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One-pot synthesis of annulated 1,8-naphthyridines

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Abstract: Annulated 1,8-naphthyridines were synthesized by one-pot reaction of aromatic aldehyde, malononitrile dimer and enehydrazinoketone.

Keywords: cyano compounds; heterocycles; Knoevenagel condensation; Michael addition; 1,8-naphthyridines.

Introduction

The naphthyridine moiety is part of many biologically active compounds possessing antimalarial [1], antibacterial [2, 3], anti-inflammatory [4–6], antiproliferative [7, 8], anticancer [9–11] and antioxidant activity [12]. In addition, naphthyridine derivatives are used as catalysts [13–15], fluorescent dyes [16] and sensors [17, 18]. Generally, 1,8-naphthyridines are synthesized by the Friedländer reaction and its modifications using pyridine derivatives as starting materials [19–21]. In recent years, multicomponent reactions have gained significant attention and have been used for the synthesis of polyfunctional compounds [22–27]. In the current work, naphthyridines were synthesized from an aromatic aldehyde, the malononitrile dimer and a 3-hydrazinylcyclohex-2-en-1-one through a sequential Michael reaction followed by two sequential heterocyclizations involving amine additions to nitriles.

Results and discussion

Previously, we have described a new method for obtaining 5*H*-chromeno[2,3-*b*]pyridines and 1,4-dihydro-1,8-naphthyridines by using double heteroannulation reactions of Michael adducts (DHARMA) strategy [28–31]. As part of our continued research, we have extended our method to obtain 2,4,10-triamino-6-oxo-5-aryl-5,6,7,8,9,10-hexahydrobenzo[*b*][1,8]naphthyridine-3-carbonitrile derivatives **2a–j** by the reaction of arylmethylidene derivatives of malononitrile dimer **1** and enehydrazinoketones (Scheme 1).

The presence of the nucleophilic and electrophilic centers in the Michael adduct **A** permits intramolecular heterocyclizations, leading to the formation of 1,8-naphthyridine **2**. Thus, following the Michael addition, the first pyridine is formed by nucleophilic attack of the enehydrazine nitrogen atom to the proximal cyano group. The resulting amine **B** is then captured by the cyano group of the dicyanomethylene moiety to give compound **2**.

The most effective way of constructing condensed heterocycles from simple substrates is the use of a multicomponent reaction. This strategy lowers the number of steps, as well as the amount of chemicals, thereby reducing the energy consumption of the process and increasing yield of the product. In this work, a three-component system comprising of aromatic aldehyde, malononitrile dimer and enehydrazinoketone was used to carry out a tandem Knoevenagel–Michael reaction that led to 1,4-dihydro-1,8-naphthyridines **2** in 65%–90% yields.

The structures of compounds **2a–j** were confirmed by spectral methods. ^{1}H NMR spectra taken at 27°C indicate that compounds **2g–j** exist as diastereomers because of the slow rate of inversion of the nitrogen atom of the dihydropyridine ring (Figure 1). To confirm this analysis, the ^{1}H NMR spectrum of **2g** was acquired at 70°C. As expected, a simpler spectrum due to averaging of signals is observed at the higher temperature.

Conclusion

A one-pot synthesis scheme of new 1,8-naphthyridines involves a double heteroannulation reaction.

Experimental

Progress of all reactions and purity of compounds were analyzed by TLC on Silufol UV-254 plates (development by UV irradiation, exposure to iodine vapor or thermal decomposition). IR spectra were recorded on an FT-IR spectrophotometer FSM-1202 using mulls in

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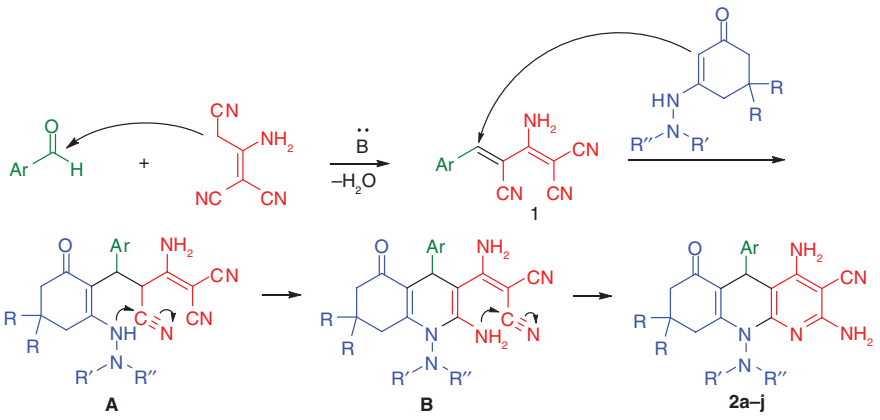

