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# Efficient Synthesis of Novel Six-Member Ring-Fused Quinoline Derivatives via the Friedländer Reaction

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ABSTRACT: *Novel quinolines fused with a six-member ring* **5a–j** *were prepared in high yields (75–95%) via the Friedländer reaction of dimethoxy-substituted o-aminobenzaldehydes of* **3a** *or* **3b** *with cyclic ketones* **4**, *respectively. The structures of* **5a–j** *were determined by IR, $^1H$ NMR, MS, and elemental analysis.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:229–233, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20356

## *INTRODUCTION*

As a potential drug candidate, quinoline derivatives have recently attracted increasing interest because of their broad range of biological activities [1]. For example, quinoline derivatives have been found to be potent, selective, and orally bioavailable inhibitors for the platelet-derived growth factor receptor [2a] and an effective inhibitor for the replication of the severe acute respiratory syndrome coronavirus in vitro [2b]. Moreover, quinoline analogues were reported to display promising antibacterial [3], anticancer and antiplatelet [4], antiasthmatic [5], anti-inflammatory [6], and antihypertensive [7] activities. In addition, quinoline's derivatives have been widely utilized as ligands for preparing metal complexes [8] and as useful materials for organic synthesis [9].

Among these quinoline derivatives, we are particularly interested in six-member ring-fused quinolines due to their promising antitumor activity [10].

One of the most widely used methods for preparing substituted quinolines is the Friedländer reaction [11], in which an aromatic *o*-aminoaldehyde or an aromatic *o*-aminoketone is condensed with an aldehyde or ketone containing an alpha active methylene group (Scheme 1).

In this paper, we report an efficient method for the synthesis of novel quinoline derivatives fused with a six-member ring via the Friedländer reaction, that is, the condensation reaction of dimethoxy-substituted *o*-aminobenzaldehydes with cyclic ketones in the presence of sodium ethoxide.

## *RESULTS AND DISCUSSION*

The starting materials, dimethoxy-substituted *o*-aminobenzaldehydes, **3a,b**, were prepared in two steps as outlined in Scheme 2.

Dimethoxy-substituted *o*-nitrobenzaldehydes of **2a** and **2b** were prepared by nitration of the corresponding dimethoxy-substituted benzaldehydes **1a,b**, respectively. Because of the electron-withdrawing effects and less stability of the

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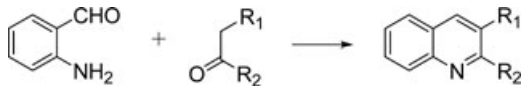
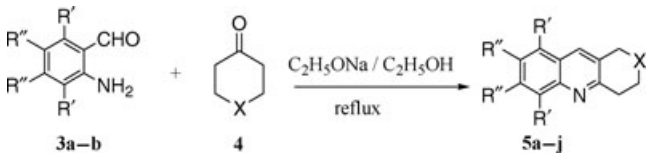


SCHEME 1



SCHEME 3

aldehdyde group in the strong acidic conditions, compounds **1a,b** were found to give the expected products **2a,b** in poor yields (less than 40%) at room temperature by using 70% nitric acid, the classic nitration method, as described in the literature [12]. We found that using nitric acid and acetic anhydride as solvent the yields of compounds **2a,b** were remarkably improved (73–80%). The reaction of **1a** under this condition gave compound **2a** (73%) as yellow needles, whereas that of **1b** gave a mixture of 2,5-dimethoxy-4-nitrobenzaldehyde (14%) and 3,6-dimethoxy-2-nitrobenzaldehyde **2b** [13] (80%), which were separated and purified through a flash silica gel chromatographic column using petroleum ether/ethyl acetate (1:1, v/v) as solvent.

