Synthesis of Benzo[3,4-*h*][1,6]naphthyridines *via* Friedländer Condensation with Active Methylenes

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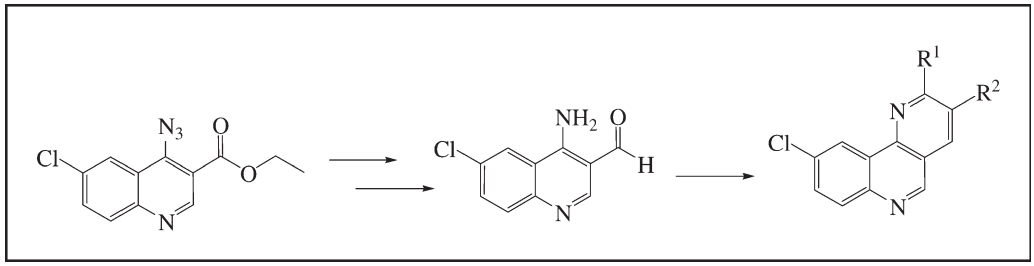

Novel 4-amino-6-chloroquinoline-3-carbaldehyde has been synthesized by synchronous reduction by lithium aluminiumhydride and finally oxidation with MnO_2. Friedländer condensation of it with reactive methylenes furnished novel benzo[3,4-*h*][1,6]naphthyridine derivatives.

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INTRODUCTION

The construction of ring structures from orthoaminoaldehyde as a starting material has wide applicability for the annulation of heterocyclic systems. This construction method predominates the direction of ring growth (angular vs. linear) and generally permits the direct and regiospecific introduction of functional groups and/or substituents in the newly formed heterocyclic ring. Among numerous possibilities for ortho joined functionalities those containing carbon and nitrogen are of particular interest, because the numerous combinations of their different oxidation states and easy accessibility of simple derivatives provide them with exceptional versatility in hetero annulation reaction. From literature, it was noted that o-aminobenzaldehyde, the first and best known member of this class of compounds has been utilized for synthesis of various heterocycles [1–17]. Annulation reaction of heterocyclic aminoaldehydes provide a synthetic entry into heterocyclic systems fused to pyridine [18–21], pyrazole [22–25], and quinoline nucleus [26,27]. The functionalized quinolines and their benzo/hetero-fused analogous present in numerous natural products along with the wide spectrum of physiological activities [28]. In our earlier communication, we have reported the synthetic utility of heterocyclic o-aminoaldehyde in which annulation of heterocyclic system on to pyrazole and pyrazolopyridine nuclei was performed [29–31].

These literature reports and our continuous interest in this area prompted us to report the novel synthesis of orthoaminoformylquinoline and study of Friedländer condensation of it with various reactive methylenes. In this communication we have synthesized benzo[3,4-*h*][1,6]naphthyridines, which may have potential biological activities such as antimalarials [32], antagonists of 5-HT_4 receptor [33], reported earlier.

Godard and Queguiner reported synthesis of 4-aminoquinoline-3-carbaldehyde by following sequence of reaction [34]. In their sequence, the anhydride **I** was treated with NH_3 to furnish carboxamide **II**. The alkaline hydrolysis of **II** with KOH yielded aminoacid **III**, which was esterified with MeOH/ H_2SO_4 to yield orthoaminoester **IV**. The lithium aluminiumhydride reduction of **IV** yielded primary alcohol **V** and finally oxidation with MnO_2 furnished a orthoaminoaldehyde **1a** (Fig. 1).

We have adopted different strategy for synthesis of 4-amino-6-chloroquinoline-3-carbaldehyde **1b** (heterocyclic orthoaminoaldehyde). Chloro-ester **A** was synthesized in the beginning by reported method [35], starting with p-chloroaniline. Then SN^2 displacement of chloro functionality at position 4 was achieved with NaN_3 in DMF at room temperature to yield **B** quantitatively. The synchronous reduction of both azido and ester group in **B** by lithium aluminiumhydride in dry THF at 0–5°C yielded the ortho amino alcohol **C** in 79% yield. Finally, oxidation of **C** with manganese (IV) oxide, without protecting amino group [34,36], in dichloromethane at room temperature furnish desire target molecule 4-amino-6-chloroquinoline-3-carbaldehyde **1b** in 71% yield. In this step, expected N-oxide was not formed as revealed by spectral and analytical data. The

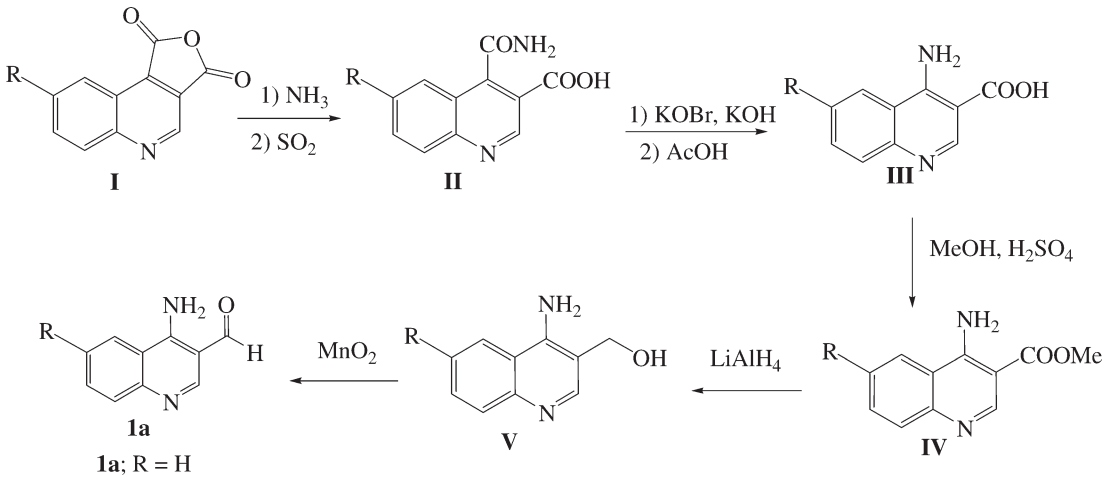


Figure 1. Godard method for synthesis of 4-aminoquinoline-3-carbaldehyde.

