A new havanensin-type limonoid from Chisocheton macrophyllus

by Mulyadi Tanjung
A new havanensin-type limonoid from Chisocheton macrophyllus

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Abstract
A new havanensin-type limonoid, 16β-hydroxydysobinin (1), along with four known limonoids (2–5), have been isolated from the seeds of Chisocheton macrophyllus. The chemical structure of the new compound was determined by referencing spectroscopic data, and by comparison to those related spectra previously reported. Each compound was evaluated for their cytotoxic effects against Michigan Cancer Foundation-7 (MCF-7) breast cancer cells and display no significant activity.

Keywords: 16β-hydroxydysobinin, Chisocheton macrophyllus, MCF-7, Limonoid, Meliaceae

Introduction
Limonoids, known as degraded triterpenes, are derived from a precursor with a 4,4,8-trimethyl-17-furanlysteroid four ring skeleton labelled as A, B, C and D rings [1]. Limonoids are a class of secondary metabolites found in the order Rutales and the Meliaceae and Rutaceae family [2]. Meliaceae is a family of timber trees that are a rich source for limonoids and are widely distributed in tropical and subtropical regions with 50 genera and more than 1400 species [3, 4]. Limonoids isolated from species of the family Meliaceae have been reported to have biologically activity as antifeedant, antimicrobial, antimalarial, and cytotoxicity [5–8]. Genus Chisocheton is the second largest in the family Meliaceae, consisting of more than 50 species distributed across Nepal, India, Bhutan, Myanmar, South China, Thailand, Indonesia, Malaysia, and Papua New Guinea [7, 9].

Chisocheton macrophyllus is a species distributed in the Nicobar Islands, peninsular Thailand, peninsular Malaysia, Singapore, Sumatera, Anambas Islands, Java and Borneo Islands [10]. Its seeds have been reported to yield bioactive limonoids such as dysobinin, 7α-hydroxyneotricolone, dysobinin and nimonol with cytotoxic activity against P-388 murine leukemia cells [11], whereas the leaves to yield Epstein-Barr virus activation of Trikerpenoids [12]. After further investigations for cytotoxic limonoids from the seeds of C. macrophyllus, we found and structural elucidation of a new havanensin-type limonoids (1) and four known limonoids (2–5), along with their cytotoxic activity against MCF-7 breast cancer cells. Herein, the isolation, structural elucidation and cytotoxic activity against MCF-7 breast cancer cells are discussed.

Materials and methods
Plant materials
Seeds of C. macrophyllus were collected from Bogor Botanical Garden, Bogor, West Java Province, Indonesia. The plant was identified by Mr. Hanto, the staff of Bogoriense Herbarium, Research Center for Biology, Indonesia Science Institute, Bogor, Indonesia and a voucher specimen (No. Bo-1295453) was deposited at the Herbarium.

Instruments and reagents
Optical rotations were measured on a Perkin Elmer 341 Polarimeter (Waltham, MA, USA). UV spectra...
was measured using a TECAN Infinite M200 pro with MeOH. Furthermore, the IR spectra and mass spectra were recorded on a One PerkinElmer spectrum-100 FT-IR in KBr and Waters Xevo QTOF MS, respectively. NMR spectra were obtained with Bruker Topspin at 500 MHz for $^1$H and 125 MHz for $^{13}$C (compound 1) and for compounds 2–5 using JEOL NM-ECZ5000R/51 at 500 MHz for $^1$H and 125 MHz for $^{13}$C, using tetramethylsilane (TMS) as the internal standard. Chromatographic separations were carried out on the silica gel 60 (70–230 and 230–400 mesh, Merck). Thin layer chromatography (TLC) analysis was carried out on 60 GF254 (Merck, 0.25 mm) using various solvent systems, and measured by irradiation under ultraviolet–visible light Vilber Lourmat (λ 254 nm dan 365 nm) followed by heating of silica gel plates, sprayed with 10% H$_2$SO$_4$ in ethanol and Ehrlich’s reagent (p-Dimethylaminobenzaldehyde in ethanol).

