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Research Article

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SYNTHESIS, CHARACTERIZATION, CRYSTAL STRUCTURE AND ANTIMICROBIAL ACTIVITIES OF A DIMERIC COPPER (I) CHLORIDE - PHENANTHROLINE COMPLEX {[CU(C$_{12}$H$_8$N$_2$)$_2$Cl].5.5H$_2$O}$_2$n

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Abstract

A novel binuclear Cu (I) Dimeric chloride complex with phenanthroline has been isolated. The structure of this compound has been elucidated using elemental analysis, infrared spectroscopy, and X-ray crystallography. The title complex crystallizes in the monoclinic system, space group, C 121, with a = 23.270(5) Å, b = 30.206(5) Å, c = 7.494 (5) Å, ß = 97.75 (0) °. The *in vitro* antibacterial activity of the complex shows considerable activity against some nine bacterial strains. The results indicate that the complex is bactericidal.

Keywords: 1,10-phenanthroline, antimicrobial, Cu(I).

Introduction

Copper is an important trace element in living organisms that plays very vital roles in different enzymatic processes; superoxide dismutase, cytochrome oxidase, tyrosinase, azurin and cerulopasmin all involving oxidation and reduction [1]. Some copper complexes catalyze radical formation while others act as antioxidants [2]. These different roles of copper in an organism are dependent on the chemical environment and the nature of the chelating agents.

Copper (I) disproportionates in solution to copper (II) and copper. However, when it is coordinated to chelating ligands, a favorable geometry around the copper (I) ion can stabilize the complex considerably [3]. Copper (I) is a highly versatile metal ion from a coordination standpoint, readily adopting coordination numbers, two, three and four. [3,4]. Five coordinate copper (I) structures are rare and have at least one significantly elongated Cu-ligand bond [3,5].

Complexes with [Cu(phen)$_2$Cl]$^+$ have received much attention due to the extensive range of geometries formed by the [Cu(phen)$_2$Cl]$^+$, from trigonal bipyramidal to square pyramidal [5].

Despite the apparent use of Cu(I) complexes in photochemical and photophysical applications, attributed to charge transfer transitions with appreciable MLCT character [6,7], the investigation of antimicrobial properties of copper (I) in the literature are remarkably few.

1,10-phenanthroline and its metal complexes represent a novel set of highly active antifungal and antimicrobial [8-10] agents whose mode of action is significantly different from that of the frequently prescribed polyene and azole drugs.

In our previous works [8-10], we reported the antibacterial and antifungal properties of mixed-ligand complexes containing 1,10-phenanthroline and 2,2'-bipyridine. The high antimicrobial activity of 1,10-phenanthroline and the upsurge of infectious disease in our country, Cameroon, caused by some bacterial strains has led us to carry out more research work on the antimicrobial activity of Cu(I) and phenantholine analogue on these pathogens. In this paper, we report on the synthesis, structural characterization and antimicrobial properties of a dimeric Cu (I) chloride phenanthroline complex against some resistant bacterial strains.

Experimental

Commercial reagents were used as obtained without further purification. 1,10-phenanthroline and picolinic acid were purchased from Riedel-de Haën Germany), while $CuCl_2.2H_2O$ was purchased from Labosi (France). The solvents, ethanol and diethylether were dried and distilled according to standard methods. The bacteria species were clinical isolates from the Centre Pasteur Laboratory of Yaoundé Cameroon.

Synthesis

The complex was prepared by adding simultaneously and dropwise, solutions of 1,10-phenanthroline (0.99 g, 5.0 mmol) and picolinic acid (1.23 g, 10.0 mmol) in 20 mL of ethanol to a solution of $CuCl_2.2H_2O$ (0.85 g, 5.0 mmol) in 10 mL of water while stirring magnetically under a water bath at room temperature. Stirring was continued for one more hour and the resulting deep blue solution was allowed to stand for four days during which green finger-like crystals were observed to form. Sufficient crystals were formed during five additional days and these were filtered, washed with diethylether and dried in *vacuum*. Yield was 85%. Elemental analysis calculated for $C_{24}H_{38}$ CuN_4ClO_{11} (%): C=43.90, N=8.58, H=5.87; found C=43.86, N=8.43, H=5.77. Characteristic IR absorption (KBr) cm^{-1}: (C=N)1625, (C=C)1420, (C-H)738/860, (M-N)680, (M-Cl) 550.

