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2,4-Diaryl-5*H*-chromeno [4,3-*b*]pyridines: Synthesis, Topoisomerase I and II Inhibitory Activity, and Cytotoxicity

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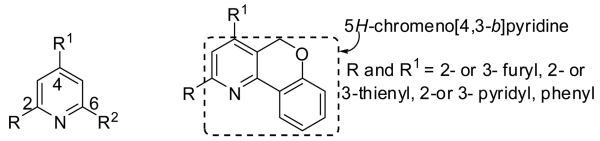
Topoisomerase enzyme, since its discovery, has been a promising target for the discovery of anticancer agents.[1] In our earlier study, we have designed and synthesized flexible 2,4,6-trisubstituted pyridine derivatives and studied their topoisomerase inhibitory activity and cytotoxicity against several human cancer cell lines.[2] Further optimization of the flexible 2,4,6-trisubstituted pyridine derivatives led us to synthesize various rigid analogues.[3] In continuation of the previously reported chromeno[4,3-*b*]pyridine derivatives,[3b] herein we have prepared eleven 2,4-diaryl-5*H*-chromeno-[4,3-*b*]pyridine derivatives (Figure 1(b)). All compounds were evaluated for their topoisomerase I and II inhibitory activity and cytotoxicity against several human cancer cell lines. Prepared compounds contain rigid chromeno[4,3-*b*]pyridine skeleton at one side of the central pyridine. Chromeno[4,3-*b*]pyridine and chromene skeleton were found to have a wide range of biological activities such as estrogen receptor β-selective ligand,[4] TNF-α inhibition,[5] and anti-inflammatory activity.[6]

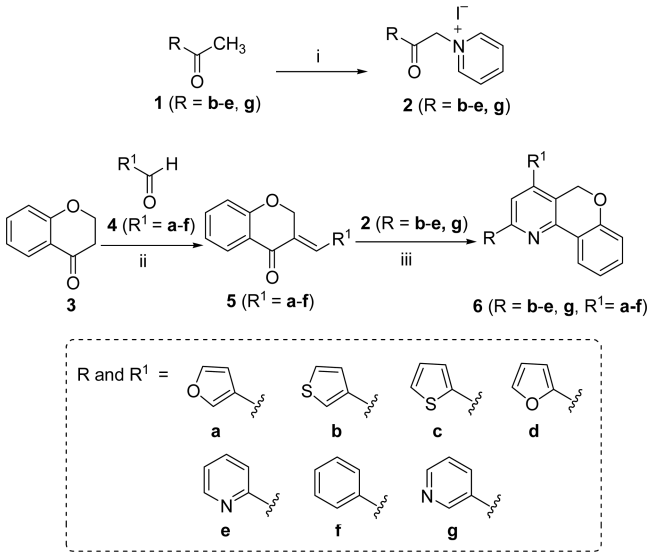
Results and Discussion

Synthetic Chemistry. At first, pyridinium iodide salts **2** (R = **b-e**, **g**) were synthesized by refluxing aryl methyl ketones **1** (R = **b-e**, **g**) with iodine and pyridine at 140 °C for 3 h in 72.5-96.2% yield. Secondly, on the basis of Claisen-schmidt condensation reaction,[7] 4-chromanone derivatives **5** (R^1 = **a-f**) were synthesized by reacting 4-chromanone (**3**) with various aryl aldehydes **4** (R^1 = **a-f**) in the presence of NaOH and ethanol at room temperature as illustrated in Scheme 1. Compounds **5** (R^1 = **a-f**) were obtained in 46.1-90.5% yield. Finally, on the basis of modified Kröhnke synthesis,[8] 2,4-diaryl-5*H*-chromeno[4,3-*b*]pyridine derivatives **6** (R = **b-e**, **g**, R^1 = **a-f**) were synthesized by reacting 4-chromanone derivatives **5** (R^1 = **a-f**) and pyridinium iodide salts **2** (R = **b-e**, **g**) in the presence of NH_4OAc and glacial acetic acid for 12-24 h at 100-110 °C. Eleven rigid analogues, 2,4-diaryl-5*H*-chromeno[4,3-*b*]pyridine derivatives (**7-17**), were synthesized in 7.5-51.9% yield as shown in Figure 2.



