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Sesquiterpenes from *Syneilesis palmata* and Their Cytotoxicity Against Human Cancer Cell Lines *In Vitro*

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The chromatographic separation of the MeOH extract from the aerial parts of *Syneilesis palmata* led to the isolation of a new sesquiterpene glycoside **4**, together with four known compounds. Their structures were characterized to be 4β,5β-epoxy-caryophill-8,(15)-ene (**1**), 3β-hydroxy-gultin-5-ene (**2**), 4α,5β-dihydroxy-caryophill-8,(15)-ene (**3**), (-)-oplopan-4-one-10-α-*O*-β-D-glucose (**4**) and 3-hexenyl-1-*O*-β-D-glucopyranose (**5**), based on spectroscopic and chemical methods. Compound **2** showed moderate cytotoxicity against five human tumor cell lines *in vitro* with its ED_{50} values ranging from 5.90~10.83 μg/mL.

Key words : *Syneilesis palmata,* Terpenoid, Oplopanone Glycoside, Cytotoxicity

INTRODUCTION

Syneilesis palmata (*Compositae*) has been used as a Korean traditional medicine in the treatment for arthritis, lumbago and bruise (Lee, 1998; An, 1998). Sesquiterpenes (Kuroda *et al.*, 1978), pyrrolizidine alkaloids (Manabu and Tsutomu, 1974), monoterpene glycosides (Bolhmann and Grenz, 1977) and flavonoids (Bolhmann and Zdero, 1978) were reported from the genus *Syneilesis*.

As part of our systematic study on the terpene constituents of the family *Compositae* (Choi *et al.*, 2002, 2003; Kwon *et al.*, 2003), we have investigated *S. palmata*, which was collected at Mt. Sul-Ak, Gangwon Province in June 2002. The aerial parts of this plant were extracted with methyl alcohol at room temperature. The repeated column chromatographic separation of the extract (250 g) resulted in the isolation of a new sesquiterpene glycoside, together with three known terpenes and a hexenyl-glucoside. The cytotoxic effects of the isolated compounds were examined on five human cancer cell lines *in vitro*, and the compound **2** showed moderate cytotoxicity. This paper describes the isolation, structural characterization and cytotoxic activities of the isolated compounds.

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MATERIALS AND METHODS

General procedure

Polarimeter: JASCO P-1020. NMR: Varian UNITY INOVA 500. EI-MS: JEOL SX102 mass spectrometer (JEOL Ltd, Japan), FAB-MS: JEOL 700 mass spectrometer (JEOL Ltd, Japan). Column chromatography : Silica gel 60 (Merck, 70~230 mesh and 230~400 mesh), Lichroprep. RP-18 (Merck) and Sephadex LH-20 (Pharmacia). TLC: Merck precoated Silica gel F254 plates and RP-18 F254s plates. LPLC: Merck Lichroprep Lobar®-A Si 60 (240×10 mm).

Plants material

The aerial parts of *S. palmata* (*Compositae*) were collected at Mt. Sul-Ak, Gangwon Province in June 2002. A voucher specimen (SKK-02-001) was deposited at the College of Pharmacy in Sungkyunkwan University.

Cytotoxicity testing

Sulforhodamin B Bioassay (SRB) was used for cytotoxicity evaluation. The activity of compound was tested at several concentration levels against five cultured human tumor cells *in vitro*, A549 (non small cell lung adenocarcinoma), SK-OV-3 (ovarian), SK-MEL-2 (skin melanoma), XF498 (CNS) and HCT15 (colon) (Skehan *et al.*, 1990).

Extraction and isolation

The aerial parts of *S. palmata* (2 kg) were extracted three times with methyl alcohol (MeOH) at room tem-

perature. The MeOH extract (250 g) was suspended in distilled water (1.6 L) and then successively partitioned with n-hexane, chloroform, ethyl acetate and n-butanol to give hexane (60 g), chloroform (4 g), ethyl acetate (8 g) and butanol (30 g) soluble fractions.