intermediates **B**, **C**, and **1b** were characterized by IR, ^{1}H, and ^{13}C NMR, mass spectroscopy and elemental analysis (Scheme 1).

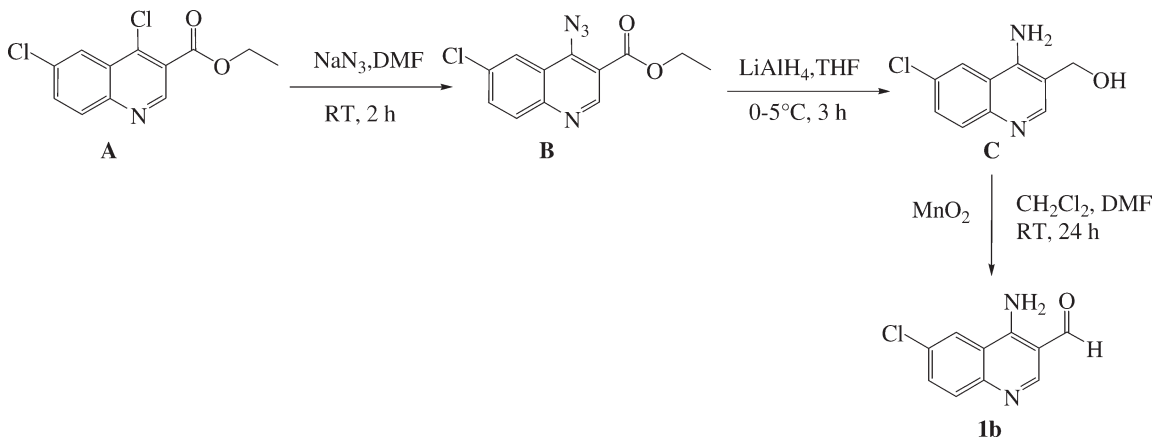
In our approach, the yields of intermediates **B**, **C**, and **1b** are excellent. This method is versatile and scalable. Compound **1b** in hand reacted with alkyl and/or aryl ketones **2a–k** in DMF at reflux using potassium hydroxide (KOH) as a base to yield benzo[*h*] naphthyridines **3a–k** in 68–80% yield. Analogously **1b** when reacted with unsymmetric dialkyl ketones **4a–b**, instead of expected mixture of two isomer [29], only single isomer **5a–b** were obtained in good yield. However, reaction of **1b** with malononitrile **6** under similar reaction condition was unsuccessful. This condensation was achieved by refluxing a mixture of **1b**, malononitrile and piperidine in ethanol to yield benzo naphthyridine **7**, having nitrile and amino functionality ortho to each other, in 78% yield (Scheme 2).

Compounds **3**, **5**, and **7** were characterized by IR, ^{1}H, and ^{13}C NMR, mass spectroscopy and elemental analysis.

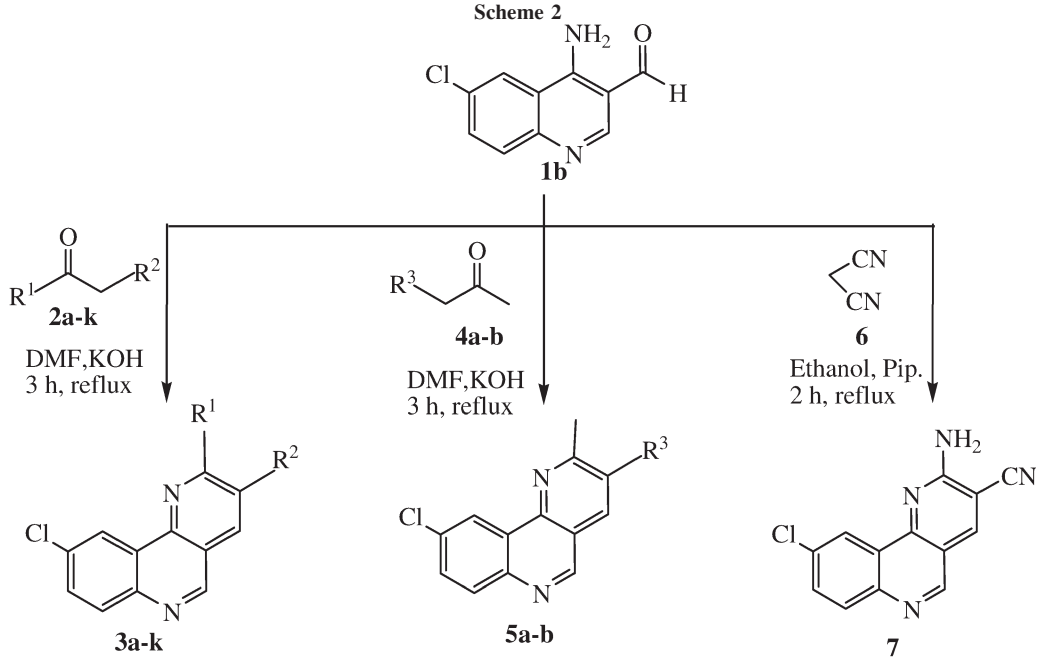
The Friedländer condensation can be catalyzed by various reagents [37]. When we extend our synthetic investigation to CH-acidic compounds such as benzoylacetonitrile **8a–d**, β-ketoester **10a**, β-ketoamide **10b**, and diethyl malonate **12**, we found that already piperidine as base was sufficient strong to catalyze the condensation reaction. Thus, cyclocondensation of **1b** with **8a–d**, **10a–b**, and **12**, afforded 9-Chloro-2-arylbenzo[*h*][1,6]-naphthyridine-3-carbonitriles **9a–d**, Ethyl 9-Chloro-2-methylbenzo[*h*][1,6]naphthyridine-3-carboxylate **11a**, 9-Chloro-2-methyl-N-phenylbenzo[*h*][1,6]naphthyridine-3-carboxamide **11b** and Ethyl 9-Chloro-1,2-dihydro-2-oxobenzo[h][1,6]naphthyridine-3-carboxylate **13**, respectively, in 75–85% yield (Scheme 3). Compounds **9**, **11**, and **13** were characterized by IR, ^{1}H, and ^{13}C NMR, mass spectroscopy and elemental analysis.

