Synthesis and Antiplasmodial Activity of 2-(4-Methoxyphenyl)-4-Phenyl-1,10-Phenanthroline Derivative Compounds

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Abstract

A unique of synthetic methods was employed to prepare 2-(4-methoxyphenyl)-4-phenyl-1,10-phenanthroline (**5**) derivatives from 4-methoxy-benzaldehyde (**1**), acetophenone (**2**), and 8-aminoquinoline (**4**) with aldol condensation and cyclization reactions. The derivatives were tested through antiplasmodial test. The synthesis of derivatives compound **5** was conducted in three steps. The 3-(4-methoxyphenyl)-1-phenylpropenone **3** was synthesized through aldol condensation of **1** and **2** which has a yield of 96.42%. The compound **5** was synthesized through cyclization of compound **4** and **3** with 84.55% yield. The derivative of compound **5** was synthesized from compound **5** using DMS and DES reagents which refluxed for 21 and 22 h, to produce (1)-*N*-methyl-9-(4-methoxyphenyl)-7-phenyl-1,10-phenanthrolinium sulfate (**6**) and (1)-*N*-ethyl-9-(4-methoxyphenyl)-7-phenyl-1,10-phenanthrolinium sulfate (**7**) with 91.42 and 86.36% yields, respectively. Results of *in vitro* testing of antiplasmodial activity of compound **5** derivatives (i.e., compound **6** and **7**) against chloroquine-resistant *P. falciparum* FCR3 strain showed that compound **7** had higher antimalarial activity than compounds **5** and **6**. Whereas, results of *in vitro* testing against chloroquine-sensitive *P. falciparum* D10 strain showed that compound **6** has higher antimalarial activity than compounds **5** and **7**.

Abstrak

Sintesis dan Aktivitas Antiplasmodium Senyawa Turunan 2-(4-Metoksifenil)-4-fenil-1,10-fenantrolin. Suatu metode sintesis yang unik telah digunakan dalam membuat senyawa turunan 2-(4-metoksifenil)-4-fenil-1,10-fenantrolin (**5**) dari 4-metoksibenzaldehida (**1**), asetofenon (**2**), dan 8-aminokuinolin (**4**) dengan reaksi kondensasi aldol dan reaksi siklisasi. Turunan-turunan senyawa tersebut diuji aktivitasnya melalui uji aktivitas antiplasmodial. Sintesis turunan senyawa **5** dilakukan dalam tiga tahap. Senyawa 3-(4-metoksifenil)-1-fenilpropenon **3** disintesis melalui reaksi kondensasi aldol dari senyawa **1** dan **2** dengan hasil 96,42%. Senyawa **5** disintesis melalui siklisasi senyawa **4** dan **3** dengan hasil 84,55%. Turunan senyawa **5** disintesis dari senyawa **5** menggunakan DMS dan DES yang direfluks berturut-turut selama 21 dan 22 jam untuk menghasilkan (1)-N-metil-9-(4-metoksifenil)-7-fenil-1,10-fenantrolinium sulfat (**6**) dan (1)-N-etil-9-(4-metoksifenil)-7-fenil-1,10-fenantrolinium sulfat (**7**) dengan rendemen hasil berturut-turut 91,42 dan 86,36%. Hasil uji in vitro aktivitas antiplasmodium dari turunan senyawa **5** (senyawa **6** dan **7**) terhadap *P. falciparum* resistan klorokuin strain FCR3 menunjukkan bahwa senyawa **7** mempunyai aktivitas antimalaria lebih tinggi dari senyawa **5** and **6**. Sedangkan, hasil uji in vitro aktivitas antiplasmodium terhadap *P. falciparum* sensitif klorokuin strain D10 menunjukkan bahwa senyawa **6** mempunyai aktivitas antimalaria lebih tinggi dari senyawa **5** and **7**.

Keywords: antimalarial activity, synthesis, 2-methoxyphenyl-4-phenyl-1,10-phenanthroline derivatives

1. Introduction

Nowadays malaria accounts for 1-3 million deaths yearly worldwide, with most of these deaths occurring in children under 5 years. Approximately 3 billions people, one half of the world's population, live in at-risk regions for malaria infections. Malaria is the main health problem in subtropical and tropical countries. This leads to about 250 million malaria cases every year and nearly one million deaths. There are 105 countries

in the world with endemic malaria and more than 500 million cases or more than 3 million deaths from malaria each year [1-8]. 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 are at risk annually (fact sheets from Malaria Foundation International). Although four species of the genus *Plasmodium* cause human malaria, *Plasmodium falciparum* is the deadliest cause. *P. falciparum* will be the subject of this review [9].

Malaria cases are constantly changing, especially through the development of parasite resistant to standard antimalarial drugs such as chloroquine. Chloroquine has been the primary medicine for falciparum malaria chemotherapy for decades: it is cheap, safe, and practicable for outpatient use. Unfortunately, chloroquine resistance is now extensively spreading in some countries, including Indonesia. In Indonesia, malaria remains a health problem especially in eastern Indonesia. In the year 2003 the Annual Parasitemia Incidence (API) was 175.558 cases and the annual malaria incidence was more than 2.48 million and there were 211 deaths among 227.5 million Indonesian people [10-12].

Chloroquine resistant has been wide spread at some endemic areas in Indonesia. Base on data from the Indonesian Ministry of Health office in 2003, the annual parasite incidence in Java-Bali was 0.22 per 1000 populations, while the annual malaria incidence in outer Java-Bali was 21.8 per 1000 populations [11]. Therefore, it is essential to find new antimalarial drugs that have higher pharmacological activity compared to current antimalarial drugs. Consequently, Quantitative Structure Activity Relationship (QSAR) analysis plays an important role to minimize trial and error in designing new antimalarial drugs [13-14].

