A Novel and Efficient Method for the Synthesis of 5-Arylnaphtho[2,1-*c*][2,7]naphthyridine Derivatives Catalyzed by Iodine

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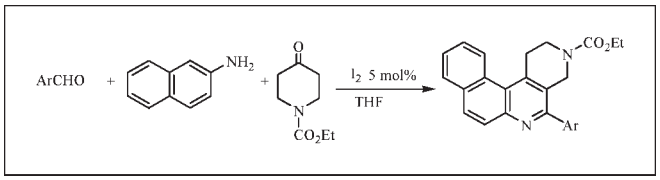

A novel method for the synthesis of 1,2-dihydro-5-arylnaphtho[2,1-*c*][2,7]naphthyridine derivatives via a three-component reaction of aromatic aldehyde, naphthalen-2-amine, and *N*-substituted piperidin-4-one derivatives is described using 5 mol % iodine as catalyst. The features of this new procedure are mild reaction condition, high yield, operational simplicity, and uses available reactants.

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INTRODUCTION

Multicomponent reactions (MCRs) can be distinguished from classical, sequential two-component chemistry synthesis processes in that they use three or more chemical starting materials as the input for product formation. Up to seven starting components have been used, and MCRs have often been shown to produce higher product yields than classical chemistry [1]. They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds, as well as small and drug-like heterocycles [2].

The naphtho[2,1-*c*][2,7]naphthyridine **1** ring system (Fig. 1) is a rare heterocycle compared with [1,8]naphthyridine **2** and [1,5]naphthyridine **3** substructures. Naphthyridines, which encompass two pyridine rings, are known to display a wide range of biological activities, including antibacterial activity [3], antimalarial activity [4], antimicrobial activity [5], anticancer activity [6], and antiinflammatory activity [7]. Moreover, it is envisioned that naphtho[2,1-*c*][2,7]naphthyridines **1**, which contained both naphthalene ring and naphthyridine moieties, may afford unique biological activities, such as Barta-Szalai et al. [8] revealed in 2003 that spiro[naphto[2,1-*c*][2,7]naphtiridine-5,4'-piperidine] derivatives were potent inhibitors of lipid peroxidation.

Previously, it has been demonstrated that naphthonaphthyridines can be obtained from 2-aminobenzo[*f*]-quinoline with glycerol in the presence of H_2SO_4 [9], or by the Skraup reaction of 3-aminobenzo[*h*]quinoline with ketone [10], or by any other methods [11]. However, despite their potential utility, many of these reported methods suffer from drawbacks such as harsh reaction conditions, unsatisfactory yields, prolonged reaction time, multistep reactions, and cumbersome product isolation procedure. This work is in connection with our previous research on the MCRs to the intriguing heterocycles [12] and successfully realized a three-component reaction of aromatic aldehyde, naphthalen-2-amine, and *N*-substituted piperidin-4-one catalyzed by iodine in THF without isolating and purifying the intermediates to afford naphtho[2,1-*c*][2,7]naphthyridine moiety.

RESULTS AND DISCUSSION

The treatment of aromatic aldehyde **4**, naphthalen-2-amine **5**, and ethyl 4-piperidinone-1-carboxylate **6** in THF in the presence of 5 mol % iodine at reflux afforded the corresponding ethyl 1,2-dihydro-5-arylnaphtho[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate derivatives **1** in high yields (Scheme 1).

In an initial endeavor, 3,4-dichlorobenzaldehyde **4a**, naphthalen-2-amine **5**, and ethyl 4-piperidinone-1-carboxylate **6** were stirred in THF in the absence of I_2. No reaction occurred at room temperature and reflux condition (Table 1, entries 1 and 2). Similar reactions were then attempted in the presence of 5, 10, and 20 mol % of I_2. The results from Table 1 (entries 5–7) showed

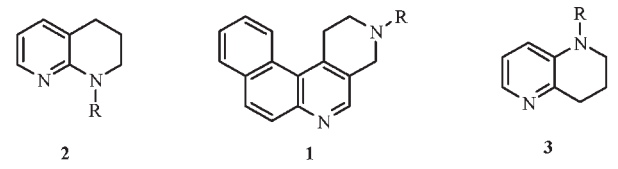


Figure 1.

that 5 mol % I_2 at reflux in THF was sufficient to push the reaction forward. Based on these observations, we have also conducted the reaction with 5 mol % of I_2 at room temperature, and 50 mol % at reflux temperature, resulting in the isolation of **1a** in trace amount, 62 and 91% yields (Table 1, entries 3–5), respectively. In addition, CH_3CN, benzene, DMF, and $CHCl_3$ (Table 1, entries 8–11) were also tested as the solvents. In these cases, product **1a** was formed in slightly lower yield (Table 1, entries 8–11).

To evaluate the efficiency of iodine as a catalyst, a range of benzaldehydes **4b–p** were subjected to react with **5** and **6** in the presence of 5 mol % I_2 to generate **1**, and the results are summarized in Table 2. It can be observed that the process tolerates both electron-donating and electron-withdrawing substituents in the benzaldehydes. In all cases, the reactions proceeded efficiently at reflux under mild conditions to afford the corresponding naphtho[2,1-*c*][2,7]naphthyridines in high yields (Table 2).

