Chinese Chemical Letters Vol. 16, No. 1, pp 38-40, 2005
http://www.imm.ac.cn/journal/ccl.html

Synthesis and Antitumor Activity of C-2/C-10 Modified Analogues of Docetaxel

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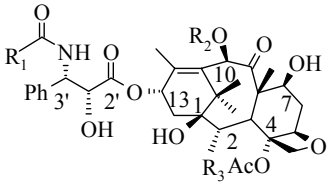
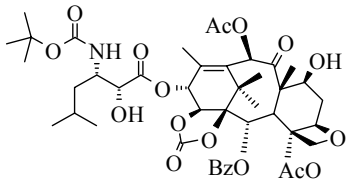
Abstract: Four 10-propionyl docetaxel analogues (**11a-d**) with 2α-amido substituents were prepared, and their antitumor activity against three solid tumor cell lines and their drug-resistant counterparts were determined.

Keywords: Paclitaxel, docetaxel, 2α-amido analogues, 10-propionate.

After many years continuing efforts, it has been recognized that the "southern hemisphere", including C-2 and C-4 substituents and C-13 side chain, is crucial to the activity of anticancer drug paclitaxel (=Taxol®, **1a**) and its analogues[1]. As an outcome of numerous structure activity relationship (SAR) studies, docetaxel (=Taxotere®, **1b**) has been launched as antitumor agent, and many other analogues **2-4** have entered clinical trials in different phases. Previous computational and spectroscopic research results have demonstrated the importance of the southern hemisphere of the molecules when binding to its receptor--tubulin dimers[2].



1a R_1=Ph, R_2=Ac, R_3=OBz
1b R_1=*t*-BuO, R_2=H, R_3=OBz
1c R_1=*t*-BuO, R_2=Ac, R_3=NHBz



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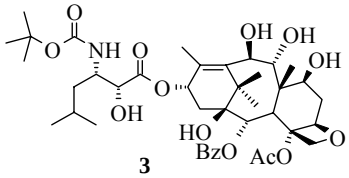

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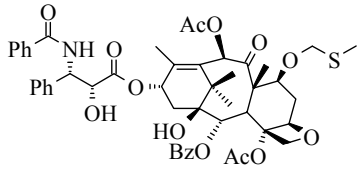

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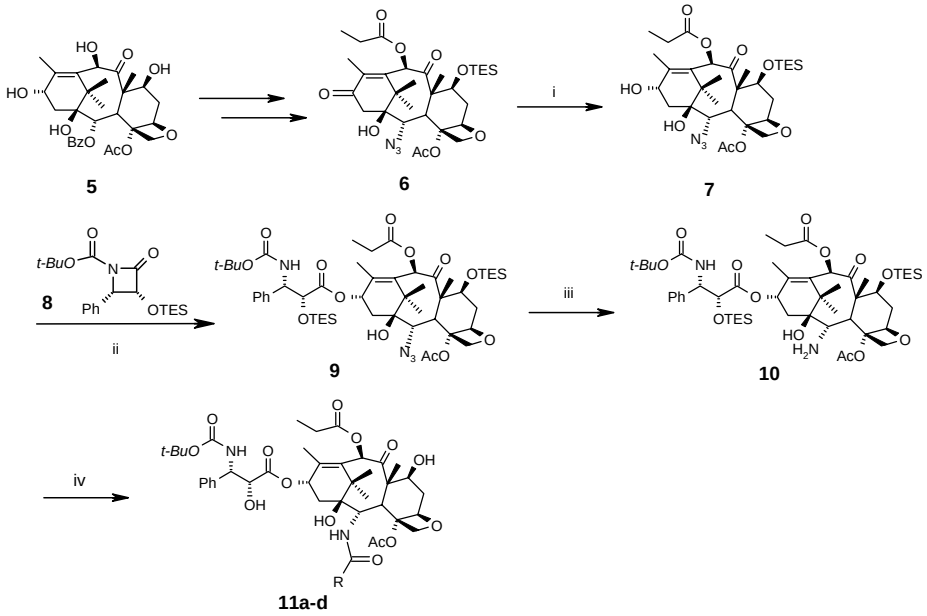
Scheme 1



