Novel aminoalkylated chalcone: Synthesis, biological evaluation, and docking simulation as potent antimalarial agents

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ARTICLE INFO
Received on: 07/02/2020
Accepted on: 22/04/2020
Available online: 05/06/2020

Key words:
Antimalarial, chalcone, docking, mannich reaction, 3D7.

ABSTRACT
Three chalcone derivatives with amine groups (4a–c) were synthesized and evaluated for their antimalarial activity. Three aminoalkylated chalcone derivatives (4a–c) have been prepared through Claisen–Schmidt condensation reaction from vanillin and chloroacetophenone, followed by the Mannich reaction to add amine group. The structure of the compounds was confirmed by the spectrophotometric analysis using mass spectrometers (MS) and proton and carbon nuclear magnetic resonance (1H- and 13C-NMR) spectroscopy. Antimalarial activity of 4a–c was evaluated against Plasmodium falciparum (3D7) strain, and the molecular docking of 4b was performed to understand the interaction against PfDHFR-TS protein (1J3I.pdb). The prepared aminoalkylated chalcone (4a–c) was obtained in a yield of 80%, 75%, and 70%. The addition of morpholine (4a), piperidine (4b), and diethylamine (4c) as amine groups significantly could improve the antimalarial activity with IC50 of 0.62, 0.54, and 1.12 µM, respectively (strong activity), compared with the chalcone without amine group (3) with IC50 of 25.84 µM (moderate activity). The molecular docking of compound 4b exhibited strong hydrogen bond interaction with ILE112, ILE64, SER111, SER108, ASP54, TYR170, and PRO113 residues with CDocker interaction energy of ~48.84 kcal/mol. Thus, aminoalkylated chalcone could be proposed for further studies and developed into antimalarial drug candidates.

INTRODUCTION
According to the global malaria programme, malaria is one of the diseases, which needs continuous monitoring and supervising, because it still has a high mortality rate (World Health Organization, 2018). The WHO has reported 228 million malaria cases worldwide, and 405 thousand died in 2018. Indonesia has been reported to have a high malaria prevalence, with more than 300 thousand incidents happened in 2017 (World Health Organization, 2019). The increasing resistance expects the high prevalence of malaria of the Plasmodium parasite to the administrated drugs (Ashley et al., 2014; Sibley, 2015). The development of new antimalarial drug agents is needed to overcome the resistance of Plasmodium parasite, so the number of the infection of malaria can be reduced.

The previous studies reported the biological activity of chalcone derivate compounds as antimalarial (Sharma et al., 2014; Syahri et al., 2017b; 2017c; Tadigoppula et al., 2013), antimicrobial (Chu et al., 2018; Khan et al., 2019), antioxidant (Wang et al., 2019), antidiabetic (Cai et al., 2017; Shin et al., 2018), anticancer (Castaño et al., 2019; Custodio et al., 2019; Muchtaridi et al., 2019), and anti-inflammatory (Ur-Rashid et al., 2019). Some functional groups such as hydroxyl, methoxy, and allyloxy in chalcone have been proved to increase the antimalarial activity (Syahri et al., 2017c) even though the activity was still categorized as low. The substitution of some amine groups into the chalcone ring could be proposed to increase the antimalarial activity of chalcone derivatives. Amine groups are expected to be the important molecule that could increase the antimalarial activity based on the fact that most of the antimalarial drugs is bearing nitrogen atoms (Fig. 1).

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The Mannich reaction is one of the methods that can be conducted to add the amine groups to the chalcone derivatives. Some compound obtained from the Mannich reaction has been reported to have antimalarial (Funk et al., 2017; Wilhelm et al., 2015), anticytotoxic (Reddy et al., 2008; Yamali et al., 2016), anticancer, and antibacterial activities (Roman, 2015). In this work, we presented the synthesis of aminoalkylated chalcones through the Mannich reaction as well as the in vitro and in silico evaluation as antiplasmodial compounds.

