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Structure–Activity Relationship Study at the 3′-*N*-Position of Paclitaxel: Synthesis and Biological Evaluation of 3′-*N*-Acyl-Paclitaxel Analogues

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Abstract—A series of 3′-*N*-acyl-paclitaxel analogues **1a**–**v** were synthesized and their cytotoxicities in vitro against several human tumor cell lines examined. It has been shown that distinct correlation between activity and *N*-acyl-substituent. The appropriate size of *N*-acyl group was indispensable for cytotoxicity, and moreover, the presence of β-substituted conjugated double and triple bond to *N*-carbonyl generally resulted in increase of cytotoxicities.

Introduction

Paclitaxel (Taxol®), a highly functionalized diterpene originally isolated from the pacific yew (*Taxus brevifolia*), has been proven to be one of the most promising antitumor compounds of the decade.[1–5] Due to its unique and effective mode of action,[6–9] paclitaxel exhibits impressive activity against various types of cancers, especially breast, ovarian, germ cell, lung, and esophageal cancers, that have not been effectively treated by other conventional anticancer agents.[10,11] Up to date, numerous analogues have been prepared to develop new taxoids with improved activity and decreased side effects.[12] Although a large body of paclitaxel structure–activity relationships (SARs) has been generated, a detailed investigation of aliphatic analogues of similar size with phenyl group of 3′-*N*-benzoyl has received little attention. Only a very few analogues having linear (*n*-pentyl) or branched (trimethylacetyl, isovaleryl, *t*-butylacetyl) alkyl group instead of phenyl group were assayed for microtubule binding affinity and cytotoxicity.[13] In these aliphatic *N*-acyl series, *n*-hexanoyl derivative [*n*-$C_5H_{11}C(O)NH$–] was shown to be slightly more active than paclitaxel against B16 melanoma cells. However, branching of the alkyl chain was detrimental to cyctotoxicity. In the course of our SAR study of taxoids, we recently found that replacement of phenyl group of 3′-*N*-benzoyl with other branched aliphatic groups such as cyclopentyl (**1j**), 1-cyclopentenyl (**1k**), cyclohexyl (**1m**) and 1-cyclohexenyl (**1n**) gave equally or more active compounds.[14] Especially, the analogues bearing cycloalkenyl groups were up to 20 times more potent than paclitaxel. These preliminary results intrigued us to carry out more detailed SAR study at the 3′-*N*-position. Here, we report the synthesis and biological evaluation of a series of 3′-*N*-acyl-paclitaxel analogues.

Results and Discussion

Chemical synthesis

A series of 3′-*N*-acyl-paclitaxel analogues **1a**–**v** were synthesized starting from 7-trichloroacetyl(TCA)-baccatin

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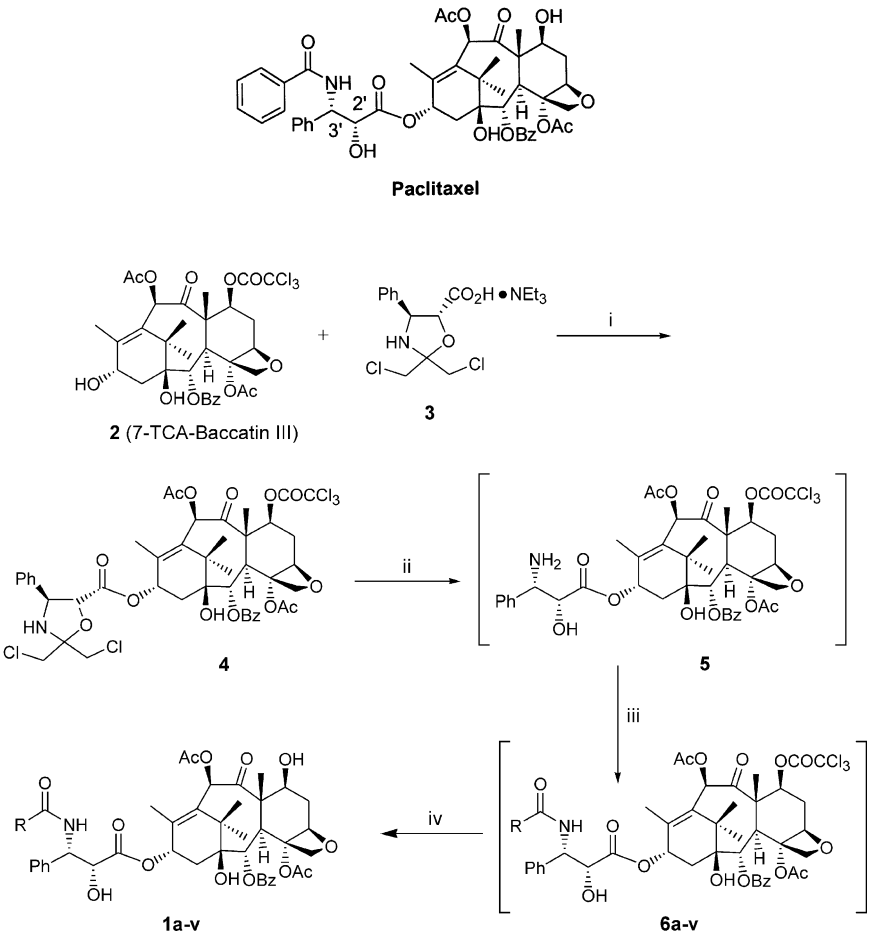

Scheme 1. Reagents and conditions: (i) DCC, toluene, 35 °C, 2 h; (ii) *c*-HCl, then aq $NaHCO_3$, EtOAc; (iii) RCOCl, pyridine; (iv) NH_4OAc, MeOH–THF.

