One-Pot Synthesis and *In Vitro* Studies of Calix[4]-2-methylresorcinarene Derivatives as Antimalarial Agents Against *Plasmodium falciparum* Chloroquine-Resistant Strain FCR-3

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Abstract: *Malaria is an endemic disease in Indonesia caused by infection from the Plasmodium parasite. Recently, antimalarial resistance significantly contributed to the decline in the cure rate of malaria sufferers. In this work, three calix[4]resorcinarenes have been synthesized from 2-methylresorcinol and different benzaldehyde derivatives, i.e., 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, and 4-dimethylaminobenzaldehyde through the one-pot synthesis procedure. The calix[4]resorcinarenes synthesis was done through a cyclo-condensation reaction by using HCl 37% as the catalyst and ethanol as the solvent in an one-pot reaction. The structures of the synthesized products were confirmed using Fourier transform infrared, proton-nuclear magnetic resonance, and liquid chromatography-mass spectrometry techniques. The antimalarial activity assay was evaluated against the* Plasmodium falciparum *FCR-3 strain through an* in vitro *study. Three synthesized compounds, i.e.,* C*-4-chlorophenylcalix[4]-2-methylresorcinarene,* C*-4-methoxyphenylcalix[4]-2-methylresorcinarene and* C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene have been successfully synthesized in up to 97% yield. The* C*-4-chlorophenylcalix[4]-2-methylresorcinerene exhibited the most potent antimalarial activity with a half-maximal inhibitory concentration (IC_{50}) value of 2.66 μM against* P. falciparum *FCR-3 while the* C*-4-methoxyphenylcalix[4]-2-methylresorcinarene and* C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene gave the IC_{50} values of 23.63 and 13.82 μM, respectively. From the results, it could be concluded that the antimalarial activity of calix[4]-2-methylresorcinarenes was influenced by the type of substituent of aromatic rings at the para position.*

Keywords: *Antimalarial; calix[4]-2-methylresorcinarene;* in vitro *assay; one-pot synthesis;* Plasmodium falciparum

■ INTRODUCTION

Malaria is one of the most fatal diseases, which is an easily spread parasite disease globally. In 2022, as many as 241 million global active malaria cases and 627 thousand deaths due to malaria have been reported. Compared to the reported data in 2019, there is an increase of 22 million active cases and 50 thousand deaths. Southeast Asia had nine countries with malaria endemic areas with 5 million cases or equal to 2.1% of global cases. Among these countries, Indonesia is the only one that reported an increase in malarial deaths in 2020. In 2019, Indonesia reported 32 deaths; however, this number increased to 49 deaths in 2020. Additionally, Indonesia is the second country in South and Southeast Asia regions with the highest number of malaria active cases after India in 2020. Indonesia reported 800 thousand malaria cases and 49 deaths in 2020, accounting for 15.6% of active cases and 22% of malaria deaths in the Southeast Asia region [1].

It is reported that malaria disease is caused by the Plasmodium infection through the mosquito (*Anopheles quadrimaculatus* Say) host. Four Plasmodium species, i.e., *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*, are responsible for the malaria diseases. The *P. falciparum* and *P. vivax* are the predominant species, accounting for 60 and 40% of global malaria cases. On the other hand, *P. ovale* is mostly found in the Sub-Saharan Africa region, while *P. malaria* is widely found in the South American region. Among them, *P. falciparum* has been reported as the most predominant species in global cases with serious symptoms, including acute respiratory dysfunction, anemia, renal failure, central nervous system damage, fever, headache, and chills [2]. Some antimalarial drugs are commercially available nowadays, but most of them are resistant to malaria parasites, including chloroquine diphosphate [3] and artemisinin [4]. Artemisinin-based combination treatments (ACTs) are currently used for malaria therapy in treating malarial disease caused by the *P. falciparum* parasite [5]. The ACT treatment consists of artemisinin and other effective malaria drugs, which can suppress artemisinin resistance. However, the effectiveness of this treatment continues to decline due to the domino effects of drug resistance and undesired side effects on human health [6]. Therefore, there is an urgent need to discover new antimalarial drugs as soon as possible to overcome these issues.

Hundreds of antimalarial agents have been isolated from natural sources as well as synthesized by organic chemists. In general, natural antimalarial agents are superior because of their safety to the human body. However, these natural compounds often suffer from poor antimalarial activity with complicated isolation and/or purification procedures. On the other hand, synthetic antimalarial agents offer higher antimalarial activity due to their rational design and higher purity than natural compounds. Recently, interest in macrocycle-based compounds has increased in medicinal chemistry, especially for calixarene. Calix[4]resorcinarene, a calixarene derivative, has gained significant interest in supramolecular chemistry as the basic framework for synthesizing cations, anions, biomolecules, gas, and neutral host molecules [7]. Calix[4]resorcinarenes have been employed in various applications, such as adsorbents [8], surfactants [9], complexation agents [10], liquid membranes [11], and chemical sensors [12]. In addition, calix[4]resorcinarenes are well known to exhibit several biological activities and uses in analytical and pharmaceutical fields [13], such as anticancer and antioxidant agents [14-15]. However, the exploration of calix[4]resorcinarene derivatives has yet to be thoroughly carried out as an active drug ingredient, especially as an antimalarial agent.

