

SYNTHESIS OF 2-HIDROXYXANTHONE FROM XANTHONE AS A BASIC MATERIAL FOR NEW ANTIMALARIAL DRUGS

AMANATIE AMANATIE¹, JUMINA JUMINA², MUSTOFA MUSTOFA³, HANAFI M⁴, LA ODE KADIDAE⁵, SAHIDIN I^{6*}¹Department of Chemistry, Faculty of Mathematics and Natural Sciences, Yogyakarta State University, Yogyakarta 55281, Indonesia.²Department of Chemistry, Faculty of Mathematics and Natural Sciences, Gadjah Mada University, Yogyakarta 55281, Indonesia. ³Department of Medicine, Faculty of Medicine, Gadjah Mada University, Yogyakarta 55281, Indonesia. ⁴Pusat Penelitian Kimia, Lembaga Ilmu Pengetahuan Indonesia, Serpong, Tangerang 15314, Indonesia. ⁵Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Halu Oleo, Kampus Baru Anduonohu, Kendari, Sulawesi, Tenggara 93232, Indonesia. ⁶Department of Pharmacy, Faculty of Pharmacy, Universitas Halu Oleo, Kampus Baru Anduonohu, Kendari, Sulawesi, Tenggara 93232, Indonesia. Email: sahidin02@yahoo.com

Received: 12 May 2017, Revised and Accepted: 01 September 2017

ABSTRACT

Objective: The purpose of this research is to synthesize 2-hydroxyxanthone from xanthone and to evaluate its antiplasmodial activity.**Methods:** The synthesis of 2-hydroxyxanthone followed the sequence of these synthetic stages, namely: 2-nitroxanthone, 2-aminoxanthone, and 2-hydroxyxanthone. The products were separated by chromatography methods including thin layer chromatography and vacuum liquid chromatography. Compound structures of the isolated products were determined based on their infrared and nuclear magnetic resonance spectra. To support these findings, the spectra were also matched to the corresponding data from literatures. The biological properties of the synthetic compound were evaluated toward *Plasmodium falciparum* 3D7.**Results:** 2-nitroxanthone was obtained as a brownish-yellow crystal in 69.00% yield with Madhya Pradesh of 181°C. Reduction of 2-nitroxanthone using SnCl₂·2H₂O/hydrogen chloride produced 2-aminoxanthone as a pale-yellow solid in 60.60% yield. Finally, the desired 2-hydroxyxanthone was achieved by initially reacting 2-aminoxanthone with sodium nitride to produce diazonium salt. Then, hydrolysis of the salt yielded 2-hydroxyxanthone as a white solid in 69.81% yield. Synthesis of 2-hydroxyxanthone from xanthone had an overall yield of 38.35%. *In vitro* antiplasmodial assay against *P. falciparum* 3D7 showed that the half maximal inhibitory concentration value was 0.44 µg/mL.**Conclusions:** An antimalarial compound (2-hydroxyxanthone) was successfully synthesized from xanthone in three steps of synthetic reactions, i.e., the formation of 2-nitroxanthone, 2-aminoxanthone, and 2-hydroxyxanthone.**Keywords:** 2-nitroxanthone, 2-aminoxanthone, 2-hydroxyxanthone, *in-vitro*, antiplasmodium, *Plasmodium falciparum* 3D7.© 2017 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2017.v10i12.19858>

INTRODUCTION

Malaria is a kind of disease, which still threatens residents in both developing and developed countries. In 2010, malaria caused 660,000 deaths, especially in children. According to the World Health Organization (WHO), malaria is actually a preventable and treatable disease. Prevention and control of this disease may decrease malaria cases in various places [1], and the WHO targets a 50% or more reduction in cases and deaths from malaria in 2000 to 2010 and 75% or more between year 2000 and 2015 [2]. Efforts to overcome malaria can be done medically and non-medically. Medical efforts, among others, are done by finding new antiplasmodium through isolation from nature and modifying it, and also synthesizing or derivatizing existing antiplasmodium compounds [3-5].

