

# Azadirone-Type Limonoids from the Fruit of *Chisocheton lasiocarpus* and Their Cytotoxic Activity Against MCF-7 Breast Cancer Lines

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**Azadirone-Type Limonoids from the Fruit of *Chisocheton lasiocarpus* and Their Cytotoxic Activity Against MCF-7 Breast Cancer Lines**Erina Hilmayanti<sup>1</sup>, Nurlelarsi<sup>1</sup>, Dewa Gede Katja<sup>2</sup>, Ace Tatang Hidayat<sup>1,3</sup>, Sofa Zuhriah<sup>4</sup>, Akhmad Darmawan<sup>4</sup>, Unang Supratman<sup>1,3,\*</sup>, Mohamad Nurul Azmi<sup>5</sup>, Yoshihito Shiono<sup>6</sup><sup>1</sup>Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran, Jatinangor 45363, Sumedang, Indonesia<sup>2</sup>Department of Chemistry, Faculty of Mathematics and Natural Sciences, Sam Ratulangi University, Kampus Kleak, Manado, 95115, North Sulawesi, Indonesia<sup>3</sup>Central Laboratory of Universitas Padjadjaran, Jatinangor 45363, Sumedang, Indonesia<sup>4</sup>Research Center for Chemistry, Indonesian Science Institute, Serpong 15311, South Tangerang, Indonesia<sup>5</sup>School of Chemical Sciences, Universiti Sains Malaysia, 11800 Minden, Penang, Malaysia<sup>6</sup>Department of Bioresources Engineering, Faculty of Agriculture Yamagata University, Tsuruoka-shi, Yamagata 997-8555, Japan

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**ABSTRACT.** Limonoid is derivatives of triterpenoid compound that have a wide variety of structures due to various ring-opening, rearrangements, and high-degree of oxidation. Limonoid is known as compounds that have wide-range of biological activities, including anticancer activity. This research was aimed to determine the chemical structure and cytotoxic activity of limonoid in the *n*-hexane extract of *Chisocheton lasiocarpus* fruit. Dried powder of *C. lasiocarpus* fruit was extracted using methanol followed by fractionated using *n*-hexane, ethyl acetate, and *n*-butanol. Five azadirone-type limonoids, 6 $\alpha$ -(acetoxyl)-14 $\beta$ ,15 $\beta$ -epoxyazadirone (**1**), dysobinin (**2**), 7 $\alpha$ -acetylneotricilenone (**3**), 6 $\alpha$ -O-acetyl-7-deacetylnimocinol (**4**), and 7 $\alpha$ -hydroxyneotricilenone (**5**), were isolated from the *n*-hexane extract of *Chisocheton lasiocarpus* fruit. The chemical structure of all compounds was identified by spectroscopic analysis, including 1D, 2D-NMR, IR, UV and HR-TOF MS as well as by comparison with previous reported spectra data. Compounds **1-5** were investigated from this plant for first time. The cytotoxic activity of the isolated compounds against MCF-7 breast cancer line were examined and the results showed that 7 $\alpha$ -hydroxyneotricilenone (**5**) showed the moderate activity with IC<sub>50</sub> values of 53  $\mu$ M.

**Keywords:** cytotoxic activity, limonoid, *Chisocheton lasiocarpus*, Meliaceae, MCF-7**INTRODUCTION**

*Chisocheton* is one genus of the of the Meliaceae Family with more than 53 species and distributed in tropical and subtropical region in Asia such as Nepal, Bhutan, India, Myanmar, South China, South East Asia and Papua New Guinea (Heyne, 1982; Vossen & Umali, 2002; Zhang et al., 2012). Plant from *Chisocheton* genus has been used traditionally as medicine for treatment of stomach illness, kidney illness, backache, fever, rheumatism and malaria (Shilpi et al., 2016; Tasyriq, et al., 2012). Plant extract or isolated compounds from *Chisocheton* plants has been reported to showed many bioactivities, including insecticidal, insect antifeedant, antiobesity, antimalarial, antibacterial, antifungal, antiviral, antimelanin, cytotoxic, and anti-inflammatory (Chie et al., 2016; Fang, Di, & Cao, 2011; Mohamad et al., 2008; Retnowati et al., 2021; Salam et al., 2021; Supratman et al., 2019,

2020; Wong et al., 2012; Yadav, Yadav, &amp; Goyal, 2014; Yadav, Katakya, &amp; Matur, 1999).

One of the compounds that responsible for these activities are limonoid which known to be abundance in *Chisocheton* genus. So far more than 50 limonoids has been isolated from *Chisocheton* plants (Shilpi et al., 2016). Limonoid compounds are highly oxygenated modified triterpenoids with moderate polarity and known as tetranortriterpenoids (Salam et al., 2021). These structures varied by the oxidation on the backbone, the side chain moiety, ring transformation and rearrangements which attracted great interest (Chong et al., 2019; Mohamad et al., 2008; Najmuldeen et al., 2012; Roy & Saraf, 2006).

*C. lasiocarpus* known as Maksang in local name and the leaves are usually used for wrapping food, while the chemical report of this species is still limited that only lasiocarpines and 14 $\beta$ ,15 $\beta$ -epoxynimonol has been reported isolated from seed

of *C. lasiocarpus* (Whitmore, Mabberley, Pannell, & Sigh, 1996; Fitriana et al., 2021). Therefore, in our continuous investigation for limonoid compounds from Indonesian *Chisocheton* plants, we have been described limonoids, dysobinol from *C. macrophyllus* (Nurlelarsi et al., 2017) and pentandricine from *C. pentandrus* stem bark (Supriatno et al., 2018). In the further search for limonoid substances from Indonesian *Chisocheton* plants, the *n*-hexane extract of *C. lasiocarpus* fruit was found to have high content of limonoid based on its TLC screening using Erlich reagent. In this contribution, we describe the isolation and structural identification of five limonoids (Figure 1), as well as their cytotoxic activity.

