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

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ABSTRACT

To develop new potential antimalarial drugs of 2-phenyl-1,10-phenanthroline **5** derivatives from 8-aminoquinoline as starting material were synthesized in good yields. The synthesis of 2-phenyl-1,10-phenanthroline **5** derivatives compounds with 8-aminoquinoline **4** as starting material through three steps has been carried out. The first step of reactions is aldol condensation of benzaldehyde **1** with acetaldehyde **2**. The result of reactions is cinnamaldehyde **3** (92.14%) in the form of yellow solid. The second step of reactions was synthesized of 2-phenyl-1,10-phenanthroline **5** (brown solid, 54.63%) through cyclization of 8-aminoquinoline **4** with cinnamaldehyde **3** compound. The third step of reactions is methylation and ethylation of 2-phenyl-1,10-phenanthroline using dimethyl sulphate (DMS) and diethyl sulphate (DES) reagents that it was refluxed for 17 and 19 h, respectively. The results of reactions are (1)-N-methyl-9-phenyl-1,10-phenanthrolinium sulphate **6** and (1)-N-ethyl-9-phenyl-1,10-phenanthrolinium sulphate **7** in yield from 90.62% and 89.70%, respectively. The results of testing *in vitro* antiplasmodial activity at chloroquine-resistant *Plasmodium falciparum* FCR3 strain to 2-phenyl-1,10-phenanthroline **5** derivatives obtained that (1)-N-ethyl-9-phenyl-1,10-phenanthrolinium sulphate **7** compound has higher antimalarial activity (IC_{50}:0.13 ± 0.02 µM) than antimalarial activity of (1)-N-methyl-9-phenyl-1,10-phenanthrolinium sulphate **6** compound (IC_{50}:0.25 ± 0.01 µM) and 2-phenyl-1,10-phenanthroline **5** compound (IC_{50}:2.45 ± 0.09 µM). While, the results of testing *in vitro* antiplasmodial activity at chloroquine-resistant *Plasmodium falciparum* D10 strain to 2-phenyl-1,10-phenanthroline **5** derivatives obtained that (1)-N-methyl-9-phenyl-1,10-phenanthrolinium sulphate **6** compound has higher antimalarial activity (IC_{50}:0.10± 0.04 µM) than antimalarial activity of (1)-N-ethyl-9-phenyl-1,10-phenanthrolinium sulphate **7** (IC_{50}:0.18 ± 0.01 µM) and 2-phenyl-1,10-phenanthroline **5** compound (IC_{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 **5** telah disintesis dari 8-aminokuinolina sebagai bahan dasar. Sintesis senyawa turunan 2-fenil-1,10-fenantrolina **5** dari 8-aminokuinolina **4** telah dilakukan melalui tiga tahap reaksi. Langkah pertama adalah reaksi aldol kondensasi benzaldehida **1** dengan asetaldehida **2** menghasilkan senyawa sinnamaldehida **3** (92,14%) dalam bentuk padatan kuning. Langkah kedua adalah sintesis senyawa 2-fenil-1,10-fenantrolina **5** (padatan coklat, 54,63%) melalui siklisasi 8-aminokuinolina **4** dengan senyawa sinnamaldehida **3**. Langkah ketiga adalah reaksi metilasi dan etilasi terhadap senyawa 2-fenil-1,10-fenantrolina **5** menggunakan reagen dimetil sulfat (DMS) dan dietil sulfat (DES) yang direfluks masing-masing selama 17 dan 19 jam. Hasil reaksi alkilasi tersebut adalah (1)-N-metil-9-fenil-1,10-phenanthrolinium sulfat **6** dan (1)-N-etil-9-fenil-1,10-phenanthrolinium sulfat **7** dengan rendemen berturut-turut sebesar 90,62% dan 89,70%. Hasil pengujian aktivitas antiplasmodial *in vitro* pada *chloroquine-resistant Plasmodium falciparum strain* FCR3 terhadap turunan 2-fenil-1,10-fenantrolin **5** diperoleh bahwa senyawa (1)-N-etil-9-fenil-1,10-phenanthrolinium sulfat **7** memiliki aktivitas antimalaria yang lebih tinggi (IC_{50}: 0,13 ± 0,02 µM) dibandingkan dengan aktivitas antimalaria dari senyawa (1)-N-metil-9-fenil-1,10-phenanthrolinium sulfat **6** (IC_{50}: 0,25 ± 0,01 µM) dan senyawa 2-fenil- 1,10-fenantrolina **5** (IC_{50}: 2,45 ± 0,09 µM). Sementara, hasil pengujian aktivitas antiplasmodial *in vitro* pada *chloroquine-sensitive P. falciparum* strain D10 terhadap senyawa 2-fenil-1,10-fenantrolina **5** diperoleh bahwa senyawa (1)-N-metil-9-fenil-1,10-fenantrolina sulfat **6** memiliki aktivitas antimalaria yang lebih tinggi (IC_{50}: 0,10 ± 0,04 µM) dibandingkan