Physical measurements

Elemental analysis for carbon, nitrogen and hydrogen were carried out on a Fisons instrument 1108 CHNS-O, while Infrared spectrum of the compound was recorded between pressed KBr discs in the range (4000-400 cm^{-1}) on a Perkin- Elmer model IR-457 spectrometer and a spectrum 100 FT-IR Perkin- Elmer spectrometer, at Institut de Chimie Moléculaire de Reims CNRS UMR 6229, Groupe de Chimie de Coordination, Faculté des Sciences, Université de Reims Champagne, Ardennes, France.

X-ray diffraction determination

A suitable single crystal of dimension, 0.3 x 0.3x 0.3 mm was mounted each on a glass fiber in a random orientation. Intensity data collection was carried out with SMART three-circle diffractometer equipped with a CCD bidimensional diffractometer using monochromatic radiation, (Mo-K) = 0.71073 Å, operating at 50kV and 40mA. Data were collected at 100 K (width of 0.30° and exposure time of 10s per frame).

The structure of the complex was solved by direct methods and refined by full matrix least squares, based on F^2 using SHELX-TL software package [11]. An empirical absorption correction based on symmetric equivalent reflections was applied using the SADABS program [12]. All the hydrogen positions were initially located in different maps and final refinement for the hydrogen atom was done by placing geometrically and holding in the riding mode. The last cycles of the refinement included atomic positions for all the atoms, anisotropic thermal parameters for all non-hydrogen atoms and isotropic thermal parameters for all the hydrogen atoms.

Anti-microbial tests

Nine species of microorganisms, *Enterobacter cloacae, Morganella morganii, Shigella flexneri, Salmonella typhi, Klebsiella pneumonia, Citrobacter freundii, Escherichia coli, Pseudomonas aeruginosa* and *Staphylococccus aureus* used for this study were provided by Centre Pasteur du Cameroon, Yaoundé. The selected microorganisms represent the causative agents for diseases that are prevalent in our environment. The microbial isolates were maintained on agar slant at 4°C in the laboratory. The strains were sub-cultured on fresh appropriate agar plate in incubators 18 hours prior to any antimicrobial test.

Nutriment Agar (NA) containing Bromocresol Purple was used for the activation of Bacillus species while NA alone was used for the other bacteria. The Colombia Agar Medium (CAM) was used for the diffusion assays determination. In-vitro antibacterial activities of the ligands, metal salts and complexes were evaluated by the well- diffusion method. Muller-Hinton broth was employed as microbial growth medium.

Diffusion tests/MIC determination

The antimicrobial diffusion tests were carried out as described by Berghe and VLietink [13] using a cell suspension of about $1.5 x 10^6$ CFU / mL obtained from

the MCFarland turbidity standard N° 0.5. The suspension was standardized by adjusting the optical density to 0.1 at 600 nm (SHIMADZU UV-120-01 spectrophotometer).

The suspension was used for inoculation by flooding the surface of the CAM plates. When the excess liquid was allowed to dry under an aspirator hood, holes of 6 mm diameter were made in the medium and filled with 60 µL of test samples. Holes with methanol were used as negative control. The plates were inoculated at 37°C for 24 hours. Antibacterial activity was evaluated by measuring the diameter of the inhibition zone (IZ) around the hole. The assay was repeated thrice and the results recorded as mean ± standard deviation of triplicated experiments. Compounds were considered as active when the IZ was greater than 6mm.

The Micro broth dilution method [14] was used to determine the minimum inhibitory concentration (MIC) of the compound and reference antibiotic (RA) on a given microorganism. The principle is based on a series of 2 fold dilution of the compound carried out in wells of a micro titer plate in the presence of a broth culture medium. After adding the inoculums and incubating, the lowest concentration of the compound that completely inhibits the growth of the microorganism is identified as the MIC.

Minimum Bactericidal concentration (MBC)

The MBC was determined by sub-culturing the last tube to show growth and all the tubes in which there was no growth. An aliquot of 100 µL from all the tubes in which no visible bacterial growth was observed was seeded in nutrient agar plates and incubated at 37° C for 24 hours. The MBC reported as the lowest concentration that showed no growth, is defined as the lowest concentration of antimicrobial agent that kills more than 99% of the initial bacteria population where no visible growth of bacteria was observed on the nutrient agar plates. Antimicrobial agents for which the ratio MBC/MIC > 4 are said to be bacteriostatic, while those for which the ratio MBC/MIC < 4 are bactericidal [15].