The structure of **1** was characterized by ^{1}H NMR, IR, and HRMS. The analyses were in agreement with their structures. For example, in the ^{1}H NMR of **1a**, the protons on the ethyl group appear at 1.31 (triplet, $J = 6.8$ Hz) and 4.22 ppm (quartet, $J = 6.8$ Hz), respectively. The adjacent methylene groups exhibit two triplets at 3.66 ($J = 5.6$ Hz) and 3.76 ($J = 5.6$ Hz), respectively. The singlet at 4.73 ppm is assigned as another methylene group in the pyridine moiety. Totally, nine corresponding protons detected make further confirmation of structure **1a**. The IR spectra for **1a** exhibit strong bands at 1715 cm^{-1} for the carboxyl group in the structure. The HRMS of **1a** is in good agreement with its structure (Calcd for $C_{25}H_{20}Cl_2N_2NaO_2$ ($M+Na^+$) 473.0800, found 473.0791) with a deviation of 1.9 ppm.

As expected, the substrate of ethyl 4-piperidinone-1-carboxylate could be extended to other 4-piperidinones.

Scheme 1

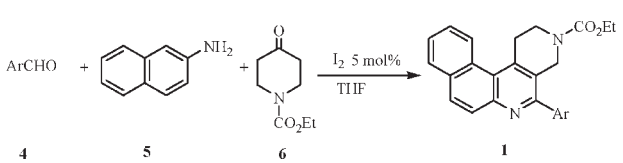


Table 1

Synthesis of **1a** in THF under different reaction conditions.[a]

Entry	Temperature (°C)	I_2 (mol %)	Solvent	Yields[b] (%)
1	RT	0	THF	0
2	Reflux	0	THF	0
3	RT	5	THF	Trace
4	50	5	THF	62
5	Reflux	5	THF	91
6	Reflux	10	THF	88
7	Reflux	20	THF	89
8	Reflux	5	CH_3CN	82
9	Reflux	5	Benzene	86
10	80	5	DMF	78
11	Reflux	5	$CHCl_3$	83

[a] Reagents and conditions: **4** (0.350 g, 2 mmol), **5** (0.286 g, 2 mmol), **6** (0.343 g, 2 mmol), solvent (10 mL).
[b] Isolated yields.

The 1-(3-chlorobenzoyl)-4-piperidinone was also chosen as reactant to react with benzaldehyde, naphthalen-2-amine (Scheme 2), and were found to generate the corresponding naphtho[2,1-*c*][2,7]naphthyridines (**8a-8d**, Table 3). However, to our surprise, we failed to get the expected products when 4-piperidinone, *N*-methyl-4-piperidinone, and *N*-benzyl-4-piperidinone were used as reactants. Perhaps the stabilities of these above-mentioned 4-piperidinones restrained their reactions.

It was interesting that the 1,4-di(1,2,3,4-tetrahydro-3-ethoxycarbonyl-naphtho[2,1-*c*][2,7]naphthyridine-5-yl) benzene **9** was obtained in 87% yield when

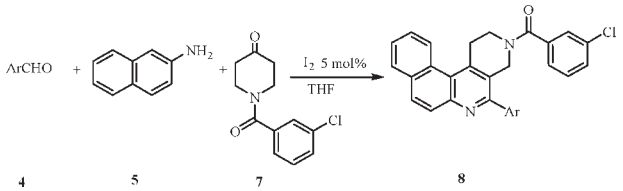
Table 2

I_2 catalyzed reaction of benzaldehydes, naphthalen-2-amine, and ethyl 4-piperidinone-1-carboxylate in THF.[a]

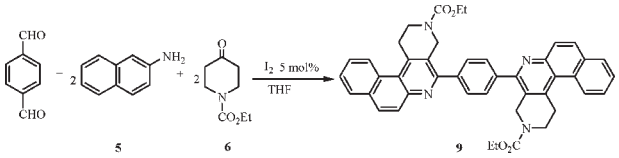
Entry	Ar	Products	Time (h)	Yields[b] (%)
1	3,4-$Cl_2C_6H_3$	**1a**	14	91
2	3-$NO_2C_6H_4$	**1b**	12	92
3	2-Thiophenyl	**1c**	16	81
4	2,4-$Cl_2C_6H_3$	**1d**	14	83
5	4-BrC_6H_4	**1e**	12	86
6	4-ClC_6H_4	**1f**	12	88
7	2,3-$Cl_2C_6H_3$	**1g**	10	90
8	4-$NO_2C_6H_4$	**1h**	10	87
9	4-FC_6H_4	**1i**	14	87
10	2-$NO_2C_6H_4$	**1j**	10	90
11	3-ClC_6H_4	**1k**	16	83
12	4-$CH_3OC_6H_4$	**1l**	18	82
13	4-Cl-2-$NO_2C_6H_3$	**1m**	10	84
14	C_6H_5	**1n**	16	83
15	2-FC_6H_4	**1o**	12	88
16	3,5-$(CH_3O)_2C_6H_3$	**1p**	16	86

[a] Reagents and conditions: **4** (2 mmol), **5** (2 mmol, 0.286 g), **6** (2 mmol, 0.342 g), I_2 (0.1 mmol, 0.026 g), THF (10 mL).
[b] Isolated yields.

