



## Synthesis of novel benzo[*h*][1,6]naphthyridine derivatives from 4-aminoquinoline and cyclic $\beta$ -ketoester

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### ABSTRACT

This paper describes the synthesis of 2,8-dichloroquinolin-4-amine **4** and 4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo[*h*][1,6]naphthyridine **8** as novel class of building blocks. Also describes the regioselective  $S_NAr$  reactions of 2,4,8-trichloroquinoline **2** on  $C_2$  and  $C_4$  positions with azide, similarly  $S_NAr$  reactions of benzo[*h*][1,6]naphthyridine **8** at  $C_4$ ,  $C_5$  positions, and  $S_N2$  reactions on  $C_3$ -(2-chloroethyl) side chain with nucleophiles such as primary aromatic amines, methoxide/ethoxide, and azide at different temperatures.

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### 1. Introduction

Synthesis of azido derivatives of hetarenes<sup>1,2</sup> raised question of regioselectivity during reactions of azide anion with 2,4-dichloroquinoline. 2,4-Dichloroquinolines are known to give nucleophilic substitution reactions both at  $\alpha$  and  $\gamma$ -positions.<sup>3,4</sup> Kinetic studies of 2,4-dichloroquinoline indicate that the chloro atom at  $C_4$  position is about two times more reactive toward nucleophiles<sup>3,5</sup> and predominantly an addition–elimination mechanism is observed.<sup>6</sup> In order to transform the literature findings for the introduction of azido groups, we have studied the reaction of 2,4,8-trichloroquinoline **2** at different temperatures. After reduction of 4-azido-2,8-dichloroquinoline **3** with sodium dithionite gives required 2,8-dichloroquinolin-4-amine **4**. Number of electrophiles failed to react with weakly nucleophilic 4-amino group of the 4-aminoquinolines.<sup>7</sup> The  $\alpha$ -acetyl  $\gamma$ -butyrolactone was relatively strong electrophile for the synthesis of tricyclic and tetracyclic heteroaromatic compounds. As noted previously<sup>8,9</sup> several heterocycles with 2-chloroethyl side chain exhibited good in vitro activity against several cell lines of clinically isolated human tumor. For further information, the reported SAR studies<sup>10</sup> of these type of compounds and replacement by quinoline nucleus as carrier of reported substituents were of particular interest because of these structures in several cytotoxic agents.<sup>11</sup> Several antimalarial candidates possess usable functional group at  $C_4$  position in tricyclic

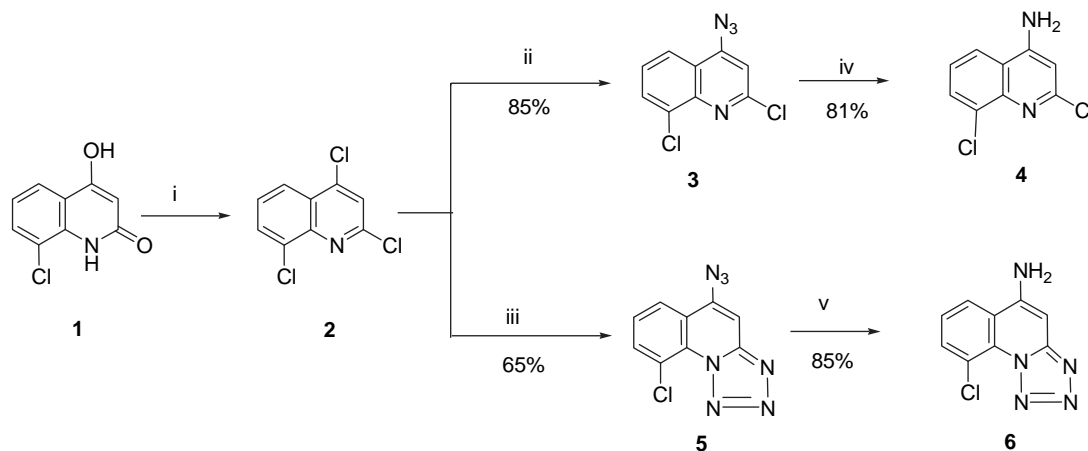
heteroaromatic nucleus were<sup>7,12</sup> synthesized by substituting chloride in the benzo[*h*][1,6]naphthyridines with various *N*-alkyl-4-piperidyl methanolate.<sup>13</sup> The benzo[*h*][1,6]naphthyridines showed broad spectrum of biological activities,<sup>14–18</sup> including high affinity on 5-HT<sub>4</sub> receptors and high selectivity versus other receptors.<sup>19,20</sup>

The acid catalyzed Conrad–Limpach reaction<sup>21</sup> of 4-aminoquinoline and acetoacetic ester has been reported and gave high yields of 2-methylbenzo[*h*][1,6]naphthyridin-4-ol. Wamhoff and co-workers<sup>22</sup> reported few thermoselective reactions of  $\alpha$ -acetyl  $\gamma$ -butyrolactone with 2-aminopyridines. Previously, we have carried out regioselective reaction of  $\beta$ -ketoesters<sup>23–26</sup> with 2-amino/4-hydroxy quinolones/pyridines. We have designed a new route for the synthesis of tri/tetracyclic quinoline derivatives from benzo[*h*][1,6]naphthyridine possessing requisite functionalities. Here, we report regioselective  $S_NAr$  reactions of 4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo[*h*][1,6]naphthyridine **8** with different nucleophiles such as primary amines, methoxide/ethoxide, and azide at different temperatures.

### 2. Results and discussion

2,4,8-Trichloroquinoline **2** was synthesized by literature methods<sup>26–28</sup> and reacted with sodium azide (added portion wise within 15 min) in DMF at 55 °C furnished 4-azido-2,8-dichloroquinoline **3** in 85% yield. The same reaction with excess of sodium azide at 80 °C gave 5-azido-9-chlorotetrazolo[1,5-*a*]quinoline **5** in 65% yield. It was observed that if sodium azide was directly poured into reaction

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**Scheme 1.** Reagents and conditions: (i)  $\text{POCl}_3$ , reflux; (ii)  $\text{NaN}_3$ , DMF,  $55^\circ\text{C}$ , 2 h; (iii)  $\text{NaN}_3$ , DMF,  $80^\circ\text{C}$ , 3.5 h; (iv)  $\text{Na}_2\text{S}_2\text{O}_4$ , methanol, reflux, 3.5 h; (v)  $\text{Na}_2\text{S}_2\text{O}_4$ , methanol, reflux, 3.5 h.

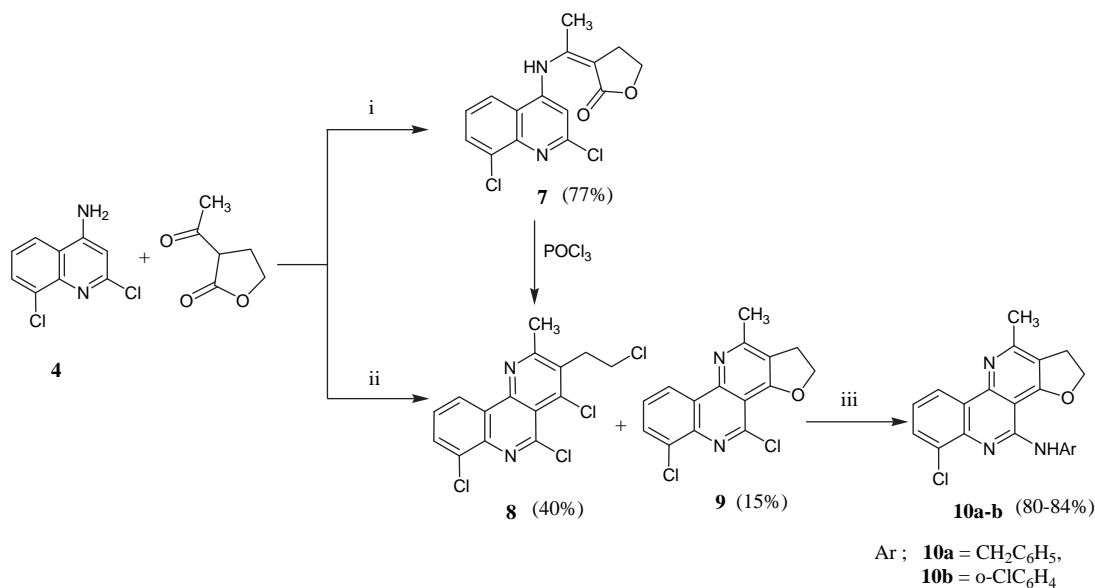
mixture at  $0^\circ\text{C}$  or at higher temperature produced green colored mixture of decomposition products. Generally, azido derivatives were reduced by triphenylphosphine via Staudinger reaction leads to iminophosphoranes, which on hydrolysis with 80% aqueous acetic acid furnished aminoquinolones.<sup>29–31</sup> We have successfully reduced 4-azido 2,8-dichloroquinoline **3** and 5-azido-9-chlorotetraza[1,5-a]quinoline **5** in one step using sodium dithionite<sup>32</sup> in methanol to afford amines **4** and **6** in 80–85% yields (Scheme 1).

