Synthesis and Antimalarial Activity of 2-Phenyl-1,10-Phenanthroline Derivative Compounds

Ruslin Hadanu\textsuperscript{1*}, Mustofa\textsuperscript{2}, and Nazudin\textsuperscript{1}\\
\textsuperscript{1}Department of Chemistry, Faculty of Teachership and Educational Science, Pattimura University, Poka, Ambon 97233  
\textsuperscript{2}Department of Pharmacology and Toxicology, Faculty of Medicine, Gadjah Mada University, Sekip Utara, Yogyakarta

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ABSTRACT

To develop new potential antimalarial drugs of 2-phenyl-1,10-phenanthroline\textsuperscript{5} derivatives from 8-aminoquinoline as starting material were synthesized in good yields. The synthesis of 2-phenyl-1,10-phenanthroline\textsuperscript{5} derivatives compounds with 8-aminoquinoline\textsuperscript{4} as starting material through three steps has been carried out. The first step of reactions is aldol condensation of benzaldehyde\textsuperscript{1} with acetaldehyde\textsuperscript{2} that it was refluxed for 17 and 19 h, respectively. The results of reactions are (1)-N-methyl-9-phenyl-1,10-phenanthrolinium sulphate\textsuperscript{6} and (1)-N-ethyl-9-phenyl-1,10-phenanthrolinium sulphate\textsuperscript{7} in yield from 90.62% and 89.70%, respectively. The results of testing in vitro antiplasmodial activity at chloroquine-resistant \textit{Plasmodium falciparum} FCR3 strain to 2-phenyl-1,10-phenanthroline\textsuperscript{5} derivatives obtained that (1)-N-ethyl-9-phenyl-1,10-phenanthrolinium sulphate\textsuperscript{7} compound has higher antimalarial activity (IC\textsubscript{50}: 0.13 ± 0.02 µM) than antimalarial activity of (1)-N-methyl-9-phenyl-1,10-phenanthrolinium sulphate\textsuperscript{6} compound (IC\textsubscript{50}: 0.25 ± 0.01 µM) and 2-phenyl-1,10-phenanthroline\textsuperscript{5} compound (IC\textsubscript{50}: 2.45 ± 0.09 µM). While, the results of testing in vitro antiplasmodial activity at chloroquine-sensitive \textit{P. falciparum} strain D10 terhadap senyawa 2-phenyl-1,10-phenanthroline\textsuperscript{5} diperoleh bahwa senyawa (1)-N-metil-9-fenil-1,10-phenanthrolinium sulfat\textsuperscript{6} memiliki aktivitas antimalaria yang lebih tinggi (IC\textsubscript{50}: 0.10± 0.04 µM) dibandingkan dengan senyawa (1)-N-etyl-9-fenil-1,10-phenanthrolinium sulfat\textsuperscript{7} (IC\textsubscript{50}: 0.18 ± 0.01 µM) dan 2-phenyl-1,10-phenanthroline\textsuperscript{5} (IC\textsubscript{50}: 0.55 ± 0.07 µM).

Keywords: 2-phenyl-1,10-phenanthroline derivatives, antimalarial activity, plasmodium, synthesis