Results and Discussion

Elemental analysis of the title complex indicates that one mole of $CuCl_2$ reacted with two moles of 1,10-phenanthroline giving the complex **{[CU($C_{12}H_8N_2$)$_2$CL]5.5H$_2$O}$_2$**n.

The green crystalline solid was obtained with a yield of 85% and is considerably air stable.

The Picolinic acid reduced the copper from +2 to +1.

In the infrared spectrum of the complex, the characteristic strong intense bands in free 1,10-phenanthroline, between 1400 and 1600 cm^{-1} region attributed to the vibration frequency of C=C and C=N of the aromatic ring [16,17],were shifted to (1420-1625) cm^{-1} in the complex. This shift by 20 and 25cm^{-1} respectively to a higher frequency shows that phen is coordinated to the metal centre [9,10]. Similarly, the strong intense bands at approximately 738 cm^{-1} and 860cm^{-1} attributed to the out- of –plane vibrations of the hydrogen atoms on the phenyl ring of phen [16,17], undergo a coordination induced higher frequency shift of 13 cm^{-1} and 10 cm^{-1} respectively. The stretching vibrations of the v (M-N) mode and v (M-Cl) appear at the 680 cm^{-1} and 550 cm^{-1} region.

The ORTEP view of the title complex, together with the atom numbering scheme is shown in figure 1 while figure 2 shows the alternate arrangement of the complex showing Face-to-face - interactions of aromatic rings and C-H…Cl hydrogen bonding in the polymeric structure. The coordination polyhedron of the copper atom is distorted square-pyramidal, where the four nitrogen atoms from two bidentate phenanthroline ligands form the base of the polyhedron and the chlorine atoms (ClO3 and ClO4) occupy the axial position and the Cu-Cl bond is significantly elongated (Fig.1). The bond lengths and angles are typical for copper diimine complexes [5, 18]. In square pyramidal coordination the axial Cu-Cl distances were 2.328-2.345 Å while the lengths of the Cu-N distances were 1.964 -2.126 Å. The coordinating ligands and copper atoms form N-Cu-N bite angles of 79.7-82.9 ° and are normal for metal-phenanthroline complexes [5,18]. The Cl atoms and water molecules form a two-dimensional network through hydrogen-bonding interactions and the cations of [Cu(phen)$_2$Cl]$^+$ further extend the two-dimensional network into three-dimensional architecture through C-H…Cl hydrogen bonding. Meanwhile the two phen rings are parallel to each other and cause significant - stacking and the two types of interactions mutually strengthen and solidify the polymer.