Scheme 2



Scheme 3



terephthalaldehyde was chosen as aromatic aldehyde to react with two equivalent of naphthalen-2-amine and ethyl 4-piperidinone-1-carboxylate (Scheme 3).

According to the literatures [13], we think that iodine catalyzes the reaction as a mild Lewis acid. The mechanism was proposed as shown in Scheme 4. In the presence of iodine, cyclophentone is in equilibrium with the enol form **I**. The enol immediately attack iodine-activated Schiff base to form intermediate **II**, followed by an intramolecular Friedel–Crafts cyclization to give **III**. The subsequent dehydration of **III** results in tetrahydronaphtho[2,1-*c*][2,7]naphthyridine **IV**, which is further oxidized by air to afford an aromatized naphtho[2,1-*c*][2,7]naphthyridine **1**.

To verify the mechanism, we individually performed each separate step. The Schiff base, *N*-(3,4-dichlorophenylidene) naphthalen-2-amine, was obtained in 92% yield, when the 3,4-dichlorobenzaldehyde (**1**, Ar = 3,4-$Cl_2C_6H_3$) was treated with naphthalen-2-amine in THF at ambient temperature (Scheme 5). As expected, Schiff base smoothly reacted with **6** to give the corresponding ethyl 1,2-dihydro-5-(3,4-dichlorophenyl) naphtha [2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate **1a**. This result suggests that a formation of Schiff base took place during the reaction. It should be noted that the overall yield was low (76%) in the above separate reaction.

In conclusion, we found an efficient method for the synthesis of naphtho[2,1-*c*][2,7]naphthyridine derivatives by three-component reaction of aromatic aldehyde, naphthalen-2-amine, and ethyl 4-piperidinone-1-carboxylate or (3-chlorobenzoyl)-4-piperidinone using 5 mol % I_2 as catalyst. The features of this procedure are mild reaction conditions, high yields, operational simplicity, and environmentally friendly procedure.

Table 3

I_2 catalyzed reaction of benzaldehyde, naphthalen-2-amine and 1-(3-chlorobenzoyl)-4-piperidinone in THF.[a]

Entry	Ar	Products	Time (h)	Yields[b] (%)
1	4-ClC_6H_4	**8a**	15	82
2	4-BrC_6H_4	**8b**	16	86
3	2,4-$Cl_2C_6H_3$	**8c**	14	78
4	4-$NO_2C_6H_4$	**8d**	12	83

[a] Reagents and conditions: **4** (2 mmol), **5** (2 mmol, 0.286 g), **7** (2 mmol, 0.474 g), I_2 (0.1 mmol, 0.026 g), THF (10 mL).
[b] Isolated yields.

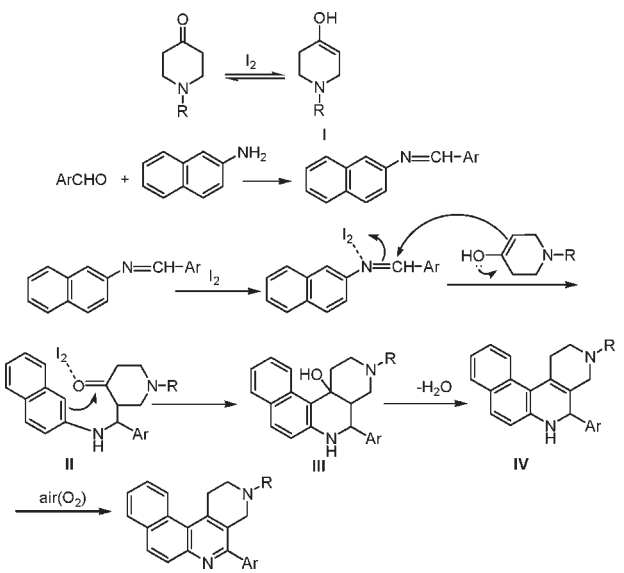
EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Infrared (IR) spectra were recorded on a TENSOR 27 spectrometer in KBr pellet. ^{1}H NMR spectra were obtained from solution in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. HRMS analyses were carried out using a Bruker-micro-TOF-Q-MS analyzer.

