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Synthesis and Biology of 3′-*N*-Acyl-*N*-debenzoylpaclitaxel Analogues

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Abstract—The 3′-*N*-acyl-*N*-debenzoylpaclitaxel analogues **1a–d** were synthesized and evaluated on biological systems. Some of the analogues **1a–d** exhibited higher cytotoxicities (up to 20-fold) and stronger abilities to induce apoptosis than paclitaxel. In an in vivo experiment against ip implanted B16 melanoma, the most cytotoxic compound **1b** in vitro caused tumor growth inhibition more than paclitaxel.

Introduction

Paclitaxel (Taxol®), a highly functionalized diterpene originally isolated from the pacific yew (*Taxus brevifolia*), is rapidly emerging as one of the most promising antitumor compounds of the decade.[1] This compound promotes microtubule stabilization[2–6] and also induces cell death via apoptosis, a process characterized by cytoskeletal changes, chromatin condensation, and genomic DNA fragmentation.[7] In the past few years, the increasing evidences have suggested that the characteristics of tumor cell death may be the most important determinant for successful chemotheraphy.[8–12] Multiple studies have concluded that paclitaxel arrests the cell cycle at G1 or G2/M, with subsequent double-stranded DNA breaks consistent with apoptosis and correlate with cell death from this agent.[13] Recent evidence has supported these findings and confirmed the presence of chemotherapy-induced apoptosis in epithelial ovarian cancer after treatment with paclitaxel.[14,15]

Structure–activity studies[16] of the paclitaxel analogues have shown that both of the C-13 phenylisoserine side chain and the diterpene part are essential for bioactivity. The natural stereochemistry of the side chain at the 2′ and 3′-positions (2′*R*,3′*S*) is also essential for maximum antitumor activity.[17] Removal of the 2′-hydroxy group[18] or the 3′-benzamide moiety[19] produces paclitaxel analogues with substantial reduced bioactivity. Deletion of the 3′-phenyl group leads to inactive derivatives,[19] however, the compounds obtained by replacement of the 3′-phenyl group with lipophilic aliphatic substituents such as cyclohexyl,[20] isobutenyl group[21] exhibited excellent bioactivity. Although a large body of paclitaxel structure–activity relationships (SAR) has been generated, a detailed investigation of aliphatic analogues of similar size with phenyl group of 3′-*N*-benzoyl has received little attention. Only the analogues having linear alkyl group instead of phenyl group were assayed for microtubule binding affinity and cytotoxicity.[22] As stated above, apoptosis along with cytotoxicity is an important factor to evaluate chemotherapeutic agents. The induction of apoptosis with tumor cell selectivity may be more important than cytotoxicity involving normal cell killing. Here we report the synthesis of 3′-*N*-acyl-paclitaxel analogues **1a–d** (Fig. 1) which were found to be highly cytotoxic and showed the strong ability to induce apoptosis in vitro.

Key words: 3′-*N*-Acyl-*N*-debenzoylpaclitaxel analogues; cytotoxicity; apoptosis; structure–activity relationship.
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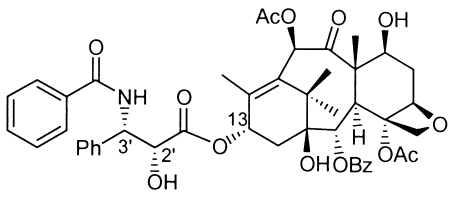
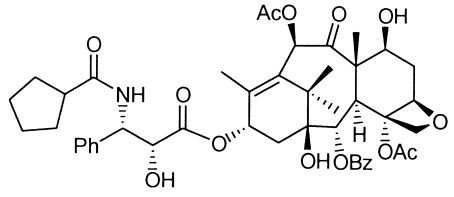
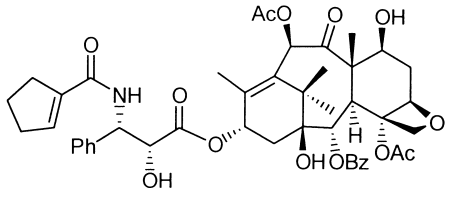