The hexane fraction (40 g) was subjected to silica gel column chromatography, eluted with a solvent mixture of hexane/ethyl acetate (10:1 to 1:1) to give six fractions (H1~H6). The H1 fraction (4.7 g) was successively applied to a silica gel column chromatography using hexane/methylene chloride (1:1), and Sephadex LH-20 using methylene chloride/methyl alcohol (1:1) to give three fractions (H11~H13). The H12 fraction (30 mg) was purified with a silica Lobar-A column using hexane/acetone (30:1) to afford **1** (5 mg). The H13 fraction (30 mg) was also purified with a silica Lobar-A column using hexane/methylene chloride (1:2) to afford **2** (5 mg). The H2 fraction (1.0 g) was applied to Sephadex LH-20 using methylene chloride/methanol (1:1), and then purified with silica HPLC using hexane/acetone (30:1) to afford **3** (10 mg).

The ethyl acetate fraction (8 g) was subjected to Sephadex LH-20 using methanol to give four fractions (E1~E4). The E1 fraction (1.5 g) was applied to a silica gel column chromatography using hexane/ethyl acetate/methanol (4:6:1) and then RP-Lobar-A using methanol/water (1:1) to give four fractions (E11~E14). The E14 fraction (350 mg) was purified with RP-HPLC using methanol/water (1:1) to afford **4** (20 mg).

The butanol fraction (30 g) was subjected to a silica gel column chromatography with ethyl acetate/methanol/water (10:2:0.5) to give four factions (B1~B4). The B1 fraction (8 g) was applied to XAD column chromatography (water to acetone), and a Sephadex LH-20 (methanol) to give five fractions (B11~B15). The B15 fraction (1.5 g) was purified with RP-HPLC using acetonitril/water (1:3) to afford **5** (30 mg).

4α,5β-Epoxy-caryopyll-8(14)-ene (1)

Colorless gum, $[\alpha]_D^{20}$: -94.3° (c=0.1, $CHCl_3$); EI-MS m/z (rel. int.) : 220 (M^+,17), 219 (100), 163 (25), 157 (13), 84 (9), 57 (81); ^{1}H-NMR ($CDCl_3$, 500 MHz, δ ppm) : 5.02 (1H, br.d, *J* = 1.4 Hz, H-14a), 4.91 (1H, br.d, *J* = 1.4 Hz, H-14b), 2.92 (1H, dd, *J* = 13.0, 4.0 Hz, H-2a), 2.63 (1H, dd, *J* = 10.0, 9.6 Hz, H-9), 2.37 (1H, dq, *J* = 8.0, 4.0 Hz, H-7a), 2.27 (1H, dq, *J* = 8.0, 4.2 Hz, H-6a), 2.12 (2H, tt, *J* = 13.0, 4.0 Hz, H-2a, 7b), 1.78 (1H, t, *J* = 10.0 Hz, H-1), 1.71 (1H, dd, *J* = 10.5, 9.6 Hz, H-10a), 1.64 (1H, t, *J* = 10.5 Hz, H-10b), 1.45 (1H, m, H-2b), 1.33 (2H, m, H-3a, 6b), 1.22 (3H, s, H-15), 1.12 (1H, d, *J* = 14.0 Hz, H-3b), 1.05 (3H, s, H-12), 1.02 (3H, s, H-13); ^{13}C-NMR ($CDCl_3$, 125 MHz, δ ppm) : 152.08 (C-8), 112.97 (C-14), 63.96 (C-5), 60.02 (C-4), 51.06 (C-1), 48.96 (C-9), 40.02 (C-10), 39.42 (C-7), 34.24 (C-11), 30.42 (C-6), 30.12 (C-3), 30.08 (C-12), 27.46 (C-2), 21.86 (C-13), 17.22 (C-15).

3β-Hydroxy glutin-5-ene (2)

