Anthracene and Anthraquinone Derivatives from the Stem Bark of *Juglans mandshurica* MAXIM.

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One new anthracene derivative, juglanthracenoside A (**1**), two new anthraquinones, juglanthraquinone A (**2**) and juglanthraquinone B (**3**), along with a new naturally occurring anthraquinone, 9,10-dihydro-4,8-dihydroxy-9,10-dioxoanthracene-2-carboxylic acid (**4**), have been isolated from the stem bark of *Juglans mandshurica*. Their structures were established by detailed spectroscopic analysis and comparison of the NMR data with those of related compounds. Compound **1** displayed noticeable antioxidant activity in both 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) free radical-scavenging assays, while compound **4** showed strong cytotoxicity against HepG2, SGC7901, HCT-8, and A549 cell lines *in vitro*.

Introduction. – *Juglans mandshurica* MAXIM. (Juglandaceae) is widely distributed in Korea and the northeast of China. Its roots, stem bark, and fruits have long been used as folk medicine for the treatment of cancer in China and Korea [1]. Previous photochemical research on *J. mandshurica* mainly involved naphthoquinones, naphthalenyl glucosides, tetralones, flavonoids, diarylheptanoid, and galloyl glycosides [1–18], and these compounds have shown cytotoxic activity, topoisomerases I and II inhibitory activity, inhibitory effect on DNA polymerase and on the ribonuclease H activity of HIV-1 reverse transcriptase, as well as inhibitory effect on pancreatic lipase [12–17]. During the course of our studies on bioactive constituents from the stem bark of this plant, one new anthracene derivative, juglanthracenoside A (**1**; *Fig. 1*), two new anthraquinones, juglanthraquinones A and B (**2** and **3**, resp.; *Fig. 2*), along with a new naturally occurring anthraquinone, 9,10-dihydro-4,8-dihydroxy-9,10-dioxoanthracene-2-carboxylic acid (**4**) were isolated. Described herein are the isolation, structure elucidation, and biological activities of these compounds.

Results and Discussion. – Compound **1** was obtained as a flavo-green amorphous powder, and its molecular formula, $C_{23}H_{20}O_{12}$, was deduced from the HR-TOF-MS

[1]) These two authors contributed equally to this work.

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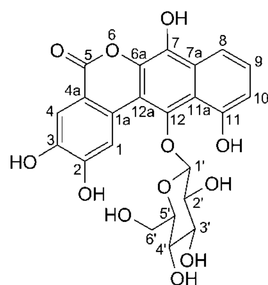

Fig. 1. *Structure of compound* **1**

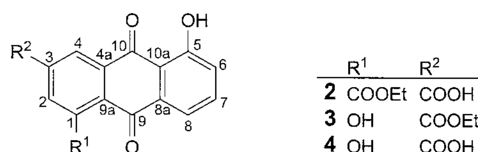

Fig. 2. *Structures of compounds* **2**, **3**, *and* **4**

(m/z 489.1023, $[M+\mathrm{H}]^+$), indicating the presence of 14 degrees of unsaturation. The presence of a hexose sugar was inferred from a fragment ion at m/z 325.0351 ($[M - C_6H_{11}O_5]^-$), consistent with the formula $C_{17}H_9O_7^-$ in HR-TOF-MS (negative-ion mode) spectrum (calc. 325.0354). The IR spectrum showed absorptions of OH (3432 cm^{-1}), conjugated CO (1669 cm^{-1}), and benzene ring (1611, 1577 cm^{-1}). Besides a set of glucopyranosyl C-atom signals at δ(C) 103.4 (C(1′)), 77.3 (C(3′)), 76.5 (C(5′)), 73.4 (C(2′)), 69.1 (C(4′)), and 60.1 (C(6′)), the ^{13}C-NMR spectrum (see *Table 1*) also exhibited 17 sp^2 C-atom signals, which were further ascribed by a DEPT experiment to five CH groups and twelve quaternary C-atoms including a conjugated ester CO C-atom at δ(C) 160.3 (C(5)). The ^{1}H-NMR spectrum exhibited signals of four H-atoms at

Table 1. *^{1}H-* (400 MHz in (D_6)DMSO) *and ^{13}C-NMR Data* (100 MHz in (D_6)DMSO) *of* **1**. δ in ppm, J in Hz.

