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Biological evaluation of new antitumor taxoids: Alteration of substitution at the C-7 and C-10 of docetaxel

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ABSTRACT

A series of new docetaxol analogues have been designed and synthesized. And their cytotoxicities against cancer cells have been evaluated by MTT method. Most of these compounds showed selective inhibitions on human cancer cell lines. Among them, compound **8** exhibited higher inhibitory activity than Paclitaxel (Taxol) against several cancer cell lines. This work indicated that appropriate modification at C-7 and C-10 of docetaxel might be a promising approach for this unique class of anticancer compounds.

Paclitaxel (i.e., Taxol) isolated from Taxus brevifolia in 1971 by Wani and Wall,[1–3] is anticancer drugs[4] of the taxoid series. Paclitaxel inhibits cells growth by interacting with microtubules.[5–7] Paclitaxel is one of the most popular chemotherapeutic agents used nowadays for treatment of ovarian, breast, and non-small cell lung cancers.[5–13] Since Paclitaxel was discovered, its structure has been extensively studied and modified. Taxols bind to different sites of β-tubulin and promote the polymerization of tubulin. This action disrupts the tubulin-microtubule equilibrium and destroys the cancer cell division process by inducing cell cycle arrest and leads ultimately to cell death by apoptosis.[14–16] Due to the aqueous solubility of Paclitaxel, docetaxel has been developed to overcome this shortcoming. Docetaxel[17–20] also exhibited stronger antitumor activity than Paclitaxel on the in vitro and in vivo experimental models.[21–23] Studies on the structure–activity relationships (SAR) of Paclitaxel and docetaxel have resulted in the discovery of cabazitaxel as the third generation of anti-cancer drugs in the taxoids. Cabazitaxel (compound **3**), a potent tubulin binding taxane drug, is used to treat resistant prostate cancer that has progressed after having had other chemotherapy.[24–27] Two methyl moieties at C-7 and C-10 of compound **3** play the essential role for its distinguished antitumor effects. We assumed that these two methyl moieties at C-7 and C-10 of compound **3** may interact with the hydrophobic pocket of tubulin. Herein, we decided to keep the side chain and oxetane ring intact and pay our attention to the substitution at the C-7 and C-10 position of compound **3** by replacing with more hydrophobic parts (Fig. 1).

To synthesize the taxol analogues **4**–**8**,[28] a parallel synthetic approach from the common precursor **13** was employed. Compound **13** was designed as shown in Scheme 1. Following the general protocol,[29–32] we synthesized compounds **4**–**8** starting from 10-deacetyl baccatinIII (**9**), and compound **13** was obtained in three steps: (1) the protection of 7,10-OH with TrocCl. The protection of 7,10-OH of compound **9** was achieved by treatment with TrocCl to give compound **10** (81% yield); (2) Fischer–Speier Esterification at C-13 of compound **10** was then prepared with 2-(4-OMe)phenyl-1,3-oxazolidine derivative of N-Boc-phenylisoserine **11**, DCC and DMAP in toluene at 85 °C leading to compound **12** with a good yield (92%); (3) selective deprotection of the Troc (2,2,2-trichloroethyloxycarbonyl) ether was accomplished using Zn/AcOH/MeOH to obtain compound **13** with a good yield (90%).

Esterification at C-7 and C-10 of compound **13** with 3-((*tert*-butyldimethylsilyl)oxy)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methylpropanoic acid, DCC and DMAP in DCM led to obtain compound **18** with 28% yield under refluxing conditions. The compounds **14**–**17** was synthesized by using POTf/DIPEA/DCE/Toluene.[33–35] (Scheme 2).

Selective deprotection of the TBS ether was accomplished using TBAF/THF (Fig. 2).[36]

