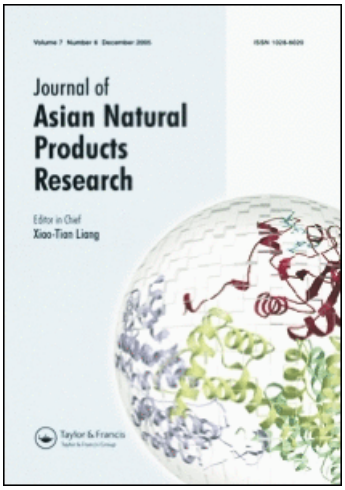

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Cytotoxic triterpene saponins from *Alternanthera philoxeroides*

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Four new pentacyclic triterpene saponins, philoxeroidesides A–D (**1**–**4**) were isolated from the aerial parts of *Alternanthera philoxeroides*. Their structures were elucidated on the basis of 1D- and 2D-NMR experiments and MS analyses. Philoxeroidesides A–D (**1**–**4**) showed cytotoxic activities against SK-N-SH and HL60 cell lines.

Keywords: *Alternanthera philoxeroides*; triterpene saponin; philoxeroidesides A–D; cytotoxic activity

1. Introduction

The genus *Alternanthera* (Amaranthacae) comprises approximately 200 species found in American tropical and subtropical zones, six of which have been used as herb drugs in clinic and four distributed in China [1]. As a folk medicine, *Alternanthera philoxeroides* (Mart.) Griseb. is used for the treatment of acute brain fever, measles, and herpes zoster [2]. It possesses various pharmacological activities, including antivirus, antibacterial, and molluscicidal activities [1]. Previous phytochemical studies on this plant resulted in the isolation of five oleanane saponins [3], two flavone *C*-glycosides, and four phenolic amides [4]. This paper deals with the isolation and structural elucidation of four new oleanane-type triterpene saponins, named philoxeroidesides A–D (**1**–**4**), as well as their cytotoxic activities. Their structures were established by spectroscopic methods, especially a series of 2D-NMR experiments (^{1}H, ^{1}H-COSY, NOESY, HSQC, and HMBC) and HRMS.

2. Results and discussion

Philoxeroideside A (**1**), exhibiting a quasi-molecular ion peaks at *m*/*z* 685.3909 $[M+Na]^+$ by positive HR-TOF-MS, indicating a molecular formula of $C_{37}H_{58}O_{10}$ for **1**. The IR spectrum of **1** indicated the existence of a hydroxyl and a γ-lactone moiety (3502 and 1756 cm^{-1}). The ^{1}H NMR spectrum showed seven methyls at δ 0.84, 0.92, 0.92, 1.00, 1.04, 1.12, and 1.15 (each 3H, s), a sugar moiety at δ 4.38 (1H, d, $J = 7.7$ Hz, H-1′), 3.25 (1H, dd, $J = 7.7, 9.2$ Hz, H-2′), 3.37 (1H, br t, $J = 9.2$ Hz, H-3′), 3.51 (1H, br t, $J = 9.7$ Hz, H-4′), and 3.82 (1H, br d, $J = 9.7$ Hz, H-5′) and a methoxyl group at δ 3.77. Its ^{13}C NMR spectrum showed 37 carbons, except for a methoxyl group at δ 52.9 and the sugar moiety at δ 107.2 (C-1′), 75.4 (C-2′), 77.6 (C-3′), 73.3 (C-4′), 76.8

