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## Cytotoxic Triterpenoid from the Stembark of *Chisocheton celebicus* (Meliaceae)

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### Cover Page Footnote

The work was supported partially by the Directorate General of Higher Education, Ministry of Research, Technology, and Higher Education, Indonesia (BPPS scholarship). We thank Mr. Ahmad Darmawan and Mrs. Sofa Fajriah in the Research Center for Chemistry, Indonesian Science Institute for NMR measurements. We are grateful to Mr. Uji Pratomo at Central Laboratory, Universitas Padjadjaran, Jatinangor, Indonesia for HR-ESITOFMS measurements and Mrs. Suzany Dwi Elitaat Department of Chemistry, Faculty of Mathematics and Natural Sciences, Institute Technology Bandung for cytotoxicity bioassay.

## Cytotoxic Triterpenoid from the Stembark of *Chisocheton celebicus* (Meliaceae)

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### Abstract

Plants belonging to the *Chisocheton* genus are a rich source of tetracyclic triterpenoids with diverse biological activities. Two triterpenoid compounds, dammar-20,24-dien-3-one (**1**) and 3 $\beta$ -hydroxy-tirucall-7-en (**2**) were isolated from the stem bark of *Chisocheton celebicus*. The chemical structures of compounds **1** and **2** were identified by spectroscopic data, including IR, NMR (<sup>1</sup>H, <sup>13</sup>C, DEPT 135°, HMQC, HMBC, <sup>1</sup>H-<sup>1</sup>H COSY), and MS, and they were compared with previously reported spectral data. Compounds **1** and **2** were evaluated for their cytotoxic effects against P-388 murine leukemia cells. The compounds showed cytotoxicity against P-388 murine leukemia cells, with IC<sub>50</sub> values of 30.2 and 4.3  $\mu$ g/mL, respectively.

### Abstrak

**Senyawa Triterpenoid yang Bersifat Sitotoksik dari Kulit Batang *Chisocheton celebicus* (Meliaceae).** Dua senyawa triterpenoid, damar-20,24-dien-3-on (**1**) dan 3 $\beta$ -hidroksi-tirucal-7-en (**2**) diisolasi dari kulit batang *Chisocheton celebicus*. Struktur kimia senyawa **1** dan **2** diidentifikasi berdasarkan data spektroskopi, meliputi IR, NMR (<sup>1</sup>H, <sup>13</sup>C, DEPT 135°, HMQC, HMBC, <sup>1</sup>H-<sup>1</sup>H COSY) dan MS, serta perbandingan dengan data spektra yang diperoleh sebelumnya. Senyawa **1** dan **2** dievaluasi sifat sitotoksiknya terhadap sel murin leukemia P-388. Senyawa **1** dan **2** menunjukkan aktivitas sitotoksik terhadap sel murin leukemia P-388 dengan nilai IC<sub>50</sub> berturut-turut 30,2 dan 4,3  $\mu$ g/mL.

*Keywords: Chisocheton celebicus, cytotoxic activity, Meliaceae, triterpenoid compounds*

### Introduction

The genus *Chisocheton* is the second largest genus of the family of Meliaceae, consisting of more than 50 species distributed in Nepal, India, Bhutan, Myanmar, South China, Thailand, Indonesia, Malaysia, and Papua New Guinea [1]. Previous phytochemical studies on this genus revealed the presence of various compounds with interesting biological activity, including sesquiterpenoids [2], dammarane-type triterpenoids [2], tirucallane-type triterpenoids [3], apo-tirucallane-type triterpenoids [4,5], limonoids [6-12], steroids [13], and phenolics [2]. Some of these compounds were shown to exhibit interesting pharmacological properties, including anticancer [12], antiplasmodial [8], anti-inflammatory [9], and apoptosis [13] properties.

