C-2 Modified Taxol Analogs with Improved Aqueous Solubility

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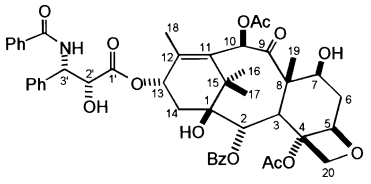
Received July 27, 1999

Paclitaxel[1] (Taxol), **1** is a novel anticancer agent isolated from the bark of the western yew[2] (*Taxus brevifolia*) that has been approved for treatment of advanced ovarian and breast cancers.



1, Taxol

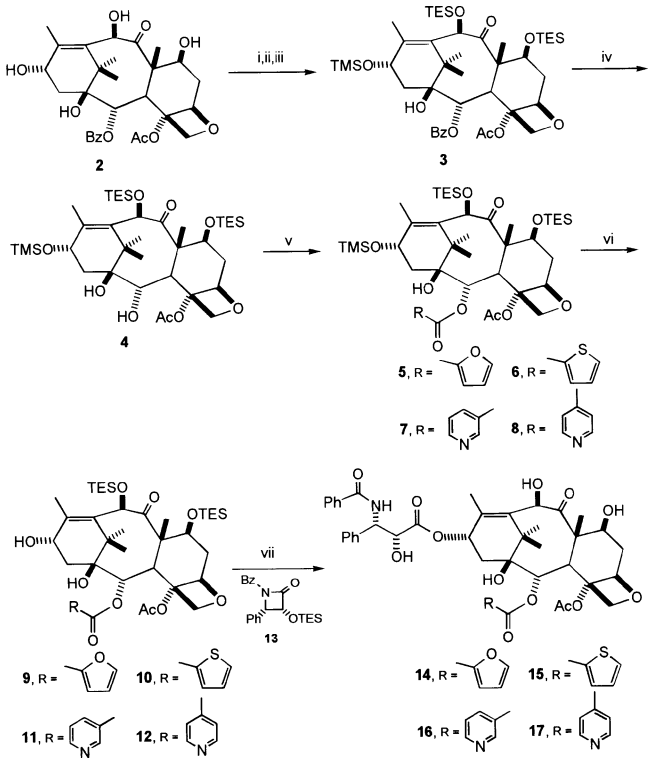
One of the problems in the pharmaceutical development of taxol is its extremely low aqueous solubility.[3] An emulsion formulation has been developed, but this is not ideal because it causes hypersensitivity in some patients.[4] Therefore, designing and synthesizing an improved aqueous solubility taxol analogs is highly desirable.

According to previous structure-activity relationship works[5] of taxol, certain substituted groups at C-2 have improved activity. It encourages us to investigate new heteroaromatic substituted analogs at C-2 which are also thought to have improved water solubility.

Our synthesis was started with 10-deacetylbaccatin (III) **2** which was selectively protected as its triethylsilyl (TES) ether. The C-10 hydroxyl group was then protected as the triethylsilyl (TES) ether through the use of n-butyllithium and triethylsilyl chloride. The C-13 hydroxyl group was subsequently protected as the trimethylsilyl (TMS) ether. This fully protected 10-deacetylbaccatin (III) **3** underwent selective reduction with Red-Al to give the diol **4** (Scheme1).[6] Attachment of new C-2 analogs has always been problematic[7] because of easy formation of THF ring between C-2 and C-20 in either basic or acidic media.

Thus, lithiation of diol **4** at low temperature (-78 °C) followed by addition of 2-furoyl chloride, 2-thiophenecarbonyl chloride, nicotinoyl chloride, and isonicotinoyl chloride afforded new C-2 heteroaromatic esters **5**, **6**, **7**, and **8**. Partial desilylation afforded 7,10-TES baccatin derivatives **9**, **10**, **11**, and **12** which coupled[8] with optically active β-lactam **13** to give new C-2 ester analogs. Finally, fluoride assisted removal of the silyl ethers resulted in new heteroaromatic substituted taxol analogs **14**, **15**, **16**, and **17**[9] (Scheme 1). *As far as we know, these four analogs are the first example of heteroaromatic substituted analogs at C-2*.

