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Synthesis of tanshinone IIA analogues and their inhibitory activities against Cdc25 phosphatases

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Abstract

Two series of tanshinone IIA derivatives were synthesized and evaluated for their antitumor activities as Cdc25 phosphatase inhibitors. Most of them demonstrated potent Cdc25 inhibitory activity and powerful cytotoxicity against A549 tumor cell line, producing IC_{50} values in very low micromolar range. At last, the preliminary SAR was discussed.

Keywords: Tanshinone IIA; Cdc25 phosphatases; Synthesis; Antitumor

Phosphatases Cdc25 function as key regulators of the cell cycle during normal eukaryotic cell division and as mediators of the checkpoint response in cells with DNA damage. Three Cdc25 homologues exist in humans: Cdc25A, Cdc25B, and Cdc25C [1–4]. Overexpression of Cdc25A and Cdc25B occurs in various forms of cancer and is strongly associated with tumor aggressiveness and poor prognosis [5–8], making Cdc25 an attractive drug target for cancer therapy.

Tanshinone IIA (**1**), which was isolated from the rhizome of *Salvia miltiorrhiza* Bunge, demonstrated moderate inhibitory activity for Cdc25 in our screening for the inhibitors of Cdc25. To explore the structure–activity relationship, two series of analogues were synthesized (Fig. 1). And their inhibitory activities against Cdc25A and Cdc25B phosphatases were evaluated. Described herein are the design and synthesis of the novel analogues of tanshinone IIA (**1**), as well as their biological profiles.

Our previous research [9,10] has revealed that some tanshinones without the A ring still demonstrated similar or even more potent antitumor activities. Thus, a series of analogue without the A ring were synthesized. Besides, different substituents were introduced into position 2 or 3 of the furan ring to probe the relationship between steric and/or electronic effects of these substituents and the biological activities.

Thus, compound **3** was first synthesized according to Ref. [11], which was brominated directly to give 2-bromo analogue **4** (Scheme 1). Subsequently, two other 2-substituted analogues were synthesized. The derivative **8** was prepared from phenol **5** in four steps, which was synthesized from **2** through reported method [12]. Thus, **5** was reacted with ethyl bromoacetate to produce compound **6**, which was subjected to cyclization to afford tricyclic compound **7** in

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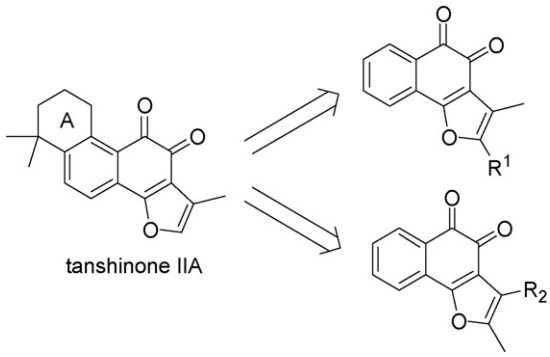
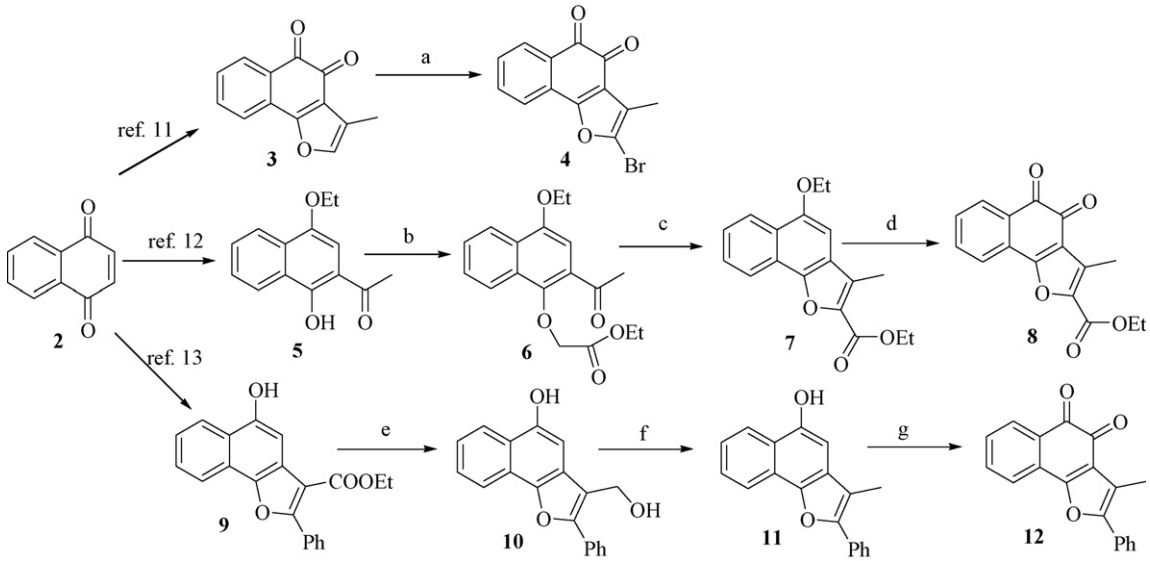


