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Iodine-catalyzed synthesis of 5-arylanthra[2,1-*c*][2,7]naphthyridine derivatives via three-component reaction

Abstract: A series of ethyl 5-aryl-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate derivatives was prepared by a three-component reaction of aromatic aldehyde, anthracen-2-amine and ethyl 4-oxopiperidine-1-carboxylate using iodine as catalyst. This iodine-catalyzed procedure has the advantages of mild reaction conditions, good yields, operational simplicity and metal-free catalyst.

Keywords: anthracen-2-amine; iodine; naphthyridine; synthesis.

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Introduction

In recent years, multi-component reactions (MCRs) have become important tools in synthetic chemistry because they increase efficiency by combining several operational steps without isolation of intermediates or changing the reaction conditions (Tietze, 1996; Vijjay et al., 2003). MCRs have emerged as valuable tools for the preparation of structurally diverse chemical libraries of drug-candidate heterocyclic compounds (Liéby et al., 2005; Wang et al., 2006, 2007; Srinivasu et al., 2010). Owing to their convergence and efficiency, MCRs have attracted considerable attention of the organic synthetic community (Dolle et al., 2008; Wang et al., 2008, 2010; Victorio et al., 2010).

Naphthyridines are an important class of heterocyclic compounds which have attracted attention, due to their significant AKT activity (Furuyama et al., 2009; Armstrong et al., 2010; Sanderson et al., 2010). Their derivatives have remarkable effects as pharmaceuticals, including antimicrobial (Ramesh et al., 2010), antitubercular (Dinakaran et al., 2009), antibacterial (Huang et al., 2010), anti-inflammatory (Roma et al., 2010) and antitumor activity (Lukka et al., 2010).

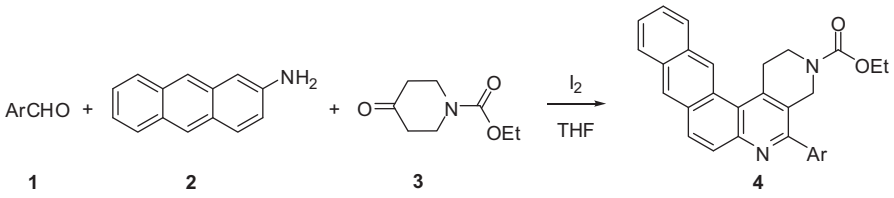
In view of the importance of naphthyridine derivatives and as a continuation of our research on the development of new methods for the preparation of heterocycles via MCRs catalyzed by iodine (Wang et al., 2009, 2012), herein we describe the synthesis of ethyl 5-aryl-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate derivatives by a reaction of aromatic aldehyde, anthracen-2-amine and ethyl 4-oxopiperidine-1-carboxylate in THF catalyzed by iodine.

Results and discussion

Treatment of aromatic aldehyde (**1**), anthracen-2-amine (**2**) and ethyl 4-oxopiperidine-1-carboxylate (**3**) in THF in the presence of 5 mol% iodine under reflux condition afforded the corresponding ethyl 5-aryl-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylates (**4**) in good to high yields (Scheme 1).

Using the conversion of 4-chlorobenzaldehyde (**1a**), anthracen-2-amine (**2**) and ethyl 4-oxopiperidine-1-carboxylate (**3**) as a model reaction, several parameters were explored initially. The reaction did not take place at reflux in the absence of iodine. Similar reactions were attempted in the presence of 1, 5 and 10 mol% of I_2. The results in Table 1 show that 5 mol% I_2 at reflux in THF is sufficient to initiate the reaction. Higher loading of the catalyst had no significant influence on the reaction yield. The yield of **4a** was also dependent on temperature, proceeding smoothly at reflux. Different solvents were also tested, and THF appeared to be the best medium for this transformation.

