An Efficient Method for the Synthesis of Naphtho[2,3-*f*]pyrano[3,4-*c*] quinoline Derivatives Catalyzed by Iodine

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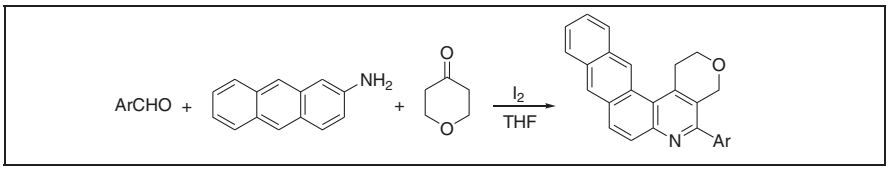

A mild and efficient method for the synthesis of naphtho[2,3-*f*]pyrano[3,4-*c*]quinoline derivatives via three-component reaction of aromatic aldehyde, anthracen-2-amine, and tetrahydropyran-4-one is described using iodine as catalyst. The features of this procedure are mild reaction conditions, good to high yields, and operational simplicity.

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INTRODUCTION

Quinoline derivatives are a very interesting class of heterocyclic system because the quinoline ring is an essential core moiety in a variety of natural and synthetic biologically active compounds [1]. In particular for polycyclic skeletons containing quinoline ring, for example, pyranoquinoline has been reported to possess antimicrobial [2], anticancer [3], selective human acetylcholinesterase inhibitory [4], antibacterial [5], and anti-inflammatory properties [6]. In addition, naphthoquinoline derivatives are also an important class of heterocycles with various bioactivities [7].

To the best of our knowledge, there are no literatures concerning about the synthesis of pentacyclic ring system of naphtho[2,3-*f*]pyrano[3,4-*c*]quinoline, which contains both naphthalene, pyran, and quinoline rings; this novel interesting skeleton may possess potential bioactive for screening. Thus, simple and efficient method to synthesize naphthopyranoquinoline would be attractive.

As a continuation of our research devoted to the development of new methods for the preparation of polycyclic heterocycles catalyzed by iodine [8], herein, we would like to synthesize 5-aryl-2,4-dihydro-1*H*-naphtho[2,3-*f*]pyrano [3,4-*c*]quinoline derivatives in THF catalyzed by iodine.

RESULTS AND DISCUSSION

Treatment of aromatic aldehyde **1** and anthracen-2-amine **2** with tetrahydropyran-4-one **3** in THF in the presence of 5 mol% iodine at reflux condition afford 5-aryl-2,4-dihydro-1*H*-naphtho[2,3-*f*]pyrano[3,4-*c*]quinoline derivatives in high yields (Scheme 1).

Using the conversion of 4-chlorobenzaldehyde **1a**, **2**, and **3** as a model, several parameters were explored as shown in Table 1. It was found that no reaction occurred at reflux condition in the absence of iodine (Table 1, entry 1), and the yield of **4a** was much greater in the presence of various quantities of the iodine, reaching a maximum of 89% yield with 5 mol% iodine (Table 1, entries 4–6). The yield of **4a** was also dependent on temperature (entries 2–4), proceeding smoothly at reflux in THF. Different solvents were also tested, and THF appeared to be the best medium for this transformation (entry 4 vs. 7–10).

This process could tolerate both electron-donating, such as alkyl and alkoxyl, and electron-withdrawing (halogen) substituents on the aromatic aldehydes (Table 2). In all cases, the reactions proceeded efficiently at reflux in THF to afford the corresponding naphtho[2,3-*f*]pyrano[3,4-*c*] quinolines in good to high yields. Alkylaldehydes, such as propyl aldehyde, *n*-butyl aldehyde, and *n*-heptaldehyde, were also selected as reactants to react with **2** and **3**. However, they all gave a mixture and were difficult to separate and purify. All the compounds were characterized by ^{1}H NMR, IR, and HRMS, and the analytical data are all in good agreement with the proposed structures.