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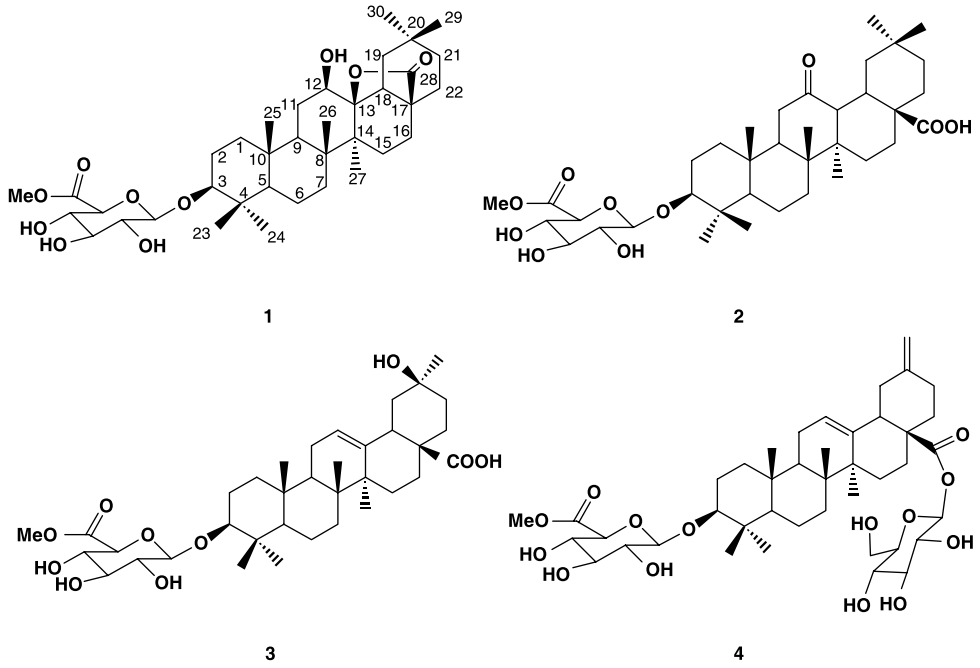

Figure 1. Structures of compounds **1**–**4**.

(C-5′), and 171.5 (C-6′) assigned as a glucuronic acid [5], the skeleton of **1** including one carbonyl, seven methyls, eight quaternary carbons, five methines, and 10 methylene carbon signals. From the above observations, compound **1** was deduced to be an oleanane-type triterpene saponin, and its ^{13}C NMR spectral data at δ 95.2 (C-13) and 182.7 (C-28) suggested a γ-lactone connecting to C-13 and C-17, that were consistent with those of 3β,12α-dihydroxyoleanan-28,13β-olide [6]. The HMBC correlation due to the methoxyl group (δ 3.77) with the carbonyl carbon [δ 171.5 (C-6′)] indicated the methylation of glucuronic acid at C-6′, and coupling constant of the anomeric proton at δ 4.38 (d, $J = 7.7$ Hz, H-1′) indicated that the presence of the β-glucuronic acid.

In the HMBC spectrum of **1**, H-12 at δ 3.80 correlated with C-11 at δ 29.4 and C-13 at δ 95.2, H_3-27 with C-13 at δ 95.2, C-14 at δ 43.8, and C-15 at δ 28.4, and H-16 at δ 2.23 with C-28 at δ 182.7. In addition, H-3 at δ 3.15 (dd, $J = 4.6$, 11.5 Hz) correlated with C-1′ at δ 107.2, H_3-23 at δ 28.3, H_3-24 at δ 16.8, and C-4 at δ 40.4. Thus, the sugar moiety and hydroxyl group were located at positions C-3 and C-12, respectively. Moreover, compound **1** had nine unsaturated degrees from its HR-TOF-MS, except for a glucuronic acid, five members ring of oleanane–triterpene and one carbonyl carbon; the remaining unsaturated degree indicated the presence of a C-13 to C-17 γ-lactone.

The NOESY correlations of H-3 with H_3-23 and H-12 with H_3-27 confirmed that H-3 was α (ax) and 12-OH had β (eq) orientations. Therefore, philoxeroideside A (**1**) was determined as 3β,12β-dihydroxyoleanan-28,13β-olide-3-*O*-β-D-6′-*O*-methylester-β-D-glucuronopyranoside (Figure 1).

Philoxeroideside B (**2**), revealed an ion peak at *m*/*z* 685.3893 $[M+Na]^+$ by positive HR-TOF-MS, corresponding to a molecular formula of $C_{37}H_{58}O_{10}$ and suggested that **2** was an isomer of **1**. The ^{1}H NMR spectrum showed seven methyls at δ 0.86, 0.91, 0.91, 0.96, 0.97, 1.04, and 1.05 (each 3H, s), an oxygenated proton at δ 3.14 (1H, dd, $J = 4.6$, 11.3 Hz, H-3), and

a β-6′-*O*-methylester-glucuronic acid, similar to those of **1**. Further comparison of ^{13}C NMR (Table 1) spectral data of **2** with those of **1**, compound **2** was also a oleanane-triterpene 28-oic acid, the differences visualize mainly in the C and D rings of the aglycon in **1** and **2**.

