Communication

Synthesis and Antitumor Activity of Tanshinone Analogues†

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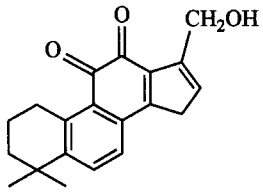
8,8-Dimethyl-5,6,7,8-tetrahydrophenanthrene-3,4-dione (3) and 8,8-dimethyl-2-(1-hydroxy ethyl)-5,6,7,8-tetrahydrophenanthrene-3,4-dione (4), two analogues of the antitumor active tanshinone, were synthesized from anisole. The synthesized compounds 3 and 4 were shown to be highly active against leukemia P-388 cell line as assayed by *in vitro* MTT method.

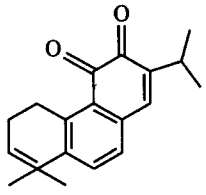
Keywords synthesis, tanshinone, analogues

Diterpenoid tanshinones which often bear an *o*-quinone moiety (such as compounds **1** and **2**), have attracted particular attention of medicinal chemists and clinicians because many of them exhibit significant antibacterial,[1] antidermatophytic,[2] antioxidant,[3] antiinflammatory,[4] antineoplastic,[5] and antiplatelet aggregation[6] activities. Przewaquinone A (**1**), a natural orthoquinone isolated from *Salvia Przewakii* Maxim. *Var. Mandarinorum* Stib,[7] showed antitumor activity in a variety of tumor models, such as Lewis lung carcinoma, melanoma B_{16}, sarcoma 180 and leukemia P-388, both *in vitro* and *in vivo*.[8] Saprorthoquinone (**2**) was isolated from the roots of *Salvia prionitis* Hance,[9] a plant used in Chinese folk medicine as an antiphlogistic, antibacterial and antitubercular drug.[10] Saprorthoquinone (**2**) was also obtained by an acidic treatment of 15-deoxyfuerstione (**2a**), a component of the roots of *Salvia moororaftiana*, by Simoes *et al*.[11] The initial bioassay showed that Saprorthoquinone had activity in leukemia P-388 test.[12] Through the comparison between **1** and **2**, it seems that the furan ring in Przewaquinone might be not essential to its biological activity. Therefore, in order to seek more effective compound easily synthesized, we designed and synthesized two analogues of tanshinone such as **3** and **4**.

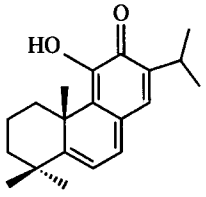
Starting from anisole (**5**), compound **10** was prepared through a five steps procedure, and then treated with methyllithium in ether to give alcohol **11**. After cyclization of compound **11** with boron trifluoride etherate in dichloromethane, the removal of methyl group of the resulting cyclization product **12** was effected with boron tribromide to afford the key intermediate **13**, which was oxidized with Fremy's salt to yield the title compound **3**.



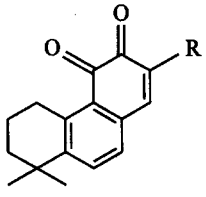
1 Przewaquinone A



2 Saprorthoquinone



2a 15-Deoxyfuerstione



3 R = H
4 R = $CHOHCH_3$

The intermediate **12** was also able to undergo smooth reaction with acetyl chloride and aluminum chloride in dichloromethane to deliver **14**, which was then converted to "phenol" **15** by demethylation with boron tribromide. Compound **15** was easily reduced to give alcohol **16**, which was oxidized with Fremy's salt to produce the target molecule **4**. The synthesized title compounds[13,14] were determined to possess the structure of **3** and **4** (Scheme 1).

The cytotoxic effects of the target compounds on tumor cells were evaluated as assayed by *in vitro* MTT method for P-388 cell line and SRB method for A-549 cell line. As shown in Table 1, the synthesized compounds **3** and **4** exhibited relatively high activity against P-388 cell line even at 10^{-6} mol/L concentration.