This process can tolerate both electron-donating (alkyl and alkoxy-) and electron-withdrawing (halogen) substituents on the aromatic aldehydes. In all cases, the



4a: Ar = 4-ClC_6H_4; **4b**: Ar = 4-MeC_6H_4; **4c**: Ar = 3-ClC_6H_4; **4d**: Ar = 3,4-$Cl_2C_6H_3$;
4e: Ar = 3,4-$(MeO)_2C_6H_3$; **4f**: Ar = 4-FC_6H_4; **4g**: Ar = 3-BrC_6H_4; **4h**: Ar = 4-$MeOC_6H_4$;
4i: Ar = Piperonyl; **4j**: Ar = 2,4-$Cl_2C_6H_3$; **4k**: Ar = 3,5-$(MeO)_2C_6H_3$; **4l**: Ar = 2-FC_6H_4

Scheme 1 The reaction for the synthesis of product **4**.

reactions proceeded efficiently at reflux to afford the corresponding anthra[2,1-*c*][2,7]naphthyridines in high yields. Products **4a–l** were characterized by IR, ^{1}H NMR and HRMS.

According to the literature (Wang et al., 2008; Bakavoli et al., 2010), iodine may catalyze the reaction as a mild Lewis acid. The proposed mechanism is shown in Scheme 2. In the presence of iodine, ethyl 4-oxopiperidine-1-carboxylate (**3**) is in equilibrium with the enol form **I**. The Schiff base may be formed by the reaction of aromatic aldehyde and anthracen-2-amine. Then imino-Diels-Alder reaction between the iodine-activated Schiff base **II** and enol form **I** takes place selectively to form the intermediate product **III**. Dehydration of **III** followed by air oxidation of the resultant dihydropyridine **IV** affords the observed aromatic product **4**.

Conclusions

A mild and efficient method for the synthesis of anthra-[2,1-*c*][2,7]naphthyridine derivatives via three-component reaction of aromatic aldehyde, anthracen-2-amine and ethyl 4-oxopiperidine-1-carboxylate using iodine as catalyst is described. The features of this procedure are mild reaction conditions, good yields, operational simplicity and metal-free catalyst.

Entry	T/°C	Solvent	I_2/mol%	Isolated yield/%
1	Reflux	THF	0	0
2	Room temperature	THF	5	Trace
3	50	THF	5	68
4	Reflux	THF	5	85
5	Reflux	THF	1	78
6	Reflux	THF	10	85
7	Reflux	$CHCl_3$	5	82
8	Reflux	Benzene	5	80
9	Reflux	CH_3CN	5	83
10	80	DMF	5	78

Table 1 Synthesis of **4a** under different reaction conditions[a].
[a]Reaction conditions: solvent (10 mL), 4-chlorobenzaldehyde (0.141 g, 1.0 mmol), anthracen-2-amine (0.193 g, 1.0 mmol), ethyl 4-oxopiperidine-1-carboxylate (0.171 g, 1.0 mmol).

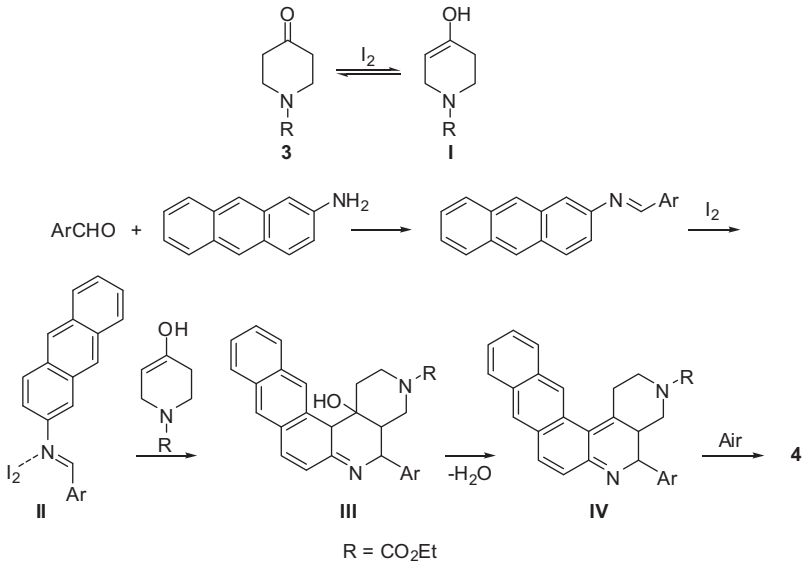
Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr pellets. ^{1}H NMR spectra were taken in $CDCl_3$ or DMSO-d_6 with Me_4Si as internal standard on a Bruker-400 (400 MHz) spectrometer. HRMS analyses were carried out on a Bruker-micro-TOF-Q-MS analyzer. Anthracen-2-amine was purchased from Sigma-Aldrich Corporation.

