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Synthesis and characterization of derivatisedArtemether complexes of Cu (II), Co (II) and Ni (II) transition metals

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Abstract

A desire to further probe structure-activity relationships (SAR), artemether, a semi-synthetic derivative of artemisinin (antimalaria drug) has been derivatised and transition metals incorporated into its organic pharmacophores to enhance its biological activity and bioavailability. Cu (II), Co (II) and Ni (II) transition metal complexes of derivatizedartemether have been synthesized and characterized by elemental analysis, electronic and infra red spectroscopy. The synthesised complexes have varying shades of colour and decomposed at a temperature above 360^{o}C. The derivatizedartemether acts as a bidentate ligand through the two nitro O- atoms. The electronic spectra are consistent with the proposed octahedral geometry around the metal ions. The metal complexes were screened for their antimicrobial activities against *Pseudomonasaeroginosa, Escherichia coli* (Extended spectrum beta lactamase strain), *Escherichia coli* (Enteropathogenicdiarrheagenic strain), *Alcagenesfaecalis*, *Proteusmirabilis* and *Staphylococcus aureus.* The nickel complex [Ni(DA)$_2$.(H$_2$O)$_2$] exhibited the greatest activity in all the organisms tested.

Keywords.artemether, spectroscopy, bidentate ligand, octhahedral

Introduction

Artemisinin (Qinghaosu) is a sesquiterpene lactone endoperoxide isolated from *Artemisia annua*L. which Chinese herbalists have traditionally used to treat malaria [1, 2], a dramatic cause of death and illness in children and adults in tropical countries [3]. The prototype arteminisinin has low solubility in water or oil, poor bioavailabilty and a short half life*in vivo* [4]. To overcome these problems, semi-synthetic and fully synthetic compounds of artemisinin have been developed [5]. Two generations of semi-synthetic derivatives of artemisinin are artesunate, arteeter, artemether and artemisone, which have been effectively used as antimalaria drugs with good clinical efficacy and tolerability [5]. Reduction of artemisinin by sodium borohydride in methanol [6] produces dihydroartemisinin (DHA, Fig. 1), which is its main metabolite with improved antimalarial potency [7]. The synthesis of DHA opened pathways for further derivatization at C-10 to give ether and ester derivatives, largely exploited by the China Cooperative Research Group [8] with the aim of tuning water and/or oil solubility and improving bioavailability.

Artemether (Art) (Fig.2) is an oily soluble semi-synthetic derivative of artemisinin and has proved to be a safe and effective treatment for uncomplicated, severe and multidrug-resistant malaria. It is also known as dihydroartemisinin methyl ether with molecular formula $C_{16}H_{26}O_5$ and molecular mass of 298.374g/mol [9]. Its structural unit consists of 1,2,4-trioxane ring constituting endoperoxide and doxepin oxygen which are simpler class of 3-aryl trioxane [10] The endoperoxide moiety is the active pharmacophore which is responsible for its antimalarial activity whereas substitution on the lactone carbonyl group markedly increase potency [10]. It is practically

insoluble in water but highly soluble in dichloromethane [9]. It is less toxic than quinine and can be taken more than once daily as it undergoes rapid conversion to dihydroartemisinin [9].

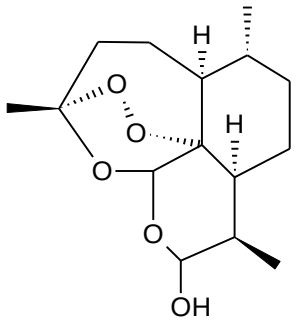


Figure 1. Structure of Dihydroartemisinin (DHA)

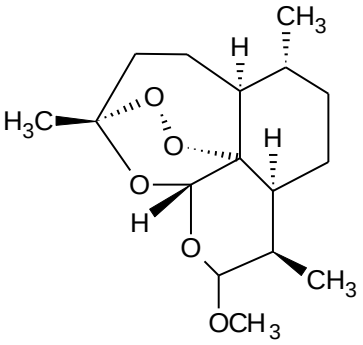


Figure 2. Structure of Artemether (Art)

A desire to further probe structure-activity relationships (SAR) has led to subsequentwork on derivatization of artemether by substitution at the methoxy group. Although there has been substantial improvement in the conventional organic synthetic strategies used for the development of antimalarial agents, researchers have sought out ways to develop more innovative approaches in order to develop more efficacious drugs to cure the disease. One of the most promising new approaches involves the use of transition metal ion complexes to produce novel antimalarial drugs [11].

