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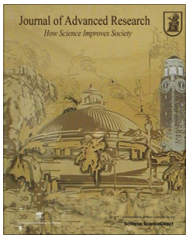

ORIGINAL ARTICLE

Benzoquinoline amines – Key intermediates for the synthesis of angular and linear dinaphthonaphthyridines

Kolandaivel Prabha, K.J. Rajendra Prasad *

Department of Chemistry, Bharathiar University, Coimbatore, Tamil Nadu, India

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ABSTRACT

A systematic study on the condensation reaction of 2,4-dichlorobenzo[*h*]quinoline and naphth-1-ylamine in the presence of CuI as catalyst to functionalised mono- and di-substituted (naphthalen-1-yl)benzo[*h*]quinoline amines was described. Subsequently these mono- and di-substituted amines on polyphosphoric acid catalysed cyclisation reaction with aromatic/heteroaromatic carboxylic acids led to the construction of angular and linear aromatic/heteroaromatic substituted dinaphthonaphthyridines in good yields.

Introduction

In a quest to obtain lead molecules in the medicinal chemistry, small molecules appended with differently substituted functional groups can be of great interest, due to their potential to create a number of chemical libraries. Among those, nitrogen containing heterocycles such as quinolines and naphthyridines draw special attention due to their wide variety of biological activities. For instance, quinoline based chemical entities were known for their anti-tuberculosis [1,2], antiproliferative [3,4], anthelmintic [5], antibacterial [6] and antioxidant activities [7]. 4-Amino-7-chloroquinoline derivatives and its modified side-chain analogs [8–10] were representative class of antimalarial drugs. Extensive studies were made to obtain biologically active quinolines and naphthyridine analogues starting from chloro quinolines [11]. The synthesis of naphthyridines [12], benzonaphthyridines [13], and dibenzonaphthyridines [14–16] from various starting precursors were also well documented in the literature. Such naphthyridines exhibit remarkable biological activities such as CB_2 selective agonists [17], anti-HIV [18], anticancer [19,20], selective 3-phosphoinositide-dependent kinase-I inhibitors [21] and topoisomerase-I inhibitors [22]. Naphthyridines were also explored as a versatile ligand in the field of inorganic chemistry [23].

Hence, there is a continuous urge to develop new methods for the synthesis of naphthyridines. There are so many reports in the literature about the utility CuI as catalyst. For example, Buchwald explored CuI-catalysed coupling of alkylamines and aryl iodides and also the *N*-arylation of sev-

* Corresponding author. Tel.: +91 422 2422311; fax: +91 422 2422387.
E-mail address: prasad_125@yahoo.com (K.J. Rajendra Prasad).
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eral nitrogen-containing substrates using specific ligands [24,25]. Recently CuI catalysts have been received good attention for *N*-arylation reaction between aryl halides and amines [26,27], which in general are high yielding reactions under mild conditions. It is also quite stable under open atmosphere, less toxic and low cost. *N*-arylation of aromatic heterocycles and amino acids catalysed by CuI catalyst under ligand free conditions were recently reported [28]. These features encouraged our interest in exploring the synthetic utility of CuI as a catalyst for the synthesis of benzoquinoline amine intermediates under ligand free condition.

To the best of our knowledge, there are no literature reports for the synthesis of angular and linear aromatic/heteroaromatic substituted dinaphthonaphthyridines. Keeping the importance of naphthyridine compounds in mind, here in we report the synthesis of titled compounds by the reaction of 2,4-dichlorobenzo[*h*]quinoline *via* benzoquinolin-amine intermediates utilising Bernthsen reaction condition. These functionalised intermediates were prepared by simple amine-halide condensation reaction between 1-naphthylamine and 2,4-dichlorobenzo[*h*]quinoline using CuI as catalyst.

Experimental

General

Melting points (Mp.) were determined on Mettler FP 51 apparatus (Mettler Instruments, Switzerland) and were uncorrected. They were expressed in degree centigrade (°C). A Nicolet Avatar Model FT-IR spectrophotometer was used to record the IR spectra (4000–400 cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AV 400 (400 M*Hz* (^{1}H) and 100 M*Hz* (^{13}C)), Bruker AV 500 (500 M*Hz* (^{1}H) and 125 M*Hz* (^{13}C)) spectrometer using tetramethylsilane (TMS) as an internal reference. The chemical shifts were expressed in parts per million (ppm). Mass spectra (MS) were recorded on Auto Spec EI + Shimadzu QP 2010 PLUS GC–MS mass spectrometer. Microanalyses were performed on a Vario EL III model CHNS analyser (Vario, Germany) at the Department of Chemistry, Bharathiar University, Coimbatore – 46, India. The solvent and the reagents used (reagent grade) were purified by standard methods. Anhydrous sodium sulphate was used to dry the solution of organic extracts. Thin layer chromatography (TLC) was performed using glass plates coated with silica gel-G containing 13% calcium sulphate as binder. Ethyl acetate and petroleum ether were used as developing solvents. A chamber containing iodine vapour was used to locate the spots. Separation and purification of the crude products were carried out using chromatographic column packed with activated silica gel (60–120 mesh). In the case of mixture of solvents used for elution, the ratio of the mixture is given in brackets.

Preparation of 2,4-dichlorobenzo[h]quinoline (3)

An equimolar mixture of naphth-1-ylamine (**1**, 0.01 mol), malonic acid (**2**, 0.01 mol) and 40 mL of phosphorous oxychloride was refluxed on water bath for 8 h and the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into crushed ice and neutralised with diluted solution of sodium hydroxide to give a white precipitate, which was filtered, dried and purified by silica column chromatography. The product was eluted with hexane, to obtain **3** as a white solid; Mp.: 70–72 °C; Yield: 45%; IR (KBr, cm^{-1}) ν_{max}: 1581 (C═N); ^{1}H NMR (400 M*Hz*, $CDCl_3$) (ppm) δ_H: 7.62 (s, 1H, C_3—H), 7.74–8.08 (m, 5H, C_5, C_6—C_9—H), 9.22 (dd, 1H, J_o = 8.20 *Hz*, J_m = 1.20 *Hz*, C_{10}—H); Anal. Calcd. for $C_{13}H_7Cl_2N$ (247): C, 62.93; H, 2.84; N, 5.65%; Found: C, 63.00; H, 2.78; N, 5.61%.

General procedure for the reaction of naphth-1-ylamine (1) with 2,4-dichlorobenzo[h] quinoline (3); preparation of 4-chloro-N-(naphth-1-yl)benzo[h]quinolin-2-amine (4) and N^2,N^4-di(naphth-1-yl)benzo[h]quinolin-2,4-diamine (5)

A mixture of 2,4-dichlorobenzo[*h*]quinoline (**3**, 0.010 mol), naphth-1-ylamine (**1**, 0.010 mol) and CuI (10 mol%) was heated in 20 mL of DMSO at 120 °C for an hour. After the completion of the reaction, water was added into the reaction mixture. The resultant precipitate was washed with water, dried and purified by column chromatography (neutral alumina). Compound **4** was eluted with petroleum ether: ethyl acetate (99:1) whereas compound **5** was eluted with ethyl acetate: methanol (95:5). Both the compounds were recrystallised using methanol.

