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## SYNTHESIS, CHARACTERIZATION, *IN-VITRO* ANTI-INFLAMMATORY AND ANTIMICROBIAL SCREENING OF METAL(II) MIXED DICLOFENAC AND ACETAMINOPHEN COMPLEXES

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**ABSTRACT.** Mixed ligand complexes derived from diclofenac potassium salt (Kdc) and acetaminophen (ace) has been synthesized and proposed to have a general formula [MB] where M = Co<sup>2+</sup>, Ni<sup>2+</sup>, Cu<sup>2+</sup> and Zn<sup>2+</sup> and B = (ace)(dc)(H<sub>2</sub>O)<sub>2</sub> except for Mn<sup>2+</sup> complex which exists as [Mn(ace)(dc)OH<sub>2</sub>]. The complexes were characterized by solubility, melting point, conductivity, elemental analyses, UV-Vis, FT-IR spectroscopy, X-ray powder diffraction (XRPD) study and magnetic susceptibility measurement. Electronic absorption spectra data are characteristic of octahedral structures for [MB]. The IR spectra revealed a bidentate coordination mode. In acetaminophen, the nitrogen and carbonyl-O atoms of the amide group were involved while the carboxylate oxygen atoms of potassium diclofenac were used; typical of a carboxylic acid derivative. The compounds were screened for *in-vitro* anti-inflammatory activity by inhibition of albumin denaturation assay and antimicrobial activity against bacteria strains: *Bacillus subtilis*, *Bacillus anthrax*, *Escherichia coli*, *Salmonella typhi* and a fungus *Aspergillus niger*. Some of the tested compounds showed moderate anti-inflammatory activity when compared to the standard drug diclofenac potassium salt. The *in-vitro* antimicrobial screening revealed an increased activity of the complexes against the bacteria isolates compared to the free ligands.

**KEY WORDS:** Metal(II) ion, NSAIDs, Anti-inflammatory activity, Diclofenac potassium salt, XRPD, Antimicrobial activity

### INTRODUCTION

Synthesis and investigation of metal complexes with active pharmaceuticals, in which the drug molecules play a role of ligand, have been regarded as a research domain of increasing interest for inorganic, pharmaceutical, and medicinal chemistry [1, 2]. Literature survey indicated that over the last decade, there had been tremendous attention towards studies on metal complexes formation using drugs as ligand [3]. A characteristic of metal ions is that they easily lose electrons from the familiar elemental or metallic state to form positively charged ions. Metal-containing compounds offer many advantages over conventional carbon-based compounds in the development of new medicinal compounds. These metal complexes are found to be interesting due to their biological applications like antifungal, antibacterial and anti-tumor activity [4]. These complexes offer a great diversity in their action; they do not only have anti-cancer properties but have also been used as antibacterial, anti-inflammatory and anti-diabetic compounds [5].

Acetaminophen (Figure 1a) otherwise known as paracetamol, is a derivative of 4-aminophenol having the chemical name N-(4-hydroxyphenyl) acetamide, molecular weight 151.16 and formula C<sub>8</sub>H<sub>9</sub>NO<sub>2</sub>. It is a widely used painkiller for mild to moderate pain, e.g. for headaches and muscular pains. It is useful in tooth ache and rheumatism. It also reduces fever and is available in 500 mg tablets or in liquid form for children. It is well tolerated with very few side-effects [2].

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Diclofenac potassium salt, (Figure 1b) a phenyl acetic acid derivative with a potent cyclooxygenase inhibiting action, is a non-steroidal anti-inflammatory drug (NSAID) taken to reduce inflammation, long term treatment of rheumatoid arthritis, and as an analgesic reducing pain in certain conditions such as menstrual pain and endometriosis [6, 7]. It is available under a variety of trade names such as Cataflam, Voltfast, Keflan, etc. Kdc is a white crystalline powder, soluble in ethanol, methanol and distilled water. Chemical name is potassium [2-(2,6-dichloroanilino)phenyl]acetate, molecular formula of  $C_{14}H_{10}Cl_2KNO_2$  and weight 334.24.

In the course of literature review, mostly metal complexes of single analgesic drugs were reported with few mixed ligand complexes. Currently used anti-inflammatory drugs although efficacious, are associated with some severe side effects such as gastro-intestinal disorders, cardiovascular and renal dysfunction, etc. Therefore, the development of potent anti-inflammatory drugs with fewer side effects is necessary and hence the increasing focuses on combinatorial products. Combination (mixed) analgesic products have been effective because they activate multiple pain-inhibitory pathways and offer a broader spectrum of relief. This may include multiple afferents and pathways as well as multiple processes [8]. Within this context and after taking into consideration the importance of NSAIDs in medicine, the enhanced activity and application of their metal complexes in drugs design, as well as a continuation of researches concerning the interaction of metal ions with drug ligands [2, 9-11], we present in this research, synthesis of metal complexes of diclofenac and acetaminophen. Evaluation of their *in-vitro* anti-inflammatory and antibacterial activities has also been discussed.