Further, we have explored the chemistry of 2,8-dichloroquinolin-4-amine **4** by reacting with  $\alpha$ -acetyl  $\gamma$ -butyrolactone in toluene and catalytic amount of PTSA at  $120^\circ\text{C}$ , furnished thermodynamically stable intermediate (*Z*)-2-aminoethylidene heterodihydrofuranone **7** in 77% yield. The weak acid PTSA selectively protonates keto carbonyl in preference to lactone carbonyl and the subsequent attack of amino moiety gave dihydrofuranone **7**. Use of other acids such as sulfuric, hydrochloric or acetic acid catalyst furnished compound **7** in low yield.

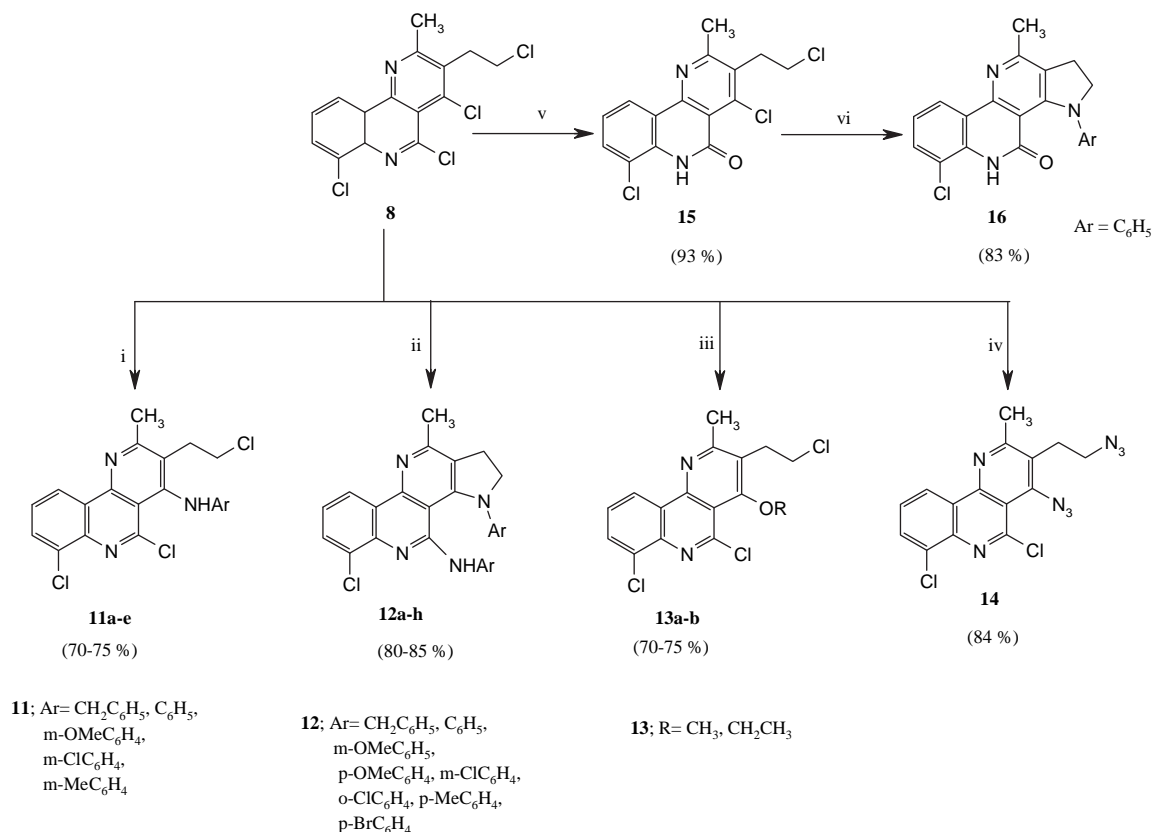
The structure of compound **7** was assigned using spectroscopic and analytical methods. For instance IR of **7** showed lactone carbonyl ( $\text{C}=\text{O}$ ) stretching at  $1689\text{ cm}^{-1}$ , NH at  $3122\text{ cm}^{-1}$ , and ( $\text{C}=\text{C}$ )

at  $1575\text{ cm}^{-1}$ . The lowering of lactone carbonyl was due to intramolecular H-bonding between CO and NH, which also supports the *Z*-configuration of furanone intermediate **7**. The  $^1\text{H}$  NMR spectrum of **7** in  $\text{CDCl}_3$  showed the resonance at 2.32 ppm for methyl protons, two triplets were observed at 3.00 and 4.43 ppm with  $J=7.5\text{ Hz}$  were assignable for  $\text{CH}_2\text{CH}_2\text{O}$ . The down field NH resonance showed sharp singlet at  $\delta$  11.03 ( $\text{D}_2\text{O}$  exchangeable), and the remaining aromatic protons resonance at expected chemical shifts and splitting pattern. The EIMS of **7** showed  $\text{M}^+$ ,  $\text{M}+2$ , and  $\text{M}+4$  at 322, 324, and 326  $m/z$ , respectively, indicating the presence of two chlorines.

Intermediate dihydrofuranone **7** was refluxed in  $\text{POCl}_3$  furnished mixture of compounds **8** and **9** in 40% and 15% yields, respectively, while direct one pot reaction of 2,8-dichloroquinolin-4-amine **4** and  $\alpha$ -acetyl  $\gamma$ -butyrolactone in  $\text{POCl}_3$  at  $115^\circ\text{C}$  furnished compounds **8** and **9** in 20% and 10% yields. Mixture of compounds **8** and **9** was separated by column chromatography eluting with toluene and structures were established by spectral and analytical data. Both compounds **8** and **9** showed absence of carbonyl and NH stretching frequency in IR. The  $^1\text{H}$  NMR spectra of compound **8** in



**Scheme 2.** Reagents and conditions: (i) PTSA, toluene,  $120^\circ\text{C}$ , 72 h; (ii)  $\text{POCl}_3$ ,  $115^\circ\text{C}$ , 5 h; (iii)  $\text{ArNH}_2$ ,  $150^\circ\text{C}$ , 15 min.



**Scheme 3.** Reagents and conditions: (i) ArNH<sub>2</sub>, 110 °C, 15 min; (ii) ArNH<sub>2</sub>, 150 °C, 30 min; (iii) CH<sub>3</sub>ONa/C<sub>2</sub>H<sub>5</sub>ONa, toluene, 120 °C, 24 h; (iv) NaN<sub>3</sub>, DMF, 30 °C, 10 h; (v) AcOH, reflux, 15 min; (vi) ArNH<sub>2</sub>, 160 °C, 1 min.

CDCl<sub>3</sub> showed resonance at 2.93 ppm singlet for methyl protons, two triplets at 3.53 and 3.81 ppm,  $J=7.2$  Hz were assignable to CH<sub>2</sub>CH<sub>2</sub>Cl. The <sup>1</sup>H NMR spectra of **9** showed singlet at 2.59 ppm assignable to methyl protons and slightly more deshielded triplets observed at 3.24 and 4.84 ppm with  $J=8.7$  Hz were assignable to four protons of pyrrole ring. The resonance of aromatic protons in both compounds **8** and **9** was observed between 7.53 and 8.95 ppm. The EIMS of **8** showed M<sup>+</sup>, M+2, M+4, M+6, and M+8 at 360, 362, 364, 366, and 368  $m/z$ , respectively, due to the presence of four chlorines and compound **9** showed M<sup>+</sup>, M+2 and M+4 at 304, 306, and 308  $m/z$  due to presence of two chlorines. Further elemental analysis was in agreement with the molecular formula of 4,5,7-dichloro-3-(2-chloroethyl)-2-methylbenzo[*h*][1,6]naphthyridine **8** and 9,11-dichloro-4-methyl-2,3-dihydrofuro[3,2-*c*]benzo[*h*][1,6]naphthyridine **9** (Scheme 2).

The 9,11-dichloro-4-methyl-2,3-dihydrofuro[3,2-*c*]benzo[*h*][1,6]naphthyridine **9** on reaction with primary aromatic amines at 150 °C gave C<sub>11</sub> substitution products **10a,b** in 80–84% yields. Both **10a,b** were characterized by spectral and analytical data (Scheme 2).

The S<sub>N</sub>Ar and S<sub>N</sub>2 reactions with different nucleophiles at varied temperatures were used to study the relative reactivities at C<sub>4</sub>, C<sub>5</sub>, C<sub>7</sub>, and C<sub>3</sub>-(2-chloroethyl) side chain in compound **8**. Compound **8** with excess primary aromatic amines at 110 °C gave C<sub>4</sub> substitution product 4-chloro-3-(2-chloroethyl)-2-methyl-*N*-phenylbenzo[*h*][1,6]naphthyridin-4-amines **11a–e**, in 70–75% yields. While at 150 °C S<sub>N</sub>Ar reaction occurs at both C<sub>4</sub> and C<sub>5</sub> position along with cyclization at C<sub>3</sub>-(2-chloroethyl) side chain furnished 2,3-dihydro-4-methyl-*N*,1-diphenyl-1*H*-pyrrolo[3,2-*c*]benzo[*h*][1,6]naphthyridin-11-amines **12a–h** in 80–85% yields. Compounds **11a–e** and **12a–h** were characterized by spectroscopic methods (given in Experimental section).

