Cytotoxic Chalcones and Flavanones from the Tree Bark of *Cryptocarya costata*

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A new flavanone, 7-hydroxy-5,6-dimethoxyflavanone (**1**), together with three other flavonoids, didymocarpin (**2**), 2′,4′-dihydroxy-5′,6′-dimethoxychalcone (**3**), and isodidymocarpin (**4**), had been isolated from the methanol extract of the tree bark of *Cryptocarya costata.* The structures of these compounds were determined based on spectral evidence, including UV, IR, 1-D and 2-D NMR, and mass spectra. Cytotoxic properties of compounds **1**–**4** were evaluated against murine leukemia P-388 cells. The chalcones **3** and **4** were found to have substantial cytotoxicity with IC_{50} of 5.7 and 11.1 μM, respectively.

Key words: 7-Hydroxy-5,6-dimethoxyflavanone, *Cryptocarya costata*, Murine Leukemia P-388 Cells

Introduction

Cryptocarya is one of the main genera of Lauraceae comprising at least 200 species (Cronquist, 1981) and it is distributed mainly in the tropical region of the world. Although the species can be found throughout the country, the center of its diversity is estimated to be in the eastern part of Indonesia (Sunarno *et al.*, 1995). Phytochemical studies reveal that the plants belonging to this genus produce a variety of aromatic compounds, including α-pyrones (see recent reports by Dumontet *et al.*, 2004; Deschamps *et al.*, 2001; Schmeda-Hirschmann *et al.*, 2001; Juliawaty *et al.*, 2000a; Cavalheiro and Yoshida, 2000), alkaloids (Lin *et al.*, 2001, 2002; Wu and Lin, 2001), and flavonoids (Dumontet *et al.*, 2001, 2004; Fu *et al.*, 1993; Timmermann *et al.*, 1995). Some of these compounds show interesting biological activities, notably as germination inhibitors (Deschamps *et al.*, 2001; Spencer *et al.*, 1984), and cytotoxic effects (Dumontet *et al.*, 2004; Fu *et al.*, 1993; Hoffmann *et al.*, 1978). As part of our program on cytotoxic constituents from the Indonesian plants (Hakim *et al.*, 2005; Suhartati *et al.*, 2001; Sahidin *et al.*, 2005; Syah *et al.*, 2001, 2004), we now report the isolation of a new flavanone, 7-hydroxy-5,6-dimethoxyflavanone (**1**), together with three other flavonoids, didymocarpin (**2**), 2′,4′-dihydroxy-5′,5′-dimethoxychalcone (*3*), and isodidymocarpin (**4**), and cytotoxic properties of these compounds isolated from the tree barks of *Cyptocarya costata* Bl.

Results and Discussion

The powdered dried tree barks of *C. costata* were macerated with methanol. After solvent evaporation under reduced pressure the concentrated methanol extract was diluted with water, and was partitionated into $CHCl_3$ and ethyl acetate fractions. TLC analysis of the fractions showed that the major flavonoids were contained in the $CHCl_3$ fraction. A portion of the $CHCl_3$ fraction was fractionated using the vacuum liquid chromatography technique on silica gel to give six major fractions, A–F. Purification of fraction F by radial chromatography and crystallization gave compound **1**. Using the same method, fraction C yielded compound **3** (Bhaskar and Seshadri, 1974) and fraction D gave compound **4** (Bose and Narayan, 1978a), while fraction F on crystallization using *n*-hexane/ethyl acetate afforded compound **2** (Bose and Narayan, 1978b).

Compound **1** was isolated as a colorless needle crystal, m.p. 189–190 °C, and $[\alpha]_D$ – 6° (MeOH, c = 0.1). The UV and IR spectra of **1** showed typical absorptions [λ_{max} = 209, 280, 324 nm; ν_{max} = 1659 (C=O)] for a flavanone (Lemos *et al.*, 2002),

Table I. ^{1}H NMR data of compounds **1**–**4** in $CDCl_3$.