According to the published literature, the presence of aromatic pharmacophoric groups is critical to enhance the antimalarial activity of organic compounds. Chloro substituent in the para position of the quinoxaline's aromatic ring gave high antimalarial activity with a half-maximal inhibitory concentration (IC_{50}) value of 0.20 μg/mL, which is more active than the chloroquine diphosphate (IC_{50} value = 0.43 μg/mL) [16]. The methoxy group is also pivotal for the antimalarial activity of hydroxy-substituted chalcones with IC_{50} values less than 10 μg/mL [17]. On the other hand, the alkylamino group in chalcone derivatives exhibits high antimalarial activity with IC_{50} values below 2 μg/mL [18]. Our previous work evaluated the antimalarial activity of

calix[4]resorcinarenes with methyl, heptyl, and nitrophenyl functional groups through an *in vitro* heme polymerization inhibition assay. The experimental data revealed that calix[4]resorcinarenes with methyl, heptyl, and nitrophenyl functional groups yielded lower IC_{50} values of 0.282, 0.814, and 0.198 μg/mL, respectively, which were lower than of chloroquine diphosphate (IC_{50} value = 1.157 μg/mL) [19]. This result demonstrated that calix[4]resorcinarene with aromatic moiety gave a higher antimalarial activity than the calix[4]resorcinarene with alkyl groups.

In another work, we also evaluated the antimalarial activity of calix[4]pyrogallolarenes through an *in vitro* heme polymerization inhibition assay. The experimental data revealed that calix[4]pyrogallolarenes with phenyl, 4-hydroxy-3-methoxyphenyl, and chlorophenyl functional groups yielded lower IC_{50} values of 1.268, 1.029, and 0.238 μg/mL, respectively, which were lower than of chloroquine diphosphate as the positive control [20]. This result demonstrated that calix[4]pyrogallolarenes yielded a weaker antimalaria activity than calix[4]resorcinarenes. This phenomenon might be caused by the stronger intramolecular hydrogen bonds in calix[4]pyrogallolarenes. The stronger intramolecular hydrogen bonds yield a weaker capacity of electron donating and/or withdrawing groups to attack the Plasmodium. Furthermore, the ability of methoxy and chloro groups to yield a stronger antimalaria has been confirmed compared with the unsubstituted aromatic ring, i.e., the phenyl group. To approve our hypothesis, we have examined the antimalarial activity of calix[4]-2-methylresorcinarenes with the nitro group at ortho and para positions at the aromatic rings through *in vitro* antiplasmodial method. The experimental data showed that the calix[4]-2-methylresorcinarenes with the nitro group at the para position gave a lower IC_{50} value (1.79 μM) than the calix[4]-2-methylresorcinarenes with the nitro group at ortho position (IC_{50} value = 2.35 μM) against *P. falciparum* [21]. These reports suggested that chloro, methoxy, and alkylamino functional groups in the para position of calix[4]-2-methylresorcinarene framework shall be considered to have potent antimalarial activity.

Therefore, this study aims to obtain potential antimalarial candidates from calix[4]-2-methylresorcinarene derivatives with various functional groups of chloro, methoxy, and dimethylamino groups at the para position. Three calix[4]-2-methylresorcinarenes were synthesized from aromatic precursors, namely 2-methylresorcinol with 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, and 4-dimethylaminobenzaldehyde in a one-pot synthesis method under acidic conditions. The chemical structure of all synthetic products was elucidated using Fourier transform infrared (FTIR), nuclear magnetic resonance (NMR), and liquid chromatography-mass spectrometry (LC-MS) techniques. Furthermore, the synthetic compounds were examined for their antimalarial activity against *P. falciparum* chloroquine-resistant strain (FCR-3) through an *in vitro* assay. The effect of the various functional groups on the antimalarial activity was also discussed from a structure-activity relationship point of view.

■ EXPERIMENTAL SECTION

Materials

Materials employed for the synthesis were 2-methylresorcinol ($C_7H_8O_2$), 4-chlorobenzaldehyde (C_7H_5ClO), 4-methoxybenzaldehyde ($C_8H_8O_2$), 4-(dimethylamino)benzaldehyde ($C_9H_{11}NO$), hydrochloric acid (HCl) 37%, and ethanol (C_2H_5OH). These reagents were purchased from Merck in pro-analytical grade and used without further purification. The materials used in the antimalarial evaluation were *P. falciparum strain* FCR-3, dimethyl sulfoxide (DMSO, C_3H_6SO, Merck), methanol (CH_3OH, Merck), serum blood, RPMI-1640 (Sigma-Aldrich), red blood cells (RBC), Giemsa 10% solution (Merck), and distilled water.

