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A facile and efficient synthesis of 1-trichloromethyl-1,2-dihydrobenzo[*b*][1,6]naphthyridines *via* three-component reaction among 2-alkynylquinoline-3-carbaldehydes, primary amines, and chloroform

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Abstract

A three-component reaction among 2-alkynylquinoline-3-carbaldehydes, primary amines, and chloroform leading to novel 1-(trichloromethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridines was developed using microwave initiation in an absence of any catalysts. This method provides a facile approach to the title compounds with moderate to higher yields.

Keywords: 2-alkynylquinoline-3-carbaldehydes; benzo[*b*][1,6]naphthyridines; microwave chemistry; three-component reaction.

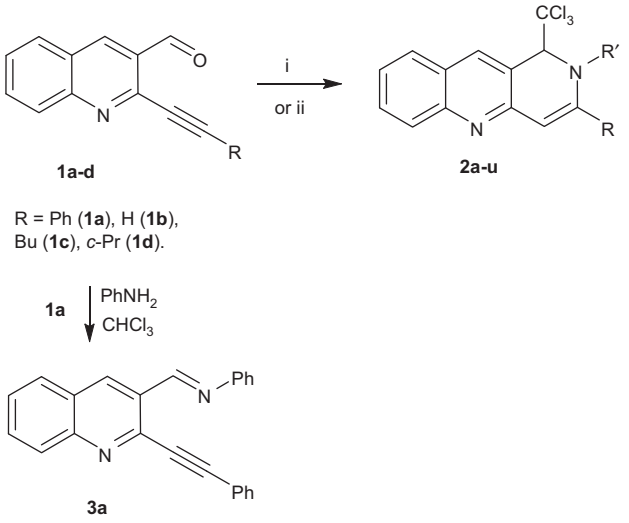
Introduction

Multicomponent reactions belong to the most efficient methods for preparation of organic compounds, allowing the formation of several bonds and the construction of complex molecular architectures from simple precursors in a single synthetic operation without the need for isolation of intermediates (Ugi et al., 1994; Armstrong et al., 1996; Bienayme et al., 2000; Doemling, 2000; Ramon and Yus, 2005; Zhu and Bienayme, 2005; Ganem, 2009; Chen and Wu, 2010; Wang et al., 2011). Recently, we have presented the straightforward synthesis of few 2-substituted 1-(trichloromethyl)-3-phenyl-1,2-dihydrobenzo[*b*][1,6]naphthyridines from 2-phenylethynylquinoline-3-carbaldehyde, primary amines, and chloroform and showed that these products induced considerably growth inhibition in some human solid cancer cell lines (Rudys et al., 2010). There also are some reports in the literature about notable antitumor activity of 1,2-dihydrobenzo[*b*][1,6]naphthyridine derivatives (Croisy-Delcey and Bisagni, 1983; Deady et al., 2003, 2005). Continuing our research on the use of ethynylazines in the synthesis of fused nitrogen nucleus-containing heterocycles (Čikotienė et al., 2008, 2009, 2010, Čikotienė, 2009, Čikotienė and Morkunas, 2009), we decided to explore the scope of the three-component reactions of 2-alkynylquinoline-3-carbaldehydes, primary amines, and *C*-pronucleophiles and the use of this method for the preparation of biologically important 1,2-dihydrobenzo[*b*][1,6]naphthyridine scaffold. Herein, we present the results of our investigations.

Results and discussion

For the synthesis of the starting compounds **1a–d**, we followed a classical Sonogashira coupling (Sonogashira et al., 1975) between commercially available 2-chloroquinoline-3-carbaldehyde and terminal acetylenes. First, we turned our attention to the multicomponent reaction among the substrates **1a–d**, amines, and chloroform by the method developed earlier by Asao et al. (2006) and Iso et al. (2008) for *o*-alkynylbenzenecarbaldehydes. However, upon the treatment of compounds **1a–d** with amines in chloroform in the presence of 3-Å molecular sieves at room temperature, the conversions of the starting compounds were incomplete and mixtures of various products were formed. Heating under reflux of aldehydes **1a,b** with 1.2 equivalents of the corresponding amine in chloroform and in the presence of the molecular sieves furnished the target compounds **2a–d,h,i** in 16–60% yields (Scheme 1). It should be noted that refluxing took 24–48 h, and the conversions of the starting compounds were still incomplete. Moreover, the reaction between **1a** and bulky cyclopentylamine in chloroform was unsuccessful, as no product was observed by thin-layer chromatography (TLC) after 48 h of heating. On the other hand, 2-hexynylquinoline-3-carbaldehyde **1d** was completely inert toward benzylamine and butylamine in refluxing chloroform.

To shorten the long reaction times, microwave-assisted chemistry was used (Gedye et al., 1986; Caddick, 1995; Strauss et al., 1995; Lew et al., 2002). When the mixtures of the starting compounds **1a–d**, amines, chloroform, and molecular sieves in 1,2-dichloroethane were placed in closed vessels and irradiated in a domestic microwave oven for 5–60 min, the target 1-(trichloromethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridines formed. The method tolerates well aliphatic amines. In the case of bulky cyclopentylamine, the reaction time is longer and the yields are slightly lower. An attempted reaction of the starting quinoline **1a** with aniline was unsuccessful, and the formation of a stable Schiff base **3a** as a sole reaction product was observed (Scheme 2). On the other hand, the attempted reaction of **1b** with aniline in chloroform did not produce any isolable product.