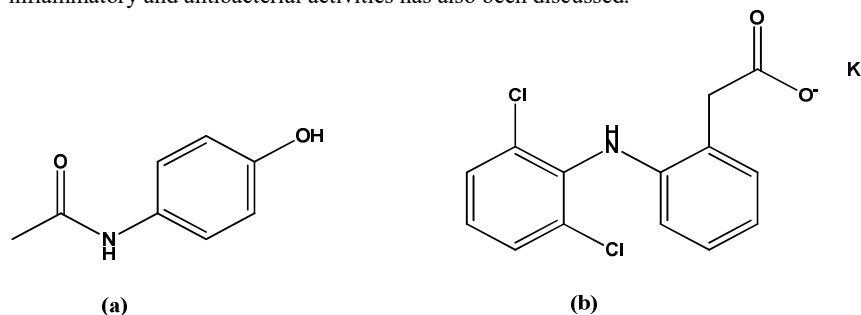


Figure 1. Chemical structures of (a) acetaminophen and (b) potassium diclofenac salt.

## EXPERIMENTAL

### *Materials*

All the chemicals for this work were used as commercially obtained (Sigma-Aldrich, BDH) without further purification. The hydrated metal salts used are  $MnCl_2 \cdot 4H_2O$ ,  $CoCl_2 \cdot 6H_2O$ ,  $NiCl_2 \cdot 6H_2O$ ,  $Cu(NO_3)_2 \cdot 3H_2O$  and  $ZnSO_4 \cdot 6H_2O$ .

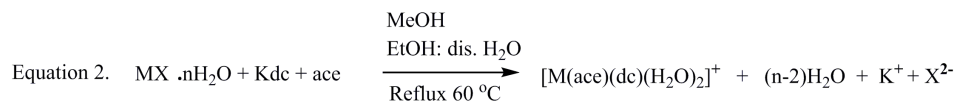
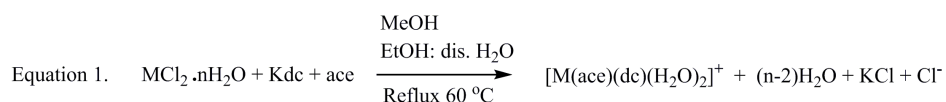
### *Physical measurements and determination*

Melting point was determined using Optimelt Automated Melting Point System with Digital Image Processing Technology (SRS). The UV-Vis spectra of  $10^{-3}$  M solutions of the complexes in DMF were determined using DU-730 Beckman Coulter UV/Vis spectrophotometer with a quartz cell of path length 1 cm. Conductivities in DMF were determined using HANNA H1763100 conductivity meter with cell constant  $0.868\text{ cm}^{-1}$  at the STEP-B Chemistry laboratory, University of Ilorin. The infra-red was recorded in KBr pellets ( $4000\text{--}500\text{ cm}^{-1}$ ) using Shimadzu FTIR spectrophotometer at Redeemers University, Osun State Nigeria. The elemental analysis (CHNO) was performed on a Perkin-Elmer CHN Analyzer at University of

York, United Kingdom. Magnetic susceptibility measurement was determined from a Gouy X-26 magnetometer at Federal University Lafia, Nassarawa State Nigeria. XRPD analysis was performed on a Bruker D8 X-ray diffractometer using CuK $\alpha$  radiation source ( $\lambda = 1.5406 \text{ \AA}$ ) at the analytical facility in University of Johannesburg, South Africa.

#### Synthesis of the complexes

The synthetic procedures described by [2, 9, 10] was adopted with slight modification. The complexes were prepared by stirring methanolic solutions (15 mL) of diclofenac potassium salt (0.334 g, 1 mmol) and acetaminophen (0.151 g, 1 mmol) for 30 min. A solution of 1 mmol of a salt of each Mn $^{2+}$ , Co $^{2+}$ , Ni $^{2+}$ , Cu $^{2+}$  and Zn $^{2+}$  was then added to the mixed ligand solution drop wise under magnetic stirring. The reaction mixture was refluxed for 3 h at 60 °C and left to evaporate slowly at room temperature, after which the resulting precipitates were filtered off, washed with methanol and distilled water and dried in a desiccator over CaCl $_2$ . The reactions are as presented in equations (1) and (2):