Thus far, several reports have shown that incorporation of transition metal ions into organic pharmacophores offer new opportunities to design unique metal-containing compounds whichcompliment the molecular diversity created by purely organic scaffolds [12, 13]. These reports show that the incorporation of transition metal ions into rationally designed ligands can result in enhancement of the biological activity [14]. There are also several reports of enhancement of the efficacy of existing drugs, e.g. chloroquine, when transition metal ions were coordinated to the parent drug structures [15]. The consistent enhancement of these drugs when coordinated to metal ions reinforces the fact that metal complexes are important resources for the generation of structural or chemical diversity in the area of antimalarial drug development [12, 15]. The complexes formed may also exhibit antibacterial activities against pathogens that are of global concerns. The menaces of multidrug resistance have made many bacterial species to be resistant to commonly used antibiotics e.g. extended spectrum beta lactamase producers (ESBL), therefore, the search is ongoing for newer and better approaches for control of pathogens. Diarrhoea resulting from E. coli is a problem in developing countries e.g. Nigeria. Therefore, the complexes will have great potentials if they can exhibit antibacterial properties as well. We have employed the metal coordination approach to prepare series of metal complexes using [16] the derivatisedartemether organic scaffold as ligands with the aim of improving their bioavailability and bioactivities against disease causing microorganisms.

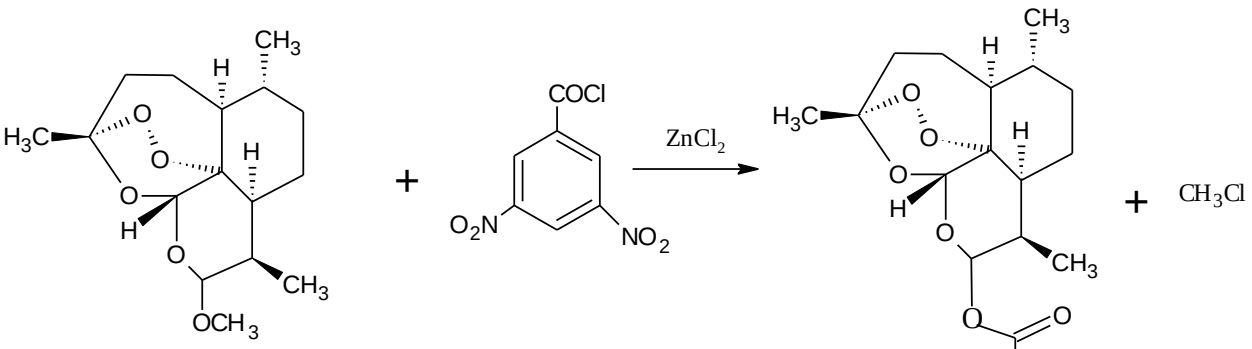
Experimental

All reagents used were obtained from Sigma Aldrich and British Drug House and were used without further purification; Artemether was a gift from Glaxo SmithclineAgbara, Ogun State. Infra red spectra were determined on Perkin Elmer BX II Spectrum FT-IR Spectrophotometer equipped with KBr discs. Metal analysis was determined by complexometric titration using EDTA solution, murexide indicator and ammonia/ammonium chloride buffer. The electronic spectra were recorded on a UVD-2960 UV/Visible PC scanning spectrophotometer. Antimicrobial study on the synthesized compounds was carried out in Department of Pharmaceutical Microbiology, University of Ibadan.

i. *Derivatization of Artemether*

Artemether was derivatised according to the standard method described by Vogel [17]: (0.05 mmol, 0.015 g) of artemether, (0.05 mmol, 0.012 g) of 3,5-dinitrobenzoyl chloride and 0.1g of anhydrous zinc chloride were added together in a round bottom flask. 10 ml methanol was added and the resulting mixture was refluxed for 1 hr. The reaction product was afterward treated with 10 ml of 0.75 M Na_2CO_3 solution, heated and then stirred for 1 mins. The resulting mixture was allowed to cool and then filtered under vacuum. This precipitate was further washed with 5 ml of 0.75 M Na_2CO_3 and twice with 5 ml ethyl ether and then air dried.