The natural product compounds that have anti-plasmodial potencies are lignan [6], quinolone [7], and xanthone derivatives [8]. Xanthone derivatives have potency not only as antiplasmodium but also as cyclooxygenase-2 inhibitor agents [9]. Tropical plants that have been used as a traditional antimalarial drug, especially in Indonesia are *Alectronseerratus* [10], *Artocarpus heterophyllus*, *Artocarpus altilis*, and *Artocarpus camansi* [11], and also *Garcinia dulcis* (Guttiferae). Further study of *G. dulcis*, potency as antimalarial have been done by *in vivo* test against Swiss Webster mice [12]. Phytochemical studies show that *Garcinia* plants commonly produce xanthone compounds. For example, the leaves of *G. dulcis* produce terpenoids, benzophenone, biflavonoid, and xanthone [13]. 7-O-methylgulinone-E, a new type of xanthone was

reported from *Garcinia cowa* [14,15]. This compound was isolated from the bark of the plant and in fact, this xanthone was found to be active as an antimalarial against *Plasmodium falciparum* with half maximal inhibitory concentration (IC₅₀) values ranging from 1.50-3.00 µg/mL. Moreover, 1,3,7-trihydroxy-prenyl-xanthone obtained from *Calophytacealedonicum* had activity as antimalarial with IC₅₀ of 1.0 µg/mL [8].

A thoroughly study of the correlation between xanthone derivatives with antiplasmodial activity showed that the antimalarial activities of hydroxyxanthenes were affected by the amount of hydroxyl groups in the xanthenes skeleton. In general, the more hydroxyl groups attached to the xanthone framework, the better anti-plasmodial activity of the compound [8]. One of the most potent antimalarial compounds derived from xanthone compounds against *P. falciparum* is 2-hydroxyxanthone from *G. dulcis* root barks with IC₅₀ value 0.44 µg/mL [15]. This compound has only one hydroxyl group, so that its anti-malarial activity may be increased by adding hydroxyl groups as substituents. However, the quantity of these compounds that could be isolated from natural products is very low. One way to increase the quantity is through synthesis.

The synthesis of 2-hydroxyxanthone from xanthone and its biological activity evaluation against *P. falciparum* strain 3D7 has not been reported yet. This article discussed 2-hydroxyxanthone synthesis and its anti-plasmodium activity evaluation. The steps of the synthesis were following this sequential order. First, xanthone was synthesized from 2-phenoxybenzoic acid, followed by preparation of 2-nitroxanthone,

then 2-aminoxanthone and finally 2-hydroxyxanthone. Furthermore, its antiplasmodial potency was evaluated toward *in vitro* *P. falciparum* strain 3D7.

MATERIALS AND METHODS

General procedures

Thin layer chromatographic (TLC) analyses were performed on Kiesel gel 60 F₂₅₄ plates from Merck. Detection was carried out under ultra violet (UV) light. Column chromatography for substance purifications was performed on silica gel 60 N, 40-50 µm. Solvents' evaporation was performed using Iwaki Rotary Evaporator REN-1000 with reduced pressure. Perkin-Elmer spectrum one Fourier-transform infrared (IR) spectrophotometers was used to record infrared spectra. JEOL nuclear magnetic resonance (NMR) of JNM ECA 500 MHz was utilized in analysis of ¹H and ¹³C NMR spectra. The operations of the JEOL spectrophotometer were at 500 MHz for ¹H NMR and at 125 MHz for ¹³C, using acetone-*d*₆ as solvent and TMS as internal standard. Anti-plasmodial evaluation used the standard facilities for *in vitro* antiplasmodium test.

Materials

Glacial acetic acid (Merck), dichloromethane (CH₂Cl₂) (Merck), ethanol (Merck), diethylether (Merck), hydrochloric acid (Merck), Na₂SO₄ anhydrous (Merck), SnCl₂·2H₂O (Merck), sodium nitride (NaNO₂) (Merck), NaOH (Merck), hydrazinium mono formate (Merck), and distilled water. The materials used for *in vitro* antiplasmodium test including chloroquine diphosphate, 10% serum, Medium roswell park memorial institute 1640 and Giemsa.

