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Cytotoxic triterpenoid saponins from *Thalictrum atriplex*

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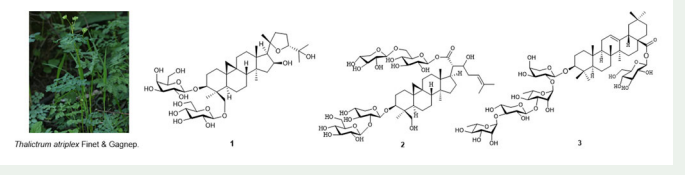
ABSTRACT

Two new cycloartane glycosides, cycloatriosides A and B (**1–2**), and a new oleanolic acid glycoside, thaliatrioside A (**3**), along with **7** known triterpenoids (**4–10**) were isolated from *Thalictrum atriplex*. The structures of the new compounds were established as 3-*O*-*β*-D-galactopyranosyl (20*S*, 24*R*)-3*β*,16*β*,25,29-tetrahydroxy-20,24-epoxy-cycloartane-29-O-*β*-D-glucopyranoside (**1**), 3-*O*-*β*-D-glucopyranosyl-(1→2)-*α*-arabinopyranosyl-3*β*,22*ξ*,30-trihydroxycycloart-24-en-21-oic acid *α*-L-arabinopyranosyl-(1→6)-*β*-D-glucopyranoside (**2**) and 3-*O*-[*α*-L-rhamnopyranosyl-(1→3)-*β*-D-xylopyranosyl-(1→3)-*α*-L-rhamnopyranosyl-(1→2)-*α*-L-arabinopyranosyl]-oleanolic acid 28-*O*-*β*-D-glucopyranosyl ester (**3**) on the basis of extensive NMR and HR-ESI-MS analyses, along with acid hydrolysis. Their cytotoxic activities against human lung cancer cells A549 and human breast cancer cells MDA-MB-231 were evaluated using MTT method. Compound **9** showed cytotoxicity against MDA-MB-231 cell line with the IC_{50} value of 72.53 ± 1.08 μM.



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1. Introduction

Thalictrum atriplex Finet & Gagnep. (*T. atriplex*), a traditional herbal medicine, belongs to the Thalictroideae subfamily (Ranunculaceae family) and mainly distributes in Tibet, Sichuan and Yunnan provinces. Its root was frequently used for the treatment of infective hepatitis, carbuncle and furuncle, etc. Modern medicinal chemistry investigations revealed that alkaloids, triterpenoids and flavonoids, the main constituents of the plants from *Thalictrum* genus possessed anti-tumor, anti-bacterial, anti-viral, immunomodulatory effects and so on (Ding et al. 2019; Li et al. 2017; Jin et al. 2020; Jin et al.

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2018; Khamidullina et al. 2006; Mushtaq et al. 2016; Gao et al. 2005; Gao et al. 2000). In our continuous study on the chemical constituents of plants from *Thalictrum* genus, three new triterpenoid saponins (Figure 1), cycloatriosides A and B (**1–2**), and thaliatrioside A (**3**), along with **7** known ones, cycloramoside A (**4**) (Meng et al. 2016), squarroside VI (**5**) (Yoshimitsu et al. 2010), squarroside VII (**6**) (Yoshimitsu et al. 2010), scabiostellatoside A (**7**) (Lehbili et al. 2018), 3-O-[β-D-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]-28-*O*-[β-D-glucopyrannosyl-(1→6)-β-D-glucopyrannoside]-oleanlic acid (**8**) (Liang et al. 2018), 3-O-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyl oleanolic acid 28-O-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl ester (**9**) (Santos et al. 2007), clematangoticoside G (**10**) (Zhao et al. 2016) were isolated from *T. atriplex*. Here we report the isolation and structural elucidation of these compounds as well as their cytotoxic effects on A549 and MDA-MB-231 cell lines.

