Cytototoxic constituents from the bark of Chisocheton cumingianus (Meliaceae)

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Cytotoxic constituents from the bark of *Chisocheton cumingianus* (Meliaceae)

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ABSTRACT

F new lanostane-type triterpenoid, 3β-hydroxy-25-ethyl-lanost-9(11),24(24′)-diene (**1**), along with 3β-hydroxy-lanost-7-ene (**2**) and β-sitosterol-3-*O*-acetate (**3**) was isolated from the stem bark of *C. cumingianus*. The chemical structure of the new compound was elucidated on the basis of spectroscopic data. All of the compounds were evaluated for their cytotoxic effects against P-388 murine leukemia cells. Compounds **1-3** showed cytotoxicity against

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Lanostane-type triterpenoid; *Chisocheton cumingianus*; cytotoxic activity; Meliaceae

1. Introduction

The genus *Chisocheton*, the second largest genus of the family Meliaceae, consists of more than 50 species and is distributed across Nepal, India, Bhutan, Myanmar, South China, Thailand, Indonesia, Malaysia, and Papua New Guinea [1]. Previous phytochemical studies on *Chisocheton* plants reported the presence of compounds with interesting biological activ-ities including sesquiterpenoids [2], dammarane-type triterpenoids [2,3], tirucallane-type triterpenoids [4], apo-tirucallane-type triterpenoids [4,5], limonoids [6–11], steroids [10], and phenolics [3].

As part of our studies on anticancer candidate compounds from Indonesian *Chicocheton* plants, the methanolic extract from the bark of *Chisocheton cuminganus* showed significant cytotoxic activity against P-388 murine leukimia cells. *C. cuminganus* is a higher plant and widely distributed in the northern part of Sulawesi island in Indonesia [12]. Its bark has been used as an Indonesian folk medicine for reducing fever, treating contused wounds, and skin diseases [12,13]. The isolation, structure elucidation, and cytotoxic evaluation of these isolated compounds are described herein.

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2. Results and discussion

Barks of *Chisocheton cumingianus* were ground and successively extracted with *n*-hexane, ethyl acetate, and methanol. All of the extracts were evaluated for cytotoxic activ-ity against P-388 murine leukemia cells. The *n*-hexane and ethyl acetate extracts exhibited a cytotoxic activity against P-388 murine leukemia cells with IC_{50} values of 2.50 ± 0.05 a[illegible]3.40 ± 0.03 µg/ml, respectively. Subsequen[illegible]ytochemical analysis was therefore focused on the *n*-hexane and ethyl acetate extracts. The *n*-hexane and ethyl acetate extracts were chromatographed over a vacuum liquid chromatography (VLC) column packed with silica gel 60 by gradient elution. The VLC fractions were repeatedly subjected to normal-phase and reversed-phase column chromatography to afford three cytotoxic compounds **1-3** (Figure 1).