Equation for the reaction

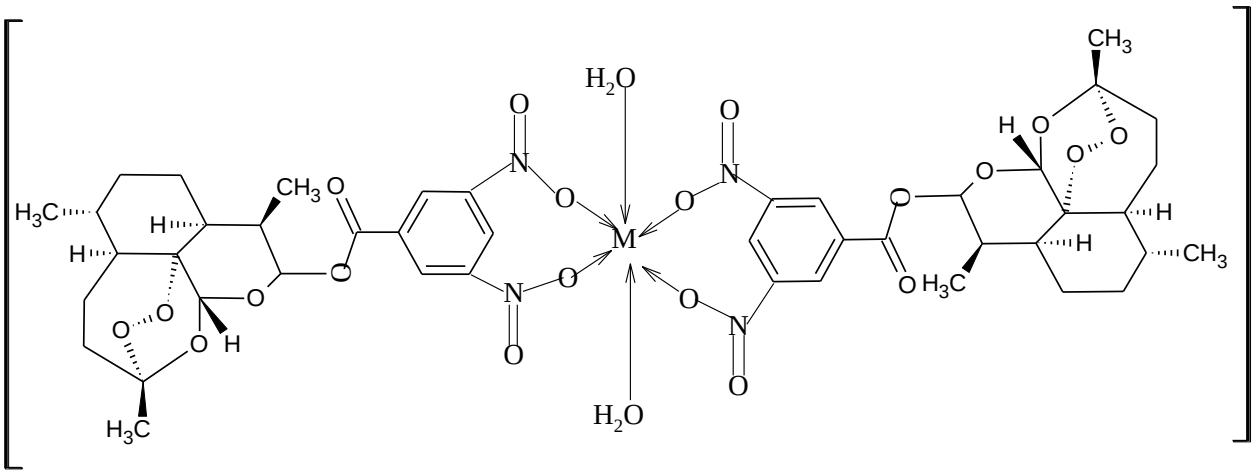


Artemether

Derivatised artemether

ii. *Synthesis of metal complexes of derivatised artemether*

The metal complexes of the derivatisedartemether were synthesized by slight modification of the method by Ogunniran *et al* [18]. (1 mmol, 0.3028 g) of derivatisedartemether was dissolved in 10 ml ethanol. The solution was transferred into a round bottom flask and stirred under reflux for 1 hr. This was followed by the addition of 0.005 mol of each metal salt (Cu (II). Ni (II) and Co(II) in 10 ml methanol. This reaction mixture was refluxed for 3 hrs, after which the solution was allowed to cool to room temperature and left on the bench for 2 weeks. The crystals formed were filtered under vacuum, washed twice with ethanol and dried in dessicator containing $CaCl_2$ as drying agent.



M = Cu, Ni, Co

Figure 3. Proposed structures of metal complexes

iii. *Antimicrobial susceptibility test*

The complexes were dissolved in Dimethylsulfoxide (DMSO) and hexane. Agar cup diffusion method was used. Bacteria were inoculated into Nutrient Broth medium and incubated overnight at 37^{o}C aerobically. 0.1 ml was then inoculated into 9.9 ml saline mixture and then a sterile swab dipped into the saline was used to streak the surface of the solidified nutrient agar plate. Holes were bored in the agar by sterile cork borer and 2 drops of the dissolved complexes were introduced into the bored holes. This was left on the bench for 1hr to allow diffusion to occur and then incubated for 24 hrs aerobically. The diameter of zones of inhibition was measured after incubation. The solvents in which they dissolved were used as negative controls.

Results and discussion

The treatment of artemether with 3,5-dinitrobenzoylchloride in methanol in the presence of zinc chloride gave derivatizedartemether($C_{22}H_{26}O_{10}N_2$ = DA), a cream coloured compound which decomposed at 360^{o}C and insoluble in most polar and non polar solvent but soluble in aprotic solvents. The synthesised metal complexes exhibited different shades of colourand also decompose on melting at temperature above 360^{o}C, they were insoluble in most solvents except the non polar hexane showing that complexation did not enhance the solubility of the derivatisedartemether. The proposed structures for the complexes are given in Figures 3. The analytical data, melting point/decomposition temperature and percentage metal analysis for the complexes are listed in Table 1.