To selectively reduce the nitro group in **2a** and **2b** in the amino group, reagents, described in the literature such as $Na_2S_2O_4$ [14], and $FeSO_4{\cdot}7H_2O$–$NH_3{\cdot}H_2O$ [15], had been first attempted. However, we found that all reactions gave products in poor yields. It is worth to point out that, when $FeSO_4{\cdot}7H_2O$–$NH_3{\cdot}H_2O$ was used, the reaction produced large amount of semisolid inorganic wastes and made the filtration process very difficult. We then attempted to use iron powder, which was able to selectively reduce the nitro group of **2a** and**2b** to give the corresponding amino products **3a** (62%) and **3b** (76%), respectively.

The condensation reaction of the dimethoxy-substituted aminoaldehydes **3a,b** with cyclic ketones **4** in anhydrous ethanol, in the presence of catalytic amount of sodium ethoxide, yielded the expected six-member ring-fused quinolines **5a–j** in high yields (Scheme 3; Table 1). Their structures were fully characterized by IR, $^1$H NMR, MS, and elemental analysis (see the Experimental).

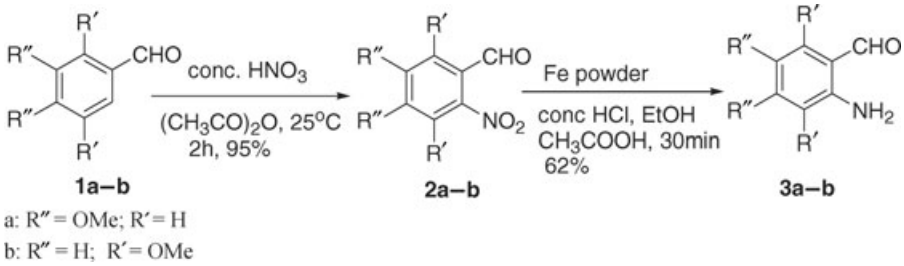
## *CONCLUSION*

We have reported an efficient method for the synthesis of novel quinoline derivatives **5a–j** through the condensation reaction of dimethoxy-substituted aminoaldehydes **3a,b** with cyclic ketones **4** via the Friedländer reaction. The experimental procedure is very simple. Our protocol can be applied to a wide range of substrates. These methods not only afford significant improvements in the reaction rates and yields but also present a more straightforward and easy work-up procedure. The anticancer activities of the new quinoline derivatives are currently under evaluation.

## *EXPERIMENTAL*

### *General*

Melting points were determined on a microscopic melting point apparatus (Kofler, Guangzhou, PRC) and were uncorrected. The IR spectra were recorded on a Perkin-Elmer 1730 FT-IR spectrometer using KBr films. The $^1$H NMR spectra were recorded on a Varian Inova 500 MHz in $CDCl_3$ solutions using TMS as an internal standard. The mass spectra were obtained on a Shimadzu Qp5050A spectrometer. Elemental analysis was performed on an elemental Varioel spectrometer. 3,4-Dimethoxybenzaldehyde, 2,5-dimethoxybenzaldehyde, cyclic ketones, and



SCHEME 2

**TABLE 1** Physical Data of Compounds **5a–j**

| *Compounds* | *R′* | *R″* | *X* | *Time (h)* | *Melting Point (°C)* | *Yield (%)* |
|---|---|---|---|---|---|---|
| **5a** | H | $CH_3O$ | $NCOOCH_2CH_3$ | 2 | 139–141 | 90 |
| **5b** | H | $CH_3O$ | $NCH_3$ | 2 | 138–140 | 95 |
| **5c** | H | $CH_3O$ | $NCOC_6H_5$ | 1.5 | 135–138 | 75 |
| **5d** | H | $CH_3O$ | S | | 117–119 | 90 |
| **5e** | H | $CH_3O$ | O | 1.5 | 140–142 | 90 |
| **5f** | $CH_3O$ | H | $NCOOCH_2CH_3$ | 2 | — | 85 |
| **5g** | $CH_3O$ | H | $NCH_3$ | 2 | 145–146 | 90 |
| **5h** | $CH_3O$ | H | $NCOC_6H_5$ | 1.5 | 141–143 | 70 |
| **5i** | $CH_3O$ | H | S | 2 | 134–136 | 95 |
| **5j** | $CH_3O$ | H | O | 2 | 160–161 | 95 |

heterocyclic 6-member ring ketones were purchased from Aldrich (Beijing, PRC).