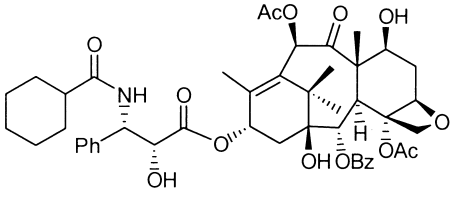
Paclitaxel (Taxol®)



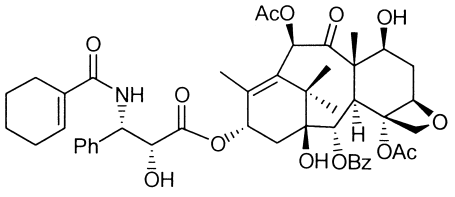
1a



1b



1c



1d

Figure 1.

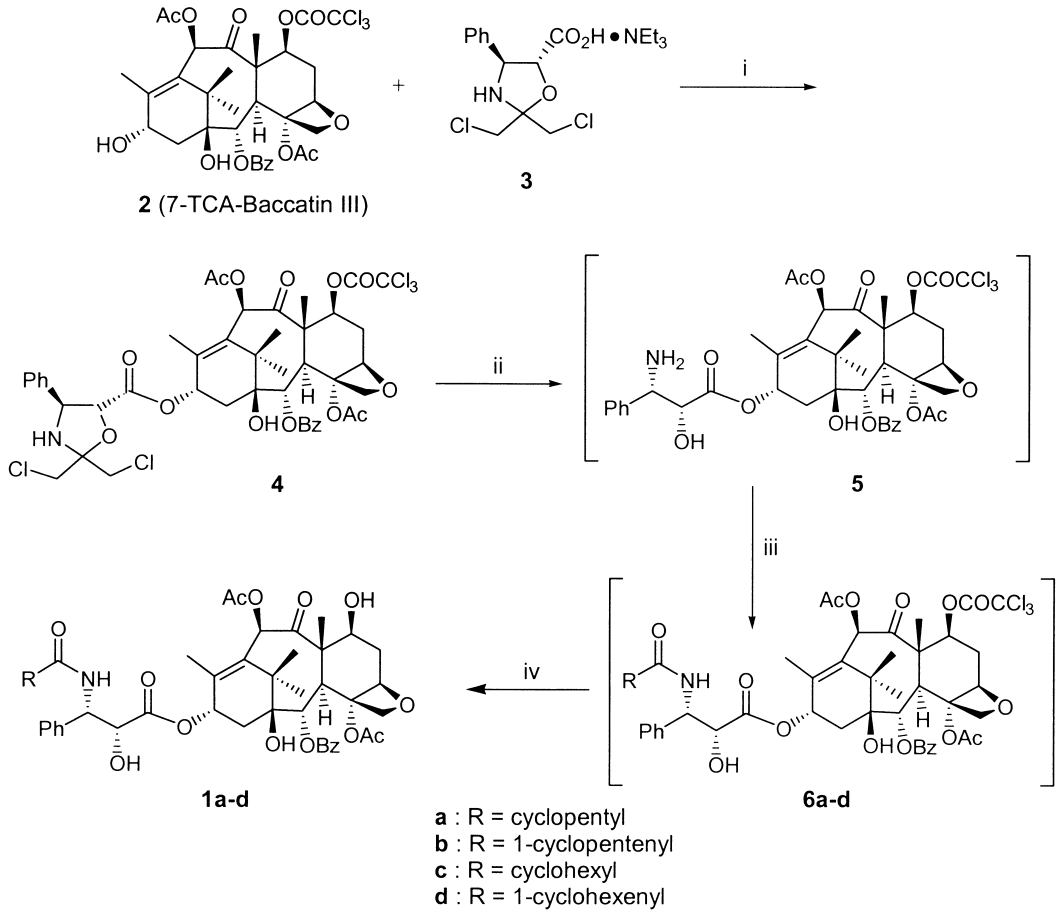
Chemistry

The synthetic route employed for the preparation of analogues **1a–d** is shown in Scheme 1. The coupling reaction of 7-TCA-baccatin III **2** with oxazolidine-protected side chain precursor **3** was carried out in the presence of DCC at ambient temperature (35°C) to afford **4** in 84% yield. Acid-mediated oxazolidine cleavage of the compound **4**, followed by *N*-acylation of the resultant free amine **5** with an appropriate acid chloride (cyclopentanoyl chloride, 1-cyclopentenoyl chloride, cyclohexanoyl chloride or 1-cyclohexenoyl chloride) gave the corresponding 3′-acyl-3′-debenzoyl-7-TCA-paclitaxels **6a–d**. Finally, the 7-trichloroacetyl group of **6a–d** was easily removed with excess of ammonium acetate (ca. 5 equiv) to give the desired 3′-acyl-3′-debenzoylpaclitaxel analogues **1a–d** in satisfactory yields. Spectroscopic data (NMR and FAB-HRMS) of **1a–d** were consistent with their assigned structures.

Results and Discussion

The biological activities of 3′-*N*-acyl-*N*-debenzoylpaclitaxel analogues **1a–d** were evaluated for their cytotoxicities against human cancer cell lines (A 549 and SK-OV 3) and their abilities to induce apoptosis against HL-60 cell line. As shown from the data in Table 1, the 3′-*N*-acyl-*N*-debenzoylpaclitaxel analogues **1a–d** were found to be highly cytotoxic. Especially, the analogues **1b** and **1d** bearing *N*-cycloalkenoyl group were more potent up to 20 times than paclitaxel. The most cytotoxic compound **1b** in vitro was further evaluated in an in vivo experiment against ip implanted B16 melanoma. As shown in Table 1, the compound **1b** caused tumor growth inhibition (T/C = 212%) more than paclitaxel (T/C = 200%). The induction of apoptosis was also studied by DNA fragmentation after treatment with