According to the literatures [9], we think that iodine catalyzes the reaction as a mild Lewis acid. The mechanism was tentatively proposed as shown in Scheme 2. In the presence of iodine, tetrahydropyran-4-one is in equilibrium with its enol form [9b]. The Schiff base **I** may be formed by the reaction of aromatic aldehyde and anthracen-2-amine firstly. And then, imino-Diels-Alder reaction between the iodine-activated Schiff base **II** and enol takes place selectively to form the intermediate **III** for its stability. The dehydration of **III** results in dihydronaphtho[2,3-*f*]pyrano [3,4-*c*]quinoline **IV**, which is further oxidized by air to afford aromatized final products **4**.

Scheme 1. The synthetic route of the products **4**.

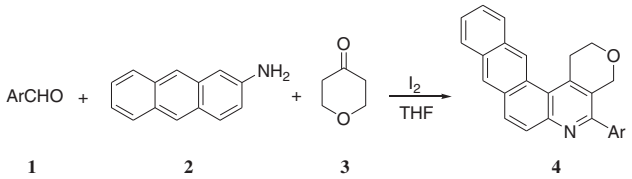


Table 1

Synthetic results of **4a** under different reaction conditions.[a]

Entry	Temp. (°C)	I_2 (mol%)	Solvent	Isolated yields (%)
1	Reflux	0	THF	0
2	RT	5	THF	trace
3	50	5	THF	72
4	Reflux	5	THF	89
5	Reflux	1	THF	78
6	Reflux	10	THF	88
7	Reflux	5	CH_3CN	82
8	Reflux	5	Benzene	83
9	80	5	DMF	76
10	Reflux	5	$CHCl_3$	82

[a]Reagents and conditions: 4-chlorobenzaldehyde **1a** (0.140 g, 1.0 mmol), **2** (0.193 g, 1.0 mmol), **3** (0.105 g, 1.05 mmol), solvent (10 mL).

Table 2

Synthetic results of **4** catalyzed by iodine in THF.[a]

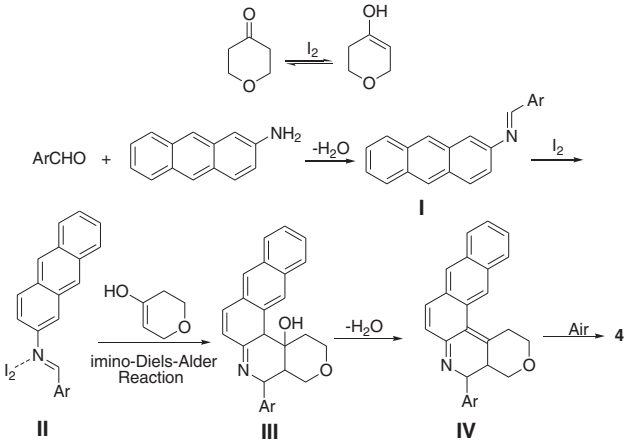
Entry	Ar	Products	Time (h)	Isolated yields (%)
1	4-ClC_6H_4	**4a**	8	89
2	4-$CH_3OC_6H_4$	**4b**	13	92
3	3,4-$(CH_3)_2C_6H_3$	**4c**	12	83
4	3-ClC_6H_4	**4d**	8	87
5	3,4-$Cl_2C_6H_3$	**4e**	6	90
6	3,4-$(CH_3O)_2C_6H_3$	**4f**	12	85
7	3-$CH_3OC_6H_4$	**4g**	10	93
8	2-ClC_6H_4	**4h**	10	90
9	4-FC_6H_4	**4i**	8	82
10	2-BrC_6H_4	**4j**	12	87
11	3-BrC_6H_4	**4k**	12	88
12	Piperonyl	**4l**	10	90

[a]Reagents and conditions: **1** (1.0 mmol), **2** (0.193 g, 1.0 mmol), **3** (0.105 g, 1.05 mmol), I_2 (0.05 mmol, 0.013 g), THF (10 mL), reflux.

CONCLUSION

In conclusion, we found a mild and efficient method for the synthesis of 5-aryl-2,4-dihydro-1*H*-naphtho[2,3-*f*]pyrano[3,4-*c*]quinoline derivatives via three-component reaction of aromatic aldehyde, anthracen-2-amine, and tetrahydropyran-4-one using iodine as catalyst. The features of this procedure are mild reaction conditions, good to high yields, and operational simplicity.

