Original Article

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New phenolic compounds from the twigs of *Artocarpus heterophyllus*

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ABSTRACT: Two new chalcones, artocarpusins A and B (1 and 2), one new flavone, artocarpusin C (3), one new 2-arylbenzofuran derivative, artocarstilene A (4), and 15 flavonoids were isolated from the twigs of *Artocarpus heterophyllus*. Their structures were established on the basis of extensive spectroscopic analysis. Compounds 9 and 16 showed moderate inhibitory activity on the proliferation of the PC-3 and H460 cell lines.

Keywords: *Artocarpus heterophyllus*, chalcone, flavone, 2-arylbenzofuran, cytotoxicity

1. Introduction

Artocarpus heterophyllus Lam, belonging to the family Moraceae (mulberry family) and popularly known as jackfruit, is a key tree found in home gardens in India and Bangladesh (*1-3*). Different parts of this species have been used for medicinal purposes, such as alleviating asthma and fever (the roots), relieving biliousness and diarrhea (the seeds), acting as a sedative for convulsions (the wood), stimulating lactation in women and animals and acting as an antisyphilitic and vermifuge in humans (the leaves), and relieving ulcers and wounds (the leaf ash) (*4,5*). The plant is known to produce prenylflavonoids, stilbenes, triterpenes, and sterols. Some of these compounds have exhibited interesting biological activities, such as cytotoxicity (*6*), antioxidative activity (*7*), anti-inflammatory activity (*8*), antimalarial activity (*9*), inhibition of tyrosinase and melanin biosynthesis (*10,11*), and inhibition of 5α-reductase (*12*). In the course of an ongoing search for anticancer metabolites from Chinese medicinal plants (*13*), the petroleum ether and EtOAc soluble fractions from the 90% EtOH extract of the twigs of *A. heterophyllus* were found to be active in an MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide) cell viability assay of the proliferation/survival of a panel of four cancer cell lines (PC3, H460, SF-268, and MCF-7). The crude extract was then investigated further and three new flavonoids, named artocarpusins A-C (**1-3**) (Figure 1), one new 2-arylbenzofuran derivative, named artocarstilbene A (**4**), and 15 known flavonoids (**5-19**) were obtained. Their structures were elucidated using spectroscopic methods, including 1D and 2D nuclear magnetic resonance (NMR) and high-resolution electrospray ionization mass spectrometry (HRESIMS). The cytotoxicity of these compounds to the PC-3 and H460 human cancer cell lines was tested.

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2. Materials and Methods

2.1. *General experimental procedures*

MTT was purchased from Sigma Chemical Co. (St. Louis, MO, USA). Doxorubicin was purchased from Shenzhen Main Luck Pharmaceuticals, Inc. (Shenzhen, China). Infrared spectra (IR) were recorded on a Nicolet iN 10 Micro FTIR spectrometer (Thermo Fisher Scientific Inc., Waltham, MA, USA) in transmission mode. Ultraviolet spectra (UV) were obtained on a Shimadzu UV-2550 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). NMR spectra were measured on a Bruker Avance DRX-600 spectrometer (Bruker Biospin Group, Billerica, MA, USA) operating at 600 (^{1}H) and 150 (^{13}C) MHz with tetramethylsilane (TMS) as an internal standard. HRESIMS were carried out on a LTQ-Orbitrap XL (Thermo Fisher Scientific Inc., Waltham, MA, USA). All solvents used were of analytical grade (Laiyang Chemical Reagent Co., Ltd., Shandong, China). High-performance liquid chromatography (HPLC) was performed on an Agilent 1100 G1310A isopump equipped with an Agilent 1100 G1322A degasser, an Agilent 1100 G1314A VWD detector (210 nm) and a ZORBAX SB-C_{18} column (9.4 mm × 250 mm, 5 μm) (Agilent Technologies, Inc., Santa Clara, CA, USA). Silica gel (200-300 mesh;

