

# ARTOPEDEN A, A NEW ANTIPLASMODIAL ISOPRENYLATED FLAVONE FROM ARTOCARPUS CHAMPEDEN

*by* Wiwied Ekasari

---

**Submission date:** 17-May-2021 12:06PM (UTC+0800)

**Submission ID:** 1587624860

**File name:** C-13 - Heterocycles\_naskah.pdf (57.07K)

**Word count:** 2215

**Character count:** 10464

HETEROCYCLES, Vol. 79, 2009, pp. 1121 - 1126. © The Japan Institute of Heterocyclic Chemistry  
Received, 17th October, 2008, Accepted, 18th December, 2008, Published online, 19th December, 2008.  
DOI: 10.3987/COM-08-S(D)72

## ARTOPEDEN A, A NEW ANTIPLASMODIAL ISOPRENYLATED FLAVONE FROM *ARTOCARPUS CHAMPEDEN*

Tutik Sri Wahyuni,<sup>a</sup> Wiwied Ekasari,<sup>a</sup> Aty Widyawaruyanti,<sup>a</sup> Yusuke Hirasawa,<sup>b</sup> Hiroshi Morita,<sup>b,\*</sup> and Noor Cholies Zaini<sup>a,\*</sup>

<sup>a</sup> Airlangga University, Jalan Dharmawangsa Dalam, Surabaya 60286, Indonesia

<sup>b</sup> Faculty of Pharmaceutical Sciences, Hoshi University, Shinagawa-ku, Tokyo 142-8501, Japan

**Abstract** – A new isoprenylated flavone, artopeden A (**1**) was isolated from the barks of *Artocarpus champeden* (Moraceae), and the structure was elucidated by NMR spectral analysis. Artopeden A (**1**) showed a potent antiplasmodial activity with an IC<sub>50</sub> of 0.045 µg/mL against *Plasmodium falciparum* 3D7.

### INTRODUCTION

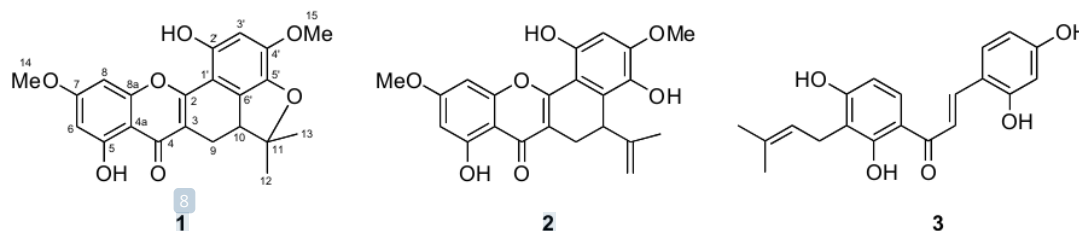
Malaria, which is caused by parasites of the genus *Plasmodium*, is a most serious infections in many tropical and subtropical regions.<sup>1</sup> Since the number of patients continues to rise mainly due to the emergence of widespread chloroquine-resistant and multiple-drug-resistant strains of malaria parasites, the discovery of new antimalarial drugs is urgently needed.<sup>2</sup>

*Artocarpus champeden* Spreng., belonging to the family Moraceae, is widely distributed throughout the tropical and subtropical regions of Southeast Asia. In Indonesia, this plant is commonly known as “Cempedak” and is traditionally used for treatment of fever, diarrhoea, and malaria.<sup>3</sup> Several isoprenyl flavonoids with cytotoxicity,<sup>4</sup> antimalarial activity,<sup>5</sup> and interaction with IgE and IgM,<sup>6</sup> have been isolated from *A. champeden*.<sup>7</sup>

As a part of our collaborative study, recent investigation of extracts from *Cassia siamea*,<sup>8</sup> *Peganum harmala*,<sup>9</sup> and *Chisocheton ceramicus*<sup>10</sup> resulted in the isolation of some new alkaloids and limonoids with antiplasmodial activity. In this paper, we report the isolation and structure elucidation of a new isoprenylated flavone, artopeden A (**1**) with an antiplasmodial activity from the barks of *Artocarpus champeden*.

