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Design, synthesis and vasodilative activity of tanshinone IIA derivatives

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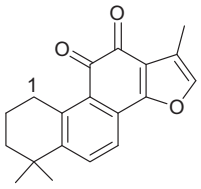
ABSTRACT

A new series of tanshinone IIA (**DIIA**) derivatives were synthesized through the reaction of brominated tanshinone IIA (**1-Br DIIA**) and aromatic acids in the presence of K_2CO_3. Twenty compounds were synthesized, and all of them were novel. Vasodilative activities for synthesized compounds were valuated in vitro on the contractile response of vascular thoracic aorta smooth muscle from Wistar rats. The results showed that most compounds exhibited a concentration-dependent inhibition on the contractile response of norepinephrine. Four prepared compounds, **4**, **5**, **8** and **13** revealed relatively remarkable vasodilative activity.

Danshen, the root of Salvia miltiorrhiza, is one of the commonly used traditional Chinese medicines which has a definite effect on cardiovascular and cerebrovascular diseases.[1–4] It has been reported that the relaxation by danshen in rat aorta ring is endothelium dependent and is possibly mediated by the nitric oxide-guanylyl cyclase pathway.[5–7] **DIIA** (Fig. 1) is one of the major lipid-soluble components extracted from danshen which shows the significant effects in cardiovascular system, antiarrhythmic activity, vasodilation and cardi protection, etc.[8,9] But there were few reports about the vasodilative activity of vascular thoracic aorta smooth muscle of **DIIA** derivatives.

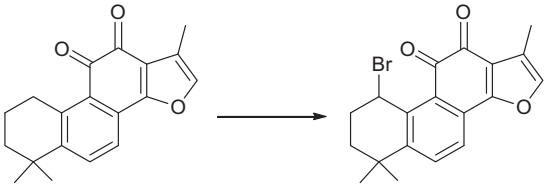
To improve the polarity and activity of **DIIA**, a series of researches were carried out in our laboratory. In our previous work, **DIIA** derivatives were synthesized through the reaction of **DIIA** with aromatic aldehyde in the presence of *p*-TsOH, their vasodilative activities were investigated in vitro and the results showed the synthetic products exhibited good activities.[10] In this study, **DIIA** derivatives were synthesized by the reactions of **1-Br DIIA** with some aromatic acids for the first time. Twenty compounds were synthesized, and all of them were novel. Their vasodilative activities were investigated on thoracic aorta rings of rats in vitro. The results showed that most compounds exhibited a concentration-dependent inhibition on the contractile response of norepinephrine. Four prepared compounds, **4**, **5**, **8** and **13** revealed relatively remarkable vasodilative activity.

1-Br DIIA was synthesized by the free radical reaction of **DIIA** and NBS in the presence of BPO (Scheme 1).[11,12] In the ^{1}H NMR spectra,[13] the shift of two hydrogen protons in the C_1 of the cycloolefin of **DIIA** at δ_H 3.18 were disappeared in comparison to that of one hydrogen proton appeared at δ_H 6.89. In the ^{13}C NMR spectra, the shift of C_1 in **DIIA** at δ 37.91 was upfield in comparison to that of **1-Br DIIA** at δ 48.12. It was concluded that one hydrogen proton was replaced by one bromine in the reaction.



DII A

Figure 1. Structures of tanshinone IIA (**DIIA**).



DII A 1-Br DIIA

Scheme 1. Reagents and condition: 1 equiv NBS, BPO, anhydrous CCl_4, 76–78 °C, reflux, 2.5 h.