No.	δ_H (multiplicity, *J* in Hz)		No.	δ_H (multiplicity, *J* in Hz)	
	1	**2**		**3**	**4**
2	5.39 (dd, 3.0, 13.0)	5.45 (dd, 3.0, 12.8)	β	7.83 (d, 15.6)	7.84 (d, 15.9)
3	2.80 (dd, 3.0, 16.8)	2.86 (dd, 3.0, 16.8)	α	7.92 (d, 15.6)	7.94 (d, 15.9)
	3.00 (dd, 13.0, 16.8)	3.02 (dd, 12.8, 16.8)			
8	6.41 (s)	–	3′	6.36 (s)	–
2′/6′	7.46 (m)	7.48 (m)	2/6	7.64 (m)	7.65 (m)
3′/5′	7.43 (m)	7.43 (m)	3/5	7.40–7.46 (m)	7.40–7.46 (m)
4′	7.38 (m)	7.38 (m)	4	7.40–7.46 (m)	7.40–7.46 (m)
5-OCH_3	3.93 (s)	3.91 (s)	5′-OCH_3	3.92 (s)	3.92 (s)
6-OCH_3	3.93 (s)	3.93 (s)	6′-OCH_3	3.91 (s)	3.90 (s)
8-OCH_3	–	3.92 (s)	3′-OCH_3	–	3.97 (s)
7-OH	6.35 (s)	6.30 (s)	4′-OH	6.38 (br s)	6,32 (s)
			2′-OH	13.60 (s)	13.60 (s)

Table II. ^{13}C NMR data of compounds **1**–**4** in $CDCl_3$.

No.	**1**	**2**	No.	**3**	**4**
2	79.1	79.4	β	143.3	143.5
3	45.6	45.9	α	126.4	126.2
4	189.4	189.4	C=O	192.8	193.6
4a	109.2	108.9	1′	109.0	108.6
5	153.2	149.7	2′	156.4	154.6
6	135.3	135.7	3′	99.5	131.4
7	155.7	149.2	4′	154.1	149.6
8	99.3	131.8	5′	133.2	133.5
8a	159.8	151.8	6′	162.7	151.0
1′	138.6	138.7	1	135.3	135.2
2′/6′	126.1	125.9	2/6	128.9	129.0
3′/5′	128.8	128.8	3/5	128.4	128.5
4′	128.7	128.6	4	130.3	130.4
5-OCH_3	61.6	61.6	5′-OCH_3	61.4	61.4
6-OCH_3	61.5	61.3	6′-OCH_3	61.5	62.0
8-OCH_3	–	61.5	3′- OCH_3	–	60.9

which was supported by its NMR spectra (Tables I and II) by the presence of three aliphatic proton signals at δ_H 2.80, 3.00, and 5.39 ppm, and three carbon signals at δ_C 45.6, 79.1, and 189.4 ppm. The mass spectrum of **1** showed a molecular ion peak at *m/z* 300, and together with the NMR data; this corresponds to the molecular formula $C_{17}H_{16}O_5$. The NMR spectra of **1** also disclosed the presence of two methoxy (δ_H 3.93, 6H, s; δ_C 61.6 and 61.5 ppm) and one hydroxy (δ_H 6.35, s) groups. These spectroscopic data, therefore, suggested that **1** is a flavanone containing one hydroxy and two methoxy groups. All these oxygenated groups were deduced to be located in ring A of the flavanone from the presence of an aromatic singlet at δ_H 6.41 ppm and a multiplet of five protons at δ_H 7.35–7.47 ppm, as well as two ion peaks at *m/z* 104 and 196 for the $[M-C_9H_8O_5]^+$ and $[M-C_8H_8]^+$, respectively, arising from a retro Diels-Alder fragmentation of the molecular ion of **1**. The exact location of the two methoxy and one hydroxy groups was determined from the analysis of HMQC and HMBC spectra. The HMBC spectrum (Fig. 1), in particular, showed correlations between the aromatic proton singlet at δ_H 6.41 ppm with four carbon signals at δ_C 109.2 (C-4a), 135.3 (C-6), 155.7 (C-7), and 159.8 ppm (C-8a), and thus, identifying three oxyaryl carbon atoms in ring A. Two of these carbon signals, *i.e.* δ_C 135.3 (C-6) and 155.7 (C-7), were also correlated with the hydroxy proton signal at δ_H 6.35 ppm, which was also correlated with the methine aromatic carbon signal at δ_C 99.3 ppm, confirming the position of the hydroxy group at C-7. The presence of HMBC correlations between the methoxy proton signal at δ_H 3.93 ppm with the fourth oxyaryl carbon signal at δ_C 153.2 ppm (C-5), in addition with the oxyaryl carbon signal at C-6 (δ_C 135.3 ppm), confirmed the position of the two methoxy groups at C-5 and C-6 as shown in structure **1**, and ruled out the alternative struc-

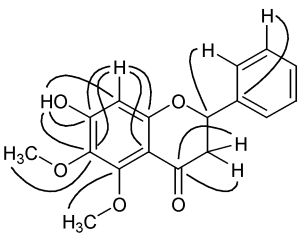

Fig. 1. Selected important HMBC correlations in **1**.