## EXPERIMENTAL SECTION

### General

UV spectra were recorded on TECAN Infinite M200 pro with methanol as solvent. The IR spectra were measured on Nicolet Summit FTIR Spectrometer with DTGS KBr detector. Mass Spectra were measured by Waters QTOF-HRTOFMS-XEVO mass spectrometer. NMR spectra were measured by JEOL JNM-ECZ500R/S1 and TMS as an internal standard. Chromatographic separation was carried out on silica gel 60 (70-230 mesh and 230-400 mesh, Merck). Thin-layer chromatography (Merck, 0.25 mm) and spots were detected under ultraviolet-visible light and followed by spraying with Ehrlich's reagent (*p*-Dimethylaminobenzaldehyde in 1:1 hydrochloric acid and ethanol).

### Plant Material

Fruit of *C. lasiocarpus* (Miq.) Valetton was found from Bogor Botanical Garden, Bogor, West Java, Indonesia in August 2019. The identification of plant was carried out by Mr. Harto, the staff of Bogoriense Herbarium, Bogor, Indonesia and voucher specimen AM. G. 168) was deposited at the herbarium.

### Extraction and Isolation

The dried fruit of *C. lasiocarpus* (1.2 kg) was extracted with methanol for 6 days (6 x 3L) and evaporated the solvent to produce dark brown residue (270 g). The residue was fractionated successively with *n*-hexane, ethyl acetate and *n*-butanol followed with solvent evaporation in vacuum to afford concentrated extract of *n*-hexane (36.5 g), ethyl acetate (28.1 g) and *n*-butanol (3.6 g). All of the extracts were examined for their cytotoxic activity against MCF-7 breast cancer cell line and showed activity with IC<sub>50</sub> values of 168; 389 and 404 µg/mL, respectively. The *n*-hexane showed the strongest cytotoxic activity and contents of limonoid compounds based on the TLC analysis under UV light and positive result on Ehrlich's reagent sprayer. Therefore, the further isolation was focused on the *n*-hexane extract.

The *n*-hexane extract was separated by vacuum liquid chromatography (VLC) on silica gel 60 using gradient system eluent of *n*-hexane, ethyl acetate,

and methanol to afford nine fractions (A-I). Fraction C (16.7 g) was subjected to VLC on silica gel with *n*-hexane and ethyl acetate as a gradient eluent give seven subfractions (C1-C7). Subfraction C3 (2.1 g) was subjected to silica gel column chromatography using gradient solvent of *n*-hexane and ethyl acetate to afford five subfractions (C3A-C3E). Furthermore, subfraction C3B was column chromatographed on a silica gel (230-400 mesh) eluted by *n*-hexane : dichloromethane : ethyl acetate (6:3:1) to give 1 (33.2 mg) and 2 (30.1 mg). Fraction C4 (1.1 g) was column chromatographed on a silica gel (230-400 mesh), eluted with *n*-hexane : ethyl acetate (8:2) to give five subfractions (C4A-C4E). In addition, subfraction C4D (280 mg) was separated by column chromatographed on ODS eluted with methanol : water (8:2) to give compound 3 (9.6 mg) and 33 (6.5 mg). Finally, subfraction C4E (59.3 mg) was separated by column chromatography on silica gel (230-400 mesh), eluted by *n*-hexane : chloroform : Ethyl acetate (6:2:2) to afford compound 5 (11.5 mg).

### 6 $\alpha$ -(acetoxyl)-14 $\beta$ ,15 $\beta$ -epoxyazadirone (1).

Colorless needle crystal; mp: 210-213 °C; UV (MeOH)  $\lambda_{max}$  (log  $\epsilon$ ): 230 nm (2.63); IR (KBr plate)  $\nu_{max}$  cm<sup>-1</sup>: 2922, 1739, 1675, 1030; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta_H$  7.36 (1H, t, *J* = 1.5 Hz, H-23), 7.14 (1H, d, *J* = 10.5 Hz, H-1), 7.09 (1H, s, H-21), 6.15 (1H, d, *J* = 1.5 Hz, H-22), 5.92 (1H, d, *J* = 10.5 Hz, H-2), 5.35 (1H, dd, *J* = 2.5, 12.5 Hz, H-6), 5.03 (1H, d, *J* = 2.5 Hz, H-7), 3.43 (1H, m, H-15), 2.62 (1H, td, *J* = 4.5, 11.5 Hz, H-17), 2.50 (1H, d, *J* = 12.5 Hz, H-5), 2.13 (1H, d, *J* = 4.5 Hz, H-16b), 2.11 (1H, s, CH<sub>3</sub>-1'), 2.01 (1H, s, CH<sub>3</sub>-1'), 1.89 (2H, m, H-12), 1.81 (1H, m, H-11), 1.59 (1H, dd, *J* = 11.0, 13.5 Hz, H-16a), 1.24 (1H, s, CH<sub>3</sub>-30), 1.22 (1H, s, CH<sub>3</sub>-29), 1.17 (1H, s, CH<sub>3</sub>-28), 1.15 (1H, s, CH<sub>3</sub>-19), 0.95 (1H, s, CH<sub>3</sub>-18); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 125 MHz), see Table 1; HR-TOF MS *m/z* 511.2693 [M+H]<sup>+</sup> (calcd. *m/z* 511.2696 for C<sub>30</sub>H<sub>39</sub>O<sub>7</sub>).