#### *In-vitro* anti-inflammatory activity

The compounds were investigated for *in-vitro* anti-inflammatory activity using protein denaturation by egg albumin assay. A 5.0 mL of solution was prepared containing 0.2 mL of egg albumin (collected from fresh hen's egg) mixed with 2.8 mL phosphate-buffered saline (PBS, pH 6.4) and 2.0 mL each of test compounds (200 ppm). A 2.0 mL of distilled water was used as control. The mixtures were heated in water bath at 37 °C for 15 min and the temperature gradually increased up to 70 °C while the samples were retained for a further 5 min. The samples were allowed to cool down to room temperature and absorbance measured at 660 nm with the use of a UV-Vis spectrophotometer [12-14]. The % inhibition of protein denaturation is calculated using equation (3) as follows:

$$\text{Equation (3) } \% \text{ inhibition} = 100 \times \left( \frac{V_t}{V_c} \right) - 1$$

where  $V_t$  = absorbance of test sample,  $V_c$  = absorbance of control

#### Antimicrobial screening

*In-vitro* antimicrobial screening was carried out using the agar diffusion technique [15]. The inhibitory action of the metal complexes was tested on bacteria isolates: *Bacillus subtilis*, *Bacillus anthrax*, *Escherichia coli*, *Salmonella typhi* and a fungus *Aspergillus niger*. A 5 mm diameter well was bored into the culture medium using a flamed cork borer. 0.5 mL each of 200

ppm and 400 ppm of the compounds were introduced into the well and allowed to disperse evenly. This process was repeated for the entire test organisms; plates were labelled and then packed carefully. The resulting medium was incubated at 37 °C for 72 hours. The zone of inhibition was measured afterwards and recorded accordingly. Experiments were done in triplicate.

## RESULTS AND DISCUSSION

The analytical and physical data are presented in Table 1. The complexes are air stable and melting points found to be slightly higher compared to the ligand acetaminophen. All the complexes were insoluble in water and most organic solvents but generally soluble in DMF suggesting their non-polar nature. The colour of the complexes varied from white, green and pink. The electrical conductivity (E.C.) values in 1 mM DMF ranges from 17.9-10.4  $\mu\text{S cm}^{-1}$  and below 90  $\Omega^{-1}\text{cm}^2\text{mol}^{-1}$ , indicating their non-electrolytic nature [16]. This result is an indication that there are no anions outside the coordination sphere of the complexes. This is further supported by the fact that  $\text{Cl}^-$  or  $\text{SO}_4^{2-}$  ions were not detected by the addition of  $\text{AgNO}_3$  or  $\text{BaCl}_2$  solutions to the solution of the complexes in nitric and hydrochloric acids respectively. The magnetic moment value for  $\text{Co}^{2+}$  complex is 4.33 BM which is within range (4.3–5.7) BM expected for high spin octahedral complexes of Co(II). For the Ni(II) complex, the value of the magnetic moment is 2.89 BM which is also within the range (2.8–3.5) BM found for paramagnetic complexes of Ni(II) with octahedral geometry. The Zn(II) complex been diamagnetic was found to have a magnetic moment of 0.16 BM as expected for complexes of metal ions with a  $d^{10}$  configuration [17]. Results of elemental analyses (Table 2) also provide evidence of stoichiometry due to the close agreement of values.

Table 1. Melting point, colour, magnetic, electrical conductance and electronic spectra data.

Compound	Empirical formula	MW (g/mol)	Colour	M.p. (°C)	Yield (%)	$\mu_{\text{eff}}$ BM	E.C. ( $\mu\text{S/cm}$ )	Electronic spectra	
								(nm)	Assignment
ace	$\text{C}_8\text{H}_9\text{NO}_2$	151.16	White	172	-	-	242.8	306	$n-\pi^*$
Kdc	$\text{C}_{14}\text{H}_{10}\text{Cl}_2\text{KNO}_2$	334.24	White	283	-	-	314.5	318 355	$\pi-\pi^*$ $n-\pi^*$
[Mn(ace)(dc)(OH) <sub>2</sub> ]	$\text{C}_{22}\text{H}_{21}\text{Cl}_2\text{MnN}_2\text{O}_5$	518.02	Pink	199.3	72	5.81	16.8	363	$n-\pi^*$
[Co-B]	$\text{C}_{22}\text{H}_{23}\text{Cl}_2\text{CoN}_2\text{O}_6$	541.27	Pink	87.9	64	4.33	16.9	554	${}^4\text{T}_{1g} \rightarrow {}^4\text{A}_{2g}$
[Ni-B]	$\text{C}_{22}\text{H}_{23}\text{Cl}_2\text{NiN}_2\text{O}_6$	541.03	Green	166.2	60	2.89	17.9	363	$n-\pi^*$
[Cu-B]	$\text{C}_{22}\text{H}_{23}\text{Cl}_2\text{CuN}_2\text{O}_6$	545.88	Green	262.1	78	2.31	14.5	388	$n-\pi^*$
[Zn-B]	$\text{C}_{22}\text{H}_{23}\text{Cl}_2\text{N}_2\text{O}_6\text{Zn}$	547.71	White	257.3	68	0.16	10.4	320	$n-\pi^*$

