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Research Article

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Synthesis pterocarpan compounds from *Erythrina crista-galli* L and their action towards *Plasmodium falciparum*

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ABSTRACT

*Synthesis of the naturally occurred 3-acetyl sandwicensin**(2)** and 2,7- dibromosandwicensin**(3)**was carried out by acetylation and bromination reaction, respectively. The pterocarpan synthesized in this study was andwicensin**(1)** isolated from stem bark of Erythrina crista galli L. Their structures were established on the basis of spectroscopic evidence. Compounds **1**–**3** were evaluated for their antimalarial properties against Plasmodium palcifarum, showing their IC_{50} were 1.83, 34.81 and 12.9 µg/mL, respectively.*

Keywords: 3-acetyl sandwicensin, 2,7-dibromosandwicensin, acetylation reaction, bromination reaction, antimalarial activity.

INTRODUCTION

Malaria remains world one of the most devastating human parasitic infection affecting more than 500 million people and causing about 1-3 million deaths each year [1]. *Plasmodium* is transmitted by anopheline mosquitoes and undergoes a complex sexual developmental cycle in the insect host. Recently, chloroquine and artemisinin have used as antimalarial drug and show resistance against *Plasmodium* parasites in Indonesia. *Erythrina* belongs to the family of *Leguminosae* and *Erythrina crista galli* L is one species of *Erythrina*. This plant has been shown to produce a number of pterocarpan and alkaloid compounds that showed activity as anticancer, antioxidant, and antimalarial. Sandwicensin is a mayor compound which has been isolated from *Erythrina crista galli*and its activity as antimalarial [2]. In continuation of these chemical investigations, we will continue research to synthesize mayor compounds that is sandwicensin with acetylation and bromination method. This paper discusses the structure elucidation of the two compounds synthesized from the reaction of acetylation and bromination and their antimalarial activity.

EXPERIMENTAL SECTION

Synthesis of pterocarpan derived from sandwicensin compounds produced from stem bark of *Erythrina crista galli* was carried out by acetylation and bromination reaction, respectively. In the acetylation synthetic route, 3 mg sandwicensin compound is added to 0.2 ml of pyridine with the addition of 0.2 ml of anhydride acetate. It was cooled to room temperature and poured over crushed ice. The separated solid was filtered, washed with distilled water, dried and it was crystallized with ether-methanol to form a 3-acetyl sandwicensin [3]. Bromination synthetic route, in the fume hood, 0.1 g or 0.2 ml of sandwicensin compound is added to 2 ml of carbon tetrachloride and 5%

solution of bromine in carbon tetrachloride is added drop wise, with shaking, and reflux for 5h until the bromine color persist and to form 2,7- dibromosandwicensin [4].

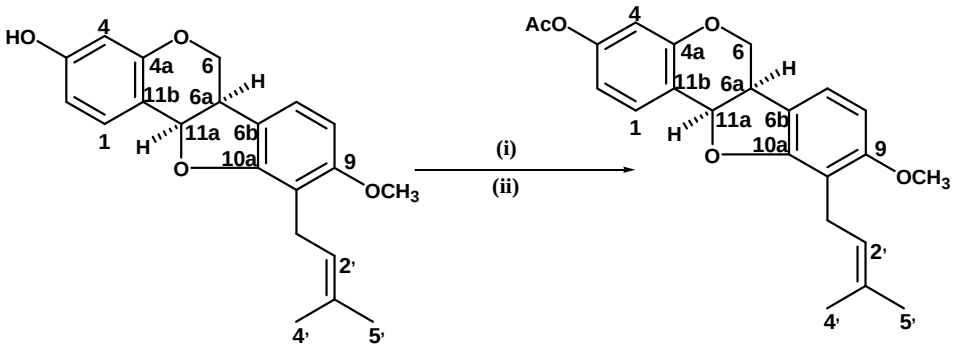
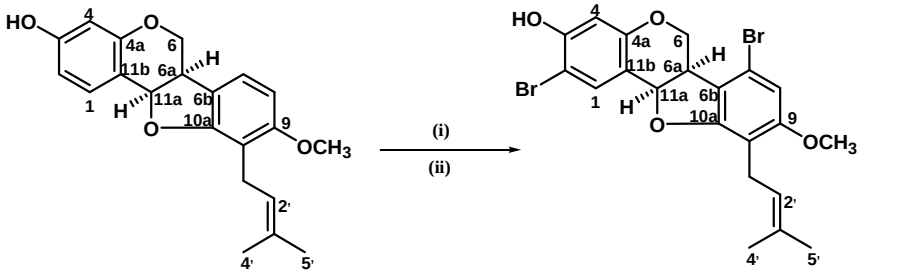