Table 1. ^{13}C NMR spectral data of **1**–**4** (75 MHz in CD_3OD solution; δ in ppm).

	Compound			
Position	**1**	**2**	**3**	**4**
1	40.1	39.2	39.8	40.0
2	27.2	27.0	27.1	27.1
3	90.9	90.8	91.2	91.2
4	40.4	40.3	40.3	40.3
5	56.6	56.7	57.0	57.0
6	18.7	19.4	19.4	19.4
7	34.6	33.1	34.1	34.0
8	43.8	42.6	40.7	40.8
9	50.3	51.2	49.0	49.9
10	37.7	37.9	38.0	38.0
11	29.4	39.5	24.3	24.6
12	67.6	214.9	124.6	124.4
13	95.2	52.9	144.3	144.3
14	43.8	43.2	42.9	43.0
15	28.4	28.8	28.8	29.0
16	21.9	23.9	24.6	24.2
17	45.4	48.3	47.1	48.7
18	43.8	50.0	42.8	49.1
19	38.1	34.4	48.5	42.7
20	32.6	31.7	72.8	149.5
21	35.4	35.6	36.8	38.5
22	28.7	34.0	34.6	31.0
23	28.3	28.4	28.5	28.6
24	16.8	16.8	17.0	17.0
25	16.9	15.9	16.0	16.1
26	19.2	16.8	17.8	17.8
27	19.8	21.1	26.3	26.5
28	182.7	181.9	181.1	177.4
29	33.7	33.3	34.6	107.5
30	24.4	23.7		
GlcA ester				
C(1′)	107.2	107.1	107.1	107.1
C(2′)	75.4	75.4	75.4	75.4
C(3′)	77.6	77.6	77.7	77.6
C(4′)	73.3	73.3	73.3	73.3
C(5′)	76.8	76.7	76.7	76.7
>C=O(6′)	171.5	171.5	171.5	171.5
OMe(6′)	52.9	52.9	52.9	52.9
Glc				
C(1″)				95.8
C(2″)				74.0
C(3″)				78.3
C(4″)				71.2
C(5″)				78.7
C(6″)				62.5

In the HMBC spectrum, H-11 at δ 2.22 correlated with C-8 at δ 42.6, C-9 at δ 51.2 and C-12 at δ 214.9, H_3-25 at δ 0.91 correlated with C-3 at δ 90.8, C-4 at δ 40.3 and C-5 at δ 56.7, and H-3 at δ 3.14 correlated with C-1′ at δ 107.1. Thus, the ketone group was located at C-12, and the sugar moiety was assigned to C-3. Assignments of the chemical shifts were obtained by analysis of ^{1}H–^{1}H COSY, HSQC, and HMBC data. Thus, philoxeroideside B (**2**) was identified as 3-*O*-β-D-6′-*O*-methylester-glucuronopyranosyl-oleanan-12-one-28-oic acid (Figure 1).

Philoxeroideside C (**3**) had a molecular formula $C_{36}H_{56}O_{10}$, as determined by negative HR-TOF-MS (quasi-molecular ion peak at *m*/*z* 647.3751 $[M-H]^-$). The ^{1}H NMR spectrum revealed six tertiary methyls at δ 0.82, 0.85, 0.95, 1.05, 1.15, and 1.60 (each 3H, s), one olefinic proton at δ 5.31 (br s), an oxygenated proton at δ 3.16 (1H, dd, $J = 4.6, 11.5$ Hz), and also had a β-6′-*O*-methylester-glucuronic acid, the same as that of **1**. The ^{13}C NMR spectral data of **3** were similar to those of **2**, except for the presence of a double bond at δ 124.6 (C-12) and 144.3 (C-13), and a hydroxyl instead of CH_3-30 at δ 23.7 in **2** (Table 1).

