Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 7654–7658

Synthesis and characterization of quinoline derivatives via the Friedländer reaction

Dingqiao Yang,* Kailing Jiang, Jingning Li and Feng Xu

School of Chemistry and Environment, South China Normal University, Guangzhou 510006, China

Received 6 August 2006; revised 29 April 2007; accepted 10 May 2007
Available online 13 May 2007

Abstract—A rapid and efficient method for the synthesis of various poly-substituted quinolines has been developed via the Friedländer condensation of 2-aminoarylaldehyde with a carbonyl compound containing a reactive α-methylene group in the presence of sodium ethoxide (10 mol %). The new tetrahydroacridine derivatives and 11*H*-indeno[1,2-*b*]quinolines were synthesized in high yield with sodium ethoxide as a catalyst via the Friedländer reaction. The conditions of reaction were discussed and the possible reaction mechanism was proposed.

1. Introduction

The quinoline nucleus occurs in several natural compounds (cincona alkaloids) and pharmacologically active substances displaying a broad range of biological activity.[1] The biological activity of quinoline compounds has been found to possess antiasthmatic, antibacterial, anti-inflammatory, and antihypertensive properties. In addition to the medicinal applications, quinolines have been employed in the study of bioorganic and bioorganometallic processes. Quinolines are also known for their formation of conjugated molecules and polymers that combine enhanced electronic, optoelectronic, or nonlinear optical properties with excellent mechanical properties.[2] The Friedländer reaction is a well-known method for preparing quinolines and polypyridyl bridging ligands,[3] it is still considered as one of the most useful methods for preparing quinolines and related bicyclic azaaromatic compounds. In its original form, the Friedländer reaction is the reaction between an aromatic *ortho*-aminoaldehyde and an aldehyde or ketone bearing α-methylene functionality. Since Friedländer's initial discovery, the reaction has been extended to a wide range of substrates, including aromatic *ortho*-aminoketones and nitrogen-containing heterocycles.[4]

In recent years, the chemists were interested in studies of the reaction with low waste and reusable reaction media for enhanced selectivity and minimized energy.[5] A number of other methods have been reported for the synthesis of quinolines involving a variety of metal catalysts and Lewis acids.[6] Brønsted acid catalysts, such as hydrochloric acid, perchloric acid, sulfuric acid, *p*-toluene sulfonic acid, sulfamic acid, phosphoric acid, and trifluoro acetic acid were widely used for the Friedländer reaction.[7] However, many of these procedures are not fully satisfactory with regard to operational simplicity, cost of the reagent, drastic reaction conditions, and relatively low yield. Therefore, a simple, general, and efficient procedure is still in demand for the preparation of these important heterocyclic compounds and continues to find a better and improved methodology. In this paper, we have demonstrated a very efficient and environmentally benign strategy for the synthesis of new tetrahydroacridine derivatives and 11*H*-indeno[1,2-*b*]quinolines with good to excellent yields.

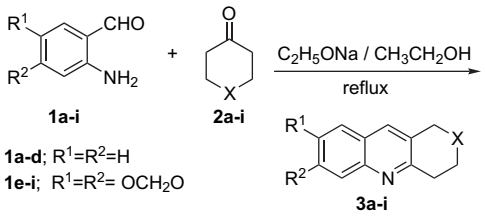
2. Results and discussion

Friedländer reaction in the presence of a catalytic amount of sodium ethoxide for about 2–3 h resulted in a complete consumption of substrates. Our approach to the synthesis of **3a–i** and **6a–i** were based on the Friedländer condensation strategy. The intermediates **1a–i** and **4a–i** were obtained by nitration of the arylaldehyde followed by reduction of *ortho*-nitroarylaldehyde. The intermediates used in the Friedländer reaction reacted with **2a–i** and **5a–i**, separately, to form quinoline derivatives. The results of these reactions were summarized in Tables 1 and 2, respectively. Friedländer reactions were carried out using sodium ethoxide under reflux in absolutely anhydrous ethanol. We tried to use NaOH as a catalyst

Keywords: The Friedländer condensation reaction; 2-Amino-3,6-dimethoxy-benzaldehyde; 11*H*-Indeno[1,2-*b*]quinoline; Tetrahydroacridine derivatives.
* Corresponding author. Tel.: +86 20 85210087; fax: +86 20 39310183; e-mail: yangdq@scnu.edu.cn

