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Synthesis of chloroquine derivatives and their *in vitro* screening for anti-malarial and anti-oxidant activity

Solomon I. Attah [1] *, Joy C. Ezugwu [1], Efeturi A. Onoabedje [1], Benjamin E. Ezema [1], Festus C. Madubuchi [1], Cosmas C. Eze [2], Ifeoma V. Okonkwo [3], Fidelia N. Ibeanu [2] and Benedict O. Onyejekwe [4]

[1] Department of Pure and Industrial Chemistry, Faculty of Physical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.

[2] School of General Studies, Natural Science Unit, University of Nigeria, Nsukka, Enugu State, Nigeria

[3] Department of Science Laboratory Technology, Faculty of Physical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.

[4] Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, University of Nigeria, Nsukka, Enugu State, Nigeria.

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Abstract

Malaria remains a major global health challenge, which is compounded by the emergence of resistance to existing drugs such as chloroquine. To address this, the search for novel derivatives with improved therapeutic profile is ongoing. The present study designed, synthesized and characterized five novel chloroquine derivatives, and evaluated them for anti-malarial and anti-oxidant activities. The synthesis began with the preparation of N1-(7-chloro-4-quinolyl)-1,2-diaminoethane via the reaction of 4,7-dichloroquinoline with ethylenediamine, affording an excellent yield. Subsequent condensation of this intermediate with various aromatic aldehydes produced the target imine derivatives in good yields. Structural elucidation was performed using ^{1}H NMR, ^{13}C NMR, and mass spectrometry. In vitro anti-malarial activity was assessed in DMSO using chloroquine diphosphate as the positive control. Three of the compounds, N1-(7-chloro-4-quinolyl)-1,2-diaminoethane (Compound A), (E)-N-(2-(benzylideneamino)ethyl)-7-chloroquinolin-4-amine (Compound E), and N-(2-((7-chloroquinolin-4-yl)amino)ethyl)-4-nitrobenzamide (Compound C) displayed remarkable inhibitory effects, with IC_{50} values of 0.015, 1.50, and 1.83 mg/ml, respectively, outperforming the standard chloroquine diphosphate (IC_{50} = 2.50 mg/ml). Anti-oxidant activity was evaluated through free radical scavenging assays using DPPH. Compounds C and D, ((E)-2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino) methyl)benzoic acid) showed potent anti-oxidant activity, with IC_{50} values of 0.57 and 0.64 mg/ml, respectively, surpassing the standard ascorbic acid (IC_{50} = 1.53 mg/ml). It was concluded that the synthesized chloroquine derivatives, particularly Compounds A, C, D and E, demonstrated in vitro anti-malarial and/or anti-oxidant activities compared to established standards. These findings suggest that structural modification of chloroquine can yield promising lead candidates for further development of treatment drugs for malaria and oxidative stress-related conditions.

Keywords: Chloroquine derivatives; Synthesis; *In vitro* evaluation; Anti-malarial; Anti-oxidant activity.

* **Correspondence:** Solomon I. Attah; Email: solomon.attah@unn.edu.ng; Phone: +23408063660524

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Introduction

Chloroquine and chloroquine derivatives have exhibited a variety of useful therapeutic properties, including treatment of malaria. Malaria treatment is facing a major challenge, due to the limited availability of effective anti-malarial drugs. The increasing resistance of *Plasmodium falciparum* to chloroquine-based treatments threatens to undermine the gains achieved in malaria control (Njara *et al*., 2015; Wellems and Plowe, 2001).

Malaria is one of the ancient diseases that have ravaged the human race, causing a lot of havoc for centuries. It kills about half a million people annually and the most vulnerable to this disease are under-aged children, pregnant women and the elderly, especially those living in tropics in Africa, Asia and Caribbean (Eikenberry and Gumel, 2018). It is a protozoan disease caused by parasites of the genus *Plasmodium*, and transmitted to humans by the vector, female anopheles mosquito. There are four species of this Plasmodium which effect humans: these are *Pl*asmodium *falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium* (Trampuz *et al*., 2003; Zekar and Sharman, 2023; Sato, 2021). These species differ in their forms or symmetry, drug responses and availability in different areas of the world (Trampuz *et al*., 2003).