paclitaxel or its *N*-acyl analogues **1a–d**, and analyzed by sub-G1% resulting from DNA fragmentation after 72 h from the time of initial exposure. All of the analogues **1a–d** exhibited stronger ability to induce apoptosis than paclitaxel. Especially, the most cytotoxic compound **1b** displayed the strongest ability for the induction of apoptosis (66.86%). It can be concluded from this study that modifications at the 3′-*N*-acyl group of paclitaxel are tolerated well in many cases.

In summary, we have prepared *N*-acyl-*N*-debenzoylpaclitaxel derivatives **1a–d** and evaluated them in different biological methods. Hydrophobic cycloalkyl and cycloalkenyl substituted 3′-*N*-acyl analogues **1a–d** showed cytotoxicity and the strong ability to induce apoptosis.



Scheme 1. Reagents and conditions: (i) DCC, toluene, 35°C, 2 h; (ii) *c*-HCl, then aq $NaHCO_3$, EtOAc; (iii) RCOCl, pyridine; (iv) NH_4OAc, MeOH-THF.

Table 1. Biological evaluation of 3′-*N*-acyl-3′-*N*-debenzoylpaclitaxel analogues **1a**–**d**

Compound	Tumor cell cytotoxicity ED_{50}/ED_{50} (paclitaxel)[a]		Apoptosis against HL 60 (%)[b]	In vivo antitumor activity in B16 melanoma tumor model[c] % T/C[d] (mg/kg/inj.)[e]
	A549	SK-OV 3		
Paclitaxel	1	1	59.70	200 (20)
1a	0.4	1.67	62.68	
1b	< 0.05	0.13	66.86	212 (20)
1c	4.44	5.68	61.96	
1d	0.56	0.83	60.41	

[a] ED_{50} = concentration which produces 50% inhibition of proliferation after 72 h of incubation. Relative to paclitaxel = 1. A 549: non-small cell lung carcinoma, SK-OV 3: ovarian carcinoma.
[b] % of sub-G1 by DNA fragmentation. The data represent the mean values of at least three separate experiments. For details of the assay, see Experimental.
[c] B16 melanoma, ip (intraperitoneal) implant model.
[d] T/C refers to the percentage of the median survival time of drug-treated mice (seven per dose) to saline-treated controls.
[e] Dose administered ip on days 1, 4, 7, and 10; vehicle used: cremophor, ethanol and saline.