**Extraction and isolation of C. macrophyllus**

The dried and powdered seeds of *C. macrophyllus* (2.5 kg) were extracted with methanol at room temperature for 3 days (3 x 5 L). After removal of the solvent under vacuum, a total of 360 g of methanol extract was obtained and partitioned with n-hexane (3 x 3 L), ethyl acetate (3 x 2 L) and n-butanol (3 x 2 L). Evaporation resulted in crude extracts of n-hexane (146.6 g), ethyl acetate (60.8 g) and n-butanol (14.6 g) respectively. The n-hexane soluble fraction (140 g) was subjected to vacuum-liquid chromatography (VLC) column packed with silica gel 60 using a gradient of n-hexane, ethyl acetate and methanol (10% stepwise) to afford thirteen fractions (A–M). Fraction D (5.4 g) was subjected to silica gel column chromatography using a gradient of n-hexane and ethyl acetate (5% stepwise) as eluting solvent to afford five subfractions (D1–D5). Subfraction D2 (165.7 mg) was chromatographed on a column of silica gel eluted with n-hexane: dichloromethane: ethyl acetate (2.7:5:0.5) to give 1 (15.3 mg). Fraction F (4.4 g) was subjected to silica gel column chromatography using a gradient of n-hexane and ethyl acetate (5% stepwise) as eluting solvent to afford twelve subfractions (F1–F12). Subfraction F5 (12.2 g) was chromatographed on a column of silica gel eluted with n-hexane: dichloromethane: ethyl acetate (2.7:5:0.5) to give 3 (19.7 mg) and four subfractions (F5A–F5D). Furthermore, subfraction F5D (308.3 mg) was chromatographed on a column of silica gel eluted with n-hexane: dichloromethane: ethyl acetate (1.8:5:0.5) to give 2 (12.8 mg). Fraction H (1.8 g) was subjected to silica gel column chromatography using a gradient of n-hexane and ethyl acetate (5% stepwise) as eluting solvent to give 5 (12.0 mg). Fraction J (1.5 g) was subjected to a silica gel column chromatography using a gradient of n-hexane and ethyl acetate (5% stepwise) to afford nineteen subfractions (J1–J19). Subfraction J9 (50.3 mg) was chromatographed on a column of silica gel eluted with n-hexane: dichloromethane: ethyl acetate (45:50:5) to give 4 (3.0 mg).

16β-hydroxydysoabinin (1): Colorless needle crystals; mp: 205–207 °C; [α]$^D_{25}$ +122.5° (c 0.2, MeOH); UV (MeOH) λ max 284 nm; IR (KBr) ν max 3509, 2929, 1744, 1670, 1502, 1366, 1386, 1248 cm$^{-1}$; HR-TOFMS m/z 511.2634 [M + H]$^+$, (calcd. for C$_{20}$H$_{28}$O$_2$ m/z 511.2696); $^1$H-NMR (CDCl$_3$, 500 MHz) and $^{13}$C-NMR (CDCl$_3$, 125 MHz) see Table 1.

| Table 1 NMR spectral data for 1 (500 MHz for $^1$H and 125 MHz for $^{13}$C in CDCl$_3$) |
|---|---|---|
| Position | $^1$H (multi.) | $^{13}$C (multi.) |
| 1 | 8.32 (H, d, 10.5) | 158 | 18 |
| 2 | 8.88 (H, d, 10.5) | 1245 | 3 |
| 3 | − | 2044 | 8 |
| 4 | − | 450 | 8 |
| 5 | 2.60 (H, d, 12.5) | 475 | 8 |
| 6 | 5.46 (H, m) | 697 | 8 |
| 7 | 5.41 (H, d, 2.6) | 740 | 8 |
| 8 | − | 416 | 8 |
| 9 | 2.12 (H, d, 6.5, 14.5) | 454 | 8 |
| 10 | − | 427 | 8 |
| 11 | 1.86 (H, d, 14.5) | 343 | 8 |
| 12 | 2.37 (H, d, 14.5) | 464 | 8 |
| 13 | 1.67 (H, m) | 468 | 8 |
| 14 | − | 1606 | 8 |
| 15 | 5.48 (H, d, 7.7) | 1193 | 8 |
| 16 | 4.49 (H, t, 7.7) | 672 | 8 |
| 17 | 2.82 (H, d, 7.7, 11.3) | 512 | 8 |
| 18 | 1.33 (H, a, 9) | 287 | 8 |
| 19 | 1.28 (H, a, 9) | 316 | 8 |
| 20 | − | 1240 | 8 |
| 21 | 1.78 (H, g) | 1397 | 8 |
| 22 | 6.30 (H, d, 1.4) | 1109 | 8 |
| 23 | 7.30 (H, d, 1.4) | 1437 | 8 |
| 24 | 9.95 (H, a, 9) | 205 | 8 |
| 25 | 1.20 (H, a, 9) | 206 | 8 |
| 26 | 1.33 (H, a, 9) | 209 | 8 |
| 27 | 2.04 (H, a, 9) | 213 | 8 |
| 28 | − | 1703 | 8 |
| 29 | 2.07 (H, s) | 220 | 8 |
| 30 | 2.07 (H, s) | 1703 | 8 |