### Ultraviolet-Visible spectra

In the ultraviolet spectrum of acetaminophen, the absorption at 306 nm is assigned to  $n-\pi^*$  while for diclofenac potassium salt, those at 318 nm and 355 nm are assigned to  $\pi-\pi^*$  and  $n-\pi^*$  transitions respectively. These bands are found to have shifted to longer wavelengths for the complexes when compared to the parent ligands. The electronic transition only reflected within the UV range and did not show sign of transition across the visible region as expected of coloured transition metal ions except for the [Co-B] complex which exhibit a band at 554 nm and was assigned to the  ${}^4\text{T}_{1g} \rightarrow {}^4\text{A}_{2g}$  transition. In addition, the [Co-B] has a broad absorption at 322 nm. The prevalent absence of transitions in the visible region may be due to the dilute concentration used [18, 19].

Table 2. Elemental analysis.

Compound	C%		H%		N%		O%	
	Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
[Mn(ace)(dc)OH <sub>2</sub> ]	51.01	51.30	4.09	3.89	5.41	5.36	15.44	16.94
[Co-B]	48.82	47.99	4.28	4.20	5.18	5.23	17.74	17.91
[Ni-B]	48.84	47.81	4.28	4.08	5.18	5.39	17.74	16.81
[Cu-B]	48.41	48.73	4.25	3.99	5.13	5.10	17.59	17.62
[Zn-B]	48.24	48.39	4.23	4.44	5.11	5.15	17.53	17.50

## FTIR

The selective infrared spectra assignment of the ligands and complexes are presented in Table 3. The assignments have been carried out based on similar compounds. A blue shift in the stretching band of the group (C=O) of acetaminophen (1654-1691) cm<sup>-1</sup> in the complexes was observed. Also, a slight shift of the in-plane bending band of the carbonyl group in the acetaminophen from 837-839 cm<sup>-1</sup> in the complexes confirms the participation of the C=O group in the coordination. A shift of the ν(N-H) band of acetaminophen from 3327 to new bands (3282-3375 cm<sup>-1</sup>) in the complexes suggests interaction of the amide nitrogen atom with the metal centre. This was confirmed by the disappearance of the in-plane δ(N-H) at 1564 cm<sup>-1</sup> in the complexes. The appearance of the stretching band of the hydroxyl group (C-O), with respect to the phenyl moiety at positions around 1200-1250 cm<sup>-1</sup> excludes the contribution of the hydroxyl oxygen atom in the coordination. Also, the appearance of the stretching band in the hydroxyl group between oxygen and hydrogen atom at positions 3248 and 3169 cm<sup>-1</sup> verifies the assumption of the exclusion of the hydroxyl oxygen atom to be chelated to the central metal ion. The absorption at 1577.82 cm<sup>-1</sup> was assigned to the C=O of diclofenac potassium salt. This frequency is found to be lowered compared to the value for the parent carboxylic acid (1700-1730 cm<sup>-1</sup>) as a result of resonance [20]. Carboxylate ions are well known to coordinate to metal ions in several ways viz: monodentate, bidentate (chelating) or bridging modes. This deduction can be made from evidence in the IR spectrum by analyzing the COO<sup>-</sup> group bands frequencies for the symmetric stretching (ν<sub>s</sub>) and the asymmetric stretching (ν<sub>as</sub>). The parameter Δν = ν<sub>as</sub> - ν<sub>s</sub> is often employed in such analysis. For the reported complexes, Δν = (100-114 cm<sup>-1</sup>) which is lower than that of potassium diclofenac (121 cm<sup>-1</sup>) and therefore is in good agreement with data for bidentately coordinated structures [9, 21, 22]. New bands found in the spectrum of the complexes which lie in the range from 516 to 545 cm<sup>-1</sup> and 453 to 478 cm<sup>-1</sup> that were not present in the spectrum of the ligands are attributed to ν(M-O) and ν(M-N) vibrations, respectively. Appearances of new vibrational bands in the range of 862-869 cm<sup>-1</sup> found in the spectrum of the complexes were therefore assigned to ν(M-OH<sub>2</sub>). The water molecules present appears to be coordinated through the metal ion rather than individual lattice.

