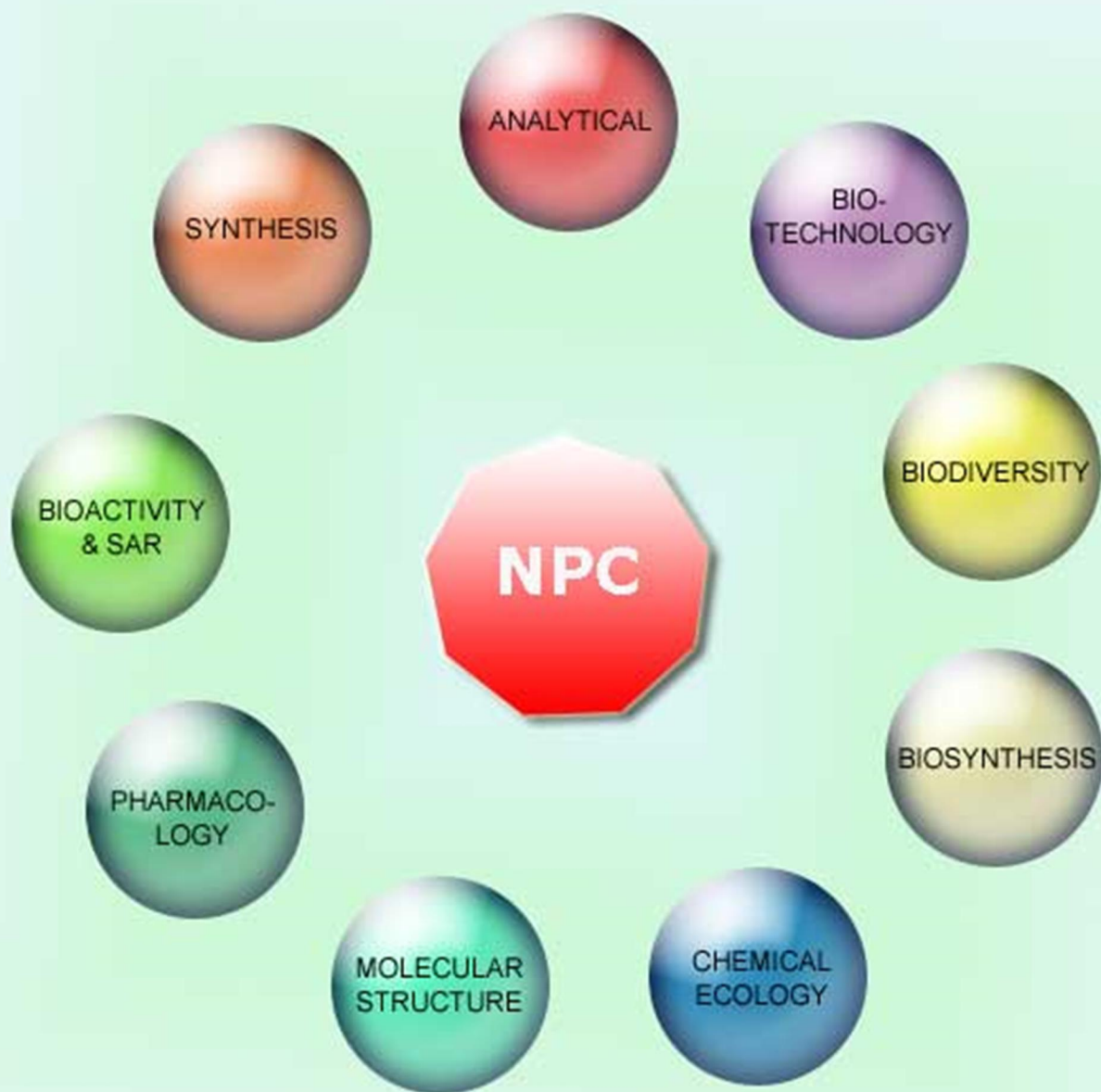


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Constituents of the Indonesian Epiphytic Medicinal Plant *Drynaria rigidula*

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The rhizome of *Drynaria rigidula* has been traditionally claimed to have anti-infective properties. A phytochemical study conducted on the rhizome successfully isolated two new aromatic glycosides as well as three known terpenoids, two benzoic acid derivatives and two known flavonoid glycosides. The rhizome methanol extract and its fractions were tested against *Mycobacterium tuberculosis*, *Plasmodium falciparum*, herpes simplex virus and KB-oral cancer cell; insignificant activity was found.