In conclusion, using anisole as the starting material, we synthesized two analogues of tanshinone such as 8,8-dimethyl-5,6,7,8-tetrahydrophenanthrene-3,4-dione (**3**) and 8,8-dimethyl-2-(1-hydroxy ethyl)-5,6,7,8-tetrahydrophenanthrene-3,4-dione (**4**). Compounds **3** and **4** exhibited high activity against leukemia P-388 cell lines. The investigations of the chemical syntheses and biological activity of a series of structural analogues of the title compounds are in progress.

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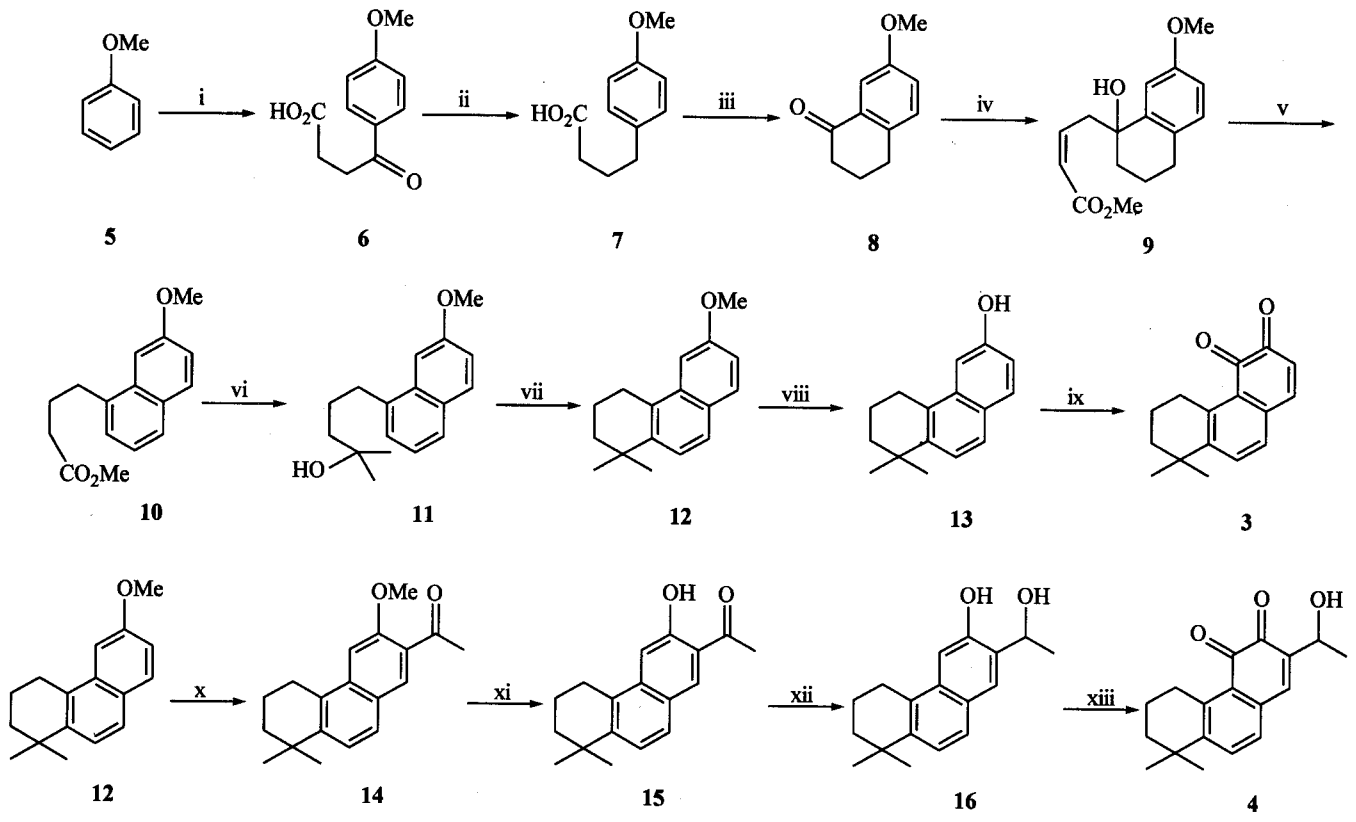
†Dedicated to Professor ZHOU Wei-Shan on the occasion of his 80th birthday.

