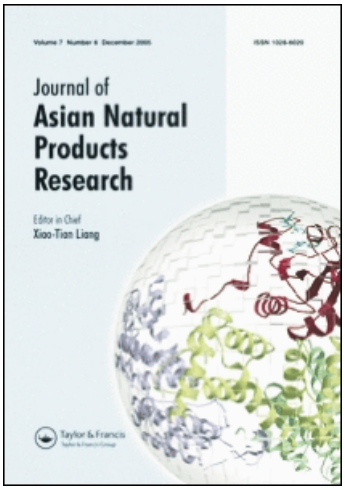

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A pair of isomeric saponins with cytotoxicity from *Albizzia julibrissin*

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Two new saponins have been isolated from the stem barks of *Albizzia julibrissin* Durazz, and their structures identified as 3-*O*-[β-D-xylopyranosyl-(1 → 2)-β-D-fucopyranosyl-(1 → 6)-β-D-2-deoxy-2-acetoamidoglucopyranosyl]-21-*O*-{(**6S**)-2-***trans***-2-hydroxymethyl-6-methyl-6-*O*-[**4**-*O*-((**6*S***)-2-***trans***-2-hydroxymethyl-6-hydroxy-6-methyl-2,7-octadienoyl)-β-D-quinovopyranosyl]-2,7-octadienoyl}-acacic acid-28-*O*-β-D-glucopyranosyl-(1 → 3)-[α-L-arabinofuranosyl-(1 → 4)]-α-L-rhamnopyranosyl-(1 → 2)-β-D-glucopyranosyl ester (**1**) and 3-*O*-[β-D-xylopyranosyl-(1 → 2)-β-D-fucopyranosyl-(1 → 6)-β-D-2-deoxy-2-acetoamidoglucopyranosyl]-21-*O*-{(6*S*)-2-*trans*-2-hydroxymethyl-6-methyl-6-*O*-[3-*O*-((6*S*)-2-*trans*-2-hydroxymethyl-6-hydroxy-6-methyl-2,7-octadienoyl)-β-D-quinovopyranosyl]-2,7-octadienoyl}acacic acid 28-*O*-β-D-glucopyranosyl-(1 → 3)-[α-L-arabinofuranosyl-(1 → 4)]-α-L-rhamnopyranosyl-(1 → 2)-β-D-glucopyranosyl ester (**2**), based on chemical and spectral evidences, named as julibroside J_{19} and julibroside J_{18}, respectively. Both compounds show significant inhibition action against HeLa, Bel-7402 and MDA-MB-435 cancer cell lines *in vitro*.

Keywords: *Albizzia julibrissin*; Triterpenoid saponin; Cytotoxicity; Julibroside J_{18}; Julibroside J_{19}

1. Introduction

Albizzia julibrissin Durazz (Leguminosae) is usually cultured as an ornamental plant in China. Its stem bark is recorded in the Chinese Pharmacopoeia as a sedative agent and anti-inflammatory drug used to treat injuries from falls and remove carbuncles [1]. In preceding papers [2–5], we reported the isolation and structure elucidation of complicated and cytotoxic julibrosides from the stem back of this plant. Recently, the modern pharmacological functions of the analogues to julibrosdies were elucidated. Haridas, *et al.* [6–8] have reported the extraction of avicins, a family of triterpenoid saponins obtained from the Australian desert tree *Acacia victoriae* (Leguminosae: Mimosoideae), which can inhibit tumor cell growth and induce cell apoptosis, in part, by perturbing mitochondrial function. These saponins also prevent chemical-induced carcinogenesis in mice, and are potent

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inhibitors of TNF-induced NF-kappa B. We report here the isolation and structure elucidation of a pair of isomeric saponins (**1** and **2**). Both **1** and **2** show significant cytotoxic activity against the HeLa, Bel-7402 and MDA-MB-435 cancer lines by the SRB method [9].

2. Results and discussion

Ethanol extracts (95%) of the stem barks of *Albizzia julibrissin* were partitioned btween H_2O and $CHCl_3$, EtOAc, n-BuOH, successively. The n-BuOH-soluble part was chromatographed over D_{101} macroporous resin and silica-gel columns to afford colorless powders (Fr 41–43). A pair of isomers, **1** and **2**, was obtained from the fractions by repeated Rp C_{18} column chromatography and preparative HPLC.