4-Chloro-N-(naphth-1-yl)benzo[h]quinolin-2-amine (4)

White amorphous powder; Mp.: 126–128 °C; Yield: 45%; IR (KBr, cm^{-1}) ν_{max}: 3066 (NH), 1636 (C═N); ^{1}H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 7.02 (s, 1H, C_2—NH), 7.17 (s, 1H, C_3—H), 7.54–7.84 (m, 8H, C_8, C_2'—C_8'—H), 7.91 (t, 1H, J = 8.00 *Hz*, C_9—H), 7.96 (d, 1H, J = 8.00 *Hz*, C_6—H), 8.01 (d, 1H, J = 8.50 *Hz*, C_7—H), 8.15 (d, 1H, J = 9.00 *Hz*, C_5—H), 9.20 (dd, 1H, J_o = 8.00 *Hz*, J_m = 1.50 *Hz*, C_{10}—H); ^{13}C NMR (125 M*Hz*, $CDCl_3$) (ppm) δ_C: 109.17 (C_3), 119.11 (C_{4a}), 121.15 (C_2'), 121.25 (C_4'), 122.12 (C_8'), 124.50 (C_5'), 124.89 (C_5), 125.95 (C_7'), 126.08 (C_6'), 126.50 (C_3'), 126.52 (C_{10}), 126.59 (C_6), 127.77 (C_9), 128.38 (C_8), 128.64 (C_7), 129.34 (C_{8a}'), 130.22 (C_{4a}'), 134.38 (C_{10a}), 134.75 (C_{6a}), 135.14 (C_1'), 143.75 (C_{10b}), 147.06 (C_4), 155.68 (C_2); MS *m*/*z* (%) 354 (M + H, 100), 356 (M + 2, 31); Anal. Calcd. for $C_{23}H_{15}ClN_2$ (354): C, 77.85; H, 4.26; N, 7.89%; Found: C, 77.79; H, 4.23; N, 7.82%.

N^2,N^4-Di(naphth-1-yl)benzo[h]quinolin-2,4-diamine (5)

Pale brown solid; Mp.: > 300 °C; Yield: 51%; IR (KBr, cm^{-1}) ν_{max}: 3136, 3054 (NH), 1629(C═N); ^{1}H NMR (500 M*Hz*, DMSO-d_6) (ppm) δ_H: 6.51 (s, 1H, C_3—H), 7.01–8.19 (m, 18H, C_6—C_9, C_2'—C_8' & C_2''—, C_8''—H), 8.77 (d, 1H, C_5—H, J = 8.00 *Hz*), 9.38 (d, 1H, C_{10}—H, J = 8.50 *Hz*), 10.74 (s, 1H, C_4—NH), 11.45 (s, 1H, C_2—NH), 14.13 (s, 1H, N_1—H); ^{13}C NMR (125 M*Hz*, DMSO-d_6) (ppm) δ_C: 86.26 116.36, 120.07, 121.05, 122.45, 122.82, 123.46, 125.16, 125.39, 126.30, 127.06 (2C), 127.20, 127.37, 128.27, 128.72, 128.95 (3C), 129.13, 129.32, 130.02, 132.35, 134.14, 134.34 (4C), 134.50, 134.88, 135.69, 152.88, 155.57; MS *m*/*z* (%) 462 (M + H, 100); Anal. Calcd. for $C_{33}H_{23}N_3$ (461): C, 85.87; H, 5.02; N, 9.10%; Found: C, 85.94; H, 4.99; N, 9.07%.

General procedure for the synthesis of dinaphtho[b,g][1,8]naphthyridines (6–12)

4-Chloro-*N*-(naphth-1-yl)benzo[*h*]quinolin-2-amine (**4**, 0.002 mol) and the appropriate carboxylic acids (0.0025 mol) were added to polyphosphoric acid (6 g of P_2O_5 in 3 mL of H_3PO_4) and then heated. The reaction time, temperature maintained and various acids used for the synthesis of respective product were mentioned in Table 2. After the completion of the reaction, it was poured into ice water, neutralised with saturated sodium bicarbonate solution to remove excess of carboxylic acids and extracted with ethyl acetate. It was then purified by column chromatography using silica gel (eluted with petroleum ether: ethyl acetate (93:7) to get the compounds (**6–12**), which was then recrystallised using methanol.

8-(4′-Methylphenyl)-dinaphtho[1,2-b:2′,1′-g][1,8]naphthyridin-7(16H)-one (6)

Yellow spongy mass; Mp.: 185–187 °C; Yield: 66%; IR (KBr, cm^{-1}) ν_{max}: 3144 (NH), 1680 (C═O), 1592 (C═N); ^{1}H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 2.50 (s, 3H, C_4'—CH_3), 7.35 (2d, 2H, C_2' & C_6'—H), 7.54–8.34 (m, 12H, C_2—C_5, C_9—C_{13}, C_3', C_5'—H & C_{16}—NH), 8.96 (d, 1H, J = 8.50 *Hz*, C_6—H), 9.29 (dd, 1H J_o = 8.00 *Hz*, J_m = 2.00 *Hz*, C_1—H), 9.64 (d, 1H, J = 8.50 *Hz*, C_{14}—H); ^{13}C NMR (125 M*Hz*, $CDCl_3$) (ppm) δ_C: 22.73, 119.51, 121.25, 121.91, 122.40, 123.95, 125.52, 126.73, 126.89, 127.05, 127.33, 127.64, 127.87, 127.98, 128.07, 128.58(2C), 128.92(2C), 129.62, 130.75, 131.41, 132.49, 133.56, 135.12, 136.27, 139.53, 142.31, 147.89, 155.93, 178.79; Anal. Calcd. for $C_{31}H_{20}N_2O$ (436): C, 85.30; H, 4.62; N, 6.42%; Found: C, 85.34; H, 4.58; N, 6.35%.

8-Methyldinaphtho[1,2-b:2′,1′-g][1,8]naphthyridin-7(16H)-one (7)

Yellow prisms; Mp.: 154–156 °C; Yield: 43%; IR (KBr, cm^{-1}) ν_{max}: 3295 (NH), 1640 (C═O), 1554 (C═N); ^{1}H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 3.07 (s, 3H, C_8—CH_3), 7.43–8.22 (m, 9H, C_2—C_5, C_9—C_{13}—H), 8.51(s, 1H, C_{16}—NH), 9.01 (d, 1H, J = 8.00 *Hz*, C_6—H), 9.31 (dd, 1H J_o = 8.50 *Hz*, J_m = 1.50 *Hz*, C_1—H), 9.63 (d, 1H, J = 9.00 *Hz*, C_{14}—H); ^{13}C NMR (125 M*Hz*, $CDCl_3$) (ppm) δ_C: 29.85, 119.66, 121.17, 121.85, 122.53, 124.05, 125.63, 126.69, 126.99, 127.00, 127.13, 127.72, 127.86, 127.91, 128.21, 129.76, 131.29, 132.55, 133.87, 135.34, 139.49, 142.50, 147.58, 154.90, 179.11; Anal. Calcd. for $C_{25}H_{16}N_2O$ (360): C, 83.31; H, 4.47; N, 7.77%; Found: C, 83.36; H, 4.54; N, 7.70%.

