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Cytotoxic prenylated flavonoids from *Macaranga indica*

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ABSTRACT

Three new prenylated flavonoids, macarindicins A–C (**1–3**), as well as seven known compounds (**4–10**) were isolated from the twigs of *Macaranga indica*. Their structures were elucidated on the basis of extensive spectroscopic interpretation. Compounds **2** and **3** enriched the diversity of prenyl moiety in genus *Macaranga* especially in the aspect of various lengths of prenyl chain. All the known compounds were isolated from *M. indica* for the first time and this plant was found to contain large number of ellagic acid. Compounds **1–10** were tested for their cytotoxicity against four cancer cell lines (MCF-7, Hep G2, Hela and P388) and showed IC_{50} values in the range of 2.61–20.35 μg/mL.

1. Introduction

Prenylated flavonoids have a relatively narrow distribution in the plant kingdom which are attracting more and more attention from the scientific community due to their structural uniqueness and remarkable biological activities [1]. The genus *Macaranga* (Euphorbiaceae) comprises approximately 300 species which are mainly distributed in tropical regions of Africa, Asia and Oceania [2]. This genus is known for a wide range of mutualistic associations with ants, ranging from facultative to strictly obligate relationships [3]. The fresh or dried leaves of certain *Macaranga* species were used in folk medicine for the treatment of cuts, swellings, sores, bruises and boils [2]. Plants in this genus have been reported to produce a number of phenolic compounds, especially prenylated flavonoids and stilbenes [2].

Macaranga indica is an arbor which grows to about 25 m in height. Previous phytochemical investigations on *M. indica* led to the isolation and identification of flavonoids, isoflavones and their prenylated derivatives [4,5]. As part of our continuous efforts towards discovering new bioactive prenylated aromatic products from the genus *Macaranga* [6,7], a phytochemical investigation on *M. indica* was conducted. As a result, three new prenylated flavonoids (**1–3**), together with six known prenylated flavonoids (**4–9**) and ellagic acid (**10**), were isolated from the twigs of this plant (Fig. 1). All the compounds were reported in *M. indica* for the first time and large quantities of ellagic acid were found in this plant. Described herein are the isolation and structure elucidation of those compounds, as well as their cytotoxicity against a small panel of cancer cell lines.

Although numbers of prenylated flavonoids have been reported in genus *Macaranga*, only two farnesylated ones were isolated from this genus [8,9] and thus the discovery of compounds **2** and **3** enriches the diversity of prenyl moiety in genus *Macaranga*, especially in the aspect of various lengths of prenyl chain. Plants in genus *Macaranga* are tall arbors with huge leaves which distribute in tropical rainforest and they can get enough sunshine during their lifetime, so it is reasonable that phenolic products are their main secondary metabolites

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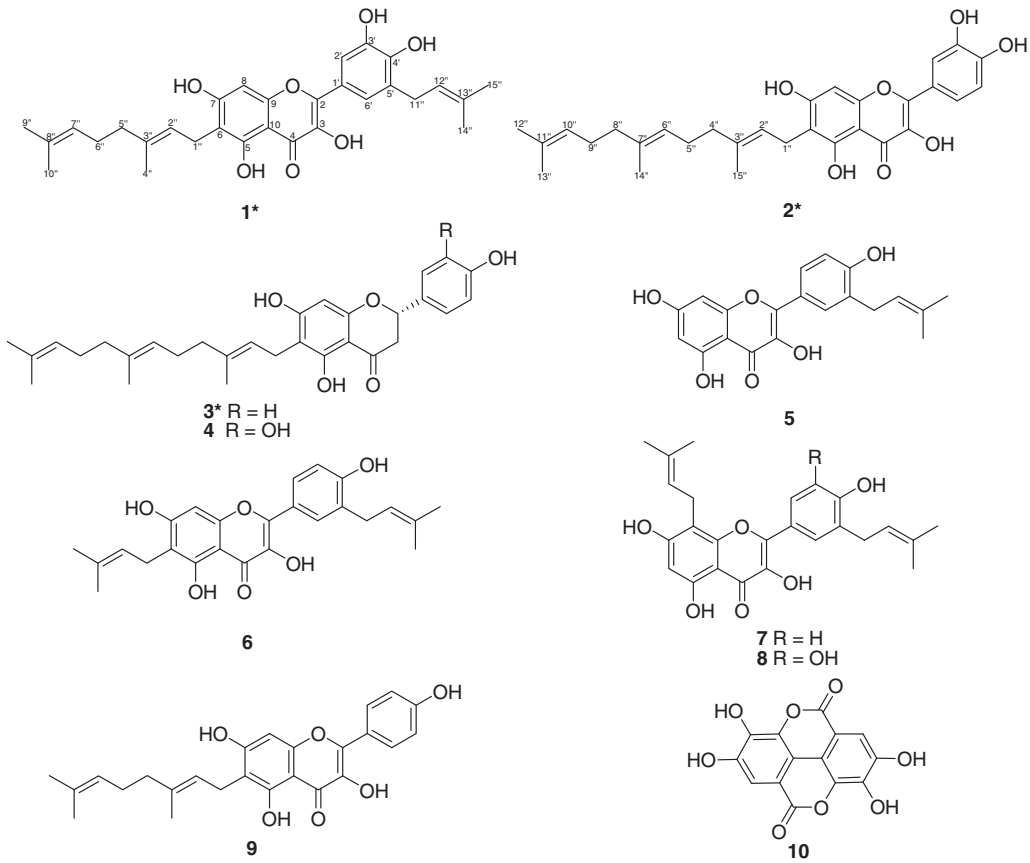