3β-Hydroxy-25-ethyl-lanost-9(11),24(24′)-diene (**1**) was obtained as colorless crystals, with m.p. 137–140 °C, and $[\ ]_{20D}$ -12 (*c*, 0.2, [illegible]Cl_3). Its molecular composition, $C_{33}H_{56}O$, was established from the HR-TOFMS found *m/z* 469.4345 $[M + H]^+$, (calcd for $C_{33}H_{56}O$, *m/z* 468.4331) and NMR data (Table[illegible]). The IR spectrum suggested the presence of a hydroxyl (3423 cm^{-1}), olefinic (1601 cm^{-1}), and ether groups (1178 cm^{-1}). The ^{13}C NMR spectrum showed 33 carbon resonances, which were classified by their chemical shifts, DEPT, and HMQC spectra as 9 methyls, 11 methylenes (one olefinic carbon), 6 methines (one oxy-genated and one olefinic carbons), and 7 quarternary c[illegible]ons (two olefinic carbons). These functionalities accounted for two out of the total six degrees of unsaturation. The remaining four degrees of unsaturation were consistent with the structure containing four rings. In addition, the presence of seven tertiary methyls (δ_H 0.88, 0.88, 0.95, 0.95, 1.01, 1.01, and 1.06; each 3H) and three olefinic protons (δ_H 4.76, 4.74 and 5.24) was evident by analysis of the ^1H NMR spectrum. These data as well as all the signals of the lanostane fused ring moiety were similar to those of the skimmiwallin which were previously isolated from *Skimmia wallichii* [16]. The ^{13}C NMR signals, however, were different from those of the latter at positions C-9, C-11, and C-19, but have same side chain structure with skimmiwallin. In the NMR spectra, the typical signals of the cycloartane methylenes at position C-19 [δ_C 29.8, δ_H 0.54; 0.31 (2H, br.s)] and sp^3 quarternary carbon at position C-9 (δ_C 19.9) were absent and the signal of an tertiary methyl [δ_C 22.2, δ_H 1.06 (3H, s)] and sp^2 quarternary carbon at position C-9 (δ_C 148.6) was newly observed in the NMR spectra, suggesting that a double bond was present at position 9(11). The skeleton and position of functional group of **1** were deduced from the ^1H-^1H COSY and HMBC spectra (Figure 2). In the HMBC spectrum, the correlations arising from the tertiary methyl protons to their neighboring carbons enabled the assignment of the seven singlet methyls. The HMBC spectrum of **1** showed cross-peaks from methyl protons at δ_H 1.06 to the sp^2 quarternary carbon at δ_C 148.6 (C-9). Olefinic proton at δ_H 5.24 showed correlations to sp^3 quartenary carbons at δ_C 26.3 (C-10), 45.3 (C-13), and a sp^3 methine carbon at δ_C 47.9 (C-8), whereas the corre-lations between sp^3 methylene proton at δ_H 1.60–1.62 and a sp^2 methine carbon at δ_C 114.9 (C-11) and s[illegible]quartenary carbon at δ_C 148.6 (C-9) suggested that the olefinic bond was at position 9(11). The HMBC cross-peaks from H-3 (δ_H 3.41–3.43) to the sp^3 m[illegible]thylene carbons at δ_C 30.7 (C-1) and 25.8 (C-2) and the cross-[illegible]k from methyl protons H-28 (δ_H 0.88) and H-29 (δ_H 0.95) to the oxymethine at δ_C 76.4 indicated the presence of a hydroxyl group at C-3. [illegible] stereochemistry of **1** was determined by NOESY experi-ment (Figure 3). [illegible]he NOESY cross-peaks observed between H-3 and H-28 indicated β-configuration of hydroxyl group at C-3. NOESY cross-peaks of H-17/H-30/CH_3-21

Table 1. ^{1}H and ^{13}C NMR spectral data (500 MHz for ^{1}H and 125 MHz for ^{13}C, in $CDCl_3$) for **1**.