III **2** and oxazolidine-type side chain precursor **3** using the coupling protocol reported previously by us[14] (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 to afford **4** in 84% yield. Acid-mediated oxazolidine cleavage of the compound **4**, followed by the reaction of the resultant free amine **5** with an appropriate acid chloride gave the corresponding 3′-*N*-acyl-7-TCA-paclitaxels **6a–v** (propanoyl chloride for **6a**, acryloyl chloride for **6b**, methacryloyl chloride for **6c**, *trans*-crotonyl chloride for **6d**, cyclopropanecarbonyl chloride for **6e**, 2-butynoyl chloride for **6f**, *trans*-2-methyl-2-butenoyl chloride for **6g**, 3,3′-dimethylacryloyl chloride for **6h**, cyclobutanecarbonyl chloride for **6i**, cyclopentanecarbonyl chloride for **6j**, 1-cyclopentenecarbonyl chloride for **6k**, *trans*-2-hexenoyl chloride for **6l**, cyclohexanecarbonyl chloride for **6m**, 1-cyclohexenecarbonyl chloride for **6n**, heptanoyl chloride for **6o,** 1-methyl-2-cyclohexenecarbonyl chloride for **6p**, 3-cyclopentylpropanoyl chloride for **6q,** octanoyl chloride for **6r**, *trans*-2-ethyl-2-hexenoyl chloride for **6s**, phenylpropynoyl chloride for **6t**, nonanoyl chloride for **6u** and 10-undecenoyl chloride for **6v**). Finally, the 7-trichloroacetyl group of **6a–v** was easily removed with excess of ammonium acetate (ca. 5 equiv) to give the desired 3′-*N*-acyl-paclitaxel analogues **1a–v** in satisfactory yields (31–58%). Spectroscopic data (^1H and ^{13}C NMR and HRMS) of **1a–v** were consistent with their assigned structures.

Biological evaluation

The in vitro cytotoxicities of these new taxoids **1a–v** were evaluated against five human tumor cell lines, A 549 (non-small cell lung carcinoma), SK-OV-3 (ovarian carcinoma), HCT-15 (colon carcinoma), SK-MEL-2 (melanoma) and XF498 (CNS carcinoma) by SRB (sulforhodamine B) method. As shown in Table 1, distinct correlation between activity and *N*-acyl-substituent was found. First, it was found that appropriate size of *N*-acyl group was indispensable for cytotoxicity. Most of analogues bearing high potency possess non-polar[15] aliphatic groups (R) with 3–6 carbons. On the other hand, the analogues having carbon atoms of R more than six (**1o–1v**) or less than three (**1a–1b**) were practically inactive. Secondly, the presence of conjugated double and triple bond to *N*-carbonyl group generally resulted similar or much higher (up to 1000 times) activity. Whereas branching of the alkyl chain was detrimental to cytotoxicity,[13] β-substitution on double and triple bond to *N*-carbonyl enhanced activity significantly, and thus these taxoids (**1d**, **1f**, **1h** and **1l**) showed 1–3 orders of magnitude stronger activity than paclitaxel. The most cytotoxic taxoids against normal

Table 1. In vitro anticancer activity of analogues against human cell lines

Taxoid [RC(O)–]		Tumor cell cytotoxicity ED_{50}/ED_{50} (paclitaxel)[a]				
		A549	SK-OV-3	HCT15	SK-MEL2	XF498
1a	Propanoyl	740	150.77	120	10	11.34
1b	Acryloyl	10.83	9.44	24.47	1.11	4.02
1c	Methacryloyl	200	133	50	20	5.37
1d	*trans*-Crotonyl	0.008	0.18	0.008	0.11	0.001
1e	Cyclopropanecarbonyl	0.39	2.46	0.31	0.22	0.22
1f	2-Butynoyl	0.067	0.98	0.0079	0.11	0.31
1g	*trans*-2-Methyl-2-butenoyl	1	5.06	4.34	1.11	1.46
1h	3,3′-Dimethylacryloyl	0.008	0.05	0.005	0.11	0.004
1i	Cyclobutanecarbonyl	1.17	4.78	2.47	1.11	1.07
1j	Cyclopentanecarbonyl	0.4	1.67			
1k	1-Cyclopentenecarbonyl	<	0.13			
1l	*trans*-2-Hexenoyl	0.0083	0.06	0.33	1	0.238
1m	Cyclohexanecarbonyl	4.44	5.68			
1n	1-Cyclohexenecarbonyl	0.56	0.83			
1o	Heptanoyl	340	79.2	210	80	4.51
1p	1-Methyl-2-cyclohexenecarbonyl	79.2	76.7	21.1	588	33.8
1q	3-Cyclopentylpropanoyl	180	104.6	90	40	3.9
1r	Octanoyl	910	750	520	150	22.9
1s	*trans*-2-Ethyl-2-hexenoyl	39.17	60	10	455	10.57
1t	Phenylpropynoyl	6	5.72	1.24	58.9	2.01
1u	Nonanoyl	3940	627.7	1300	820	44.8
1v	10-Undecenoyl	5260	748.5	3050	1055	47.1

[a]ED_{50} = concentration which produces 50% inhibition of proliferation after 72 h of incubation. Relative to paclitaxel = 1.0. A 549: non-small cell lung carcinoma, SK-OV-3: ovarian carcinoma, HCT-15: colon carcinoma, SK-MEL-2: melanoma, XF498: CNS carcinoma.

human cancer cell lines are **1d** and **1h**. But, the α-substitution on double bond to *N*-carbonyl gave the adverse effect in activity (compare activities! **1c** and **1d**, **1g** and **1h**).

Although paclitaxel has made great milestones in the treatment of various cancers, clinical reports have revealed that their use often results in a number of undesirable side effects. These side effects, along with the onset of multi-drug resistance (MDR), clearly indicate the necessity of developing new taxoids with fewer side effects and much improved activity.[10,16] Thus, five (**1d**, **1h**, **1k**, **1l** and **1n**) of the taxoids **1a**–**v**, which displayed better activities than paclitaxel were further evaluated for their cytotoxicities against human cancer cell lines (MES-SA and MCF7) and their corresponding drug-resistant cell lines (MES-SA/DX5 and MCF7/DOX). As shown from the data in Table 2, all of the tested compounds (**1d**, **1h**, **1k**, **1l** and **1n**) were highly cytotoxic against both sensitive and resistant cell lines. Especially, these analogues were up to ca. 7 times more cytotoxic than paclitaxel toward MDR variant cell lines.