Saponin **1** was obtained as a white powder, and showed positive Molish and Liebermann–Buchard reactions, The ^{1}H NMR spectrum shows seven angular methyl signals at δ 1.18, 1.02, 0.96, 1.15, 1.87, 1.03, 1.08 (each 3H, s) and sugar proton signals at δ 3.3–6.24, which suggest a saponin skeleton for **1**. When **1** was hydrolyzed with refluxing HCl (2.0 mol L^{-1}), the resultant sapogenin was identical to an authentic sample of acacic acid lactone on HPTLC, which was confirmed by the proton and carbon signals of the acacic acid moiety (see table 1 and Experimental section), and glucose, arabinose, rhamnose, fucose, xylose and quinovose were also found to be present in the hydrolysate. The ^{1}H NMR spectrum of **1** exhibits eight signals for anomeric protons of the sugar moieties, at δ 4.89 (1H, d, $J = 7.7$ Hz, 2-deoxy-2-acetoamidoglc-H-1), 4.97 (1H, br s, H-fuc-1), 5.07 (1H, d, $J = 6.5$ Hz, H-xyl-1), 6.03 (1H, d, $J = 7.9$ Hz, H-glc′-1), 5.88 (1H, s, H-rha-1), 6.24 (1H, s, H-araf-1), 5.31 (1H, d, $J = 7.5$ Hz, H-glc″-1) and 4.79 (1H, d, $J = 7.8$ Hz, H-qui-1). Three proton doublets at δ 1.50 (3H, $J = 6.4$ Hz, H-fuc-6), 1.75 (3H, d, $J = 5.8$ Hz, H-rha-6) and 1.35 (3H, d, $J = 5.9$ Hz, H-qui-6) due to methyls of deoxy-sugar moieties: fucose, rhamnose and quivonose, along with a distinct singlet at δ 2.10 (3H, s, H-$NHCOCH_3$) due to amido-methyl, were also observed. The ^{13}C NMR spectrum of **1** shows eight carbon signals due to the anomeric carbons of sugar moieties at δ 95.7, 99.3, 101.8, 103.3, 104.7, 105.7, 106.8, 111.0, three methyl signals due to sugar moieties at δ 17.1, 17.8, 18.7, a methyl signal due to amido-methyl at δ 24.6, a carbonyl signal at δ 170.1 and a typical amide carbon signal at δ 58.0. Combined with the results of HCl-hydrolysis, **1** is deduced to contain two units of β-D-glucose, and one unit each of β-D-2-deoxy-2-amidoglucose, β-D-xylose, β-D-fucose, α-L-arabinose, α-L-rhamnose and β-D-quivonose. In the ^{13}C NMR spectrum of **1**, the signals of

Table 1. ^{13}C NMR spectral data of aglycone moieties in **1** and **2** (Py-d_5).

C	*1*	*2*	*C*	*1*	*2*	*C*	*1*	*2*
1	38.8	39.0	11	23.9	23.6	21	77.1	76.8
2	26.6	26.8	12	123.1	123.1	22	36.4	36.4
3	88.8	88.8	13	143.3	143.4	23	28.2	28.2
4	40.0	39.6	14	42.0	42.1	24	17.2	17.2
5	56.0	56.1	15	35.9	36.0	25	15.8	15.9
6	18.8	18.7	16	73.9	73.9	26	17.2	17.4
7	33.6	33.7	17	51.6	51.7	27	27.3	27.3
8	40.2	40.2	18	40.9	41.0	28	174.4	174.5
9	47.2	47.2	19	47.9	47.9	29	29.2	29.2
10	37.1	37.2	20	35.4	35.5	30	19.1	19.2

Table 2. ^{13}C NMR spectral data of monosaccharide moieties in **1** and **2** (Py-d_5).