Figure-1.Preparation of compound 3-acetyl sandwicensin (2),colorless solid :(i) pyridine,anhydride acetate,temperature 37^{o}C; (ii) crystallized eter-metanol



Sandwicensin 2,7-Dibromo sandwicensin

Figure-2. Preparation of compound 2,7-dibromo sandwicensin (3), yellow solid: (i) CCl_4, 5% Br_2 in CCl_4; (ii) reflux 5h, bromine color persist

Sandwicensin**(1)**, yellow solid,1H NMR (500 MHz, $CDCl_3$) data, see Table-1; UV (MeOH) λmax nm (log ε) : 223 (4.60), 285 (3.84), and 287 nm (3.89).HR-ESI-mass spectra (m/z 339.1642 $[M+H]^+$, calcd. for $C_{21}H_{23}O_4$, 325.1440). 3-Acetyl sandwicensin**(2)**, colourless solid, 1H-NMR (500 MHz,$CDCl_3$) data, see Table-1;UV (MeOH) λmax nm (log ε) : 285 (3.90), and 289 nm (4,10).

2,7-Dibromo sandwicensin**(3)** ,yellow solid,1H-NMR (500 MHz, $CDCl_3$) data, see Table-1;UV (MeOH) λmax nm (log ε) : 229 (4.13), 286 (3.84), and 289 nm (3.86).

Antimalarial properties ofcompound**1-3** against *Plasmodium palcifarum* were obtained from the Institute of Tropical Diseases, Universitas Airlangga, Surabaya, Indonesia. In vitro antimalarial activity against *Plasmodium palcifarum* was carried out according to a modified method of Trager and Jensen using RPMI 1640medium with10% O+ serum [5]. The antimalarial activity of three phenolic compounds and chloroquine (positive control) were measured in triplicate. Fresh red blood cells were used as a negative control. The active compound was dissolved in DMSO and diluted with RPMI 1640 medium to prepare a series of concentration. Parasitaemia was evaluated after 48 by Giemsa stain and the average percentage suppression of parasitaemia was calculated by following equation [6,7]:

$$\%\ average\ suppression\ = \frac{100\ \times\ (\%\ average\ in\ control - \%\ average\ in\ active\ compound)}{\%\ average\ parasitemia\ in\ control}$$

The influence of the active compound on the growth of parasites were expressed by the 50% inhibitory concentrations (IC_{50}) which were determined using linier regression analysis.

RESULTS AND DISCUSSION

Sandwicensin is a mayor compound produced from stem bark *Erythrina crista galli* L [8]. Sandwicensin (**1**)was isolated as a yellow solid, and its UV spectrum exhibited absorption maxima λ_{maks}(nm) (log ε): 223 (4.60), 285 (3.84), and287 nm (3.89) a typical for a pterocarpan. From HR-ESI-mass spectra (m/z 339.1642 $[M+H]^+$, calcd. for $C_{21}H_{23}O_4$, 325.1440).The ^1H and ^{13}C NMR can be seen in Table 1. There is one methoxyl groups attached to the aromatic ring from compound **1** that showed proton signal at δ_H3.81 and the carbon signal at 55.9.The placement of a methoxy group in the C-3or C-9 confirmed by the HMQC and HMBC spectra. The HMBC spectrum shows a correlation between the proton signal at δ_H3.81with carbonoxyaril signal at δ_C 155.8. Furthermore, the correlation between aromatic proton signals at δ_H7.02 (*d*, 8.1, H-7)with oxyaril carbon signal at δ_C 155.8 indicated that the methoxyl group attached at C-9.