Five years ago, our research concerned with the synthesis and biological activity of 1,10-phenanthroline derivatives. In this program follow up, this paper report 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 [11]. Based on the 1,10-phenanthroline skeleton, Mustofa, [15] we have also synthesized thirteen derivatives of 1,10-phenanthroline and evaluated the *in vitro* antiplasmodial activity and their QSAR. The results of the QSAR analysis found the best theoretical activity of six new compounds and synthesized and evaluated their *in vitro* antiplasmodial activity through laboratory experiment.

Recently, our research reported the antiplasmodial activity of (1)-*N*-alkyl- and (1)-*N*-benzyl-1,10-phenanthrolinium showed that (1)-*N*-methyl-1,10-phenanthrolinium sulfate, (1)-*N*-ethyl-1,10-phenanthrolinium sulfate, (1)-*N*-benzyl-1,10-phenanthrolinium chloride, (1)-*N*-benzyl-1,10-phenanthrolinium bromide and (1)-*N*-benzyl-1,10-phenanthrolinium iodide were active against *P. falciparum* FCR3 with an IC_{50} 0.18±0.01-0.10±0.04 μM and D10 strains with an IC_{50} 0.74±0.20-0.34±0.07 μM [16].

This study synthesized compound **5** derivatives i.e: **6** and **7** compounds (Fig. 1). A unique of synthetic methods has been employed to prepare **5** derivatives from **1, 3**, and **4** compounds with aldol condensation and cyclization reactions.

2. Methods

Materials. Two strains of chloroquine-resistant *P. falciparum*, FCR-3 ($IC_{50} > 100$ nM) and chloroquine-sensitive, D10 strain ($IC_{50} < 100$ nM) were obtained from Eijkman Institute for Molecular Biology Jakarta, *p*-methoxybenzaldehyde p.a. (Merck), 8-aminoquinoline p.a. (Merck), dimethyl sulfate (DMS) p.a. (Merck), diethyl sulfate (DES) p.a. (Merck), H_2SO_4 70% p.a. (Merck), acetophenone, 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), $NaHCO_3$ p.a. (Merck), acetone 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), CH_2Cl_2 p.a. (Merck), and ethanol 95%.

Characterization of compounds. In general, the melting point of compounds was determined on melting point electro thermal 9100. The spectrum measurements of compound structures were taken using the following instruments: FTIR spectrums were taken on Shimadzu FTIR-8201 PC; ^{1}H-NMR spectrums were obtained on JEOL 60 MHz and JEOL 500 MHz MS spectrums were recorded on GC-MS Shimadzu QP 5000 (EI method).

Synthesis of 3-(4-Methoxyphenyl)-1-phenylpropenone (3). The ethanol (15 ml) was transferred into a 125 ml Erlenmeyer flask, and 20 ml of 10% KOH solution was added. Using a thermometer, the solution was cooled to 20 ºC. In a medium size tube, compound **2** was mixed (2.72 g; 20 mmol) with compound **1** (2.40 g; 20 mmol), and then the mix compound was left at room temperature for 5 minutes. Then, small portions of ethanol-NaOH solution mixture were added and stirred with a magnetic stirrer (if available) for 30 minutes. The mixture was cooled in ice-water bath. The product was filtrated and hand-dried to collect the yellow oils to yield compound **3**.

Synthesis of 2-(4-Methoxyphenyl)-4-phenyl-1,10-phenanthroline (5). The compound **3** (6.13 g; 20 mmol) was added over 6 h to a stirred solution of the

compound **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 at room temperature, added to 1 M Na_2CO_3 (50 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic layers were extracted with CH_2Cl_2. Subsequently, the filtrates were evaporated under reduced pressure to yield 1,10-phenanthroline skeleton as a product of reaction. The products were purified by filtration through silica gel using CH_2Cl_2 as a solvent to produce brown solid of compound **5.**

Synthesis of (1)-*N*-Methyl-9-(4-methoxyphenyl)-7-phenyl-1,10-phenanthrolinium sulfat (6). The compound **6** (0.73 g; 2 mmol) and dimethylsulfate (DMS; 1.26 g, 10 mmol) in acetone (20 ml) were refluxed for 21 hours. The resulting mixture was then cooled. The precipitate which formed was filtered, and washed with acetone and recrystalized with dichloromethane : diethyl ether (1:1). The precipitate which formed was filtered and washed with acetone to produce brown solid of compound **6.**

Synthesis of (1)-*N*-ethyl-9-(4-methoxyphenyl)-7-phenyl-1,10-phenanthrolinium sulfate (7). The compound **6** (0.73 g; 2 mmol) and diethylsulfate (DES; 1.54 g; 10 mmol) in acetone (25 ml) were refluxed for 22 hours. The resulting mixture was then cooled. The precipitate which formed was filtered, and washed with acetone and recrystalized with dichloromethane : diethyl ether (1:1). The precipitate which formed was filtered and washed with acetone to produce brown solid of compound **8.**

Biological Activity. Parasites were cultured according to the modified method described by Trager and Jensen [17]. The parasites were maintained *in vitro* in human red blood cells (O±), diluted to 1-2% hematocrit in RPMI-1640 medium (Sigma-Aldrich, USA), supplemented with 25 mM HEPES (Sigma Chemical, USA) and 30 mM $NaHCO_3$ (Sigma-Aldrich, USA) and supplemented with 5% human O± serum. Parasite cultures were synchronized by 5% of D-sorbitol (Sigma-Aldrich, USA) in distilled water as reported by Lambros and Vanderburgh [18]. The method used for *in vitro* antiplasmodial activity testing was adapted from a radioactive method as described [19]. Strain FCR3 was considered as a chloroquine resistant strain and strain D10 was considered as a chloroquine sensitive strain. The method used for *in vitro* antimalarial activity testing was adapted from visual method. The moleculer 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. Parasite growth was estimated by coloring with Giemsa (10%) for 30 seconds and calculated using 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 (IC_{50}) were determined by SPPS 13.0 software.

