Iridoid Glucosides and *p*-Coumaroyl Iridoids from *Viburnum luzonicum* and Their Cytotoxicity

Yoshiyasu Fukuyama,*,† Yuka Minoshima,† Yoshiko Kishimoto,† Ih-Sheng Chen,‡ Hironobu Takahashi,† and Tomoyuki Esumi†

Institute of Pharmacognosy, Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan, and Department of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan, Republic of China

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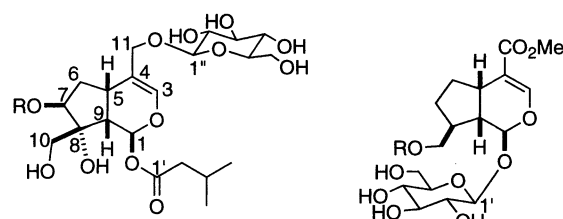
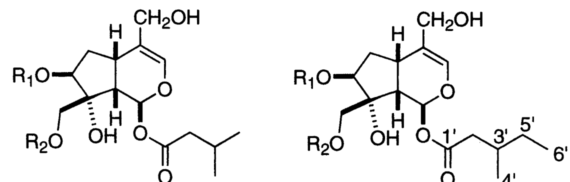
Four new iridoids glucosides (**1**−**4**) and seven new iridoid aglycons (**5**−**11**) bearing (*E*)- or (*Z*)-*p*-coumaroyl groups were isolated from a methanol extract of the dried leaves of *Viburnum luzonicum* collected in Kaoshiung, Taiwan. The structures of the new compounds, named luzonoside A (**1**), luzonoside B (**2**), luzonoside C (**3**), luzonoside D (**4**), luzonoid A (**5**), luzonoid B (**6**), luzonoid C (**7**), luzonoid D (**8**), luzonoid E (**9**), luzonoid F (**10**), and luzonoid G (**11**), were elucidated by analysis of spectroscopic data and comparison with values for previously known analogues. Among the iridoids isolated in the present study, glucosides **1** and **2**, and their aglycons **5**−**9**, exhibited moderate inhibitory activity against HeLa S3 cancer cells, whereas **3** and **4** showed no cytotoxicity even at 100 μM.

Several *Viburnum* species such as *V. opulus* and *V. prunifolium* are used in folk medicine for their diuretic, antispasmodic, and sedative properties.[1−5] *Viburnum* species contain iridoid glycosides,[6] triterpenoids,[7] and diterpenoids, among which vibsane-type diterpenes occur only in *V. awabuki*[8] and *V. odoratissimum*.[9] Our continuing efforts have led to the isolation of over 30 vibsane-type diterpenes from *V. awabuki*, which are dividable into three structural subclasses.[10,11] As part of our ongoing studies on biologically active compounds from *Viburnum* species, we have examined the chemical constituents of the leaves of *V. luzonicum* Rolfe, an evergreen shrub widely distributed in Taiwan. Since an earlier paper reported that a 70% acetone extract of this plant inhibited KB cell growth,[12] we have examined specifically the cytotoxic principles of this species, thereby resulting in the isolation of four new iridoid glucosides (**1**−**4**), named luzonosides A−D, and seven new iridoids (**5**−**11**), named luzonoids A−G, which bear a *p*-coumaroyl group at position C-7 or C-10. In this paper, we report the structure elucidation of these new compounds and their inhibitory activity against HeLa S3 cancer cells.



1 R = (*E*)-*p*-coumaroy
2 R = (*Z*)-*p*-coumaroyl
12 R = H

3 R = (*E*)-*p*-coumaroyl
4 R = (*Z*)-*p*-coumaroyl
13 R = H



5 R_1 = (*E*)-*p*-coumaroyl, R_2 = H
6 R_1 = (*Z*)-*p*-coumaroyl, R_2 = H
7 R_1 = H, R_2 = (*E*)-*p*-coumaroyl
8 R_1 = H, R_2 = (*Z*)-*p*-coumaroyl

9 R_1 = (*E*)-*p*-coumaroyl, R_2 = H
10 R_1 = (*Z*)-*p*-coumaroyl, R_2 = H
11 R_1 = H, R_2 = (*E*)-*p*-coumaroyl

Results and Discussion

The methanol extract of the leaves of *V. luzonicum* was fractionated by silica gel column chromatography to afford fractions 1−17. The iridoid-rich fractions 23, 24, and 30 were purified by a combination of column chromatography and preparative HPLC to give four new iridoid glucosides, luzonoside A (**1**), luzonoside B (**2**), luzonoside C (**3**), and luzonoside D (**4**), and seven new iridoids, luzonoid A (**5**), luzonoid B (**6**), luzonoid C (**7**), luzonoid D (**8**), luzonoid E (**9**), luzonoid F (**10**), and luzonoid G (**11**).

Luzonoside A (**1**) exhibited a $[M + Na]^+$ ion peak at *m/z* 647.2310 in the high-resolution FABMS, corresponding to the molecular formula $C_{30}H_{40}O_{14}$, and its IR spectrum displayed absorptions due to hydroxyl groups at 3364 cm^{-1}, carbonyl groups at 1720 and 1684, and an aromatic moiety at 1589 and 1515 cm^{-1}. The NMR spectral data (Table 1) of **1** were closely related to those of suspensolide F (**12**)[13] except for the presence of an (*E*)-*p*-coumaroyl group [δ_H 6.34 (d, J = 15.9 Hz, H-2), 7.61 (d, J = 15.9 Hz, H-3), 6.80 (2H, d, J = 8.8 Hz, H-6, 8), 7.47 (2H, d, J = 8.8 Hz, H-5, 9); δ_C 167.7 (C-1)]. Indeed, the NMR data of **1** indicated the presence of the functional groups identical with those of **12**, such as an isovaleryl ester substituent [δ_H 0.97 (6H, d, J = 6.6 Hz, H-4′, 5′), 2.09 (1H, tq, J = 6.6, 6.6 Hz, H-3′), 2.22 (2H, d, J = 6.6 Hz, H-2′); δ_C 173.1 (C-1′)], a β-glucopyranose unit [δ_H 4.30 (d, J = 8.0 Hz, H-1″); δ_C 62.8 (C-6″), 71.7 (C-4″), 75.2 (C-2″), 78.0 (C-5″), 78.1 (C-3″), 103.4 (C-1″)], and an acetal moiety [δ_H 6.21 (d, J = 4.4 Hz, H-1); δ_C 91.5 (C-1)]. The latter unit was involved in the fragment −O−C(1)H−C(9)H−C(5)H−C(6)H_2−C(7)H−O−, inferred by the COSY and HMQC spectral data. Also present were a singlet olefinic proton at δ_H 6.41 and two isolated oxymethylenes [δ_H 3.67 (d, J = 11.5 Hz, H-10) and 3.73 (d, J = 11.5 Hz, H-10), δ_C 66.0 (C-10), and δ_H 4.13 (d, J = 11.5 Hz, H-11) and 4.29 (d, J = 11.5 Hz, H-11), δ_C 69.8

* To whom correspondence should be addressed. Tel: +81-88-622-9611 (5911). Fax: +81-88-655-3051. E-mail: fukuyama@ph.bunri-u.ac.jp.
† Tokushima Bunri University.
‡ Kaohsiung Medical University.