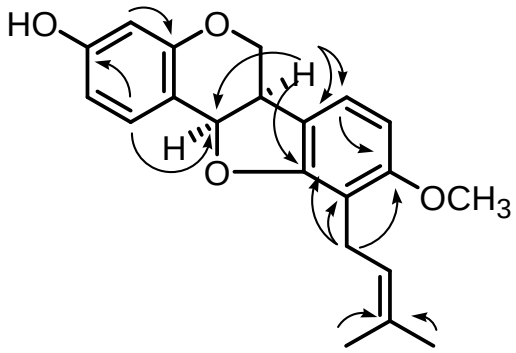
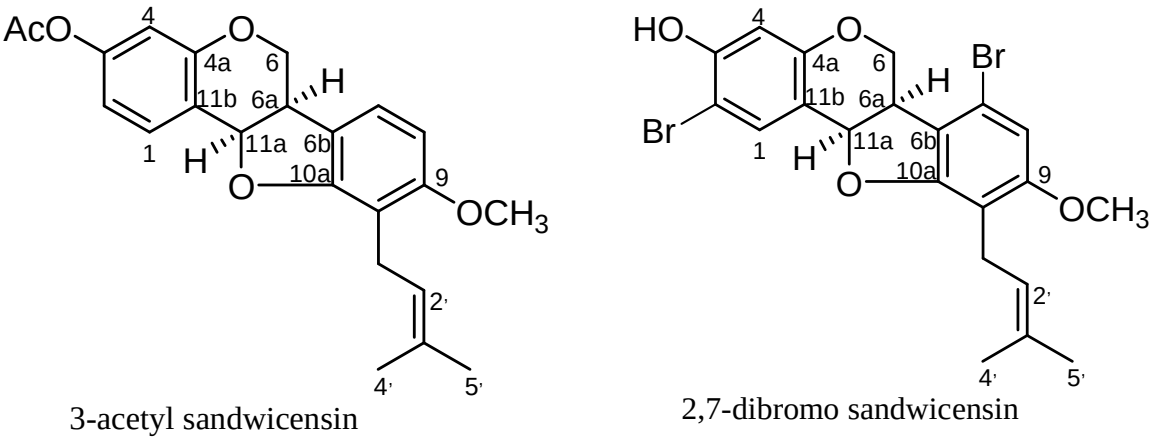


Figure 3.The significant HMBC correlations of 1

3-Acetyl sandwicensin**(2)** produced from synthesis sandwicensin (**1**) using acetylation methods. 3-Acetyl sandwicensin obtained as colourless solid, its UV spectrum exhibited absorption maxima λ_{maks}(nm) (log ε): 223 (4.60), 285 (3.84), and287 nm (3.89).

Based on ^{1}H-NMR proton spectrum showed four proton signal atδ_H 5.46 (1H, *d*, *J* = 6.7 Hz); 4.25 (1H, *t*, *J* = 10.8 Hz; 3.64 (1H, *dd*, *J* = 10.8 Hz); and 3.54 (1H, *m*)which is typical for pterocarpan structure.^{1}H-NMR spectrum of compound **1** shows two signals of aromatic unit, there are a pair of doublet signals *ortho* (*J* = 8.1 Hz) atδ_H7.01 dan 6.40 and the presence of three other aromatic proton signals with ABX system atδ_H7.54 (1H, *d*, *J* = 8.4 Hz); 6.78 (1H, *dd*, *J* = 8.4 and 2.4 Hz); and6.68 ppm (1H, *d*, *J* = 2.4 Hz). The presence of the methyl group δ_H1.56 at C-3 shows that acetyl bond to sandwicensin skeleton and compound **2** was identified 3-acetyl sandwicensin.

2,7-Dibromo sandwicensin**(3)** produced from synthesis sandwicensin (**1**)using bromination methods. 2,7-Dibromo sandwicensin isolated as yellow solid, its UV spectrum exhibited absorption maxima λ_{maks}(nm) (log ε): 229 (4.13), 286 (3.84), and 289 nm (3.86). Based on ^{1}H-NMR spectral data of compounds **3** shows similar pattern of the ^{1}H and ^{13}C chemical shifts of NMR with compound **2**. The difference with compound **3** is the addition of two bromide groups. Two proton singlets at δ_H7.59(1H, H-1) and 6.25 (1H, H-4) showed the presence of four substituents attached to the ring A and also shows that the presence of bromide group attached to the C-2. The presence of one proton singlets δ_H7.31 at H-8 and methoxy group at C-9 showed that the bromide group in the position at C-7. Based on 1D NMR data, compound **3** was identified 2,7-dibromo sandwicensin.