The spread of malaria is prevented by the use of the insecticide treated nets and an indoor residual spraying to control the population of the mosquito vectors (Hemingway, 2014; Rabinovich *et al*., 2017). There are many nature-derived agents for combating malaria, such as plant extracts that are rich in naturally occurring anti-malarials. Examples are quinine and cinchonine alkaloids obtained from cinchona plant (Willcox and Bodeker, 2004). In addition to these naturally occurring anti-malarials, there are many other synthetic and semi-synthetic anti-malarial drugs, most of which have their molecular frame derived from some naturally occurring anti-malarials**.** Among these groups of anti-malarials, quinolone family of anti-malarials has shown a prolonged, fruitful and progressive history due to their unique inhibitory activity against the blood stage parasites (Aguiar *et al*., 2012).

Chloroquine, a 4-aminoquinoline, is an excellent representative of the quinoline family, well known for its exceptional mode of elimination of malarial parasites (Slater, 1993; Edwards, 2001). The powerful anti-malarial activity of chloroquine is attributed to its unique mode of action: its ability to hinder the polymerization of toxic free heme released when malaria parasites digest haemoglobin into amino acids that are incorporated into their protein (Coy *et al*., 2003). The structure of chloroquine is composed of an amine side chain and a quinoline nucleus bearing chlorine atom (Figure 1) (Jochen *et al.*, 2003). The amine side chain helps in the accumulation of the drug into the acidic vacuole of malaria parasites whereas the latter is responsible for its anti-malarial activity (Titus, 1989; Ginsburg and Krugliak, 1999).

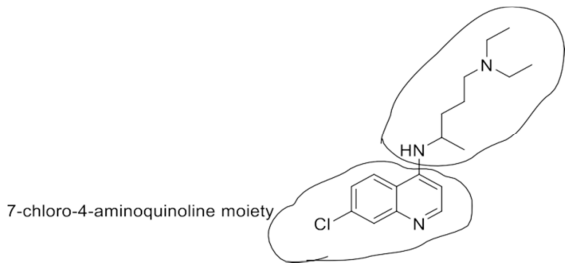

Figure 1. The structure of chloroquine: an amine side chain and a quinoline nucleus bearing chlorine atom.

Previous studies relating the structure of chloroquine to its function has focused on the modification of the side chain and of the quinoline ring (Kaschulla, 2002). Studies have also revealed that structural changes on the 7-chloroaminoquinoline reduced the anti-malarial activity of chloroquine while variations of the side chain gave a more promising anti-malarial activity (Park *et al*., 2002). However, the propensity of the parasites to become resistant to the available anti-malarial drugs has posed a significant barrier to the treatment of malaria for several decades, as drug-resistant parasites have continued to emerge after the medicine was first used.

Based on earlier reports, the modification of the side chain of chloroquine is an important approach for the development of drugs with better anti-malarial activity (Solomon *et al*., 2007). Currently, Schiff bases are of interest due to the valuable function of the imino group in the anti-malarial activity (Nawaz *et al*., 2025). The nitrogen atom of the imine functional group has sp^2 hybridized orbital, in which its lone pair of electrons contributes large enough to the potent anti-malarial activities of this group (Dzeikala and Sykula, 2018). Studies have also shown that chloroquine and its analogues play a vital role in neutralizing oxygen-containing molecules with an uneven number of electrons, known as free radicals which cause large chains of chemical reactions in the body (Magwere *et al*., 1997). In this study, we designed, synthesized, characterized imine derivatives of chloroquine and evaluated their antimalarial and antioxidant potentials.