3. Results and Discussion

A unique of synthetic methods was employed to prepare compound **5** derivatives from compounds **2**, **1**, and **4** with aldol condensation and cyclization reactions. The synthesis of compound **5** derived through three steps (Fig. 1). The first step was synthesizing of compound **3** by aldol condensation reaction. The second step was synthesizing compound **5** from **4** and **3** through cyclization reaction. The third step was synthesizing the (1)-*N*-alkyl-9-phenyl-1,10-phenantrolinium salts derivative from compound **5** using DMS and DES as reagent to produce compounds **6** and **7**, respectively (Figure 1).

Compound 3-(4-Methoxyphenyl)-1-phenylpropenone (3). The synthesis of compound **3** was conducted through condensation reaction using the NaOH as base catalyst. The condensation of compound **1** and **2** to produce compound **3** as a product of reaction (4.76 g, m.p. : 61-62 °C) in 96.42% yield. The product was characterized by means of IR spectrometry, proton NMR and mass spectrometry. **IR (KBr) ύ (/cm)**: 3026,8 (C_{sp2}-H), 2923.9 (C_{sp3}-H), 1700.1 (C=O), 1629.5 and
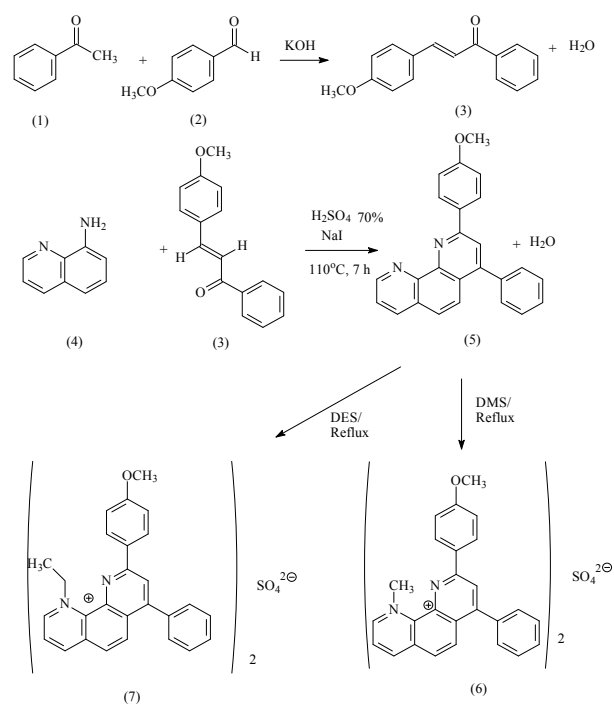

Figure 1. Synthesis of Compound 5 Derivatives

1527.5 (C=C aromatic); ^{1}**HNMR (60 MHz, DMSO-d$_6$, TMS) δ (ppm)**: 8.0-7.8 (3H, *d*, H$_A$), 7.5-7.3 (4H, *d*, H$_B$), 7.0-6.8 (2H, *d*, H$_C$), 7.0-6.8 (2H, *s*, H$_D$), and 3.7 (3H, *s*, -CH$_3$); **MS (EI) *m/z***: 238 (M), 208 (238-.OCH$_2$), 179 (207-C=O), 131 (207-.Ph), 103 (M-PhC.=O), and 77 (103- C$_2$H$_2$).

The product of condensation reaction was characterized by FTIR, ^{1}H-NMR and mass spectrometry. The FTIR spectrum showed the peaks at ύ 1629.5 and 1527.9/cm these indicated that the product of condensation reaction had C=C bonding from aromatic group. Absorption bands of C=O, C-H$_{sp3}$, and C-O at ύ 1700.1, 1377.1, and 1161.1/cm, respectively corroborated the existence of the compound **3** as a product of this reaction. In the ^{1}H-NMR spectrum, compound **3** did not have signals at 10-13 ppm, which indicates no aldehyde group (-CHO) existed. Mass spectrometry spectrum, showed the peak of molecular ion at *m/z* 238 which indicated the presence compound **3**. The result of the FTIR, ^{1}H-NMR and mass spectrum of compound **3** is showed in Figure 2 and 3, respectively.

Compound 2-(4-Methoxyphenyl)-4-phenyl-1,10-phenanthroline (5). The synthesis of compound **5** was conducted from compound **4** and **3** through cyclization reaction using NaI and H$_2$SO$_4$ 70% as the catalyst. The product of cyclization reaction was characterized by FTIR, ^{1}H-NMR and mass spectrometry. The products were purified by filtration through silica gel using CH$_2$Cl$_2$ as solvent to produce a brown solid of compound **5** (12.66 g, 84.55%): m.p. = 169-170 ^{o}C. The product was characterized by means of IR spectrometry, proton NMR and mass spectrometry. **IR** (KBr) ύ (/cm): 3473.6 dan 3365.6 (O-H O-H hydrogen bonding), 3035.7 (C$_{sp2}$-H), 2925.8 and 2854.5 (C$_{sp3}$-H), 1616.2 and 1506.3 (C=C aromatic); ^{1}**HNMR** (500 MHz, DMSO-d$_6$, TMS) δ (ppm): 8.8 (1H, *s*, H$_A$), 8.5-8.4 (2H, *s*,