Fig. 1. Structures of compounds **1–10**.

both in structure diversity and quantities [10]. Ellagic acid possess a wide range of biological activities, such as antioxidant functions, estrogenic activities, anti-inflammatory and prebiotic effects, which suggest that it could have beneficial effects on human health [11] and the high content of ellagic acid in *M. indica* indicate that it might be a new source for industrial extraction.

2. Experimental

2.1. General

ORD spectra were recorded on a Horiba SEPA-300 polarimeter. CD spectra were obtained on an Automated Circular Dichroism spectrometer (Applied Photophysics). UV data were obtained on a Shimadzu UV-2401PC spectrophotometer. IR spectra were recorded on a Bio-Rad FTS-135 spectrometer with KBr pellets. 1D and 2D NMR experiments were recorded on Bruker Avance III 600 spectrometers with TMS as internal standard. Chemical shifts (δ) are expressed in ppm with reference to the solvent signals. ESI-MS were recorded using a Finnigan MAT 90 instrument. HR-EI-MS were performed on a Waters AutoSpec Premier P776. Column chromatography (CC) was performed on Sephadex LH-20 (Amersham Biosciences, Piscataway, USA), silica gel (200–300 mesh, Qingdao Marine Chemical inc., Qingdao, PR China), RP-18 gel (LiChroprep, 40–63 μm, Merck, Darmstadt, Germany), and MCI gel CHP20P (75–150 μm, Mitsubishi Chemical Corporation, Tokyo, Japan). Semipreparative HPLC was performed on a Hewlett-Packard instrument (column: Zorbax SB–C18, 250 × 9.4 mm, DAD detector). Fractions were monitored by TLC and visualized by heating plates sprayed with 15% H_2SO_4 in EtOH.

2.2. Plant material

The twigs of *M. indica* were collected from Jinping county of Yunnan province, PR China, in June 2013. A voucher specimen (Yangyp–20130612) was deposited in the Herbarium of Kunming Institute of Botany, Chinese Academy of Sciences, which was identified by one of the authors (Prof. Yong-Ping Yang).

2.3. Extraction and isolation

The air-dried and powdered twigs of *M. indica* (17.0 kg) were extracted with 90% aqueous EtOH (3 × 40 L) for 24 h at room temperature. The solvent was concentrated under vacuum to give a crude extract (903.0 g), which was partitioned between H_2O and EtOAc. The EtOAc portion was further decolorized on MCI gel CC (EtOH/H_2O, 95:5). The residue (720.0 g) was dissolved with MeOH and the soluble part was subjected to RP-18 CC (MeOH/H_2O, 40:60 to 100:0) to afford four fractions (Fr.1–4). The MeOH insoluble solid was

