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CYTOTOXIC XANTHONOIDS FROM THE STEM BARK OF *GARCINIA HANBURYI* COLLECTED IN VIETNAM

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Abstract. Five prenylated caged xanthones: desoxymorellin (**1**), morellic acid (**2**), gambogic acid (**3**), isogambogic acid (**4**) and 10α-butoxy gambogic acid (**5**), were isolated from the stem bark of *Garcinia hanburyi* collected in Vietnam. Their structures were elucidated by detailed 1D, 2D NMR, MS spectroscopic analyses and compared with reported data. Two major constituents, gambogic acid and isogambogic acid, displayed strong cytotoxicity against LLC and SK-LU-1cell lines with IC_{50} values in the range from 0.35±0.05 µM to 2.26±0.19 µM. This is the first study on the cytotoxicity of gambogic acid and isogambogic acid against LLC and SK-LU-1 lung cancer cell lines.

Keywords: prenylated caged xanthones, *Garcinia hanburyi*, gambogic acid, cytotoxicity, LLC and SK-LU-1.

Classification numbers: 1.1.1, 1.1.6, 1.4.7.

1. INTRODUCTION

Garcinia hanburyi Hook. f. (*G. hanburyi*), an evergreen tree belonging to the Guttiferae family, distributes in the rainforest of Vietnam, Thailand, Cambodia and the southern part of China. The resin of *G. hanburyi*, which is also called gamboge, has been used as pigment and in folk medicine as a potent purgative and for infected wounds [1]. Previous phytochemical studies revealed that prenylated caged xanthones which contain a unique 4-oxatricyclo[4.3.1.$0^{3,7}$]dec-8-en-2-one scaffold were found from the resin, fruits and other parts of the plant [2-10]. This special group of xanthones is considered as main bioactive group with potent biological activities such as anti-tumor [3-11], anti-HIV [1], anti-bacterial [2], anti- inflammatory [12] and neurotrophic activities [12].

The phytochemical of resin of *G. hanburyi* collected in Phu Quoc, Vietnam was investigated with the isolation of five caged xanthones, assigned as gambogic acid, isogambogic acid, isomorellic acid, isomorellin and isomoreollin B [13]. In this continuing investigation on the sterm bark of this species, we report herein the isolation, structural elucidation and cytotoxicity evaluation against lung cancer cell lines of five prenylated caged xanthones (**1**-**5**), namely desoxymorellin (**1**), morellic acid (**2**), gambogic acid (**3**), isogambogic acid (**4**) and 10α-butoxy gambogic acid (**5**) from the dichloromethane (DCM) extract of the stem bark of *G. hanburyi* collected in Phu Quoc island.

2. MATERIALS AND METHODS

2.1. General

NMR spectra were recorded on a Bruker Avance 500 spectrometer at 500 and 125 MHz for ^{1}H and ^{13}C, respectively, at Institute of Chemistry - Vietnam Academy of Science and Technology (VAST). Chemical shifts are shown in δ (ppm) with tetramethylsilane (TMS) as an internal reference. ESI-MS spectra were performed on an Agilent 1100 LC/MS at Institute of Natural Products Chemistry – VAST. Melting points were measured on Buchi B545 apparatus (no correction). Column chromatographic separations were conducted by using silica gel 60 (Merck, 5-40 μm), silica gel 60 (Merck, 40-63 μm), silica gel 100 (Merck, 63-200 μm), and C_{18}-reversed-phase silica gel (RP-18, Merck, 15-25 μm). Visualization of TLC plates was detected under UV light (at 254 and 365 nm) and staining with vanilin-H_2SO_4 10% solution.

Ellipticine and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Fetal bovine serum (FBS), DMEM medium, trichloroacetic acid (TCA) and acetic acid were obtained from GIBCO-Invitrogen (Carlsbad, CA, USA). Lung cancer cell lines were provided by Professor J. M. Pezzuto, Long-Island University, US and Professor Jeanette Maier, University of Milan, Italy.

