

ISOLATION OF ARTONIN E FROM THE ROOT BARK OF ARTOCARPUS RIGIDA, SYNTHESIS OF ARTONIN E ACETATE AND EVALUATION OF ANTICANCER ACTIVITY

By Tati Suhartati

ISOLATION OF ARTONIN E FROM THE ROOT BARK OF *ARTOCARPUS RIGIDA*, SYNTHESIS OF ARTONIN E ACETATE AND EVALUATION OF ANTICANCER ACTIVITY

Tati Suhartati^{1*}, Hernawan¹, Jhons F. Suwandi², Yandri¹ and Sutopo Hadi^{1#}

¹Department of Chemistry, University of Lampung, Jl. S. Brojonegoro No. 1, Bandar Lampung, Indonesia 35145

²Faculty of Medicine, University of Lampung, Jl. S. Brojonegoro No. 1, Bandar Lampung, Indonesia 35145

tati.suhartati@fmipa.unila.ac.id, sutopo.hadi@fmipa.unila.ac.id

Artonin E was isolated from the root bark of *A. rigida*. The isolated compound was then esterified using a known procedure by the addition of acetic anhydride with pyridine catalyst. The structure of the synthesized compound was carefully determined by physical and spectroscopic techniques and compared to the data in the literature. The anticancer activity test against murine leukemia cancer cells P-388 showed that the ester compound has good activity with an IC_{50} of 2.79 $\mu\text{g/ml}$ and much better stability during storage compared to artonin E itself.

Keywords: *A. rigida*; artonin E acetate; esterification; anticancer activity

ИЗОЛАЦИЈА НА АРТОНИН Е ОД КОРАТА НА КОРЕНОТ НА *ARTOCARPUS RIGIDA*, СИНТЕЗА НА АРТОНИН Е АЦЕТАТ И ОЦЕНУВАЊЕ НА АНТИКАНЦЕГЕНОТО ДЕЈСТВО

Артонин Е беше изолиран од кората на коренот на *A. rigida*. Изолираното соединение потоа беше естерифицирано со примена на позната постапка со додавање на анхидрид на оцетна киселина со пиридин како катализатор. Структурата на синтетизираното соединение беше внимателно определена со физички и спектроскопски техники и споредена со податоци од литературата. Тестот на антиканцерогеното дејство против леукогени канцерогени клетки P-388 покажа дека естерското соединение добро дејствува со IC_{50} од 2,79 $\mu\text{g/ml}$ и многу подобра стабилност при складирање споредено со самиот артонин Е.

Клучни зборови: *A. rigida*; артонин Е; естерификација; антиканцерогено дејство

1. INTRODUCTION

Some flavonoid compounds have been isolated from some species of *Artocarpus* and some of the compounds isolated have shown interesting biological activities [1–6]; one of the compounds is artonin E. Artonin E is a flavonoid compound which potential anticancer and antimalaria activity [7, 8] and can easily be isolated from various *Artocarpus* plant such as *A. communis*, *A. rotunda*, *A. altilis*, *A. elasticus* and *A. rigida* [3, 4, 7, 9–12].

As a flavone compound, artonin E has four hydroxyl groups. Two of these are in the *ortho* position, which makes them easily oxidized. One of the ways to protect the oxidation reaction occurring at these hydroxyl groups is by esterification.

In this work, artonin E was isolated from *A. rigida*, which is native of Indonesia. The plant was obtained from Keputran village, Sukoharjo, Pringsewu, Lampung, Indonesia. The artonin E was then esterified with acetic anhydride. The ester compound obtained was well characterized by physical

and spectroscopic techniques and then tested for bioactivity against murine leukemia cancer cells P-388.

2. EXPERIMENTAL

10 2.1. General

Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. The UV-vis and IR spectra were measured with Agilent Cary 100 and Agilent Cary 620 FTIR spectrophotometers, respectively. The ^1H and ^{13}C NMR spectra were obtained with an Agilent spectrometer with DD2 console system at 500 MHz and 125 MHz, respectively. Vacuum liquid chromatography (VLC) was performed using a Merck Si-gel 60, and thin layer chromatography (TLC) analysis was carried out on pre-coated Si-gel plates (Merck Kieselgel 60 F254, 0.25 mm).