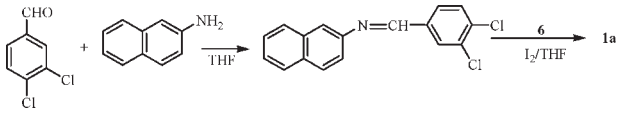
General procedure for the syntheses of 1,2-dihydro-5-arylnaphtho [2,1-*c*] [2,7]naphthyridine derivatives 1 and 8. A dry 50-mL flask was charged with aromatic aldehyde (2.0 mmol), naphthalen-2-amine (2.0 mmol, 0.286 g), ethyl 4-piperidinone-1-carboxylate or (3-chlorobenzoyl)-4-piperidinone (2.0 mmol), I_2 (0.1 mmol, 0.026 g), and THF (10 mL). The reaction mixture was stirred at reflux for 10–18 h. After completion of the reaction, as indicated by TLC, a little DMF was added to the mixture until the all yellow solid was dissolved. The generated crystals were collected by filtration to give 1 or 8 when the mixture was cooled to room temperature.

Ethyl 1,2-dihydro-5-(3,4-dichlorophenyl)naphtho[2,1-c][2,7] naphthyridine-3(4H)-carboxylate (1a). This compound was obtained as pale yellow crystals (0.819 g, 91%), mp 192–194°C. IR (KBr): ν_{max} 3057, 2983, 2957, 2869, 1715, 1564, 1549, 1473, 1451, 1381, 1338, 1282, 1255, 1203, 1169, 1138, 1110, 1087, 1059, 1029, 966, 954, 894, 838, 808, 788, 779, 755 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.31 (t, J = 6.8 Hz, 3H,

Scheme 4



Scheme 5



CH_3), 3.66 (t, J = 5.6 Hz, 2H, CH_2), 3.76 (t, J = 5.6 Hz, 2H, CH_2), 4.22 (q, J = 6.8 Hz, 2H, CH_2O), 4.73 (s, 2H, CH_2), 7.42 (dd, J = 8.0 Hz, J' = 2.0 Hz, 1H, ArH), 7.60 (d, J = 8.0 Hz, 1H, ArH), 7.66–7.70 (m, 2H, ArH), 7.74 (d, J = 2.0 Hz, 1H, ArH), 7.96–8.00 (m, 3H, ArH), 8.00–8.63 (m, 1H, ArH). HRMS (ESI, *m*/*z*): calcd for $C_{25}H_{20}Cl_2N_2NaO_2$ ($M+Na^+$) 473.0800, found 473.0791.

Ethyl 1,2-dihydro-5-(3-nitrophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1b). This compound was obtained as pale yellow crystals (0.785 g, 92%), mp 156−157°C. IR (KBr): ν_{max} 3090, 2960, 1694, 1534, 1466, 1447, 1382, 1348, 1303, 1260, 1204, 1095, 1081, 1001, 832, 807, 771, 759, 738, 708 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.20 (b, 3H, CH_3), 3.58–3.60 (m, 2H, CH_2), 3.74–3.76 (m, 2H, CH_2), 4.08 (q, J = 6.4 Hz, 2H, CH_2), 4.69 (s, 2H, CH_2), 7.75 (dd, J = 6.0 Hz, J' = 3.2 Hz, 2H, ArH), 7.86–7.91 (m, 2H, ArH), 8.11–8.13 (m, 3H, ArH), 8.40 (dd, J = 8.0 Hz, J' = 1.6 Hz, 1H, ArH), 8.49 (s, 1H, ArH), 8.74–8.76 (m, 1H, ArH). HRMS (ESI, *m*/*z*): calcd for $C_{25}H_{22}N_3O_4$ ($M+H^+$) 428.1610, found 428.1611.

Ethyl 1,2-dihydro-5-(2-thiophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1c). This compound was obtained as pale yellow crystals (0.629 g, 81%), mp 111−112°C. IR (KBr): ν_{max} 3057, 2981, 1697, 1606, 1551, 1478, 1436, 1379, 1359, 1332, 1304, 1258, 1227, 1199, 1169, 1134, 1117, 1074, 1028, 969, 827, 817, 767, 749, 712 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.26 (t, J = 7.2 Hz, 3H, CH_3), 3.62–3.63 (m, 2H, CH_2), 3.73–3.74 (m, 2H, CH_2), 4.16 (q, J = 7.2 Hz, 2H, CH_2), 5.01 (s, 2H, CH_2), 7.29–7.31 (m, 1H, ArH), 7.62 (d, J = 3.6 Hz, 1H, ArH), 7.72–7.74 (m, 2H, ArH), 7.81–7.85 (m, 2H, ArH), 8.08–8.11 (m, 2H, ArH), 8.71–8.73 (m, 1H, ArH). HRMS (ESI, *m*/*z*): calcd for $C_{23}H_{20}N_2NaO_2S$ ($M+Na^+$) 411.1143, found 411.1130.