Table 3. Infrared spectral data of ligands and complexes (cm<sup>-1</sup>).

Compound	ν(N-H)	ν(OH)	ν(C=O)	ν <sub>s</sub> (CO <sub>2</sub> <sup>-</sup> )	ν <sub>as</sub> (CO <sub>2</sub> <sup>-</sup> )	Δν = ν <sub>as</sub> -ν <sub>s</sub>	ν(M-OH <sub>2</sub> )	ν(M-O)	ν(M-N)
ace	3327sh	3161	1654s	-	-	-	-	-	-
Kdc	3634m	-	1577s	1383s	1504s	121	-	-	-
[Mn(ace)(dc)OH <sub>2</sub> ]	3350sh	3292	1606s	1450s	1552s	102	866w	534w	453w
[Co-B]	3375sh	3248	1691m	1398s	1508s	110	868w	534w	468w
[Ni-B]	3315sh	3196	1566m	1452s	1566m	114	866w	534w	464w
[Cu-B]	3323sh	3452	1620s	1396s	1496m	100	868w	524w	474w
[Zn-B]	3282sh	3169	1691m	1402s	1510s	108	869w	545w	478w

m-medium, sh-sharp, s-strong, br-broad, w-weak.

*X-Ray powder diffraction (XRPD) study*

Powder X-ray diffraction studies were carried out by using X-ray diffractometer (Bruker D8 equipped with PW-3064 spinner). The samples were irradiated with CuK $\alpha$  radiation source ( $\lambda = 1.5406\text{\AA}$ ) and analyzed over the range of Bragg angles  $20.003^\circ$  to  $90.006^\circ$  ( $2\theta$ ). The superimposed XRPD patterns are shown in Figure 2. The patterns obtained for the ligands and complexes were different. Peaks observed are at  $2\theta$ : (25.07, 27.86, 30.87, 55.79, and  $76.42^\circ$ ) and (38.24, 61.50 and  $68.49^\circ$ ) for ace and Kdc, respectively. The complex [Co-B] has peaks at  $2\theta$ : (38.22, 44.47 and  $82.21^\circ$ ). As a result of the absence of some peaks in the complexes which were originally present in the free ligands, it shows the occurrence of possible complexation [23].

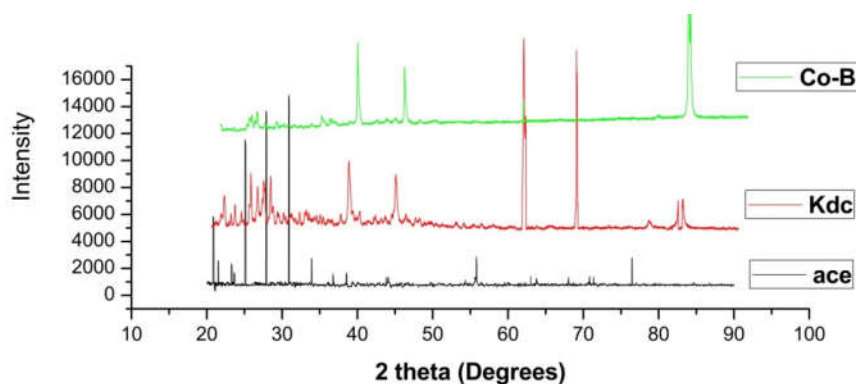


Figure 2. XRPD patterns collected from CuK $\alpha$  radiation on a Bruker D8 diffractometer. The pattern was recorded from a PW-3064 spinner using a step scan over the range of Bragg angles  $20^\circ \leq 2\theta \leq 90^\circ$  with a  $0.0167^\circ$  of  $2\theta$  step and counting time of 88 s per step.

*Anti-inflammatory screening*

The result presented in Table 4 indicated that the compounds possessed moderate anti-inflammatory activity by their protein denaturation inhibition. For instance, the complex [Cu-B] has 45.17% inhibition when compared to 58.24% for diclofenac potassium salt (standard) all at a concentration of 200 ppm. The experiments were done in triplicate determinations and the results depicted as mean  $\pm$  Standard error of mean (SEM).

Table 4. Anti-inflammatory activity data by egg albumin denaturation.