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Table 1. ^{13}C NMR (150 MHz) and ^{1}H NMR (600 MHz) Spectral Data of Compounds **1** and **2** in CD_3OD^a

	1		**2**	
position	δ_C	δ_H	δ_C	δ_H
1	91.5	6.21 d (4.4)	91.4	6.17 d (4.4)
3	140.7	6.41 s	140.5	6.34 s
4	115.9		115.9	
5	33.0	3.09 ddd (7.4, 7.4, 9.9)	33.0	2.92 ddd (8.0, 8.0, 9.9)
6	35.9	2.24 ddd (4.4, 7.4, 11.8)	36.0	2.10 ddd (4.1, 8.0, 11.3)
		2.17 ddd (4.4, 7.4, 11.8)		2.17 ddd (4.1, 8.0, 11.3)
7	81.6	5.10 dd (4.4, 4.4)	81.3	5.04 dd (4.1, 4.1)
8	83.4		83.4	
9	45.3	2.45 dd (4.4, 9.9)	45.3	2.27 dd (4.4, 9.9)
10	66.0	3.67 d (11.5)	65.8	3.56 d (11.3)
		3.73 d (11.5)		3.59 d (11.3)
11	69.8	4.13 d (11.5)	69.8	4.11 d (11.7)
		4.29 d (11.5)		4.28 d (11.7)
1′	173.1		173.1	
2′	44.2	2.22 d (6.6)	44.2	2.22 d (7.1)
3′	26.8	2.09 tq (6.6, 6.6)	26.8	2.08 tq (5.2, 7.1)
4′	22.7	0.97 d (6.6)	22.7	0.96 d (5.2)
5′	22.7	0.97 d (6.6)	22.7	0.96 d (5.2)
glc 1″	103.4	4.30 d (8.0)	103.4	4.31 d (7.7)
2″	75.2	3.19 dd (8.0, 9.3)	75.1	3.20 dd (7.7, 9.1)
3″	78.1	3.34 t (9.3)	78.1	3.34 t (9.1)
4″	71.7	3.26 m	71.8	3.27 m
5″	78.0	3.26 m	78.0	3.27 m
6″	62.8	3.75 dd (1.4, 11.5)	62.8	3.65 dd (1.6, 11.8)
		3.86 dd (1.4, 11.5)		3.87 dd (1.6, 11.8)
coumaroyl				
1	167.7		168.7	
2	115.2	6.34 d (15.9)	116.9	5.79 d (12.6)
3	146.9	7.61 d (15.9)	145.4	6.91 d (12.6)
4	127.8		128.0	
5, 9	131.3	7.47 d (8.8)	133.4	7.54 d (8.5)
6, 8	116.8	6.80 d (8.8)	115.9	6.76 d (8.5)
7	161.4		161.4	

[a] All assignments were made by extensive analyses of 1D and 2D NMR (COSY, DEPT, HMQC, and HMBC).

Table 2. ^{13}C NMR (150 MHz) and ^{1}H NMR (600 MHz) Spectral Data of Compounds **3** and **4** in CD_3OD^a

	3		**4**	
position	δ_C	δ_H	δ_C	δ_H
1	98.5	5.20 d (4.9)	98.4	5.13 d (4.7)
3	153.5	7.47 s	153.5	7.46 s
4	111.9		111.8	
5	36.6	2.89 ddd (8.2, 8.2, 13.0)	36.8	2.73 ddd (7.4, 7.4, 12.8)
6	33.5	2.20 m	33.5	2.17 m
		1.45 m		1.37 m
7	28.8	1.45 m	28.6	1.37 m
		1.90 m		1.80 m
8	41.2	2.41 m	41.0	2.32 m
9	44.4	2.03 ddd (6.9, 6.9, 13.0)	44.3	1.92 ddd (6.9, 6.9, 12.8)
10	68.4	4.15 dd (6.5, 11.0)	68.3	4.10 dd (5.8, 11.0)
		4.21 dd (6.5, 11.0)		4.14 dd (6.0, 11.0)
11	169.5		169.6	
OMe	51.7	3.70 s	51.7	3.70 s
glc 1′	100.7	4.66 d (8.0)	100.5	4.65 d (8.0)
2′	74.7	3.20 dd (8.0, 9.3)	74.7	3.22 dd (8.0, 9.3)
3′	78.0	3.35 t (9.3)	78.0	3.35 t (9.3)
4′	71.4	3.30 m	71.5	3.30 m
5′	78.3	3.28 m	78.4	3.27 m
6′	62.7	3.65 dd (1.8, 11.0)	62.7	3.88 dd (1.8, 11.8)
		3.85 dd (1.8, 11.0)		3.86 dd (1.8, 11.8)
coumaroyl				
1	169.5		169.6	
2	115.1	6.34 d (15.9)	117.0	5.80 d (12.6)
3	146.7	7.61 d (15.9)	144.9	6.89 d (12.6)
4	127.1		127.8	
5, 9	131.3	7.48 d (8.5)	133.3	7.55 d (8.5)
6, 8	116.9	6.80 d (8.5)	115.9	6.80 d (8.5)
7	161.4		161.4	

[a] All assignments were made by extensive analyses of 1D and 2D NMR (COSY, DEPT, HMQC, and HMBC).