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Cytotoxic activity test
The cytotoxicity of compounds 1–5 was determined with a cell viability test using PrestoBlue® assay. The cells were maintained in a Roswell Park Memorial Institute (RPMI) medium with 10% (v/v) Fetal Bovine Serum (FBS) and 1 μL/1 mL antibiotics (1% Penicillin–Streptomycin). Cultures were incubated at 37 °C in a humidified atmosphere of 5% CO₂. MCF-7 cells plated in 96 multiwell culture plates at a density of 1.7 × 10⁴ cells/well. After twenty-four hours, 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 24 h, PrestoBlue® reagent (resazurin dye) was added. The PrestoBlue® assay results were read using a multimode reader at 570 nm. The IC₅₀ values were determined by linear regression method using Microsoft Excel software. The IC₅₀ 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.

Results and discussion
The n-hexane fraction from the seeds of C. macrophyllus was subjected to vacuum-liquid chromatography (VLC) column packed with silica gel 60 by gradient elution. The VLC fractions were repeatedly subjected to normal phase column chromatography on silica gel to yield compounds 1–5 (Fig. 1).

Compound 1 was isolated as colorless needle crystals. The molecular formula was determined to be C₉₀H₁₃₃O₂₇ based on the high resolution time-of-flight mass spectrometry (HR-TOFMS) spectra (Additional file 1; Fig. S8) at m/z 511.2696 [M + H]⁺ (calcd. for C₉₀H₁₃₃O₂₇ m/z 511.2696) and nuclear magnetic resonance (NMR) data (Table 1), indicating the presence of twelve degrees of unsaturation. The ultraviolet (UV) spectrum showed maximum absorption at 284 nm, indicating the presence of an α, β-unsaturated ketone [13, 14]. Infrared (IR) absorptions spectra suggested the presence of hydroxyl (3509 cm⁻¹), aliphatic (2929 cm⁻¹), carbonyl ester (1744 cm⁻¹), α, β-unsaturated carbonyl (1670 cm⁻¹), olefinic (1502 cm⁻¹), gem-dimethyl (1366 and 1386 cm⁻¹) and ether groups (1248 cm⁻¹).