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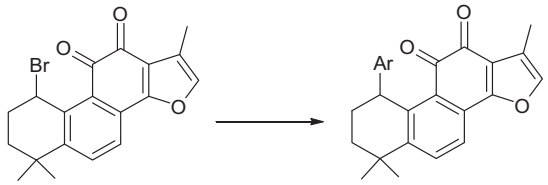
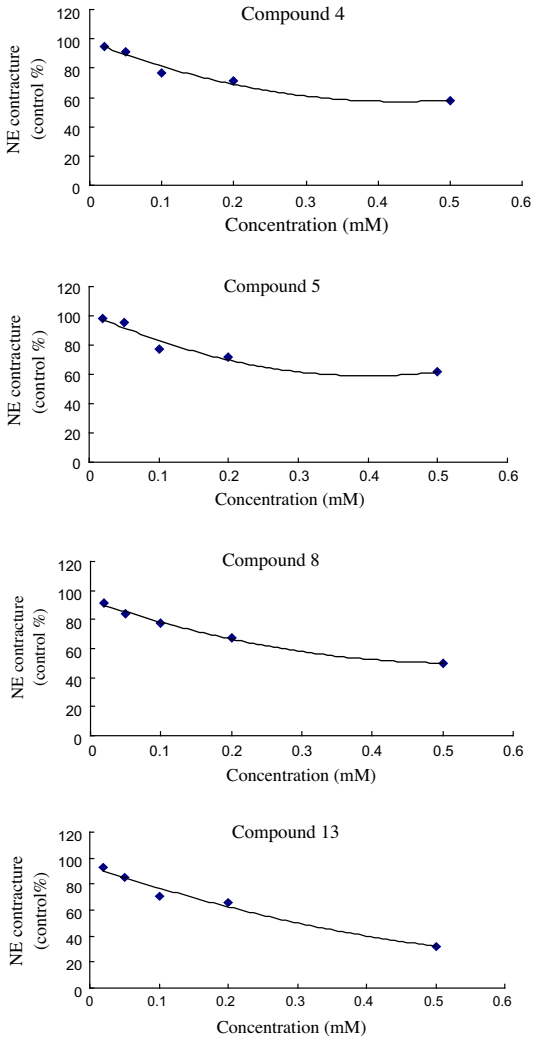


Scheme 2. Reagents and condition: 1 equiv K_2CO_3, aromatic acid, anhydrous DMF, 45–50 °C, 2–3 h.

Those **DIIA** derivatives were synthesized through the reaction of **1-Br DIIA** and aromatic acids in the presence of K_2CO_3 (Scheme 2).[14,15] Vasodilative activities for synthesized compounds were valuated in vitro on the contractile response of vascular thoracic aorta smooth muscle from male Wistar rats pre-contracted with norepinephrine bitartrate (1×10^{-6} M) according to the known standard procedure.[16,17] The results were presented in terms of percentage of the maximal control norepinephrine-induced responses. Most

Table 1
The relaxant effects of norepinephrine (10^{-6} mol/L) induced contraction in rat thoracic aorta (X ± SEM) (*n*, the number of cases used)

%Inhibition of norepinephrine contraction in rat thoracic aorta					
Compound	1×10^{-4} M	*n*	Compound	1×10^{-4} M	*n*
1	−9.41 ± 2.96	3	**11**	−17.83 ± 8.81	3
2	7.58 ± 3.37	6	**12**	12.80 ± 4.45	5
3	−0.25 ± 3.08	4	**13**	29.38 ± 7.41	4
4	23.48 ± 10.04	4	**14**	20.22 ± 1.13	3
5	22.40 ± 4.74	4	**15**	−0.37 ± 1.78	5
6	19.05 ± 3.36	3	**16**	−4.92 ± 2.80	3
7	9.39 ± 1.30	5	**17**	−1.67 ± 2.74	4
8	21.77 ± 1.24	3	**18**	1.92 ± 1.97	4
9	−3.59 ± 0.14	5	**19**	−2.78 ± 3.92	4
10	−3.30 ± 1.37	3	**20**	−13.30 ± 3.76	3
DIIA	1.86 ± 2.75	3			
The raw material of 4	3.86 ± 1.43	5	The raw material of 5	5.75 ± 4.30	5
The raw material of 8	7.78 ± 1.72	5	The raw material of 13	3.67 ± 2.86	5



P_1-P_{20}

Compound	Ar	Compound	Ar
1	COO—	**11**	CH_2COO—
2	COO—, OCH_3	**12**	CH_2COO—, OCH_3
3	COO—, OCH_3	**13**	CH_2COO—, OCH_3
4	COO—, OCH_3	**14**	CH_2COO—, OCH_3
5	COO—, OH	**15**	CH_2COO—, OH
6	COO—, OH	**16**	CH_2COO—, OH
7	COO—, OH	**17**	CH_2COO—, OH
8	COO—, F	**18**	CH_2COO—, F
9	COO—, F	**19**	CH_2COO—, F
10	COO—, F	**20**	CH_2COO—, F

Figure 2. Influence of synthesized compounds on contracture induced by norepinephrine bitartrate (NE) in thoracic aortic rings of rats.

of compounds showed a concentration-dependent inhibition on the contractile response of norepinephrine (Table 1). Especially **4, 5, 8** and **13**, exhibited better activity (Fig. 2),[18] and compared to their raw materials, the relaxant effects of bioactive products (**4, 5, 8** and **13**) were improved in varying degrees (Table 1).

