



Abstract

The need for further structure-activity relationships of artemether (ART), a semi-synthetic derivative of artemisinin has led to formation of its 3,5-dinitrobenzoylchloride derivatives (DA), and the incorporation of transition metals into its organic pharmacophores to enhance its biological activity and bioavailability. The DA and its Cu (II), Co (II) and Ni (II) transition metal complexes have been synthesized and characterized by percentage metal analysis, melting points, infrared spectroscopy and electronic spectroscopies. The Infrared spectral data established that DA acts as a bidentate ligand bonding through the two nitro oxygen atoms. The electronic spectral data indicated that the metal (II) complexes have octahedral geometries. The in-vitro antimicrobial studies carried out against *Pseudomonas aeruginosa*, *Escherichia coli* (Extended spectrum beta lactamase strain), *Escherichia coli* (Enteropathogenicdiarrheagenic strain), *Alcagenes faecalis*, *Proteus mirabilis* and *Staphylococcus aureus* showed enhancement in antimicrobial activities due to coordination to metals with the nickel complex [Ni(DA)₂.(H₂O)₂] exhibiting the greatest activity in all the organisms tested.

Keywords: Derivatized-artemether, spectroscopy, bidentate ligand, antimicrobial

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 artemisinin has low solubility in water or oil, poor bioavailability 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, arteether, artemether and artemisone, which have been effectively used as antimalaria drugs with good clinical efficacy and tolerability ⁵.

Artemether (Art) (Fig.1) 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. Its structure consists of 1,2,4-trioxane ring constituting endoperoxide and doxepin oxygen. The endoperoxide moiety is the active pharmacophore which is responsible for its antimalarial activity¹⁰

Derivatized-Artemether complexes of Cu (II), Co (II) and Ni (II) transition metals: Synthesis, characterisation and antimicrobial studies.

Eugene-Osoikhia, T.T.,^{1*} Okunade, R. F.¹ and Ayeni, F².

¹Department of Chemistry, University of Ibadan, Ibadan, Nigeria

²Department of Pharmaceutical Microbiology, University of Ibadan, Ibadan, Nigeria

*Correspondence Email: kemtunmise@yahoo.co.uk

A desire to further probe structure-activity relationships (SAR) has led to subsequent work on derivatization of artemether by substitution at the methoxy group.

