Phytochemistry Letters 4 (2011) 129–133

Contents lists available at ScienceDirect

Phytochemistry Letters

journal homepage: www.elsevier.com/locate/phytol

Guttiferones Q-S, cytotoxic polyisoprenylated benzophenones from the pericarp of *Garcinia cochinchinensis*

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ARTICLE INFO

Article history:
Received 16 September 2010
Received in revised form 17 January 2011
Accepted 24 January 2011
Available online 8 February 2011

Keywords:
Garcinia cochinchinensis
Guttiferae
Guttiferones Q-S
Xanthones
Structure elucidation
Cytotoxicity

ABSTRACT

Three new polyisoprenylated benzophenones, guttiferones Q-S, the known guttiferone I and four xanthones, dulxanthone A, 1,3,5-trihydroxy-6-methoxy-7-(3-methylbut-2-enyl)xanthone, 1,3,5-trihydroxy-13,13-dimethyl-2H-pyran[7,6-b]xanthen-9-one and 1,3-dihydroxy-5,6-dimethoxy-7-(3-methylbut-2-enyl)xanthone, as well as trimethyl citrate, were isolated from the pericarp of *Garcinia cochinchinensis* collected in Vietnam. Their structures were elucidated using spectroscopic methods (mainly 1-D and 2-D NMR). All the guttiferones were tested for their cytotoxicity towards three human cancer cell lines, MCF-7, Hela, and NCI-H460. Among the tested compounds, guttiferone Q showed potent cytotoxicity, having IC_{50} values in the range of 2.74–4.04 μg/ml, against the investigated cells.

1. Introduction

The genus *Garcinia* (Guttiferae) is known for the biosynthesis of a variety of polyisoprenylated benzophenones (Hamed et al., 2006; Gustafson et al., 1992; Magadula et al., 2008), a class of compounds which is not only chemically interesting due to their structurally complex features but also pharmacologically valuable. Polyisoprenylated benzophenones have been reported to possess various biological activities including antibacterial (Lokvam et al., 2000), antioxidant (Sang et al., 2002), HIV-inhibitory (Gustafson et al., 1992), cytotoxic (Matsumoto et al., 2003; Baggett et al., 2005), and cancer chemopreventive (Ito et al., 2003) properties. In Vietnamese folk medicine, the bark of *Garcinia cochinchinensis* is used to cure allergy, itches and skin diseases while the buds are used for the treatment of threatened abortion (Vo, 1997). Previous work on the bark of the species collected in south Vietnam resulted in the isolation of guttiferone G, a strong inhibitor of human sirtuins SIRT1 and SIRT2 (Gey et al., 2007). To continue our search for new cytotoxic compounds from medicinal plants, we have examined the chemical constituents of the pericarp of *G. cochinchinensis* collected in Dong Nai Province and now report the isolation, structure elucidation and cytotoxicity of three new polyisoprenylated benzophenones, guttiferones Q-S (**1**–**3**). In addition, the benzophenone guttiferone I and four known xanthones, together with trimethyl citrate, were obtained.

2. Results and discussion

A chloroform extract of the pericarp of *G. cochinchinensis* was subjected to silica gel, RP_{18} and Sephadex LH-20 column chromatography to produce guttiferones Q-S (**1**–**3**), guttiferone I (**4**) (Merza et al., 2006), dulxanthone A (Ito et al., 1997), 1,3,5-trihydroxy-6-methoxy-7-(3-methylbut-2-enyl)xanthone (Han et al., 2008), 1,3,5-trihydroxy-13,13-dimethyl-2H-pyran[7,6-b]xanthen-9-one (Nilar et al., 2005), 1,3-dihydroxy-5,6-dimethoxy-7-(3-methylbut-2-enyl)xanthone (Han et al., 2008), and trimethyl ester of citric acid (Han et al., 2001).