Position	δ(H)	δ(C)	Position	δ(H)	δ(C)
1a		115.2	11		153.5
1	9.05 (*s*)	108.0	11a		114.06
2		146.7	12		149.8
3		140.5	12a		112.4
4	7.41 (*s*)	107.1	1′	5.04 (*d*, J = 7.6)	103.4
4a		114.13	2′		73.4
5		160.3	3′		77.3
6a		143.8	4′		69.1
7		140.0	5′		76.5
7a		125.4	6′		60.1
8	7.84 (*d*, J = 8.0)	112.1			
9	7.50 (*dd*, J = 8.0, 8.0)	128.2			
10	6.94 (*d*, J = 8.0)	111.9			

δ(H) 10.50 (br. *s*), 10.09 (br. *s*), 9.74 (br. *s*), and 9.44 (br. *s*), three aromatic H-atoms as an *ABC* system at δ(H) 7.84 (*d*, *J* = 8.0, H–C(8)), 7.50 (*dd*, *J* = 8.0, 8.0, H–C(9)), and 6.94 (*d*, *J* = 8.0, H–C(10)), as well as two aromatic *singlet*s at δ(H) 9.05 (*s*, H–C(1)) and 7.41(*s*, H–C(4)). Additionally, the anomeric H-atom of glucopyranosyl was observed at δ(H) 5.04 (*d*, *J* = 7.6, H–C(1′)), so the anomeric configuration of the glucopyranosyl was β judging from the *J* value. The aglycone of **1** could be divided into two substructures by analysis of HMBC spectrum and comparison of the NMR data with those of related compounds. Substructure A (C(1)–C(5), C(1a), and C(4a)) was assembled on the basis of HMBCs (from H–C(1) to C(3) and C(4a), from H–C(4) to C(5), C(2), C(1a), and C(3); see *Fig. 3*) and the comparison of the ^{13}C-NMR data with those of 3,4-dihydroxybenzoic acid. Substructure B (C(7)–C(12), C(6a), C(7a), C(11a), and C(12a)) was established on the basis of HMBCs (from H–C(8) to C(7), from H–C(9) to C(11), and from H–C(10) to C(11a)) and the comparison of the NMR data with those of naphthalene glucopyranosides [15]. The linkage between the glucopyranosyl and substructure B was determined to be through C(1′) and C(12) based on the HMBC from H–C(1′) to C(12). Substructures A and B could be linked through a C(1a)–C(12a) bond, judging from the long-range correlation from H–C(1) to C(12a) in the HMBC spectrum and the NOE correlation (H–C(1)/H–C(1′)) in the NOESY spectrum. Further analysis of the ^{13}C-NMR data and the molecular formula, the conjugated ester C=O C-atom (C(5)) should be attached to C(6a) (δ(C) 143.8) through an O-bridge, forming a six-membered lactone between substructures A and B, and the remaining positions C(2), C(3), C(7), and C(11) should all be substituted by OH groups. The ^{1}H- and ^{13}C-NMR data of **1** were assigned on the basis of DEPT, HMQC, and HMBC experiments (*Table 1*). Thus, the structure of **1** was determined as 12-*O*-β-D-glucopyranosyl-2,3,7,11-tetrahydroxy-6-oxabenzo[*a*]anthracen-5-one, named juglanthracenoside A[2]) (*Fig. 1*).

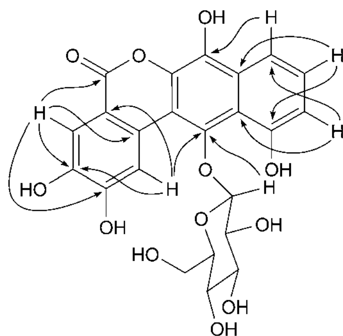

Fig. 3. *Key HMBCs of compound* **1**

Compound **2** was isolated as yellow needles, which gave a positive *Bornträger*'s test characteristic of anthraquinone derivatives. It reacted positively with bromocresol green and $FeCl_3$ reagent, suggesting the presence of COOH group and its phenolic