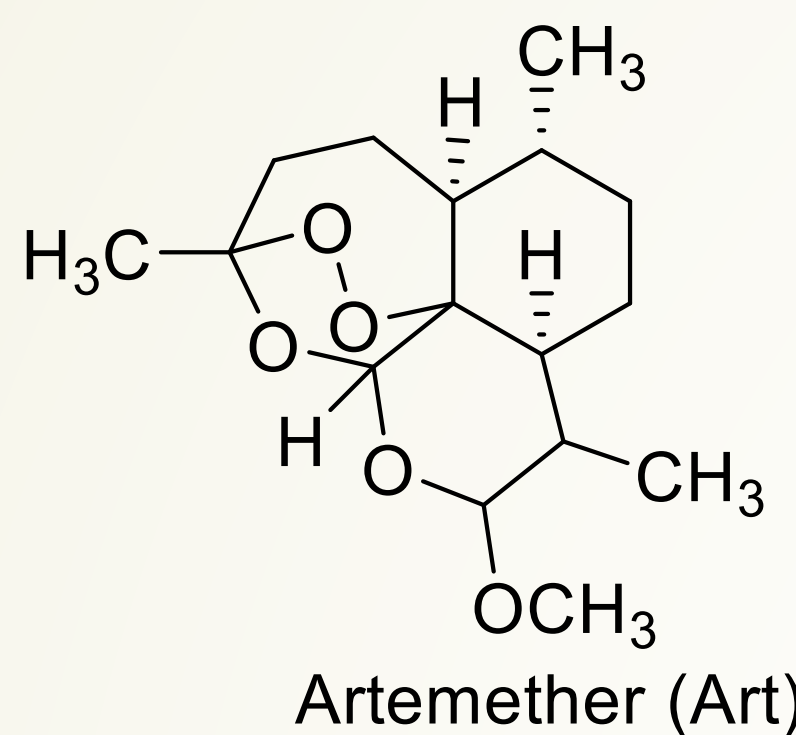


Fig. 1: Artemether

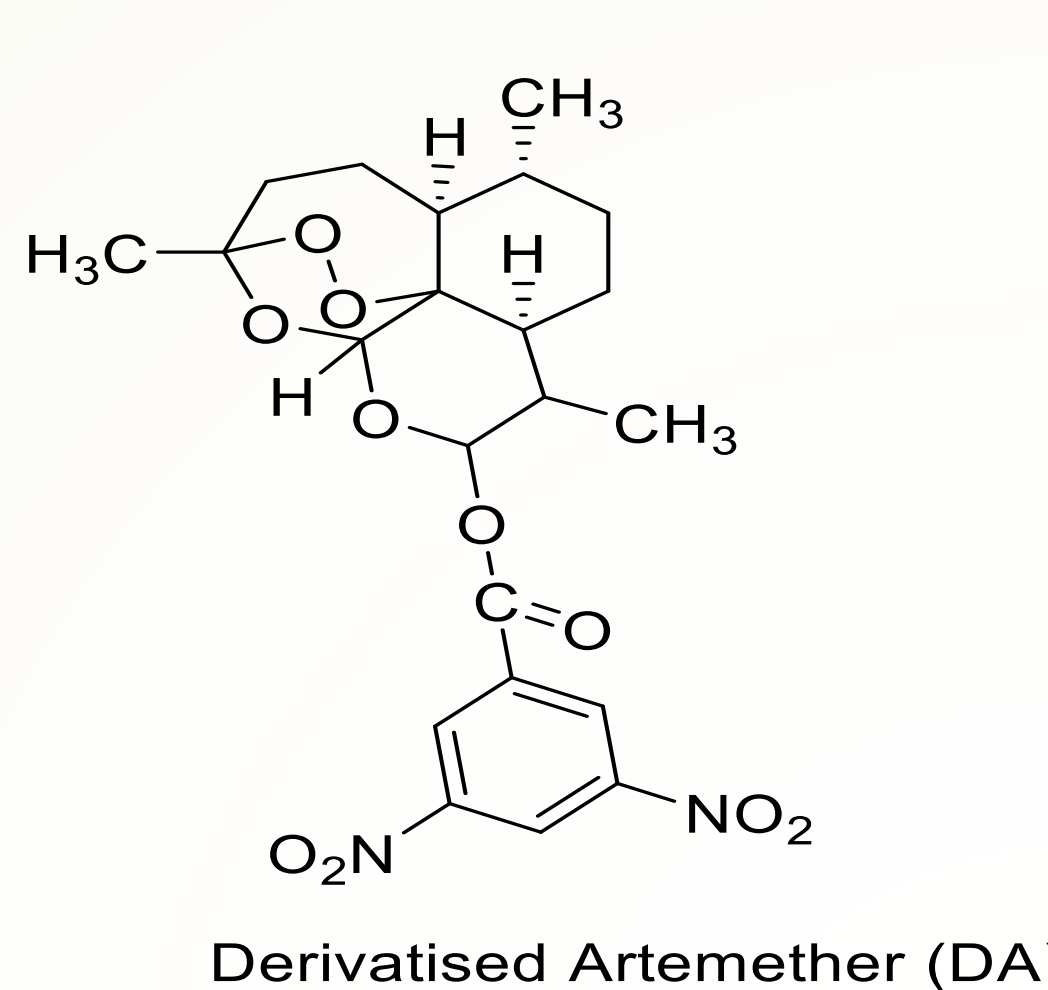


Fig.2: Derivatized Artemether (DA)

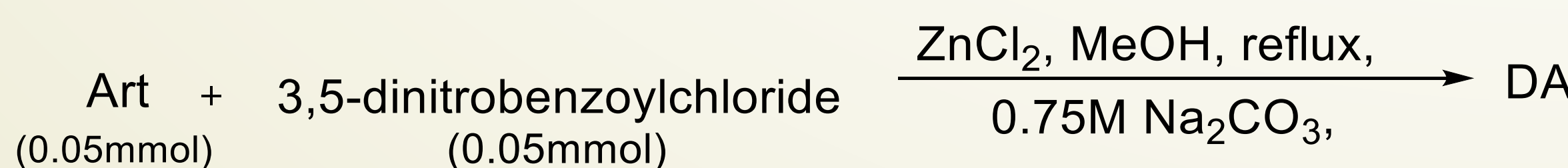
Several reports have shown that incorporation of transition metal ions into organic pharmacophores offer new opportunities to design unique metal-containing compounds which complement the molecular diversity created by purely organic scaffolds which can result enhancement in biological activity.