	1	
Position carbon	^{13}C NMR δc (mult.)	^{1}H NMR δ_H (Integral, mult., J = Hz)
1	30.7 (t)	1.49 (1H, t, 3.9)
		1.51 (1H, t, 3.9)
2	25.8 (t)	1.63 (1H, dt, 9.5, 6.0)
		1.70 (1H, dt, 9.5, 6.0)
3	76.4 (d)	3.41–3.43 (1H, m)
4	38.0 (s)	–
5	46.9 (d)	1.29 (1H, t, 1.3)
6	28.2 (t)	1.38–1.40 (1H, m)
		1.41–1.43 (1H, m)
7	25.9 (t)	1.40–1.42 (1H, m)
		1.34–1.36 (1H, m)
8	47.9 (d)	1.51–1.53 (1H, m)
9	148.6 (s)	–
10	26.3 (s)	–
11	114.9 (d)	5.34 (1H, d, 5.8)
12	32.9 (t)	1.59–1.61 (1H, m)
		1.60–1.62 (1H, m)
13	45.3 (s)	–
14	48.8 (s)	–
15	35.5 (t)	1.25–1.27 (1H, m)
		1.26–1.28 (1H, m)
16	28.2 (t)	1.28–1.30 (1H, m)
		1.79–1.81 (1H, m)
17	52.1 (d)	1.61–1.63 (1H, m)
18	18.1 (q)	0.95 (3H, s)
19	22.2 (q)	1.06 (3H, s)
20	36.8 (d)	2.07–2.09 (1H, m)
21	18.7 (q)	0.88 (3H, d, 6.5)
22	36.9 (t)	1.13–1.15 (1H, m)
		1.56–1.60 (1H, m)
23	27.4 (t)	1.74–1.76 (1H, m)
		2.03–2.05 (1H, m)
24	157.9 (s)	–
25	39.3 (s)	–
26	27.7 (q)	1.01 (3H, s)
27	28.0 (q)	1.01 (3H, s)
28	22.7 (q)	0.88 (3H, s)
29	28.5 (q)	0.95 (3H, s)
30	18.7 (q)	0.88 (3H, s)
24′	106.5 (t)	4.74 (1H, d, 1.3)
		4.76 (1H, d, 1.3)
25′	33.1 (t)	1.66 (2H, q, 7.1)
25″	13.1 (q)	1.03 (3H, t, 7.1)

indicated β-configuration of CH_3-18 and α-configuration of CH_3-30. This configuration was very important to distinguish tirucallane-type (C-18α, C-30β) with lanostane-type (C-18β, C-30α) triterpenoids [17]. Consequently, compound **1** was determined as a new lanostane-type triterpenoid and named 3β-hydroxy-25-ethyl-lanost-9(11),24(24′)-diene.

The known compounds were identified to be 3β-hydroxy-lanost-7-ene (**2**) [18] and β-sitosterol-3-*O*-acetate (**3**) [19] on the basis of NMR and MS techniques, as well as by comparison of their spectral data with those reported previously.

The cytotoxicity effects of the isolated compounds against the P-388 murine leukemia cells were conducted according to the method described in previous paper [14,15,20] and an artonin E (IC_{50} 0.3 μg/ml) was used as a positive control [21].

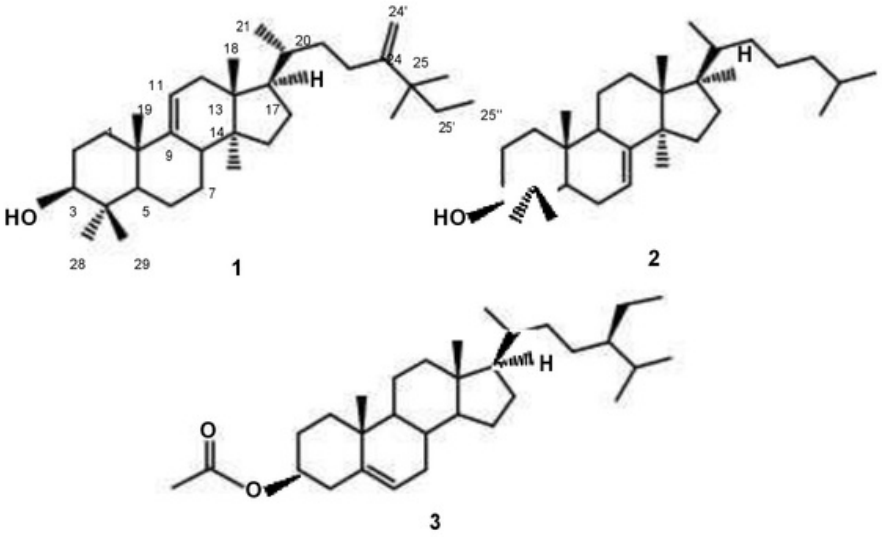

Figure 1. Structures of compounds **1-3**.