In conclusion herein, we report novel and scalable route towards orthoaminoformylquinoline **1b**. A series of novel benzo[3,4-*h*][1,6]naphthyridines and benzo[3,4-

Scheme 1



Scheme 2



2,3	R^1	R^2
a	CH_3	H
b	C_6H_5	H
c	C_6H_5	CH_3
d	2-Cl-C_6H_4	H
e	4-Cl-C_6H_4	H
f	4-F-C_6H_4	H
g	4-Br-C_6H_4	H
h	3,4-di-OMe-C_6H_3	H
i	2,6-di-OMe-C_6H_3	H
j	4-Me-C_6H_4	H
k	3,5-di-CF_3-C_6H_3	H

5	R^3
a	CH_3
b	C_6H_5

h][1,6]naphthyridone was synthesized by Friedländer condensation reaction of 4-amino-6-chloroquinoline-3-carbaldehyde **1b** with reactive methylene compounds.

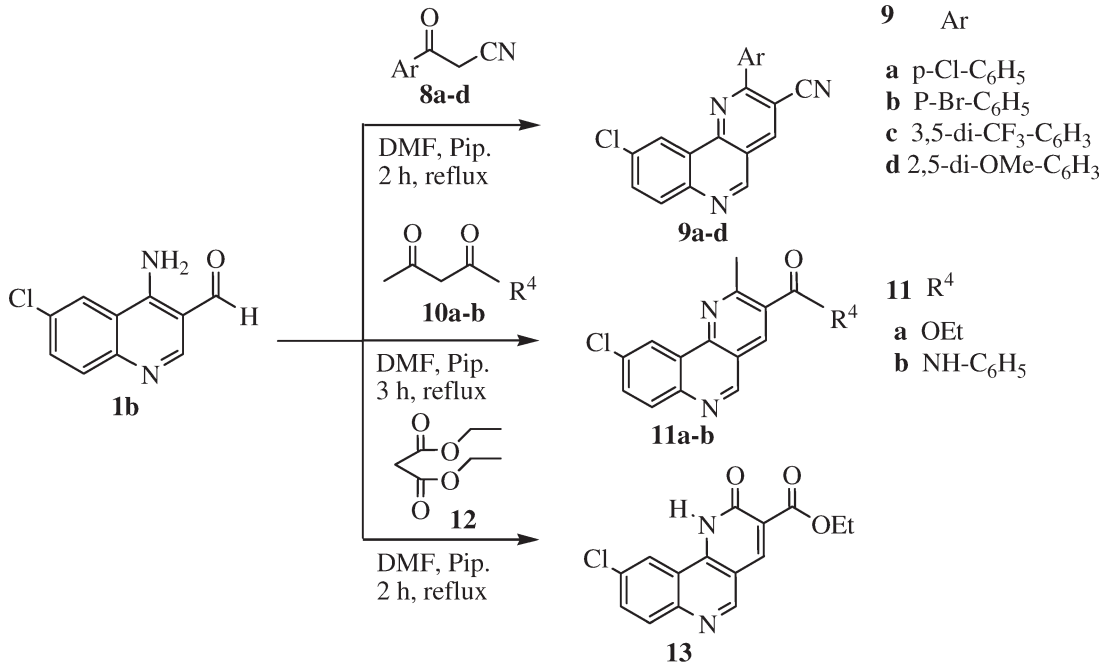
EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus, Mod. MFB595 in open capillary tubes and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were measured on a Varian XL-300 spectrometer using tetramethylsilane as the internal standard. IR spectra were recorded using a Shimadzu IR-408, a Shimadzu FTIR instrument with potassium bromide discs. Mass spectrum was recorded on Shimadzu GC-MS QP mass spectrometer with an ionization potential of 70 eV. Elemental analyses were obtained on a Hosli CH-Analyzer and are within ±0.3 of the theoretical percentage.

All reactions were monitored by thin layer chromatography on 0.2 mm silica gel F-254 (Merck) plates using UV light (254 and 366 nm) for detection. Common reagents were either commercially available and were used without further purification or prepared by standard literature procedures.

