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A new antiplasmodial sterol from Indonesian marine sponge, *Xestospongia* sp

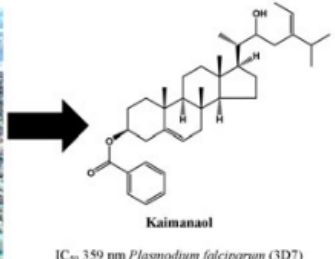
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ABSTRACT

A new antimalar sterol, kaimanol (**1**), along with a known sterol, saringosterol (**2**) was isolated from the Indonesian Marine sponge, *Xestospongia* sp. The chemical structure of the new compound was determined on the basis of spectroscopic evidences and by comparison to those related compounds previously reported. Isolated compounds, **1** and **2** were evaluated for their antiplasmodial effect against *Plasmodium falciparum* 3D7 strains. Compounds **1** and **2** exhibited antiplasmodial activity with IC₅₀ values of 359 and 0.250 nM, respectively.



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1. Introduction

Malaria is the most severe and infectious disease in the world and infected to 2.4 billion people over more than 100 countries (Bickii et al. 2006; Bagavan et al. 2011; Poostchi et al. 2017). Despite more than a century of effort to eradicate or control malaria, the disease remains a major and growing threat to the public health and economic development of countries in the tropical regions (Snow et al. 2005; Nayyar et al. 2012; Kabaria et al. 2017). WHO (2008), state that in Indonesia, cases of malaria are estimated about ninety millions cases by 2011, when one person died per a hundred thousand cases. This infectious disease has spread across the Indonesian archipelago including Sumatera, Borneo, Java, Sulawesi, Maluku and Papua. Especially, in the Papua Island, malaria has infected seventy people per a hundred population (WHO 2008). In the search for new, safe and effective antimalarial drugs, screening of the extract from marine sponge was indicated.

Xestospongia is marine sponge genus belong to Petrosiidae family, consist more than 33 species that are distributed mainly in the tropical sea (Indo-Pacific) and inhabits the intertidal zones (Allen and Steene 2002; Correia and Sovierzoski 2013). Phytochemical studies on *Xestospongia* species have reported a number compounds, such as antimalarial alkaloids (Williams et al. 1998; Girard et al. 2004; Ashok et al. 2014), antifungal alkaloids (Moon et al. 2002), cytotoxic and inhibition of the aspartic protease of the quinones and hydroquinones (Aguinaga et al. 2010; Dai et al. 2010), antimalarial quinones (Laurent et al. 2006), antiplasmodial benzaldehyde (Murtihapsari et al. 2018) and antiplasmodial sterol (Renga et al. 2012).

A part the course of our research for novel antimalarial substances from Indonesian *Xestospongia* species, we obtained a new antiplasmodial benzaldehyde and propionic acid derivative from *Xestospongia* sp (Murtihapsari et al. 2013; 2018). In continuing search for novel antiplasmodial compounds from Papuan *Xestospongia* species, we obtain the *n*-hexane extract of *Xestospongia* sp, showed a significant antiplasmodial activity against *P. falciparum* 3D7 strains. In this communication, isolation, structural elucidation and antiplasmodial activity against *P. falciparum* 3D7 strains of new sterol, kaimanol (**1**) and known sterol, saringosterol (**2**) were described.

2. Results and discussion

The *n*-hexane extract of *Xestospongia* sp was separated by vacuum-liquid chromatographed (VLC) on silica gel 60 by gradient elution, *n*-hexane-EtOAc-MeOH (10% increasing of polarity). The VLC fraction was further separated by column chromatography and preparative thin layer chromatography to afford compounds **1** and **2** (Figure 1).

Kaimanol (**1**) was isolated as white crystals and showed melting point of 115.6 °C, possessed molecular formula C₃₆H₅₂O₃ by HR-TOFMS spectra (*m/z* 531.3838 [M+H]⁺) and NMR spectra showed a hydrogen deficiency index of eleven. The UV spectrum displayed maximum absorption at 240 nm (log ε 3.2), suggesting the presence of a benzoyl moiety. The IR spectrum exhibited absorption bands ascribed to a hydroxyl (ν_{max} 3264 cm⁻¹), an aliphatic (ν_{max} 2980 and 2870 cm⁻¹), a conjugated carbonyl (ν_{max} 1701 cm⁻¹), an aromatic (ν_{max} 1601 cm⁻¹) and an ether groups