One of the phen rings in the [Cu(phen)$_2$Cl]$^+$ cation takes part in the formation of the dimer unit via - interactions. The remaining one also produces - interactions resulting in the polymer shown in fig. 2. Thus, the binuclear [Cu(phen)$_2$Cl]$_2$$^{2+}$ units are linked to each other in 3D space. The crystal lattice water molecules are involved in the hydrogen bonding network, making the system stable, thus a unique dimer structure constructed through C-H…Cl hydrogen bonding, and - interactions.
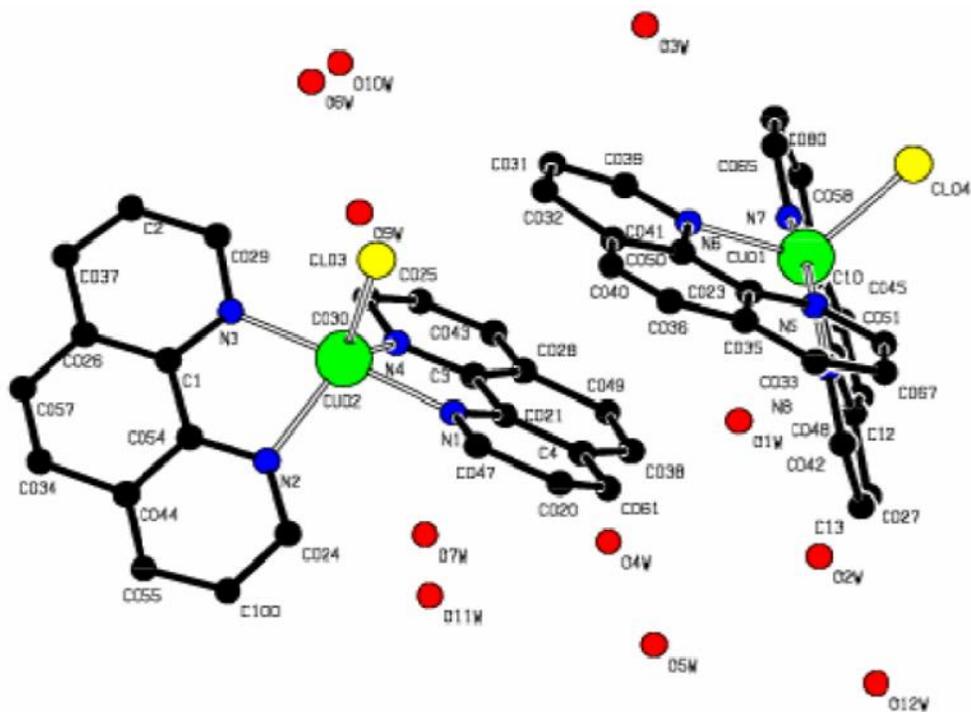
Figure 1: ORTEP diagram of the complex with the atom numbering scheme. Thermal ellipsoids are drawn at the 30% probability level
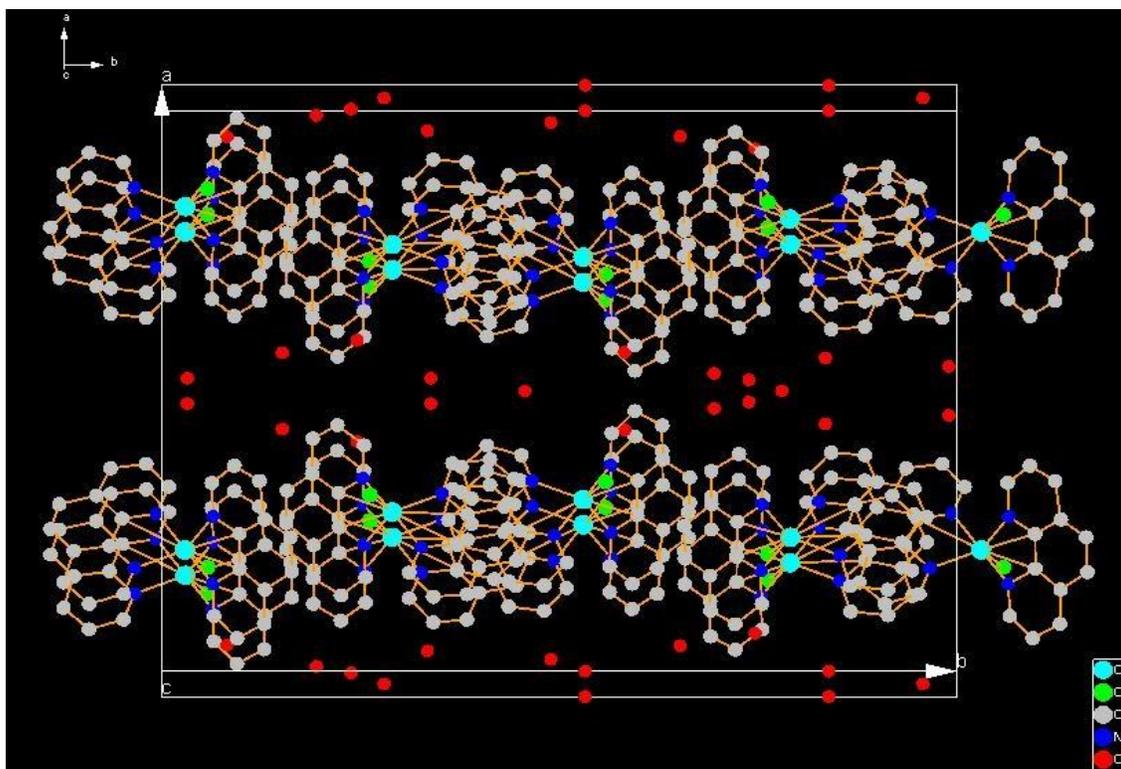
Figure 2: A view of the polymeric structure extended via C-H…Cl hydrogen bonding, and - interactions.