Procedure for the synthesis of anthra[2,1-*c*][2,7]naphthyridines (4) A dry 50 mL flask was charged with aromatic aldehyde (**1**) (1.0 mmol), anthracen-2-amine (**2**) (0.193 g, 1.0 mmol), ethyl 4-oxopiperidine-1-carboxylate (**3**) (0.171 g, 1.0 mmol), THF (10 mL) and I_2 (0.013 g, 0.05 mmol). The mixture was stirred under reflux for 10–18 h, and then treated hot with a small amount of DMF to dissolve the precipitate. The product **4** crystallized from a filtered solution after cooling to room temperature.

Ethyl 5-(4-chlorophenyl)-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate (4a) This compound was obtained in 85% yield as a pale yellow powder; mp 196–198°C; ^{1}H NMR ($CDCl_3$): δ 1.32 (t, *J* = 7 Hz, 3H), 3.69 (s, 2H), 3.86 (t, *J* = 5 Hz, 2H), 4.23 (q, *J* = 7 Hz, 2H), 4.75 (s, 2H), 7.51–7.58 (m, 4H), 7.61–7.64 (m, 2H), 7.82 (d, *J* = 8 Hz, 1H), 8.02 (s, 1H), 8.08–8.13 (m, 2H), 8.44 (s, 1H), 9.05 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 155.6, 147.6, 147.3, 135.7, 134.8, 132.6, 131.6, 131.5, 131.4, 131.3, 130.2, 129.0, 128.67, 128.65, 128.01, 127.97, 127.94, 127.61, 127.59, 127.2, 126.7, 126.3, 61.8, 44.5, 40.8, 31.4, 14.8; IR: ν 2985, 2866, 1709, 1672, 1594, 1553, 1477, 1413, 1378, 1334, 1277, 1265, 1247, 1229, 1201, 1131, 1106, 1040, 1015, 894, 841, 768, 748 cm^{-1}. HRMS (ESI, m/z): Calcd for $C_{29}H_{23}ClN_2O_2Na$ $[M+Na]^+$ 489.1346, found 489.1357.

Ethyl 5-(*p*-tolyl)-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate (4b) This compound was obtained in 82% yield as a pale yellow powder; mp 194–195°C; ^{1}H NMR ($CDCl_3$): δ 1.31 (t, *J* = 7 Hz, 3H), 2.45 (s, 3H), 3.69 (m, 2H), 3.86 (m, 2H), 4.22 (q, *J* = 7 Hz, 2H), 4.78 (s, 2H), 7.34 (d, *J* = 7 Hz, 2H), 7.50 (d, *J* = 7 Hz, 2H), 7.60–7.63 (m, 2H), 7.85 (d, *J* = 9 Hz, 1H), 8.01 (d, *J* = 8 Hz, 1H), 8.07–8.13 (m, 2H), 8.43 (s, 1H), 9.05 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 155.8, 154.6, 146.7, 143.2, 137.9,



Scheme 2 Possible mechanism for the formation of product **4**.

136.5, 131.2, 131.03, 131.0, 130.8, 128.91, 128.87, 128.7, 128.3, 127.9, 127.3, 127.0, 126.8, 126.7, 126.2, 125.5, 125.4, 60.9, 43.9, 40.3, 31.3, 20.9, 14.6; IR: ν 3055, 2987, 2915, 2861, 1699, 1672, 1613, 1556, 1513, 1477, 1413, 1378, 1331, 1273, 1229, 1201, 1131, 1107, 1072, 1040, 1019, 988, 954, 942, 893, 848, 832, 804, 768, 743 cm^{-1}. HRMS (ESI, m/z): Calcd for $C_{30}H_{27}N_2O_2$ $[M+H]^+$ 447.2073, found 447.2071.