(a) 2,4,6-trisubstitued pyridines (b) 2,4-diaryl-5*H*-chromeno[4,3-*b*]pyridine

Figure 1. Structure of (a) 2,4,6-trisubstituted pyridines, and (b) 2,4-diaryl-5*H*-chromeno[4,3-*b*]pyridine.



Scheme 1. Synthesis of 2,4-diaryl-5*H*-chromeno[4,3-*b*]pyridine derivatives, Reagents and conditions; i) I_2, pyridine, 140 °C, 3 h, 72.5-96.2%; ii) NaOH, EtOH, room temperature, 46.1-90.5% ; iii) NH_4OAc, glacial AcOH, 12-24 h, 100-110 °C, 7.5-51.9%.

Topo I and II Inhibitory Activity. Synthesized 2,4-diaryl-5*H*-chromeno[4,3-*b*]pyridine derivatives (**7-17**) were evaluated for their topo I and II inhibitory activities. The results of topo inhibitory activities of evaluated compounds are displayed in Figure 3, and Table 1. Camptothecin and etoposide, well known topo I and II inhibitors respectively, were used as positive controls.

Compounds **7-17** were evaluated for topo I inhibitory activity both at 100 and 20 μM concentration. It is found that entire compounds showed strong topo I inhibitory activity in the range of 61.3-96.0% (as compared to 57.5% of camptothecin) at 100 μM. Compound **17** showed the most significant activity. Only compound **8** showed topo I inhibition of 17.0% (as compared to 18.4% of camptothecin) at 20 μM. The topo I inhibitory activity of evaluated compounds is summarized in Figure 3, and Table 1.

Compounds **7-17** were tested for topo II inhibition at 100 μM and only those with considerable topo II inhibitory activity at 100 μM were evaluated for 20 μM. From the

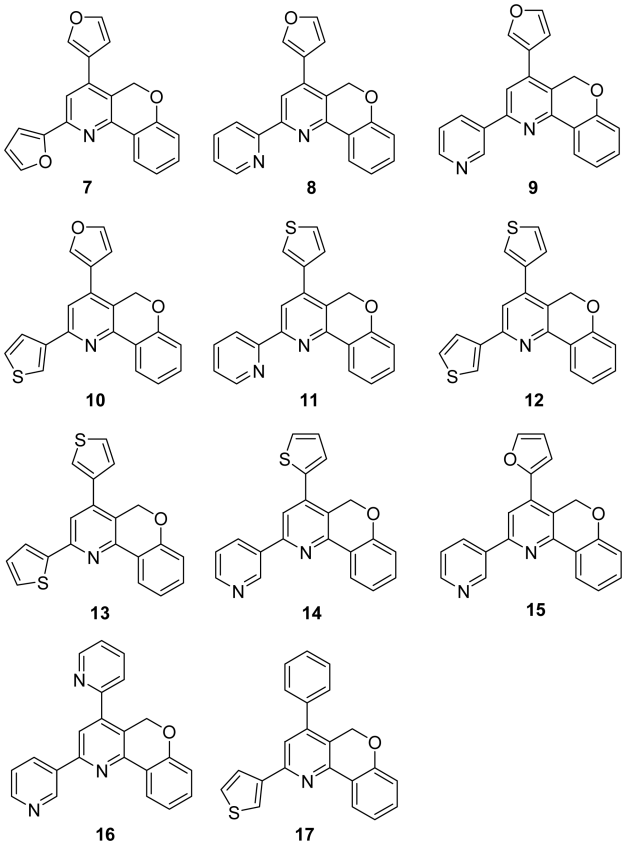


Figure 2. Structure of synthesized 2,4-diaryl-chromeno[4,3-*b*]pyridines.

results, compounds **7**, **10**, **12**, **13**, and **17** showed considerable topo II inhibitory activity in the range of 62.3-100% (as compared to 88.7% of etoposide) at 100 μM. Among them, compound **17** showed the higher topo II inhibitory activity (100%) than etoposide.