![Fig. 1 Structures of compounds 1–5](image-url)
The $^1$H-NMR spectrum (Additional file 1; Fig. S1) showed five tertiary methyls at $\delta_H$ 0.95 (3H, s, Me-28), 1.20 (3H, s, Me-29), 1.28 (3H, s, Me-19), and 1.33 (6H, s, Me-18 and Me-30) as well as two acetoxyl groups at $\delta_H$ 2.64 (3H, s, Me-1') and 2.67 (3H, s, Me-1''). In addition, three oxygenated protons at $\delta_H$ 5.46 (1H, m, H-6), 5.41 (1H, d, $J$ = 2.6 Hz, H-7) and 4.49 (1H, t, $J$ = 7.7 Hz, H-16), a $\beta$-furan moiety at $\delta_H$ 6.30 (1H, d, $J$ = 1.45 Hz, H-22), 7.28 (1H, s, H-21), and 7.40 (1H, d, $J$ = 1.45 Hz, H-23) and three olefinic protons at $\delta_H$ 5.48 (1H, d, $J$ = 7.7 Hz, H-15), 5.88 (1H, d, $J$ = 10.5 Hz, H-2) and 8.32 (1H, d, $J$ = 10.5 Hz, H-1) were also observed in the $^1$H-NMR spectrum. The $^{13}$C-NMR (Additional file 1; Fig. S2) along with distortions enhancement by polarization transfer (DEPT) (Additional file 1; Fig. S3) and heteronuclear single quantum coherence (HSQC) spectra (Additional file 1; Fig. S4) showed thirty carbons consisting of an $\alpha$-$\beta$-unsaturated carbonyl at $\delta_C$ 204.4 (C-3), two acetoxyl groups at $\delta_C$ 21.3 (C-1'), 170.1 (C-2') and 170.3 (C-2'') and five methyls at $\delta_C$ 20.5 (Me-28), 20.6 (Me-29), 20.9 (Me-30), 28.7 (Me-18) and 31.6 (Me-19). The spectra also showed two methylene carbons at $\delta_C$ 34.3 (C-11) and 46.4 (C-12), three sp$^3$ methine carbons at $\delta_C$ 45.4 (C-9), 47.5 (C-5) and 51.2 (C-17), four sp$^3$ methine carbons at $\delta_C$ 110.9 (C-22), 119.3 (C-15), 124.5 (C-2) and 158.1 (C-1), three oxygenated sp$^3$ methine carbons at $\delta_C$ 67.2 (C-16), 69.7 (C-6) and 74.0 (C-7), two oxygenated sp$^3$ methine carbons at $\delta_C$ 139.7 (C-21) and 142.7 (C-23), four sp$^3$ quaternary carbons at $\delta_C$ 41.6 (C-8), 42.7 (C-10), 45.0 (C-4), and 46.8 (C-13) and two sp$^2$ quaternary carbons at $\delta_C$ 124.0 (C-20) and 160.6 (C-14). These functionalities accounted for seven out of the twelve degrees of unsaturation, while the remaining five degrees of unsaturation corresponded to the pentacyclic limonoid structure [6, 11, 15, 16]. The NMR spectra data of 1 resembled those of previously reported dysobinin [16, 17], except for the appearance of oxygenated signals at $\delta_H$ 4.49 (1H, t, $J$ = 7.7 Hz), $\delta_C$ 67.2, thus suggesting that 1 was a hydroxy analog of dysobinin. Position of the hydroxyl group at C-16 was determined through the $^1$H-$^1$H correlated spectroscopy ($^1$H-$^1$H COSY) and proton multiple bond connectivity (HMBC) experiments (Fig. 2, Additional file 1; Fig. S5 and Fig. S6). Correlations from methyl protons at $\delta_H$ 1.33 (CH$_3$-18) to $\delta_C$ 51.2 (C-17), oxygenated sp$^3$ methine at $\delta_H$ 4.49 (H-16) to $\delta_C$ 124.0 (C-20) and methyne proton $\delta_H$ 2.82 (H-17) to $\delta_C$ 139.7 (C-21) and $\delta_C$ 110.9 (C-22) were used to assign the hydroxyl group and a furan ring attached at C-16 and C-17, respectively.