2.2. Plant collection

Samples of the root bark of *A. rigida* Blume were collected from Keputran village, Sukoharjo Pringsewu Lampung, in August 2015 and were identified at the Herbarium Bogoriense, Research Centre for Biology, Indonesia, Institute of Sciences Bogor, Indonesia and a voucher specimen has been deposited at the herbarium.

2.3. Extraction and isolation

The powder of root bark of *A. rigida* (1 kg) was extracted exhaustively with *n*-hexane and a mixture of methanol-ethyl acetate (EtOAc) 1:1 for 3 days for each process. Removal of the solvents by vacuum rotatory evaporator produced methanol/EtOAc extract (150.9 g). The methanol/EtOAc extract was then fractionated by Si-gel VLC eluted with EtOAc/*n*-hexane in the ratio 0–100%, to produce six main fractions (A–F). Fraction B weighed 38.7 g and fraction C 23.8 g. Fractions B and C were then subjected again to VLC using Si-gel with the same eluent system. The result of fractionation was a yellow solid, which was recrystallized to produce yellow crystals (1.6343 g) with m.p. 250–252 °C and the same R_f with three eluent systems.

2.4. Esterification of artonin E

The isolated artonin E was then esterified using the method employed by Hano [9] as follows: 9.5 mg artonin E was placed in a reaction tube and reacted 0.3 ml acetic anhydride in the presence of 0.1 ml of pyridine catalyst. The reac-

tion mixture was then left in the sealed reaction tube for 72 h. Every 24 h the purified product was tested with TLC. After 72 h, the reaction mixture was added to H₂O, so the clear mixture became cloudy and formed clumps. The cloudy solution was then filtered off and vacuumed to produce white crystals and recrystallized in *n*-hexane/ether.

Artonin E was found as yellow crystals, m.p. 250–252 °C, UV-vis (MeOH) λ_{max} : 211, 268, and 347 nm.

Ester of Artonin E acetate **1** was found as clear crystals, m.p. 190–192 °C, UV-vis (MeOH) λ_{max} : 211, 236 (shoulder), 261 and 319. IR (KBr) ν_{max} : 3343 (wide), 2918, 1770, 1635, 1573, 1492, 1421, 1373, 1283, 1226 and 1081 cm^{-1} .

^1H NMR (CDCl_3) δ (ppm): 1.36 (H-13); 1.46 (H-17 and H-18); 1.57 (H-9); 1.58 (H-12); 2.11; 2.31; 2.32; 2.44 (four CH₃ groups from acetyl group); 5.05 (2H); 5.62 (H-15); 6.47 (H-6); 6.62 (H-14); 7.22 (H-3') and 7.28 (H-6').

^{13}C NMR (CDCl_3) δ (ppm): 17.64; 20.71; 20.85; 20.98; 21.44; 24.48; 25.71; 28.46; 78.44; 107.57; 109.28; 110.38; 114.78; 118.98; 121.14; 123.73; 123.91; 125.11; 129.78; 132.58; 139.57; 143.78; 146.03; 149.76; 153.11; 155.47; 157.14; 167.6; 167.8; 168.6 and 176.08.

2.5. Bioactivity

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The bioactivity test performed was a cytotoxicity test of compound **1** based on the method of Alley et al. [13] and was conducted at Laboratory of Natural Product Chemistry, Department of Chemistry, Bandung Institute of Technology, Bandung, Indonesia. Leukemia cancer cells P-388 were supplied by Dr. S Tsukagoshi of the Japan Foundation for Cancer Research and were kept on RPMI-1640 media (Nissui Pharm. Co., Ltd) with 5% fetal calf serum (Mitsubishi Chemical Industry Co., Ltd.) and kanamycin (100 $\mu\text{g}/\text{ml}$). The cancer cells (3×10^3 cells/well) were cultured on 96-well Corning disposable plates containing 100 μl growth media and incubated at 37 °C with an atmosphere of 5% CO₂. Samples (10 μl) with various concentrations of the tested compound were added to the culture one day after transfer. On the third day, 20 μl of MTT solution (5 mg/ml) 5 μl well was added to each culture medium. After 4 h of incubation, 100 μl of 10% SDS solution in 0.01 N HCl was added to each well and formazan crystals were dissolved in each well by stirring with a pipette. The optical density measurement was performed with a Tohsu MPR-A4i microplate reader using two wavelength systems (550 and 700 nm). For all experiments, three replicates were conducted to determine each test point.