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.05.037

Table 1. Reaction results of the Friedländer condensation reaction for the synthesis of poly-substituted quinolines

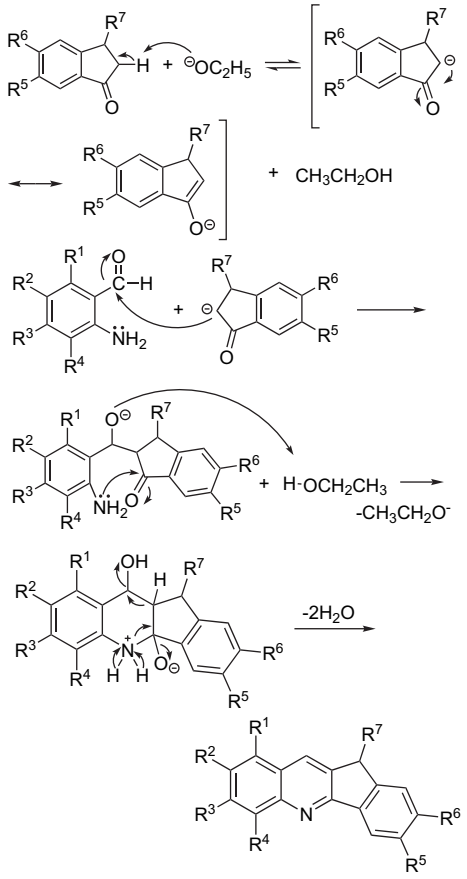


Entry	Compounds	R^1	R^2	X	Time (h)	Yield (%)
1	**3a**	H	H	O	2	51
2	**3b**	H	H	S	2	82
3	**3c**	H	H	NCH_3	2	88
4	**3d**	H	H	NCH_2CH_2Ph	2	80
5	**3e**	OCH_2O	R^1	O	2	53
6	**3f**	OCH_2O	R^1	S	2	93
7	**3g**	OCH_2O	R^1	NCH_3	2	90
8	**3h**	OCH_2O	R^1	NCH_2CH_2Ph	2	83
9	**3i**	OCH_2O	R^1	$NCOOCH_2CH_3$	2	65

for the Friedländer reactions; we got target compounds in a low yield. Sodium ethoxide is better catalyst than sodium hydroxide for the Friedländer reactions, because it is much stronger base than sodium hydroxide. The use of 10 mol % of the catalyst was sufficient to promote the reaction. Higher amounts of the catalyst did not improve the yields. That is why we choose sodium ethoxide as a catalyst in a low loading for the Friedländer reactions. Interesting, cyclic ketones also underwent smooth condensation with 2-aminoarylaldehyde to afford the respective tricyclic and tetracyclic quinolines (Tables 1 and 2). In most cases, the products were isolated by simple filtration. The crude products were purified either by recrystallization from a mixture of diethyl acetate/*n*-hexane or by silica gel column chromatography. Target compounds of **3a–i** and **6a–i** were obtained in good yield from the Friedländer reaction under sodium ethoxide as a catalyst (catalyst loading is 10 mol %). The yields of **3a–i** and **6a–i** were in the range of 53–93%.

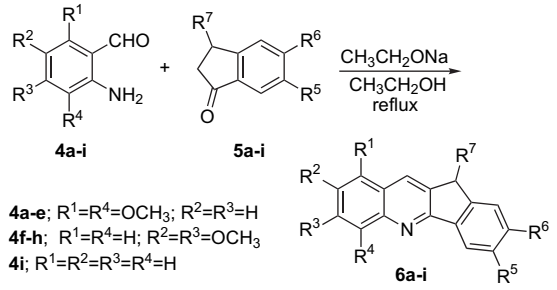
All the compounds of **3a–i** and **6a–i** were well characterized by UV, IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis.

The possible reaction mechanism for the Friedländer reaction was proposed in Scheme 1. A nucleophilic reaction



Scheme 1. The possible mechanism of formation of 11*H*-indeno[1,2-*b*]-quinoline derivatives.