(C-11)]. The above spectral similarities between **1** and **12** implied that **1** was acylated at C-7 or C-10 with an (*E*)-*p*-coumaroyl group. From the significant downfield shift (δ_H 5.10) of H-7 in comparison with **12**, the coumaroyl group was assigned to the C-7 hydroxyl group via an ester bond. This was supported by an HMBC correlation of H-7 to the ester carbonyl at δ_C 167.7 of the coumaroyl group. Since the H-11 signals showed HMBC correlations to the anomeric C-1″ of the glucose unit that resonated at δ_C 103.4, the linkage position of this β-glucopyranose unit was inferred at C-11. The relative stereochemistry of **1** was found to be the same as **12** on the basis of not only the *J* value (4.4 Hz) for H-1 but also the following NOESY correlations: H-5/H-9, H-5/H-6β, H-7/H-6α, and H-10/H-1. Accordingly, luzonoside A (**1**) was assigned as 7-*O*-(*E*)-*p*-coumaroylsuspensolide F.

Luzonoside B (**2**) had the same molecular formula $C_{30}H_{40}O_{14}$ as **1**, obtained from high-resolution FABMS at *m/z* 647.2310 $[M + Na]^+$, and exhibited physical and NMR data (Table 1) very similar to those of compound **1** except for the NMR data assignable to the *p*-coumaroyl group. Specifically, a small *J* value (12.6 Hz) was observed for two vicinal olefinic protons, indicating the presence of a (*Z*)-*p*-coumaroyl ester unit. It was evident from the HMBC correlation of the H-7 signal at δ_H 5.04 to the ester carbonyl at δ_C 168.7 that this *p*-coumaroyl group is located at the C-7 position. The other NMR data including the HMBC and NOESY spectra for **2** were consistent with those of **1**. Thus, the structure of luzonoside B (**2**) was determined to be 7-*O*-(*Z*)-*p*-coumaroylsuspensolide F.

Luzonoside C (**3**) had a molecular formula, $C_{26}H_{32}O_{12}$, determined by high-resolution FABMS at *m/z* 559.1750 $[M + Na]^+$, and its IR spectrum displayed absorptions due to a hydroxyl group at 3392 cm^{-1}, a conjugated carbonyl group at 1684 cm^{-1}, and an aromatic moiety at 1604 and 1512 cm^{-1}. The NMR spectral data of **3** (Table 2) showed the presence of a β-glucopyranose unit (δ_C 62.7, 71.4, 74.7, 78.0, 78.3, 100.7; δ_H 4.66 (d, J = 8.0 Hz, H-1′), a conjugated methyl ester (δ_H 3.70; δ_C 51.7, 169.5), which was confirmed by an HMBC correlation between the singlet olefinic proton at δ_H 7.47 and the ester carbonyl resonance at δ_C 169.5, an acetal carbon at δ_C 98.5, and a *p*-coumaroyl group, which was assigned with an *E*-geometry from its large *J* value (15.9 Hz). In addition, a partial structure, $-O-C(10)H_2-C(8)H-C(7)H_2-C(6)H_2-C(5)H-C(9)H-C(1)H-O-$, was generated from the analysis of the COSY and HMQC spectral data. The HMBC correlations of the H-1 signal at δ_H 5.20 to the C-1′ anomeric carbon at δ_C 100.7 and the C-3 olefinic carbon at δ_C 153.5 indicated that a β-glucopyranose unit was attached to C-1, which was further linked to C-3 through an ether bond. These spectral data disclosed that the structure of **3** was similar to that of adoxoside (**13**)[14] except for the presence of a *p*-coumaroyl group. The

Table 3. ^{13}C NMR (150 MHz) Spectral Data of Compounds **5**−**11** in CD_3OD

C	5	6	7	8	9	10	11
1	91.6	91.5	91.8	91.8	91.6	91.5	91.8
3	138.9	138.7	138.4	138.4	139.0	138.7	138.5
4	119.0	119.1	119.7	119.8	119.1	119.2	119.7
5	32.5	32.4	32.1	32.3	32.6	32.4	32.1
6	36.0	35.9	38.4	38.4	36.0	35.9	38.4
7	81.3	81.1	79.1	78.9	81.3	81.2	79.1
8	83.5	83.5	83.0	83.0	83.6	83.5	83.0
9	45.3	45.3	45.8	45.7	45.4	45.4	45.8
10	65.8	65.7	69.1	68.5	65.9	65.7	69.2
11	62.1	62.2	62.3	62.3	62.1	62.2	62.3
1′	173.1	173.1	173.2	173.1	173.3	173.3	173.4
2′	44.2	44.2	44.3	44.3	42.3	42.2	42.4
3′	26.7	26.7	26.9	26.8	33.1	33.1	33.2
4′	22.7	22.7	22.7	22.7	19.6	19.6	19.5
5′	22.7	22.7	22.7	22.7	30.3	30.3	30.3
6′					11.6	11.6	11.6
coumaroyl							
1	168.6	167.5	169.5	168.4	168.6	167.5	169.5
2	115.1	117.1	115.1	116.5	115.2	117.1	115.1
3	146.8	145.5	146.8	145.4	146.8	145.5	146.8
4	127.1	127.8	127.2	127.6	127.1	127.8	127.2
5, 9	131.2	133.4	131.2	133.8	131.3	133.4	131.2
6, 8	116.8	115.9	116.8	115.8	116.8	115.9	116.8
7	161.3	160.0	161.4	160.2	161.4	160.0	161.3

linkage position of this extra aromatic group was determined to be at the C-10 position on the basis of characteristic downfield shifts for the H_2-10 oxymethylene as well as the HMBC correlations between H_2-10 (δ_H 4.15 and 4.21) and an ester carbonyl (δ_C 169.5) of the *p*-coumaroyl group. The relative configuration for **3** was found to be the same as that of **13** by comparison of the *J* values for each proton and the ^{13}C NMR chemical shifts with those of **13**.[14] Thus, the structure of luzonoside C (**3**) could be represented as 10-*O*-(*E*)-*p*-coumaroyladoxoside.

Luzonoside D (**4**) was found to have the same molecular formula, $C_{26}H_{32}O_{12}$, as that of **3**, as determined by high-resolution FABMS at *m/z* 559.1792 [M + Na]$^+$. The IR spectrum displayed absorptions attributable to a hydroxyl group at 3395 cm^{-1}, a conjugated carbonyl group at 1692 cm^{-1}, and an aromatic moiety at 1624 and 1512 cm^{-1}. The ^{1}H and ^{13}C NMR spectral data (Table 2) of **4** showed signals similar to those of **3** except for differences of the chemical shifts and *J* values corresponding to the coumaroyl H-2 and H-3. The small $J_{2,3}$ value (12.6 Hz) indicated the double-bond geometry for this *p*-coumaroyl unit to be *Z*. NOESY NMR experiments indicated that the relative stereochemistry for **4** was the same as that of **3**. Thus, the structure of **4** was assigned as 10-*O*-(*Z*)-*p*-coumaroyladoxoside.