H$_B$), 8.0 (3H, *s*, H$_C$), 7.4-7.3 (3H, *s*, H$_D$), 6.8-6.7 (3H, *s*, H$_E$), 6.4-6.3 (3H, *s*, H$_F$) and 3.6-3.5 (3H, *s*, -CH$_3$). **MS (EI) *m/z***: 362 (M), 331 (M-OCH$_2$), 306 (331-C$_2$H$_2$), 280 (306-C$_2$H$_2$), 255 (280-.C$_2$H$_2$), 229 (255-C$_2$H$_2$), 203 (229-C$_2$H$_2$), 178 (203-.C$_2$H$_2$), 127 (178-.NCCCH), 101 (127-.C$_2$H) and 77 (102-.C$_2$H).

The FTIR spectrum showed the peaks at 1616.2, 1595.6, and the absorption bands of C-H$_{sp2}$ *stretching* at 3035.7/cm these indicated the C=C aromatic functional group from product of cyclization reaction. The absorption bands of C-H$_{sp3}$ at 1373.2 and 2925.8/cm corroborated the existence of the compound **5** as product of this reaction. The ^{1}H-NMR spectrum of
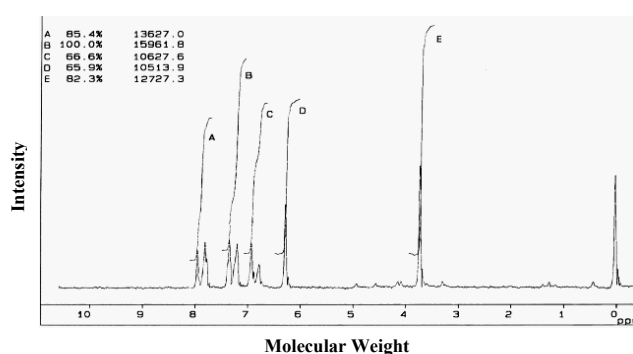
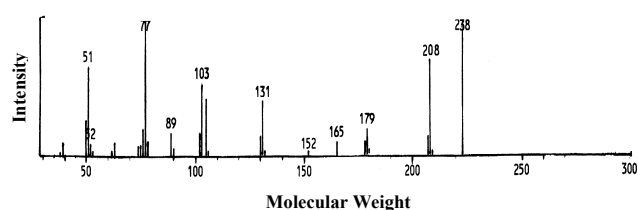**Figure 2.** The ^{1}H-NMR Spectrum of Compound 3 (CDCl$_3$, 60 MHz)
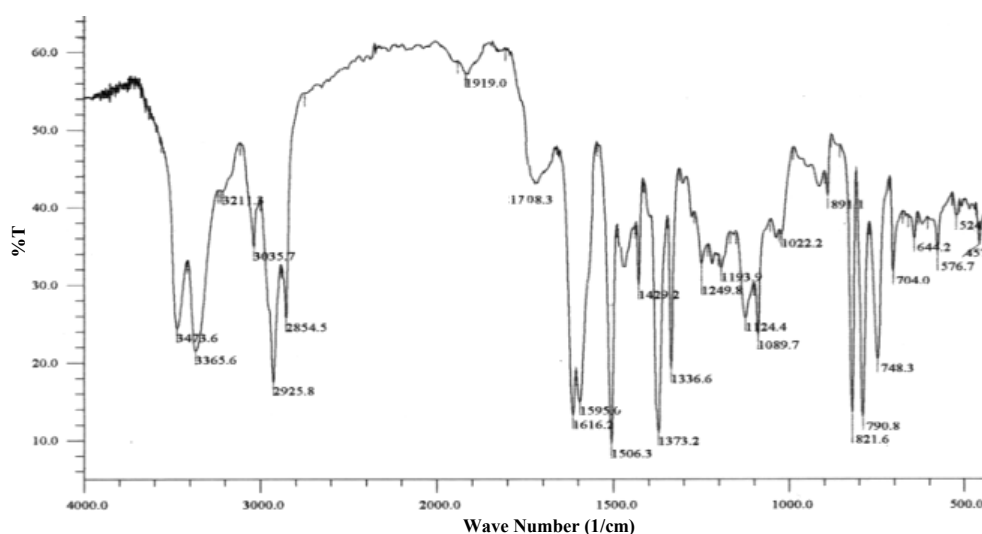
Figure 3. The Mass Spectrum of Compound 3

Figure 4. The FTIR Spectrum of Compound 5 (KBr pellet)

compound **5** showed seven signals at: 8.9, 8.6-8.5; 8.2, 7.3, 6.8, 6.4, and 3.7 ppm, which were assigned as H_A (1H), H_B (2H), H_C (3H), H_D (3H), H_E (3H), H_F (3H), and H_G (3H), respectively. The mass spectrometry spectrum, showed the peak of molecular ion at m/z 362. This indicated the presence of compound **5**. The result of FTIR and mass spectrum of compound **5** showed in Fig. **4** and **5**, respectively.