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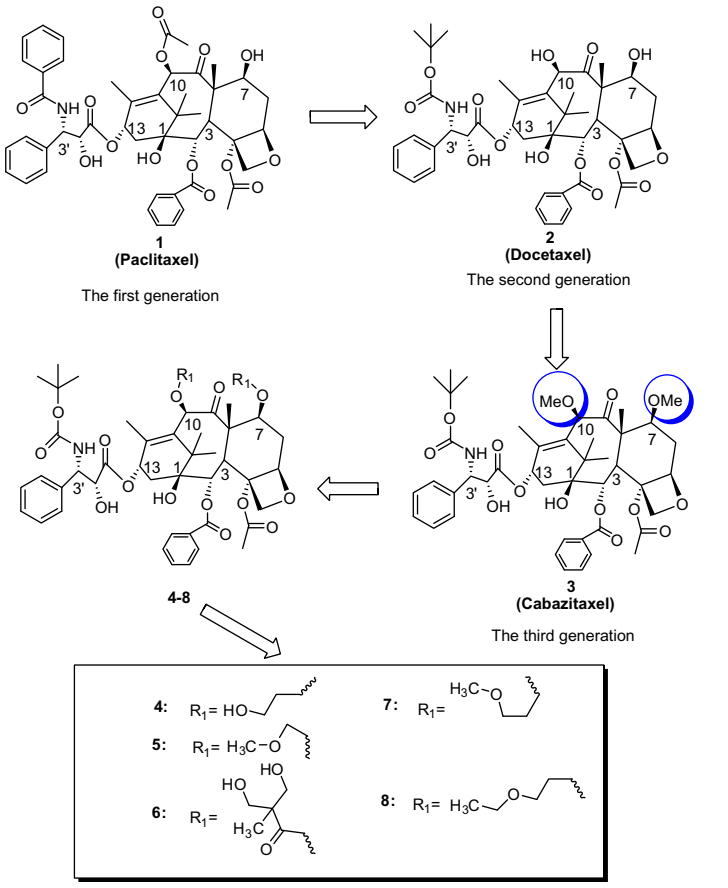
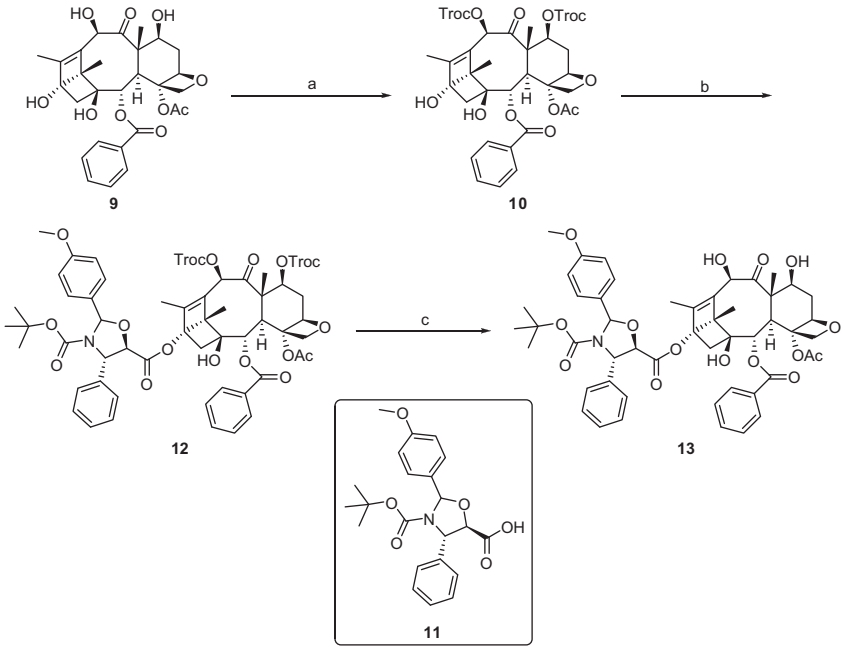


Figure 1. Design of new taxol-like molecules.



Scheme 1. Reagents and conditions: (a) TrocCl, Pyridine, rt, 81%; (b) **11**, DCC, DMAP, toluene, 85 °C, 92%; (c) Zn, AcOH, MeOH, 30 °C, 90%.

Finally, removal of all the protective groups in one step with *p*-toluenesulfonic acid in methanol afforded the desired compounds **4**–**8**. (Fig. 3).