Table 2. Reaction results of the Friedländer condensation reaction for the synthesis of 11*H*-indeno[1,2-*b*]quinoline and its derivatives



Compounds	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)
6a	OCH_3	H	H	OCH_3	H	F	H	65
6b	OCH_3	H	H	OCH_3	H	Cl	H	71
6c	OCH_3	H	H	OCH_3	H	Br	H	75
6d	OCH_3	H	H	OCH_3	OCH_3	OCH_3	H	85
6e	OCH_3	H	H	OCH_3	H	H	Ph	67
6f	H	OCH_3	OCH_3	H	H	Cl	H	72
6g	H	OCH_3	OCH_3	H	H	Br	H	75
6h	H	OCH_3	OCH_3	H	H	H	Ph	66
6i	H	H	H	H	OCH_3	OCH_3	H	75

took place between *ortho*-aminoaldehyde and indenone substrate. In the basic medium used in the current work, a resonance-stabilized enolate anion for indenone was formed. The enolate anion attacked the carbonyl carbon in *ortho*-aminoarylaldehyde and the amino group in the *ortho*-aminoarylaldehyde attacked the carbonyl group in the enolate anion, as a result, the cyclized intermediate was formed, eliminating 2 equiv of H_2O to give a quinoline.

In conclusion, we have demonstrated a simple and efficient procedure for the synthesis of quinolines, utilizing sodium ethoxide as a catalyst via Friedländer reaction. The reaction offers a potential strategy for the preparation of qunolines bearing indeno functional groups. This method not only provides an excellent complement to quinoline synthesis via Friedländer reaction, but also avoids the use of hazardous acids and harsh reaction conditions. The advantages of this method include good substrate generality, the use of inexpensive reagents and catalyst under mild conditions, and experimental operational ease. This approach would provide a useful tool for the construction of large quinoline and related azaheterocycle libraries. Reactions employing ionic liquid as solvent and catalyst are currently under investigation in our research group, and will be reported in due course.

3. Experimental

3.1. General

All reagents and solvents were of reagent grade. Melting points were determined on a microscopic melting point apparatus (Kofler) and were uncorrected. ^{1}H NMR (400 MHz) and ^{19}F NMR (282 MHz) were recorded in $CDCl_3$ or DMSO-d_6 solutions with TMS as the respective internal standards. Mass spectra were obtained with Thermofinnigan MAT95XL spectrometer system. Relevant data were tabulated as *m*/*z*. The IR spectra were recorded on a Perkin–Elmer Model 1730 FTIR spectrometer using KBr film. The ^{1}H NMR spectra were recorded on a Varian Inova 500 MHz in $CDCl_3$ solutions using TMS as an internal standard. Elemental analyses were performed on a Elemental Varioel spectrometer. 3,4-Dimethoxy benzaldehyde, 2,5-dimethoxybenzaldehyde, cyclic ketones, and heterocyclic 6-member ring ketones were purchased from Aldrich. 3,4-Dimethoxy-6-amino benzaldehyde[8] and 3,6-dimethoxy-2-aminobenzaldehyde were prepared according to previous reports.[9]

3.2. General procedure for the synthesis of quinoline derivatives via Friedländer condensation reaction

To a solution of *ortho*-aminobenzaldehyde **1a** (0.1150 g, 0.95 mmol) and tetrahydro-4*H*-pyran-4-one **2a** (0.095 mL, 0.95 mmol) in anhydrous ethanol (10 mL) was added sodium ethoxide (6.8 mg, 0.10 mmol). The solution was stirred at reflux for 2 h. The mixture was cooled down to room temperature. The solvent was removed under vacuum (30–40 mmHg). Evaporation of the solvent afforded the crude product as a solid, which was further purified by column chromatography to afford the product **3a** (0.089 g, 51%) as a colorless crystal.

3.2.1. 3,4-Dihydro-1*H*-pyrano[4,3-*b*]quinoline (3a). A colorless crystal, mp 74–77 °C; ^{1}H NMR ($CDCl_3$) δ 8.01 (d, 1H), 7.74 (d, J=8.1 Hz, 1H), 7.72 (s, 1H), 7.66 (t, J=7.1 and 8.3 Hz, 1H), 7.48 (t, J=7.1 and 7.9 Hz, 1H), 4.96 (s, 2H), 4.17 (t, J=5.6 and 5.5 Hz, 2H), 3.24 (t, J=5.8 and 5.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 155.18, 147.24, 131.17, 129.29, 128.68, 127.39, 127.09, 127.09, 126.23, 67.91, 66.14, 32.90; UV–vis (CH_3OH) λ_{max}: 222.00 nm; IR (KBr) ν 3054, 2964, 2938, 2830, 1725, 1621, 1598, 1556, 1491, 1417, 1162, 863, 761 cm^{-1}; MS (*m*/*z*, %): 185 (M^+, 100), 184 (M−H, 82), 156 (78), 128 (28); Found: C, 77.55; H, 6.19; N, 7.28%. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56%.