**Dysobinin (2).** White crystal; mp: 190-194 °C; UV (MeOH)  $\lambda_{max}$  (log  $\epsilon$ ): 229 nm (2.45); IR (KBr)  $\nu_{max}$  cm<sup>-1</sup>: 2938, 1721, 1664, 1503, 1022; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta_H$  7.37 (1H, t, *J* = 1.5 Hz, H-23), 7.23 (1H, s, H-21), 7.14 (1H, d, *J* = 10.0 Hz, H-1), 6.27 (1H, d, *J* = 1.5 Hz, H-22), 5.91 (1H, d, *J* = 10.0 Hz, H-2), 5.45 (1H, d, *J* = 3.0 Hz, H-15), 5.42 (1H, d, *J* = 3.0 Hz, H-7), 5.37 (1H, m, H-6), 2.81 (1H, dd, *J* = 7.5, 10.5 Hz, H-17), 2.50 (1H, d, *J* = 12.0 Hz, H-5), 2.39-2.42 (1H, m, H-12b), 2.34-2.36 (1H, m, H-12a), 2.25 (1H, dd, *J* = 4.5, 10.5 Hz, H-16b), 2.04 (3H, s, CH<sub>3</sub>-1'), 2.02 (1H, d, *J* = 3.0 Hz, H-16a), 2.00 (3H, s, CH<sub>3</sub>-1'), 1.93 (1H, m, H-11b), 1.73 (1H, m, H-11a), 1.65 (1H, m, H-9), 1.32 (3H, s, CH<sub>3</sub>-30), 1.25 (3H, s, CH<sub>3</sub>-29), 1.18 (3H, s, CH<sub>3</sub>-19), 1.18 (3H, s, CH<sub>3</sub>-28), 0.79 (3H, s, CH<sub>3</sub>-18); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 125 MHz), see Table 1; HR-TOFMS *m/z* 495.2743 [M+H]<sup>+</sup> (calcd. *m/z* 495.2747 for C<sub>30</sub>H<sub>39</sub>O<sub>6</sub>).

**7 $\alpha$ -acetylnatricilene (3).** White crystal; m.p 207-210 °C; UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ): 230 nm (2.68); IR (KBr)  $\nu_{\max}$   $\text{cm}^{-1}$ : 2956, 1722, 1662, 1026;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 500 MHz):  $\delta_{\text{H}}$  7.39 (1H, t,  $J = 1.5$  Hz, H-23), 7.28 (1H, s, H-21), 7.15 (1H, d,  $J = 10.0$  Hz, H-1), 6.29 (1H, t,  $J = 1.5$  Hz, H-22), 5.88 (1H, d,  $J = 10.0$  Hz, H-2), 4.96 (1H, t,  $J = 2.5$  Hz, H-7), 3.48 (1H, t,  $J = 10.0$  Hz, H-17), 2.50 (1H, t,  $J = 10.0$  Hz, H-16), 2.43 (1H, s, H-14), 2.08 (1H, s,  $\text{CH}_3$ -1'), 2.07 (1H, dd,  $J = 5.0, 10.5$  Hz, H-5), 1.99 (1H, td,  $J = 3.0, 14$  Hz, H-12b), 1.87-1.90 (2H, m, H-6), 1.69-1.79 (2H, m, H-11), 1.38 (1H, dd,  $J = 2.5, 11.5$  Hz, H-9), 1.25-1.32 (1H, m, H-12a), 1.15 (3H, s,  $\text{CH}_3$ -30), 1.13 (3H, s,  $\text{CH}_3$ -19), 1.06 (3H, s,  $\text{CH}_3$ -29), 1.05 (3H, s,  $\text{CH}_3$ -28), 0.78 (3H, s,  $\text{CH}_3$ -18);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 125 MHz), see Table 1; HR-TOFMS  $m/z$  475.2462  $[\text{M}+\text{Na}]^+$ , (calcd.  $m/z$  475.2460 for  $\text{C}_{28}\text{H}_{36}\text{O}_5\text{Na}$ ).

**6 $\alpha$ -O-acetyl-7-deacetyl nimocinol (4).** Colorless crystal; m.p 189-191 °C; UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ): 229 nm (2.64); IR (KBr)  $\nu_{\max}$   $\text{cm}^{-1}$ : 3384, 2943, 1739, 1658, 1019.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 500 MHz):  $\delta_{\text{H}}$  7.38 (1H, t,  $J = 1.5$  Hz, H-23), 7.27 (1H, s, H-21), 7.11 (1H, d,  $J = 10.0$  Hz, H-1), 6.28 (1H, d,  $J = 1.5$  Hz, H-22), 5.88 (1H, d,  $J = 10.0$  Hz, H-2), 5.57 (1H, d,  $J = 3.5$  Hz, H-15), 5.46 (1H, dd,  $J = 2.0, 12.0$  Hz, H-6), 4.07 (1H, d,  $J = 2.0$  Hz, H-7), 2.86 (1H, dd,  $J = 7.5, 11.0$  Hz, H-17), 2.74 (1H, d,

H-16b), 2.42 (1H, dd,  $J = 3.5, 7.5, 15.0$  Hz,  $J = 12.0$  Hz, H-8), 2.57 (1H, dd,  $J = 11.0, 15.0$  Hz, H-16a), 2.29 (1H, dd,  $J = 12.0, 6.5$  Hz, H-9), 2.18 (3H, s,  $\text{CH}_3$ -1'), 1.93-1.96 (1H, m, H-11b), 1.88-1.92 (1H, m, H-12b), 1.70-1.77 (1H, m, H-11a), 1.63-1.66 (1H, m, H-12a), 1.32 (3H, s,  $\text{CH}_3$ -29), 1.28 (3H, s,  $\text{CH}_3$ -30), 1.19 (3H, s,  $\text{CH}_3$ -28), 1.17 (3H, s,  $\text{CH}_3$ -19), 0.83 (3H, s,  $\text{CH}_3$ -18);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 125 MHz), see Table 1; HR-TOFMS  $m/z$  475.2462  $[\text{M}+\text{H}]^+$ , (calcd.  $m/z$  475.2460 for  $\text{C}_{28}\text{H}_{36}\text{O}_5\text{Na}$ ).