3. RESULTS AND DISCUSSION

3.1. Spectroscopic analyses

Artonin E acetate **1**, the product of esterification of artonin E with acetic anhydride, was carefully analyzed based on the spectroscopic data. The data from UV-vis (Fig. 1), IR (Fig. 2), ^1H NMR (Fig. 3) and ^{13}C NMR (Fig. 4) of compound **1** were compared to the data for isolated artonin E.

Table 1 shows the comparison of ^1H NMR data of artonin E tetraacetate [9] and compound **1**. The data clearly suggest that the esterification of artonin E was successfully achieved although there are slightly changes in the chemical shifts, which

might be due to the different solvents used in the measurements.

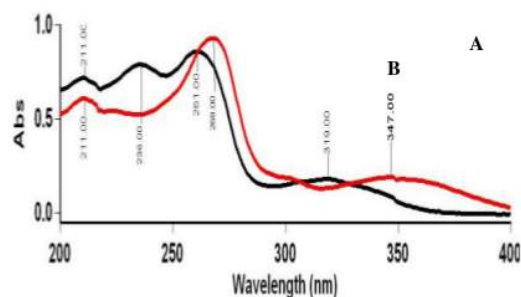


Fig. 1. UV-vis spectra of (A) isolated artonin E; (B) the ester compound of artonin E acetate (in methanol)

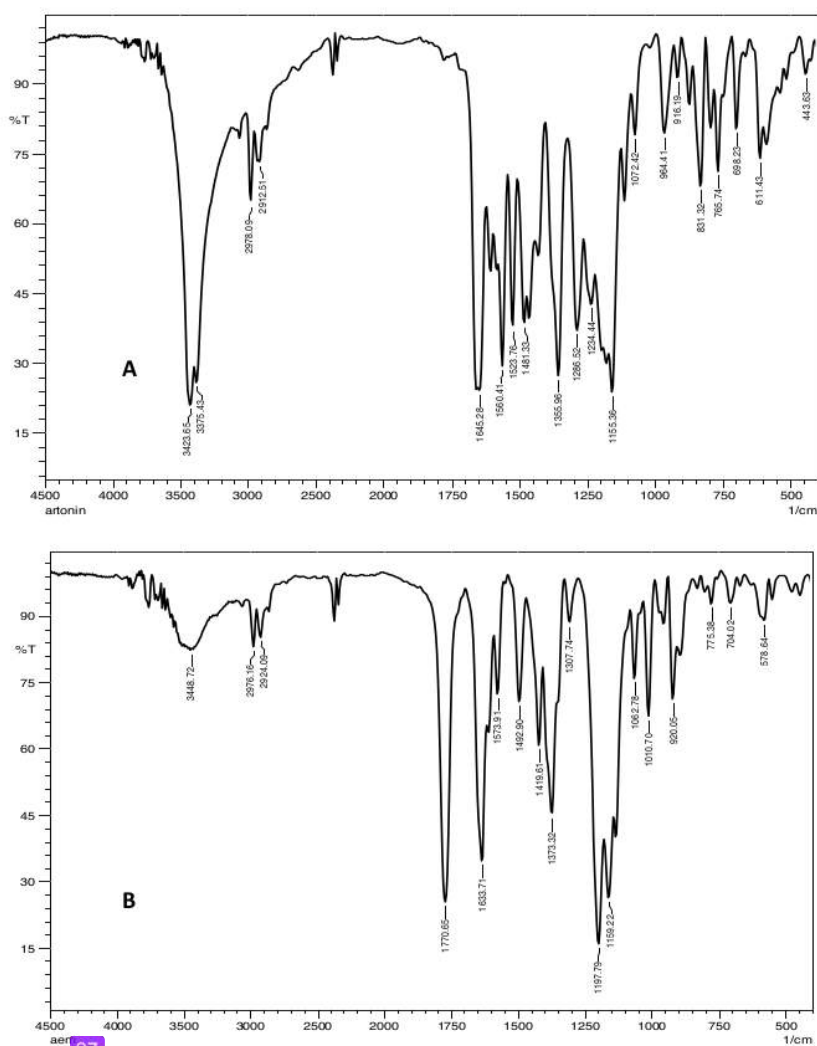


Fig. 2. The comparison of IR spectra of (A) isolated artonin E [1]; (B) compound **1**