Conclusion

A series of novel 3′-*N*-acyl-paclitaxel analogues **1a**–**v** were synthesized and their biological activities examined. Through detailed investigation on 3′-*N*-acyl analogues, we found distinct correlation between activity and *N*-acyl-substituent [RC(O)–]. It was clear that the β-substituted conjugated double and triple bond to *N*-carbonyl affected positively to activity. However, the α-substitution on double bond to *N*-carbonyl lowered the activity significantly. The size of R group was also indispensable for cytotoxicity of paclitaxel analogues. Without multiple modification at taxane ring and side chain, the analogues simply derivatized on 3′-*N*-position can exhibit superior potency in both sensitive and resistant cell lines. On the basis of these findings, further

Table 2. In vitro anticancer activity of paclitaxel and 3′-*N*-modified taxoids

Taxoids [RC(O)–]	Tumor cell cytotoxicity ED_{50} (μM)[a]			
	MES-SA	MES-SA/DX5	MCF7	MCF7/DOX
Paclitaxel (benzoyl)	0.00001	0.984	0.00001	1.167
1d (*trans*-crotonyl)	<0.00001	0.924	<0.00001	0.753
1h (3,3′-dimethylacryloyl)	<0.00001	0.227	<0.00001	0.186
1k (1-cyclopentenecarbonyl)	<0.00001	0.188	<0.00001	0.179
1l (*trans*-2-hexenoyl)	<0.00001	0.173	0.00001	0.176
1n (1-cyclohexenecarbonyl)	0.00001	0.197	0.00001	0.211

[a]ED_{50} = concentration which produces 50% inhibition of proliferation after 72 h of incubation. Relative to paclitaxel = 1.0. MES-SA: human uterine sarcoma, MES-SA/DX5: a MDR variant of MES-SA, MCF: human breast adenocarcinoma, MCF7/DOX: a MDR variant of MCF.

SAR studies at 3′-*N* position of paclitaxel will be followed to get more potent analogues.

Experimental

Chemical synthesis

General methods. 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. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.0 MHz) spectra were recorded on a Varian Gemini 300 spectrometer using TMS as an internal standard. HRMS (FAB) analysis was carried out by the Mass Spectrometry Analysis Group at Korea Basic Science Institute.

Materials. The chemicals were purchased from Aldrich Co. and purified before use by standard methods. The 7-TCA-baccatin III (**2**) and oxazolidine-protected sidechain precursor **3** were prepared according to the reported procedure.[14] 7-Trichloroacetyl-3′-acyl-3′-debenzoylpaclitaxel **6a**–**v** were prepared using our published procedure[14] and then used for the next reaction without purification.

General procedure for the synthesis of 3′-*N*-debenzoyl-3′-*N*-substituted paclitaxel 1a–v. To a stirred solution of the crude product of **6a**–**v** in MeOH/THF (1:1, v/v, ca. 5 mM solution) was added ammonium acetate (5 equiv) 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) to give the corresponding 3′-*N*-debenzoyl-3′-*N*-substituted paclitaxel **1a**–**v** as a white solid.

3′-*N*-Propanoyl-3′-debenzoylpaclitaxel (1a). Yield 22 mg (57%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.10 (t, J = 7.6 Hz, 3H), 1.26 (s, 3H), 1.56 (s, 3H), 1.67 (s, 3H), 1.81 (s, 3H), 2.22–2.34 (m, 9H), 2.46–2.59 (m, 2H), 3.77 (d, J = 6.9 Hz, 1H), 3.83 (d, J = 5.5 Hz, 1H), 4.19 (d, J = 8.4 Hz, 1H), 4.29 (d, J = 8.4 Hz, 1H), 4.38–4.43 (m, 1H), 4.67 (q, J = 2.6 Hz, 1H), 4.93 (d, J = 7.9 Hz, 1H), 5.57 (dd, J = 2.5, 8.9 Hz, 1H), 5.68 (d, J = 7.0 Hz, 1H), 6.18 (t, J = 8.5 Hz, 1H), 6.28 (s, 1H), 6.45 (d, J = 8.9 Hz, 1H), 7.33–7.61 (m, 8H), 8.10 (d, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 8.58, 8.85, 13.17, 13.78, 19.86, 20.88, 21.55, 25.77, 28.56, 34.61, 42.19, 44.62, 53.59, 57.49, 59.42, 71.08, 71.23, 72.19, 73.93, 74.58, 77.83, 80.08, 83.37, 125.94, 127.21, 127.68, 127.91, 128.17, 129.17, 132.11, 132.67, 137.04, 140.97, 165.86, 169.29, 170.25, 171.79, 172.87, 202.88; HRMS (FAB) calcd for $C_{43}H_{52}NO_{14}$ ($M+H^+$) 806.3388, found 806.3391.

3′-*N*-Acryloyl-3′-*N*-debenzoylpaclitaxel (1b). Yield 18 mg (46%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.19 (t, J = 7.1 Hz, 3H), 1.74 (s, 3H), 1.81 (s, 3H), 2.25 (s, 3H), 2.29 (s, 3H), 2.42–2.63 (m, 1H), 3.72 (d, J = 6.9 Hz, 1H), 4.11 (d, J = 8.3 Hz, 1H), 4.22 (d, J = 8.3 Hz, 1H), 4.28–4.34 (m, 1H), 4.65 (d, J = 2.6 Hz, 1H), 4.87 (d, J = 7.9 Hz, 1H), 5.57–5.61 (m, 3H), 6.08 (d, J = 9.9 Hz, 1H), 6.14–6.21 (m, 3H), 6.34 (d, J = 8.7 Hz, 1H), 7.29–7.55 (m, 8H), 8.05 (d, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.97, 14.59, 15.25, 21.25, 21.44, 22.27, 23.01, 27.26, 36.02, 43.59, 46.02, 55.22, 59.01, 60.79, 72.58, 72.73, 73.65, 75.36, 75.97, 79.47, 81.54, 84.80, 127.42, 128.28, 128.76, 129.12, 129.40, 129.55, 130.45, 130.62, 133.57, 134.14, 138.26, 142.42, 165.55, 167.41, 170.77, 171.66, 173.0, 204.04; HRMS (FAB) calcd for $C_{43}H_{50}NO_{14}$ ($M+H^+$) 804.3231, found 804.3211.