Cytotoxicities of compounds **4**–**8** against several human solid tumor cell lines, such as K562, HL60, PANC-1, Huh-7, Molt-4, BGC823, HT1080, Hela, A549, MCF-7, A431, BEL-7402, Hela,

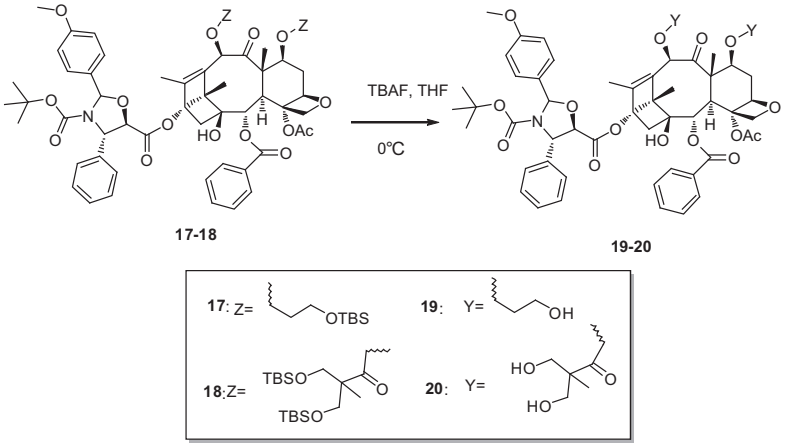
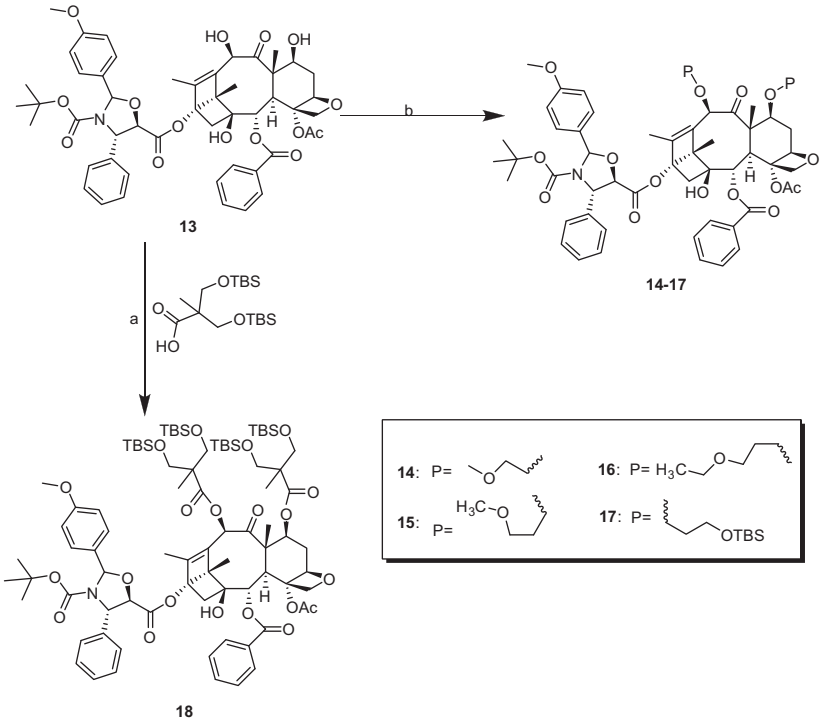


Figure 2. The synthsis of **19** and **20**.



Scheme 2. Reagents and conditions: (a) DCC, DMAP, DCM, rt (28%); (b) POTf, DIPEA, DCE/Toluene = 1:1, 55 °C.

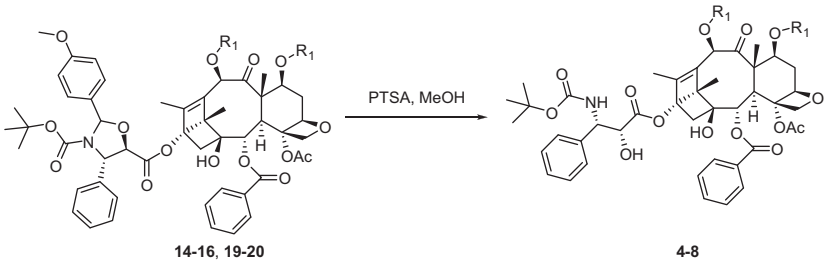


Figure 3. The synthesis of new taxol-like molecules.