Reagents and conditions: (i)$NaBH_4$, MeOH-THF, -15℃, 83%; (ii)LHMDS, THF, -45℃→-15℃, 68%; (iii)H_2, Pd-C (10%), EtOH, rt, 44%; (iv)RCOCl, $NaHCO_3$, EtOAc-H_2O, rt; then 40% aq. HF in Py, MeCN, rt, 50% for **11a**, 52% for **11b**, 45% fro **11c**, 40% for **11d** (2 steps)

It has been shown that benzoate-like esters and stereochemistry at C-2 were of great importance to activity[3-5], debenzoyl or 2β-analogues were almost inactive. Our group has succeeded in the synthesis of 2-benzoylamido analogues (example see **1c**)[6] which retained cytotoxicity to a great extent, while 2-debenzoyloxy-2α-PhS analogue did not show activity[7]. In summary, they exhibited similar SAR to their counterparts of paclitaxel. Since multi-drug resistance (MDR) has been an ever increasing problem in chemotherapy and some 10-deacetyl-10-acyl analogues showed more potent activity against MDR tumors than paclitaxel[8], we decide to incorporate propionyl group at C-10 to replace acetate in paclitaxel. As an ongoing efforts of systematic SAR exploration of C-2 of paclitaxel, we report here the preparation of its 2α-amido analogues with 10-propionate.

With the established methodology[6], 2α-N_3 product **6** was prepared from naturally abundant taxoid 10-deacetylbaccatin III **5** and used as the key intermediate for the successive transformations. Reduction of **6** with sodium borohydride in THF-MeOH led to formation of 13α-OH compound **7** in 83% yield (C-9 ketone was not reduced under the reaction condition due to its very hindered nature), which is readily coupled with an enantiopure β-lactam **8** to furnish **9**. Further 2-debenzoyloxy-2α-azido docetaxel analogue **9** underwent hydrogenation to furnish 2α-amino docetaxel analogue **10** (C-11, 12 double bond was not reduced under the reaction condition due to its very hindered nature as well). Schotten-Baumann acylation of **10** with acyl chloride (see **Table 1**) and subsequent desilylation with HF·Py at room temperature yielded **11a-d**.

In MTT assay toward several tumor cell lines (KB, A549 and MCF-7) and their MDR counterparts (KB/VCR, A549/Taxol and MCF-7/Adr), only **11b** showed comparable activity to that of paclitaxel against KB, KB/VCR and A549/taxol cell lines, while in most of other cases decreased activities were observed. The result indicated that 10-propionate does not increase the activity of 2α-amido analogues when comparing with those 10-acetyl-2α-amido analogues[6]. Although the result is disappointing, but it provided information that simultaneously replacing two positions with the groups, known to increase activity, does not necessarily lead to an additive result.

The preparation and evaluation of other C-2 paclitaxel/docetaxel analogues with different atomic linkage are in progress.

Table 1 Cytotoxicity of **11a-d** against three tumor cell lines and their MDR counterparts

compounds	IC_{50} (μg/mL)					
	KB	KB /VCR	A549	A549 /Taxol	MCF-7	MCF-7/Adr
11a (R= Ph)	>0.1	>1	>0.1	0.658	0.093	>1
11b (R=*m*-MeO-Ph)	0.009	0.697	0.031	0.053	0.008	>1
11c (R=*m*-Cl-Ph)	>0.1	>1	>0.1	0.873	>0.1	>1
11d (R=*i*-Pr)	>0.1	>1	>0.1	>1	>0.1	>1
1a (paclitaxel)	0.0014	0.659	0.0029	0.025	<0.001	>1
1b (docetaxel)	<0.001	0.353	<0.001	0.01	<0.001	>1

Acknowledgment

Financial support from Funding to Outstanding Doctor Thesis Authors of Chinese Universities (Grant No. 199949) is gratefully acknowledged by W. S. Fang.

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Received 11 December, 2003