Keywords: Epiphytic medicinal plant, Indonesia, Bondowoso, *Drynaria rigidula*, Terpenes, Flavonoids, Glycosides, Anti-cancer, Anti-malaria, Anti-TB, Anti-HSV.

Since early Indonesian civilization, medicinal plants have been used to treat ailments from generation to generation with knowledge of their healing properties being passed through verbal and non-verbal records. Throughout the archipelago, more than 9,000 plants have been recorded to have medicinal properties. However, a recent study [1] concluded that only a small percentage of them have been studied – this includes the particularly neglected Indonesian epiphytic plants, both parasitic and non parasitic varieties.

Epiphytes occupy more than 10% of the world's total plant species and the majority exists in the Magnoliophyta division [2]. Currently, our laboratory is developing a record of epiphytic medicinal plants that covers the ethnopharmacology, ethnopharmacy, phytochemistry and pharmacology of 260 epiphytic medicinal plants.

Our study started in early 2010, with field trips in the Malabar Forest, East Java, Indonesia where we surveyed, selected and collected epiphytic medicinal plants used traditionally for infection therapy. In this paper, we report the phytochemical study of *Drynaria rigidula*, used traditionally as an anti-viral and anti-inflammatory agent, and to treat eye infections and gonorrhoea.

Drynaria species are common epiphytes in tropical forests. The genus is composed of at least 16 species with only 5 being claimed to have medicinal properties: *D. fortunei*, *D. quercifolia*, *D. propinqua*, *D. sparsisora* and *D. rigidula*. *D. fortunei* is highly prescribed in China for osteoporosis therapy with recent findings revealing that the flavonoids present significantly suppress osteoclast activities. Phytochemical studies have been performed on the first three species, with 30 compounds being isolated, including steroids, flavonoids and their glycosides [3-7].

D. rigidula is an epiphytic bird's-nest fern locally named as *simbar layangan* or *pasilan kelapa*. It has fertile and sterile leaves. The species is distributed throughout the Indonesian Islands as well as southeast Asia to Polynesia (Fiji) and Australia. To the people of

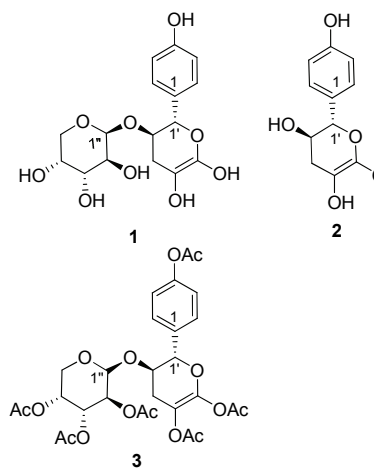


Figure 1: Aromatic glycosides isolated from *D. rigidula* rhizome. Compound 3 was obtained from acetylation of 1.

Java, the rhizome of *D. rigidula* has been used in traditional medicine, but, to date, there has been no phytochemical investigation of this species. We report here the results of our study into the bioactive constituents of this plant [8].

The crude extract of the rhizomes was fractionation into *n*-hexane, dichloromethane, ethyl acetate and residual fractions. Column chromatography of the *n*-hexane and dichloromethane fractions, followed by preparative thin layer chromatography, produced three isolated compounds. EIMS and nuclear magnetic resonance spectral analyses suggested these were the known compounds fern-9(11)ene [9], hop-22(29)-ene [10], and γ -sitosterol [11]. These terpenes are common in ferns, but are reported here for the first time from *D. rigidula*.

The ethyl acetate and residual fractions produced similar HPLC profiles; therefore, our study only focused on the ethyl acetate

fraction. The first two peaks with t_R of 6 and 8 minutes were identified from subsequent NMR spectral comparison as the known benzoic acids, 3,4-dihydroxybenzoic acid and 4-hydroxybenzoic acid. Two other known glycosidic flavonoids, kaempferitrin [12] and 3,5-dihydroxy-flavone-7-*O*- β -rhamnopyranosyl-4'-*O*- β -glucopyranoside [13], came with t_R of 35 and 42 minutes, respectively. For two previously unreported compounds, isolated with t_R of 14 and 17 minutes, we propose the glycoside structures **1** and **2** (Figure 1).