Table 1. Analytical data for the compounds

Compounds	Colour	Formularweight	Yield %	M.P/D.T (^{o}C)	% Metal (observed)	% Metal (expected)
Art ($C_{16}H_{26}O_5$)	white	298.37	-		-	-
DA($C_{22}H_{26}O_{10}N_2$)	cream	478	58	360	-	-
[Cu(DA)$_2$.(H$_2$O)$_2$]	leafy green	1055.55	81.34	>360	5.29	5.17
[Ni(DA)$_2$.(H$_2$O)$_2$]	light green	1050.69	56.70	>360	5.10	5.53
[Co(DA)$_2$.(H$_2$O)$_2$]	pink	1050.93	88.51	>360	5.18	5.55

DA = Derivatizedartemether ligand, Art = Artemether

Infra red spectra studies of synthesized compounds

In order to clarify the mode of bonding and the effect of the metal ion on the ligand, the IR spectra of the free ligand, the derivatised ligand and the metal complexes were studied and assigned based on careful comparison of their spectra with that of the free and the derivatised ligand. Relevant IR bands for the ligand and metal complexes are presented in Table 2. The FTIR spectra of Artemether (Fig.4) presented here showed characteristics bands 2923cm^{-1} (Fermi resonance of the symmetric stretching vibration of CH_3), 2853cm^{-1} (V_{asym} C-H), 1034cm^{-1}(C-O str of cyclic ether), 821cm^{-1} (O-O str) and 874cm^{-1} (O-O-C str vibration) which indicates the properties of 1,2,4-trioxane ring which are consistent with the reported studies [19, 20] and additional methyl which correspond to the peak at 1374cm^{-1} [21] The spectra of derivatisedArtemether (Fig.5) showed similarity to that of Artemether but with the presence of new bands at 3313.77cm^{-1}attributed to O-H str due to water of crystallization, bands at 1652.5cm^{-1} 1463cm^{-1} are assigned to asymmetric vibration of the nitro group with an additional band at 1506cm^{-1} although this is different from those reported for nitroaromatics compounds [22], this might be as a result of steric hindrance caused by the attached artemether moiety to 3,5-dinitrobenzoylchloride. The observation of the N-O stretching vibration at a longer wavelengths as compared to the reported values might be as a result of the planarity of the two nitro groups in 3,5-dinitrobenzoyl moiety in which the NO_2 group electrons are conjugated with the π electrons of the benzene ring and thus caused a decrease in electron density in the benzene ring therefore a bathochromic shift [23-24]. Coordination of the metals was through the oxygen atom of the nitro group as the nitrogen site is already attached to the benzene ring and thus is unavailable. This was evidence by the shift to higher frequency (hypsochromic shift) in the N-O stretching vibrations of the complexes (Fig.6-8). The M-ONO bands were observed at 605cm^{-1}, 611cm^{-1} and 595cm^{-1} for Cu-O, Ni-O and Co-O complexes respectively. It was also observed that O-O endoperoxide and O-O-C bands were observed in Ni complex spectra.

Table 2. IR data (cm^{-1}) for Artemether, derivatisedArtemether and the complexes

Compounds	ν(C-H) sym	ν (C-H) asy	ν(C-O)	ν(O-O)	ν(O-O-C)	ν(O-H)	ν (N-O) asy	ν (N-O) sym	ν(M-ONO)
A ($C_{16}H_{26}O_5$)	2923	2853	1034	821	874	-	-	-	-
DA($C_{22}H_{26}O_{10}N_2$)	2923	2853	1098	802	870	3313_b	1652	1463	-
[Cu(DA)$_2$.(H$_2$O)$_2$]	2924	2854	1082	805	-	3440_b	1642	1460	605
[Ni(DA)$_2$.(H$_2$O)$_2$]	2923	2854	1098	-	-	3433_b	1642	1461	611
[Co(DA)$_2$.(H$_2$O)$_2$]	2923	2854	1034	842	864	3390_b	1812	1456	595

