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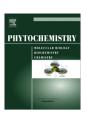
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Highly oxygenated chromones from mangrove-derived endophytic fungus Rhytidhysteron rufulum

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ABSTRACT

Five highly oxygenated chromones, rhytidchromones A-E, were isolated from the culture broth of a mangrove-derived endophytic fungus, Rhytidhysteron rufulum, isolated from Thai Bruguiera gymnorrhiza. Their structures were determined by analysis of 1D and 2D NMR spectroscopic data. The structure of rhytidchromone A was further confirmed by single-crystal X-ray diffraction analysis. These compounds were evaluated for cytotoxicity against four cancer cell lines (MCF-7, Hep-G2, Kato-3 and CaSki). All compounds, except for rhytidchromone D, displayed cytotoxicity against Kato-3 cell lines with IC50 values ranging from 16.0 to 23.3 μ M, while rhytidchromones A and C were active against MCF-7 cells with IC_{50} values of 19.3 and 17.7 μ M, respectively.

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1. Introduction

Endophytic fungi, microorganisms which reside in the healthy tissue of their host harmoniously without causing any apparent negative effect (Strobel and Daisy, 2003; Faeth, 2002), are known as an exceptionally valuable resource for the discovery of structurally interesting and biologically active secondary metabolites, some of which are promising candidates for drug development or agrochemical applications (Zhang et al., 2006; Tan and Zou, 2001; Kusari and Spiteller, 2011; Strobel et al., 2004). Currently, an increasing number of fungal endophytes have been isolated and their metabolites are receiving considerable attention, with a number of structurally unique and biologically active compounds having been thus obtained from their cultures (Kharwar et al., 2011; Macías-Rubalcava et al., 2014; Liu et al., 2015; Amrani et al., 2014; Li et al., 2011). Among plant-derived fungi, those associated with a marine habitat, including mangrove plants, have received much interest from natural product researchers due to this ecosystem (Debbab et al., 2013; Xu, 2015; Zhou et al., 2014; Xiao et al., 2013). Moreover, Thailand has some of the largest mangrove formations in the world, with only those found in Bangla-

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desh. Brazil, Indonesia and India being larger. This prompted us to embark on the study of bioactive metabolites from Thai mangrove-derived fungi (Pudhom and Teerawatananond, 2014; Pudhom et al., 2014; Chokpaiboon et al., 2011, 2010).

Recently, a chemical investigation of the endophytic fungal strain BG2-Y was performed. This fungus was isolated from the leaves of the Thai mangrove plant Bruguiera gymnorrhiza and was identified as Rhytidhysteron rufulum. Five new chromones, namely rhytidchromones A–E (**1–5**), were obtained from the ethyl acetate (EtOAc) extract of the culture broth grown in a Sabouraud dextrose broth (SDB). These compounds contained a highly oxygenated side-chain in their structures. Herein, the isolation, structure elucidation, and cytotoxic activity against human cancer cell lines of these metabolites are described.

2. Results and discussion

The EtOAc extract of the mangrove-derived endophytic R. rufulum cultured in SDB was subjected to chromatographic fractionation over Sephadex LH20 and silica gel to yield compounds 1-5 (Fig. 1).

Rhytidchromone A (1), obtained as colorless crystals, was assigned a molecular formula of C₁₆H₁₆O₇ by the HRESIMS ion at m/z 343.0784 [M+Na]⁺, implying nine degrees of unsaturation. The ¹H NMR spectrum (Table 1) contained signals for one phenolic

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Fig. 1. Structures of compounds 1-5.

Table 1 1 H (400 MHz) and 13 C (100 MHz) NMR spectroscopic data for 1–3 (CDCl₃).