Guttiferone Q (**1**) was isolated as bright yellow needles, mp. 104–106 °C, $[\alpha]_D^{25}$ −50.0 (*c* 0.21, MeOH), UV: (λ_{max}) 261 nm. The HR-ESIMS showed a $[M+H]^+$ molecular ion peak at *m*/*z* 503.3156, which suggested a molecular formula of $C_{33}H_{42}O_4$ with 13° of unsaturation. The IR spectrum exhibited a hydroxyl band (3411 cm^{-1}), and three carbonyl bands (1728, 1671, 1641 cm^{-1}). The ^1H NMR spectrum (Table 1) revealed the presence of a monosubstituted benzene ring in the molecule [δ_H 7.56 (2H, m, H-12 and H-16), 7.40 (2H, t, *J* = 7.7 Hz, H-13 and H-15) and 7.54 (1H, m, H-14)]. There were also resonances for a tertiary methyl [δ_H 0.93 (3H, s, H_3-17)], three olefinic protons [δ_H 5.18 (1H, br t, *J* = 7.3 Hz, H-30), 5.12 (1H, br t, *J* = 7.0 Hz, H-20) and 5.05 (1H, br t, *J* = 6.5 Hz, H-25)], six vinylic methyls [δ_H 1.73, 1.70, 1.69, 1.66, 1.65 and 1.60 (3H each, s, H_3-32, H_3-23, H_3-27, H_3-22, H_3-33 and H_3-28)] and four allylic methylenes [δ_H 1.45–1.70 and 2.02–2.44 (8H, m)], which suggested the presence of two 3-methylbut-2-enyl and one 4-methylpent-3-enyl side chains. The ^{13}C NMR spectrum (Table 1) showed resonances for six aromatic carbons and a conjugated

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doi:10.1016/j.phytol.2011.01.001

Table 1
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data for guttiferones Q-S (**1**–**3**) (*J* in Hz in parentheses).

Position	Guttiferone Q (**1**)[a]		Guttiferone R (**2**)[b]		Guttiferone S (**3**)[b]	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	–	196.6	–	177.9	–	194.9
2	–	118.4	–	117.5	–	118.0
3	–	188.4	–	192.1	–	173.2
4	3.35 s	67.7	3.14 s	69.7	3.94 s	59.7
5	–	48.3	–	46.6	–	44.3
6	1.78 m	42.1	2.04 m	42.2	2.05 m	43.4
7	2.06 dd (13.2, 4.0)	42.9	2.44 dd (13.7, 4.8)	38.8	1.97 dd (13.3, 4.5)	42.1
	1.60 t (13.2)		1.90 dd (13.7, 12.5)		1.48 t (13.3)	
8	–	64.9	–	61.5	–	64.6
9	–	208.0	–	203.5	–	206.9
10	–	198.3	–	192.3	–	194.0
11	–	139.5	–	138.3	–	138.6
12	7.56 m	129.7	7.81 dd (8.0, 1.3)	129.8	7.83 dd (7.8, 1.0)	129.6
13	7.40 t (7.7)	128.9	7.50 br t (8.0)	129.4	7.49 br t (7.8)	129.4
14	7.54 m	133.3	7.61 tt (8.0, 1.3)	134.1	7.60 tt (7.8, 1.0)	133.9
15	7.40 t (7.7)	128.9	7.50 br t (8.0)	129.4	7.49 br t (7.8)	129.4
16	7.56 m	129.7	7.81 dd (8.0, 1.3)	129.8	7.83 dd (7.8, 1.0)	129.6
17	0.93 s	18.4	0.96 s	17.7	0.98 s	18.2
18	1.67 m	39.8	1.60 m	39.1	2.12 m	36.4
	1.46 td (12.8, 4.1)		1.42 td (12.5, 4.5)		1.61 m	
19	2.36 m	23.0	2.42 m	22.5	2.25 m	22.8
	2.06 m		1.92 m		2.02 m	
20	5.12 br t (7.0)	125.4	5.01 br t (7.3)	125.3	4.16 dd (11.3, 7.8)	91.1
21	–	132.5	–	131.8	–	72.6
22	1.66 s	18.2	1.60 s	17.8	1.12 s	26.6
23	1.70 s	26.0	1.63 s	25.8	1.04 s	27.2
24	2.20 m	29.1	2.36 m	28.0	2.18 m	28.4
	1.70 m		1.84 m		1.81 m	
25	5.05 br t (6.5)	123.6	5.21 br t (7.3)	123.4	5.16 br t (6.8)	123.5
26	–	134.4	–	133.8	–	133.8
27	1.60 s	17.8	1.64 s	18.0	1.64 s	18.0
28	1.69 s	25.9	1.71 s	26.0	1.71 s	26.0
29	2.42 m	31.1	2.77 dd (13.0, 5.8)	29.6	2.35 m	30.1
			1.96 dd (13.0, 10.8)		2.05 m	
30	5.18 br t (7.3)	121.1	4.80 dd (10.8, 5.8)	93.6	5.08 br t (7.0)	121.3
31	–	135.2	–	70.5	–	133.6
32	1.65 s	18.0	1.08 s	26.2	1.59 s	18.1
33	1.73 s	26.2	1.10 s	25.7	1.61 s	26.1