ABSTRAK

Untuk mengembangkan obat baru antimalaria yang potensial dari senyawa turunan 2-fenil-1,10-fenantrolina\textsuperscript{5} telah disintesis dari 8-aminokuinolina sebagai bahan dasar. Sintesis senyawa turunan 2-fenil-1,10-fenantrolina\textsuperscript{5} diperoleh dari 8-aminokuinolina\textsuperscript{4} telah dilakukan melalui reaksi aldol kondensasi benzaldehida\textsuperscript{1} dengan asetaldehida\textsuperscript{2} menghasilkan senyawa sinnamaldehida\textsuperscript{3} (92,14%) dalam bentuk padatan kuning. Langkah ketiga adalah reaksi alkilasi terhadap senyawa 2-fenil-1,10-phenanthrolina\textsuperscript{5} menggunakan reagen dimetil sulfat (DMS) dan dietil sulfat (DES) yang direfluks selama 17 dan 19 jam. Hasil reaksi alkilasi tersebut adalah (1)-N-metil-9-fenil-1,10-phenanthrolinium sulfat\textsuperscript{6} dan (1)-N-etyl-9-fenil-1,10-phenanthrolinium sulfat\textsuperscript{7} dengan rendemen berturut-turut sebesar 90.62% dan 89.70%. Hasil pengujian aktivitas antiplasmodial in vitro pada \textit{chloroquine-resistant Plasmodium falciparum} FCR3 terhadap senyawa 2-fenil-1,10-fenantrolina\textsuperscript{5} diperoleh bahwa senyawa (1)-N-metil-9-fenil-1,10-phenanthrolinium sulfat\textsuperscript{6} memiliki aktivitas antimalaria yang lebih tinggi (IC\textsubscript{50}: 0.13 ± 0.02 µM) dibandingkan dengan aktivitas antimalaria dari senyawa (1)-N-metil-9-fenil-1,10-phenanthrolinium sulfat\textsuperscript{6} (IC\textsubscript{50}: 0.25 ± 0.01 µM) dan senyawa 2-fenil-1,10-phenanthrolina\textsuperscript{5} (IC\textsubscript{50}: 2.45 ± 0.09 µM). Sementara, hasil pengujian aktivitas antiplasmodial in vitro pada \textit{chloroquine-sensitive P. falciparum} strain D10 terhadap senyawa 2-fenil-1,10-fenantrolina\textsuperscript{5} diperoleh bahwa senyawa (1)-N-metil-9-fenil-1,10-phenanthrolinium sulfat\textsuperscript{6} memiliki aktivitas antimalaria yang lebih tinggi (IC\textsubscript{50}: 0.10 ± 0.04 µM) dibandingkan...
INTRODUCTION

Malaria is the most important parasitic disease in the world. Its etiological agents are protozoa of the genus *Plasmodium*. *Plasmodium falciparum* is the most virulent among the four species infecting humans and is responsible for most of mortality. In 2008, among 3.3 billion people at risk, there were 243 million malaria cases, causing an estimated 863,000 deaths, mostly of children under five years. From 109 countries endemic for malaria, 45 were within the World Health Organization (WHO 2009) especially in African Region (Fernández et al. 2011; Fidock et al. 2004; Olumes 2005; Kayembe et al. 2010). Malaria remains one of the most important diseases of the developing world, killing 1–3 million people and causing disease in 300–500 million people annually (Fidock et al. 2004; Olumes 2005, Kayembe et al. 2010). Malaria endemic areas include Africa, South East Asia, India and South America; however, the disease is spreading to new areas, such as Central Asia, and Eastern Europe. Local transmission of malaria in the United States, unheard of in the era between World War II and 1980, now accounts for an increasing number of cases (Molyneux et al. 1989). Clinical cases in the US now average 1,300 per year (Wernsdorfer 1991). Worldwide, the majority of deaths occur in children; other high risk groups include pregnant women, refugees, migrant workers, and non immune travelers-over 20 million Western tourists at risk annually (fact sheets from Malaria Foundation International). Although four species of the genus *Plasmodium* cause human malaria, *P. falciparum* is the deadliest and will be the subject of this review.

The traditional remedies are no longer effective and the incidence of malarial by *P. falciparum*, the most dangerous species of parasite, continues to grow, while some traditional drugs such as chloroquine and its congeners are losing their activity due to the increasing multi drug resistance (Yapi et al. 2000; Yapi et al. 2006). Therefore, it is essential to find new drugs of anti malaria having a pharmacological activity higher than of currently available drugs of anti malaria. In this connection, quantitative structure-activity relationship (QSAR) analysis plays an important role to minimize trial and error in designing new antimalarial drugs.

The halofantrine as new anti malaria has good therapeutic effects (Basco et al. 1994). Halofantrine as more active against strains of *P. falciparum* that are resistant to chloroquine, pyrimethamine, and quine (Rang et al. 2003). However, halofantrine is known to have some unwanted side effects, such as abdominal pain, nausea, vomiting, diarrhea, orthostatic, hypertension, prolongation of QTc intervals, pruritus, rash, and hepatotoxic (Karbwang et al. 1991; Bassi et al. 2006). The 1,10-phenanthroline derivatives are similar to halofantrine as antimalarial drug which its added at heterocyclic with two nitrogen atoms. (In 2000, Yapi reported) that the 1,10-phenanthroline ring system appeared as new class of potential antimalarial compound (Yapi et al. 2000).