Luzonoid A (**5**) gave the molecular formula $C_{24}H_{30}O_9$, as determined by the high-resolution FABMS at *m/z* 485.1787 [M + Na]$^+$, and its IR spectrum displayed absorptions due to a hydroxyl group at 3429 cm^{-1} and carbonyl groups at 1734 and 1694 cm^{-1}. The ^{1}H and ^{13}C NMR spectral data (Table 3) of luzonoid A (**5**) showed the presence of a *p*-coumaroyl group with an *E* double bond ($J_{2,3}$ = 15.8 Hz), an isovaleroyl group, and an iridoid skeleton identical to that of **1**, but no signal corresponding to a sugar moiety. Acetylation of **5** gave a triacetate (δ_H 2.32, 2.09, 2.06), which suggested the presence of one phenolic hydroxyl and two aliphatic hydroxyl groups, indicating the absence of a glucose unit in **5**. These data were consistent with **5** being the aglycon of **1**. In the HMBC NMR experiment, the H-1 acetal signal at δ_H 6.18 (J = 4.9 Hz) correlated to both the ester carbonyl at δ_C 173.1 of the isovaleroyl group and the C-3 olefinic carbon at δ_C 138.9, and also the H-7 signal at δ_H 5.09 (dd, J = 4.1, 4.1 Hz) showed a cross-peak to the ester carbonyl of a *p*-coumaroyl group at δ_C 168.6. The NOESY spectrum and the *J* values for each proton in **5** were comparable with those of **1**, thereby indicating that the relative stereochemistry of **5** was the same as **1**. Thus, the structure of luzonoid A (**5**) was determined to be the aglycon of luzonoside A (**1**).

Luzonoide B (**6**) was assigned the molecular formula $C_{24}H_{30}O_9$, as determined by the high-resolution FABMS at *m/z* 485.1775 [M + Na]$^+$, which was in accordance with that of **5**. All the spectral data for **6** were found to be very similar to those of **5** except for the chemical shifts and *J* values (12.6 Hz) for H-2 and H-3 of the *p*-coumaroyl group. This led to the conclusion that in the case of **6** a (*Z*)-*p*-coumaroyl group was attached to the C-7 position in place of an *E* geometry existing in **5**.

Luzonoids C (**7**) and D (**8**) showed the same molecular formula of $C_{24}H_{30}O_9$ as **5** and **6**. The spectral data of **7** and **8** were very similar not only to each other but also to **5** and **6**, respectively. The ^{13}C NMR data (Table 3) of **7** and **8** revealed that the C-7 resonance (δ_C 79.1 for **7**; δ_C 78.9 for **8**) shifted upfield by 2.2 ppm in comparison with those of **5** and **6**, whereas the C-10 (δ_C 69.1 for **7**; δ_C 68.5 for **8**) and C-6 (δ_C 38.4 for **7** and **8**) signals shifted downfield (Table 3). Additionally, the H-7 and H-10 signals for **7** and **8** exhibited characteristic upfield and downfield shifts of 1.0 and 0.7 ppm, respectively, in comparison with those of **5** and **6**. These spectral data implied that in the case of **7** and **8** an (*E*)- and a (*Z*)-*p*-coumaroyl group was attached at the C-10 position, respectively, and there was a free hydroxyl group at C-7. These assignments were supported by the HMBC correlations of the H_2-10 signals to ester carbonyls (δ_C 169.5 for **7**; δ_C 168.4 for **8**) of *p*-coumaroyl groups existing in **7** and **8**. Thus, luzonoids C (**7**) and D (**8**) were assigned as the 10-*O*-*p*-coumaroyl isomers of **5** and **6**, respectively.

Luzonoid E (**9**) had a molecular formula of $C_{25}H_{32}O_9$, as determined by the high-resolution FABMS at *m/z* 499.1939 [M + Na]$^+$, indicative of a CH_2 increase over the molecular formulas of **5**−**8**. The ^{13}C NMR spectral data (Table 3) of **9** were identical with those of luzonoid A (**5**) except for the data assignable to an isovaleroyl group. These spectral data indicated that **9** represents a 7-*O*-(*E*)-*p*-coumaroyl iridoid analogue of **5**. The ^{1}H NMR spectrum of **9** showed the presence of an ethyl group at δ_H 0.91 (3H, dd, J = 7.4, 7.4 Hz), 1.25 and 1.40 (each 1H, ddq, J = 14.8, 7.4, 7.4 Hz), showing characteristic nonequivalent signals when being next to a chiral center. This ethyl group was found to be involved in a 3-methylpentanone unit, as determined from the analysis of the COSY and HMBC NMR spectra of **9**. The presence of this new 3-methylvaleroyl group was supported by the observation of a prominent fragment peak at *m/z* 99 in the EIMS and the FABMS. The HMBC correlation of the H-1 acetal proton at δ_H 6.17 (d, J = 4.9 Hz) to an ester carbonyl resonance at δ_C 173.3 verified the 3-methylvaleroyl group attached to C-1. The NOESY and the NMR data for the remaining parts of **9** were consistent with those of **5**. Thus, the structure of luzonoid E (**9**) was determined to be 1-*O*-deisovaeroyl-1-*O*-3-methylvaleroyl-luzonoid A.

All physical and spectral data for luzonoid F (**10**) were identical with those of **9** except for the chemical shifts and *J* values due to H-2 and H-3 of the *p*-coumaroyl unit. A small *J* value (12.6 Hz) between H-2 and H-3 of the *p*-coumaroyl group was observed, indicating the *Z* isomer. Additionally, the H-7 signal at δ_H 5.02 (dd, J = 4.0, 4.0 Hz) showed an HMBC correlation to an ester carbonyl (δ_C 167.5) of a *p*-coumaroyl group, confirming its linkage

Table 4. Cytotoxic Activities of Compounds **1**−**9** against HeLa S3 Cells[a]

compound	IC_{50} (μM)
1	3.39
2	4.67
3	>100
4	>100
5	2.89
6	3.11
7	3.57
8	4.56
9	7.40
fluorouracil	5.40
cisplatin	2.46

[a] Human epithelial cancer cell line.

position to be at C-7. Thus, luzonoid F (**10**) was assigned as the *Z* isomer of a *p*-coumaroyl group in luzonoid E (**9**).

