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A New Antiplasmodial Compound from the Papuan Marine Sponge *Xestospongia* sp.

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Abstract

A new antiplasmodial compound, 2-(3*H*-diazirine-3-yl)benzaldehyde (**1**), has been isolated from the Papuan marine sponge *Xestospongia* sp. The structure elucidation of compound **1** was determined by spectroscopic evidences including UV, IR, MS, 1D and 2D-NMR analysis. Compound **1** showed moderate antiplasmodial activity against *Plasmodium falciparum* with IC_{50} value of 1.08×10^{-6} µM.

Keywords: 2-(3*H*-diazirine-3-yl)benzaldehyde, *Plasmodium falciparum*, Sponge, *Xestospongia* sp.

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1. INTRODUCTION

In tropical countries, malaria is known as the most severe disease infected more than two billion people across the world (Bagavan *et al*., 2011; Poostchi *et al*., 2017). This disease is also responsible of the human death (Weiss *et al*., 2018), most of the death cases occurred in Africa, Asia, and other tropical countries (Snow *et al*., 2005; Nayyar *et al*., 2012; Kabaria *et al*., 2017).

Currently, Indonesia harbours twenty vectors malaria associating with four species of Malaria (Elyazar *et al*., 2011). In Indonesia, cases of malaria are estimated about ninety millions cases by 2011 where one people died per a hundred thousand cases (WHO, 2008). Most cases of malaria are reported in the eastern provinces of Indonesia (Papua and West Papua) (Nagesha *et al*., 2001; Douglas *et al*., 2017). In the region, malaria have infected seventy people per a hundred population, most of them are women and children (WHO, 2008).

It is estimated about 30% of antimalarial medicaments are obtained from nature herbs, including terrestrial plants and marine biota's (Sanon *et al*., 2013; Boampong *et al*., 2015). In marine drug exploration, marine sponges (*Xestopongia* sp. and *Haliclona* sp.) are intensively studied in recent decades, since its potential antiplasmodial and bacterial properties, in which dozen patents already obtained from this unique biota (Inbaneson and Ravikumar, 2012; Davis *et al*., 2012; Beesoo *et al*., 2017). Marine sponge of the genus *Xestospongia* is one of the world's potential antimalarial agents containing xestoquinone (Laurent *et al*., 2006; Nogueira and Lopes, 2011; Bottee *et al*., 2012).

In the present study, a new antiplasmodial compound obtained from the

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Papuan marine sponge is desribed, and exhibited ability against *Plasmodium falciparum*.

2. MATERIAL AND METHODS

General Experimental Procedure

The IR spectra were recorded on a SHIMADZU IR Prestige-21 in KBr. The mass spectra were recorded with a Waters Xevo QTOF MS. NMR spectra were recorded on a Bruker Topspin spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C using TMS as an internal standard. Column chromatography was conducted on silica gel 60. TLC plates were precoated with silica gel GF_{254} (Merck, 0.25 mm) and detection was achieved by spraying with 10% H_2SO_4 in EtOH, followed by heating and under UV light at wave length at 254 and 367 nm.

Sponge Collection and Cultured Parasites

The study was based on material Porifera genus *Xestospongia*, collected 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., (Lamarck, 1813), the species belongs to the *Xestospongia* (Order Haplosclerida: Family Petrosiidae). 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-V/2016, Catalogue: MS041.1-5). Subject of the study was the protozoan parasite *P. falciparum* strain 3D7 (chloroquine-sensitive) obtained from University of Tokyo and cultured by the Eijkman Institute for Molecular Biology in Jakarta.

Extraction and Isolation

The milled fresh of sponge *Xestospongia* sp. (38 kg) was extracted with EtOH (40 L) at room temperature. After removing solvent under the vacuum, viscous concentrated of EtOH extract (376 g) was first suspended in H_2O and then partitioned successively with *n*-hexane, EtOAc, and *n*-BuOH. Evaporation resulting in the crude extracts of *n*-hexane (10 g), EtOAc (11 g), and *n*-BuOH (30 g), respectively. The EtOAc was selected for fractionation due to uniqueness of this assay. The EtOAc extract (11 g) was fractionated by column chromatography on silica gel using a gradient *n*-hexane-EtOAc-MeOH to give eleven fractions (A–K). Fraction B (2.6 g) was subjected to column chromatography on silica gel, eluted *n*-hexane:acetone (8:2) to give twelve subfractions (B1-B12). Subfraction B11 (450 mg) was column chromatography on octa desyl silane (ODS), eluted with MeOH:H_2O (7:3) to yield five subfractions (B11A-B11E). Subfraction B11C (86 mg) was separated by preparative TLC on silica gel GF_{254}, eluted with *n*-hexane:acetone (7:3) to give **1** (12 mg).