MATERIALS AND METHODS

Materials

All of the materials used in synthesis were purchased from Sigma-Aldrich and Merck in analytical grade and used without further purification, i.e., 4-chloroacetophenone, vanillin, sodium hydroxide (NaOH), morpholine, piperidine, diethylamine, formaldehyde, ethanol, hexane, and ethyl acetate. Meanwhile, chloroform-d₆ (CDCl₃) and acetone-d₆ were used in the nuclear magnetic resonance (NMR) spectroscopy analysis. The silica gel 60 GF₃₄ was used for column chromatography, and the silica gel 60 F₂₅₄ thin-layer chromatography (TLC) aluminum sheet was utilized in monitoring the reaction. The materials used in the in vitro antimalarial activity assay follow the previous work (Syahri et al., 2017c).

Instrumentation

Melting points of the prepared compounds were determined in an open capillary tube on Electrothermal 9100 (uncorrected). The molecular weight of the compounds was determined based on the MS from Shimadzu QP2010S. The ¹H and ¹³C-NMR spectra were recorded using tetramethylsilane as an internal standard on JEOL JNMECA (500 MHz).

General procedure for the synthesis of aminoalkylated chalcone derivates (4a–c)

The preparation of chalcone 3 has been reported before (Syahri et al., 2017c). The synthesis of aminoalkylated chalcone 4a–c was carried out through the Mannich reaction (Wilhelm et al., 2015) by dissolving chalcone 3 (10 mmol) in ethanol (75 ml) until homogenous solution obtained. To this solution, 10 mmol of formaldehyde solution (37%) and 10 mmol of secondary amines (morpholine for 4a, piperidine for 4b, and diethylamine for 4c) were added while stirring at room temperature. The mixture was then heated and refluxed for 20 hours or until no starting materials remain (monitored by TLC using hexane:ethyl acetate in 3:1 ratio). After the completion of the reaction, the solvent was evaporated under a reduced pressure rotary evaporator, and the solid product obtained was purified using column chromatography with hexane:ethyl acetate mixture (0%–50% gradient) as the eluent.

Antimalarial activity

An in vitro antimalarial activity assay was conducted against Plasmodium falciparum 3D7 strain (sensitive chloroquine) according to the method of Rieckmann et al. (1978) in 96-well microtiter plates with minor modifications as it was reported before (Syahri et al., 2017a). The antimalarial activity test was carried out by dissolving the test compounds in DMSO and then diluted the solution into serial concentration in the RPMI-1640 media to obtain a final concentration of 100, 10, 1, 0.1, and 0.01 µg/ml. To the test solution, a parasite suspension was added with a parasitemia level of ± 1% and a hematocrit of 5%. The culture was then incubated at 37°C for 48 hours. The culture was collected, and a thin layer of blood was prepared with 20% Giemsa stain. The percentage of parasitemia and also the percentage of the growth inhibition of P. falciparum were calculated by counting the number of infected erythrocytes for every 1,000 erythrocytes. The antimalarial activity (IC₅₀ value) was determined by performing the statistical analysis using Probit log analysis based on the percentage inhibition data and the concentration of the test compound.

Molecular docking

Molecular docking was performed to dihydrofolate reductase–thymidylate synthase (PDHFR-TS) protein with a code of 1J31.pdb (2.33 Å) (Yuvaniyama et al., 2003). The docking procedure followed the standard protocol implemented from Discovery Studio® 3.1 software (Accelrys, San Diego). The ligands were prepared, and the energy was minimized first before the docking process. Hydrogen atoms were added to the protein structure before the docking process, and all of the ionizable amino acids (residues) were adjusted at pH 7.4 (default protonation). The ligands were allowed to flex, and the receptor was maintained rigid during the docking process. The docked conformer of ligand–receptor was set in a docking tolerance of 0.25 Å with a number of nonpolar or polar hotspots in the receptor, to start the conformer fitting, which were set at 500. Meanwhile, the conformations of

![Figure 1. Some commercial antimalarial drugs bearing amine in their structure: Chloroquine (a), Amodiaquine (b), and Quinine (c).](image-url)
the ligands produced from the docking process were fixed at 500 within the relative energy threshold of 20.

