VLADINOL F, NEOLIGNAN COMPOUND FROM THE STEM BARK OF *Dryobalanops oblongifolia* (DIPTEROCARPACEAE) AND ANTIPLASMODIAL ACTIVITY

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ABSTRACT

Dryobalanops oblongifolia known as kayu kapur is a plant member of Dipterocarpaceae family. A neolignan, vladinol F, was successfully isolated from the dissolved fraction in acetone-ether of *Dryobalanops oblongifolia* stem bark. The chemical structure's determination was done based on an analysis of UV-Vis, NMR, and MS spectra and a comparison with the reference. *In vitro* test of this compound against *Plasmodium falciparum* 3D7 showed that IC₅₀ value was 3.51 µg/mL.

Keywords: *Dryobalanops oblongifolia*, Neolignan, Vladinol F, Antiplasmodial Activity, *Plasmodium falciparum*
RASĀYAN J. Chem., Vol. 14, No.1, 2021

INTRODUCTION

Various researches to find new drug candidates have been carried out.¹⁻³ Malaria is a parasitic infectious disease which causes millions of deaths every year. Besides that, the resistance of *P. falciparum* to nearly all available antimalarial drugs are increasing today.⁴ Thus, the new antimalarial drugs are urgently needed that will be used to prevent the spread of the infection and to cure infected patients. *Dryobalanops oblongifolia* is a species of the *Dryobalanops* genus belonging to the Dipterocarpaceae family. *Dryobalanops* is called Kayu Kapur by the local community^{5,6} and is recognized as a source of oligostilbene agents.⁷⁻¹⁰ A previously isolated constituent from *D. oblongifolia* reported that dimerstilbene, (-) ampelopsin F, had a potential activity as antiplasmodium.¹¹

In continuation of our research program on biologically active compounds from plants, we investigated this plant's antiplasmodial constituent. From this research, we have isolated vladinol F from the acetone extract of *D. oblongifolia* stem bark.

EXPERIMENTAL

Material and Methods

The stem bark of *D. oblongifolia* was gathered from Gunung Mali, Tempunak, Sintang, West Kalimantan in 2012. The plant was identified at the Biological Research Center, LIPI, Bogor, Indonesia, and the specimen's voucher was stored at the herbarium.

General Procedure

Using acetone, as many as 5 kg of *D. oblongifolia* stem bark powder was macerated twice at room temperature and then concentrated by vacuum evaporator. The acetone extract was divided into two fractions, that were soluble or insoluble in acetone – ether. By vacuum liquid chromatography (VLC) (*n*-hexane-EtOAc, rising polarity), 48 g dissolved part in acetone-ether was fractionated to yield fractions A-D. 1.2 g of fraction D was repeatedly GCC separated using *n*-heksane – EtOAc 5:5 – EtOAc 100% to give subfractions D1 - D3. Subfraction D3 (50 mg), on repeated separation and

purification using radial chromatography (gradient system of CHCl_3 – MeOH), acquired vladinol F (10 mg) (Fig.-1).

Detection Method

The elucidation structure of the vladinol F molecule using UV-Vis, ^1H and ^{13}C NMR and 2D NMR spectroscopy. ESI-MS spectrometer was used to record the molecular mass of this compound.

RESULTS AND DISCUSSION

Vladinol F, a colorless amorphous solid, mp. $105^0 - 107^0$; UV λ_{max} (MeOH): 216, 230, dan 284nm. ESI-MS: m/z $[\text{M}-\text{H}]^-$ 359,2 (Fig.-2, supplementary data). ^1H -NMR (methanol- d_4 , 500 MHz) (Fig.-1, supplementary data), δ_{H} (ppm): 1.87 (2H, *m*, H-8a); 2.63 (2H, *t*, H-7a); 3.46 (1H, *q*, H-8); 3.57 (2H, *t*, H-9a); 3.75 (2H, *dd* & *dd*, H-9); 3.81 (3H, *s*); 3.85 (3H, *s*); 6.72 (1H, *s*, H-2a); 6.73 (1H, *s*, H-6a); 6.76 (1H, *d*, H-3); 6.82 (1H, *dd*, H-2); 6.95 (1H, *d*, H-6). ^{13}C -NMR (methanol- d_4 , 125 MHz) (Fig.-3, Supplementary data), δ_{C} (ppm): 32.9 (C-7a); 35.8 (C-8a); 55.5 (C-8); 56.4 (C5a-OCH₃); 56.8 (C5-OCH₃); 62.2 (C-9a); 65.0 (C-9); 88.9 (C-7); 110.6 (C-6); 129.9 (C-3a); 114.2 (C-6a); 115.9 (C-3); 117.9 (C-2a); 119.7 (C-2); 134.8 (C-1); 136.9 (C-1a); 145.2 (C-5a); 147.5 (C-4a); 147.6 (C-4); 149.1 (C-5).