further dissolved in the mix solvent of $CHCl_3$–MeOH (1:1) and chromatographed on silica gel ($CHCl_3$/MeOH, 10:1 to 2:1) to afford **10** (310 g). Fr.1 was subjected to silica gel CC ($CHCl_3$/acetone, 10:1 to 3:2) and then purified by Sephadex LH–20 CC ($CHCl_3$/MeOH, 1:1) to afford **5** (21.6 mg). Fr.2 was subjected to silica gel CC ($CHCl_3$/EtOAc, 10:1 to 1:1) to yield three major subfractions (Fr.2a–2c). Fr.2a was purified by semipreparative HPLC (MeOH/H_2O, 65:35) to afford **6** (7.3 mg), **7** (3.6 mg) and **8** (6.4 mg). Fr.2c was subjected to Sephadex LH–20 CC ($CHCl_3$/MeOH, 1:1) to obtain **9** (11.9 mg). Fr.3 was chromatographed on silica gel ($CHCl_3$/EtOAc, 10:1 to 2:1) to yield four major subfractions (Fr.3a–3d). Fr.3b was purified by Sephadex LH–20 CC ($CHCl_3$/MeOH, 1:1), followed by semipreparative HPLC (MeOH/H_2O, 73:27) to afford **3** (11.4 mg) and **4** (6.1 mg). Fr.3c was subjected to Sephadex LH–20 CC ($CHCl_3$/MeOH, 1:1), followed by preparative TLC with $CHCl_3$/EtOAc (4:1), to give **1** (5.2 mg) and **2** (4.7 mg).

2.4. Spectroscopic data

2.4.1. Macarindicin A (*1*)

Yellow oil; $[\alpha]^{21}_{D}$ −13.6 (*c* 0.12, MeOH); UV (MeOH) λ_{max} (log ε) 204 (5.03), 274 (4.69), 350 (4.11), 436 (4.70) nm; IR (KBr) ν_{max} 3418, 2968, 2917, 1648, 1624, 1601, 1562, 1484, 1439, 1370, 1318, 1196, 1153, 1090, 1046, 973 cm^{-1}; ^1H NMR (acetone-d_6, 600 MHz) and ^{13}C NMR (acetone-d_6, 150 MHz) data, see Table 1; negative ESIMS *m/z* 505 $[M–H]^-$, 1011 $[2M–H]^-$; HR-EI-MS *m/z* 506.2308 $[M]^+$ (calcd for $C_{30}H_{34}O_7$, 506.2305).

2.4.2. Macarindicin B (*2*)

Yellow oil; $[\alpha]^{22}_{D}$ −2.96 (*c* 0.21, MeOH); UV (MeOH) λ_{max} (log ε) 204 (4.65), 273 (4.36), 432 (4.33) nm; IR (KBr) ν_{max} 3450, 2923, 1650, 1615, 1601, 1551, 1514, 1483, 1360, 1319, 1257, 1213, 1196, 1161, 1091, 1029, 960, 805, 598 cm^{-1}; ^1H NMR (acetone-d_6, 600 MHz) and ^{13}C NMR (acetone-d_6, 150 MHz) data, see Table 1; negative ESI-MS *m/z* 505 $[M–H]^-$, 1011 $[2M–H]^-$; HR-EI-MS *m/z* 506.2318 $[M]^+$ (calcd for $C_{30}H_{34}O_7$, 506.2305).

2.4.3. Macarindicin C (*3*)

Yellow oil; $[\alpha]^{21}_{D}$ −4.49 (*c* 0.42, MeOH); UV (MeOH) λ_{max} (log ε) 202 (4.80), 295 (4.38) nm; IR (KBr) ν_{max} 3419, 2966, 2917, 1634, 1596, 1517, 1490, 1450, 1338, 1297, 1224, 1155, 1084, 830 cm^{-1}; ^1H NMR (acetone-d_6, 600 MHz) and ^{13}C NMR (acetone-d_6, 150 MHz) data, see Table 1; negative ESI-MS *m/z*

Table 1
^1H and ^{13}C NMR data of compounds **1–3** in acetone-d_6[a] (δ in ppm, *J* in Hz).