Scheme 2. The possible mechanism for the formation of products **4**.



EXPERIMENTAL

Melting points were determined in open capillaries and were uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr pellet. ^{1}H NMR spectra was obtained from a solution in DMSO-d_6 or $CDCl_3$ with Me_4Si as internal standard using a Bruker-400 spectrometer. HRMS analyses were carried out using a Bruker-micro-TOF-Q-MS analyzer (Bruker Corporation, Karlsruhe, Germany). All of the reagents were purchased from China National Pharmaceutical Group Corporation (Shanghai, China); the solvent of THF was dried by Na and redistilled before use.

General procedure for the synthesis of 5-aryl-2,4-dihydro-1*H*-naphtho[2,3-f]pyrano[3,4-c]quinolines 4. A dry 50 mL flask was charged with aromatic aldehyde (1.0 mmol), anthracen-2-amine (0.193 g, 1.0 mmol), tetrahydropyran-4-one (0.105 g, 1.05 mmol), I_2 (0.05 mmol, 0.013 g), and THF (10 mL). The reaction mixture was stirred at reflux for 6–13 h, and then, a small amount of DMF was added to the mixture, until all the precipitate was dissolved. The products **4** were obtained by filtration, when the mixture was allowed to cool down to room temperature.

5-(4-Chlorophenyl)-2,4-dihydro-1H-naphtho[2,3-f]pyrano[3,4-c]quinoline 4a. m.p. 259–261°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.85 (s, 2H, CH_2), 4.07 (d, J = 5.2 Hz, 2H, CH_2), 4.94 (s, 2H, CH_2), 7.52 (s, 4H, ArH), 7.63–7.65 (m, 2H, ArH), 7.86 (d, J = 9.2 Hz, 1H, ArH), 8.03 (d, J = 9.2 Hz, 1H, ArH), 8.09–8.17 (m, 2H, ArH), 8.46 (s, 1H, ArH), 9.22 (s, 1H, ArH). IR (KBr, cm^{-1}): ν 3050, 2966, 2944, 2850, 1552, 1534, 1492, 1476, 1433, 1422, 1365, 1312, 1249, 1223, 1160, 1136, 1107, 1090, 1034, 1015, 979, 955, 890, 878, 829, 739. HRMS (ESI, *m/z*): Calcd for $C_{26}H_{19}ClNO$ $[M+H]^+$ 396.1155, found 396.1152.

5-(4-Methoxyphenyl)-2,4-dihydro-1H-naphtho[2,3-f]pyrano[3,4-c]quinoline 4b. m.p. 234–235°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.83 (t, J = 5.2 Hz, 2H, CH_2), 3.89 (s, 3H, CH_3O), 4.06 (t, J = 5.2 Hz, 2H, CH_2), 4.96 (s, 2H, CH_2), 7.04 (d, J = 8.8 Hz, 2H, ArH), 7.51 (d, J = 8.4 Hz, 2H, ArH), 7.59–7.63 (m, 2H, ArH), 7.88 (d, J = 9.2 Hz, 1H, ArH), 8.00 (d, J = 9.2 Hz, 1H, ArH), 8.07–8.09 (m, 1H, ArH), 8.12–8.15 (m, 1H, ArH), 8.44 (s, 1H, ArH), 9.20 (s, 1H, ArH). IR (KBr, cm^{-1}): ν 2970, 2934, 2840, 1606, 1560, 1531, 1513, 1474, 1424, 1366, 1289, 1242, 1178, 1147, 1108, 1030, 981, 898, 876, 833, 747. HRMS (ESI, *m/z*): Calcd for $C_{27}H_{21}NO_2Na$ $[M+Na]^+$ 414.1470, found 414.1484.