3′-*N*-Methacryloyl-3′-*N*-debenzoylpaclitaxel (1c). Yield 19 mg (48%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.14 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.68 (s, 3H), 1.79 (s, 4H), 1.92 (s, 6H), 2.24–2.33 (m, 5H), 2.36 (s, 3H), 2.49–2.59 (m, 2H), 3.78 (d, J = 7.0 Hz, 1H), 4.18 (d, J = 8.4 Hz, 1H), 4.29 (d, J = 8.4 Hz, 1H), 4.39 (dd, J = 10.5, 6.7 Hz, 1H), 4.71 (d, J = 2.7 Hz, 1H), 4.93 (d, J = 8.2 Hz, 1H), 5.36 (s, 1H), 5.60–5.70 (m, 3H), 6.21 (t, J = 8.8 Hz, 1H), 6.27 (s, 1H), 6.68 (d, J = 8.8 Hz, 1H), 7.31–7.64 (m, 8H), 8.11 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.57, 14.84, 18.64, 20.88, 21.85, 22.59, 26.83, 35.60, 43.17, 45.61, 54.68, 58.57, 72.17, 72.28, 73.21, 74.91, 75.56, 76.49, 79.01, 81.10, 84.39, 120.51, 126.95, 128.31, 128.71, 128.99, 129.11, 130.21, 133.13, 133.74, 137.90, 139.42, 142.00, 166.99, 168.04, 170.37, 171.29, 172.67, 203.65; HRMS (FAB) calcd for $C_{44}H_{52}NO_{14}$ ($M+H^+$) 818.3388, found 818.3371.

3′-*N*-(*trans*-Crotonyl)-3′-*N*-debenzoylpaclitaxel (1d). Yield 21 mg (52%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.15 (s, 3H), 1.26 (t, J = 7.1 Hz, 6H), 1.68 (s, 6H), 1.80–1.93 (m, 9H), 2.25–2.33 (m, 6H), 2.34 (s, 3H), 2.49–2.62 (m, 2H), 3.78 (d, J = 7.0 Hz, 1H), 4.18 (d, J = 8.4 Hz, 1H), 4.29 (d, J = 8.4 Hz, 1H), 4.40 (dd, J = 10.8, 6.7 Hz, 1H), 4.93 (d, J = 8.3 Hz, 1H), 5.61 (d, J = 7.7 Hz, 1H), 5.67 (d, J = 7.0 Hz, 1H), 6.41–6.49 (m, 3H), 6.74–6.86 (m, 1H), 7.35–7.63 (m, 8H), 8.12 (d, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.97, 14.60, 15.27, 18.19, 21.27, 22.28, 23.02, 27.27, 30.10, 36.0, 43.59, 46.0, 55.27, 59.01, 60.80, 72.59, 72.68, 73.75, 75.36, 75.99, 79.45, 81.51, 84.81, 124.65, 127.43, 128.71, 129.12, 129.39, 129.55, 130.62, 133.49, 134.13, 138.45, 142.07, 142.55, 166.03, 167.40, 170.74, 171.68, 173.09, 204.08; HRMS (FAB) calcd for $C_{44}H_{51}NO_{14}$ ($M+H^+$) 840.3207, found 840.3207.

3′-*N*-Cyclopropanecarbonyl-3′-*N*-debenzoylpaclitaxel (1e). Yield 19 mg (48%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.15 (s, 2H), 1.27 (m, 4H), 1.50–1.90 (m, 9H), 1.83 (s, 3H), 2.25 (s, 3H), 2.37 (s, 2H), 2.51–2.54 (m, 1H), 3.78 (d, J = 7.0 Hz, 1H), 4.18 (d, J = 8.6 Hz, 1H), 4.29 (d, J = 8.4 Hz, 1H), 4.40 (dd, J = 10.8, 6.7 Hz, 1H), 4.69 (d, J = 2.8 Hz, 1H), 4.93 (d, J = 7.6 Hz, 1H), 5.58 (dd, J = 2.8, 8.9 Hz, 1H), 5.67 (d, J = 7.0 Hz, 1H), 6.22–6.28 (m, 2H), 6.44 (d, J = 10.7 Hz, 1H), 7.33–7.62 (m, 8H), 8.11 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 8.06, 8.19, 9.97, 14.59, 15.12, 15.23, 21.26, 21.44, 22.34, 22.99, 27.22, 35.99, 43.62, 45.99, 55.29, 58.99, 60.79, 72.58, 72.69, 73.87, 75.36,

75.97, 79.51, 81.48, 84.81, 127.36, 128.66, 129.09, 129.37, 129.51, 130.63, 133.45, 134.12, 138.42, 142.57, 167.45, 170.76, 171.68, 173.16, 174.06, 204.08; HRMS (FAB) calcd for $C_{44}H_{51}NO_{14}$ ($M+H^+$) 840.3207, found 840.3211.