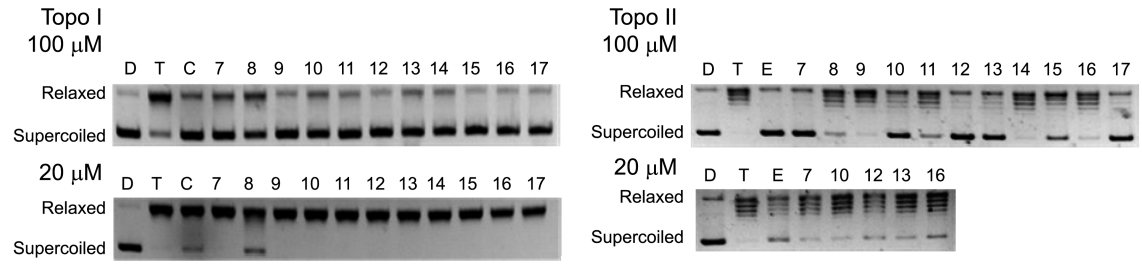
Cytotoxicity. All compounds **7-17** were evaluated for cytotoxicity against four different human cancer cell lines: human embryonic kidney cell line (HEK293), human prostate tumor cell line (DU145), human colorectal adenocarcinoma cell line (HCT15) and human breast ductal carcinoma cell line (T47D). Inhibitory activities were presented as micromolar concentrations of the compounds that cause 50% inhibition of cell growth (IC_{50}) under the assay conditions and compared with that of adriamycin. The cytotoxicity results are summarized in Table 1. Among the tested compounds, **7**, **14**, and **15** has shown the moderate cytotoxicity against all four cancer cell lines. Rest of the compounds has shown weaker cytotoxicity against all tested cancer cell lines. No direct correlation between cytotoxicity and topoisomerase inhibitory activity was observed.

Structure-Activity Relationship (SAR) Study. SAR was performed according to the results of topo I and II inhibitory activity and cytotoxicity of the evaluated compounds. All compounds **7-17** showed considerable topo I inhibitory activity better than camptothecin at 100 μM. Compounds **7**, **10**, **12**, **13**, and **17** showed considerable topo II inhibitory activity but lesser than etoposide. This indicates the importance of rigid planar structure for topo I inhibitory activity over topo II inhibitory activity. Since all compounds showed weaker cytotoxicity, concrete SAR could not be determined regarding cytotoxicity.

In conclusion, we have designed and synthesized eleven 2,4-diaryl-5*H*-chromeno[4,3-*b*]pyridine derivatives (**7-17**) as rigid analogues of 2,4,6-trisubstituted pyridine and evaluated their topo I and II inhibitory activity, and cytotoxicity against several human cancer cell lines. All the prepared compounds showed strong topo I inhibitory activity at 100 μM. Similarly, several compounds showed good topo II inhibitory activity at 100 μM. Compound **17** showed the most significant topo I and II inhibitory activity at 100 μM. SAR revealed the importance of rigid structure for topo I inhibitory activity.

Experimental Section

Compounds used as starting materials and reagents were obtained from Aldrich Chemicals Co., Junsei or other chemical companies, and utilized without further purification. HPLC grade acetonitrile (ACN) and methanol were purchased from Burdick and Jackson, USA. Thin-layer chromatography (TLC) and column chromatography (CC) were performed with Kieselgel 60 F_{254} (Merck) and silica gel (Kieselgel 60, 230-400 mesh, Merck), respectively. NMR spectra were recorded on a Bruker AMX 250 (250 MHz, FT) for ^{1}H NMR and 62.5 MHz for ^{13}C NMR, and chemical shifts were calibrated to solvent peaks. Chemical shifts (δ) were recorded in ppm and coupling constants (J) in hertz (Hz). Melting points were



Lane D: pBR322 only,
Lane T: pBR322+Topo I or Topo II
Lane C: pBR322+Topo I+camptothecin,
Lane E: pBR322+Topo II+etoposide
Lane **7-17**: pBR322+Topo I or Topo II+samples (**7-17**) at 100 or 20 μM

Figure 3. Topo I and II inhibitory activity of synthesized compounds at 100 μM and 20 μM.