Although secondary metabolites from other *Chisocheton* species have been reported previously, the chemical

constituents of *C. celebicus* have yet to be reported. *C. celebicus* is a higher plant that is widely distributed in the northern part of Sulawesi island in Indonesia [14]. Its bark has been used as an Indonesian folk medicine for reducing fever, treating contused wounds, and for skin diseases [14,15]. The isolation, structure elucidation, and cytotoxic evaluation of these isolated compounds are described herein.

### Material and Methods

**Equipment.** Melting points were measured with a Fisher John melting point apparatus and are uncorrected. Optical rotations were recorded using a Perkin-Elmer 341 polarimeter. The IR spectra were recorded with a Perkin-Elmer 1760X FT-IR in KBr. Mass spectra were obtained with a Water Qtof HR-MS XEVO<sup>tm</sup> mass spectrometer. <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were obtained with a JEOL JNM A-500 spectrometer using TMS as an

internal standard. Chromatographic separations were carried out on silica gel 60 (Merck) and octa desyl silane (ODS) (Fuji Silysia). Thin layer chromatography (TLC) plates were precoated with silica gel GF<sub>254</sub> (Merck, 0.25 mm) and ODS, and detection was achieved by spraying with 10% H<sub>2</sub>SO<sub>4</sub> in ethanol, followed by heating.

**Plant material.** The stem bark of *C. celebicus* was collected in Bogor Botanical Garden, Bogor, West Java Province, Indonesia, in April 2012. The plant was identified by the staff of the Bogoriense Herbarium, Bogor, Indonesia, and a voucher specimen was deposited at the herbarium.

**Plant extraction.** Dried ground stem bark of *C. celebicus* (2 kg) was extracted successively with *n*-hexane, EtOAc, and MeOH. Evaporation resulted in the crude extracts of *n*-hexane (26.8 g), EtOAc (22.4 g), and MeOH (20.6 g), respectively. The *n*-hexane, ethyl acetate, and methanol extracts exhibited cytotoxic activity against P-388 murine leukemia cells, with IC<sub>50</sub> values of 19.9, 16.9, and 75.9 µg/mL, respectively. The EtOAc extract (22.4 g) was subjected to vacuum liquid chromatography over silica gel using a gradient elution mixture of *n*-hexane-EtOAc (10:0-0:10) as an eluting solvent, yielding 8 fractions (A–H). Fraction E (3.2 g) was subjected to column chromatography over silica gel using a mixture of CHCl<sub>3</sub>:EtOAc (9:1) as an eluting solvent, affording 7 fractions (E01–E07). Fraction E04 (0.22 g) was subjected to column chromatography over ODS using a mixture of MeOH:H<sub>2</sub>O (2:3) as an eluting solvent to form **1** (5.2 mg). Fraction E06 (80.1 mg) was subjected to column chromatography over silica gel using a mixture of CHCl<sub>3</sub>:Me<sub>2</sub>CO (7:3) to give **2** (4.7 mg). The purification results of both compounds were determined by TLC on silica gel and ODS with several solvent systems and showed a single spot (> 95% pure).

**Determination of cytotoxic activities.** The P-388 cells were seeded into 96-well plates at an initial cell density of approximately 3 × 10<sup>4</sup> cells cm<sup>-3</sup>, supplemented with a growth medium containing various concentrations of NABV or vinblastine in 0.5% dimethyl sulfoxide (DMSO) for 72 h. After 24 h of incubation for cell attachment and growth, sample with various concentration was added. The added compounds were first dissolved in DMSO at the required concentration. Subsequently, six desirable concentrations were prepared using PBS (phosphate buffered saline, pH = 7.30–7.65). Control wells received only DMSO. The assay was terminated after a 48 h incubation period by adding MTT reagent [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; also named as thiazol blue], and the incubation was continued for another 4 h, after which the MTT-stop solution containing SDS (sodium dodecyl sulphate) was added and another 24 h incubation was conducted. Optical density was measured using a microplate reader at 550 nm. IC<sub>50</sub> values were taken from the plotted

graph of the percentage of live cells compared to the control (%), which received only PBS and DMSO, versus the tested concentrations of the compounds (µg/mL). The IC<sub>50</sub> value is the concentration required for 50% growth inhibition of cells. All analyses were carried out in triplicate, and the results were expressed as mean ± standard deviation (SD) and compared using the Waller–Duncan test. A value of *p* < 0.05 was considered statistically significant.