a: Ar = Ph; R = R′ = R″ = Me
b: Ar = 4-F-C_6H_6; R = R′ = R″ = Me
c: Ar = 4-CH_3-C_6H_4; R = R′ = R″ = Me
d: Ar = 3-Cl-C_6H_4; R = R′ = R″ = Me
e: Ar = Ph; R = H; R′ = R″ = Me
f: Ar = 4-F-C_6H_4; R = H; R′ = R″ = Me
g: Ar = Ph; R = Me; R′ = H; R″ = Ph
h: Ar = 2-Cl-C_6H_4; R = Me; R′ = H; R″ = Ph
i: Ar = 4-Me-C_6H_4; R = Me; R′ = H; R″ = Ph
j: Ar = 3-NO_2-C_6H_4; R = Me; R′ = H; R″ = Ph

Scheme 1 Synthesis of 2,4,10-triamino-6-oxo-5-aryl-5,6,7,8,9,10-hexahydrobenzo[*b*][1,8]naphthyridine-3-carbonitrile derivatives **2a–j**.

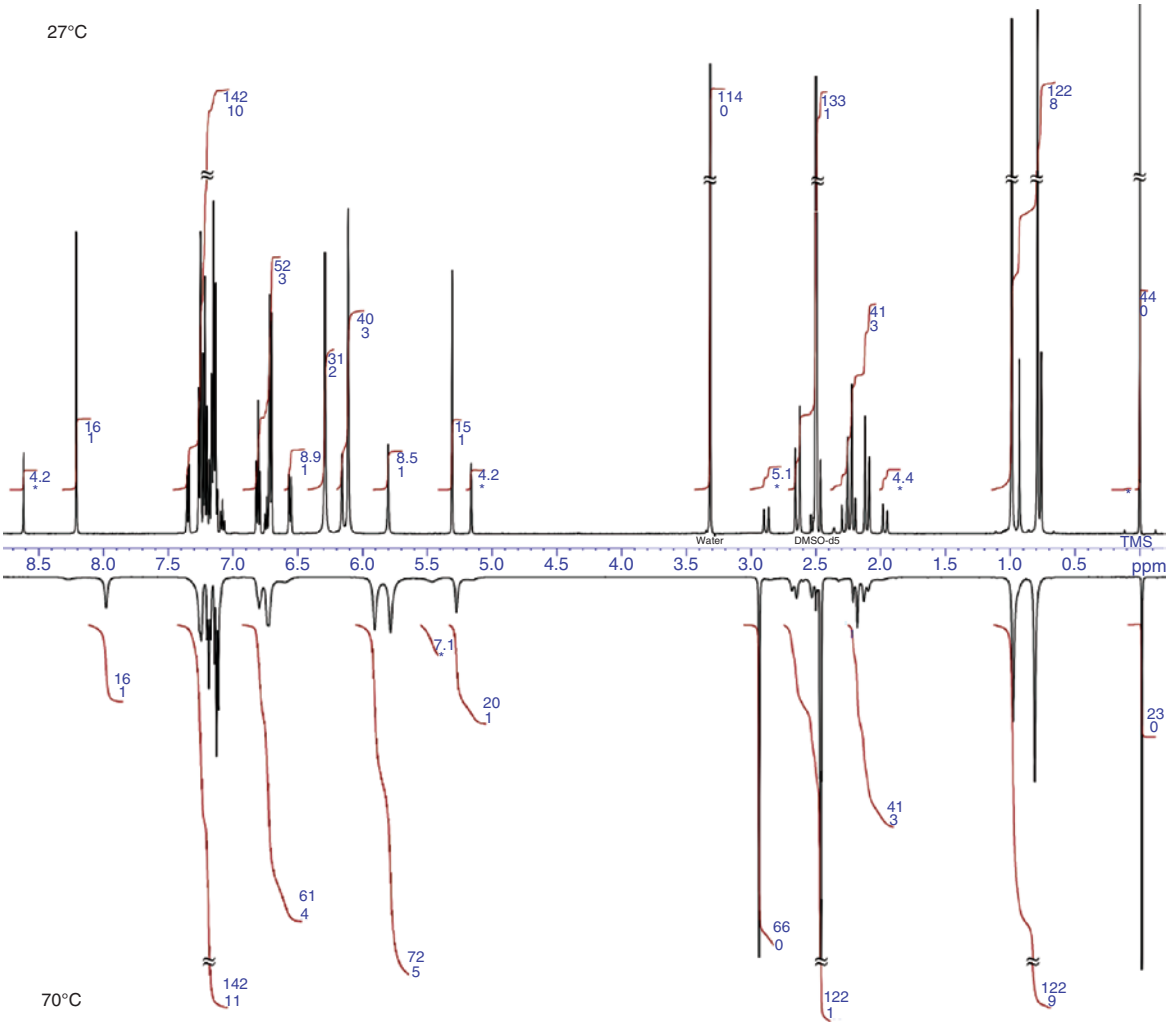

Figure 1 ^{1}H NMR spectra of compound **2g** at 27°C and at 70°C.

mineral oil. ^{1}H NMR spectra were registered on a spectrometer Bruker DRX-500 (500.13 MHz) in DMSO-d_6 using TMS as the internal standard. Mass spectra (EI, 70 eV) were obtained using a Finnigan MAT INCOS-50 instrument. The signals of a second isomer in NMR spectra of compounds **2g–j** are indicated by an asterisk.

General procedure for the synthesis of a series of 2,4-diamino-6-oxo-5-aryl-5,6,7,8,9,10-hexahydrobenzo[*b*][1,8]naphthyridine-3-carbonitriles 2

A solution of enehydrazinoketone (10 mmol) and piperidine in EtOH (10 mL) was added to a mixture of aromatic aldehyde (10 mmol) and malononitrile dimer (10 mmol) in EtOH (10 mL). The mixture was stirred at 40–50°C for 30 min and the resulting precipitate was filtered and washed with *i*-PrOH. Crude products were crystallized from a mixture of dioxane and acetonitrile.

