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Cylindroxanthones A–C, three new xanthones and their cytotoxicity from the stem bark of *Garcinia cylindrocarpa*

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ABSTRACT

Three new xanthones, cylindroxanthones A–C (**1**–**3**), were isolated from the stem bark of *Garcinia cylindrocarpa*. The structures were established on the basis of spectroscopic analysis. The molecular structure of **1** was unequivocally confirmed by single-crystal X-ray diffraction analysis. These three xanthones were evaluated regarding their cytotoxicity against KB, HeLa S-3, HT-29, MCF-7, and Hep G2 cancer cell lines. Compound **1** exhibited good cytotoxicity against KB cell with IC_{50} value of 2.36 μM.

1. Introduction

The genus *Garcinia* belongs to the Clusiaceae family and comprises 77 species in Indonesia [1,2]. In the previous phytochemical investigation, this genus was well known to contain xanthones as chemotaxonomic marker [3–7], flavonoids [8], phloroglucinols [9,10], and triterpenoids [11,12]. Many of these compounds have demonstrated a number of interesting biological activities such as anticancer [4,7,12], antioxidant [3], antidiabetes [6,13], and anti-inflammatory [10]. *Garcinia cylindrocarpa* Kosterm locally known as "Kogbirat" is the woody plant distributed mainly in Maluku Island, Indonesia [14]. This plant has been used in Indonesian traditional medicine as fever remedy. In continuation on phytochemical investigation for bioactive compounds [4,15–18], we report the isolation and structure elucidation of three new xanthones, cylindroxanthones A–C (**1**–**3**), as well as cytotoxicity of these compounds against five cancer cell lines (KB, HeLa S-3, HT-29, MCF-7, and Hep G2).

2. Experimental

2.1. General experiment procedures

The melting points were determined by micro-melting point apparatus Fischer John. UV spectra were analyzed by UV–vis 1700 Shimadzu spectrophotometer. IR data were obtained on FTIR 8400 Shimadzu spectrophotometer using KBr disk methods. 1D and 2D NMR spectra were measured respectively at 600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR on JNM ECA-600 spectrometer in $CDCl_3$, with TMS as internal standard. HR-ESI-MS were analyzed using Bruker MICROTOF model mass spectrometer. Vacuum liquid (VLC) and column chromatography were carried out using Merck silica gel 60 GF_{254} and silica gel 60 (70–230 mesh ASTM). For TLC analysis, precoated silica gel plates (Merck silica gel 60 GF_{254}, 0.25 mm) were used. Spots were visualized under UV light and sprayed with cerium sulfate ($Ce(SO_4)_2$) followed by heating.

2.2. Plant material

The stem bark of *G. cylindrocarpa* was collected from Saumlaki Forest, Southeast West Maluku Islands, Indonesia. The plant was identified by Mrs. Ritmita Sari (a botanist at Bogor Botanical Garden, Indonesia). A voucher specimen (No. 630) was deposited at the Herbarium Bogoriense, Bogor Botanical Garden, Indonesia.

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Table 1
NMR spectroscopic data (in $CDCl_3$) for **1**, **2**, and **3**.

Position	**1**			**2**			**3**		
	δ_H (*J* in Hz)	δ_C	HMBC	δ_H (*J* in Hz)	δ_C	HMBC	δ_H (*J* in Hz)	δ_C	HMBC
1		158.0			158.0			157.5	
2		104.8			104.9			104.7	
3		160.3			160.2			160.3	
4	6.36 (1H, s)	94.6	9, 4a, 3, 2	6.35 (1H, s)	94.6	9, 8b, 4a, 3, 2	6.42 (1H, s)	95.2	9, 8b, 4a, 3, 2
4a		156.1			156.0			156.8	
4b		152.7			147.1			145.9	
5		137.3			131.3			134.6	
6		147.4			148.5			145.1	
7		143.2			137.7			144.8	
8		149.4			148.5		7.40 (1H, s)	99.8	9, 8a, 7, 6, 5, 4b
8a		111.1			108.5			113.0	
8b		103.6			103.5			103.2	
9		180.4			180.3			179.9	
1′	6.73 (1H, d, 9.9)	115.6	1, 2, 3, 4, 3′, 4′, 5′	6.73 (1H, d, 10.2)	115.6	2, 3, 2′, 3′, 4′, 5′	6.72 (1H, d, 10.2)	115.5	1, 2, 3, 4, 2′, 3′, 4′, 5′
2′	5.59 (1H, d, 9.9)	127.4	2, 3, 3′, 4′, 5′	5.58 (1H, d, 10.2)	127.4	2, 3, 4, 3′, 4′, 5′	5.60 (1H, d, 10.2)	127.6	2, 3, 3′, 4′, 5′
3′		78.2			78.1			78.2	
4′	1.47 (3H, s)	28.4	2′, 3′, 5′	1.47 (3H, s)	28.4	1′, 2′, 3′, 5′	1.46 (3H, s)	28.4	3, 2′, 3′, 5′
5′	1.47 (3H, s)	28.4	2′, 3′, 4′	1.47 (3H, s)	28.4	1′, 2′, 3′, 4′	1.46 (3H, s)	28.4	3, 2′, 3′, 4′
1-OH	13.56 (1H, s)		9, 8b, 1, 2, 1′	13.63 (1H, s)		9, 8b, 1, 2	13.24 (1H, s)		
6-OH				6.39 (1H, s)		5, 6, 7	6.29 (1H, s)		5, 6
5-OMe	3.93 (3H, s)	61.7	5	3.90 (3H, s)	62.1	5	4.01 (3H, s)	61.7	5
6-OMe	3.97 (3H, s)	61.8	6						
7-OMe	3.97 (3H, s)	62.0	7	4.08 (3H, s)	61.8	7	4.08 (3H, s)	56.6	7
8-OMe	4.12 (3H, s)	62.2	8	4.09 (3H, s)	61.8	8			