DA = Derivatizedartemether ligand, A = Artemether

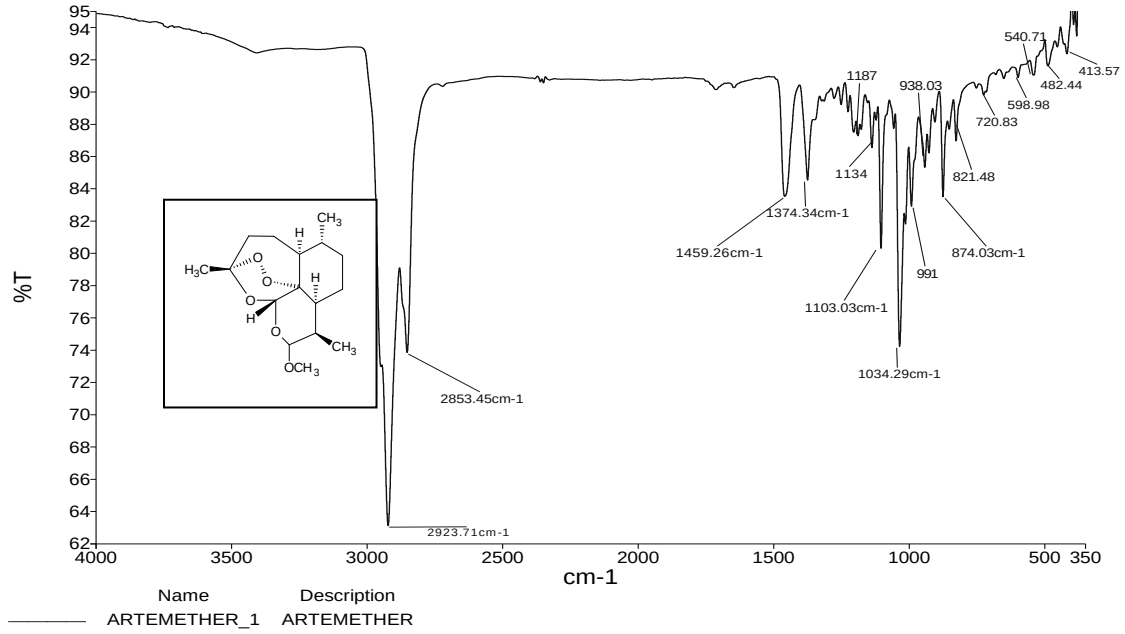


Figure 4.FTIR spectrum of Artemether

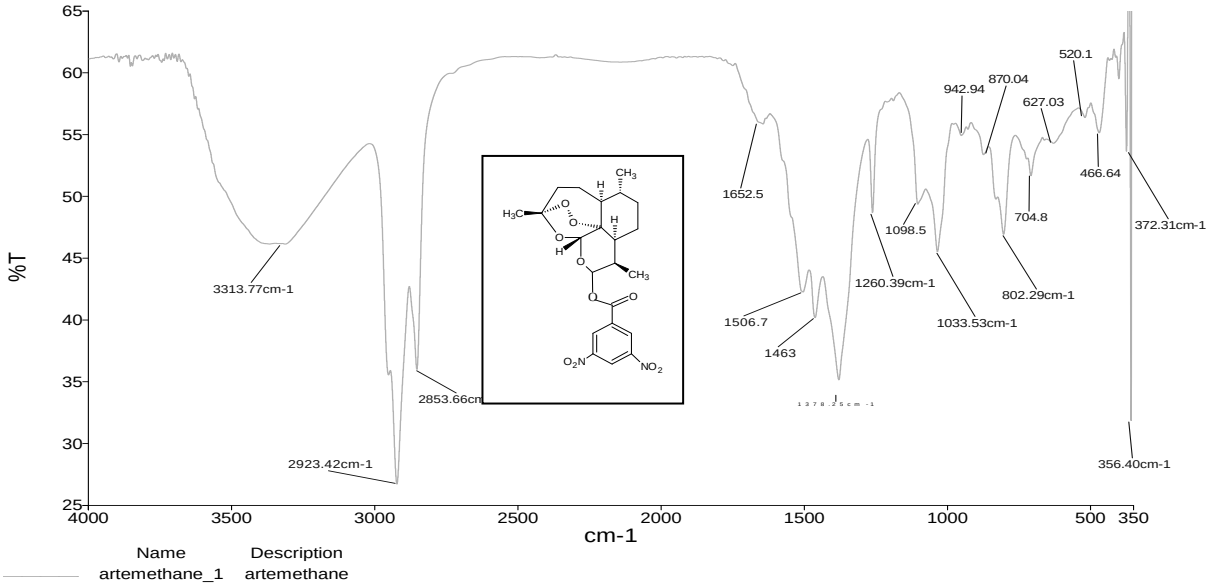


