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## Cover Page Footnote

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# Synthesis of 1-(4-Ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium Bromide and Its Evaluation as Antiplasmodium through Heme Polymerization Inhibitory Activity (HPIA) Assay

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## Abstract

This study describes the development of *N*-benzyl-1,10-phenantrolinium salt as an antiplasmodium agent. The salt, that is, 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide, was prepared using vanillin as the starting material in four simple synthetic steps. First, the alkylation of vanillin using diethyl sulfate produced 4-ethoxy-3-methoxybenzaldehyde in 79% yield. Second, the reduction of the protected vanillin by $NaBH_4$ through the grinding method allowed us to obtain 4-ethoxy-3-methoxybenzyl alcohol in 96% yield. Next, the bromination of the benzyl alcohol under solvent-free condition led to the formation of the corresponding benzyl bromide, which in turn underwent bimolecular nucleophilic substitution with 1,10-phenanthroline to produce the desired product, that is, 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide, in 58% yield. The evaluation of *N*-benzyl-1,10-phenantrolinium salt as an antiplasmodium agent was conducted through heme polymerization inhibitory activity (HPIA) assay. The results showed that the phenantroline salt and chloroquine displayed the HPIA half maximal inhibitory concentrations of 3.63 and 4.37 mM, respectively. Therefore, 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide displays desirable HPIA and has a great potential to be further developed as an antiplasmodium.

***Keywords:*** *antiplasmodium, HPIA assay, 1,10-phenantroline salt, vanillin*

## Introduction

Malaria is a global disease affecting developing and developed countries. According to data from World Health Organization, 219 million cases of malaria were diagnosed worldwide, and 435,000 malaria-caused mortalities were recorded in 2017 [1]. Efforts to overcome malaria have been carried out for a long time, but the outcomes are still not optimal. The efforts are mainly constrained on the resistance of malaria parasites to standard antimalaria drugs, such as chloroquine and artemisinin [2,3]. Moreover, the resistance to antimalaria drugs rapidly spread almost all over the world, prompting researchers to find new antimalarial candidates [4].

Our groups have been developing phenanthrene-based-antiplasmodium agents [5]. The 1,10-phenantroline scaffolds [6,7], particularly *N*-benzyl-1,10-phenantrolinium salts, display great potential as antiplasmodium agents [8–10]. The activity of the drug is also correlated to their anion counterpart, where large anions, such as bromide or iodide, may give good antiplasmodium profile [11–13].

According to the literature, the convenient synthetic route to access *N*-benzyl-1,10-phenantrolinium salts is by nucleophilic substitution between 10-phenantroline and benzyl halides [14,15]. The former is commercially available, and the latter may be generated from benzaldehydes. In connection to our interests on the application of Indonesian natural products in the synthesis biologically active products, we have screened natural products whose major components are benzaldehyde derivatives and found out that vanillin (4-hydroxy-3-methoxybenzaldehyde) should be an excellent precursor for *N*-benzyl-1,10-phenantrolinium salts.

In this study, we aimed to develop a new antiplasmodium agent made of 1,10-phenantrolinium salt, that is, 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide, by using vanillin. Before performing the study, the antiplasmodium activity of the salt was predicted based on the previously formulated quantitative structure activity relationship (QSAR) equation [16]. The calculation showed that the predicted half maximal inhibitory concentration ($IC_{50}$) value of salt was 0.01 µM, whereas that of chloroquine was 0.076 µM. Based on the results, 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide displays a good antiplasmodium activity.

## Materials and Methods

The materials for this study included vanillin, 1,10-phenanthroline monohydrate, diethyl sulfate, $NaBH_4$, $PBr_3$, NaOH, $NaHCO_3$, NaCl, $Na_2SO_4$, hematin, acetic acid, acetone, dimethyl sulfoxide (DMSO), dichloromethane, and chloroform. The materials were purchased from E. Merck and used without purification.

Proton nuclear magnetic resonance ($^1$H-NMR) spectra were recorded on a 500 MHz JEOL JNM-ECA using TMS as an internal reference. Chromatogram and mass spectra were measured on a Shimadzu QP-2010 GC-MS spectrometer. Infrared spectra were obtained from a Shimadzu-Prestige 21 spectrophotometer. The melting point (m.p.) was determined on an Electrothermal 9100 m.p. apparatus and was not corrected.