---

<sup>†</sup>Dedicated to Dr. John Daly, National Institutes of Health scientist emeritus.



## RESULTS AND DISCUSSION

The dried stem bark of *A. champeden* was extracted successively with hexane,  $\text{CH}_2\text{Cl}_2$ , and MeOH.  $\text{CH}_2\text{Cl}_2$ -soluble materials were subjected to a vacuum silica gel column ( $\text{CHCl}_3$ -EtOAc-MeOH mixture as gradient mobile phase). Fractionation was continued by an open silica gel column chromatography with  $\text{CHCl}_3$ -EtOAc-MeOH mixture as gradient mobile phase. The active fraction was purified by preparative thin layer chromatography ( $\text{CH}_3\text{CN}$ -MeOH- $\text{H}_2\text{O}$ , 4:1:1 as mobile phase) followed by preparative thin layer chromatography ( $\text{CHCl}_3$ -MeOH, 19:1 as mobile phase) and an ODS column (MeOH/ $\text{H}_2\text{O}$  7:3  $\rightarrow$  1:0) to afford artopeden A (**1**, 0.000016%) together with artoindonesianin S (**2**, 0.00004%),<sup>11</sup> artoindonesianin E (12.0 mg: 0.00048%),<sup>5b</sup> artonin A (12.0 mg: 0.00048%),<sup>12</sup> and cycloheterophyllin (19.3 mg: 0.00077%).<sup>13</sup> MeOH-soluble materials were subjected to a silica gel column ( $\text{CHCl}_3$ -MeOH mixtures as mobile phase), followed by an ODS column (MeOH/ $\text{H}_2\text{O}$  3:2  $\rightarrow$  4:1) to give morachalcone A<sup>14</sup> (**3**, 0.00002%).

Artopeden A (**1**,  $[\alpha]_{\text{D}}^0$ ) showed the pseudomolecular ion peak at  $m/z$  397 ( $\text{M}+\text{H}^+$ ) in ESIMS, and the molecular formula,  $\text{C}_{22}\text{H}_{20}\text{O}_7$ , was established by HRTOFMS [ $m/z$  397.1268, ( $\text{M}+\text{H}^+$ )  $\Delta$  -1.9 mDa]. IR spectrum suggested the presence of OH ( $3450\text{ cm}^{-1}$ ) and conjugated carbonyl ( $1640\text{ cm}^{-1}$ ) groups. The  $^{13}\text{C}$  NMR (Table 1) spectrum of **1** disclosed twenty-two carbon signals due to one conjugated carbonyl ( $\delta_{\text{C}}$  179.7), eleven  $sp^2$  quaternary carbons ( $\delta_{\text{C}}$  104.4, 104.5, 112.0, 133.4, 135.3, 148.3, 150.6, 156.2, 160.2, 161.3, and 164.6), one  $sp^3$  quaternary carbon ( $\delta_{\text{C}}$  93.7), three  $sp^2$  methines ( $\delta_{\text{C}}$  93.1, 98.8, and 102.8), one  $sp^3$  methine ( $\delta_{\text{C}}$  47.2), one  $sp^3$  methylene ( $\delta_{\text{C}}$  20.4), two methyls ( $\delta_{\text{C}}$  22.8 and 28.3), and two methoxy groups ( $\delta_{\text{C}}$  56.3 and 56.6).  $^1\text{H}$  and  $^{13}\text{C}$  signals for **1** were assigned by detailed analysis of the 2D NMR spectra.

The  $^1\text{H}$  NMR spectrum of **1** showed the signals for the following protons: three aromatic protons [ $\delta_{\text{H}}$  6.33 (1H, d, 2.2), 6.72 (1H, d, 2.2), and 6.45 (1H, s)], two methyl protons [ $\delta_{\text{H}}$  1.36 (3H, s) and 1.68 (3H, s)], ABX type protons [ $\delta_{\text{H}}$  2.40 (1H, dd, 15.2, 15.2), 3.24 (1H, dd, 15.2, 7.1), and 3.44 (1H, dd, 15.2, 7.1)], and two methoxy protons [ $\delta_{\text{H}}$  3.89 (3H, s) and 3.92 (3H, s)]. The chemical shifts and coupling patterns of **1** were similar to those of artonin L,<sup>15</sup> which has already been isolated from *Artocarpus heterophyllus*.<sup>13</sup> The chemical shifts of all the carbons were similar to those of the relevant carbons of artonin L with the exception of the shifts of the four carbons (C-2', 3', 4', and 5') (Table 1). In the case