Figure 5.FTIR spectrum of derivatisedArtemether

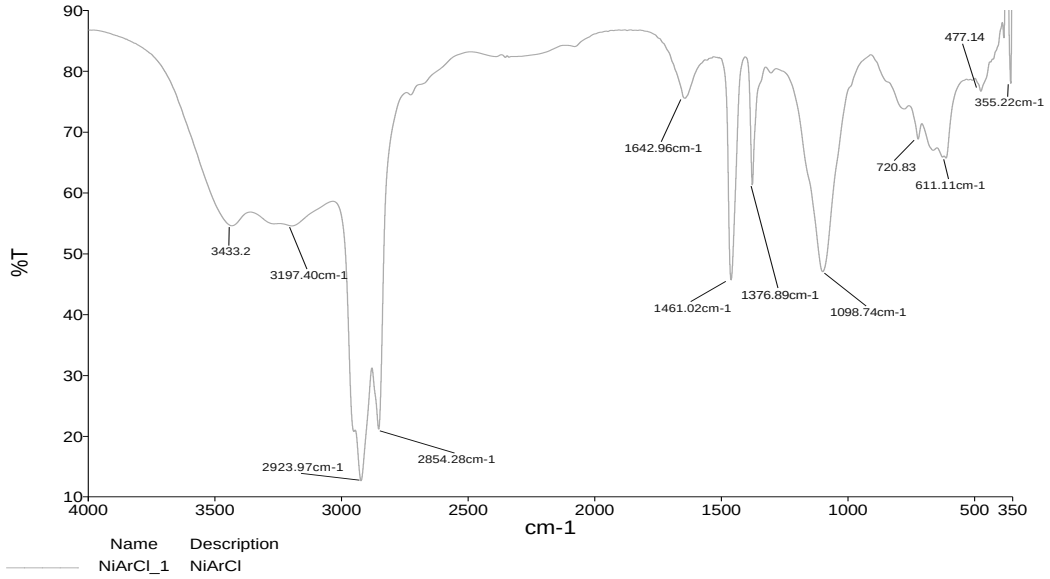


Figure 6. FTIR spectrum of Ni complex of derivatisedArtemether ($[Ni(DA)_2.(H_2O)_2]$)