Now, part of our research was concerning the synthesis and biological activity of 1,10-phenanthroline derivatives. In this program continuation of these studies, we report in this paper our results concerning the synthesis and the determination of the biological activity of compound type (1)-N-alkyl- and (1)-N-benzyl-1,10-phenanthroline (Widjayanti et al. 2006). Yapi et al. (2006) have synthesized diaza-analogs of phenanthrene by substituting the two nitrogen atoms in the phenanthrene skeleton. Antiplasmodial activity of series of diaza-analogs of phenanthrene derived from 3-amino-, 5-amino-, 6-amino-, 8-aminoquinoline and 5-isoquinoline showed that among the molecules evaluated the 1,10-phenanthroline skeleton was the most active compound in vitro on both chloroquine-resistant (FcB1) and chloroquine-sensitive (Nigerian) strain with an IC_{50} of about 0.13 M. Based on the skeleton, (Mustofa et al. 2003) have also synthesized thirteen derivatives of 1,10-phenanthroline and evaluated the in vitro antiplasmodial activity (Yapi et al. 2000) and their Quantitative Structure Activity Relationship (QSAR) Mustofa et al. 2003. The resulting of the QSAR analysis found the best theoretical activity of six new compounds and its was synthesized and evaluated their in vitro antiplasmodial activity through experiment in laboratory.

This study were synthesized of 2-phenyl-1,10-phenanthroline derivatives from 8-aminoquinoline as starting material. The halofantrine were obtained two compounds of 2-phenyl-1,10-phenanthroline derivatives (1) N-methyl-9-phenyl-
1,10-phenanthroline sulphate 6 and (1)-N-ethyl-9-phenyl-1,10-phenanthroline sulphate 7 which were synthesized through 3 stages reaction. The reactions condition and the results of synthesis of 2-phenyl-1,10-phenanthroline 5 derivative compounds were described in Figure 1.

**MATERIALS AND METHODS**

**Materials.** The 8-aminoquinoline p.a. (Merck), dymethyl sulphate (DMS) p.a. (Merck), dymethyl sulphate (DES) p.a. (Merck), HSO₄ 70% p.a. (Merck), acetaldehyde p.a. (Merck), benzaldehyde p.a. (Merck), HCl p.a. (Merck), NaOH p.a. (Merck), NaI p.a. (Merck), KOH p.a. (Merck), Na₂SO₄ anhydrous p.a. (Merck), HBr p.a. (Merck), NaHCO₃ p.a. (Merck), acetone p.a. (Merck), CH₃Cl p.a. (Merck), CHCl₃ p.a. (Merck), CCl₄ p.a. (Merck), dimethyl sulfoxide (DMSO) p.a. (Merck), gas N₂, Na₂SO₄ p.a. (Merck), TLC plat, silica gel, hexane p.a. (Merck), benzene p.a. (Merck).

**Instruments.** The melting point of compound were determined with melting point electro thermal 9100. The spectrum of structures compound measurements were taken using the instruments: Shimadzu FTIR-8201 PC; 1H-NMR JEOL 60 MHz, JEOL 500 MHz and GC-MS Shimadzu QP 5000. In general, the melting point of compounds were determined on melting point electro thermal 9100 and are not corrected. The spectrum of structures compound measurements were taken using the following instruments: FTIR spectrum were taken on Shimadzu FTIR-8201 PC; 1H-NMR spectrum were obtained on JEOL 60 MHz and JEOL 500 MHz. MS spectrum were recorded on GC-MS Shimadzu QP 5000.

**Procedure.** Synthesis of Cinnamaldehyde (3). Ethanol (15 mL) was transferred into a 125-mL Erlenmeyer flask, and 20 mL of 10% NaOH solution. Using a thermometer, cool the solution to 20°C. In a medium size tube, mix 2 mL of benzaldehyde with 15 drops of acetaldehyde, and leave it at room temperature for 5 minutes. Then, add the mixture to the ethanol-NaOH solution in small portions and stir with magnetic stirrer for 30 minutes. Cool the mixture using the ice-water bath. The product was filtrated and hand-dried to collect the yellow oils to give of the cinnamaldehyde 3 product (6.09 g; 92.04%). The product was characterized by means of spectrum. IR spectrum (KBr) υ (cm⁻¹): 3062.7-3031.9 (HC=), 2927.7 (-C-H), 1685.7 (C=O), 1600.8 and 1462.8 (C=C aromatic); NMR spectrum (60 MHz, DMSO-d₆, TMS) δ (ppm): 10.1 (1H, s, CHO), 8.2-7.9 (3H, CHO), 7.3 (4H, s), 7.1-6.2 (5H, m, H₃C₆H₄), and 7.8-7.3 (4H, m, H₃C₆H₄). MS spectrum (El) m/z: 132 (M), 131 (M-H), 103 (131-C=O), 77 (103-C₆H₄), and 51 (77-C₆H₄).