In the HMBC spectrum, H-3 at δ 3.16 correlated with anomeric carbon of the sugar at δ 107.1; H_3-27 at δ 1.15 correlated with C-8 at δ 40.7, C-13 at δ 144.3 (C-13), C-14 at δ 42.9, and C-15 at δ 28.8; and H_3-29 at δ 1.60 correlated with C-19 at δ 34.4, C-20 at δ 72.8, and C-21 at δ 36.8. Thus, the hydroxyl group was located at C-20 and the double bond was located at C-12 and C-13. The relative configuration of the hydroxyl group was assigned as C-20 β-OH mainly by the chemical shift comparison on Me-29 (δ 34.6) with those of related compound [3β,20α-dihydroxy-29-norolean-12-en-28-oic acid 3-*O*-β-D-xylopyranosyl-(1 → 2)-β-D-glucopyranoside, Me-30 (δ 25.7)] [7]. Based on the above results, the structure of philoxeroideside C (**3**) was established as 3β,20β-dihydroxy-30-norolean-12-en-28-oic acid-3-*O*-β-D-6′-*O*-methyl ester-β-D-glucuronopyranoside (Figure 1).

High-resolution mass spectrometry (positive HR-TOF-MS) of philoxeroideside D (**4**) gave an ion peak $[M+Na]^+$ at *m/z* 815.4240, corresponding to a molecular formula of $C_{42}H_{64}O_{14}$. The ^1H NMR spectrum of **4** showed two anomeric proton signals at δ 4.38 (d, $J = 7.8$ Hz) and 5.37 (d, $J = 7.8$ Hz), an olefinic proton signal at δ 5.32 (1H, br s), a terminal double bond methylene [δ 4.61 (2H, br s)], five tertiary methyls at δ 0.80, 0.85, 0.95, 1.05, and 1.19 (each 3H, s). The ^{13}C NMR spectral data of **4** were very similar to those of 3-*O*-[β-D-glucuronopyranosyl]-30-norolean-12,20(29)-dien-28-*O*-[β-D-glucopyranosyl] ester [8], except for the sugar moiety at C-3. The difference consisted in the addition of the methoxy group (δ 52.9), which connected to D-glucuronoic acid at C-6′ according to the correlation between the signal at δ 3.77 (OMe) with C-6′ at δ 171.5 in the HMBC spectrum. A glucopyranoside portion linked at C-28 as revealed by the HMBC correlation between the anomeric proton at δ 5.37 ($J = 7.8$ Hz, Glc-1″) and C-28 at δ 177.4. Therefore, philoxeroideside D (**4**) was identified as 3-*O*-[β-D-glucuronopyranosyl-6′-*O*-methyl ester]-30-norolean-12,20(29)-dien-28-*O*-[β-D-glucopyranosyl] ester (Figure 1).

The antineoplastic activity of compounds **1**–**4** was determined by using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide colorimetric assay with two tumor cell lines: human neuroblastoma cell line (SK-N-SH) and human leukemia cell (HL60). Compounds **1**–**4** exhibited cytotoxic activity against these tumor cells *in vitro* as shown in Table 2.

Table 2. The IC_{50} (μg/ml) values for cytotoxic activity of compounds **1**–**4**.

	Compound			
Cell line	**1**	**2**	**3**	**4**
SK-N-SH	51.00	118.69	60.60	37.29
HL60	185.29	185.57	>200 (271.45)	45.93

3. Experimental

3.1 General experimental procedures

The IR spectra were detected by a Perkin-Elmer 577 spectrometer in cm^{-1}, and optical rotations were obtained on a Perkin-Elmer 241-MC digital polarimeter. The NMR analysis of samples was performed with a Bruker Avance 300 instrument (^1H NMR 300 MHz ^{13}C NMR 75 MHz), both with tetramethylsilane as an internal standard. HRFTIMS data were obtained on a IonSpec 4.7 Tesla FTMS in *m/z*. Column chromatography was performed on silica gel (Qingdao Haiyang Chemical Co. Ltd, Qingdao, China) and Toyopearl HW-40 (TOSOH). TLC were detected by silica gel GF_{254} plates visualization under UV light and by spraying with Ce_2SO_4, followed by heating. HPLC separations were performed on a JASCO Gulliver Series with PU-2089 (pump), RI-2031, and UV-2075 (detector). Preparative HPLC column was used as below: ODS (YMC-Pack ODS-A, SH-343-5) and GPC (Shodex, Asahipak GS-310, 20G, MeOH).

3.2 Plant material

The aerial parts of *A. philoxeroides* (Mart.) Griseb were collected in Wuhan, Hubei Province of China in November 2003 and identified by Prof. Ding-Rong Wan (School of Life Sciences, South-Central University for Nationalities). A voucher specimen (D20030802) has been deposited at School of Pharmaceutical Sciences, Tianjin Medical University, China.