**Synthesis of 4-ethoxy-3-methoxybenzaldehyde 2**. Vanillin **1** (1 equiv. 33 mmol, 5 g) and 12 mL pre-heated Aquadest were added to a 250 mL three-necked flask until complete dissolution. As much as 12 mL aqueous solution of 5 M NaOH was heated until 100 °C and added to the mixture. Diethyl sulfate (4.6 mL) was added dropwise to the mixture. After 45 min, 1.3 mL diethyl sulfate was added to the mixture. The mixture was heated for 10 min, and 3 mL aqueous solution of 5 M NaOH was dropwise added. The addition of NaOH solution and diethyl sulfate was repeated until 8.4 mL diethyl sulfate was consumed. The reaction mixture was heated for 15 min, rapidly cooled to rt while stirring, and then extracted thrice with dichloromethane. The combined organic layers were dried over $Na_2SO_4$ and evaporated under reduced pressure.

Light-brown solid; m.p.: 63 °C–65 °C; isolated yield: 79%; $^1$H-NMR (500 MHz, $CDCl_3$, ppm): δ 9.81 (CHO, s, 1H), 7.42 ($H_{Ar}$, d, $J$ = 7.9 Hz, 1H), 7.40 ($H_{Ar}$, d, $J$ = 7.9 Hz, 1H), 6.97 ($H_{Ar}$, s, 1H), 4.21 ($CH_2$, q, $J$ = 7.5 Hz), 3.92 ($CH_3$, s, 3H), 1.51 ($CH_2$, t, $J$ = 7.5 Hz); Fourier transform infrared spectroscopy (FTIR) (KBr) νmax: 3078, 2723, 2681, 1683, 1589, 1512, and 1396; gas chromatography-mass spectrometry (GC-MS) (EI): m/z (%): 180 [M+], 151 (base peak), 123, 95, and 65.

**Synthesis of 4-ethoxy-3-methoxybenzyl alcohol 3**. A mixture of 4-ethoxy-3-methoxybenzaldehyde **2** (1 equiv. 10 mmol 1.8 g) and $NaBH_4$ (1 equiv., 10 mmol, 0.38 g) was ground with an agate mortar and a pestle at rt for 10 min. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The mixture was then extracted twice with dichloromethane. The organic layer was dried over $Na_2SO_4$ anhydrous and evaporated under reduced pressure.

Yellow oil; isolated yield: 96%; $^1$H-NMR (500 MHz, $CDCl_3$, ppm): δ 6.86–6.99 ($H_{Ar}$, m, 3H), 4.58 ($CH_2$, d, 2H, $J$ = 5.9 Hz), 4.10 ($CH_2$, q, $J$ = 7.3 Hz, 2H), 3.85 ($CH_3$, s, 3H), 1.46 ($CH_3$, t, $J$ = 7.3 Hz 3H); FTIR (neat) νmax: 3078, 2978, 1597, 1519, 1465, and 1234; GC-MS (EI): m/z (%): 182 [M+, base peak], 153, 137, 121, and 93.

**Synthesis of 4-ethoxy-3-methoxybenzyl bromide 4**. Benzyl alcohol derivative **3** (1 equiv., 10 mmol) was placed in a 25 mL three-necked flask equipped with a condenser and a dropping funnel. Phosphorus tribromide (1 equiv., 10 mmol, 0.95 mL) was added dropwise at 0 °C, and the mixture was stirred for 30 min in an ice bath at rt for 1 h. The reaction was then refluxed for 3 h. Next, cold water (15 mL) was added to the reaction mixture. The mixture was then extracted with chloroform for three times. The organic layer was dried over $Na_2SO_4$ anhydrous and evaporated under reduced pressure to yield benzyl bromide derivative **4,** which was directly used in the next step without further purification.

Dark brown oil; isolated yield: 97%; GC-MS (EI): m/z (%): 244 [M+], 165, 151, 137 (base peak), and 77.

**Synthesis of 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide 5**. Benzyl bromide derivative **4** (1 mmol), 1,10-phenanthroline monohydrate (1 equiv., 1 mmol, 0.2 g), and 15 mL acetone were introduced to a 100 mL three-necked flask. The mixture was refluxed for 12 h and then cooled to rt. The precipitate was then washed with acetone to yield 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide **5**.