Experimental

Chromatographic purification of products was carried out by flash chromatography using Merck silica gel 60 (230–400 mesh). Thin layer chromatography was carried out on Merck silica gel 60F plates. Melting points were measured with a Thomas Hoover capillary melting point apparatus and were uncorrected. ^1H NMR (300 MHz) and ^{13}C NMR (75.0 Hz) spectra were recorded on a Varian Gemini 300 spectrometer using TMS as an internal standard. IR spectra were recorded on a MIDAC 101025 FT–IR spectrometer and main absorption frequencies were given in cm^{-1}. HRMS (FAB) analysis was carried out by the Mass Spectrometry Analysis Group at Korea Basic Science Institute. The 7-TCA-baccatin III (**2**) and oxazolidine-protected side chain precursor **3** were prepared according to the reported procedure.[23]

General procedure for the synthesis of 3′-acyl-3′-debenzoylpaclitaxel 1a-d

Synthesis of the compound 4. To the mixture of 7-trichloroacetylbaccatin III (**2**) (630 mg, 0.89 mmol), DCC (530 g, 2.57 mmol) and DMAP (6 mg, 0.05 mmol) in toluene (15 mL), was added a solution of (4*S*,5*R*)-2,2-di(chloromethyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid triethylamine salt (**3**) (1 g, 2.55 mmol) in toluene (10 mL) at room temperature and the reaction mixture was warmed to 35°C. After stirring at this temperature for 2 h, the reaction mixture was diluted with ethyl acetate and washed with brine. After concentration in vacuo, the crude product was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:2) to give **4** (740 mg, 84%) as a white solid: ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.15 (s, 3H), 1.24 (s, 3H), 1.79 (s, 3H), 1.84 (s, 3H), 1.99 (s, 3H), 2.16 (s, 3H), 2.60–2.71 (m, 1H), 3.78 (d, J = 12.0 Hz, 1H), 3.86 (d, J = 12.0 Hz, 1H), 3.91 (d, J = 7.0 Hz, 1H), 4.04 (s, 2H), 4.12 (d, J = 8.5 Hz, 1H), 4.27 (d, J = 8.3 Hz, 1H), 4.43 (d, J = 8.3 Hz, 1H), 4.65 (d, J = 8.1 Hz, 1H), 4.89 (d, J = 9.3 Hz, 1H), 5.63 (d, J = 7.7 Hz, 1H), 5.66 (d, J = 7.1 Hz, 1H), 6.25 (t, J = 8.9 Hz, 1H), 6.39 (s, 1H), 7.44–7.70 (m, 8H), 8.03 (d, J = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 11.06, 14.96, 21.00, 21.58, 21.74, 26.78, 32.50, 35.78, 43.57, 46.51, 46.81, 48.09, 56.14, 66.49, 71.53, 74.79, 74.93, 76.55, 79.43, 80.59, 83.79, 98.87, 127.57, 129.07, 129.31, 129.43, 129.66, 130.50, 133.29, 134.35, 137.35, 141.77, 160.87, 167.32, 169.23, 170.48, 170.87, 190.31, 201.55.

7-Trichloroacetyl-3′-debenzoylpaclitaxel 5. To a solution of oxazolidine-protected 7-trichloroacetylpaclitaxel (**4**) (0.2 g, 0.20 mmol) in ethyl acetate (5 mL) was added concd -HCl (0.05 mL) at 0°C. After stirring for 30 min, the reaction mixture was neutralized by addition of aqueous $NaHCO_3$ and the organic phase was washed with brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford the crude product of 7-trichloroacetyl-3′-debenzoylpaclitaxel **5**, which was used for the next reaction without purification.

7-Trichloroacetyl-3′-acyl-3′-debenzoylpaclitaxel 6a–d. To a stirred solution of the crude product of free amine **5** (50 mg) in pyridine (5 mL) was added dropwise an appropriate acid chloride [cyclopentanoyl chloride, 1-cyclopentenoyl chloride, cyclohexanoyl chloride or 1-cyclohexenoyl chloride] (0.17 mmol) at 0°C. After stirring for 2 h at the same temperature, the reaction mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give the crude residue of the corresponding 7-trichloroacetyl-3′-acyl-3′-debenzoylpaclitaxel (**6a–d**), which was used for the next reaction without purification.