Scheme 1 (i) R′NH_2 (1.2 equiv.), 3-Å molecular sieves, $CHCl_3$, reflux. (ii) R′NH_2 (1.2 equiv.), 3-Å molecular sieves, $CHCl_3$ (3 equiv.) in 1,2-dichloroethane, microwave irradiation, 600 W.

We believe that at the beginning, the formation of imines **3** from the starting substrates and amines takes place. Nucleophilic attack of the imine nitrogen at the triple bond would lead to the formation of zwitterion salt **A.** Abstraction of proton from chloroform and subsequent attack of trichloromethyl anion would produce the final compounds **2a–u** (Scheme 2). A similar mechanism was proposed by Asao et al. (2006) for *o*-alkynylbenzenecarbaldehydes.

The examination of the results suggests that there are several factors affecting the successful cyclization. These include steric factors (hindrance or geometrical alignment of substituents on alkynyl and imine moieties), stability of the intermediate products, and reaction conditions. The observed failure of the attempted reaction of aniline can be explained in two ways. First, the imine nitrogen in compound **3a** is relatively nonnucleophilic due to conjugation with the aromatic ring. However, Asao et al. (2006) have found that the reaction among *o*-ethynylbenzaldehyde, aniline, and chloroform proceeded successfully. It can be suggested that, in our case, there is a steric hindrance between two planar phenyl rings in compound **3a**, thus the formation of intermediate **A** becomes impossible.

The reaction was studied by ^{1}H NMR experiments. Upon dissolution of **1a** and benzylamine in $CDCl_3$ and before the heating, the immediate disappearance of aldehyde signal at 10.81 ppm and the appearance of new singlets at 9.11 ppm (CH=N) and 4.98 ppm (N-CH_2) were observed. These signals were attributed to the corresponding imine derivative **3** (Figure 1A). Upon heating the solution for 3 h, the gradual appearance of new singlets at 5.27 and 6.49 ppm together with the AB pattern at 4.54 and 4.86 ppm with a coupling constant 15.9 Hz for the final compound **2a** were observed (Figure 1B). This reaction is highly regioselective in that only the formation of 6-*endo*-dig cyclization products is observed.

As an extension of this work, similar three-component reactions with other pronucleophiles, such as nitromethane, diethyl malonate, phenylacetylene, and trimetoxymethane, were attempted. In all cases, mixtures of various undefined products were formed.

Conclusions

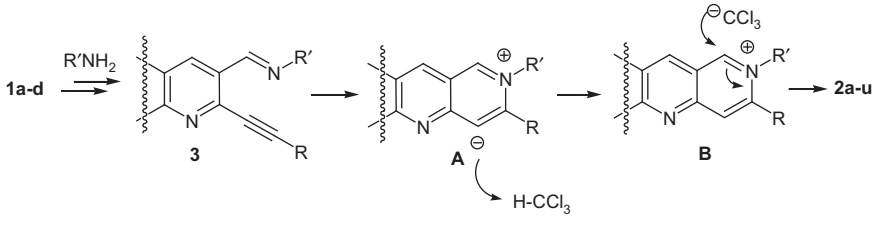
An efficient microwave-assisted three-component reaction among 2-alkynylquinoline-3-carbaldehydes, primary amines, and chloroform leading to novel 1-(trichloromethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridines was described. The presented method opens the way to biologically important 1,2-dihydrobenzo[*b*][1,6]naphthyridine derivatives.

Experimental section

Melting points were determined in open capillaries and are uncorrected. Infrared spectra were run in Nujol mulls or in KBr discs on a Perkin-Elmer FT spectrophotometer Spectrum BX II. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, on a Varian Unity INOVA spectrometer (300 MHz). The three-component reactions were carried out in closed 15-mL vessels in the domestic microwave oven (model Daewoo KOR6305A). All reactions and the purity of the synthesized compounds were monitored by TLC using silica gel 60 F254 aluminum plates (Merck). Visualization was accomplished by ultraviolet light.

General procedure for the synthesis of 2,3-disubstituted 1-(trichloromethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridines (2)

Method A (conventional heating) To a mixture of the corresponding compound **1a,b** (0.39 mmol) and 3-Å molecular sieves (0.3 g) in chloroform (3 mL), the corresponding amine (0.39 mmol) was added. The reaction mixture was heated under reflux for 24–48 h. After completion of the reaction, as observed by TLC, the solvent was removed to leave the crude product that was purified by basic silica gel column chromatography using a mixture of toluene and ethyl acetate as an eluent to give **2a–d,h,i.**



Scheme 2 The plausible mechanism of the three-component reaction.

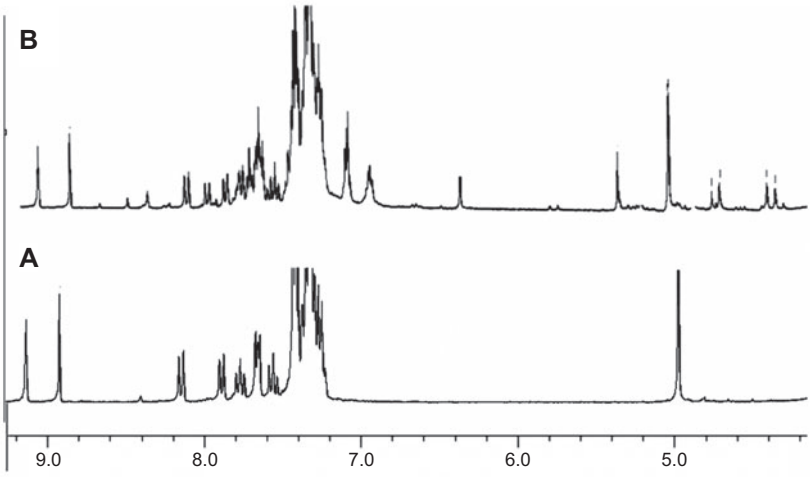


Figure 1 Fragments of ^{1}H NMR spectra.
(A) Immediately after mixing of **1a** with excess of benzylamine in $CDCl_3$. (B) After 3 h of heating.