2.2. Plant materials

The stem bark of *G. hanburyi* was collected in Phu Quoc island - Kien Giang province, in December 2015. The plant materials were identified by Dr. Nguyen Quoc Binh, Vietnam National Museum of Nature. The voucher specimen (GH2015129) is deposited at Institute of Natural Products Chemistry - Vietnam Academy of Science and Technology.

2.3. Extraction and isolation

The stem bark of *G. hanburyi* (2.5 kg) was cut into small pieces and then were dried in the oven at 45 ^{o}C in three days to achieve 2.1 kg dried stem bark. The dried stem bark was grounded into powder and extracted with methanol (MeOH) (3 L x 3) at room temperature using conventional ultrasound-assisted technique. The solvent was evaporated under reduced pressure to give a dark brown residue (325.0 g). The residue was further extracted with DCM (500 mL × 3) to yield DCM extract (71.9 g). The left residue was then extracted with ethyl acetate (EtOAc) (500 mL × 3) to afford EtOAc extract (122.4 g).

The crude DCM extract was subjected to column chromatography (CC) over silica gel, eluted successively with a gradient of *n*-hexane-EtOAc (v/v, 100:0 to 3:1), DCM-EtOAc (v/v, 15:1 to 3:1) and DCM-MeOH (v/v, 9:1 to 1:2) to afford ten fractions (Frs. GHT1-GHT10).

Fraction GHT1 (3.4 g) was separated by CC using eluent of 2% acetone in *n*-hexane to give five subfractions (GHT1.1-GHT1.5). Further chromatography of subfraction GHT1.4 (0.5 g) over silica gel using *n*-hexane-acetone (v/v, 50:1) as the mobile phase to yield compound **1** (30 mg). Fraction GHT7 (7.5 g) was fractionated by CC with a gradient of *n*-hexane-acetone (v/v, 50:1 to 0:100) to give eight subfractions, GHT7.1-GHT7.8. Subfraction GHT7.3 (1.85 g) was separated by chromatography over RP-18 silica gel eluting with MeOH-H_2O (v/v, 6:1) to give nine subfractions (Frs. GHT7.3.1-GHT7.3.9). Subfraction GHT7.3.6 (0.25 g) was further purified by CC (*n*-hexane-acetone, v/v, 50:1) to obtain compound **2** (10 mg). Fraction GHT4 (11.9 g) was chromatographed over silica gel, eluting with a gradient of hexane-EtOAc-CH_3COOH (v/v/v, 50:1:0.01 to 10:1:0.01) to produce four subfractions (GHT4.1-GHT4.4). Subfraction GHT4.1 (1.8 g) was separated by CC using eluent of 10 % acetone in *n*-hexane follow by purifying on RP-18 silica gel (MeOH-H_2O, v/v, 5:1), to give compound **3** (820 mg). Fraction GHT8 (9.5 g) was loaded to a silica gel CC with a gradient of *n*-hexane-acetone (v/v, 20:1 to 0:100) to yield five subfractions (Frs. GHT8.1-GHT8.5). Compound **4** (470 mg), was derived from subfraction GHT8.4 (3.84 g) by repeated purification on C_{18}-reversed-phase silica gel chromatography with eluent of MeOH-H_2O (v/v, 5:1). Fraction GHT6 (7.4 g) was fractionated by employing CC over silica gel eluting with a gradient of *n*-hexane-EtOAc (v/v, 60:1 to 0:100) to yield five subfractions (Frs. GHT6.1-GHT6.5). Subfraction GHT6.3 (0.9 g) was further isolated by CC over RP-18 silica gel using MeOH-H_2O (v/v, 6:1) as the mobile phase. Compound **5** (0.03 g) was achieved from subfractions GHT6.3.4 by repeating separation on RP-18 silica gel eluting with MeOH-H_2O (v/v, 5:1).

Desoxymorellin (1): yellow oil; ^1H and ^{13}C NMR ($CDCl_3$), see Tables 1 and 2. ESI-MS *m/z* 531.25 $[M+H]^+$ (calcd for $C_{33}H_{39}O_6$, 531.27).

Morellic acid (2): bright yellow solid, m.p. 90-92 ^oC; ^1H and ^{13}C NMR ($CDCl_3$), see Tables 1 and 2. ESI-MS *m/z* 561.22 $[M+H]^+$ (calcd for $C_{33}H_{37}O_8$, 561.25).