White powder, $[\alpha]_D^{20}$ +10.3° (c=0.1, $CHCl_3$); EI-MS *m/z* (rel. int.) : 426 (M^+, 15), 411 (30), 393 (23), 337 (4), 311 (8), 274 (92), 259 (70), 205 (27), 153 (29), 111 (44), 69 (100); ^{1}H-NMR ($CDCl_3$, 500 MHz, δ ppm) : 5.65 (1H, d, *J* = 6.0 Hz, H-6), 3.49 (1H, d, *J* = 2.5 Hz, H-3), 2.03-1.96 (2H, m), 1.92-1.83 (3H, m), 1.78 (1H, dd, *J* = 9.0, 5.0 Hz), 1.73 (1H, dd, *J* = 9.0, 3.0 Hz), 1.68 (1H, m), 1.61 (1H, d, *J* = 3.5 Hz), 1.55 (10H, br.m), 1.49 (1H, dd, *J* = 6.0, 2.5 Hz), 1.46 (1H, br.t), 1.43 (1H, m), 1.41 (1H, d, *J* = 4.0 Hz), 1.38 (2H, dd, *J* = 9.0, 3.5 Hz), 1.34 (1H, t, *J* = 6.0 Hz), 1.27 (4H, m), 1.18 (3H, s), 1.16 (3H, s), 1.11 (3H, s), 1.09 (2H, s), 1.06 (2H, s), 1.05 (3H, tm, *J* = 5.0 Hz), 1.03 (3H, s), 1.01 (3H, s), 0.99 (2H, s), 0.97 (3H, s), 0.93 (3H, dd, *J* = 9.0, 2.5 Hz), 0.90 (3H, s), 0.87 (3H, s); ^{13}C-NMR ($CDCl_3$, 125 MHz, δ ppm) : 141.88 (C-5), 122.30 (C-6), 76.57 (C-3), 49.95 (C-10), 47.69 (C-8), 43.33 (C-18), 41.06 (C-4), 39.56 (C-14), 39.20 (C-22), 38.09 (C-13), 35.54 (C-19), 35.34 (C-16), 35.01 (C-9), 34.85 (C-15), 34.76 (C-29), 33.37 (C-11), 32.57 (C-28), 32.34 (C-21), 32.27 (C-30), 30.60 (C-12), 30.34 (C-17), 29.18 (C-23), 28.48 (C-20), 27.48 (C-2), 25.68 (C-24), 23.86 (C-7), 19.85 (C-27), 18.64 (C-26), 18.50 (C-1), 16.43 (C-25).

4α,5β-Dihydroxy-caryophyll-8(14)-ene (3)

Colorless gum, $[\alpha]_D^{20}$: -34.5° (c=1.2, $CHCl_3$); EI-MS *m/z* (rel. int.) : 239 ($[M+H]^+$, 10), 236 (9), 211 (10), 183 (12), 125 (22), 71 (70), 57 (100); ^{1}H-NMR ($CDCl_3$, 500 MHz, δ ppm) : 4.99 (1H, br.s, H-14a), 4.88 (1H, br.s, H-14b), 2.89 (1H, dd, *J* = 10.0, 3.5 Hz, H-5), 2.63 (1H, dd, *J* = 18.0, 10.0 Hz, H-9), 2.36 (1H, td, *J* = 8.0, 5.0 Hz, H-7a), 2.26 (1H, ddd, *J* = 13.0, 8.0, 5.0 Hz, H-6a), 2.12 (2H, tt, *J* = 13.0, 5.0 Hz, H-2a, 7b), 1.78 (1H, t, *J* = 10.0 Hz, H-1), 1.73-1.62 (3H, m, H-3a, 10a, 10b), 1.45 (1H, t, *J* = 13.0 Hz, H-2b), 1.32 (1H, m, H-6b), 1.22 (3H, s, H-15), 1.15 (1H, m, H-3b), 1.03 (3H, s, H-12), 1.00 (3H, s, H-13); ^{13}C-NMR ($CDCl_3$, 125 MHz, δ ppm) : 140.32 (C-8), 122.93 (C-14), 85.40 (C-5), 80.75 (C-4), 49.56 (C-1), 45.97 (C-9), 36.43 (C-7), 34.82 (C-11), 13.34 (C-10), 31.48 (C-6), 30.08 (C-3), 29.87 (C-2), 26.72 (C-13), 26.32 (C-15), 21.29 (C-12).

(-)-Oplopan-4-one-10-α-*O*-β-glucose (4)

Colorless needle, $[\alpha]_D^{20}$: -36.8° (c=0.03, MeOH); IR (KBr) ν_{max} (cm^{-1}) : 3376, 2936, 1706, 1359, 1026; HRFAB-MS : 423.2359 ($[M+Na]^+$); ^{1}H-NMR (DMSO-d_6, 500 MHz, δ ppm) : see Table I; ^{13}C-NMR (DMSO-d_6, 125 MHz, δ ppm) : see Table I; ^{1}H-^{1}H COSY : see Table I; HMBC : see Table I.