Method B (microwave irradiation) A mixture of the corresponding compound **1a–d** (0.39 mmol), the corresponding amine (0.39 mmol), chloroform (1 mL), and 3-Å molecular sieves (0.3 g) in 1,2-dichloroethane (3 mL) was irradiated in a closed 15-mL vessel in the domestic microwave oven (model Daewoo KOR6305A) at 600 W for 10–25 min. After completion of the reaction, as observed by TLC, the solvent was removed to leave the crude product that was purified by basic silica gel column chromatography using a mixture of toluene and ethyl acetate as an eluent to give **2a–u**.

1-(Trichloromethyl)-3-phenyl-2-(phenylmethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2a) Yield 48% (method A), 81% (method B); yellow solid; mp 146–148°C; ^{1}H NMR: δ 8.04 (d, 1H, *J* = 8.4 Hz, ArH), 7.97 [s, 1H, C(10)H], 7.69–7.81 (m, 4H, ArH), 7.41–7.51 (m, 4H, ArH), 7.08–7.10 (m, 3H, ArH), 6.98–6.99 (m, 2H, ArH), 6.49 [s, 1H, C(4)H], 5.27 [s, 1H, C(1)H], 4.86 (d, 1H, J^2 = 15.9 Hz, PhCH), 4.54 (d, 1H, J^2 = 15.9 Hz, PhCH); ^{13}C NMR: δ 152.8, 148.7, 137.9, 137.5, 136.9, 130.3, 129.5, 128.8, 128.6, 128.4, 128.0, 127.6, 127.3, 126.6, 124.9, 119.0, 109.2, 104.9, 74.9, 59.2. Anal. Calcd for $C_{26}H_{19}Cl_3N_2$: C, 67.04; H, 4.11; N, 6.01. Found: C, 67.01; H, 4.25; N, 5.97.

1-(Trichloromethyl)-3-phenyl-2-(phenylethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2b) Yield 56% (method A), 84% (method B); yellow solid; mp 139–140°C; ^{1}H NMR: δ 8.04 (d, 1H, *J* = 8.7 Hz, ArH), 7.79 [s, 1H, C(10)H], 7.74–7.78 (m, 4H, ArH), 7.47–7.51 (m, 4H, ArH), 6.89–6.92 (m, 3H, ArH), 6.79–6.82 (m, 2H, ArH), 6.45 [s, 1H, C(4)H], 4.93 [s, 1H, C(1)H], 4.09–4.18 (m, 1H, PhCH$_2$**CH$_2$**N), 3.48–3.58 (m, 1H, PhCH$_2$**CH$_2$**N), 2.50–2.57 (m, 2H, Ph**CH$_2$**CH$_2$N); ^{13}C NMR: δ 152.8, 151.3, 148.7, 138.0, 137.5, 136.8, 130.2, 129.4, 128.8, 128.4, 128.2, 127.9, 126.9, 126.7, 126.3, 124.9, 119.2, 110.5, 104.8, 77.2, 58.1, 35.8. Anal. Calcd for $C_{27}H_{21}Cl_3N_2$: C, 67.58; H, 4.41; N, 5.84. Found: C, 67.61; H, 4.33; N, 5.90.

2-Allyl-1-(trichloromethyl)-3-phenyl-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2c) Yield 60% (method A), 89% (method B); yellow solid; mp 127–128°C; ^{1}H NMR: δ 8.23 [s, 1H, C(10)H], 8.09 (d, 1H, *J* = 8.4 Hz, ArH), 7.86 (dd, 1H, *J* = 7.95, 1.2 Hz, ArH), 7.74–7.79 (m, 3H, ArH), 7.46–7.51 (m, 4H, ArH), 5.47–5.61 (m, 1H, CH$_2$**CH** = CH$_2$), 6.52 [s, 1H, C(4)H], 5.28 [s, 1H, C(1)H], 4.97–5.07 (m, 2H, CH$_2$CH = **CH$_2$**), 4.19–4.26 (m, 1H, **CH$_2$**CH = CH$_2$), 3.88–3.96 (m, 1H, **CH$_2$**CH = CH$_2$); ^{13}C NMR: δ 152.2, 148.3, 137.9, 136.6, 133.2, 130.3, 129.3, 128.8, 128.6, 128.0, 127.9, 127.8, 126.6, 124.9, 118.9, 117.9, 109.4, 104.5, 74.3, 58.1. Anal. Calcd for $C_{22}H_{17}Cl_3N_2$: C, 63.56; H, 4.12; N, 6.74. Found: C, 63.68; H, 4.05; N, 6.80.