Table 1. Topoisomerase I and II inhibitory activity of compounds **7-17**

Compounds	Topo I (% Inhibition)		Topo II (% Inhibition)		IC_{50} (μM)			
	100 μM	20 μM	100 μM	20 μM	[a]HEK293	[b]DU145	[c]HCT15	[d]T47D
[e]**Adriamycin**					1.59 ± 0.02	1.76 ± 0.01	1.74 ± 0.32	1.61 ± 0.17
[f]**Etoposide**			88.7	32.3	1.54 ± 0.16	1.89 ± 0.02	2.74 ± 0.23	2.08 ± 0.05
[g]**Camptothecin**	57.5	18.4			1.54 ± 0.19	1.77 ± 0.01	2.47 ± 0.18	2.20 ± 0.15
7	69.2	1.2	79.3	7.1	13.34 ± 0.98	11.75 ± 1.35	11.37 ± 1.13	13.49 ± 1.08
8	61.3	17.0	11.2	ND	>50	>50	>50	>50
9	77.9	N	3.1	ND	>50	>50	>50	>50
10	66.7	N	62.3	3.6	>50	>50	>50	>50
11	80.4	N	11.4	ND	>50	>50	>50	>50
12	81.7	N	79.5	15.5	>50	>50	>50	>50
13	75.7	N	64.6	6.6	>50	>50	>50	>50
14	80.5	N	1.3	ND	12.47 ± 1.21	13.93 ± 0.57	19.01 ± 1.86	17.78 ± 1.58
15	87.2	N	19.1	ND	10.64 ± 0.62	12.09 ± 1.72	19.02 ± 1.20	18.03 ± 1.08
16	90.9	N	N	ND	>50	>50	>50	>50
17	96.0	N	100	12.2	>50	>50	>50	>50

N: none, ND: Not determined. Each data represents mean S.D. from three different experiments performed in triplicate; [a]HEK293: human embryonic kidney cell line. [b]DU145: human prostate tumor. [c]HCT15 human colorectal adenocarcinoma. [d]T47D: Human breast ductal carcinoma. [e]Adriamycin: positive control for cytotoxicity. [f]Etoposide: positive control for topo II and cytotoxicity. [g]Camptothecin: positive control for topo I and cytotoxicity.

determined in open capillary tubes on electrothermal 1A 9100 digital melting point apparatus and were uncorrected.

HPLC analyses were performed using previously reported method.[3c] Purity of compound is described as percent (%) and retention time is given in minutes. ESI MS analyses were performed with API 4000 LC-MS/MS system (Applied Biosystems, Foster City, CA, USA) equipped with an electrospray ionization interface. The Turbolon Spray (Applied Biosystems, Foster City, CA, USA) interface was operated in the positive ion mode at 5500 V and 450 °C.

General Method for Preparation of 2 (R = b-e, g). Aryl methyl ketones **1** (R = **b-e**, **g**) with equivalent amount of iodine in pyridine was refluxed at 140 °C for 3 h. Precipitate occurred during reaction was cooled to room temperature. Then it was filtered and washed with cold pyridine followed by drying overnight to yield 72.5-96.2% of **2** (R = **b-e**, **g**).

General Method for the Preparation of 5 (R^1 = a-f). Aryl aldehydes **4** (R^1 = **a-f**) (1.0 equiv), and **3** (1.0 equiv) were dissolved in ethanol and 5% aqueous solution of NaOH was added dropwise to the mixture at room temperature. On addition of NaOH, precipitation was observed, cooled for 30 min, filtered, and washed with water and cold methanol. Compounds **5** (R^1 = **a-f**) were obtained in the yield of 46.1-90.5%.

General Method for the Preparation of 6 (R = b-e, g, R^1 = a-f). 5 (R^1 = **a-f**) (1.0 equiv), pyridinium iodide salts **2** (R = **b-e**, **g**) (1.0 equiv) and NH_4OAc (10.0 equiv) in glacial AcOH was heated at 100-110 °C for 12-24 h under nitrogen gas. The reaction mixture was then extracted with ethyl acetate, washed with water and brine solution. The organic layer was dried with magnesium sulfate and filtered. The filtrate was evaporated at reduced pressure, which was then purified with silica gel column chromatography with the gradient elution of ethyl acetate/*n*-hexane to afford solid compounds **7-17** in 7.5-51.9% yield.