3.2.2. 3,4-Dihydro-1*H*-2-thia-10-aza-anthracene (3b). A white solid, mp 96–99 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (d, J=8.1 Hz, 1H), 7.87 (d, J=5.2 Hz, 1H), 7.76 (d, J=8.1 Hz, 1H), 7.68 (t, J=7.1 and 8.2 Hz, 1H), 7.51 (t, J=7.5 and 7.4 Hz, 1H), 3.95 (s, 2H), 3.41 (m, J=6.4, 3.5 and 2.8 Hz, 2H), 3.11 (t, J=6.5 and 6.3 Hz, 2H); UV–vis (CH_3OH) λ_{max}: 231.00 nm; IR (KBr) ν 3042, 2906, 2924, 2862, 1724, 1620, 1598, 1556, 1490, 1460, 763 cm^{-1}; MS (*m*/*z*, %): 201 (M^+, 100), 200 (M−H, 36), 186 (16), 168 (72), 154 (39), 129 (7); Found: C, 71.40; H, 5.37; N, 6.66; S, 15.70%. Calcd for $C_{12}H_{11}NS$: C, 71.60; H, 5.51; N, 6.96; S, 15.93%.

3.2.3. 2-Methyl-1,2,3,4-tetrahydro-benzo[*b*][1,6]naphthyridine (3c). A yellow solid, mp 76–79 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J=8.5 Hz, 1H), 7.78 (s, 1H), 7.73 (d, J=8.1 Hz, 1H), 7.64 (m, 1H), 7.46 (m, 1H), 3.79 (s, 2H), 3.30 (t, J=6.1 Hz, 2H), 2.90 (t, J=5.6 and 6.1 Hz, 2H), 2.54 (d, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 156.21, 147.14, 132.87, 129.00, 128.50, 127.26, 126.95, 126.95, 125.89, 57.84, 53.33, 46.18, 32.38; UV–vis (CH_3OH) λ_{max}: 232.00 nm; IR (KBr) ν 3054, 2937, 2851, 2790, 2755, 1730, 1603, 1496, 1451, 1420, 747 cm^{-1}; MS (*m*/*z*, %): 198 (M^+, 46), 197 (M−H, 100), 168 (3), 154 (25), 140 (4), 128 (6); Found: C, 78.50; H, 7.20; N, 14.10%. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13%.

3.2.4. 2-Phenethyl-1,2,3,4-tetrahydro-benzo[*b*][1,6]naphthyridine (3d). A yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J=8.5 Hz, 1H), 7.78 (s, 1H), 7.71 (d, J=6.8 Hz, 1H), 7.63 (d, J=1.3 Hz, 1H), 7.46 (d, J=7.8 Hz, 1H), 7.31 (d, J=7.5 Hz, 1H), 7.28 (d, J=2.9 Hz, 1H), 7.23–7.25 (m, 3H), 3.90 (s, 2H), 3.28 (t, J=6.1 Hz, 2H), 3.01 (t, J=6.0 Hz, 2H), 2.94 (t, J=4.7 and 4.5 Hz, 2H), 2.85 (t, J=4.6 and 3.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 156.57, 147.10, 140.15, 133.01, 129.19, 128.94, 128.86, 128.75, 128.65, 128.49, 127.17, 126.60, 126.20, 125.84, 65.57, 59.93, 55.80, 51.10, 34.04, 33.19; UV–vis (CH_3OH) λ_{max}: 236.00 nm; IR (KBr) ν 3061, 2924, 2853, 1728, 1651, 1601, 1558, 1494, 1456, 1383, 750, 700 cm^{-1}; MS (*m*/*z*, %): 289 (M−H, 100); Found: C, 83.30; H, 7.10; N, 9.81%. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71%.