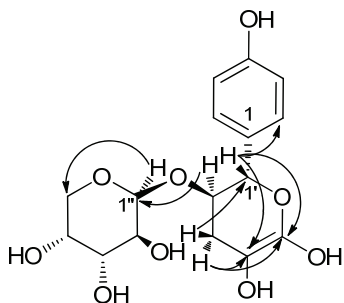


Figure 2: Selected proton-carbon correlations in compound **1**.

Compound **1**, with a t_R of 14 minutes, was a UV-active brown solid. ^1H NMR and ^{13}C NMR analyses indicated a glycoside molecule with an aromatic aglycon and two sugar moieties, for which gCOSY and TOCSY spectral analysis clearly indicated one aromatic proton system (aglycon) and two proton systems (two sugar units). The aglycon (proton system) was assigned as a 1,4-disubstituted benzene ring with the quaternary carbon at 158 ppm assigned as attached to an -OH substitution (C4). The COSY and TOCSY spectra clearly indicated proton H1' to H3' of the first sugar unit. Through gHMBC spectral analysis, two quaternary alkene carbons, δ 100 (C4') and 156 (C5'), were assigned to be components of the first sugar ring system.

The chemical shift of the anomeric carbon C1' at 80 ppm was lower than that of the common anomeric sugar carbon chemical shifts. This suggested a C-C bond which, through gHMBC spectral analysis, clearly indicated a C-C bond bridge between C1' and C1. COSY and TOCSY spectral analyses were also able to assign proton H1'' to H5'' of the second sugar ring system, with coupling constant patterns of $^3J_{\text{H1-H2}} = 7.5$ Hz, $^3J_{\text{H2-H3}} = 9.0$ Hz, $^3J_{\text{H3-H4}} = 9.0$ Hz, and $^3J_{\text{H4-H5}} = 5.5$ Hz, which suggest proton-proton configuration patterns of axial-axial, axial-axial, axial-axial, and axial-equatorial, respectively [14]. In combination, this suggested an arabinopyranose moiety, which was confirmed by a MS/MS experiment, which showed a fragment loss of 132 a.m.u. The coupling constant of the anomeric proton ($^3J_{\text{H1-H2}} = 7.0$ Hz, H1'') suggested a β configuration. The anomeric carbon chemical shift at 104 ppm of the second sugar clearly indicated a C-O bond bridge as the gHMBC was able to allocate a C-O-C bond between C2' and C1''. The proposed molecular structure of **1** is illustrated in Figure 2, along with selected H-C correlations.

Interestingly, we have assigned **1** as the ene-diol and not the corresponding keto molecule. There was no stretch in the IR spectrum typical of a carbonyl bond, and in the ^{13}C NMR spectrum, there were no signals that could be assigned to a carbonyl. Furthermore, there were chemical shifts at δ 156.5 (C5') and δ 100.7 (C4') assigned to the alkene attached to 2 x oxygen substituents (i.e. OH) in the pyran ring system. Therefore, the NMR analysis suggests an unusual ene-diol structure instead of the 'keto' form.

In order to confirm the assignment of **1**, we undertook exhaustive acetylation of the isolated natural product. Analysis of the ESI MS of this product revealed a peak at m/z 681, an extra 252 a.m.u over **1**, corresponding to the addition of six acetyl groups, confirming that six hydroxyl groups had been acetylated. Based on the NMR spectral analysis we found 16 carbons, 14 hydrogens and the carbon chemical shift analysis indicated 3 oxygens and 5 hydroxyl groups. Therefore, **1** had a molecular formula of $\text{C}_{16}\text{H}_{20}\text{O}_9$, with molecular weight of 356 a.m.u.

Spectral analysis of compound **2** indicated that the compound was identical to compound **1**, but without the second sugar moiety.

Biological testing: The anti-microbial activity of the crude rhizome extract, as well as the *n*-hexane, dichloromethane and ethyl acetate fractions were screened for activity against *Plasmodium falciparum*, *Mycobacterium tuberculosis*, and herpes simplex virus, and also for their cytotoxicity against KB-oral cavity, breast and lung cancers. No activity was detected, which suggests that the isolated compounds do not possess significant biological activity.

Experimental

Plant material: *Drynaria rigidula* (Sw.) Bedd. (Polypodiaceae) rhizomes were collected from Malabar forest, Bondowoso, Indonesia and identified at the School of Pharmacy, University of Jember, Indonesia, where sample vouchers are kept under accession codes DRR. The rhizomes were cleaned, washed, sliced, sun-dried and then powdered.