2-Butyl-1-(trichloromethyl)-3-phenyl-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2d) Yield 39% (method A), 70% (method B); yellow solid; mp 103–104°C; ^{1}H NMR: δ 8.27 [s, 1H, C(10)H], 8.10 (d, 1H, *J* = 8.1 Hz, ArH), 7.87 (dd, 1H, *J* = 8.1, 1.2 Hz, ArH), 7.75–7.78 (m, 3H, ArH), 7.47–7.52 (m, 4H, ArH), 6.47 [s, 1H, C(4)H], 5.26 [s, 1H, C(1)H], 3.65–3.72 (m, 1H, **CH$_2$**CH$_2$CH$_2$CH$_3$), 3.27–3.36 (m, 1H, **CH$_2$**CH$_2$CH$_2$CH$_3$), 2.30–2.39 (m, 2H, CH$_2$**CH$_2$**CH$_2$CH$_3$), 0.99–1.10 (m, 2H, CH$_2$CH$_2$**CH$_2$**CH$_3$), 0.68 (t, 3H, *J* = 7.5 Hz, CH$_2$CH$_2$CH$_2$**CH$_3$**); ^{13}C NMR: δ 152.9, 137.9, 136.9, 130.4, 129.4, 129.0, 128.7, 128.2, 127.9, 126.7, 125.9, 125.0, 109.4, 109.3, 104.9, 99.9, 75.9, 55.9, 31.1, 19.7, 13.7. Anal. Calcd for $C_{23}H_{21}Cl_3N_2$: C, 63.98; H, 4.90; N, 6.49. Found: C, 64.03; H, 4.89; N, 6.55.

1-(Trichloromethyl)-2-cyclopentyl-3-phenyl-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2e) Yield 45% (method B); yellow solid; mp 110–112°C; ^{1}H NMR: δ 8.27 [s, 1H, C(10)H], 8.08 (1H, d, *J* = 8.7 Hz, ArH), 7.83–7.87 (m, 3H, ArH), 7.69–7.75 (m, 1H, ArH), 7.44–7.49 (m, 4H, ArH), 6.71 [s, 1H, C(4)H], 5.23 [s, 1H, C(1)H], 3.74–3.85 [m, 1H, **CH**(CH$_2$CH$_2$)$_2$], 1.97–2.04 [m, 2H, CH(**CH$_2$**CH$_2$)$_2$], 1.64–1.68 [m, 2H, CH(**CH$_2$**CH$_2$)$_2$], 1.41–1.47 [m, 2H, CH(CH$_2$**CH$_2$**)$_2$], 1.25–1.28 [m, 2H, CH(CH$_2$**CH$_2$**)$_2$]; ^{13}C NMR: δ 153.3, 152.8, 148.4, 137.6, 130.2, 129.2, 128.7, 128.5, 128.2, 127.8, 127.6, 126.8, 125.1, 120.7, 112.2, 104.1, 69.5, 64.7, 29.7, 29.1, 22.6, 22.2. Anal. Calcd for $C_{24}H_{21}Cl_3N_2$: C, 64.95; H, 4.77; N, 6.31. Found: C, 65.01; H, 4.80; N, 6.27.

1-(Trichloromethyl)-2-(phenylmethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2f) Yield 71% (method B); yellow solid; mp 125–128°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 [s, 1H, C(10)H], 8.03 (br. s., 1H, ArH), 7.78 (dd, 1H, *J* = 8.1, 1.2 Hz, ArH), 7.68–7.74 (m, 1H, ArH), 7.40–7.45 (m, 1H, ArH), 7.25–7.28 (m, 3H, ArH), 7.13–7.16 (m, 3H, ArH), 6.85 [dd, 1H, *J* = 7.8, 1.5 Hz, C(3)H], 6.09 [dd, 1H, *J* = 7.8, 0.6 Hz, C(4)H], 5.30 [dd, 1H, *J* = 1.5, 0.6 Hz, C(1)H], 5.04 (d, 1H, J^2 = 15.9 Hz, PhCH), 4.82 (d, 1H, J^2 = 15.9 Hz, PhCH); ^{13}C NMR: δ 152.3, 148.4, 141.9, 138.2, 137.4, 130.4, 128.9, 128.1, 127.9, 127.8, 126.9, 126.4, 124.7, 117.3, 103.1, 84.1,

75.0, 62.3. Anal. Calcd for $C_{20}H_{15}Cl_3N_2$: C, 61.64; H, 3.88; N, 7.19. Found: C, 61.55; H, 4.00; N, 7.23.

1-(Trichloromethyl)-2-(phenylethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2g) Yield 76% (method B); yellow solid; mp 110–112°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* = 8.4 Hz, ArH), 7.70–7.77 (3H, m, ArH), 7.42–7.48 (1H, m, ArH), 6.98–7.05 (5H, m, ArH), 6.79 [1H, dd, *J* = 7.3, 0.9 Hz, C(3)H], 6.14 [1H, d, *J* = 7.3 Hz, C(4)H], 4.78 [1H, d, *J* = 0.9 Hz, C(1)H], 3.91–3.99 (2H, m, $PhCH_2\mathbf{CH_2}N$), 2.73–2.92 (2H, m, $Ph\mathbf{CH_2}CH_2N$); ^{13}C NMR: δ 152.4, 141.1, 138.7, 138.2, 130.8, 129.2, 128.8, 128.2, 126.8, 126.5, 125.8, 125.1, 124.2, 117.8, 104.7, 103.7, 76.7, 60.1, 37.7. Anal. Calcd for $C_{21}H_{17}Cl_3N_2$: C, 62.47; H, 4.24; N, 6.94. Found: C, 62.55; H, 4.15; N, 7.09.