3.2.5. 6,9-Dihydro-7*H*-1,3,8-trioxa-5-aza-cyclopenta-[*b*]anthracene (3e). A white solid, mp 194–196 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (s, 1H), 7.30 (s, 1H), 6.97 (s, 1H), 6.09 (s, 2H, OCH_2O), 4.90 (s, 2H), 4.15 (t, J=5.9 Hz, 2H), 3.15 (t, J=5.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 155.32, 150.66, 147.71, 145.14, 133.13, 127.08, 124.03, 105.11, 102.35, 101.75, 34.12, 29.77, 26.76; UV–vis (CH_3OH) λ_{max}:

231.00 nm; IR (KBr) ν 3048, 2963, 2845, 1729, 1620, 1495, 1460, 1140, 946, 876, 787 cm^{-1}; MS (*m/z*, %): 229 (M^+, 100), 228 (M−H, 60), 200 (75), 169 (7), 141 (13); Found: C, 68.04; H, 5.01; N, 5.91%. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11%.

3.2.6. 6,9-Dihydro-7*H*-1,3-dioxa-8-thia-5-aza-cyclopenta-[*b*]anthracene (3f). A white crystal, mp 203–205 °C; ^1H NMR ($CDCl_3$) δ 7.67 (s, 1H), 7.30 (s, 1H), 6.98 (s, 1H), 6.09 (s, 2H, OCH_2O), 3.88 (s, 2H), 3.33 (t, J=6.3 and 6.4 Hz, 2H), 3.07 (t, J=6.4 and 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 151.92, 150.04, 147.08, 144.81, 129.68, 126.22, 123.31, 104.61, 101.77, 101.11, 67.13, 65.56, 32.45; UV–vis (CH_3OH) λ_{max}: 225 nm; IR (KBr) ν 3020, 2958, 2924, 2851, 1727, 1614, 1492, 1461, 1409, 942, 842 cm^{-1}; MS (*m/z*, %): 245 (M^+, 100), 244 (M−H, 37), 212 (67), 199 (44), 187 (11), 141 (9); Found: C, 63.83; H, 4.57; N, 6.01; S, 12.98%. Calcd for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71; S, 13.07%.

3.2.7. 8-Methyl-6,7,8,9-tetrahydro-1,3-dioxa-5,8-diaza-cyclopenta[*b*]anthracene (3g). A yellow crystal, mp 190–192 °C; ^1H NMR ($CDCl_3$) δ 7.58 (s, 1H), 7.28 (s, 1H), 6.95 (s, 1H), 6.06 (s, 2H, OCH_2O), 3.71 (s, 2H), 3.19 (t, J=6.1 Hz, 2H), 2.86 (t, J=6.1 Hz, 2H), 2.51 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 153.52, 150.45, 147.45, 145.27, 132.11, 131.00, 128.95, 126.56, 123.76, 105.06, 102.28, 101.60, 57.59, 53.36, 46.09, 32.85; UV–vis (CH_3OH) λ_{max}: 230.00 nm; IR (KBr) ν 3037, 2963, 2936, 2845, 2761, 1727, 1621, 1498, 1459, 1320, 923, 854 cm^{-1}; MS (*m/z*, %): 242 (M−H, 64), 241 (M^+, 100), 227 (8), 169 (9), 141 (11); Found: C, 69.11; H, 5.93; N, 11.33%. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56%.

3.2.8. 8-Phenethyl-6,7,8,9-tetrahydro-1,3-dioxa-5,8-diaza-cyclopenta[*b*]anthracene (3h). A brown solid, mp 150–152 °C; ^1H NMR ($CDCl_3$) δ 7.58 (s, 1H), 7.32 (s, 1H), 7.29 (d, J=7.3 Hz, 2H), 7.23 (t, J=4.2 Hz, 2H), 7.20 (d, J=7.0 Hz, 1H), 6.94 (s, 1H), 6.05 (s, 2H, OCH_2O), 3.83 (s, 2H), 3.20 (t, J=6.1 and 6.0 Hz, 2H), 2.98 (t, J=6.2 and 7.1 Hz, 2H), 2.93 (t, J=4.1 and 4.7 Hz, 2H), 2.83–2.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 153.85, 150.36, 147.36, 145.23, 140.18, 132.19, 128.74, 128.48, 126.51, 126.18, 123.69, 105.03, 102.18, 101.51, 55.93, 55.57, 51.14, 34.05, 32.74; UV–vis (CH_3OH) λ_{max}: 229.00 nm; IR (KBr) ν 3028, 2949, 2801, 1620, 1558, 1493, 1451, 1402, 945, 748, 698 cm^{-1}; MS (*m/z*, %): 333 (M−H, 100); Found: C, 75.81; H, 5.93; N, 8.43%. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43%.