[a] Measured in methanol-d_4.
[b] In acetone-d_6.

carbonyl group [δ_C 198.3 (C-10)], revealing the presence of a benzoyl group. Resonances for a bicyclo[3.3.1]nonane ring system including a non-conjugated ketone [δ_C 208.0 (C-9)], an enolised 1,3-diketone [δ_C 196.6 (C-1), 188.4 (C-3) and 118.4 (C-2)], two quaternary carbons [δ_C 64.9 (C-8) and 48.3 (C-5)], two methines [δ_C 67.7 (C-4) and 42.1 (C-6)] and a methylene [δ_C 42.9 (C-7)] were also observed. The spectral data were similar to those of the polyisoprenylated benzophenone guttiferone I (Merza et al., 2006) with one less isoprenyl group.

In the HMBC plot (Fig. 1), the tertiary methyl group attached to C-5 [δ_H 0.93 (H_3-17)] showed correlations to a quaternary carbon [δ_C 48.3 (C-5) and two methine carbons [δ_C 67.7 (C-4) and 42.1 (C-6)]. The more shielded methylene protons of the 4-methylpent-3-enyl side chain correlated to C-4, C-5, C-6 and C-17, indicating that the group was linked to the skeleton at C-5. C-4 was therefore protonated instead of carrying an isoprenyl group as seen in guttiferone I. Correlations of C-24 methylene protons (^2J: C-6, ^3J: C-7) confirmed the placement of a 3-methylbut-2-enyl group at C-6 while those of C-29 methylene protons (^2J: C-8, ^3J: C-1 and C-7) required the other 3-methylbut-2-enyl group to be bonded to C-8. The correlations observed in the ^1H–^1H COSY spectrum confirmed the structure.

The bicyclic ring system in compound **1** required both H-4 and the C-8 isoprenyl side chain to be equatorial. The relative configuration of C-6 was deduced from the coupling constant of 13.2 Hz between H-6 and H_β-7, which required the protons to be *trans*-diaxial. The 3-methylbut-2-enyl group located at C-6 therefore had an α-orientation. Assignment of the relative stereochemistry of the substituents at C-5 was made by comparison with that of guttiferone I (**4**) (Merza et al., 2006). The absolute configuration of **1** remains undetermined.

Guttiferone R (**2**) was obtained as bright yellow needles, mp. 86–88 °C, $[\alpha]_D^{25}$ −57.5 (*c* 0.33, MeOH), UV: (λ_{max}) 253 nm, IR: (ν_{max}) 3433 cm^{-1} (O–H), 1736, 1673, 1618 cm^{-1} (C=O), $C_{33}H_{42}O_5$ (*m*/*z* 519.3105 $[M+H]^+$). The ^1H and ^{13}C NMR spectra (Table 1) closely resembled those of **1** apart from the chemical shifts of C-1 and the C_5 unit attached to C-8, suggesting that the difference was only in the structure of the side chain. In the HMBC spectrum, correlations of protons at δ_H 2.77 and 1.96 (H_2-29), 1.08 (H_3-32) and 1.10 (H_3-33) to the carbons at δ_C 93.6 (C-30) and 70.5 (C-31) indicated that the side chain was a 2,3-dioxygenated 3-methylbutyl group. Key HMBC correlations (Fig. 1) of H_2-29 to the carbons at δ_C 177.9 (C-1) revealed that the side chain formed a 2-(1-hydroxy-1-methylethyl)-2,3-dihydrofuran ring fused with the phloroglucinol moiety at C-1 and C-8 with C-1 being oxygenated. Guttiferone R therefore had structure **2** which was supported by the ^1H–^1H COSY experiment.