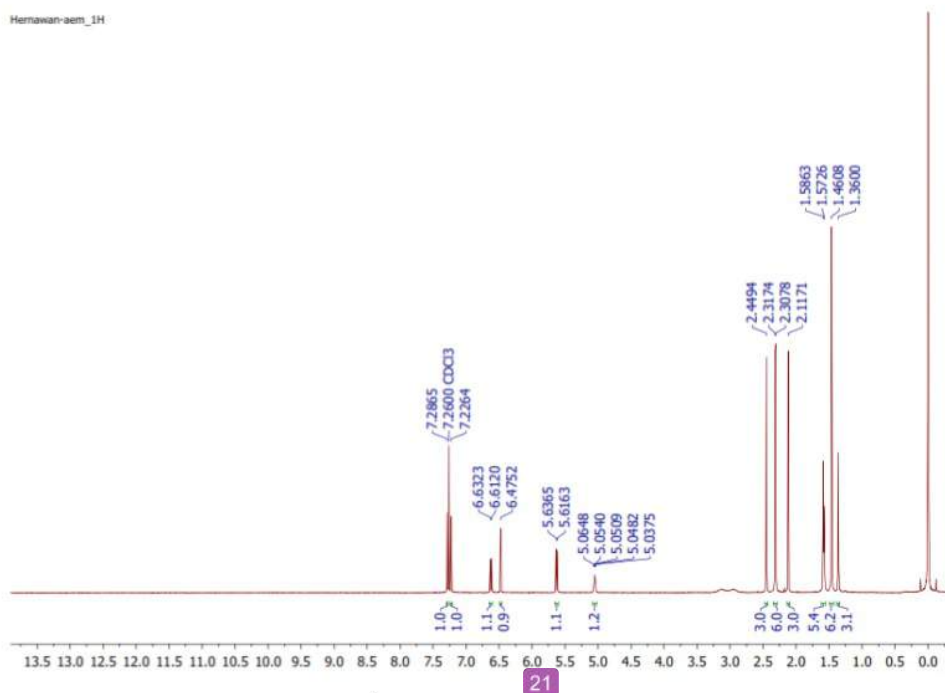
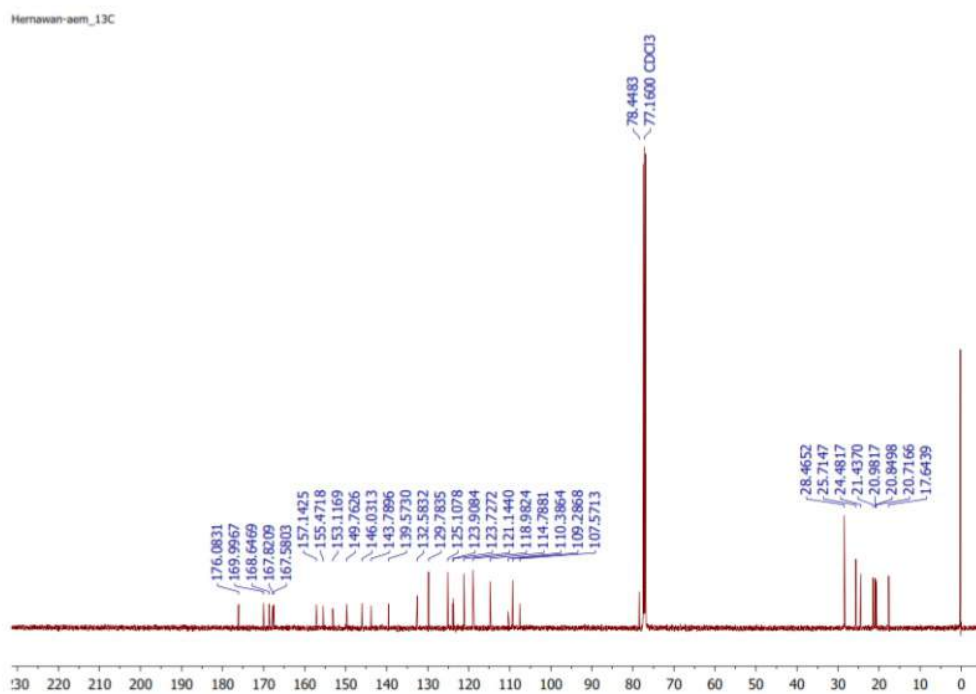
Fig. 3. ^1H NMR spectrum of compound IFig. 4. ^{13}C NMR spectrum of compound I