## Result and Discussion

The stem bark of *C. celebicus* was ground and successively extracted with *n*-hexane, ethyl acetate, and methanol. All the extracts were evaluated for their cytotoxic activity against P-388 murine leukemia cells, with the ethyl acetate extract showing the strongest cytotoxic activity. Therefore, the subsequent phytochemical analysis was focused on the ethyl acetate extract, which was chromatographed over a vacuum-liquid chromatographed (VLC) column packed with silica gel 60 with gradient elution. The VLC fractions were repeatedly subjected to normal-phase and reverse-phase column chromatography, yielding two cytotoxic triterpenoids, **1** and **2** (Figure 1).

**Dammar-20,24-dien-3-one (1)**, White needle-like crystals, m.p. 141–143 °C, IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>) 3082 (C-H *sp*<sup>2</sup> stretch), 2949 (C-H *sp*<sup>3</sup> stretch), 1705 (C=O stretch), and 1641 (C=C stretch). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz), see Table 1; <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 125 MHz), see Table 1; HR-TOFMS (positive ion mode) *m/z* 425.3698 [M+H]<sup>+</sup>, (calcd. for C<sub>30</sub>H<sub>48</sub>O, *m/z* 424.3695).

**3β-hydroxy-tirucall-7-en (2)**, White amorphous powder, m.p. 136–139 °C, IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>) 3406 (O-H stretch), 1623 (C=C stretch), 1165 (C-O stretch), and 901 (C-H *sp*<sup>2</sup> bend). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz), see

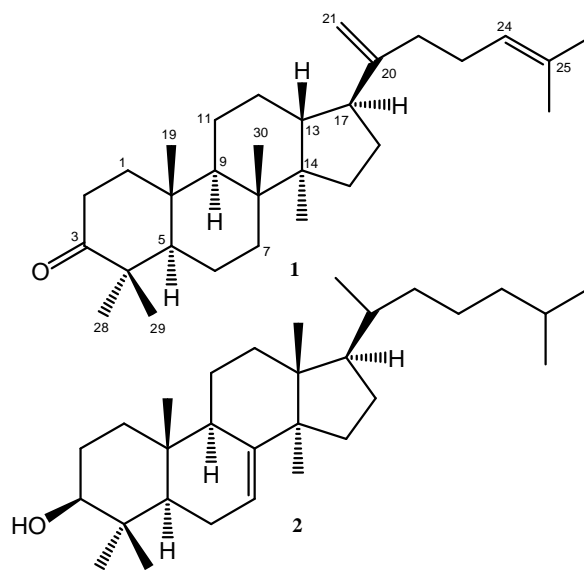


Figure 1. Chemical Structures of Compounds **1** and **2**

Table 1. NMR data (500 MHz for  $^1\text{H}$  and 125 MHz for  $^{13}\text{C}$ , in  $\text{CDCl}_3$ ) for **1** and **2**