3.3 Extraction and isolation

The dried aerial parts (9.0 kg) of *A. philoxeroides* were crushed and extracted three times with EtOH (95%, 60 l each) under reflux for 6 h. The EtOH extract was concentrated *in vacuo* to give a residue (960 g), which was suspended in H_2O, and then partitioned with petroleum ether, EtOAc and *n*-BuOH, successively. The *n*-BuOH extract (28 g) was chromatographed on silica gel (300–400 mesh) column eluting with

solvents of increasing polarity [700 g silica gel; $CHCl_3$–MeOH–H_2O (95:5:0, 93:7:0, 9:1:0, 85:15:0, 8:2:0.2, 7:3:0.3, and 6:4:0.5, 100% MeOH)] to yield 16 fractions (1–16). Fraction 9 (1.6 g) was chromatographed on Toyopearl HW-40 ($CHCl_3$–MeOH, 2:1) and then HPLC (ODS-A, MeOH–H_2O, 85:15) to give **1** (20.4 mg), **2** (16.6 mg), and **3** (17.4 mg). Fraction 12 (2 g) was chromatographed on Toyopearl HW-40 ($CHCl_3$–MeOH, 2:1) to yield five fractions (12.1–12.5). Fraction 12.2 (0.12 g) was chromatographed on HPLC (ODS-A, MeOH–H_2O, 8:2) and then HPLC (MeOH GPC) to give **4** (18.9 mg).

3.3.1 *Philoxeroideside A (**1**)*

White powder; $[\alpha]_D^{25}$ −20.05 ($c = 0.4$, MeOH). IR (KBr) ν_{max}: 3502, 2948, 1756, 1463, 1364, 1248, 1215, 1170, 1029, and 910 cm^{-1}. ^1H NMR (CD_3OD): 3.15 (1H, dd, $J = 4.6$, 11.5 Hz, H-3), 3.80 (1H, m, H-12), 2.72 (1H, br d, $J = 11.4$ Hz, H-18), 2.24 (1H, m, H-16a), 1.25 (1H, m, H-16b), 1.04 (3H, s, Me-23), 0.84 (3H, s, Me-24), 0.92 (3H, s, Me-25), 1.15 (3H, s, Me-26), 1.12 (3H, s, Me-27), 1.00 (3H, s, Me-29), and 0.92 (3H, s, Me-30); 6′-*O*-methylester-β-glucuronic acid: 4.38 (1H, d, $J = 7.7$ Hz, H-1′), 3.25 (1H, dd, $J = 7.7$, 9.2 Hz, H-2′), 3.37 (1H, br t, $J = 9.2$ Hz, H-3′), 3.51 (1H, br t, $J = 9.7$ Hz, H-4′), 3.82 (1H, br d, $J = 9.7$ Hz, H-5′), and 3.77 (3H, s, 6′-OMe). ^{13}C NMR spectral data, see Table 1. HR-TOF-MS (pos.) *m/z*: 685.3909 $[M+Na]^+$ (calcd for $C_{37}H_{58}O_{10}Na$, 685.3928).

3.3.2 *Philoxeroideside B (**2**)*

White powder; $[\alpha]_D^{25}$ −40.58 ($c = 0.8$, MeOH). IR (KBr) ν_{max}: 3433, 2945, 1742, 1695, 1541, 1467, 1386, 1207, 1169, 1083, 1033, 975, and 910 cm^{-1}. ^1H NMR (CD_3OD): 3.14 (1H, dd, $J = 4.6$, 11.3 Hz, H-3), 2.22 (1H, m), 2.72 (1H, br d, $J = 11.4$ Hz, H-18), 1.05 (3H, s, Me-23), 0.86 (3H, s, Me-24), 0.91 (3H, s, Me-25), 1.04 (3H, s, Me-26), 0.97 (3H, s, Me-27), 0.96 (3H, s, Me-29), and 0.91 (3H, s, Me-30); 6′-*O*-methylester-β-glucuronic acid: 4.38 (1H, d, $J = 7.7$ Hz, H-1′), 3.23 (1H, dd, $J = 7.7$, 9.2 Hz, H-2′), 3.36 (1H, br t, $J = 9.2$ Hz, H-3′), 3.51 (1H, br t, $J = 9.7$ Hz, H-4′), 3.82 (1H, br d, $J = 9.7$ Hz, H-5′), and 3.78 (3H, s, 6′-OMe). ^{13}C NMR spectral data, see Table 1. HR-TOF-MS (pos.) *m/z*: 685.3893 $[M+Na]^+$ (calcd for $C_{37}H_{58}O_{10}Na$, 685.3928).