of artonin L, the presence of methoxy group at C-2' caused higher field shift ( $\Delta +0.15$  ppm) of the proton at the C-8 position when compared to that of hydroxy group (artoinin L: 6.51 ppm at C-8; artopeden A: 6.72 ppm at C-8).<sup>15</sup> Thus, the gross structure of artopeden A was assigned as **1** with a methoxy group at C-4', which was an isomer of artonin L. Since artopeden A (**1**) did not show the optical rotation, **1** might be biogenetically derived from artoindonesianin S (**2**) through the oxidative coupling, which was the same case as in artonins A and B.<sup>12</sup>

Malaria is the most prevalent parasitic disease. According to World Health Organization (WHO), as many as 300–500 million people suffer from malaria. *Artocarpus champeden* has been traditionally used for treatment of malaria,<sup>3</sup> and some isoprenylated flavonoids and stilbenes from *Artocarpus* species have already been reported on inhibitory activity against some parasites.<sup>5</sup> Artopeden A (**1**) showed a potent *in vitro* antiplasmodial activity against *Plasmodium falciparum* 3D7 (artopeden A: IC<sub>50</sub> 0.045  $\mu\text{g/ml}$ ; chloroquine: IC<sub>50</sub> 0.0061  $\mu\text{g/ml}$ ).

Table 1. <sup>1</sup>H and <sup>13</sup>C NMR Data [ $\delta_{\text{H}}$  (J, Hz) and  $\delta_{\text{C}}$ ] of artopeden A (**1**) in acetone-*d*<sub>6</sub> at 300K

Position	$\delta_{\text{H}}$	$\delta_{\text{C}}$
2		161.3
3		112.0
4		179.7
4a		104.5
5		160.2
6	6.33 (1H, d, 2.2)	98.8
7		164.6
8	6.72 (1H, d, 2.2)	93.1
8a		156.2
1'		104.4
2'		150.6
3'	6.45 (1H, s)	102.8
4'		148.3
5'		135.3
6'		133.4
9a	2.40 (1H, dd, 15.2, 15.2)	20.4
9b	3.24 (1H, dd, 15.2, 7.1)	
10	3.44 (1H, dd, 15.2, 7.1)	47.2
11		93.7
12	1.68 (3H, s)	28.3
13	1.36 (3H, s)	22.8
14	3.89 (3H, s)	56.3
15	3.92 (3H, s)	56.6

## EXPERIMENTAL

**General Experimental Procedures.** <sup>4</sup> <sup>1</sup>H and 2D NMR spectra were recorded on a Bruker AV 400 spectrometer and chemical shifts were reported using residual acetone-*d*<sub>6</sub> ( $\delta_{\text{H}}$  2.06 and  $\delta_{\text{C}}$  29.8) as internal standards. Standard pulse sequences were employed for the 2D NMR experiments. Mass spectra were obtained with a Micromass LCT spectrometer.

**Plant Material.** Dried stem bark of *A. champeden* was collected from "Mak Balim" village, Sorong, Irian Jaya, Indonesia, in August 2004. A voucher specimen was identified by Dr. Eko Baroto Walujo at the Herbarium Bogoriense, LIPI - Research center For Biology, Bogor, Indonesia, and it was deposited at the herbarium of Bogor Botanical Garden.