*Preparation of 4,5-Dimethoxy-2-nitrobenzaldehyde (**2a**).* Nitric acid (4 mL; 89 mmol), acetic anhydride (4 mL; 42 mmol), and **1a** (2.0 g; 12 mmol) were added at 0°C with stirring, respectively. After 2 h stirring, the mixture was poured onto 10 mL ice water. The resultant yellow solid was filtered, washed with cold water and then cold ethanol, and recrystallized from 95% ethanol; a yellow needle compound **2a** (1.85 g, yield 73%, mp 132−133°C (Lit. 132–133°C) [13]) was obtained.

*Preparation of 3,6-Dimethoxy-2-nitrobenzaldehyde (**2b**).* Compound **2b** was prepared by following the same experimental procedure described for **2a**. **2b** was recrystallized from 95% ethanol, and a yellow, needle-shaped compound **2b** (2.0 g, yield 80%, mp 162–163°C (Lit. 163–165°C) [13]) was obtained.

*Preparation of 3,4-Dimethoxy-6-aminobenzaldehyde (**3a**) [16].* 4,5-Dimethoxy-2-nitrobenzaldehyde **2a** (0.43 g; 2 mmol), iron powder (0.42 g; 74 mmol), and 0.01 mL of concentrated HCl were introduced into a solution of EtOH (5.0 mL), AcCOOH (5.0 mL ), and $H_2O$ (3.0 mL). The resultant mixture was refluxed for 30 min with stirring prior to the filtration. The filtrate was diluted with $H_2O$ (30 mL) and was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 15 mL) and $H_2O$ (2 × 15 mL), dried over anhydrous $Na_2SO_4$. After removing the solvent under reduced pressure, the residue was separated by column chromatography to get **3a** (0.23 g, 62%) as an orange oil. $^1$H NMR (500 MHz, $CDCl_3$), δ (ppm) : 9.70 (s, 1H, CHO), 6.65 (s, 2H, ArH), 6.10 (br s, 2H, $NH_2$), 3.85 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$).

*Preparation of 3,6-Dimethoxy-2-aminobenzaldehyde (**3b**).* Compound **3b** was prepared by following the same experimental procedure described for **3a**. **3b** was recrystallized from 95% ethanol, and a yellow solid **3b** (1.60 g, yield 76%, mp 67−68°C (Lit. 67–68°C) [16]) was obtained. $^1$H NMR (500 MHz, $CDCl_3$), δ (ppm) : 10.32 (s, 1H, CHO), 6.69 (d, 1H, $J_{4,5}$ = 8.7 Hz, $H_4$), 6.8–6.5 (br s, 2H, $NH_2$), 5.90 (d, 1H, $H_5$), 3.74 (s, 6H, $OCH_3$).

## *General Procedure for the Synthesis of Novel Six-Member Ring-Fused Quinoline Derivatives via the Friedländer Reaction*

To a solution of dimethoxy-substituted aminoaldehyde **3** (0.90 mmol) and heterocyclic six-member ring ketone **4** (0.90 mmol) in anhydrous ethanol (10 mL), sodium ethoxide (3 mL; prepared by 0.01 g sodium and 3 mL anhydrous ethanol) was added. The solution was stirred at reflux about 2 h. The mixture was cooled to room temperature. The solvent was removed under vacuum (30–40 mmHg). The residue was purified through silica gel chromatographic column to get products **5**.

