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Synthesis of New Benzoimidazole Derivatives

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Abstract: The reactions of cryptotanshinone and tanshinone IIA with cadaverine and putrescine were investigated. Six new compounds, four with imidazole functional groups and two with oxazole groups, were obtained. The possible reaction mechanism was proposed.

Keywords: Cryptotanshinone, tanshinone IIA, putrescine, cadaverine, biogenic bisamines.

Tanshinones are naturally occurring diterpeniods isolated from *Salvia miltiorrhiza* Bunge. This type of compounds has shown comprehensive pharmacological activities such as enzyme inhibitory activity and cytotoxicity[1,2]. In this paper, the reactions of cryptotanshinone **1** and tanshinone IIA **2** with biogenic bisamines were investigated. Biogenic bisamines such as cadaverine (1, 5-diamino pentane) and putrescine (1, 4-diamino butane) were considered to be involved in the process of cell multiplication and regulation[3,4], we believe that the current work may provide some evidence for the mechanisms on enzymatic inhibitory activities and cytotoxicity of tanshinones.

The reaction of **1** with putrescine or cadaverine gave major products of **3** or **4**, respectively (**Scheme 1**). FAB-MS and elemental analysis of **4** suggested a formula of $C_{24}H_{28}N_2O$. ^{13}C NMR and IR data indicated that **4** had no *O*-quinone carbon, because there was no absorption signal of quinone function group in the UV spectrum, indicating that the *O*-quinone moiety was changed during reaction. NMR data showed that the product contained three methyl, eight methylene groups and three methenyl. An additional aromatic quaternary carbon signal (δ 152.0) appeared at lower field that could be assigned to C-1'. Two protons with an AMX type splitting at δ 4.38 and δ 4.87 could be assigned to CH_2-16, which was made diastereotopic by the chirality of CH-15. Signals of aromatic protons (CH-6 and CH-7) of **4** appeared at δ 7.46 and δ 7.91 as a sharp AB-quartet. H-H COSY spectrum showed that **4** contained a -$CH_2CH_2CH_2CH_2$- moiety which was not found in **1**, indicating that the fragment was probably derived from cadaverine. In NOE spectrum, irradiating CH_3-17 (δ 1.53) resulted in the enhancement of CH-15 and CH_2-16, and irradiating one proton of CH_2-1 (δ 3.20) resulted in the enhancement of CH-5' (δ 4.41), indicating that CH_2-1 and CH_2-5' were spatially

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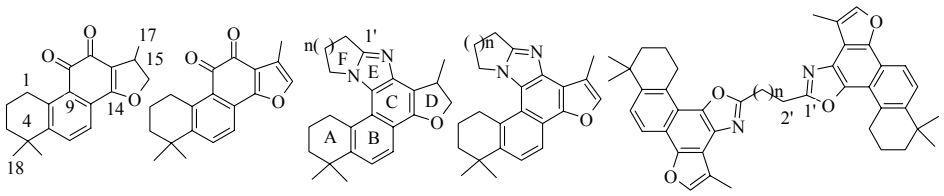
neighboring protons. The CH_2-1 protons were anisochronic and their ^1H NMR signals appeared at δ 3.18-3.23 and δ 3.27-3.32 as multiple peaks. The signals differ from those of **1**, which were triplet peaks (δ 3.22, J = 7 Hz)[5]. Similarly, the two proton signals of CH_2-5' appeared at δ 4.30-4.34 and δ 4.39-4.44, splitting as multiple peaks, respectively. According to all of the spectral data[6], product **4** could be assigned as 2, 7, 7-trimethyl-2, 3, 7, 8, 9, 10, 11, 12, 13, 14-decahydro [furo[2, 3-*d*]phenanthro][1, 2-*d*] pyrido[1, 2-*a*]imidazole.

