Synthesis and Biological Evaluation of 3'-Deazapaclitaxel

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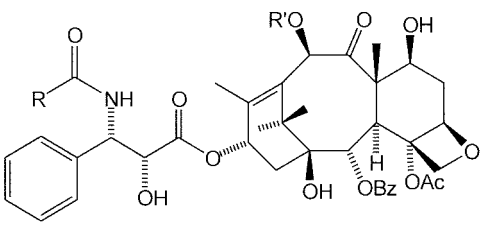
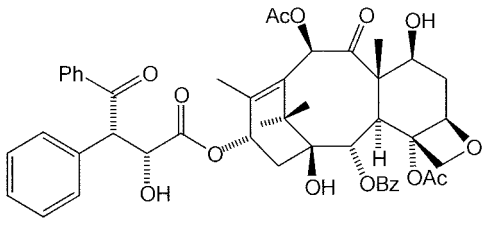
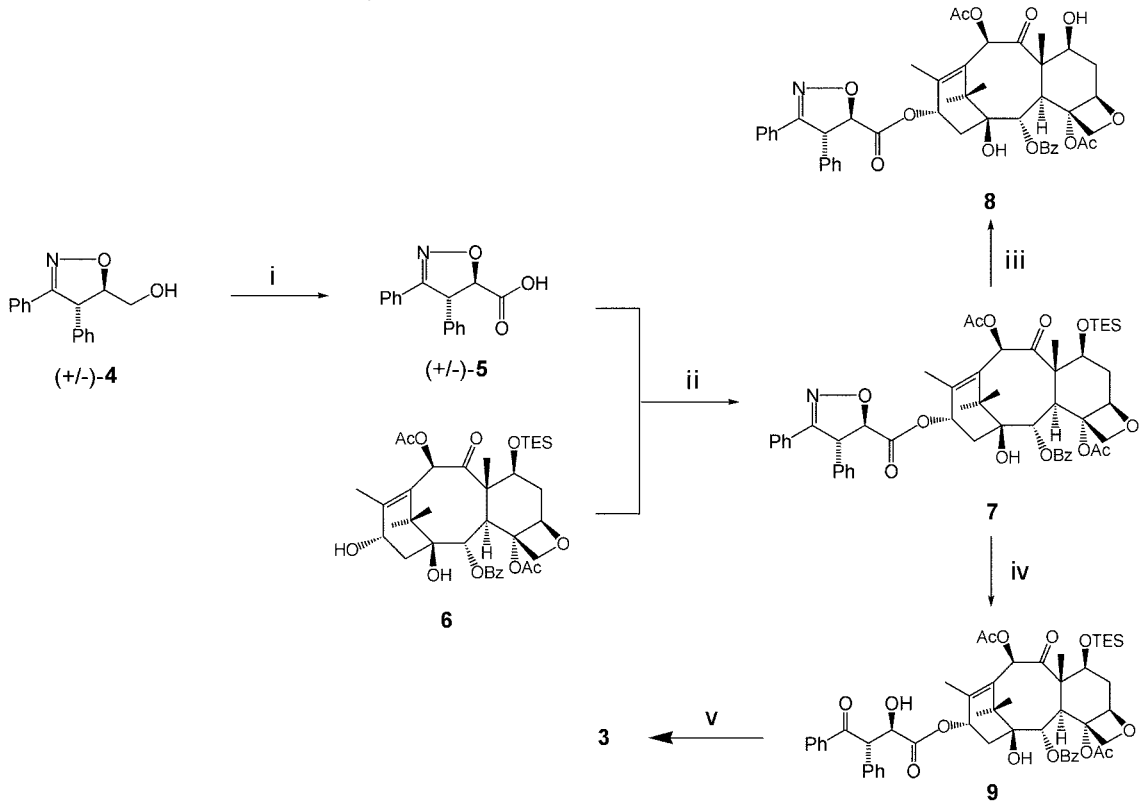
Paclitaxel (**1**), originally isolated from the Pacific yew tree *Taxus brevofolia*,[1] has attracted much attention as a target for chemical and medicinal research[2,3] due to its structural complexity and biological activity.[4] It has been shown to have strong antitumor activity against a variety of malignancies including ovarian, breast, and lung cancers.[5] The structure-activity relationship (SAR) studies have demonstrated that the side chain at the C-13 position of A-ring in paciltaxel is essential for the anticancer activity.[6] A number of analogues with modifications at the side chain have been synthesized and evaluated for the biological activity.[7] A representative example is docetaxel **2** with a *N-t*-Boc moiety



Paclitaxlel **1** : R = Ph, R' = Ac
Docetaxel **2** : R = ^{t}BuO, R' = H



3' - Deaza - Paclitaxel **3**



Scheme 1. The Synthesis of Deazapaclitaxel. *Reagents and conditions*; (i) $RuCl_3/NaIO_4/CCl_4$-CH_3CN-H_2O/rt, 85%; (ii) DCC/DMAP/toluene-THF/rt, 65%; (iii) 1 N HCl/CH_3CN/0 °C, 87%; (iv) H_2/Raney-Ni/$B(OH)_3$/MeOH-H_2O/0 °C, 72%; (v) HF-Py/0 °C/rt, 88%.