3′-*N*-(2-Butynoyl)-3′-*N*-debenzoylpaclitaxel (1f). Yield 12 mg (32%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.15 (s, 4H), 1.22 (s, 3H), 1.68 (s, 4H), 2.22–2.37 (m, 8H), 2.41–2.59 (m, 1H), 3.79 (d, $J=7.0$ Hz, 1H), 4.18 (d, $J=8.4$ Hz, 1H), 4.29 (d, $J=8.5$ Hz, 1H), 4.41 (dd, $J=10.7$, 6.7 Hz, 1H), 4.65 (d, $J=2.2$ Hz, 1H), 4.94 (d, $J=7.8$ Hz, 1H), 5.27–5.32 (m, 1H), 5.53 (d, $J=9.3$ Hz, 1H), 5.67 (d, $J=7.1$ Hz, 1H), 6.23–6.33 (m, 2H), 7.38–7.62 (m, 8H), 8.11 (d, $J=7.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.72, 14.63, 19.45, 20.77, 21.23, 21.83, 28.70, 34.52, 41.16, 44.33, 45.91, 46.88, 57.44, 65.26, 69.82, 70.97, 71.89, 73.92, 74.99, 78.26, 79.92, 83.02, 83.97, 87.32, 97.92, 126.97, 127.91, 128.81, 128.94, 129.21, 130.22, 133.45, 136.82, 141.87, 166.92, 170.32, 170.81, 171.86, 203.91; HRMS (FAB) calcd for $C_{44}H_{50}NO_{14}$ ($M+H^+$) 816.3231, found 816.3277.

3′-*N*-(*trans*-2-Methyl-2-butenoyl)-3′-*N*-debenzoylpaclitaxel (1g). Yield 14 mg (36%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.05 (s, 5H), 1.20 (s, 5H), 1.60–1.65 (m, 5H), 1.72–1.81 (m, 5H), 1.97 (s, 3H), 2.17–2.29 (m, 9H), 2.21–2.45 (m, 2H), 3.61–3.72 (m, 1H), 3.91–3.96 (m, 1H), 4.11 (d, $J=7.32$ Hz, 1H), 4.23 (d, $J=8.38$ Hz, 1H), 4.27–4.32 (m, 1H), 4.82 (d, $J=7.32$ Hz, 1H), 5.42–5.62 (m, 2H), 6.10–6.21 (m, 2H), 7.23–7.63 (m, 8H), 8.03 (d, $J=7.62$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.86, 14.20, 14.34, 20.59, 21.06, 22.52, 23.24, 26.56, 29.70, 31.49, 33.22, 35.84, 36.97, 43.04, 46.47, 54.65, 57.68, 60.42, 72.01, 72.28, 73.37, 74.79, 78.73, 81.08, 84.15, 127.03, 128.23, 128.73, 128.92, 129.18, 130.18, 133.73, 136.07, 138.06, 138.24, 138.56, 139.57, 165.11, 166.96, 170.46, 171.22, 211.28; HRMS (FAB) calcd for $C_{45}H_{54}NO_{14}$ ($M+H^+$) 832.3544, found 832.3541.

3′-*N*-(3,3′-Dimethylacryloyl)-3′-*N*-debenzoylpaclitaxel (1h). Yield 21 mg (53%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.08 (s, 3H), 1.18 (t, $J=7.3$ Hz, 6H), 1.55–1.75 (m, 14H), 1.96 (d, $J=7.4$ Hz, 4H), 2.17–2.27 (m, 6H), 2.30 (s, 3H), 2.49–2.42 (m, 1H), 3.72 (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, $J=10.8$, 6.7 Hz, 1H), 4.86 (d, $J=9.4$ Hz, 1H), 5.49–5.53 (m, 1H), 5.60 (d, $J=7.0$ Hz, 1H), 6.06–6.21 (m, 2H), 7.32–7.54 (m, 8H), 8.03 (d, $J=7.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.95, 14.59, 15.25, 20.29, 21.26, 21.44, 22.25, 23.02, 27.02, 27.63, 36.01, 43.61, 46.02, 55.06, 59.0, 60.8, 72.59, 72.72, 73.94, 75.36, 76.01, 79.42, 81.49, 84.80, 117.94, 127.42, 128.59, 129.10, 129.34, 129.52, 130.59, 133.41, 134.10, 138.65, 142.68, 153.64, 166.97, 167.40, 170.68, 171.67, 173.26, 204.10; HRMS (FAB) calcd for $C_{45}H_{54}NO_{14}$ ($M+H^+$) 832.3544, found 832.3524.

3′-*N*-Cyclobutanecarbonyl-3′-*N*-debenzoylpaclitaxel (1i). Yield 24 mg (58%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.09 (s, 2H), 1.20 (s, 4H), 1.61 (s, 6H), 1.75–1.98 (m, 8H), 2.15–2.29 (m, 14H), 2.43–2.51 (m, 2H), 3.72 (d, $J=7.1$ Hz, 1H), 4.12 (d, $J=8.4$ Hz, 1H), 4.23 (d, $J=8.3$ Hz, 1H), 4.33 (dd, $J=10.8$, 6.7 Hz, 1H), 4.61 (d, $J=2.8$ Hz, 1H), 4.87 (d, $J=7.7$ Hz, 1H), 5.49 (dd, $J=2.7$, 8.9 Hz, 1H), 5.60 (d, $J=7.0$ Hz, 1H), 6.04 (d, $J=9.0$ Hz, 1H), 6.15 (t, $J=9.1$ Hz, 1H), 6.21 (s, 1H), 7.29–7.55 (m, 8H), 8.05 (d, $J=7.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.97, 15.22, 21.26, 22.31, 22.99, 25.66, 25.84, 27.23, 36.03, 40.12, 43.63, 45.99, 54.83, 59.01, 72.58, 72.80, 73.62, 75.37, 75.98, 79.42, 81.53, 84.81, 127.33, 128.67, 129.11, 129.38, 129.55, 130.63, 133.56, 134.10, 138.41, 142.48, 167.40, 170.70, 171.67, 173.21, 175.31, 204.07; HRMS (FAB) calcd for $C_{45}H_{53}NO_{14}$ ($M+H^+$) 854.3364, found 854.3365.