Position	1		2		3	
	δ_{C} , type	δ _H , mult (<i>J</i> in Hz)	δ_{C} , type	δ _H , mult (<i>J</i> in Hz)	δ_{C} , type	δ _H , mult (J in Hz)
2	167.1, qC		166.9, qC		166.9, qC	
3	108.7, CH	6.04, s	108.4, CH	6.05, s	108.4, CH	6.04, s
4	182.5, qC		182.9, qC		182.9, qC	
4a	104.9, qC		105.3, qC		105.8, qC	
5	163.4, qC		162.5, qC		162.3, qC	
6	95.2, CH	6.36, s	95.3, CH	6.40, s	95.3, CH	6.38, s
7	162.9, qC		164.1, qC		164.0, qC	
8	103.4, qC		104.8, qC		104.7, qC	
8a	155.7, qC		156.1, qC		155.9, qC	
1′	69.2, CH	6.00, dd (7.2, 9.6)	70.6, CH	5.10, t (7.2)	70.2, CH	5.09, dd (3.9, 9.9)
2′	33.6, CH ₂	2.55, ddd (7.2, 10.0, 12.8)	36.9, CH ₂	2.30, m	37.4, CH ₂	1.97, ddd (3.9, 9.7, 14.1)
		2.86, ddd (7.2, 9.6, 12.8)		2.60, dt (7.2, 14.0)		2.70, ddd (3.7, 9.9, 14.1)
3′	76.1, CH	4.29, t (10.0)	78.2, CH	3.63, dd (4.8, 12.8)	77.9, CH	4.06, dd (3.7, 9.7)
4'	174.9, qC	. , ,	172.8, qC	•	173.3, qC	
2-Me	20.4, CH ₃	2.35, s	20.5, CH ₃	2.38, s	20.5, CH ₃	2.38, s
5-OH		13.04, br s		13.01, br s		13.03, s
7-OMe	56.3, CH ₃	3.89, s	56.2, CH ₃	3.90, s	56.2, CH ₃	3.89, s
1'-OMe	· =		56.7, CH ₃	3.17, s	56.6, CH ₃	3.19, s
3'-OMe	58.6, CH ₃	3.64, s	58.1, CH₃	3.29, s	58.4, CH ₃	3.43, s
4'-OMe			51.8, CH₃	3.73, s	51.8, CH₃	3.71, s

proton bonded to a carbonyl group (δ_H 13.04 s), one aromatic proton (δ_H 6.36 s) attributed to a pentasubstituted aromatic ring, one olefinic proton (δ_H 6.04 s) assigned to a trisubstituted olefin, two methoxy singlets (δ_H 3.64 and 3.89), and one methyl singlet (δ_H 2.35). Combined analysis of ¹³C NMR and HSQC data further established the presence of one conjugated ketone carbonyl (δ_C 182.5), one ester carbonyl (δ_C 174.9), six quaternary carbons (δ_C 167.1, 163.4, 162.9, 155.7, 104.9 and 103.4), four methines (δ_C 108.7, 95.2, 76.1 and 69.2), two methoxys (δ_C 58.6 and 56.3), one methylene (δ_C 33.6), and one methyl (δ_C 20.4). In addition, the UV absorption maxima at 237, 255, 290, and 319 nm indicated that compound 1 should be a chromone derivative. According to its double bond equivalent (DBE), the seven units of unsaturation for a chromone skeleton and one unit for an ester carbonyl, suggested that compound 1 contains an additional ring in the structure. The ¹H-¹H COSY spectrum indicated the existence of one isolated spin system, CH-1'-CH₂-2'-CH-3', as well as the HMBC cross-peaks from H-1' (δ_H 6.00, dd, J = 7.2, 9.6 Hz) and H-3' (δ_H 4.29, t, I = 10.0 Hz) to an ester carbonyl at δ_C 174.9 (C-4'); this led to the corroboration of the γ -lactone ring (Fig. 2). Further HMBC correlations from H-1' to C-7, C-8 and C-8a indicated that the C-1' oxymethine of the γ -lactone ring was attached on C-8 of the chromone nucleus. One methoxy group (δ_{H} 3.64, δ_{C} 58.6) was located on C-3' due to its HMBC correlation with C-3', whereas another methoxy group (δ_H 3.89, δ_C 56.3) was placed on C-7 from its HMBC cross-peak to C-7. The singlet methyl proton (δ_H 2.35) showed HMBC correlations with C-2 and C-3, indicating the location of the methyl group at C-2. Additionally, observed HMBC

correlations of 5-OH with C-4a, C-5, and C-6 verified the location of the hydroxy group on C-5. This assignment was also supported by the appearance of the hydroxy proton downfield due to a chelation effect. Thus, the structure of 1 was established as shown. The proposed structure of 1 was further confirmed, along with the establishment of its relative configuration by single-crystal X-ray diffraction analysis using Mo K α radiation, and a perspective ORTEP plot is depicted in Fig. 3. To the best of our knowledge, chromones possessing a γ -lactone ring as a side chain seem to be rare. The only precedents include lachnones C-D from a filamentous fungus *Lachnum* sp. (Rukachaisirikul et al., 2006).

Rhytidchromone B (2) was obtained as a pale yellow gum. The HRESIMS afforded an $[M+Na]^+$ ion peak at m/z 389.1207, consistent with a molecular formula of $C_{18}H_{22}O_{8}$, indicating eight degrees of

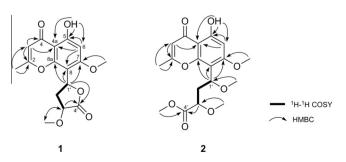


Fig. 2. ¹H-¹H COSY and key HMBC correlations of 1 and 2.

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