2. Results and discussion

Compound **1** was obtained as a white amorphous powder. Its molecular formula was determined as $C_{42}H_{70}O_{15}$ according to the HR ESI MS data (*m/z* 815.4779 $[M+H]^+$, calcd. for $C_{42}H_{71}O_{15}$ 815.4793, *m/z* 859.4678 $[M+HCOO]^-$ calcd. for $C_{43}H_{71}O_{17}$ 859.4691). The IR absorption of compound **1** at 3356 cm^{-1} indicated the presence of hydroxyl groups. The signals at 2939, 1458 and 1382 cm^{-1} suggested the presence of methyl groups. The IR absorption at 1058 cm^{-1} was due to the bending vibration of C-O bond. Detailed comparison of the ^1H and ^{13}C NMR data, it was found that the data of the aglycone was in good agreement with those of Sieberoside I (Verotta et al. 1998) except for C-3, C-5, C-6, C-29 and C-30. The chemical shift of C-6 (δ_C 26.8) revealed the absence of the hydroxyl group. The chemical shift of C-29 (δ_C 71.6) revealed the presence of oxygenated methyl at C-29. Two anomeric proton signals of glycosyl units were observed at δ_H 5.34 (1H, d, $J = 7.8$ Hz) and 5.52 (1H, d, $J = 7.8$ Hz). The ^{13}C and DEPT135 NMR spectra displayed 42 carbon signals including the signals for β-glucopyranosyl and β-galactopyranosyl. All these data revealed that compound **1** could be a cycloartane-type triterpene glycosylated by a β-glucopyranosyl and a β-galactopyranosyl. This deduction was confirmed by analysis the ^1H-^1H COSY, HSQC and HMBC data. In the HMBC spectrum, the correlation between H-1′ of β-glucopyranosyl (δ_H 5.52) and C-29 suggested that the β-glucopyranosyl was linked at C-29. The correlation between H-1" of β-galactopyranosyl (δ_H 5.34) and C-3 suggested that the β-galactopyranosyl was linked at C-3.

In the ROESY spectrum of **1**, NOE correlations from H-5 (δ_H 1.98) to H-3 (δ_H 4.51) and H-28 (δ_H 0.85), from H-3 (δ_H 4.51) to H-30 (δ_H 0.92), from H-16 (δ_H 4.51) to H-28 (δ_H 0.85) and H-17 (δ_H 2.20) were observed. The correlations from H-21 (δ_H 1.36) to H-24 (δ_H 3.96), from H-16 (δ_H 4.80) to H-22a (δ_H 2.50), from H-17 to H-28 were also observed. Thus, the configurations of **1** were determined to be 3β, 16β, 17 *R*, 20*S*, 24 *R*. HPLC analysis of the acid hydrolysate of compound **1** proved the presences of D-glucopyranosyl and D-galactopyranosyl units. Finally, the structure of compound **1** was elucidated as 3-*O*-β-D-galactopyranosyl (20*S*, 24 *R*)-3β, 16β, 25, 29-tetrahydroxy-20,24-epoxycycloartane-29-O-β-D-glucopyranoside and named as cycloatrioside A.