Ethyl 4-Azido-6-chloroquinoline-3-carboxylate (B). A mixture of **A** [35] (0.246 g, 1 mmol) and sodium azide (0.065 g, 1 mmol) in DMF (2 mL) was stirred at RT for 2 h. After completion of the reaction (TLC check), the solvent was distilled out by vacuum distillation. The reaction mass was quenched in ice cold water (10 mL) and extracted with three fraction of ethyl acetate (12 mL × 3). The organic layer was dried over sodium sulphate and solvent was evaporated under reduced pressure. The crude solid was washed with methanol, filtered, and dried to furnish **B** as colorless solid; (0.182 g, 74%), mp 292–293°C; ir (potassium bromide): 3086(w), 2920(m), 2134(m), 1770(s), 1563(s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (t, J = 6.9 Hz, 3H), 4.45 (q, J = 6.9 Hz, 2H), 7.73 (dd, J = 8.5, 2.2 Hz, 1H), 7.81 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.92 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.02, 60.3, 124.5, 128.6, 129.4, 131.7, 133.1, 133.9, 138.4, 146.2, 146.9, 166.2; ms: *m/z* (%) 276 (M^+,100), 278 (M+2, 32); Anal. Calcd. for $C_{12}H_9ClN_4O_2$ (276.68): C, 52.09; H, 3.28; N, 20.25. Found: C, 52.25; H, 3.37; N, 20.43.

Scheme 3



(4-Amino-6-chloroquinolin-3-yl)methanol (C). A solution of **B** (0.276 g, 1 mmol) in tetrahydrofuran (2 mL) was added slowly into the dispersed lithium aluminium hydride (0.144 g, 4 mmol) in tetrahydrofuran (2 mL) at 0–5°C, after addition, the reaction mass was allowed to stand at RT and further stirred for 3 h. After completion of reaction (TLC check), the reaction mass was quenched in saturated sodium sulphate solution (2–3 mL) at 0–5°C and extracted in three fraction of ethyl acetate (5 mL × 3). The combined organic layer was washed with water (5 mL × 3), then dried over anhydrous sodium sulphate, filtered, and the solvent was evaporated under reduced pressure, the crude solid was washed with methanol, filtered, dried under high vacuum, and recrystallized from ethanol: DMF (8:2) to give **C** as colorless solid; (0.218 g, 79%); mp 221–222°C; ir (potassium bromide): 3443(m), 3354(m), 3248(s), 2895(w), 1660(s), 1564(s), 1500(s) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.56 (d, J = 5.4 Hz, 2H, CH_2), 5.13 (t, J = 5.4 Hz, 1H, OH), 6.62 (s, 2H, NH_2), 7.55 (d, J = 9 Hz, 1H), 7.76 (d, J = 9 Hz, 1H), 8.36 (s, 1H), 8.37 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 56.3, 116.7, 119.4, 122.9, 129.7, 130.5, 131.1, 146.4, 149.2, 151.9; ms: *m/z* (%) 208 (M^+,100), 210 (M+2, 33); Anal. Calcd. For $C_{10}H_9ClN_2O$ (208.64): C, 57.57; H 4.35; N, 13.43. Found: C, 57.63; H, 4.46; N, 13.51.

4-Amino-6-chloroquinoline-3-carbaldehyde (1b). To the solution of **C** (0.208 g, 1 mmol) in dichloromethane (2 mL), manganese (IV) dioxide (0.170 g, 2 mmol) was added. The reaction mixture was stirred at 25°C for 24 h. After completion of the reaction (TLC check), the reaction mass was filtered through celite and solvent was evaporated under reduced pressure, the crude solid was washed with methanol, filtered, dried under high vacuum, and recrystallized from ethanol: DMF (6:4) to give **1b** as pale brown needles; (0.147 g, 71%); mp 319–320°C; ir (potassium bromide): 3323(m), 3093(m), 2926(m), 2783(w), 1714(s), 1657(s), 1589(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.77 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 8.7 Hz, 1H), 8.67 (s, 1H), 8.73 (s, 1H), 8.91 (s, 2H, NH_2), 9.96 (s, 1H, CHO); ^{13}C NMR (DMSO-d_6): δ 115.2, 121.5, 123.7, 130.7, 131.8, 133.0, 142.6, 145.3, 159.9, 193.0; ms: *m/z* (%) 206 (M^+, 100), 208 (M+2, 31); Anal. Calcd. For $C_{10}H_7ClN_2O$ (206.63): C, 58.13; H, 3.41; N, 13.56. Found. C, 58.23; H, 3.47; N, 13.62.

General procedure for the synthesis of compounds 3a–k. A mixture of **1b** (0.206 g, 1 mmol) and **2a–k** (1 mmol) in DMF with catalytic amount of KOH was heated under reflux for 3 h, after completion of the reaction (TLC check), solvent was evaporated under reduced pressure. The crude solid was washed with methanol, filtered, dried under high vacuum, and recrystallized from ethanol: DMF (7:3) to furnish compounds **3a–k** in 68–80% yield.

9-Chloro-2-methylbenzo[h][1,6]naphthyridine (3a). Pale yellow solid; (0.148 g, 72%); mp 282–283°C; ir (potassium bromide): 3111(w), 3040(w), 2833(m), 2830(m), 2905(m), 1671(s), 1659(w), 1561(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.47 (s, 3H), 7.73 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 8.54 (d, J = 8.4 Hz, 1H), 8.75 (d, J = 8.4 Hz, 1H), 9.24 (s, 1H), 9.33 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 24.2, 119.9, 121.4, 122.7, 125.3, 125.9, 130.1, 130.8, 131.1, 133.8, 135.3, 145.6, 156.2; ms: *m/z* (%) 228 (M^+, 100), 230 (M+2, 34); Anal. Calcd. For $C_{13}H_9ClN_2$ (228.66): C, 68.28; H, 3.97; N, 12.25. Found. C, 68.34; H, 4.1; N, 12.31.