Table 1. *In vivo* activities (IC_{50}, μg/mL)[a] of paclitaxel analogs (**3a**, **3b**, and **8**) against human cancer cell lines

Compound	MCF7	MDA-MB-435	BT-549	OVCAR-4	PC-3	LOX-IMVI	UACC62	HCT-116	A549
3a	5	>10	>10	10	6	>10	>10	>10	>10
3b	9	>10	>10	>10	7	>10	>10	>10	>10
8	>10	>10	>10	>10	>10	>10	>10	>10	>10
Paclitaxel	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1

[a]The concentration which produces 50% inhibition of cell proliferation after 48 h of incubation.

replacing the *N*-benzoyl group at the 3'-position of the 13-side chain.[8] The *t*-Boc analogue has been shown to have some increased potency in cytotoxicity or tubulin polymerization assays.[9] As an extension of our continuing efforts in paclitaxel chemistry,[10] we became interested in paclitaxel analogues with new structural modifications at the 13-side chain: particularly, the one (**3**) with no nitrogen at the 3'-position. We herein report the results from the studies on its synthesis and biological evaluation.

The synthesis of **3** started from *trans*-3,4-diphenyl-2-isoxazoline-5-methanol (**4**) which had been prepared in three steps from benzaldehyde according to the literature procedure.[11] The racemic isoxazoline derivative was first oxidized using $RuCl_3$ and $NaIO_4$ in the 2 : 2 : 3 mixture of CCl_4-CH_3CN-Phosphate Buffer (pH 7.2)[12] to give *trans*-3,4-diphenyl-5-carboxy-2-isoxazoline (**5**) in good yield (85%). The isoxazoline carboxylic acid was then coupled using DCC/DMAP with 7-TES-baccatin III (**6**)[13] to afford **7** as a 6 : 4 diastereomeric mixture in 65% yield. The triethylsilyl group at C-7 of **7** was removed readily under the acidic conditions to yield **8** in 87% yield. The isoxazoline ring in the side chain of **7** was cleaved by catalytic hydrogenolysis (H_2, $B(OH)_3$, Raney-Ni, 7 : 1 MeOH-H_2O)[14] to produce a mixture of two separable diastereomers in 72% yield (**9a**, major product, 47%; **9b**, minor product, 25%). Finally, the diastereomers were separately desilylated with the treatment of HF/Py to obtain two diastereomers (**3a** and **3b)** of the target molecule in 88% yield (Scheme 1). The absolute configurations of the stereocenters at the side chain of each diastereomer were not established.

The biological activities of deazapaclitaxel isomers (**3a** and **3b**) and isoxazoline intermediate (**8**) were evaluated in *in vitro* cytotoxicity assays against several human tumor cell lines. The results are given in Table 1. All of them exhibited no significant anticancer activities in all assays. The deaza analogs displayed very weak activities against a few cell lines and no activities against most cell lines. The isoxazoline molecule was virtually inactive against all the cell lines. These observations clearly indicate that 1) the amide functionality of the side chain is an essential structural element required for the anticancer activity; and 2) the major structural modification of the C-13 side chain such as the incorporation of a ring results in the complete loss of the anticancer activity.

Experimental Section

Preparation of compound 5. *trans*-3,4-Diphenyl-2-isoxazoline-5-methanol (**4**) (50 mg, 0.197 mmol) was dissolved in CCl_4/CH_3CN/phosphate buffer (pH 7.5) (0.35 mL/0.35 mL/0.5 mL, 2/2/3). To this solution at 0°C was added $RuCl_3$ (2 mg, 0.00985 mmol), $NaIO_4$(42 mg, 0.591 mmol). After stirring at room temperature for 12h, the reaction mixture was diluted with EtOAc (50 mL) and extracted with saturated $NaHCO_3$ (2 × 50 mL). To the aqueous solution was added 3 *N* HCl (120 mL) and the resulting mixture was extracted with EtOAc (3 × 50 mL). The organic layer was dried and concentrated *in vacuo* to yield **5** (45 mg, 85%): m.p. 187-189 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.61 (m, 2H), 7.26-7.38 (m, 8 H), 5.08 (d, *J* = 3.2 Hz, 1H), 5.00 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 172.2, 158.4, 138.5, 130.5, 129.7, 129.0, 128.9, 128.4, 127.8, 126.3, 86.7, 58.5; HRMS m/z calcd for $C_{16}H_{13}NO_3$ + H 268.0974, obsd 268.0975.