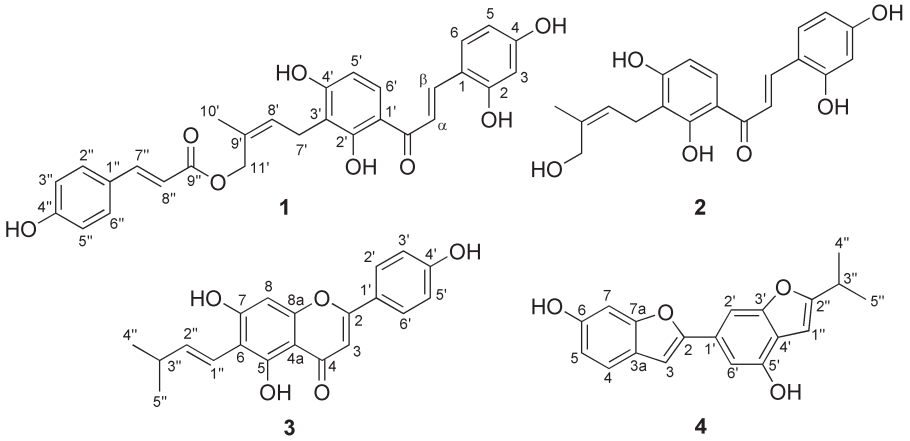

Figure 1. Structures of compounds 1-4.

Qingdao Haiyang Chemical Co., Ltd., Qingdao, China), C_{18} reversed-phase silica gel (YMC ODS-A gel, YMC Co., Ltd., Kyoto, Japan), MCI-gel (CHP20P, 75-150 μm, Mitsubishi Chemical Industries Ltd., Tokyo, Japan), and Sephadex LH-20 (GE Health, Uppsala Sweden) were used for column chromatography (CC). Thin layer chromatography (TLC) was carried out with high-performance TLC plates precoated with silica gel GF254 (Qingdao Haiyang Chemical Co., Ltd.). Spots of TLC were visualized within iodine vapor or by spraying with H_2SO_4-EtOH (1:9) followed by heating.

2.2. *Plant material*

The twigs of *A. heterophyllus* were collected from Xishuangbanna County, Yunnan Province, China in July 2009. The plant material was identified by Dr. Tao Shen, Shandong University. A voucher specimen (AH01-2009-07) was deposited with the Department of Natural Products Chemistry, School of Pharmaceutical Sciences, Shandong University.