**7 $\alpha$ -hydroxynatricilene (5).** White needle crystal; m.p 217-217 °C; UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ): 230 nm (2.63); IR (KBr)  $\nu_{\max}$   $\text{cm}^{-1}$ : 3435, 2939, 1715, 1666, 1636, 1025;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 500 MHz):  $\delta_{\text{H}}$  7.40 (1H, t,  $J = 1.5$  Hz, H-23), 7.29 (1H, s, H-21), 7.13 (1H, d,  $J = 10.0$  Hz, H-1), 6.30 (1H, d,  $J = 1.5$  Hz, H-22), 5.86 (1H, d,  $J = 10.0$  Hz, H-2), 3.89 (1H, br.s, H-7), 3.49 (1H, s, H-17), 2.72 (1H, s, H-14), 2.52 (2H, dd,  $J = 10.5$  Hz, H-16), 2.29 (1H, dd,  $J = 2.5, 13.0$  Hz, H-12b), 2.27 (1H, dd,  $J = 2.5, 13$ , H-5), 2.01 (1H, dt,  $J = 3.5, 14.5$  Hz, H-12a), 1.94 (1H, td,  $J = 2.5, 13.0, 14.5$  Hz, H-6a), 1.72 (1H, m, H-6b), 1.37 (1H, dd,  $J = 2.5, 11.0$  Hz, H-9), 1.15 (3H, s,  $\text{CH}_3$ -29), 1.10 (3H, s,  $\text{CH}_3$ -19), 1.09 (3H, s,  $\text{CH}_3$ -28), 1.09 (3H, s,  $\text{CH}_3$ -30), 0.79 (3H, s,  $\text{CH}_3$ -18);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 125 MHz), see Table 1; HR-TOFMS  $m/z$  433.2353  $[\text{M}+\text{H}]^+$ , (calcd.  $m/z$  433.2355 for  $\text{C}_{26}\text{H}_{34}\text{O}_4$  Na).

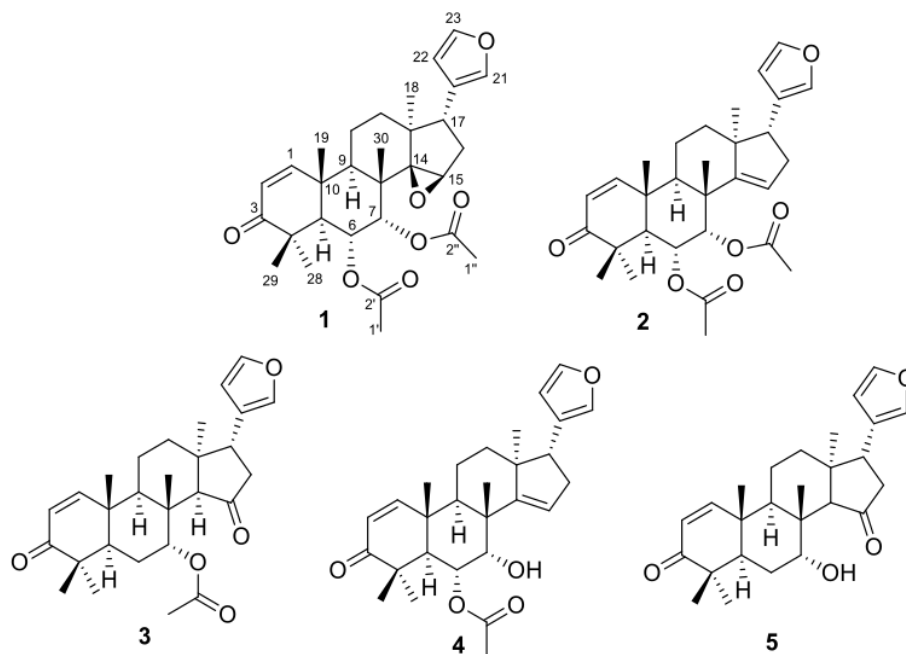


Figure 1. Structures of Compounds 1-5



### Determination of Cytotoxic Activity

The cytotoxicity of compounds **1-5** was measured in a cell viability test by PrestoBlue® assay. The cells were maintained in Roswell Park Memorial Institute (RPMI) medium with 10% (v/v) Fetal Bovine Serum (FBS) and 1 µL/mL antibiotics (1% Penicillin-Streptomycin). Cultures were incubated at 37 °C in a humidified atmosphere of 5% CO<sub>2</sub>. MCF-7 cells plated in 96 multi-well culture plates at a density of  $1.7 \times 10^4$  cells/well. After 24 h, the medium was discarded and fresh medium containing sample with different concentrations 7.81, 15.63, 31.25, 62.50, 125.00, 250.00, 500.00, 1000.00 µg/mL and control was added. After incubation with the sample for 48h, PrestoBlue® reagent (resazurin dye) was added. The PrestoBlue® assay results were read using a multimode reader at 570 nm. The IC<sub>50</sub> values were determined by linear regression method using Microsoft Excel software. The IC<sub>50</sub> value corresponds to the concentration of compounds that decreases by 50% the number of viable cells and the absorbance in control corresponds to 100% viability (Nurlelasari et al., 2021).

