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Research Article

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Antimalarial Activity of 3-(4-Nitrophenyl)-1-Phenylprop-2-en-1-one and Its Metal Complexes

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Abstract Antimalarial resistance is currently the greatest challenge to the effective treatment of malaria globally. In this work, 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one, as well as the Fe(III), Ni(II) and Mn(II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one were synthesized and characterized using Fourier Transform Infrared (FTIR) Spectroscopy, Thin Layer Chromatography (TLC) and melting point analysis. The obtained yields of the Fe(III), Ni(II) and Mn(II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one are 56.9%, 52.2% and 49.3%, respectively. The uncomplexed 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one as well as the Fe(III), Ni(II) and Mn(II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one were subjected to in-vitro antimalarial screening using Plasmodium berghii cysteine enzyme inhibition assay at concentrations of 1000 ug/ml, 500 ug/ml, and 250 ug/ml. 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one shows promising activity for inhibiting the cysteine enzymes. The antimalarial activity of Fe(III) and Mn(II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one was found to be much higher that of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one. However, the Ni(II) complex of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one did not show enhanced antimalarial activity.

Keywords 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one, metal complex, malaria, synthesis, characterization

Introduction

Malaria is an infectious disease that affects about half of the world's population. Each year, about one million deaths and nearly 250 million cases are reported due to malaria. Sub-Saharan Africa has the highest risk of contracting malaria, with an estimation of 81% cases and 91% deaths in 2010 alone. Children below the five years of age and pregnant women are the most severely affected [1]. Malaria is caused by five species of parasites of the genus *Plasmodium* that affect humans (*P. falciparum, P. vivax, P. ovale, P.malariae and P. knowlesi*). However, malaria due to *P.falciparum* predominates in Africa [2]. For several decades, chloroquine (a 4-aminoquinoline) which was previously characterized by its efficacy, minimal host toxicity and affordability was the main standard for the treatment of malaria. Extensive worldwide use of chloroquine in the beginning of the late 1940s, led to the first reports of chloroquine-resistant strains of *P. falciparum* after a decade later. Today, there is massive spread of chloroquine resistance in majority of malaria-endemic regions, rendering chloroquine ineffective. Currently, artemisinin-based combination therapy is the first line treatment in *P. falciparum* malaria [3]. However, limited accessibility of artemisinin-based combination therapy together with reduced susceptibility of *P.falciparum* to artemisinin derivatives has necessitated the development of novel antimalarial drugs [4].

Quinine and derivatives of artemisinin are the two most important antimalarial drugs which are used to treat severe *falciparum* malaria. Quinine and derivatives of artemisinin are derived from plant sources. In the case of artemisinin, moderate chemical modifications of the natural product parent nuclei have led to arrays of exceptionally potent antimalarial agents that are now widely used for the treatment of malaria. However, Artimisnin-based antimalarial therapies are too expensive to be afforded by developing countries. Since, malaria is strongly associated with poverty, it has been estimated that mortality rates from malaria are highest in countries with a lower gross national income. Thus, to combat malaria, new drugs at reasonable cost are highly needed.

Chalcones constitute an important group of plant secondary metabolite with selective inhibition against *P.falciparum*, first reported for licochalcone A [3], with low cost of production, ease availability, thus making them promising antimalarial compounds[5,6]. Chalcones are versatile molecules possessing a wide range of activity; antimalarial, antifungal, anti-inflammatory, anti-oxidant, antimicrobial activities. Compounds with electron releasing groups such as methoxy and hydroxyl showed better antimalarial activity than the others not having such groups. Compound having pharmacophores such as chloro, dichloro and fluoro groups have exhibited high antifungal activity [7,8]. Chalcones can be synthesized using a conventional base catalyzed Claisen Schmidt condensation reaction, which involves the condensation of an equimolar quantity of a substituted acetophenone with a benzaldehyde in the presence of an aqueous alcoholic alkali [9]. This paper focuses on microwave assisted synthesis and evaluation of the antimalarial activity of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one, and Fe(III), Ni(II) and Mn(II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one.