3.2.9. 6,9-Dihydro-7*H*-1,3-dioxa-5,8-diaza-cyclopenta-[*b*]anthracene-8-carboxylic acid ethyl ester (3i). A white solid, mp 168–170 °C; ^1H NMR ($CDCl_3$) δ 7.67 (s, 1H), 7.29 (s, 1H), 6.97 (s, 1H), 6.08 (s, 2H, OCH_2O), 4.74 (s, 2H), 4.21–4.56 (m, 2H), 3.85 (s, 2H), 3.13 (t, J=6.0 Hz, 2H), 1.30 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.71, 153.55, 150.71, 147.70, 145.26, 132.04, 130.93, 123.95, 105.10, 102.23, 101.70, 61.69, 45.23, 41.76, 32.67, 14.80; IR (KBr) ν 3037, 2997, 2985, 2913, 2851, 1716, 1621, 1497, 1458, 1423, 1238, 1093, 943, 771 cm^{-1}; MS (*m/z*, %): 300 (M^+, 3), 299 (M−H, 0.28), 271 (26), 227 (13), 199 (2), 169 (1), 141 (1); Found: C, 64.28; H, 5.61; N, 9.11%. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33%.

3.2.10. 2-Fluoro-6,9-dimethoxy-11*H*-indeno[1,2-*b*]quinoline (6a). A yellow crystal, mp 160–161 °C; ^1H NMR ($CDCl_3$) δ 8.69 (s, 1H), 8.60 (s, 1H), 7.72 (d, J=8.8 Hz, 1H), 7.55 (d, J=2.2 Hz, 1H), 7.01 (d, J=8.4 Hz, 1H), 6.82 (d, J=8.4 Hz, 1H), 4.11 (s, 3H, $-OCH_3$), 4.09 (s, 2H), 4.02 (s, 3H, $-OCH_3$); UV–vis (CH_3OH) λ_{max}: 296.50 nm, 286.50 nm; IR (KBr) ν 2986, 1615, 1487, 1250, 1105, 950, 856, 787 cm^{-1}; MS (*m/z*, %): 295 (M^+, 100), 280 (35), 252 (48); Found: C, 73.03; H, 4.83; N, 4.49%. Calcd for $C_{18}H_{14}FNO_2$: C, 73.21; H, 4.78; N, 4.74%.

3.2.11. 2-Chloro-6,9-dimethoxy-11*H*-indeno[1,2-*b*]quinoline (6b). A yellow crystal, mp 198–200 °C; ^1H NMR ($CDCl_3$) δ 8.64 (s, 1H), 8.32 (d, J=8.4 Hz, 1H), 7.58 (s, 1H), 7.47 (d, J=10.0 Hz, 1H), 6.96 (d, J=10.0 Hz, 1H), 6.78 (d, J=8.4 Hz, 1H), 4.09 (s, 3H, $-OCH_3$), 4.07 (s, 2H), 3.99 (s, 3H, $-OCH_3$); UV–vis (CH_3OH) λ_{max}: 300.50 nm, 292.60 mm; IR (KBr) ν 2928, 1615, 1463, 1462, 1122, 795 cm^{-1}; MS (*m/z*, %): 311 (M^+, 100), 296 (21), 207 (50); Found: C, 69.66; H, 4.83; N, 4.28%. Calcd for $C_{18}H_{14}ClNO_2$: C, 69.35; H, 4.53; N, 4.49%.

3.2.12. 2-Bromo-6,9-dimethoxy-11*H*-indeno[1,2-*b*]quinoline (6c). A light green crystal, mp 208–209 °C; ^1H NMR ($CDCl_3$) δ 8.62 (s, 1H), 8.24 (d, J=8.0 Hz, 1H), 7.73 (s, 1H), 7.61 (d, J=1.0 Hz, 1H), 6.76 (d, J=8.5 Hz, 1H), 6.69 (d, J=8.5 Hz, 1H), 4.07 (s, 3H, $-OCH_3$), 4.02 (s, 2H), 3.98 (s, 3H, $-OCH_3$); UV–vis (CH_3OH) λ_{max}: 301.00 nm, 292.50 nm; IR (KBr) ν 2923, 1622, 1460, 1260, 1073, 950, 787 cm^{-1}; MS (*m/z*, %): 355 (M^+, 50), 339 (100), 328 (21); Found: C, 60.95; H, 4.23; N, 3.75%. Calcd for $C_{18}H_{14}BrNO_2$: C, 60.69; H, 3.96; N, 3.93%.