Based on the $^1$H-$^1$H COSY spectrum of 1, correlation in H$_1$-H$_2$, H$_2$-H$_6$, H$_3$-H$_{12}$, H$_{10}$-H$_{17}$ and H$_{12}$-H$_{23}$ supported the presence of a havaensim-type limonoid structure in 1 [15, 17, 18]. The HMBC spectrum showed $^3$ J correlations between sp$^3$ methine proton signal $\delta_H$ 8.32 (H-1) to $\delta_C$ 47.5 (C-5) and carbonyl at $\delta_C$ 204.4 (C-3) and $\delta_H$ 5.88 (H-2) to $\delta_C$ 42.7 (C-10), indicating the presence of $\alpha$-$\beta$-unsaturation ketone located at C-1, C-2 and C-3, respectively. Correlations from oxygenated sp$^3$ methine protons at $\delta_H$ 5.46 (H-6) to $\delta_C$ 45.0 (C-4) and $\delta_C$ 170.1 (C-2') and $\delta_H$ 5.41 (H-7) to $\delta_C$ 45.4 (C-9) as well as $\delta_H$ 2.04 (H-1') to $\delta_C$ 170.1 (C-2') and $\delta_H$ 2.07 (H-1') to $\delta_C$ 170.3 (C-2''), indicate that an acetyl group was attached at C-6 and C-7, respectively.
The relative stereochemistry of hydroxyl group at C-16 of 1 was determined by a nuclear overhauser and exchange spectroscopy (NOESY) experiment (Fig. 3 and Additional file 1; Fig. S7). Comparison of oxygenated sp² methine protons at δH 4.49 (H-16) and CH₃-18 (δH 1.33) with α-oriented, indicated that H-16 was α-oriented and hydroxyl group at C-16 is β-oriented. Correlations between δH 5.41 (H-7) and CH₃-30 (δH 1.33) with β-oriented, indicated that H-7 was β-oriented and acetyl group at C-7 is α-oriented. Correlations between δH 5.46 (H-6) and CH₃-19 (δH 1.28) with β-oriented, indicated that H-6 was β-oriented and acetyl group at C-6 is α-oriented. Furthermore, the optical rotation of [α]Dp +122.5° (c 0.2, MeOH) is the same sign to those of previously reported dysobin (6) ([α]Dp +150°) [17, 18]. Therefore, the structure of 1 was elucidated as the new havanusin-type of limonoid derivative and named 16β-hydroxydysobin.

Four known compounds, 7-deacetyl epoxazadiradione (2), were previously synthesized as a derivative of epoxazadiradione [19, 20], but isolated from a natural source for the first time. In addition, 6α-acetoxyl epoxazadiradione (3) and 6α-acetoxydysobin (4) [21] as well as dysobin (5) [11, 17, 18] were identified by comparison of their spectroscopic data with previously reported values.

Cytotoxic activity
All isolated compounds were evaluated for the cytotoxic activity against MCF-7 breast cancer cell line and cisplatin is used as a positive control according to the method previously described [16, 22] and the results are shown in Table 2. Compound 1 showed the strongest activity against MCF-7 breast cancer cell with IC₅₀ (inhibitory concentration, 50%) values of 45.91 μM, suggesting that the presence of hydroxyl at C-16 can increase the cytotoxic activity. In addition, the presence of epoxy ring and ketone group, like in compound 2–4, showed weak activity, indicating the presence of epoxy ring and ketone group can decrease activity.

| Compounds                  | IC₅₀ (μM) |
|----------------------------|-----------|
| 16β-hydroxydysobin (1)    | 45.91     |
| 7-deacetyl epoxazadiradione (2) | 94.62     |
| 6α-acetoxyl epoxazadiradione (3) | 105.16    |
| 6α-acetoxydysobin (4)     | 121.82    |
| Dysobin (5)               | 68.15     |
| Cisplatin*                | 38.96     |

* Positive control

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Declarations

Competing interests
There is no conflict of interests.