Luzonoid G (**11**) had the same molecular formula of $C_{25}H_{32}O_9$ as **9** and **10** and similar spectral data to those of **9**. On comparison of the ^{13}C NMR data (Table 3) of **11** and **9**, the C-7 (δ_C 79.1) and C-10 (δ_C 69.2) resonances for **11** were shifted upfield and downfield by 2.2 and 3.3 ppm, respectively, compared to **9**. Additionally, its H-7 and H-10 signals exhibited characteristic upfield and downfield shifts of 1.6 and 0.7 ppm, respectively, in comparison with those of **9**. These spectral data suggested that **11** has an (*E*)-*p*-coumaroyl group at the C-10 position, and the hydroxyl group at C-7 is unsubstituted. This was supported by the HMBC correlations of the H_2-10 signals at δ_H 4.36 and 4.38 (each d, J = 11.5 Hz) to an ester carbonyl (δ_C 169.5) of a *p*-coumaroyl group. Thus, the structure of luzonoid G (**11**) was assigned as the 10-*O*-(*E*)-*p*-coumaroyl isomer of **9**.

All the new iridoid glucosides and iridoids isolated in this study are structurally analogous to those found in many other species of *Viburnum* and in some species of *Valeriana*. They are characterized by (*E*)- or (*Z*)-*p*-coumaroyloxy groups attached to position 7 or 10. Although these iridoids bearing (*E*)- or (*Z*)-*p*-coumaroyl groups are readily isolated in a pure form, they gradually interconvert into a mixture of the *E* and *Z* forms at room temperature, but remain unchanged while being kept in a refrigerator. In a cytotoxicity assay with the HeLa S3 (human epithelial cancer) cell line, iridoid glucosides **1** and **2** and their aglycons **5**−**9** exhibited moderate inhibitory activity, with IC_{50} values of 3−7 μM, whereas **3** and **4** showed no cytotoxicity even at 100 μM, as summarized in Table 4.[15] Furthermore, cytotoxic iridoids **1** and **2** and **5**−**9** inhibited the growth and the cell viability in primary-cultured rat cortical neurons at 10 μM.[16] Although catalposide,[17] pulmercin, and allamcin[18] are known as typical cytotoxic iridoids, this is the first report of the cytotoxic activities in 1-*O*-isovaleroyl and 1-*O*-3-methylvaleroyl iridoids.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. IR spectra were measured on a JASCO FT-IR 5300 infrared spectrophotometer. 1D and 2D NMR spectra were recorded on a Varian Unity 600 instrument. Chemical shifts are given as δ (ppm) with TMS as internal standard. MS were recorded on a JEOL AX-500 instrument. Column chromatography was carried out on Kieselgel 60 (70−230 mesh) and Wako gel C-300.

Plant Material. The leaves of *Viburnum luzonicum* were collected in Kaoshiung, Taiwan, in May 2002. One of the authors (I.-S.C.) identified the plant, and a voucher specimen (1714LF) has been deposited at the Institute of Pharmacognosy, TBU, Tokushima, Japan.

Extraction and Isolation. The dried leaves of *V. luzonicum* (7.0 kg) were extracted with MeOH to yield 800 g of the MeOH extract. The extract (150 g) was chromatographed on a Si gel (Kieselgel 60) column eluting with a step gradient of CH_2Cl_2 (100%), CH_2Cl_2−EtOAc (9:1), CH_2Cl_2−EtOAc (3:2), CH_2Cl_2−EtOAc (2:3), EtOAc (100%), EtOAc−MeOH (9:1), and EtOAc−MeOH (4:1) to give 17 fractions (1−17).

Fraction 10 (7.7 g) was first subjected to Si gel (Wako C-300) chromatography eluting with $CHCl_3$−EtOAc (1:1) to give fractions 18−27. Fraction 24 (450 mg) was separated by Si gel chromatography with $CHCl_3$−MeOH−H_2O (8:2:0.2), followed by reversed-phase HPLC [Cosmosil $5C_{18}$-AR-II, ϕ 10 × 250 mm; H_2O−MeOH (2:3), 2.5 mL/min] to give compounds **1** (2.1 mg), **2** (2.9 mg), **3** (2.8 mg), and **4** (2.8 mg). Fraction 22 (777 mg) was separated by reversed-phase HPLC (Cosmosil $5C_{18}$-AR-II, ϕ 10 × 250 mm) using MeOH−H_2O (11:9, 2 mL/min) to give compounds **5** (43 mg), **6** (26 mg), **9** (8 mg), and **10** (1.6 mg). Fraction 23 (73 mg) was chromatographed by Si gel column chromatography eluting with CH_2Cl_2−EtOAc (2:1) to give fractions 28−35. Fraction 30 (15 mg) was separated by reversed-phase HPLC (Cosmosil $5C_{18}$-AR-II, ϕ 10 × 250 mm) using MeOH−H_2O (3:2, 2.5 mL/min) as a solvent to give compounds **7** (9 mg), **8** (3.4 mg), and **11** (1.5 mg).

Luzonoside A (1): yellow paste; $[\alpha]^{21}_D$ −18.6° (*c* 0.60, MeOH); IR (film) ν_{max} 3364 (OH), 1720 (C=O), 1684 (conjugated C=O), 1589, 1515 (aromatic) cm^{-1}; UV (EtOH) λ_{max} 315 (ϵ 17 800), 226 (ϵ 11 100) nm; ^{1}H and ^{13}C NMR, see Table 1; HRFABMS *m/z* 647.2310 [M + Na]$^+$ (calcd 647.2316 for $C_{30}H_{40}O_{14}Na$).

Luzonoside B (2): yellow paste; $[\alpha]^{21}_D$ −41.1° (*c* 0.45, MeOH); IR (film) ν_{max} 3370 (OH), 1732 (C=O), 1687 (conjugated C=O), 1589, 1515 (aromatic) cm^{-1}; UV (EtOH) λ_{max} 315 (ϵ 21 600), 225 (ϵ 13 300) nm; ^{1}H and ^{13}C NMR, see Table 1; HRFABMS *m/z* 647.2310 [M + Na]$^+$ (calcd 647.2316 for $C_{30}H_{40}O_{14}Na$).