Compound **8** on reaction with sodium methoxide/ethoxide at 120 °C in toluene afforded C<sub>4</sub>-OR substitution products **13a,b** in 70–75% yields. Where as reaction of compound **8** with sodium azide in DMF at 30 °C gave C<sub>4</sub> and C<sub>3</sub>-(2-chloroethyl) substitution product 4-azido-3-(2-azidoethyl)-5,7-dichloro-2-methylbenzo[*h*][1,6]naphthyridine **14** in 84% yield. Compounds **13a,b** and **14** were characterized by IR, <sup>1</sup>H NMR, elemental analysis, and mass spectroscopic methods (Scheme 3).

The iminechloride (–N=C–Cl) moiety in compound **8** was converted to secondary amide by refluxing in glacial acetic acid furnished 4,7-dichloro-3-(2-chloroethyl)-2-methylbenzo[*h*][1,6]naphthyridin-5(6*H*)-one **15** in 93% yield. The S<sub>N</sub>Ar reaction of compound **15** with primary aromatic amine at 160 °C furnished 9-chloro-2,3-dihydro-4-methylbenzo-[*h*][1,6]naphthyridin-1-phenyl-1*H*-pyrrolo[3,2-*c*]-11(10*H*)-one **16** with 83% yield. The formation of compounds **10a,b**, **12a,b**, and **16** occurred at relatively higher temperature, while compounds **11a–e**, **13a,b**, and **14** formed at relatively lower temperature. All these observations proved that C<sub>4</sub> position in compound **8** is more reactive than C<sub>5</sub> position toward nucleophilic substitution reactions.

### 3. Conclusion

In summary, we have disclosed the convenient synthesis of 4-aminoquinoline as useful tools in development of 4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo[*h*][1,6]naphthyridine **8** by using  $\alpha$ -acetyl  $\gamma$ -butyrolactone. Our main interest was concerned with regioselective synthesis of substituted benzo[*h*][1,6]naphthyridine with nucleophiles at different temperature and also the synthesis of tetracyclic furano[3,2-*c*] and pyrrolo[3,2-*c*]benzo[*h*][1,6]naphthyridine derivatives.

## 4. Experimental

### 4.1. General

Common reagents grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures. The melting points were measured on Barnstead Electro Thermal melting point apparatus Mod. No. IA-9200 in open capillary tubes and are uncorrected. Elemental analyses were determined using Thermo Quest Model No. flash EA 1112-Elemental Analyzer. The IR spectra of compounds were recorded on Shimadzu IR-408 instrument in potassium bromide pellets. All mass spectra were recorded on Mat 112 Varian Mat Bremen mass spectrometer. Routine  $^1\text{H}$  NMR (300 MHz) and  $^{13}\text{C}$  NMR (75 MHz) spectra were recorded on VARIAN XL-300 instrument at 25 °C. The measurements were done using protiated solvents— $\text{CDCl}_3$  and  $\text{DMSO}-d_6$ , with TMS as an internal standard reference. Coupling constants ( $J$ ) are quoted to the nearest 0.1 Hz and chemical shift ( $\delta$ -scale) are quoted in parts per million (ppm) and following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Column chromatography was performed using silica gel with particle size (60–120 mesh, Merck). All reactions were monitored by TLC carried out 0.2 mm silica gel 60 F<sub>254</sub> (Merck) plates using 254 and 366 nm UV light for detection.

### 4.2. Synthetic procedures

**4.2.1. 4-Azido-2,8-dichloroquinoline (3).** To a vigorously stirred solution of 2,4,8-trichloroquinoline **2** (11.55 g, 0.05 mol) in DMF (100 mL) at 55 °C, sodium azide (3.90 g, 0.06 mol) was added slowly within 15 min. The resulting red colored solution was kept stirring for 2 h. The progress of the reaction was monitored by TLC till the trichloroquinoline was consumed. After completion, the reaction mixture was poured in cold water (2 L). The obtained solid was filtered, washed with water, dried, and recrystallized from ethanol to give title compound **3** (10.11 g, 85%) as a colorless needles;  $R_f$  (toluene) 0.62, mp 105 °C; IR (KBr):  $\nu$  3051, 2922, 2219, 2133 ( $\text{N}_3$ ), 1516, 1500, 1307, 1105, 906, 767  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  6.50 (s, 1H, C<sub>3</sub>H), 7.10 (t,  $J=7.4$  Hz, 1H, C<sub>6</sub>H), 7.73 (d,  $J=7.4$  Hz, 1H, C<sub>7</sub>H), 8.30 (d,  $J=7.4$  Hz, 1H, C<sub>5</sub>H); MS:  $m/z$  (%): 243 (M+4, 10), 241 (M+2, 50), 239 (M, 100), 197 (70), 77 (20). Anal. Calcd for  $\text{C}_9\text{H}_4\text{Cl}_2\text{N}_4$  (239.06): C, 45.22; H, 1.69; N, 23.44. Found: C, 45.18; H, 1.73; N, 23.31.

**4.2.2. 2,8-Dichloroquinolin-4-amine (4).** A mixture of 4-azido-2,8-dichloroquinoline **3** (11.95 g, 0.05 mol) and sodium dithionite (10.44 g, 0.06 mol) in methanol (150 mL) was heated to reflux for 3.5 h (TLC checked, toluene). The solvent was evaporated in vacuo and residue was stirred into ice water (1 L). The obtained solid was filtered, washed with water (10 mL). The product was further purified by dissolving in 1:1 hydrochloric acid (500 mL) at 50 °C, stirred by adding activated charcoal (5 g). After filtering out charcoal, the resulting solution was neutralized with 2 N NaOH. The precipitated solid was filtered, washed with water, and recrystallized from ethanol to give title compound **4** (7.90 g, 85%) as colorless prisms;  $R_f$  (10% toluene/ethyl acetate) 0.31, mp 235 °C; IR (KBr):  $\nu$  3462, 3319 ( $\text{NH}_2$ ), 3197, 1645, 1575, 1355, 1116, 759  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  4.90 (br s, 2H,  $\text{NH}_2$ ,  $\text{D}_2\text{O}$  exchangeable), 6.59 (s, 1H, C<sub>3</sub>H), 7.56 (t,  $J=7.5$  Hz, 1H, C<sub>6</sub>H), 7.59 (d,  $J=7.5$  Hz, 1H, C<sub>7</sub>H), 8.93 (d,  $J=7.5$  Hz, 1H, C<sub>5</sub>H); MS:  $m/z$  (%): 216 (M+4, 40), 214 (M+2, 50), 212 (M, 90), 173 (20), 141 (20), 127 (30), 77 (10), 44 (31). Anal. Calcd for  $\text{C}_9\text{H}_6\text{Cl}_2\text{N}_2$  (213.06): C, 50.73; H, 2.84; N, 13.15. Found: C, 50.65; H, 2.79; N, 13.21.

**4.2.3. 5-Azido-9-chlorotetrazolo[1,5-a]quinoline (5).** A solution of 2,4,8-trichloroquinoline **2** (1.16 g, 0.005 mol) and sodium azide (0.650 g, 0.01 mol) in DMF (10 mL) was stirred at 80 °C for 10 h. The progress of the reaction was monitored by TLC till trichloroquinoline was consumed. After completion, the reaction mixture was stirred into cold water (2 L). The formed crude product was filtered off, dried, and further purified by column chromatography using silica gel eluting with toluene gave title compound **5** (0.796 g, 65%) as yellow colored needles;  $R_f$  (10% toluene/ethyl acetate) 0.64, mp 159 °C; IR (KBr):  $\nu$  3042, 2922, 2146 ( $\text{N}_3$ ), 1616, 1553, 1401, 1250, 854  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  6.90 (s, 1H, C<sub>4</sub>H), 7.43 (t,  $J=7.2$  Hz, 1H, C<sub>7</sub>H), 7.77 (d,  $J=7.2$  Hz, 1H, C<sub>8</sub>H), 8.54 (d,  $J=7.2$  Hz, 1H, C<sub>6</sub>H); MS:  $m/z$  (%): 247 (M+2, 10), 245 (M, 100), 203 (50), 161 (30). Anal. Calcd for  $\text{C}_9\text{H}_4\text{ClN}_7$  (245.63): C, 44.01; H, 1.64; N, 39.92. Found: C, 44.10; H, 1.50; N, 39.92.