Instrumentation

The melting point of the synthesized calix[4]resorcinarene was determined by a Electrothermal 9100 apparatus. Structure elucidation of the synthesized products was performed using an FTIR spectrometer (Shimadzu Prestige 21), proton NMR spectrometer (^{1}H-

NMR, JEOL JNMECA 500 MHz), and LC-MS instrument (ACQUITY UPLC®H-Class System waters, USA). Pieces of equipment used for the antimalarial assay were glass slides, 96-well microplate, micropipette (Gilson and Thermo Scientific), candle jar, microcentrifuge (Thermo Sorvall Legend Micro 17R), and microscope (Nikon eclipse E100).

Procedure

One-pot synthesis of calix[4]-2-methylresorcinarene

The synthesis procedure of calix[4]-2-methylresorcinarene was carried out using an adapted method from the previously published literature [22]. The 2-methylresorcinol (5 mmol) was completely dissolved in 50 mL of ethanol and then separately mixed with benzaldehyde derivatives, i.e., 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, 4-dimethylaminobenzaldehyde (5 mmol). Afterward, as much as 1 mL of HCl 37% was slowly poured into the mixture and the mixture was heated at 78 °C. After 24 h, the mixture was cooled and added with 50 mL of distilled water to precipitate the desired products. Next, the solid residue was filtered and washed with cold ethanol and water to remove the unreacted precursors. Then, the solid product was recrystallized from ethanol to obtain the title compound as a pure chemical and finally characterized by FTIR, ^{1}H-NMR, and LC-MS analyses.

***C*-4-chlorophenylcalix[4]-2-methylresorcinarene.** The desired compound was obtained in 97% yield as an orange solid. melting point (m.p.) 263 °C; FTIR ν_{max} (KBr, cm^{-1}): 3441 (O–H stretching), 2924 and 2862 (C_{sp3}–H stretching), 1604 and 1481 (C=C aromatic stretching), 1435 (C–H methine stretching), 1288 and 1188 (C–O stretching), 725 (C–Cl stretching); ^{1}H-NMR (DMSO-d_6; 500 MHz) δ (ppm): 1.95 and 1.97 (s, 12H, $ArCH_3$), 5.71, 5.76 and 5.96 (s, 4H, ArCH), 5.99 and 6.23 (s, 8H, ArH meta to OH), 6.51 and 6.62 (d, coupling constant (*J*) = 8.6 Hz, 8H, ArH), 6.91 and 7.05 (d, *J* = 8.5 Hz, 8H, ArH), 7.79, 7.88, 7.99, and 8.17 (s, 8H, ArOH); LC-MS: two signals at 12.81 and 13.14 min with *m/z* of $[M+K+H]^+$ = 1004.

***C*-4-methoxyphenylcalix[4]-2-methylresorcinarene.** The title molecule was obtained in 95% yield as an orange solid. m.p. > 367 °C (decomposition); FTIR ν_{max} (KBr, cm^{-1}): 3487 (O–H stretching), 2931 and 2839 (C_{sp3}–H stretching), 1604 and 1512 (C=C aromatic stretching), 1473 (C–H methine stretching), 1242 and 1180 and 1033 (C–O stretching); ^{1}H-NMR ($CDCl_3$; 500 MHz) δ (ppm): 2.06 (s, 12H, $ArCH_3$), 3.77 (s, 12H, OCH_3), 4.54 (s, 8H, ArOH), 5.37 (s, 4H, ArCH), 5.58 (s, 4H, ArH meta to OH), 6.62 (d, 8H, *J* = 8.5 Hz, ArH), 6.70 (d, 8H, *J* = 9.0 Hz, ArH); LC-MS: a single signal at 10.81 min with *m/z* of $[M+NH_4]^+$ = 986.

***C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene.** The product was obtained in 35% yield as a purple solid. m.p. > 289 °C (decomposition); FTIR ν_{max} (KBr, cm^{-1}): 3394 (O–H stretching), 2924 (C_{sp3}–H stretching), 1604 and 1473 (C=C aromatic stretching), 1435 (C–H methine stretching), 1180 (C–O stretching), 1342 (C–N stretching); ^{1}H-NMR (D_2O; 500 MHz) δ (ppm): 1.92 and 1.97 (s, 12H, $ArCH_3$), 3.09 and 3.16 (s, 24H, $-N(CH_3)_2$), 5.62, 5.71 and 5.86 (s, 4H, ArCH), 5.77, 5.89 and 5.92 (s, 4H, meta to OH), 6.88–6.79 (d, 8H, *J* = 8.5 Hz, ArH), 7.11–7.37 (d, 8H, *J* = 8.5 Hz, ArH); LCMS: two signals at 8.55 and 9.35 min with *m/z* of $[M]^+$ = 1021.