Material and Methods

All the chemicals used for the study were of analytical grade and were purchased from Sigma Aldrich, USA. The melting points were determined using Gallenkamp melting point apparatus (England). The infra-red spectra were recorded on FTIR-8400s Fourier Transform Infrared Spectrophotometer using KBr disc at Docchy Analytical Laboratory Awka, Nigeria, with absorptions given in wave number (cm^{-1}). The nuclear magnetic resonance (^{1}H-NMR) were recorded with Brucker DPX 400 MHZ spectrophotometer relative to DMSO as internal standard, at the North Carolina State University. All shifts were reported in ppm (δ) in relation to the residual peak of the solvent.

Procedure for synthesis of the key intermediate – Synthesis of N^1-(-7-chloro-4-quinolyl-)-1,2-diaminoethane intermediate: A mixture of 4,7-dichloroquinoline (2.5 g, 0.0126 mol) and ethylene diamine (9.1 g, 0.152 mol) was heated to 110^{o}C under reflux, with continuous stirring in an inert atmosphere for 7 hours and allowed to cool to room temperature. About 100 ml of water was added and the mixture was then filtered to get the product, which was then washed with another 100 ml of water and allowed to dry.

Synthesis of Chloroquine derivatives:

Synthesis of (E)-7-chloro-N-(2-((4-nitrobenzylidene)amino)ethyl)quinolin-4-amine: A mixture of 4-nitobenzaldehyde (0.14 g, 9 mmol) and N^1-(-7-chloro-4-quinolyl-)-1, 2-diamino ethane (0.2g, 9.3mmol) in ethanol (10mL), was stirred under reflux for 3 hours. It was cooled and precipitates formed were collected by filtration, washed with ethanol and recrystallized from ethanol.

Synthesis of N-(2-((7-chloroquinolin-4-yl)amino)ethyl-4-nitrobenzamide: A mixture of 4-nitrobenzoylchloride (0.43 g, 2.3 mmol) and N^1-(-7-chloro-4-quinolyl-)-1, 2- diamine ethane (0.2g, 2.3mmol) in ethanol (10mL), was stirred under reflux for 3 hours. After cooling, precipitates were formed and collected by filtration, washed with ethanol and recrystallized from ethanol.

Synthesis of (E)-2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino)methyl)benzoicacid: A mixture of 2-carboxybenzaldehyde (0.14 g, 0.9

mmol) and N^1-(-7-chloro-4-quinolyl-)-1, 2-diamino ethane (0.2g, 0.9mmol) in ethanol (10mL), was stirred under reflux for 3 hours. After cooling, precipitates were formed and collected by filtration, washed with ethanol and recrystallized from ethanol.

Synthesis of (E)-N-(2-(benzylideneamino) ethyl)-7-chloroquinolin-4-amine: A mixture of benzaldehyde (0.48g, 4.5mmol) and N^1-(-7-chloro-4-quinolyl-)-1,2-diaminoethane (1 g, 4.5 mmol) in ethanol (10 mL), was stirred under reflux for 3 hours. After cooling, precipitates were formed and collected by filtration, washed with ethanol and recrystallized from ethanol.

Determination of Antioxidant Activity: The abilities of the newly synthesized chloroquine derivatives to scavenge DPPH free radicals were determined using ascorbic acid as a standard. The half-maximal inhibitory concentration (IC_{50}) values were deduced from a graph of the percentage inhibition against the concentration for each of the synthesized compounds (Attah *et al*., 2022).

Determination of Anti-malarial activity: An *in vitro* assay was used to assess the abilities of the chloroquine derivatives to inhibit hemozoin formation by their activities against cultured *Plasmodium falciparum* parasites, using chloroquine diphosphate as the standard (Panda *et al*., 2013)

Results

Synthesis of N^1-(-7-chloro-4-quinolyl-)-1,2-diaminoethane intermediate (Compound A): Yield = 2.30 g (82%), Melting point = 180^{o}C. FTIR (cm^{-1}, KBr): 1251 (C-N), 1631(C=C, Ar), 3000 (C-H, aliphatic), 3119 (C-H, aromatic), 3435 and 3569 (N-H stretch). ^{1}HNMR (DMSO, 500 MHz) δ (ppm): 6.40 – 8.20 (5H, m, Ar – H), 3.0 (3H, s, –NH), 2.5(4H, m, CH_2).