C	***1***	***2***	*C*	***1***	***2***	*C*	***1***	***2***
2-amido-glc			xyl					
1	104.7	104.6	1	106.2	106.8	1	101.0	101.1
2	58.0	58.1	2	75.7	75.3	2	84.4	84.4
3	76.1	75.7	3	78.2	78.2	3	78.6	78.4
4	72.2	72.2	4	70.8	70.9	4	85.4	85.5
5	77.4	77.7	5	67.3	67.3	5	62.6	62.6
6	69.5	69.6	glc′			glc″		
C=O	170.1	170.1	1	95.7	95.7	1	105.8	105.8
Me	23.6	23.9	2	76.8	76.9	2	75.3	75.6
			3	77.9	78.2	3	78.4	78.4
Fuc			4	71.1	71.2	4	71.9	71.9
1	103.3	103.4	5	79.0	79.4	5	78.4	78.2
2	82.1	82.1	6	62.0	62.1	6	62.8	62.9
3	75.4	75.4	rha			qui		
4	72.5	72.3	1	101.8	101.8	1	99.3	99.2
5	71.3	71.9	2	70.6	70.6	2	75.5	72.6
6	17.1	17.2	3	82.1	82.0	3	75.6	80.0
			4	79.0	79.0	4	77.1	74.9
			5	69.2	69.2	5	70.1	70.5
			6	18.8	18.8	6	18.7	18.7

the aglycone and sugar moieties (table 2) are almost superimposable on those of julibroside III [10], except that **1** exhibits one group of signals due to inner quivonose, instead of the signals of two groups due to the two quivonoses of julibroside III, indicating that **1**, unlike julibroside III, does not have an outer quivonose.

As well as the resonances belonging to aglycone and sugar moieties, two groups of proton and carbon signals are observed in the ^1H (table 3) and ^{13}C (table 4) NMR spectra of **1**, *i.e.* proton signals at δ 7.01 (1H, t, $J = 7.5$ Hz, H-MT-3), 6.18 (1H, dd, $J = 11.4$, 17.1 Hz, H-MT-7), 5.20 (1H, d, $J = 11.4$ Hz, H-MT-8a), 5.40 (1H, d, $J = 14.1$ Hz, H-MT-8b), 4.70 (2H, s, H-MT-9), 1.48 (3H, s, H-MT-10) and 7.24 (1H, d, $J = 7.8$ Hz, H-MT′-3), 6.07 (1H, $J = 10.8$, 17.2 Hz, H-MT′-7), 5.11 (1H, d, $J = 10.8$ Hz, H-MT′-8a), 5.50 (1H, d, $J = 17.2$ Hz, H-MT′-8b), 4.70 (2H, s, H-MT′-9), 1.35 (3H, s, H-MT′-10). These resonances are very similar to those of julibrosides J_2 and J_7 [2], which indicate the presence of two units of (6*S*)-2-hydroxymethyl-6-methyl-6-hydroxy-2-*trans*-2,7-octadienoic acid moiety in saponin **1**. Thus, compound **1** is composed of acacic acid, eight monosaccharides and two monoterpenoids, which is supported by the MS data of **1**. The FABMS of **1** in positive ion mode exhibits a quasi-molecular ion peak at *m/z*: 2105 $[M + Na + 1]^+$. Therefore, saponin **1** was identified as 3-*O*-[β-D-xylopyranosyl-(1 → 2)-β-D-fucopyranosyl-(1 → 6)-β-D-2-deoxy-2-acetoamido-glucopyranosyl]-21-*O*-{(6*S*)-2-*trans*-2-hydroxymethyl-6-methyl-6-*O*-[4-*O*-((6*S*)-2-*trans*-2-hydroxymethyl-6-hydroxy-6-methyl-2,

Table 3. ^1H NMR spectral data of MT and MT′ moieties in **1** and **2** (Py-d_5).