5-(p-Tolyl)-2,4-dihydro-1H-naphtho[2,3-f]pyrano[3,4-c] quinoline 4c. m.p. 225–226°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 2.44 (s, 3H, CH_3), 3.83 (t, J = 5.2 Hz, 2H, CH_2), 4.06 (t, J = 5.2 Hz, 2H, CH_2), 4.95 (s, 2H, CH_2), 7.32 (d, J = 8.0 Hz, 2H, ArH), 7.44 (d, J = 8.0 Hz, 2H, ArH), 7.59–7.63 (m, 2H, ArH), 7.87 (d, J = 9.2 Hz, 1H, ArH), 7.99 (d, J = 8.8 Hz, 1H, ArH), 8.07–8.09 (m, 1H, ArH), 8.12–8.15 (m, 1H, ArH), 8.43 (s, 1H, ArH), 9.21 (s, 1H, ArH). IR (KBr, cm^{-1}): *v* 3046, 2937, 2851, 1548, 1531, 1472, 1421, 1364, 1325, 1304, 1247, 1185, 1147, 1108, 1033, 1019, 980, 892, 828, 747. HRMS (ESI, *m/z*): Calcd for $C_{27}H_{21}NONa$ $[M + Na]^+$ 398.1521, found 398.1531.

5-(3-Chlorophenyl)-2,4-dihydro-1H-naphtho[2,3-f]pyrano [3,4-c]quinoline 4d. m.p. 213–214°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.83 (t, J = 5.2 Hz, 2H, CH_2), 4.06 (t, J = 5.2 Hz, 2H, CH_2), 4.92 (s, 2H, CH_2), 7.42–7.46 (m, 3H, ArH), 7.56 (s, 1H, ArH), 7.60–7.65 (m, 2H, ArH), 7.85 (d, J = 8.8 Hz, 1H, ArH), 8.01 (d, J = 9.2 Hz, 1H, ArH), 8.07–8.10 (m, 1H, ArH), 8.13–8.15 (m, 1H, ArH), 8.44 (s, 1H, ArH), 9.21 (s, 1H, ArH). IR (KBr, cm^{-1}): *v* 3044, 2967, 2945, 2882, 2831, 1596, 1570, 1548, 1533, 1475, 1435, 1419, 1383, 1353, 1325, 1306, 1248, 1163, 1139, 1111, 1083, 1058, 1036, 981, 950, 901, 884, 873, 837, 819, 788, 739, 722, 703. HRMS (ESI, *m/z*): Calcd for $C_{26}H_{19}ClNO$ $[M + H]^+$ 396.1155, found 396.1200.

5-(3,4-Dichlorophenyl)-2,4-dihydro-1H-naphtho[2,3-f] pyrano[3,4-c]quinoline 4e. m.p. 242–243°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.83 (t, J = 5.2 Hz, 2H, CH_2), 4.06 (t, J = 5.2 Hz, 2H, CH_2), 4.92 (s, 2H, CH_2), 7.39–7.41 (m, 1H, ArH), 7.58–7.65 (m, 3H, ArH), 7.69 (d, J = 2.0 Hz, 1H, ArH), 7.82 (d, J = 9.2 Hz, 1H, ArH), 8.02 (d, J = 9.2 Hz, 1H, ArH), 8.08–8.15 (m, 2H, ArH), 8.45 (s, 1H, ArH), 9.20 (s, 1H, ArH). IR (KBr, cm^{-1}): *v* 3048, 2947, 2880, 2848, 1556, 1533, 1472, 1433, 1378, 1353, 1307, 1248, 1140, 1110, 1028, 982, 949, 905, 882, 873, 829, 808, 791, 734, 710. HRMS (ESI, *m/z*): Calcd for $C_{26}H_{18}Cl_2NO$ $[M + H]^+$ 430.0765, found 430.0793.