9-Chloro-2-phenylbenzo[h][1,6]naphthyridine (3b). Colorless solid; (0.154 g, 75%); mp 298–299°C; ir (potassium bromide): 3022(w), 2979(m), 1668(m), 1639(w), 1567(m), 1559(m), 1518(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.66 (m, 3H, Ar—H), 7.81 (d, J = 8.1 Hz, 1H), 8.13 (d, J = 8.1 Hz, 1H), 8.46 (m, 3H), 8.71 (d, J = 8.4 Hz, 1H), 9.12 (s, 1H), 9.40 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 121.2, 123.9, 126.7 (2 C's), 128.0, 128.1, 128.3, 128.9 (2 C's), 130.0, 131.6, 132.7, 133.4, 136.1, 136.9, 144.7, 148.2, 154.3; ms: *m/z* (%) 290 (M^+, 100), 292 (M+2, 35); Anal. Calcd. For $C_{18}H_{11}ClN_2$ (290.75): C, 74.36; H, 3.81; N, 9.63. Found. C, 74.48; H, 3.79; N, 9.77.

9-Chloro-3-methyl-2-phenylbenzo[h][1,6]naphthyridine (3c). Pale yellow solid; (0.164 g, 80%); mp 294–295°C; ir (potassium bromide): 3093(w), 2973(w), 1643(s), 1631(m), 1612(m), 1582(m), 1567(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.31 (s, 3H), 7.22–7.56 (m, 5H), 7.84 (d, J = 7.4 Hz, 1H), 8.01 (d, J = 7.4 Hz, 1H), 8.37 (s, 1H), 8.82 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 14.5, 121.7, 124.0, 126.9, 128.6, 129.1, 129.7, 130.1, 130.3, 132.0, 132.4, 132.9, 133.1, 135.2, 135.3, 137.3, 146.6, 150.1, 160.8; ms: *m/z* (%) 304 (M^+, 100), 306 (M+2, 32); Anal. Calcd. For $C_{19}H_{13}ClN_2$ (304.77): C, 74.88; H, 4.30; N, 9.19. Found. C, 74.91; H, 4.43; N, 9.24.

9-Chloro-2-(2-chlorophenyl)benzo[h][1,6]naphthyridine (3d). Colorless solid; (0.140 g, 68%); mp 276–277°C; ir (potassium bromide): 2985(m), 2822(w), 2818(m), 1691(m), 1637(w), 1583(w), 1501(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.44 (m, 2H), 7.51 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H,), 8.12 (d, J = 7.5 Hz, 1H), 8.24 (d, J = 6.7 Hz, 1H), 8.42 (d, J = 6.7 Hz, 1H), 9.27 (s, 1H), 9.33 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 120.5, 123.3, 124.9, 126.8, 127.5, 127.9, 128.2, 129.1, 130.3, 131.1, 131.9, 132.4, 132.7, 134.0, 134.7, 145.1, 149.1, 152.7; ms: *m/z* (%) 324 (M^+, 100), 326 (M+2, 31), 328 (M+4, 18); Anal. Calcd. For $C_{18}H_{10}Cl_2N_2$ (325.19): C, 66.48; H, 3.10; N, 8.16. Found. C, 66.52; H, 3.19; N, 8.27.

9-Chloro-2-(4-chlorophenyl)benzo[h][1,6]naphthyridine (3e). Pale yellow solid; (0.142 g, 69%); mp 269–270°C; ir (potassium bromide): 3012(m), 2921(m), 2817(w), 1658(m), 1649(s), 1486(m), 1422(w), 1583(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.37 (d, J = 7.9 Hz, 2H), 7.91 (d, J = 8.3 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H), 8.36 (d, J = 7.2 Hz, 1H,), 8.52 (d, J = 7.9 Hz, 2H), 8.65 (d, J = 7.2 Hz, 1H), 9.00 (s, 1H), 9.24 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 118.3, 123.0, 127.2, 127.9, 128.9 (2 C's) 130.0, 130.7, 130.9, 131.2, 133.3, 134.1, 134.7, 143.8 (2 C's) 147.2, 154.0, 157.1; ms: *m/z* (%) 324 (M^+,100), 326 (M+2, 36), 328 (M+4, 13); Anal. Calcd. For $C_{18}H_{10}Cl_2N_2$ (325.19): C, 66.48; H, 3.10; N, 8.16. Found. C, 66.49; H, 3.21; N, 8.29.

9-Chloro-2-(4-fluorophenyl)benzo[h][1,6]naphthyridine (3f). Colorless solid; (0.150 g, 73%); mp 297–298°C; ir (potassium bromide): 2989(m), 2817(w), 1631(m), 1604(m), 1588(m), 1563(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.55 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 7.4 Hz, 1H), 7.93 (d, J = 7.4 Hz, 1H), 8.06 (d, J = 7.5 Hz, 1H), 8.19 (d, J = 7.5 Hz, 1H), 8.58 (d, J = 8.4 Hz, 2H), 8.90 (s, 1H), 9.26 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 113.4 (2 C's), 120.7, 122.9, 125.6, 125.8, 129.1(2 C's), 129.9, 131.1, 131.9, 132.0, 133.7, 135.1, 144.6, 147.9, 154.1, 159.3; ms: *m/z* (%) 308 (M^+, 100), 310 (M+2, 33); Anal. Calcd. For $C_{18}H_{10}ClFN_2$ (308.74): C, 70.03; H, 3.26; N, 9.07. Found. C, 70.11; H, 3.37; N, 9.19.