Compounds **1-3** were evaluated for their cytotoxicity against the P-388 murine leukemia cells and showed IC_{50} values of 28.8 ± 0.10, 4.29 ± 0.03, and 100.18 ± 0.16 µg/ml. Among these compounds, 3β-hydroxy-lanost-7-ene (**2**) having a hydroxyl and an olefinic group showed strong activity, whereas β-sitosterol-3-*O*-acetate (**3**) having 3-acetyl group and 3β-hydroxy-25-ethyl-lanost-9(11),24(24′)-diene having one more olefinic bond showed inactive and weak activity, suggesting that the hydroxyl and the olefinic bonds are important functional groups for cytotoxic activity.

3. Experimental

3.1. General experimental procedures

Melting points were measured on an electrothermal melting point apparatus IA9000 (Bibby Scientific Limited, Staffordshire, UK). Optical rotations were recorded on a Perkin Elmer 341 polarimeter (Waltham, MA, USA). The IR spectra were recorded on a Perkin Elmer 1760X FT-IR in KBr (Waltham, MA, USA). Mass spectra were obtained with a Water Qtof HR-MS XEV^{otm} mass spectrometer (Waters, Milford, MA, USA). ^{1}H- and ^{13}C-NMR spectra were obtained with a JEOL JNM A-500 spectrometer (Tokyo, Japan) using TMS as an internal standard. Chromatographic separations were carried out on silica gel 60 (Merck, Darmstadt, Germany). TLC plates were precoated with silica gel GF_{254} (Merck, 0.25 mm) and detection was achieved by spraying with 10% H_2SO_4 in ethanol, followed by heating.

3.2. Plant material

The stem barks of *Chisocheton cumingianus* were collected in Bogor Botanical Garden, Bogor, West Java Province, Indonesia, in April 2014. The plant was identified by the staff of the Bogoriense Herbarium, Bogor, Indonesia, and a voucher specimen (No. Bo-1305315) was deposited at the herbarium.

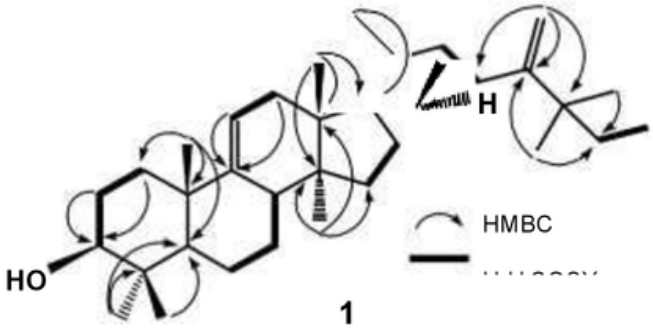

Figure 2. Selected HMBC and ^{1}H-^{1}H COSY correlations for 1.

3.3. Extraction and isolation

Dried ground stem barks (2.2 kg) of *C. cumingianus* were extracted successively with *n*-hexane, EtOAc, and MeOH. Evaporation resulted in the crude extracts of *n*-hexane (36.9 g), EtOAc (23.6 g), and MeOH (30.0 g), respectively. The *n*-hexane, ethyl acetate, and methanol extracts exhibited a cytotoxic activity against P-388 murine leukemia cells with IC_{50} values of 2.50 ± 0.05, 3.40 ± 0.03, and 33.85 ± 0.05 µg/ml, respectively.