Gambogic acid (3): orange solid, m.p. 86-89 ^oC; ^1H and ^{13}C NMR data ($CDCl_3$), see Tables 1 and 2. ESI-MS *m/z* 629.35 $[M+H]^+$ (calcd for $C_{38}H_{45}O_8$, 629.31).

Isogambogic acid (4): orange solid, m.p. 88-90 ^oC; ^1H and ^{13}C NMR ($CDCl_3$), see Tables 1 and 2. ESI-MS *m/z* 629.32 $[M+H]^+$ (calcd for $C_{38}H_{45}O_8$, 629.31).

10α-butoxy gambogic acid (5): light yellow oil; ^1H and ^{13}C NMR ($CDCl_3$), see Tables 1 and 2. ESI-MS *m/z* 701.34 $[M+H]^+$ (calcd for $C_{42}H_{53}O_9$, 701.37).

2.4. Cytotoxicity assay

Cytotoxicity against human lung carcinoma (SK-LU-1) and Lewis lung carcinoma (LLC) cell lines was evaluated by using MTT method according to the described protocol [14] at Institute of Biotechnology – VAST.

SK-LU-1 and LLC cell lines were cultured in a DMEM media mixed with 10 % heat-inactivated fetal bovine serum (FBS), 1 % antibiotic PSF (100 units/mL penicilline, 100 µg/mL streptomycin and fungizone), 2 mM L-glutamine, 1.5 g/L sodium bicarbonate, 4.5 g/L glucose, 10 mM HEPES and 1.0 mM sodium pyruvate using incubator with 5 % CO_2 at 37 ^oC.

Cultured cells were added in 96 well plates at the density of 4 x 10^4 cells/well and grown for 48 h. Compounds **1-5** with various concentrations in DMSO (10 µL) and control (0.5 % of dimethyl sulfoxide) were added to cells. After incubating cells for 48 h, media was removed and the cell monolayer attached to the wall was fixed with cold 20 % (wt/vol) TCA for 1 h at 4 ^oC and stained with 1X SRB staining solution at room temperature (22-25 ^oC) for 30 min. The

unbound dye was removed by washing repeatedly with 1 % (v/v) acetic acid. Finally, the protein-bound dye was dissolved in 10 mM Tris base solution for OD determination at 515-540 nm on an ELISA Plate Reader (Bio-Rad). Cell viability was assessed through MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay as described previously [14].

Ellipticine, with concentrations of 10 μg/mL, 2 μg/mL, 0.4 μg/mL, 0.08 μg/mL, was used as a positive control.

3. RESULTS AND DISCUSSION

3.1. Isolation of the caged xanthones 1-5

Compounds **1-5** were isolated from the DCM extract of the stem bark of *G. hanburyi* using repeated column chromatography on silica gel and C_{18}-reversed-phase silica gel eluting with appropriate solvent mixtures. The structures of the isolated compounds are shown in Figure 1.