8-(4′-Methoxyphenyl)dinaphtho[1,2-b:2′,1′-g][1,8]naphthyridin-7(16H)-one (8)

Yellow solid; Mp.: 191–193 °C; Yield: 69%; IR (KBr, cm^{-1}) ν_{max}: 3166 (NH), 1626 (C═O), 1567 (C═N); ^{1}H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 4.05 (s, 3H, C_4'—CH_3), 7.26 (2d, 2H, C_2' & C_6'—H), 7.38 (2d, 2H, C_3' & C_5'—H), 7.40–8.09 (m, 9H, C_2—C_5, C_9—C_{13}—H), 8.22 (s, 1H, C_{16}—NH), 8.86 (d, 1H, J = 7.50 *Hz*, C_6—H), 9.30 (d, 1H J = 8.00 *Hz*, C_1—H), 9.61 (d, 1H, J = 8.50 *Hz*, C_{14}—H); ^{13}C NMR (125 M*Hz*, DMSO-d_6) (ppm) δ_C: 53.86, 118.96, 121.16, 121.86, 122.27, 124.15, 125.64, 126.68, 126.78, 127.15, 127.41, 127.51, 127.79, 127.90, 128.11, 128.46(2C), 129.09 (2C), 129.70, 130.64, 131.36, 132.50, 133.30, 135.30, 136.31, 139.42, 142.27, 148.90, 155.70, 178.49; Anal. Calcd. for $C_{31}H_{20}N_2O_2$ (452): C, 82.28; H, 4.45; N, 6.19%; Found: C, 82.34; H, 4.51; N, 6.14%.

8-(4′-Chlorophenyl)dinaphtho[1,2-b:2′,1′-g][1,8]naphthyridin-7(16H)-one (9)

Yellow solid; Mp.: 176–178 °C; Yield: 71%; IR (KBr, cm^{-1}) ν_{max}: 3210 (NH), 1639 (C═O), 1598 (C═N); ^{1}H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 7.40 (2d, 2H, C_2' & C_6'—H), 7.55–8.54 (m, 12H, C_2—C_5, C_9—C_{13}, C_3', C_5'—H & C_{16}—NH), 8.85 (d, 1H, J = 8.00 *Hz*, C_6—H), 9.22 (dd, 1H J_o = 8.00 *Hz*, J_m = 2.00 *Hz*, C_1—H), 9.59 (d, 1H, J = 8.50 *Hz*, C_{14}—H); ^{13}C NMR (125 M*Hz*, DMSO-d_6) (ppm) δ_C: 118.99, 121.09, 121.76, 122.39, 123.88, 125.67, 126.81, 126.90, 127.20, 127.29, 127.59, 127.80, 127.94, 128.21, 128.33(2C), 129.87, 130.01(2C), 130.59, 131.50, 132.38, 133.50, 135.23, 136.18, 139.61, 142.40, 147.64, 153.76, 180.06; Anal. Calcd. for $C_{30}H_{17}ClN_2O$ (456): C, 78.86; H, 3.75; N, 6.13%; Found: C, 78.81; H, 3.82; N, 6.07%%.

8-(4′-Nitrophenyl)dinaphtho[1,2-b:2′,1′-g][1,8]naphthyridin-7(16H)-one (10)

Dark yellow solid; Mp.: 167–169 °C; Yield: 61%; IR (KBr, cm^{-1}) ν_{max}: 3131 (NH), 1641 (C═O), 1599 (C═N); ^{1}H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 7.34–8.36 (m, 13H, C_2—C_5, C_9—C_{13}, C_2', C_6', C_3' & C_5'—H), 8.50 (s, IH, C_{16}—NH), 8.91 (d, 1H, J = 7.50 *Hz*, C_6—H), 9.34 (dd, 1H, J_o = 8.50 *Hz*, J_m = 1.50 *Hz*, C_1—H), 9.65 (d, 1H, J = 9.00 *Hz*, C_{14}—H); ^{13}C NMR (125 M*Hz*, $CDCl_3$) (ppm) δ_C: 119.19, 121.36, 121.84, 122.61, 123.87, 125.73, 126.81, 126.93, 127.17, 127.41, 127.59, 127.76, 127.88, 128.11, 128.49(2C), 129.77, 130.10(2C), 130.65, 131.39, 132.33, 133.65, 134.98, 136.47, 139.62, 143.86, 148.78, 154.57, 180.11; Anal. Calcd. for $C_{30}H_{17}N_3O_3$ (467): C, 77.08; H, 3.67; N, 8.99%; Found: C, 77.01; H, 3.73; N, 9.04%.

8-(Pyridin-3′-yl)dinaphtho[1,2-b:2′,1′-g][1,8]naphthyridin-7(16H)-one (11)

Yellow solid; Mp.: 183–185 °C; Yield: 57%; IR (KBr, cm^{-1}) ν_{max}: 3243 (NH), 1655 (C═O), 1590 & 1521 (C═N); ^{1}H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 7.40 (t, 1H, J = 5.00 *Hz* C_5'—H), 7.44–8.29 (m, 9H, C_2—C_5, C_9—C_{13}—H), 8.32 (d, 1H, J = 5.50 *Hz*, C_4'—H), 8.40 (s, 1H, C_{16}—NH), 8.51 (d, 1H, J = 4.50 *Hz*, C_6'—H), 8.86 (s, 1H, C_2'—H), 8.93 (d, 1H, J = 8.50 *Hz*, C_6—H), 9.27 (dd, 1H J_o = 9.00 *Hz*, J_m = 2.00 *Hz*, C_1—H), 9.58 (d, 1H, J = 8.00 *Hz*, C_{14}—H); ^{13}C NMR (125 M*Hz*, $CDCl_3$) (ppm) δ_C: 117.55, 120.97, 121.75, 123.13, 124.67, 125.82, 125.99, 126.09, 126.77, 127.05, 127.43, 127.58, 127.81, 128.11, 128.74, 129.90, 130.19, 131.46, 132.67, 133.39, 134.70, 136.54, 138.03, 143.70, 146.75, 147.58, 149.29, 155.14, 178.88; Anal. Calcd. for $C_{29}H_{17}N_3O$ (423): C, 82.25; H, 4.05; N, 9.92%; Found: C, 82.30; H, 4.01; N, 9.88%.