2-Allyl-1-(trichloromethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2h) Yield 16% (method A), 75% (method B); yellow solid; mp 124–126°C; ^{1}H NMR: δ 8.13 [s, 1H, C(10)H], 8.00 (d, 1H, *J* = 8.25 Hz, ArH), 7.78 (dd, 1H, *J* = 8.1, 1.2 Hz, ArH), 7.65–7.71 (m, 1H, ArH), 7.38–7.43 (m, 1H, ArH), 6.72 [dd, 1H, *J* = 7.5, 1.2 Hz, C(3)H], 6.02 [d, 1H, *J* = 7.5 Hz, C(4)H], 5.71–5.83 (m, 1H, $CH_2\mathbf{CH} = CH_2$), 5.23 [d, 1H, *J* = 1.2 Hz, C(1)H], 5.07–5.16 (m, 2H, $CH_2CH = \mathbf{CH_2}$), 4.28–4.36 (m, 1H, $\mathbf{CH_2}CH = CH_2$), 4.11–4.19 (m, 1H, $\mathbf{CH_2}CH = CH_2$); ^{13}C NMR: δ 152.4, 148.3, 141.3, 138.3, 133.5, 130.5, 128.0, 127.9, 126.4, 124.7, 118.4, 117.3, 104.7, 103.2, 74.9, 60.2. Anal. Calcd for $C_{16}H_{13}Cl_3N_2$: C, 56.58; H, 3.86; N, 8.25. Found: C, 56.71; H, 4.00; N, 8.33.

2-Butyl-1-(trichloromethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2i) Yield 45% (method A), 85% (method B); yellow solid; mp 102–104°C; ^{1}H NMR: δ 8.14 [s, 1H, C(10)H], 8.02 (d, 1H, *J* = 8.4 Hz, ArH), 7.78 (dd, 1H, *J* = 8.1, 0.9 Hz, ArH), 7.64–7.70 (m, 1H, ArH), 7.37–7.43 (m, 1H, ArH), 6.73 [dd, 1H, *J* = 7.5, 1.2 Hz, C(3)H], 6.03 [d, 1H, *J* = 7.5 Hz, C(4)H], 5.21 [d, 1H, *J* = 1.2 Hz, C(1)H], 3.53–3.73 (m, 2H, $\mathbf{CH_2}CH_2CH_2CH_3$), 1.47–1.57 (m, 2H, $CH_2\mathbf{CH_2}CH_2CH_3$), 1.16–1.28 (m, 2H, $CH_2CH_2\mathbf{CH_2}CH_3$), 0.85 (t, 3H, *J* = 7.5 Hz, $CH_2CH_2CH_2\mathbf{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 147.9, 141.5, 138.3, 130.6, 127.9, 127.7, 126.3, 124.7, 117.5, 104.7, 102.5, 75.7, 57.8, 32.4, 19.8, 13.7. Anal. Calcd for $C_{17}H_{17}Cl_3N_2$: C, 57.40; H, 4.82; N, 7.88. Found: C, 57.66; H, 4.75; N, 7.99.

1-(Trichloromethyl)-2-cyclopentyl-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2j) Yield 75% (method B); yellow solid; mp 137–138°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 [s, 1H, C(10)H], 8.05 (d, 1H, *J* = 8.7 Hz, ArH), 7.79 (dd, 1H, *J* = 7.95, 0.9 Hz, ArH), 7.68–7.74 (m, 1H, ArH), 7.41–7.47 (m, 1H, ArH), 6.90 [dd, 1H, *J* = 7.8, 1.2 C(3)H], 6.12 [d, 1H, *J* = 7.8 Hz, C(4)H], 5.31 [d, 1H, *J* = 1.2 Hz, C(1)H], 4.09 [pent., 1H, *J* = 7.8 Hz, $\mathbf{CH}(CH_2CH_2)_2$], 2.21–2.30 [m, 1H, $CH(\mathbf{CH_2}CH_2)_2$], 1.91–2.00 [m, 2H, $CH(\mathbf{CH_2}CH_2)_2$], 1.69–1.85 [m, 4H, $CH(CH_2\mathbf{CH_2})_2$], 1.36–1.46 [m, 1H, $CH(CH_2\mathbf{CH_2})_2$]; ^{13}C NMR: δ 152.3, 147.4, 138.8, 137.6, 130.7, 127.9, 127.3, 126.3, 124.7, 117.6, 104.3, 102.9, 77.3, 68.7, 33.5, 29.7, 24.0, 23.9. Anal. Calcd for $C_{18}H_{17}Cl_3N_2$: C, 58.80; H, 4.66; N, 7.62. Found: C, 59.01; H, 4.75; N, 7.49.

3-Cyclopropyl-1-(trichloromethyl)-2-(phenylmethyl)-1,2-dihydrobenzo[*b*][1,6]-naphthyridine (2k) Yield 65% (method B); yellow solid; mp 146–148°C; ^{1}H NMR: δ 8.05 (d, 1H, *J* = 8.4 Hz, ArH), 8.04 [s, 1H, C(10)H], 7.76 (dd, 1H, *J* = 8.25, 1.2 Hz, ArH), 7.67–7.71 (m, 1H, ArH), 7.38–7.44 (m, 1H, ArH), 7.17–7.20 (m, 3H, ArH), 6.97–7.00 (m, 2H, ArH), 6.08 [s, 1H, C(4)H], 5.64 (d, 1H, J^2 = 17.4 Hz, PhCH), 5.25 [s, 1H, C(1)H], 4.88 (d, 1H, J^2 = 17.4 Hz, PhCH), 1.62–1.73 [m, 1H, $\mathbf{CH}(CH_2)_2$], 1.02–1.09 [m, 1H, $CH(\mathbf{CH_2})_2$], 0.83–0.91 [m, 2H, $CH(\mathbf{CH_2})_2$], 0.52–0.58 [m, 1H, $CH(\mathbf{CH_2})_2$]; ^{13}C NMR: δ 152.8, 148.1, 138.3, 137.4, 130.3, 128.6, 127.8, 127.6, 127.2, 126.0, 125.9, 124.4, 117.9, 104.7, 101.8, 76.4, 57.1, 14.2, 8.6, 4.5. Anal. Calcd for $C_{23}H_{19}Cl_3N_2$: C, 64.28; H, 4.46; N, 6.52. Found: C, 64.16; H, 4.49; N, 6.88.