The structure–activity relationship showed that the benzoic acids substituted derivatives presented better pharmacological vasodilative properties than that of phenylacetic acids substituted derivatives. Most methoxy-substituing derivatives presented good pharmacological vasodilative properties, suggesting that, methoxy has a distinct role to improve the vasodilative activity. In addition, the electron donating group substituted derivatives presented better vasodilative activity than the electron attracting group substituted derivatives.

In summary, a series of **DIIA** derivatives have been synthesized for the first time and the vasodilative activities in vitro of them were valuated on the contractile response of vascular thoracic aorta smooth muscle from Wistar rats. The results revealed that the polarity of products contrasted with **DIIA** was increase and some synthetic products exhibited good activity. The preliminary structure–activity relationship showed that it is valuable to develop potent vasodilatve activity of tanshinone IIA derivatives.

Acknowledgment

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12. Reagents and condition: 1 equiv NBS, BPO, anhydrous CCl_4, 76–78 °C, reflux, 2.5 h.
13. All newly synthesized compounds have adequate spectral data, for example, compound **4**, IR (KBr, cm^{-1}): 3420, 2959, 2932, 2867, 1719, 1678, 1606, 1587, 1537, 1510, 1255, 1164, 1098. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.90 (d, 2H, J = 8.8 Hz, H-22, 26), 7.23 (s, 1H, H-15), 6.83 (d, 2H, J = 8.8 Hz, H-23, 25), 6.71(d, 1H, J = 2.7 Hz, H-1), 3.81 (s, 3H, H-27), 2.30–2.37 (m, 1H, H-2a), 2.22 (s, 3H, H-17), 1.96–2.04 (m, 2H, H-2b,3a), 1.56–1.59 (m, 1H, H-3b), 1.44 (s, 3H, H-18), 1.31 (s, 3H, H-19). ^{13}C NMR (400 MHz, $CDCl_3$, TMS): δ 182.40 (C-11), 174.86 (C-12), 165.24 (C-20), 163.09 (C-24), 161.05 (C-14), 150.83 (C-5), 141.55 (C-15), 138.09 (C-10), 134.10 (C-6), 131.68 (C-22, 26), 128.39 (C-8), 127.01 (C-9), 123.18 (C-21), 122.98 (C-7), 121.36 (C-13), 120.27 (C-16), 113.41 (C-23, 25), 67.25 (C-1), 55.37 (C-27), 34.88 (C-4), 32.37 (C-3), 31.78 (C-18), 31.11 (C-19), 24.80 (C-2), 8.75 (C-17). MS ($[M+Na]^+$): 467.1470.
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18. Screening of vasodilative activity synthesized compounds was carried out on the thoracic aortic rings of male Wistar rats (200–300 g), which were stunned and dislocated in the cervical. Then thoracic aortas were immediately dislodged from Wistar rats and placed in a Krebs–Henseleit solution which was composed of (in mM): NaCl, 118.0; KCl, 4.7; $NaHCO_3$, 25.0; $CaCl_2$, 2.5; NaH_2PO_4, 1.2; $MgSO_4$, 1.2; EDTA, 0.016; glucose, 12 and was saturated in a gas of 95% O_2/5% CO_2 at 4 °C. After surface tissues were removed, the aortas were cut in 2–3 mm ring and fastened in 10 ml organ baths, which maintained at 37 °C in a gas of 95% O_2/5% CO_2. The preparations were allowed to balance for 2 h under 1.5 g basal tension and the Krebs–Henseleit solution in the organ baths was changed every 20 min. The integrality of aorta's endothelium was checked before synthesized compounds were added to the organ baths. If the percentage of relaxation of pre-contracted aorta by norepinephrine bitartrate (1×10^{-6} M) by acetylcholine (1×10^{-5} M) was greater than 80%, endothelium was deemed to be intact. Removal of functional endothelium which was confirmed by the lack of relaxation (<10%) in the presence of acetylcholine. The tested compounds were dissolved in dimethylsulfoxide (DMSO) as stock solution (50 mg/mL). Contrast tests were performed in the presence of DMSO alone, at the same concentrations as those used with the synthesized compounds, in order to check contractile response of aorta rings was not affected. All the results were performed as mean ± the standard error of the mean (SEM). Dose–response curves were used to exhibit different effects of compounds. Differences between different concentrations were considered statistically significant when paired Student's t-test was under the condition of P <0.05.