Guttiferone S (**3**) was obtained as a pale yellow gum and had an $[\alpha]_D^{25}$ value of −10.0 (*c* 0.28, MeOH), UV: (λ_{max}) 253 nm, $C_{33}H_{42}O_5$ (*m*/*z* 519.3105 $[M+H]^+$). The IR spectrum (see Section 3) was virtually identical to those of **1**. The ^1H and ^{13}C NMR spectra (Table 1) also compared well with those of **1** apart from the absence of signals due to a C_5 side chain. These were replaced by resonances which could be ascribed to a 3,4-dioxygenated 4-methylpentyl group [δ_H 4.16 (1H, dd, *J* = 11.3, 7.8 Hz, H-20), 2.25 and 2.02 (1H

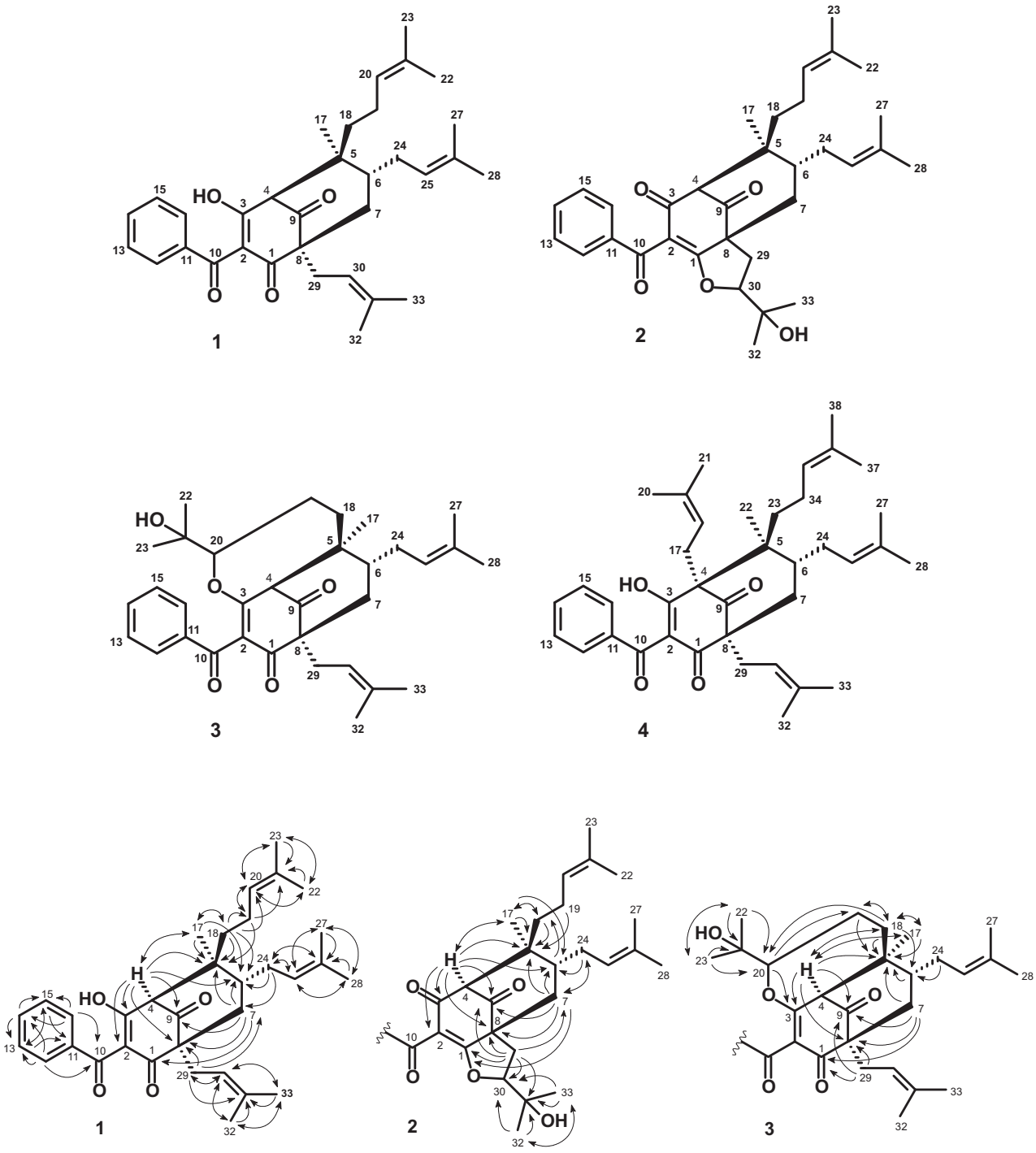

Fig. 1. HMBC correlations for guttiferones Q-S (**1**–**3**).

each, m, H_2-19), 2.12 and 1.61 (1H each, m, H_2-18), 1.12 (3H, s, H_3-23) and 1.04 (3H, s, H_3-22); δ_C 91.1 (C-20), 72.6 (C-21), 36.4 (C-19), 27.2 (C-22), 26.6 (C-23) and 22.8 (C-19)]. Correlations of H-20 to C-3 (δ_C 173.2) observed in the HMBC spectrum (Fig. 1) confirmed the presence of a 2-(1-hydroxy-1-methylethyl)-2,3,4,5-tetrahydrooxepine ring fused with the phloroglucinol moiety at C-3 and C-5 with the oxygen atom bonded to C-3. Guttiferone S was thus identified as **3**. The structure was consistent with the ^1H–^1H COSY spectrum.