Compound   (1)-*N*-Methyl-9-(4-methoxyphenyl)-7-phenyl-1,10-phenanthrolinium sulfat (6). Compound **6** (brown solid, 0.778 g; 91.42%; m.p. : 203-204 °C) was obtained through methylation reaction of compound **5** with DMS reagent in acetone with 21 hours refluxing. The product was characterized by means of IR spectrometry and proton NMR. **IR** (KBr) ύ (/cm): 3421.5 (O-H hydrogen bonding), 3101.7 and 3041.8 (C_{sp2}-H), 2970.2 and 2862.2 (C_{sp3}-H), 1624.0 and 1527.5 (C=C aromatic); and 1369.4 (CH_3); **1H-NMR** (500 MHz, DMSO-d_6, TMS) δ (ppm): δ 9.10 (1H, H_A; *s*), 8.71 (2H, H_B; *d*), 8.42 (2H, H_C; *t*), 8.07-8.05 (2H, H_D; *d*, J=8.6 Hz), 7.85 (1H, H_E; *t*), 7.58-7.44 (2H, H_F; *t*), 7.35-7.33 (1H, H_G; *t*, J=7.35 Hz), 7.68-7.64 (1H, H_H; *d*, J=7.35 Hz), 6.64-6.62 (1H, H_I; *d*, J=7.30 Hz), 3.83 (3H, H_J, *s*) and 3.47 (3H, H_K, *s*).

The structure of compound **6** was determined by FTIR and 1H-NMR spectrum (Figure 6 and 7). The FTIR spectrum showed typical spectra at 1369.4 and 2970.2/cm which indicated presence of the methyl functional group. One singlet at 3.83 ($3H_J$) and 3.47 ppm ($3H_I$) in the 1H-NMR spectrum indicated existence of the methyl group too.
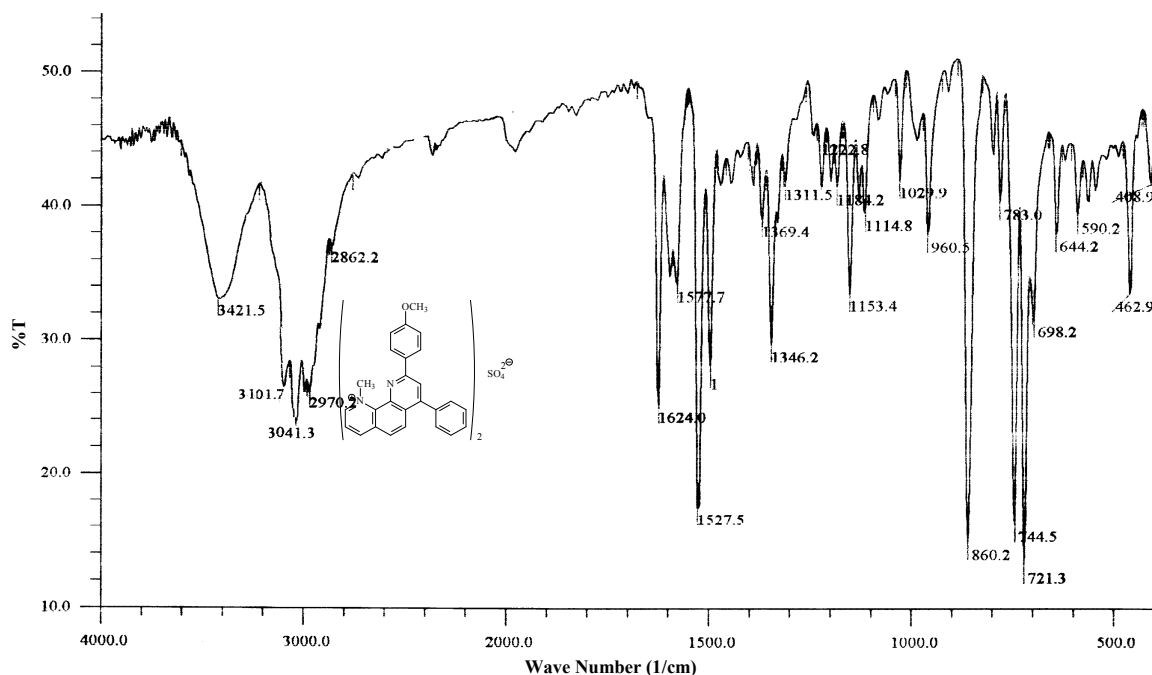
Compound   (1)-*N*-ethyl-9-(4-methoxyphenyl)-7-phenyl-1,10-phenanthrolinium sulfate (7). Compound **7** (brown solid, m.p: = 205-206 °C in 86.36% yield) was obtained through ethylation reaction of compound **5** using DES reagent in acetone with 22 hours refluxing. The product was characterized by means of IR spectrometry and proton NMR. **IR** (KBr) ύ (/cm): 3425.3 (O-H hydrogen bonding), 3004.9 (C_{sp2}-H), 2958.6 and 2815.5 (C_{sp3}-H), 1612,4 and 1512.1 (C=C aromatic); 1461.9 (CH_2), and 1367.3 (CH_3); **1H-NMR** (500 MHz, DMSO-d_6, TMS) δ (ppm): δ 8.42-8.39 (1H, H_A; *m*), 8.33-8.32 (2H, H_B; *d*, J=7.35 Hz), 8.24-8.22 (2H, H_C; *d*, J=10.05 Hz), 8.14-8.12 (2H, H_D; *d*, J=10.75 Hz), 8.02-8.00 (2H, H_E; *d*, J=7.75 Hz), 7.95-7.93 (1H, H_F; *s*), 7.83-7.80 (2H, H_G; *s*), 7.67 (1H, H_H; *s*), 7.22-7.19 (2H, H_I; *d*, J=10.85 Hz), 3.74-3.72 (3H, O-CH_3, *s*), 1.90-1.82 (2H, -CH_2-, *m*, J=6.75-7.30 Hz) and 1.10-1.07 (3H, C-CH_3, *t*, J=6.70-7.35).