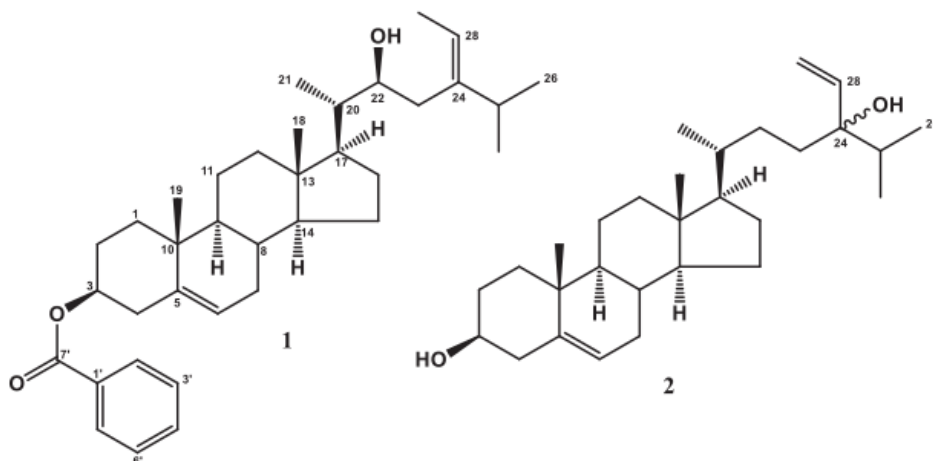


Figure 1. Structures of Compounds 1–2.

(ν_{\max} 1182 cm^{-1}). The $^1\text{H-NMR}$ spectrum indicated the presence of a mono-substituted benzene ring at [δ_{H} 8.09 (2H, d, $J=7.8$ Hz), 7.47 (2H, dd, $J=7.8, 5.6$ Hz) and 7.61 (1H, d, $J=5.6$ Hz)], two sp^2 methines at [δ_{H} 5.35 (1H, dd, $J=2.8, 6.2$ Hz) and 5.10 (1H, d, $J=4.6$ Hz)], two oxygenated sp^3 methines at [δ_{H} 3.66 (1H, m) and 3.53 (1H, m)], two tertiary methyls at δ_{H} 0.82 and 1.00 (each 3H, s), four secondary methyls at [δ_{H} 1.38 (3H, d, $J=5.2$ Hz), 0.89 (3H, d, $J=3.4$ Hz), 0.67 (3H, d, $J=2.8$ Hz) and 0.64 (3H, d, $J=3.6$ Hz)] and some aliphatic proton signals at upfield region. The ^{13}C NMR along with the DEPT spectra revealed thirty six carbon signals, including a carbonyl ester at δ_{C} 170.9, seven sp^2 methines at δ_{C} 128.6 (2 \times), 133.8 (2 \times), 130.3, 121.9 and 116.6, three sp^2 quaternary carbons at δ_{C} 130.3, 140.8 and 146.1, two tertiary methyl signals at δ_{C} 12.5 and 19.6, four secondary methyl signals at δ_{C} 18.9, 12.9, 12.2 and 12.0, nine sp^3 methylenes, eight sp^3 methines and two sp^3 quaternary carbons at δ_{C} 36.7 and 42.5. Five remaining hydrogen deficiency index corresponded to the tetracyclic steroidal skeleton (Renga et al. 2012; Bouzidi et al. 2014) with an additional benzoyl group. A comparison of the NMR data of **1** to those of saringosterol isolated from brown alga, *Cystoseira foeniculaceae* (Bouzidi et al. 2014), revealed that both structures were similar. The main difference was absence one of the oxygenated methines and the position of newly hydroxyl group as well as the appearance of a benzoyl group in downfield region, suggesting that **1** was a sterol derivative with a benzoyl group. To confirm the position of partial structure, $^1\text{H-}^1\text{H}$ COSY and HMBC experiments were carried out, and the results were shown in Figure S6 (supplementary materials). The $^1\text{H-}^1\text{H}$ COSY spectrum of **1** showed correlations in H_1 to H_4 , H_6 to H_9 , H_9 - H_{11} - H_{12} , H_{14} to H_{17} , H_{20} - H_{22} - H_{23} , and $\text{H}_{2'}$ to $\text{H}_{6'}$ supporting the presence of steroidal structure and benzoyl ring in **1**. The correlations arising from the tertiary methyl protons at δ_{H} 0.82 and 1.00 to their neighbouring carbons enabled the assignment of the two singlet methyls at C-10 and C-13, respectively. Furthermore, an olefinic proton at δ_{H} 5.35 was correlated to C-5 (δ_{C} 140.8) and C-7 (δ_{C} 31.7), indicated one of the olefinic moiety was located at C-5 to C-6 ($\Delta^{5,6}$). Another olefinic was located at C-24 to C-28 ($\Delta^{24,28}$) based on the correlation from of an olefinic proton at δ_{H} 5.10 to C-24 (δ_{C} 146.1) and secondary methyl at δ_{H} 0.89 to C-28 (δ_{C} 116.6) and C-24 (146.1). Correlations from oxygenated