Experiments

Synthesis of 2-nitroxanthone

The slurry mixture of 4.90 g (25 mol) of the xanthone in 10 mL of glacial acetic acid was reacted at 0°C (ice cooling) with 1.039 ml nitric acid (concentrated). To the reaction mixture, 1.31 mL of sulphuric acid (concentrated) was added, and the mixture was stirred for 4 hrs. The progress of the synthetic reaction was monitored with TLC in which after starting to form a yellow solution, the product was tested with TLC using CH₂Cl₂ as an eluent and the R_f was compared to the starting material (xanthone) R_f. Once the TLC indicating there was a difference in the R_f value, then the heating was stopped and let it overnight to cool to room temperature. The resulted yellow solids were filtered and washed it in a sequential order with 25 mL of dichloromethane, 10 mL of water, 10 mL of ethanol, and 10 mL of diethylether. The organic layer was collected and dried with Na₂SO₄ anhydrous. After filtration, the solvents were removed through evaporation with Buchi rotary evaporator. The obtained solid was recrystallized to remove the reaction residue; finally, the desired product was obtained. Identification of the products was determined by measuring its melting point and assessing its UV-vis and IR spectra.

Synthesis of 2-aminoxanthone

2-Nitroxanthone (10 mg, 0.0413 mmol) was suspended in 12.5 mL of ethanol, stirred and cooled at 5°C. The cooled suspension was added drop wisely with SnCl₂·2H₂O (0.6688 g, 0.0413 mmol) in 1.25 mL hydrogen chloride (HCl) (concentrated) at maintained temperature under 100°C. After completion of the addition of SnCl₂·2H₂O, the reaction mixture was refluxed it at 80°C for 2 hrs and let it to cool to room temperature overnight. After that, it was diluted with distilled water, extracted with 15 mL dichloromethane, filtered, and extracted with 15 mL of ethyl acetate. The organic layer was dried with Na₂SO₄

anh. and after filtration the solvents were removed by evaporation. The obtained product was dried. The product was characterized using IR spectrophotometer.

Synthesis of 2-hydroxyxanthone

Into a three-neck flask containing 2-aminoxanthone (0.01 g, 0.00005 mol) suspended in HCl, 10 mL of NaNO₂ 2.8 M was added at 5°C and the solution changed entirely to yellow. The reaction mixture was stirred at 5°C for 30 minutes and added with 15 ml of HCl 1 M and then cooled. The reaction mixture was continually stirred at 5°C for 1 hr, and acidified with phosphoric acid. The product was recrystallized with ethanol-distilled water. Furthermore, the crystal was analyzed using IR and NMR spectrometer.

In vitro antiplasmodial activity test

Testing the effect of *in vitro* antiplasmodium of the compound against *P. falciparum* 3D7 utilized a procedure outlined by Trager and Jensen and it was modified by Waruyanti [16,17]. To determine the IC₅₀ (concentration of test compound which could inhibit parasitic growth by 50%), the obtained data were analyzed using probit analysis method.

RESULTS

Rendement of reaction steps in 2-hydroxyxanthone synthesis are displayed in Table 1.

¹H NMR data of 2-nitroxanthone

The ¹H NMR spectrum of 2-nitroxanthone (500 MHz) δ_H (ppm) 8.75 (2H, d, J=2.3, H₁ and H₈); 8.36 (1H, d, J=8.3, H₄); 8.34 (2H, dd, J=8.3, 2.3, H₃ and H₆); 7.30 (1H, d, J=8.3); 7.10 (1H, d, J=8.3, H₇); and 6.86 (1H, d, J=8.3, H₅).

¹H and ¹³C NMR data of 2-hydroxyxanthone

The ¹H NMR spectrum of 2-hydroxyxanthone (500 MHz) δ_H (ppm): 11.93 (1H, s, O-H); 7.56 (2H, J=8.3 Hz); 7.28 (2H, J=8.3 Hz); 7.20 (1H, s); 6.91 (1H, J=8.3 Hz); and 6.85 (1H, J=8.3 Hz). The spectrum of ¹³C-NMR (JEOL, JNM ECA 125 MHz) showed aryl carbons at δ_C 96; 106; 110; 117; 137 and 155 ppm. The peak at δ_C 179 came from the carbonyl group while the peak at δ 155 ppm was the peak for the carbon next to the hydroxyl group.