SGC-7901, U937, and DU145, were evaluated by MTT assays with taxol as positive control. The results were listed in Table 1. Some of these compounds were found excellent selective inhibitory effects between these human cancer cell lines. For instance, compound **8** showed significant inhibitiory preference to human cancer cell lines Huh-7, HT1080, A549, MCF-7, BEL-7402, SGC-7901,

Table 1
Inhibitory activities of Taxol and compounds **4**–**8** against cell growth

Cell lines[a]	GI50[b] (nM)						
	Taxol	3	4	5	6	7	8
HT1080	3.889	1.406	471.8	NA	165.8	479.9	2.831
Huh-7	206.7	ND	112.6	257.1	103.8	226.8	87.5
A549	18.73	1.483	6.76	562.7	159.3	3.105	1.943
Hela	3.206	1.799	6.654	1.239	225.1	407.3	2.533
HL60	ND	4.736	118.5	1233	376	57.9	63.7
A431	2.355	1.483	38.5	275	1.25	6.73	2.27
MCF-7	1.29	1.187	7.413	615.2	130.3	344.8	1.193
DU145	5.568	1.429	412.6	2.091	65.13	982.5	3.685
U937	2.392	0.5391	7.413	6.152	198.5	38.75	1.952
BEL-7402	1.792	ND	56.03	660.8	11.9	57.3	1.558
SGC-7901	3.088	0.3553	92.45	966	558	68.2	2.273
K562	7.014	4.186	469.9	NA	554.5	935.6	483.3
PANC-1	2.409	1.283	295.7	1.889	170.5	294.7	149.8
BGC823	3.605	467.2	128.3	80.55	983.5	1.995	816.3
Molt-4	2.232	ND	ND	ND	263.3	749.4	267.8

[a] HT1080: fibrosarcoma cells; Huh-7: a human hepatoma cell line; A549: human lung adenocarcinoma cell line; Hela: human cervical carcinoma cell; HL60: the human promyelocytic leukaemia cell line;A431: epidermoid carcinoma cells; MCF-7: human breast cancer; DU145: human prostatic cancer cells; U937: the human histiocytic lymphoma cell line; BEL-7402: human hepatocellular carcinoma; SGC-7901: human gastric cancer cell line; K562: human myelogenous leukemiac; PANC-1: the human pancreatic carcinoma cell line; Molt-4: lymphocytic leukemia; BGC823: human gastric carcinoma cells.
[b] NA: not active; ND: not detectable.

U937, and DU145. What's more, its inhibition against A549 cell growth was 9–10 times more potent than taxol. And its inhibition against human cancer cell lines (MCF-7, and A549) growth was as good as compound **3**. Compound **5** showed significant inhibition preference to human cancer cell lines Molt-4, Hela and PANC-1, but no cytotoxicity was observed against K562 and HT1080.

Compound **5** with methoxymethane linker at the C-7 and C-10 didn't show inhibition against HT1080 and K562 cell lines which was unlike with that compound **4**. To our surprise, compound **8** with diethyl ether linkage was identified as the best compound in this series.

In summary, we have successfully designed and synthesized a series of taxols by introducting of conformational constraints to the skeleton of compound **3**. Biological evaluation of these taxols showed that most dimeric compounds retained the inhibitory selectivity on different human cancer cell lines. Compound **8** with diethyl ether linkage exhibited the most potent inhibitory activities in this series of compounds. We also found that hydrophobic groups linkage had most potent inhibitory activities.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.12.083.