Synthesis of (E)-7-chloro-N-(2-((4-nitrobenzylidene)amino)ethyl)quinolin-4-amine (Compound B): Yield = 0.22 g (68.75%), Melting point =124 ^{o}C. FTIR (cm^{-1} KBr): 800 (C – Cl), 1277 (C-N), 1394 (NO_2), 1594 (C=C,Ar), 1630(N=C), 3325 and 3452 (R_2NH). ^{1}HNMR (DMSO,500 MHz)δ (ppm):6.50–8.00 (9H,m,Ar-H), 4.7 (1H,s,–NH), 3.4 (4H,m, CH_2), 1.40 (1H,s,-CH).

Synthesis of N-(2-((7-chloroquinolin-4-yl)amino)ethyl-4-nitrobenzamide (Compound C): Yield = 0.72 g (81.8%), Melting point = 220 ^{o}C. FTIR (cm^{-1} KBr): 755 (C – Cl), 851 (C – C),1312(C–N),1437(C=Caromatics), 1625 (C=Oamides), 2914(C–Halkanes), 3090(C–Haromatics), 3301(N–Hamides). ^{1}HNMR (DMSO, 500MHz) δ (ppm):6.80–8.70(9H,m, Ar – H), 3.7 (2H, s –NH), 3.4 (4H, m, –CH_2).

Synthesis of (E)-2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino)methyl) benzoic acid (Compound D): Yield = 0.14 g (44%), Melting point = 193 ^{o}C. FTIR (cm^{-1} KBr): 1437 (C=C, Ar), 1618 (N–H amines), 1625(C=O), 2891 (C–H aliphatic), 3048, 3126 (C–H aromatics), 3260 (O–H carboxylic acid). H^1NMR (DMSO, 500 MHz) δ (ppm):10 (1H, S, COOH), 6.70 – 8.90 (9H, m, Ar – H), 3.9 (2H, s, –NH), 3.2 (4H, m, CH_2), 3.40 (1H, s, –CH).

Synthesis of (E)-N-(2-(benzylideneamino) ethyl)-7-chloroquinolin-4-amine (Compound E): Yield= 0.38 g (80%), Melting point = 222 ^{o}C. FTIR (cm^{-1} KBr): 719 (C – Cl), 1335-1431(C-N), 1611 (C = C), 2960 (C –H aliphatic), 3075 (Aromatic C – H), 3424 (N – H). H^1NMR (DMSO, 500 MHz) δ (ppm): 6.00 – 8.50 (9H, m, Ar), 4.6 (1H, s =C-H), 3.2 (4H, m, methylene-H), 3.6(1H, s, N – H).

Anti-oxidant activity: Two of the synthesized compounds N-(2-((7-chloroquinolin-4-yl)amino)ethyl-4-nitrobenzamide (Compound C) and Compound D ((E)-2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino)methyl) benzoic acid) exhibited good antioxidant activity based on their potent reduction of DPPH free radicals, when compared with others and with the standard ascorbic acid (Table 1).

Table 1. *In vitro* anti-oxidant activity of five new chloroquine derivatives (A, B, C, D and E) synthesized during the study.

Concentration	DPPH percentage inhibition					
	A	B	C	D	E	AA
5 mg/mL	69.4	63.5	54.1	37.6	42.0	82.8
2.5 mg/mL	55.8	50.5	46.9	36.2	39.0	75.2
1.25 mg/mL	56.6	36.7	68.1	31.0	23.0	63.4
0.063 mg/mL	40.6	23.9	53.5	1.4	19.8	49.7
IC50 (mg/ml)	**27.63**	**2.34**	**0.57**	**0.64**	**1.76**	**1.53**

AA – Ascorbic acid; IC50 – half maximal inhibitory concentration

Table 2. *In vitro* anti-malarial activity of five new chloroquine derivatives (A, B, C, D and E) synthesized during the study.