2-(4-Bromophenyl)-9-chlorobenzo[h][1,6]naphthyridine (3g). Pale yellow solid; (0.150 g, 73%); mp 267–268°C; ir (potassium bromide): 3005(w), 2918(m), 1645(m), 1623(w), 1522(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.25 (d, J = 7.5 Hz, 2H), 7.81 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.37 (d, J = 7.6 Hz, 1H,), 8.56 (d, J = 7.5 Hz, 2H), 8.53 (d, J = 7.6 Hz, 1H), 9.08 (s, 1H), 9.31 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 117.7, 123.5, 126.9, 128.0, 129.0 (2 C's) 131.0, 131.2, 131.3, 131.4, 134.0, 134.2, 134.6, 144 (2 C's) 147.0, 154.4, 159.8; ms: *m/z* (%) 368 (M^+, 78), 370 (M+2, 95), 372 (M+4, 19); Anal. Calcd. For $C_{18}H_{10}BrClN_2$ (369.64): C, 58.49; H, 2.73; N, 7.58. Found. C, 58.58; H, 2.75; N, 7.69.

9-Chloro-2-(3,4-dimethoxyphenyl)benzo[h][1,6]naphthyridine (3h). Pale yellow solid; (0.154 g, 75%); mp 294–295°C; ir (potassium bromide): 3018(m), 2963(w), 1683(w), 1669(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.67 (s, 6H), 7.06 (d, J = 7.5 Hz, 1H), 7.30 (dd, J = 7.2,2.2 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.35 (d, J = 7.4 Hz, 1H), 8.50 (d, J = 8.4 Hz, 1H), 8.75 (d, J = 7.4 Hz, 1H), 9.11 (s, 1H), 9.23 (s, 1H); ms: *m/z* (%) 350 (M^+, 100), 352 (M+2, 34); Anal. Calcd. For $C_{20}H_{15}ClN_2O_2$ (350.80): C, 68.48; H, 4.31; N, 7.99. Found. C, 68.53; H, 4.42; N, 8.1.

9-Chloro-2-(2,6-dimethoxyphenyl)benzo[h][1,6]naphthyridine (3i). Colorless solid; (0.158 g, 77%); mp 297–298°C; ir (potassium bromide): 2981(m), 2897(w), 1676(m), 1632(m), 1548(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.79 (s, 6H), 7.43 (m, 3H, Ar—H), 8.3 1(d, J = 8.2 Hz, 1H), 8.42 (d, J = 7.8 Hz, 1H), 8.45 (d, J = 8.2 Hz, 1H), 8.73 (d, J = 7.8 Hz, 1H), 9.10 (s, 1H), 9.17 (s, 1H); ms: *m/z* (%) 350 (M^+, 100), 352 (M+2, 36); Anal. Calcd. For $C_{20}H_{15}ClN_2O_2$ (350.80): C, 68.48; H, 4.31; N, 7.99. Found. C, 68.50; H, 4.37; N, 8.2.

9-Chloro-2-p-tolylbenzo[h][1,6]naphthyridine (3j). Colorless solid; (0.156 g, 76%); mp 297–298°C; ir (potassium bromide): 2981(m), 2978(w), 2896(m), 1635(m), 1618(m), 1512(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.43 (s, 3H, CH_3), 7.37 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 8.27 (d, J = 8.5 Hz, 1H), 8.44 (d, J = 8.2 Hz, 1H), 8.91 (s, 1H), 9.13 (s, 1H); ms: *m/z* (%) 304 (M^+, 100), 306 (M+2, 31); Anal. Calcd. For $C_{19}H_{13}ClN_2$ (304.77): C, 74.88; H, 4.30; N, 9.19. Found. C, 74.91; H, 4.33; N, 9.27.

2-(3,5-Bis(trifluoromethyl)phenyl)-9-chlorobenzo[h][1,6]-naphthyridine (3k). Colorless solid; (0.154 g, 75%); mp 283–284°C; ir (potassium bromide): 3012(m), 2937(m), 1683(w), 1662(s), 1544(m), 1537(w); ^1H NMR (DMSO-d_6): δ 7.87 (m, 1H), 8.16 (m, 2H), 8.65 (dd, J = 2.7,8.4 Hz, 1H), 8.80 (dd, J = 2.7,8.4 Hz,1H), 8.93 (s,2H), 9.01 (s, 1H), 9.44 (s, 1H); ms: m/z (%) 426 (M^+, 100), 428 (M+2, 33); Anal. Calcd. For $C_{20}H_9ClF_6N_2$ (426.74): C, 56.33; H, 2.11; N, 6.57. Found. C, 56.31; H, 2.17; N, 6.56.

General procedure for the synthesis of compounds 5a and b. A mixture of **1b** (0.206 g, 1 mmol) and corresponding ketones **4a–b** (1 mmol) in DMF with catalytic amount of KOH was heated under reflux for 3 h. After completion of the reaction (TLC check), solvent was evaporated under reduced pressure, the crude solid was washed with methanol, filtered, dried under high vacuum, and recrystallized from ethanol: DMF (6:4) to furnish **5a–b** in 76–79% yield.