Vladinol F was obtained as a colorless amorphous solid having a melting point of $105^0 - 107^0$. Its molecular formula was determined as $\text{C}_{20}\text{H}_{24}\text{O}_6$ by ESI-MS ($[\text{M}-\text{H}]^-$ ion at m/z 359.2). The UV (216, 230, and 284 nm) spectra of this compound were typical for a phenolic chromophore. The ^{13}C -NMR (Nuclear Magnetic Resonance) (Table-1) and DEPT (Distortion less Enhancement by Polarization Transverse) (90, 135) spectra of the isolated compound revealed 20 carbon signals including two aromatic rings (δ_{C} 110.6-149.1), one oxygenated methine group (δ_{C} 88.9), one methine group (δ_{C} 55.5), two methylene groups (δ_{C} 32.9, 35.8), two oxygenated methylene groups (δ_{C} 62.2, 65.0), and two methoxy groups (δ_{C} 56.4, 56.8). The ^1H -NMR spectra indicated five protons of two aromatic regions, one was at δ_{H} 6.82 (1H, *dd*, $J=8.1$, 1.9, H-2), δ_{H} 6.76 (1H, *d*, $J=8.1$, H-3), δ_{H} 6.95 (1H, *d*, $J=1.9$, H-6), and another was δ_{H} 6.72 (1H, *s*, H-2a) and δ_{H} 6.73 (1H, *s*, H-6a). Two singlet signals of methoxy group were at δ_{H} 3.81(3H) and δ_{H} 3.85 (3H). Furthermore, in the ^1H -NMR spectra showed a structure of propanol side chain at δ_{H} 2.63 (2H, *t*, $J=6.5$, H-7a), δ_{H} 1.87 (2H, *m*, H-8a), δ_{H} 3.57 (2H, *t*, $J=5.4$, H-9a). Four hydrogen proton signals at δ_{H} 5.49 (1H, *d*, $J=6.3$, H-7), δ_{H} 3.46 (1H, *q*, H-8) δ_{H} 3.75 (1H, *dd*, $J=6.0$, 9.2, H-9'), and δ_{H} 3.83 (1H, *dd*, $J=5.6$, 9.6, H-9'') were a -CH-CH-CH₂- a structural unit which formed a dihydrofuran ring. The HMBC spectrum of this compound showed correlations between H-7/C-4a, H-7/C-3a, H-7/C-2, H-7/C-6, H-2/C-7, H-6/C-1, H-6/C-7, and H-6a/C-4a. These correlations indicated that dihydrofuran ring fused at C-3a and C-4a of the aromatic ring and a phenyl group was located at C-7 of dihydrofuran ring. Long-range couplings determined the placement propanol group at position C-1a of the aromatic ring in the HMBC spectrum between H-2a/C-7a and H-8a/C-1a. Based on the spectroscopic analysis, the isolated compound was established as vladinol F (Fig.-1), 7-phenyldihydrobenzofuranpropanol-type neolignan.^{12,13} We compared it with the previously reported Vladinol F (see Table-1) to validate the isolated compound.