Luzonoside C (3): yellow paste; $[\alpha]^{21}_D$ −9.6° (*c* 0.31, MeOH); IR (film) ν_{max} 3392 (OH), 1684 (C=O), 1604, 1512 (aromatic) cm^{-1}; UV (EtOH) λ_{max} 313 (ϵ 23 000), 204 (ϵ 22 600) nm; ^{1}H and ^{13}C NMR, see Table 2; HRFABMS *m/z* 559.1750 [M + Na]$^+$ (calcd 559.1792 for $C_{26}H_{32}O_{12}Na$).

Luzonoside D (4): yellow paste; $[\alpha]^{21}_D$ +32.6° (*c* 0.27, MeOH); IR (film) ν_{max} 3395 (OH), 1692 (C=O), 1624, 1512 (aromatic) cm^{-1}; UV (EtOH) λ_{max} 312 (ϵ 7600), 203 (ϵ 283 000) nm; ^{1}H and ^{13}C NMR, see Table 2; HRFABMS *m/z* 559.1750 [M + Na]$^+$ (calcd 559.1792 for $C_{26}H_{32}O_{12}Na$).

Luzonoid A (5): yellow oil; $[\alpha]^{21}_D$ +41.0° (*c* 0.64, MeOH); IR (film) ν_{max} 3429 (OH), 1734 (C=O), 1694 (conjugated C=O), 1587, 1516 (aromatic) cm^{-1}; UV (EtOH) λ_{max} 316 (ϵ 22 400), 300 (ϵ 18 200), 229 (ϵ 11 000) nm; ^{1}H NMR (CD_3OD) δ 0.97 (6H, d, J = 6.9 Hz, H_3-4′, 5′), 2.09 (1H, tq, J = 7.1, 6.9 Hz, H-3′), 2.12 (1H, ddd, J = 11.0, 8.2, 4.1 Hz, H-6), 2.15 (1H, ddd, J = 11.0, 8.2, 4.1 Hz, H-6), 2.22 (2H, d, J = 7.1 Hz, H_2-2′), 2.43 (1H, dd, J = 9.8, 4.9 Hz, H-9), 3.02 (1H, ddd, J = 9.8, 8.2, 8.2 Hz, H-5), 3.68 (1H, d, J = 11.3 Hz, H-10), 3.76 (1H, d, J = 11.3 Hz, H-10), 3.94 (1H, d, J = 12.4 Hz, H-11), 4.09 (1H, d, J = 12.4 Hz, H-11), 5.09 (1H, dd, J = 4.1, 4.1 Hz, H-7), 6.18 (1H, d, J = 4.9 Hz, H-1), 6.34 (1H, s, H-3), 6.34 (1H, d, J = 15.8 Hz, coumaroyl H-2), 6.80 (2H, d, J = 8.5 Hz, coumaroyl H-6, 8), 7.46 (2H, d, J = 8.5 Hz, coumaroyl H-5, 9), 7.61 (1H, d, J = 15.8 Hz, coumaroyl H-3); ^{13}C NMR, see Table 3; FABMS *m/z* 485 [M + Na]$^+$, 147 (80), 85 (20); HRFABMS *m/z* 485.1787 (calcd 485.1788 for $C_{24}H_{30}O_9Na$).

Acetylation of 5. A solution of **5** (3.5 mg) in acetic anhydride (0.5 mL) and pyridine (1.0 mL) was stood at room temperature for 12 h. The mixture was condensed under reduced pressure to give a residue, which was purified by preparative TLC ($CHCl_3$−EtOAC, 1:1) to afford a triacetate of **5** as a colorless oil: IR (film) ν_{max} 3479 (OH), 1769, 1731 (C=O), 1697 (conjugated C=O), 1582, 1505 (aromatic) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (6H, d, J = 6.6 Hz, H_3-4′, 5′), 2.06 (3H, s), 2.09 (3H, s), 2.12 (1H, tq, J = 7.0, 6.6 Hz, H-3′), 2.25 (2H, d, J = 7.0 Hz, H-2′), 2.32 (3H, s), 2.50 (1H, dd, J = 9.5, 4.7 Hz, H-9), 2.95 (1H, m, H-5), 4.25 (2H, s, H-11), 4.64 (1H, d, J = 12.4 Hz, H-10), 4.64 (1H, d, J = 12.4 Hz, H-10), 5.17 (1H, t, J = 4.7 Hz, H-7), 6.45 (1H, s, H-3), 6.35 (1H, d, J = 4.7

Hz, H-1), 6.38 (1H, d, J = 15.8 Hz, coumaroyl H-2), 7.15 (2H, d, J = 8.5 Hz, coumaroyl H-6, 8), 7.55 (2H, d, J = 8.5 Hz, H-5, 9), 7.65 (1H, d, J = 15.8 Hz, H-3); HRFABMS *m/z* 611.2090 (calcd 611.2104 for $C_{30}H_{36}O_{12}Na$).

Luzonoid B (6): yellow oil; $[\alpha]^{21}_{D}$ −53.7° (c 2.11, MeOH); IR (film) ν_{max} 3443 (OH), 1736 (C=O), 1697 (conjugated C=O), 1590, 1514 (aromatic); UV (EtOH) λ_{max} 314 (ϵ 16 500), 300 (ϵ 14 200), 230 (ϵ 9800) nm; ^{1}H NMR (CD_3OD) δ 0.96 (6H, d, J = 6.6 Hz, H-4′, 5′), 2.09 (1H, tq, J = 7.1, 6.6 Hz, H-3′), 2.09 (1H, ddd, J = 11.3, 8.2, 4.0 Hz, H-6), 2.11 (1H, ddd, J = 11.3, 8.2, 4.0 Hz, H-6), 2.22 (2H, d, J = 7.1 Hz, H_2-2′), 2.26 (1H, dd, J = 9.9, 4.7 Hz, H-9), 2.92 (1H, ddd, J = 9.9, 8.2, 8.2 Hz, H-5), 3.57 (1H, d, J = 11.3 Hz, H-10), 3.61 (1H, d, J = 11.3 Hz, H-10), 3.92 (1H, d, J = 12.6 Hz, H-11), 4.08 (1H, d, J = 12.6 Hz, H-11), 5.02 (1H, dd, J = 4.0, 4.0 Hz, H-7), 5.78 (1H, d, J = 12.6 Hz, coumaroyl H-2), 6.14 (1H, d, J = 4.7 Hz, H-1), 6.31 (1H, s, H-3), 6.75 (2H, d, J = 8.7 Hz, coumaroyl H-6, 8), 6.90 (1H, d, J = 12.6 Hz, coumaroyl H-3), 7.58 (2H, d, J = 8.7 Hz, coumaroyl H-5, 9); ^{13}C NMR, see Table 3; FABMS *m/z* 485 [M + Na]$^+$, 147 (89), 85 (32); HRFABMS *m/z* 485.1775 [M + Na]$^+$ (calcd 485.1788 for $C_{24}H_{30}O_9Na$).