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dengan aktivitas antimalaria dari senyawa (1)-*N*-etil-9-fenil-1,10-phenanthrolinium sulfat **7** (IC_{50}: $0,18 \pm 0,01$ M) dan senyawa 2-fenil-1,10-fenantrolina **5** (IC_{50}: $0,55 \pm 0,07$ pM).

Kata Kunci: aktivitas antimalaria, plasmodium, sintesis, turunan 2-fenil-1,10-fenantrolina

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; Olumese 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; Olumese 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-phenanthrolinium (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 μM. 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 **5** derivatives from 8-aminoquinoline **4** as starting material were obtained two compounds of 2-phenyl-1,10-phenanthroline **5** derivatives i.e. (1)-*N*-methyl-9-phenyl-

1,10-phenanthrolinium sulphate **6** and (1)-*N*-ethyl-9-phenyl-1,10-phenanthrolinium 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), H_2SO_4 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), Na_2SO_4 anhydrous p.a. (Merck), HBr p.a. (Merck), $NaHCO_3$ p.a. (Merck), acetone p.a. (Merck), CH_2Cl_2 p.a. (Merck), $CHCl_3$ p.a. (Merck), CCl_4 p.a. (Merck), dimethyl sulfoxide (DMSO) p.a. (Merck), gas N_2, Na_2SO_4 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; ^{1}H-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; ^{1}H-NMR spectrum were obtained on JEOL 60 MHz and JEOL

Figure 1 Synthesis of 2-phenyl-1,10-phenanthroline **5** derivatives

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)   (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-d$_6$, TMS)   (ppm): 10.1 (1H, *s*, CHO), 8.2-7.9 (3H, *m*, H$_{B,C,\&G}$), and 7.8-7.3 (4H, *m*, H$_{A,D,E\&F}$). MS spectrum (EI) *m/z*: 132 (M), 131 (M-.H), 103 (131-C=O), 77 (103-C_2H_2), and 51 (77- C_2H_2).

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 H_2SO_4 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 Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combination of organic layers were extracted with CH_2Cl_2. Removal of the solvent in vacuo afforded the appropriate 1,10-phenanthroline skeleton. The products were purified by filtration through silica gel using CH_2Cl_2 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) (cm-1): 3409.9 (O-H hydrogen bonding), 3028.0 (HC=), 2900.0-2854.5 (-C-H), 1596.9 and 1462.8 (C=C aromatic); NMR spectrum (500 MHz, DMSO-d6, TMS)   (ppm): 8.30-6.43 (12H, *m*, Ph); MS spectrum (EI) *m/z*: 256 (M), 230 (M-C_2H_2), 204 (230-C_2H_2), 179 (204-C_2H_2), 127 (179-NC$_3$H$_2$), 101 (127-.C_2H) and 77 (102-.C_2H).