Antimalarial activity assay

The synthesized calix[4]-2-methylresorcinarene derivatives were evaluated for their antimalarial activity against *P. falciparum* FCR-3 as a chloroquine-resistant strain. In this study, the antimalarial activity evaluation was conducted using an *in vitro* hybrid microtechnical method as reported by Congpoung et al. [23]. As much as 100 µL of inoculum solution containing the *P. falciparum* FCR-3 parasite in serum blood and red blood cells was added to each well of the 96-well assay plate. Several concentrations of calix[4]-2-methylresorcinarene compounds (1, 2, 10, 20, and 25 µg/mL) in DMSO were prepared. Then, as much as 100 µL of each solution concentration was added to the 96-well assay plate, in which each concentration was subjected to triplicates in a row. The incubation was carried out for 72 h in a 5% CO_2 incubator at 37 °C, using the previously reported procedure [24]. Afterward, the blood suspension was subjected to a vortex separation to obtain supernatant and blood precipitate. The blood precipitate was placed in the glass slide to make a thin blood smear. The blood smear was fixed through

methanol washing and then stained by using a 10% Giemsa solution containing methylene blue, eosin, and azure B dyes. These dyes were added for better visualization of health and infected red blood cells by *P. falciparum* parasites. The growth of *P. falciparum* was observed during the schizont phase. The number of schizonts was counted by using a microscope and then compared for at least 1,000 normal red blood cells. The inhibition percentage is calculated by using Eq. (1);

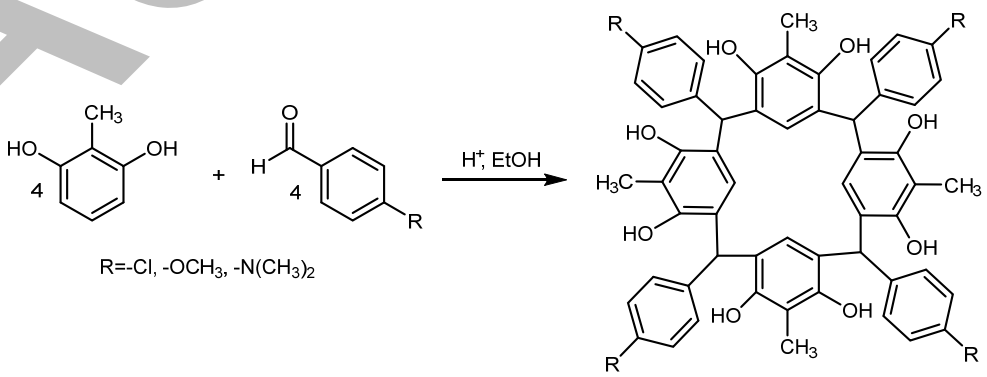
$$\text{Inhibition } (\%) = \frac{A - B}{A} \times 100\% \quad (1)$$

where A and B represent the negative control and sample parasitemia percentage, respectively. The IC_{50} value of each synthesized compound was calculated through a probit analysis using IBM SPSS Statistics 26 software. Chloroquine diphosphate and DMSO were employed as the positive and negative controls, respectively.

■ RESULTS AND DISCUSSION

One-pot Synthesis of Calix[4]-2-methylresorcinarenes Derivatives

All of the synthesized compounds are produced through a cyclo-condensation reaction between 2-methylresorcinol and benzaldehyde derivatives. This cyclo-condensation reaction produced a cyclic tetramer of calix[4]-2-methylresorcinarene, as shown in Scheme 1. The reaction mechanism for the production of calix[4]-2-methylresorcinarene has been investigated in our previous work for calix[4]resorcinarenes and calix[4]pyrogallolarenes [19]. Due to the similar structure of calix[4]resorcinarenes, calix[4]pyrogallolarenes, and calix[4]-2-methylresorcinarenes, the reaction mechanism shall not be significantly different. Briefly, the carbonyl group of benzaldehyde derivative was protonated by hydrochloric acid in ethanol media, thus increasing the electrophilicity properties as reported before. The 2-methylresorcinol has three electron-donating groups, i.e., two hydroxyl groups and one methyl group. Therefore, 2-methylresorcinol could act as a nucleophile for an electrophilic aromatic substitution reaction with activated benzaldehyde ones. This coupling reaction happens until a cyclic tetramer structure is formed through the elimination of water molecules. Through this reaction mechanism, three calix[4]-2-methylresorcinarene derivatives, i.e., *C*-4-chlorophenylcalix[4]-2-methylresorcinarene, *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene, and *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene have been successfully obtained in 97, 95, and 35% yield, respectively. The *C*-4-chlorophenylcalix[4]-2-methylresorcinarene compound was obtained in the highest yield due to the presence of chloro substituent as an electron-withdrawing group, thus contributing to the higher electrophilicity properties of benzaldehyde. Meanwhile, *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene compound was obtained in the lowest yield due to the presence of the polar dimethylamino group. This *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene compound has eight hydroxyl groups and four dimethylamino groups; thus, it is highly soluble in water and ethanol media. Consequently, this high solubility might lead to the lowest isolation yield during the recrystallization process.