Similar to **4**, the product **3** could be assigned as 2, 7, 7-trimethyl-2, 3, 7, 8, 9, 10, 11,12, 13-enneahydro[furo[2, 3-*d*]phenanthro][1, 2-*d*]pyrrolo[1, 2-*a*]imidazole according to its spectral data[6]. The difference between the structure of compound **3** and **4** was the F ring. The pyrrolidine moiety was formed from the reaction of **1** with putrescine, while the reaction of cadaverine with **1** gave F ring as piperidine moiety. As can be seen from its structure, the spatial distance between the CH_2-1 and CH_2-4' in **4** was longer than that in **3**, this in turn resulted that **3** has less sterical hindrance comparing to **4**. Consequently, the ^1H NMR signals of CH_2-1 appeared at δ 3.31 as multiple peaks, and those of CH_2-4' appeared at δ 4.66.

The reaction of **2** with cadaverine gave two major products of **6** and **8** as shown in **Scheme 1**. FAB-MS and elemental analysis showed that the molecular formula of product **6** was $C_{24}H_{26}N_2O$. According to the spectral data[6], similar to compound **4**, product **6** was determined to be 2, 7, 7-trimethyl-7, 8, 9, 10, 11, 12, 13, 14-octahydro [furo[2, 3-d]phenanthro][1, 2-d]pyrido[1, 2-a]imidazole.

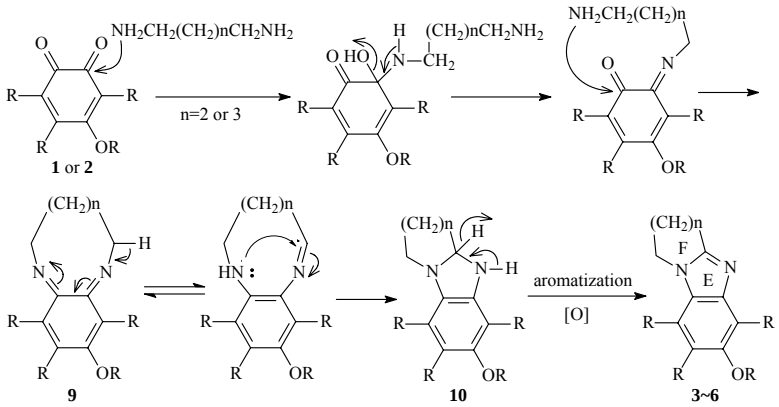
FAB-MS and elemental analysis indicated that the molecular formula of **8** was $C_{43}H_{42}N_2O_4$. ^1H NMR showed that the structure of **8** [10] was probably symmetric. The signal area of the CH_2-2' methylene groups appeared as four protons, while the CH_2-3' signal at δ 2.71 appeared as two protons and was quintuplet splitting peaks (J = 7 Hz). In ^1H NMR spectrum, product **8** had AX_3 style long-range coupling, δ 2.35 (d, J=1 Hz) and δ 7.40 (q, J=1 Hz), character of the signals of β-methyl furan moiety. The singlet peak at δ 1.37 could be assigned as the signal of the geminal dimethyl groups in **8**. Comparing its NMR data with that of compound **2**, it could be confirmed that compound **8** contained the same molecular framework with compound **2**. According to all of spectral data, compound **8** could be assigned as 1, 3-di(4, 9, 9-trimethyl-9, 10, 11, 12-tetrahydro-1, 6-dioxa-3-azadicyclopenta[*a*, *c*]phenanthren-2-yl)-propane[7].

Scheme 1



1 **2** **3**: n=1 **4**: n=2 **5**: n=1 **6**: n=2 **7**: n=1 **8**: n=2

Scheme 2 Possible mechanism of the formation of imidazole derivatives



Two major products **5** and **7** [10] were obtained from the reaction of **2** with putrescine. Their structures were similar to that of products **6** and **8**. According to the spectral data, compounds **5** and **7** could be assigned as 2, 7, 7-trimethyl-7, 8, 9, 10, 11, 12, 13-heptahydro[furo[2, 3-*d*]phenanthro][1, 2-*d*]pyrrolo[1, 2-*a*]imidazole and 1, 2-di(4, 9, 9-trimethyl-9, 10, 11, 12-tetrahydro-1, 6-dioxa-3-azadicyclopenta[*a*, *c*]phenanthren-2-yl)-ethane, respectively.