No.	**1**		**2**		**3**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2		145.0 s		146.5 s	5.36, dd (13.0, 2.8)	79.8 d
3		136.6 s		136.6 s	2.67, dd (17.0, 2.8) 3.11, dd (17.0, 13.0)	43.5 t
4		176.4 s		176.4 s		197.2 s
5		158.9 s		158.9 s		162.2 s
6		111.6 s		111.7 s		109.0 s
7		162.6 s		162.6 s		164.7 s
8	6.55, s	93.7 d	6.57, s	93.7 d	6.00, s	95.2 d
9		155.5 s		155.5 s		161.9 s
10		103.9 s		103.9 s		103.0 s
1′		122.8 s		123.8 s		130.8 s
2′	7.70, d (1.6)	113.2 d	7.80, d (2.1)	115.6 d	7.35, d (8.5)	128.9 d
3′		146.8 s		145.7 s	6.87, d (8.5)	116.0 d
4′		146.2 s		148.1 s		158.5 s
5′		129.0 s	6.98, d (8.5)	116.1 d	6.87, d (8.5)	116.0 d
6′	7.60, d (1.6)	121.7 d	7.67, dd (8.5, 2.1)	121.3 d	7.35, d (8.5)	128.9 d
1″	3.36, d (7.3)	21.8 t	3.36, d (6.9)	21.9 t	3.25, d (7.2)	21.5 t
2″	5.28, t (7.3)	123.0 d	5.28, t (6.9)	123.2 d	5.24, t (6.8)	123.4 d
3″		135.3 s		135.3 s		135.3 s
4″	1.78, s	16.2 q	1.96, t (7.4)	40.4 t	1.94, t (7.5)	40.4 t
5″	1.95, t (8.2)	40.5 t	2.06, overlapped	27.0 t	2.05, q (7.5)	27.1 t
6″	2.02, overlapped	27.3 t	5.05, t (7.0)	124.8 d	5.08, t (7.5)	124.9 d
7″	5.06, t (7.1)	125.0 d		135.0 s		134.8 s
8″		131.6 s	1.85, t (6.9)	40.3 t	1.90, t (7.1)	40.4 t
9″	1.59, s	25.8 q	1.92, q (6.9)	27.3 t	1.99, q (7.1)	27.3 t
10″	1.54, s	17.6 q	4.99, t (6.9)	125.0 d	5.06, t (7.1)	125.1 d
11″	3.40, d (7.4)	29.0 t		131.5 s		131.5 s
12″	5.37, t (7.4)	123.4 d	1.56, s	25.8 q	1.62, s	25.8 q
13″		132.8 s	1.50, s	17.6 q	1.55, s	17.7 q
14″	1.75, s	17.9 q	1.53, s	16.2 q	1.75, s	16.0 q
15″	1.73, s	25.9 q	1.79, s	16.1 q	1.55, s	16.2 q
3-OH			8.56, brs			
5-OH	12.43, s		12.40, s		12.45, s	
7-OH			9.75, brs		9.61, brs	
3′-OH			7.97, brs			
4′-OH			8.35, brs		8.58, brs	

[a] ^1H and ^{13}C NMR data measured at 600 and 150 MHz, respectively.

475 [M–H]$^-$, 951 [2M–H]$^-$; HR-EI-MS *m/z* 476.2574 [M]$^+$ (calcd for $C_{30}H_{36}O_5$, 476.2563).

2.5. Cytotoxicity assay

Compounds **1–10** were tested for their cytotoxicity against human breast adenocarcinoma (MCF-7), human hepatocellular (Hep G2), human cervical carcinoma (Hela), mouse leukemia (P388) by the MTT method, 5-fluorouracil was used as a positive control. Briefly, 100 μL of cell suspension (1×10^5 cells/mL) was seeded into 96-well microtiter plates and cultured for 24 h before the compound was added. Then, different concentrations of the compounds were added to the plates, the cells were cultivated for 48 h, and 10 μL of MTT (5 mg/mL) was added to each well. After 4 h, the culture medium was removed and the formazan crystals were completely dissolved with 150 μL DMSO in each well by vigorously shaking the plate. Finally, formazan absorbance was assessed by a BioRad microplate reader at 570 nm.