5-(3,4-Dimethoxyphenyl)-2,4-dihydro-1H-naphtho[2,3-f] pyrano[3,4-c]quinoline 4f. m.p. 233–235°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.86 (t, J = 5.2 Hz, 2H, CH_2), 3.95 (s, 3H, CH_3O), 3.96 (s, 3H, CH_3O), 4.07 (m, J = 5.2 Hz, 2H, CH_2), 4.98 (s, 2H, CH_2), 7.00 (d, J = 8.8 Hz, 1H, ArH), 7.10 (d, J = 6.8 Hz, 2H, ArH), 7.60–7.63 (m, 2H, ArH), 7.88 (d, J = 9.2 Hz, 1H, ArH), 8.00 (d, J = 9.2 Hz, 1H, ArH), 8.07–8.15 (m, 2H, ArH), 8.44 (s, 1H, ArH), 9.21 (s, 1H, ArH). IR (KBr, cm^{-1}): *v* 3057, 2997, 2946, 2877, 2817, 1586, 1515, 1476, 1462, 1473, 1362, 1313, 1252, 1229, 1181, 1142, 1102, 1029, 970, 895, 881, 811, 750, 700. HRMS (ESI, *m/z*): Calcd for $C_{28}H_{23}NO_3Na$ $[M + Na]^+$ 444.1576, found 444.1588.

5-(3-Methoxyphenyl)-2,4-dihydro-1H-naphtho[2,3-f] pyrano[3,4-c]quinoline 4g. m.p. 214–215°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.84 (t, J = 5.2 Hz,2H, CH_2), 3.88 (s, 3H, CH_3O), 4.06 (t, J = 5.2 Hz, 2H, CH_2), 4.94 (s, 2H, CH_2), 7.00–7.03 (m, 1H, ArH), 7.08–7.11 (m, 2H, ArH), 7.40–7.44 (m, 1H, ArH), 7.59–7.64 (m, 2H, ArH), 7.88 (d, J = 9.2 Hz, 1H, ArH), 8.00 (d, J = 9.2 Hz, 1H, ArH), 8.07–8.15 (m, 2H, ArH), 8.44 (s, 1H, ArH), 9.21 (s, 1H, ArH). IR (KBr, cm^{-1}): *v* 3048, 2969, 2934, 2870, 2838, 1589, 1536, 1477, 1464, 1426, 1363, 1318, 1269, 1242, 1184, 1160, 1105, 1080, 1033, 982, 969, 882, 826, 796, 739, 713. HRMS (ESI, *m/z*): Calcd for $C_{27}H_{21}NO_2Na$ $[M + Na]^+$ 414.1470, found 414.1509.

5-(2-Chlorophenyl)-2,4-dihydro-1H-naphtho[2,3-f]pyrano[3,4-c]quinoline 4h. m.p. 223–224°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.77–3.90 (m, 2H, CH_2), 3.99–4.13 (m, 2H, CH_2), 4.64–4.85 (m, 2H, CH_2), 7.39–7.44 (m, 3H, ArH), 7.52–7.54 (m, 1H, ArH), 7.60–7.65 (m, 2H, ArH), 7.87 (d, J = 9.2 Hz, 1H, ArH), 8.01 (d, J = 9.2 Hz, 1H, ArH), 8.07–8.16 (m, 2H, ArH), 8.45 (s, 1H, ArH), 9.22 (s, 1H, ArH). IR (KBr, cm^{-1}): *v* 3052, 2937, 2899, 2858, 1553, 1537, 1471, 1425, 1364, 1309, 1289, 1271, 1245, 1160, 1139, 1102, 1076, 1047, 1034, 970, 952, 894, 824, 763, 741, 709. HRMS (ESI, *m/z*): Calcd for $C_{26}H_{19}ClNO$ $[M + H]^+$ 396.1155, found 396.1289.

5-(4-Fluorophenyl)-2,4-dihydro-1H-naphtho[2,3-f]pyrano [3,4-c]quinoline 4. m.p. 271–274°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.83 (t, J = 5.2 Hz, 2H, CH_2), 4.06 (t, J = 5.2 Hz,2H, CH_2), 4.91 (s, 2H, CH_2), 7.19–7.23 (m, 2H, ArH), 7.52–7.63 (m, 4H, ArH), 7.85 (d, J = 9.2 Hz, 1H, ArH), 8.01 (d, J = 9.2 Hz, 1H, ArH), 8.07–8.15 (m, 2H, ArH), 8.44 (s, 1H, ArH), 9.20 (s, 1H, ArH). IR (KBr, cm^{-1}): *v* 3048, 2987, 2936, 2902, 2850, 1602, 1534, 1509, 1470, 1434, 1322, 1363, 1305, 1217, 1157, 1107, 1079, 1033, 1017, 978, 956, 898, 877, 833, 791, 739. HRMS (ESI, *m/z*): Calcd for $C_{26}H_{19}FNO$ $[M + H]^+$ 380.1451, found 380.1475.