Preparation of compound 7. To a toluene/THF (4 mL, 1/3, v/v) mixture of 7-TES-baccatin III 6 (100 mg, 0.14 mmol) and 5 (75 mg, 0.28 mmol) were added DCC (56 mg, 0.28 mmol) and DMAP (17 mg, 0.14 mmol). The reaction mixture was stirred at room temperature for 10 h and then subjected to silica gel chromatography (50% ethyl acetate in hexane) to afford **7** (96 mg, 65%): m.p. 86-88 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 8.09 (d, *J* = 8.28 Hz, 2H), 7.61-7.64 (m, 3H), 7.46-7.53(m, 2H), 7.29-7.38 (m, 8H), 6.44 (s, 1H), 6.27 (m, 1H), 5.69 (d, J = 6.98 Hz, 1H), 5.28 (d, *J* = 3Hz, 0.35H, minor), 5.15 d, *J* = 2 Hz, 0.65H, major), 5.04 (d, *J* = 4.3 Hz, 0.35H, minor), 5.02 (d, *J* = 4.2 Hz, 0.65H, major), 4.95 (m, 1H), 4.74 (s, OH), 4.50 (m. 1H), 4.31 (d, *J* = 8.27 Hz, 1H), 4.15 (d, J = 8.26 Hz, 1H), 3.86 (d, *J* = 6.99, 1H) 2.59 (m, 1H), 2.32 (s, 3H), 2.30 (m, 2H), 2.16 (s, 3H), 2.02 (s, 3H), 1.90 (m, 1H), 1.70 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H), 0.93 (m, 9H), 0.55 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 202.5, 171.3, 170.7, 169.9, 167.8, 159.0, 140.9, 138.1, 134.5, 134.45, 134.4, 130.8, 130.4, 130.3, 129.5, 129.4, 129.3, 129.2, 128.31, 128.26, 128.23, 87.2, 87.0, 85.0, 84.9, 81.6, 81.4, 79.7, 79.5, 78.9, 77.9, 77.5, 75.8, 75.7, 75.6, 72.9, 72.3, 59.3, 59.2, 58.2, 47.6, 43.9, 37.9 35.8, 27.3, 23.2, 22.6, 21.8, 21.6, 21.5, 15.3, 15.1, 10.77, 10.72, 7.4, 6.0; HRMS m/z calcd for $C_{53}H_{64}O_{13}NSi$ + H 950.4147, obsd 950.4152.

Preparation of compound 8. Compound **7** (50 mg, 0.056 mmol) was dissolved in CH_3CN (1 mL) and treated at 0 °C with 1 *N* HCl (0.5 mL). After stirring at 0 °C for 8h, the reaction mixture was diluted with EtOAc (100 mL) and washed with saturated solution $NaHCO_3$ (2 × 50 mL) and then brine (50 mL). The organic layer was dried and concentrated *in vacuo*. Silica gel chromatography (1 : 1 ethyl acetatehexane) gave 8 (10 mg, 88%): m.p. 146-148 °C; ^{1}H

NMR (300 MHz, $CDCl_3$, ppm) 8.07 (d. *J* = 7.32 Hz, 2H), 7.60-7.63 (m, 3H), 7.46-7.51 (m, 2H), 7.27-7.38 (m, 8H), 6.30 (m, 2H), 5.66 (d, *J* = 7.11 Hz, 1H), 5.23 (d, *J* = 4.23 Hz, 0.35H, minor), 5.16 (d, *J* = 4.32 Hz, 0.65H, major), 5.04 (d, *J* = 4.32 Hz, 0.35H, minor), 5.02 (d, *J* = 4.29 Hz, 0.65H, major), 4.97 (m, 1H), 4.47 (m, 1H), 4.31 (d, *J* = 8.34 Hz, 1H), 4.15 (d, *J* = 8.31 Hz, 1H), 3.84 (d, *J* = 7.11 Hz, 1H), 2.57 (m, 1H), 2.33 (s, 3H), 2.27 (m, 2H), 2.24 (s, 1.5H), 2.22 (s, 1.5H), 1.89 (s, 3H), 1.76 (m, 1H), 1.67 (s, 3H), 1.25 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 204.4, 204.3 171.9, 171.2, 170.9, 170.8, 167.7, 159.03, 143.2, 138.0, 137.9, 134.4, 133.7, 131.2, 130.8, 130.4, 130.3, 130.0, 129.9, 129.5, 129.4, 129.3, 129.2, 129.1, 128.25, 128.2, 87.2, 86.98, 85.2, 85.13, 81.5, 81.4, 80.2, 79.9, 78.7, 77.91, 77.50, 76.2, 75.9, 75.7, 72.8, 72.3, 59.3, 59.2, 59.1, 58.4, 46.4, 43.9, 36.4, 36.2, 32.3, 30.4, 27.5, 23.3, 23.1, 22.6, 21.5, 15.8, 15.7, 10.3; HRMS m/z calcd for $C_{47}H_{50}O_{13}N$ + H 836.3282, obsd 836.3285.