3-Cyclopropyl-1-(trichloromethyl)-2-(phenylethyl)-1,2-dihydrobenzo[*b*][1,6]-naphthyridine (2l) Yield 71% (method B); yellow oil; ^{1}H NMR: δ 8.02 (dd, 1H, *J* = 8.25, 1.2 Hz, ArH), 7.65–7.73 (m, 3H, ArH), 7.37–7.43 (m, 1H, ArH), 6.95–7.05 (m, 5H, ArH), 6.05 [s, 1H, C(4)H], 4.80 [s, 1H, C(1)H], 4.58–4.67 (m, 1H, $PhCH_2\mathbf{CH_2}N$), 3.67–3.77 [m, 1H, $PhCH_2\mathbf{CH_2}N$], 2.76–2.80 (m, 2H, $Ph\mathbf{CH_2}CH_2N$), 1.72–1.79 [m, 1H, $\mathbf{CH}(CH_2)_2$], 1.05–1.10 [m, 1H, $CH(\mathbf{CH_2})_2$], 0.89–0.94 [m, 2H, $CH(\mathbf{CH_2})_2$], 0.78–0.82 [m, 1H, $CH(\mathbf{CH_2})_2$]; ^{13}C NMR: δ 153.1, 152.9, 148.2, 137.9, 137.2, 130.0, 128.7, 128.3, 127.8, 127.7, 126.3, 124.3, 118.1, 104.6, 102.7, 77.1, 56.5, 36.1, 13.8, 9.3, 4.9. Anal. Calcd for $C_{24}H_{21}Cl_3N_2$: C, 64.95; H, 4.77; N, 6.31. Found: C, 65.09; H, 4.96; N, 6.49.

2-Allyl-1-(trichloromethyl)-3-cyclopropyl-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2m) Yield 64% (method B); yellow oil; ^{1}H NMR: δ 8.13 [s, 1H, C(10)H], 8.03 (d, 1H, *J* = 8.4 Hz, ArH), 7.79 (dd, 1H, *J* = 8.1, 1.2 Hz, ArH), 7.66–7.71 (m, 1H, ArH), 7.38–7.44 (m, 1H, ArH), 6.04 [s, 1H, C(4)H], 5.64–5.76 (m, 1H, $CH_2\mathbf{CH} = CH_2$), 5.19 [s, 1H, C(1)H], 4.92–5.05 (m, 3H, $\mathbf{CH_2}CH = CH_2$ and $CH_2CH = \mathbf{CH_2}$), 4.18 (ddt, 1H, *J* = 18, 4.8, 1.2 Hz, $\mathbf{CH_2}CH = CH_2$), 1.63–1.73 [m, 1H, $\mathbf{CH}(CH_2)_2$], 0.84–1.06 [m, 3H, $CH(\mathbf{CH_2})_2$], 0.64–0.72 [m, 1H, $CH(\mathbf{CH_2})_2$]; ^{13}C NMR: δ 154.1, 152.9, 148.0, 137.7, 133.8, 130.4, 127.9, 127.6, 124.6, 118.2, 116.6, 104.7, 101.9, 75.6, 56.0, 14.2, 8.7, 4.4. Anal. Calcd for $C_{19}H_{17}Cl_3N_2$: C, 60.10; H, 4.51; N, 7.38. Found: C, 59.87; H, 4.45; N, 7.40.

2-Butyl-1-(trichloromethyl)-3-cyclopropyl-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2n) Yield 57% (method B); yellow solid; mp 112–114°C; ^{1}H NMR: δ 8.17 [s, 1H, C(10)H], 8.04 (d, 1H, *J* = 8.4 Hz, ArH), 7.80 (dd, 1H, *J* = 7.8, 1.2 Hz, ArH), 7.67–7.72 (m, 1H, ArH), 7.39–7.45 (m, 4H, ArH), 6.03 [s, 1H, C(4)H], 5.19 [s, 1H, C(1)H], 4.26–4.36 (m, 1H, $\mathbf{CH_2}CH_2CH_2CH_3$), 3.45–3.55 (m, 1H, $\mathbf{CH_2}CH_2CH_2CH_3$), 1.68–1.77 [m, 1H, $\mathbf{CH}(CH_2)_2$], 1.40–1.50 (m, 2H, $CH_2\mathbf{CH_2}CH_2CH_3$), 1.22–1.29 (m, 2H, $CH_2CH_2\mathbf{CH_2}CH_3$), 1.01–1.08 [m, 2H, $CH(\mathbf{CH_2})_2$], 0.89–0.93 [m, 1H, $CH(\mathbf{CH_2})_2$], 0.87 (t, 3H, *J* = 7.5 Hz, $CH_2CH_2CH_2\mathbf{CH_3}$), 0.72–0.84 [m, 1H, $CH(\mathbf{CH_2})_2$]; ^{13}C NMR: δ 152.9, 147.6, 137.9, 130.6, 127.9, 127.2, 126.1, 124.6, 118.3, 104.6, 101.3, 76.2, 54.4, 31.5, 19.9, 14.1, 13.8, 9.3, 5.0. Anal. Calcd for $C_{20}H_{21}Cl_3N_2$: C, 60.70; H, 5.35; N, 7.08. Found: C, 60.64; H, 5.48; N, 6.99.