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References
1. Fang X, Di VT, Hao XJ (2011) The advances in the limonoid chemistry of the Melaleuca family. Curr Org Chem 15:1363–1391
2. Li H, Feng Y, Zheng J (2014) Metabolic activation and toxicities of fututrepeptosid A, B, and C. Toxicon 88:1055–1059
3. Pantzia V, Chrmveva R, Thammanin C, Ghanta RG, Mohamed A (2013) Phytochemicals and antimicrobial potentials of mahogany family. Rev BrasFarmacognos 23:81–83
4. Tan GD, Luo XD (2011) Mammalian limonoids: chemistry and biological activities. Chem Rev 111:7437–7522
5. Yang MH, Wang JS, Luo QG, Wang M, Li K (2009) Tetrahydrofuran derivatives from Chrysophyllum pascuata. Nat Prod Res 22:7014–2016
6. Wong CP, Shinada M, Nogakura Y, Noguchi AE, Hisawa Y, Taneja R, Awang K, Hadi AA, Mohamad K, Shino M, Morita H (2011) Ceramidines E–I: new limonoids from Chrysophyllum ceratocerasus. Chem Pharm Bull 59:407–411
7. Shih SM, Siah S, Chong SL, Nahar L, Sarkar SD, Awang K (2016) Advances in chemistry and bioactivity of the genus Chrysophyllum BLUME. Chem Biol Di 13:483–503
8. Chong SL, Hematpoor A, Hazi H, Azran MS, Utudon M, Supaman M, Musata M, Awang K (2019) Mosquitolike larvicidal limonoids from the fruits of Chroococcus cyanophorus Hee. Phytochem Lett 30:99–103
9. Katja DG, Farabi K, Nurulsafl H, Awang K, Supaman M, Utudon M, Hazi H (2017) Cytotoxic constituents from the bark of Chroococcus cyanophorus. Molecules. Asian Nat Prod Res 6:1–5
10. Vossen VDand Umbel BE (2002) Plant Resources of South East Asia, No. 14, Vegetable oil and fats, Prosea Foundation, Bogor, Indonesia.
11. Nurulsafl H, Awang K, Utudon M, Supaman M, Hazi H (2017) Limonoids from the seeds of Chroococcus cyanophorus. Chem Nat Compd 53:83–87
12. Tanaka A, Somekawa M, Murata H, Nakanishi T, Takuda H, Nishino H, Iwashina A, Dameed D, Musata M (1999) Phytochemical studies on melastomatous plants. VIII. Structures and inhibition effects on Epstein-Barr virus activation of interperiplamidin from leaves of Chroococcus cyanophorus. Phytochemistry. Asian Nat Prod Res 6:1–5
13. Shirato K, Miyazaki N, Matsuyama T, Kozeki T, Harazono KDG, Supaman M, Nakata J, Kasai H, Sanek M, Yoshida J, Uesugi S, Kimura K (2016) GSK-3β inhibitory activities of novel dichiocerein-derivative alkaloids from Cosmopoulos japonicus isolated from a mangrove plant. Phytochemistry. Asian Nat Prod Res 6:1–5
14. Ashiy EH, Van YF, Helena T, Juliana E, Keide E, Nurulsafl M, Hazi H, Utudon M, Shaw NY, Supaman M, Hazi H (2017) Limonoids from the leaves of Chroococcus cyanophorus. Molecules. Asian Nat Prod Res 6:1–5
16. Supaman M, Nurulsafl H, Awang K, Malawan B, Hidaya T, Marlan T, Supaman U, Ramzi RR, Shirone Y (2018) A new limonoid from stem bark of Chroococcus cyanophorus. Molecules. Asian Nat Prod Res 6:1–5
17. Singh S, Garg HS, Khanna NM (1978) Dysosmin, a new tetraoxotriepoxide from Dysosma broussonetii. Phytochemistry. Asian Nat Prod Res 6:1–5
18. Moreau JR, Van YF, Jompo River K, Keide E, Nurulsafl M, Hazi H (2018) Anti-malarial, antihyperglycemic and anti-inflammatory effects of limonoids from Chroococcus cyanophorus. Molecules. Asian Nat Prod Res 6:1–5
19. Halder S, Kole K, Thakur BN (2013) Biocatalytic fungi mediated novel and selective 13B or 17B hydroxylation on the basic limonoid skeleton. Green Chem. Asian Nat Prod Res 6:1–5
20. Yodap RA, Kumar CP, Siva R, Babu KG, Allari AD, Siwe PS, Jain N, Rao AV (2017) Synthesis and evaluation of anti-plasmodial and cytotoxic activities of o-phenylthiophene derivatives. Eur J Med Chem. Asian Nat Prod Res 6:1–5
21. Perekia TB, Siaka I, Amorini R, Mba M, Soupa R, Eberin M, Luma ES, Voccelli MC, Peltz AM (2014) In vitro and in vivo anti-malarial activity of Limonoids isolated from the residual seed biomass from Cotesia gueneei (Andricida) oil production. Mollele. Asian Nat Prod Res 6:1–5
22. Examinor RR, Wulandari AP, Harman D, Poniah A (2018) Cytotoxicity of artemisinin compound from an endophytic fungus, Cladosporium sp EN501. J. Curr Pharm Res. Asian Nat Prod Res 6:1–5

