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Synthesis and biological evaluation of novel 3′-*N*-*tert*-butylsulfonyl analogues of docetaxel

Bowen Ke [a], Yong Qin [a,*], Fengyan Zhao [b], Yi Qu [b,*]

[a] Department of Chemistry of Medicinal Natural Products, Key Laboratory of Drug Targeting and Drug Delivery System of Ministry of Education, West China School of Pharmacy, Sichuan University, Chengdu 610041, PR China
[b] Department of Pediatrcs, West China Second University Hospital, Sichuan University, Chengdu 610041, PR China

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ABSTRACT

Novel 3′-*N*-*tert*-butylsulfonyl analogues **10a**–**c** of docetaxel were synthesized and their biological evaluation in cytotoxicity in vitro against several human tumor cell lines were presented. The biologically tested results showed that *N*-oxide pyridyl substituted**10b**–**c** had potent cytotoxicities against human tumor cell lines Eca-109, SKOV3, SMMC-7721, HCT-8, PC3, MCF-7, HeLa and KB.

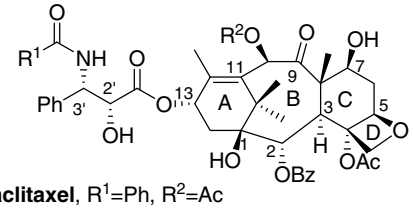
Paclitaxel (Taxol, Fig. 1), a naturally occurring diterpenoid, isolated from the bark of Pacific yew tree *Taxus brevofolia* in 1971 (Fig. 1),[1] has shown remarkably high antitumor activity.[2] It has been considered as one of the most important antitumor agents[3] and was approved by FDA for the treatment of advanced ovarian cancer and breast cancer in 1992 and 1994, respectively. Clinical trials have demonstrated that paclitaxel also was of utility for treatment of lung, skin, and head and neck cancers.[4] Docetaxel (Taxotere, Fig. 1),[5] a semisynthetic analogues, has also exhibited encouraging clinical usage and was approved by FDA for the treatment of breast cancer in 1996. The anti-cancer activity of these compounds is ascribed to their unique mechanism of action as promoters of tubulin assembly and inhibitors of microtubule disassembly.[6] Although both paclitaxel and docetaxel possess potent antitumor activity, utility of these drugs results in some undesirable side effects, such as low tumor selectivity, development of multi-drug resistance (MDR),[7] and poor solubility in aqueous solutions.[8] Therefore, development of new anticancer agents with fewer side effects, improved pharmacological properties and activity against various cancers has been a long term effort by medicinal chemists.

Extensive structure–activity relationship (SAR) studies over the past two decades have led to several promising clinical candidates of paclitaxel and docetaxel analogues. These SAR studies were mainly focused on changes to A, B, C, D-rings[9–12] and the side-chain.[13]

SAR studies so far indicate that the C-13 side chain is essential for antitumor activity. The stereochemistry of the side chain at the C2′ and C3′ is crucial for biological activity.[14] Deletion of either 2′-hydroxy group or 3′-phenyl group leads to analogues with reduced biologic activity.[15] It is also known that analogues without a 3′-*N*-acyl group are significantly less active than paclitaxel and aliphatic and heteroaromatic 3′-*N*-acyl analogues are slightly more active than paclitaxel.[16]

Although a large number of 3′-*N*-acyl analogues were investigated, SAR studies of 3′-*N*-sulfonyl analogues have received little attention. A few of paclitaxel analogues with 3′-*N*-phenylsulfonyl group were reported with significant loss of antitumor activity.[17] In this letter, we report our efforts on the synthesis and biological evaluation of several novel 3′-*N*-*tert*-butylsulfonyl docetaxel analogues **10a–c**.

The synthesis of novel 3′-*N*-*tert*-butylsulfonyl analogues **10a–c** of docetaxel was accomplished by following two synthetic proce-



Paclitaxel, R^1=Ph, R^2=Ac
Docataxel, R^1=*tert*-BuO, R^2=H

Figure 1. The Structures of Paclitaxel and Docataxel.

* Corresponding authors. Tel./fax: +86 28 85503842.
E-mail address: yongqin@scu.edu.cn (Y. Qin).