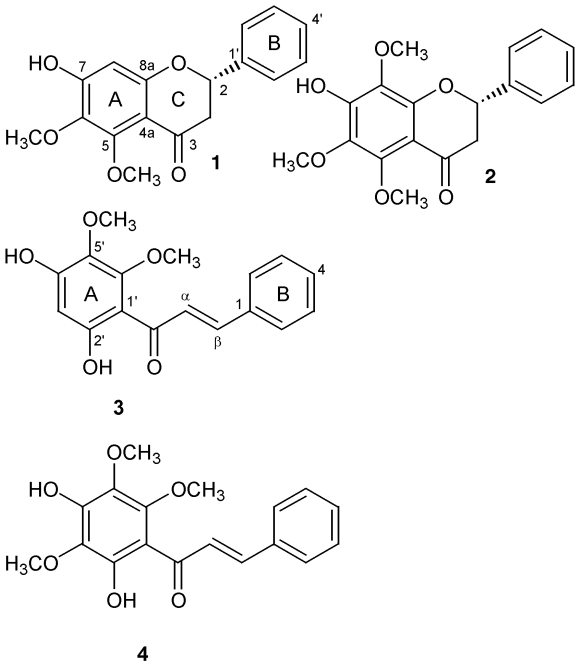

Fig. 2. The flavonoid constituents isolated from *C. costata*: 7-hydroxy-5,6-dimethoxyflavanone (**1**), didymocarpin (**2**), 2′,4′-dihydroxy-5′,6′-dimethoxychalcone (**3**), and isodidymocarpin (**4**).

ture in which these two methoxy groups are at C-5 and C-8. From these HMBC correlations, therefore, compound **1** was assigned as 7-hydroxy-5,6-dimethoxyflavanone (Fig. 2). As shown in the ^{1}H NMR spectrum of **1** there is a *trans* diaxial coupling (J = 13.0 Hz) between H-2 and H-3, and together with a minus sign of its specific optical rotation, **1** must have the *S* configuration at C-2 (Li *et al.*, 1992). Using the same argument the *S* configuration at C-2 was also assigned for compound **2** ($[\alpha]_D$ − 5°, MeOH, c = 0.1).

A number of flavonoids have been isolated from some *Cryptocarya* species. They include dihydrochalcone, chalcone, dihydroflavanone, flavanone, and biflavonoid derivatives (Dumontet *et al.*, 2001, 2004; Fu *et al.*, 1993; Govindachari *et al.*, 1973; Juliawaty *et al.*, 2000b). The presence of compounds **1**–**4** in *C. costata* represents two pairs of flavanone-chalcone containing a highly oxygenated functionality in ring A, which is the first time in *Cryptocarya.* Compounds **2** (didymocarpin) and **4** (isodidymocarpin) have been isolated previously from an Indian plant, *Didymocarpus pedicellata* (Bose and Narayan, 1978a, b), while compound **3** has not been reported previously as a natural compound. The use of 2-D NMR spectra, HMQC and HMBC, for compounds **2** and **4** allow to assign precisely both their proton and carbon signals as shown in the Tables I and II.

The cytotoxic properties of compounds **1**–**4** (Table III) were evaluated against murine leukemia P-388 cells according to the method described previously (Alley *et al.*, 1988). The results showed that the two chalcones (compounds **3** and **4**) strongly inhibited the growth of the cells and a change from the chalcones to the flavanones (compounds **1** and **2**) dramatically decreased cytotoxic properties. These phenomena were consistent with the results obtained by Bhat *et al.* (2005) using a number of cell lines, in which converting the α,β-unsaturated ketone moieties of chalcones to the corresponding epoxides abolished cytotoxicities. However, the presence of an additional methoxy group in ring A affected the cytotoxic properties of the flavanones and chalcones differently. While the addition of a methoxy group in ring A of the chalcones (compounds **3** to **4**) decreased cytotoxicities, the same changes in ring A of the flavanones (compounds **1** to **2**) affected cytotoxicities in an opposite manner. The different responses of cytotoxicities on the structural changes in ring A of the chalcones and flavanones could be rationalized that these two classes of flavonoids exert cytotoxicities on the P-388 cells via different mechanisms. Interestingly a recent study (Shen *et al.*, 2004) had demonstrated that flavanones with a single -OH group at C-2′, -4′, -6, or -7 show greater cytotoxicities on three colorectal carcinoma cell lines, and increasing -OH substitutions at both rings A and B reduced the cytotoxic effects. Thus, more studies are needed to clarify the contribution of oxygenated

Table III. IC_{50} values of compounds **1**–**4** against P-388 cells.

Compound	IC_{50} [μM]
7-Hydroxy-5,6-dimethoxyflavanone (**1**)	130.0 ± 4.7
Didymocarpin (7-hydroxy-5,6,8-trimethoxyflavanone (**2**)	84.1 ± 1.1
2′,4′-Dihydroxy-5′,6′-dimethoxychalcone (**3**)	5.7 ± 0.9
Isodidymocarpin (2′,4′-Dihydroxy-3′,5′,6′-trimethoxychalcone (**4**)	11.1 ± 0.2

functionalities, including the hydroxy and methoxy groups, on the cytotoxic properties of chalcones and flavanones.