It was noticeable that every reaction of compound **1** or **2** with bisamines gave imidazole derivative products. The possible reaction mechanism was proposed in **Scheme 2**. A nucleophilic reaction took place between tanshinone and amine. One of the amino groups in bisamine attacked one *O*-quinone carbonyl groups, and a quinone-imine intermediate was formed and one equivalent H_2O was eliminated. Then, another amino group of the bisamine attacked another carbonyl group of the tanshinone. The rearrangement of intermediate **9** to the aromatic Schiff base might be spontaneous because of the stability of the latter[8]. Intermolecular additional reactions took place in the Schiff base intermediate, and resulted in intermediate **10**, which, in the presence of an oxidant such as tanshinone or air[5], underwent aromatization to give the imidazole product[9].

Two major products were isolated from the reaction of tanshinone IIA with biogenic bisamines. One of the two products was oxazole derivative. The formation of oxazole product might be through a previously proposed pathway[5,7].

In conclusion, the reaction of tanshinones with biogenic bisamines revealed a possible mechanism of the enzymatic inhibitory activities and cytotoxicity of tanshinones. The reaction offers a potential strategy for the preparation of quinine derivatives bearing imidazole functional groups. Modification of the reaction conditions to get higher yields of functionalized quinines is currently underway.

Acknowledgments

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References and Notes

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6. The data of products **3, 4, 5, 6**.
   Product **3**: light yellow needle crystals, yield 15%. $C_{23}H_{26}N_2O$, calcd: C, 79.73; H, 7.56; N, 8.09; O, 4.62; found: C, 79.69; H, 7.60; N, 8.02. m.p. 227-230 ºC. FAB-MS *m/z* (rel. int.): 347 $[M+1]^+$ (95), 346 (100). UV λ (EtOH): 348.0, 333.0, 258.0, 233.0 nm. IR *v* (KBr): 3060, 2957, 2928, 2868, 1543, 1513, 1455, 1397, 1295 cm^{-1}. ^1H NMR (500 MHz, Acetone, δ ppm) 1.36 (s, 3H), 1.38 (s, 3H), 1.53 (d, 3H, *J* 6.5Hz), 1.81 (m, 2H), 1.83 (m, 2H), 2.65 (m, 2H), 3.01 (m, 2H), 3.31 (m, 2H), 4.02 (m, 1H), 4.30 (dd, AMX, 1H, *J* 6.3, 8.8Hz), 4.66 (m, 2H), 4.87 (t, AMX, 1H, *J* 8.8Hz,), 7.45 (d, AB, 1H, *J* 9Hz), 7.85 (d, AB, 1H, *J* 8.5Hz). ^{13}C NMR-DEPT (500 MHz, Acetone, δ ppm) 19.8q, 21.0t, 24.0t, 27.3t, 32.6q, 34.1t, 35.5s, 38.2d, 40.0t, 52.6t, 79.5t, 116.8s, 117.6s, 121.2d, 123.5d, 125.0s, 129.8s, 142.9s, 145.3s, 152.3s, 161.6s. The structure was confirmed by HMQC and HMBC. Product **4**: light yellow needle crystals, yield 