3. Results and discussion

Macarindicin A (**1**), a yellow oil, was assigned a molecular formula of $C_{30}H_{34}O_7$ by HR-EI-MS (*m/z* 506.2308 [M]$^+$), requiring 14° of unsaturation. The IR spectrum showed absorption bands for hydroxyl (3418 cm^{-1}), carbonyl group (1648 cm^{-1}), double bonds (1624 cm^{-1}) and benzene rings (1601 and 1484 cm^{-1}). The UV absorption maxima at λ_{max} 204, 274 and 350 nm suggested the presence of a flavonol skeleton [12]. Analysis of the ^{1}H and ^{13}C NMR (Table 1) data of **1** aided by HSQC revealed resonances for one prenyl group [δ_C 29.0 (t), 123.4 (d), 132.8 (s), 17.9 (q), 25.9 (q); δ_H 3.40 (2H, d, $J = 7.4$ Hz), 5.37 (1H, t, $J = 7.4$ Hz), 1.75 (3H, s), 1.73 (3H, s)] [12], one geranyl group [two pair of trisubstituted double bonds: δ_H 5.06 (1H, t, $J = 7.1$ Hz), 5.28 (1H, t, $J = 7.3$ Hz), δ_C 125.0 (d), 131.6 (s), 123.0 (d), 135.3 (s); three methylenes: δ_C 21.8, 40.5, 27.3; three methyls: δ_H 1.78, 1.59, 1.54, 3H each, s] [13], one diprenylated quercetin [δ_C 136.6 (s), 176.4 (s), 93.7 (d), 146.8 (s), 146.2 (s); δ_H 6.55 (1H, s), 7.60 (1H, d, $J = 1.6$ Hz), 7.70 (1H, d, $J = 1.6$ Hz)] [12]. The HMBC correlations of H-1″/C-5, C-6, C-7; H-2″/C-6, H-11″/C-4′, C-5′, C-6′ (Fig. 2) indicated the attachment of the prenyl group to C-5′ and the geranyl group to C-6. Therefore, the structure of **1** was determined as 5′-prenyl-6-geranylquercetin (Fig. 1).

Macarindicin B (**2**) possessed a molecular formula of $C_{30}H_{34}O_7$ as deduced from its HR-EI-MS (*m/z* 506.2318 [M]$^+$). It was regarded as a mono-prenylated flavonol by comparison of the UV, IR and NMR spectroscopic data of **2** with **1**. The NMR data (Table 1) exhibited four phenolic hydroxy groups [δ_H 9.75, 8.56, 8.35 and 7.97 (1H each, brs)], one hydrogen-bonded hydroxy group [δ_H 12.40 (1H, s, 5-OH)] [14], one 6-prenylated quercetin [δ_C 136.6 (s), 176.4 (s), 93.7 (d), 145.7 (s), 148.1 (s); δ_H 6.57 (1H, s), 7.80 (1H, d, $J = 2.1$ Hz), 7.67 (1H, dd, $J = 8.5$, 2.1 Hz), 6.98 (1H, d, $J = 8.5$ Hz)] [15,16], and one farnesyl [three pair of trisubstituted double bonds: δ_H 4.99 (1H, t, $J = 6.9$ Hz), 5.05 (1H, t, $J = 7.0$ Hz), 5.28 (1H, t, $J = 6.9$ Hz), δ_C 125.0 (d), 131.5 (s), 124.8 (d), 135.0 (s), 123.2 (d), 135.3 (s); five methylenes: δ_C 21.9, 27.0, 27.3, 40.3, 40.4; four methyls: δ_H 1.50, 1.53, 1.56, 1.79, 3H each, s] [8]. The location of farnesyl group at C-6 was confirmed by HMBC correlations of H-1″/C-5, C-6, C-7 and H-2″/C-6 (Fig. 2). As a result, the structure of **2** was determined as 6-farnesylquercetin.

Macarindicin C (**3**) was obtained as optically active yellow oil ($[\alpha]^{21}_D$ −4.49, *c* 0.42, MeOH). The UV spectrum showed the characteristic absorbances for a dihydroflavonol [λ_{max} (log ε) 202 nm (4.80) and 295 nm (4.38)] [17]. Analysis of the NMR data of **3** (Table 1) suggested the presence of one 6-prenylated naringenin [δ_C 79.8 (d), 43.5 (t), 197.2 (s), 95.2 (d); δ_H 6.87 (2H, d, $J = 8.5$ Hz), 7.35 (2H, d, $J = 8.5$ Hz)] [17,18] and one farnesyl [19]. Comparison of the NMR data of **3** with those of **4** indicated that they were very similar except that an oxygenated quaternary carbon (C-3′, δ_C 144.1) in **4** was replaced by a non-oxygenated methine (δ_C 116.0) in **3** [19], which was further confirmed by the COSY correlation of H-2′/H-3′ and HMBC correlation of H-3′/C-4′ (Fig. 2). The observed HMBC-correlations of H-1″/C-5, C-6, C-7, and H-2″/C-6 demonstrated that the farnesyl group was located at C-6 (Fig. 2). The absolute configuration at C-2 was assigned as *S* from the positive (+1.64) and negative (−8.44) Cotton effects in the CD spectra at 331 nm (n → π^* transition) and 291 nm ($\pi \rightarrow \pi^*$ transition) [20]. Therefore, the structure of **3** was determined as (2*S*)-6-farnesylnaringenin.