2.3. *Extraction and isolation*

The air-dried and powdered plant material (10.0 kg) was extracted with 90% EtOH (4 × 20 L, each for 5 days) at room temperature. The combined extracts were concentrated under reduced pressure to yield a dark gum (150.0 g), which was suspended in H_2O, and fractionated successively with petroleum ether (5 × 1 L), EtOAc (5 × 1 L), and *n*-BuOH (5 × 1 L). The petroleum ether soluble fraction (10.0 g) had TLC like that of the EtOAc soluble fraction (50.0 g), hence they were combined together and subjected to silica gel CC eluted with petroleum ether-EtOAc (20:1→1:1) to yield 14 fractions (Fr. 1-Fr. 14). Fr. 6 (7.0 g) was subjected to CC of MCI-gel (MeOH-H_2O, 30:70→90:10) to yield six subfractions (Fr. 6.1-Fr. 6.6). Fr. 6.4 (1.1 g) was first subjected to CC of silica gel (petroleum ether-acetone, 20:1→2:1) to obtain the major portion, which was further separated by Sephadex LH-20 CC (MeOH) and then purified by preparative HPLC (MeOH-H_2O, 82:18, 1.8 mL/min) to yield **4** (5.9 mg, t_R = 9.06 min) and **7** (13.9 mg, t_R = 16.02 min). Fr. 6.6 (1.2 g) was first separated by CC of silica gel (petroleum ether-acetone, 20:1→1:1) to obtain the major portion, which was subjected to CC of C_{18} reversed-phase silica gel (MeOH-H_2O, 30:70→90:10) to yield **16** (8.0 mg). Fr. 7 (8.0 g) was subjected to CC of MCI-gel (MeOH-H_2O, 30:70→90:10) to yield six subfractions (Fr. 7.1−Fr. 7.6). Fr. 7.1 (0.72 g) was first subjected to Sephadex LH-20 CC (EtOH) and then purified by preparative HPLC (MeOH-H_2O, 78:22, 1.8 mL/min) to yield **18** (15.0 mg, t_R = 10.02 min). Fr. 7.3 (1.1 g) was first subjected to CC of silica gel (dichloromethane-acetone, 50:1→10:1) to obtain the major portion, which was further separated by CC of Sephadex LH-20 (MeOH) and then purified by preparative HPLC (MeOH-H_2O, 78:22, 1.8 mL/min) to yield **13** (8.0 mg, t_R = 16.02 min), **3** (10.5 mg, t_R = 19.50 min), **17** (5.0 mg, t_R = 22.02 min), and **15** (6.0 mg, t_R = 24.02 min). Fr. 8 (8.2 g) was further separated by a column of MCI-gel (MeOH-H_2O, 30:70→90:10) to yield seven subfractions (Fr. 8.1−Fr. 8.7). Fr. 8.3 (1.1 g) was first subjected to CC of silica gel (dichloromethane-acetone, 50:1→10:1) to obtain the major portion, which was further separated by Sephadex LH-20 CC (MeOH) and then purified by preparative HPLC (MeOH-H_2O, 75:15, 1.8 mL/min) to give **6** (5.1 mg, t_R = 20.06 min), **8** (10.1 mg, t_R= 21.26 min), and **14** (5.1 mg, t_R = 23.06 min). Fr. 9 (9.9 g) was subjected to CC of MCI-gel (MeOH-H_2O, 30:70→90:10) to yield eleven subfractions (Fr. 9.1−Fr. 9.11). Fr. 9.4 (1.2 g) was first separated by CC of silica gel (dichloromethane-acetone, 50:1→10:1) to obtain the major portion, which was purified by CC of C_{18} reversed-phase silica gel (MeOH-H_2O, 30:70→90:10) to yield **2** (8.0 mg) and **19** (20.0 mg). Fr. 9.5 (0.61 g) was first separated by Sephadex LH-20 CC (MeOH) and then purified by preparative HPLC (MeOH-H_2O, 78:22, 1.8 mL/min) to yield **5** (3.0 mg, t_R = 12.02 min). Fr. 9.9 (1.0 g) was first subjected to CC of silica gel (dichloromethane-acetone, 100:1→10:1) to obtain the major portion, which was further separated by Sephadex LH-20 CC (EtOH) and then purified by CC of silica gel (dichloromethane-

acetone, 50:1→10:1) to yield **9** (10.5 mg), **10** (7.5 mg), **11** (8.3 mg), **12** (3.3 mg), and **1** (2.5 mg).

2.4. *Cell lines and cell culture*

PC-3 cells (ATCC CRL-1435 human prostate adenocarcinoma) and NCI-H460 cells (ATCC HTB 177 human lung carcinoma) were cultured in RPMI-1640 medium (HyClone, Thermo Fisher Scientific Inc., Waltham, MA, USA). The medium was supplemented with 10% fetal bovine serum (FBS) (Gibco, Invitrogen, Carlsbad, CA, USA), 100 µg/mL penicillin, and 100 µg/mL streptomycin. Cells were cultured in a humidified atmosphere of 5% CO_2 at 37°C.

2.5. *Cytotoxicity assay*

A tetrazolium-based colorimetric assay (MTT assay) was used to determine cell viability (*14*). The cancer cells were all cultured under standard culture conditions. The test compounds or vehicle control (dimethyl sulfoxide, DMSO) were added to appropriate wells and the cells were incubated for 72 h. Then MTT solution was added to the assay plates (final concentration, 0.5 mg/mL). After shaking for 10 sec, plates were returned to the incubator and incubated for 4 h. The supernatants were carefully removed and then100 µL of DMSO was added to each well to dissolve the precipitate. Next, the absorbance was measured at 570 nm with a Model 680 microplate reader (Bio-Rad, Hercules, CA, USA). The percent viability was expressed as absorbance in the presence of test compound as a percentage of that in the vehicle control. Doxorubicin and DMSO were used as positive and negative controls.