***N*-Acyl-*N*-debenzoylpaclitaxel 1a–d**. To a stirred solution of the crude product of **6a–d** in MeOH (5 mL) and THF (5 mL) was added ammonium acetate (13 mg, 0.16 mmol) at room temperature. After completion of the reaction (ca. 2 h), the reaction mixture was diluted with ethyl acetate and washed with brine. After concentration in vacuo, the crude product was purified by flash column chromatography on silica gel (EtOAc: *n*-hexane = 1:1) to give the corresponding *N*-acyl-*N*-debenzoylpaclitaxel **1a–d** as a white solid.

3′-Cyclopentanoyl-3′-debenzoylpaclitaxel (1a). ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.08 (s, 3H), 1.20 (s, 3H), 1.61 (s, 3H), 1.75 (s, 3H), 2.10 (s, 3H), 2.18 (s, 3H), 2.29 (s, 3H), 2.40–2.60 (m, 2H), 3.71 (d, J = 7.0 Hz, 1H), 4.11 (d, J = 8.4 Hz, 1H), 4.23 (d, J = 8.4 Hz, 1H), 4.33 (dd, J = 6.8, 10.6 Hz, 1H), 4.61 (d, J = 2.5 Hz, 1H), 4.87 (d, J = 8.3 Hz, 1H), 5.50 (dd, J = 2.4, 8.9 Hz, 1H), 5.60 (d, J = 7.0 Hz, 1H), 6.13 (t, J = 9.4 Hz, 1H), 6.21 (s, 1H), 7.20–7.60 (m, 8H), 8.05 (d, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.97, 15.20, 21.25, 22.33, 23.00, 26.21, 27.20, 30.66, 31.05, 43.64, 46.00, 54.84, 59.00, 72.57, 72.84, 73.61, 75.38, 75.98, 79.39, 81.52, 84.81, 127.30, 128.61, 129.10, 129.36, 129.56, 130.62, 133.53, 134.08, 138.47, 142.50, 167.39, 170.68, 171.66, 173.31, 176.61, 204.08; HRMS (FAB) calcd for $C_{46}H_{56}NO_{14}$ ($M+H^+$) 846.3701, found 846.3698.

3′-(1-Cyclopentenoyl)-3′-debenzoylpaclitaxel (1b). ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.08 (s, 3H), 1.19 (t, 3H), 1.61 (s, 3H), 1.73 (s, 3H), 2.18 (s, 3H), 2.28 (s, 3H), 2.46 (m, 3H), 3.71 (d, J = 7.0 Hz, 1H), 4.11 (d, J = 8.4 Hz, 1H), 4.22 (d, J = 8.4 Hz, 1H), 4.33 (dd, J = 6.6, 10.7 Hz, 1H), 4.65 (d, J = 2.8 Hz, 1H), 4.87 (d, J = 7.8 Hz, 1H), 5.55 (dd, J = 2.7, 8.7 Hz, 1H), 5.60 (d, J = 7.0 Hz, 1H), 6.14 (t, J = 8.6 Hz, 1H), 6.20 (s, 1H), 6.37 (d, J = 8.8 Hz, 1H), 6.47 (m, 1H), 7.30–7.55 (m, 8H), 8.04 (d, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.96, 15.22, 21.26, 22.26, 22.98, 23.62, 27.27, 31.89, 33.61, 36.02, 43.60, 46.01, 55.03, 59.01, 72.57, 72.69, 73.69, 75.37, 75.99, 79.38, 81.53, 84.80, 127.40, 128.68, 129.10, 129.37, 129.58, 130.60, 133.57, 134.09, 138.49, 138.90, 139.99, 142.45, 165.58, 167.36, 170.73, 171.65, 173.11, 204.06; HRMS (FAB) calcd for $C_{46}H_{54}NO_{14}$ ($M+H^+$) 844.3544, found 844.3577.