2) Systematic names are given in the *Exper. Part.*

nature. The molecular formula was established as $C_{18}H_{12}O_7$ from its *quasi*-molecular ion at m/z 341.0651 ($[M+H]^+$) in the HR-TOF-MS. The UV spectrum displayed specific absorptions with maxima at 233, 307, and 353 nm. The IR spectrum revealed absorption bands at 1649 and 1596 cm^{-1}, due to the free and chelated CO groups, respectively. Both UV and IR data indicated that compound **2** was a 9,10-anthraquinone derivative. The ^{1}H-NMR spectrum (see *Table 2*) of **2** showed the presence of two *meta*-coupled aromatic H-atoms with signals at δ(H) 8.41 (d, $J = 1.6$, H–C(2)) and 9.10 (d, $J = 1.6$, H–C(4)), and those of three aromatic H-atoms as an *ABC* system at δ(H) 7.38 (d, $J = 8.4$, H–C(6)), 7.73 (dd, $J = 7.6, 8.4$, H–C(7)), and 7.83 (d, $J = 7.6$, H–C(8)). In addition, a signal of a chelated OH group was observed at δ(H) 12.38, and EtO signals were observed at δ(H) 1.45 (t, $J = 7.2$) and 4.55 (q, $J = 7.2$). The ^{13}C-NMR spectrum of **2** exhibited 18 C-atom signals, shared between two quinone C=O group signals at δ(C) 186.7 (C(10)) and 181.0 (C(9)), two C=O groups at δ(C) 168.3 and 167.0, and 12 aromatic C-atoms except for an EtO group (δ(C) 14.0 and 62.2) mentioned above. The complete ^{1}H- and ^{13}C-NMR assignments and connectivities of **2** were determined from the HMQC and HMBC spectra (*Table 2*). In the HMBC spectrum (*Fig. 4*), the long-range correlation from δ(H) 4.55 (MeC*H*$_2$OOC–C(1)) to δ(C) 168.3 (MeCH$_2$OO*C*–C(1)) revealed the presence of an EtOCO group, thus another CO (δ(C) 167.0) should be a COOH group according to the positive bromocresol green reaction. The COOH group was at C(3) due to the HMBCs (from

Table 2. *^{1}H-* (400 MHz in (D$_6$)DMSO) *and ^{13}C-NMR Data* (100 MHz in (D$_6$)DMSO) *of* **2** *and* **3**. δ in ppm, J in Hz.

Position	**2**		**3**	
	δ(H)	δ(C)	δ(H)	δ(C)
1		128.8[a])		162.7
2	8.41 (d, $J = 1.6$)	134.0	7.96 (d, $J = 1.2$)	125.7
3		135.9[b])		138.0
4	9.10 (d, $J = 1.6$)	129.9	8.44 (d, $J = 1.2$)	119.7
4a		130.9[a])		133.0[c])
5		162.8		163.0
6	7.38 (d, $J = 8.4$)	125.0	7.37 (br. d, $J = 8.4$)	125.4
7	7.73 (dd, $J = 8.4, 7.6$)	137.4	7.72 (dd, $J = 8.4, 7.6$)	137.0
8	7.83 (d, $J = 7.6$)	120.2	7.88 (br. d, $J = 7.6$)	119.7
8a		133.2		133.5[c])
9		181.0		187.8
9a		134.0[b])		118.3
10		186.7		187.2
10a		115.7		116.1
*H*O–C(1)	–	–	12.57 (s)	–
*H*O–C(5)	12.38 (s)	–	12.56 (s)	–
COOH	12.12 (br. s)	167.0	–	–
MeCH$_2$O*C*O	–	168.3	–	164.4
Me*CH*$_2$	4.55 (q, $J = 7.2$)	62.6	4.47 (q, $J = 7.2$)	62.1
*Me*CH$_2$	1.45 (t, $J = 7.2$)	14.0	1.45 (t, $J = 7.2$)	14.2

[a]) Data may be interchanged. [b]) Data may be interchanged. [c]) Data may be interchanged.