### RESULTS AND DISCUSSIONS

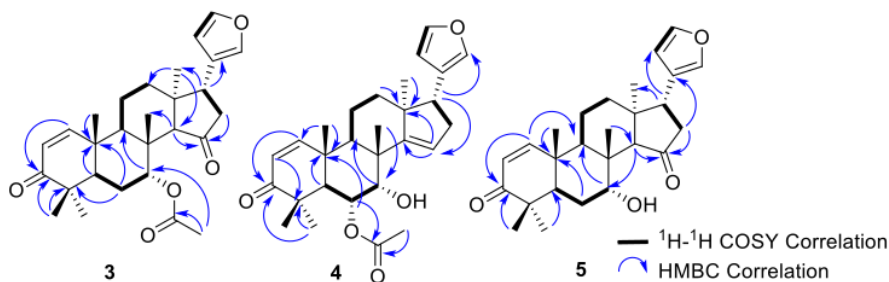
Dried and grinded fruit of *C. lasiocarpus* (1.2 kg) was extracted with methanol and further evaporated to afford dark brown residue (270 g) and fractionated successively with *n*-hexane, Ac and *n*-butanol. The *n*-hexane extract (36.5 g) was subjected to several chromatography procedures including vacuum-liquid chromatography (VLC), column chromatography and crystallization, the separation process was observed by TLC using silica gel GF<sub>254</sub> to afford five limonoid compound **1-5** (Figure 1).

Compound **1** was obtained as a colorless needle crystal (MeOH), having the molecular formula of C<sub>30</sub>H<sub>38</sub>O<sub>7</sub> based on analysis of HR-TOFMS spectra with peak ion molecule [M+H]<sup>+</sup> *m/z* 511.2693 (calcd. for C<sub>30</sub>H<sub>39</sub>O<sub>7</sub>, *m/z* 511.2696), with twelve degrees of unsaturation. The UV spectrum showed maximum absorption at 230 nm (log ε 2.63), suggesting the presence of an enone group. The IR spectrum showed the presence of aliphatic (2922), carbonyl ester (1739 cm<sup>-1</sup>), carbonyl (1775 cm<sup>-1</sup>) and ether group (1030 cm<sup>-1</sup>). The <sup>1</sup>H-NMR spectrum displayed seven tertiary methyl singlets, consisting of five from limonoid skeleton and two from acetoxy group δ<sub>H</sub> 0.95 (3H, s, CH<sub>3</sub>-18), 1.15 (3H, s, CH<sub>3</sub>-19), 1.17 (3H, s, CH<sub>3</sub>-28), 1.22 (3H, s, CH<sub>3</sub>-29), 1.24 (3H, s, CH<sub>3</sub>-30), 2.11 (3H, s, CH<sub>3</sub>-1') and 2.01 (3H, s, CH<sub>3</sub>-1''), five olefinic protons δ<sub>H</sub> 5.92 (1H, d, *J* = 10.5, H-2), 6.15 (1H, d, *J* = 1.5 Hz, H-22), 7.14 (1H, d, *J* = 10.5 Hz, H-1), 7.09 (1H, s, H-21), and 7.36 (1H, s, *J* = 1.5 Hz, H-23), three oxymethines δ<sub>H</sub> 5.35 (1H, dd, *J* = 2.5, 12.5 Hz, H-6), 5.03 (1H, d, *J* = 2.5 Hz, H-7) and 3.43 (1H, m, H-15). The <sup>13</sup>C NMR and DEPT 135° spectra revealed

30 carbon signals, exhibited the presence of five quaternary methyl groups that is characteristic of intact limonoid at δ<sub>C</sub> 21.5 (C-18), 21.8 (C-19), 31.6 (C-28), 20.1 (C-29), 18.8 (C-30), and two additional quaternary methyl groups came from acetoxy group at δ<sub>C</sub> 21.2 (C-1') and 21.1 (C-1''). The <sup>13</sup>C-NMR spectrum also showed signals at δ<sub>C</sub> 157.6 (C-6), 126.1 (C-2) and 204.6 (C-3), a characteristic of an α,β-unsaturated ketone at the ring A. In addition, signals at 123.6 (C-20), 139.5 (C-21), 110.8 (C-22) and 142.9 (C-23) is a typical peak for a furan side chain. Four oxygenated carbon signals at δ<sub>C</sub> 70.1 (C-6), 73.5 (C-7), 72.7 (C-14) and 57.1 (C-15), two oxygenated carbons are the carbon that bond to the acetoxy group and the signal at chemical shift region of C-14 (δ<sub>C</sub> 72.7) and C-15 (δ<sub>C</sub> 57.1) inferred a pair of carbon signal for epoxide ring. The functionalities accounted for seven out of the twelve degrees of unsaturation, and five degrees of unsaturation belongs to pentacyclic of limonoid skeleton (Nurlelasari et al., 2021; Wong et al., 2011; Yang, Wang, Luo, Wang, & Kong, 2012). The NMR data of compound **1** resembled a similar result with reported for compound 6α-(acetoxy)-14β,15β-epoxyazadirone that isolated from seeds of *Toona ciliata* (Neto et al., 1995). Therefore, the structure of compound **1** was identified as 6α-(acetoxy)-14β,15β-epoxyazadirone.

To determine the stereochemistry of the substituents at C-6 and C-7 besides from NOESY experiment, it also can be defined based on its vicinal coupling constant, the vicinal coupling constant for proton at C-5, C-6 and C-7 is (*J*<sub>HH</sub> = 12.3 Hz), (*J*<sub>HH</sub> = 12.3 and 2.5 Hz), and (*J*<sub>HH</sub> = 2.5 Hz) respectively. The orientation of H-5 based on biosynthesis approach is β-oriented with axial position, the large vicinal coupling constant (*J*<sub>HH</sub> = 12.3 Hz) indicate axial-axial correlation (vicinal coupling constant correlation value *J*<sub>aa</sub> = 7-12 Hz; *J*<sub>ee</sub> = *J*<sub>oe</sub> = 2-5 Hz), inferred the proton on C-6 at the axial position which is β-orientation and the acetoxy group at the opposite plane at α-orientation. The vicinal coupling constant between H-6 and H-7 have small value (*J*<sub>HH</sub> = 2.5 Hz) that indicate axial-equatorial correlation and it inferred H-7 at the equatorial position (β-orientation) and the acetoxy group at axial position at α-orientation.