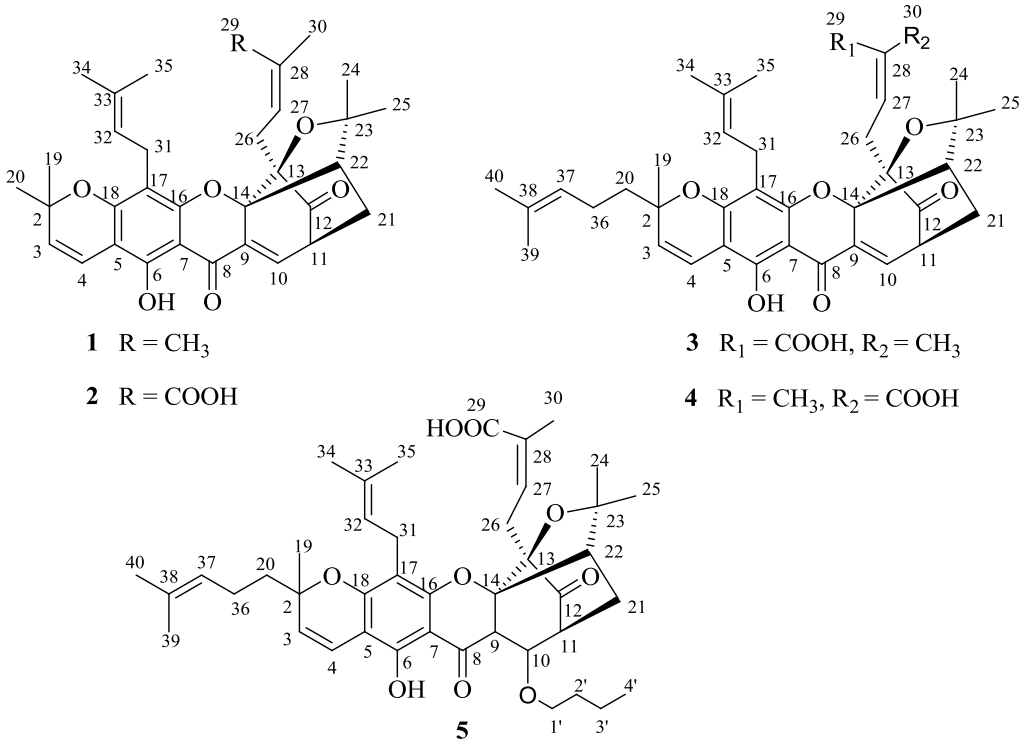

Figure 1. Structures of compounds **1-5**.

Compound **1** was obtained as yellow oil. The ^{1}H NMR spectrum of **1** revealed the presence of one chelated *ortho*-hydroxy group [δ_H 12.90 (1H, s, OH-6)], eight tertiary methyl groups [δ_H 1.09 (3H, s), 1.31 (3H,s), 1.39 (3H, s), 1.46 (6H, s), 1.69 (3H, s), 1.73 (3H, s), 1.79 (3H, s)], two prenyl olefinic protons [δ_H 4.46 (1H, t, J = 7.0 Hz, H-27), 5.24 (1H, dd, J = 6.5, 7.5 Hz, H-32)], a *cis*-double bond [δ_H 5.54 (1H, d, J = 10.0 Hz, H-3), 6.66 (1H, d, J = 10.0 Hz, H-4)] and one proton of α,β-unsaturated ketone group [δ_H 7.46 (1H, d, J = 7.0 Hz, H-10)] (Table 1). The ^{13}C NMR and HSQC spectra contained signals due to eight methyl, three methylene, seven methine, and fifteen quaternary carbons including two carbonyl carbons at δ_C 203.5 and 179.6, which

were characterized as signals of C-12 and C-8 of the caged xanthonoid skeleton (Table 2). The NMR spectra of **1** also contained characteristic signals of a bicyclo[2,2,2]octane ring at [δ_H 3.51 (dd, J = 6.5, 5.0 Hz), δ_C 47.0, CH-11] , [δ_H 2.35 and 1.34 (dd), δ_C 25.5, CH_2-21] and [δ_H 2.51 (d, J = 9.5), δ_C 49.2, CH-22] (Tables 1, 2). These spectral data suggested that **1** contained a caged xanthonoid moeity [15-19] with two prenyl side chains. The positions of the substituents at C-2, C-17 and C-13 were determined by HMBC experiment with correlations between: H-19, H-20 (δ_H 1.46) /C-3 (δ_C 126.1); H-31(δ_H 3.35)/C-16 (δ_C 157.5) and C-18 (δ_C 160.6); H-26 (δ_H 2.59)/C-12 (δ_C 203.5), C-13 (δ_C 84.7) and C-14 (δ_C 90.5). In addition, the HMBC correlations of H-10/C-11, C-21; H-21/C=O (C-12); H-22, H-24 (δ_H 1.73), H-25 (δ_H 1.31)/C-23 (δ_C 83.2) confirmed the presence of a bicyclo[2,2,2]octane ring. On the basis of the evidences and upon comparison the spectral data of compound **1** with those of previously reported [20], compound **1** was assigned as desoxymorellin.