Yellow solid; m.p.: 178 °C–183 °C; isolated yield: 58%; $^1$H-NMR (500 MHz, DMSO-$d_6$, ppm): δ: 9.75 ($H_{Ar}$, d, $J$ = 8.5 Hz, 1H), 9.48 ($H_{Ar}$, d, $J$ = 8.5 Hz, 1H), 9.30 ($H_{Ar}$, d, $J$ = 7.8 Hz, 1H), 8.78 ($H_{Ar}$, d, $J$ = 7.8 Hz, 1H), 8.50 ($H_{Ar}$, d, $J$ = 8.5 Hz, 1H), 8.35–8.37 ($H_{Ar}$, m, 1H), 8.05 ($H_{Ar}$, d, $J$ = 7.8 Hz, 1H), 7.28 ($CH_2$, s, 2H), 7.17 ($H_{Ar}$, s, 1H), 6.77 ($H_{Ar}$, d, $J$ = 8.5 Hz, 1H), 6.63 ($H_{Ar}$, d, $J$ = 8.5 Hz, 1H), 3.87 ($CH_2$, q, $J$ = 7.1 Hz, 2H), 3.71 ($CH_3$, s, 3H), 1.25 ($CH_3$, t, $J$ = 7.1 Hz, 3H); FTIR (KBr) νmax: 3032, 2985, 1597, 1512, 1465, and 1265.

**Heme polymerization inhibitory activity (HPIA) assay of 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-**

**1-ium bromide 5.** The *in vitro* antiplasmodium assay was carried out through HPIA assay, which was developed by Basilico [17], by slightly modifying the hematin solution and sample dosages. As much as 100 mL solution of 1 mM hematin in 0.2 M NaOH was introduced into a microtube. Next, 50 mL 1,10-phenantroline salt **5** with various dose levels of 20, 10, 5, 2.5, and 1.25 mg/mL was added to the solution. The assay was performed in triplicate for each dose.

To initiate the heme polymerization reaction, we added 50 mL glacial acetic acid solution (pH 2.6) to the microtube containing the hematin solution and sample. The microtube was incubated at 37 °C for 24 h. In this study, chloroquine diphosphate was used as the positive control and distilled water as the negative control.

After incubation at 37 °C for 24 h, the microtube was centrifuged at 8000 rpm for 10 min to obtain the supernatant and precipitate. The former was removed, whereas the latter was washed thrice with 200 mL DMSO. The precipitate was then treated with 200 mL 0.1 M NaOH. Each 100 mL of the obtained solution was placed in a 96-well microplate. The determination of optical density values was carried out by means of an ELISA reader at 405 nm.

The HPIA was expressed as $IC_{50}$, *i.e.*, the concentration which can allow the inhibition of heme polymerization by 50% compared with the negative control. The standard curve was generated by preparing the concentrations of hematin series (which was dissolved in 0.2 M NaOH). The $IC_{50}$ of phenanthroline salt was calculated using the probit analysis.

## Results and Discussion

In this report, we synthesized a new antiplasmodium agent of 1,10-phenantrolinium salt, that is, 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide, from vanillin. Vanillin offers several advantages, such as good availability and accessibility, as a precursor in synthetic processes. From the structural point of view, the presence of aldehyde and phenolic groups enable vanillin to undergo various chemical transformations.

The 1,10-phenantrolinium salt was prepared *via* four simple synthetic steps, including alkylation, reduction, bromination, and bimolecular nucleophilic substitution reactions (Figure 1). Initially, vanillin was introduced to the alkylation reaction using diethyl sulfate as an alkylating agent to protect the phenolic group which is prone to reduction reaction (the next step). The product (4-ethoxy-3-methoxy-benzaldehyde) was obtained in 79% yield.

The protected vanillin underwent reduction reaction with $NaBH_4$ to give 4-ethoxy-3-methoxy-benzyl alcohol [18]. The reduction reaction was conducted by grinding method at rt for a very short period of time, *i.e.*, 10 min, forming the desired product in a high yield (96%). In addition, no solvent was employed to facilitate the reaction. These aspects are in a good agreement with green chemistry principles [19].