Compound	% Inhibition
Kdc	$58.24 \pm 1.96$
[Mn(ace)(dc)OH <sub>2</sub> ]	$38.72 \pm 1.08$
[Co-B]	$36.28 \pm 1.55$
[Ni-B]	$35.45 \pm 1.97$
[Cu-B]	$45.17 \pm 2.15$
[Zn-B]	$39.22 \pm 1.35$

Results are expressed as mean  $\pm$  SEM (n = 3).

*Antimicrobial screening*

Antimicrobial activities at 200 ppm and 400 ppm are shown in Figure 3. Zones of inhibition against the test organisms are shown in Figure 4. The results of antimicrobial activity screening are as shown in Table 5. The complexes were found to have an increased activity against the strains of microorganisms as compared to the parent ligands. A slight increase in activity with increased concentration was observed. [Ni-B] has the highest inhibitory activity at 400 ppm against *Bacillus anthrax*. [Zn-B] showed the highest inhibitory activity against *Bacillus subtilis* while the complexes were moderately active against the gram(-ve) bacteria. However, there was no activity against the fungus, *Aspergillus niger*. The increased activity is expectedly due to chelation which reduced the polarity of the metal ion, mainly because of partial sharing of its positive charge with donor groups of the ligand and possible  $\pi$ -electron delocalization on the aromatic rings. Thus, the lipophilicity of the drug is enhanced and the drug action is significantly increased due to effective permeability of the drug into the site of action [24].

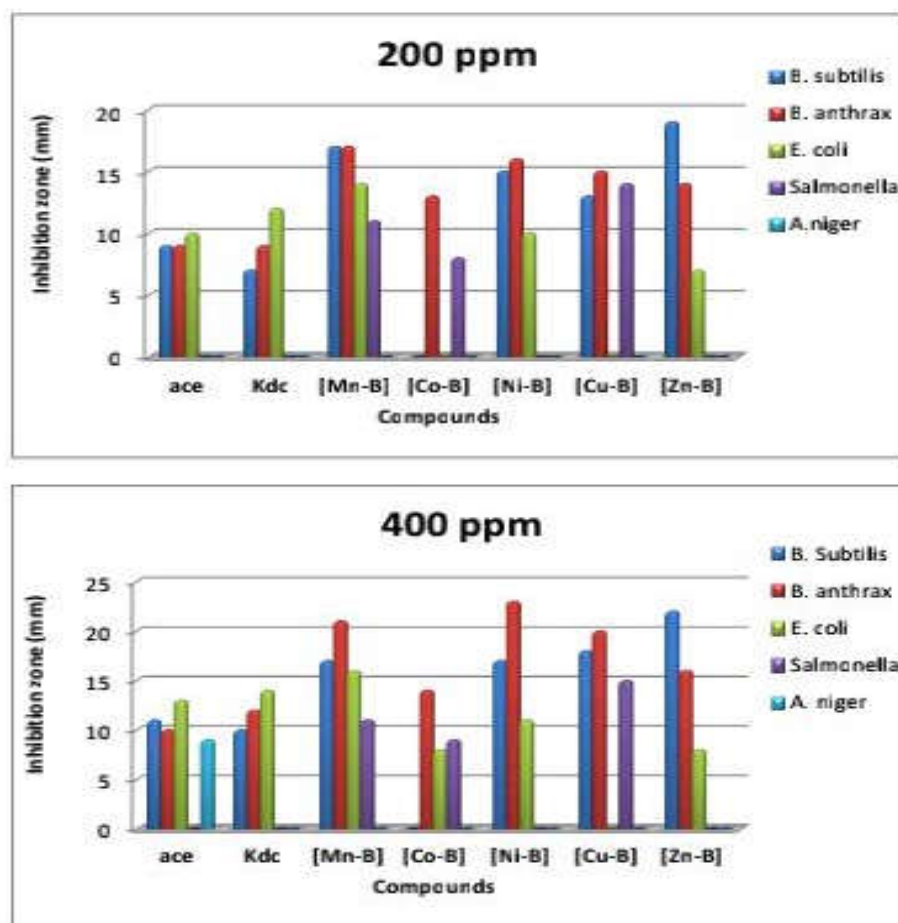


Figure 3. Chart showing antimicrobial activity at 200 ppm and 400 ppm.