Materials and Methods

Synthesis and characterization of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one and its metal complexes

A mixture of acetophenone (0.1 mole), 4-nitrobenzaldehyde (0.1 mole) and sodium hydroxide (0.1 mole) were placed in a mortar and grinded using a pestle until a uniform mixture was formed. The product was diluted using distilled water, and one drop of 5% HCl was added, and the mixture was kept overnight. The mixture was then neutralized with 5% HCl, and further diluted with cold distilled water with constant stirring. The progress of the reaction was monitored using thin layer chromatography (TLC) with n-hexane and ethyl acetate in a ratio of 4:1 as the developing solvent. Appearance of a single new spot and disappearance of the reactants spots indicate formation of the product.

To synthesize the metal complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one**,** 0.02 mole of the synthesized3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one was mixed with 0.01 mole of ferric chloride in a round bottom flask containing methanol. The mixture was then refluxed for two hours and the solid mass obtained, was filtered through a sintered glass crucible and the residue was washed with hot methanol until solid mass was free of excess ligand and the crystals obtained was weighed and measured. The same procedure was followed for the synthesis of Ni(II) and Mn(II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one using manganese (II) sulfate, and Nickel (II) chloride, respectively.

The melting point of the synthesized of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one and its metal complexes was determined using Gallenklamp melting point Apparatus. The reported melting point was uncorrected. Fourier Transform Infrared (FTIR) spectra were recorded on a shimadzu FTIR 8201 PC spectrophotometer. For the Shinoda's test, 1 ml of 10% ethanolic solution of the studied sample was mixed with 0.5ml of hydrochloric acid 10% and magnesium metal,and the colour change observed.

Antimalarial screening of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one and its metal complexes

Three different concentrations1000ug/ml, 500ug/ml, and 250ug/ml each of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one and its metal complexes [Fe(III), Mn(II), Ni(II)] were prepared. 200ul of crude enzyme source was added in each of the 39 test tubes, previously washed and dried. 2000ul of 100Mm sodium acetate buffer pH 4.5, 400ml of 3% casein at 37^{o}c were also added into each of the test tubes were made-up to 4000ul with distilled water. Out of 39 test tubes, three test tubes were used as control. Bland solution (200ul distilled water) was also prepared for each of the concentration (1000ug/ml, 500ug/ml, and 250ug/ml) of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one and the metal complexes, the remaining reagents were added as described above. To the 36 test tubes of the crude enzymes source the various concentrations of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one and its metal complexes were added each in triplicate, and the remaining 3 test tubes were left as the control (negative). All the test tubes were arranged in a test tube rack and placed in an incubator at 37^{o}C for 1 hour. The reaction was stopped by the addition of 800ul of 20% trichloroacetic acid. All test tubes were centrifuged for 30 minutes and the absorbance of each sample was determined and recorded.

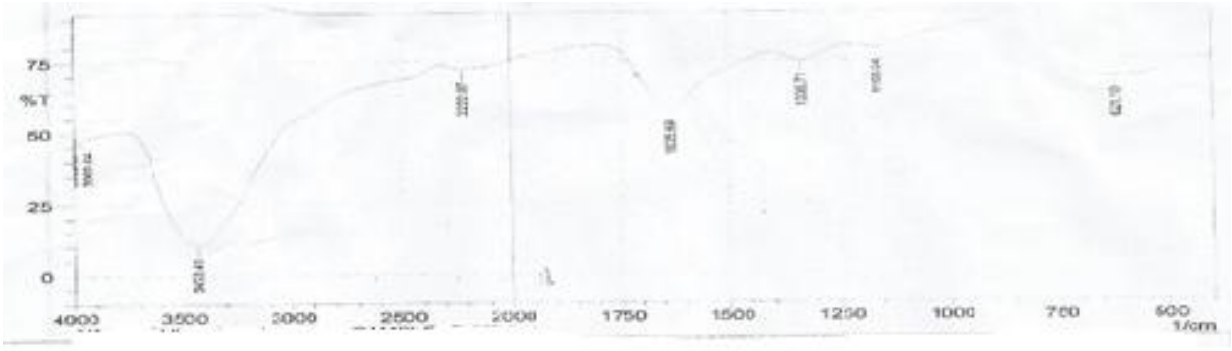
Results And Discussion.