Enzymatic hydrolysis of 4

The mixture of the compound **4** (3 mg) in H_2O (3 mL) and β-cellulase (45 mg) were stirred at 37°C for 4 days.

Table I. ^{1}H-NMR (500 MHz, DMSO-d_6) and ^{13}C-NMR (125 MHz, DMSO-d_6) spectral data of compound **4**

Position	δ_H	δ_C	^{1}H-^{1}H COSY	HMBC (C→H)
1	1.62 (td, 12.0, 5.3)	54.4	2b, 6	6, 7, 3b, 14
2a	1.02	26.0	3a	1, 3b
2b	1.23 (t, 10.5)		1, 3b	
3a	1.53 (ddd, 13.0, 3.1, 2.8)	28.7	2a	2a, 5
3b	1.42 (m)		5, 2b	
4		211.6		3b, 5, 6, 15
5	2.62 (ddd, 11.3, 9.5, 5.1)	55.4	3b, 6, 7	3b, 6, 7, 15
6	1.70 (dt, 12.0, 9.5)	46.5	1, 5, 8a	1, 5, 7, 11
7	1.84 (m)	49.2	5, 8b, 11	5, 6, 7, 8a, 12, 13
8a	1.02 (m)	22.9	6, 9a, 9b	9b, 13
8b	1.84 (m)		7, 11	
9a	1.89 (d, 11.5)	38.6	8a	14
9b	1.42 (m)		8a	
10		79.3		1, 6, 9b, 14, 1'
11	1.42 (m, 7.0)	29.8	7, 8b, 12, 13	12, 13
12	0.86 (d, 7.0)	22.5	11	11, 13
13	0.61 (d, 7.0)	16.2	11	11, 12
14	1.14 (s)	18.6		1, 9b
15	2.13 (s)	29.5		5
1'	4.32 (d, 7.9)	97.1	2'	2'
2'	2.86 (dd, 9.0, 7.9)	74.3	1', 3', 6'a, 6'b	1', 4', 6'b
3'	3.13 (dd, 9.0, 8.4)	77.3	2', 4'	3'
4'	3.02 (dd, 9.6, 8.4)	71.0	3', 6'a	3', 4'
5'	3.06 (ddd, 9.6, 5.9, 2.0)	77.7	6'b	
6'a	3.41 (dd, 11.8, 5.9)	61.9	2', 4', 6'b	
6'b	3.62 (d, 11.8, 2.0)		2', 5', 6'a	

The reaction mixture was extracted with ethyl acetate (3ml) three times. The ethyl acetate extract (1.5 mg) was subjected to silica gel column chromatography using hexane/ethyl acetate (1:1) to afford **4a** (1 mg) (Ye *et al.*, 2002). The glucose in the aqueous layer was identified by comparison with D-glucose standard using a co-TLC (ethyl acetate/methanol/water/acetic acid 13:3:3:4 and 6:2:1:1).

(-)-Oplopan-4-one (4a)

Colorless needle, $[\alpha]_D^{20}$: -16.0° (c=0.033, $CHCl_3$); EI-MS :238.19 $[M]^+$; ^{1}H-NMR (CD_3OD, 500 MHz, δppm) : 2.65 (1H, ddd, *J* = 5.4, 5.7, 10.5 Hz, H-5), 2.19 (3H, s, H-15), 1.97 (1H, m, H-3b), 1.83 (1H, m, H-2b), 1.82 (1H, m, H-6), 1.80 (1H, m, H-9b), 1.60 (1H, m, H-8b), 1.58 (1H, m, H-3a), 1.45 (2H, m, H-1, 11), 1.42 (1H, m, H-2a), 1.38 (1H, m, H-9a), 1.20 (3H, s, H-14), 1.10 (1H, m, H-8a), 1.08 (1H, m, H-7), 0.90 (3H, d, *J* = 6.9 Hz, H-12), 0.69 (3H, d, *J* = 6.9Hz, H-13).