3. Results and Discussion

The petroleum ether and EtOAc soluble fraction was subjected to repeated column chromatography over silica gel, Sephadex LH-20, and HPLC to yield four new compounds **1**-**4**, together with 15 known ones, artocarmitin A (**5**) (*15*), 3'-[γ-hydroxymethyl-(*Z*)-γ-methylallyl]-2',4',4-trihydroxychalcone (**6**) (*16*), isobavachalcone (**7**) (*17*), 2',4',2,4-tetrahydroxy-3-(3-methyl-2-butenyl)-chalcone (**8**) (*18*), gemichalcones A (**9**) and B (**10**), isogemichalcone B (**11**) (*15*), artocarmitin B (**12**) (*15*), 6-(3-methylbut-2-enyl)-apigenin (**13**) (*19*), arthocarpesin (**14**) (*20*), norartocarpin (**15**) (*21*), artocarpin (**16**) (*22*), cudraflavone C (**17**) (*23*), 5,7,4'-trihydroxyflavone (**18**) (*24*), and norartocarpesin (**19**) (*25*). Compounds were identified by comparison of their spectroscopic data (*see Supplemental Data*) with values reported in the literature.

Artocarpusin A (**1**) was obtained as an orange powder. The molecular formula was established as $C_{29}H_{26}O_8$ according to HRESIMS with a pseudo molecular ion $[M + H]^+$ peak at *m/z* 503.1709 (calcd for $C_{29}H_{27}O_8$, 503.1706).

Table 1. ^{1}H- (600 MHz) and ^{13}C- (150 MHz) NMR data for compounds 1 and 2

Position	Compound **1**[a]		Compound **2**[b]	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1	---	115.2	---	114.1
2	---	160.0	---	159.3
3	6.53, d (2.0)	103.5	6.39, s	102.4
4	---	162.5	---	162.0
5	6.45, dd (8.5, 2.0)	109.1	6.32, d (8.5)	108.1
6	7.69, d (8.5)	131.7	7.72, d (8.5)	129.5
α	7.80, d (15.6)	117.4	7.68, d (15.5)	115.5
β	8.22, d (15.6)	140.9	8.07, d (15.5)	139.8
CO	---	193.4	---	192.0
1'	---	114.5	---	112.8
2'	---	165.0	---	161.7
3'	---	114.9	---	113.2
4'	---	162.3	---	163.4
5'	6.55, d (8.5)	107.9	6.46, d (8.8)	107.3
6'	7.92, d (8.5)	130.3	7.93, d (8.8)	130.5
7'	3.50, d (7.2)	22.1	3.27, d (7.2)	21.2
8'	5.58, t (7.2)	128.4	5.22, t (7.2)	123.4
9'	---	131.0	---	135.2
10'	1.75, s	63.5	1.65, s	20.8
11'	4.96, s	21.7	4.12, s	59.6
1"	---	127.0	---	---
2", 6"	7.57, d (8.5)	131.0	---	---
3", 5"	6.90, d (8.5)	116.6	---	---
4"	---	160.5	---	---
7"	7.63, d (16.0)	145.3	---	---
8"	6.39, d (16.0)	115.6	---	---
9"	---	167.6	---	---
2'-OH	14.26, s	---	14.18, s	---

[a] Data collected in acetone-d_6. [b] Data collected in DMSO-d_6.

The ^{1}H-NMR spectrum (Table 1) of **1** showed resonance for a methyl attached to a double bond at δ 1.75 (s, 3H), a methylene at δ 3.50 (d, *J* = 7.2 Hz, 2H), an oxygenated methylene at δ 4.96 (s, 2H), two *trans* olefinic protons at δ 7.63 (1H, d, *J* = 16.0 Hz, H-7") and 6.39 (1H, d, *J* = 16.0 Hz, H-8"), an olefinic proton at δ 5.58 (t, *J* = 7.2 Hz, H-8'), a 1,2,4-trisubstituted benzene ring at δ_H 6.53 (1H, d, *J* = 2.0 Hz, H-3), 6.45 (1H, dd, *J* = 2.0, 8.5 Hz, H-5), and 7.69 (1H, d, *J* = 8.5 Hz, H-6), a l,2,3,4-tetrasubstituted benzene ring at δ 6.55 (1H, d, *J* = 8.5 Hz, H-5') and 7.92 (1H, d, *J* = 8.5 Hz, H-6'), a *para*-disubstituted benzene ring at δ 6.90 (d, *J* = 8.5 Hz, H-3" and H-5") and 7.57 (d, *J* = 8.5 Hz, H-2" and H-6"), two olefinic protons of a chalcone skeleton at δ 7.80 (1H, d, *J* = 15.6 Hz, H-α) and 8.22 (1H, d, *J* = 15.6 Hz, H-β), and a hydrogen-bonded hydroxyl group at δ 14.26 (1H, s, 2'-OH). The ^{13}C-NMR spectrum (Table 1) revealed 29 carbon signals, which included the signals of a conjugated ketone carbonyl (δ 193.4 ppm), an esteric carbonyl (δ 167.6 ppm), three benzene rings, three double bonds, two methylenes (including one oxygenated at δ 63.5 ppm), and one methyl. The NMR data for **1** were very similar to those for 3'-[γ-hydroxymethyl-(*E*)-γ-methylallyl]-2,4,2',4'-tetra-hydroxychalcone 11'-*O*-coumarate (*26*), except for a change in the chemical shift values for H-8' and H-11'. The NOESY correlations of H-7'/H-11' and H-8'/H-10' (Figure 2) indicated that the double bond