Table 1

The comparison of ^1H NMR data between artonin E tetraacetate [9] and compound **1**

^1H NMR, (ppm)	
(2) (DMSO- d_6)	(1) (CDCl $_3$)
31 (3H. s. C-11-CH $_3$)	1.36 (3H. s. C-11-CH $_3$)
1.45 (6H. s. C-16-CH $_3$ x2)	1.46 (6H. s. C-16-CH $_3$ x2)
3.32	1.57 (2H. d. C-9-H)
(2H. s. overlapping H $_2$ O signal. C-9-H)	14 (3H. s. C-11-CH $_3$)
1.53 (3H. s. C-11-CH $_3$)	2.11 (3H. s. COCH $_3$)
2.10 (3H. s. COCH $_3$)	2.32 (3H. s. COCH $_3$)
2.32 (6H. s. COCH $_3$ x2)	2.31 (3H. s. COCH $_3$)
2.33 (7. s. COCH $_3$)	2.44 (3H. s. COCH $_3$)
4.92 (1H. m. C-10-H)	5.05 (1H. m. C-10-H)
5.87 (1H. d. $J=10$ Hz. C-15-H)	5.62 (1H. d. $J=10$ Hz. C-15-H)
6.53 (1H. dd. $J=0.6$ & 10 Hz C-14-H)	6.62 (1H. d. $J=10$ Hz C-14-H)
6.65 (1H. 13 = 0.6 Hz. C-6-H)	6.47 (1H. 13 -6-H)
7.45 (1H. s. C-3'-H)	7.22 (1H. s. C-3'-H)
7.61 (1H. s. H-6'-H)	7.28 (1H. s. H-6'-H)

Table 2

The comparison of ^{13}C NMR data between artonin E tetraacetate [9] and compound **1**

No C	^{13}C NMR, (ppm)	
	(2) DMSO- d_6	(1) CDCl $_3$
2	162.20	155.47
3	121.70	123.91
4	183.30	176.08
4a	105.60	110.38
5	162.80	149.76
6	99.70	109.28
7	160.00	157.14
8	101.60	107.57
8a	153.30	153.11
1'	111.60	123.73
2'	149.80	146.03
3'	104.80	125.11
4'	149.50	143.78
5'	139.10	139.57
6'	117.10	118.98
9	24.70	21.44
10	122.50	121.14
11	132.30	132.58
12	25.80	25.71
13	17.70	17.64
14	115.50	114.78
15	128.00	129.78
16	78.80	78.44
17	28.30	28.46
18	28.30	28.46
CH $_3$ CO		
C=O	178.0; 168.6; 167.8;	167.6
CH $_3$	24.48; 20.71; 20.98;	20.85

The comparison of ^{13}C NMR data between artonin E tetraacetate [9] and compound **1** can be seen in Table 2.

The binding of hydrogen atoms to certain carbon atoms in compound **1** is shown by the heteronuclear single quantum correlation (HSQC) spectrum as can be seen in Table 3. The HSQC technique normally provides information about the correlation between the proton and the carbon in a single bond [14].

The relative position of hydrogen atoms and the two isoprenyl substituents on the flavone carbon frame is shown by the heteronuclear multiple bond correlation (HMBC) of compound **1**, as shown in Figure 5.