(*Z*)-3-Hexenyl-1-*O*-β-D-glucopyranose (5)

Colorless gum, $[\alpha]_D^{20}$: -30.6° (c=0.5, MeOH); FAB-MS : 285.4 $[M+Na]^+$; ^{1}H-NMR (CD_3OD, 500 MHz, δ ppm) : 5.47 (1H, dtt, *J* = 11.0, 7.0, 1.7 Hz, H-3), 5.39 (1H, dtt, *J* = 11.0, 7.0, 1.7 Hz, H-4), 4.28 (1H, d, *J* = 8.0 Hz, Glc-1), 3.88 (1H, td, *J* = 14.0 Hz, 1.4 Hz, Glc-6), 3.68 (1H, dd, *J* = 11.5 Hz, 5.5 Hz, Glc-3)*, 3.56 (1H, td, *J* = 10.0 Hz, 7.0 Hz, Glc-5)*, 3.36 (1H, t, *J* = 9.0 Hz, Glc-2), 3.32 (1H, quint., *J* = 1.7 Hz, Glc-4), 3.29 (1H, d, *J* = 8.4 Hz, H-1), 2.40 (2H, q, *J* = 7.0 Hz, H-2), 2.09 (2H, quint., *J* = 7.5 Hz, H-5), 0.98 (3H, t, *J* = 7.5 Hz, H-6); ^{13}C-NMR (CD_3OD, 125 MHz, δ ppm) : 133.34 (C-3), 124.70 (C-4), 103.18 (Glc-1), 76.97 (Glc-3)*, 76.78 (Glc-5)*, 73.95 (Glc-2), 70.50 (Glc-4), 69.30 (C-1), 61.61 (Glc-6), 27.62 (C-2), 20.25 (C-5), 13.43 (C-6) (* Exchangeable).

RESULTS AND DISCUSSION

Compounds **1**, **2**, **3**, and **5** were identified to be 4β,5β-epoxy-caryophill-8,(15)-ene (**1**) (Tatarova *et al.*, 2002), 3β-hydroxy-gultin-5-ene (**2**) (Antionio *et al.*, 1987), 4α,5β-dihydroxy-caryophill-8,(15)-ene (**3**) (Collado *et al.*, 1997) and 3-hexenyl-1-*O*-β-D-glycoside (**5**) (Mizutani *et al.*, 1988) by comparison of ^{1}H-, ^{13}C-NMR and MS data with those reported in the literature. Compounds **1**, **2**, **3**, and **5** were isolated for the first time from the genus *Syneilesis*.

Compound **4** was obtained as colorless gum and $[\alpha]_D^{20}$ was -36.8° (c=0.03, MeOH). The IR spectrum showed absorption bands at 3376 and 1706 cm^{-1} due to OH and C=O functional groups, respectively. The HR-FAB-MS of **4** produced a molecular ion at 423.2359 $[M+Na]^+$, providing the molecular formula of $C_{21}H_{36}O_7$ (calcd. for $C_{21}H_{36}O_7Na$: 423.2360) and four unsaturation degrees. Anomeric proton at δ4.32 (1H, d, *J* = 7.9 Hz), and six oxygenated protons at δ3.62 (1H, dd, *J* = 11.8, 2.0 Hz), δ3.41 (1H, dd, *J* = 11.8, 5.9 Hz), δ3.13 (1H, dd, *J* = 9.0, 8.4 Hz), δ3.06 (1H, ddd, *J* = 9.6, 5.9, 2.0 Hz), 3.02 (1H, dd, *J* = 9.6, 8.4 Hz), and 2.86 (1H, dd, *J* = 9.0, 7.9 Hz) in the ^{1}H-NMR spectrum indicated the presence of glucose. The ^{13}C-NMR spectrum of **4** showed 15 carbon signals besides glucose signals indicated that the compound **4** was supposed to be a sesquiterpene glucoside. The signals at δ0.86 (3H, d, *J* = 7.0 Hz, H-12), δ0.61 (3H, d, *J* = 7.0 Hz, H-13) and δ1.42 (1H, m, H-11) in the ^{1}H-NMR spectrum indicated the presence of isopropyl group (Alberto *et al.*, 1993). The signal at δ2.13 (3H, s, H-15) in the ^{1}H-NMR spectrum and the signal at δ211.6 (C-4) in the ^{13}C-NMR spectrum indicated the presence of an acetyl group. The signal at δ1.62 (1H, td, *J* = 12.0, 5.3 Hz), δ2.62 (1H, ddd, *J* = 11.3, 9.5, 5.1 Hz), δ1.70 (1H, td, *J* = 12.0, 9.5 Hz) and δ1.84 (1H, m) in the ^{1}H-NMR spectrum and the signals at δ54.4, δ55.4 δ46.5 and δ49.2 in the ^{13}C-NMR spectrum implied that the compound **4**