Ethyl 1,2-dihydro-5-(2,4-dichlorophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1d). This compound was obtained as pale yellow crystals (0.729 g, 83%), mp 168−169°C. IR (KBr): ν_{max} 3083, 2975, 1708, 1587, 1557, 1474, 1426, 1379, 1360, 1341, 1303, 1281, 1247, 1201, 1170, 1139, 1116, 1098, 1064, 1051, 947, 863, 837, 800, 767, 746 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.22 (b, 3H, CH_3), 3.42–3.45 (m, 1H, CH), 3.68–3.70 (m, 1H, CH), 3.78–3.84 (m, 2H, CH_2), 4.08–4.13 (m, 2H, CH_2), 4.34–4.38 (m, 1H, CH), 4.48–4.51 (m, 1H, CH), 7.59 (d, J = 8.4 Hz, 1H, ArH), 7.66 (dd, J = 8.4 Hz, J' = 2.0 Hz, 1H, ArH), 7.74–7.77 (m, 2H, ArH), 7.86–7.88 (m, 2H, ArH), 8.11–8.14 (m, 2H, ArH), 8.77–8.80 (m, 1H, ArH). HRMS (ESI, *m*/*z*): calcd for $C_{25}H_{21}Cl_2N_2O_2$ ($M+H^+$) 451.0980, found 451.0983.

Ethyl 1,2-dihydro-5-(4-bromophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1e). This compound was obtained as pale yellow crystals (0.790 g, 86%), mp 188−190°C. IR (KBr): ν_{max} 3050, 2980, 1687, 1590, 1564, 1516, 1429, 1380, 1321, 1300, 1248, 1204, 1169, 1136, 1115, 1084, 1010, 953, 911, 886, 832, 765 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.20 (b, 3H, CH_3), 3.54–3.57 (m, 2H, CH_2), 3.70–3.73 (m, 2H, CH_2), 4.09 (q, J = 7.2 Hz, 2H, CH_2), 4.65 (s, 2H, CH_2), 7.59 (d, J = 8.4 Hz, 2H, ArH), 7.72–7.75 (m, 4H, ArH), 7.86 (d, J = 8.8 Hz, 1H, ArH), 8.07–8.11 (m, 2H, ArH), 8.70–8.72 (m, 1H, ArH). HRMS (ESI, *m*/*z*): calcd for $C_{25}H_{22}BrN_2O_2$ ($M+H^+$) 461.0865, found 461.0831.

Ethyl 1,2-dihydro-5-(4-chlorophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1f). This compound was obtained as pale yellow crystals (0.730 g, 88%), mp 210−212°C. IR (KBr): ν_{max} 3055, 2979, 1695, 1595, 1559, 1481, 1460, 1432, 1382, 1362, 1337, 1321, 1302, 1284, 1246, 1203, 1169, 1138, 1114, 1087, 1046, 1014, 979, 945, 870, 837, 757 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.20 (b, 3H, CH_3), 3.58 (t, J = 5.6 Hz, 2H, CH_2), 3.75 (t, J = 5.6 Hz, 2H, CH_2), 4.09 (q, J = 6.8 Hz, 2H, CH_2O), 4.66 (s, 2H, CH_2), 7.63–7.74 (m, 4H, ArH), 7.75–7.76 (m, 2H, ArH), 7.87 (d, J = 8.8 Hz, 1H, ArH), 8.09–8.13 (m, 2H, ArH), 8.73–8.75 (m, 1H, ArH). HRMS (ESI, *m*/*z*): calcd for $C_{25}H_{22}ClN_2O_2$ ($M+H^+$) 417.1370, found 417.1387.

Ethyl 1,2-dihydro-5-(2,3-dichlorophenyl)naphtho[2,1-c][2,7]naphthyri-dine-3(4H)-carboxylate (1g). This compound was obtained as pale yellow crystals (0.810 g, 90%), mp 165−167°C. IR (KBr): ν_{max} 3057, 2979, 2905, 1694, 1604, 1561, 1482, 1430, 1379, 1362, 1343, 1253, 1207, 1170, 1142, 1117, 1048, 1028, 870, 833, 788, 770, 753, 717, 701 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.29 (b, 3H, CH_3), 3.67–3.76 (m, 4H, $2CH_2$), 4.16–4.23 (m, 2H, CH_2O), 4.57 (s, 2H, CH_2), 7.33–7.40 (m, 2H, ArH), 7.60 (d, J = 8.8 Hz, 1H, ArH), 7.67–7.70 (m, 2H, ArH), 7.97–8.00 (m, 3H, ArH), 8.67–8.69 (m, 1H, ArH). HRMS (ESI, *m*/*z*): calcd for $C_{25}H_{21}Cl_2N_2O_2$ ($M+H^+$) 451.0980, found 451.0956.

Ethyl 1,2-dihydro-5-(4-nitrophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1h). This compound was obtained as pale yellow crystals (0.743 g, 87%), mp 209−211°C. IR (KBr): ν_{max} 3063, 2999, 2982, 2960, 2941, 2902, 1684, 1600, 1581, 1515, 1468, 1451, 1385, 1347, 1261, 1228, 1170, 1140, 1098, 1083, 1017, 968, 952, 886, 858, 837, 770, 751, 700 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.20 (b, 3H, CH_3), 3.58–3.59 (m, 2H, CH_2), 3.74–3.75 (m, 2H, CH_2), 4.07 (q, J = 7.2 Hz, 2H, CH_2), 4.65 (m, 2H, CH_2), 7.76 (dd, J = 6.0 Hz, J' = 3.2 Hz, 2H, ArH), 7.87–7.92 (m, 3H, ArH), 8.11–8.13 (m, 2H, ArH), 8.41 (d, J = 8.8 Hz, 2H, ArH), 8.73–8.76 (m, 1H, ArH). HRMS (ESI, *m*/*z*): calcd for $C_{25}H_{22}N_3O_4$ ($M+H^+$) 428.1610, found 428.1605.