These new C-2 modified analogs were evaluated against human breast (MCF-7), human ovarian (SK-OV-3), and human lung (A549) cell lines (Table 1). For comparison, taxol was also evaluated. We found that all new analogs had negligible activity in all assay. In Table 2 the solubility data



Scheme 1. Reagents and Conditions: (i) TESCl, Pyr., rt., 97%; (ii) n-BuLi, THF, -78 °C, then TESCl, 89%; (iii) TMSCl, imidazole, DMAP, DMF, rt., 97%; (iv) Red-Al, THF, 0 °C, 97%; (v) LHMDS, THF, -78 °C, then, 2-furoyl chloride for **5** (76%), 2-thiophenecarbonyl chloride for **6** (72%), nicotinoyl chloride for **7** (52.5%), and isonicotinoyl chloride for **8** (48.4%); (vi) Pyr., 48% HF, CH_3CN, **9** (76.6%), **10** (78.6%), **11** (72.4%), and **12** (71.3%); (vii) LHMDS, THF, -45 °C, **13,** then, Pyr., 48% HF, CH_3CN, **14** (71.9%), **15** (72.9%), **16** (49.1%), and **17** (45.7%).

Table 1. *In Vitro* Cytotoxicities of C-2 Modified Taxols

	Cytotoxicity ED_{50} (μg/mL)[a]		
Compd	MCF-7[b]	SK-OV-3[c]	A549[d]
1	0.004	0.002	0.004
14	> 10.0	> 10.0	> 10.0
15	> 0.1	> 0.1	> 0.1
16	> 0.1	> 0.1	> 0.1
17	> 0.1	> 0.1	> 0.1

[a] ED_{50} is the concentration of compound that cause a 50% reduction in absorbance at 540 nm relative to untreated cells using SRB assay. [b,c,d] MCF-7, SK-OV-3, A549 are human breast, ovarian, lung cancer cell line, respectively.

Table 2. Solubility Data for Taxol Analogs

Compd	Aqueous solubility[a]
1	0.0008
14	0.1664
15	0.0701
16	1647
17	0.1887

[a] In mg/mL, determined by reverse phase HPLC.

for C-2 modified analogs is presented. All analogs shows excellent water solubility compared to taxol.

In conclusion, the introduction in the C-2 position of heteroaromatic rings causes a significant increase of their water solubility. These new analogs offer the hope of acceptable solubility in the pharmaceutical development.[10] New taxol analogs with improved water solubility and their evaluation study are under investigation in our laboratory.

Acknowledgment. We would like to thank Hanmi Pharm. Co., Ltd for free donation of 10-deacetylbaccatin (III) and financial support of this work.