**Synthesis of 2-phenyl-1,10-phenanthroline (5).** The cinnamaldehyde 3 compound (2.64 g; 20 mmol) was added over 5 h to a stirred solution of the 8-aminoquinoline 4 (1.73 g; 10 mmol) and NaI (12 mmol) in H₂SO₄ 70% (5 mL) at 110°C. After 1 h at 110°C the dark brown reaction mixture was cooled to room temperature, poured into 1 M Na₂CO₃ (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combination of organic layers were extracted with CH₂Cl₂. Removal of the solvent in vacuo afforded the appropriate 1,10-phenanthroline skeleton. The products were purified by filtration through silica gel using CH₂Cl₂ as solvent to give brown solid compound of 2-phenyl-1,10-phenanthroline 5 (2.80 g, 54.63%, m.p.: 145-148°C. The product was characterized by means of spectrum. IR spectrum (KBr) υ (cm⁻¹): 3409.9 (O-Hydrogen bonding), 3028.0 (HC=), 2980.0-2854.5 (-C-H), 1596.9 and 1462.8 (C=C aromatic); NMR spectrum (500 MHz, DMSO-d₆, TMS) δ (ppm): 8.30-6.43 (12H, m, Ph); MS spectrum (El) m/z: 256 (M), 230 (M-C₆H₄), 204 (230-C₆H₄), 179 (204-C₆H₄), 227 (179-C₆H₄), 101 (127-C₆H₄) and 77 (102-C₆H₄).

**Synthesis of (1)-N-methyl-9-phenyl-1,10-phenanthroline sulphate (6).** The 2-phenyl-1,10-phenanthroline 5 (0.51 g; 2 mmol) and DMS (1.26 g, 20 mmol) in acetone (20 mL) was refluxed for 17 h. The resulting mixture was then cooled. The precipitate which formed was filtered, and washed with acetone. Recrystallization with dichloromethane:diethyl ether (1:1). The precipitate which
formed was filtered and washed with acetone to give brown solid compound (0.58 g; 90.62%) of (1)-N-methyl-6-nitro-1,10-phenanthrolinium sulphate 6; m.p.: 188-190°C. The product was characterized by spectroscopy method. IR spectrum (KBr) δ (cm⁻¹): 3429.2 (O-H hydrogen bonding), 2950.9; 2923.9; and 2866.0 (-C-H), 1600.8 and 1500.0 (C=C aromatic); 1365.5 (CH₃); NMR spectrum (500 MHz, DMSO-d₆, TMS) δ (ppm): 9.37 (1H, d, H₉), 9.10 (1H, d, H₆), 8.75-8.74 (1H, t, H₈), 8.58-8.54 (1H, d, H₈), 7.94-7.93 (1H, d, H₆), 7.83-7.82 (1H, d, H₈), 7.76-7.72 (1H, d, H₆), 7.68-7.64 (1H, s, H₅), 7.50-7.30 (1H, t, H₇), 7.21-7.13 (1H, t, H₇), 6.94-6.92 (1H, t, H₈), 6.80-6.75 (1H, s, CH₃), 4.78 (3H, s, CH₃), and 3.57-3.49 (H₂O, s; hydrogen bonding).

Synthesis of (1)-N-ethyl-9-phenyl-1,10-phenanthroline sulphate (7). The 2-phenyl-1,10-phenanthroline 5 (0.51 g; 2 mmol) and DES (0.51 g; 20 mmol) in acetone (25 mL) was refluxed for 19 h. The resulting mixture was then cooled. The precipitate which formed was filtered, and washed with acetone. Recrystallization with dichloromethane: diethyl ether (1:1). The precipitate which was filtered and washed with acetone to give brown solid compound (0.61 g; 89.70%) of (1)-N-ethyl-6-nitro-1,10-phenanthroline sulphate 7; m.p.: 188-190°C. The product was characterized by means of spectroscopic. IR spectrum (KBr) δ (cm⁻¹): 3438.8 (O-H hydrogen bonding), 3058.9 (C=CH₂, H), 2989.5; 2923.9; and 2866.0 (-C-H), 1600.8 and 1500.0 (C=C aromatic); 1438.8 (CH₃); and 1357.8 (CH₂); NMR spectrum (500 MHz, DMSO-d₆, TMS) δ (ppm): 9.20-8.20 (12H, H₉), 7.50-7.40 (3H, m, H₄), 2.49 (3H, s, CH₃), and 1.1 (3H, t, H₃).