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   - Publication

3. Celia Bustos-Brito, Antonio Nieto-Camacho, Simón Hernandez-Ortega, José Rivera-Chávez et al. "Structural Elucidation of Malonylcommunol and 6β-Hydroxy-trans-communic Acid, Two Undescribed Diterpenes from Salvia cinnabarina. First Examples of Labdane Diterpenoids from a Mexican Salvia Species", Molecules, 2020

   - Publication

4. S. A. M. Abdelgaleil. "Antifeeding activity of limonoids from Khaya senegalensis
Bin Wu, Wen Hui Lin, Hui Yuan Gao, Lu Zheng, Li Jun Wu, Chul Sa Kim. "Four New Antibacterial Constituents from . ", Pharmaceutical Biology, 2008

Yuan Li. "A New Stilbene from Cercis chinensis Bunge", Journal of Integrative Plant Biology, 8/2005

Hong-Ying Wang, Jun-Song Wang, Si-Ming Shan, Xiao-Bing Wang, Jun Luo, Ming-Hua Yang, Ling-Yi Kong. "Chemical Constituents from Trichilia connaroides and Their Nitric Oxide Production and α-Glucosidase Inhibitory Activities", Planta Medica, 2013

Kai-Long Ji, Shang-Gao Liao, Xiao-Ling Zheng, Zhi Na, Hua-Bin Hu, Ping Zhang, You-Kai Xu. "Limonoids from the Fruits of Khaya ivorensis", Molecules, 2014
11. thieme-connect.de
   Internet Source

12. Claudio Madeddu, Maria Cinta Roda-Serrat, Knud Villy Christensen, Rime B. El-Houri, Massimiliano Errico. "A Biocascade Approach Towards the Recovery of High-Value Natural Products from Biowaste: State-of-Art and Future Trends", Waste and Biomass Valorization, 2020

13. M. Mostafa, Nilufar Nahar, M. Mosihuzzaman, Selestin D. Sokeng, Naheed Fatima, Atta-ur-Rahman, M. Iqbal Choudhary. "Phosphodiesterase-I inhibitor quinovic acid glycosides from ", Natural Product Research, 2006

14. Dan Yuan. "Inhibitory activity of isoflavones of Pueraria flowers on nitric oxide production from lipopolysaccharide-activated primary rat microglia", Journal of Asian Natural Products Research, 06/2009

15. mbio.asm.org
   Internet Source

16. vjs.ac.vn
   Internet Source
Zhao-Qing Zeng, Wen-Ying Zhuang. "Our current understanding of the genus Pseudocosmospora (Hypocreales, Nectriaceae) in China", Mycological Progress, 2021

Poitras, Marie-Eve, Martin Fortin, Catherine Hudon, Jeannie Haggerty, and José Almirall. "Validation of the disease burden morbidity assessment by self-report in a French-speaking population", BMC Health Services Research, 2012.

Di, Ying-Tong, Hong-Ping He, Chun-Shun Li, Jun-Mian Tian, Shu-Zhen Mu, Shun-Lin Li, Suo Gao, and Xiao-Jiang Hao. "Yuzurimine-Type Alkaloids from Daphniphyllum yunnanense", Journal of Natural Products, 2006.

Qing-Wen Shi, Zuo-Ping Li, Ding Zhao, Ji-Shun Gu, Hiromasa Kiyota. "Isolation and structure
revision of 10-deacetyltaxinine from the seeds of the Chinese yew, "Natural Product Research, 2006"

Ahmed I. Khodair. "SYNTHESIS OF 2-THIOHYDANTOINS AND THEIR -GLUCOSYLATED DERIVATIVES AS POTENTIAL ANTIViral AND ANTITumor AGENTS ", Nucleosides, Nucleotides and Nucleic Acids, 2001

Marc Litaudon, Hadjira Bousserouel, Khalijah Awang, Olivier Nosjean et al. "A Dimeric Sesquiterpene from a Malaysian as a New Inhibitor of Bcl-xL/BakBH3 Domain Peptide Interaction ", Journal of Natural Products, 2009

Wen-Chen Chen, Jyh-Horng Sheu, Lee-Shing Fang, Wan-Ping Hu, Ping-Jyun Sung. "3α,7α,12α-Triacetoxy-5β-cholanic acid, a steroid from the Formosan soft coral sp. (Alcyoniidae) ", Natural Product Research, 2006