1-(Trichloromethyl)-2-cyclopentyl-3-cyclopropyl-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2o) Yield 72% (method B); yellow oil; ^{1}H NMR: δ 8.17 [s, 1H, C(10)H], 8.00 (dd, 1H, *J* = 8.4, 0.6 Hz, ArH), 7.80 (dd, 1H, *J* = 8.1, 1.2 Hz, ArH), 7.64–7.68 (m, 1H, ArH), 7.39–7.44 (m, 1H, ArH), 6.14 [s, 1H, C(4)H], 5.18 [s, 1H, C(1)H], 4.51–4.62 [m, 1H, $\mathbf{CH}(CH_2CH_2)_2$], 2.12–2.16 [m, 1H, $\mathbf{CH}(CH_2)_2$], 1.45–1.74 (m, 6H), 1.92–2.00 (m, 1H), 0.96–1.17 (m, 3H) [$CH(\mathbf{CH}2)_2$, and $CH(\mathbf{CH_2CH_2})_2$], 0.83–0.92 [m, 1H, $CH(\mathbf{CH_2})_2$], 0.64–0.73 [m, 1H, $CH(\mathbf{CH_2})_2$]; ^{13}C NMR: δ 155.7, 153.2, 148.3, 136.9, 130.0, 128.0, 127.8, 126.5, 124.6, 119.9, 105.8, 70.3, 62.9, 30.2, 30.0, 23.1, 22.5, 14.5, 10.0, 5.0. Anal. Calcd for $C_{21}H_{21}Cl_3N_2$: C, 61.86; H, 5.19; N, 6.87. Found: C, 62.00; H, 5.22; N, 6.90.

3-Butyl-1-(trichloromethyl)-2-(phenylmethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2p) Yield 64% (method B); yellow

solid; mp 150–152°C; ^{1}H NMR: δ 8.08 [s, 1H, C(10)H], 8.07 (d, 1H, *J* = 8.7 Hz, ArH), 7.78 (dd, 1H, *J* = 8.1, 1.2 Hz, ArH), 7.69–7.72 (m, 1H, ArH), 7.41–7.46 (m, 1H, ArH), 7.19–7.22 (m, 3H, ArH), 6.99–7.01 (m, 2H, ArH), 6.15 [s, 1H, C(4)H], 5.24 [s, 1H, C(1)H], 5.14 (d, 1H, J^2 = 17.4 Hz, PhCH), 4.79 (d, 1H, J^2 = 17.4 Hz, PhCH), 2.50–2.60 (m, 1H, **CH$_2$**CH$_2$CH$_2$CH$_3$), 2.27–2.38 (m, 1H, **CH$_2$**CH$_2$CH$_2$CH$_3$), 1.70–1.83 (m, 2H, CH$_2$**CH$_2$**CH$_2$CH$_3$), 1.38–1.50 (m, 2H, CH$_2$CH$_2$**CH$_2$**CH$_3$), 0.99 (t, 3H, *J* = 7.5 Hz, CH$_2$CH$_2$CH$_2$**CH$_3$**); ^{13}C NMR: δ 152.8, 149.4, 148.3, 138.2, 137.6, 130.5, 128.9, 127.9, 127.8, 127.5, 126.3, 125.9, 124.6, 118.1, 104.9, 76.8, 57.3, 33.7, 29.8, 22.4, 13.8. Anal. Calcd for $C_{24}H_{23}Cl_3N_2$: C, 64.66; H, 5.20; N, 6.28. Found: C, 64.77; H, 5.12; N, 6.44.

3-Butyl-1-(trichloromethyl)-2-(phenylethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2r) Yield 62% (method B); yellow solid; mp 116–118°C; ^{1}H NMR: δ 8.00 (dd, 1H, *J* = 8.4, 0.6 Hz, ArH), 7.67 (d, 1H, *J* = 7.8 Hz, ArH), 7.58 (s, 1H, CH), 7.35–7.40 (m, 1H, ArH), 6.90–6.98 (m, 6H, ArH), 6.13 (s, 1H, CH), 4.65 (s, 1H, CH), 4.14–4.23 (m, 1H, PhCH$_2$**CH**), 3.53–3.63 (m, 1H, PhCH$_2$**CH**), 2.55–2.78 (2m, 3H, **CH$_2$**CH$_2$CH$_2$CH$_3$, and Ph**CH**), 2.32–2.42 (m, 1H, Ph**CH**), 1.66–1.80 (m, 2H, CH$_2$**CH$_2$**CH$_2$CH$_3$), 1.40–1.56 (m, 2H, CH$_2$CH$_2$**CH$_2$**CH$_3$), 0.98 (t, 3H, *J* = 7.5 Hz, CH$_2$CH$_2$CH$_2$**CH$_3$**); ^{13}C NMR: δ 152.8, 151.8, 148.0, 137.8, 137.2, 130.1, 128.8, 128.3, 127.7, 126.3, 126.1, 124.4, 118.2, 106.2, 104.6, 77.6, 56.5, 36.4, 33.6, 29.9, 22.5, 13.8. Anal. Calcd for $C_{25}H_{25}Cl_3N_2$: C, 65.30; H, 5.48; N, 6.09. Found: C, 65.40; H, 5.35; N, 5.98.