protons at δ_{H} 3.66 (H-3) to carbonyl carbon at δ_{C} 170.9 (C-7'), were used to assign a benzoyl group was attached at C-3. Furthermore, correlations from methine proton at δ_{H} 1.38 (H-20) and methylene protons at δ_{H} 1.38 (H-23a) and 1.84 (H-23b) to oxygenated carbon at δ_{C} 72.0, suggesting that a secondary alcohol at located at C-22.

The relative stereochemistry of **1** was identified by a NOESY experiment (Figure S8 (supplementary materials)). The NOESY correlations between H-9/H-3, supported that the benzoyl group at C-3 was β -oriented. The NOESY cross peak also observed between H-14, H-17 and H-22, indicated that the secondary hydroxyl group at C-22 was β -oriented. Other correlations in the NOE spectra supported that the relative configuration of **1** was similar to those saringosterol (Letourneux et al. 1975; Terasaki et al. 2009; Bouzidi et al. 2014). The stereochemistry of **1** was supported also by a coupling constant values in the $^1\text{H-NMR}$ spectrum and by comparison with those of related compound previously reported, fucosterol (Hwang et al. 2012) and saringosterol (Letourneux et al. 1975; Terasaki et al. 2009; Bouzidi et al. 2014) and langcoesterol A, isolated from marine sponge *Xestospongia testudinaria* collected in Vietnam (Nguyen et al. 2018), as well as biogenetic point of view to those sterols in *Xestospongia* genus (Hwang et al. 2012; Renga et al. 2012; Nguyen et al. 2018). In addition the specific optical rotation of **1** $[\alpha]_{\text{D}}^{25} - 13.7^\circ$ (c 0.1, CHCl_3), is same negative sign to that of the previously reported, fucosterol ($[\alpha]_{\text{D}}^{20} - 38.4^\circ$ (c 0.25, CHCl_3) (Brooks et al. 1972) and langcoesterol A ($[\alpha]_{\text{D}}^{23} - 23.0^\circ$ (c 0.1, CHCl_3) (Nguyen et al. 2018), therefore, the structure of **1** was determined as the new sterol derivative and namely kaimanol.

The known compound, saringosterol (**2**) (Bouzidi et al. 2014) was identified by comparison of their spectroscopic evidence previously reported.

The antiplasmodial activity of the compounds **1** and **2** was evaluated against the against *P. falciparum* parasites using emisinin as a positive control ($\text{IC}_{50} 5.207 \times 10^{-3} \text{ nM}$) (Frohlich et al. 2016). Compounds **1** and **2** showed antiplasmodial activity with an IC_{50} values of 359 and 0.250 nM, respectively, suggesting the the presence of a benzoyl moiety decrease antiplasmodial activity in sterol structure, whereas the presence of an olefinic moiety no effect on antiplasmodial activity.

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3. Experimental

3.1. General experimental procedures

Melting points were obtained on an electrothermal melting point apparatus. Optical rotations were performed on an ATAGO AP-300 automatic polarimeter. UV spectra were measured on a TECAN Infinite M200 pro, with MeOH. IR spectra (KBr disks, in cm^{-1}) were recorded on a SHIMADZU IR-Prestige-21 in KBr . HRTOF mass spectra were acquired on Waters Xevo QTOF MS. IR spectra were obtained on a Bruker Topspin spectrometer at 500 MHz for ^1H and 125 MHz for ^{13}C with TMS as an internal standard. Silica gel G60, 70–230 and 200–400 mesh (Merck). TLC plates were precoated with silica gel GF₂₅₄ (Merck, 0.25 mm) and detection was achieved by spraying with 10% H_2SO_4 in EtOH, followed by heating.