The typical spectra in ύ 1461.9 /cm of the FTIR spectrum (Figure 8) indicated the presence of the methylene group. The singlet peak at δ 1.10-1.07 ppm in the 1H-NMR spectrum (Figures 9 and 10) indicated the existence of the methylene group.
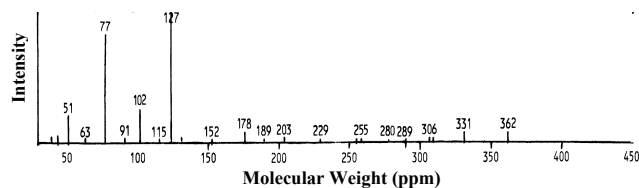

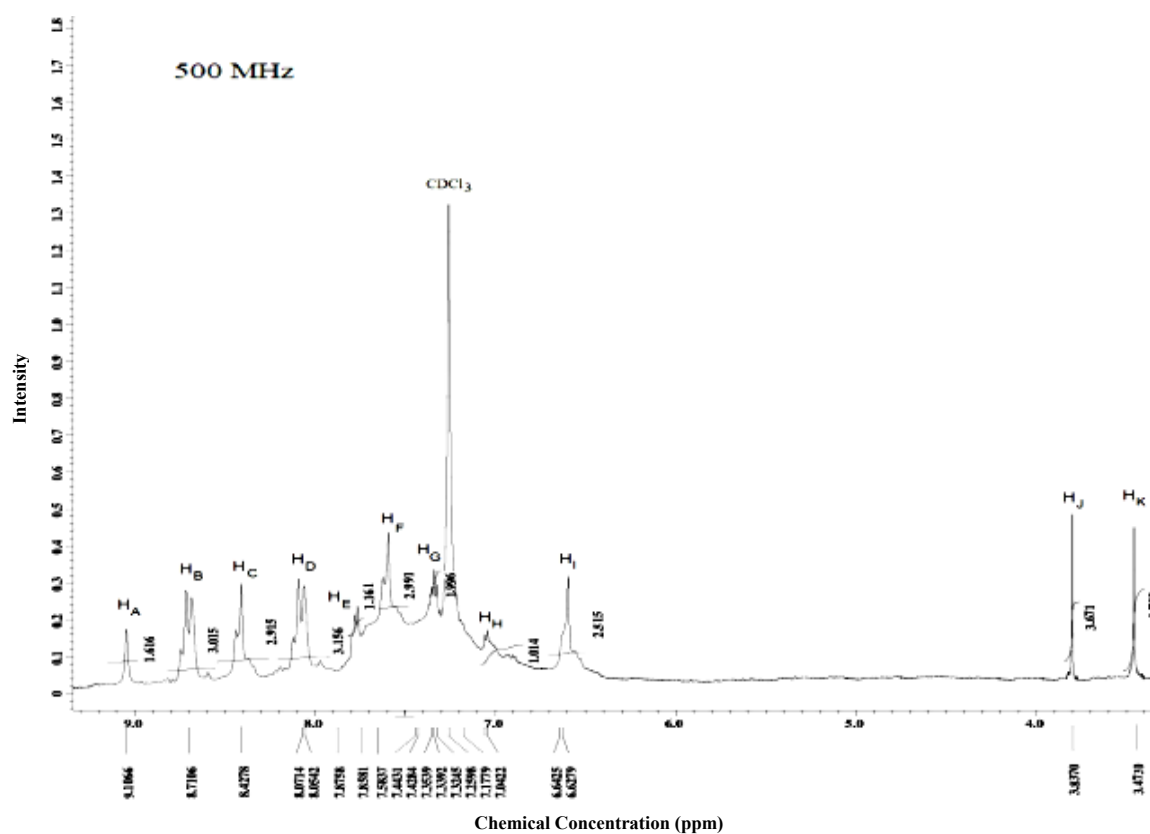**Figure 5. The Mass Spectrum of Compound 5 (EI)**

Figure 6. The FTIR Spectrum of Compound 6 (KBr pellet)