*7,8-Dimethoxy-3,4-dihydro-1H-benzo[b][1,6]-naphthyridine-2-carboxylic Acid Ethyl Ester (**5a**).* The compound was purified by flash silica gel chromatographic column (ethyl acetate/petroleum ether = 3:1, v/v) to give **5a** as a white solid in yield of 90%. It has $R_f$ 0.30 (ethyl acetate/petroleum ether = 3/1, v/v), and mp 139–141°C. IR (KBr), $\nu$ ($cm^{-1}$): 2958, 1695, 1500, 1434, 1395, 893, 850. $^1$H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.21 (t, $J$ = 7.0 Hz, 3H, $CH_3$), 3.16 (t, $J$ = 6.0 Hz, 2H, $CH_2$), 3.87 (t, $J$ = 6.0 Hz, 2H, $CH_2$), 4.00 (s, 3H, $OCH_3$), 4.01 (s, 3H, $OCH_3$), 4.22–4.60 (m, $J$ = 7.0 Hz, 2H, $CH_2$), 4.78 (s, 2H, $CH_2$), 6.98 (s, 1H, H-6), 7.34 (s, 1H, H-3), 7.72 (s, 1H, H-10). MS (*m/z*, %): 316 ($M^+$, 18), 287 (100), 243 (19).

Anal. Calcd. for $C_{17}H_{20}N_2O_4$(316.14), C, 64.54; H, 6.37; N, 8.86. Found: C, 64.16; H, 6.51; N, 8.58.

*7,8-Dimethoxy-2-methyl-1,2,3,4-tetrahydro-benzo-[b][1,6]naphthyridine (***5b***)*. The compound was purified by flash chromatographic column (dichloromethane/ethanol = 4:1, v/v) to give **5b** as a white solid in yield of 95%. It has $R_f$ 0.40 (dichloromethane/ethanol = 4:1, v/v) and mp 138–140°C. IR (KBr), $\nu$ ($cm^{-1}$): 2938, 1624, 1503, 1464, 1395, 1251, 850. $^1H$ NMR (500 MHz, $CDCl_3$), $\delta$ (ppm): 2.53 (s, 3H, $CH_3$), 2.88 (t, $J = 6.5$ Hz, 2H, $CH_2$), 3.22 (t, $J = 6.5$ Hz, 2H, $CH_2$), 3.74 (s, 2H, $CH_2$), 4.00 (s, 3H, $OCH_3$), 4.02 (s, 3H, $OCH_3$), 6.96 (s, 1H, H-6), 7.33 (s, 1H, H-3), 7.63 (s, 1H, H-10). MS (*m/z*, %): 258 ($M^+$, 60), 257 (100), 215 (44), 128 (23).

Anal. Calcd for $C_{15}H_{18}N_2O_2$(258.13). C, 69.74; H, 7.02; N, 10.84. Found: C, 69.69; H, 7.27; N, 10.70.

*(7,8-Dimethoxy-3,4-dihydro-1H-benzo[b][1,6]-naphthyridin-2-yl)-phenyl-methanone (***5c***)*. The compound was purified by flash chromatographic column (ethyl acetate/petroleum ether = 3:1, v/v) to give **5c** as a white solid in yield of 75%. It has $R_f$ 0.22 (ethyl acetate/petroleum ether = 3:1, v/v). mp 135–138°C. IR (KBr), $\nu$ ($cm^{-1}$): 2933, 1628, 1500, 1434, 1395, 1250, 1011, 877. H NMR (500 MHz, $CDCl_3$), $\delta$ (ppm): 3.21 (s, 2H, $CH_2$), 3.81 (s, 2H, $CH_2$), 4.00 (s, 3H, $OCH_3$), 4.02 (s, 3H, $OCH_3$), 5.02 (s, 2H, $CH_2$), 6.99 (s, 1H, H-6), 7.37 (s, 1H, H-3), 7.42–7.48 (m, 5H, $C_6H_5$), 7.81 (s, 1H, H-10). MS (*m/z*, %): 349 (25), 348 ($M^+$, 100), 243 (36), 228 (34), 105 (80), 77 (56).

Anal. Calcd for $C_{21}H_{20}N_2O_3$(348.15), C, 72.40; H, 5.79; N, 8.04. Found: C, 72.35; H, 6.02; N, 7.98.