Ethyl 1,2-dihydro-5-(4-fluorophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1i). This compound was obtained as pale yellow crystals (0.695 g, 87%), mp 207−209°C. IR (KBr): ν_{max} 3060, 2982, 2943, 2906, 1697, 1602, 1561, 1509, 1482, 1461, 1433, 1384, 1361, 1337, 1321, 1285, 1248, 1159, 1113, 1046, 1030, 979, 944, 869, 837, 808, 758 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.20 (b, 3H, CH_3), 3.54–3.57 (m, 2H, CH_2), 3.71–3.74 (m, 2H, CH_2), 4.07 (q, J = 6.8 Hz, 2H, CH_2O), 4.64 (s, 2H, CH_2), 7.37–7.42 (m, 2H, ArH), 7.66–7.76 (m, 4H, ArH), 7.86 (d, J = 9.2 Hz, 1H, ArH), 8.07–8.11 (m, 2H, ArH), 8.70–8.73 (m, 1H, ArH). HRMS (ESI, *m*/*z*): calcd for $C_{25}H_{22}FN_2O_2$ ($M+H^+$) 401.1665, found 401.1661.

Ethyl 1,2-dihydro-5-(2-nitrophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1j). This compound was obtained as pale yellow crystals (0.769 g, 90%), mp 218−220°C. IR (KBr): ν_{max} 3057, 2978, 2924, 2905, 2851, 2684, 1608, 1560, 1529, 1468, 1442, 1383, 1350, 1302, 1266, 1224, 1140, 1118, 1092, 1028, 979, 954, 895, 860, 840, 790, 758, 740, 705, 693 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.13–1.22 (m, 3H, CH_3), 3.64 (b, 2H, CH_2), 3.75 (b, 2H, CH_2), 4.08 (b, 2H, CH_2), 4.51 (s,

2H, CH_2), 7.74–7.85 (m, 5H, ArH), 7.92–7.96 (m, 1H, ArH), 8.08–8.12 (m, 2H, ArH), 8.27 (d, J = 8.0 Hz, 1H, ArH), 8.78–8.80 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{22}N_3O_4$ ($M+H^+$) 428.1610, found 428.1610.

Ethyl 1,2-dihydro-5-(3-chlorophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1k). This compound was obtained as pale yellow crystals (0.691 g, 83%), mp 131−132°C. IR (KBr): ν_{max} 3053, 2969, 2869, 1700, 1568, 1479, 1466, 1417, 1363, 1346, 1280, 1255, 1202, 1170, 1137, 1111, 1060, 1027, 997, 957, 875, 837, 794, 768, 752, 722, 696 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.22 (b, 3H, CH_3), 3.57–3.58 (m, 2H, CH_2), 3.71–3.72 (m, 2H, CH_2), 4.09 (q, J = 6.4 Hz, 2H, CH_2), 4.66 (s, 2H, CH_2), 7.59–7.60 (m, 3H, ArH), 7.73–7.76 (m, 3H, ArH), 7.87 (d, J = 8.8 Hz, 1H, ArH), 8.09–8.13 (m, 2H, ArH), 8.71–8.74 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{22}ClN_2O_2$ ($M+H^+$) 417.1370, found 417.1350.

Ethyl 1,2-dihydro-5-(4-methoxyphenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1l). This compound was obtained as pale yellow crystals (0.674 g, 82%), mp 193−194°C. IR (KBr): ν_{max} 3018, 2978, 2958, 2934, 2903, 2871, 2841, 1702, 1610, 1556, 1518, 1418, 1367, 1292, 1204, 1135, 1109, 1087, 1060, 964, 952, 858, 836, 795, 759 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.20 (b, 3H, CH_3), 3.55 (t, J = 5.2 Hz, 2H, CH_2), 3.72 (s, 2H, CH_2), 3.86 (s, 3H, CH_3O), 4.08 (q, J = 7.2 Hz, 2H, CH_2), 4.69 (s, 2H, CH_2), 7.11 (d, J = 8.4 Hz, 2H, ArH), 7.59 (d, J = 8.4 Hz, 2H, ArH), 7.73 (t, J = 4.4 Hz, 2H, ArH), 7.86 (d, J = 8.8 Hz, 1H, ArH), 8.06–8.11 (m, 2H, ArH), 8.69–8.71 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{26}H_{25}N_2O_2$ ($M+H^+$) 413.1865, found 413.1865.