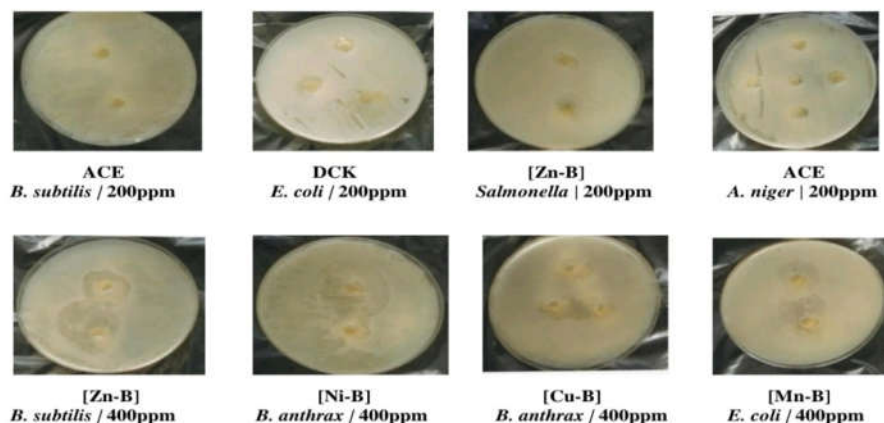


Figure 4. Plates showing zones of inhibition against the test organisms.

Table 5. Antimicrobial screening result.

Compound	<i>Bacillus subtilis</i>		<i>Bacillus anthrax</i>		<i>E. coli</i>		<i>S. typhi</i>		<i>A. Niger</i>	
	Zones of inhibition (mm)									
Concentration (ppm)	200	400	200	400	200	400	200	400	200	400
ace	9	11	9	10	10	13	0	0	0	9
Kdc	7	10	9	12	12	14	0	0	0	0
[Mn(ace)(dc)OH <sub>2</sub> ]	17	17	17	21	14	16	11	11	0	0
[Co-B]	0	0	13	14	0	8	8	9	0	0
[Ni-B]	15	17	16	23	10	11	0	0	0	0
[Cu-B]	13	18	15	20	0	0	14	15	0	0
[Zn-B]	19	22	14	16	7	8	0	0	0	0

## CONCLUSION

In this research, refluxing method has been used to prepare  $Mn^{2+}$ ,  $Co^{2+}$ ,  $Ni^{2+}$ ,  $Cu^{2+}$  and  $Zn^{2+}$  complexes of mixed acetaminophen and diclofenac potassium salt. The complexes were characterized using some physicochemical and spectroscopic techniques. [Ni-B] complex has the highest inhibitory activity at 400 ppm against *Bacillus anthrax*. The anti-inflammatory activity revealed the [Cu-B] complex to be the best with a 45.17% inhibition at a concentration of 200 ppm. Some of the compounds showed moderate anti-inflammatory activity when compared to the diclofenac potassium salt which served as the test standard. It is evident to say that nearly all the metal complexes possess mild zone of inhibition against bacterial species, thus suggesting them as promising antidotes in metal chemotherapy. Further investigation of the complexes could be extended towards their thermal behavior using TGA/DTG as well as toxicological studies.