Guttiferones Q-S (**1**–**3**) and guttiferone I (**4**) were tested for their cytotoxicity towards three human cancer cell lines, MCF-7 (breast adenocarcinoma), HeLa (human cervical cancer), and NCI-H460 (human lung cancer). As shown in Table 2, guttiferone Q (**1**) exhibited strong activity with IC_{50} values of 2.74, 3.03, and 4.04 μg/ml, respectively, while both guttiferones R (**2**) and S (**3**) were found to be inactive. IC_{50} of guttiferone I (**4**) was not determined due to the lack of sample amount but **4** had promising cytotoxicity for inhibiting 91.9% growth of NCI-H460 cells at the concentration of 100 μg/ml and inhibiting 82.7 and 80.0% growth of Hela and MCF-7 cells at 50 μg/ml, respectively.

It could be assumed that guttiferones R and S (**2**–**3**) were produced from guttiferone Q (**1**) by cyclisation of the 3-methylbut-2-enyl side chain at C-8 to the oxygen atom at C-1, and the 4-methylpent-3-enyl group at C-5 to the oxygen atom at C-3, respectively. Such cyclisations led to the disappearance of a hydroxyl group in the phloroglucinol moiety which decreased

Table 2
Cytotoxicity of guttiferones Q (**1**) and I (**4**).

Cell line	$IC_{50} \pm SD$ (μg/ml)[a]	Growth inhibition (%)
	1	4
MCF-7	2.74 ± 0.12	80.0 ± 0.3[b]
Hela	3.03 ± 0.15	82.7 ± 3.4[b]
NCI-H460	4.04 ± 0.22	91.9 ± 1.0[c]

[a] Mean of three measurements.
[b] % Growth inhibition of **4** at concentration 50 μg/ml, mean of two measurements.
[c] % Growth inhibition of **4** at concentration 100 μg/ml, mean of three measurements.

dramatically cytotoxicity of the compounds towards the tested cells. In addition, it is possible that guttiferone I (**4**) was yielded from prenylation at C-4 of guttiferone Q (**1**).

3. Experimental

3.1. General experimental procedures

Optical rotations were measured on an A. Krüss Optronic polarimeter. Melting points were determined on a Wagner & Munz Polytherm A hot stage microscope and were uncorrected. UV spectra were obtained with an Agilent 8453 spectrophotometer and IR spectra were recorded in KBr using a Bruker Tensor 37 spectrophotometer. HR-ESIMS was performed on a Bruker micrOTOF-QII (80 eV). NMR spectra were measured using a Bruker AV 500 [500 MHz (^{1}H) and 125 MHz (^{13}C)] with TMS as an internal standard. Multiplicities were determined using the DEPT pulse sequence.

Column chromatography (CC) was run on silica gel (Merck, 40–63 μm) or RP_{18} (Merck, 40–63 μm) bonded phases. For gel permeation chromatography (GPC), Sephadex LH-20 (GE Healthcare) with $CHCl_3$–MeOH 1:1 as eluent was used. TLC was carried out on precoated glass TLC plates normal phase (Merck, 250 μm) and RP_{18} (Merck, 200 μm). TLC plates were visualized using UV light, staining with I_2 or spraying with methanolic $FeCl_3$ (for detection of phenolic compounds). Petroleum ether refers to the fraction of bp. 50–90 °C.

Cytotoxic activity was set up in Costar 96 wells. Sulforhodamine B (SRB), EMEM medium, FBS, and camptothecin were bought from Sigma.

3.2. Plant material

The fruit of *Garcinia cochinchinensis* Pierre was collected in Dong Nai Province and identified by Nguyen Thien Tich, Department of Botany, Ho Chi Minh City University of Science (HCMUS). Herbarium samples are deposited in Natural Product and Medicinal Chemistry Lab, Faculty of Chemistry, HCMUS.