Compound **2** was obtained as a white crystal (MeOH) with melting point, 210-213 °C. The molecular formula was identified to be C<sub>30</sub>H<sub>38</sub>O<sub>6</sub> with twelve degrees of unsaturation based on analysis of HR-TOFMS spectra with peak ion molecule [M+H]<sup>+</sup> *m/z* 495.2743 (calcd. *m/z* 495.2747 for C<sub>30</sub>H<sub>39</sub>O<sub>6</sub>). The IR and UV spectra of compound **2** exhibited similar spectral data to compound **1**, and the <sup>1</sup>H-NMR spectrum displayed seven tertiary methyl singlets δ<sub>H</sub> 0.79 (3H, s, CH<sub>3</sub>-18), 1.18 (3H, s, CH<sub>3</sub>-19), 1.18 (3H, s, CH<sub>3</sub>-28), 1.25 (3H, s, CH<sub>3</sub>-29), 1.32 (3H, s, CH<sub>3</sub>-30), 2.04 (3H, s, CH<sub>3</sub>-1') and



**Figure 2** Selected HMBC and  $^1\text{H}$ - $^1\text{H}$  COSY correlation of compound 3-5.

61.0 (3H, s,  $\text{CH}_3$ -1"), but different from compound 1, compound 2 have six olefinic protons at  $\delta_{\text{H}}$  7.14 (1H, d,  $J=10.0$  Hz, H-1), 7.23 (1H, s, H-21), 7.27 (1H, d,  $J=1.5$  Hz, H-22), 7.37 (1H, t,  $J=1.5$  Hz, H-23), 5.42 (1H, d,  $J=3.0$  Hz, H-15) and only two oxygenated methine proton  $\delta_{\text{H}}$  5.42 (1H, d,  $J=3.0$  Hz, H-7) and 5.37 (1H, m, H-6), indicating one oxygenated group was changed into double bond group. The  $^{13}\text{C}$ -NMR and DEPT 135° spectra revealed 30 carbon signals, including one ketone  $\delta_{\text{C}}$  204.6 (C-3), two ester  $\delta_{\text{C}}$  170.1 (C-2) and 170.2 (C-2'), unlike compound 1, compound 2 have eight  $\text{sp}^2$  carbons  $\delta_{\text{C}}$  158.1 (C-14), 157.2 (C-1), 142.6 (C-23), 139.7 (C-21), 126.1 (C-2), 124.4 (C-20), 119.7 (C-15), and 110.9 (C-22) while the four of them represent furan group, seven methyl groups  $\delta_{\text{C}}$  26.7 (C-18), 31.6 (C-19), 20.4 (C-28), 20.7 (C-29), 20.8 (C-30), 21.4 ( $\text{CH}_3$ -1') and 21.0 ( $\text{CH}_3$ -1''), two oxygenated methines  $\delta_{\text{C}}$  74.5 (C-7) and 69.9 (C-6), three methines, four quaternary carbons, and three methylenes. A comparison of the NMR data of 2 with dysobinin isolated from fruit of *Dysoxylum binectariferum* (Singh, Garg & Khanna, 1976) inferred that the two compounds were similar, compound 2 was identified as dysobinin.

Compound 3 was obtained as a white crystal (MeOH). The molecular formula was identified as  $\text{C}_{28}\text{H}_{36}\text{O}_5$  with eleven degrees of unsaturation based on analysis of HR-TOFMS spectra with peak ion molecule  $[\text{M}+\text{H}]^+$   $m/z$  475.2462 (calcd.  $m/z$  475.2460 for  $\text{C}_{28}\text{H}_{36}\text{O}_5\text{Na}$ ). The UV spectrum showed maximum absorption at 230 nm ( $\log \epsilon$  2.68), indicating the presence of an enone group. The IR spectrum showed the presence of carbonyl ester ( $1652\text{ cm}^{-1}$ ) and an  $\alpha,\beta$ -unsaturated carbonyl ( $1662\text{ cm}^{-1}$ ) functionalities. The  $^1\text{H}$ -NMR spectrum displayed six tertiary methyl singlets, five from intact limonoid and one from acetoxy group  $\delta_{\text{H}}$  0.78 (3H, s,  $\text{CH}_3$ -18), 1.13 (3H, s,  $\text{CH}_3$ -19), 1.05 (3H, s,  $\text{CH}_3$ -28), 1.15 (3H, s,  $\text{CH}_3$ -30), 1.06 (3H, s,  $\text{CH}_3$ -29), and 2.08 (3H, s,  $\text{CH}_3$ -1'), five olefinic protons  $\delta_{\text{H}}$  7.15 (1H, d,  $J=10.0$  Hz, H-1) and 5.88 (1H, d,  $J=10.0$  Hz, H-2), a typical proton for ring A 1-en-3 one, 7.28 (1H, s, H-21), 6.29 (1H, t,  $J=1.5$  Hz, H-22),