Ethyl 1,2-dihydro-5-(4-chloro-2-nitrophenyl)naphtha [2,1-c][2,7] naphthyridine-3(4H)-carboxylate (1m). This compound was obtained as pale yellow crystals (0.774 g, 84%), mp 185−186°C. IR (KBr): ν_{max} 3061, 2986, 2906, 1698, 1683, 1605, 1567, 1537, 1484, 1470, 1435, 1383, 1339, 1297, 1246, 1224, 1204, 1144, 1117, 1026, 980, 960, 894, 868, 834, 756 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.31 (b, 3H, CH_3), 3.75 (b, 4H, $2CH_2$), 4.20 (b, 2H, CH_2), 4.54 (b, 2H, CH_2), 7.51 (s, 1H, ArH), 7.62–7.69 (m, 3H, ArH), 7.86 (d, J = 9.2 Hz, 1H, ArH), 7.94–8.01 (m, 2H, ArH), 8.22 (d, J = 8.8 Hz, 1H, ArH), 8.65–8.67 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{21}ClN_3O_4$ ($M+H^+$) 462.1221, found 462.1201.

Ethyl 1,2-dihydro-5-phenylnaphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1n). This compound was obtained as pale yellow crystals (0.634 g, 83%), mp 175−177°C. IR (KBr): ν_{max} 3056, 2975, 2931, 2869, 1703, 1565, 1478, 1446, 1419, 1376, 1364, 1344, 1278, 1261, 1231, 1200, 1169, 1135, 1110, 1088, 1060, 1029, 954, 880, 853, 838, 782, 757, 737, 700 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.29 (b, 3H, CH_3), 3.65–3.66 (m, 2H, CH_2), 3.73–3.75 (m, 2H, CH_2), 4.20 (q, J = 6.8 Hz, 2H, CH_2), 4.74 (s, 2H, CH_2), 7.47–7.60 (m, 5H, ArH), 7.64–7.68 (m, 2H, ArH), 7.93–8.00 (m, 3H, ArH), 8.60–8.63 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{22}N_2NaO_2$ ($M+Na^+$) 405.1579, found 405.1579.

Ethyl 1,2-dihydro-5-(2-fluorophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1o). This compound was obtained as pale yellow crystals (0.704 g, 88%), mp 95−97°C. IR (KBr): ν_{max} 3059, 2990, 2964, 2902, 2851, 1701, 1616, 1579, 1561, 1528, 1489, 1438, 1385, 1365, 1247, 1216, 1141, 1046, 1024, 978, 951, 896, 858, 842, 814, 755 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.22 (b, 3H, CH_3), 3.60–3.74 (m, 4H, $2CH_2$), 4.08 (b, 2H, CH_2O), 4.52 (b, 2H, CH_2), 7.41–7.45 (m, 2H, ArH), 7.57–7.65 (m, 2H, ArH), 7.74–7.76 (m, 2H, ArH), 7.88 (d, J = 8.8 Hz, 1H, ArH), 8.10–8.13 (m, 2H, ArH), 8.75–8.77 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{21}FN_2NaO_2$ ($M+Na^+$) 423.1485, found 423.1467.

Ethyl 1,2-dihydro-5-(3,5-dimethoxyphenyl)naphtha [2,1-c][2,7] naphthyridine-3(4H)-carboxylate (1p). This compound was obtained as pale yellow crystals (0.760 g, 86%), mp 157−159°C. IR (KBr): ν_{max} 3052, 2985, 2936, 2843, 1694, 1599, 1454, 1423, 1372, 1321, 1301, 1247, 1204, 1193, 1112, 1088, 1058, 969, 897, 852, 836, 802, 770, 752, 729 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.30 (b, 3H, CH_3), 3.66–3.69 (m, 2H, CH_2), 3.74–3.76 (m, 2H, CH_2), 3.85 (s, 6H, $2CH_3O$), 4.21 (q, J = 6.8Hz, 2H, CH_2O), 4.77 (s, 2H, CH_2), 6.57 (s, 1H, ArH), 6.70 (d, J = 2.0 Hz, 2H, ArH), 7.65–7.68 (m, 2H, ArH), 7.94–8.01 (m, 3H, ArH), 8.61–8.64 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{27}H_{27}N_2O_4$ ($M+H^+$) 443.1971, found 443.1948.

1,2,3,4-Tetrahydro-3-(3-chlorobenzoyl)-5-(4-chlorophenyl)-naphtho[2,1-c][2,7]naphthyridine (8a). This compound was obtained as pale yellow crystals (0.789 g, 82%), mp 184−185°C. IR (KBr): ν_{max} 3062, 3014, 2977, 2899, 2853, 1623, 1560, 1479, 1430, 1361, 1322, 1259, 1211, 1165, 1126, 1085, 1055, 1045, 1012, 965, 946, 900, 838, 805, 744, 699 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.54–3.80 (m, 4H, $2CH_2$), 4.67–4.85 (m, 2H, CH_2), 7.43–7.75 (m, 10H, ArH), 7.89 (d, J = 8.8 Hz, 1H, ArH), 8.10–8.13 (m, 2H, ArH), 8.14 (s, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{29}H_{20}Cl_2N_2NaO$ ($M+Na^+$) 505.0850, found 505.0857.