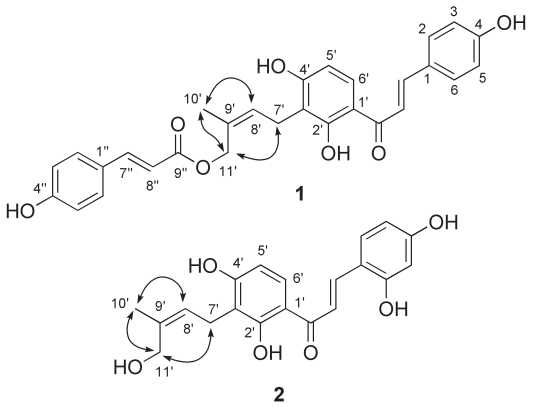

Figure 2. Key NOESY correlations (H↔H) of 1 and 2.

at C-8' was *Z*-configured. Thus, **1** was determined to be 3'-[γ-hydroxymethyl-(*Z*)-γ-methylallyl]-2,4,2',4'-tetrahydroxychalcone 11'-*O*-coumarate.

Artocarpusin B (**2**) was obtained as a yellow solid. HRESIMS revealed a pseudo molecular ion $[M + H]^+$ peak at *m/z* 357.1334 (calcd for $C_{20}H_{21}O_6$, 357.1338), which agreed with the molecular formula $C_{20}H_{20}O_6$. The ^{1}H- and ^{13}C-NMR data (Table 1) for **2** closely resembled those for **6** (*16*), except for the absence of signals for one of the methyls at C-9' and appearance of one oxygenated methylene (δ 4.12, s and δ 59.6 ppm, CH_2-11') in **2**. The NOESY spectrum showed intense correlations of H-10'/H-8' and H-11'/H-7', indicating that the double bond at C-8' was *Z*-configured. Thus, **2** was determined to be 3'-[γ-hydroxymethyl-(*Z*)-γ-methylallyl]-2',4',2,4-tetra-hydroxychalcone.

Artocarpusin C (**3**) was obtained as a yellow solid. HRESIMS revealed an $[M + H]^+$ ion peak at *m/z* 339.1227 (calcd for $C_{20}H_{19}O_5$, 339.1232), corresponding to the molecular formula $C_{20}H_{18}O_5$. The ^{1}H- and ^{13}C-NMR data (Table 2) for **3** were similar to those for isoartocarpesin (*18*) except for a difference in ring-B of the flavonoids. The absence of the AMX-type proton signals and presence of the AA'XX'-type proton signals at δ 7.90 (2H, d, *J* = 8.0 Hz, H-3' and H-5') and 6.91 (2H, d, *J* = 8.0 Hz, H-2' and H-6') indicated that **3** has a *para*-disubstituted phenyl moiety. Thus, **3** was determined to be 2'-dehydroxyisoartocarpesin.

Artocarstilbene A (**4**) was obtained as a brown solid. HRESIMS revealed an $[M-H]^-$ ion peak at *m/z* 307.0969, corresponding to the molecular formula $C_{19}H_{16}O_4$ (calcd for $C_{19}H_{15}O_4$, 307.0970). The ^{1}H- and ^{13}C-NMR data (Table 2) for **4** closely resembled those for moracin D (*27*), except for changing of the 2,2-dimethylpyran ring fused at C-3' and C-4' in moracin D to a 2-isopropylfuran ring at C-3' and C-4'. Further evidence for structure **4** came from HMBC correlations of H-1"/C-3', C-5', C-2", and C-3". Thus, **4** was determined to be 2'-isopropyl-2,6'-bibenzofuran-4',6-diol.