and 7.39 (1H, t,  $J=1.5$  Hz, H-23), the three proton signals that belong to furan group and one oxygenated methine proton  $\delta_{\text{H}}$  4.96 (1H, d,  $J=2.5$  Hz, H-7). The  $^{13}\text{C}$  NMR and DEPT 135° spectra revealed 28 carbon signals (Table 1). In the HMBC spectrum of compound 3, cross peak from H-1 ( $\delta_{\text{H}}$  7.15) to C-3 ( $\delta_{\text{C}}$  204.6) and C-10 ( $\delta_{\text{C}}$  39.5) and from H-28 ( $\delta_{\text{H}}$  1.05) and H-29 ( $\delta_{\text{H}}$  1.06) to C-3 ( $\delta_{\text{C}}$  204.6) support the presence of  $\alpha,\beta$ -unsaturated carbonyl in ring-A. The carbonyl at position C-15 was indicated by the correlation on the COSY spectra according for position of ring D that only showed between H-17 ( $\delta_{\text{H}}$  3.48) and H-16 ( $\delta_{\text{H}}$  2.50), and cross peak shown from the HMBC spectra of H-14 ( $\delta_{\text{H}}$  2.43) to C-15 ( $\delta_{\text{C}}$  218.8), H-16 ( $\delta_{\text{H}}$  2.50) to C-15 ( $\delta_{\text{C}}$  218.8) and H-17 ( $\delta_{\text{H}}$  3.48) to C-21 ( $\delta_{\text{C}}$  40.2). Additionally, one acetoxy group located at C-7 was revealed by the COSY correlation between H-5 ( $\delta_{\text{H}}$  2.07), H-6 ( $\delta_{\text{H}}$  1.89) and H-7 ( $\delta_{\text{H}}$  4.96) and cross peak from proton  $\text{CH}_3$ -1' ( $\delta_{\text{H}}$  2.08) to C-2' ( $\delta_{\text{C}}$  169.4) and C-7 ( $\delta_{\text{C}}$  73.2) (Figure 2). The NMR spectra of 3 were similar with that reported 7 $\alpha$ -acetylneotricilenone that was isolated previously from seeds of *Azadirachta indica* (Kraus et al., 1981), therefore, compound 3 was identified as a 7 $\alpha$ -acetylneotricilenone.

Compound 4 was isolated as a colorless crystal (MeOH) and the molecular formula of  $\text{C}_{28}\text{H}_{36}\text{O}_5$  was identified based on analysis of HR-TOFMS spectra with peak ion molecule  $[\text{M}+\text{H}]^+$   $m/z$  475.2462 (calcd.  $m/z$  475.2460 for  $\text{C}_{28}\text{H}_{36}\text{O}_5\text{Na}$ ) with eleven degrees of unsaturation. The spectra of compound 2 exhibited similar spectral data to compound 4, therefore, it is possible to assign the  $^1\text{H}$  and  $^{13}\text{C}$ -NMR signal of rings A - D and the signal of furan, methyl and C-6 acetoxy by comparison of the spectra. The presence of the acetoxy at C-6 was indicated from the proton signal at  $\delta_{\text{H}}$  5.46 (1H, dd,  $J=2.0, 12.0$  Hz, H-6) from the COSY spectra showed correlation with proton at  $\delta_{\text{H}}$  2.74 (1H, d,  $J=12.0$  Hz, H-5) and 4.07 (1H, d,  $J=2.0$  Hz, H-7), and in the HMBC spectrum showed cross peak from H-6 ( $\delta_{\text{H}}$  5.46) to C-5 ( $\delta_{\text{C}}$  46.3), C-10 ( $\delta_{\text{C}}$  41.0) and C-7 ( $\delta_{\text{C}}$  170.4). Furthermore, the hydroxyl at C-7 was

inferred by the cross peak from H-7 ( $\delta_H$  4.07) to C-9 ( $\delta_C$  35.6) and 43-30 ( $\delta_C$  26.5) (Figure 2). The stereochemistry of the hydroxyl and acetoxy group was determined by NOESY experiment, the spectrum showed correlation between H-6/H-7 and CH<sub>3</sub>-19/CH<sub>3</sub>-30, therefore H-6/H-7 was at the same plane as CH<sub>3</sub>-19/CH<sub>3</sub>-30 at  $\beta$ -oriented. Thus, the hydroxyl and acetoxy group was  $\alpha$ -oriented. The NMR data of compound 4 compared with 6 $\alpha$ -O-acetyl-7-deacetylnimocinol that was isolated from leaves of *Azadirachta indica* (Siddi et al., 2000) showed similar data. Therefore, the structure of compound 4 was inferred as 6 $\alpha$ -O-acetyl-7-deacetylnimocinol.<sup>14</sup>

Compound 5 was obtained as a white needle crystal (MeOH) and the molecular formula of C<sub>26</sub>H<sub>34</sub>O<sub>5</sub> was identified based on analysis of HR-TOFMS spectra with peak ion molecule [M+H]<sup>+</sup> *m/z* 433.2353 (calcd. *m/z* 433.2355 for C<sub>26</sub>H<sub>36</sub>O<sub>5</sub>Na), therefore ten degrees of unsaturation are required. The spectra of compound 5 exhibited similar spectral data to compound 3. The <sup>1</sup>H-NMR spectrum showed

the difference of the absence of singlet signal worth three proton a typical methyl for acetyl group signal at  $\delta_H$  2.10 ppm. It was supported by the peak ion molecule of 5 [*m/z* 433.2355; C<sub>26</sub>H<sub>34</sub>O<sub>4</sub>Na] and 3 [*m/z* 475.2460; C<sub>28</sub>H<sub>36</sub>O<sub>5</sub>Na] that inferred the lost of acetyl group for compound 5. Furthermore, the hydroxyl group bond to C-7 ( $\delta_C$  69.9) was inferred by its correlation based on COSY experiment that showed cross peak between H-7 ( $\delta_H$  3.89) to H-6 ( $\delta_H$  1.94 and 1.72) and H-6 to H-5 ( $\delta_H$  2.27). From these revealed data indicated that compound 5 is a neotrichilenone derivative limonoid. Therefore, based on the comparison with NMR data of 7 $\alpha$ -hydroxynetricilenone from *Trichilia havanensis* (Chan, Gibbs, & Taylor, 1967), the structure of compound 5 was defined<sup>46</sup> as 7 $\alpha$ -hydroxynetricilenone.