**4.2.4. 9-Chlorotetrazolo[1,5-a]quinolin-5-amine (6).** A mixture of 5-azido-9-chlorotetrazolo[1,5-a]quinoline **5** (0.956 g, 0.004 mol) and sodium dithionite (0.86 g, 0.005 mol) in methanol (10 mL) was heated to reflux for 3.5 h (TLC checked, toluene). The solvent was evaporated in vacuo and residue poured into ice water (200 mL). The formed crude product was filtered off, washed with water, and purified by dissolving it in 1:1 HCl (100 mL) at 50 °C, stirred by adding activated charcoal (0.50 g). After filtering out charcoal, the resulting solution was neutralized with 2 N NaOH. The precipitate solid was filtered off, washed with water, and recrystallized from ethanol to give title compound **6** (0.740 g, 85%) as colorless prisms;  $R_f$  (20% toluene/ethyl acetate) 0.48, mp 230 °C; IR (KBr):  $\nu$  3390, 3348 ( $\text{NH}_2$ ), 3234, 2923, 1642, 1431, 976  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  6.30 (br s, 2H,  $\text{NH}_2$ ,  $\text{D}_2\text{O}$  exchangeable), 7.20 (t,  $J=8.3$  Hz, 1H, C<sub>7</sub>H), 7.51 (d,  $J=8.3$  Hz, 1H, C<sub>8</sub>H), 7.90 (s, 1H, C<sub>4</sub>H), 8.81 (d,  $J=8.3$  Hz, 1H, C<sub>6</sub>H); MS:  $m/z$  (%): 221 (M+2, 20), 219 (M, 100), 177 (40), 161 (30), 77 (10). Anal. Calcd for  $\text{C}_9\text{H}_6\text{ClN}_5$  (219.63): C, 49.22; H, 2.75; N, 31.89. Found: C, 49.14; H, 2.79; N, 31.92.

**4.2.5. (Z)-3-(1-(2,8-Dichloroquinolin-4-ylamino)ethylidene)-dihydrofuran-2(3H)-one (7).** The solution of 2,8-dichloroquinolin-4-amine **4** (10.65 g, 0.05 mol),  $\alpha$ -acetyl- $\gamma$ -butyrolactone (8.96 mL, 0.07 mol), and catalytic amount of PTSA in toluene (500 mL) was heated to reflux for 72 h. Azeotropic water separation was done by using Dean Stark apparatus to monitor the reaction by collecting equivalent amount of water. The solvent was evaporated in vacuo and the red colored oily residue obtained was poured into ethanol (200 mL). The solid separated was collected by suction filtration, dried, and recrystallized from ethanol/DMF (9:1) to furnish title compound **7** (12.43 g, 77%) as pale yellow colored prisms;  $R_f$  (10% toluene/ethyl acetate) 0.41, mp 208 °C; IR (KBr):  $\nu$  3122 ( $\text{NH}$ ), 1689 ( $\text{C}=\text{O}_{\text{lactone}}$ ), 1662, 1575, 1477, 1334, 1240, 1134, 968, 773  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.32 (s, 3H,  $\text{CH}_3$ ), 3.00 (t,  $J=7.5$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{O}$ ), 4.43 (t,  $J=7.5$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{O}$ ), 6.98 (s, 1H, C<sub>3</sub>H), 7.43 (t,  $J=7.2$  Hz, 1H, C<sub>6</sub>H), 7.78 (d,  $J=7.2$  Hz, 1H, C<sub>7</sub>H), 7.96 (d,  $J=7.2$  Hz, 1H, C<sub>5</sub>H), 11.03 (s, 1H,  $\text{NH}$ ,  $\text{D}_2\text{O}$  exchangeable);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  14.11, 60.82, 61.34, 105.32, 119.17, 119.38, 130.80, 132.03, 133.22, 143.76, 148.67, 151.33, 164.48, 168.57; MS:  $m/z$  (%): 326 (M+4, 10), 324 (M+2, 20), 322 (M, 70), 274 (40), 198 (50), 147 (40), 129 (20), 44 (40). Anal. Calcd for  $\text{C}_{15}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_2$  (323.17): C, 55.75; H, 3.74; N, 8.67. Found: C, 55.65; H, 3.81; N, 8.57.

**4.2.6. 4,5,7-Trichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridine (8) and 9,11-dichloro-4-methyl-2,3-dihydrofuro[3,2-c]benzo[h][1,6]naphthyridine (9).** Method A. The solution of (Z)-3-(1-(2,8-dichloroquinolin-4-ylamino)ethylidene)-dihydrofuran-2(3H)-one **7** (9.69 g, 0.03 mol) in phosphorous oxychloride (80 mL) was

heated to reflux for 4 h. After completion of reaction, excess POCl<sub>3</sub> was evaporated in vacuo. The red colored residue obtained was poured into ice water (1 L) and solution was neutralized with solid sodium carbonate (10 g). The separated solid product was collected by suction filtration. The TLC analysis in toluene showed two products. The mixture of crude product was separated by column chromatography on silica gel eluting with toluene, yields title compounds **8** (4.32 g, 40%) and **9** (1.36 g, 15%).

**Method B.** The mixture of 2,8-dichloroquinolin-4-amine **4** (6.39 g, 0.03 mol) and  $\alpha$ -acetyl  $\gamma$ -butyrolactone (5.12 mL, 0.04 mol) in POCl<sub>3</sub> (80 mL) was heated to reflux for 3 h. After completion of reaction, the workup was carried out as described in method A. The TLC analysis in toluene showed two products. The mixtures of crude product were separated by column chromatography on silica gel eluting with toluene. The solvent was evaporated in vacuo to give title compounds **8** (2.16 g, 20%) and **9** (0.90 g, 10%).

**4.2.6.1. 4,5,7-Trichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridine (8).** Recrystallized from ethanol to afford yellow prisms; *R<sub>f</sub>* (toluene) 0.64, mp 151 °C; IR (KBr):  $\nu$  2958, 2922, 2854, 1568, 1545, 1433, 1329, 1122, 941, 844, 785 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.93 (s, 3H, CH<sub>3</sub>), 3.53 (t, *J*=7.2 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>Cl), 3.81 (t, *J*=7.2 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>Cl), 7.56 (t, *J*=7.5 Hz, 1H, C<sub>9</sub>H), 7.83 (d, *J*=7.5 Hz, 1H, C<sub>8</sub>H), 8.93 (d, *J*=7.5 Hz, 1H, C<sub>10</sub>H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  25.13, 33.85, 41.08, 123.38, 126.01, 127.65, 127.81, 131.41, 132.32, 132.54, 140.69, 142.21, 147.42, 149.80, 163.11; MS: *m/z* (%): 368 (M+8, 10), 366 (M+6, 20), 364 (M+4, 50), 362 (M+2, 90), 360 (M, 90), 323 (08), 311 (100), 287 (07), 274 (20), 239 (10), 198 (20), 116 (12), 99 (10), 49 (15). Anal. Calcd for C<sub>15</sub>H<sub>10</sub>Cl<sub>4</sub>N<sub>2</sub> (360.07): C, 50.04; H, 2.80; N, 7.78. Found: C, 49.93; H, 2.85; N, 7.69.

**4.2.6.2. 9,11-Dichloro-4-methyl-2,3-dihydrofuro[3,2-c]benzo[h][1,6]naphthyridine (9).** Recrystallized from ethanol to afford yellow prisms; *R<sub>f</sub>* (toluene) 0.14, mp 231 °C; IR (KBr):  $\nu$  2972, 2918, 1604, 1573, 1428, 1314, 1187, 945, 777 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.59 (s, 3H, CH<sub>3</sub>), 3.24 (t, *J*=8.7 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>O), 4.84 (t, *J*=8.7 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>O), 7.54 (t, *J*=7.5 Hz, 1H, C<sub>7</sub>H), 7.82 (d, *J*=7.5 Hz, 1H, C<sub>8</sub>H), 8.95 (d, *J*=7.5 Hz, 1H, C<sub>6</sub>H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  26.10, 32.96, 33.56, 124.40, 124.75, 127.31, 130.69, 131.25, 132.60, 139.50, 141.10, 146.23, 149.21, 150.33, 161.37; MS: *m/z* (%): 308 (M+4, 40), 306 (M+2, 70), 304 (M, 100), 269 (20), 263 (20), 227 (10), 164 (10). Anal. Calcd for C<sub>15</sub>H<sub>10</sub>Cl<sub>2</sub>N<sub>2</sub>O (305.16): C, 59.04; H, 3.30; N, 9.18. Found: C, 59.01; H, 3.23; N, 9.15.

**4.2.7. 9-Chloro-2,3-dihydro-4-methyl-N-substitutedfuro[3,2-c]benzo[h][1,6]naphthyridine-11-amines (10a,b).** A mixture of 9,11-dichloro-4-methyl-2,3-dihydrofuro[3,2-c]benzo[h][1,6]naphthyridine **9** (0.304 g, 0.001 mol) and primary aromatic amine (0.01 mol) was heated at 110 °C for 15 min. After cooled down to room temperature, methanol (10 mL) was added. The crude product separated was collected by suction filtration give title compounds **10a,b**.