3.2. Sponge collection and cultured parasites

Material of porifera *Xestospongia* sp, was obtained by scuba in about 10 m depth in the south west of Kaimana, West Papua, Indonesia (GPS: 4°20.341'S-133°30.265'E). It has been identified taxonomically as *Xestospongia* sp. (Darumas et al. 2007; Khairunnisa Kurnianda 2017; Kieattisak et al. 2017), the species belongs to the *Xestospongia*. Identification taxonomic and nomenclature were provided by the Laboratory Biology and Conservation, Jakarta Fisheries University, Ministry of Marine Affairs and Fisheries (LIN BIOVASI, No: 041/STP/2016, Catalogue: MS041.1-5). The protozoan parasite of *P. falciparum* strain 3D7 (chloroquine-sensitive) obtained from University of Tokyo and cultured by the Eijkman Institute for Molecular Biology in Jakarta.

3.3. Extraction and isolation

The fresh of sponge *Xestospongia* sp. (38 kg) was macerated with ethanol (3×10 L) at room temperature. After removal of the solvent under reduced pressure, the crude extract (376 g) was suspended in H₂O (1 L) and partitioned successively with *n*-hexane, EtOAc and *n*-BuOH. The *n*-hexane soluble fraction (10.0 g) was crudely separated by vacuum liquid chromatography on silica gel G60 eluting with a gradient of *n*-hexane and EtOAc to afford nine fractions (A-I), as monitored by TLC. Fraction C (1.56 g) was chromatographed on a column of silica gel, eluted with a gradient of *n*-hexane-EtOAc (10:0-1:1), to give nine subfractions (C01-C09). Subfraction C05 was subjected to silica gel column using CHCl₃:MeOH (9.75:0.25), to give four subfraction (C05A-C05D). Subfraction C05B was separated on preparative TLC on silica gel GF₂₅₄, eluted with *n*-hexane-EtOAc (9:1), to give **1** (10.0 mg). Fraction D (2.25 g) was subjected silica gel column eluting with a gradient of *n*-hexane-EtOAc (10:1-1:10), to give six subfractions (D01-D06). Subfraction D04 was recrystallized in EtOAc, to give **2** (14.2 mg).

Kaimanol (**1**), a white crystals, $[\alpha]_D^{25} -13.7^\circ$ (c 0.1, CHCl₃), UV (MeOH) λ_{max} 240 nm (log ϵ 3.2); IR (KBr) ν_{max} 3264, 2980, 2870, 1710, 1601, 1182 cm⁻¹; HR-TOFMS m/z 532.3838 [M + H]⁺, (Calcd. C₃₆H₅₂O₃ m/z 532.3836). ¹H-NMR (CDCl₃, 500 MHz): δ_H 0.67 (3H, d, $J = 5.6$ Hz, CH₃-26), 0.64 (3H, d, $J = 5.6$ Hz, CH₃-27), 0.82 (3H, s, CH₃-18), 0.96 (3H, d, $J = 1.8$ Hz, CH₃-21), 1.00 (3H, s, CH₃-19), 1.02 (1H, dd, $J = 1.9, 5.4$ Hz, H-17), 1.10 (1H, m, H-14), 1.13 (1H, m, H-11b), 1.17 (1H, m, H-9), 1.16 (1H, m, H-11a), 1.27 (1H, m, H-8), 1.38 (1H, ddd, $J = 1.8, 2.3, 5.8$ Hz, H-20), 1.49 (1H, m, H-16b), 1.56 (1H, m, H-16a), 1.59 (3H, d, $J = 4.2$ Hz, CH₃-22), 1.66 (1H, m, H-15b), 1.73 (1H, dd, $J = 2.1, 7.8$ Hz, H-2b), 1.83 (1H, m, H-2a), 1.84 (1H, dd, $J = 2.3, 7.8$ Hz, H-23b), 1.84 (1H, m, H-1a), 1.88 (1H, m, H-1b), 1.94 (1H, m, H-15a), 1.95 (1H, m, H-7b), 1.99 (1H, m, H-2b), 2.06 (1H, m, H-12a), 2.09 (1H, m, H-7a), 2.21 (1H, dd, $J = 3.4, 7.8$ Hz, H-23a), 2.25 (1H, dd, $J = 4.2, 5.6$ Hz, H-4a), 2.29 (1H, m, H-4b), 2.36 (1H, m, H-25), 3.53 (1H, ddd, $J = 2.3, 3.4, 6.7$ Hz, H-22), 3.66 (1H, dd, $J = 2.1, 4.3$ Hz, H-3), 5.10 (1H, d, $J = 4.2$ Hz, H-28), 5.35 (1H, dd, $J = 2.5, 5.7$ Hz, H-6), 7.47 (2H, dd, $J = 7.8, 5.6$ Hz, H-3', H-5'), 7.61 (1H, d, $J = 5.6$ Hz, H-4'), 8.09 (2H, d, $J = 7.8$ Hz, H-2', H-6'); ¹³C-NMR (CDCl₃, 125 MHz): 12.0 (CH₃-27), 12.2 (CH₃-26), 12.5 (CH₃-18), 12.9 (CH₃-29), 18.9 (CH₃-21), 19.6 (CH₃-19), 22.7 (C-25), 28.4 (C-23), 31.6 (C-2), 31.7 (C-7), 32.1 (C-15), 32.3 (C-16), 35.9 (C-20), 36.7 (C-10), 37.4 (C-1), 39.7 (C-11), 39.9 (C-12), 42.4 (C-4), 42.5 (C-13), 45.0 (C-14), 50.3 (C-9), 54.5 (C-8), 56.7 (C-17), 71.6