8-(Thiophen-2′-yl)dinaphtho[1,2-b:2′,1′-g][1,8]naphthyridin-7(16H)-one (12)

Yellow solid; Mp.: 177–179 °C; Yield: 41%; IR (KBr, cm^{-1}) ν_{max}: 3209 (NH), 1645 (C═O), 1592 & 1528 (C═N); ^1H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 7.19 (t, 1H, J = 5.00 *Hz* C_4'—H), 7.31–8.18 (m, 11H, C_2—C_5, C_9—C_{13}, C_3' & C_5'—H), 8.38(s, 1H, C_{16}—NH), 9.03 (d, 1H, J = 7.50 *Hz*, C_6—H), 9.28 (dd, 1H, J_o = 8.00 *Hz*, J_m = 2.50 *Hz*, C_1—H), 9.52 (d, 1H, J = 8.50 *Hz*, C_{14}—H); Anal. Calcd. for $C_{28}H_{16}N_2OS$ (428): C, 78.48; H, 3.76; N, 6.54; S, 7.48%; Found: C, 78.53; H, 3.80; N, 6.49; S, 7.51%.

General procedure for the synthesis of dinaphtho[b,h][1,6]naphthyridines (13–20)

A mixture of N^2,N^4-di(naphth-1-yl)benzo[*h*]quinoline-2,4-diamine (**5**, 0.002 mol) and appropriate carboxylic acids (0.0025 mol) were added to polyphosphoric acid (6 g of P_2O_5 in 3 mL of H_3PO_4). The reaction time, temperature maintained and various acids used for synthesis of the respective product were mentioned in Table 2. The reaction was monitored by TLC. After the completion of the reaction, it was poured into ice water, neutralised with saturated solution of sodium bicarbonate to remove excess of carboxylic acids, extracted with ethyl acetate, purified by column chromatography using silica gel and product was eluted with petroleum ether:ethyl acetate (97:3) mixture to get (**13–20**) which was recrystallised using methanol.

N-(Naphth-1″-yl)-7-(4′-methylphenyl)-dinaphtho[1,2-b:1′,2′-h][1,6]naphthyridin-6-amine (13)

Orange prisms; Mp.: 262–264 °C; Yield: 75%; IR (KBr, cm^{-1}) ν_{max}: 3048 (NH), 1655, 1601 (C═N); ^1H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 2.48 (s, 3H, C_4'—CH_3), 7.25–8.32 (m, 20H, C_2, C_3, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{16}, C_2', C_3', C_5', C_6', C_2''—C_8'' and C_6—NH), 8.87 (d, 1H, C_1—H, J = 8.00 *Hz*), 8.95 (d, 1H, C_{16}—H, J = 7.50 *Hz*), 9.27 (d, 1H, C_4—H J = 8.00 *Hz*), 9.51 (d, 1H, C_{15}—H, J = 8.00 *Hz*), 9.87 (d, 1H, C_{13}—H, J = 7.50 *Hz*); ^{13}C NMR (125 M*Hz*, $CDCl_3$) (ppm) δ_C: 22.56 (C_4'—CH_3), 114.27, 119.33, 120.57, 121.07, 121.86, 122.11, 122.96, 123.41, 124.25, 125.18, 126.01, 126.59, 126.68, 126.92, 127.22, 127.34, 127.41, 127.50, 127.63, 127.77, 127.89, 128.35 (2C), 128.90 (2C), 129.06, 129.42, 130.24, 130.86, 131.57, 132.69, 133.48, 134.03, 134.85, 136.13, 140.72, 144.55, 147.71, 149.90, 158.07; MS (EI) m/z (%) 561 (M^+, 75); Anal. Calcd. for $C_{41}H_{27}N_3$ (561): C, 87.67; H, 4.85; N, 7.48%; Found: C, 87.61; H, 4.90; N, 7.51%.

7-Methyl-N-(naphth-1″-yl)dinaphtho[1,2-b:1′,2′-h][1,6]naphthyridin-6-amine (15)

Orange solid; Mp.: 241–243 °C; Yield: 57%; IR (KBr, cm^{-1}) ν_{max}: 3098 (NH), 1635, 1611 (C═N); ^1H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 3.26 (s, 3H, C_7—CH_3), 7.39–8.29 (m, 15H, C_2, C_3, C_8, C_9, C_{10}, C_{11}, C_{12}, C_2''—C_8'' and C_6—NH), 8.76 (d, 1H, C_1—H, J = 8.00 *Hz*), 8.95 (d, 1H, C_{16}—H, J = 7.50 *Hz*), 9.30 (d, 1H, C_4—H J = 8.00 *Hz*), 9.55 (d, 1H, C_{15}—H, J = 8.00 *Hz*), 9.85 (d, 1H, C_{13}—H, J = 7.50 *Hz*); ^{13}C NMR (125 M*Hz*, $CDCl_3$) (ppm) δ_C: 26.6 (C_7—CH_3), 113.89, 118.61, 120.09, 121.11, 121.72, 122.26, 122.73, 123.50, 124.39, 125.24, 126.11, 126.47, 126.59, 126.89, 127.14, 127.26, 127.31, 127.60, 127.71, 127.82, 127.99, 129.00, 129.37, 130.51, 131.66, 132.73, 133.53, 134.16, 135.24, 141.03, 144.62, 147.31, 148.76, 157.12; MS (EI) m/z (%) 485 (M^+, 79); Anal. Calcd. for $C_{35}H_{23}N_3$ (485): C, 86.57; H, 4.77; N, 8.65%; Found: C, 86.61; H, 4.84; N, 8.59%.

7-(4′-Methoxyphenyl)-N-(naphth-1″-yl)dinaphtho[1,2-b:1′,2′-h][1,6]naphthyridin-6-amine (16)

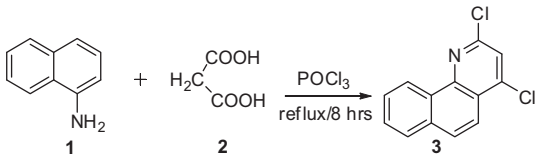
Orange prisms; Mp.: 271–273 °C; Yield: 61%; IR (KBr, cm^{-1}) ν_{max}: 3123 (NH), 1617, 1581(C═N); ^1H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 3.81 (s, 3H, C_4'—OCH_3), 7.27–8.23 (m, 19H, C_2, C_3, C_8, C_9, C_{10}, C_{11}, C_{12}, C_2', C_3', C_5', C_6', C_2''—C_8'' and C_6—NH), 8.85 (d, 1H, C_1—H, J = 8.50 *Hz*), 8.98 (d, 1H, C_{16}—H, J = 8.00 *Hz*), 9.33 (d, 1H, C_4—H J = 8.00 *Hz*), 9.49 (d, 1H, C_{15}—H, J = 8.50 *Hz*), 9.90 (d, 1H, C_{13}—H, J = 8.00 *Hz*); ^{13}C NMR (125 M*Hz*, $CDCl_3$) (ppm) δ_C: 55.99 (C_4'—OCH_3), 113.94, 119.45, 120.66, 121.12, 121.70, 122.02, 122.76, 123.53, 124.44, 125.26, 126.18, 126.47, 126.71, 126.88, 127.30, 127.42, 127.53, 127.64, 127.76, 127.85, 127.91, 128.45 (2C), 128.86 (2C), 129.19, 129.50, 130.42, 130.77, 131.65, 132.52, 133.64, 134.41, 134.67, 135.28, 141.25, 143.48, 146.17, 149.56, 157.71; MS (EI) m/z (%) 577 (M^+, 91); Anal. Calcd. for $C_{41}H_{27}N_3O$ (577): C, 85.25; H, 4.71; N, 7.27%; Found: C, 85.31; H, 4.77; N, 7.20%.