Table 3

The HSQC spectrum data of compound **1**

No C	^1H NMR, ppm	^{13}C NMR, ppm
6	6.47	109.28
10	5.05	121.14
12	1.58	25.71
13	1.36	17.64
14	6.62	114.78
15	5.62	129.78
17	1.46	28.46
18	1.46	28.46
3'	7.22	125.12
6'	7.28	118.98

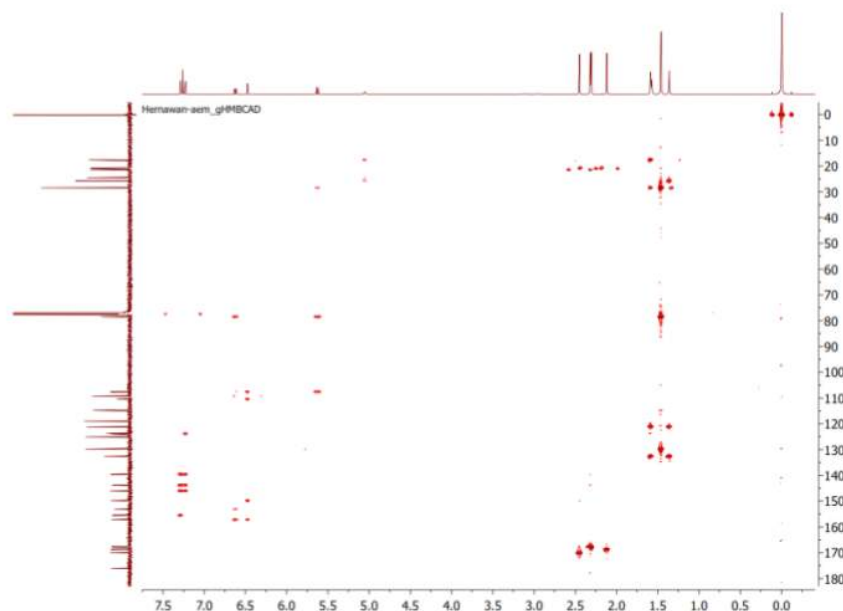


Fig. 5. Correlation spectrum of heteronuclear multiple bond correlation (HMBC) of compound 1

There are four ester groups in artonin E and the use of CDCl_3 solvent causes the multiple bond correlation of carbonyl on C-4 and hydrogen to not appear in the HMBC spectrum. However, based on the analysis of the HMBC spectrum, the structure of compound 1 is as shown in Figure 6.

The UV-vis spectra of the isolated artonin E showed maximum absorbances at λ_{max} 211, 268, and 347 nm in methanol with solution concentration of 5 ppm (1 mg/20 mL). The UV spectrum of artonin E shows absorbances characteristic of a

flavone compound. The maximum absorbance at λ_{max} 347 nm is specific flavone absorption of a band I cinnamoyl group, which indicates the presence of free hydroxyl groups on the flavonoid B ring. The maximum absorbance at λ_{max} 267 nm is a specific absorption of flavone on band II and is characteristic of a benzoyl group on the A ring. The absorbances of compound 1 were at λ_{max} 211, 236 (shoulder) and 319 nm in methanol at a concentration of 10 ppm (1 mg/10 ml).

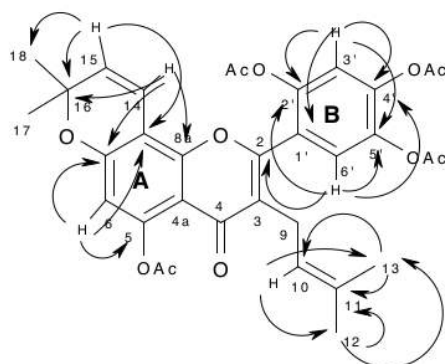


Fig. 6. The important structure correlation of compound 1 based on the HMBC spectrum

The UV spectrum of compound **1** still shows absorbances characteristic of a flavone. The maximum absorbances of **1** with λ_{\max} 319 and 261 nm show changes in the B ring and A ring of artonin E, since there are absorption decreases of 28 nm on band I and 7 nm on band II. The decrease of absorption on band I indicates that the free hydroxyl group of artonin E on the B ring has been esterified by acetic anhydride. The same observation also occurred on the B ring where the maximum absorbance decreased by 7 nm, indicating that the hydroxyl group at C-5 on the A ring had also been esterified.

The success in the esterification reaction was also supported by the IR spectrum of **1**, where the transmittance intensity of the -OH vibration at 3423 cm^{-1} and hydrogen bonding between carbonyl and the -OH group on C-5 is no longer observed, as shown by the vibration change of the carbonyl group of artonin E at 1645 cm^{-1} (the spectrum obtained for artonin E is identical to that reported previously by Suhartati et al. [1]) to 1770 cm^{-1} for compound **1**. The comparison of the IR spectra of artonin E and **1** is shown in Figure 2.