Extraction and fractionation: A suspension of the above powder (500 g) in methanol (5.0 L) was stirred for 48 h at room temperature. The mixture was then filtered and the supernatant vacuum dried to produce the rhizome extract (24.07 g). Liquid-liquid fractionation of the rhizome extract produced *n*-hexane (10.44 g), CH_2Cl_2 (0.93 g), and EtOAc (4.33 g) fractions, along with a residue (8.22 g).

Isolation: Part of the *n*-hexane fraction (1501.8 mg) was subjected to flash silica gel CC (2 cm diameter, 40 cm length) and elution with a *n*-hexane to ethyl acetate gradient, followed by an ethyl acetate to acetonitrile gradient, followed by acetonitrile-methanol (9:1). This produced 115 fractions. Crystal needles were obtained from fractions 5-9 (116.4 mg), and 21-24 (11.5 mg). Separately, these fractions were subjected to preparative TLC with *n*-hexane as the developing solvent to obtain needle crystals of fern-9(11)ene (75.2 mg) and hop-22(29)-ene (5.1 mg) from fraction 5-9 and 21-24, respectively. Pale yellow needle crystals were also collected from fraction 50 - 59 (30.5 mg). Fraction 50 - 59 was subjected to preparative TLC with 20% EtOAc in *n*-hexane as the developing solvent, which produced γ -sitosterol (12.7 mg).

The dichloromethane fraction (698.2 mg) was subjected to silica gel CC and elution with a gradient solvent system from *n*-hexane to ethyl acetate, and then ethyl acetate to acetonitrile, produced 71 fractions. Needle crystals were collected from fractions 2 - 3, which contained fern-9(11)ene, and fractions 22 - 23, which contained γ -sitosterol. These compounds were identified using EIMS analysis followed by database searching.

The ethyl acetate fraction (500 mg) was subjected to silica gel CC (2 cm x 5 cm). Elution with ACN: MeOH: H_2O (8:1:1) produced 200 mL of solution, which was reduced to 10 mL. This was injected into 8 blocks for preparative HPLC (19 x 150 mm, 5 μm , SunfireTM C₁₈) with gradient elution from 88% to 80% solvent A (0.1 % TFA

in H₂O) in 40 min (15 mL/min) with solvent B (0.1 % TFA in ACN) to produce 3,4-dihydroxybenzoic acid, 4-hydroxybenzoic acid, kaempferitrin, 3,5-dihydroxy-flavone-7-*O*- β -rhamnopyranosyl-4'-*O*- β -glucopyranoside and compounds **1** and **2**.

Compound 1

Brown powder, 0.12 mg/g dried sample.

IR (cm⁻¹) ν_{\max} : 3333 (m), 2926 (w), 1672 (m), 1611 (m), 1202, (m) 1140 (m), 1037 (s), 820 (w).

¹H NMR (CD₃OD, 500 MHz): 7.21 (d, ³J= 8.5, 2H, H₂, H₆), 6.76 (d, ³J= 8.5, 2H, H₃, H₅), 4.87 (d, ³J= 7.0, 1H, H_{1'}), 4.10 (dd, ³J= 7.0, 5.5, 1H, H_{2'}), 4.06 (d, ³J= 7.5, 1H, H_{1''}), 3.84 (dd, ²J= 11.5, ³J= 5.5, 1H, H_{5''A}), 3.44 (ddd, ³J= 9.0, 5.0, 5.0, 1H, H_{4''}) 3.18 (dd, ³J= 9.0, 9.0, 1H, H_{3''}), 3.12 (dd, ²J= 11.5, ³J= 5.5, 1H, H_{5''B}), 3.08 (dd, ³J= 9.0, 7.5, 1H, H_{2''}), 2.77 (dd, ²J= 16.5, ³J= 5.5, 1H, H_{3'A}), 2.67 (dd, ²J= 16.5, ³J= 5.5, 1H, H_{3'B}).

¹³C NMR (CD₃OD, 125 MHz): 158.3 (C₄), 156.5 (C_{5'}), 131.3 (C₁), 129.2 (C₂, C₆), 116.1 (C₃, C₅), 104.6 (C_{1''}), 100.7 (C_{4'}), 80.3 (C_{1'}), 77.1 (C_{4''}), 76.5 (C_{2'}), 75.7 (C_{2''}), 71.1 (C_{4''}), 66.6 (C_{5''}), 27.0 (C_{3'}).