Ethyl 5-(3-chlorophenyl)-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate (4c) This compound was obtained in 89% yield as a pale yellow powder; mp 203–204°C; ^{1}H NMR (DMSO-d_6): δ 1.23 (m, 3H), 3.62 (m, 2H), 3.87 (m, 2H), 4.11 (d, *J* = 6 Hz, 2H), 4.69 (m, 2H), 7.61–7.75 (m, 7H), 8.12–8.18 (m, 2H), 8.34 (s, 1H), 8.63 (s, 1H), 9.26 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 154.6, 154.2, 146.8, 141.4, 133.3, 133.1, 131.5, 131.1, 131.0, 130.8, 130.1, 130.3, 129.0, 128.6, 128.5, 128.11, 128.08, 127.5, 127.3, 126.9, 126.8, 126.3, 125.6, 124.8, 61.0, 43.8, 40.3, 31.4, 14.6; IR: ν 3050, 2984, 2937, 1696, 1598, 1562, 1537, 1473, 1426, 1381, 1368, 1348, 1315, 1248, 1205, 1142, 1112, 1080, 1015, 962, 888, 781, 747, 726, 708 cm^{-1}. HRMS (ESI, m/z): Calcd for $C_{29}H_{24}ClN_2O_2$ $[M+H]^+$ 467.1526, found 467.1514.

Ethyl 5-(3,4-dichlorophenyl)-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate (4d) This compound was obtained in 89% yield as a white powder; mp 215–216°C; ^{1}H NMR (DMSO-d_6): δ 1.23 (m, 3H), 3.62 (m, 2H), 3.88 (m, 2H), 4.12 (d, *J* = 6 Hz, 2H), 4.70 (m, 2H), 7.65–7.69 (m, 3H), 7.74 (d, *J* = 8 Hz, 1H), 7.84 (d, *J* = 8 Hz, 1H), 7.95 (s, 1H), 8.14–8.18 (m, 2H), 8.35 (d, *J* = 6 Hz, 1H), 8.64 (s, 1H), 9.27 (s, 1H); IR: ν 3053, 2977, 2906, 2868, 1711, 1557, 1536, 1471, 1413, 1382, 1361, 1330, 1286, 1248, 1201, 1138, 1107, 1072, 1057, 1031, 964, 894, 840, 828, 810, 752 cm^{-1}. HRMS (ESI, m/z): Calcd for $C_{29}H_{23}Cl_2N_2O_2$ $[M+H]^+$ 501.1137, found 501.1158.

Ethyl 5-(3,4-dimethoxyphenyl)-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate (4e) This compound was obtained in 79% yield as a yellow powder; mp 160–162°C; ^{1}H NMR (DMSO-d_6): δ 1.22 (m, 3H), 3.60 (t, *J* = 5 Hz, 2H), 3.83 (s, 3H), 3.86 (s, 5H), 4.10 (q, *J* = 7 Hz, 2H), 4.73–4.77 (m, 2H), 7.12–7.18 (m, 2H), 7.25 (s, 1H), 7.66–7.68 (m, 2H), 7.74 (d, *J* = 9 Hz, 1H), 8.12 (d, *J* = 9 Hz, 1H), 8.16–8.18 (m, 1H), 8.34 (d, *J* = 5 Hz, 1H), 8.63 (s, 1H), 9.24 (s, 1H); IR: ν 3203, 3142, 3051, 2885, 1664, 1606, 1563, 1520, 1476, 1428, 1366, 1326, 1294, 1269, 1196, 1158, 1133, 1108, 1093, 1051, 1031, 966, 937, 844, 828, 806, 788, 755, 735, 705 cm^{-1}. HRMS (ESI, m/z): Calcd for $C_{31}H_{29}N_2O_4$ $[M+H]^+$ 493.2127, found 493.2094.