RESULTS AND DISCUSSION

Synthesis

The synthesis of chalcone 4a–c was carried out via the Claisen–Schmidt condensation reaction from vanillin and 4-chloroacetophenone, followed by the Mannich reaction to add secondary amine groups such as morpholine, piperidine, and diethylamine (Scheme 1). Vanillin is an aldehyde compound with hydroxyl (–OH) and methoxy (–OCH₃) groups present in its structure, and it is abundantly available in nature. According to the previous studies, both hydroxyl and methoxy groups showed a positive effect on the increasing of antimalarial activity (Neto and Lavarda, 2014; Syahri et al., 2017c). The addition of chloro (–Cl) group is expected to increase the antimalarial activity as it is seen in chloroquine that has –Cl group in the structure. Based on the literature studies, compound 4a–c is a new compound that the structure elucidation of all the prepared compounds was confirmed using MS to calculate the molecular weight and NMR spectrometers to determine the electronic (chemical) environment of each proton and carbon peaks. According to the ¹H-NMR spectra, all of the synthesized chalcone compounds (4a–c) were afforded in trans (E) conformation as it can be seen from the coupling constant (J) of H-α (H-8) and H-β (H-7) with 15.5 Hz.

(E)-1-(4-chlorophenyl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one (5)

Yellow crystals, yield 60%, melting point 110°C–112°C. ¹H-NMR (500 MHz, CDCl₃) δ (ppm): 7.98 (d, J = 8.5 Hz, 2H, H-11;15); 7.79 (d, J = 15.5 Hz, 1H, H-7); 7.72 (d, J = 15.57 Hz, 1H, H-8); 7.43 (d, J = 8.50 Hz, 2H, H-12;14); 7.36 (s, 1H, H-4); 7.22 (dd, J = 1.9, 8.4 Hz, 1H, H-1); 6.88 (d, J = 8.20 Hz, 1H, H-6); 3.74 (s, 3H, OCH₃). ¹³C NMR (125 MHz, CDCl₃) δ (ppm) 188.8 (C-9); 150.6 (C-3); 148.9 (C-2); 146.2 (C-7); 139.1 (C-13); 138.2 (C-10); 131.0 (C-11;15); 129.7 (C-12;14); 128.0 (C-5); 124.8 (C-6); 119.5 (C-8); 116.2 (C-1); 112.1 (C-4); 56.4 (C-17). MS (C₁₅H₁₃ClO₂) [M]+: 288.

\[
\begin{array}{c}
\text{Cl} \quad \text{O} \quad \text{CH}_3 \\
\text{1} + \quad \text{Cl} \quad \text{H} \quad \text{2} \quad \text{O} \quad \text{O} \quad \text{CH}_3 \\
\text{ii} \quad \text{Cl} \quad \text{H} \quad \text{3} \quad 4a\text{-c} \\
\end{array}
\]

Scheme 1. Reagents and conditions of synthesis: (i) Sodium hydroxide (60%), ethanol, stir at RT overnight; (ii) Secondary amine (R), formaldehyde, ethanol, stir for 20 hours.

Yellow crystals, yield 80%, melting point 151°C–152°C. ¹H-NMR (500 MHz, acetone-d₆) δ (ppm): 8.13 (d, J = 8.5 Hz, 2H, H-11;15); 7.75 (d, J = 15.5 Hz, 1H, H-7); 7.71 (d, J = 15.5 Hz, 1H, H-8); 7.58 (d, J = 8.5 Hz, 2H, H-12;14); 7.41 (s, 1H, H-4); 7.18 (s, 1H, H-6); 3.88 (s, 3H, H-17); 3.87 (s, 2H, H-18); 2.67 (m, 4H, H-19;23); 1.13 (m, 6H, H-20;21;22). ¹³C NMR (125 MHz, acetone-d₆) δ (ppm) 138.9 (C-9); 151.4 (C-3); 148.8 (C-4); 146.2 (C-5); 138.96 (C-13); 137.09 (C-10); 129.98 (C-11;15); 128.98 (C-12;14); 125.0 (C-5); 122.90 (C-1); 121.72 (C-8); 118.46 (C-6); 110.20 (C-4); 61.82 (C-18); 56.15 (C-17); 53.98 (C-19;21). MS (C₁₆H₂₂ClNO) [M]+: 385.