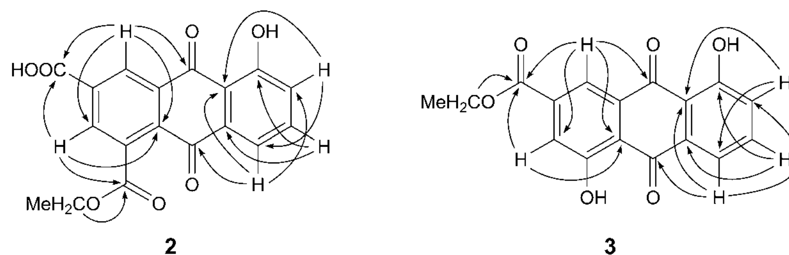

Fig. 4. *Key HMBCs of compounds* **2** *and* **3**

H–C(4) to the COO C-atom (δ(C) 167.0) and C(10), and from H–C(2) to the COO C-atom (δ(C) 167.0)). Accordingly, the EtOCO was assigned to C(1), based on the HMBC between H–C(2) and the CO C-atom (δ(C) 168.3 $MeCH_2OOC$–C(1)). In addition, the chelated OH group was at C(5) due to the HMBCs (from HO–C(5) to C(5), from H–C(7) to C(5), and from H–C(8) to C(9)). Therefore, the structure of compound **2** was elucidated as 1-(ethoxycarbonyl)-5-hydroxyanthraquinone-3-carboxylic acid[2]), named juglanthraquinone A (*Fig. 2*).

Compound **3** was obtained as yellow needles, and also showed a positive *Bornträger*'s test characteristic of anthraquinone derivatives. It reacted positively with $FeCl_3$, indicating its phenolic nature. Its molecular formula was determined as $C_{17}H_{12}O_6$ on the basis of HR-TOF-MS peak at *m/z* 313.0704 ($[M+H]^+$) combined with 1D- and 2D-NMR experiments. Like compound **2**, **3** appeared to be a 9,10-anthraquinone derivative based on its UV spectrum with maxima at 216, 245, and 332 nm and its IR spectrum which exhibited absorption bands at 1639 and 1610 cm^{-1} due to the two chelated CO groups. The IR spectrum also revealed important bands at 3418 and 1721 cm^{-1} due to the OH and the ester C=O groups, respectively. The ^{1}H- and ^{13}C-NMR data of **3** were very similar to those of **4**, except for an additional EtO group (δ(H) 1.45 (*t*, $J = 7.2$) and 4.47 (*q*, $J = 7.2$), δ(C) 14.2 and 62.1). The EtO group was connected to the ester CO group (δ(C) 164.4), on the basis of the long-range correlation between δ(H) 4.47 (MeC*H*$_2$OOC–C(3)) and δ(C) 164.4 ($MeCH_2OO$*C*–C(3)) in the HMBC spectrum (*Fig. 4*). The complete ^{1}H- and ^{13}C-NMR assignments of **3** were accomplished from the HMQC and HMBC spectra (*Table 2*). With the data above, compound **3** was established as ethyl 1,5-dihydroxyanthraquinone-3-carboxylate[2]), named juglanthraquinone B (*Fig. 2*).

Compound **4** was identified as 9,10-dihydro-4,8-dihydroxy-9,10-dioxoanthracene-2-carboxylic acid, which has been mentioned in previous literature [19]. However, it is firstly reported herein as a natural compound.

The antioxidant activity of **1** was tested by both DPPH (=1,1-diphenyl-2-picrylhydrazyl) and ABTS (=2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)) radical scavenging activity assays and compared with the reference antioxidant, gallic acid. Compound **1** exhibited considerable antioxidant activity in both DPPH and ABTS assays, with IC_{50} values of 2.78 and 1.34 μg/ml, respectively, which was comparable with the positive control (1.64 and 2.27 μg/ml).

The cytotoxicities of compounds **2**–**4** against four cultured human tumor cell lines, HepG2, SGC7901, HCT-8, and A549, were determined *in vitro* by MTT (=3-(4,5-

dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide) method, using adriamycin as a positive control. As shown in *Table 3*, compound **4** displayed strong cytotoxicity with IC_{50} values ranging from 4.62 ± 1.45 to 10.21 ± 4.22 μg/ml, whereas compounds **2** and **3** showed no obvious inhibitory activity ($IC_{50} > 30$ μg/ml).