(C-3), 72.0 (C-22), 116.6 (C-28), 121.9 (C-6), 128.6 (3 ×, C-2', C-4' and C-6'), 130.3 (C-1'), 133.8 (2 ×, C-3' and C-5'), 140.8 (C-5), 146.1 (C-24), 170.9 (C-7').

3.4. *In vitro* antimalarial assay

3.4.1. Cultivation of *P. falciparum*

P. falciparum strain 3D7, which is resistant to chloroquine, was cultured in sealed flask at 37 °C, in a 3% O₂, 5% CO₂ and 91% N₂ atmosphere in RPMI 1640, 25 μM HEPES, PH 7.4, supplemented with heat inactivated 10% human serum and human erythrocytes to achieve a 2% hematocrit. Parasites were synchronized in the ring stage by serial treatment with 5% sorbitol (Lambros and Vanderberg 1979) and studied at 1% parasitemia.

Compounds were prepared as 20 mg/mL stock solutions in DMSO, diluted as needed for individual experiment and tested in triplicate. The stock solutions were diluted in supplemented RPMI 1640 medium so as to have, at most, 0.2% DMSO in the final reaction medium. An equal volume of 1% parasitemia, 4% haematocrit culture was there after added and gently mixed thoroughly. Negative controls contained equal concentration of DMSO. Positive control contained artemisinin. Cultures were incubated at 37 °C for 48 hours (1 parasite erythrocytic life cycle). Parasites at ring stage were there after fixed by replacing the serum medium by an equal volume of 1% formaldehyde in PBS. Aliquots (50 μL) of each culture were then added to 5 mL round-bottom polystyrenes tubes containing 0.5 mL 0.1% Triton X-100 and 1 nM YOYO nuclear dye (Molecular Probes) in PBS. Parasitemias of treated and control cultures were compared using a Becton-Dickinson FACSsort flow cytometer to count nucleated (parasitized) erythrocytes. Antiplasmodial examination was used 96 wells, each well filled by parasitemia culture 1%. About 50 μL of the compounds filled into the well with the following concentration 10⁻⁹ to 10⁻² μg/mL. These data were normalized to percent control activity and 50% inhibitory concentration (IC₅₀) calculated using Table probit.

Different concentration of the compounds were incubated at 37 °C with cultured 3D7 strain of *P. falciparum* parasites for 48 hours. Parasites were there after fixed and strained, and parasitemias of treated and control cultures were determined. Results are means, compared to untreated controls from 3 experiments. Error bars represent standard deviations of results.

4. Conclusions

A new antiplasmodial sterol, namely kaimanol (1), along with a known sterol, saringosterol (2), was isolated from Indonesian marine sponge, *Xestospongia* sp. Compounds 1 and 2 showed strong antiplasmodial activity against *P. falciparum* 3D7 strains. The presence of a benzoyl moiety in sterol structure can decrease antiplasmodial activity.

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