Table 1. ^{1}H (500 MHz) NMR data of compounds **1**-**5** in $CDCl_3$: δ_H (ppm) J (Hz).

Position	**1**	**2**	**3**	**4**	**5**
3	5.54 (d, 10.0)	5.48 (d, 10.0)	5.38 (d, 10.0)	5.44 (dd, 10.5, 7.0)	5.44 (d, 10.0)
4	6.66 (d, 10.0)	6.58 (d, 10.0)	6.60 (d, 10.0)	6.67 (dd, 10.5, 2.5)	6.66 (dd, 10.0, 1.5)
6-OH	12.90 (s)	12.80 (br s)	12.77 (s)	12.75 (br s)	11.95 (s)
9	-	-	-	-	3.18 (m)
10	7.46 (d,7.0)	7.55 (d, 6.5)	7.55 (d, 7.0)	7.55 (dd, 7.0, 2.5)	4.42 (dd, 4.5, 1.5)
11	3.51 (dd, 6.5, 5.0)	3.48 (m)	3.47 (m)	3.50 (dt, 7.0, 2.5)	2.81 (m)
19	1.46 (s)	1.40 (s)	1.38 (s)	1.38 (s)	1.36 (s)
20	1.46 (s)	1.44 (s)	1.76 (overlapped), 1.59 (m)	1.78 (overlapped), 1.65 (overlapped)	1.77 (m), 1.63 (m)
21	2.35 (dd, 13.5, 4.5); 1.34 (overlapped)	1.38 (overlapped); 2.32 (dd, 13.5, 4.5)	2.31 (dd, 13.5, 5.0); 1.34-1.36 (m)	2.33 (dd, 13.5, 4.5); 1.34-1.36 (m)	1.94 (m), 1.38 (m)
22	2.51 (d, 9.5)	2.53 (d, 9.5)	2.51 (d, 9.0)	2.52 (d, 9.5)	2.50 (d, 8.5)
24	1.73 (s)	1.29 (s)	1.69 (s)	1.71 (s)	1.35 (s)
25	1.31 (s)	1.65 (s)	1.29 (s)	1.29 (s)	1.15 (s)
26	2.59 (d, 7.5)	2.92 (t, 7.5, 7.0)	2.95 (dd, 15.5, 8.0)	2.63 (dd, 6.0, 3.0), 2.58 (dd, 6.0)	3.20 (m), 3.10 (m)

27	4.46 (t, 7.0)	6.02 (t, 7.0, 6.5)	6.09 (t, 7.5)	6.49 (t, 7.0)	6.61 (dt, 7.0, 1.0)
29	1.09 (s)	-	-	1.36 (s)	-
30	1.39 (s)	1.74 (s)	1.74 (s)	-	1.96 (s)
31	3.35 (m)	3.16 (dd, 14.5, 5.0), 3.32 (dd, 9.0, 8.0)	3.29 (dd, 15.0, 8.0), 3.14 (dd, 15.0, 5.0)	3.29 (dd, 16.0, 6.5)	3.28 (m), 3.19 (m)
32	5.24 (dd, 7.5, 6.5)	5.05 (t, 6.5, 6.0)	5.04 (overlapped)	5.13 (dt, 7.0, 1.5)	5.03 (dt, 6.0, 1.5)
34	1.79 (s)	1.74 (s)	1.72 (s)	1.73 (s)	1.73 (s)
35	1.69 (s)	1.65 (s)	1.62 (s)	1.65 (s)	1.62 (s)
36	-	-	2.01 (m)	2.03 (m)	2.08 (m)
37	-	-	5.04 (overlapped)	5.07 (dt, 8.5, 2.5)	5.09 (dt, 7.0, 1.5)
39	-	-	1.64 (s)	1.66 (s)	1.56 (s)
40	-	-	1.55 (s)	1.55 (s)	1.66 (s)

Table 2. ^{13}C (125 MHz) NMR data of compounds **1**-**5** in $CDCl_3$: δ_C (ppm).