3′-*N*-(*trans*-2-Hexenoyl)-3′-*N*-debenzoylpaclitaxel (1l). Yield 17 mg (42%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 0.80 (t, $J=7.4$ Hz, 3H), 1.08 (s, 3H), 1.20 (t, $J=7.1$ Hz, 4H), 1.30–1.34 (m, 2H), 1.61 (s, 3H), 1.75 (s, 4H), 1.98–2.11 (m, 4H), 2.17 (s, 5H), 2.29 (s, 3H), 2.32–2.49 (m, 1H), 3.71 (d, $J=7.0$ Hz, 1H), 4.11 (d, $J=8.4$ Hz, 1H), 4.23 (d, $J=8.5$ Hz, 1H), 4.32 (dd, $J=10.5$, 6.4 Hz, 1H) 4.64 (d, $J=2.7$ Hz, 1H), 4.87 (d, $J=8.1$ Hz, 1H), 5.55 (dd, $J=2.6$, 8.7 Hz, 1H), 5.60 (d, $J=7.1$ Hz, 1H), 5.73 (d, $J=15.3$ Hz, 1H), 6.14 (d, $J=6.7$ Hz, 1H), 6.21 (s, 1H), 6.68–6.74 (m, 1H), 7.33–7.55 (m, 8H), 8.05 (d, $J=7.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.96, 14.03, 15.26, 21.24, 21.44, 21.54, 21.69, 22.29, 23.01, 27.27, 34.46, 34.67, 43.59, 45.99, 55.33, 59.01, 60.79, 72.59, 72.67, 73.85, 75.38, 75.98, 79.47, 81.51, 84.81, 123.17, 127.16, 127.44, 128.69, 129.11, 129.37, 129.55, 130.63, 133.49, 134.11, 138.45, 142.55, 146.93, 166.18, 167.40, 170.76, 171.66, 173.08, 204.08; HRMS (FAB) calcd for $C_{46}H_{56}NO_{14}$ ($M+H^+$) 846.3701, found 846.3703.

3′-*N*-Heptanoyl-3′-*N*-debenzoylpaclitaxel (1o). Yield 21 mg (51%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 0.81–0.86 (m, 3H), 1.15 (s, 2H), 1.22–1.29 (m, 8H), 1.51–1.58 (m, 2H), 1.68 (s, 3H), 1.81 (d, $J=2.9$ Hz, 3H), 2.14–2.38 (m, 8H), 2.48–2.59 (m, 2H), 3.52 (d, $J=5.3$ Hz, 1H), 3.78 (d, $J=7.0$ Hz, 1H), 4.18 (d, $J=8.5$ Hz, 1H), 4.30 (d, $J=8.3$ Hz, 1H), 4.39–4.42 (m, 1H), 4.68 (q, $J=2.6$ Hz, 1H), 4.93 (d, $J=7.9$ Hz, 1H), 5.57 (dd, $J=2.5$, 8.9 Hz, 1H), 5.67 (d, $J=7.0$ Hz, 1H), 6.21 (t, $J=8.7$ Hz, 2H), 6.28 (s, 1H), 7.32–7.65 (m, 8H), 8.11 (d, $J=7.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.55, 14.03, 14.88, 20.89, 21.87, 22.45, 25.67, 26.79, 28.85, 31.45, 35.55, 36.64, 43.17, 45.54, 54.52, 58.57, 72.19, 72.34, 73.14, 74.88, 75.55, 78.99, 81.05, 84.38, 126.96, 128.29, 128.72, 128.98, 129.04, 130.22, 133.06, 133.75, 137.99, 142.12, 166.99, 170.26, 171.34, 172.82, 173.02, 203.70; HRMS (FAB) calcd for $C_{47}H_{60}NO_{14}$ ($M+H^+$) 862.4014, found 862.4016.

3′-*N*-(1-Methyl-2-cyclohexenecarbonyl)-3′-*N*-debenzoylpaclitaxel (1p). Yield 14 mg (33%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.08–1.10 (m, 6H), 1.11–1.20 (m, 5H), 1.61 (s, 3H), 1.74–1.98 (m, 14H), 2.16–2.32 (m, 10H), 2.35–2.42 (m, 1H), 3.71 (d, $J=6.93$ Hz, 1H), 4.03–4.14 (m, 1H), 4.20 (d, $J=7.3$ Hz, 1H), 4.31–4.35 (m, 1H), 4.52–4.61

(m, 1H), 4.82 (d, $J=7.3$ Hz, 1H), 5.54–5.62 (m, 4H), 6.11–6.18 (m, 1H), 6.21 (s, 1H), 6.45–6.61 (m, 1H), 7.19–7.47 (m, 8H), 8.05 (d, $J=7.14$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 8.27, 9.01, 9.58, 11.28, 12.72, 13.65, 14.87, 19.21, 20.86, 21.31, 21.89, 22.86, 27.91, 29.23, 34.07, 35.62, 43.19, 45.62, 54.96, 58.59, 72.18, 72.22, 73.48, 74.98, 75.59, 79.05, 81.09, 84.42, 122.79, 127.05, 128.28, 128.72, 128.96, 129.16, 130.24, 130.98, 131.22, 131.83, 133.07, 133.72, 138.07, 142.16, 146.50, 165.81, 166.99, 170.38, 171.28, 172.68, 203.69; HRMS (FAB) calcd for $C_{48}H_{58}NO_{14}$ ($M+H^+$) 872.3857, found 872.3859.

3′-*N*-(3-Cyclopentylpropanoyl)-3′-*N*-debenzoylpaclitaxel (1q). Yield 18 mg (43%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.15 (s, 3H), 1.26 (s, 4H), 1.53–1.57 (m, 6H), 1.68 (s, 7H), 1.82–1.91 (m, 5H), 2.19–2.34 (m, 10H), 2.45–2.55 (m, 2H), 3.47 (d, $J=2.3$ Hz, 1H), 3.75 (d, $J=7.2$ Hz, 1H), 4.18 (d, $J=8.5$ Hz, 1H), 4.29 (d, $J=8.3$ Hz, 1H), 4.32–4.48 (m, 1H), 4.93 (d, $J=9.4$ Hz, 1H), 5.57 (d, $J=8.9$ Hz, 1H), 5.67 (d, $J=7.0$ Hz, 1H), 6.18–6.28 (m, 3H), 7.35–7.62 (m, 8H), 8.10 (d, $J=8.5$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.56, 14.85, 20.88, 21.90, 22.62, 25.07, 26.81, 31.88, 32.32, 32.38, 35.58, 35.89, 39.56, 43.19, 45.56, 54.51, 58.58, 72.19, 72.34, 73.18, 74.93, 75.56, 79.03, 81.07, 84.39, 126.96, 128.28, 128.73, 128.96, 129.07, 130.24, 133.10, 133.73, 138.04, 142.11, 167.00, 170.27, 171.30, 172.84, 173.07, 203.69; HRMS (FAB) calcd for $C_{48}H_{60}NO_{14}$($M+H^+$) 874.4014, found 874.4019.