2-Allyl-3-butyl-1-(trichloromethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2s) Yield 58% (method B); yellow solid; mp 121–123°C; ^{1}H NMR: δ 8.14 [s, 1H, C(10)H], 8.02 (d, 1H, *J* = 8.7 Hz, ArH), 7.79 (dd, 1H, *J* = 8.1, 1.2 Hz, ArH), 7.66–7.72 (m, 1H, ArH), 7.39–7.42 (m, 1H, ArH), 6.09 [s, 1H, C(4)H], 5.64–5.75 (m, 1H, CH$_2$**CH** = CH$_2$), 5.15 [s, 1H, C(1)H], 4.91–5.04 (m, 2H, CH$_2$CH = **CH$_2$**), 4.44–4.52 (m, 1H, **CH$_2$**CH = CH$_2$), 4.04–4.12 (m, 1H, **CH$_2$**CH = CH$_2$), 2.49–2.59 (m, 1H, **CH$_2$**CH$_2$CH$_2$CH$_3$), 2.30–2.38 (m, 1H, **CH$_2$**CH$_2$CH$_2$CH$_3$), 1.67–1.78 (m, 2H, CH$_2$**CH$_2$**CH$_2$CH$_3$), 1.41–1.55 (m, 2H, CH$_2$CH$_2$**CH$_2$**CH$_3$), 0.99 (t, 3H, *J* = 7.5 Hz, CH$_2$CH$_2$CH$_2$**CH$_3$**); ^{13}C NMR: δ 152.9, 148.4, 137.4, 133.7, 130.3, 128.1, 128.0, 127.9, 126.3, 124.5, 118.1, 116.5, 105.1, 104.9, 76.2, 55.9, 33.5, 29.8, 22.4, 13.8. Anal. Calcd for $C_{20}H_{21}Cl_3N_2$: C, 60.70; H, 5.35; N, 7.08. Found: C, 60.79; H, 5.49; N, 6.89.

2,3-Dibutyl-1-(trichloromethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2t) Yield 48% (method B); yellow oil; ^{1}H NMR: δ 8.15 [s, 1H, C(10)H], 8.02 (d, 1H, *J* = 8.4 Hz, ArH), 7.79 (dd, 1H, *J* = 8.1, 0.9 Hz, ArH), 7.65–7.71 (m, 1H, ArH), 7.38–7.44 (m, 1H, ArH), 6.09 [s, 1H, C(4)H], 5.13 [s, 1H, C(1)H], 3.80–3.89 (m, 1H, N**CH$_2$**CH$_2$CH$_2$CH$_3$), 3.32–3.42 (m, 1H, N**CH$_2$**CH$_2$CH$_2$CH$_3$), 2.52–2.62 (m, 1H, **CH$_2$**CH$_2$CH$_2$CH$_3$), 2.28–2.39 (m, 1H, **CH$_2$**CH$_2$CH$_2$CH$_3$), 1.68–1.80 (m, 2H, CH$_2$**CH$_2$**CH$_2$CH$_3$), 1.40–1.55 (m, 4H, CH$_2$CH$_2$**CH$_2$**CH$_3$, and CH$_2$**CH$_2$**CH$_2$CH$_3$), 1.16–1.29 (m, 2H, CH$_2$CH$_2$**CH$_2$**CH$_3$), 1.00 (t, 3H, *J* = 7.5 Hz, CH$_2$CH$_2$CH$_2$**CH$_3$**), 0.85 (t, 3H, *J* = 7.5 Hz, CH$_2$CH$_2$CH$_2$**CH$_3$**); ^{13}C NMR: δ 153.1, 152.8, 148.3, 137.3, 130.2, 127.8, 127.0, 126.3, 124.4, 118.4, 105.4, 104.9, 76.7, 54.3, 33.6, 31.8, 29.9, 22.4, 19.9, 13.9, 13.8. Anal. Calcd for $C_{21}H_{25}Cl_3N_2$: C, 61.25; H, 6.12; N, 6.80. Found: C, 60.99; H, 5.93; N, 6.95.

3-Butyl-1-(trichloromethyl)-2-cyclopentyl-1,2-dihydrobenzo[*b*][1,6]naphthyridine (2u) Yield 38% (method B); yellow oil; ^{1}H NMR: δ 8.20 [s, 1H, C(10)H], 8.04 (d, 1H, *J* = 8.4 Hz, ArH), 7.81 (dd, 1H, *J* = 8.1, 1.2 Hz, ArH), 7.66–7.72 (m, 1H, ArH), 7.43–7.46 (m, 1H, ArH), 6.30 [s, 1H, C(4)H], 5.19 [s, 1H, C(1)H], 4.08–4.19 [m, 1H, **CH**(CH$_2$CH$_2$)$_2$], 2.61–2.72 (m, 1H, **CH$_2$**CH$_2$CH$_2$CH$_3$), 2.34–2.44 (m, 1H, **CH$_2$**CH$_2$CH$_2$CH$_3$), 1.94–1.98 and 2.10–2.14 [2m, 2H, CH(**CH$_2$**CH$_2$)$_2$], 1.45–1.78 [m, 10H, CH$_2$**CH$_2$**CH$_2$CH$_3$, CH$_2$**CH$_2$**CH$_2$CH$_3$, CH(**CH$_2$CH$_2$**)$_2$], 0.99 (t, 3H, *J* = 7.5 Hz, CH$_2$CH$_2$CH$_2$**CH$_3$**); ^{13}C NMR: δ 154.4, 152.8, 148.1, 137.1, 130.1, 127.9, 127.8, 126.6, 124.7, 119.7, 109.7, 104.6, 70.3, 62.3, 34.2, 30.6, 30.1, 30.0, 23.2, 22.6, 22.5, 13.8. Anal. Calcd for $C_{22}H_{25}Cl_3N_2$: C, 62.35; H, 5.95; N, 6.61. Found: C, 62.66; H, 6.02; N, 6.67.

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