Fig. 1. Design of tanshinone IIA analogues

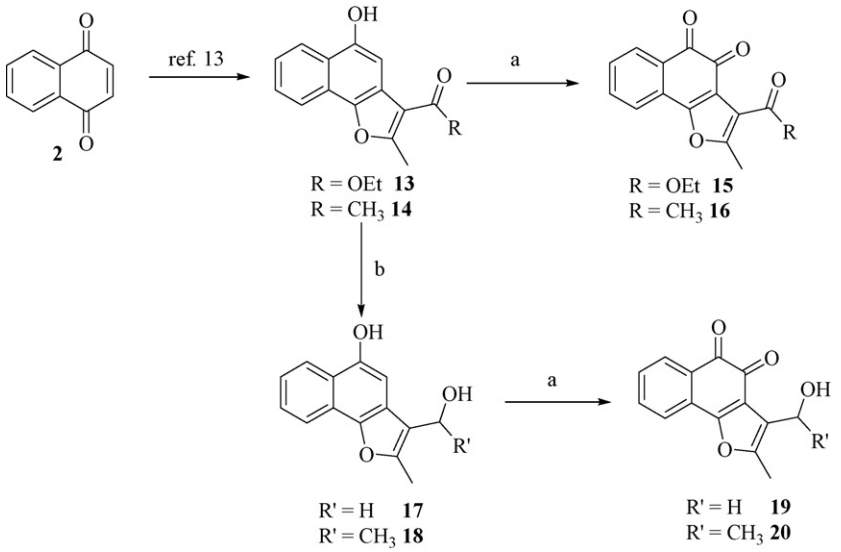


Scheme 1. (a) Br_2, HOAc, 77%; (b) $BrCH_2COOEt$, K_2CO_3, acetone, 96%; (c) NaOAc, Ac_2O, HOAc, 51%; (d) (i) BBr_3, CH_2Cl_2; (ii) HNO_3, HOAc, 72% from **7**; (e) $LiAlH_4$, THF, 90%; (f) H_2, 10% Pd/C, HOAc, EtOH, 96%; (g) HNO_3, HOAc, 70%.

77% yield. Then deprotection and subsequent oxidation proceeded smoothly to give the target compound **8**. Afterwards, 2-phenyl derivative **12** was also synthesized from the common starting material. Thus, compound **9**, prepared from **2** by the literature method [13], was reduced with $LiAlH_4$ to afford compound **10**, which was subjected to hydrogenation and oxidation to give **12** [14].

To further explore the substitutents' effect at positions 2 and 3 of the furan ring, the second series of derivatives were designed and synthesized as 2-methyl analogues (Scheme 2). The intermediates **13** and **14** were obtained by the literature method [13], which were oxidized with HNO_3 in acetic acid to produce the corresponding products **15** and **16** in excellent yields. Reduction of the intermediates **13** and **14** produced compounds **17** and **18**, which were transformed into **19** and **20**, respectively.