9-Chloro-2,3-dimethylbenzo[h][1,6]naphthyridine (5a). Pale yellow solid; (0.160 g, 78%); mp 302–303°C; ir (potassium bromide): 3012(w), 2982(m), 2811(m), 1683(m), 1661(w), 1537(m), 1518(s) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.55 (s, 3H), 2.71 (s, 3H), 7.86 (d, J = 6.6 Hz, 1H), 8.10 (d, J = 6.6 Hz, 1H), 8.32 (s, 1H) 8.96 (s, 1H), 9.30 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 16.3, 18.1, 120.7, 126.6, 127.8, 130.1, 131.3, 132.6, 133.1, 133.2, 135.0, 145.7, 150.0, 159.1; ms: m/z (%) 242 (M^+, 100), 244 (M+2, 37); Anal. Calcd. For $C_{14}H_{11}ClN_2$ (242.70): C, 69.28; H, 4.57; N, 11.54. Found. C, 69.37; H, 4.58; N, 11.63.

9-Chloro-2-methyl-3-phenylbenzo[h][1,6]naphthyridine (5b). Pale yellow solid; (0.156 g, 76%); mp 291–292°C; ir (potassium bromide): 3314(m), 3017(m), 2983(w), 1683(m), 1676(w), 1560(w), 1553(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ

2.60 (s, 3H), 7.22–7.56 (m, 5H), 8.07 (d, J = 7.4 Hz, 1H), 8.29 (d, J = 7.4 Hz, 1H), 8.45 (s, 1H), 9.03 (s, 1H), 9.25 (s, 1H); ms: m/z (%) 304 (M^+, 100), 306 (M+2, 32); Anal. Calcd. For $C_{19}H_{13}ClN_2$ (304.77): C, 74.88: H, 4.30; N, 9.19. Found. C, 74.93; H, 4.48; N, 9.21.

2-Amino-9-chlorobenzo[*h*][1,6]naphthyridine-3-carbonitrile (7). A mixture of **1b** (0.206 g, 1 mmol) and malononitrile **6** (0.066 g, 1 mmol) in ethanol with catalytic amount of piperidine was heated under reflux for 2 h. After completion of reaction (TLC check), separated solid was collected by filtration and recrystallized from DMF to furnish compound **7** as colorless needles; (0.160 g, 78%); mp 279–280°C; ir (potassium bromide): 3406(s), 3315(w), 3084(m), 2962(w), 2744(w), 2218(m), 1660(s), 1599(s), 1489(s) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.86 (d, J = 8.7 Hz, 1H), 7.88 (s, 2H, NH_2), 8.02 (d, J = 8.7 Hz, 1H), 8.75 (s, 1H), 8.89 (s, 1H), 9.05 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 95.2, 119.6, 120.5, 127.3, 127.9, 129.1, 131.2, 133.1, 135.9, 142.7, 146.8, 149.6, 163.0; ms: m/z (%) 254 (M^+, 100), 256 (M+2, 35); Anal. Calcd. For $C_{13}H_7ClN_4$ (254.67): C, 61.31: H, 2.77; N, 22.00. Found. C, 61.36; H, 2.86; N, 22.09.

General procedure for the synthesis of compounds 9a–d. A mixture of **1b** (0.206 g, 1 mmol) and corresponding benzoylacetonitrile **8a–d** (1 mmol) in DMF with catalytic amount of piperidine was heated under reflux for 2 h. After completion of the reaction (TLC check), solvent was evaporated under reduced pressure. The crude solid was washed with methanol, filtered, dried under high vacuum, and recrystallized from ethanol: DMF (8:2) to furnish compounds **9a–d** in 75–85% yield.

9-Chloro-2-(4-chlorophenyl)benzo[h][1,6]naphthyridine-3-carbonitrile (9a). Pale brown solid; (0.170 g, 83%); mp 297–298°C; ir (potassium bromide): 3002(w), 2987(m), 2811(m), 2217(m), 1678(s), 1657(m), 1583(w), 1559(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.62 (d, J = 7.6 Hz, 2H), 7.91 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 7.6 Hz, 2H), 8.23 (d, J = 8.2 Hz, 1H), 8.54 (s, 1H), 8.81 (s, 1H), 9.17 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 91.9, 117.6, 122.2, 123.8, 126.7, 129.1, 129.3, 129.7, (2 C's), 130.1, 131.8, 132.6, 133.1, 133.3, 135.5, 140.3, 144.2, 149.1, 164.4; ms: m/z (%) 349 (M^+, 100), 351 (M+2, 36), 353 (M+4, 14); Anal. Calcd. For $C_{19}H_9Cl_2N_3$ (350.20): C, 65.16; H, 2.59; N, 12.00. Found. C, 65.21; H, 2.66; N, 12.11.

2-(4-Bromophenyl)-9-chlorobenzo[h][1,6]naphthyridine-3-carbonitrile (9b). Pale brown solid; (0.166 g, 81%); mp 297–298°C; ir (potassium bromide): 2963(m), 2917(m), 2221(m), 1682(w), 1667(m), 1591(m), 1551(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.75 (d, J = 7.5 Hz, 2H), 8.01 (d, J = 8.4 Hz, 1H), 8.15 (d, J = 7.5 Hz, 2H), 8.33 (d, J = 8.4 Hz, 1H), 8.64 (s, 1H), 8.81 (s, 1H), 9.01 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 90.0, 118.0, 123.2, 126.4, 126.8, 130.2, 130.3, 130.7, (2 C's), 131.1, 131.7, 132.9, 134.1, 134.3, 135.7, 141.0, 143.2, 150.1, 165.3; ms: m/z (%) 394 (M^+, 81), 396 (M+2, 97), 398 (M+4, 22); Anal. Calcd. For $C_{19}H_9BrClN_3$ (394.65): C, 57.82; H, 2.30; N, 10.65. Found. C, 57.83; H, 2.41; N, 10.72.