**4.2.7.1. 9-Chloro-2,3-dihydro-4-methyl-N-benzylfuro[3,2-c]benzo[h][1,6]naphthyridine-11-amine (10a).** Recrystallized from ethanol to afford colorless prisms; yield (0.295 g, 80%); *R<sub>f</sub>* (20% toluene/ethyl acetate) 0.53, mp 227 °C; IR (KBr):  $\nu$  3417 (NH), 2922, 1616, 1591, 1594, 1199, 950 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.59 (s, 3H, CH<sub>3</sub>), 3.24 (t, *J*=8.7 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>O), 4.84 (t, *J*=8.7 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>O), 4.97 (d, *J*=5.1 Hz, 2H, CH<sub>2</sub>NH), 7.09 (t, *J*=7 Hz, 2H, ArH), 7.12 (d, *J*=7 Hz, 2H, ArH), 7.32 (t, *J*=7 Hz, 1H, ArH), 7.58 (t, *J*=7.5 Hz, 1H, C<sub>7</sub>H), 7.68 (d, *J*=7.5 Hz, 1H, C<sub>8</sub>H), 8.10 (d, *J*=5.1 Hz, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 8.72 (d, *J*=7.5 Hz, 1H, C<sub>6</sub>H); MS: *m/z* (%): 377 (M+2, 30), 375 (M, 100), 227 (20), 177 (30), 113 (30), 99 (10). Anal. Calcd for C<sub>22</sub>H<sub>18</sub>ClN<sub>3</sub>O (375.85): C, 70.30; H, 4.83; N, 11.18. Found: C, 70.35; H, 4.76; N, 11.12.

**4.2.7.2. 9-Chloro-2,3-dihydro-4-methyl-N-(2-chloropenyl)furo[3,2-c]benzo[h][1,6]naphthyridine-11-amine (10b).** Recrystallized from ethanol to afford colorless prisms; yield (0.332 g, 84%); *R<sub>f</sub>* (20% toluene/ethyl acetate) 0.37, mp 237 °C; IR (KBr):  $\nu$  3415, 3060, 1627, 1597, 1534, 1033, 742 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.39 (s, 3H, CH<sub>3</sub>), 2.94 (t, *J*=7.2 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>O), 3.41 (t, *J*=7.2 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>O), 6.57 (t, *J*=6.7 Hz, 1H, ArH), 6.72 (d, *J*=6.7 Hz, 1H, ArH), 7.12 (m, 2H, ArH), 7.41 (t, *J*=7.2 Hz, 1H, C<sub>7</sub>H), 7.65 (d, *J*=7.2 Hz, 1H, C<sub>8</sub>H), 8.3 (s, 1H, NH, D<sub>2</sub>O exchangeable), 8.87 (d, *J*=7.2 Hz, 1H, C<sub>6</sub>H); MS: *m/z* (%): 400 (M+4, 10), 398 (M+2, 50), 396 (M, 100), 276 (20), 176 (20), 130 (20), 99 (15). Anal. Calcd for C<sub>21</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>3</sub>O (396.27): C, 63.65; H, 3.82; N, 10.60. Found: C, 63.70; H, 3.76; N, 10.65.

**4.2.8. 5,7-Dichloro-3-(2-chloroethyl)-2-methyl-N-phenylbenzo[h][1,6]naphthyridine-4-amines (11a–e).** A mixture of 4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridine **8** (0.360 g, 0.001 mol) and primary aromatic amine (0.01 mL) was heated at 110 °C for about 15–25 min. After cooling down to room temperature, methanol (100 mL) was added, the crude product separated was collected by suction filtration, dried, and recrystallized from the suitable solvent to furnish compounds **11a–e** in good yields.

**4.2.8.1. N-Benzyl-5,7-dichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridine-4-amine (11a).** Recrystallized from ethanol/DMF (8:2) to afford colorless prisms; yield (0.301 g, 70%); *R<sub>f</sub>* (toluene) 0.62, mp 190 °C; IR (KBr):  $\nu$  3481 (NH), 3077, 2922, 1563, 1525, 1306, 1187, 1028, 827, 736, 697, 648 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.86 (s, 3H, CH<sub>3</sub>), 3.45 (t, *J*=7.1 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>Cl), 3.74 (t, *J*=7.1 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>Cl), 5.00 (d, *J*=4.5 Hz, 2H, CH<sub>2</sub>NH), 7.28–7.38 (m, 5H, ArH), 7.53 (t, *J*=7.2 Hz, 1H, C<sub>9</sub>H), 7.68 (d, *J*=7.2 Hz, 1H, C<sub>8</sub>H), 8.72 (t, *J*=4.5 Hz, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 8.74 (d, *J*=7.2 Hz, 1H, C<sub>10</sub>H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  24.63, 33.54, 40.99, 46.39, 110.57, 122.16, 122.34, 123.20, 127.32, 128.34, 128.58, 129.50, 129.71, 130.83, 139.07, 140.11, 142.37, 150.33, 151.36, 160.94; MS: *m/z* (%): 436 (M+6, 20), 434 (M+4, 25), 432 (M+2, 50), 430 (M, 90), 405 (50), 390 (60), 377 (15), 345 (20), 307 (20), 141 (30), 127 (30), 77 (20), 44 (50). Anal. Calcd for C<sub>22</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>3</sub> (430.76): C, 61.34; H, 4.21; N, 9.75. Found: C, 61.27; H, 4.49; N, 9.68.

**4.2.8.2. 5,7-Dichloro-3-(2-chloroethyl)-2-methyl-N-phenylbenzo[h][1,6]naphthyridine-4-amine (11b).** Recrystallized from ethanol/DMF (8:2) to afford pale yellow prisms; yield (0.304 g, 73%); *R<sub>f</sub>* (toluene) 0.64, mp 186 °C; IR (KBr):  $\nu$  3430 (NH), 2835, 1572, 1534, 1456, 1205, 1157, 1051, 769, 787 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.91 (s, 3H, CH<sub>3</sub>), 3.46 (t, *J*=7.1 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>Cl), 3.74 (t, *J*=7.1 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>Cl), 7.26–7.33 (m, 5H, ArH), 7.55 (t, *J*=7.2 Hz, 1H, C<sub>9</sub>H), 7.75 (d, *J*=7.2 Hz, 1H, C<sub>8</sub>H), 8.79 (d, *J*=7.2 Hz, 1H, C<sub>10</sub>H), 9.0 (s, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  24.66, 33.71, 40.94, 110.48, 120.07, 122.86, 123.06, 123.17, 123.26, 128.84, 130.05, 130.16, 130.84, 139.30, 139.51, 141.70, 148.08, 150.23, 161.37; MS: *m/z* (%): 422 (M+6, 10), 420 (M+4, 20), 418 (M+2, 70), 416 (M, 100), 415 (100), 410 (80), 347 (20), 317 (20), 173 (20), 141 (40), 127 (30), 77 (20). Anal. Calcd for C<sub>21</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>3</sub> (416.73): C, 60.52; H, 3.87; N, 10.08. Found: C, 60.67; H, 3.79; N, 10.11.

**4.2.8.3. 5,7-Dichloro-3-(2-chloroethyl)-N-(3-methoxyphenyl)-2-methylbenzo[h][1,6]naphthyridine-4-amine (11c).** Recrystallized from ethanol/DMF (8:2) to afford yellow prisms; yield (0.308 g, 69%); *R<sub>f</sub>* (toluene) 0.48, mp 176 °C; IR (KBr):  $\nu$  3425 (NH), 2833, 1575, 1536, 1457, 1313, 1159, 1051, 767, 787 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.92 (s, 3H, CH<sub>3</sub>), 3.49 (t, *J*=7.1 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>Cl), 3.76 (t, *J*=7.1 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>Cl), 3.92 (s, 3H, OCH<sub>3</sub>), 6.73 (d, *J*=7.5 Hz, 1H, ArH), 7.29 (s, 1H, ArH), 7.30–7.35 (m, 2H, ArH), 7.36 (t, *J*=7.5 Hz, 1H, C<sub>9</sub>H), 7.75 (d, *J*=7.5 Hz, 1H, C<sub>8</sub>H), 8.1 (s, 1H, NH, D<sub>2</sub>O exchangeable), 8.81 (d, *J*=7.5 Hz, 1H, C<sub>10</sub>H); MS: *m/z* (%): 452 (M+6, 10), 450 (M+4, 20), 448 (M+2, 70), 446 (M, 100), 410 (90), 395 (10), 347 (20), 317 (20), 223

(15), 173 (20), 141 (40), 127 (30), 77 (20). Anal. Calcd for  $C_{22}H_{18}Cl_3N_3O$  (446.76): C, 59.15; H, 4.06; N, 9.41. Found: C, 59.23; H, 4.09; N, 9.37.