7-(4′-Chlorophenyl)-N-(naphth-1″-yl)dinaphtho[1,2-b:1′,2′-h][1,6]naphthyridin-6-amine (17)

Orange prisms; Mp.: 255–257 °C; Yield: 69%; IR (KBr, cm^{-1}) ν_{max}: 3134(NH), 1609, 1590(C═N); ^1H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 7.30–8.13 (m, 19H, C_2, C_3, C_8, C_9, C_{10}, C_{11}, C_{12}, C_2', C_3', C_5', C_6', C_2''—C_8'' and C_6—NH), 8.71 (d, 1H, C_1—H, J = 7.50 *Hz*), 8.96 (d, 1H, C_{16}—H, J = 8.50 *Hz*), 9.38 (d, 1H, C_4—H J = 9.00 *Hz*), 9.59 (d, 1H, C_{15}—H, J = 8.00 *Hz*), 9.87 (d, 1H, C_{13}—H, J = 8.50 *Hz*); ^{13}C NMR (125 M*Hz*, $CDCl_3$) (ppm) δ_C: 114.32, 118.90, 120.46, 121.00, 121.51, 122.31, 122.78, 123.55, 124.39, 125.30, 126.14, 126.60, 126.76, 126.81, 127.19, 127.28, 127.37, 127.47, 127.56, 127.66, 127.75, 128.40 (2C), 128.87 (2C), 129.19, 129.37, 130.46, 130.68, 131.94, 132.75, 133.71, 134.42, 134.73, 135.28, 140.44, 145.16, 148.54, 149.70, 158.24; MS (EI) m/z (%) 581 (M^+, 81), 583 (M+2, 31); Anal. Calcd. For $C_{40}H_{24}ClN_3$ (581): C, 82.53; H, 4.16; N, 7.22%; Found: C, 82.59; H, 4.09; N, 7.160%.

N-(Naphth-1″-yl)-7-(4′-nitrophenyl)dinaphtho[1,2-b:1′,2′-h][1,6]naphthyridin-6-amine (18)

Pale orange prisms; Mp.: 251–253 °C; Yield: 57%; IR (KBr, cm^{-1}) ν_{max}: 3201, 1644, 1571; ^1H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 7.32–8.27 (m, 19H, C_2, C_3, C_8, C_9, C_{10}, C_{11}, C_{12}, C_2', C_3', C_5', C_6', C_2''—C_8'' and C_6—NH), 8.84 (d, 1H, C_1—H, J = 8.00 *Hz*), 8.96 (d, 1H, C_{16}—H, J = 9.00 *Hz*), 9.31 (d, 1H, C_4—H J = 8.00 *Hz*), 9.58 (d, 1H, C_{15}—H, J = 8.50 *Hz*), 9.91 (d, 1H, C_{13}—H, J = 8.00 *Hz*); ^{13}C NMR (125 M*Hz*, $CDCl_3$) (ppm) δ_C: 113.94, 118.80, 120.76, 121.33, 121.90, 122.27, 122.81, 123.65, 124.84, 125.37, 126.25, 126.48, 126.70, 126.95, 127.01, 127.26, 127.39, 127.47, 127.56, 127.64,



Scheme 1 Synthesis of 2,4-dichlorobenzo[*h*]quinoline (3).

127.99, 128.51 (2C), 128.99 (2C), 129.13, 129.59, 130.42, 130.68, 131.77, 132.36, 133.84, 134.22, 134.49, 135.30, 140.57, 143.67, 146.85, 148.70, 159.19; MS (EI) *m*/*z* (%) 592 (M^+, 90); Anal. Calcd. for $C_{40}H_{24}N_4O_2$ (592): C, 81.07; H, 4.08; N, 9.45%; Found: C, 81.14; H, 4.03; N, 9.51%.

N-(Naphth-1″-yl)-7-(pyridin-3′-yl)dinaphtho[1,2-b:1′,2′-h][1,6]naphthyridin-6-amine (19)

Orange solid; Mp.: 233–235 °C; Yield: 41%; IR (KBr, cm^{-1}) ν_{max}: 3086 (NH), 1625, 1603 (C═N); ^{1}H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 7.39–8.29 (m, 16H, C_2, C_3, C_8, C_9, C_{10}, C_{11}, C_{12}, C_5', C_2''—C_8'' and C_6—NH), 8.41 (d, 1H, C_4'—H, J = 4.50 *Hz*), 8.59 (d, 1H, C_6'—H, J = 5.50 *Hz*), 8.77 (s, 1H, C_2'—H), 8.81 (d, 1H, C_1—H, J = 8.50 *Hz*), 8.99 (d, 1H, C_{16}—H, J = 7.50 *Hz*), 9.27 (d, 1H, C_4—H J = 8.50 *Hz*), 9.49 (d, 1H, C_{15}—H, J = 9.00 *Hz*), 9.78 (d, 1H, C_{13}—H, J = 7.50 *Hz*); ^{13}C NMR (125 M*Hz*, $CDCl_3$) (ppm) δ_C: 114.65, 117.43, 129.99, 120.82, 121.09, 122.04, 122.59, 123.00, 124.71, 125.69, 126.26, 126.49, 126.60, 126.98, 127.09, 127.31, 127.42, 127.56, 127.76, 127.89, 127.95, 128.34, 129.13, 129.59, 130.66, 131.73, 132.65, 133.38, 133.72, 134.27, 135.54, 136.09, 141.36, 144.71, 145.54, 147.37, 148.82, 149.47, 156.90; MS (EI) *m*/*z* (%) 548 (M^+, 100); Anal. Calcd. for $C_{39}H_{24}N_4$ (548): C, 85.38; H, 4.41; N, 10.21%; Found: C, 85.42; H, 4.40; N, 10.18%.

N-(Naphth-1″-yl)-7-(thiophen-2′-yl)dinaphtho[1,2-b:1′,2′-h][1,6]naphthyridin-6-amine (20)

Orange solid; Mp.: 228–230 °C; Yield: 33%; IR (KBr, cm^{-1}) ν_{max}: 3077 (NH), 1643, 1621 (C═N); ^{1}H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 7.22 (t, 1H, C_4'—H, J = 5.50 *Hz*), 7.32–8.34 (m, 18H, C_2, C_3, C_8, C_9, C_{10}, C_{11}, C_{12}, C_3', C_5', C_2''—C_8'' and C_6—NH), 8.46 (d, 1H, C_4'—H, J = 4.50 *Hz*), 8.66 (d, 1H, C_6'—H, J = 5.50 *Hz*), 8.80 (s, 1H, C_2'—H), 8.92 (d, 1H, C_1—H, J = 8.50 *Hz*), 9.17 (d, 1H, C_{16}—H, J = 7.50 *Hz*), 9.31 (d, 1H, C_4—H J = 8.50 *Hz*), 9.54 (d, 1H, C_{15}—H, J = 9.00 *Hz*), 9.74 (d, 1H, C_{13}—H, J = 7.50 *Hz*); MS (EI) *m*/*z* (%) 553 (M^+, 100); Anal. Calcd. for $C_{38}H_{23}N_3S$ (553): C, 82.43; H, 4.19; N, 7.59; S, 5.79%; Found: C, 82.38; H, 4.21; N, 7.60; S, 5.81%.