Yellow crystals, yield 75%, melting point 150°C–151°C. ¹H-NMR (500 MHz, acetone-d₆) δ (ppm): 8.11 (d, J = 8.4 Hz, 2H, H-11;15); 7.73 (d, J = 15.5 Hz, 1H, H-7); 7.69 (d, J = 15.5 Hz, 1H, H-8); 7.57 (d, J = 8.5 Hz, 2H, H-12;14); 7.40 (s, 1H, H-4); 7.14 (s, 1H, H-6); 3.87 (s, 3H, H-17); 3.72 (s, 2H, H-18); 2.54 (m, 4H, H-19;21;23); 1.63 (m, 2H, H-20;22). ¹³C NMR (125 MHz, acetone-d₆) δ (ppm) 189.36 (C-9); 151.44 (C-3); 148.49 (C-7); 146.9 (C-5); 138.96 (C-13); 137.09 (C-10); 129.98 (C-11;15); 128.98 (C-12;14); 125.50 (C-5); 122.90 (C-1); 121.72 (C-8); 118.46 (C-6); 110.20 (C-4); 61.82 (C-18); 56.15 (C-17); 53.98 (C-19;23;21). 25.88 (C-20;22); 23.96 (C-21). MS (C₁₆H₂₂ClNO) [M]+: 385.

Yellow crystals, yield 70%, melting point 84°C–85°C. ¹H-NMR (500 MHz, acetone-d₆) δ (ppm): 8.11 (d, J = 8.4 Hz, 2H, H-11;15); 7.73 (d, J = 15.5 Hz, 1H, H-7); 7.69 (d, J = 15.5 Hz, 1H, H-8); 7.57 (d, J = 8.5 Hz, 2H, H-12;14); 7.40 (s, 1H, H-4); 7.14 (s, 1H, H-6); 3.87 (s, 3H, H-17); 3.72 (s, 2H, H-18); 2.54 (m, 4H, H-19;21;23); 1.63 (m, 2H, H-20;22). ¹³C NMR (125 MHz, acetone-d₆) δ (ppm) 138.9 (C-9); 151.44 (C-3); 148.49 (C-7); 146.2 (C-5); 138.95 (C-13); 137.09 (C-10); 129.98 (C-11;15); 128.98 (C-12;14); 125.50 (C-5); 122.90 (C-1); 121.72 (C-8); 118.45 (C-6); 110.19 (C-4); 61.82 (C-18); 56.14 (C-17); 53.98 (C-19;21;23). 25.88 (C-20;22); 23.96 (C-21). MS (C₁₆H₂₂ClNO) [M]+: 385.
**Antimalarial activity**

An *in vitro* antimalarial activity assay of chalcone 3 (without amine group) and aminoalkylated chalcone 4a–c was performed against chloroquine-sensitive *P. falciparum* (P3D7) strain. Based on the data in Table 1, it can be seen that there is a significant increase in antimalarial activity with the addition of a secondary amine to the chalcone compound. Chalcone 3 without secondary amine group showed an IC$_{50}$ of 25.84 µM, and the addition of diethylamine (4c) could improve the antimalarial activity significantly to 1.12 µM. The substitution of piperidine (4b) and morpholine group (4a) showed a better antimalarial activity with IC$_{50}$ of 0.54 and 0.62 µM, respectively. This result proposed the important role of the amine group in the antimalarial activity. This fact also can be seen from the excellent antimalarial activity of chloroquine as a positive control (0.06 µM), which has three amine functional groups. Suwito *et al.* (2014) stated that amines can form electrostatic interactions with carbonyl groups from the protein of the *Plasmodium* parasite, so they can kill parasites. This study revealed that the prepared compound 4a–c could be categorized as an antimalarial compound with strong activity (IC$_{50}$ ≤ 1 µM), based on the category by Batista *et al.* (2009).