**4.2.8.4. 5,7-Dichloro-3-(2-chloroethyl)-N-(3-chlorophenyl)-2-methylbenzo[h][1,6]naphthyridin-4-amine (11d).** Recrystallized from ethanol/DMF (8:2) to afford yellow prisms; yield (0.347 g, 77%);  $R_f$  (toluene) 0.64, mp 163 °C; IR (KBr):  $\nu$  3436 (NH), 2966, 1600, 1568, 1538, 1425, 1335, 1166, 886, 767  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.93 (s, 3H,  $CH_3$ ), 3.46 (t,  $J=7.5$  Hz, 2H,  $CH_2CH_2Cl$ ), 3.75 (t,  $J=7.5$  Hz, 2H,  $CH_2CH_2Cl$ ), 7.12 (d,  $J=7.5$  Hz, 1H, ArH), 7.23 (s, 1H, ArH), 7.25–7.34 (m, 2H, ArH), 7.39 (t,  $J=7.8$  Hz, 1H,  $C_9H$ ), 7.76 (d,  $J=7.8$  Hz, 1H,  $C_8H$ ), 8.1 (s, 1H, NH,  $D_2O$  exchangeable), 8.81 (d,  $J=7.8$  Hz, 1H,  $C_{10}H$ ); MS:  $m/z$  (%): 459 (M+8, 15), 457 (M+6, 20), 455 (M+4, 40), 453 (M+2, 70), 451 (M, 100), 449 (42), 430 (20), 378 (10), 317 (23), 245 (20), 170 (45), 123 (25), 77 (20). Anal. Calcd for  $C_{21}H_{15}Cl_4N_3$  (451.18): C, 55.90; H, 3.35; N, 9.31. Found: C, 55.33; H, 3.31; N, 9.23.

**4.2.8.5. 4,7-Dichloro-3-(2-chloroethyl)-2-methyl-N-m-tolylbenzo[h][1,6]naphthyridin-5-amine (11e).** Recrystallized from ethanol/DMF (8:2) to afford yellow prisms; yield (0.301 g, 70%);  $R_f$  (toluene) 0.48, mp 164 °C; IR (KBr):  $\nu$  3431 (NH), 2960, 1611, 1561, 1537, 1435, 1345, 1163, 883, 767  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.45 (s, 3H,  $ArCH_3$ ), 2.89 (s, 3H,  $CH_3$ ), 3.51 (t,  $J=7.5$  Hz, 2H,  $CH_2CH_2Cl$ ), 3.79 (t,  $J=7.5$  Hz, 2H,  $CH_2CH_2Cl$ ), 6.74 (d,  $J=7.8$  Hz, 1H, ArH), 6.93 (s, 1H, ArH), 7.15–7.27 (m, 2H, ArH), 7.30 (t,  $J=7.5$  Hz, 1H,  $C_9H$ ), 7.74 (d,  $J=7.5$  Hz, 1H,  $C_8H$ ), 8.81 (s, 1H, NH,  $D_2O$  exchangeable), 8.78 (d,  $J=7.5$  Hz, 1H,  $C_{10}H$ ); MS:  $m/z$  (%): 436 (M+6, 19), 434 (M+4, 20), 432 (M+2, 50), 430 (M, 70), 402 (20), 365 (10), 317 (23), 245 (20), 170 (47), 123 (25), 77 (22). Anal. Calcd for  $C_{22}H_{18}Cl_3N_3$  (430.76): C, 61.34; H, 4.21; N, 9.75. Found: C, 61.24; H, 4.49; N, 9.68.

**4.2.9. 9-Chloro-N,1-dibenzyl-2,3-dihydro-4-methyl-1H-pyrrolo[3,2-c]benzo[h][1,6]naphthyridin-11-amine (12a–h).** A mixture of 4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridine **8** (0.360 g, 0.001 mol) and primary aromatic amine (0.01 mol) was heated at 150 °C for about 30 min. After cooling down to room temperature, methanol (100 mL) was added, the crude product obtained was collected by suction filtration, washed with methanol, dried, and recrystallized from suitable solvent to furnish compounds **12a–h** in good yields.

**4.2.9.1. 9-Chloro-N,1-dibenzyl-2,3-dihydro-4-methyl-1H-pyrrolo[3,2-c]benzo[h][1,6]naphthyridin-11-amine (12a).** Recrystallized from ethanol/DMF (5:5) to afford colorless prisms; yield (0.385 g, 83%);  $R_f$  (10% toluene/ethyl acetate) 0.40, mp 189 °C; IR (KBr):  $\nu$  3372 (NH), 3053, 2929, 1590, 1535, 1356, 1194, 779, 744  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.56 (s, 3H,  $CH_3$ ), 2.89 (t,  $J=8.5$  Hz, 2H,  $CH_2CH_2N$ ), 3.60 (t,  $J=8.5$  Hz, 2H,  $CH_2CH_2N$ ), 4.33 (s, 2H,  $CH_2$ ), 4.69 (d,  $J=4.8$  Hz, 2H,  $CH_2$ ), 7.06–7.22 (m, 10H, Ar–H), 7.33 (t,  $J=7.2$  Hz, 1H,  $C_7H$ ), 7.75 (d,  $J=7.2$  Hz, 1H,  $C_8H$ ), 8.79 (d,  $J=4.8$  Hz, 1H, NH,  $D_2O$  exchangeable), 8.85 (d,  $J=7.2$  Hz, 1H,  $C_6H$ );  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta$  22.96, 26.81, 45.29, 53.52, 60.54, 103.68, 121.59, 122.91, 123.44, 126.81, 127.04, 127.38, 127.44, 128.29, 128.69, 128.78, 129.65, 129.93, 136.99, 139.15, 142.95, 150.72, 152.46, 156.97, 157.87; MS:  $m/z$  (%): 466 (M+2, 10), 464 (M, 10), 372 (80), 373 (100), 295 (10), 268 (20), 217 (10), 106 (15), 91 (70). Anal. Calcd for  $C_{29}H_{25}ClN_4$  (464.99): C, 74.91; H, 5.42; N, 12.05. Found: C, 73.01; H, 5.33; N, 12.13.

**4.2.9.2. 9-Chloro-N,1-diphenyl-2,3-dihydro-4-methyl-1H-pyrrolo[3,2-c]benzo[h][1,6]naphthyridin-11-amine (12b).** Recrystallized from ethanol/DMF (5:5) to afford yellow prisms; yield (0.358 g, 82%);  $R_f$  (20% toluene/ethyl acetate) 0.31, mp 272 °C; IR (KBr):  $\nu$  3322 (NH), 2934, 2880, 1576, 1532, 1467, 1233, 1150, 1054, 765, 767  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.68 (s, 3H,  $CH_3$ ), 3.17 (t,  $J=8.2$  Hz, 2H,  $CH_2CH_2N$ ), 4.44 (t,  $J=8.2$  Hz, 2H,  $CH_2CH_2N$ ), 6.93–7.26 (m, 10H,

Ar–H), 7.34 (t,  $J=7.5$  Hz, 1H,  $C_7H$ ), 7.73 (d,  $J=7.5$  Hz, 1H,  $C_8H$ ), 8.40 (s, 1H, NH,  $D_2O$  exchangeable), 8.84 (d,  $J=7.5$  Hz, 1H,  $C_6H$ );  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta$  22.89, 26.72, 59.05, 104.59, 118.97, 119.47, 122.17, 122.75, 123.06, 123.78, 124.57, 127.94, 128.42, 129.64, 130.03, 130.25, 139.65, 142.44, 148.11, 148.76, 150.46, 150.76, 157.80; MS:  $m/z$  (%): 438 (M+2, 30), 436 (M, 100), 354 (20), 254 (20), 232 (30), 216 (10), 106 (15), 91 (40). Anal. Calcd for  $C_{27}H_{21}ClN_4$  (436.94): C, 74.22; H, 4.84; N, 12.82. Found: C, 74.33; H, 4.49; N, 11.91.

**4.2.9.3. 9-Chloro-N,1-(di-3-methoxyphenyl)-2,3-dihydro-4-methyl-1H-pyrrolo[3,2-c]benzo[h][1,6]naphthyridin-11-amine (12c).** Recrystallized from ethanol/DMF (5:5) to afford yellow prisms; yield (0.402 g, 81%);  $R_f$  (10% toluene/ethyl acetate) 0.33, mp 185 °C; IR (KBr):  $\nu$  3353 (NH), 2933, 2870, 1554, 1542, 1433, 1254, 1110, 1067, 1020, 768, 749, 663  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.67 (s, 3H,  $CH_3$ ), 3.26 (t,  $J=7.5$  Hz, 2H,  $CH_2CH_2N$ ), 3.61 (t,  $J=7.5$  Hz, 2H,  $CH_2CH_2N$ ), 3.85 (s, 3H,  $OCH_3$ ), 3.87 (s, 3H,  $OCH_3$ ), 6.45–6.6 (m, 6H, ArH), 7.00–7.20 (m, 2H, ArH), 7.29 (t,  $J=7.2$  Hz, 1H,  $C_7H$ ), 7.6 (d,  $J=7.2$  Hz, 1H,  $C_8H$ ), 7.8 (s, 1H, NH,  $D_2O$  exchangeable), 8.98 (d,  $J=7.2$  Hz, 1H,  $C_6H$ ); MS:  $m/z$  (%): 498 (M+2, 70), 496 (M, 100), 481 (40), 374 (70), 331 (20), 248 (30), 92 (40). Anal. Calcd for  $C_{29}H_{25}ClN_4O_2$  (496.99): C, 70.08; H, 5.07; N, 11.27. Found: C, 69.96; H, 4.99; N, 11.21.