DISCUSSION

Synthesis of 2-hydroxyxanthone

Nitration of xanthone with concentrated nitric acid was conducted at 5°C. This was performed by adapting No K, Noh Y and Firdaus method [18,19]. The nitration product was a brownish-yellow crystal in 69.71% yield, with Madhya Pradesh of 181°C. The product was characterized using UV-Vis and IR spectrometers. From UV-Vis spectra, it was found that there were 2 maximum wavelengths at 215 and 311 nm. The appearance of the two peaks agreed with those of Harborne findings [20], namely, at 202-215; 254-258; 278-284; and 330-358 nm. The IR spectrum of the product showed strong absorption of carbonyl group at 1689 cm⁻¹, while aromatic-ether group absorbed at 1288 and 1087 cm⁻¹. The presence of strong absorption bands at 1543 and 1350 cm⁻¹ was from the vibration of nitro groups.

The nitration mechanism was displayed in Fig. 1. The concentrated nitric acid acted as a direct nitrating agent. The formed nitronium agent would be attacked by the aromatic ring of xanthone to give 2-nitroxanthone.

Table 1: Reaction products (%) of each reaction step

Source of compound	Yield (%)		
	2-nitroxanthone	2-aminoxanthone	2-hydroxyxanthone
Xanthone	69.71 from xanthone	78.81 from 2-nitroxanthone	69.81 from 2-aminoxanthone

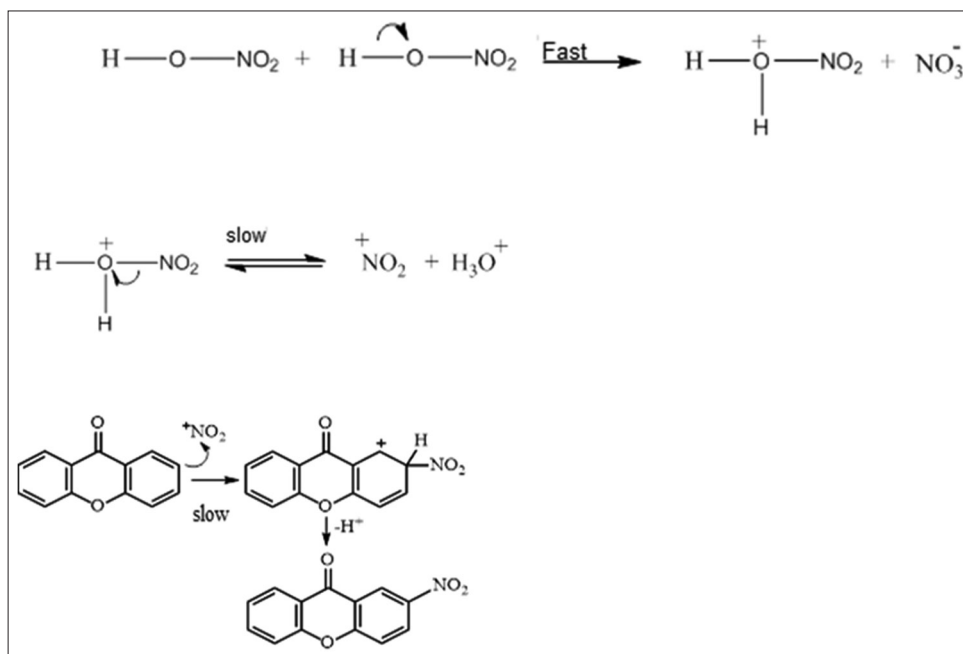


Fig. 1: Reaction mechanism of xanthone nitration

However, the formation of nitronium ion was relatively slow, thus the yield was not optimal. For this reason a mixture of sulfuric acid and nitric acid was required the reaction rate-stopping-agent.

Conversion of aliphatic nitro group into aliphatic amino group could be carried out using boron as a reductor in THF, while aromatic nitro group was usually performed using Zn as a reductor in neutral condition [17,21] or Zn-NH₄Cl/ H₂O at 50-55°C. The reduction of nitro group could also be done using SnCl₂·2H₂O/HCl [13,14]. In this research, the reduction of 2-nitro-xanthone was employed 3 equivalent of SnCl₂·2H₂O in HCl per one nitro group. 2-Aminoxanthone was obtained as a pale-yellow solid in 60.60% yield. The solid product was slightly soluble in ethyl acetate. The low yield was probably due to the less solubility of product in extractor solvent and the competition with the formation of Sn(OH)₂. Absorption band in IR spectrum at 3093 cm⁻¹ confirmed the existence of the amino group of the 2-aminoxanthone. The presence of this group and the disappearance of a band at 1543 cm⁻¹ from nitro group, indicated that the nitro group has been completely reduced into amino group. The vibrations of C-N and C-O bonds were shown by the presence of the absorption band sat 1288 and 1234 cm⁻¹, respectively. Based on the IR spectrum, it seemed that the desired product of 2-aminoxanthone was successfully achieved from the reduction of 2-nitroxanthone using SnCl₂·2H₂O/HCl, with 78.81% yield. The scheme of the formation of 2-aminoxanthone was presented in Fig. 2.