Results and discussion

Synthesis of dinaphtho[b,g][1,8]naphthyridines

The required precursor for the synthesis of substituted angular and linear dinaphthonaphthyridines, 2,4-dichlorobenzo[*h*]quinoline (**3**) was obtained from naphth-1-ylamine **1** and malonic acid (**2**) under reflux in $POCl_3$ for 8 h as depicted in Scheme 1.

Compound **3** was then reacted with naphth-1-ylamine **1** in the presence of CuI catalyst, afforded **4** and **5**. The reaction conditions and the yields of the two compounds obtained were depicted in Table 1. In the absence of catalyst the reaction in methanol gave 31% of compound 4 and 28% of compound **5** in 8 h (entry **1** in Table 1), whereas by using 10 mol% of CuI as catalyst reduces the reaction time from 8 h to 2 h and increased the yield of the products marginally (entry **2** in Table 1). When the solvent was changed from methanol to ethanol, we obtained the compounds **4** & **5** in 40% and 38% respectively in 2 h using 10 mol% of CuI (entry **4** in Table 1). To our surprise, when the reaction was performed in DMSO as solvent (using 10 mol% of CuI) within 0.5 h we obtained 57% and 31% of compounds **4** & **5** (entry **6** in Table 1). Interestingly, when the reaction was allowed for another half an hour (entry **7** in Table 1) product **5** was obtained as a major product (51%) along with 45% yield of compound **4.** It is noteworthy to mention here that, reaction in DMSO in the absence of catalyst, (entry **8** in Table 1) even after 8 h resulted in 30% and 27% of the compounds **4** and **5**. In the presence of catalyst the reaction time came down from 8 h to 0.5 h with the combined (**4** + **5**) yield of 96%. But in the absence of catalyst, the combined yield of **4** & **5** was 57%. Reduction of time and substantial increase in yield clearly indicate the effect of CuI catalyst in the reaction.

It is documented that in S_NAr, the reaction rate gets accelerated by activating the amine through hydrogen bonding when the reaction was performed in polar aprotic solvent like DMSO [29,30]. Hence it is anticipated that the second step (**I** to **II** in Scheme 3) was accelerated in the presence of DMSO and hence the possible explanation for the increased yield when the reaction was performed in DMSO/CuI (entry **7** in Table 1). The present finding showed that the combination

Table 1 The reaction conditions and the yields of the two compounds **4** and **5.**

Entry	Catalyst[a]	Solvent	*T* (°C)	*t* (h)	Yield (%) of the products	
					4	5
1	–	MeOH	Reflux	8	31	28
2	CuI	MeOH	Reflux	2	37	32
3	–	Ethanol	Reflux	8	31	29
4	CuI	Ethanol	Reflux	2	40	38
5	CuI	DMF	Reflux	8	NR	NR
6	CuI	DMSO	120	0.5	57	31
7	CuI	DMSO	120	1	45	51
8	–	DMSO	120	8	30	27

[a] 10 mol% of catalyst.

Table 2 Synthesis and reaction conditions of compound **6–20.**

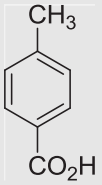
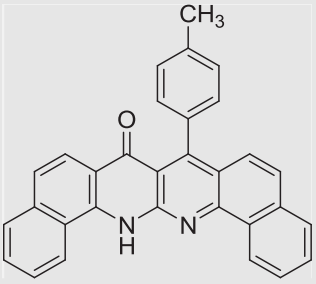
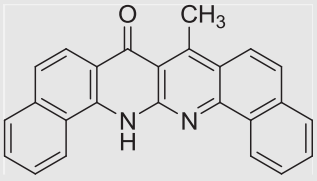
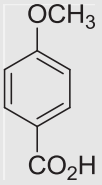
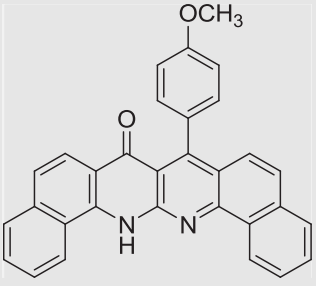
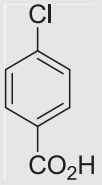
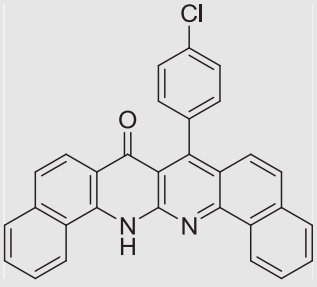
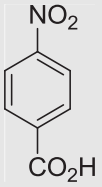
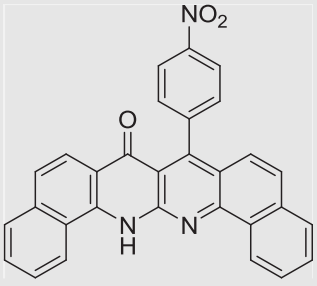
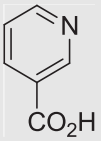
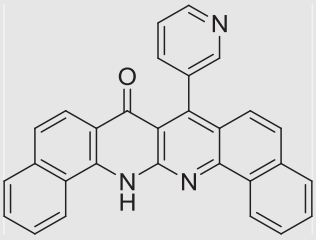
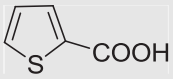
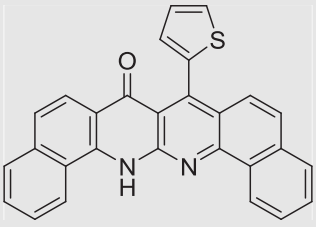
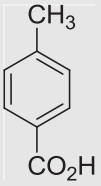
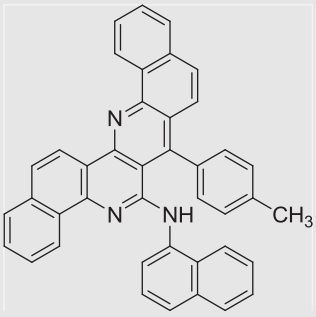
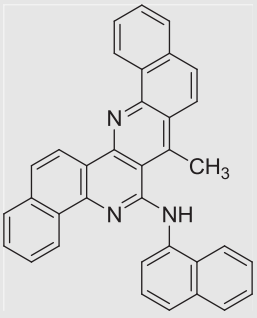
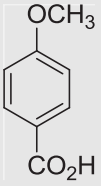
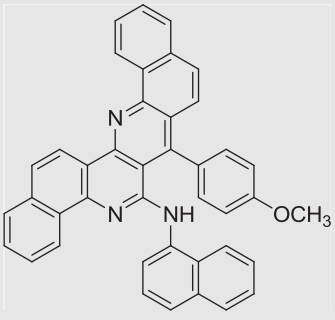
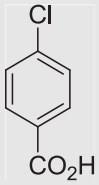
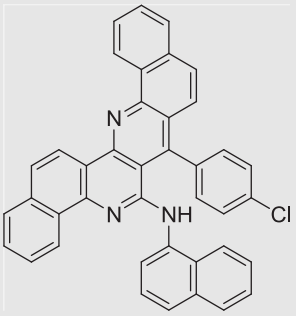
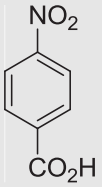
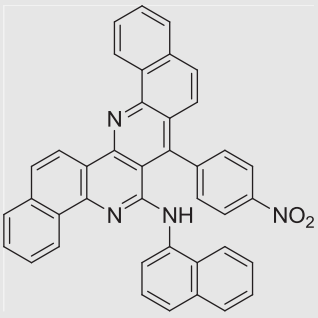
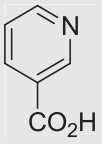
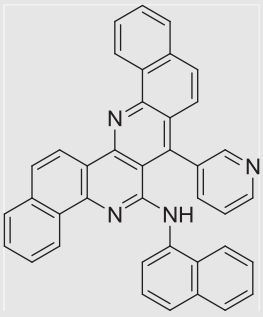
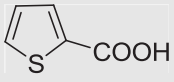
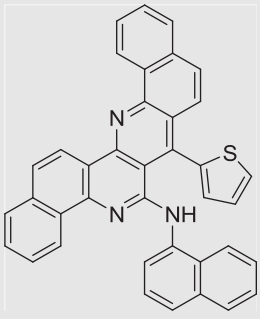
Compounds	Acid	Products[a]	*t* (h)	*T* (°C)
6			3.5	230
7	CH_3COOH		4	230
8			3	230
9			3	230
10			2.5	190