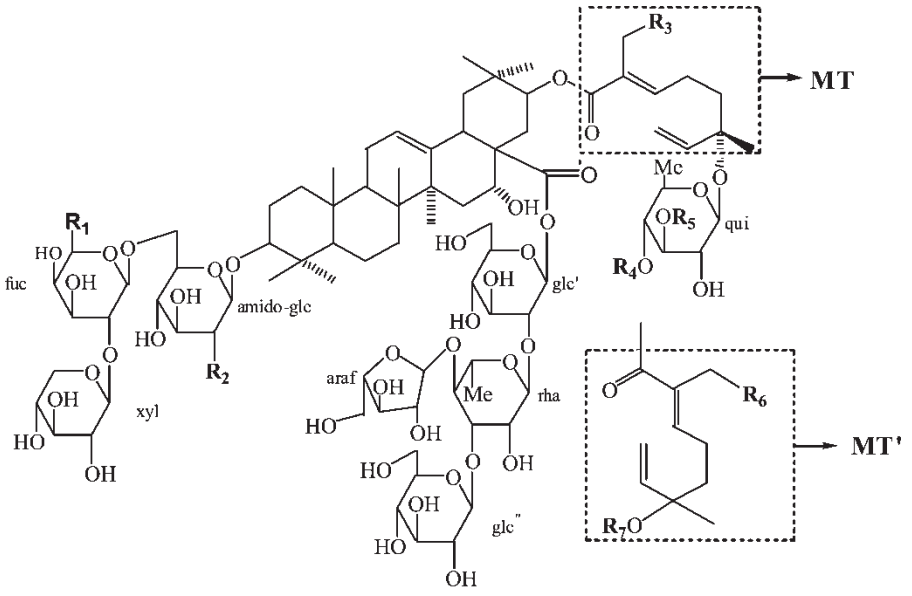
MT	***1***	***2***	*MT′*	***1***	***2***
3	7.01, t, 7.5	7.04, t, 7.0	3	7.24, t, 7.8	7.34, br s
7	6.18, dd, 11.4, 17.1	6.26, dd, 10.4, 16.9	7	6.07, dd, 10.8, 17.2	6.08, dd, 11.6, 17.0
8a	5.20, d, 11.4	5.15, d, 10.4	8a	5.11, d, 10.8	5.09, d, 10.4
8b	5.40, d, 17.1	5.36, d, 16.9	8b	5.50, d, 17.2	5.48, d, 17.0
9	4.70 s	4.71 s	9	4.70 s	4.71 s
10	1.48 s	1.49 s	10	1.35 s	1.38 s

Table 4. ^{13}C NMR spectral data of MT and MT′ in **1** and **2** (Py-d_5).

MT	*1*	*2*	*MT′*	*1*	*2*
1	167.5	167.6	1	167.6	168.1
2	133.8	133.5	2	133.4	133.8
3	146.5	145.3	3	145.2	145.9
4	23.7	23.8	4	23.7	23.8
5	40.8	41.0	5	41.9	41.9
6	79.7	79.9	6	72.5	72.3
7	143.9	143.7	7	146.3	146.6
8	115.0	115.1	8	111.7	111.7
9	56.4	56.4	9	56.4	56.6
10	23.5	23.9	10	28.5	28.5

7-octadienoyl)-β-D-quinovopyranosyl]2,7-octadienoyl}acacic acid–28-*O*-β-D-glucopyranosyl-(1 → 3)-[α-L-arabinofuranosyl-(1 → 4)]-α-L-rhamnopyranosyl-(1 → 2)-β-D-glucopyranosyl ester, being a new compound, named julibroside J_{19} (figure 1).

Saponin **2** contains structure units consistent with saponin **1** – acacic acid, two units of monoterpenoyl acid moieties and eight sugar moieties. The FABMS of **2** in positive mode exhibits a quasi-molecular ion peak at *m/z* 2105 $[M + Na + 1]^+$. In the ^{13}C NMR spectrum of **2** the signals agree well with those of **1**, except for the C-2 and C-4 signals due to



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
1	Me	NHAc	OH	MT'	H	OH	H
2	Me	NHAc	OH	H	MT'	OH	H
Julibroside J_7	OH	OH	OH	H	MT'	OH	H
Julibroside J_2	OH	OH	OH	MT'	H	OH	H
Julibroside III	Me	NHAc	H	MT'	H	H	qui'

Figure 1. Structures of julibrosides J_2, J_7, J_{19} (**1**), J_{18} (**2**) and julibroside III.