3.2.13. 2,3,6,9-Tetramethoxy-11*H*-indeno[1,2-*b*]quinoline (6d). A yellow solid, mp 196–197 °C; ^1H NMR ($CDCl_3$) δ 8.60 (s, J=8.0 Hz, 1H), 7.73 (d, J=8.0 Hz, 1H), 7.53 (s, 1H), 7.10 (s, 1H), 6.96 (s, 1H), 4.11 (s, 6H, $-OCH_3$), 4.09 (s, 6H, $-OCH_3$), 3.98 (s, 2H); UV–vis (CH_3OH) λ_{max}: 314.00 nm, 287.50 nm; IR (KBr) ν 2928, 1615, 1462, 1260, 1080, 1031, 790 cm^{-1}; MS (*m/z*, %): 337 (M^+, 58), 322 (100), 308 (22); Found: C, 71.50; H, 5.88; N, 4.37%. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15%.

3.2.14. 6,9-Dimethoxy-11-phenyl-11*H*-indeno[1,2-*b*]quinoline (6e). A light red solid, mp 162–163 °C; ^1H NMR ($CDCl_3$) δ 8.50 (s, 1H), 8.44 (d, J=12 Hz, 1H), 7.52 (t, J=10 Hz, 1H), 7.45 (t, J=12 Hz, 1H), 7.39 (d, J=12 Hz, 1H), 7.33–7.26 (m, 4H, Ar-H), 7.14 (d, J=8 Hz, 1H, Ar-H), 6.98 (d, J=8 Hz, 1H), 6.76 (d, J=8 Hz, 1H), 5.20 (s, J=8 Hz, 1H), 4.12 (s, 3H, $-OCH_3$), 3.94 (s, 3H, $-OCH_3$); UV–vis (CH_3OH) λ_{max}: 300.50 nm, 291.50 nm; IR (KBr) ν 2923, 1615, 1460, 1260, 1090, 790 cm^{-1}; MS (*m/z*, %): 353 (M^+, 100), 338 (21), 322 (50); Found: C, 81.79; H, 5.67; N, 4.13%. Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96%.

3.2.15. 2-Chloro-7,8-dimethoxy-11*H*-indeno[1,2-*b*]quinoline (6f). A light yellow crystal, mp 202–203 °C; ^1H NMR ($CDCl_3$) δ 8.14 (d, J=8 Hz, 1H), 8.01 (s, 1H), 7.71 (s, 1H), 7.53 (s, 1H), 7.46 (d, J=8 Hz, 1H), 7.05 (s, 1H), 4.06 (s, 3H, $-OCH_3$), 4.02 (s, 3H, $-OCH_3$), 3.94 (s, 2H); UV–vis (CH_3OH) λ_{max}: 363.00 nm, 232.60 nm; IR (KBr)

ν 2931, 1620, 1503, 1258, 1132, 795 cm^{-1}; MS (*m/z*, %): 311 (M^+, 100), 296 (22), 207 (50); Found: C, 69.66; H, 4.67; N, 4.33%. Calcd for $C_{18}H_{14}ClNO_2$: C, 69.35; H, 4.53; N, 4.49%.

3.2.16. 2-Bromo-7,8-dimethoxy-11*H*-indeno[1,2-*b*]quinoline (6g). A light green solid, mp 214–215 °C; ^1H NMR ($CDCl_3$) δ 8.09 (s, 1H), 7.75 (s, 1H), 7.71 (s, 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.62 (s, 1H), 7.09 (s, 1H), 4.10 (s, 3H, $-OCH_3$), 4.05 (s, 3H, $-OCH_3$), 4.00 (s, 2H); UV–vis (CH_3OH) λ_{max}: 363.00 nm, 233.00 nm; IR (KBr) ν 2927, 1624, 1503, 1252, 1134, 1017, 846 cm^{-1}; MS (*m/z*, %): 355 (M^+, 100), 338 (21), 322 (54); Found: C, 60.37; H, 4.18; N, 3.75%. Calcd for $C_{18}H_{14}BrNO_2$: C, 60.69; H, 3.96; N, 3.93%.