Figure 3 shows the ^1H NMR spectrum of compound **1**. Three singlets at chemical shift (δ) of 1.28, 1.46 ($2 \times \text{CH}_3$) and 1.58 ppm from the four CH_3 groups are observed. The multiplet peaks appear at δ 5.03 ppm (1H, m) due to the two neighboring protons having different chemical shifts. The doublet peaks of sp^2 carbon appear at δ 5.62 and 6.62 ppm (1H, d, $J = 10\text{ Hz}$) from the two neighboring protons of the alkene carbon. In the proton shift region of sp^2 aromatic carbon, there are two singlet protons with δ 7.22 ppm and 7.28 ppm from the protons on the B ring, which indicates that C-2', C-4' and C-5' are containing oxygen atom [15].

The singlet proton of one proton on the A ring appears at δ 6.47 ppm. The specific differences between artonin E and compound **1** are the appearance of singlet peaks at δ 2.11, 2.31, 2.32 and 2.44 ppm, indicating the presence of four methyl groups from the ester of artonin E acetate [16].

The success of esterification is strengthened by ^{13}C NMR spectrum of compound **1** (Figure 4) which shows the presence of 33 carbon atoms, where some of them show the appearance of C carbonyl at chemical shifts of δ 176.08 (C-4), 169.99, 168.64, 167.82 and 167.58 ppm, where the last four signals are from the carbonyls of four acetyl groups, and also the chemical shifts at 20.71, 20.84, 20.98 and 21.43 ppm due to the presence of four methyl groups of the acetyl group.

3.2. Anticancer activity test

The cytotoxicity test using murine leukemia cancer cells P-388 showed that compound **1** was active, with an IC_{50} 2.79 $\mu\text{g/ml}$. The determination of IC_{50} was processed from the data in Table 4 using Origin 8.5 software, as shown in Figure 7.

According to Suhartati et al. [10], artonin E shows much higher activity with an IC_{50} of 0.06 $\mu\text{g/ml}$; however, artonin E is less stable towards oxidation. Compound **1** is more stable compared to artonin E. This is because artonin E is easily oxidized due to the presence of two *ortho* hydroxy groups on the B ring; thus, although the activity of artonin E is higher, the stability is very low, while compound **1** still shows excellent anticancer activity [8], with good stability. The results obtained indicate that compound **1** is potentially useful as a future drug in the treatment of cancer, since it is very stable and can thus be stored for longer period than can artonin E.

Table 4

P-388 test data of compound **1**

Optical density of compound (1)				The average optical density of (1)	
100	0.013	0.01	0.016	0.013	0.013
30	0.01	0.005	0.01	0.008333	0.008333
10	0.012	-0.004	0.001	0.003	0.003
3	0.056	0.074	0.043	0.057667	0.057667
1	0.828	0.803	0.659	0.763333	0.763333
0.3	0.705	0.633	0.636	0.658	0.658
0.1	0.542	0.743	0.671	0.652	0.652
Positive blank				100%	50%
0.573	0.628	0.649	0.629	0.576	0.603
				0.609667	0.304833

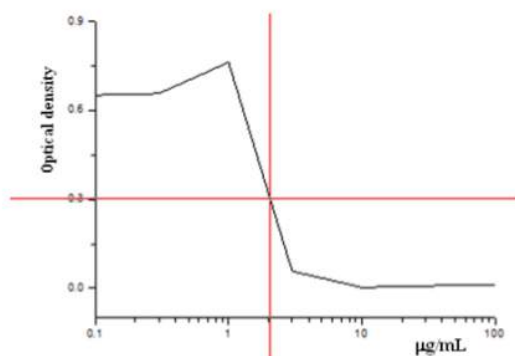


Fig. 7. The graph of cytotoxicity test of compound I using leukemia cells P-388

4. CONCLUSIONS

Artonin E has been successfully isolated from the root bark of *A. rigida* and has also been modified to an ester: artonin E acetate. The synthesized compound has been shown to have excellent anticancer activity against murine cancer cells P-388 with an IC_{50} of 2.79 $\mu\text{g/ml}$.

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