**Molecular docking**

Dihydrofolate reductase–thymidylate synthase (PfDHFR-TS) protein was chosen as the molecular target in the docking process as it has an essential mechanism in the biosynthesis of folate that needed in DNA synthesis (Singh and Mishra, 2018). The inhibition of the folate biosynthesis is the target in the discovery of new antimalarial drugs because this step can inhibit the formation of the nucleotide deoxythymidine monophosphate, and in sequence, it can prevent the synthesis of DNA in *Plasmodium* parasite in thymidylate cycle. As a result, *Plasmodium* could not grow and eventually die (Yuvaniyama *et al.*, 2003).

In this work, the molecular docking was performed in 4b, as this compound exhibited the best *in vitro* antimalarial activity. The molecular docking was performed to predict the interaction of secondary amine functional group in 4b to the amino acid of PfDHFR-TS protein. The molecular docking result of 4b to the protein 1J3L.pdb is shown in Figure 2.

The result of the molecular docking of compound 4b to 1J3L.pdb protein displayed seven hydrogen bond interactions with ILE112, ILE164, SER111, SER108, ASP54, TYR170, and PRO113 amino acid residues (Fig. 2). The number of hydrogen bonds formed was similar to the interaction by co-crystallized ligands WR99210. This result is proposed to determine the strong *in vitro* antimalarial activity of 4b. The calculation of CDOCKER interaction energy of 4b was −48.84 kcal/mol, which is lower than the interaction energy of co-crystallized ligands WR99210 (−54.32 kcal/mol) (Syahri *et al.*, 2017c). This result implies that co-crystallized ligands WR99210 form a more stable interaction than 4b. The remarkable part from the interaction formed in Figure 2 was the hydrogen bond interaction of 4b to amino acid residue SER108 and SER111. Both of these amino acid residues are the essential amino acid in the DHFR-TS protein of chloroquine-sensitive and chloroquine-resistance *P. falciparum* (Yuvaniyama *et al.*, 2003). It can be concluded that the increasing antimalarial activity of 3 (25.84 µM) to 4b (0.54 µM) was affected by the presence of the amine group. Thus, it can be proposed that aminoalkylated chalcone 4b would show a good antimalarial activity against chloroquine-resistance *P. falciparum* strain.

**CONCLUSION**

This work showed that the addition of secondary amine groups such as morpholine, piperidine, and diethylamine could increase the antimalarial activity of chalcone derivatives from moderate (25.84 µM) to strong activity (0.54–1.12 µM). The molecular docking of 4b has also supported this result by indicating the interaction of the amine groups in the chalcone compound to SER111 and SER108 amino acid residues from the P/DHFR-TS protein. Thus, the secondary amine groups were essential in the development of new candidate antimalarial drugs.

**ACKNOWLEDGMENTS**

The authors are gratitude to the Ministry of Research, Technology, and Higher Education, Indonesia, for the financial support of this work through the Penelitian Dasar (PD) Scheme (the fiscal year of 2019) with contract number of 015/K10/KM/KONTRAK-PENELITIAN-3/2019.

**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.

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**Table 1. An *in vitro* antimalarial activity (IC$_{50}$) against P3D7.**

| Compound          | IC$_{50}$ (µM) |
|-------------------|---------------|
| 3                 | 25.84 ± 0.412 |
| 4a                | 0.62 ± 0.299  |
| 4b                | 0.54 ± 0.649  |
| 4c                | 1.12 ± 0.369  |
| Chloroquine       | 0.06 ± 0.387  |

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![Figure 2](image-url)
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How to cite this article: Syahri J, Nasution H, Nurohmah BA, Purwono B, Yuanita E. Aminolkaledyl chalcone: Synthesis, biological evaluation, and docking simulation as potent antimalarial agents. J Appl Pharm Sci, 2020; 10(06):001–005.