Table 2 (Continued)

Compounds	Acid	Products[a]	*t* (h)	*T* (°C)
11			1	160
12			1	140
13			0.5	rt
15	CH_3COOH		1	rt
16			1	rt

(*continued on next page*)

Table 2 (Continued)

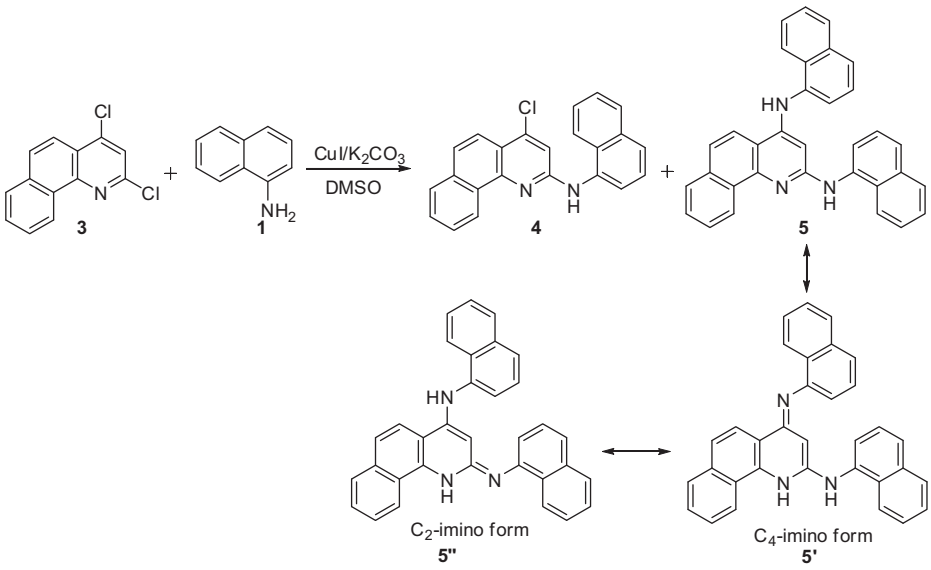
Compounds	Acid	Products[a]	*t* (h)	*T* (°C)
17			1	rt
18			0.5	rt
19			0.5	90
20			0.5	90

rt – Room temperature.

[a] The products were characterised by IR, NMR, MASS and elemental analysis (refer experimental section).

of DMSO and CuI turns out to be the best among the combination screened.

IR spectrum of the first eluted product showed stretching vibrations at 3066 cm^{-1} and 1636 cm^{-1} due to NH and C═N groups. In its ^1H NMR spectrum, C_4─NH appeared as a broad singlet at δ 7.02, C_3─H appeared as a singlet at δ 7.17 and all the aromatic protons appeared between the region δ 7.54 and 9.20. Its ^{13}C NMR spectrum showed the presence of



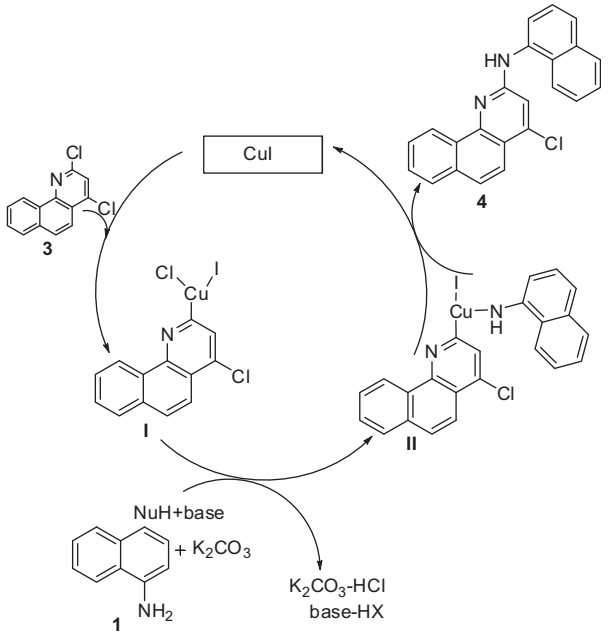
Scheme 2 Synthesis of benzoquinolin-amines (4) and (5).

twenty-three carbons and its mass spectrum showed the molecular ion peak at m/z 354. On the basis of the reactivity of chlorine atom in the 2 and 4 positions of the 2,4-dichloroquinoline [31,32], the first compound was assigned as 2-substituted product namely, 4-chloro-*N*-(naphth-1-yl)benzo[*h*]quinolin-2-amine (**4**).

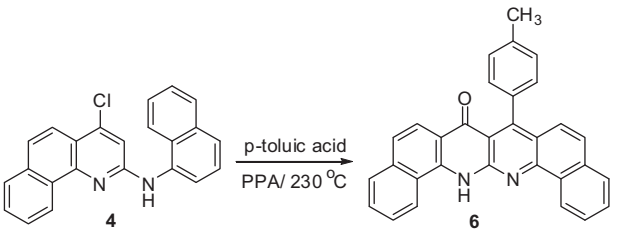
The second product showed stretching frequencies at 3136 cm^{-1}, 3054 cm^{-1} and 1629 cm^{-1} in the IR spectrum due to two NH and C═N functional groups. In its ^{1}H NMR spectrum C_3—H appeared as a singlet at δ 6.51, all the aromatic protons appeared between the region δ 7.01 and 9.38. Three broad singlets appeared at δ 10.74, 11.45 and 14.13 were assigned for C_4—NH, C_2—NH and N_1—H, respectively. Its ^{13}C NMR spectrum showed the presence of 33 carbons. All the aforesaid data attest the obtained product as 2,4-disubstituted product, namely, N^2,N^4-di(naphth-1-yl)benzo[*h*]quinoline-2,4-diamine (**5**) which was found to be in resonance with the two imino forms on the basis of its IR and ^{1}H NMR spectra (Scheme 2).