Furthermore, the isolated compound was checked out as antiplasmodial. Methods previously described by Widyawaruyanti determined the antiplasmodial activity of the isolated compound.¹⁴ The samples were dissolved in DMSO and kept at -20°C until use. The parasite *P. falciparum* (3D7) clone was propagated in a 24-well culture plate in the presence of 100, 10, 1, 0.1 and 0.01 $\mu\text{g/ml}$ range of concentrations of the sample. Parasitaemia was monitored over 48 hours by making a blood smear fixed with MeOH and stained with Geimsa (Merck). The antiplasmodial activity test of the vladinol F toward *P. falciparum* showed the IC_{50} value of 3.51 $\mu\text{g/ml}$. This result showed that vladinol F was good as an antiplasmodial agent.¹⁵

Fig.-1: (1a) Structure and (1b) HMBC Correlations ($^1\text{H} \rightleftharpoons ^{13}\text{C}$) of the isolated compound

Table-1: ^1H -NMR (500 Mhz) and ^{13}C -NMR (125 MHz) Spectral Data of Isolated Compound in methanol- d_4 (Figure 3 & 4, supplementary data) and Vladinol F (Isao Kouno, 1993)¹²

C	Isolated Compound			Vladinol F (Isao Kouno, 1993) ⁹	
	δ_{H} (ppm) (multiplet, J in Hz)	δ_{C} (ppm)	HMBC ($^1\text{H} \rightleftharpoons ^{13}\text{C}$)	δ_{H} (ppm) (multiplet, J in Hz)	δ_{C} (ppm)
1	-	134.8	-	-	137.9
2	6.82 (<i>dd</i> , 8.1 & 1.9)	119.7	C-4, C-6, C-7	6.93 (<i>dd</i> , 8.1 & 1.8)	119.4
3	6.76 (<i>d</i> , 8.1)	115.9	C-1, C-4, C-5	7.06 (<i>d</i> , 8.1)	118.9
4	-	147.6	-	-	148.5
5	-	149.1	-	-	152.1
6	6.95 (<i>d</i> , 1.9)	110.6	C-1, C-2, C-4, C-5, C-7	7.03 (<i>d</i> , 1.8)	111.3
7	5.49 (<i>d</i> , 6.3)	88.9	C-2, C-6, C-8, C-3a, C-4a	5.5 (<i>d</i> , 5.9)	88.6
8	3.46 (<i>brd q</i>)	55.5	-	3.46 (<i>dd</i> , 12.5 & 5.5)	55.6
9	3.75 & 3.83 (<i>dd</i> & <i>dd</i>)	65.0	C-7, C-8	3.73 & 3.84 (<i>m</i>)	65.1
1a	-	136.9	-	-	137.0
2a	6.72 (<i>s</i>)	117.9	C-6a, C-7a	6.72 (<i>s</i>)	118.0
3a	-	129.9	-	-	129.7
4a	-	147.5	-	-	147.5
5a	-	145.2	-	-	145.3
6a	6.73 (<i>s</i>)	114.3	C-2a, C-4a, C-5a	6.73 (<i>s</i>)	114.3
7a	2.63 (<i>t</i>)	32.9	C-8a, C-9a	2.62 (<i>t</i> , 7.7)	32.9
8a	1.87 (<i>p</i>)	35.8	C-1a, C-7a, C-9a	1.82 (<i>m</i>)	35.8
9a	3.57 (<i>t</i>)	62.2	C-7a, C-8a	3.56 (<i>t</i> , 6.4)	62.3
5a-OCH ₃	3.81 (<i>s</i>)	56.4	-	3.82 (<i>s</i>)	56.5
8-OCH ₃	3.85 (<i>s</i>)	56.8	-	3.85 (<i>s</i>)	56.9

Fig.-2: ESI-MS Spectral Data of the Isolated Compound

NSA_JND12 (4mg) in methanol-d4 // com @300

Fig.-3 ¹³C-NMR and DEPT Spectral Data of the Isolated Compound

CONCLUSION

A neolignan, vladinol F, was successfully isolated from the dissolved fraction in acetone-ether of *Dryobalanops oblongifolia* stem bark. The antiplasmodial activity test of the vladinol F toward *P. falciparum* showed the IC₅₀ value of 3.51 µg/mL. This result showed that vladinol F was good as an antiplasmodial agent.