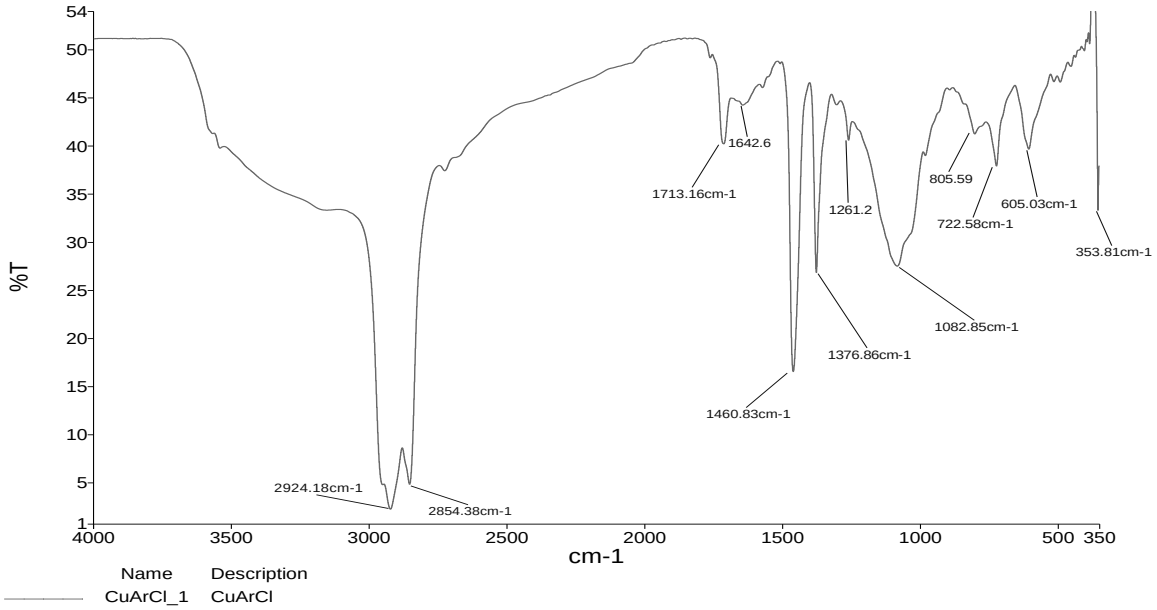


Figure 7. FTIR spectrum of Copper complex of derivatisedArtemether $[Cu(DA)_2.(H_2O)_2]$

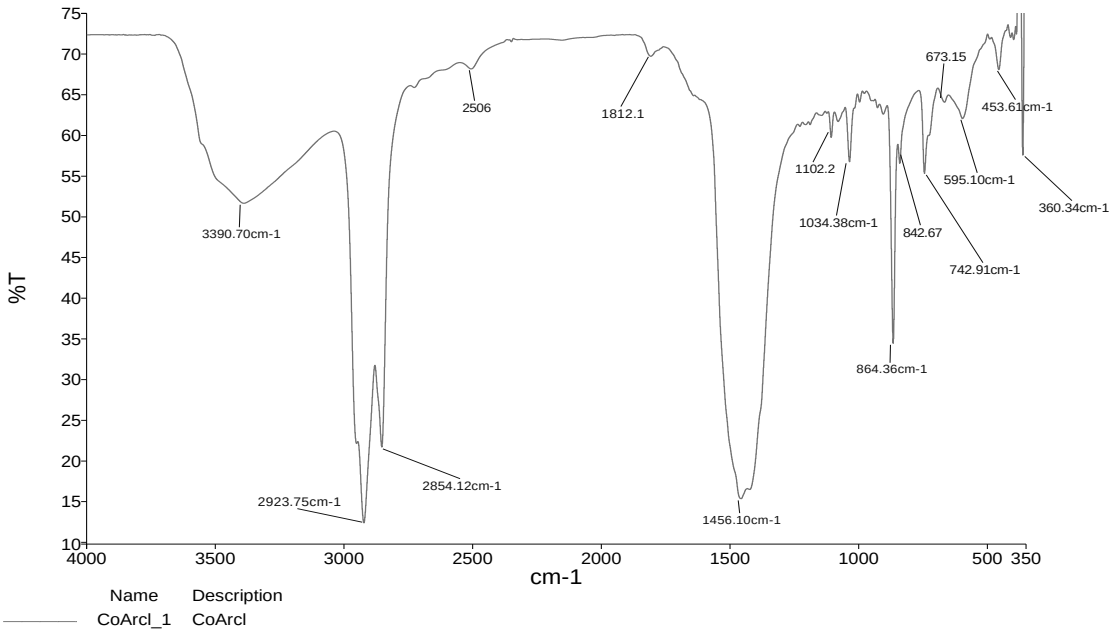


Figure 8.FTIR spectrum of Cobalt complex of derivatisedArtemether $[Co(DA)_2.(H_2O)_2]$

Electronic spectra of synthesized compounds

The electronic spectral absorptions of the complexes of Co (II), Ni(II) and Cu(II) are presented in Table 3. The electronic configuration of cobalt (II) complex is d^7 with a spectroscopic ground term ^4F. $[Co(DA)_2.(H_2O)_2]$ showed three bands in the visible region. The absorption bands at 30303cm^{-1} is due to charge transfer while the three spectral absorptions at 19417cm^{-1}, 19801cm^{-1} and 19920cm^{-1} in the visible region is assigned to the transitions: $^4T_1g(F) \rightarrow {}^4T_{2g}(F)$, $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$, these are in agreement with octahedral geometry [25]. The electronic spectra of Cu (II) complexes show a single absorption at 13141cm^{-1} which is attributed to $^2Eg \rightarrow {}^2T_{2g}$ transition.[26]. Electronic spectra of Ni(II) complexes show three absorptions in the region 10300 – 24400 cm^{-1} and they may be attributed to the transitions to the excited states from the ground state $^3A_{2g}$ [27]:

$^3A_{2g}$ (F) → $^3T_{2g}$ (F) (ν1); $^3A_{2g}$ (F) → $^3T_{1g}$ (F) (ν2); $^3A_{2g}$ (F) → $^3T_{1g}$ (P) (ν3) which are characteristic of octahedral Ni(II) species [27].