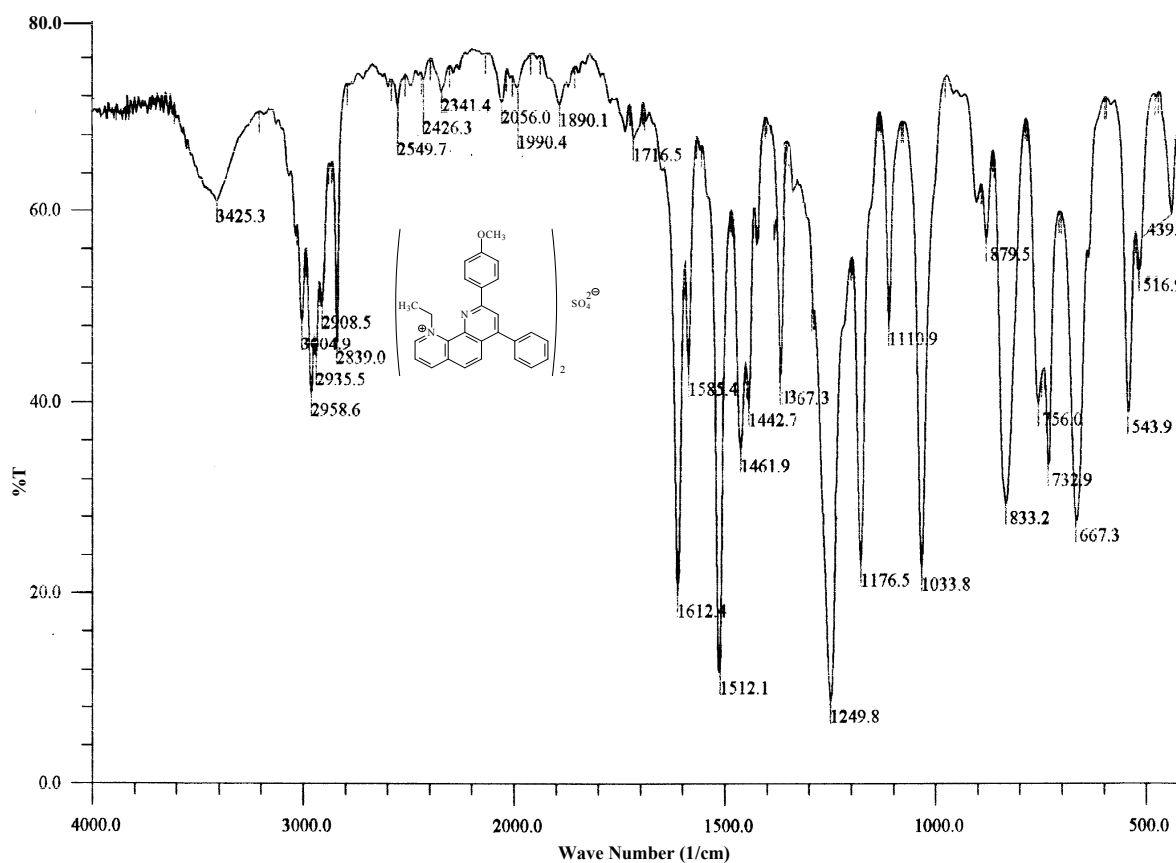**Figure 7. The ¹H-NMR Spectrum of Compound 6 (CDCl₃, 500 MHz)**
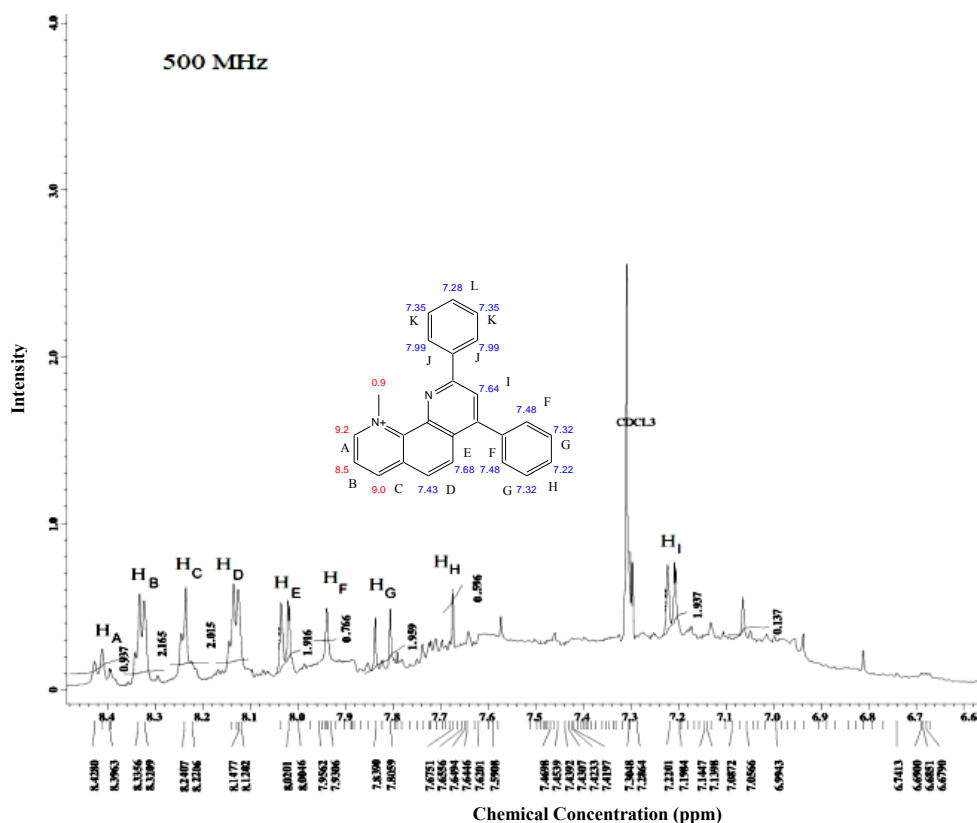

Figure 8. The FTIR Spectrum of Compound 7 (KBr pellet)

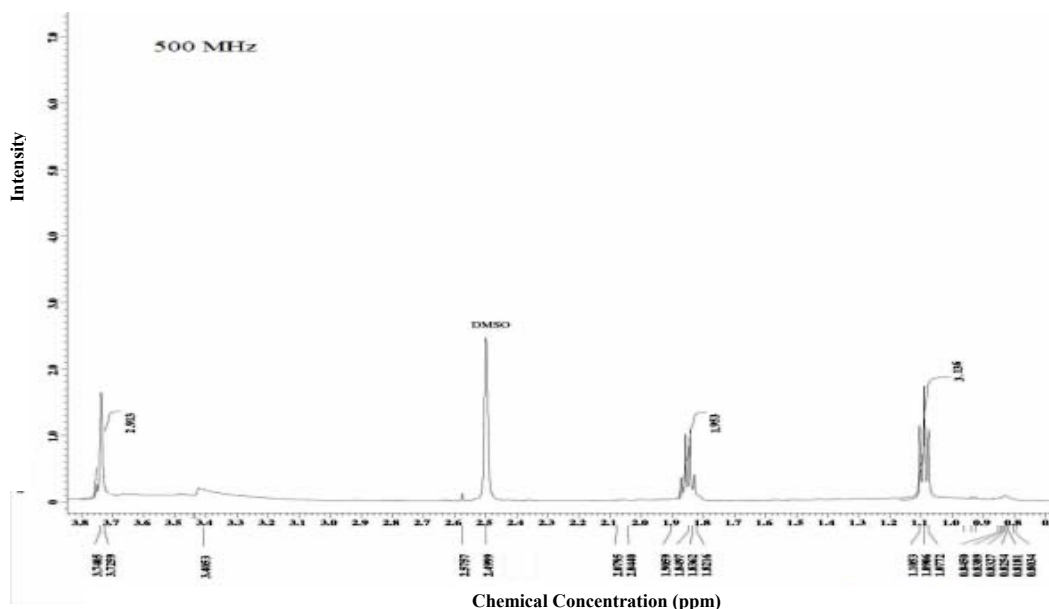**Figure 9. The ¹H-NMR Spectrum of Compound 7 at δ 6.6-8.5 ppm (DMSO, 500 MHz)**