ACKNOWLEDGMENT

We would like to thank: (1) Directorate General of Higher Education of Indonesia for financial supporting of this research and (2) Faculty of Pharmacy, Meijo University, Nagoya, Japan for measuring NMR and MS data.

REFERENCES

1. D. Kesuma¹, A.L. Nasyanka, M. Rudyanto, Siswandono, B.T. Purwanto, And I.G.A. Sumartha, *Rasayan Journal of Chemistry*, **13(3)**, 1914(2020), DOI:10.31788/RJC.2020.1335694
2. D. Handayani, R. Amilia, I. Aminah, T. Hertiani, N. P. Ariantari, and P. Proksch, *Rasayan Journal of Chemistry*, **13(3)**, 1817(2020), DOI:10.31788/RJC.2020.1335549
3. G. Swapna, D. Rakesh, and M. Estari, *Rasayan Journal of Chemistry*, **13(4)**, 4 (2020), DOI:10.31788/RJC.2020.1345889
4. WHO, World Malaria Report (2015), www.who.int/malaria
5. Purwaningsih, Ecological Distribution of Dipterocarpaceae Species in Indonesia, *Biodeversitas*, **5**, 2 (2004), DOI:10.13057/biodiv/d050210
6. M.F. Newman, P.F. Burges, T.C. Whitmore, Manual of Dipterocarps Series (Sumatra, Kalimantan, Jawa to Nuigini), Prosea-Indonesia, Bogor, pp.5-45, (1999)
7. N.S. Aminah, Y.M. Syah, E.H. Hakim, N. Aimi, M. Kitajima, H. Takayama, S.A. Achmad, *Phytochemistry*, **63** (2003), DOI:10.1016/s0031-9422(03)00274-7
8. N.S. Aminah, Y.M. Syah, E.H. Hakim, N. Aimi, S.A. Achmad, M. Niwa, *Indonesia Journal Chemistry*, **6(1)**(2006), DOI:10.22146/ijc.21778
9. A. Wibowo, N. Ahmat, A.S. Hamzah, A.L.M. Low, S.A.S. Mohamad, H.Y. Khong, A.S. Sufian, N. Manshoor, H. Takayama, *Fitoterapia*, **83**, 8 (2012), DOI:10.1016/j.fitote.2012.09.004
10. A. Wibowo, N. Ahmat, A.S. Hamzah, A.S. Sufian, N.H. Ismail, R. Ahmad, F.M. Jaafar, H. Takayama, *Fitoterapia*, **82**, 4 (2011), DOI:10.1016/j.fitote.2011.02.006
11. Indriani, Yoshiaki Takaya, N.N.T. Puspaningsih, N.S. Aminah, *Chemistry of Natural Compound*, **53**, 31 (2017), DOI:10.1007/s10600-017-2049-5

12. Isao Kouno, Y. Yukari, S. Satomi, S. Miki, I. Yumi, and Y. Chun-Shu, *Phytochemistry*, **32**, 6 (1993), [DOI:10.1016/0031-9422\(93\)85182-Q](https://doi.org/10.1016/0031-9422(93)85182-Q)
13. Qiu-Fen HU, Huai-Xue MU, Hai-Tao HUANG, Hua-Ying LV, Shu-Li LI, Pen-Fei TU, and Gan-Peng LI, *Chemical and Pharmaceutical Bulletin*, **59**,11 (2011), [DOI:10.1248/cpb.59.1421](https://doi.org/10.1248/cpb.59.1421)
14. Widyawaruyanti, S.K. Subehan, Kalauni, S. Awale, M. Nindatu. N.C. Zaini, D. Syafruddin, P.B. Setia Asih, Y. Tezuka, and S. Kadota, *Journal of Natural Medicine*, **61**, 410(2007), [DOI:10.1007/s11418-007-0153-8](https://doi.org/10.1007/s11418-007-0153-8)
15. Ronan, J.S.J. Ademir, and B.O. Alaide, *Molecules*, **14(8)**, 3037(2009), [DOI:10.3390/molecules14083037](https://doi.org/10.3390/molecules14083037)

[RJC-6017/2020]