**Extraction and Isolation.** <sup>9</sup> Dried powder of *A. champeden* stem bark (2.5 kg) was macerated successively in hexane, CH<sub>2</sub>Cl<sub>2</sub>, and MeOH. The CH<sub>2</sub>Cl<sub>2</sub> extract (32.0 g) was fractionated by a vacuum silica gel column chromatography with CHCl<sub>3</sub>-EtOAc-MeOH mixtures as mobile phases. Fractionation was continued by an open silica gel column chromatography with CHCl<sub>3</sub>-EtOAc-MeOH mixture as gradient mobile phase. The active fraction was purified by preparative thin layer chromatography (CH<sub>3</sub>CN-MeOH-H<sub>2</sub>O, 4:1:1 as mobile phase) followed by preparative thin layer chromatography (CHCl<sub>3</sub>-MeOH, 19:1 as mobile phase) and an ODS column (MeOH/H<sub>2</sub>O 7:3 → 1:0) to afford artopeden A (**1**, 0.4 mg: 0.000016%) together with artoindonesianin S (**2**, 1.0 mg: 0.00004%), artoindonesianin E (12.0 mg: 0.00048%), <sup>5b</sup> artontonin A (12.0 mg: 0.00048%), <sup>12</sup> and cycloheterophyllin (19.3 mg: 0.00077%). <sup>13</sup> The MeOH fraction was further chromatographed on silica gel column chromatography, with CHCl<sub>3</sub>-MeOH mixtures as mobile phases, followed by repeated purification by reversed-phase column chromatography with MeOH-H<sub>2</sub>O mixture as mobile phases to yield morachalcone A<sup>14</sup> (**3**, 0.5 mg: 0.00002%).

**Artopeden A (1):** yellow powder;  $[\alpha]_{\text{D}}^{23}$  0 (*c* 1.0, MeOH); IR (KBr)  $\nu_{\text{max}}$  3450, 2940, and 1640 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{\text{max}}$  370 (log  $\epsilon$  4.3) and 205 (log  $\epsilon$  4.3) nm; <sup>1</sup>H and <sup>13</sup>C NMR data (Table 1); ESIMS *m/z* 397 (M+H)<sup>+</sup>; HRTOFMS *m/z* 397.1268 [(M+H)<sup>+</sup>, calcd for C<sub>22</sub>H<sub>21</sub>O<sub>7</sub>, 397.1287].

**Antiplasmodial Assay.** Human malaria parasites were cultured according to the method by W. Trager *et al.*<sup>16</sup> The antimalarial activity of the isolated compounds was determined by the procedure described by Budimulja *et al.*<sup>17</sup> In brief, Stock solution of the samples were prepared in DMSO (final DMSO concentrations of < 0.5%) and were diluted to the required concentration with complete medium (RPMI 1640 supplemented with 10% human plasma, 25 mM HEPES and 25 mM NaHCO<sub>3</sub>) until the final concentration of samples at well culture plate were : 10; 1; 0.1; 0.01; 0.001  $\mu\text{g/mL}$ . The malarial parasite *P. falciparum* 3D7 clone was propagated in a 24-well culture plate in the presence of a wide range of concentrations of each compound. The growth of the parasite was monitored by making a blood smear fixed with MeOH and stained with Geimsa solution. The antimalarial activity of each

compound was expressed as an IC<sub>50</sub> value, defined as the concentration of the compound causing 50% inhibition of parasite growth relative to an untreated control.

The percentage of growth inhibition was expressed according to following equation : Growth inhibition % = 100 - [(test parasitaemia/control parasitemia) × 100. Chloroquine: IC<sub>50</sub> = 0.0061 µg/mL.

#### ACKNOWLEDGMENTS

We acknowledge the financial support provided by Assessment Service Unit, Faculty of Pharmacy, Airlangga University. This work was also supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and The Open Research Center Project.