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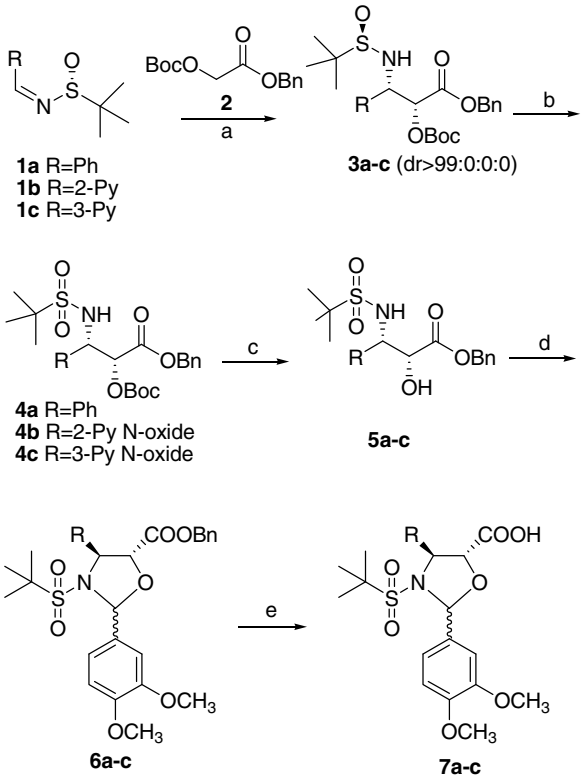
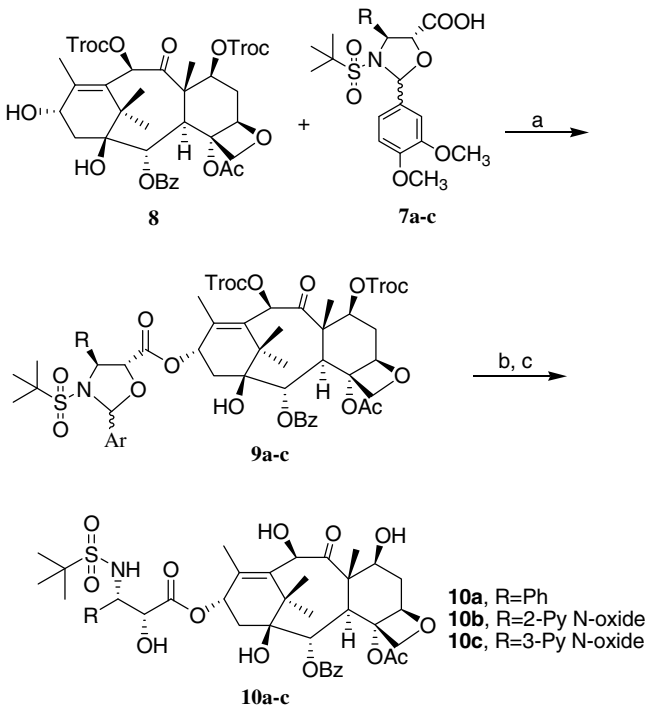
Table 1
Cytotoxicity data (IC_{50}, μM) for taxoids **10a–c** against human cancer cell lines[a]

Taxoids	Eca-109	SKOV3	SMMC-7721	HCT-8	PC3	MCF-7	Hela	KB	K562
Paclitaxe	2.73 (±0.28)	2.43 (±0.26)	2.86 (±0.26)	3.29 (±0.30)	2.85 (±0.28)	2.98 (±0.27)	3.11 (±0.28)	2.54 (±0.22)	3.65 (±0.35)
Docetaxel	2.60 (±0.24)	2.35 (±0.24)	2.73 (±0.25)	3.07 (±0.26)	2.77 (±0.28)	3.29 (±0.30)	3.03 (±0.31)	2.35 (±0.29)	2.96 (±0.28)
10a	7.14 (±0.54)	7.09 (±0.22)	>10	9.12 (±0.88)	6.83 (±0.45)	7.88 (±0.56)	9.54 (±0.87)	7.68 (±0.56)	>10
10b	1.95 (±0.21)	2.28 (±0.24)	2.54 (±0.25)	2.85 (±0.29)	1.98 (±0.22)	2.11 (±0.18)	2.54 (±0.23)	2.12 (±0.23)	2.89 (±0.26)
10c	2.52 (±0.23)	2.41 (±0.26)	2.45 (±0.26)	3.03 (±0.27)	2.64 (±0.27)	2.68 (±0.28)	2.67 (±0.28)	2.32 (±0.22)	3.33 (±0.23)

[a] Values are means of three experiments, standard deviation is given in parentheses.