2-Aminoxanthone as the product of 2-nitroxanthone reduction was then reacted with NaNO₂, HCl, and H₃PO₄ to yield 2-hydroxyxanthone, as presented in Fig. 3.

2-Hydroxyxanthone could be synthesized from aminoxanthones with NaNO₂ and hydrochloric acid through diazonium salt. This compound was obtained by reacting 2-aminoxanthone with NaNO₂ to first produce its diazonium salt. Then, hydrolysis of the salt gave 2-hydroxyxanthone as the desired product. The product was a white solid in 69.81% yield. The IR spectrum showed that the absorption at 3433 cm⁻¹ indicated the stretch of OH, while the stretching of aromatic C=C appeared at 1620 cm⁻¹.

The spectrum of ¹H-NMR (JEOL, JNM ECA 500 MHz), showed that the aryl protons appeared in the region of δ 6.85-7.56 ppm. In this region, there were 4 doublet at δ_H 6.85 (2H, J=8.3 Hz), 6.91 (2H, J=8.3 Hz),

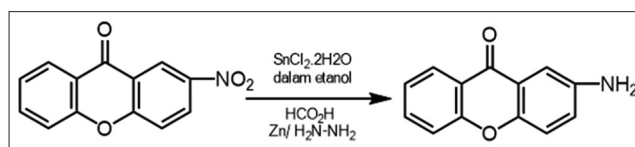


Fig. 2: Reduction of 2-nitroxanthone into 2-aminoxanthone using SnCl₂·2H₂O/HCl

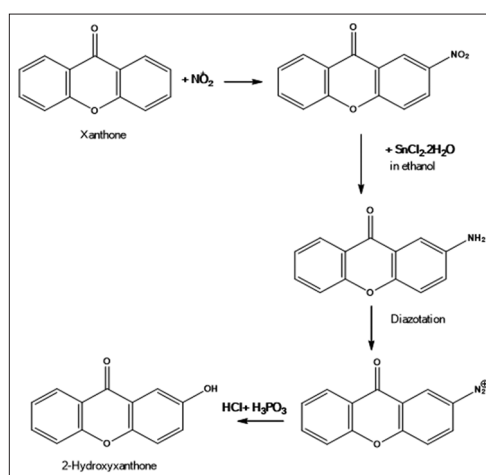


Fig. 3: Reaction of 2-hydroxyxanthone

7.28 (2H, J=8.3 Hz), and 7.56 (2H, J=8.3 Hz) ppm as well as one triplet peak at δ 7.20 ppm. One singlet peak from hydroxyl proton appeared at δ_H 11.93 ppm. Identification of the product using ¹³C-NMR (JOEL, JNM ECA 500 MHz) showed aryl carbons at δ_C 96, 106, 110, 117, 137, and 155 ppm. The peak at δ_C 179 came from the carbonyl group while the peak at δ 155 ppm was the peak for the carbon next to hydroxyl group.

Based on spectroscopy analyses, it could be stated that the reaction of 2-aminoxanthone with NaNO₂/HCl and H₃PO₄ had successfully produced 2-hydroxyxanthone. The reaction mechanism was presented in Fig. 4.