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| Hosoya, T.. "Antioxidant phenylpropanoid glycosides from the leaves of Wasabia japonica", Phytochemistry, 200802 | <1 % |
| Shadid, K.A.. "Cytotoxic caged-polyprenylated xanthonoids and a xanthone from Garcinia cantleyana", Phytochemistry, 200710 | <1 % |
39 Swati P. Kolet, Saikat Haldar, Siddiqui Niloferjahan, Hirekodathakallu V. Thulasiram. "Mucor hiemalis mediated 14α-hydroxylation on steroids: In vivo and in vitro investigations of 14α-hydroxylase activity", Steroids, 2014

40 Y. Venkateswarlu, P. Ramesh, N. Srinivasa Reddy, T. Prabhakara Rao. "A Novel Polyhydroxylated Epoxy Steroid From the Soft Coral Sinularia Dissecta", Natural Product Letters, 1999

41 downloads.hindawi.com Internet Source

42 spandidos-publications.com Internet Source

43 ugspace.ug.edu.gh Internet Source

44 univmed.org Internet Source

45 J. G. Urones, D. Díez, P. M. Gómez, I. S. Marcos, P. Basabe, R. F. Moro. "Drimane Homochiral Semisynthesis: Pereniporin a, -Warburganal and C-9 Nitrogenated Drimanes", Natural Product Letters, 1998
| Page | Author(s)                                                                 | Title                                                                                                     | Journal                                                                                       |
|------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| 46   | Mireku, Evelyn Afua, Souvik Kusari, Dennis Eckelmann, Abraham Yeboah Mensah, Ferdinand M. Talontsi, and Michael Spiteller. | "Anti-inflammatory tirucallane triterpenoids from Anopyxis klaineana Pierre (Engl.), (Rhizophoraceae)" | Fitoterapia, 2015                                                                             |
| 47   | P. Ashok Yadav, Ch. Pavan Kumar, Bandi Siva, K. Suresh Babu et al.        | "Synthesis and evaluation of anti-plasmodial and cytotoxic activities of epoxyazadiradione derivatives" | European Journal of Medicinal Chemistry, 2017                                                  |
| 48   | Qiang-Qiang Shi, Jing Lu, Xing-Rong Peng, Da-Shan Li, Lin Zhou, Ming-Hua Qiu. | "Cimitriteromone A–G, Macromolecular Triterpenoid–Chromone Hybrids from the Rhizomes of" | The Journal of Organic Chemistry, 2018                                                         |
| 49   | Sasaki, Hisako, Hirofumi Shibata, Kiyoshi Imabayashi, Yoshihisa Takaishi, and Yoshiki Kashiwada. | "Prenylated Flavonoids from the Stems and Leaves of Desmodium caudatum and Evaluation of Their Inhibitory Activity against the Film-Forming Growth of" |                                                                                               |
Zygosaccharomyces rouxii F51", Journal of Agricultural and Food Chemistry

Sato, Kimihiko, Yasunori Inaba, Hyun-Sun Park, Toshiyuki Akiyama, Tetsuo Koyama, Haruhiko Fukaya, Yutaka Aoyagi, and Koichi Takeya. "Cytotoxic Bisnor- and Norditerpene Dilactones Having 7\(\pm\),8\(\pm\)-Epoxy-9,11-enolide Substructure from Podocarpus macrophyllus D. DON", CHEMICAL & PHARMACEUTICAL BULLETIN, 2009.

Uppuluri V. Mallavadhani, Anita Mahapatra, Satyabrata Mohapatra. "An efficient chemical method for separation of corsolic acid from its isomeric maslinic acid", Natural Product Research, 2006
Judit Hohmann, Ferenc Evanics, György Dombi, Pál Szabó. "Salicifoline and salicinolide, new diterpene polyesters from Euphorbia salicifolia", Tetrahedron Letters, 2001
Publication

Michel Souza Passos, Thalya Soares Ribeiro Nogueira, Otoniel de Aquino Azevedo, Milena Gonçalves Curcino Vieira et al. "Limonoids from the genus Trichilia and biological activities: review", Phytochemistry Reviews, 2021
Publication
A new havanensin-type limonoid from Chisocheton macrophyllus

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