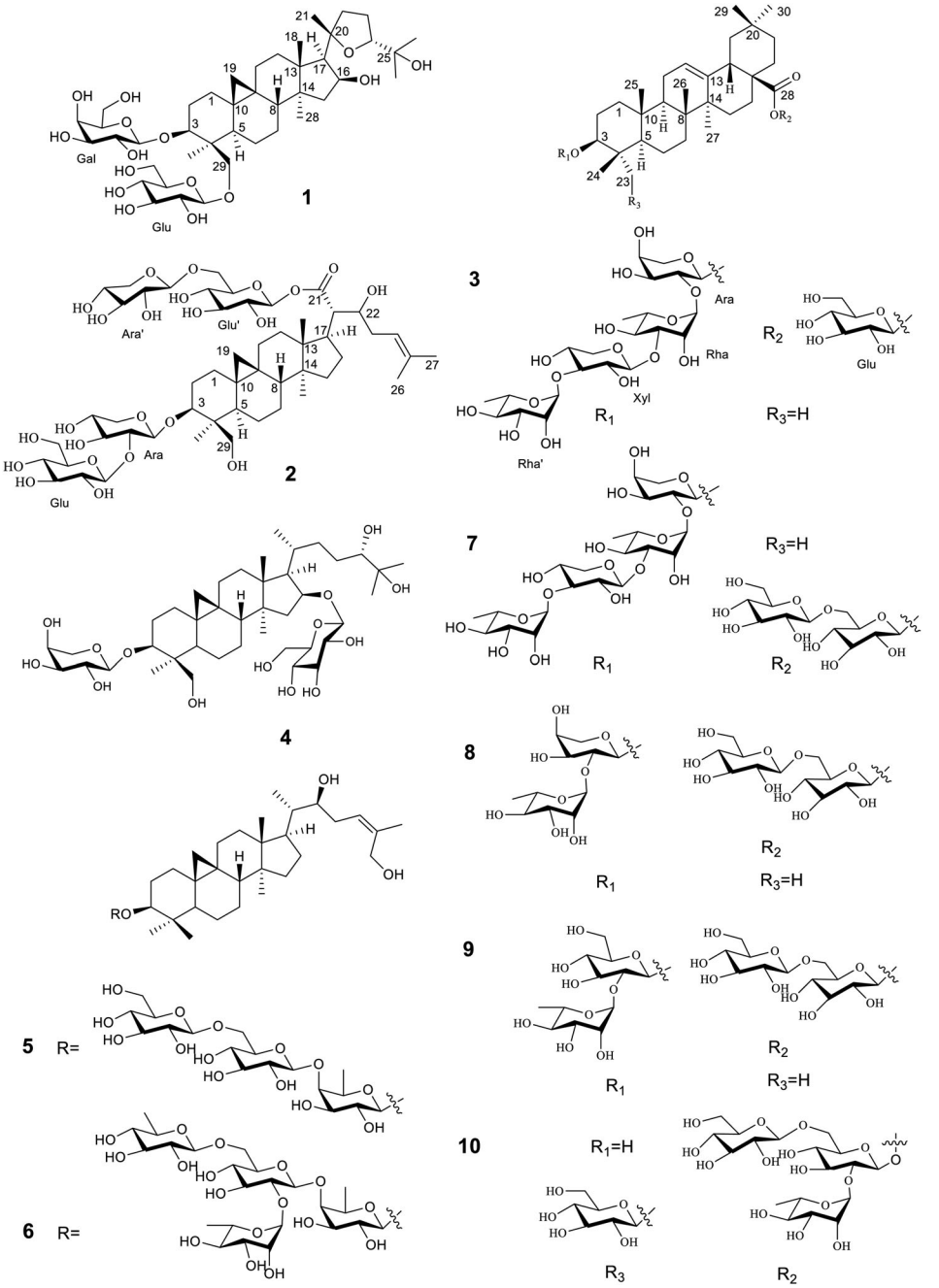

Figure 1. Compounds isolated form *Thalictrum atriplex*.

Compound **2** was obtained as a white amorphous powder. The molecular formula of **2** was determined to be $C_{52}H_{84}O_{23}$ from its HR ESIMS data (*m/z* 1121.5359 $[M+HCOO]^-$, calcd. for $C_{53}H_{85}O_{25}$ 1121.5380; *m/z* 1077.5493 $[M+H]^+$, calcd. for $C_{52}H_{85}O_{23}$ 1077.5482). The IR spectrum of compound **2** showed the absorptions of methyl and methylene groups at 2962, 2935, 1456 and 1375 cm^{-1}. The absorption of