The cytotoxic activity against MCF-7 breast cancer cell line of these isolated compounds (1-5) were evaluated and cisplatin was used as a positive control based on the method previously reported (Skehan et al., 1990; Supratman et al., 2020; Supriatno et al., 2018) and the results shown in Table 2.

<sup>51</sup> Table 1. <sup>13</sup>C-NMR Data for compound 1-5

Carbon Position	Compounds				
	31 1 $\delta_C$ (mult.)	2 $\delta_C$ (mult.)	3 $\delta_C$ (mult.)	4 $\delta_C$ (mult.)	5 $\delta_C$ (mult.)
1	157.6 (d)	157.2 (d)	157.9 (d)	157.2 (d)	158.2 (d)
2	126.1 (d)	126.1 (d)	125.8 (d)	126.0 (d)	125.8 (d)
3	204.6 (s)	204.6 (s)	204.6 (s)	204.9 (s)	204.1 (s)
4	42.8 (s)	44.9 (s)	44.0 (s)	44.9 (s)	44.2 (s)
5	48.4 (d)	47.8 (d)	45.0 (d)	46.3 (s)	43.7 (d)
6	70.1 (d)	69.9 (d)	22.2 (t)	71.4 (d)	25.3 (t)
7	73.5 (d)	74.5 (d)	73.2 (d)	73.5 (d)	69.9 (d)
8	41.8 (s)	42.9 (s)	40.9 (s)	44.8 (s)	42.4 (s)
9	39.3 (d)	37.2 (d)	46.9 (d)	35.6 (d)	45.9 (d)
10	40.5 (s)	40.7 (s)	39.5 (s)	41.0 (s)	39.4 (s)
11	16.3 (t)	16.4 (t)	17.6 (t)	16.2 (t)	17.7 (t)
12	29.1 (t)	34.5 (t)	34.2 (t)	32.2 (t)	34.1 (t)
13	45.1 (s)	47.1 (s)	42.1 (s)	47.2 (s)	42.1 (s)
14	72.7 (s)	158.1 (s)	61.1 (d)	160.0 (s)	62.0 (d)
15	57.1 (d)	119.7 (d)	218.9 (s)	120.5 (d)	221.4 (s)
16	32.0 (t)	32.6 (t)	43.1 (t)	34.3 (t)	43.2 (t)
17	38.9 (d)	51.5 (s)	37.8 (d)	51.6 (t)	37.9 (d)
18	21.5 (q)	26.7 (q)	27.8 (q)	20.5 (q)	27.7 (q)
19	21.8 (q)	31.6 (q)	19.1 (q)	20.6 (q)	19.1 (q)
20	123.6 (s)	124.1 (s)	122.7 (s)	124.1 (s)	122.8 (s)
21	139.5 (d)	139.7 (d)	140.7 (d)	139.7 (d)	140.1 (d)
22	110.8 (d)	110.9 (d)	110.7 (d)	110.9 (d)	110.7 (d)
23	142.9 (d)	142.6 (d)	142.9 (d)	142.7 (d)	142.9 (d)
28	31.6 (q)	20.4 (q)	27.3 (q)	20.6 (q)	21.3 (q)
29	20.1 (q)	20.7 (q)	21.1 (q)	31.6 (q)	27.4 (q)
30	18.8 (q)	20.8 (q)	18.1 (q)	26.5 (q)	18.6 (q)
2'	169.9 (s)	170.1 (s)	169.4 (s)	170.4 (s)	
1'	21.2 (q)	21.4 (q)	21.2 (q)	21.7 (q)	
2''	170.0 (s)	170.2 (s)			
1''	21.1 (q)	21.0 (q)			

(CDCl<sub>3</sub>, <sup>13</sup>C-NMR 125 MHz)



**Table 2.** Cytotoxic activity of compounds **1-5** against MCF-7 breast cancer line

Compounds	IC <sub>50</sub> (μM)
1	3201.8
2	119.5
3	3609.6
4	7283.5
5	53.4
Cisplatin*	15.9

\*positive control

Compound **5** showed the best cytotoxic activity against MCF-7 breast cancer cell with IC<sub>50</sub> value of 53.4 μM, classified as weak activity. The result indicating that the presence of hydroxyl group at C-7 of compound **5** can increase the cytotoxic activity. Furthermore, compound **1-4** based on the IC<sub>50</sub> value classified as no active compounds against MCF-7 breast cancer cells, and suggesting the presence of epoxy ring and ketone group can decrease activity of each compound.

### CONCLUSIONS

Five azadirone-type limonoids, 6α-(acetoxy)-14β,15β-epoxyazadirone (**1**), dysobinin (**2**), 7α-acetylneotricilenone (**3**), 6α-O-acetyl-7-deacetylneotricilenone (**4**), and 7α-hydroxynotricilenone (**5**), were isolated from the *n*-hexane of the fruit of *Chisocheton lasiocarpus*. Compound **5** (7α-hydroxynotricilenone) showed strongest cytotoxic activity with IC<sub>50</sub> values of 53.4 μM suggesting that hydroxyl group at C-7 can increase the cytotoxic activity, but the presence of epoxy ring and ketone group can decrease activity in azadirone-type limonoid.

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# Azadirone-Type Limonoids from the Fruit of *Chisocheton lasiocarpus* and Their Cytotoxic Activity Against MCF-7 Breast Cancer Lines

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