Antiplasmodial Assay *in Vitro*

Strain 3D7 of *P. falciparum* was cultured and developed by Eijkman Institute for Molecular Biology in Jakarta. Antimalarial examination was used 96 wells, each well filled by parasitemia culture 1%. About 50 μL of the sponge fractions filled in to the well with the following concentration 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2} µg/mL. All wells were then stored in the Laminar Airflow cabinets, until all solvents are evaporated. Further, we added 50 μL of parasitemia red blood cell into the well then were incubated at 37ºC. After 48 h, slides preparation were stained using Giemsa 20% (WHO, 2008).

3. RESULT AND DISCUSSION

The ethanol extract from the milled fresh of sponge of *Xestospongia* sp. was concentrated and extracted successively with *n*-hexane, ethyl acetate, and *n*-butanol. The ethyl acetate fraction was separated by combination of column chromatography on silica gel G60, ODS, and preparative TLC on silica gel GF_{254} to afford compound **1**.

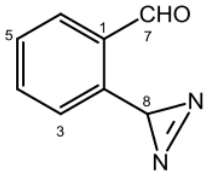

Figure 1. The Structure of Compound **1**

2-(3*H*-diazirine-3-yl)benzaldehyde (1)

Yellow oily; UV (MeOH) λ_{max} nm (log ε) 260 (3.74); IR (KBr) ν_{max}(cm^{-1}) 1725, 1620, 1510, and 820. ^{1}H-NMR (DMSO-d_6, 500

MHz) and ^{13}C-NMR (DMSO-d_6, 125 MHz), see **Table 1**. QTOF MS *m/z* 146.3106.

Table 1. NMR data for Compound **1** (500 MHz for ^{1}H and 125 MHz for ^{13}C in DMSO-d_6)

Position of Carbon	^{1}H NMR δ_H (Int., mult., *J*=Hz)	^{13}C NMR δc (mult.)
1	-	125.6 (*s*)
	-	120.2 (*s*)
3	7.50 (1H, *d*, 7.8)	113.0 (*d*)
4	7.27 (1H, *dd*, 7.1, 7.8)	124.5 (*d*)
5	7.23 (1H, *dd*, 6.8, 7.1)	123.0 (*d*)
6	8.21 (1H, *d*, 6.8)	122.3 (*d*)
7	10.03 (1H, *s*)	185.4 (*s*)
8	8.20 (1H, *s*)	138.1 (*d*)

Compound **1** was obtained as yellow oily. QTOF-MS of **1** showed *m/z* 146.3106, which in line to the molecular formula of $C_8H_6ON_2$ thus requiring seven degrees of unsaturation. UV spectra in MeOH showed λ_{max} nm (log ε) 260 (3.74), indicated the presence of benzene ring attached to electron with drawing group (Ursula and Stanley, 1987). The IR spectrum showed absorption peaks due to of aldehyde group (1720 cm^{-1}), C=C aromatic ring (1515 cm^{-1}), N=N group (1620 cm^{-1}), and disubstituted aromatic ring (1020 and 820 cm^{-1}). The ^{1}H-NMR spectrum of **1** showed the presence of an aldehyde proton at δ_H 10.03 (1H, *s*, H-7), aromatic protons at δ_H 7.50 (1H, *d*, *J*=7.8 Hz, H-3), 7.27 (1H, *dd*, *J*=7.8 Hz, H-4), 7.23 (1H, *dd*, *J*=6.8 and 7.1 Hz, H-5) and 8.21 (1H, *d*, *J*=6.8 Hz, H-6) as well as a deshielded aliphatic proton at δ_H 8.20 (1H, *s*, H-8). The ^{13}C NMR spectrum showed seven carbon resonances, which were classified by their chemical shift sand the DEPT spectra as one aldehyde (δ_C 185.4), two sp^2 quartenary carbons at δ_C 125.6 and 120.2, four sp^2 methine carbons at δ_C 113.0, 124.5, 123.0 and 122.3 as well as one sp^3 deshielded carbon at δ_C 138.1. These functionalities accounted for five out of the total seven degrees of unsaturation and the remaining two degrees of unsaturation were consistent with the diazirine-benzaldehyde derivative sructure (Sakurai *et al*., 2014).