Table 1: Crystallographic data

Formula sum	$C_{96}Cl_4Cu_4N_{16}O_{18}$ (H atoms omitted)
Formula weight	2061.08 g/mol
Crystal system	Monoclinic
Space group	C1 2 1
Cell parameters	a = 23.270(5) Å, b = 30.206(5) Å, c = 7.494 (5)Å, ß = 97.75 (0) °
Cell ratio	a/b = 0.7704, b/c = 4.0307, c/ a = 0.3220
Cell volume	5219.32 (517) Å^3
Z	2
Calc. density	1.3114 g/cm^3
R-factor %	8.79
Refinement method	Full covariance matrix least squares
Data / restraints / parameters	3815/6/118
Goodness-of-fit on F^2	1.000
Final R indices [I>2sigma(I)]	R_I = 0.0264, wR_2 = 0.0684
R indices (all data]	R_I = 0.0347, wR_2 = 0.0745

Table 2: Selected bond lengths (Å) and angles (°) for compound

CuO1-ClO4	2.345(3)	CuO2-ClO3	2.328(3)
CuO1-N8	2.086(7)	CuO2-N4	2.081(7)
CuO1-N7	1.964(7)	CuO2-N1	1.998(9)
CuO1-N6	2.119(9)	CuO2-N2	2.168(8)
CuO1-N5	1.981(8)	CuO2-N3	1.995(8)
ClO4-CuO1-N8	121.6(2)	ClO3-CuO2-N2	122.6(2)
ClO4-CuO1-N7	92.5(2)	ClO3-CuO2-N3	92.5(2)
ClO4-CuO1-N6	114.6(2)	ClO3-CuO2-N4	115.6(2)
ClO4-CuO1-N5	92.9(2)	ClO3-CuO2-N1	89.9(3)
N8-CuO1-N7	82.9(3)	N4-CuO2-N1	81.4(3)
N8-CuO1-N6	123.7(3)	N4-CuO2-N3	99.5(3)
N8-CuO1-N5	93.5(3)	N4-CuO2-N2	121.7(3)
N7-CuO1-N6	98.0(3)	N1-CuO2-N3	176.8(3)
N7-CuO1-N5	174.5(3)	N1-CuO2-N2	97.1(3)
N6-CuO1-N5	80.5(3)	N3-CuO2-N2	79.7(3)

Anti-microbial Tests

The results of susceptibility of these microbes towards the compounds, judged by measuring the inhibition zone growth diameter (IZ), are presented in Table 3. A compound was considered as active when the IZ was greater than 6mm.

The ligand, 1,10-phenanthroline exhibited the greatest activity (9/9) pathogens with high inhibition zones ranging from (28 to 32) mm, followed by metal complex, with high activity (9/9) with inhibition zones ranging from (21-29) mm, while the metal salt showed relatively very low inhibition zones (7-8) mm. Therefore the metal complex has greater antimicrobial activity than the free metal ion which is in agreement with the literature. [19,20]. This shows that bioactivity of the metal ions increases upon coordination. The increase in activity on coordination could be explained

by Overtone's concept and chelation theory [21]. According to Overtone's concept of cell permeability, the lipid membranes that surround the cell favour the passage of only lipid-soluble material and lipid-solubility is an important factor that controls antimicrobial activity. On coordination, the polarity of the metal ion is reduced due to overlap of the ligand orbital and the partial sharing of the positive charge of the metal ion with the donor atoms of the ligand and possible -electron delocalization over the whole chelate ring. Such chelation may increase the lipophilic character of the metal complex, enabling it to permeate the lipid membrane of the bacteria. Furthermore, the mode of action of the complexes may involve formation of a hydrogen bond through the azomethine (>C N) group with the active centers of cell constituents, resulting in interference with the normal cell processes [22].

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The ratio, MBC/MIC $\leq$ 4 indicates that the complex is bactericidal, thus could further be studied as a potential relief for the fight against antimicrobial resistance.

