic behaved as a bidentate ligand towards transition metals employed in this study while the preferred coordination sites are the nitrogen atom of the secondary amide and  $\beta$ -lactam ring carbonyl group. The endocyclic nitrogen of  $\beta$ -lactam and the carboxylate were not involved in the coordination of the six-coordinate metal complexes suggested to have octahedral structure. Antimicrobial susceptibility test on selected bacteria and fungi revealed that one of the Fe (II) complex,  $Fe(clox)_{2}(H_{2}O)_{2}]SO_{4}.2H_{2}O$  showed remarkable and improved activity against two of the four bacteria species tested at the concentration. The complex may be a potential substitute for cloxacillin for combating antibiotic resistance.

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