Scheme 1 Synthesis of compounds **3** and **4**



Reagents and conditions: (i) 1.2 eq. succinic anhydride, 2.5 eq. $AlCl_3$, CH_3NO_2, 0 ℃→25 ℃, 12 h, 73.4%; (ii) 3.0 eq. NH_2-$NH_2 \cdot H_2O$, 5.0 eq. KOH, DEG, 130—150 ℃ 3 h, then 175—195 ℃ 4 h, 95%; (iii) 25 eq. 85% H_3PO_4, 20 eq. P_2O_5, 70—80 ℃ 3 h, 87.7%; (iv) 4 eq. Zn, 3.5 eq. methyl 4-bromocrotonate, THF, 85.5%; (v) 0.3 eq. Palladium black, 230—260 ℃ 2 h, 48.3%; (vi) 7 eq. methyllithium, 0 ℃ 4 h, 81.7%; (vii) 25 eq. $BF_3 \cdot Et_2O$, CH_2Cl_2, 20 ℃ 1 h, 92.5%; (viii) 3 eq. BBr_3, CH_2Cl_2, 0 ℃ 3 h, 95.4%; (ix) 4 eq. Fremy's salt, KH_2PO_4 buffer, acetone, 30 ℃ 10 h, 42.4%; (x) 5.8 eq. $AlCl_3$, 7.5 eq. acetyl chloride, CH_2Cl_2, 0—25 ℃ 12 h, 75%; (xi) 12 eq. BBr_3, CH_2Cl_2, 0 ℃ 6 h, 78.9%; (xii) 4 eq. $LiAlH_4$, 0—25 ℃ 10 h, 70.9%; (xiii) 4 eq. Fremy's salt, KH_2PO_4 buffer, acetone, 25 ℃, 40%; THF = tetrahydrofuran, DEG = diethylene glycol.

Table 1 Inhibition (%) of P-388 and A-549 tumor cell line *in vitro*

compd	Cell line	*c* (mol/L)				
		10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}
3	P-388[a]	97.0	97.0	98.5	6.1	3.0
	A-549[b]	89.3	83.9	32.1	30.4	30.0
4	P-388[a]	100.0	100.0	98.9	33.0	4.3
	A-549[b]	94.5	70.9	0	0	0

[a] 48 h, MTT assay; [b] 72 h, SRB assay.

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13 The data for **3**: m.p. 142—145 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.32 (s, 6H, CH_3), 1.65—1.67 (m, 2H, CH_2), 1.76—1.85 (m, 2H, CH_2), 3.20 (t, J = 6.4 Hz, 2H, CH_2), 6.38 (d, J = 9.9Hz, 1H, ArH), 7.16 (d, J = 8.0 Hz, 1H, ArH), 7.38 (d, J = 9.9 Hz, 1H, ArH), 7.63 (d, J = 8.0 Hz, 1H, ArH); IR (KBr) ν: 1686, 1657, 1578, 1248 cm^{-1}; EIMS m/z: 240 (M^+), 226, 212, 197. Anal. calcd for $C_{16}H_{16}O_2$: C 79.97, H 6.71; found C 79.91, H 6.61.

14 The data for **4**: m.p. 47—50 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 6H, CH_3), 1.38 (d, J = 6.3 Hz, 3H, CH_3), 1.58 (t, J = 5.6 Hz, 2H, CH_2), 1.71—1.74 (m, 2H, CH_2), 2.25 (br, 1H, OH), 3.11 (t, J = 6.3 Hz, 2H, CH_2-Ar), 4.74—4.79 (m, 1H, CH), 7.05 (d, J = 8.0 Hz, 1H, ArH), 7.18 (s, 1H, ArH), 7.53 (d, J = 7.7 Hz, 1H, ArH); IR (KBr) ν: 1655, 1261, 1144 cm^{-1}; EIMS m/z: 284 (M^+), 268, 254, 240, 225. HRMS calcd for $C_{18}H_{20}O_3$ 284.1407, found 284.1412.

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