*6,7-Dimethoxy-3,4-dihydro-1H-2-thia-10-aza-anthracene (***5d***)*. The compound was purified by flash chromatographic column (ethyl acetate/petroleum ether = 1:1, v/v) to give **5d** as a white solid in yield of 90%. It has $R_f$ 0.40 (ethyl acetate/petroleum ether = 1:1, v/v). mp 117–119°C. IR (KBr), $\nu$ ($cm^{-1}$): 2928, 1621, 1500, 1390, 1252, 1154, 1010, 851. $^1H$ NMR (500 MHz, $CDCl_3$), $\delta$ (ppm): 3.08 (t, $J = 6.0$ Hz, 2H, $CH_2$), 3.35 (t, $J = 6.0$ Hz, 2H, $CH_2$), 3.90 (s, 2H, $CH_2$), 4.00 (s, 3H, $OCH_3$), 4.02 (s, 3H, $OCH_3$), 6.98 (s, 1H, H-6), 7.35 (s, 1H, H-3), 7.70 (s, 1H, H-10). MS (*m/z*, %): 262 (16), 261 ($M^+$,100), 260 (17), 246 (12), 230 (10), 228 (56), 215 (32), 77 (7).

Anal. Calcd for $C_{14}H_{15}NO_2S$ (261.08), C, 64.34; H, 5.79; N, 5.36. Found: C, 64.74; H, 6.00; N, 5.10.

*7,8-Dimethoxy-3,4-dihydro-1H-pyrano[4,3-b]quinoline (***5e***)*. The compound was purified by flash chromatographic column (ethyl acetate/petroleum ether = 1:1, v/v) to give **5e** as a white solid in yield of 90%. It has $R_f$ 0.34 (ethyl acetate/petroleum ether, 1:1, v/v). mp 140–142°C. IR (KBr), $\nu$ ($cm^{-1}$): 2933, 1622, 1504, 1393, 1249, 1155, 1013, 891, 851. $^1H$ NMR (500 MHz, $CDCl_3$), $\delta$ (ppm): 3.08 (t, $J = 6.0$ Hz, 2H, $CH_2$), 3.90 (3H, $OCH_3$), 3.92 (3H, $OCH_3$), 4.06 (t, $J = 6.0$ Hz, 2H, $CH_2$), 4.82 (s, 2H, $CH_2$), 6.86 (s, 1H, H-6), 7.26 (s, 1H, H-3), 7.49 (s, 1H, H-10). MS (*m/z*, %): 246 (15), 245 ($M^+$, 100), 244 (40), 217 (19), 115 (5), 77 (6).

Anal. Calcd for $C_{14}H_{15}NO_3$(245.11), C, 68.56; H, 6.16; N, 5.71. Found: C, 68.61; H, 6.44; N, 5.64.

*6,9-Dimethoxy-3,4-dihydro-1H-benzo[b][1,6]-naphthyridine-2-carboxylic Acid Ethyl Ester (***5f***)*. The compound was purified by flash chromatographic column (ethyl acetate/petroleum ether = 3:1, v/v) to give **5f** as a yellow oil in yield of 85%. It has $R_f$ 0.39 (ethyl acetate/petroleum ether = 3:1, v/v). IR (KBr), $\nu$ ($cm^{-1}$): 2936, 1697,1479, 1435, 1262, 1097, 725. $^1H$ NMR (500 MHz, $CDCl_3$), $\delta$ (ppm): 1.29 (t, $J = 7.0$ Hz, 3H, $CH_3$), 3.28 (t, $J = 6.0$ Hz, 2H, $CH_2$), 3.86 (t, $J = 6.0$ Hz, 2H, $CH_2$), 3.96 (s, 3H, $OCH_3$), 4.03 (s, 3H, $OCH_3$), 4.21–4.60 (m, $J = 7.0$ Hz, 2H, $CH_2$), 4.83 (s, 2H, $CH_2$), 6.70 (d, $J = 8.5$ Hz, 1H, H-1), 6.87 (d, $J = 8.5$ Hz, 1H, H-2), 8.29 (s, 1H, H-10). MS (*m/z*, %): 317 (29), 316 ($M^+$, 89), 315 (27), 301 (100), 287 (62), 243 (20).