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## REFERENCES

- Demertzi, D.K. Recent advances on nonsteroidal anti-inflammatory drugs, NSAIDs: Organotin complexes of NSAIDs. *J. Organomet. Chem.* **2006**, 691, 1767-1774.
- Lawal, A.; Obaleye, J.A. Synthesis, characterization and antibacterial activity of aspirin and paracetamol-metal complexes. *Biokemistri* **2007**, 19, 9-15.
- Hariprasath, K.; Deepthi, B.; Sudheer, B.I.; Venkatesh, P.; Sharfudeen, S.; Soumya, V. Metal complexes in drug research - A review. *J. Chem. Pharm. Res.* **2010**, 2, 496-499.
- Farrell, N.P. *Transition Metal Complexes as Drugs and Chemotherapeutic Agents in Catalysis by Metal Complexes*. James, B.R.; Ugo, R. (Eds.), Reidel-Kluwer Academic Press: Dordrecht, Netherlands; **1989**; Vol. 11, p 304.
- Warra, A.A. Transition metal complexes and their application in drugs and cosmetics – A review. *J. Chem. Pharm. Res.* **2011**, 3, 951-958.
- Imran, T.; Ahmad, M.M.; Tariq, S.; Pervaiz, A.S.; Syed, A.R.; Najam ul Hassan, J.; Ali, M.Y.; Ghulam, A. In vitro release studies of diclofenac potassium tablet from pure and blended mixture of hydrophilic and hydrophobic polymers. *Lat. Am. J. Pharm.* **2012**, 31, 380-387.
- Sweetman, S.C. Martindale, A. *The Complete Drug Reference*, 33rd ed., Pharmaceutical Press: London; **2012**; p 89.
- Pandeya, S.N.; Sriram, D.; Nath, G.; DeClereq, E. Synthesis, antibacterial, antifungal and anti-HIV activities of Schiff and Mannich bases derived from isatin derivatives and N-[4-(4'-chlorophenyl)thiazol-2-yl]thiosemicarbazide. *Eur. J. Pharm. Sci.* **1999**, 9, 25-31.
- Pramila, S.; Anuradha, S. Synthesis, characterization and anti-inflammatory effects of Cr(III), Mn(II), Fe(III) and Zn(II) complexes with diclofenac sodium. *Indian J. Chem.* **2000**, 39(A), 874-876.
- Refat, M.S.; Mohamed, G.G.; El-Sayed, M.Y.; Killa, H.M.A.; Fetooh, H. Spectroscopic and thermal degradation behavior of Mg(II), Ca(II), Ba(II) and Sr(II) complexes with paracetamol drug. *Arab. J. Chem.* **2013**, 4, 1878-5352.
- Rajee A.O.; Aliyu, A.A.; Babamale, H.F.; Lawal, A.; Ayinla, S.O.; Osunniran, W.A.; Obaleye, J.A. Preparation, characterization and antibacterial activity of Mn(II), Cu(II) and Zn(II) complexes of methionine and 2,2-bipyridine co-ligands. *J. Kenya Chem. Soc.* **2020**, 13, 16-21.
- Sen, S.; Chakraborty, R.; Maramsa, N.; Basak, M.; Deka, S.; Dey, B.K. In vitro anti-inflammatory activity of *Amaranthus caudatus* L. leaves. *Indian J. Nat. Prod. Resour.* **2015**, 6, 326-329.
- Fernandes, J.; Revanasiddappa, B.C.; Ishwarbhat, K.; Vijay Kumar, M.; D'Souza, L.; Alva, S.S. Synthesis and in-vitro anti-inflammatory activity of novel pyrazoline derivatives. *Res. J. Pharm. Technol.* **2017**, 10, 1679-1682.
- Konda, R.K.; Kumar, Y.P.; Mohamed Saleem, T.S. Microwave assisted synthesis and anti-inflammatory activity of Schiff base complexes derived from meta chloro aniline and salicylaldehyde. *EJPMR* **2016**, 3, 321-325.
- Bauer, A.W.; Kirbi, W.M.; Sherris, J.C. Antibiotic susceptibility testing standardized single disc method. *Am. J. Clin. Pathol.* **1996**, 45, 493-496.
- Vogel, V.T. *Textbook of Practical Organic Chemistry*, 4th ed., John Wiley Inc.: England; **1989**; pp 133-325.
- Agarwal, R.K.; Sharma, D.K.; Shing, L. Synthesis, spectral, and biological properties of copper(II) complexes of thiosemicarbazones of Schiff bases derived from 4-aminoantipyrine and aromatic aldehydes. *Bioinorg. Chem. Appl.* **2006**, 3, 29238.
- Shoab, K.; Rehman, W.; Mohammad, B.; Ali, S. Synthesis, characterization and biological applications of transition metal complexes of [NO] donor Schiff bases. *J. Proteomics Bioinform.* **2013**, 6, 7.

19. Bagihalli, G.B.; Patil, S.A. Synthesis, physico-chemical investigations, and in vitro microbial, studies of VO(IV) complexes with novel ONON donor Schiff bases. *Main Group Chem.* **2010**, *8*, 71-88.
20. Pavia, D.L.; Lampman, G.M.; George, S.K. *Introduction to Spectroscopy, A Guide for Students of Organic Chemistry*, 3rd ed., Online Publication; **2007**; p 78.
21. Ali, H.A.; Omar, S.N.; Darawsheh, M.D.; Fares, H. Synthesis, characterization and antimicrobial activity of zinc(II) ibuprofen complexes with nitrogen-based ligands. *J. Coord. Chem.* **2016**, *69*, 1110-1122.
22. Nakamoto, K. *Infrared and Raman spectra of Inorganic and Coordination Compounds, Part B: Applications in Coordination, Organometallic, and Bioinorganic Chemistry*, 6th ed., Wiley: New Jersey; **2009**.
23. Tita, B.; Stefanescu, M.; Tita, D. Complexes of anti-inflammatory non-steroidal drugs from carboxylic acids family: Synthesis and characterization of Zn(II) complex with Ibuprofen. *Rev. Chim.* **2011**, *62*, 1060-1064.
24. Chohan, Z.H. Antibacterial copper(II) complexes of 1,1-symmetric ferrocene-derived Schiff-base ligands: Studies of the effect of anions on their antibacterial properties. *Appl. Organomet. Chem.* **2002**, *16*, 17-20.