2,4-Diamino-10-(dimethylamino)-8,8-dimethyl-6-oxo-5-phenyl-5,6,7,8,9,10-hexahydrobenzo[*b*][1,8]naphthyridine-3-carbonitrile (2a) This compound was obtained in 70% yield (0.28 g) as a pale yellow solid; mp 237–238°C (dec); ^{1}H NMR: δ 0.78 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.96 (d, 1H, J = 16 Hz, CH_2), 2.17 (d, 1H, J = 16 Hz, CH_2), 2.48 (d, 1H, J = 17 Hz, CH_2), 2.92 (d, 1H, J = 17 Hz, CH_2), 2.98 (s, 3H, $N(CH_3)_2$), 3.00 (s, 3H, $N(CH_3)_2$), 5.03 (s, 1H, CH), 6.08 (s, 2H, NH_2), 6.25 (s, 2H, NH_2), 7.06 (t, 1H, J = 7 Hz, C_6H_5), 7.16 (t, 2H, J = 7 Hz, C_6H_5), 7.23 (d, 2H, J = 7 Hz, C_6H_5); IR: 3456, 3427, 3337 (NH_2), 2190 (CN), 1630 cm^{-1} (C=O); MS: *m/z* (%) 402 [M]$^+$ (10), 358 [M–44]$^+$ (25), 325 [M–77]$^+$ (38), 281 [M–120]$^+$ (100). Anal. Calcd for $C_{23}H_{26}N_6O$: C, 68.63; H, 6.51; N, 20.88. Found: C, 68.77; H, 6.42; N, 20.72.

2,4-Diamino-10-(dimethylamino)-5-(4-fluorophenyl)-8,8-dimethyl-6-oxo-5,6,7,8,9,10-hexahydrobenzo[*b*][1,8]naphthyridine-3-carbonitrile (2b) This compound was obtained in 76% yield (0.32 g) as a white solid; mp 254–255°C (dec); ^{1}H NMR: δ 0.78 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.96 (d, 1H, J = 16 Hz, CH_2), 2.17 (d, 1H, J = 16 Hz, CH_2), 2.48 (d, 1H, J = 17 Hz, CH_2), 2.92 (d, 1H, J = 17 Hz, CH_2), 2.98 (s, 3H, $N(CH_3)_2$), 3.00 (s, 3H, $N(CH_3)_2$), 5.06 (s, 1H, CH), 6.14 (s, 2H, NH_2), 6.27 (s, 2H, NH_2), 6.99 (t, 2H, J = 9 Hz, C_6H_4), 7.25 (dd, 2H, J = 9 Hz, J = 6 Hz, C_6H_4); IR: 3459, 3320 (NH_2), 2190 (CN), 1680 cm^{-1} (C=O); MS: *m/z* (%) 420 [M]$^+$ (18), 377 [M–43]$^+$ (100), 325 [M–95]$^+$ (59). Anal. Calcd for $C_{23}H_{25}FN_6O$: C, 65.70; H, 5.99; N, 19.99. Found: C, 65.54; H, 5.87; N, 20.12.