The flavonoids **2**, **3**, **5-10**, and **13-19** were evaluated for their *in vitro* inhibition of cell proliferation using

Table 2. ^{1}H- (600 MHz) and ^{13}C- (150 MHz) NMR data for compounds 3 and 4

Position	Compound **3**[a]		Position	Compound **4**[a]	
	δ_H (*J* in Hz)	δ_C		δ_H (*J* in Hz)	δ_C
2	---	163.5	2	---	154.7
3	6.73, s	103.0	3	7.17, s	101.2
4	---	182.0	3a	---	121.0
4a	---	103.0	4	7.37, d (8.0)	112.5
5	---	159.3	5	6.74, d (8.0)	121.0
6	---	108.7	6	---	156.3
7	---	163.5	7	6.94, s	97.9
8	6.48, s	94.2	7a	---	155.7
8a	---	155.7	1'	---	127.0
1'	---	121.6	2'	7.44, s	98.8
2'	7.90, d (8.0)	128.8	3'	---	151.1
3'	6.91, d (8.0)	116.4	4'	---	118.2
4'	---	161.6	5'	---	156.1
5'	6.91, d (8.0)	116.4	6'	7.08, s	104.0
6'	7.90, d (8.0)	128.8	1"	6.58, s	98.3
1"	6.52, d (16.2)	117.3	2"	---	163.5
2"	6.70, dd (16.2, 8.0)	140.4	3"	3.06, m	27.6
			4"	1.29, d (6.4)	20.8
3"	1.23, m	33.0	5"	1.29, d (6.4)	20.8
4"	1.05, d (6.2)	23.2			
5"	1.05, d (6.2)	23.2			
5-OH	13.88, s	---			

[a] Data collected in DMSO-d_6.

Table 3. Cytotoxicity of some compounds against human tumor cells

Compound	PC-3	H460
1	14.1 ± 0.3	16.2 ± 0.5
2	> 100	> 100
3	> 100	65.9 ± 7.1
4	> 100	> 100
5	41.6 ± 0.5	37.5 ± 4.4
6	26.2 ± 2.8	22.9 ± 1.0
7	15.6 ± 0.0	16.1 ± 1.6
8	22.2 ± 0.5	29.9 ± 0.5
9	8.2 ± 0.3	9.5 ± 0.4
10	9.8 ± 0.2	13.1 ± 1.6
11	14.9 ± 0.5	17.6 ± 1.1
12	11.2 ± 0.7	16.2 ± 0.5
13	43.8 ± 1.9	40.6 ± 1.7
14	16.3 ± 0.1	11.6 ± 0.3
15	22.3 ± 0.9	20.7 ± 0.7
16	7.9 ± 0.6	8.3 ± 0.4
17	16.0 ± 0.1	19.8 ± 1.9
18	75.4 ± 1.5	59.0 ± 1.1
19	47.7 ± 0.1	18.6 ± 3.0
Doxorubicin	0.2 ± 0.1	0.3 ± 0.1

Results are expressed as IC_{50} values in μM. Doxorubicin and DMSO were used as positive and negative controls.

two cancer cell lines, PC-3 (human prostate cancer cells) and H460 (human lung cancer cells). As shown in Table 3, compounds **9** and **16** showed cytotoxic activity with IC_{50} values of 8.2 ± 0.3 and 7.9 ± 0.6 μM for PC-3 and 9.5 ± 0.4 and 8.3 ± 0.4 μM for H460, respectively, and **10** showed inhibitory activity against PC-3 cells (IC_{50} = 9.8 ± 0.2 μM). Compounds **1**, **7**, **11**, **12**, and **14** showed weak activity against PC-3 and H460 cells (10 μM < IC_{50} < 20 μM). The other compounds showed

inactivity against PC-3 and H460 cells (IC_{50} > 20 μM). Doxorubicin was used as a positive control, with IC_{50} values of 0.2 ± 0.1 μM and 0.3 ± 0.1 μM against PC-3 cells and H460 cells, respectively.

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