A comparison of the NMR data of **1** with those of 2-methoxy-5-[3-(trifluoromethyl)-3H-diazirine-3-yl]-benzaldehyde (Sakurai *et al*., 2014), revealed that the structures of the two compounds are closely related, the main differences are the absence of methoxyl and trifluoromethyl group and the presence additional aromatic protons in **1.** The gross structure of **1** was deduced from the ^{1}H-^{1}H COSY and HMBC spectra (Fig. 2). The ^{1}H–^{1}H COSY spectrum of **1** showed correlations in C_1–C_2–C_3–C_4, supporting the presence of terasubstituted benzene ring and remaining the aldehyde group and diazirine ring. In the HMBC spectrum, an aldehyde proton at δ_H 10.03 was correlated to C-1 (δ_C 125.6) and C-2 (δ_C 120.2), indicating that an aldehyde group was located at C-1. A downfield proton resonance at δ_H 8.20 was correlated to C-2 (δ_C 120.2), whereas aromatic proton at δ_H 7.50 was correlated to a downfield resonance carbon at δ_C 138.1 (C-8), indicating that a diazirine ring was located at C-2. The aromatic proton at δ_H 7.23 was correlated to C-6 (δ_C 122.3) and C-4 (δ_C 124.5), whereas another aromatic proton at δ_H 7.50 was correlated to C-2 (δ_C 120.2) and C-4 (δ_C 124.5), supporting the presence of *ortho*-tetrasubtituted benzene ring. The relative stereochemistry of C-8 was determined by comparing with the similar compounds, 2-methoxy-5-[3-(trifluoromethyl)-3H-diazirin-il]-benzaldehyde (Sakurai *et al*., 2014) and 3,7-dimethyl-9-(4'-(3H-diazirinyl)-2',6'-dimethylphenyl)-2*E*,4*E*,6*E*,8*E*-nonatetrenal-1-3H (Ursula and Stanley, 1987), thus the relative stereochemistry of C-8 was *R*. Consequently, the structure of a new diazirine benzaldehyde (**1**), was established as 2-(3*H*-diazirine-3-yl)-benzaldehyde and was isolated from marine sponge for the first time.

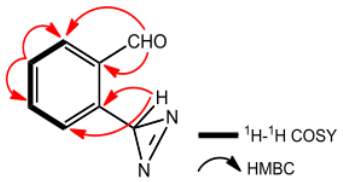

Figure 2. Selected ^{1}H-^{1}H-COSY and HMBC Correlations of **1**

2-(3*H*-diazirine-3-yl)benzaldehyde (**1**) showed moderate antiplasmodial activity against *P. falciparum* strain 3D7 *in vitro* with

IC_{50} value of 1.08×10^{-6} µM. The smallest value of IC_{50} indicates the effectiveness to inhibit a given *P. falciparum* (Baniecki *et al*., 2007; Koleala *et al*., 2015). A slight value IC_{50} indicates also that a compound has highly potential antimalarial agent. The obtained value of IC_{50} in the present work lower than dihydroartemisinin, commonly obtained by researchers (IC_{50} < 25 μg/mL) (Ringwald, 1999; Ravikumar *et al*., 2012), indicated that the compound 2-(3*H*-diazirine-3-yl)benzaldehyde as a promising sources against *Plasmodium*.

Currently, the marine sponges are pointed as one of the potential object of biomedical research due to its richness bioactive properties. In recent decades, marine sponges are known as marine drugs resources such as anticancer, antimicrobe, antivirus, and antimalaria (Sipkema *et al*., 2004; Kutluay *et al*., 2016). In the present study, we reported here the presence of a compound was recognised from derivate of benzaldehyde, which is highly capable of inhibiting *Plasmodium* (IC_{50} 1.08×10^{-6} µM). The obtained value of IC_{50} in the present work was far lowest compared to commonly IC_{50} obtained from the same type of biota, such as sponge of Northern New Guinea IC_{50} 34.6 μM (Murtihapsari *et al*., 2013), sponge of New Caledonia 3 µM. (Laurent *et al*., 2006; Nogueira and Lopes, 2011). Our finding of antiplasmodial activity is rangked as very active compound according to norms (Rasoanaivo *et al*., 1992; Ringwald, 1999; Ravikumar *et al*., 2012a; 2012b).

Malaria has been one of the most deadly disease in eastern part of Indonesia. In respond to the Indonesia and international program of reducing malarial effects, research on malaria was recently attracted much attention and has been supported by government. The eastern part of Indonesia was known as center of World Coral Triangle, a vast richness of marine landscape harboring potential marine drugs for Malaria. Recently (Tapilatu, 2015) summarized a list of newly compound from the marine life of eastern part of the country where antimalarial source remain poorly studied. We conclude that our finding exhibit a strongly signal antimalarial compound from Papuan sponge, which is need a continuation and comprehensive studied.

4. CONCLUSIONS

A new antiplasmodial compound, namely, 2-(3*H*-diazirine-3-yl)benzaldehyde (**1**) was isolated from the Papuan marine sponge *Xestospongia* sp. 2-(3*H*-diazirine-3-yl)benzaldehyde showed moderate antiplasmodial activity against *P. falciparum* with IC_{50} value of 1.08×10^{-6} µM.

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