2,4-Diamino-10-(dimethylamino)-8,8-dimethyl-6-oxo-5-(p-tolyl)-5,6,7,8,9,10-hexahydrobenzo[*b*][1,8]naphthyridine-3-carbonitrile (2c) This compound was obtained in 67% yield (0.28 g) as a pale yellow solid; mp 265–266°C (dec); ^{1}H NMR: δ 0.79 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.95 (d, 1H, J = 16 Hz, CH_2), 2.16 (d, 1H, J = 16 Hz, CH_2), 2.18 (s, 3H, CH_3), 2.47 (d, 1H, J = 18 Hz, CH_2), 2.91 (d, 1H, J = 18 Hz, CH_2), 2.97 (s, 3H, $N(CH_3)_2$), 3.00 (s, 3H, $N(CH_3)_2$), 4.97 (s, 1H, CH), 6.03 (s, 2H, NH_2), 6.23 (s, 2H, NH_2), 6.96 (d, 2H, J = 8 Hz, C_6H_4), 7.11 (d, 2H, J = 8 Hz, C_6H_4); IR: 3430, 3333, 3239 (NH_2), 2187 (CN), 1641 cm^{-1} (C=O); MS: *m/z* (%) 416 [M]$^+$ (20), 373 [M–43]$^+$ (90), 325 [M–91]$^+$ (50), 282 [M–134]$^+$ (100). Anal. Calcd for $C_{24}H_{28}N_6O$: C, 69.21; H, 6.78; N, 20.18. Found: C, 69.08; H, 6.79; N, 20.30.

2,4-Diamino-5-(3-chlorophenyl)-10-(dimethylamino)-8,8-dimethyl-6-oxo-5,6,7,8,9,10-hexahydrobenzo[*b*][1,8]naphthyridine-3-carbonitrile (2d) This compound was obtained in 80% yield (0.35 g) as a pale yellow solid; mp 251–252°C (dec); ^{1}H NMR: δ 0.78 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.98 (d, 1H, J = 16 Hz, CH_2), 2.18 (d, 1H, J = 16 Hz, CH_2), 2.48 (d, 1H, J = 18 Hz, CH_2), 2.92 (d, 1H, J = 18 Hz, CH_2), 2.98 (s, 3H, $N(CH_3)_2$), 3.00 (s, 3H, $N(CH_3)_2$), 5.07 (s, 1H, CH), 6.22 (s, 2H, NH_2), 6.30 (s, 2H, NH_2), 7.08–7.14 (m, 2H, C_6H_4), 7.21 (t, 1H, J = 8 Hz, C_6H_4), 7.37 (t, 1H, J = 2 Hz, C_6H_4); IR: 3465, 3343, 3211 (NH_2), 2196 (CN), 1625 cm^{-1} (C=O); MS: *m/z* (%) 436 [M]$^+$ (3), 393 [M–43]$^+$ (20). Anal. Calcd for $C_{23}H_{25}ClN_6O$: C, 63.22; H, 5.77; N, 19.23. Found: C, 63.09; H, 5.86; N, 19.37.

2,4-Diamino-10-(dimethylamino)-6-oxo-5-phenyl-5,6,7,8,9,10-hexahydrobenzo[*b*][1,8]naphthyridine-3-carbonitrile (2e) This compound was obtained in 65% yield (0.24 g) as a pale yellow solid; mp 239–240°C (dec); ^{1}H NMR: δ 1.60–1.69 (m, 2H, CH_2), 1.88–1.94 (m, 2H, CH_2), 2.12–2.24 (m, 2H, CH_2), 2.98 (s, 3H, CH_3), 3.01 (s, 3H, CH_3), 5.07 (s, 1H, CH), 6.08 (s, 2H, NH_2), 6.24 (s, 2H, NH_2), 7.06 (t, 1H, J = 7 Hz, C_6H_5), 7.14–7.25 (m, 4H, C_6H_5); IR: 3474, 3360 (NH_2), 2201 (CN), 1650 cm^{-1} (C=O); MS: *m/z* (%) 374 [M]$^+$ (5), 330 [M–44]$^+$ (16), 297 [M–77]$^+$ (25), 254 [M–120]$^+$ (100). Anal. Calcd for $C_{21}H_{22}N_6O$: C, 67.36; H, 5.92; N, 22.44. Found: C, 67.50; H, 5.83; N, 22.35.