The benzyl alcohol was then converted into the corresponding benzyl bromide *via* bromination reaction. The reaction was performed using an equimolar amount of phosphorus tribromide under solvent-free condition to give 4-ethoxy-3-methoxy-benzyl bromide, which was directly subjected to the last step.

Using the benzyl bromide, we then performed the bimolecular nucleophilic reaction with 1,10-phenantroline as the nucleophile [20]. Finally, we obtained the desired product, that is, 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide, as a yellow solid in 58% yield.

After its successful preparation from vanillin, we then subjected the 1,10-phenantrolinium salt HPIA assay for the initial evaluation of the phenanthroline derivative as an antiplasmodium agent. The assay was conducted in accordance with the method developed by Basilico [17].

The assay showed that the HPIA $IC_{50}$ of 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide was 3.63 mM, whereas the positive control of chloroquine yielded the HPIA $IC_{50}$ of 4.37 mM, which is higher than that of the phenanthroline salt. Thus, the phenantroline salt displayed better activity than the commercial drug chloroquine. The results are in line with the prediction of antiplasmodium activity using the previously formulated QSAR equation [16].

Figure 2 illustrates the proposed mechanism of heme polymerization inhibition by 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide.
The free aromatic amine (N10) on the salt may act as a Lewis base and may interact with Fe(II) of heme (red

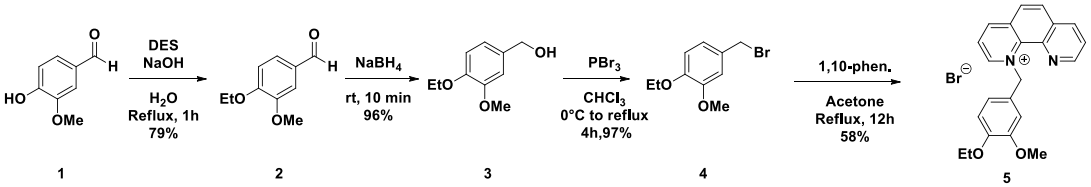


**Figure 1. Synthesis of 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide from vanillin**

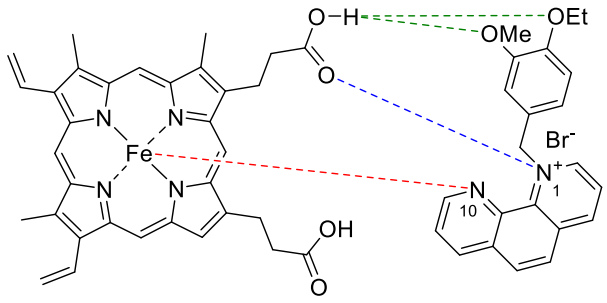


**Figure 2. Proposed Antiplasmodium Activity Interaction between Heme and 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide**

dashed line), thus lowering the reaction rate of hemozoin formation. Moreover, the benzyl unit derived from vanillin may play roles in the inhibition of heme polymerization. The presence of the methoxy group as an electron-withdrawing group may increase the positive charge of N1, thus promoting the formation of hydrogen bond with the oxygen of carboxylate group in heme (blue dashed line). Other hydrogen bond interactions (green dashed line) may occur among the oxygen atoms of ethoxy and methoxy groups with a hydrogen atom of the heme carboxylate group [8,21]. These interactions may inhibit the heme polymerization process and the formation of hemozoin, leading to the death of *Plasmodium* parasites. Moreover, the soft anion of bromide ($Br^-$) may aid the salt in penetrating the cell wall of plasmodium [11].

According to Baelsman, the phenanthroline salt exhibits a good HPIA because its $IC_{50}$ value (3.63 mM) is lower than 37.5 mM. Therefore, 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide has a great potential to be developed as an antiplasmodium.

## Conclusion

1,10-Phenantrolinium salt of 1-(4-ethoxy-3-methoxybenzyl)-1,10-phenanthrolin-1-ium bromide was successfully synthesized from vanillin in four steps: alkylation, reduction, bromination, and bimolecular nucleophilic substitution. The HPIA assay showed that the 1,10-phenantrolinium salt displayed a heme polymerization activity with the $IC_{50}$ value of 3.63 mM.

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