12%, $C_{24}H_{28}N_2O$, calcd: C, 79.96; H, 7.83; N, 7.77; O, 4.44; found: C, 79.91; H, 7.85; N, 7.70. m.p. 103-104.5 ºC. FAB-MS *m/z* (rel. int.): 361 $[M+1]^+$ (100). UV λ (EtOH): 352.0, 263.0, 236.0, 203.0 nm. IR *v* (KBr): 3067, 2927, 2859, 1461, 1402, 1118, 824 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm) 1.37 (s, 3H), 1.42 (s, 3H), 1.53 (d, 3H, *J* 7Hz), 1.76 (m, 2H), 1.82 (m, 2H), 1.93 (m, 2H), 2.09 (m, 2H), 3.18-3.23 (m, 1H), 3.28 (t, 2H, *J* 7Hz), 3.27-3.32 (m, 1H), 4.09 (m, 1H), 4.30-4.34 (m, 1H), 4.38 (dd, AMX, 1H, *J* 5.3, 8.3Hz), 4.39-4.44 (m, 1H), 4.87 (t, 1H, *J* 8.8Hz), 7.46 (d, AB, 1H, *J* 9Hz,), 7.91 (d, AB, 1H, *J* 8.5Hz). ^{13}C NMR-DEPT (500 MHz, $CDCl_3$, δ ppm) 20.0q, 20.2t, 21.4t, 24.7t, 25.6t, 32.7q, 34.3t, 35.2s, 36.9d, 40.1t, 51.3t, 79.3t, 115.2s, 117.4s, 120.4d, 122.9s, 123.6d, 126.6s, 129.5s, 138.9s, 142.9s, 151.9s, 152.0s. The structure was confinmed by H-H COSY、NOE、HMQC and HMBC together. Product **5**: colorless needle crystals, yield 14%, $C_{23}H_{24}N_2O$, calcd: C, 80.20; H, 7.02; N, 8.13; O, 4.64; found: C, 80.15; H, 7.09; N, 8.07. m.p. 282.0-284.0 ºC. FAB-MS *m/z* (rel. int.): 345 $[M+1]^+$ (100). UV λ (EtOH): 266.0, 203.0 nm. IR *v* (KBr): 2925, 2854, 1543, 1513, 1458, 1375 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm) 1.34 (s, 6H), 1.74 (m, 2H), 1.79 (m, 2H), 2.57 (d, 3H, *J* 1Hz), 2.61 (m, 2H), 3.17 (t, 2H, *J* 7.8Hz), 3.25 (t, 2H, *J* 5.5Hz), 4.58 (t, 2H, *J* 7Hz), 7.44 (q, 1H, *J* 1Hz), 7.49 (d, AB, 1H, *J* 8.5Hz), 8.16 (d, AB, 1H, *J* 9Hz). ^{13}C NMR-DEPT (500 MHz, $CDCl_3$, δ ppm) 9.9q, 20.6t, 23.9t, 27.1t, 32.5q, 33.8t, 35.0s, 39.3t, 52.4t, 116.2s, 116.7s, 118.0s, 119.2d, 120.4s, 124.4d, 124.7s, 127.3s, 129.3s, 140.6d, 142.3s, 149.3s, 159.4s. Product **6**: colorless solid, yield 19%, $C_{24}H_{26}N_2O$, calcd: C, 80.41; H, 7.31; N, 7.81; O, 4.46; found: C, 80.43; H, 7.35; N, 7.76. m.p. 126-128 ºC. FAB-MS m/z (rel. int.): 359 $[M+1]^+$ (20), 154 (100). UV λ (EtOH): 348.0, 332.0, 269.0, 205.0 nm. IR *v* (KBr): 3061, 2929, 2860, 1607, 1499, 1457, 1329 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm) 1.41 (s, 6H), 1.72 (m, 2H), 1.80 (m, 2H), 1.84 (m, 2H), 2.13 (m, 2H), 2.64 (d, 3H, *J* 1.5Hz), 3.27 (t, 2H, *J* 5.8Hz), 3.35 (t, 2H, *J* 7Hz), 4.38 (t, 2H, *J* 5.5Hz), 7.50 (q, br, 1H, *J* 1.5Hz), 7.55 (d, AB, 1H, *J* 8.5Hz), 8.21 (d, AB, 1H, *J* 8Hz). ^{13}C NMR-DEPT (500 MHz, $CDCl_3$, δ ppm) 9.9q, 20.2t, 21.5t, 24.7t, 25.4t, 32.8q, 34.1t, 35.1s, 40.2t, 51.3t, 116.2s, 116.7s, 118.5s, 119.0d, 120.7s, 124.0s, 124.4d, 127.5s, 130.2s, 140.6d, 142.4s, 149.2s, 151.4s.
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