Synthesis of (1)-*N*-methyl-9-phenyl-1,10-phenanthrolinium 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. Recrystalization with dichloromethane:diethyl ether (1:1). The precipitate which
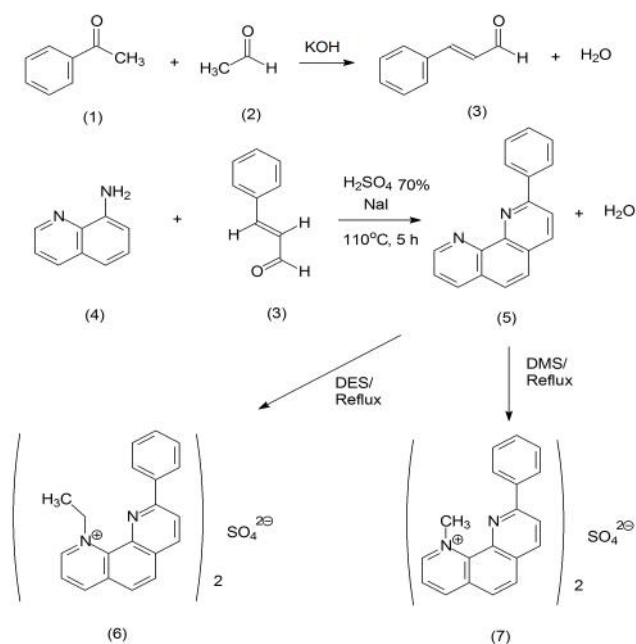
formed was filtered and washed with acetone to give brown solid compound (0.58 g; 90.62%) of (1)-*N*-methyl-6-nitro-1,10-phenanthrolinium sulphate **6**; m.p.: 188-190ºC. The product was characterized by spectroscopy method. **IR** spectrum (KBr)   (cm^{-1}): 3429.2 (O-H hydrogen bonding), 2950.9; 2923.9; and 2866.0 (-C-H), 1600.8 and 1500.0 (C=C aromatic); 1365.5 (CH$_3$); **NMR** spectrum (500 MHz, DMSO-d$_6$, TMS)   (ppm): 9.37 (1H, *d*, H$_A$), 9.10 (1H, *d*, H$_C$), 8.75-8.74 (1H, *t*, H$_B$), 8.58-8.54 (1H, *d*, H$_J$), 7.94-7.93 (1H, *d*, H$_E$), 7.83-7.82 (1H, *d*, H$_I$), 7.76-7.72 (1H, *d*, H$_D$), 7.68-7.64 (1H, *s*, H$_F$), 7.50-7.30 (1H, *t*, H$_K$), 7.21-7.13 (1H, *t*, H$_G$), 6.94-6.92 (1H, *t*, H$_L$), 6.80-6.75 (1H, *t*, H$_H$), 4.78 (3H, *s*, CH$_3$)**,** and 3.57-3.49 (H$_2$O, *s*; hydrogen bonding).

Synthesis of (1)-*N*-ethyl-9-phenyl-1,10 phenanthrolinium 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. Recrystalization with dichloromethane: diethyl ether (1:1). The precipitate which formed was filtered and washed with acetone to give brown solid compound (0.61 g; 89.70%) of (1)-*N*-ethyl-6-nitro-1,10-phenanthrolinium sulphate **7**; m.p.: 188-190ºC. The product was characterized by means of spectroscopic. **IR** spectrum (KBr) (cm^{-1}): 3438.8 (O-H hydrogen bonding), 3058.9 (C$_{sp2}$-H), 2989.5 and 2879.5 (-C-H), 1625.9 and 1525.6 (C=C aromatic); 1438.8 (CH$_2$), and 1357.8 (CH$_3$); **NMR** spectrum (500 MHz, DMSO-d$_6$, TMS)   (ppm): 9.20-8.20 (12H, H$_{Ph}$), 2.49 (3H, *m*, H$_{CH2}$) and 1.1 (3H, *t*, H$_{CH3}$).

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 perfomed 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 -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 (IC$_{50}$) were determined by SPPS 13.0 software. The IC$_{50}$ 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-phenanthrolinium salts compound from 2-phenyl-1,10-phenanthroline **5** using DMS and DES reagent as donor of (1)-*N*-methyl-9-phenyl-1,10-phenanthrolinium sulphate **6** and (1)-*N*-ethyl-9-phenyl-1,10-phenanthrolinium sulphate **7** compounds (Figure 1).

Synthesis of (1)-*N*-methyl-9-phenyl-1,10 phenanthrolinium 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-phenanthrolinium 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. Treatment of (1)-*N*-ethyl-9-phenyl-1,10-phenanthrolinium 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-phenanthrolinium 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-phenanthrolinium sulphate **7** compounds showed one triplet at ʊ 2.49 (3H, *m*, H$_{CH2}$) and 1.1 (3H, *t*, H$_{CH3}$), respectively, that indicated the presence of methyl and methylene groups.

Widjayanti *et al.* (2006) reported the activities of 8 new

Table 1 Parasite growth inhibition and IC_{50} of 2-phenyl-1,10-phenanthroline on FCR-3 strain

Concentration (ng/mL)	% Inhibition (mean ± SD)		
	Compound of 5	Compound of 6	Compound of 7
50	28.71 ± 1.60	37.20 ± 8.09	44.72 ± 6.75
100	35.97 ± 4.96	45.36 ± 6.87	70.07 ± 3.17
200	42.74 ± 4.11	53.75 ± 2.37	77.76 ± 0.15
400	48.88 ± 5.37	61.12 ± 5.77	89.10 ± 1.26
800	60.51 ± 3.68	69.30 ± 2.07	93.36 ± 2.43
1600	67.34 ± 6.89	83.85 ± 3.05	97.19 ± 1.01
IC_{50} (µM)	2.45 ± 0.09	0.25 ± 0.01	0.13 ± 0.02