Concentration	Hemozoin percentage inhibition					
	A	B	C	D	E	CDP
5mg/mL	56.9	48.0	38.3	27.6	52.5	82.6
2.5mg/mL	36.8	40.7	29.6	15.3	49.3	80.0
1.25mg/mL	47.1	37.9	15.7	11.7	21.3	77.4
0.063mg/mL	50.7	24.4	5.1	7.4	8.7	74.6
IC50 (mg/ml)	**0.015**	**12.87**	**1.83**	**14.42**	**1.50**	**2.50**

CDP – Chloroquine diphosphate; IC50 – half maximal inhibitory concentration

Anti-malarial activity: Three among the synthesized compounds, N^1-(-7-chloro-4-quinolyl-)-1,2-diaminoethane (Compound A), (E)-N-(2-(benzylideneamino)ethyl)-7-chloroquinolin-4- amine (Compound E and N-(2-((7-chloroquinolin-4-yl) amino ethyl-4-nitrobenzamide (Compound C) exhibited excellent antimalarial activities comparable with other compounds and with the standard chloroquine diphosphate. (Table 2)

Discussion

The dual assessment of the five newly synthesized chloroquine derivatives (Compounds A–E) for their antioxidant potential and antimalarial activity is particularly relevant given the established role of oxidative stress in malaria pathophysiology (Gomes *et al*., 2022) and the therapeutic importance of compounds that can simultaneously disrupt parasite metabolism and mitigate host oxidative damage (Percário, 2012).

All the synthesized compounds demonstrated concentration-dependent DPPH radical scavenging activity, though with marked variability in potency. Among the derivatives, Compound C exhibited the strongest antioxidant activity, with an IC_{50} of 0.57 mg/ml, surpassing even the reference standard ascorbic acid (IC_{50} = 1.53 mg/ml). Compound D also showed notable activity (IC_{50} = 0.64 mg/ml), followed by compounds E (1.76 mg/ml) and B (2.34 mg/ml). In contrast, compound A showed the weakest antioxidant activity (IC_{50} = 27.63 mg/ml), despite demonstrating relatively high percentage inhibition at higher concentrations. Minor non-monotonic variations in percentage inhibition observed at certain concentrations

may reflect assay variability, compound solubility effects, or differences in interaction kinetics; therefore, IC_{50} values were considered the primary metric for comparative anti-oxidant potency (Blois, 1958).

The DPPH radical scavenging assay revealed that antioxidant activity was highly dependent on aromatic substitution, molecular conjugation, and the balance of electron-withdrawing and electron-donating functional groups (Kareem *et al*.., 2016). The reduced activity of compound A may be attributed to the absence of extended aromatic substituents or conjugated electron-donating systems within its side chain, as confirmed by spectral analysis. The predominance of flexible aliphatic amine functionalities limits electron delocalization and radical stabilization, indicating that aliphatic amines alone are insufficient to confer potent antioxidant activity (Rice-Evans *et al*., 1997).

In contrast, the superior antioxidant performance of Compound C may be attributed to the presence of an amide linkage, which facilitated hydrogen bonding and contributed to stabilization of radical intermediates, consistent with the well-established role of amide groups as hydrogen-bond donors and acceptors in proteins and drug molecules (Montalbetti and Falque, 2005), as well as a para-nitrobenzamide moiety which has been reported to enhance electron delocalization across the aromatic system (Adeniyi and Conradie, 2019). Compound D exhibited strong antioxidant activity, which can be attributed to the presence of its carboxylic acid group capable of proton donation and the extended π-conjugation provided by the Schiff base linkage. These structural features are well known to enhance free radical scavenging efficiency, as demonstrated by Bakır *et al*. (2024), who reported that Schiff bases bearing carboxyl substituents showed significantly improved antioxidant properties due to their ability to donate protons and stabilize radicals through conjugation.