Anal. Calcd for $C_{17}H_{20}N_2O_4$(316.14), C, 64.54; H, 6.37; N, 8.86. Found: C, 64.53; H, 6.64; N, 8.56.

*6,9-Dimethoxy-2-methyl-1,2,3,4-tetrahydro-benzo-[b][1,6]naphthyridine (***5g***)*. The compound was purified by flash chromatographic column (dichloromethane/ethanol = 9:1, v/v) to give **5g** as a yellow solid in yield of 90%. It has $R_f$ 0.55 (dichloromethane/ethano l = 9:1, v/v). mp 145–146°C. IR (KBr), $\nu$ ($cm^{-1}$): 2946, 1607, 1480, 1389, 1258, 971, 812. $^1H$ NMR (500 MHz, $CDCl_3$), $\delta$ (ppm): 2.52 (s, 3H, $CH_3$), 2.88 (t, $J = 6.0$ Hz, 2H, $CH_2$), 3.34 (t, $J = 6.0$ Hz, 2H, $CH_2$), 3.79 (s, 2H, $CH_2$), 3.94 (s, 3H, $OCH_3$), 4.02 (s, 3H, $OCH_3$), 6.66 (d, $J = 8.5$ Hz, 1H, H-1), 6.83 (d, $J = 8.5$ Hz, 1H, H-2), 8.17 (s, 1H, H-10). MS (*m/z*, %): 259 (16), 258 ($M^+$, 100), 243 (53), 227 (33), 128 (26), 77 (6).

Anal. Calcd for $C_{15}H_{18}N_2O_2$(258.13), C, 69.74; H, 7.02; N, 10.84. Found: C, 69.28; H, 7.35; N, 10.60.

*(6,9-Dimethoxy-3,4-dihydro-1H-benzo[b][1,6]-naphthyridin-2-yl)-phenyl-methanone (***5h***)*. The compound was purified by flash chromatographic column (ethyl acetate/petroleum ether = 3:1, v/v) to give **5h** as a yellow solid in the yield of 70%. It has $R_f$ 0.28 (ethyl acetate/petroleum ether = 3:1, v/v). mp 141–143°C. IR (KBr), $\nu$ ($cm^{-1}$): 3055, 2936,

1622, 1479, 1435, 1264, 1077, 725. $^1$H NMR (500 MHz, $CDCl_3$), δ (ppm): 3.33 (s, 2H, $CH_2$), 3.95 (s, 2H, $CH_2$), 4.03 (s, 6H, $2OCH_3$), 5.09 (s, 2H, $CH_2$), 6.72 (d, $J = 8.5$ Hz, 1H, H-1), 6.90 (d, $J = 8.5$ Hz, 1H, H-2) 7.44–7.47 (m, 5H, $C_6H_5$), 8.20 (s, 1H, H-10). MS (*m/z*, %): 349 (11), 348 ($M^+$, 49), 333 (53), 213 (23), 200 (13), 105 (79), 77 (100).

Anal. Calcd for $C_{21}H_{20}N_2O_3$(348.15), C, 72.40; H, 5.79; N, 8.04. Found: C, 72.19; H, 6.05; N, 7.96.