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28. *Compound **4**:* ^{1}H NMR (400 MHz, CDCl3): δ 8.08 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.39–7.40 (m, 4H), 7.34–7.31 (m, 1H), 6.20 (t, J = 9 Hz, 1H), 5.62(d, J = 7.5 Hz, 1H), 5.43 (d, J = 10.0 Hz, 1H), 5.27 (s, 1H), 4.96 (d, J = 10 Hz, 1H), 4.80 (s, 1H), 4.62 (s, 1H), 4.29 (d, J = 8.5 Hz, 1H), 4.17 (d, J = 8.5 Hz, 1H), 3.85 (dd, J = 11.0 Hz, J = 6.5 Hz, 1H), 3.81–3.76 (m, 5H), 3.55–3.72 (m, 4H), 3.45 (s, 1H), 2.24–2.29 (m, 2H), 2.04 (s, 3H), 1.87 (s, 3H), 1.79–1.82 (m, 1H), 1.76 (s, 3H), 1.59–1.71 (m, 4H), 1.36 (s, 9H), 1.27 (s, 3H), 1.25 (s, 3H) ppm.
*Compound **5**:* ^{1}H NMR (400 MHz, CDCl3): δ 8.08 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.39–7.40 (m, 4H), 7.34–7.31 (m, 1H), 6.20 (t, J = 9 Hz, 1H), 5.62(d, J = 7.5 Hz, 1H), 5.43–5.47 (m, 5H), 5.27 (s, 1H), 4.96 (d, J = 10 Hz, 1H), 4.80 (s, 1H), 4.62 (s, 1H), 4.29 (d, J = 8.5 Hz, 1H), 4.17 (d, J = 8.5 Hz, 1H), 3.85 (dd, J = 11.0 Hz, J = 6.5 Hz, 1H), 3.80 (d, J = 7.5 Hz, 1H), 3.45 (s, 1H), 3.32 (s, 3H), 3.28 (s, 3H), 2.24–2.29 (m, 2H), 2.04 (s, 3H), 1.87 (s, 3H), 1.79–1.82 (m, 1H), 1.76 (s, 3H), 1.59–1.71 (m, 4H), 1.36 (s, 9H), 1.27 (s, 3H), 1.25 (s, 3H) ppm.
*Compound **6**:* ^{1}H NMR (400 MHz, CDCl3): δ 8.08 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.39–7.40 (m, 4H), 7.34–7.31 (m, 1H), 6.20 (t, J = 9 Hz, 1H), 5.62(d, J = 7.5 Hz, 1H), 5.43 (d, J = 10.0 Hz, 1H), 5.27 (s, 1H), 4.96 (d, J = 10 Hz, 1H), 4.80 (s, 1H), 4.62 (s, 1H), 4.29 (d, J = 8.5 Hz, 1H), 4.17 (d, J = 8.5 Hz, 1H), 3.85 (dd, J = 11.0 Hz, J = 6.5 Hz, 1H), 3.82–3.84 (m, 8H), 3.80 (d, J = 7.5 Hz, 1H), 3.45 (s, 1H), 2.24–2.29 (m, 2H), 2.04 (s, 3H), 1.87 (s, 3H), 1.79–1.82 (m, 1H), 1.76 (s, 3H), 1.59–1.71 (m, 4H), 1.36 (s, 6H), 1.36 (s, 9H), 1.27 (s, 3H), 1.25 (s, 3H) ppm.
Compound 7: ^{1}H NMR (400 MHz, CDCl3): δ 8.08 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.39–7.40 (m, 4H), 7.34–7.31 (m, 1H), 6.20 (t, J = 9 Hz, 1H), 5.62(d, J = 7.5 Hz, 1H), 5.43 (d, J = 10.0 Hz, 1H), 5.27 (s, 1H), 4.96 (d, J = 10 Hz, 1H), 4.80 (s, 1H), 4.62 (s, 1H), 4.29 (d, J = 8.5 Hz, 1H), 4.17 (d, J = 8.5 Hz, 1H), 3.85 (dd, J = 11.0 Hz, J = 6.5 Hz, 1H), 3.81–3.76 (m, 5H), 3.55–3.72 (m, 4H), 3.45 (s, 1H), 3.32 (s, 3H), 3.28 (s, 3H), 2.24–2.29 (m, 2H), 2.04 (s, 3H), 1.87 (s, 3H), 1.79–1.82 (m, 1H), 1.76 (s, 3H), 1.59–1.71 (m, 4H), 1.36 (s, 9H), 1.27 (s, 3H), 1.25 (s, 3H) ppm.
*Compound **8**:* ^{1}H NMR (400 MHz, CDCl3): δ 8.08 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H) , 7.48 (t, J = 7.5 Hz, 2H), 7.39–7.40 (m, 4H), 7.34–7.31 (m, 1H), 6.20 (t, J = 9 Hz, 1H), 5.62(d, J = 7.5 Hz, 1H), 5.43 (d, J = 10.0 Hz, 1H), 5.27 (s, 1H), 4.96 (d, J = 10 Hz, 1H), 4.80 (s, 1H), 4.62 (s, 1H), 4.29 (d, J = 8.5 Hz, 1H), 4.17 (d, J = 8.5 Hz, 1H), 3.85 (dd, J = 11.0 Hz, J = 6.5 Hz, 1H), 3.81–3.76 (m, 5H), 3.55–3.72 (m, 4H), 3.47–3.52 (m, 4H) , 3.45 (s, 1H), 2.24–2.29 (m, 2H), 2.04 (s, 3H), 1.87 (s, 3H), 1.79–1.82 (m, 1H), 1.76 (s, 3H), 1.59–1.71 (m, 4H), 1.36 (s, 9H), 1.27 (s, 3H), 1.25 (s, 3H), 1.10 (s, 6H) ppm.

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