ESI-MS: *m/z* 405 [M-H]⁻, 407 [M+H]⁺, 429 [M+Na]⁺.

ESI-MS2: *m/z* 405 [M-H]⁻, 273 [M-H-132]⁻.

Compound 2

Brown powder, 0.03 mg/g dried sample.

IR (cm⁻¹) ν_{\max} : 3336 (m), 2928 (w), 1675 (w), 1611 (m), 1201 (s), 1140 (s), 1096 (s), 800 (m).

¹H NMR (CD₃OD, 500 MHz): 7.22 (d, ³J= 8.0, 2H, H₂, H₆), 6.79 (d, ³J= 8.0, 2H, H₃, H₅), 4.60 (d, ³J= 8.0, 1H, H_{1'}), 3.99 (dd,

³J= 8.0, 6.0, 1H, H_{2'}), 2.86 (dd, ²J= 16.0, ³J= 6.0, 1H, H_{3'A}), 2.50 (dd, ²J= 16.0, ³J= 6.0, 1H, H_{3'B}).

¹³C NMR (CD₃OD, 125 MHz): 158.3 (C₄), 156.9 (C_{5'}), 131.5 (C₁), 129.7 (C₂, C₆), 116.0 (C₃, C₅), 100.9 (C_{1'}), 82.8 (C_{4'}), 68.9 (C_{4'}), 28.8 (C_{3'}).

ESI-MS: *m/z* 275 [M+H]⁺.

Acetylation of 1: Compound **1** (1.5 mg) was stirred with acetic anhydride (0.25 mL) and pyridine (0.25 mL) under nitrogen for 24 h. The reaction was then quenched by the addition of distilled water (1.0 mL) and the aqueous mixture extracted with ethyl acetate (2 x 5 mL). A sample of the ethyl acetate layer was added to methanol (2 mL), which was then used for mass spectrometric analysis. A peak at *m/z* 681 [M+Na]⁺ was assigned to **3**.

Bioactivity testing: Anti-malarial activity was determined against *Plasmodium falciparum* K1 based on the microculture radioisotope technique [15]. Cytotoxicity was tested against KB-oral cancer cell, lung cancer cell NCI-H187 and breast cancer cell based on the resazurinmicroplate assay. Anti-TB was tested against *Mycobacterium tuberculosis* H37Ra strain using a green fluorescent protein microplate assay. Anti-viral activity was tested against herpes simplex virus type 1 using a green fluorescent protein assay [16].