Table 3. *Cytotoxicities of Compounds* **2**–**4** *against Four Cultured Human Tumor Cell Lines*[a])

Cell lines	IC_{50} value [μg/ml]			
	2	**3**	**4**	Adriamycin[b])
HepG2	66.38 ± 0.69	38.80 ± 3.29	4.62 ± 1.45	1.93 ± 0.11
HCT-8	44.37 ± 3.25	50.11 ± 2.01	8.88 ± 4.88	10.52 ± 1.76
A549	68.91 ± 1.48	78.54 ± 0.76	10.01 ± 1.01	1.78 ± 0.16
SGC7901	100.26 ± 2.01	66.73 ± 2.19	10.21 ± 4.22	2.09 ± 0.14

[a]) Data are expressed as the mean ± SD of three distinct experiments. [b]) Positive control.

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Experimental Part

General. Column chromatography (CC): silica gel (SiO_2; 300–400 mesh; *Qingdao Marine Chemical Group, Co.*); *Sephadex LH-20* (*Pharmacia, Co.*). M.p.: *Yanaco-53* micro melting-point apparatus; uncorrected. Optical rotation: *Perkin-Elmer 241 MC* automatic digital polarimeter. UV Spectra: *Shimadzu UV-2201* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Bruker Vertex-70 FTIR* instrument; with KBr disks; in cm^{-1}. NMR spectra: *Bruker AV-400* spectrometer, δ in ppm rel. to TMS as internal standard, *J* in Hz. ESI-MS: *Finnigan LCQ* mass spectrometer; in *m*/*z*. EI-MS: *VG-5050E* mass spectrometer; in *m*/*z*. HR-TOF-MS: *micrOTOF-Q Bruker* mass spectrometer; in *m*/*z*.

Plant Material. The stem bark of *Juglans mandshurica* MAXIM. was collected at mountain area of Jian (Jilin Province, P. R. of China) and was identified by Prof. *Shaobo Fan* (Jilin Agricultural University). A voucher specimen (NO. 2007007) was deposited with Research Center of Agriculture and Medicine Gene Engineering of Ministry of Education, Northeast Normal University.

Extraction and Isolation. The air-dried and powdered stem bark of *Juglans mandshurica* MAXIM. (5 kg) was extracted with 70% EtOH (3 × 10 l, 3 × 1.5 h, 80°) under reflux conditions to give a crude extract, which was suspended in H_2O and extracted with petroleum ether (PE), $CHCl_3$, AcOEt, and BuOH, successively, to yield a PE-soluble fraction (90.5 g), a $CHCl_3$-soluble fraction (100.4 g), an AcOEt-soluble fraction (200.6 g), and a BuOH-soluble fraction (120.0 g). A part of the $CHCl_3$ extract (80 g) was subjected to CC (SiO_2; gradient of PE/AcOEt) to obtain eight fractions, *FC1*–*FC8*. *FC1* (PE/AcOEt 90 : 10) was resubjected to CC (SiO_2; gradient of PE/AcOEt) and was further purified by *Sephadex LH-20* CC ($CHCl_3$/MeOH 1 : 1) to afford **3** (15 mg). *FC3* (PE/AcOEt 80 : 20) was recrystallized using MeOH to give **4** (41 mg). *FC4* (PE/AcOEt 70 : 30) was separated by CC (*Sephadex LH-20*; $CHCl_3$ containing increasing amount of MeOH) to furnish **2** (20 mg). A part of the AcOEt extract (100 g) was subjected to CC (SiO_2; gradient of $CHCl_3$/MeOH) to obtain twelve fractions, *FE1*–*FE12*. *FE8* ($CHCl_3$/MeOH 80 : 20) was resubjected to CC (*Sephadex LH-20*; $CHCl_3$/MeOH, 1 : 1) and recrystallized using MeOH/DMSO 10 : 1 to afford **1** (60 mg).