The yield and measured physical properties of the synthesized 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one as well as Fe(III), Ni(II) and Mn(II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one are presented in Table 1. The microwave assisted synthesis afforded high yield (77.2%) of 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one. As seen in Table 1, the yields of the three metal complexes are relatively lower than that of the of 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one. The metal complexes have higher melting points when compared with the uncomplexed of 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one. The appearance of; a single spot in the thin layer chromatograps indicates the purity of the synthesized 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one, as well as Fe(III), Ni(II) and

Mn(II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one with R_f values in the range of 0.45-0.50. The synthesized 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one tested positive for flavonoids based on the Shinoda's test which gave orange colour. The FTIR spectrum of 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one is shown in Figure 1. Characteristic peaks of aromatic rings at about 1599 cm^{-1} and aromatic nitro group at 1518cm^{-1}. An overtone C=O stretch was observed at about 3446 cm^{-1}, C-H stretch band was found at about 2929 cm^{-1}, an Aromatic C-N stretch was also observed at about 1500 cm^{-1}.

Table 1: Yield and some physical properties of 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one and it metal complexes

	3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one	**Fe(III) complex of 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one**	**Mn(II) complex of 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one**	**Ni(II) complex of 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one**
Yield, (%)	77.2	56.9	52.2	49.3
Melting point, (^oC)	152-154	202-206	233-239	190-195
R_f value	0.49	0.50	0.47	0.45
Colour	Light yellow	yellow	Pale yellow	yellow



(a)

(b)

(c)

(d)

Figure 1: FTIR spectra of (a) 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one (b) Fe(III) complex of 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one, (c) Mn(II) complex of 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one, (d) Ni(II) complex of 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one

Antimalarial screening

The in-vitro Antimalarial screening of chalcone and it metal complexes was carried out on protease enzyme. As can be seen in Tables 2-5, the percentage inhibition for3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one and its metal complexes are concentration dependent. The higher the concentration, the higher the antimalarial activity. The percentage inhibition for the indole acetic acid (IAA) and EDTA were 100% and 90% which were used as standard.

Table 2: Absorbance and percentage inhibition for 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one at 366nm

Concentration	Absorbance	Inhibition (%)
1. 1000ug/ml		
A.	0.010	
B.	0.005	= 64.4%
C.	0.007	
2. 500ug/m		
A.	0.011	
B	0.011	= 44.88%
C	0.012	
3. 250ug/ml		
A.	0.017	
B.	0.014	= 18.54%
C.	0.019	

Table 3: Absorbance and percentage inhibition for Fe(III) complex of 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one at 366nm

Concentration	Absorbance	Inhibition (%)
1. 1000ug/ml		
A.	0.003	
B.	0.002	= 85.0%
C.	0.004	
2. 500ug/ml		
A.	0.004	
B.	0.005	= 80.48%
C.	0.003	
3. 250ug/ml		
A.	0.009	
B.	0.018	= 36.58%
C.	0.012	

Table 4: Absorbance and percentage inhibition for Mn(II) complex of 3-(-4-nitrophenyl)-1-phenylprop-2-ene-1-one at 366nm

Concentration	Absorbance	inhibition (%)
1. 1000ug/ml		
A.	0.006	
B.	0.005	= 72.2%
C.	0.006	
2. 500ug/ml		
A.	0.008	
B.	0.009	= 59.5%
C.	0.008	
3. 250ug/ml		
A.	0.035	
B.	0.036	= -81.95%
C.	0.041	

Conclusion

Microwave assisted synthesis of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one and its three metal complexes was successfully carried out with a yield of 77.2%. The obtained yields of the Fe(III), Ni(II) and Mn(II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one are 56.9%, 52.2% and 49.3%, respectively. The uncomplexed 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one as well as the Fe(III), Ni(II) and Mn(II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one were subjected to in-vitro antimalarial screening using Plasmodium berghii cysteine enzyme inhibition assay at concentrations of 1000 ug/ml, 500 ug/ml, and 250 ug/ml. 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one shows promising activity for inhibiting the cysteine enzymes. The antimalarial activity of Fe(III) and Mn(II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one was found to be much higher that of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one. However, the Ni(II) complex of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one did not show enhanced antimalarial activity.

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