2-(3,5-Bis(trifluoromethyl)phenyl)-9-chlorobenzo[h][1,6]-naphthyridine-3-carbonitrile (9c). Colorless solid; (0.164 g, 80%); mp 291–292°C; ir (potassium bromide): 3012(m), 2969(m), 2219(m), 1673(w), 1656(m), 1569(m), 1533(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.76 (s, 1H), 8.03 (s, 2H), 8.14 (d, J = 7.5 Hz, 1H), 8.18 (d, J = 7.5 Hz, 1H), 8.64 (s, 1H), 8.83 (s, 1H), 9.38 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 89.5, 105.3, 124.1, 124.3, 124.9, 125.7, 126.8, 128.2, 128.8 (2 C's), 131.1, 132.2 (2 C's), 132.9 133.0, 134.7, 138.2, 140.1, 144.3, 147.9, 163.8; ms: m/z (%) 451 (M^+, 100), 453 (M+2, 31); Anal. Calcd. For $C_{21}H_8ClF_6N_3$ (451.75): C, 55.87; H, 1.77; N, 9.31. Found. C, 55.83; H, 1.90; N, 9.28.

9-Chloro-(2,5-dimethoxyphenyl)benzo[h][1,6]naphthyridine-3-carbonitrile (9d). Pale yellow solid; (0.175 g, 85%); mp 293–294°C; ir (potassium bromide): 2986(m), 2947(w), 2218(m), 1683(w), 1669(w), 1527(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.65 (s, 6H), 7.01–7.35 (m, 3H, Ar—H), 8.01 (d, J = 8.2 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 8.59 (s, 1H), 8.73 (s, 1H), 9.10 (s, 1H); ms: m/z (%) 375 (M^+, 100), 377 (M+2, 33); Anal. Calcd. For $C_{21}H_{14}ClN_3O_2$ (375.81): C, 69.12; H, 3.75; N, 11.18. Found. C, 69.17; H, 3.81; N, 11.27.

General procedure for the synthesis of compounds 11a and b. A mixture of **1b** (0.206 g, 1 mmol) and corresponding diketone **10a–b** (1 mmol) in DMF with catalytic amount of piperidine was heated under reflux for 3 h. After completion of the reaction (TLC check), solvent was evaporated under reduced pressure. The crude solid was washed with methanol, filtered, dried under high vacuum, and recrystallized from ethanol: DMF (6:4) to furnish compound **11a–b** in 77–79% yield.

Ethyl 9-Chloro-2-methylbenzo[h][1,6]naphthyridine-3-carboxylate (11a). Colorless solid; (0.158 g, 77%); mp 297–298°C; ir (potassium bromide): 3161(w), 3073(m), 2981(m), 2935(m), 1767(s), 1661(s), 1624(m), 1510(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.33 (s, 3H), 3.78 (t, J = 6.9 Hz, 3H), 4.35 (q, J = 6.9 Hz, 2H, OCH_2), 7.92 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.54 (s, 1H), 8.86 (s, 1H), 9.14 (s, 1H); ms: m/z (%) 300 (M^+, 100), 302 (M+2, 33); Anal. Calcd. For $C_{16}H_{13}ClN_2O_2$ (300.74): C, 63.90; H, 4.36; N, 9.31. Found. C, 63.97; H, 4.49; N, 9.30.

9-Chloro-2-methyl-N-phenylbenzo[h][1,6]naphthyridine-3-carboxamide (11b). Pale yellow solid; (0.150 g, 73%); mp 271–272°C; ir (potassium bromide): 3336(s), 3152(m), 3017(w), 2880(m), 1693(s), 1642(s), 1624(m), 1517(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.36 (s, 3H, CH_3), 7.34 (m, 5H, Ar—H), 8.01 (d, J = 8.2 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H), 8.34 (s, 1H), 8.80 (s, 1H), 9.14 (s, 1H), 11.80 (s, 1H, NH); ms: m/z (%) 347 (M^+, 100), 349 (M+2, 35); Anal. Calcd. For $C_{20}H_{14}ClN_3O$ (347.80): C, 69.07; H, 4.06; N, 12.0. Found. C, 69.14; H, 4.01; N, 12.06.

Ethyl 9-Chloro-1,2-dihydro-2-oxobenzo[*h*][1,6]naphthyridine-3-carboxylate (13). Colorless solid; (0.152 g, 74%); mp 247–248°C; ir (potassium bromide) 3398(w), 3167(m), 3072(m), 2980(s), 1741(m), 1699(s), 1662(s), 1604(s), 1500(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.33 (t, J = 6.9 Hz, 3H, CH_3), 4.34 (q, J = 6.9 Hz, 2H, OCH_2), 7.83 (d, J = 7.8 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 8.71 (s, 1H), 9.00 (s, 1H), 9.16 (s, 1H), 12.8 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 14.1, 60.9, 110.4, 116.9, 122.4, 123.4 131.5, 131.6, 131.8, 142.0, 143.1, 146.2, 151.5, 159.2, 163.6; ms: m/z (%) 302 (M^+, 100), 304 (M+2, 34); Anal. Calcd. For $C_{15}H_{11}ClN_2O_3$ (302.71): C, 59.52; H, 3.66; N, 9.25. Found. C, 59.41; H, 3.67; N, 9.19.

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