Juglanthracenoside A (=*2,3,7,11-Tetrahydroxy-5-oxo-5*H*-dibenzo[*c,g*]chromen-12-yl β-*D*-Glucopyranoside*; **1**). Flavo-green amorphous powder. M.p.: 294–296°. UV (MeOH): 374 (0.71), 265 (2.21). $[\alpha]^{25}_{D} = +23.1$ ($c = 0.09$, MeOH). IR (KBr): 3432, 1669, 1610, 1577, 1524, 1493, 1430, 1384, 1356, 1312, 1225, 1081, 987, 871, 774, 732. ^{1}H- and ^{13}C-NMR: see *Table 1*. ESI-MS: 487.2 ($[M-H]^-$), 511.2 ($[M+Na]^+$), 999.3 ($[2M+Na]^+$), 325.1 ($[M-C_6H_{11}O_5]^-$). HR-TOF-MS: 489.1023 ($[M+H]^+$, $C_{23}H_{21}O_{12}^+$; calc. 489.1027), 325.0351 ($[M-C_6H_{11}O_5]^-$, $C_{17}H_9O_7^-$; calc. 325.0354).

Juglanthraquinone A (=*4-(Ethoxycarbonyl)-9,10-dihydro-8-hydroxy-9,10-dioxoanthracene-2-carboxylic Acid*; **2**). Yellow needles (MeOH). M.p.: 254–256°. UV (MeOH): 233 (3.63), 307 (2.18), 353 (2.01). IR (KBr): 3418, 2985, 2956, 2919, 1739, 1702, 1649, 1596, 1576, 1459, 1368, 1272, 1158, 749, 712. ^{1}H- and ^{13}C-NMR: see *Table 2*. ESI-MS: 339.0 ($[M-H]^-$), 295.1 ($[M-COOH]^-$), 341.0 ($[M+H]^+$). HR-TOF-MS: 341.0651 ($[M+H]^+$, $C_{18}H_{13}O_7^+$; calc. 341.0655).

Juglanthraquinone B (=*Ethyl 9,10-Dihydro-4,8-dihydroxy-9,10-dioxoanthracene-2-carboxylate*; **3**). Yellow needles (MeOH). M.p.: 208–210°. UV (MeOH): 216 (3.27), 245 (1.75), 332 (0.93). IR (KBr): 3418, 3083, 2956, 2924, 2852, 1721, 1639, 1610, 1562, 1454, 1380, 1291, 1153, 774, 712. ^{1}H- and ^{13}C-NMR: see *Table 2*. EI-MS: 312.0 (M^+), 283.0 ($[M-Et]^+$), 267.0 ($[M-EtO]^+$), 239.0 ($[M-COOEt]^+$). HR-TOF-MS: 313.0704 ($[M+H]^+$, $C_{17}H_{13}O_6^+$; calc. 313.0706).

1,1-Diphenyl-2-picrylhydrazyl (DPPH) *Radical Scavenging Assay.* The DPPH radical scavenging activity was investigated according to the method described in [20][21]. Gallic acid was used as a positive control. The antioxidant capacity is given as a percent inhibition of DPPH scavenging by samples and comparison with DMSO-treated controls.

2,2′-Azinobis(3-ethylbenzothiazoline-6-sulfonic Acid) (ABTS) Radical Cation Decolorization Assay. The ABTS assay was performed according to the method described in [22], with some modifications [21]. Gallic acid was used as a positive control. The antioxidant capacity is given as a percent inhibition of ABTS scavenging and was calculated in the same way as described for DPPH assay.

Cell Culture and Growth Inhibition Assay. Cell lines were maintained in *Dulbecco*'s modified *Eagle*'s medium (*DMEM*, *Gibco*), supplemented with 10% fetal bovine serum (FBS; *TBD*, China) and antibiotics (100 U/ml penicillin and 100 μg/ml astreptomycin). Cell growth-inhibition assay (MTT assay) was performed as reported in [23]. Cells were harvested with trypsin and resuspended in a final concentration of 1×10^5 cells/ml. Aliquots (0.1 ml) of each cell suspension were distributed evenly into 96-well multiplates and incubated for 24 h. Designated wells were treated with different concentration of the tested compounds. After 44 h, 20 μl of MTT soln. (5 mg/ml in PBS) was added to each well, and the plates were incubated for an additional 4 h in a 37° incubator containing 5% CO_2, allowing viable cells to reduce the yellow MTT into dark-blue formazan crystals. Hundred μl of DMSO were added to each well and agitated for 10 min to dissolve the formazan crystals. Absorbance in each well was read at 570 nm by an *Automated Microplate Reader* (*Bio-Rad*). Adriamycin was used as a positive control, and IC_{50} values were calculated by SPSS method. All assays were performed in triplicate.

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