The known compounds were identified as 6-farnesyl-3′,4′,5,7-tetrahydroxyflavanone (**4**) [19], isolicoflavonol

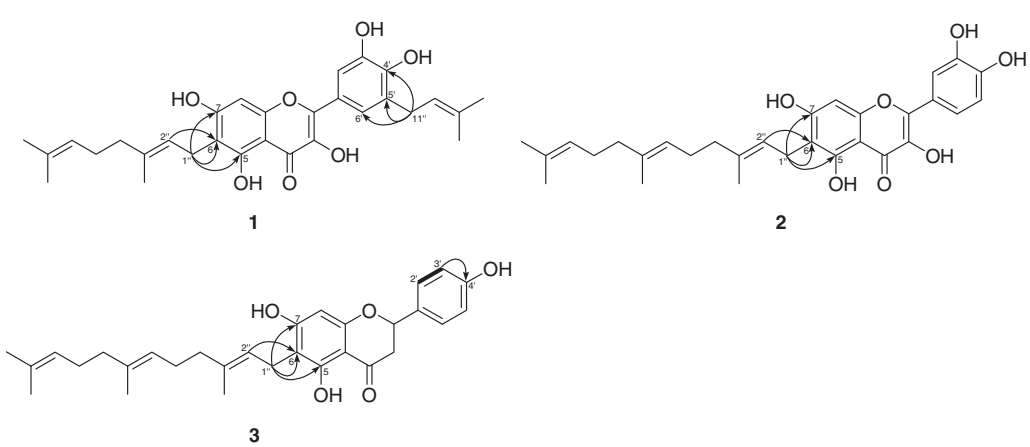

Fig. 2. Key HMBC (⌒) and COSY (—) correlations of compounds **1–3**.

Table 2
Cytotoxicities of compounds **1–10**.

compounds	IC_{50} (μg/mL)			
	MCF-7	Hep G2	Hela	P388
5-fluorouracil	15.14	13.27	13.85	16.97
1	15.23	>30	>30	11.82
2	>30	>30	>30	18.94
3	10.72	>30	>30	3.27
4	>30	13.52	>30	2.61
5	9.74	>30	>30	>30
6	>30	>30	>30	>30
7	>30	11.84	8.71	>30
8	7.88	>30	>30	>30
9	>30	20.35	16.06	>30
10	11.39	>30	3.70	>30

(**5**) [21], glyasperin A (**6**) [22], broussoflavonol F (**7**) [21], broussonol D (**8**) [12], macarangin (**9**) [23] and ellagic acid (**10**) [24] by comparison of their experimental and reported spectroscopic data. All the compounds were isolated from *M. indica* for the first time and this plant was found to contain large quantities of ellagic acid.

Since prenylated flavonoids are reported to have modest or strong anticancer activities [1,6], the cytotoxicity of compounds **1–10** were evaluated against human breast adenocarcinoma (MCF-7), human hepatocellular (Hep G2), human cervical carcinoma (Hela), mouse leukemia (P388) cell lines by MTT method, with 5-fluorouracil as a positive control [25]. The results are shown in Table 2. Compounds **1**, **3**, **5**, **8** and **10** inhibit the proliferation of MCF-7 cell line with IC_{50} values of 15.23, 10.72, 9.74, 7.88 and 11.39 μg/mL, respectively. Compounds **4**, **7** and **9** exhibit cytotoxicity against Hep G2 cell line with IC_{50} values of 13.52, 11.84 and 20.35 μg/mL, respectively. Compounds **7** and **9** exhibit cytotoxicity against Hela cell line with IC_{50} values of 8.71 and 16.06 μg/mL, respectively. Compounds **1–4** exhibit cytotoxicity against P388 cell line with IC_{50} values of 11.82, 18.94, 3.27 and 2.61 μg/mL, respectively. The other compounds were inactive in the tests.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.fitote.2015.04.002.

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