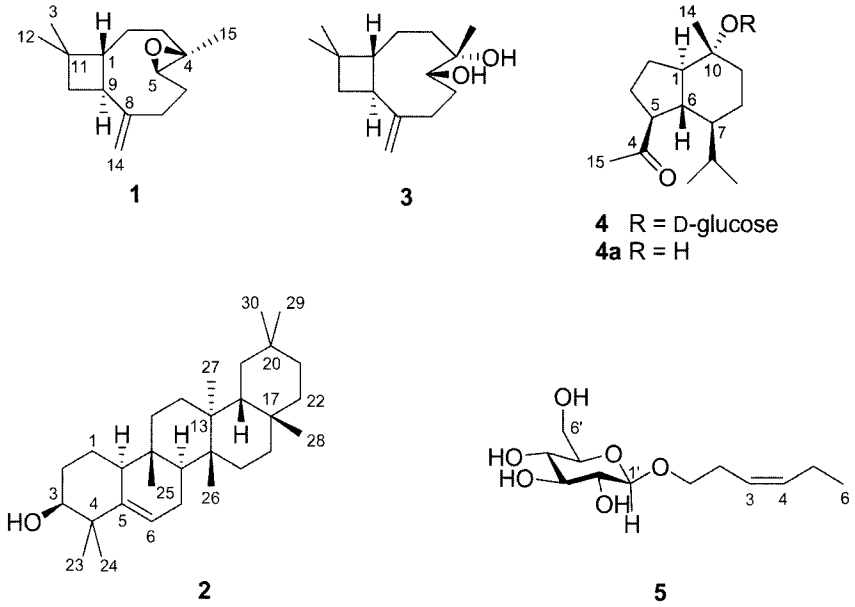

Fig. 1. The structures of compounds **1**~**5** isolated from *Syneilesis palmata*

was to be oplopanone type sesquiterpene (Kitagawa *et al.*, 1987; Takeda *et al.*, 1965; Sung *et al.*, 1992). The position of glucose was determined to be at C-10, based on the HMBC correlation of signal of δ79.3 (C-10) with δ4.32 (1H, d, 7.9 Hz, H-1') (Table I).

The stereochemical structures of the oplopanone sesquiterpenoid were reported in two types (Kitagawa *et al.*, 1987; Takeda *et al.*, 1965; Sung *et al.*, 1992), *normal* form with stereostructure of 1-α-H, 5-α-H, 6-β-H, 7-α-H and 10-α-OH (Takeda *et al.*, 1965), and *ent* form with stereostructure of 1-β-H, 5-β-H, 6-α-H, 7-β-H and 10-β-OH (Kitagawa *et al.*, 1987), respectively. The another major difference between *ent*-form and *normal*-form was the specific rotation; *normal* form was –20.0° (Sung, *et al.*, 1992) and *ent* form +19.0° (Kitagawa *et al.*, 1987), The $[\alpha]_D^{20}$ of compound **4a,** which was isolated from the reaction mixture of enzymatic hydrolysis of **4**, showed –16.0°. This data indicated that the compound **4** was assigned to be *normal* form. The D-glucose was also identified by co-TLC (EtOAc/MeOH/H_2O/HOAc=13:3:3:4 and 6:2:1:1) with D-glucose standard in the reaction mixture of enzymatic hydrolysis of **4**. And the configuration of D-glucose was determined to be β form by the ^{1}H- and ^{13}C-NMR data of anomeric proton [δ4.32 (1H, d, J = 7.9 Hz)] and carbon (δ97.1) (Vignon and Vottero, 1976).

Therefore, the structure of compound **4** was determined to be (-)-oplopan-4-one-10-α-*O*-D-β-glucose. The compound **4** was first isolated from natural sources.

Compounds (**1**~**5**) were evaluated for their cytotoxicity against five human tumor cell lines. Compound **2** showed non-specific moderate cytotoxicity against the human non-small cell lung cancer cells (A549, 9.46 μg/mL; SK-OV-3, 10.83 μg/mL; SK-MEL-2, 5.90 μg/mL, XF498, 8,62 μg/mL; HCT15, 6.64 μg/mL, respectively). The other compounds showed little activity against the five human cancer cell lines tested (>10 μg/mL).

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