Preparation of compounds 9a and 9b. To a MeOH-H_2O (2 mL, 7/1, v/v) solution of **7** (50 mg, 0.0526 mmol) were added Raney-Ni (10 mol%) and $B(OH)_3$ (13 mg, 0.21 mmol). Under the pressure of H_2 gas (1 atm, balloon), the reaction mixture was stirred at 0 °C for 8h. The reaction mixture was then diluted with EtOAc (50 mL), filtered to remove Raney-Ni, and washed with 1 *N* HCl (50 mL) and brine (50 mL). The organic layer was dried and concentrated *in vacuo*. The residue was chromatographed (1 : 1 ethyl acetatehexane) to give the desired products **9a** (23 mg, 47%) and **9b** (13 mg, 25%).

9a: m.p. 134-136 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 8.07 (d, *J* = 7.40 Hz, 2H), 7.90 (d, *J* = 7.48 Hz, 2H), 7.59-7.64 (m, 1H), 7.46-7.51 (m, 3), 7.32-7.3 (m, 7H), 6.48 (s, 1H), 6.06 (m, 1H), 5.64 (d, *J* = 6.99 Hz, 1H), 5.21 (d, *J* = 5.18 Hz, 1H), 4.94 (d, *J* = 8.67 Hz, 1H), 4.67 (dd, *J* = 9.81, 5.18 Hz, 1H), 4.50 (m. 1H), 4.27 (d, *J* = 8.20 Hz, 1H), 4.13 (d, *J* = 8.29 Hz, 1H), 3.93 (d, *J* = 10.08, OH), 3.82 (d, *J* = 6.89, 1H), 2.53 (m, 1H), 2.32 (s, 3H), 2.27-2.35 (m, 2H), 2.19 (s, 3H), 2.17 (s, 3H), 1.87 (m, 1H), 1.68 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 0.94 (m, 9H), 0.59 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 202.6, 200.8, 173.6, 170.9, 169.8, 167.7, 141.3, 136.2, 135.6, 134.44, 134.36, 134.1, 130.7, 130.0, 129.9, 129.8, 129.3, 129.2, 128.8, 84.9, 81.4, 79.7, 77.1, 75.6, 75.4, 72.9, 71.7, 59.1, 57.5, 47.5, 43.8, 37.9, 35.9, 27.2, 22.9, 21.6, 21.5, 15.2 10.7, 7.4, 5.95; HRMS m/z calcd for $C_{53}H_{64}O_{14}Si$ + H 953.4144, obsd 953.4137

9b: m.p. 124-127 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 8.07 (d. *J* = 7.32 Hz, 2H), 7.94 (d, *J* = 7.44 Hz, 2H), 7.58-7.63 (m, 1H), 7.45-7.50 (m, 3H), 7.35-7.40 (m, 7H), 6.31 (s, 1H), 6.03 (m, 1H), 5.64 (d, *J* = 6.93 Hz, 1H), 5.17 (d, *J* = 6.45 Hz, 1H), 4.96 (d, *J* = 8.31 Hz, 1H), 4.79 (m, 1H), 4.69 (s, OH), 4.38 (m, 1H), 4.29 (d, *J* = 8.37 Hz, 1H), 4.15 (d, *J* = 8.28 Hz, 1H), 3.83 (d, *J* = 7.47, 1H), 3.74 (d, *J* = 6.90, OH), 2.55 (m, 1H), 2.43 (s, 3H), 2.31 (m, 2H), 2.14 (s, 3H), 1.88 (m, 1H), 1.67 (s, 3H), 1.43 (s, 3H), 1.18 (s, 3H), 1.11 (s, 3H), 0.91 (m, 9H), 0.57 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 202.4, 200.0, 172.5, 170.7, 169.8, 167.7, 140.5, 136.3, 134.9, 134.4, 134.3, 130.7, 130.1, 129.9, 129.7, 129.3, 129.2, 129.0, 84.8, 81.7, 79.4, 77.9, 75.7, 75.4, 73.0, 71.8, 59.2, 57,4, 47.6, 43.7, 37.9, 36.3, 27.2, 23.4, 21.5, 21.3, 14.6 10.6, 7.4, 5.9.