Position	<b>1</b>		<b>2</b>	
	$^{13}\text{C}$ NMR $\delta_{\text{C}}$ (mult.)	$^1\text{H}$ NMR $\delta_{\text{H}}$ (Integral, mult., $J$ =Hz)	$^{13}\text{C}$ NMR $\delta_{\text{C}}$ (mult.)	$^1\text{H}$ NMR $\delta_{\text{H}}$ (Integral, mult., $J$ =Hz)
1	40.5 (t)	1.44 (1H, m) 1.93 (1H, m)	29.5 (t)	1.43 (1H, t, 3.7) 1.52 (1H, t, 3.7)
2	34.3 (t)	1.96 (1H, m) 2.48 (1H, m)	20.3 (t)	1.35 (1H, dt, 9.3, 5.7) 1.45 (1H, dt, 9.3, 5.7)
3	218.4 (s)	-	79.3 (d)	3.20 (1H, t, 5.8)
4	47.6 (s)	-	39.5 (s)	-
5	55.6 (d)	1.39 (1H, t, 5.3)	44.5 (d)	1.28 (1H, t, 1.3)
6	19.9 (t)	1.46 (1H, m) 1.86 (1H, m)	18.1 (t)	1.37 (1H, m) 1.54 (1H, m)
7	34.9 (t)	1.33 (1H, m) 1.78 (1H, m)	116.4 (d)	5.30 (1H, t, 3.2)
8	40.6 (s)	-	151.2 (s)	-
9	50.5 (d)	1.41 (1H, t, 5.3)	40.2 (d)	2.02 (1H, t, 10.2)
10	37.1 (s)	-	37.9 (s)	-
11	22.1 (t)	1.54 (1H, m) 1.84 (1H, m)	19.3 (t)	1.72 (1H, m) 1.80 (1H, m)
12	29.1 (t)	1.91 (1H, m) 1.76 (1H, m)	36.3 (t)	1.41 (1H, m) 1.54 (1H, m)
13	45.6 (d)	1.69 (1H, m)	43.1 (s)	-
14	49.6 (s)	-	37.8 (s)	-
15	31.5 (t)	1.61 (1H, m) 2.01 (1H, m)	39.5 (t)	1.90 (1H, t, 3.9) 1.93 (1H, t, 3.9)
16	25.2 (t)	1.51 (1H, m) 1.98 (1H, m)	28.3 (t)	1.83 (1H, m) 1.76 (1H, m)
17	47.9 (d)	2.20 (1H, m)	31.0 (d)	1.98 (1H, m)
18	15.5 (q)	0.98 (3H, s)	15.6 (q)	0.95 (3H, s)
19	16.3 (q)	0.85 (3H, s)	14.2 (q)	0.75 (3H, s)
20	152.8 (s)	-	52.1 (d)	1.57 (1H, m)
21	107.8 (t)	4.71 (1H, d, 1.9) 4.75 (1H, d, 1.9)	25.4 (q)	0.81 (3H, s)
22	34.3 (t)	1.96 (1H, m) 1.80 (1H, m)	36.9 (t)	1.51 (1H, m) 1.56 (1H, m)
23	27.3 (t)	2.11 (1H, m) 1.70 (1H, m)	28.3 (t)	1.63 (1H, m) 1.60 (1H, m)
24	124.6 (d)	5.11 (1H, dd, 2.1, 5.6)	29.9 (t)	1.25 (1H, m)
25	131.7 (s)	-	-	1.40 (1H, m)
26	39.8 (q)	1.68 (3H, s)	17.9 (q)	0.82 (3H, d, 6.5)
27	22.3 (q)	1.61 (3H, s)	23.2 (q)	0.88 (3H, d, 6.5)
28	21.2 (q)	1.05 (3H, s)	15.2 (q)	0.87 (3H, s)
29	26.9 (q)	1.08 (3H, s)	27.6 (q)	0.86 (3H, s)
30	16.0 (q)	0.87 (3H, s)	16.0 (q)	1.06 (3H, s)

Table 1;  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 125 MHz), see Table 1; HR-TOFMS (positive ion mode)  $m/z$  429.7355  $[\text{M}+\text{H}]^+$ , (calcd. for  $\text{C}_{30}\text{H}_{52}\text{O}$   $m/z$  428.7353).