the bending vibration of C-O bond was observed at 1078 cm^{-1}. The ^{1}H NMR spectrum of compound **2** showed the signals owing to a cyclopropane methylene at δ_H 0.43 (1H, d, $J = 3.8$ Hz) and 0.45 (1H, d, $J = 3.8$ Hz), five methyl groups at δ_H 0.87, 1.26, 1.58, 1.60 and 1.65 (each 3H), four anomeric protons at δ_H 4.84 (1H, d, $J = 6.5$ Hz), 4.96 (1H, d, $J = 6.6$ Hz), 5.72 (1H, d, $J = 7.9$ Hz) and 6.18 (1H, d, $J = 8.1$ Hz), and one olefinic proton at δ_H 5.57 (1H, t, $J = 6.6$ Hz), which indicated that compound **2** was a cycloartane tetraglycoside derivative. The ^{13}C NMR spectrum of **2** also showed the carbon signals of the cycloartane aglycone moiety, which was coincidence with those of thalictoside IX (Yoshimitsu et al. 1995). The ^{1}H and ^{13}C data of the aglycone moiety was authenticated by carefully analysis of the HSQC and HMBC data. Besides, a diglycosyl of β-glucopyranosyl-(1→2)-α-arabinopyranosyl attached to C-3 of the aglycone and a diglycosyl of α-arabinopyranosyl-(1→6)-β-glucopyranosyl linked at C-21 of the aglycone were also determined. Their absolute configurations were identified based on the $^{3}J_{H1/H2}$ coupling constants. The absolute configurations of compound **2** were determined as 3β, 17*R*, 20*S* based on the ROESY data. Acid hydrolysis of compound **2** yield L-arabinose and D-glucose. Thus, the structure of **2** were determined to be 3-*O*-β-D-glucopyranosyl-(1→2)-α-arabinopyranosyl-3β,22ξ,30-trihydroxycycloart-24-en-21-oic acid α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside, named as cycloatrioside B.

Compound **3** was also obtained as a white amorphous powder, whose molecular formula was determined as $C_{58}H_{94}O_{24}$ based on the quasi-molecular ion peaks at *m/z* 1219.6090 $[M + HCOO]^-$ (calcd. for $C_{59}H_{95}O_{26}$ 1219.6112) and 1197.6051 $[M + Na]^+$ (calcd. for $C_{58}H_{94}O_{24}Na$ 1197.6033) in the negative and positive HR ESIMS experiments. In the IR spectrum of compound **3**, the absorption of hydroxy group was observed at 3383 cm^{-1}. The signal at 2941 cm^{-1} was attributed to the C-H stretching vibration of methyl group. The absorptions of C-H bending vibration were observed at 1462 and 1388 cm^{-1}. Comparison of the ^{1}H and ^{13}C NMR data of **3** with those of the known compound scabiostellatoside A (Lehbili et al. 2018) showed a good agreement except for the absence of the signals of a glucopyranosyl. Detailed analysis of its HMBC data suggested a tetra-saccharide of rhamnopyranosyl-(1→3)-xylopyranosyl-(1→3)-rhamnopyranosyl-(1→2)-arabinopyranosyl linked at C-3 of the aglycone and a glucopyranosyl linked at C-28 of the aglycone. The absolute configurations of the sugar residues were determined as L-rhamnopyranosyl, D-xylopyranosyl, L-arabinopyranosyl and D-glucopyranosyl based on the HPLC analysis of the acid hydrolysate of compound **3**. Therefore, compound **3** was determined as 3-*O*-[α-L-rhamnopyranosyl-(1→3)-β-D-xylopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]-oleanolic acid 28-*O*-β-D-glucopyranosyl ester, named as thaliatrioside A.

Their cytotoxic activities against human lung cancer cells A549 and human breast cancer cells MDA-MB-231 were evaluated using MTT method. Compound **9** showed cytotoxicity against MDA-MB-231 cell line with the IC_{50} value of 72.53 ± 1.08 μM (10.90 ± 0.67 μM for taxol). The other compounds did not exhibit significant cytotoxic activities.

3. Experimental

3.1. General experimental procedures

HR ESIMS were measured on a Thermo LTQ Orbitrap XL mass spectrometer (Thermo Electron, Bremen, Germany). IR spectra were recorded on an Avatar 360 E.S.P

spectrophotometer (Termo Nicolet Co. Boston, MA, USA). 1 D (^{1}H and ^{13}C) and 2 D (^{1}H-^{1}H COSY, HSQC, HMBC, ROESY) NMR spectra were recorded on a Bruker AV-400 spectrometer (Fallanden, Switzerland) with C_5D_5N ($\delta_{H/C}$ 7.58/135.91) or CD_3OD ($\delta_{H/C}$ 3.31/49.0) as reference. HPLC analysis was performed on a SHIMADZU Chromatograph equipped with LC-20AD pumps, SPD-20A detector and a 250 mm × 4.6 mm i.d. Cosmosil 5C18-MS-II column (Nacalai Tesque Inc., Kyoto, Japan). D-Galactose, D-Glucose, D-xylose, L-Rhamnose, L-arabinose, *O*-tolyl isothiocyanate and L-cysteine methyl ester were purchased from Sigma (Sigma-Aldrich, Missouri, USA). Human cancer cell lines (A549, MDA-MB-231 and HepG2) were obtained from Cell bank of Chinese Academy of Sciences (Shanghai, China).