2-(Furan-2-yl)-4-(furan-3-yl)-5*H*-chromeno[4,3-*b*]pyridine (7): White solid (20.1%), TLC (EtOAc/*n*-hexane 1:5 v/v), R_f = 0.30, mp 105.3-108.1 °C, HPLC: purity: 95.8%, retention time: 6.78 min, ESI MS: $[MH]^+$: 316.2, ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.35 (dd, J = 7.7, 1.4 Hz, 1H, chromeno H-10), 7.60-7.54 (m, 4H, pyridine H-3, 2-furan H-5, 4-furan H-2 and H-5), 7.33 (td, J = 8.1, 1.6 Hz, 1H, chromeno H-8), 7.22 (d, J = 4.3 Hz, 1H, 2-furan H-3), 7.13 (td, J = 7.6, 1.0 Hz, 1H, chromeno H-9), 6.97 (d, J = 8.1 Hz, 1H, chromeno H-7), 6.60 (dd, J = 1.5, 0.9 Hz, 1H, 4-furan H-4), 6.56 (dd, J = 3.3, 1.7 Hz, 1H, 2-furan H-4), 5.34 (s, 2H, chromeno -CH_2-); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.23, 153.70, 148.79, 148.56, 143.80, 143.22, 141.02, 137.69, 131.26, 125.21, 123.28, 122.31, 122.17, 121.92, 116.97, 116.69, 112.10, 110.54, 108.92, 65.85.

4-(Furan-3-yl)-2-(thiophen-3-yl)-5*H*-chromeno[4,3-*b*]-pyridine (10): Light yellow solid (8.2%), TLC (EtOAc/*n*-hexane 1:5 v/v), R_f = 0.50, mp 185.9-188.6 °C, HPLC: purity: 97.4%, retention time: 7.62 min, ESI MS: $[MH]^+$: 332.32, ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.40 (dd, J = 7.7, 1.6 Hz, 1H, chromeno H-10), 8.02 (dd, J = 3.0, 1.2 Hz, 1H, 2-thiophene H-2), 7.78 (dd, J = 5.0, 1.2 Hz, 1H, 2-thiophene H-4), 7.59-7.57 (m, 2H, 4-furan H-2, H-5), 7.50 (s, 1H, pyridine H-3), 7.42 (dd, J = 5.0, 3.0 Hz, 1H, 2-thiophene H-5), 7.33 (td, J = 7.7, 1.7 Hz, 1H, chromeno H-8), 7.14 (td, J = 7.5, 1.1 Hz, 1H, chromeno H-9), 6.90 (dd, J = 8.1, 0.8 Hz, 1H, chromeno H-7), 6.60 (dd, J = 1.7, 0.8 Hz, 1H, 4-furan H-4), 5.34 (s, 2H, chromeno -CH_2-); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.23, 152.53, 148.66, 143.83, 141.99, 140.90, 137.77, 131.19, 126.24, 125.18, 123.71, 123.46, 122.26, 122.21, 121.79, 118.81, 116.69, 110.54, 65.82.

2,4-Di(thiophen-3-yl)-5*H*-chromeno[4,3-*b*]pyridine (12): Yellow solid (7.5%), TLC (EtOAc/*n*-hexane 1:5 v/v), R_f = 0.50, mp 162.5-165.2 °C, HPLC: purity: 95.6%, retention time: 8.64 min, ESI MS: $[MH]^+$: 348.2, ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.40 (dd, J = 7.8, 1.5 Hz, 1H, chromeno H-10), 8.03 (dd, J = 3.0, 1.0 Hz, 1H, 2-thiophene H-2), 7.77 (dd, J =

5.0, 1.0 Hz, 1H, 2-thiophene H-4), 7.53 (s, 1H, pyridine H-3), 7.50 (dd, J = 5.0, 2.0 Hz, 1H, 4-thiophene H-5), 7.42 (dd, J = 5.0, 3.0 Hz, 1H, 2-thiophene H-5), 7.37-7.30 (m, 2H, chromeno H-8 and 4-thiophene H-2), 7.20 (dd, J = 4.8, 1.1 Hz, 1H, 4-thiophene H-4), 7.14 (td, J = 7.5, 1.1 Hz, 1H, chromeno H-9), 6.96 (d, J = 8.0 Hz, 1H, chromeno H-7), 5.31 (s, 2H, chromeno -CH_2-); ^{13}C NMR (62.5 MHz, $CHCl_3$) δ 156.32, 152.44, 148.74, 142.04 141.76, 137.85, 131.19, 127.80, 126.72, 126.27, 126.23, 125.22, 124.45, 123.72, 123.60, 122.27, 121.81, 119.33, 116.73, 65.93.