3′-*N*-Octanoyl-3′-*N*-debenzoylpaclitaxel (1r). Yield 22 mg (52%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 0.84 (t, $J=6.6$ Hz, 3H), 1.15–1.26 (m, 13H), 1.51–1.57 (m, 2H), 1.63 (s, 2H), 1.81 (s, 2H), 2.18 (t, $J=7.6$ Hz, 2H), 2.23–2.34 (m, 7H), 2.47–2.59 (m, 2H), 3.72 (s, 1H), 3.77 (d, $J=6.9$ Hz, 1H), 4.18 (d, $J=8.4$ Hz, 1H), 4.28 (d, $J=8.4$ Hz, 1H), 4.32–4.42 (m, 1H), 4.67 (s, 1H), 4.93 (d, $J=8.3$ Hz, 1H), 5.57 (dd, $J=2.4$, 8.9 Hz, 1H), 5.67 (d, $J=7.0$ Hz, 1H), 6.19 (t, $J=8.7$ Hz, 1H), 6.35 (d, $J=8.9$ Hz, 1H), 7.29–7.64 (m, 8H), 8.10 (d, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.58, 14.05, 14.82, 20.87, 21.89, 22.57, 25.74, 26.80, 28.94, 29.14, 31.62, 35.62, 36.61, 43.19, 45.61, 54.56, 58.55, 72.15, 72.28, 73.16, 74.96, 75.59, 78.92, 81.09, 84.39, 126.97, 128.23, 128.71, 128.94, 129.15, 130.22, 133.13, 133.69, 138.09, 142.06, 166.93, 170.28, 171.27, 172.82, 173.15, 203.69; HRMS (FAB) calcd for $C_{48}H_{61}NO_{14}Na$ ($M+Na^+$) 898.3990, found 898.3987.

3′-*N*-(*trans*-2-Ethyl-2-hexenoyl)-3′-*N*-debenzoylpaclitaxel (1s). Yield 14 mg (34%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.15 (s, 3H), 1.26 (s, 4H), 1.59 (s, 12H), 1.68 (s, 3H), 1.80–2.04 (m, 8H), 2.36 (s, 5H), 2.49 (s, 3H), 2.52–2.63 (m, 2H), 3.33 (d, $J=5.1$ Hz, 1H), 3.79 (d, $J=7.0$ Hz, 1H), 4.18 (d, $J=8.5$ Hz, 1H), 4.29 (d, $J=8.4$ Hz, 1H), 4.35–4.42 (m, 1H), 4.51 (s, 1H), 4.64–4.68 (m, 2H), 4.94 (d, $J=7.8$ Hz, 1H), 5.29 (d, $J=8.9$ Hz, 1H), 5.68 (t, $J=9.6$ Hz, 2H), 6.28 (s, 2H), 7.39–7.61 (m, 8H), 8.09 (d, $J=7.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.96, 15.24, 19.93, 21.24, 22.17, 22.34, 23.0, 27.22, 31.30, 35.97, 43.62, 46.04, 56.97, 59.0, 59.95, 72.56, 72.81, 73.74, 75.33, 75.96, 79.45, 79.80, 80.86, 81.20, 81.60, 84.79, 101.95, 126.54, 127.18, 128.76, 129.09, 129.37, 129.48, 130.48, 130.58, 133.63, 133.83, 134.08, 134.24, 138.19, 138.57, 142.05, 142.34, 153.07, 154.19, 157.19, 167.43, 168.78, 170.67, 171.64, 203.99; HRMS (FAB) calcd for $C_{48}H_{60}NO_{14}$ ($M+H^+$) 874.4014, found 874.3978.

3′-*N*-Phenylpropynoyl-3′-*N*-debenzoylpaclitaxel (1t). Yield 13 mg (31%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.07 (s, 3H), 1.26 (s, 4H), 1.63 (s, 4H), 1.67 (s, 3H), 1.89 (s, 3H), 2.08 (d, $J=8.96$ Hz, 2H), 2.24 (s, 3H), 2.46–2.56 (m, 2H), 3.22 (d, $J=10.22$ Hz, 1H), 3.71 (d, $J=7.11$ Hz, 1H), 3.82 (d, $J=9.92$ Hz, 2H), 4.06–4.12 (m, 2H), 4.22 (d, $J=8.38$ Hz, 1H), 4.42 (d, $J=8.22$ Hz, 2H), 4.61 (t, $J=9.05$ Hz, 1H), 4.89 (d, $J=7.69$ Hz, 1H), 5.61 (d, $J=7.12$ Hz, 1H), 6.26–6.29 (m, 2H), 7.35–7.71 (m, 12H), 8.02 (d, $J=8.47$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.52, 14.93, 20.86, 21.43, 21.89, 26.73, 35.41, 43.13, 45.53, 46.12, 47.62, 58.44, 62.61, 64.72, 66.26, 71.35, 72.06, 74.99, 75.51, 79.31, 80.70, 83.43, 84.37, 98.50, 122.23, 124.52, 125.44, 126.52, 126.94, 127.12, 128.62, 128.88, 129.03, 129.31, 130.13, 133.92, 136.94, 142.44, 167.03, 170.02, 170.61, 171.33, 203.73; HRMS (FAB) calcd for $C_{49}H_{52}NO_{14}$ ($M+H^+$) 878.3388, found 878.3396.