#### REFERENCES

1. J. Wiesner, R. Ortmann, H. Jomaa, and M. Schlitzer, *Angew. Chem. Int. Ed.*, 2003, **42**, 5274.
2. (a) M. H. Gelb and W. G. Hol, *Science*, 2002, **297**, 343; (b) P. A. G. N. De Smet, *Drugs*, 1997, **54**, 801.
3. S. A. Achmad, *Bull. Soc. Nat. Prod. Chem. (Indonesia)*, 2004, **4**, 35.
4. E. H. Hakim, A. Fahriyati, M. S. Kau, S. A. Achmad, L. Makmur, E. L. Ghisalberty, and T. Nomura, *J. Nat. Prod.*, 1999, **62**, 613.
5. (a) C. Boonlaksiri, W. Oonant, P. Kongsaree, P. Kittakooop, M. Tanticharoen, and Y. Thebtharanonth, *Phytochemistry*, 2000, **54**, 415; (b) A. Widyawaruyanti, Subehan, S. K. Kalauni, S. Awale, M. Nindatu, N. C. Zaini, D. Syafruddin, P. B. S. Asih, Y. Tezuka, and S. Kadota, *J. Nat. Med.*, 2007, **61**, 410.
6. S. A. Achmad, E. H. Hakim, L. D. Juliawaty, L. Makmur, Suyatno, N. Aimi, and E. L. Ghisalberty, *J. Nat. Prod.*, 1996, **59**, 878.
7. Y. M. Syah, L. D. Juliawaty, S. A. Achmad, E. H. Hakim, and E. L. Ghisalberty, *J. Nat. Med.*, 2007, **60**, 308.
8. (a) H. Morita, S. Oshimi, Y. Hirasawa, K. Koyama, T. Honda, W. Ekasari, G. Indrayanto, and N. C. Zaini, *Org. Lett.*, 2007, **9**, 3691; (b) S. Oshimi, Y. Tomizawa, Y. Hirasawa, T. Honda, W. Ekasari, A. Widyawaruyanti, M. Rudyanto, G. Indrayanto, N. C. Zaini, and H. Morita, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3761.
9. A. Astulla, K. Zaima, Y. Matsuno, Y. Hirasawa, W. Ekasari, A. Widyawaruyanti, N. C. Zaini, and H. Morita, *J. Nat. Med.*, 2008, **62**, 470.
10. K. Mohamad, Y. Hirasawa, M. Litaudon, K. Awang, A. H. A. Hadi, K. Takeya, W. Ekasari, A. Widyawaruyanti, N. C. Zaini, and H. Morita, *Bioorg. Med. Chem.*, in press.

11. Y. M. Syah, S. A. Achmad, E. L. Ghisalberty, E. H. Hakim, L. Makmur, and D. Mujahidin, *Phytochemistry*, 2002, **61**, 949.
12. Y. Hano, M. Aida, M. Shiina, T. Nomura, T. Kawai, H. Ohe, and K. Kagei, *Heterocycles*, 1989, **29**, 1447.
13. B. L. Wei, J. R. Weng, P. H. Chiu, C. F. Hung, J. P. Wang, and C. N. Lin, *J. Agric. Food Chem.*, 2005, **53**, 3867.
14. Y. Hano, S. Suzuki, T. Nomura, and S. Ueda, *Heterocycles*, 1989, **29**, 807.
15. M. Aida, K. Shinomiya, Y. Hano, and T. Nomura, *Heterocycles*, 1993, **36**, 575.
16. W. Trager and J. B. Jensen, *Science*, 1976, **193**, 673.
17. A. S. Budimulja, Syafruddin, P. Tapchaisri, P. Wilairat, and S. Marzuki, *Mol. Biochem. Parasitol.*, 1997, **84**, 137.

# ARTOPEDEN A, A NEW ANTIPLASMODIAL ISOPRENYLATED FLAVONE FROM ARTOCARPUS CHAMPEDEN

## ORIGINALITY REPORT

15%

SIMILARITY INDEX

9%

INTERNET SOURCES

12%

PUBLICATIONS

0%

STUDENT PAPERS

## PRIMARY SOURCES

- |   |  |    |
|---|--|----|
| 1 | <a href="http://www.thieme-connect.com">www.thieme-connect.com</a><br>Internet Source  | 1% |
| 2 | <a href="http://protocolexchange.researchsquare.com">protocolexchange.researchsquare.com</a><br>Internet Source  | 1% |
| 3 | Y.-B. Liu. "Two eudesmane sesquiterpenes from <i>Laggera pterodonta</i> ", <i>Journal of Asian Natural Products Research</i> , 6/1/2006<br>Publication | 1% |
| 4 | <a href="http://pubs.rsc.org">pubs.rsc.org</a><br>Internet Source  | 1% |
| 5 | <a href="http://bmccomplementmedtherapies.biomedcentral.com">bmccomplementmedtherapies.biomedcentral.com</a><br>Internet Source                        | 1% |
| 6 | Adebayo, J.O.. "Potential antimalarials from Nigerian plants: A review", <i>Journal of Ethnopharmacology</i> , 20110127<br>Publication                 | 1% |
| 7 | Liu, Qi-Bing, Ling Huang, Li Zhang, Qiang Liu, Qiao-Qin Xu, Xian-Jing Qin, Xing-Yue Fang, and Yu Zeng. "Two new cassane-type diterpenes                | 1% |