Compound **1** took the form of white needle-like crystals. The HR-TOFMS spectrum showed  $[\text{M}+\text{H}]^+$   $m/z$  425.3698 (calcd  $m/z$  424.3695), which corresponded to the molecular formula of  $\text{C}_{30}\text{H}_{48}\text{O}$  and thus required seven degrees of unsaturation, originating from two pairs of C  $sp^2$ , one C=O, and the remaining tetracyclic triterpenoids. The  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 500 MHz) spectrum showed the presence of seven tertiary methyl groups, resonating at  $\delta_{\text{H}}$  1.00 (H-18), 0.95 (H-19), 1.68 (H-26), 1.61 (H-27), 1.05 (H-28), 1.08 (H-29), and 0.87 (H-30).

There was one olefinic methine group, resonating at  $\delta_{\text{H}}$  5.11 (1H, t,  $J = 2.6$  Hz, H-24), and one methylene group, resonating at  $\delta_{\text{H}}$  4.71 (1H, d,  $J = 1.9$  Hz) and 4.75 (1H, d,  $J = 1.9$  Hz, H-21), which indicates that the olefinic protons were in the geminal position. The proton pairing was also confirmed with the  $^1\text{H}$ - $^1\text{H}$  COSY spectrum (Figure 2). The  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 125 MHz) and DEPT  $135^\circ$  spectra showed the presence of seven methyl groups, exhibiting the characteristics of triterpenoid compounds [16], one olefinic methine, one olefinic methylene, two olefinic quaternary carbons, and a ketone group, resonating at  $\delta_{\text{C}}$  218.4. The HMBC crosspeaks (Figure 2) from H-28 ( $\delta_{\text{H}}$  1.05) and H-29 ( $\delta_{\text{H}}$  1.05) and the methylene protons from H-2 ( $\delta_{\text{H}}$  1.44 and

1.93) to the quaternary carbon at  $\delta_C$  218.4 indicated the presence of a ketone group at C-3. These functionalities accounted for three of seven total degrees of unsaturation, and the remaining four degrees of unsaturation were consistent with the triterpenoid skeleton. A comparison of the NMR data of **1** with dammar-20,24-dien-3-one [17] revealed that the structures of the two compounds were very similar; consequently, compound **1** was identified as dammar-20,24-dien-3-one and was shown in this species for the first time.

Compound **2** was obtained as a white amorphous powder. The HR-TOFMS spectrum showed  $[M+H]^+$   $m/z$  429.7355 (calculated  $m/z$  428.7353), which corresponded to the molecular formula of  $C_{30}H_{52}O$  and thus required five degrees of unsaturation, originating from one pair of  $C sp^2$  and the remaining tetracyclic triterpenoids. The  $^1H$ -NMR ( $CDCl_3$  500 MHz) spectrum showed the presence of five tertiary methyl groups, resonating at  $\delta_H$  0.73 (H-19), 0.75 (H-18), 0.87 (H-28), 0.86 (H-29), and 1.06 (H-30), and two secondary methyl groups, resonating at  $\delta_H$  0.82 (3H, d,  $J = 6.5$  Hz, H-26) and 0.89 (3H, d,  $J = 6.5$  Hz, H-27), indicated the presence of triterpenoid in **1** [17]. One olefinic methine group, resonating at  $\delta_H$  5.30 (1H, t,  $J = 3.2$  Hz, H-7), and one oxymethine group, resonating at  $\delta_H$  3.20 (1H, t,  $J = 5.8$  Hz, H-3), indicating that the configuration was  $3\beta$ -OH. The proton pairing was also confirmed with the  $^1H$ - $^1H$  COSY spectrum (Figure 2). The  $^{13}C$ -NMR ( $CDCl_3$  125 MHz) and DEPT  $135^\circ$  spectra showed the presence of eight methyl groups, one olefinic methine, and one oxymethine, resonating at  $\delta_C$  79.3, supporting the presence of triterpenoid compound in **1** [16]. The HMBC crosspeaks (Figure 2) from H-28 ( $\delta_H$  0.87) and H-29 ( $\delta_H$  0.86) and methylene protons from H-2 ( $\delta_H$  1.35 and 1.45) to the oxymethine at  $\delta_C$  79.3, indicated the presence of a hydroxyl