*5,8-Dimethoxy-3,4-dihydro-1H-2-thia-10-aza-anthracene (***5i***).* The compound was purified by flash chromatographic column (ethyl acetate/petroleum ether = 1:1, v/v) to give **5i** as a yellow solid in yield of 95%. It has $R_f$ 0.35 (ethyl acetate/petroleum ether = 1/1, v/v). mp 134–136°C. IR (KBr), ν ($cm^{-1}$): 3080, 2952, 1620, 1477, 1385, 1266, 1163, 1097, 973, 813. $^1$H NMR (500 MHz, $CDCl_3$), δ (ppm): 3.08 (t, $J = 6.0$ Hz, 2H, $CH_2$), 3.47 (t, $J = 6.0$ Hz, 2H, $CH_2$), 3.95 (s, 2H, $CH_2$), 3.95 (s, 3H, $OCH_3$), 4.03 (s, 3H, $OCH_3$), 6.72 (d, $J = 8.5$ Hz, 1H, H-1), 6.88 (d, $J = 8.5$ Hz, 1H, H-2), 8.26 (s, 1H, H-10). MS (*m/z*, %): 262 (11), 261 ($M^+$, 55), 246 (100), 232 (26), 200 (31), 186 (6), 115 (17), 77 (7).

Anal. Calcd for $C_{14}H_{15}NO_2S$ (261.08), C, 64.34; H, 5.79; N, 5.36. Found: C, 64.46; H, 6.12; N, 5.18.

*6,9-Dimethoxy-3,4-dihydro-1H-pyrano[4,3-b]quinoline (***5j***).* The compound was purified by flash chromatographic column (ethyl acetate/petroleum ether = 1:1, v/v) to give **5j** as a yellow solid in a yield of 95%. It has $R_f$ 0.28 (ethyl acetate/petroleum ether = 1:1, v/v. mp 160–161°C. IR (KBr), ν ($cm^{-1}$): 2962, 1621, 1606, 1482, 1391, 1180, 1076, 812. $^1$H NMR (500 MHz, $CDCl_3$), δ (ppm): 3.30 (t, $J = 6.0$ Hz, 2H, $CH_2$), 3.94 (s, 3H, $OCH_3$), 4.03 (s, 3H, $OCH_3$), 4.15 (t, $J = 6.0$ Hz, 2H, $CH_2$), 4.96 (s, 2H, $CH_2$), 6.68 (d, $J = 8.5$ Hz, 1H, H-1), 6.86 (d, $J = 8.5$ Hz, 1H, H-2), 8.16 (s, 1H, H-10). MS (*m/z*, %): 246 (4), 245 ($M^+$, 28), 244 (14), 230 (100), 216(19), 200 (35), 186 (11), 115 (6), 77 (8).

Anal. Calcd for $C_{14}H_{15}NO_3$ (245.11), C, 68.56; H, 6.16; N, 5.71. Found: C, 68.37; H, 6.36; N, 5.55.

## *REFERENCES*


[1] Chauhan, P. M. S.; Srivastav, S. K. Curr Med Chem 2001, 8, 1535–1542.

[2] (a) Heath, J. A.; Mehrotra, M. M.; Chi, S.; Yu, J. C.; Hutchaleelaha, A.; Hollenbach, S. J.; Giese, N. A.; Scarborough, R. M.; Pandey, A. Bioorg Med Chem Lett 2004, 14, 4867–4872; (b) Keyaerts, E.; Vijgen, L.; Maes, P.; Neyts. J.; Ranst, M. V. Biochem Biophys Res Commun 2004, 323, 264–268.

[3] (a) Vaitilingam, B.; Nayyar, A.; Palde, P. B.; Monga, V.; Jain, R.; Kaur, S.; Singh, P. P. Bioorg Med Chem 2004, 12, 4179–4188; (b) Chen, Y.-L.; Fang, K.-C.; Sheu, J.-Y.; Hsu, S.-L.; Tzeng, C. C. J Med Chem 2001, 44, 2374–2377.

[4] (a) Lee, B. D.; Li, Z.; French, K. J.; Zhuang, Y.; Xia, Z.; Smith, C. D. J Med Chem 2004, 47, 1413–1422; (b) Gopal, M.; Shenoy, S.; Doddamani, L. S. J Photochem Photobiol B 2003, 72, 69–78; (c) Tara, F.; Hanna, I. P.; Walter, T. G.; Kurtis, C. B.; Stephen, J. G.; Alexandra, M. Z. S.; Howard, D. B.; Christopher, J. M. Bioorg Med Chem 2004, 12, 1667–1687; (d) Ko, T.-C.; Hour, M.-J.; Lien, J.-C.; Teng, C.-M.; Lee, K.-H.; Kuo, S.-C.; Huang, L.-J. Bioorg Med Chem Lett 2001, 11, 279–282.