2.3. Extraction and isolation

The air-dried stem bark of *G. cylindrocarpa* (3.0 kg) was extracted with methanol (3 × 15 L) by maceration at room temperature for three days. The extract was concentrated in vacuo to yield 138.0 g of brown crude extract and separated then into vacuum liquid chromatography (VLC) on silica gel (1.5 kg) using hexane, CH_2Cl_2, EtOAc, and MeOH, respectively, for each 3 × 2 L to get hexane, CH_2Cl_2, EtOAc, and MeOH extracts. CH_2Cl_2 extract (48.0 g) was further subjected to VLC on silica gel (500.0 g) with gradient of EtOAc–CH_2Cl_2 (20:80, 40:60, 60:40, 80:20, 100:0, *v*/*v*, each 500 mL) to get three fractions (A–C). Fraction A (8.9 g) was separated by VLC on silica gel (300.0 g) with gradient of CH_2Cl_2–hexane (5:95, 10:90, 15:85, 20:80, 30:70, 40:60, 50:50, *v*/*v*, each 300 mL) to yield compound **1** (50.4 mg). Fraction B (10.3 g) was chromatographed into VLC on silica gel (300.0 g) with EtOAc–hexane (5:95, 10:90, 20:80, 30:70, 40:60, 50:50, *v*/*v*, each 300 mL) to give six subfractions (B1–B6). Subfraction B5 (1.5 g) was then applied to the same chromatography technique on silica gel (70.0 g) by eluent CH_2Cl_2–hexane (10:90, 25:85, 40:60, 55:45, 70:30, 85:15, 100:0, *v*/*v*, each 150 mL) to yield four subfractions (B5.1–B5.4). Subfraction B5.1 (220.0 mg) was subjected to column chromatography over silica gel (15.0 g) using EtOAc–CH_2Cl_2 (5:95) to afford compound **2** (107.2 mg). Compound **3** (89.0 mg) was obtained by separation of subfraction B5.2 (350.0 mg) using column chromatography over silica gel (10.0 g) eluted with a gradient of EtOAc–CH_2Cl_2 (40:60, 45:55, 50:50, 55:45, *v*/*v*, each 100 mL).

2.3.1. Cylindroxanthone A (**1**)

Yellow crystal; mp: 103–105 °C; UV (MeOH) λ_{max}: 330, 283, and 241 nm; IR ν_{max} (KBr): 3310, 2970, 2939, 1649, 1609, 1448, and 1200 cm^{-1}; for ^1H (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) spectroscopic data, see Table 1; and HRESIMS *m*/*z* 437.1210 $[M + Na]^+$ (calcd. For $C_{22}H_{22}O_8Na$, 437.1212).

2.3.2. Cylindroxanthone B (**2**)

Yellow powder; mp: 144–145 °C; UV (MeOH) λ_{max}: 332, 280, and 243 nm; IR ν_{max} (KBr): 3163, 2974, 2926, 1656, 1605, 1466, and 1180 cm^{-1}; for ^1H (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$)

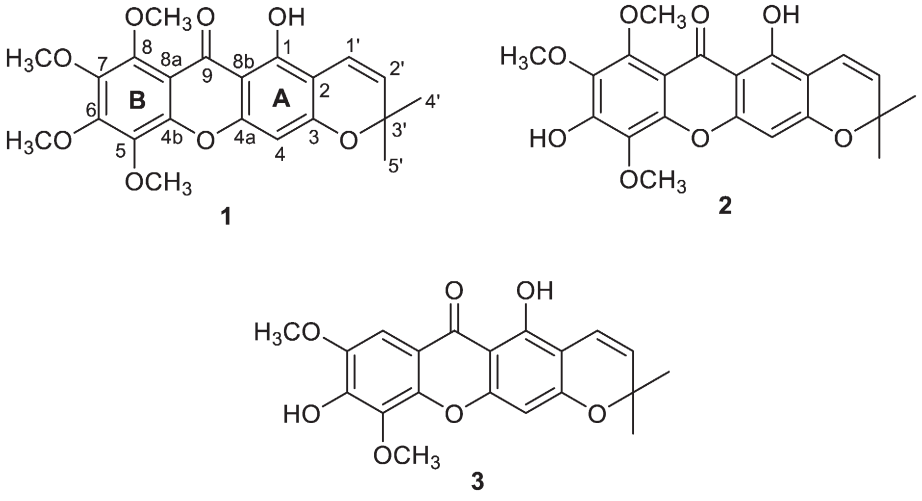

Fig. 1. The structures of **1**–**3** isolated from the stem bark of *G. cylindrocarpa*.