a β-D-quinovopyranosyl moiety of **2** show an upfield shift of δ 2.9 and 2.2 from δ 75.5 and 77.1 in **1** to 72.6 and 74.9 in **2**, respectively; the chemical shift of C-3 shows a downfield shift of δ 4.4, from δ 75.6 in 1 to 80.0 in **2**. These can be considered as glycosidation shifts, which suggest different esterified locations of the outer monoterpenic acid moieties at β-D-quinovopyranosyl moieties in **1** and **2**. A typical triplet proton signal at δ 5.79 (1H, t, $J = 9.1$ Hz) in the ^{1}H NMR spectrum of **2** indicates the attachment of an outer monoterpenic acid moiety to C-3 of a β-D-quinovopyranosyl moiety in **2**, instead of to C-4 in **1** [2]. Accordingly, **2** was identified as 3-*O*-[β-D-xylopyranosyl-(1 → 2)-β-D-fucopyranosyl-(1 → 6)-β-D-2-deoxy-2-acetoamido-glucopyranosyl]-21-*O*-{(6*S*)-2-*trans*-2-hydroxymethyl-6-methyl-6-*O*-[3-*O*-((6*S*)-2-*trans*-2-hydroxymethyl-6-hydroxy-6-methyl-2,7-octadienoyl)-β-D-quinovopyranosyl]-2,7-octadienoyl}acacic acid-28-*O*-β-D-glucopyranosyl-(1 → 3)-[α-L-arabinofuranosyl-(1 → 4)]-α-L-rhamnopyranosyl-(1 → 2)-β-D-glucopyranosyl ester, being a new compound, named as julibroside J_{18} (figure 1).

3. Experimental

3.1 General experimental procedures

IR spectra were measured on a Perkin-Elmer 983 FT-IR instrument as pressed KBr disks. 1D and 2D NMR spectra were recorded using Bruker AM-500 and Varian-300 instruments. FABMS were recorded using a ZABspec mass spectrometer. High-performance liquid chromatography was carried out using a Gilson automatic system for preparative HPLC with an Alltima C_{18} (5 μ, 60 Å, 22 × 250 mm id and 10 μ, 60 Å, 22 × 250 mm id) chromatography column, using a Waters 600 HPLC meter for semi-preparative HPLC with a μ Bondpak C_{18} (6 μ, 60 Å, 7.8 × 300 mm ID) chromatography column. Macroporous resin D_{101} (Nankai University,China) chromatography column, silica gel (10–40 μ Qingdao, China), Sephadex LH-20 (Pharmacia) and Rp C_{18} silica gel (100–200 mesh, Ouya) were used as normal or reversed-phase for chromatographic separations.

3.2 Plant material

Dried stem barks of *A. julibrissin* were purchased from the Mianyang Medicinal Company of Sichuan Province in October 1995 and were identified by Professor Shen-hua Li. A voucher specimen has been deposited in the Department of Natural Medicines, Peking University.

3.2.1 Extraction and isolation. Air-dried powdered stem barks were extracted with 95% ethanol at room temperature. The ethanol extracts were then suspended in H_2O, and then extracted successively with $CHCl_3$, EtOAc and n-BuOH. The n-BuOH-soluble part was dissolved in MeOH, and then poured into acetone dropwise. The resultant precipitates were further chromatographed over D_{101} resin column by elution with a gradient solvent system (100% H_2O → 100% MeOH), and the MeOH part was then subjected to silica-gel column chromatography, eluting with a gradient solvent system ($CHCl_3$–MeOH–H_2O, 100:0:0 → 6:4:1), to afford 68 fractions. Fractions 41–43 were decolorized by active charcoal in MeOH to give a white powder (10.5 g) that was successively subjected to repeated chromatography on Sephadex LH-20, an Rp C_{18} silica-gel column and preparative HPLC to

afford 1 (64.5% MeOH–H_2O, 8.0 ml min^{-1}, 216 nm, t_R: 37.6 min, 28.5 mg) and 2 (61.5% MeOH–H_2O, 6.0 ml min^{-1}, 216 nm, t_R: 55.0 min, 15.6 mg).