3′-*N*-Nonanoyl-3′-*N*-debenzoylpaclitaxel (1u). Yield 18 mg (43%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 0.86 (t, $J=6.9$ Hz, 3H), 1.15–1.26 (m, 17H), 1.51–1.59 (m, 2H), 1.68 (s, 4H), 1.82–1.91 (m, 5H), 2.17–2.35 (m, 10H), 2.47–2.54 (m, 2H), 3.51 (d, $J=5.1$ Hz, 1H), 3.78 (d, $J=6.8$ Hz, 1H), 4.18 (d, $J=8.4$ Hz, 1H), 4.29 (d, $J=8.3$ Hz, 1H), 4.39–4.42 (m, 1H), 4.67 (s, 1H), 4.93 (d, $J=9.1$ Hz, 1H), 5.55 (d, $J=8.7$ Hz, 1H), 5.67 (d, $J=6.9$ Hz, 1H), 6.21 (t, $J=8.7$ Hz, 3H), 7.33–7.64 (m, 8H), 8.11 (d, $J=7.5$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.57, 14.08, 14.84, 20.87, 22.61, 25.74, 26.84, 29.10, 29.21, 29.25, 31.78, 35.63, 36.66, 43.21, 45.59, 54.55, 58.61, 72.36, 73.17, 74.97, 75.59, 79.04, 81.11, 84.41, 126.98, 128.28, 128.72, 128.98, 129.13, 130.24, 133.15, 133.72, 138.08, 142.10, 167.01, 170.27, 171.28, 172.83, 173.00, 203.68; HRMS (FAB) calcd for $C_{49}H_{64}NO_{14}$ ($M+H^+$) 890.4327, found 890.4324.

3′-*N*-(10-Undecenoyl)-3′-*N*-debenzoylpaclitaxel (1v). Yield 21 mg (47%: overall yield from 50 mg of **4**); ^{1}H NMR ($CDCl_3$, selected diagnostic peaks) δ 1.14–1.33 (m, 10H), 1.51–1.57 (m, 2H), 1.67 (s, 2H), 1.81 (s, 2H), 1.87–2.04 (m, 4H), 2.18 (t, $J=7.3$ Hz, 2H), 2.24–2.34 (m, 6H), 2.47–2.59 (m, 2H), 3.65 (s, 1H), 3.77 (d, $J=6.8$ Hz, 1H), 4.18 (d, $J=8.4$ Hz, 1H), 4.28 (d, $J=8.4$ Hz, 1H), 4.32–4.42 (m, 1H), 4.67 (s, 1H), 4.91–5.00 (m, 3H), 5.57 (d, $J=8.8$ Hz, 1H), 5.67 (d, $J=6.9$ Hz, 1H), 5.75–5.84 (m, 1H), 6.19 (t, $J=8.6$ Hz, 1H), 6.28–6.33 (m, 2H), 7.31–7.64 (m, 8H), 8.10 (d, $J=8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.57, 14.83, 20.87, 21.89, 22.60, 25.72, 26.81, 28.84, 29.03, 29.17, 29.23, 29.26, 33.75, 35.60, 36.61, 43.19, 45.60, 54.55, 58.55, 72.15, 72.30, 73.15, 74.95, 75.58, 78.96, 81.08, 84.39, 114.17, 126.97, 128.25, 128.71, 128.95, 129.13, 129.62, 130.22, 133.11, 133.71, 138.07, 139.14, 142.07, 166.95, 170.27, 171.28, 172.83, 173.06, 203.68; HRMS (FAB) calcd for $C_{51}H_{66}NO_{14}$($M+H^+$) 916.4483, found 916.4481.

Cytotoxicity assay

Materials and methods. The human non-small cell lung cancer cell line A549, the ovarian cancer cell line SK-OV-3, the colorectal cancer cell line HCT15, the skin cancer cell line SK-MEL2, the central nerve system cancer cell line XF498, the breast cancer cell line MCF7 and its doxorubicin-resistant subline MCF7/DOX, and the uterus cancer cell line MES-SA and its doxorubicin-resistant subline MES-SA/DX5 were used in this study. The A549, SK-OV-3, HCT15, SK-MEL2 and XF498 cells were grown in RPMI1640 medium supplied with 5% fetal bovine serum (FBS). The MCF7, MCF7/DOX, MES-SA and MES-SA/DX5 cells were grown in Dulbecco's modified eagle medium (DMEM) supplied with 10% FBS. All the cells were cultured in a 95% air/5% CO_2 atmosphere at 37 °C in a humidified incubator, and the cells were dissociated with 0.25% trypsin and 3 mM EDTA in phosphate buffered solution in case of transferring or dispensing before experiment.

Growth inhibition assay. All experimental procedures followed the NCI's protocol in some minor changes based on the SRB method as described previously.[17,18] Briefly, after 72 h of continuous drug-exposure time, the cells were fixed with 10% cold TCA, followed by staining with 0.4% SRB solution. Then, the cells were washed, and the cell membrane-bound stains were solubilized with 10 mM unbuffered Trisma base solution (pH 10.5). The value of optical density (OD value) was measured spectrophotometrically at 520 and 690 nm in a microtiter plate reader (Molecular Devices E-max, Sunnyvale, CA, USA), and the OD value at 690 nm was subtracted from that at 520 nm so as to eliminate the effects of non-specific absorbance. Cell survival fractions were calculated with the aid of three basic measurements; a time zero (T_z) at the beginning of drug incubation, a cell control (CC) at the end of incubation without drug, and a drug-treatment (DT) at the end of the drug incubation period. If DT $\geq T_z$, the net percent of cell growth inhibition was calculated by $(DT-T_z)/(CC-T_z)\times 100$. If DT $< T_z$, the net percent of cell killing activity was calculated by $(DT-T_z)/T_z\times 100$. All the data represented the average values of three wells in each experiment.

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References and Notes

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