Biological Activity. Parasites were cultured according to method described by Trager and Jensen (1976) with modification. FCBr3 was considered as a chloroquine resistant strain and D10 were considered as a chloroquine sensitive strain. Culture medium was replaced daily and the cultures were synchronized by 5% D-sorbitol lysis (Merk, Darmstadt, Germany). The method used for in vitro antimalarial activity testing was adapted from visual method. The molecules were tested 3 times in triplicate in 96-well plates (TPP, Switzerland) with cultures at ring stage at 0.5-1.0% parasitemia (hematocrit 1%). For each test, the parasite cultures were incubated with the chemicals at decreasing concentrations for 24 and 72 h. The first dilution of the product (10 mg/mL) was performed with dimethylsulfoxide (DMSO, Merck), and the following with RPMI 1640. Parasites growth was estimated by coloring with giemsa (10%) for 30 second and calculated by β-caunter.

The parasite control in the presence without chemicals (mean of the corresponding wells was referred to as 100%). Concentrations inhibiting 50% of the parasite (IC₅₀) were determined by SPSS 13.0 software. The IC₅₀ that indicated antiplasmodial activity of chemicals compound to determine by probit analysis method with percentage of concentration inhibition versus chemical doses.

RESULTS AND DISCUSSION

The synthesis of 2-phenyl-1,10-phenanthroline 5 derivate was carried out through three steps (Figure 1). The first step is synthesis of cinnamaldehyde 3 compound by aldol condensation reaction. This reaction used sodium hydroxide (NaOH) as base catalyst. The condensation of acetaldehyde with benzaldehyde to give cinnamaldehyde 3 compound as product of reaction (6.09 g; 92.04%). The second step is synthesis of 2-phenyl-1,10-phenanthroline 5 from 8-aminoquinoline 4 and cinnamaldehyde 3 through cyclization reaction. The third step is synthesis of the (1)-N-alkyl-9-phenyl-1,10-phenanthroline salts compound from 2-phenyl-1,10-phenanthroline 5 using DMS and DES reagent as donor of (1)-N-methyl-9-phenyl-1,10-phenanthroline sulphate 6 and (1)-N-ethyl-9-phenyl-1,10-phenanthroline sulphate 7 compounds (Figure 1).

Synthesis of (1)-N-methyl-9-phenyl-1,10-phenanthroline sulphate 6 was conducted from 2-phenyl-1,10-phenanthroline 5 by DMS reagent in acetone which refluxing 17 hours. The structure of (1)-N-methyl-9-phenyl-1,10-phenanthroline sulphate 6 was determined by FTIR and ¹H-NMR spectrum. The FTIR spectrum showed typical spectra at 1357.8 cm⁻¹ that to indicate the presence of methyl group, while the ¹H-NMR spectrum showed one singlet at 4.78 (3H), assigned to the methyl group. The treatment of (1)-N-ethyl-9-phenyl-1,10-phenanthroline sulphate 7 compound with DES in acetone which refluxing for 19 hours gave the salt compound. The product of ethylation of reaction washing with acetone and the structure was determined by FTIR and ¹H-NMR spectrum. Similarly, the FTIR spectrum of (1)-N-ethyl-9-phenyl-1,10-phenanthroline sulphate 7 showed typical spectrum at 1438.8 and 1357.8 cm⁻¹, respectively, assigned to the methyl and methylene groups, while the ¹H-NMR spectrum of (1)-N-ethyl-9-phenyl-1,10-phenanthroline sulphate 7 compounds showed one triplet at δ 2.49 (3H, m, H₄), and 1.1 (3H, t, H₃), respectively, that indicated the presence of methyl and methylene groups.