from the seeds of *Caesalpinia crista*", *Journal of Asian Natural Products Research*, 2015.

Publication

---

8

Nunuk H Soekamto, Sjamsul A Achmad, Emilio L Ghisalberty, Euis H Hakim, Yana M Syah. "Artoindonesianins X and Y, two isoprenylated 2-arylbenzofurans, from *Artocarpus fretessi* (Moraceae)", *Phytochemistry*, 2003

Publication

---

9

Yana M Syah, Sjamsul A Achmad, Emilio L Ghisalberty, Euis H Hakim, Lukman Makmur, Didin Mujahidin. "Artoindonesianins Q–T, four isoprenylated flavones from *Artocarpus champeden* Spreng. (Moraceae)", *Phytochemistry*, 2002

Publication

---

10

Yana M. Syah, Sjamsul A. Achmad, Emilio L. Ghisalberty, Euis H. Hakim, Didin Mujahidin. "Two new cytotoxic isoprenylated flavones, artoindonesianins U and V, from the heartwood of *Artocarpus champeden*", *Fitoterapia*, 2004

Publication

---

11

Sabine Van Miert, Steven Hostyn, Bert U. W. Maes, Kanyanga Cimanga et al. "Isonocryptolepine, a Synthetic Indoloquinoline Alkaloid, as an Antiplasmodial

1 %

1 %

1 %

1 %

Lead Compound", Journal of Natural Products,  
2005

Publication

12

Ting Zhang. "Two new eudesmanolides from  
*Inula racemosa*", Journal of Asian Natural  
Products Research, 09/2010

Publication

1 %

13

[mafiadoc.com](http://mafiadoc.com)

Internet Source

1 %

14

[www.icuc-iwmi.org](http://www.icuc-iwmi.org)

Internet Source

1 %

15

Sarfraz Khan Marwat, Fazal ur Rehman.  
"Medicinal and Pharmacological Potential of  
*Harmala* (*Peganum harmala* L.) Seeds",  
Elsevier BV, 2011

Publication

<1 %

16

[www.hindawi.com](http://www.hindawi.com)

Internet Source

<1 %

17

Minoru Ishikura, Koji Yamada, Takumi Abe.  
"Simple indole alkaloids and those with a  
nonrearranged monoterpenoid unit", Natural  
Product Reports, 2010

Publication

<1 %

18

Srinivas Gadthula, Chung K. Chu, Raymond F.  
Schinazi. " Synthesis and Anti-HIV Activity of -  
D-3'-Azido-2',3'-unsaturated Nucleosides and -  
D-3'-Azido-3'-deoxyribofuranosyl nucleosides ",

<1 %

# Nucleosides, Nucleotides and Nucleic Acids, 2005

Publication

---

19

Xue-Shi Huang. "A novel steroid from  
Tylophora atrofoliculata Metc.", Journal of  
Asian Natural Products Research, 1/1/2002

Publication

---

<1 %

20

[kclpure.kcl.ac.uk](http://kclpure.kcl.ac.uk)

Internet Source

---

<1 %

---

Exclude quotes      Off

Exclude matches      Off

Exclude bibliography      On

# ARTOPEDEN A, A NEW ANTIPLASMODIAL ISOPRENYLATED FLAVONE FROM ARTOCARPUS CHAMPEDEN

---

## GRADEMARK REPORT

---

FINAL GRADE

**/0**

GENERAL COMMENTS

**Instructor**

---

PAGE 1

---

PAGE 2

---

PAGE 3

---

PAGE 4

---

PAGE 5

---

PAGE 6

---