In this report, we employed the metal coordination approach to prepare series of metal complexes using the derivatized-artemether (DA) Fig.2 organic scaffold as ligands with the aim of screening their bioactivities against disease causing microorganisms

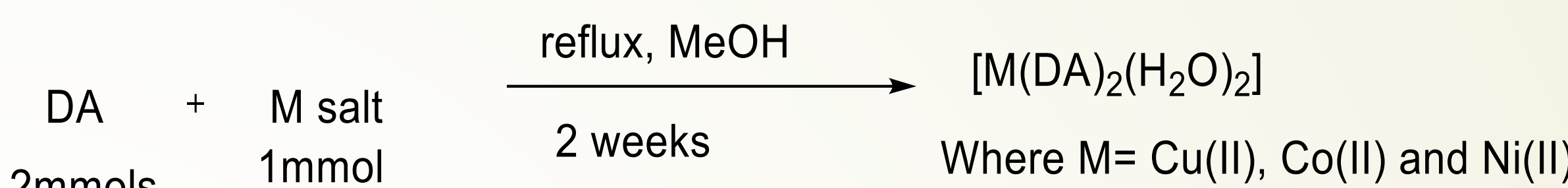
Materials and methods: Artemether were gifts from GlaxoSmithline pharmaceutical Companies, Agbara, Ogun State Nigeria. While other chemicals and reagents were obtained from Sigma Aldrich.

Physical measurements: Infra red spectra were determined on Perkin Elmer BX II Spectrum FT-IR Spectrophotometer equipped with KBr discs at 4000–370 cm⁻¹. Metal analysis was determined by complexometric titration. The electronic spectra was recorded on a UVD-2960 UV/Visible PC scanning spectrophotometer. Melting points were determined with Stuart SMP10. Antimicrobial study on the synthesized compounds was carried out in Department of Pharmaceutical Microbiology, University of Ibadan

Derivatization of Artemether



Synthesis of metal complexes of [M(DA)₂(H₂O)₂] where M = Cu(II), Co(II) and Ni(II)



Antimicrobial studies: Antimicrobial screening in vitro by Agar diffusion method against identified clinical strains of gram positive and gram negative bacteria: *Pseudomonas aeruginosa*, *Escherichia coli* (ESBL), *Escherichia coli* (EPEC), *Alcagenes faecalis*, *Proteus mirabilis* and *Staphylococcus aureus*

Results and discussions

The reaction of the synthesized DA with the metal (II) salts of Cu, Co and Ni gave varying shades of coloured complexes Fig.3 in the yields in the range 56.70-88.50%. The derivatized artemether (DA) ligand, decomposed at 360°C while its metal complexes decomposed above 300 °C

IR studies

The spectra of DA (Fig.2) 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, and 1506cm⁻¹ are assigned to asymmetric vibration of the nitro group of aromatics group. The DA ligand acts as a bidentate ligand through coordinating to the metals through the two nitro O- atoms on the aromatic moiety..

Electronic spectra, magnetic moment studies and conductivity .

Electronic spectra data indicated that all the metal (II) complexes were monomeric and octahedral..

Antimicrobial studies :

The insolubility of DA in most solvents poses a serious challenge for the antimicrobial study. 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.(H₂O)₂] exhibited the greatest activity in all the organisms tested; which includes the Extended spectrum beta-lactamase strains which often hydrolyze broad spectrum beta-lactams antibiotics posing difficulties in treatment.