Widjayanti et al. (2006) reported the activities of 8 new...
In this study, the synthesis of N-alkyl- and N-benzyl-1,10-phenanthroline derivatives: 1) (1)-N-methyl-1,10-phenanthroline sulphate, 2) (1)-N-ethyl-1,10-phenanthroline sulphate, 3) (1)-N-t-buthyl-1,10-phenanthroline chloride, 4) (1)-N-benzyl-1,10-phenanthroline chloride, 5) (1)-N-benzyl-1,10-phenanthroline bromide, 6) (1)-N-benzyl-1,10-phenanthroline iodide, 7) (1)-N-(4-methoxybenzyl)-1,10-phenanthroline chloride, and 8) (1)-N-(4-benzyloxy-3-methoxybenzyl)-1,10-phenanthroline chloride compounds were presented. In another compound, Hadanu et al. (2007) reported the activities of 1 new compound of (1)-N-(4-methoxybenzyl)-1,10-phenanthroline bromide. All compounds tested showed antimalarial activities, with the compound of (1)-N-benzyl-1,10-phenanthroline bromide having the highest activities (0.10 ± 0.13 μM) against P. falciparum strain FCR3 and the (1)-N-benzyl-1,10-phenanthroline bromide having highest activity (IC50 = 0.33 ± 0.34 μM) on P. falciparum strain D10.

In this research, the result of evaluation antimalarial activities using chloroquine-resistant FCR3 strain is summarized in Table 1. While, the result of investigation antimalarial activities using chloroquine sensitive D10 strains is summarized in Table 2. In this study, the antimalarial activity of 1,10-phenanthroline derivatives showed that 2-phenyl-1,10-phenanthroline 5, (1)-N-methyl-9-phenyl-1,10-phenanthroline sulphate 6, and (1)-N-ethyl-9-phenyl-1,10-phenanthroline sulphate 7 were active against P. falciparum FCR3 with an IC50, 2.45 ± 0.09, 0.25 ± 0.01 and 0.13 ± 0.02 μM, respectively, and D10 strains with an IC50, 0.55 ± 0.07, 0.10 ± 0.03, and 0.18 ± 0.02 μM, respectively. The result of antimalarial evaluation to all 2-phenyl-1,10-phenanthroline derivatives toward FCR 3 and D10 strain of P. falciparum were presented in Table 1 and 2, respectively.

Table 1 Parasite growth inhibition and IC50 of 2-phenyl-1,10-phenanthroline on FCR-3 strain

<table>
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<tr>
<th>Concentration (ng/mL)</th>
<th>Compound of 5</th>
<th>% Inhibition (mean ± SD)</th>
<th>Compound of 6</th>
<th>% Inhibition (mean ± SD)</th>
<th>Compound of 7</th>
<th>% Inhibition (mean ± SD)</th>
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<td>93.36 ± 2.43</td>
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<td>IC50(μM)</td>
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ND : Not Determined

Table 2 Parasite growth inhibition and IC50 of 2-phenyl-1,10-phenanthroline on D10 strain

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<td>IC50(μM)</td>
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</tbody>
</table>

This treatment with 2-phenyl-1,10-phenanthroline derivative compounds significantly inhibited parasitemia of P. falciparum FCR3 strain D10. Although the suppression of parasitemia was never complete (100% inhibition of parasite growth), the results indicated antimalarial potency. In the P. falciparum FCR3 strain, the (1)-N-ethyl-9-phenyl-1,10-phenanthroline sulphate 7 compound have higher activity than (1)-N-methyl-9-phenyl-1,10-phenanthroline sulphate 6 and (1)-N-ethyl-1,10-phenanthroline 5 compound, but in the P. falciparum D10 strain, the (1)-N-methyl-9-phenyl-1,10-phenanthroline sulphate 6 compound have higher activity than (1)-N-ethyl-9-phenyl-1,10-phenanthroline sulphate 7 and 2-phenyl-1,10-phenanthroline 5 compound.

**CONCLUSIONS**

The 1,10-phenanthroline derivative compounds i.e. 2-phenyl-1,10-phenanthroline 5, (1)-N-methyl-9-phenyl-1,10-phenanthroline sulphate 6 and (1)-N-ethyl-9-phenyl-1,10-phenanthroline sulphate 7 were synthesized,
characterized, and evaluated of in vitro antiplasmodial activity. Results of in vitro antiplasmodial activity on chloroquine-resistant P. falciparum FCR3 strain were determined by microscopic method after 72 h incubation showing the highest antiplasmodial activity in FCR3 strain is (1)-N-ethyl-9-phenyl-1,10-phenanthroline sulphate 7 to equal 0.13 ± 0.02 µM, while in the D10 strain having the highest antiplasmodial activity is (1)-N-methyl-9-phenyl-1,10-phenanthroline sulphate 6 to equal 0.10 ± 0.03 µM.

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