The *n*-hexane extract of *C. cumingianus* (36.9 g) was subjected to vacuum liquid chromatography over silica gel using a gradient elution mixture of *n*-hexane–EtOAc (10:0–0:10) as eluting solvent to afford 15 fractions (A01–A015). Fractions A01–A06 were combined (200 mg) and subjected to column chromatography over silica gel using a gradient mixture of *n*-hexane–$CHCl_3$ (4:1–3:2) as eluting solvent to afford nine fractions (B01–B09). Fraction B03 (64.7 mg) was subjected to column chromatography over silica gel using a mixture of *n*-hexane–EtOAc (9.5:0.5) as eluting solvent to give **1** (6.8 mg). Fractions A07–A08 were combined (170 mg) and subjected to column chromatography over silica gel using a gradient mixture of *n*-hexane–Me_2CO (10:0–9:1) as eluting solvent to afford seven fractions (C01–C07). Fraction C05 (80.1 mg) was subjected to column chromatography over silica gel using a mixture of $CHCl_3$:Me_2CO (7:3) to give **2** (4.7 mg). The ethyl acetate extract of *C. cumingianus* (23.6 g) was subjected to vacuum liquid chromatography over silica gel using a gradient elution mixture of *n*-hexane–EtOAc (10:0–0:10) as eluting solvent to afford nine fractions (D01–D09). Fraction D04 (3.8 g) was subjected to column chromatography over silica gel using a mixture of CH_2Cl_2/Me_2CO (9:1) as eluting solvent to afford eight fractions (E01–E08). Fraction E05 (1.5 g) was subjected to column chromatography over silica gel using a mixture of $CHCl_3$:MeOH (8:2) as eluting solvent to afford 40 fractions (F01–F040). Fractions F08–F020 were combined (82 mg) and subjected to column chromatography over ODS using a mixture of MeOH:H_2O (7:3) to give **3** (6.0 mg).

3.3.1. 3β-Hydroxy-25-ethyl-lanost-9(11),24(24')-diene (1)

Colorless crystals; m.p. 137–140 °C; $[\alpha]_{20D}$ -12 (*c* 0.2, $CHCl_3$); IR (KBr) ν_{max} 3423, 1601, 1178, 879 cm^{-1}; ^{1}H NMR spectral data ($CDCl_3$, 500 MHz), Table 1; ^{13}C NMR spectral data ($CDCl_3$, 125 MHz), see Table 1; HR-TOFMS: *m/z* 469.4345 $[M + H]^+$ (calcd for $C_{33}H_{56}O$, 468.4331).

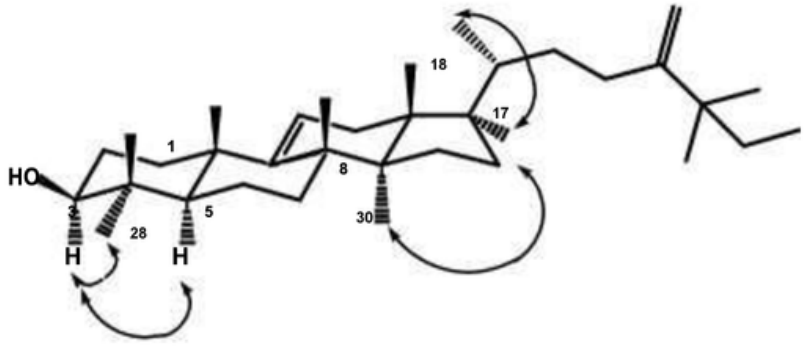

Figure 3. Selected NOESY correlations for 1.

3.4. Determination of cytotoxic activities

The cytotoxicity assay was conducted according to the method described by Sahidin *et al.* and Alley *et al.* [14,15]. P388 cells were seeded into 96-well plates at an initial cell density of approximately 3×10^4 cells cm^{-3}. After 24 h of incubation for cell attachment and growth, varying concentrations of samples were added. The compounds added were first dissolved in DMSO at the required concentration. Subsequently, six desirable concentrations were prepared using PBS (phosphoric buffer solution, 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, in which the MTT-stop solution containing sodium dodecyl sulfate was added and another 24-h incubation was conducted. Optical density was read using a microplate reader at 550 nm. IC_{50} values were taken from the plotted graph of percentage live cells compared to control (%), receiving only PBS and DMSO vs. the tested concentration of compounds (μg/ml). The IC_{50} value is the concentration required for 50% growth inhibition. All analyses were carried out in triplicate, and the results were expressed as the mean ± standard deviation and compared using Waller–Duncan test. A value of $p < 0.05$ was considered statistically significant.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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