group at C-3. HMBC crosspeaks were also observed from H-30 ( $\delta_H$  1.06) to the quaternary carbon at C-8 ( $\delta_C$  151.2) and olefinic methine from H-7 ( $\delta_H$  5.30) to the methine group at C-9 ( $\delta_C$  40.2), indicating the presence of an olefinic group at 7 and 8 ( $\Delta^{7,8}$ ). These functionalities accounted for one of the five total degrees of unsaturation, and the remaining four degrees of unsaturation were consistent with the triterpenoid skeleton. A comparison of the NMR data of **2** with the data for  $3\beta$ -hydroxy-tirucall-7-en [18] revealed that the structures of the two compounds were very similar, and thus compound **2** was identified as  $3\beta$ -hydroxy-tirucall-7-en and shown in this species for the first time.

The cytotoxicity effects of the two isolated compounds (**1** and **2**) against P-388 murine leukemia cells were investigated according to the method described in previous papers [16], and artonin E ( $IC_{50}$  0.3  $\mu g/mL$ ) was used as a positive control [19].

The cytotoxicity activity of isolated compounds **1** and **2** in terms of  $IC_{50}$  values was  $30.5 \pm 0.24$  and  $4.3 \pm 0.08$   $\mu g/mL$ , respectively. These results suggested that the activity of  $3\beta$ -hydroxy-tirucall-7-en (**2**) was influenced by the hydroxy group at C-3, the position of the methyl group at C-18, and the position of olefinic carbon. In dammar-20,24-dien-3-one (**1**), the presence of a ketone group at C-3, the position of C-18 (which is different from compound **2**), and the position of an olefinic group at the side chain can decrease cytotoxic activity. The cytotoxic activity of both compounds (**1** and **2**) was weaker than that of the control (artoinin E), so neither can be used as a model compound for anticancer directly; their partial structures need to be modified to increase cytotoxic activity.

## Conclusions

Two known triterpenoid compounds, **1** and **2**, have been isolated from the stem bark of *Chisocheton celebicus*. These compounds were evaluated for their cytotoxic activity against P-388 murine leukemia cells *in vitro*. The result indicated that the presence of a hydroxyl group at C-3 and the location of the methyl and olefinic groups can increase cytotoxic activity. Both compounds require modification of their partial structures to increase cytotoxic activity.

## Acknowledgements

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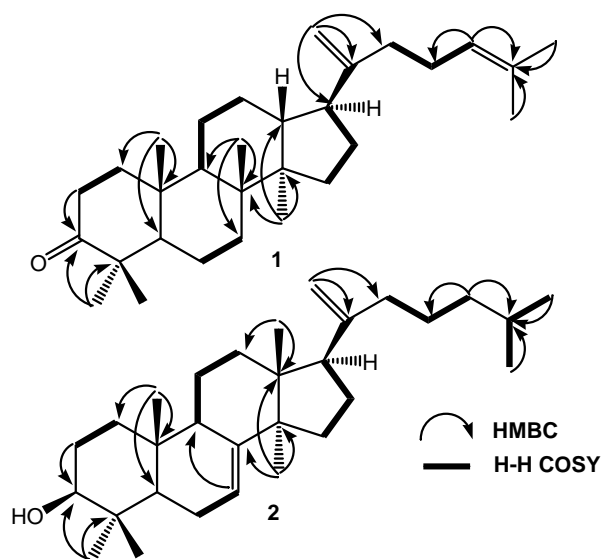


Figure 2. Selected HMBC and H-H COSY Correlations for **1** and **2**

Universitas Padjadjaran, Jatinangor, Indonesia for HR-ESITOFMS measurements and Mrs. Suzany Dwi Elita at Department of Chemistry, Faculty of Mathematics and Natural Sciences, Institute Technology Bandung for cytotoxicity bioassay.

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