Position	**1**	**2**	**3**	**4**	**5**
2	78.4	78.7	81.3	81.3	81.0
3	126.1	126.1	124.5	124.8	125.1
4	115.6	115.4	115.9	115.9	115.9
5	103.0	103.2	102.8	102.9	102.8
6	157.8	157.6	157.6	157.6	156.4
7	100.6	100.6	100.5	100.5	101.8
8	179.6	179.0	178.9	178.8	193.8
9	133.8	133.8	133.4	133.4	48.6
10	133.8	135.4	135.3	135.3	72.3
11	47.0	46.9	46.8	46.9	44.2
12	203.5	203.5	203.3	202.9	208.4
13	84.7	84.1	83.8	83.7	86.4
14	90.5	90.9	90.9	90.7	88.4
16	157.5	157.3	157.4	157.4	155.7
17	108.3	108.1	107.6	107.9	108.9

18	160.6	161.2	161.5	161.4	161.2
19	28.3	28.3	27.7	27.4	27.2
20	28.3	28.3	42.0	41.9	41.9
21	25.5	25.2	25.2	25.4	20.0
22	49.2	49.1	49.0	49.1	43.6
23	83.2	83.8	84.1	83.7	82.4
24	30.1	28.9	29.9	30.0	29.7
25	29.1	29.9	28.8	29.1	27.2
26	28.8	29.4	29.3	29.0	28.0
27	117.9	136.8	137.8	136.8	139.0
28	134.9	126.1	127.8	128.9	127.6
29	16.7	170.1	170.2	11.4	171.6
30	25.6	20.8	20.7	171.1	20.6
31	21.7	21.7	21.6	21.6	21.5
32	122.2	122.2	122.3	122.2	122.6
33	131.6	131.6	131.5	131.9	131.3
34	18.2	18.2	18.2	18.1	18.1
35	25.7	25.7	25.6	25.5	25.6
36	-	-	22.7	22.7	22.9
37	-	-	123.8	123.8	123.8
38	-	-	131.8	131.8	131.9
39	-	-	25.6	25.7	25.6
40	-	-	17.6	17.6	17.6

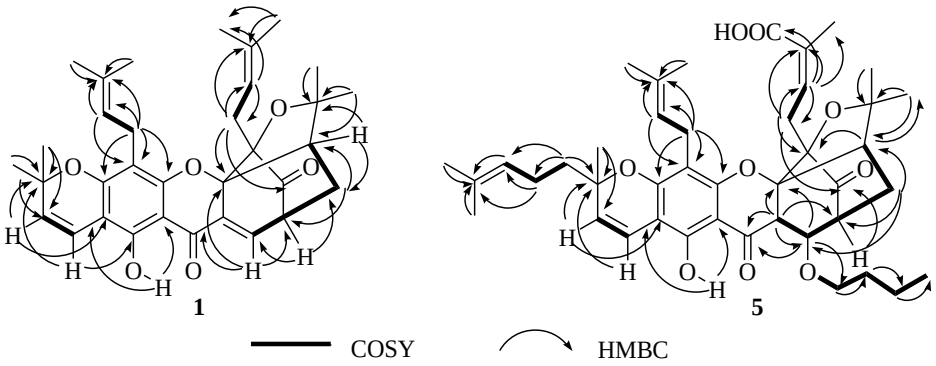

Figure 2. COSY correlations, key HMBC correlations and/or NOESY correlations of compounds **1** and **5**.

Compound **2** was isolated as a bright yellow solid. The NMR spectra of compound **2** exhibited 33 carbon signals, equal to the number of carbons in **1** (Table 2). However, the ^{1}H-NMR spectrum of **2** demonstrated the disappearance of a methyl group and the shift to the upperfield of the olefinic proton H-27 (at δ_H 6.02 in **2** compared to 4.46 in **1**) (Table 1). Moreover, the ^{13}C-NMR spectrum exhibited the appearance of one more carbonyl carbon at δ_C 170.1 besides the two carbonyl carbons C-8, -12 (at δ_C 179.0 and 203.5, respectively). Thus, the NMR data of **2** suggested the replacement of the methyl group in compound **1** by a carboxyl group (C-29). By comparing the NMR data of **2** with reported data of morellic acid [21], we concluded that compound **2** was morellic acid.