3′-Cyclohexanoyl-3′-debenzoylpaclitaxel (1c). ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.09 (s, 3H), 1.20 (s, 3H), 1.61 (s, 3H), 2.10 (s, 3H), 2.18 (s, 3H), 2.28 (s, 3H), 2.21–2.26 (m, 2H), 2.28 (s, 3H), 2.42–2.51 (m, 2H), 3.71 (d, J = 7.0 Hz, 1H), 4.12 (d, J = 8.4 Hz, 1H), 4.23 (d, J = 8.4 Hz, 1H), 4.33 (dd, J = 6.9, 10.8 Hz, 1H), 4.61 (d, J = 2.4 Hz, 1H), 4.87 (d, J = 7.7 Hz, 1H), 5.49 (dd, J = 2.6, 8.9 Hz, 1H), 5.61 (d, J = 7.0 Hz, 1H), 6.13 (t, J = 9.0 Hz, 2H), 6.21 (s, 1H), 7.25–7.55 (m, 8H), 8.05 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.97, 15.19, 21.26, 22.33, 22.99, 25.95, 27.21, 29.96, 30.10, 36.00, 43.64, 45.83, 45.98, 54.54, 59.00, 72.57, 72.91, 73.47, 75.39, 75.99, 79.33, 81.53, 84.81, 127.29, 128.62, 129.11, 129.37, 129.59, 130.63, 133.57, 134.07, 138.42, 142.47, 167.35, 170.64, 171.67, 173.36, 176.43, 204.09; HRMS (FAB) calcd for $C_{47}H_{58}NO_{14}$ ($M+H^+$) 860.3857, found 860.3867.

3′-(1-Cyclohexenoyl)-3′-debenzoylpaclitaxel (1d). ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.08 (s, 3H), 1.21 (s, 3H), 1.61 (s, 3H), 1.72 (s, 3H), 1.72 (s, 3H), 2.17 (s, 3H), 2.28 (s, 3H), 3.71 (d, J = 7.0 Hz, 1H), 4.11 (d, J = 8.4 Hz, 1H), 4.22 (d, J = 8.4 Hz, 1H), 4.32 (dd, J = 6.7, 10.8 Hz, 1H), 4.63 (d, J = 2.9 Hz, 1H), 4.86 (d,

$J=7.7$ Hz, 1H), 5.53 (dd, $J=2.8$, 8.7 Hz, 1H), 5.60 (d, $J=7.0$ Hz, 1H), 6.13 (t, $J=8.2$ Hz, 1H), 6.20 (s, 1H), 6.45 (d, $J=8.7$ Hz, 1H), 6.57 (m, 1H), 7.20–7.55 (m, 8H), 8.04 (d, $J=7.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 8.55, 13.80, 19.84, 20.36, 20.97, 21.57, 23.23, 24.37, 25.87, 34.61, 42.19, 44.60, 53.79, 57.61, 71.17, 71.29, 72.35, 73.97, 74.58, 78.02, 80.11, 83.40, 126.01, 127.25, 127.69, 127.96, 128.16, 129.19, 131.61, 132.12, 132.69, 133.84, 137.15, 141.11, 165.98, 167.28, 169.30, 170.24, 171.78, 202.68; HRMS (FAB) calcd for $C_{47}H_{56}NO_{14}$ ($M+H^+$) 858.3701, found 858.3714.

Biological assays for apoptosis

Cell cultures. The human promyelocytic leukemia HL-60 cell line was maintained at 5×10^5 cells/mL in RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum, penicillin G (100 IU/mL), streptomycin (100 μg/mL), and L-glutamine (2 mM). HL-60 cells were cultured at 37°C in a humidified atmosphere containing 5% CO_2 and 95% air. Exponentially growing HL-60 cells were seeded at 1×10^6 per 6-well plate, and then the cells were exposed to paclitaxel or its *N*-acyl analogues **1a**–**d**.

Assays for apoptosis. The measurement of nuclear DNA content for apoptosis and cell distribution was carried out using an ethanol fixation procedure and analyzed on a FACStar^{plus} flow cytometer (Becton Dickinson, Mountain View, CA). Briefly, washed cell pellets were resuspended in 70% ethanol and incubated at −20°C for at least 20 min. The fixed cells were then washed twice, resuspended in PBS, and incubated at 37°C for 20 min. The cells were stained with propidium iodide (50 μg/mL) and analyzed by flow cytometry within 6 h. Analyses of the resulting histogram profiles were performed using ModFit LT software. The histogram profile of untreated cells was used to define the positions of the G1 and G2/M peaks. The intervening region is defined as S region and the region below the G1 peak is defined the sub-G1 region. The delineation of region from untreated cells was applied to profiles of treated cells.

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