Table 3. Electronic spectra data for Artemether, derivatised Artemether and their metal (II) complexes.

Complex/Ligand	Absorptions (cm-1)	Tentative assignment	Probable geometry
Artemether	30303	n→π*	
	30769	π→π*	
	37175	π→π*	
DerivatisedArtemether	30303	n→π*	
	33670	π→π*	
	41152	π→π*	
$[Co(DA)_2.(H_2O)_2]$	30303	Charge Transfer	Octahedral
	19920	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$	
	19801	$^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$	
	19417	$^4T_1g(F) \rightarrow {}^4T_{2g}(F)$	
$[Cu(DA)_2.(H_2O)_2]$	131410	$^2Eg \rightarrow {}^2T_{2g}$	Octahedral
$[Ni(DA)_2.(H_2O)_2]$	48309	Charge Transfer	Octahedral
	23529	$^3A_{2g}$ (F) → $^3T_{1g}$ (P)	
	23041	$^3A_{2g}$ (F) → $^3T_{1g}$ (F)	
	15060	$^3A_{2g}$ (F) → $^3T_{2g}$ (F	

Antimicrobial studies

The metal complexes were screened for their antimicrobial activities against *Pseudomonas aeruginosa*, *Escherichia coli* (ESBL), *Escherichia coli* (EPEC), *Alcagenes faecalis*, *Proteus mirabilis* and *Staphylococcus aureus*,. The antimicrobial report is summarized on Table 4. The insolubility of derivatised artemether in most solvent pose a serious challenge for the antimicrobial study as the solvents are used as the negative control. Antimicrobial activities of cobalt complex could not be estimated due to its insolubility. The copper and the nickel complexes exhibit high antibacterial ability. The nickel complex $[Ni(DA)_2.(H_2O)_2]$ exhibited the greatest activity in all the organisms tested. Extended spectrum beta-lactamases strains are often acquired plasmid mediated beta lactamases that hydrolyze broad spectrum beta-lactams antibiotics therefore leading to difficulties in treatment [28]. However, the copper and nickel complexes in this study produce antibacterial activities against the tested ESBL strain. Strains of *Pseudomonas aeruginosa*, Enteropathogenicdiarrheagenic strain of *E. coli*, *Alcagenes faecalis*, *Proteus mirabilis* and *Staphylococcus aureus* have been implicated in various infectious states and the infections could lead to mortality [29-31]. Of more concern are the multidrug resistant strains of these organisms. Interestingly, the Copper and Nickel complexes (Table 4) have good antimicrobial activities against these organisms. Further pharmacological investigation of these compounds will reveal their possible use in treatment of these bacterial infections.

Table 4. Antimicrobial screening of ofderivatisedArtemether and their metal complexes

Complexes/ ligand	***Pseudomonas aeruginosa***	***Escherichia coli* (ESBL)**	***Staphylococcus aureus***	***Escherichia coli* (EPEC)**	***Alcagenes faecalis***	***Proteus mirabilis***
DMSO(-ve control)	-	-	-	-	-	-
Hexane (-ve)	-	-	-	-	-	-
$[Cu(DA)_2.(H_2O)_2]$	10mm	22mm	30mm	30mm	34mm	16mm
$[Ni(DA)_2.(H_2O)_2]$	40mm	38mm	42mm	40mm	40mm	40mm

Conclusion

The derivatisation of artemether with 3,5-dinitrobenzoylchloride gave derivatisedartemether a cream coloured solid which decomposes at 360^{o}C. The incorporation of metal (II) ions of Copper, Cobalt and Nickel into its organic scaffold resulted into their metal (II) complexes which are characterized by the spectroscopic methods. From the analytical and spectral data the derivatisedartemether was found to coordinate to the metal ions through the oxygen atom of nitro group as a bidentate ligand to give an octahedral geometry. Antimicrobial screening of the complexes showed that $[Ni(DA)_2.(H_2O)_2]$ is the most active of the complexes against all the tested microorganisms.

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