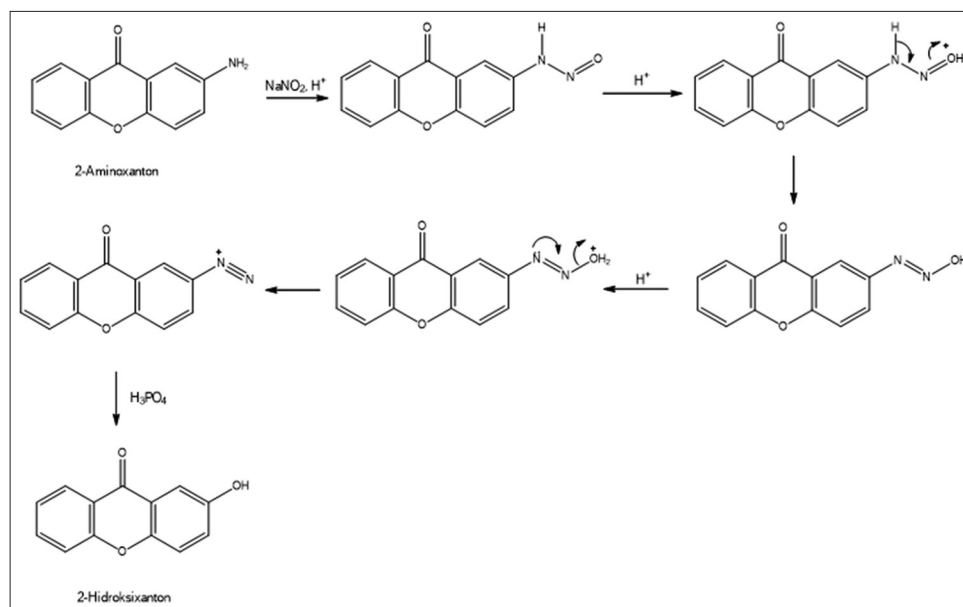


Fig. 4: Mechanism of synthesis of 2-hydroxyxanthone

Calculation of 2-hydroxyxanthone rendement

Their action products or rendements starting from nitration of xanthone to 2-hydroxyxanthone are shown in Table 1. The data in this Table are stoichiometric calculation results for each step of the reactions.

Synthesis of 2-nitroxanthone

$$\text{Xanthone} = 4.9 \text{ g} = \frac{4.9}{196} = 0.025 \text{ mol}$$

$$\text{2-nitroxanthone product (theory)} = 0.025 \text{ mol} = 0.025 \times 241 = 6.025 \text{ g}$$

$$\text{Product (2-nitroxanthone) from xanthone (product of synthesis)} = 4.2 \text{ g}$$

$$\text{Rendement} = \frac{\text{Weight of product}}{\text{Weight of product (theory)}}$$

$$\times 100\% = \frac{4.2 \text{ g}}{6.025 \text{ g}} \times 100\% = 69.71\%$$

Synthesis of 2-aminoxanthone

$$\text{2-nitroxanthone} = 10 \text{ g} = \frac{10}{241} = 0.0414 \text{ mmol}$$

$$\text{2-aminoxanthone product (theory)} = 0.0414 \text{ mmol} = 0.0414 \times 211 \text{ mg} = 8.7354 \text{ mg}$$

$$\text{Product (2-aminoxanthone) from synthesis} = 6.884 \text{ mg}$$

$$\text{Rendement} = \frac{\text{Weight of product}}{\text{Weight of product (theory)}}$$

$$\times 100\% = \frac{6.884 \text{ g}}{8.7354 \text{ g}} \times 100\% = 78.81\%$$

Synthesis of 2-hydroxyxanthone

$$\text{2-aminoxanthone} = 10 \text{ mg} = \frac{10}{211} = 0.0473 \text{ mmol}$$

$$\text{Product (2-hydroxyxanthone) from synthesized (theory)} = 0.0473 \text{ mmol} = 0.0473 \times 212 = 10.0276 \text{ mg}$$

Product 2-hydroxyxanthone from 2-aminoxanthone = 7.0 mg.

$$\text{Rendement} = \frac{\text{Weight of product}}{\text{Weight of product (theory)}}$$

$$\times 100\% = \frac{7.0 \text{ mg}}{10.0276 \text{ mg}} \times 100\% = 69.81\%$$

In general, synthesis of 2-hydroxyxanthone from xanthone can produce 38.35% of 2-hydroxyxanthone which came from 69.71% of 2-nitroxanthone, 78.81% of 2-aminoxanthone, and 69.81% of 2-hydroxyxanthone.

Evaluation of antimalarial activity

The *in vitro* antimalarial assay of 2-hydroxyxanthone was conducted using microscopic method with the incubation time of 48 hrs. The assay was carried out against *P. falciparum* strain of 3D7. The parasite was sensitive to chloroquine diphosphate. The parasite inhibitory activity was reported as IC_{50} .