Scheme 1. The one-pot synthesis route of calix[4]-2-methylresorcinarene derivatives

All of the synthetic calix[4]-2-methylresorcinarene products were elucidated using FTIR, ^{1}H-NMR, and LC-MS analyses. The FTIR spectra of *C*-4-chlorophenylcalix[4]-2-methylresorcinarene, *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene, and *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene are shown in Fig. 1. In the FTIR spectrum of each calix[4]-2-methylresorcinarene, the formation of calix[4]-2-methylresorcinarene structure was indicated by the loss of strong absorption of the carbonyl group (C=O) stretching and C–H stretching of benzaldehyde at 1700–1660 and 2700–2800 cm^{-1}, respectively [25]. The appearance of the methine bridge (C–H) absorption at 1435–1437 cm^{-1} strengthened the evidence of the formation of calix[4]-2-methylresorcinarene as this absorption signal is quite characteristic of calix[4]resorcinarene framework [21]. The other functional groups such as hydroxyl (O–H), C_{sp3}–H of methylresorcinol structure, C=C aromatic and C–O phenolic were also observed in 3487–3394, 2931–2839, 1604–1473, and 1288–1180 cm^{-1}, respectively, giving a stronger evidence that the calix[4]-2-methylresorcinarene structure has been successfully generated. The presence of these functional groups has also been reported for a successful synthesis of calixarenes, calix[4]resorcinarenes, and calix[4]pyrogallolarenes in other published works [7,10-11,15,22]. Additionally, the presence of the C–Cl functional group in *C*-4-chlorophenylcalix[4]-2-methylresorcinarene was confirmed by an absorption signal at 725 cm^{-1} on its FTIR spectrum. The C–O methoxy functional group of *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene was also observed at 1033 cm^{-1}, while the C–N functional group of *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene was detected as a signal at 1342 cm^{-1}. These FTIR data indicated the successful production of calix[4]-2-methylresorcinarene derivatives.

The ^{1}H-NMR spectra of *C*-4-chlorophenylcalix[4]-2-methylresorcinarene, *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene, and *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene are shown in Fig. 2. In ^{1}H-NMR analysis, the C–H aldehyde signal of benzaldehyde at around 10 ppm was not found due to the cyclo-condensation reaction. Instead, new singlet

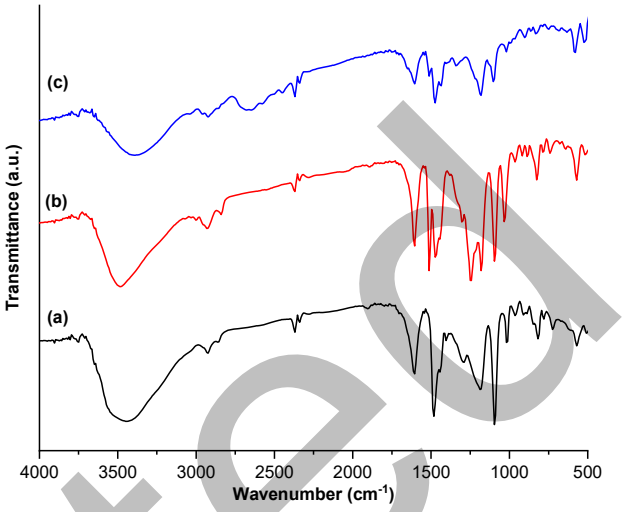


Fig 1. The FTIR spectra of (a) *C*-4-chlorophenylcalix[4]-2-methylresorcinarene, (b) *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene, and (c) *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene

peaks from the methine proton at 5.37–5.76 ppm gave solid evidence for the successful formation of the calix[4]-2-methylresorcinarene [26]. It was well-known that the ^{1}H-NMR characterization data are the key to elucidating the supramolecular structures, including calix[4]resorcinarenes, calixarenes, and calix[4]pyrogallolarenes. Ohto [8] reported that there are four possible conformations of calix[4]resorcinarene, i.e., crown (C_{4v}), boat (C_{2v}), chair (C_{2h}), diamond (C_s), and saddle (S_4) conformations. Crown conformation of calix[4]resorcinarene is defined when a singlet signal of methine proton is observed in the ^{1}H-NMR spectrum. Boat and chair conformations of calix[4]resorcinarene are interpreted when there are two methine proton signals with the same integral value. On the other hand, diamond and saddle conformation of calix[4]resorcinarene are clarified when there are four methine proton signals with the same integral value [27-29]. This spectroscopic evidence aligns with the crystallographic data of each conformation, demonstrating the meaningful ^{1}H-NMR characterization data as proved by previous works [30-34]. With only the difference of a methyl group between the hydroxyl groups of calix[4]resorcinarene, the existing conformations of calix[4]-2-methylresorcinarene and calix[4]resorcinarene are not significantly different.