Preparation of compounds 3a and 3b. To a pyridine solution (1 mL) of **9a** or **9b** (20 mg, 0.021 mmol) was added HF-Pyridine (50 μL) at 0 °C. After stirring at room temperature for 4 h, the reaction mixture was diluted with EtOAc (100 mL) and washed first with a saturated solution of $CuSO_4$ (2 × 50 mL) and then brine (50 mL). The organic layer was dried and concentrated *in vacuo*. The residue was chromatographed (1 : 1 ethyl acetatehexane) to give desired product (15.5 mg, 0.018 mmol, 88%).

3a: m.p. 153-156 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 8.07 (d, *J* = 7.20 Hz, 2H), 7.90 (d, *J* = 7.53 Hz, 2H), 7.60-7.63 (m, 1H), 7.49-7.52 (m, 3H), 7.32-7.4 (m, 7H), 6.32 (s, 1H), 6.08 (m, 1H), 5.63 (d, *J* = 6.96 Hz, 1H), 5.29 (s, OH), 5.21 (d, *J* = 5.19 Hz, 1H), 4.96 (d, *J* = 8.88 Hz, 1H), 4.69 (dd, *J* = 8.37, 4.78 Hz, 1H), 4.47 (m, 1H), 4.27 (d, *J* = 8.40 Hz, 1H), 4.13 (d, *J* = 8.21 Hz, 1H), 3.90 (d, *J* = 9.23, OH), 3.81(d, *J* = 5.74 Hz, 1H), 2.53 (m, 1H), 2.32 (s, 3H), 2.27-2.35 (m, 1H), 2.24 (s, 3H), 2.05 (s, 3H), 1.91 (m, 1H), 1.66 (s, 3H), 1.21 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 204.5, 200.8, 173.6, 171.9, 171.0, 167.7, 141.6, 136.2, 135.5, 134.52, 134.48, 133.3, 130.8, 130.0, 129.9, 129.8, 129.4, 129.3, 128.9, 85.1, 81.4, 80.0, 77.9, 77.0, 76.3, 75.7, 75.5, 72.8, 71.7, 59.2, 57.6, 46.3, 43.7, 36.2, 36.1, 30.4, 27.4, 22.9, 22.5, 21.5, 15.8 10.2; HRMS m/z calcd for $C_{47}H_{51}O_{14}$ + H 839.3279, obsd 839.3290.

3b: m.p. 157-160 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 8.07 (d, *J* = 7.23 Hz, 2H), 7.93 (d, *J* = 7.35 Hz, 2H), 7.60-7.65 (m, 1H), 7.47-7.54 (m, 3H), 7.29-7.42 (m, 7H), 6.17 (s, 1H), 6.03 (m, 1H), 5.64 (d, *J* = 6.93 Hz, 1H), 5.15 (d, *J* = 6.42 Hz, 1H), 4.97 (d, *J* = 8.07 Hz, 1H), 4.78 (m, 1H), 4.37 (m, 1H), 4.31(d, *J* = 8.07 Hz, 1H), 4.16 (d, *J* = 8.34 Hz, 1H), 3.75 (d, *J* = 7.02 Hz, 1H), 3.74 (d, *J* = 8.49 Hz, OH), 2.55 (m, 1H), 2.42 (s, 3H), 2.31-2.42 (m, 2H), 2.22 (s, 3H), 2.17 (s, 3H), 1.88 (m, 1H), 1.66 (s, 3H), 1.19 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 202.4, 200.0, 172.5, 171.9, 170.8, 167.7, 142.8, 136.2, 134.9, 134.5, 134.48, 134.0, 130.7, 130.2, 129.8, 129.7, 129.4, 129.1, 85.1, 81.7, 79.8, 77.9, 77.1, 76.3, 75.5, 75.1, 72.9, 71.9, 59.3, 57,6, 46.4, 43.7, 36.6, 36.3, 27.4, 23.4, 22.2, 21.5, 15.2, 10.2; HRMS m/z calcd for $C_{47}H_{51}O_{14}$ + H 839.3279, obsd 839.3289.

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