The antimalarial assay against *P. falciparum* was performed using candle jar methods [15,21]. The parasite culture was cultivated and then employed in the assay. From the *in vitro* assay, the IC_{50} value could be obtained. This value was the parameter indicating the potential of the 2-hydroxyxanthone as new antimalarial. In the antimalarial assay, the synthesized 2-hydroxyxanthone was dissolved in dimethyl sulfoxide (DMSO) to give concentrations of 10, 1, 0.1, 0.01, and 0,001 $\mu\text{g/mL}$. The concentration of DMSO used was less than 0.5% as such concentration would not affect the parasite growth [19]. Distilled water was used as the negative control and used as the comparison in the calculation of parasite inhibitory activity of xanthone derivatives. In addition, chloroquine diphosphate was used as the positive control [16,22] since *P. falciparum* strain of 3D7 was sensitive to chloroquine diphosphate. Moreover, the additional reason is that the drug is still applied as standard antimalarial drug in Indonesia.

The assay was performed in 48 hrs as the asexual cycle of parasite in blood. In this phase, clinical symptoms of malaria such as fever and anemia were observed. Synchronization was carried out to make the parasite stadium to be the same. The inhibitory activity of each concentration was determined by calculating the inhibitory percentage of the test compound to the growth of *P. falciparum*. Parasitemia percentage was the amount of infected eritrosit compared to the total

Table 2: IC₅₀ value of some compounds against *P. falciparum*

Compound	% Inhibition of test dose (µg/mL)					IC ₅₀ (µg/mL)
	10	1	0.1	0.01	0.001	
Xanthone	63.01	55.17	37.62	33.22	5.02	0.688
2-hydroxyxanthone	69.35	20.98	13.37	10.00	1.96	0.440
Chloroquine diphosphate	88.55	75.32	60.31	39.19	9.67	0.056

IC₅₀: Half maximal inhibitory concentration, *P. falciparum*: *Plasmodium falciparum*

eritrosit. The total eritrosit was the amount of eritrosit in the field of view. The calculation of the average parasitemia percentage was required to calculate the parasite inhibitory percentage to the negative control using statistical method of probit analysis and finally to give IC₅₀ value. Based on the results obtained from *in vitro* antimalarial assay, it showed that the IC₅₀ value of 2-hydroxyxanthone was 0.44 µg/mL, which is better than IC₅₀ value of xanthone (0.688 µg/mL) as shown in Table 2.

CONCLUSION

According to the results and discussion, it could be concluded that: (1) Synthesis of 2-hydroxyxanthone from xanthone was successfully done in three steps of synthetic reactions: 2-nitroxanthone, 2-aminoxanthone, and 2-hydroxyxanthone. These reactions had an overall yield of 38.35%. *In vitro* antiplasmodial assay of 2-hydroxyxanthones against *P. falciparum* strain of 3D7 showed that the IC₅₀ values of 2-hydroxyxanthone is 0.44 µg/mL.

ACKNOWLEDGMENTS

We would like to thank to the Ministry of Research, Technology and Higher Education of the Republic of Indonesia for the research grant "Program of Doctoral Grant."