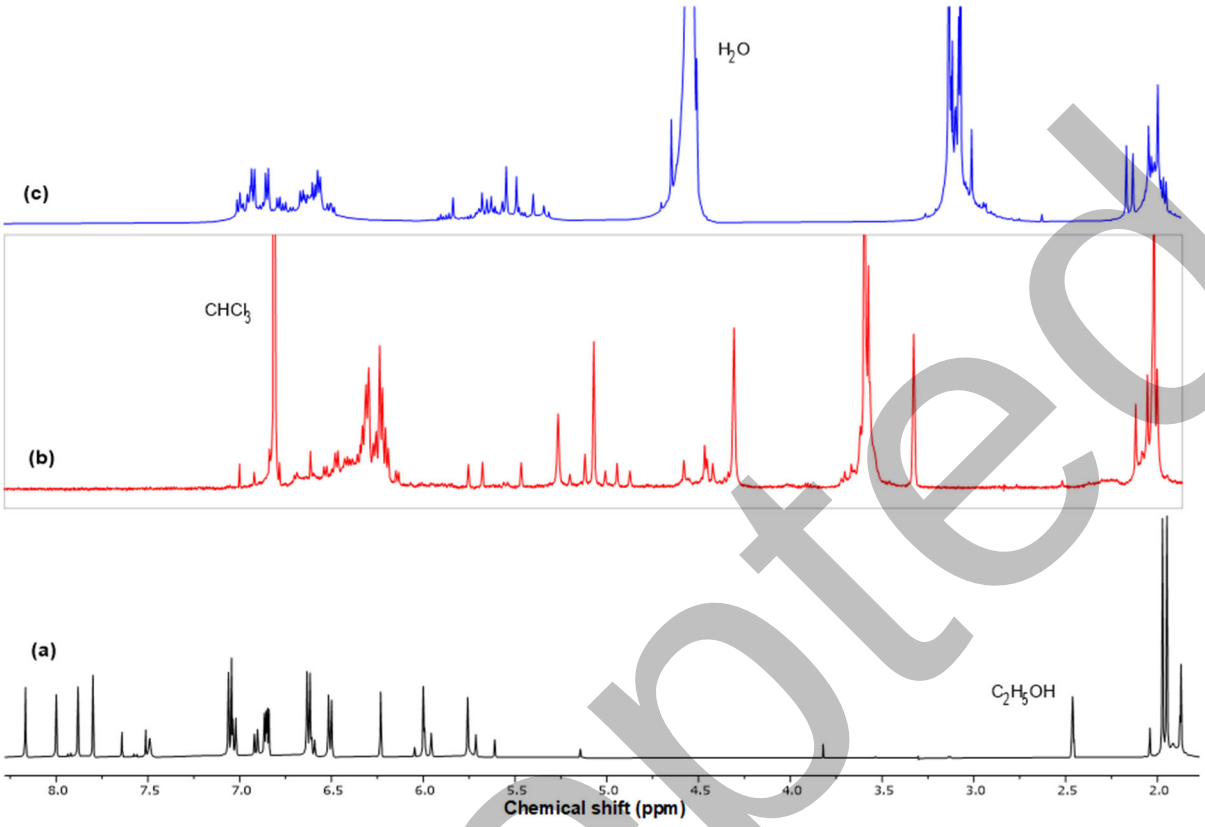


Fig 2. The ^{1}H-NMR spectra of (a) *C*-4-chlorophenylcalix[4]-2-methylresorcinarene, (b) *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene, and (c) *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene

The ^{1}H-NMR spectrum analysis showed that *C*-4-chlorophenylcalix[4]-2-methylresorcinarene and *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene compounds form two conformations due to variable possible intramolecular and intermolecular hydrogen bonds. The *C*-4-chlorophenylcalix[4]-2-methylresorcinarene compound existed in boat and chair conformations, while *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene compound observed in the crown and chair conformations. Boat and chair conformations of *C*-4-chlorophenylcalix[4]-2-methylresorcinarene compound were strongly indicated by four singlet proton signals of resorcinol OH group at a chemical shift value of 7.79, 7.88, 7.99, and 8.17 ppm. The boat and chair conformations have OH groups divided in two directions of different chemical environments, axial and equatorial; thus, these hydroxyl groups appeared as two proton signals [35-36]. The *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene compound existed in crown and chair conformations, as indicated by the presence of peaks for the same proton type, but appeared with different proton integrations, similar to the trend of *C*-4-chlorophenylcalix[4]-2-methylresorcinarene. The crown conformation shows a singlet signal with one proton integral because all methine protons are symmetrical with each other. In contrast, the chair will show two proton peaks of the same type with the proton integration value half of the crown proton integral. The observed crown and chair conformations in this study have similarities with the results of research by Castillo-Aguirre et al. [26]. On the other hand, *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene was found in a single crown conformation, as confirmed by a singlet signal of C–H methine at a chemical shift value of 5.37 ppm. This prediction was also confirmed by the appearance of two peaks in the LC chromatogram of both *C*-4-chlorophenylcalix[4]-2-methylresorcinarene and *C*-4-dimethylaminophenylcalix[4]-2-

methylresorcinarene compounds. On the other hand, the single conformation of *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene, i.e., in a crown conformation, agreed with a single peak in the LC chromatogram of *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene.