Experimental

General experimental procedures

All melting points were determined on a micro-melting point apparatus and were uncorrected. UV spectra were measured with a Varian Conc. 100 instrument. IR spectra were determined with a Perkin Elmer FTIR Spectrum One spectrometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded either with a JEOL JNM A500, operating at 500 (^{1}H) and 125 (^{13}C) MHz, or with a JEOL AS400 spectrometer, operating at 400 (^{1}H) and 100 (^{13}C) MHz, using residual and deuterated solvent peaks as reference standards. Mass spectra were obtained with a JEOL GCmate instrument (direct probe on EI mode). Vacuum liquid (VLC) and column chromatography were carried out using Merck silica gel 60 GF_{254} and silica gel G60, 35–70 mesh. For TLC analysis, precoated silica gel plates (Merck Kieselgel 60 GF_{254}, 0.25 mm) were used.

Plant material

The tree barks of *Cryptocarya costata* were collected from National Garden of Leralindu, Central Sulawesi, Indonesia, in March 2004, and identified by the staff of Herbarium Bogoriense, Bogor, Indonesia. The voucher specimen (E-377L) was deposited at the herbarium of Department of Biology, University of Tadulako, Central Sulawesi.

Extraction and isolation

The powdered dried tree barks (2.5 kg) of *C. costata* were macerated with methanol at room temperature for 24 h. The mixture was filtered and the methanol was evaporated under reduced pressure to give a concentrated methanol extract. The extract was diluted with water and the resulting aqueous methanol extract was partitioned into $CHCl_3$ and ethyl acetate to give $CHCl_3$ (140 g) and ethyl acetate (40 g) fractions. A portion (20 g) of the $CHCl_3$ fraction was fractionated using vacuum liquid chromatography (silica gel; eluted with *n*-hexane/ethyl acetate 9:1–1:1) to give six major fractions, A–F (0.7, 0.9, 3.0, 5.9, 3.6, and 2.6 g, respectively). Purification of a portion (100 mg) of fraction F by radial chromatography (silica gel; eluted with *n*-hexane/ethyl acetate 9:2) and crystallization from *n*-hexane/ethyl acetate afforded compound **1** (50 mg). Using the same method, fraction C (0.2 g) yielded compound **3** (50 mg) and fraction D (400 mg) gave compound **4** (290 mg), while fraction F (500 mg) on crystallization using *n*-hexane/ethyl acetate afforded compound **2** (460 mg).

7-Hydroxy-5,6-dimethoxyflavanone (**1**)

Colorless needle crystals; m.p. 189–190 °C; $[\alpha]_D$ – 6° (MeOH, *c* 0.1). – UV: λ_{max} (MeOH) (log ε) = 209 (3.67), 280 (2.94), 324 (2.54) nm; λ_{max} (MeOH+NaOH) 208 (3.83), 253 (2.76), 332 (3.18) nm. – IR (KBr): ν_{max} = 3220, 2934, 1659, 1596, 1497, 1458 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): see Table I. – ^{13}C NMR (125 MHz, $CDCl_3$): see Table II. – EIMS: *m/z* (% rel. int.) = 300 $[M]^+$ (72), 285 (12), 223 (23), 196 (79), 181 (100), 167 (8), 153 (23), 125 (10), 104 (6), 103 (8), 78 (5), 77 (7), 69 (25).

Cytotoxicity assay

The cytotoxicity assay was conducted according to the method described by Alley *et al.* (1988). P-388 cells were seeded into 96-well plates at an initial cell density of approximately 3×10^4 cells cm^{-3}. After 24 h of incubation for cell attachment and growth, varying concentrations of samples were added. The compounds added were first dissolved in DMSO at the required concentration. Subsequent six desirable concentrations were prepared using PBS (phosphoric buffer solution, pH = 7.30–7.65). Control wells received only DMSO. The assay was terminated after a 48 h incubation period by adding MTT reagent [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; also named as thiazol blue] and the incubation was continued for another 4 h, in which the MTT-stop solution containing SDS (sodium dodecyl sulphate) was added and another 24 h incubation was conducted. Optical density was read by using a micro plate reader at 550 nm. IC_{50} values were taken from the plotted graph of percentage life cells compared to control (%), receiving only PBS and DMSO, versus the tested concentration of compounds (μM). The IC_{50} value is the concentration required for 50% growth inhibition. Each assay and analysis was run in triplicate and averaged.

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