[5] (a) Larsen, R. D.; Corley, E. G.; King, A. O.; Carrol, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y.; Xiang, Y. B.; Zamboni, R. J. J Org Chem 1996, 61, 3398–3405; (b) Zwaagstra, M. E.; Timmerman, H.; Van De Stolpe, A. C.; De Kanter, F. J.; Tamura, M.; Wada, Y.; Zhang, M. Q. J Med Chem 1998, 41, 1428–1438; (c) Von Sprecher, A.; Gerspacher, M.; Beck, A.; Kimmel, S.; Wiestner, H.; Anderson, G. P.; Niederhauser, U.; Subramanian, N.; Bray, M. A. Bioorg Med Chem Lett 1998, 8, 965–970; (d) Doubè, D.; Blouin, M.; Brideau. C.; Chan, C.; Desmarais, S.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Girard, M.; Girard, Y.; Guay, J.; Tagari. P.; Young, R. N. Bioorg Med Chem Lett 1998, 8, 1255–1260.

[6] Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, M. Eur J Med Chem 2000, 35, 1021–1035.

[7] (a) Morizawa, Y.; Okazoe, T.; Wang, S.-Z.; Sasaki, J.; Ebisu, H.; Nishikawa, M.; Shinyama, H. J Flu Chem 2001, 109, 83–86; (b) Ferrarini, P. L.; Mori, C.; Badawneh, M.; Calderonem, V.; Greco, R.; Manera, C.; Martinelli, A.; Nieri, P.; Saccomanni, G. Eur J Med Chem 2000, 35, 815–826.

[8] (a) Hu, Y. Z.; Zhang, G.; Randolph, P. T. Org Lett 2003, 5, 2251–2253; (b) Ohashi, A.; Tsuguchi, A.; Imura, H.; Ohashi, K. Anal Sci 2004, 20, 1091–1093; (c) Wang, H.; Liu, Z.; Liu, C.; Zhang, D.; Lu, Z.; Geng, H.; Shuai, Z.; Zhu, D. Inorg Chem 2004, 43, 4091–4098.

[9] (a) Chiang, C.-L.; Shu, C.-F. Chem Mater 2002, 14, 682–686; (b) Nakatani, K.; Sando, S.; Saito, I. Bioorg Med Chem 2001, 9, 2381–2385; (c) Nakatani, K.; Sando, S.; Saito, I. J Am Chem Soc 2000, 122, 2172–2177; (d) Nguyen, C. H.; Marchand, C.; Delane, S.; Sun, J.-S.; Garestier, H.; Bisagni, E. J Am Chem Soc 1998, 120, 2501–2507.

[10] Sugimori, M.; Ejima. A.; Qhsuki. S.; Uoto. K.; Mitsui. I.; Kawato, Y. J Med Chem 1998, 41, 2308–2318.

[11] Brian, R, M.; Benjamin, L, M. Org Lett 2003, 5, 4257–4259.

[12] Sandeep, K.; Ellen, J. W.; Ehud, K. J Org Chem 1993, 58, 3821–3827.

[13] Randolph, P. T.; Sara, C.; Christophe, H.; Jean-Lue, L.; Tie-Lin, W. J Org Chem 1993, 58, 1666–1671.

[14] Christiane, V.; Jean-Luc, V.; Georges, D. Tetrahedron 2001, 57, 3087–3098.

[15] Yang, D.-Q.; Zeng, H.-P.; Liu, C.-Y. J South China Normal Uni 2000, 4, 44–46.

[16] Guo, W.; Jiang, Q.-J.; Lü, F.; Yang, D.-Q. Chin J Synth Chem 2004, 12, 12–14.