References

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9. **14**: mp. 156-157 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (s, 3H, Me16), 1.14 (s, 3H, Me17), 1.68 (s, 3H, Me19), 1.69 (s, 3H, Me18), 1.79 (m, 1H, H6β), 2.18 (m, 2H, H14), 2.31 (s, 3H, 4Ac), 2.48 (m, 1H, H6α), 3.80 (d, 1H, *J* = 7.0 Hz, H3), 4.17 (m, 1H, H7), 4.19 (d, 1H, *J* = 8.3 Hz, H20β), 4.35 (d, 1H, *J* = 8.3 Hz, H20β), 4.75 (d, 1H, *J* = 2.2 Hz, H2′), 4.88 (d, 1H, *J* = 9.5 Hz, H5), 5.15 (s, 1H, H10), 5.51 (d, 1H, *J* = 7.0 Hz, H2), 5.73 (dd, 1H, *J* = 2.4, 9.0 Hz, H3′), 6.14 (dd, 1H, *J* = 8.5, 8.8 Hz, H13), 6.54 (dd, 1H, *J* = 1.7, 3.4 Hz, furoyl), 7.21 (d, 1H, *J* = 9.0 Hz, NH), 7.38 (m, 1H, furoyl), 7.38 (m, 8H, 2′-NBz and 3′-Ph), 7.62 (d, 1H, *J* = 1.7 Hz, furoyl), 7.71 (m, 2H, 2′-NBz and 3′-Ph). **15**: mp. 161-163 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 3H, Me16), 1.16 (s, 3H, Me17), 1.71 (s, 3H, Me19), 1.71 (s, 3H, Me18), 1.81 (m, 1H, H6β), 2.24 (m, 2H, H14), 2.33 (s, 3H, 4Ac), 2.53 (m, 1H, H6α), 3.82 (d, 1H, *J* = 7.1 Hz, H3), 4.23 (dd, 1H, *J* = 7.1, 11.0 Hz, H7), 4.24 (d, 1H, *J* = 8.4 Hz, H20β), 4.40 (d, 1H, *J* = 8.3 Hz, H20α), 4.75 (d, 1H, *J* = 2.4 Hz, H2′), 4.91 (d, 1H, *J* = 8.6 Hz, H5), 5.15 (s, 1H, H10), 5.53 (d, 1H, *J* = 7.1 Hz, H2), 5.73 (dd, 1H, *J* = 2.4, 9.0 Hz, H3′), 6.13 (dd, 1H, *J* = 7.6, 8.3 Hz, H13), 7.13 (dd, 1H, *J* = 3.7, 4.9 Hz, thiophene), 7.15 (d, 1H, *J* = 9.1 Hz, NH), 7.41 (m, 8H, 2′-NBz and 3′-Ph), 7.63 (dd, 1H, *J* = 1.2, 4.9 Hz, thiophene), 7.74 (m, 2H, 2′-NBz and 3′-Ph), 7.88 (dd, 1H, *J* = 1.2, 3.7 Hz, thiophene). **16**: mp. 156-157 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10 (s, 3H, Me16), 1.19 (s, 3H, Me17), 1.74 (s, 3H, Me19), 1.77 (s, 3H, Me18), 1.85 (m, 1H, H6β), 2.30 (m, 2H, H14), 2.36 (s, 3H, 4Ac), 2.56 (m, 1H, H6α), 3.89 (d, 1H, *J* = 7.3 Hz, H3), 4.19 (d, 1H, *J* = 8.2 Hz, H20β), 4.21 (m, 1H, 2OH), 4.26 (d, 1H, *J* = 8.2 Hz, H20α), 4.27 (dd, 1H, *J* = 6.8, 13.5 Hz, H7), 4.75 (d, 1H, *J* = 2.8 Hz, H2¢), 4.92 (dd, 1H, *J* = 1.1, 9.3 Hz, H5), 5.17 (s, 1H, H10), 5.67 (d, 1H, *J* = 7.3 Hz, H2), 5.74 (dd, 1H, *J* = 2.2, 8.9 Hz, H3′), 6.16 (t, 1H, *J* = 8.3 Hz, H13), 7.04 (d, 1H, *J* = 8.9 Hz, NH), 7.42 (m, 1H, nicotinoyl), 7.57 (m, 10H, 2′-NBz and 3′-Ph), 8.38 (d, 1H, *J* = 7.9 Hz, nicotinoyl), 8.81 (s, 1H, nicotinoyl), 9.30 (s, 1H, nicotinoyl). **17**: mp 171-173 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07 (s, 3H, Me16), 1.19 (s, 3H, Me17), 1.73 (s, 3H, Me19), 1.77 (s, 3H, Me18), 1.86 (m, 1H, H6β), 2.28 (m, 2H, H14), 2.38 (s, 3H, 4Ac), 2.54 (m, 1H, H6α), 3.88 (d, 1H, *J* = 7.3 Hz, H3), 4.15 (d, 1H, *J* = 8.2 Hz, H20β), 4.17 (m, 1H, 2'OH), 4.22 (d, 1H, *J* = 8.2 Hz, H20α), 4.22 (m, 1H, H7), 4.78 (d, 1H, *J* = 2.5 Hz, H2′), 4.90 (dd, 1H, *J* = 1.1, 9.3 Hz, H5), 5.17 (s, 1H, H10), 5.64 (d, 1H, *J* = 7.3 Hz, H2), 5.78 (dd, 1H, *J* = 2.3, 9.3 Hz, H3′), 6.20 (t, 1H, *J* = 8.1 Hz, H13), 7.09 (d, 1H, *J* = 9.1 Hz, NH), 7.55 (m, 10H, 2′-NBz and 3′-Ph), 7.90 (d, 1H, *J* = 1.8 Hz, isonicotinoyl), 7.91 (d, 1H, *J* = 1.6 Hz, isonicotinoyl), 8.79 (d, 1H, *J* = 1.6 Hz, isonicotinoyl), 8.80 (d, 1H, *J* = 1.8 Hz, isonicotinoyl).
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