Table 3: Antimicrobial activities of ligand, metal salt, Reference antibiotic and complex

Bacteria	IZ/mm				MIC Of complex/ μL	MBC Of complex/ μL	MBC/ MIC
	D	E	F	RA			
E. cloacae	32	-	26	21	625	625	1
S. aureus	31	7	21	18	1250	2500	2
E. coli	31	8	29	24	625	1250	2
M.morganii	30	-	27	23	625	1250	2
S. thyphi	32	-	28	24	625	1250	2
K.pneumoniae	28	7	29	23	625	1250	2
S. flexineri	31	8	34	27	625	1250	2
C. freundi	30	-	24	24	1250	2500	2
P. aeruginosa	31	-	23	23	1250	2500	2

IZ = inhibition zone; D = 1,10-phenanthroline (phen) ; E = $CuCl_2.2H_2O$,
F = $\{[CU(C_{12}H_8N_2)_2CL]5.5H_2O\}_2n$;
RA = Reference antibiotic = Gentamycin

Conclusion

A square pyramidal, $[Cu(phen)_2Cl]^+$ type compound has been synthesized having a dimer structure. The mononuclear units of $[Cu(phen)_2Cl]^+$ were connected via C-H…Cl hydrogen bonding and - stacking interactions, giving rise to a polymeric structure.

The dimer, $\{[CU(C_{12}H_8N_2)_2Cl]5.5H_2O\}_2n$ crystallizes in the monoclinic crystal system, space group *C 1 2 1*, with coordinates a = 23.270(5) Å , b = 30.206(5) Å, c = 7.494(5) Å, ß = 97.75°. The axial Cu-Cl distances in the complex were 2.328-2.345 Å, while the ligands and the copper (I) atoms form N-Cu-N bite angles of 79.7-82.9.

In vitro antimicrobial studies of the ligand, metal salt and complex against nine bacterial strains reveal enhanced activity of metal salt upon coordination. The ratio, MBC/MIC $\leq$ 4 shows that the complex is bactericidal and could be a potential remedy for antimicrobial resistance.

References

1. M. Pavelka, V. Jaroslav, Burda, "Theoretical description of copper (I)/Cu(II) complexes in mixed ammine-aqua environment. DFT and ab initio quantum chemical study", *Chemical Physics*, **2005**, 312, 193-204.

2. M. Pellei, G.G. Lobbia, C. santini, R.Spagna, M.Camalli, D. Fedeli, G. Falcioni, "Synthesis, characterization and antioxidant activity of New Copper (I) complexes of Scorpionate and Water Soluble Phosphane Ligands", **Dalton Trans**., **2004**, 17, 2822-2828.

3. F. Cotton, G. Wilkinson, C. Murillo, M. Boschmann, Advanced Inorganic Chemistry, **1999**, 6th Edn., John Wiley and sons, 855-876.

4. L.M Marica, X. Ottenwaelder, T.D.P. Stack, "Structure and Spectroscopy of Copper-Dioxygen Complexes", *Chem. Rev.*, **2004**, 104, 1013-1046.

5. H.-Y. He, Y.-L. Zou, Y.- N. Chen, L.-G. Zhu , "Crystal structure of [chlorobis(1,10-phenanthroline) copper (II)"] chloride 3,5-dihydroxybenzoic acid solvate monohydrate,$[CuCl(C_{12}H_8N_2)Cl.C_6H_3(OH)_2COOH.H_2O]$", *Z. Kristallogr.*, **2005** NCS 220, 448-450.

6. D.-M. Zink, D. Volz, T.B.M. Mydlak, H. Flügge, J.F.M. Nieger, S. Brase, "Heteroleptic, Dinuclear Copper(I) Complexes for Application in Organic Light-Emitting Diodes", Chemistry of materials, **2013,** 25(**22**), 4471-4486.

7. J.-P. Zhang, Y.-Y. Lin, X.-C. Huang, X.-M. Cheng, "Copper (I) 1,2,3- Triazolates and related complexes; studies of the solvothermal ligand reactions, network topologies and photoluminescence properties", J. AM. Chem. Soc., **2005**, 127(**15**), pp 5495- 5506.

8. M.O. Agwara, P.T. Ndifon, N.B. Ndosiri, A.G. Paboudam, D.M. Yufanyi, A. Mohamadou, "Synthesis, Characterization and Antibacterial Activities of Co(II), Cu(II), and Zn(II) Mixed-ligand complexes containing 1,10 -phenanthroline and 2,2'-bipyridine", *Bull. Chem. Soc. Ethiop.*, **2010**, 24(3), 001-007.