Scheme 1. Reagents and conditions: (a) LiHMDS, THF, −78 °C, 3 h, 72–97%; (b) *m*-CPBA, MeOH, 60 °C, 2 h, 50–63%; (c) TFA, CH_2Cl_2, rt, 1 h; (d) 3,4-dimethoxybenzaldehyde dimethyl acetal, toluene, PPTS, 76–85%; (e) $Pd(OH)_2$, AcOEt, 1 atm H_2, 2 h, 93–99%.



Scheme 2. Reagents and conditions: (a) DCC or DPC, DMAP, toluene, 80 °C, 18 h, 45–72%; (b) TFA, CH_2Cl_2, rt, 2 h, 58–63%; (c) Zn, AcOH, MeOH, 60 °C, 2 h, 50–63%.

dures: (1) asymmetric synthesis of side chain oxazolidines **7a–c** and (2) condensation of the side chain **7a–c** with 7,10-ditrocbaccatin III.

Oxazolidines **7a–c** were synthesized via a five-step route from benzyl *O*-Boc-α-hydroxyacetate**2** (Scheme 1). The substituted isoserines **3a–c** with S_R,2*R*,3*S* absolute configurations were prepared in 72–97% yields by a diastereoselective enolate addition of **2** with (S_R)-*tert*-butylsulfinylimine **1a–c** by adopting our previous methord.[18] Oxidation of **3a–c** to the corresponding sulfonamides **4a–c** with *m*-CPBA, followed by deprotection of Boc group in **4a–c** with TFA afforded alcohols **5a–c**. Alcohols **5a–c** were condensed with 3,4-dimethoxybenzaldehyde dimethyl acetal in the presence of PPTS to afford oxazolidines **6a–c** as a diastereomeric mixture in a 3:1 ratio. Removal of the benzyl group in **6a–c** afforded the corresponding carboxylic acids **7a–c** by hydrogenolysis with 5% $Pd(OH)_2$ (Pearlman's catalyst). Coupling of acids **7a–c** with 7,10-ditrocbaccatin III (**8**)[19] was carried out by using DCC or DPC as coupling reagents to afford **9a–c** in 45–72% yields (Scheme 2). Treatment of **9a–c** with TFA, followed by removal of Troc groups with Zn/AcOH at 60 °C provided taxoids **10a–c**[20] in 50–63% yields.

The synthesized taxoids **10a–c** were tested for their cytotoxicity against various cancer cells. As a result of in vitro studies, **10b–c** showed the same level of potencies against human cancer cell lines such as Eca-109, SKOV3, SMMC-7721, HCT-8, PC3, MCF-7, HeLa and KB, while **10a** showed less cytotoxic activity in comparison to paclitaxel and docetaxel (Table 1).

In conclusion, we have synthesized the novel 3′-*N*-*tert*-butylsulfonyl docetaxel analogues **10a–c** and found that *N*-oxide pyridyl substituted 3′-*N*-*tert*-butylsulfonyl analogues **10b–c** showed potent activities against human cancer cell lines used in our study.