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Synthesis and Mass Spectral Fragmentation Patterns of Brassinolide Early Biosynthetic Precursors Labeled at C-26 Vladimir A. Khripach, Danuše Tarkowská, Vladimir N. Zhabinskii, Olga V. Gulyakevich, Yurii V. Ermolovich, Pavel Drašar and Miroslav Strnad	771
Severibuxine, Isolated from <i>Severinia buxifolia</i>, Induces Apoptosis in HL-60 Leukemia Cells Chihiro Ito, Tomiyasu Murata, Midori Kato, Natsu Suzuki, Tian-Shung Wu, Norio Kaneda, Hiroshi Furukawa and Masataka Itoigawa	775
Two New Morphinandienone Alkaloids from <i>Croton micradenus</i> Armando L. Payo-Hill, Daysi Sandoval-López, Hermán T. Vélez-Castro, Iraida Spengler-Salabarría and Luca Rastrelli	779
Isolation and Cholinesterase Inhibitory Activity of <i>Narcissus</i> Extracts and Amaryllidaceae Alkaloid Lucie Cahliková, Miroslav Ločárek, Nina Benešová, Radim Kučera, Jakub Chlebek, Zdeněk Novák and Lubomír Opletal	781
Antioxidant Activity and Mechanism of Tetrahydroamentoflavone <i>in vitro</i> Xican Li, Weijuan Han, Wenqiong Mai and Li Wang	787
Blue Mood for Superfood Kari Taulavuori, Riitta Julkunen-Tiitto, Valteri Hyöky and Erja Taulavuori	791
Acetylcholinesterase Inhibitors from <i>Croton sylvaticus</i> Ethyl Acetate Leaf Extract and their Mutagenic Effects Mutalib A. Aderogba, Ashwell R. Ndhlala and Johannes Van Staden	795
Coumarin Precursor from <i>Micromelum integerrimum</i> Leaves Wong Phakhodee, Preetiya Pongparn, Angkana Saovapakhiran and Surat Laphookhieo	799
Antifilarial Activity of Constituents of <i>Calophyllum inophyllum</i> and their Derivatives Jankiprasad, Gunaganti Naresh, Jyoti Gupta, Shailja M. Bhattacharya, Siron M. Rajendran, Shailendra K. Awasthi and TadiGOPpula Narender	803
Two New Lignans from the Wood of <i>Cunninghamia konishii</i> Chi-I Chang, Yen-Cheng Li, Ching-Chuan Kuo, Che-Yi Chao, Hsun-Shuo Chang, Jyh-Horng Wu, Sheng-Yang Wang and Yueh-Hsiung Kuo	805
Biological Studies of Turmeric Oil, Part 1: Selective <i>in vitro</i> Anticancer Activity of Turmeric Oil (TO) and TO-Paclitaxel Combination James N. Jacob and Masoud Toloue	807
Biological Studies of Turmeric Oil, Part 2: Isolation and Characterization of Turmeric Oil Components; Cytotoxic Activity Against Pancreatic Cancer Cells Wudan Yan, Wayne D. Bowen, Russell Hopson, Abraham E. Mathew and James N. Jacob	811
Ushikulide C, a New Immunosuppressant from <i>Streptomyces</i> sp. IUK-102 Kosaku Takahashi, Eri Fukushi, Jun Kawabata, Hideyuki Matsuura and Kazuhiko Kurosawa	815
Influence of the Bioclimatic Area on the Polyphenolic Composition, and Antioxidant and Bacteriostatic Activities of <i>Rosmarinus officinalis</i> Maria J. Jordán, Vanesa Lax, Maria C. Rota, Susana Lorán and José A. Sotomayor	817
Antibacterial and Antioxidant Activities of Various Medicinal Plants Used in Oriental Medicine Junho Seo, Jiyeon Kim, Geon Go, Jung-Suk Sung and Kwang-Geun Lee	823
Aconitamide, a Novel Alkaloid from the Roots of <i>Aconitum carmichaeli</i> Tzong-Huei Lee, Yu-Chang Chen, Ching-Kuo Lee, Hsun-Shuo Chang, Ching-Chuan Kuo, Che-Yi Chao, Jing-Jer Lin, Lee-Chiang Lo and Yueh-Hsiung Kuo	827
The Chemical Composition and Antibacterial Activities of the Essential Oils from Three <i>Aframomum</i> Species from Cameroon, and Their Potential as Sources of (<i>E</i>)-(<i>R</i>)-Nerolidol Sylvie Kwanga Nguikwie, Maximilienne A. Nyegue, Florentine Ndoye-Foe Belinga, Rosalie A. Ngono Ngane, Bernard Romestand, Achraf Kouzayha, Hervé Casabianca, Paul H. Amvam Zollo and Chantal Menuet	829
Chemical Composition and Antimicrobial Activity of <i>Daucus aureus</i> Essential Oils from Algeria Nawel Meliani, Mohammed El Amine Dib, Nassim Djabou, Jean Costa, Hocine Allali, Boufeldja Tabti and Alain Muselli	835
Chemical Composition of the Essential Oils of Three Species of Apiaceae Growing Wild in Sicily: <i>Bonannia graeca</i>, <i>Eryngium maritimum</i> and <i>Opanax chironium</i> Antonella Maggio, Maurizio Bruno, Carmen Formisano, Daniela Rigano and Felice Senatore	841

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Volume 8, Number 6

Contents

Australasian Natural Product Studies

(Guest Editor: Sylvia Urban)