3.2. Plant material

The whole plants of *T. atriplex* were collected in Jiacha, Linzhi, Tibet, China in June 2018, and authenticated by Dr. Xiaozhong Lan (TAAHC-SWU Medicinal Plant R&D Center, Tibet Agricultural and Animal Husbandry University). A voucher specimen (2018-CM-0603) was deposited in College of Pharmaceutical Sciences, Southwest University.

3.3. Extract and isolation

Dried powdered plants of *T. atriplex* (3.5 Kg) were refluxing extracted with 20 L 95% ethanol for 3 times. The ethanol extract was suspended in water and then successively extracted with petroleum ether, EtOAc and *n*-BuOH. The *n*-BuOH soluble extract (118.3 g) was subjected to a silica gel column using CH_2Cl_2-MeOH (20:1 → 5:4) as the eluent, giving 5 fractions (Fr. 1-5). Fr. 4 (17.8 g) was further fractionated by silica gel column using EtOAc-MeOH (20:1 → 10:3) as the eluent to afford 5 subfractions (Fr. 4.1-4.5). Fr. 4.3 (7.0 g) was further purified by repeated silica gel column to afford compound **4** (2.2 g). Fr. 4.4 (3.2 g) was fractionated by silica gel column, ODS and sephadex LH-20, successively, and finally purified by preparative HPLC (Cosmosil 5C18-MS-II 250 mm × 10 mm i.d., MeOH-H_2O 80: 20) to give compounds **1** (23.4 mg), **3** (6.2 mg), **5** (3.8 mg), **6** (4.3 mg) **8** (11.2 mg). Fr. 5 (10.6 g) was fractionated by sephadex LH-20 using CH_2Cl_2-MeOH (1:1) as the eluent to afford 4 subfractions (Fr. 5.1-5.4). Fr. 5.1 subjected to an ODS column using MeOH-H_2O (70:30) as eluent to give 5 subfractions. Fr. 5.1.1 (53 mg) was further purified by preparative HPLC (YMC ODS 250 mm × 10 mm i.d., CH_3CN-H_2O 33: 67) to give compounds **2** (6.7 mg), **9** (4.9 mg) and **10** (3.4 mg). Fr. 5.1.2 (5.3 g) was subjected to an ODS column using MeOH-H_2O (70:30) as eluent to yield compound **7** (2.7 g).

Cycloartioside A (**1**) Amorphous white powder, $C_{42}H_{70}O_{15}$, $[\alpha]_D^{20}$ = + 5.7 (c 0.20 MeOH), IR (KBr) ν_{max}: 3356, 2939, 1647, 1458, 1382, 1074, 1058 cm^{-1}; HR ESIMS: *m/z* 815.4779 $[M+H]^+$ (calcd. for $C_{42}H_{71}O_{15}$ 815.4793), *m/z* 859.4678 $[M+HCOO]^-$ (calcd. for $C_{43}H_{71}O_{17}$ 859.4691); ^{1}H NMR (C_5D_5N, 400 MHz) and ^{13}C (C_5D_5N, 100 MHz) data see Table **S1** and Table **S2**.

Cycloartioside B (**2**) Amorphous white powder, $C_{42}H_{70}O_{15}$, $[\alpha]_D^{20}$ = − 17.2 (c 0.20 MeOH), IR (KBr) ν_{max}: 3354, 2962, 2935, 1651, 1633, 1456, 1379, 1361, 1338, 1163, 1134, 1078, 1018 cm^{-1}; HR ESIMS: *m/z* 1121.5359 $[M+HCOO]^-$ (calcd. for $C_{53}H_{85}O_{25}$

1121.5380), *m/z* 1077.5493 $[M+H]^+$, (calcd. for $C_{52}H_{85}O_{23}$ 1077.5482); ^1H NMR (C_5D_5N, 400 MHz) and ^{13}C (C_5D_5N, 100 MHz) data see Table **S1** and Table **S2**.