All the tanshinone IIA analogues were evaluated for inhibitory activity against protein phosphatases Cdc25A and Cdc25B (Table 1). All the analogues, except **15** and **16**, were potent inhibitors against Cdc25 phosphatase, with IC_{50} values in micromolar range. The simplified analogues (**3**) exhibited more potent inhibitory activities than tanshinone IIA (**1**), as we expected. However, introduction of different substituents into position 2 of the furan ring did not reduce the inhibitory activity, which suggested that there might be wide space to accommodate fairly large substituents without disrupting the biological profiles. While replacement of the 3-methyl group with an ester group or an acetyl group (analogues **15** and **16**) significantly reduced the Cdc25 inhibitory activity,



Scheme 2. (a) HNO_3, HOAc, 60–80%; (b) $LiAlH_4$, THF, 90%.

Table 1
Inhibitory activities against Cdc25A and Cdc25B phosphatases.

Compounds	Cdc25A, $IC_{50} \pm SD$ (μmol/L)[a]	Cdc25B, $IC_{50} \pm SD$ (μmol/L)[a]
Tanshinone IIA (**1**)	6.11 ± 0.45	8.42 ± 1.02
3	0.73 ± 0.10	0.65 ± 0.09
4	0.73 ± 0.04	0.48 ± 0.03
8	1.10 ± 0.11	0.89 ± 0.07
12	5.52 ± 0.83	2.67 ± 0.41
15	>20	9.45 ± 1.72
16	>20	>20
19	1.26 ± 0.18	0.98 ± 0.12
20	1.65 ± 0.24	1.59 ± 0.14

[a] The IC_{50} values are means of three distinct experiments.

reduction of the ester group and the acetyl group to alcohol (**19** and **20**) slightly increased the inhibitory activity. This suggested that electro-withdrawing groups at position 3 would be harmful to the Cdc25 inhibitory activities. Thereafter, the most potent three Cdc25 inhibitors (compounds **3**, **4** and **8**) [14] were chosen for further *in vitro* antitumor activity assay. As expected, all of them exhibited powerful cytotoxic activity against A549 tumor cell line, with IC_{50} values in micromolar range (Table 2).

To sum up, novel tanshinone IIA analogues were synthesized and evaluated for their antitumor activities. Most of these compounds demonstrated potent inhibitory activities for Cdc25A and Cdc25B, producing IC_{50} values in very low micromolar range. As expected, these Cdc25 inhibitors also exhibited powerful antitumor activities *in vitro*.

Table 2
In vitro cytotoxic activity against A549 tumor cell line.

Compounds	IC_{50} (μmol/L)[a]
3	1.66 ± 0.13
4	3.14 ± 0.03
8	2.80 ± 0.20

[a] The IC_{50} values are means of three distinct experiments.

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[14] Compound **3**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.26 (d, 3H, J = 1.2 Hz), 7.26 (d, 1H, J = 1.2 Hz), 7.43 (dd, 1H, J = 8.0, 8.0 Hz), 7.64–7.68 (m, 2H), 8.05 (d, 1H, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 8.7, 121.0, 121.5, 122.0, 128.4, 128.6, 129.9, 130.1, 135.2, 141.6, 160.4, 175.2, 180.5. EI-MS (m/z): 212 (M^+). Compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.22 (s, 3H), 7.46 (dd, 1H, J = 7.6, 7.7 Hz), 7.61–7.71 (m, 2H), 8.06 (d, 1H, J = 7.9 Hz). EI-MS (m/z): 293, 291 (M^+). Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.40 (t, 3H, J = 6.9 Hz), 2.60 (s, 3H), 4.40 (q, 2H, J = 6.9 Hz), 7.53 (dd, 1H, J = 7.8, 7.6 Hz), 7.69 (dd, 1H, J = 7.6, 7.6 Hz), 7.89 (d, 1H, J = 7.7 Hz), 8.09 (d, 1H, J = 7.7 Hz). EI-MS (m/z): 284 (M^+).