**4.2.9.4. 9-Chloro-N,1-(di-4-methoxyphenyl)-2,3-dihydro-4-methyl-1H-pyrrolo[3,2-c]benzo[h][1,6]naphthyridin-11-amine (12d).** Recrystallized from ethanol/DMF (5:5) to afford yellow prisms, yield (0.362 g, 73%);  $R_f$  (10% toluene/ethyl acetate) 0.29, mp 205 °C; IR (KBr):  $\nu$  3360 (NH), 2919, 1580, 1525, 1323, 1045, 746  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.62 (s, 3H,  $CH_3$ ), 3.09 (t,  $J=7.2$  Hz, 2H,  $CH_2CH_2N$ ), 3.45 (t,  $J=7.2$  Hz, 2H,  $CH_2CH_2N$ ), 3.67 (s, 3H,  $OCH_3$ ), 3.81 (s, 3H,  $OCH_3$ ), 6.67–7.00 (m, 8H, ArH), 7.63 (t,  $J=7.8$  Hz, 1H,  $C_7H$ ), 7.82 (d,  $J=7.8$  Hz, 1H,  $C_8H$ ), 8.61 (s, 1H, NH,  $D_2O$  exchangeable), 8.89 (d,  $J=7.8$  Hz, 1H,  $C_6H$ ); MS:  $m/z$  (%): 498 (M+2, 80), 496 (M, 90), 481 (40), 409 (30), 318 (20), 248 (30), 77 (50). Anal. Calcd for  $C_{29}H_{25}ClN_4O_2$  (496.99): C, 70.08; H, 5.07; N, 11.27. Found: C, 69.76; H, 4.91; N, 11.31.

**4.2.9.5. 9-Chloro-N,1-(di-3-chlorophenyl)-2,3-dihydro-4-methyl-1H-pyrrolo[3,2-c]benzo[h][1,6]naphthyridin-11-amine (12e).** Recrystallized from DMF to afford yellow prisms, yield (0.421 g, 85%);  $R_f$  (10% toluene/ethyl acetate) 0.44, mp 288 °C; IR (KBr):  $\nu$  3365 (NH), 2823, 1565, 1532, 1470, 1332, 1168, 1054, 925  $cm^{-1}$ ;  $^1H$  NMR ( $DMSO-d_6$ ):  $\delta$  2.71 (s, 3H,  $CH_3$ ), 3.01 (t,  $J=8.1$  Hz, 2H,  $CH_2CH_2N$ ), 3.99 (t,  $J=8.1$  Hz, 2H,  $CH_2CH_2N$ ), 6.89–7.22 (m, 8H, ArH), 7.74 (t,  $J=7.6$  Hz, 1H,  $C_7H$ ), 7.86 (d,  $J=7.6$  Hz, 1H,  $C_8H$ ), 8.31 (s, 1H, NH,  $D_2O$  exchangeable), 8.88 (d,  $J=7.6$  Hz, 1H,  $C_6H$ ); MS:  $m/z$  (%): 511 (M+6, 20), 509 (M+4, 50), 507 (M+2, 100), 505 (M, 100), 469 (20), 378 (80), 330 (20), 235 (50), 216 (20), 164 (15), 75 (80), 63 (20). Anal. Calcd for  $C_{27}H_{19}Cl_3N_4$  (505.83): C, 64.11; H, 3.79; N, 11.08. Found: C, 64.21; H, 4.08; N, 11.02.

**4.2.9.6. 9-Chloro-N,1-(di-2-chlorophenyl)-2,3-dihydro-4-methyl-1H-pyrrolo[3,2-c]benzo[h][1,6]naphthyridin-11-amine (12f).** Recrystallized from ethanol/DMF (5:5) to afford yellow prisms; yield (0.398 g, 79%);  $R_f$  (10% toluene/ethyl acetate) 0.58, mp 293 °C; IR (KBr):  $\nu$  3353 (NH), 2918, 2848, 1579, 1521, 1473, 1328, 1197, 1054, 925, 775, 746, 688  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.71 (s, 3H,  $CH_3$ ), 3.01 (t,  $J=8.1$  Hz, 2H,  $CH_2CH_2N$ ), 3.99 (t,  $J=8.1$  Hz, 2H,  $CH_2CH_2N$ ), 6.89–7.22 (m, 8H, ArH), 7.67 (t,  $J=7.2$  Hz, 1H,  $C_7H$ ), 7.79 (d,  $J=7.2$  Hz, 1H,  $C_8H$ ), 8.25 (s, 1H, NH,  $D_2O$  exchangeable), 8.85 (d,  $J=7.2$  Hz, 1H,  $C_6H$ ); MS:  $m/z$  (%): 511 (M+6, 20), 509 (M+4, 50), 507 (M+2, 100), 505 (M, 100), 469 (20), 378 (80), 330 (20), 253 (20), 235 (50), 216 (20), 164 (15), 111 (50), 75 (80), 63 (20), 44 (30). Anal. Calcd for  $C_{27}H_{19}Cl_3N_4$  (505.83): C, 64.11; H, 3.79; N, 11.08. Found: C, 64.23; H, 3.76; N, 11.23.



4.2.9.7. 9-Chloro-N,1-(di-4-methylphenyl)-2,3-dihydro-4-methyl-1H-pyrrolo[3,2-c]benzo[h][1,6]naphthyridin-11-amine (**12g**).

Recrystallized from ethanol/DMF (5:5) to afford yellow prisms; yield (0.375 g, 81%);  $R_f$  (10% toluene/ethyl acetate) 0.38, mp 249 °C; IR (KBr):  $\nu$  3427 (NH), 2914, 3087, 1585, 1529, 1409, 1269, 1080, 975, 750, 688  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.13 (s, 3H,  $\text{ArCH}_3$ ), 2.27 (s, 3H,  $\text{ArCH}_3$ ), 2.65 (s, 3H,  $\text{CH}_3$ ), 3.14 (t,  $J=8.4$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{N}$ ), 4.35 (t,  $J=8.4$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{N}$ ), 6.87–7.00 (m, 8H, ArH), 7.63 (t,  $J=7.2$  Hz, 1H,  $\text{C}_7\text{H}$ ), 7.69 (d,  $J=7.2$  Hz, 1H,  $\text{C}_8\text{H}$ ), 8.33 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable), 8.87 (d,  $J=7.2$  Hz, 1H,  $\text{C}_6\text{H}$ ); MS:  $m/z$  (%): 466 (M+2, 60), 464 (M, 90), 373 (50), 282 (60), 246 (10), 192 (10), 104 (20), 93 (100), 77 (50). Anal. Calcd for  $\text{C}_{29}\text{H}_{25}\text{ClN}_4$  (464.99): C, 74.91; H, 5.42; N, 12.05. Found: C, 74.33; H, 5.49; N, 11.91.

4.2.9.8. 9-Chloro-N,1-(di-4-bromophenyl)-2,3-dihydro-4-methyl-1H-pyrrolo[3,2-c]benzo[h][1,6]naphthyridin-11-amine (**12h**).

Recrystallized from ethanol/DMF (5:5) to afford yellow prisms; yield (0.433 g, 73%);  $R_f$  (10% toluene/ethyl acetate) 0.33, mp 315 °C; IR (KBr):  $\nu$  3353 (NH), 2960, 2698, 2663, 1587, 1153, 1497, 1328, 1142, 927, 831, 775, 744, 626  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.79 (s, 3H,  $\text{CH}_3$ ), 2.98 (t,  $J=8.5$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{N}$ ), 3.90 (t,  $J=8.5$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{N}$ ), 6.89–7.34 (m, 8H, ArH), 7.37 (t,  $J=7.5$  Hz, 1H,  $\text{C}_7\text{H}$ ), 7.78 (d,  $J=7.5$  Hz, 1H,  $\text{C}_8\text{H}$ ), 8.90 (d,  $J=7.5$  Hz, 1H,  $\text{C}_6\text{H}$ ), 9.01 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable); MS:  $m/z$  (%): 600 (M+6, 10), 598 (M+4, 10), 596 (M+2, 10), 594 (M, 20), 513 (10), 410 (10), 342 (10), 281 (10), 207 (20), 149 (20), 135 (80), 108 (90), 81 (50), 66 (50), 44 (100). Anal. Calcd for  $\text{C}_{27}\text{H}_{19}\text{Br}_2\text{ClN}_4$  (594.73): C, 54.53; H, 3.22; N, 9.42. Found: C, 54.60; H, 3.27; N, 9.32.