Luzonoid C (7): yellow oil; $[\alpha]^{21}_{D}$ −54.1° (c 0.35, MeOH); IR (film) ν_{max} 3379 (OH), 1739 (C=O), 1691 (conjugated C=O), 1587, 1515 (aromatic) cm^{-1}; UV (EtOH) λ_{max} 314 (ϵ 12 700), 300 (ϵ 10 700), 228 (ϵ 6480) nm; ^{1}H NMR (CD_3OD) δ 0.93 (6H, d, J = 6.9 Hz, H_3-4′, 5′), 2.01 (1H, ddd, J = 10.3, 8.4, 4.0 Hz, H-6), 2.03 (1H, ddd, J = 10.3, 8.4, 4.0 Hz, H-6), 2.07 (1H, tq, J = 7.4, 6.9 Hz, H-3′), 2.21 (2H, m, H_2-2′), 2.44 (1H, dd, J = 10.2, 4.4 Hz, H-9), 3.05 (1H, ddd, J = 10.2, 8.4, 8.4 Hz, H-5), 3.93 (1H, d, J = 12.6 Hz, H-11), 4.02 (1H, dd, J = 4.0, 4.0 Hz, H-7), 4.08 (1H, d, J = 12.6 Hz, H-11), 4.38 (2H, s, H-10), 6.30 (1H, s, H-3), 6.31 (1H, d, J = 4.4 Hz, H-1), 6.38 (1H, d, J = 16.1 Hz, coumaroyl H-2), 6.80 (2H, d, J = 8.5 Hz, coumaroyl H-6, 8), 7.48 (2H, d, J = 8.5 Hz, coumaroyl H-5, 9), 7.68 (1H, d, J = 16.1 Hz, coumaroyl H-3); ^{13}C NMR, see Table 3; FABMS *m/z* 485 [M + Na]$^+$, 147 (43), 85 (16); HRFABMS *m/z* 485.1770 (calcd 485.1788 for $C_{24}H_{30}O_9Na$).

Luzonoid D (8): yellow oil; $[\alpha]^{21}_{D}$ −43.3° (c 1.03, MeOH); IR (film) ν_{max} 3409 (OH), 1733 (C=O), 1696 (conjugated C=O), 1586, 1513 (aromatic) cm^{-1}; UV (EtOH) λ_{max} 313 (ϵ 12 400), 300 (ϵ 10 700), 225 (ϵ 11 000) nm; ^{1}H NMR (CD_3OD) δ 0.94 (6H, d, J = 6.9 Hz, H_3-4′, 5′), 1.98 (1H, ddd, J = 11.5, 8.4, 3.8 Hz, H-6), 2.02 (1H, ddd, J = 11.5, 8.4, 3.8 Hz, H-6), 2.07 (1H, tq, J = 7.7, 6.9 Hz, H-3′), 2.20 (2H, m, H_2-2′), 2.38 (1H, dd, J = 10.2, 4.4 Hz, H-9), 3.02 (1H, ddd, J = 10.2, 8.4, 8.4 Hz, H-5), 3.92 (1H, d, J = 12.5 Hz, H-11), 3.97 (1H, dd, J = 3.8, 3.8 Hz, H-7), 4.06 (1H, d, J = 12.5 Hz, H-11), 4.31 (1H, d, J = 11.5 Hz, H-10), 4.35 (1H, d, J = 11.5 Hz, H-10), 5.86 (1H, d, J = 12.8 Hz, coumaroyl H-2), 6.20 (1H, d, J = 4.4 Hz, H-1), 6.29 (1H, s, H-3), 6.74 (2H, d, J = 8.8 Hz, coumaroyl H-6, 8), 6.87 (1H, d, J = 12.8 Hz, coumaroyl H-3), 7.67 (2H, d, J = 8.8 Hz, coumaroyl H-5, 9); ^{13}C NMR, see Table 3; FABMS *m/z* 485 [M + Na]$^+$, 147 (100), 85 (61); HRFABMS *m/z* 485.1808 (calcd 485.1788 for $C_{24}H_{30}O_9Na$).

Luzonoid E (9): yellow oil; $[\alpha]^{21}_{D}$ +54.1° (c 0.21, MeOH); IR (film) ν_{max} 3422 (OH), 1732 (C=O), 1687 (conjugated C=O), 1587, 1515 (aromatic) cm^{-1}; UV (EtOH) λ_{max} 315 (ϵ 20 600), 300 (ϵ 17 100), 229 (ϵ 10 600) nm; ^{1}H NMR (CD_3OD) δ 0.91 (3H, dd, J = 7.4, 7.4 Hz, H_3-6′), 0.95 (3H, d, J = 6.6 Hz, H_3-4′), 1.25 (1H, ddq, J = 14.8, 7.4, 7.4 Hz, H-5′), 1.40 (1H, ddq, J = 14.8, 7.6, 7.4 Hz, H-5′), 1.87 (1H, m, H-3′), 2.12 (1H, ddd, J = 11.5, 8.1, 4.1 Hz, H-6), 2.15 (1H, ddd, J = 11.5, 8.1, 4.1 Hz, H-6), 2.14 (1H, dd, J = 14.8, 8.2 Hz, H-2′), 2.35 (1H, dd, J = 14.8, 6.0 Hz, H-2′), 2.43 (1H, dd, J = 9.9, 4.9 Hz, H-9), 3.02 (1H, ddd, J = 9.9, 8.1, 8.1 Hz, H-5), 3.68 (1H, d, J = 11.5 Hz, H-10), 3.75 (1H, d, J = 11.5 Hz, H-10), 3.94 (1H, d, J = 12.5 Hz, H-11), 4.09 (1H, d, J = 12.5 Hz, H-11), 5.08 (1H, dd, J = 4.1, 4.1 Hz, H-7), 6.17 (1H, d, J = 4.9 Hz, H-1), 6.34 (1H, s, H-3), 6.34 (1H, d, J = 15.8 Hz, coumaroyl H-2), 6.80 (2H, d, J = 8.7 Hz, coumaroyl H-6, 8), 7.61 (1H, d, J = 15.8 Hz, coumaroyl H-3), 7.47 (2H, d, J = 8.7 Hz, coumaroyl H-5, 9); ^{13}C NMR, see Table 3; FABMS *m/z* 499 [M + Na]$^+$, 147 (62), 99 (20); HRFABMS *m/z* 499.1939 (calcd 499.1944 for $C_{25}H_{32}O_9Na$).