9. M.O Agwara, A.G. Paboudam, J .T. Musongong, F. Tekom, N.B. Ndosiri, I.P. Binda, "Synthesis, Characterization and Antibacterial Activities of Manganese(II), Nickel(II), Zinc(II) and Cadmium(II) Mixed-ligand complexes containing 1,10-phenanthroline and 2,2'-bipyridine", Annales de la Faculté des Sciences. Université de Yaoundé I, Vol. 37, (**1**), **2010**, série Chimie.

10. N.B. Ndosiri, M.O. Agwara, A.G. Paboudam, P.T. Ndifon, D.M. Yufanyi, C. Amah, "Synthesis, Characterization and Antifungal Activities of Mn(II), Co(II), Cu(II), and Zn(II) Mixed-ligand complexes containing 1,10 -phenanthroline and 2,2'-bipyridine", *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, **2013**, 4(**1**), 386-397.

11. V. A. Berghe, A. J. Vlietinct, "Screening Methods for Antibacterial and Antiviral Agents from Higher Plants", *Methods for Biochemistry*, **1991**, 6, 47-68.

12. J .S. Carvallert,…[et al.], "Manual of Antimicrobial Susceptibility Testing, Library of Congress Cataloging-in-Publication Data", *American Society for microbiology*, **2005**, 1-231.

13. B. Carbonnelle, F. Denis, A. Marmonier, G. Pinon, R. Vague, Bactériologie Médicale : Techniques Visuelles, **1987**, SIMED, South Africa, 228-282.

14. C. Barry, K. Kwanagh, M. Mcxcann, M. Devereux, M. Geraghty, "Mode of antifungal activity of 1,10-Phenanthroline and its Cu(II), Mn(II) and Ag(I) Complexes", *Biometals*, **2003**, 16 (2), 1572-1773.

15. M.O. Agwara, P.T. Ndifon, M.K. Ndikontar, M.A. Atamba, "Synthesis, Characterisation and Antimicrobial Activities of Co(II), Ni(II) and Cu(II) Complexes of Hexamethylenetetramine Ligand", Res. J. Chem. Soc. Ethiop., **2008**, 18(2), 143-148.

16. A.A. Schilt, R.C. Taylor, "Infrared Spectra of 1,10-phenanthroline Metal Complexes in the Rock Salt Region below 2000 cm^{-1}", *J. Inorg. Nucl. Chem.*, **1959**, 9, 211-221.

17. A.K. Boudalis, V. Nastopoulos, S.P. Perlepes, "Reactions of 2,2'-bipyridine and 1,10-phenanthroline with Yittrium(III) nitrate: Preparation, X-ray of Bis-bipy and Bis-phen complexes", *Transition Metal Chem.*, **2001**, 26, 276-281.

18. B.-Q Ma, S. Gao, T. Yi, C.-H Yan, G.-X. Xu, "A dimer structure {Cu(phen)$_2$Cl][OH].6H$_2$O}$_2$ constructed through C-H…Cl hydrogen bondings and - interactions",*Inorganic Chemistry Communications*, **2000**, 3, 93-95.

19. A.A. Nejo, G. A. Kolawole, A.O. Nejo, "Synthesis, Characterisation, Antibacterial and Thermal Thermal Studies of unsymmetrical Complexes of Cobalt(II)", *Journal of Coordination Chemistry*, **2010**, 63(24), 4398-441.

20. S.C. Singh Jadon, N. Gupta, R.V. Singh, *Ind. J. Chem.*, **1995,** 34 A, 733.

21. Z. H. Chohan, A. Munawar, C.T. Supuran, "Transition Metal Ion Complexes of Schiff Bases. Synthesis, Characterisation and Antibacterial Properties", *Metal Basesd Drugs*, **2001**, 8(3), 132-143.

22. Z. H. Chohan, S. Kuausar, "Synthesis, Characterisation and Biological Properties of Tridentate NNO, NNS and NNN Donor Thiazole-derived Furanyl, Thiophenyl and and Pyrrolyl Schiff Bases and Their Co(II), Cu(II), Ni(II) and Zn(II) Metal Chelates", *Metal Based Drugs*, **2000**, 7(1), 17-22.