Thalioatrioside A (**3**) Amorphous white powder, $C_{58}H_{94}O_{24}$, $[\alpha]_D^{20} = +23.6$ (c 0.10 MeOH), IR (KBr) ν_{max}: 3383, 2941, 1735, 1633, 1462, 1388, 1365, 1261, 1232, 1053 cm^{-1}; HR ESIMS: *m/z* 1219.6090 $[M+HCOO]^-$ (calcd. for $C_{59}H_{95}O_{26}$ 1219.6112), *m/z* 1197.6051 $[M+Na]^+$ (calcd. for $C_{58}H_{94}O_{24}Na$ 1197.6033); ^1H NMR (CD_3OD, 400 MHz) and ^{13}C (CD_3OD, 100 MHz) data see Table **S1** and Table **S2**.

3.4. Acid hydrolysis

Acid hydrolysis analysis of the monosaccharide compositions of compound **1 − 3** were carried out as described before (Meng et al. 2016). Briefly, compounds **1 − 3** (1 − 2 mg) were dissolved in 2 mL of 2 M HCl and heated at 80 °C water-bath for 2 h, respectively. Remove the solvent and the residue was re-dissolved in 0.5 mL of pyridine. Add 5 mg of L-cysteine methyl ester and the mixture was heated at 60 °C for 1 h. Then, *O*-tolyl isothiocyanate (5 mg) was added into the mixture and heated further for 30 min. Finally, the solution was passed through a 0.45 mm syringe filter for HPLC analysis (SHIMADZU, 250 mm × 4.6 mm i.d. Cosmosil 5C18-MS-II, acetonitrile: 0.5% aqueous acetic acid solution: 25: 75, flow rate 0.8 mL/min, detection wavelength 250 nm). The standard solutions of monosaccharides (each 5 mg) were treated as described above. The peaks of each monosaccharide derivative were observed at t_R (min): **1**: D-galactose 18.77, D-glucose 21.59; **2**: D-glucose 21.28, L-arabinose 23.82; **3**: D-glucose 21.18, L-arabinose 23.71, D-xylose 24.68, L-rhamnose 35.92 (standard monosaccharide derivatives: D-galactose 18.62, D-glucose 21.20, L-arabinose 23.83, D-xylose 24.88 and L-rhamnose 35.95).

3.5. Cytotoxic activity

The cytotoxic activities of all isolates were evaluated against human non-small cell lung cancer A549, human breast cancer MDA-MB-231 and human liver cancer HepG2 cell lines using MTT method with taxol as positive control (Ma et al. 2019). Briefly, A549, MDA-MB-231, HepG2 cell lines were seeded in 96-well microplates, 5000 cells per well, and cultured in DMEM medium for 24 h under 5% CO_2 atmosphere at 37 °C. After remove the medium, 100 μL fresh medium containing 3.125, 6.25, 12.5, 25, 50 μM taxol or each isolate was added and the plates were further incubated for 48 h. Then, 10 μL of 5 mg/ml MTT solution in phosphate buffered saline was added to each well, and the cell lines were incubated for another 4 h. The supernatants were removed and 100 μL of DMSO was added to each well to dissolve the formazan crystals. Finally, the optical density at 490 nm were measured using a microplate reader and IC_{50} values were calculated.

4. Conclusions

In this study, two new cycloartane glycosides, cycloatriosides A and B (**1–2**), and a new oleanolic acid glycoside, thaliatrioside A (**3**), along with **7** known triterpenoids (**4–10**) were isolated from *Thalictrum atriplex*. Their structures were established on the

basis of extensive NMR and HR-ESI-MS analysis along with acid hydrolysis. Compound **9** showed cytotoxicity against MDA-MB-231 cell line with the IC_{50} value of $72.53 \pm 1.08\,\mu M$ *in vitro* antitumor assay.

Disclosure statement

The author declares that there is no conflict of interest.

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