2-(Thiophen-2-yl)-4-(thiophen-3-yl)-5*H*-chromeno[4,3-*b*]pyridine (13): Yellow solid (51.9%), TLC (EtOAc/*n*-hexane 1:5 v/v), R_f = 0.50, mp 121.9-124.8 °C, HPLC: purity: 95.3%, retention time: 8.80 min, ESI MS: $[MH]^+$: 348.2, ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.38 (dd, J = 8.6, 1.3 Hz, 1H, chromeno H-10), 7.65 (dd, J = 3.6, 1.0 Hz, 1H, 2-thiophene H-3), 7.55 (s, 1H, pyridine H-3), 7.48 (dd, J = 2.9, 1.9 Hz, 1H, 4-thiophene H-2), 7.42 (d, J = 4.9 Hz, 1H, 2-thiophene H-5), 7.37-7.31 (m, 2H, 4-thiophene H-5 and chromeno H-8), 7.20 (d, J = 4.9 Hz, 1H, 4-thiophene H-4), 7.15-7.11 (m, 2H, chromeno H-9 and 2-thiophene H-4), 6.96 (d, J = 8.0 Hz, 1H, chromeno H-7), 5.30 (s, 2H, chromeno -CH_2-); ^{13}C NMR (62.5 MHz, $CHCl_3$) δ 156.30, 151.58, 148.72, 144.92 141.78, 137.68, 131.30, 127.96, 127.76, 127.67, 126.75, 125.34, 124.59, 124.54, 123.30, 122.34, 121.92, 117.78, 116.68, 65.91.

4-Phenyl-2-(thiophen-3-yl)-5*H*-chromeno[4,3-*b*]pyridine (17): White solid (38.3%), TLC (EtOAc/*n*-hexane 1:5 v/v), R_f = 0.30, mp 114.2-115.9 °C, HPLC: purity: 97.4%, retention time: 9.33 min, ESI MS: $[MH]^+$: 342.2, ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.43 (dd, J = 7.6, 1.6 Hz, 1H, chromeno H-10), 8.03 (dd, J = 2.9, 1.1 Hz, 1H, 2-thiophene H-2), 7.78 (dd, J = 5.0, 1.1 Hz, 1H, 2-thiophene H-5), 7.53-7.49 (m, 4H, pyridine H-3, 4-phenyl H-2,6 and chromeno H-8), 7.41 (dd, J = 5.0, 3.0 Hz, 1H, 2-thiophene H-4), 7.36-7.30 (m, 3H, 4-phenyl H-3,4,5), 7.15 (td, J = 7.6, 1.0 Hz, 1H, chromeno H-9), 6.97 (dd, J = 8.0, 0.8 Hz, 1H, chromeno H-7), 5.23 (s, 2H, chromeno -CH_2-); ^{13}C NMR (62.5 MHz, $CHCl_3$) δ 156.41, 152.38, 148.68, 147.26 142.10, 137.41, 131.18, 128.75, 128.60, 128.40, 126.30, 126.21, 125.24, 123.71, 123.68, 122.26, 121.80, 119.72, 116.74, 65.90.

Pharmacology. DNA topo I and II inhibition assays were determined following the previously reported method.[2(l)] Cytotoxicity was determined in four different cancer cell lines: human embryonic kidney cell line (HEK293), human prostate tumor cell line (DU145), human colorectal adenocarcinoma cell line (HCT15) and human breast ductal carcinoma cell line (T47D) by following the previously reported method.[2(l)] Cancer cells were cultured according to the supplier's instructions. Cells were seeded in 96-well plates at a density of 2~4 × 10^4 cells per well and incubated for overnight in 0.1 mL of media supplied with 10% Fetal Bovine Serum (Hyclone, USA) in 5% CO_2 incubator at 37 °C. On day 2, after FBS starvation for 4 h, culture medium in each well was exchanged with 0.1 mL aliquots of medium containing graded concentrations of compounds. On day 4, each well was added with 5 mL of the cell counting kit-8 solution (Dojindo, Japan) then incubated for additional 4 h under the same condition. The absorbance of each well was determined by an Automatic Elisa Reader System (Bio-Rad 3550) at 450 nm wavelength. For determination of the IC_{50} values, the absorbance readings at 450 nm were fitted to the four-parameter logistic equation. The compounds like adriamycin, etoposide, and camptothecin were purchased from Sigma and used as positive controls.

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