1,2,3,4-Tetrahydro-3-(3-chlorobenzoyl)-5-(4-bromophenyl)-naphtho[2,1-c][2,7]naphthyridine (8b). This compound was obtained as pale yellow crystals (0.902 g, 86%), mp 171−172°C. IR (KBr): ν_{max} 3060, 3016, 2980, 2946, 2898, 2852, 1634, 1563, 1518, 1479, 1430, 1362, 1321, 1259, 1227, 1211, 1165, 1125, 1083, 1068, 1009, 966, 900, 833, 805, 745, 703, 683 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.79–3.85 (m, 4H, $2CH_2$), 4.67–4.85 (m, 2H, CH_2), 7.32–7.80 (m, 10H, ArH), 7.89 (d, J = 8.8 Hz, 1H, ArH), 8.09–8.12 (m, 2H, ArH), 8.74 (s, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{29}H_{21}BrClN_2O$ ($M+H^+$) 527.0526, found 527.0525.

1,2,3,4-Tetrahydro-3-(3-chlorobenzoyl)-5-(2,4-dichlorophenyl)naphtho[2,1-c][2,7]naphthyridine (8c). This compound was obtained as pale yellow crystals (0.805 g, 78%), mp 217−218°C. IR (KBr): ν_{max} 3058, 3022, 2944, 1641, 1588, 1562, 1518, 1477, 1460, 1439, 1380, 1360, 1343, 1321, 1263, 1228, 1170, 1131, 1099, 1049, 971, 906, 870, 834, 798, 781, 759, 745, 698 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.49–3.95 (m, 4H, $2CH_2$), 4.44–4.74 (m, 2H, CH_2), 7.43–7.78 (m, 9H, ArH), 7.89 (d, J = 8.8 Hz, 1H, ArH), 8.12–8.14 (m, 2H, ArH), 8.80 (s, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{29}H_{19}Cl_3N_2NaO$ ($M+Na^+$) 539.0461, found 539.0456.

1,2,3,4-Tetrahydro-3-(3-chlorobenzoyl)-5-(4-nitrophenyl)-naphtho[2,1-c][2,7]naphthyridine (8d). This compound was obtained as pale yellow crystals (0.818 g, 83%), mp 133−134°C. IR (KBr): ν_{max} 3055, 2944, 2887, 2855, 1658, 1629, 1564, 1515, 1478, 1430, 1349, 1322, 1258, 1211, 1098, 1045, 859, 837, 807, 757, 737, 701 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.57–3.87 (m, 4H, $2CH_2$), 4.67–4.86 (m, 2H, CH_2), 7.36–7.58 (m, 4H, ArH), 7.76–7.78(m, 2H, ArH), 7.91 (d, J = 8.8 Hz, 1H, ArH), 7.96–7.99 (m, 2H, ArH), 8.13 (d, J = 9.2 Hz, 2H, ArH), 8.26–8.45 (m, 2H, ArH), 8.76–8.78 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{29}H_{20}ClN_3NaO_3$ ($M+Na^+$) 516.1091, found 516.1099.

General procedure for the syntheses of binaphtho[2,1-*c*][2,7]naphthyridine 9. A dry 50-mL flask was charged with terephthalaldehyde (1.0 mmol, 0.134 g), naphthalen-2-amine (2.0 mmol, 0.286 g), ethyl 4-piperidinone-1-carboxylate (2.0 mmol, 0.342 g), I_2 (0.05 mmol, 0.013 g), and THF (10 mL). The reaction mixture was stirred at reflux for 10 h. After completion of the reaction, as indicated by TLC, a little DMF was added to the mixture until the all yellow solid was dissolved. The generated crystals were collected by filtration to give **9** when the mixture was cooled to room temperature.

1,4-di(1,2,3,4-tetrahydro-3-ethoxycarbonyl-naphtho[2,1-c][2,7]naphthyri-dine-5-yl)benzene (9). This compound was obtained as pale yellow crystals (0.597 g, 87%), mp 249−250°C. IR (KBr): ν_{max} 3054, 2987, 2872, 1708, 1564, 1479, 1449, 1419, 1379, 1362, 1259, 1205, 1137, 1112, 1086, 853, 837, 752cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.21–1.23 (b, 6H, $2CH_3$), 3.61–3.64 (m, 4H, $2CH_2$), 3.78–3.80 (m, 4H, $2CH_2$), 4.12 (q, J = 6.8 Hz, 4H, $2CH_2O$), 4.80 (s, 4H, $2CH_2$), 7.75–7.77 (m, 4H, ArH), 7.83 (s, 4H, ArH), 7.95 (d, J = 9.2 Hz, 2H, ArH), 8.12–8.15 (m, 4H, ArH), 8.76–8.78 (m, 2H, ArH). HRMS (ESI, *m*/*z*): calcd for $C_{44}H_{39}N_4O_4$ ($M+H^+$) 687.2971, found 687.2936.

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