Ethyl 5-(4-fluorophenyl)-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate (4f) This compound was obtained in 84% yield as a yellow powder; mp 218–219°C; ^{1}H NMR (DMSO-d_6): δ 1.22 (s, 3H), 3.61 (s, 2H), 3.87 (s, 2H), 4.11 (d, *J* = 6 Hz, 2H), 4.68 (s, 2H), 7.41 (t, *J* = 8 Hz, 2H), 7.68–7.74 (m, 5H), 8.12–8.17 (m, 2H), 8.34 (d, *J* = 5 Hz, 1H), 8.63 (s, 1H), 9.25 (s, 1H); IR: ν 3056, 2972, 2931, 2873, 1700, 1604, 1556, 1537, 1511, 1477, 1425, 1378, 1335, 1287, 1227, 1204, 1165, 1132, 1110, 1072, 1040, 1013, 953, 892, 855, 828, 816, 768, 750 cm^{-1}. HRMS (ESI, m/z): Calcd for $C_{29}H_{24}FN_2O_2$ $[M+H]^+$ 451.1822, found 451.1823.

Ethyl 5-(3-bromophenyl)-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate (4g) This compound was obtained in 80% yield as a yellow powder; mp 188–189°C; ^{1}H NMR (DMSO-d_6): δ 1.23 (m, 3H), 3.62 (s, 2H), 3.87 (s, 2H), 4.11 (d, *J* = 5 Hz, 2H), 4.69 (s, 2H), 7.52–7.56 (m, 1H), 7.64–7.75 (m, 5H), 7.85 (s, 1H), 8.13–8.16 (m, 2H), 8.34 (s, 1H), 8.63 (s, 1H), 9.26 (s, 1H); IR: ν 3049, 2981, 2935, 1696, 1596, 1560, 1535, 1472, 1423, 1380, 1367, 1247, 1247, 1204, 1140, 1110, 1072, 1036, 1015, 957, 886, 849, 809, 780, 746, 715, 705 cm^{-1}. HRMS (ESI, m/z): Calcd for $C_{29}H_{24}BrN_2O_2$ $[M+H]^+$ 511.1021, found 511.1036.

Ethyl 5-(3-methoxyphenyl)-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate (4h) This compound was obtained in 90% yield as a pale yellow powder; mp 188–190°C; ^{1}H NMR (DMSO-d_6): δ 1.22 (m, 3H), 3.62 (s, 2H), 3.85 (s, 5H), 4.11 (d, *J* = 5 Hz, 2H), 4.70 (s, 2H), 7.11 (d, *J* = 8 Hz, 1H), 7.18 (s, 2H), 7.47–7.51 (m, 1H), 7.68 (d, *J* = 5 Hz, 2H), 7.74 (d, *J* = 9 Hz, 1H), 8.12–8.18 (m, 2H), 8.34 (s, 1H), 8.64 (s, 1H), 9.27 (s, 1H); IR: ν 3053, 2977, 2935, 1695, 1588, 1551, 1466, 1434, 1387, 1361, 1328, 1317, 1269, 1243, 1135, 1108, 1035, 976, 884, 825, 793, 747, 714 cm^{-1}. HRMS (ESI, m/z): Calcd for $C_{30}H_{27}N_2O_2$ $[M+H]^+$ 463.2022, found 463.2020.

Ethyl 5-(piperonyl)-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate (4i) This compound was obtained in 83% yield as a pale yellow powder; mp 225–226°C; ^{1}H NMR (DMSO-d_6): δ 1.22 (m, 3H), 3.60 (s, 2H), 3.86 (s, 2H), 4.12 (s, 2H), 4.72 (s, 2H), 6.15 (s, 2H), 7.10 (s, 2H), 7.22 (s, 1H), 7.68 (s, 2H), 7.72 (d, J = 8 Hz, 1H), 8.11–8.17 (m, 2H), 8.34 (s, 1H), 8.62 (s, 1H), 9.24 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 152.1, 148.03, 147.96, 147.5, 131.6, 131.41, 131.37, 131.35, 131.33, 131.26, 131.2, 128.8, 128.6, 127.9, 127.8, 127.7, 127.6, 127.1, 126.6, 126.3, 122.7, 113.2, 109.5, 108.6, 101.3. 61.7, 44.6, 40.9, 32.3, 14.8; IR: ν 3054, 2978, 2896, 2874, 1700, 1556, 1502, 1494, 1475, 1445, 1418, 1377, 1361, 1283, 1254, 1235, 1203, 1130, 1109, 1038, 929, 892, 828, 769, 746 cm^{-1}. HRMS (ESI, m/z): Calcd for $C_{30}H_{25}N_2O_4$ $[M+H]^+$ 477.1814, found 477.1817.