3-acetyl sandwicensin 2,7-dibromo sandwicensin

Figure 4.Synthesis of pterocarpan derived from sandwicensin

Table 1. NMR spectroscopic data of sandwicensin(1), 3-acetyl sandwicensin (2), and 2,7-dibromo sandwicensin(3) in $CDCl_3$

No.H	δ_H (mult, *J* Hz) Sandwicensin (1)	δ_H (mult, *J* Hz) 3-Acetyl sandwicensin (2)	δ_H (mult, *J* Hz) 2,7-Dibromo sandwicensin (3)
1	7.41 (*d*, 8.4)	7.54 (*d*, 8.4)	7.59 (*s*)
2	6.58 (*dd*, 8.4; 2.4)	6.78 (*dd*, 8.4; 2.4)	-
3	-	-	-
4	6.44 (*d*, 2.4)	6.68 (*d*, 2.4)	6.05 (*s*)
4a	-	-	-
6	4.23 (*t*, 10.9); 3.66 (*dd*,10.9; 5.1)	4.25 (*t*, 10.8); 3.64 (*dd*,10.8)	4.48 (*dd*;8); 3.26 (*dd*,8)
6a	3.52 (*m*)	3.54 (*m*)	3.53 (*m*)
6b	-	-	-
7	7.02 (*d*, 8.1)	7.01 (*d*, 8.1)	-
8	6.42 (*d*,8.1)	6.40 (*d*,8.1)	7.31 (*s*)
9	-	-	-
10	-	-	-
10a	-	-	-
11a	5.46 (*d*, 6.8)	5.46 (*d*, 6.7)	5.48(d; 7.4)
11b	-	-	-
1'	3.31 (*d*, 7.9)	3.26 (*d*, 6.4)	3.31 (*d*;8.6)
2'	5.26 (*t*, 7.2)	5.21 (*t*, 8.3)	5.54 (*d*;6.9)
3'	-	-	-
4'	1.78 (*s*)	1.74 (*s*)	1.57 (*s*)
5'	1.67 (*s*)	1.64 (*s*)	1.41 (*s*)
9-OCH_3	3.81 (*s*)	3.78 (*s*)	3.83 (*s*)
3-CH_3	-	1.56 (*s*)	-

Compound **1** isolated from the stem bark of *E.crista-galli* and synthesis compound **2-3** was assessed for their antimalarial activity against *Plasmodium falciparum*. The results are presented in **Table-3**.Compounds **1**–**3** were evaluated for their antimalarial properties against *Plasmodium palcifarum*, showing their IC_{50} were 1.83, 34.81, and 12.9 µg/mL, respectively (chloroquine as a positive control, IC_{50}1.02 µg/mL). These antimalarial data suggested that the compound **1-3** showed activity against *Plasmodium palcifarum*.

Table 2. ^{13}C-NMR spectroscopic data of sandwicensin(1), and 3-acetyl sandwicensin(2) in $CDCl_3$

No.C	δ_C (Sandwicensin)	δ_C (3-Acetyl sandwicensin)
1	132.3	132,2
2	109.9	110.6
3	157.5	158.4
4	103.1	103.1
4a	156.5	156.4
6	66.4	66.6
6a	39.9	40.0
6b	119.4	119.0
7	122.3	122.2
8	103.5	103.0
9	155.8	156.3
10	112.6	111.2
10a	158.5	158.6
11a	78.0	77.8
11b	113.3	113.4
1’	22.9	22.8
2’	121.6	121.7
3’	132.2	132.0
4’	17.4	18.4
5’	25.8	26.3
9-OCH_3	55.9	56.0
3-CH_3	-	21.3

Table 3. Antimalarial and DPPH scavenging assay of 1-3

Compound	Antimalarial IC_{50} (µg/mL)
Sandwicensin	1.83
3-Acetyl sandwicensin	34.81
2,7-Dibromo sandwicensin	12.9
Chloroquine	1.02

CONCLUSION

In summary, 3-Acetyl sandwicensin**(2)** and 2,7-dibromo sandwicensin**(3)**can be performed by acetylation and bromination of sandwicensin. Evaluation for their antimalarial properties against *Plasmodium palcifarum*, showing their IC_{50} were 34.81, and 12.9 µg/mL which activities are lower than sandwicensin with $IC_{50}$of 1.83.

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