The other proton signals of each calix[4]-2-methylresorcinarene were also observed in their ^{1}H-NMR spectra. The methyl protons of 2-methylresorcinol were observed as a singlet signal at a chemical shift range of 1.95–2.06 ppm. The aromatic protons of 2-methylresorcinol moiety were also detected as a singlet signal at a chemical shift range of 5.58–6.23 ppm. Meanwhile, the aromatic protons of the benzaldehyde structure were found as two doublet signals with a *J* value of 8.5–9.0 Hz at a chemical shift range of 6.51–7.37 ppm. The OH protons of calix[4]-2-methylresorcinarene were observed as a singlet signal at a chemical shift range of 4.54 to 8.17 ppm. It is well-known that hydroxyl protons can be found in a wide range of chemical shifts in the ^{1}H-NMR spectra. The methoxy protons of *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene were observed as a singlet signal at 3.77 ppm, while the dimethylamino protons of *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene were detected as singlet signals at a chemical shift range of 3.09–3.16 ppm.

Another characterization that proves the formation of calix[4]-2-methylresorcinarene compounds is done through LC-MS analysis. Characterization of *C*-4-chlorophenylcalix[4]-2-methylresorcinarene compound showed two signals with the same *m/z* value of 1005 for $[M+H+K]^+$ at the retention time of 12.81 and 13.14 min. Both peaks had the same *m/z* value, indicating that two conformations existed as suggested by the ^{1}H-NMR analysis, i.e., boat and chair conformations. The *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene compound showed an *m/z* value of 986 $[M+NH_4]^+$ as a single peak at the retention time of 10.81 min, confirming that *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene existed in one conformation only (crown conformation). Meanwhile, the *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene compound was observed as two signals with the same *m/z* value of 1021 $[M]^+$ at 8.55 and 9.35 min, confirming the presence of crown and chair conformations as revealed by the ^{1}H-NMR analysis. Based on the FTIR, ^{1}H-NMR, and LC-MS data, it can be concluded that *C*-4-chlorophenylcalix[4]-2-methylresorcinarene, *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene, and *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene have been successfully synthesized in the present work.

Antimalarial Activity of Calix[4]-2-methylresorcinarenes

The antimalarial activity of the synthesized calix[4]-2-methylresorcinarene derivatives was examined through an *in vitro* assay against chloroquine-resistant *P. falciparum* FCR-3. This resistant strain (FCR-3) was selected due to serious concern about malarial resistance against chloroquine diphosphate as a commercial drug during the last decade. This *in vitro* assay observes the schizont growth in the red blood cells in RPMI-1640 media. Table 1 shows the inhibition percentage of *P. falciparum* FCR-3 in the presence of various calix[4]-2-methylresorcinarene concentrations. Increasing the calix[4]-2-methylresorcinarene concentrations generally increased the inhibition percentage. At the highest concentration (12.5 μg/mL), *C*-4-chlorophenylcalix[4]-2-methylresorcinarene gave a higher inhibition percentage (82.17%) than *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene (53.77%) and much higher than *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene (41.12%). A similar trend was also observed for the lowest concentration (0.5 μg/mL), whereas the inhibition percentage of *C*-4-chlorophenylcalix[4]-2-methylresorcinarene (22.72%) > *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene (17.87%) > *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene (14.31%). This result shows that *C*-4-chlorophenylcalix[4]-2-methylresorcinarene was the best antimalarial agent against *P. falciparum* FCR-3 parasites among the synthesized calix[4]-2-methylresorcinarenes in this work.

The antimalarial activity is classified based on the IC_{50} values by Batista et al. [36]. These classifications are

Table 1. *Plasmodium falciparum* FCR-3 parasites inhibition percentages in a various concentration of calix[4]-2-methylresorcinarenes

Compound	Concentration (μg/mL)	Inhibition percentage (%)
C-4-chlorophenylcalix[4]-2-methylresorcinarene	12.5	82.17
	10.0	72.55
	5.0	57.99
	1.0	31.33
	0.5	22.72
C-4-methoxyphenylcalix[4]-2-methylresorcinarene	12.5	43.56
	10.0	43.11
	5.0	35.42
	1.0	22.94
	0.5	14.31
C-4-dimethylaminophenylcalix[4]-2-methylresorcinarene	12.5	53.77
	10.0	41.12
	5.0	35.62
	1.0	23.98
	0.5	17.87