REFERENCES

- WHO. Malaria. Available from: <http://www.who.int/mediacentre/factsheets/fs094/en>. [Last accessed on 2013 Mar 23].
- WHO. World Malaria Report 2009. Geneva: WHO; 2009.
- Vial A. Reseacher de novalis molecules antipaludieeneents, uneurdeence, un espoir. *Pathol Biol* 1994;42:138-44.
- Mustofa M. Malaria between hope and reality, speech inauguration of professor of Gadjah Mada university. Yogyakarta: Indonesia; 2009.
- Sholikah EN. New Anti-Plasmodium N-Alkyl and N-Benzyl 1,10-Fenantrolin Derivatives: Study *in vitro* Activity, Cytotoxicity, Physical Properties of Chemistry, and Pharmacokinetics Profile, Dissertation, Doctoral Program, Faculty of Medicine. Yogyakarta: Gadjah Mada University; 2010.
- Rosmalena R, Prasasti VD, Hanafi M, Budianto E, Elya B. Lignan derivatives potential as *Plasmodium falciparum* lactate dehydrogenase inhibitors: Molecular docking approach of antiplasmodial drug design. *Int J Pharm Pharm Sci* 2015;7(10):394-8.
- Mahanteshappa SS, Satyanarayan ND, Mahadevan KN, Bommegowda YD, Tangaraj M. Synthesis, antiplasmodial and ADMET studies of 4-methylamino-2-phenylquinoline analogs. *Int J Pharm Pharm Sci* 2016;8(11):173-9.
- Hay AE, Helesbeux JJ, Duval O, Labaied M, Grellier P, Richomme P. Antiplasmodiumxanthone from *Calophyllum caledonicum* and *Garcinia viellardii*. *Life Sci* 2004;75:3077-85.
- Miladiyah I, Jumina J, Haryana SM, Mustofa M. *In silico* molecular docking of xanthone derivatives as cyclooxygenase-2 inhibitor agents. *Int J Pharm Pharm Sci* 2017;9(3):98-104.
- Wydawaruyanti A, Khasanah U, Tumewu L, Ilmi H, Hafid AF, Tantular IS. Antimalarial activity and cytotoxicity study of ethanol extract and fraction from *Alectronserattus* leaves. *Int J Pharm Pharm Sci* 2015;7(12):250-3.
- Hafid AF, Septiani RP, Fabriana LH, Febrianty N, Ranggaditya D, Wydawaruyanti A. Antimalarial activity of crude extracts *Artocarpus heterophyllus*, *Artocarpus altilis* and *Artocarpus camansi*. *Asian J Pharm Clin Res* 2016;9(1):279-81.
- Rahayu MK, Harmastuti N, Pamudji G, Klodengan D, Supargiyono S, Wijayanti MA. *In vivo* test of antimalarial activity from dichloromethane-ethylacetate-methanol fractions of mundu's barks (*Garcinia dulcis*) in Swiss Webster mice. *Asian J Pharm Clin Res* 2017;10:113-5.
- Kosela S, Hu LH, Rachmatia T, Hanafi M, Sim KY. Dulxanthones F-H, three new pyranoxanthones from *Garcinia dulcis*. *J Nat Prod* 2000;63(3):406-7.
- Hanafi M, Soemiati A, Kosela S, Leslie JH. Identification and Cytotoxic L1210 Cell Evaluation of Prenylatedpyranoxanthonoids from *Garcinia dulcis* Fruit (Gutteferae) n-Hexane Extract. *Prosiding Seminar Internasional UGM*; 2004.
- Likhitwitayawuid K, Chanmahasathien W, Ruangrunsi N, Krungkrai J. Antiplasmodiumxanthones from *Garcinia cowa*. *Plana Med* 2000;64:70-2.
- Wijayanti MA, Supargiyono S, Mustofa M, Sholikah EN, Jumina J, Tahir I, et al. Heme Polymerization Inhibitory Activity (HPIA) of N-Alkyl and N-Benzyl-1,10-Phenanthroline Derivatives as Antiplasmodium, Proceeding of International Conference on Chemical Sciences (ICCS-2007): Jointly held by Department of Chemistry Gadjah Mada University and Department of Chemistry Universiti Sains Malaysia, Yogyakarta; 2007. p. 237-42.
- Tomar N, Singh SV, Chottes LJ, Verma G, Anirban P, Singh V. Synthesis and anti-plasmodial activity of some novel chalcone derivatives. *Asian J Pharm Res* 2015;8(2):47-50.
- No K, Noh Y. The synthesis of calix(4) arene. *Bull Korean Chem Soc* 1986;7:4.
- Firdaus. Sintesis Seri Senyawa Aminokalisarenadan Penerapannya untuk Menjerat Ion Logam Berat, PhD Thesis. Yogyakarta: Pascasarjana Universitas Gadjah Mada; 2008.
- Harborne JB. *Method of Phytopharmaca, Guide Modern Way of Analyzing Plants, Translation Kosasih Padmawinata and Iwang Sudiro*. Bandung: ITB; 1987.
- Amanatie A, Jumina J, Mustofa M, Hanafi M. Development of new xanthone compound derivatives from *Garcinia dulcis* root as antiplasmodium. Research Report on Incentive Grant of Applied Research in the Field of Health and Pharmaceutical Technology Year II and III). Yogyakarta: Research Institute of Yogyakarta State University; 2009.
- Naidoo JM. Novel Methodology for the Synthesis of Xanthones, Tesis. Johannesburg: Witwatersrand University; 2009.