Saponin 1. Saponin **1**, obtained as a white powder, gave a positive FAB-MS of *m/z* 2105 $[M + Na + H]^+$, 1503 $[M + Na + H\text{-}(2glc + rha + ara)]^+$,1841$[M + Na + H\text{-}ara\text{-}xyl]^+$, 1739 $[M + H\text{-}MT'\text{-}glc]^+$,1593 $[M + H\text{-}MT'\text{-}glc\text{-}qui]^+$; IR (KBr) ν_{max} (cm^1): 3402, 2932, 1689, 1638, 1562,1372, 1282, 1228, 1073, 644; ^1H NMR (500 MHz, py-d_5) δ (ppm): 1.18, 1.02, 0.96, 1.15, 1.87, 1.03, 1.08 (each 3H, each s, H-23, 24, 25, 26, 27, 29, 30), 5.61 (1H, br s, H-12), 4.89 (1H, d, $J = 7.7$ Hz, 2-NHAc-glc-H-1), 4.97 (1H, br s, H-fuc-1), 5.07 (1H, d, $J = 6.5$ Hz, H-xyl-1), 6.03 (1H, d, $J = 7.9$ Hz, H-glc′-1), 5.88 (1H, s, H-rha-1), 6.24 (1H, s, H-araf-1), 5.31 (1H, d, $J = 7.5$ Hz, H-glc″-1) and 4.79 (1H, d, $J = 7.8$ Hz, H-qui-1), 1.75 (3H, d, $J = 5.8$ Hz, H-rha-6), 1.50 (3H, $J = 6.4$ Hz, H-fuc-6), 1.35 (3H, d, $J = 5.9$ Hz, H-qui-6), 2.10 (3H, s, H-NHCOMe); for ^1H and ^{13}C NMR data of MT and MT′ see tables 3 and 4.

Saponin 2. Saponin **2** was obtained as a white powder, positive FAB-MS *m/z* 2105 $[M + Na + 1]^+$, 1579 $[M + Na + 2\text{-}(MT' + qui + MT) - 16]^+$, 1432 $[M + Na + 2\text{-}(MT' + qui + MT)\text{-}glc]^+$; IR (KBr) ν_{max} (cm^1): 3386, 2924, 1689, 1639, 1563, 1412, 1382, 1285, 1072; ^1H NMR (500 MHz, py-d_5) δ (ppm): 1.18, 1.01, 0.97, 1.16, 1.87, 1.03, 1.09 (each 3H, each s, H-23, 24, 25, 26, 27, 29, 30), 5.62 (1H, br s, H-12), 4.93 (1H, d, $J = 7.8$ Hz, 2-NHAc-glc H-1), 4.98 (1H, $J = 6.9$ Hz, fuc H-1), 5.04 (1H, d, $J = 7.0$ Hz, xyl H-1), 6.03 (1H, d, $J = 7.3$ Hz, glc′ H-1), 5.8 (1H, s, rha H-1), 6.23 (1H, s, araf H-1), 5.30 (1H, d, $J = 7.5$ Hz, glc″ H-1), 4.78 (1H, d, $J = 7.0$ Hz, qui H-1), 1.75 (3H, d, $J = 5.8$ Hz, rha-Me), 1.47 (3H, d, $J = 6.2$ Hz, rha-Me),1.57 (3H, d, $J = 6.2$ Hz, qu-Me), 2.09 (3H, s, H-NHAc-Me), 5.79 (1H, t, $J = 9.0$ Hz, fuc H-3). ^1H and ^{13}C NMR data of MT and MT′ are given in tables 3 and 4.

Compounds **1** and **2** were hydrolyzed and the hydrolysates detected according to the literature method [2]. When **1** and **2** were hydrolyzed with refluxing 2.0M HCl their sapogenins was found to be identical to an authentic sample of acacic acid lactone on HPTLC [$CHCl_3$–MeOH (95:5)], and glucose, arabinose, rhamnose, fucose, xylose and quinovose were also found in the hydrolysate also, compared with authentic samples on PC [n-BOH–HOAc–H_2O (4:1:2)] (the literature value was used in the case of D-quinovose).

Table 5. Inhibition rate (%) of **1** and **2** to the cancer cell lines.

		Inhibition rate (%)		
Compound	*Concentration ($\mu g\ ml^{-1}$)*	*HeLa*	*Bel-7402*	*MDA-MB-435*
	1	− 28.55	0.80	18.66
1	10	59.80	69.40	43.80
	100	89.71	80.23	77.56
	1	3.85	− 14.37	16.91
2	10	18.74	1.72	17.10
	100	78.26	64.93	80.00

3.3 Cytotoxicity bioassays against cancer cells

MTT and SRB methods were used to assay cytotoxicity to HL-60 (MTT method), PC-3MIE8, MDA-MB-435, BGC-823, Bel-7402 and HeLa cancer cell lines *in vitro* at 1, 10 and 100 $\mu g\,ml^{-1}$, respectively. Both **1** and **2** show significant cytotoxicities against the cancer cell lines at 100 $\mu g\,ml^{-1}$ assayed by SRB method (table 5).

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