3.2.17. 7,8-Dimethoxy-11-phenyl-11*H*-indeno[1,2-*b*]quinoline (6h). A light red solid, mp 167–168 °C; ^1H NMR ($CDCl_3$) δ 8.44 (s, 1H), 7.90 (s, 1H), 7.55 (t, *J*=12 Hz, 1H), 7.45 (t, *J*=12 Hz, 2H), 7.40 (s, 1H), 7.31–7.27 (m, 3H, Ar-H), 7.15–7.16 (m, 2H, Ar-H), 7.02 (s, 1H), 5.20 (s, 1H), 4.10 (s, 3H, $-OCH_3$), 3.08 (s, 3H, $-OCH_3$); UV–vis (CH_3OH) λ_{max}: 363.00 nm, 232.00 nm; IR (KBr) ν 2924, 1621, 1463, 1287, 1071, 750 cm^{-1}; MS (*m/z*, %): 353 (M^+, 100), 338 (21), 322 (54); Found: C, 81.32; H, 5.27; N, 4.02%. Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96%.

3.2.18. 2,3-Dimethoxy-11*H*-indeno[1,2-*b*]quinoline (6i). A yellow crystal, mp 102–103 °C; ^1H NMR ($CDCl_3$) δ 8.13 (d, *J*=8.0 Hz, 1H), 7.98 (s, 1H), 7.73 (d, *J*=4.0 Hz, 1H), 7.70 (s, 1H), 7.64 (t, *J*=12 Hz, 1H), 7.43 (t, *J*=8.0 Hz, 1H), 6.99 (s, 1H), 4.03 (s, 3H, $-OCH_3$), 3.92 (s, 3H, $-OCH_3$), 3.79 (s, 2H, $-CH_2-$); UV–vis (CH_3OH) λ_{max}: 347.00 nm, 261.50 nm; IR (KBr) ν 2833, 1626, 1607, 1506, 1459, 1295, 1219 cm^{-1}; MS (*m/z*, %): 277 (M^+, 100), 262 (26), 336 (26); Found: C, 78.25; H, 5.67; N, 5.13%. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05%.

Acknowledgements

We would like to thank the Natural Science Foundation of Guangdong Province for the financial support (No. 04010404).

References and notes

1. (a) Maguire, M. P.; Sheets, K. R.; Vety, K. M.; Spada, A. P.; Zilberstein, A. *J. Med. Chem.* **1994**, *37*, 2129–2137; (b) Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, M. *Eur. J. Med. Chem.* **2000**, *35*, 1021–1035; (c) Chen, Y.-L.; Fang, K.-C.; Sheu, J.-Y.; Hsu, S.-L.; Tzeng, C.-C. *J. Med. Chem.* **2001**, *44*, 2374–2377.
2. Palimkar, S. S.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2003**, *68*, 9371–9378.
3. Zong, R.; Wang, D.; Hammitt, R.; Thummel, R. P. *J. Org. Chem.* **2006**, *71*, 167–175.
4. Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G.; Mcwilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, *68*, 467–477.
5. Horvath, I. T.; Rabai, J. *Science* **1994**, *266*, 72–75.
6. (a) Huma, H. Z. S.; Halder, R.; Kalra, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485–6488; (b) Yadav, J. S.; Rao, P. P.; Sreenu, D.; Rao, R. S.; Kumar, V. N.; Nagaiah, K.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 7249–7253; (c) Bose, D. S.; Kumar, R. K. *Tetrahedron Lett.* **2006**, *47*, 813–816; (d) Atechian, S.; Nock, N.; Norcross, R. D.; Ratni, H.; Thomas, A. W.; Verron, J.; Masciadri, R. *Tetrahedron* **2007**, *63*, 2811–2823.
7. (a) Wang, G.-W.; Jia, C.-S.; Dong, Y.-W. *Tetrahedron Lett.* **2006**, *47*, 1059–1063; (b) Narasimhulu, M.; Reddy, T. S.; Mahesh, K. C.; Prabhakar, P.; Rao, C. B.; Venkateswarlu, Y. *J. Mol. Catal. A: Chem.* **2006**, *266*, 114–147; (c) Muscia, G. C.; Bollini, M.; Carnevale, J. P.; Bruno, A. M.; Asís, S. E. *Tetrahedron Lett.* **2006**, *47*, 8811–8815.
8. Guo, W.; Jiang, Q.-J.; Lü, F.; Yang, D.-Q. *Chin. J. Syn. Chem.* **2004**, *12*, 12–14.
9. Thummel, R. P.; Chirayil, S.; Hery, C.; Lim, J. L.; Wang, T.-L. *J. Org. Chem.* **1993**, *58*, 1666–1671.