The proposed plausible mechanism for the formation of compound **4** is as follows. The first step involves the oxidative addition of compound **3** with CuI to form the intermediate **I**. Then the elimination of H and Cl elements between the intermediate **I** and compound **1** leads to the formation of intermediate **II**. This further undergoes reductive elimination to give compound **4** and regenerated the catalyst. Compound **4** undergoes a similar catalytic cycle to afford compound **5** (Scheme 3).

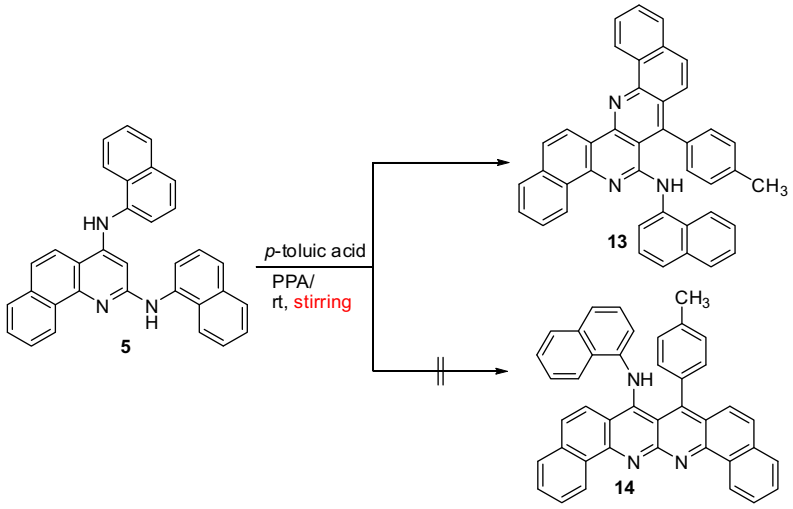
In order to get the target linear dinaphthonaphthyridine, 4-chloro-*N*-(naphth-1-yl)benzo[*h*] quinolin-2-amine (**4**) was reacted with *p*-toluic acid in the presence of poly phosphoric acid at 230 °C which afforded a single product. The IR spectrum showed stretching frequencies at 3144 cm^{-1}, 1680 cm^{-1} and 1592 cm^{-1} revealed the presence of NH, C═O and C═N functional groups respectively. In its ^{1}H NMR spectrum a singlet at δ 2.50 was due to the presence of C_4'—CH_3 proton. Rest of the aromatic protons resonated in the region between δ 7.35 and 9.64 including C_{16}—NH. Its ^{13}C NMR spectrum showed the peak at δ 178.79 due to the presence of C═O group. The molecular formula of the product was found to be $C_{31}H_{20}N_2O$ calculated from elemental analysis. From the aforementioned spectral and analytical information, the structure of compound has been assigned as 8-(4′-methyl-



Scheme 3 Mechanism for the formation of compound (4).



Scheme 4 Synthesis of dinaphtho[*b*,*g*][1,8]naphthyridine (6).



Scheme 5 Synthesis of dinaphtho[*b,h*][1,6]naphthyridine (13).

phenyl)-dinaphtho[1,2-*b*:2′,1′-*g*][1,8]naphthyridin-7(16*H*)-one (**6**) (Scheme 4).

To explore the generality of the reaction, we have also tried the same reaction with other carboxylic acids like acetic acid, *p*-methoxy benzoic acid, *p*-chloro benzoic acid, *p*-nitro benzoic acid, pyridine-3-carboxylic acid and thiophen-2-carboxylic acid to get the corresponding linear 8-substituted dinaphtho[1,2-*b*:2′,1′-*g*][1,8]naphthyridin-7(16*H*)-one (**7–12**) Table 2. The structures of all compounds were confirmed by elemental and spectral analysis (refer experimental section and supporting data).

Synthesis of dinaphtho[b,h][1,6]naphthyridines

Next, in order to construct angular naphthyridines N^2,N^4-di(naphth-1-yl) benzo[*h*]quinoline-2,4-diamine (**5**) was reacted with *p*-toluic acid in the presence of poly phosphoric acid as catalyst at room temperature (stirring for half an hour). The IR spectrum showed stretching frequencies at 3048 cm^{-1}, 1655 cm^{-1} and 1601 cm^{-1} which were due to the presence of NH and two C=N functional groups respectively. In its ^1H NMR spectrum, methyl protons appeared as a singlet at δ 2.48 for C_4'—CH_3. All the aromatic protons appeared between the region δ 7.25 and 8.95 except for C_4—H, C_{15}—H and C_{13}—H which appeared as three doublets at δ 9.27 (J = 8.00 *Hz*, J = 1.50 *Hz*), 9.51 (J = 8.00 *Hz*) and 9.87 (J = 7.50 *Hz*) respectively. The ^{13}C NMR spectrum showed the presence of 41 carbons. All the spectral data revealed the formation of the compound **13**. Here the chance of getting the linear naphthyridine **14** has not been observed and the only formed product was assigned as the thermodynamically more stable angular isomer namely, *N*-(naphth-1″-yl)-7-(4′-methylphenyl)-dinaphtho[1,2-*b*:1′,2′-*h*][1,6]naphthyridin-6-amine **13**, on the basis of its higher melting point and literature data [33,34] (Scheme 5).

Encouraged by these results, this procedure was then further evaluated for its scope and general applicability. A similar set of reaction was extended to **5** with acetic acid, *p*-methoxy benzoic acid, *p*-chloro benzoic acid, *p*-nitro benzoic, pyridine-3-carboxylic acid and thiophen-2-carboxylic acid in the presence of polyphosphoric acid to afford the respective 7-substituted dinaphtho[1,2-*b*:1′,2′-*h*][1,6]naphthyridin-6-amine (**15–20**) as a single compound (Table 2). Very interestingly electron withdrawing group substituted benzoic acid undergoes cyclisation in shorter reaction time when compared to electron donating group substituted benzoic acid. The structures of all compounds were confirmed by elemental and spectral analysis (refer experimental section and supporting data).

Conclusions

A useful method for the synthesis of intermediates **4** and **5** using 10 mol% of CuI catalyst was developed. Both the intermediates undergo facile cyclisation under poly phosphoric acid condition with aliphatic and various aromatic/heteroaromatic carboxylic acids afforded angular and linear dinaphthonaphthyridines. This method has the potential to create new libraries of substituted dinaphthonaphthyridines which may find applications in medicinal chemistry.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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