3.3. Extraction and isolation

The fresh fruit (1.7 kg) was peeled off to obtain its pericarp which was initially homogenised in MeOH and let stand at room temperature for a week followed by filtration. The cake layer was soaked in MeOH overnight, filtered and the process was repeated three times. The filtrates were combined and concentrated to yield a MeOH crude extract which was exhaustedly extracted with $CHCl_3$ using a separating funnel. Removing of the solvent afforded a $CHCl_3$ extract (42 g).

The $CHCl_3$ extract was fractionated over a column of silica gel with EtOAc–hexane gradient to give seven fractions (GC1–7). Fraction GC1 (2.1 g) was separated using CC (silica gel, acetone–hexane followed by isopropanol–hexane) to afford trimethyl citrate (18 mg). Fraction GC2 (3.8 g) was subjected to repeated CC on silica gel and finally purified using GPC to yield guttiferone I (**4**) (4.0 mg) and guttiferone Q (**1**) (10.9 mg). Fraction GC4 (4.1 g) was fractionated using CC (silica gel, EtOAc–hexane and isopropanol–hexane, respectively) followed by GPC and finally CC on RP_{18} (MeOH–H_2O) to give guttiferone R (**2**) (6.2 mg) and guttiferone S (**3**) (6.0 mg). Fraction GC5 (4.3 g) was separated using CC (silica gel, EtOAc–hexane and EtOAc–$CHCl_3$, respectively) followed by reversed-phase CC (C_{18}, CH_3CN–H_2O) to furnish dulxanthone A and 1,3,5-trihydroxy-6-methoxy-7-(3-methylbut-2-enyl)xanthone. Fraction GC6 (5.5 g) was purified using CC (silica gel, isopropanol–hexane and $CHCl_3$–MeOH, respectively) followed by CC on RP_{18} (MeOH–H_2O) to produce 1,3,5-trihydroxy-13,13-dimethyl-2H-pyran[7,6-b]xanthen-9-one (6.7 mg) and 1,3-dihydroxy-5,6-dimethoxy-7-(3-methylbut-2-enyl)xanthone (5.4 mg).

3.3.1. Guttiferone Q (1)

Bright yellow needles, mp. 104–106 °C (acetone–hexane), $[\alpha]_D^{25}$ −50.0 (*c* 0.21, MeOH); UV (MeOH) λ_{max} 203 and 261 nm; IR (KBr) ν_{max} 3411, 2971, 2925, 1728, 1671, 1641, 1586, 1384, 847 cm^{-1}; ^{1}H and ^{13}C NMR: see Table 1; HR-ESIMS *m*/*z* 503.3156 $[M+H]^+$ (calcd for $C_{33}H_{43}O_4$, 503.3163).

3.3.2. Guttiferone R (2)

Bright yellow needles, mp. 86–88 °C (acetone–hexane), $[\alpha]_D^{25}$ −57.5 (*c* 0.33, MeOH); UV (MeOH) λ_{max} 203 and 253 nm; IR (KBr) ν_{max} 3433, 2975, 2929, 1736, 1673, 1618, 1373, 757 cm^{-1}; ^{1}H and ^{13}C NMR: see Table 1; HR-ESIMS *m*/*z* 519.3105 $[M+H]^+$ (calcd for $C_{33}H_{43}O_5$, 519.3112).

3.3.3. Guttiferone S (3)

Pale yellow gum, $[\alpha]_D^{25}$ −10.0 (*c* 0.28, MeOH); UV (MeOH) λ_{max} 203 and 253 nm; IR (KBr) ν_{max} 3437, 2971, 2930, 1732, 1677, 1641, 1594, 1411, 755 cm^{-1}; ^{1}H and ^{13}C NMR: see Table 1; HR-ESIMS *m*/*z* 519.3105 $[M+H]^+$ (calcd for $C_{33}H_{43}O_5$, 519.3112).

3.4. Cytotoxicity assay

The cells for cytotoxicity assays, MCF-7, HeLa, and NCI-H460, were obtained from Division of Cancer Treatment and Diagnosis (NCI, Maryland, U.S.A.). The *in vitro* cytotoxicity assay was carried out according to the procedures described previously using SRB (Skehan et al., 1990) with 0.01% campothecin as the positive control. The absorbance at 492 and 620 nm (reference wavelength) was recorded using Synergy HT microplate reader (Bio-Tek).

Acknowledgements

We would like to thank Vietnam's National Foundation for Science and Technology Development (NAFOSTED) for a grant in the field of basic research.

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