It is important to note that the structure-activity trends demonstrated in antioxidant activity did not directly correlate with antimalarial potency, indicating that distinct molecular features independently modulate redox behavior and parasite inhibition.

The anti-malarial screening revealed that the chloroquine derivatives exhibited diverse inhibitory effects on hemozoin formation, a critical detoxification pathway in *Plasmodium falciparum* (Egan, 2008). Notably, Compound A emerged as the most potent antimalarial agent, with an IC_{50} value of 0.015 mg/ml, demonstrating activity markedly superior to that of chloroquine diphosphate (CDP; IC_{50} = 2.50 mg/ml). Compounds E and C also showed strong anti-malarial activity, exceeding that of the standard drug.

The exceptional potency of Compound A may be attributed to enhanced electrostatic and π–π interactions with ferriprotoporphyrin IX, resulting in effective inhibition of hemozoin crystallization (Pagola *et al*., 2000). In addition, the presence of a flexible diaminoethyl side chain is consistent with structural features characteristic of weakly basic anti-malarial quinolines, which are known to undergo protonation and accumulate within the parasite's acidic food vacuole (Fitch, 2004). Structurally, Compound A closely resembles classical chloroquine, while lacking bulky substituents that could otherwise compromise vacuolar access or target engagement.

Compounds C and E also showed strong anti-malarial activity. Both compounds retained the 4-aminoquinoline nucleus, a scaffold widely associated with an optimal balance between basicity and lipophilicity that promotes efficient membrane permeation while enabling protonation-dependent accumulation in acidic intracellular compartments via ion trapping. Such physicochemical properties are characteristic

of potent dibasic quinolones and are consistent with their accumulation in parasite digestive vacuoles. (Martin and Kirk, 2004; Romero, 2025).

On the other hand, compounds B and D showed poor antimalarial activity. Compound D contains a carboxylic acid group, which reduces basicity, limits protonation and accumulation within the parasite's acidic food vacuole, and increases polarity, thereby impairing membrane permeability (Krogstad, 1987). Interestingly, this finding contrasts with previous reports suggesting that carboxylic ionophores, such as monensin and nigericin, can exhibit potent anti-malarial activity by alkalinizing the food vacuole (Adovelande & Schrével, 1996). In contrast, Compound B bears a bulky nitro–Schiff base moiety, which may sterically hinder effective interaction with ferriprotoporphyrin IX (Egan, 2008).

When both biological activities are considered together, Compound C stands out as the most balanced derivative, exhibiting strong antioxidant activity and potent antimalarial effects. This dual functionality is therapeutically significant, as oxidative stress contributes to erythrocyte damage and inflammatory complications during malaria infection (Percário, 2012). A compound combining parasite inhibition with antioxidant protection may therefore offer added clinical advantage.

In contrast, compound A, while highly potent as an anti-malarial, displayed poor antioxidant capacity, suggesting a more target-specific mechanism of action rather than broad redox modulation. Compounds B and D were generally less effective across both assays, indicating that their structural features may compromise both redox activity and antimalarial efficacy.

Conclusion: A series of new derivatives of chloroquine were successfully synthesized and tested for their activities against chloroquine resistant *Plasmodium falciparum* and also free radical scavenging activity. Three of the analogues of chloroquine showed excellent anti-malarial activities. Also, two of the new derivatives of chloroquine showed potent antioxidant activities in their reduction of DPPH free radicals. The impressive activity of the new analogues of chloroquine show that introducing an imine functional group to the side chain of chloroquine, gives rise to new group of compounds that can overcome the resistance developed by these protozoans and also in the reduction of free radicals.

Conflict of interest

The authors declare no conflict of interest.

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