Acknowledgments

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20. Compound **10a**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 8.07 (d, J = 7.6 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.4 Hz, 2H), 7.31–7.42 (m, 5H), 6.14 (t, J = 8.3 Hz, 1H), 5.68 (s, 1H), 5.64 (d, J = 7.2 Hz, 1H), 5.18 (s, 1H), 4.90 (d, J = 2 Hz, 1H), 4.57 (s, 1H), 4.19 and 4.28 (2d, J = 8.8, 8.4 Hz, 2H), 3.85 (d, J = 8.4 Hz, 1H), 2.50–2.58 (m, 1H), 2.31 (s, 3H), 2.21–2.27 (m, 2H), 2.17 (s, 3H), 1.99–2.06 (m, 1H), 1.74 (s, 3H), 1.26 (s, 9 H), 1.20 (s, 3H), 1.04 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.8, 170.1, 169.9, 166.8, 162.7, 153.2, 153.1, 149.8, 148.8, 142.7, 139.6, 133.7, 131.8, 130.0, 129.6, 129.1, 128.7, 128.6, 128.5, 128.3, 128.1, 127.8, 127.5, 120.9, 111.0, 110.6, 83.7, 83.6, 80.5, 79.1, 79.0, 77.4, 77.1, 76.4, 76.2, 74.3, 72.1, 66.8, 61.4, 56.1, 55.9, 55.8, 46.9, 43.1, 35.8, 33.9, 33.2, 26.3, 24.1, 21.7, 21.1, 15.3, 10.7 ppm; Anal. Calcd for $C_{42}H_{53}NO_{14}S$: C, 60.92; H, 6.45; N, 1.69. Found: C, 60.81; H, 6.38; N, 1.74; HRMS (FAB) calcd for $C_{42}H_{53}NO_{14}S$ (M+Na$^+$) 850.3079, found 850.3050. Compound **10b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 6.4 Hz, 1H), 8.10 (d, J = 7.4 Hz, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.33–7.37 (m, 4H), 6.22 (m, 1H), 5.68 (s, 1H), 5.56 (d, J = 7.2 Hz, 1H), 5.18 (s, 1H), 4.93 (d, J = 2 Hz, 1H), 4.60 (s, 1H), 4.19 and 4.30 (2d, J = 8.8, 8.4 Hz, 2H), 3.87 (d, J = 8.4 Hz, 1H), 2.50–2.58 (m, 1H), 2.37 (s, 3H), 2.22–2.27 (m, 2H), 2.17 (s, 3H), 1.99–2.06 (m, 1H), 1.75 (s, 3H), 1.24 (s, 9 H), 1.18 (s, 3H), 1.04 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.1, 172.0, 170.6, 166.7, 159.8, 142.0, 138.8, 133.8, 132.2, 130.1, 129.8, 129.0, 128.9, 128.6, 127.5, 127.8, 126.8, 106.1, 83.5, 80.9, 79.1, 78.5, 77.4, 75.1, 74.0, 72.1, 68.3, 59.7, 56.3, 55.9, 46.9, 42.9, 35.5, 33.3, 26.5, 24.1, 22.4, 20.5, 14.8, 9.8 ppm; Anal. Calcd for $C_{42}H_{53}NO_{14}S$: C, 58.28; H, 6.20; N, 3.32. Found: C, 58.11; H, 6.28; N, 3.21; HRMS (FAB) calcd for $C_{41}H_{52}N_2O_{15}S$ (M+Na$^+$) 867.2880, found 867.2850. Compound **10c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.14 (d, J = 6.4 Hz, 1H), 8.11 (d, J = 7.4 Hz, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.33–7.43 (m, 4H), 6.13 (m, 1H), 5.67 (d, J = 7.0 Hz, 1H), 5.64 (d, J = 7.2 Hz, 1H), 5.22 (s, 1H), 4.93 (d, J = 9.3 Hz, 1H), 4.64 (s, 1H), 4.20 and 4.30(2d, J = 8.8, 8.4 Hz, 2H), 3.93 (d, J = 8.4 Hz, 1H), 2.56–2.63 (m, 1H), 2.40 (s, 3H), 2.21–2.27 (m, 2H), 2.09 (s, 3H), 1.99–2.08 (m, 1H), 1.77 (s, 3H), 1.26 (s, 9 H), 1.20 (s, 3H), 1.15 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.4, 174.7, 170.3, 166.8, 159.8, 142.0, 138.8, 134.4, 132.2, 129.8, 129.0, 128.8, 128.5, 127.8, 127.5, 126.8, 106.1, 83.5, 80.9, 79.1, 78.5, 76.8, 75.1, 74.0, 72.1, 68.4, 60.3, 56.3, 55.9, 46.9, 42.9, 35.5, 33.3, 27.4, 23.9, 22.4, 20.5, 13.6, 9.9 ppm; Anal. Calcd for $C_{42}H_{53}NO_{14}S$: C, 58.28; H, 6.20; N, 3.32. Found: C, 58.13; H, 6.29; N, 3.43; HRMS (FAB) calcd for $C_{41}H_{52}N_2O_{15}S$ (M+Na$^+$) 867.2880, found 850.2861.