3.3.3 *Philoxeroideside C (**3**)*

White powder; $[\alpha]_D^{25}$ +4.58 ($c = 0.4$, MeOH). IR (KBr) ν_{max}: 3429, 2944, 1740, 1628, 1446, 1386, 1168, and 1027 cm^{-1}. ^1H NMR (CD_3OD): 3.16 (dd, $J = 4.6$, 11.5 Hz, H-3), 5.31 (1H, br s, H-12), 2.72 (1H, br d, $J = 11.4$ Hz, H-18), 1.05 (3H, s, Me-23), 0.85 (3H, s, Me-24), 0.95 (3H, s, Me-25), 0.82 (3H, s, Me-26), 1.15 (3H, s, Me-27), and 1.60 (3H, s, Me-29); 6′-*O*-methylester-β-glucuronic acid: 4.38 (1H, d, $J = 7.7$ Hz, H-1′), 3.24 (1H, dd, $J = 7.7$, 9.2 Hz, H-2′), 3.36 (1H, br t, $J = 9.2$ Hz, H-3′), 3.51 (1H, br t, $J = 9.7$ Hz, H-4′), 3.82 (1H, br d, $J = 9.7$ Hz, H-5′), and 3.77 (3H, s, 6′-OMe). ^{13}C NMR spectral data, see Table 1. HR-TOF-MS *m/z*: 647.3751 $[M-H]^-$ (calcd for $C_{37}H_{55}O_{10}$, 647.3795).

3.3.4 *Philoxeroideside D (**4**)*

White powder; $[\alpha]_D^{25}$ +29.01 ($c = 0.62$, MeOH). IR (KBr) ν_{max}: 3434, 2929, 2360, 2339, 1736, 1650, 1558, 1540, 1458, 1392, 1287, 1168, 1074, 1021, and 950 cm^{-1}. ^1H NMR (CD_3OD): 3.14 (dd, $J = 4.6$, 11.3 Hz, H-3), 5.32 (1H, br s, H-12), 2.72 (1H, br d, $J = 11.4$ Hz, H-18), 1.05 (3H, s, Me-23), 0.85 (3H, s, Me-24), 0.95 (3H, s, Me-25), 0.80 (3H, s, Me-26), 1.19 (3H, s, Me-27), and 4.61 (2H, br s, CH_2-29); 6′-*O*-methylester-β-glucuronic acid: 4.38 (1H, d, $J = 7.8$ Hz, H-1′), 3.25 (1H, dd, $J = 7.7$, 9.2 Hz, H-2′), 3.38 (1H, br t, $J = 9.2$ Hz, H-3′), 3.51 (1H, br t, $J = 9.7$ Hz, H-4′), 3.83 (1H, br d, $J = 9.7$ Hz, H-5′), and 3.77 (3H, s, 6′-OMe); Glc: 5.37 ($J = 7.8$ Hz, H-1″), 3.69 (1H, m), and 3.30–3.45 (5H, m). ^{13}C NMR spectral data, see Table 1. HR-TOF-MS (pos.) *m/z*: 815.4240

$[M+Na]^+$ (calcd for $C_{42}H_{64}O_{14}Na$, 815.4194).

3.4 Acid hydrolysis of compounds **1–4**

Each compound (**1–4**, 1.0 mg) dissolved in EtOH–H_2O (7:3 v/v, 2 ml) was heated under reflux in 1 N aq. CF_3COOH (1 ml) for 6 h [9]. After removal of the solvent *in vacuo*, the residue was dissolved in MeOH–H_2O (7:3 v/v, 0.3 ml) and identified by TLC by comparison with authentic glucuronic acid and glucose, in $CHCl_3$–MeOH–1% acetic acid (12:8:2) sprayed with aminobenzene-1,2-benzenedicarboxylic acid (R_f: 0.44, glucuronic acid; R_f: 0.58, glucose).

3.5 Cytotoxicity assay

Procedure of bioassay was reported in the previous paper [10].

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