Conclusion

The derivatization of artemether with 3,5-dinitrobenzoylchloride gave DA, a cream coloured solid which decomposes at 360°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 DA 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.(H₂O)₂] is the most active of the complexes against all the tested microorganisms

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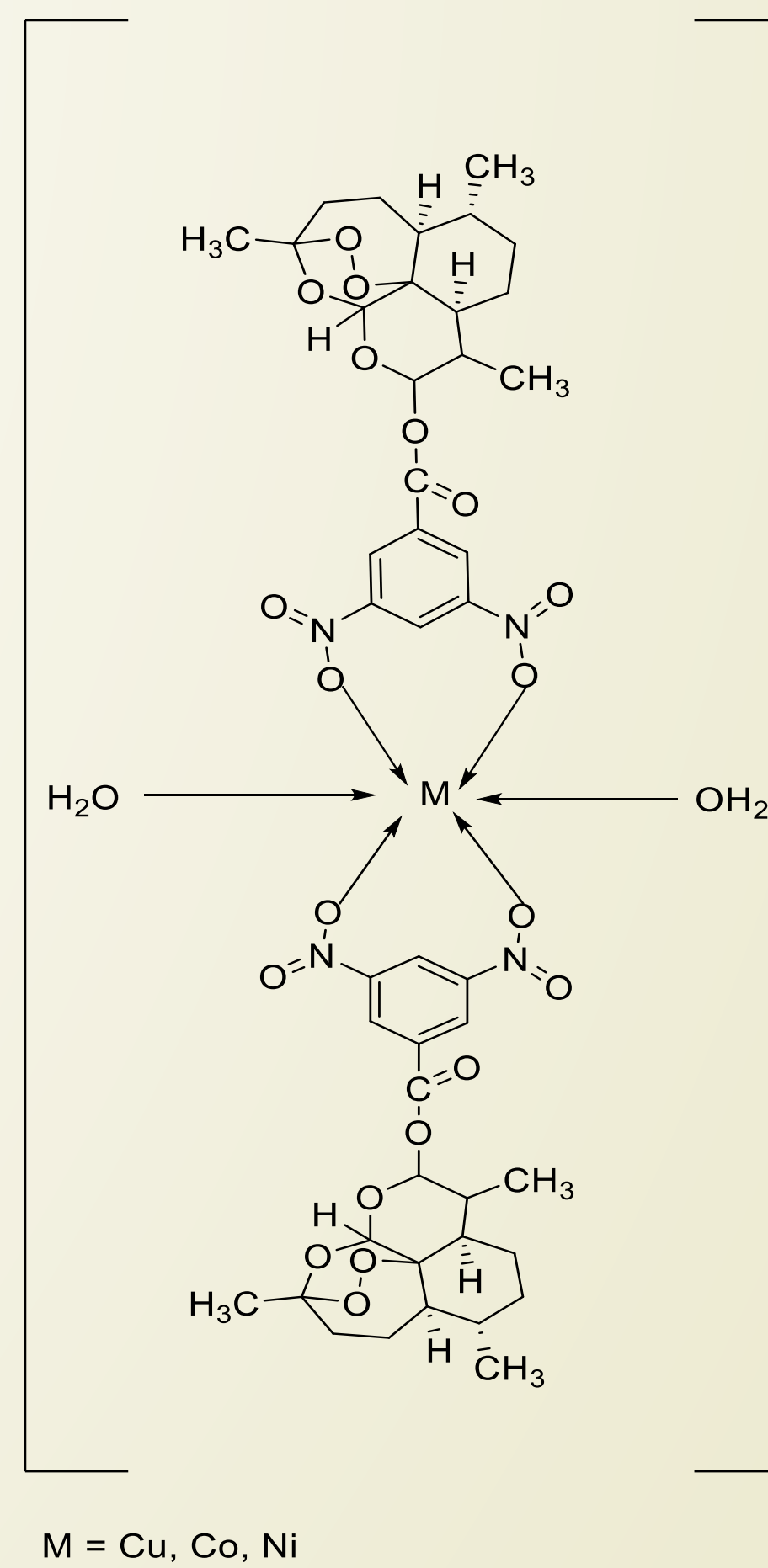


Fig. 3 metal complex