Compounds **3** and **4** were separated as yellow solids. Comparison of NMR data of **3** or **4** and **2** (morellic acid) revealed the only difference was that one of the methyl groups bonded to C-2 in **2** was replaced by a prenyl group in **3** and **4** (Tables 1-2). The structures of **3** and **4** were elucidated as gambogic acid and isogambogic acid from their NMR data and by comparison with reported data [3, 21-22]. These compounds were previously isolated from the resin of *G. hanburyi* growing in Phu Quoc island [13].

Compound **5** was obtained as light yellow oil. The NMR spectra of compound **5** were quite similar to those of compounds **3** and **4**, except for the disappearance of H-10 signal at δ_H 7.55 ppm (1H, s) and the appearance of one *n*-butoxy group and two methine protons at δ_H 3.18 (1H, m, H-9) and 4.42 (1H, dd, J = 4.5 & 1.5Hz, H-10). The COSY and HSQC spectra of compound **5** illustrated the correlations of six ^{1}H - ^{1}H and ^{1}H - ^{13}C spin systems represented as bold lines (Figure 2), in which the *n*-butoxy group was appeared at [δ_H 3.51 (1H, m), 3.38 (1H, m), δ_C 68.1, CH-1'], [δ_H 1.47 (2H, m), δ_C 31.6, CH-2'], [δ_H 1.27 (2H, m,), δ_C 19.2, CH-3'] and [δ_H 0.85 (3H, t, J = 7.0, 7.5), δ_C 13.8, CH-4']. Moreover, the HMBC correlations of H-9/C-10 (δ_C 72.3), C-11 (δ_C 44.2); H-21 (δ_H 1.94, 1.38)/C-10; H-22 (δ_H 2.50)/C-10, C-14 (δ_C 88.4) and H-10/C-1' indicated that the double bond between C-9 and C-10 was oxidized. Furthermore, the signal of the metyl group in the 4-methylbut-3-en-4-oic group was assigned at δ_C 20.6 ppm (C-30) suggested the Z form of the double bond C-27 and C-28. Based on the above evidences and upon comparison of the reported values [23], compound **5** was identified as 10α-butoxy gambogic acid.

3.2. *In vitro* cytotoxicity

Table 3. Cytotoxicity of compounds **1-5** against LLC and SK-LU-1 cells.

Compound	IC_{50} (μM)	
	LLC	SK-LU-1
1	N/A	N/A
2	N/A	N/A
3	0.37 ± 0.08	0.35 ± 0.05
4	2.26 ± 0.19	2.02 ± 0.27
5	N/A	N/A
Ellipticine	1.99 ± 0.16	1.79 ± 0.33

N/A: no activities

Five isolated compounds were evaluated for their cytotoxicity against lung cancer cells (LLC, SK-LU-1), with ellipticine as the positive control. Deoxymorelline (**1**), morellic acid (**2**)

and 10-butoxy-gambogic acid (**5**) showed no activities whereas gambogic acid (**4**) and isogambogic acid displayed potent toxicity against tested cancer cell lines. The IC_{50} values of gambogic acid (**3**) and isogambogic acid (**4**) are given in the Table 3. The test result also revealed that these two compounds displayed higher cytotoxic activity against SK-LU-1 cell line than against LLC cell line. Furthermore, gambogic acid (**3)** showed higher activity, with IC_{50} values of 0.37 and 0.35 μM against LLC and SK-LU-1 cell lines, respectively.

4. CONCLUSIONS

Chemical constituents study of the sterm bark of *Garcinia hanburyi* Hook. f. (Guttiferae) collected from Phu Quoc island leads to the isolation and identification of five prenylated caged xanthones, desoxymorellin (**1**), morellic acid (**2**), gambogic acid (**3**), isogambogic acid (**4**) and 10α-butoxy gambogic acid (**5**). Among these xanthones, gambogic acid (**3**) and isogambogic acid (**4**) presented potent cytotoxic activities to LLC and SK-LU-1 cancer cells. Especially, gambogic acid (**3**) may provide us a clue for a lead structure of anticancer agents.

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