Luzonoid F (10): colorless oil; $[\alpha]^{21}_{D}$ −32.1° (c 2.10, MeOH); IR (film) ν_{max} 3428 (OH), 1734 (C=O), 1688 (conjugated C=O), 1590, 1514 (aromatic) cm^{-1}; UV (EtOH) λ_{max} 315 (ϵ 21 400), 300 (ϵ 18 300), 226 (ϵ 18 000) nm; ^{1}H NMR (CD_3OD) δ 0.91 (3H, dd, J = 7.4, 7.4 Hz, H_3-6′), 0.94 (3H, d, J = 6.6 Hz, H_3-4′), 1.24 (1H, ddq, J = 14.8, 7.4, 7.4 Hz, H-5′), 1.39 (1H, ddq, J = 14.8, 7.6, 7.4 Hz, H-5′), 1.86 (1H, m, H-3′), 2.09 (1H, ddd, J = 11.0, 8.5, 4.0 Hz, H-6), 2.11 (1H, ddd, J = 11.0, 8.5, 4.0 Hz, H-6), 2.14 (1H, dd, J = 15.1, 8.1 Hz, H-2′), 2.26 (1H, dd, J = 10.0, 4.7 Hz, H-9), 2.35 (1H, dd, J = 15,1, 6.0 Hz, H-2′), 2.92 (1H, ddd, J = 9.9, 8.5, 8.5 Hz, H-5), 3.57 (1H, d, J = 11.5 Hz, H-10), 3.61 (1H, d, J = 11.5 Hz, H-10), 3.93 (1H, d, J = 12.4 Hz, H-11), 4.08 (1H, d, J = 12.4 Hz, H-11), 5.02 (1H, dd, J = 4.0, 4.0 Hz, H-7), 5.78 (1H, d, J = 12.6 Hz, coumaroyl H-2), 6.14 (1H, d, J = 4.7 Hz, H-1), 6.31 (1H, s, H-3), 6.75 (2H, d, J = 8.7 Hz, coumaroyl H-6, 8), 6.91 (1H, d, J = 12.6 Hz, coumaroyl H-3), 7.58 (2H, d, J = 8.7 Hz, coumaroyl H-5, 9); ^{13}C NMR, see Table 3; FABMS *m/z* 499 [M + Na]$^+$, 147 (55), 99 (12); HRFABMS *m/z* 499.1909 (calcd 499.1944 for $C_{25}H_{32}O_9Na$).

Luzonoid G (11): colorless oil; $[\alpha]^{21}_{D}$ −36.1° (c 0.80, MeOH); IR (film) ν_{max} 3380 (OH), 1738 (C=O), 1689 (conjugated C=O), 1588, 1515 (aromatic) cm^{-1}; UV (EtOH) λ_{max} 314 (ϵ 12 800), 300 (ϵ 10 900), 226 (ϵ 7490) nm; ^{1}H NMR (CD_3OD) δ 0.86 (3H, dd, J = 7.4, 7.4 Hz, H_3-6′), 0.91 (3H, d, J = 6.9 Hz, H_3-4′), 1.20 (1H, ddq, J = 14.1, 7.4, 6.0 Hz, H-5′), 1.35 (1H, ddq, J = 14.1, 7.4, 6.0 Hz, H-5′), 1.87 (1H, m, H-3′), 2.01 (1H, ddd, J = 11.9, 8.8, 4.0 Hz, H-6), 2.03 (1H, ddd, J = 11.9, 8.8, 4.0 Hz, H-6), 2.13 (1H, dd, J = 14.9, 8.2 Hz, H-2′), 2.33 (1H, dd, J = 14.9, 6.2 Hz, H-2′), 2.44 (1H, dd, J = 9.9, 4.1 Hz, H-9), 3.04 (1H, ddd, J = 9.9, 8.8, 8.8 Hz, H-5), 3.93 (1H, d, J = 12.5 Hz, H-11), 4.02 (1H, dd, J = 4.0, 4.0 Hz, H-7), 4.08 (1H, d, J = 12.5 Hz, H-11), 4.36 (1H, d, J = 11.5 Hz, H-10), 4.38 (1H, d, J = 11.5 Hz, H-10), 6.30 (1H, s, H-3), 6.31 (1H, d, J = 4.4 Hz, H-1), 6.39 (1H, d, J = 15.8 Hz, coumaroyl H-2), 6.80 (1H, d, J = 8.5 Hz, coumaroyl H-6, 8), 7.68 (1H, d, J = 15.8 Hz, coumaroyl H-3), 7.48 (2H, d, J = 8.5 Hz, coumaroyl H-5, 9); ^{13}C NMR, see Table 3; FABMS *m/z* 499 [M + Na]$^+$, 147 (74), 99 (20); HRFABMS *m/z* 499.1929 (calcd 499.1944 for $C_{25}H_{32}O_9Na$).

Cell Proliferation Assay. The cell proliferation assay was carried out using a cell counting kit (Wako Pure Chemical Industries ltd., Osaka, Japan). In brief, HeLa S3 cells were plated in 384-well plates at a density of 500 cells/well in minimum essential medium. Following overnight culture, drugs were added to final concentrations of 0.1, 1, 10, and 100 μM, and the cells were incubated for 72 h. After 72 h, WST-1 [2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2*H* tetrazolium, monosodium salt] was added according to the manufacturer's protocol and the cells were incubated for a further 2 h. The plates were read at a wavelength of 450 nm using a Wallac 1420 ARVOsx microplate reader (Perkin-Elmer Life and Analytical Sciences, Inc., Boston, MA).

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