Table 2 Parasite growth inhibition and IC_{50} of 2-phenyl-1,10-phenanthroline on D10 strain

Concentration (ng/mL)	% Inhibition (mean ± SD)		
	Compound of 5	Compound of 6	Compound of 7
	ND	31.20 ± 3.28	4.80 ± 1.24
50	24.58 ± 7.40	64.48 ± 0.66	43.55 ± 0.34
100	31.61 ± 20.35	88.89 ± 2.26	60.66 ± 14.97
200	46.58 ± 6.88	94.72 ± 5.68	90.16 ± 10.00
400	54.91 ± 3.14	97.87 ± 1.89	96.26 ± 3.34
800	72.02 ± 8.06	ND	ND
1600	78.59 ± 7.53	ND	ND
IC_{50} (µM)	0.55 ± 0.07	0.10 ± 0.03	0.18 ± 0.02

ND : *Not Determined*

compounds of *N*-alkyl- and *N*-benzyl-1,10-phenanthrolinium derivatives: 1) (1)-*N*-methyl-1,10-phenanthrolinium sulphate, 2) (1)-*N*-ethyl-1,10-phenanthrolinium sulphate, 3) (1)-*N*-t-butyl-1,10-phenanthrolinium chloride, 4) (1)-*N*-benzyl-1, 10-phenanthrolinium chloride, 5) (1)-*N*-benzyl-1, 10-phenanthrolinium bromide, 6) (1)-*N*-benzyl-1,10-phenanthrolinium iodide, 7) (1)-*N*-(4-methoxybenzyl-1,10-phenanthrolinium chloride, and 8) (1)-*N*-(4-benzyloxy-3-methoxybenzyl-1,10-phenanthrolinium chloride compounds. In another compound, Hadanu *et al.* (2007) reported the activities of 1 new compound of (1)-*N*-(4-methoxybenzyl-1,10-phenanthrolinium bromide. All compounds tested antiplasmodial activities, the compound of (1)-*N*-benzyl-1,10-phenanthrolinium bromide had the highest activities (0.10 ± 0.13 µM) against *P. falciparum* strain FCR3 and the (1)-*N*-benzyl-1,10-phenanthrolinium bromide had highest activity (IC_{50} : 0.33 ± 0.34 µM) on *P. falciparum* strain D10.

In this research, the result of evaluation antiplasmodial activities using chloroquine-resistant FCR3 strain is summarized in Table 1. While, the result of investigation antiplasmodial activities using chloroquine sensitive D10 strains is summarized in Table 2. In this study, the antiplasmodial activity of 1,10-phenanthroline derivatives showed that 2-phenyl-1,10-phenanthroline 5, (1)-*N*-methyl-9-phenyl-1,10-phenantrolinium sulphate 6, and (1)-*N*-ethyl-9-phenyl-1,10-phenantrolinium sulphate 7 were active against *P. falciparum* FCR3 with an IC_{50} 2.45 ± 0.09, 0.25 ± 0.01 and 0.13 ± 0.02 µM, respectively, and D10 strains with an IC_{50} 0.55 ± 0.07, 0.10 ± 0.04, and 0.18 ± 0.01 µM, respec-

tively. The result of antiplasmodium 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, completely. Based on the Table 1 and 2 showed having the highest antiplasmodial activity in FCR3 strain is (1)-*N*-ethyl-9-phenyl-1,10-phenanthrolinium 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-phenanthrolinium sulfate 6 to equal 0.10 ± 0.04 µM.

This treatment with 2-phenyl-1,10-phenanthroline derivative compounds significantly inhibited parasitemia of *P. falciparum* FCR3 strain D10 strain (Table 1 and 2). Although the suppression of parasitemia was never complete (100% inhibition of parasite growth), the results indicated antiplasmodial potency. In the *P. falciparum* FCR3 strain, the (1)-*N*-ethyl-9-phenyl-1,10-phenantrolinium sulfate 7 compound have higher activity than (1)-*N*-methyl-9-phenyl-1,10-phenanthrolinium sulphate 6 and 2-phenyl-1,10-phenanthroline 5 compound, but in the *P. falciparum* D10 strain, the (1)-*N*-methyl-9-phenyl-1,10-phenanthrolinium sulphate 6 compound have higher activity than (1)-*N*-ethyl-9-phenyl-1,10-phenanthrolinium 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-phenanthrolinium sulphate 6 and (1)-*N*-ethyl-9-phenyl-1,10-phenanthrolinium 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-phenanthrolinium 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-phenanthrolinium sulphate **6** to equal 0.10 ± 0.03 µM.

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