Figure 10. The ¹H-NMR Spectrum of Compound 7 at δ 0.7-3.8 ppm (DMSO, 500 MHz)

Solikhah [20] reported the activities of 8 new compounds of *N*-alkyl- and *N*-benzyl-1,10-phenanthrolinium derivatives: 1) (1)-*N*-methyl-1,10-phenanthrolinium sulfate, 2) (1)-*N*-ethyl-1,10-phenanthrolinium sulfate, 3) (1)-*N*-t-buthyl-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 [12] reported the activities of one new compound of (1)-*N*-(4-methoxybenzyl-1,10-phenanthrolinium bromide. In all compounds tested for antiplasmodial activities, the (1)-*N*-benzyl-1,10-phenanthrolinium bromide showed the highest activity (0.10 ± 0.13 μM) against *P. falciparum* strain FCR3, whereas the (1)-*N*-benzyl-1,10-phenanthrolinium bromide showed the highest activity (IC_{50} : 0.33 ± 0.34 μM) on *P. falciparum* strain D10.

In this research, the result of antiplasmodial activities using chloroquine-resistant strain FCR-3 was summarized in Table 1. Meanwhile, the result of investigation antiplasmodial activities using chloroquine sensitive strain D10 was summarized in Table 2. In this study, the antiplasmodial activity of 1,10-phenanthroline derivatives showed that compounds **5**, **6** and **7** were active against *P. falciparum* strain FCR3 with an IC_{50} 1.28 ± 0.05, 0.16 ± 0.05, and 0.07 ± 0.01 μM, respectively and strain D10 with an IC_{50} 0.55 ± 0.07, 0.01 ± 0.01, and 0.03 ± 0.01 μM, respectively. The result of antiplasmodium evaluation to all of **5** compound derivatives toward strain FCR-3 and strain D10 of *P. falciparum* were presented in Table 1 and 2, completely. Based on the result presented in Table 1 and 2, the compound **7** (IC_{50} : 0.07 ± 0.01 μM) has highest antiplasmodial activity in strain FCR-3, while the compound **6** (IC_{50} : 0.01 ± 0.01μM) has the highest antiplasmodial activity in the D10 strain.

Table 1. Parasite Growth Inhibition and IC_{50} of Compound 5 Derivatives on Strain FCR-3

Concentration (ng/ml)	% Inhibition (mean±SD)		
	Compound **5**	Compound **6**	Compound **7**
50	0.00	53.11±5.62	58.92± 7.62
100	11.48±5.04	58.04±8.49	49.64±19.17
200	30.48±6.29	66.61±2.79	58.96±11.20
400	53.10±2.05	71.99±4.69	62.56±14.03
800	89.55±1.04	83.24±3.38	73.11± 4.04
1600	ND	93.72±2.45	82.39± 8.36
IC_{50} (μM)	1.28±0.05	0.16±0.05	0.07±0.01

ND: *not determined*

Table 2. Parasite Growth Inhibition and IC_{50} of Compound 3 Derivatives on Strain D10

Concentration (ng/ml)	% Inhibition (mean±SD)		
	Compound **5**	Compound **6**	Compound **7**
50	24.58±7.40	79.30±0.36	54.58±1.02
100	31.61±20.35	71.04±4.71	63.29±4.20
200	46.58±6.88	75.82±4.27	78.43±5.58
400	54.91±3.14	82.55±0.35	77.54±3.49
800	72.02±8.06	82.16±4.60	79.09±2.33
1600	78.59±7.53	96.67±1.50	85.82±4.12
IC_{50} (μM)	0.55±0.07	0.01±0.01	0.03±0.01

This treatment with compound **5** derivatives significantly inhibited parasitemia of *P. falciparum* FCR3 and D10 strain (Table **1** and **2**). Although the suppression of parasitemia was never complete (100% inhibition of parasite growth), the results indicated antiplasmodial potential. In the *P. falciparum* strain FCR3, the compound **7** had higher activity than compounds **6** and **5**, but in the *P. falciparum* strain D10, the compound **6** had higher activity than compounds **7** and **5**.

4. Conclusions

Three derivative compounds of 1,10-phenanthroline i.e. compounds **5**, **6** and **7** were successfully obtained in this study by a unique of synthetic methods. Results of *in vitro* antiplasmodial activity of these compounds on chloroquine-resistant *P. falciparum* strain FCR-3 showed that compound **7** has the highest antiplasmodial activity which is equal to 0.07 ± 0.01 μM. However, the highest activity on chloroquine-sensitive strain D10 was exhibited by the compound **6**, i.e equal to 0.01 ± 0.01 μM.

Acknowledgement

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