Original Paper

Page

- Epimanool and a New 2,6-Dideoxy-hexopyran-3-olose Derivative from *Celmisia viscosa***
Catherine E. Sansom, Lesley Larsen, Alison C. Evans and Nigel B. Perry 689
- 7-Bromo-1-ethyl- β -carboline, an Alkaloid from the New Zealand Marine Bryozoan *Pterocella vesiculosa***
Michèle R. Prinsep and Méline Dumté 693
- Alkaloids from the Roots and Leaves of *Stichoneuron halabalensis* and their Acetylcholinesterase Inhibitory Activities**
Rosdayati Alino Ramli, Wilford Lie and Stephen G. Pyne 695
- Establishment of a Phenotypic-based Sand Dollar *Fellaster zelandiae* Embryo Development Assay and its Application in Defining the Structure-Activity Relationship of Discorhabdin Alkaloids**
Tanja Grkovic and Brent R. Copp 699
- Sharing of Pyrazine Semochemicals Between Genera of Sexually Deceptive Orchids**
Bjorn Bohman, Ryan D. Phillips, Gavin Flematti, Rod Peakall and Russell A. Barrow 701
- Constituents of the Indonesian Epiphytic Medicinal Plant *Drynaria rigidula***
Ari S. Nugraha, Rachada Haritakun and Paul A. Keller 703
- Variability of the Polyphenolic Content and Antioxidant Capacity of Methanolic Extracts of Pomegranate Peel**
Antony Kam, Kong M Li, Valentina Razmovski-Naumovski, Srinivas Nammi, Kelvin Chan and George Q Li 707
- Combination Effects of Curcumin and Aqueous Extract of *Lignosus rhinocerotis* Mycelium on Neurite Outgrowth Stimulation Activity in PC-12 Cells**
Priscilla A. John, Kah-Hui Wong, Murali Naidu, Vikineswary Sabaratnam and Pamela David 711
- HPLC-NMR Chemical Profiling and Dereplication Studies of the Marine Brown Alga, *Cystophora torulosa***
Sylvia Urban and Michael Timmers 715
- Two Polyketides from a Co-culture of Two Marine-derived Fungal Strains**
Miriam H. Kossuga, Antonio G. Ferreira, Lara D. Sette and Roberto G. S. Berlink 721
- Cyclic Peroxides from a Two-Sponge Association of *Plakortis communis*-*Agelas mauritiana***
Pinus Jumaryatno, Lynette K. Lambert, John N. A. Hooper, Joanne T. Blanchfield and Mary J. Garson 725
- Relative Configuration of the Marine Natural Product Elatenyne using NMR Spectroscopic and Chemical Derivatization Methodologies**
Robert Brkljača and Sylvia Urban 729
- Antimicrobial, Antimalarial and Cytotoxicity Activities of Constituents of a Bhutanese Variety of *Ajania nubigena***
Phurpa Wangchuk, Paul A. Keller, Stephen G. Pyne, John Korth, Samten, Malai Taweechotipatr, Roonglawan Rattanajak and Sumalee Kamchonwongpaisan 733
- Dihydrotagetone, an Unusual Fruity Ketone, is Found in Enantiopure and Enantioenriched Forms in Additional Australian Native Taxa of *Phebalium* (Rutaceae: Boronieae)**
Nicholas J. Sadgrove, Ian R. H. Telford, Ben W. Greatrex, Ashley Dowell and Graham L. Jones 737
- Antimicrobial Activity of Essential Oils and Solvent Extracts from *Zieria* species (Rutaceae)**
Nicholas J. Sadgrove and Graham L. Jones 741
- Characterization and Bioactivity of Essential Oils from *Geijera parviflora* (Rutaceae): A Native Bush Medicine from Australia**
Nicholas J. Sadgrove and Graham L. Jones 747
- Synthesis and Insecticidal Activities of Novel Derivatives of 1 β ,4 α ,6 α ,9 α -Tetrahydroxy-2 β ,12-epoxymethano- β -dihydroagarofuran**
Jiwen Zhang, Zhan Hu, Shengkun Li, Shuding Yang and Wenjun Wu 753
- Novel α -Glucosidase Activator from *Pulicaria undulata***
Nasir Rasool, Muhammad Abid Rashid, Saleha Suleman Khan, Zulfiqar Ali, Muhammd Zubair, Viqar Uddin Ahmad, Shamsun Nahar Khan, M. Iqbal Choudhary and Rasool Bakhsh Tareen 757
- Phytochemical, Antimicrobial and Antiplasmodial Investigations of *Terminalia brownii***
Francis Machumi, Jacob O. Midiwo, Melissa R. Jacob, Shabana I. Khan, Babu L. Tekwani, Jin Zhang, Larry A. Walker and Ilias Muhammad 761
- A New Sulfated Triterpene Saponin from *Gypsophila trichotoma***
Irina Krasteva, Maya Yotova, Kristina Jenett-Siems, Petranka Zdraveva and Stefan Nikolov 765
- Bioactive Triterpene Saponins from the Leaves of *Schefflera elegantissima***
Amira S. Wanas, Mostafa A. Fouad, Mohamed S, Kamel, Katsuyoshi Matsunami and Hideaki Otsuka 767

Continued Inside backcover