4.2.10. 5,7-Dichloro-3-(2-chloroethyl)-4-alkoxy-2-ethylbenzo[h][1,6]naphthyridines (**13a,b**). A mixture of 4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridine **8** (0.360 g, 0.001 mol) and sodium alkoxide (0.002 mol) in toluene was heated to reflux for 24 h. (TLC checked, Toluene) The solvent was evaporated in vacuo, the residue obtained was stirred into methanol. The formed crude product was collected by suction filtration washed with methanol, dried, and recrystallized from suitable solvent.

4.2.10.1. 5,7-Dichloro-3-(2-chloroethyl)-4-methoxy-2-methylbenzo[h][1,6]naphthyridine (**13a**). Recrystallized from ethanol to afford colorless prisms; yield (0.298 g, 84%);  $R_f$  (toluene) 0.81, mp 180 °C; IR (KBr):  $\nu$  2962, 2837, 1583, 1425, 1321, 1162, 1033, 776  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.89 (s, 3H,  $\text{CH}_3$ ), 3.44 (t,  $J=7.6$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{Cl}$ ), 3.92 (t,  $J=7.6$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{Cl}$ ), 4.19 (s, 3H,  $\text{OCH}_3$ ), 7.54 (t,  $J=7.5$  Hz, 1H,  $\text{C}_9\text{H}$ ), 7.94 (d,  $J=7.5$  Hz, 1H,  $\text{C}_8\text{H}$ ), 8.83 (d,  $J=7.5$  Hz, 1H,  $\text{C}_{10}\text{H}$ ); MS:  $m/z$  (%): 360 (M+6, 50), 358 (M+4, 60), 356 (M+2, 80), 354 (M, 100), 325 (100), 319 (60), 275 (70), 198 (20), 138 (50), 49 (70). Anal. Calcd for  $\text{C}_{16}\text{H}_{13}\text{Cl}_3\text{N}_2\text{O}$  (355.65): C, 54.03; H, 3.68; N, 7.88. Found: C, 54.22; H, 3.57; N, 7.81.

4.2.10.2. 5,7-Dichloro-3-(2-chloroethyl)-4-ethoxy-2-methylbenzo[h][1,6]naphthyridine (**13b**). Recrystallized from ethanol to afford yellow prisms; yield (0.258 g, 70%);  $R_f$  (toluene) 0.81, mp 197 °C; IR (KBr):  $\nu$  2976, 2893, 1583, 1315, 1190, 1035, 750  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.58 (t,  $J=7.5$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 2.89 (s, 3H,  $\text{CH}_3$ ), 3.51 (t,  $J=7.8$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{Cl}$ ), 3.80 (t,  $J=7.8$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{Cl}$ ), 4.75 (q,  $J=7.5$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 7.39 (t,  $J=7.8$  Hz, 1H,  $\text{C}_9\text{H}$ ), 7.76 (d,  $J=7.8$  Hz, 1H,  $\text{C}_8\text{H}$ ), 8.85 (d,  $J=7.8$  Hz, 1H,  $\text{C}_{10}\text{H}$ ); MS:  $m/z$  (%): 375 (M+6, 50), 373 (M+4, 60), 371 (M+2, 80), 369 (M, 100), 325 (100), 319 (60), 275 (70), 198 (20), 138 (50), 49 (70). Anal. Calcd for  $\text{C}_{17}\text{H}_{15}\text{Cl}_3\text{N}_2\text{O}$  (369.67): C, 55.23; H, 4.09; N, 7.58. Found: C, 55.22; H, 4.11; N, 7.53.

4.2.11. 4-Azido-3-(2-azidoethyl)-5,7-dichloro-2-methylbenzo[h][1,6]naphthyridine (**14**). A mixture of 4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridine **8** (0.360 g, 0.001 mol) and sodium azide (0.195 g 0.003 mol) in DMF (15 mL) was stirred at

room temperature for 10 h. The progress of reaction was monitored by TLC. After completion, the reaction mixture was slowly added over cold water (200 mL). The obtained solid was filtered off and recrystallized from ethanol to give title compound **14** (0.313 g, 84%) as colorless prisms;  $R_f$  (10% toluene/ethyl acetate) 0.60, mp 191 °C; IR (KBr):  $\nu$  2964, 2147 ( $\text{N}_3$ ), 1594, 1544, 1383, 1234, 1077, 785  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.90 (s, 3H,  $\text{CH}_3$ ), 3.50 (t,  $J=7.2$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{N}_3$ ), 3.86 (t,  $J=7.2$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{N}_3$ ), 7.68 (t,  $J=7.8$  Hz, 1H,  $\text{C}_9\text{H}$ ), 7.98 (d,  $J=7.8$  Hz, 1H,  $\text{C}_8\text{H}$ ), 9.16 (d,  $J=7.8$  Hz, 1H,  $\text{C}_{10}\text{H}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  24.29, 31.16, 42.36, 124.07, 125.41, 125.91, 127.01, 128.20, 131.11, 134.69, 140.23, 142.69, 146.06, 148.21, 163.37; MS:  $m/z$  (%): 376 (M+4, 10), 374 (M+2, 10), 372 (M, 20), 323 (20), 308 (60), 279 (100), 245 (100), 140 (90), 91 (90). Anal. Calcd for  $\text{C}_{15}\text{H}_{10}\text{Cl}_2\text{N}_8$  (373.2): C, 48.27; H, 2.70; N, 30.03. Found: C, 48.39; H, 2.50; N, 30.17.

4.2.12. 4,7-Dichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridin-5(6H)-one (**15**). A mixture of 4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridine **8** (1.08 g, 0.003 mol) in glacial acetic acid (10 mL) was heated to reflux for 15 min. After cooling down to room temperature, methanol (50 mL) was added, the crude product obtained was collected by suction filtration, dried, and recrystallized from ethanol/DMF (9:1) to give title compound **15** (0.317 g, 93%) as pink colored prisms;  $R_f$  (10% toluene/ethyl acetate) 0.51, mp 254 °C; IR (KBr):  $\nu$  3339 (NH), 3186, 3143, 1676 ( $\text{C}=\text{O}_{\text{lactum}}$ ), 1249, 734  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.91 (s, 3H,  $\text{CH}_3$ ), 3.57 (t,  $J=7.1$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{Cl}$ ), 3.83 (t,  $J=7.1$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{Cl}$ ), 7.59 (t,  $J=7.5$  Hz, 1H,  $\text{C}_9\text{H}$ ), 7.77 (d,  $J=7.5$  Hz, 1H,  $\text{C}_8\text{H}$ ), 8.1 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable), 8.97 (d,  $J=7.5$  Hz, 1H,  $\text{C}_{10}\text{H}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  23.26, 30.95, 42.65, 119.40, 121.72, 122.14, 126.75, 128.00, 128.20, 128.63, 128.74, 136.66, 142.23, 161.54, 170.61; MS:  $m/z$  (%): 347 (M+6, 10), 345 (M+4, 30), 343 (M+2, 50), 341 (M, 100), 274 (20), 198 (20), 99 (10). Anal. Calcd for  $\text{C}_{15}\text{H}_{11}\text{Cl}_3\text{N}_2\text{O}$  (341.62): C, 52.74; H, 3.25; N, 8.20. Found: C, 52.47; H, 3.31; N, 8.29.

4.2.13. 9-Chloro-2,3-dihydro-4-methylbenzo[h][1,6]naphthyridin-1-phenyl-1H-pyrrolo[3,2-c]-11(10H)-one (**16**). A mixture of 4,7-dichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridine-5(6H)-one **15** (0.360 g, 0.001 mol) and primary aromatic amine (0.01 mol) was heated to 160 °C for 30 min. After reaction had completed, the reaction mixture was cooled to room temperature, methanol (10 mL) was added, and resulting solid formed was collected by suction filtration, dried, and recrystallized from ethanol to give title compound **16** (0.299 g, 83%) as yellow prisms;  $R_f$  (10% toluene/ethyl acetate) 0.40, mp 272 °C; IR (KBr):  $\nu$  3339 (NH), 3186, 3143, 1676 ( $\text{C}=\text{O}_{\text{lactum}}$ ), 1249, 734  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.70 (s, 3H,  $\text{CH}_3$ ), 3.23 (t,  $J=7.8$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{N}$ ), 4.43 (t,  $J=7.8$  Hz, 2H,  $\text{CH}_2\text{CH}_2\text{N}$ ), 7.00–7.30 (m, 5H, ArH), 7.46 (t,  $J=7.2$  Hz, 1H,  $\text{C}_7\text{H}$ ), 7.70 (d,  $J=7.2$  Hz, 1H,  $\text{C}_8\text{H}$ ), 8.10 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable), 8.89 (d,  $J=7.2$  Hz, 1H,  $\text{C}_6\text{H}$ ); MS:  $m/z$  (%): 363 (M+2, 30), 361 (M, 100), 254 (20), 221 (10), 91 (50). Anal. Calcd for  $\text{C}_{21}\text{H}_{16}\text{ClN}_3\text{O}$  (361.82): C, 69.71; H, 4.46; N, 11.61. Found: C, 69.70; H, 4.49; N, 11.67.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.04.085.

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