Ethyl 5-(2,4-dichlorophenyl)-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate (4j) This compound was obtained in 89% yield as a yellow powder; mp 197–199°C; ^{1}H NMR (DMSO-d_6): δ 1.23 (m, 3H), 3.47–3.52 (m, 1H), 3.83 (s, 2H), 3.94–3.98 (m, 1H), 4.12 (d, J = 6 Hz, 2H), 4.37–4.48 (m, 2H), 7.60 (d, J = 8 Hz, 1H), 7.66–7.75 (m, 4H), 7.88 (s, 1H), 8.14–8.18 (m, 2H), 8.36 (d, J = 6.0 Hz, 1H), 8.65 (s, 1H), 9.32 (s, 1H). IR: ν 3055, 2976, 2933, 2872, 1710, 1587, 1552, 1472, 1425, 1379, 1339, 1280, 1246, 1205, 1169, 1144, 1135, 1112, 1077, 1050, 1011, 950, 890, 860, 828, 809, 767, 741 cm^{-1}. HRMS (ESI, m/z): Calcd for $C_{29}H_{23}Cl_2N_2O_2$ $[M+H]^+$ 501.1137, found 501.1117.

Ethyl 5-(3,5-dimethoxyphenyl)-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate (4k) This was obtained in 81% yield as a pale yellow powder; mp 220–221°C; ^{1}H NMR (DMSO-d_6): δ 1.23 (m, 3H), 3.63 (s, 2H), 3.83 (s, 6H), 3.86 (s, 2H), 4.11 (d, J = 5 Hz, 2H), 4.71 (s, 2H), 6.66 (s, 1H), 6.75 (s, 2H), 7.68 (d, J = 5 Hz, 2H), 7.74 (d, J = 9 Hz, 1H), 8.12–8.18 (m, 2H), 8.34 (s, 1H), 8.64 (s, 1H), 9.26 (s, 1H). IR: ν 3059, 2997, 2936, 2868, 1699, 1590, 1558, 1448, 1418, 1372, 1335, 1279, 1248, 1201, 1154, 1131, 1108, 1062, 1011, 961, 924, 894, 862, 831, 755 cm^{-1}. HRMS (ESI, m/z): Calcd for $C_{31}H_{29}N_2O_4$ $[M+H]^+$ 493.2127, found 493.2132.

Ethyl 5-(2-fluorophenyl)-1,2-dihydroanthra[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate (4l) This compound was obtained in 88% yield as a brown powder; mp 169–171°C; ^{1}H NMR (DMSO-d_6): δ 1.24 (m, 3H), 3.65 (s, 2H), 3.88 (s, 2H), 4.12 (s, 2H), 4.55 (s, 2H), 7.42–7.46 (m, 2H), 7.60–7.69 (m, 4H), 7.74 (d, J = 9 Hz, 1H), 8.13–8.17 (m, 2H), 8.34 (s, 1H), 8.64 (s, 1H), 9.29 (s, 1H); IR: ν 3047, 2982, 2933, 2896, 1704, 1618, 1578, 1556, 1496, 1476, 1452, 1426, 1378, 1334, 1285, 1255, 1222, 1200, 1136, 1117, 1068, 1016, 953, 889, 820, 757, 744 cm^{-1}. HRMS (ESI, m/z): Calcd for $C_{29}H_{22}FN_2O_2$ $[M-H]^+$ 449.1665, found 449.1647.

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