Table 2. The IC_{50} value of antimalarial compounds based on calix-structure

Compounds	IC_{50} value (μM)
C-4-chlorophenylcalix[4]-2-methylresorcinarene	2.66
C-4-methoxyphenylcalix[4]-2-methylresorcinarene	23.63
C-4-dimethylaminophenylcalix[4]-2-methylresorcinarene	13.82
C-4-nitrophenylcalix[4]-2-methylresorcinarene [21]	1.79
C-8-hydroxyquinolinecalix[4]arene [39]	0.07
C-2-aminopyrimidinecalix[4]arene [39]	0.04
Chloroquine	0.62
1,6-dihydroxyxanthone [24]	81.77
1,4,5-trihydroxyxanthone [40]	14.54
1,3,5-trihydroxyxanthone [40]	102.33

very active (IC_{50} value < 1 μM), active (IC_{50} value = 1–20 μM), moderate (IC_{50} value = 20–100 μM), and inactive (IC_{50} value > 100 μM) antimalarial agents. Table 2 shows that *C*-4-chlorophenylcalix[4]-2-methylresorcinarene, *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene, and *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene compounds gave IC_{50} values of 2.66, 23.63, and 13.82 μM, respectively, against *P. falciparum*. The *C*-4-chlorophenylcalix[4]-2-methylresorcinarene compound was found as an active antimalarial agent with the lowest IC_{50} value of 2.88 μM, demonstrating the strongest antimalarial activity. The *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene compound was found as a moderate antimalarial agent with an IC_{50} value of 23.63 μM while the *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene compound was an active antimalarial agent with an IC_{50} value of 13.82 μM. These *in vitro* results showed that the antimalarial activities of calix[4]-2-methylresorcinarene derivatives were influenced by the various functional groups at the para position of the aromatic rings. The chloro functional group exhibited a higher antimalarial activity than the dimethylamino and methoxy functional groups. Both polar functional groups, i.e., chloro and dimethylamino,

exhibited higher antimalarial activity than the non-polar methoxy group. This phenomenon was in agreement with other reported publications [19-21,28,37]. More polar calix derivatives, *i.e.*, *C*-4-nitrophenylcalix[4]-2-methylresorcinarene (IC_{50} value = 1.79 μM), *C*-8-hydroxyquinolinecalix[4]arene (IC_{50} value = 0.07 μM), and *C*-2-aminopyrimidinecalix[4]arene (IC_{50} value = 0.04 μM) yield much lower IC_{50} values than *C*-4-chlorophenylcalix[4]-2-methylresorcinarene (IC_{50} value = 2.66 μM). However, the antimalarial activity of calix[4]-2-methylresorcinarenes in this work was much stronger than hydroxyxanthone derivatives, i.e., 1,6-dihydroxyxanthone (IC_{50} value = 81.77 μM), 1,5,6-trihydroxyxanthone (IC_{50} value = 27.64 μM), 1,6,8-trihydroxyxanthone (IC_{50} value = 6.76 μM), 1,4,5-trihydroxyxanthone (IC_{50} value = 14.54 μM), and 1,3,5-trihydroxyxanthone (IC_{50} value = 102.33 μM),as a representative of polyphenolic compounds, which was remarkable. This meant that the cyclization reaction of the polyphenolic compound significantly enhanced the antimalarial activity. Even though the calix[4]-2-methylresorcinarenes exhibit lower activity than chloroquine diphosphate, the *C*-4-chlorocalix[4]-2-methylresorcinarenes may have great potential to overcome chloroquine resistance as they have a different geometry from chloroquine diphosphate [38]. Thus, *C*-4-chlorocalix[4]-2-methylresorcinarenes could be further functionalized to have a better and stronger antimalarial agent in the future.

■ CONCLUSION

Three calix[4]-2-methylresorcinerene have been successfully synthesized from 2-methylresorcinol through a one-pot reaction method under acidic conditions. Their chemical structures were confirmed through spectroscopic elucidation analyses. The *C*-4-chlorophenylcalix[4]-2-methylresorcinarene product was obtained in boat and chair conformations in 97% yield. The *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene compound was produced in a single crown conformation in 95% yield. Meanwhile, the *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene compound was constructed in crown and chair conformations in 35% yield. The *in vitro* antimalarial activity assay against *P. falciparum* FCR-3 showed that the *C*-4-chlorophenylcalix[4]-2-methylresorcinarene compound exhibited the most potent antimalarial activity with an IC_{50} value of 2.66 μM, followed by *C*-4-dimethylaminophenylcalix[4]-2-methylresorcinarene compound (IC_{50} value = 13.82 μM) and *C*-4-methoxyphenylcalix[4]-2-methylresorcinarene compound (IC_{50} value = 23.63 μM). Therefore, the antimalarial activity of calix[4]-2-methylresorcinarenes depends on the type of functional group attached to the aromatic ring at the para position.

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■ CONFLICT OF INTEREST

The authors have no competing interests to be declared.

■ AUTHOR CONTRIBUTIONS

Jumina did conceptualization of this work. Jumina, Harno Dwi Pranowo, Eti Nurwening Sholikhah, Jeffry Julianus, and Susalit Setya Wibowo did supervision. Baiq Ike Nursofia conducted the experiment. Baiq Ike Nursofia, Krisfian Tata Aneka Priyangga, Yehezkiel Steven Kurniawan, Jeffry Julianus, Eti Nurwening Sholikhah, Harno Dwi Pranowo, and Hana Anisa Fatimi did formal analysis. Baiq Ike Nursofia, Krisfian Tata Aneka Priyangga, Yehezkiel Steven Kurniawan, and Yoga Priastomo wrote and revised the manuscript. All authors agreed to the final version of this manuscript.

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