5-(2-Bromophenyl)-2,4-dihydro-1H-naphtho[2,3-f]pyrano[3,4-c]quinoline 4j. m.p. 218–220°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.77–3.92 (m, 2H, CH_2), 3.98–4.04 (m, 1H, CH), 4.08–4.14 (m, 1H, CH), 4.62–4.83 (m, 2H, CH_2), 7.32–7.41 (m, 2H, ArH), 7.46–7.50 (m, 1H, ArH), 7.60–7.65 (m, 2H, ArH), 7.72 (d, J = 8.0 Hz, 1H, ArH), 7.87 (d, J = 9.2 Hz, 1H, ArH), 8.02 (d, J = 8.8 Hz, 1H, ArH), 8.08–8.16 (m, 2H, ArH), 8.45 (s, 1H, ArH), 9.23 (s, 1H, ArH). IR (KBr, cm^{-1}): *v* 3048, 2935, 2868, 2835, 1558, 1536, 1469, 1422, 1364, 1313, 1247, 1221, 1161, 1135, 1104, 1078, 1042, 1026, 977, 956, 883, 822, 762, 747, 730. HRMS (ESI, *m/z*): Calcd for $C_{26}H_{19}BrNO$ $[M + H]^+$ 440.0650, found 440.0654.

5-(3-Bromophenyl)-2,4-dihydro-1H-naphtho[2,3-f]pyrano[3,4-c]quinoline 4k. m.p. 225–226°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.84 (t, J = 5.2 Hz, 2H, CH_2), 4.06 (t, J = 5.2 Hz, 2H, CH_2), 4.92 (s, 2H, CH_2), 7.37–7.41 (m, 1H, ArH), 7.48 (d, J = 7.6 Hz, 1H, ArH), 7.60–7.65 (m, 3H, ArH), 7.72 (s, 1H, ArH), 7.85 (d, J = 9.2 Hz, 1H, ArH), 8.02 (d, J = 9.2 Hz, 1H, ArH), 8.08–8.15 (m, 2H, ArH), 8.45 (s, 1H, ArH), 9.21 (s, 1H, ArH). IR (KBr, cm^{-1}): *v* 3050, 2962, 2843, 1591, 1553, 1531, 1472, 1432, 1407, 1358, 1312, 1291, 1250, 1161, 1136, 1110, 1069, 1037, 997, 982, 955, 898, 875, 809, 792, 742, 704. HRMS (ESI, *m/z*): Calcd for $C_{26}H_{19}BrNO$ $[M + H]^+$ 440.0650, found 440.0693.

5-Piperonyl-2,4-dihydro-1H-naphtho[2,3-f]pyrano[3,4-c] quinoline 4l. m.p. 235–238°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.8 (s, 2H, CH_2), 4.06 (s, 2H, CH_2), 4.96 (s, 2H, CH_2), 6.04 (s, 2H, CH_2), 6.94 (d, J = 8.0 Hz, 1H, ArH), 7.01–7.05 (m, 2H, ArH), 7.61 (d, J = 5.2 Hz, 2H, ArH), 7.85 (d, J = 9.2 Hz, 1H, ArH), 7.99 (d, J = 9.2 Hz, 1H, ArH), 8.08 (d, J = 5.2 Hz, 1H, ArH), 8.13 (d, J = 5.2 Hz, 1H, ArH), 8.43 (s, 1H, ArH), 9.20 (s, 1H, ArH). IR (KBr, cm^{-1}): *v* 3052, 2956, 2931, 2878, 1551, 1536, 1499, 1476, 1433, 1357, 1305, 1233, 1179, 1164, 1141, 1116, 1082, 1042, 978, 941, 896, 872, 861, 801, 733. HRMS (ESI, *m/z*): Calcd for $C_{27}H_{20}NO_3$ $[M + H]^+$ 406.1443, found 406.1427.

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