2,4-Diamino-10-(dimethylamino)-5-(4-fluorophenyl)-6-oxo-5,6,7,8,9,10-hexahydrobenzo[*b*][1,8]naphthyridine-3-carbonitrile (2f) This compound was obtained in 68% yield (0.27 g) as a pale yellow solid; mp 237–238°C (dec); ^{1}H NMR: δ 1.64–1.68 (m, 2H, CH_2), 1.89–1.94 (m, 2H, CH_2), 2.14–2.22 (m, 2H, CH_2), 2.97 (s, 3H, CH_3), 3.01 (s, 3H, CH_3), 5.09 (s, 1H, CH), 6.13 (s, 2H, NH_2), 6.24 (s, 2H, NH_2), 6.98 (t, 2H, J = 9 Hz, C_6H_4), 7.23 (m, 4H, C_6H_4); IR: 3460, 3340 (NH_2), 2204 (CN), 1656 cm^{-1} (C=O); MS: *m/z* (%) 392 [M]$^+$ (1), 348 [M–44]$^+$ (4), 254 [M–138]$^+$ (43). Anal. Calcd for $C_{21}H_{21}FN_6O$: C, 64.27; H, 5.39; N, 21.42. Found: C, 64.38; H, 5.28; N, 21.30.

2,4-Diamino-8,8-dimethyl-6-oxo-5-phenyl-10-(phenylamino)-5,6,7,8,9,10-hexahydrobenzo[*b*][1,8]naphthyridine-3-carbonitrile (2g) This compound was obtained in 70% yield (0.32 g) as a white solid; mp 229–230°C (dec); ^{1}H NMR: δ 0.76 (s, 3H, CH_3)*, 0.79 (s, 3H, CH_3), 0.93 (s, 3H, CH_3)*, 0.99 (s, 3H, CH_3), 1.97 (d, 1H, J = 17 Hz, CH_2)*, 2.11 (d, 1H, J = 16 Hz, CH_2), 2.21 (d, 1H, J = 14 Hz, CH_2)*, 2.24 (d, 1H, J = 16 Hz, CH_2), 2.28 (d, 1H, J = 18.0 Hz, CH_2)*, 2.48 (d, 1H, J = 18 Hz, CH_2), 2.64 (d, 1H, J = 18 Hz, CH_2), 2.89 (d, 1H, J = 17 Hz, CH_2)*, 5.16 (s, 1H, CH)*, 5.31 (s, 1H, CH), 5.80 (s, 2H, NH_2)*, 6.11 (s, 2H, NH_2), 6.16 (s, 2H, NH_2)*, 6.29 (s, 2H, NH_2), 6.56 (d, 2H, J = 8 Hz, C_6H_5)*, 6.71 (d, 2H, J = 8 Hz, C_6H_5), 6.74 (t, 1H, J = 7 Hz, C_6H_5)*, 6.81 (t, 1H, J = 7 Hz, C_6H_5), 7.08 (t, 1H, J = 7 Hz, C_6H_5)*, 7.12–7.27 (m, 7H, $2C_6H_5$), 7.12–7.27 (m, 4H, $2C_6H_5$)*, 7.35 (d, 2H, J = 7 Hz, C_6H_5)*, 8.21 (s, 1H, NH), 8.62 (s, 1H, NH)*; IR: 3430, 3347 (NH_2), 3217 (NH), 2196 (CN), 1620 cm^{-1} (C=O); MS: *m/z* (%) 450 [M]$^+$ (55), 373 [M–77]$^+$ (95), 358 [M–92]$^+$ (56), 282 [M–168]$^+$ (100). Anal. Calcd for $C_{27}H_{26}N_6O$: C, 71.98; H, 5.82; N, 18.65. Found: C, 71.88; H, 5.90; N, 18.78.

2,4-Diamino-5-(2-chlorophenyl)-8,8-dimethyl-6-oxo-10-(phenylamino)-5,6,7,8,9,10-hexahydrobenzo[*b*][1,8]naphthyridine-3-carbonitrile (2h) This compound was obtained in 90% yield (0.44 g) as a white solid; mp 225–226°C (dec); ^{1}H NMR: δ 0.82 (s, 3H, CH_3)*, 0.86 (s, 3H, CH_3), 0.95 (s, 3H, CH_3)*, 1.00 (s, 3H, CH_3), 1.93 (d, 1H, J = 16 Hz, CH_2)*, 2.01 (d, 1H, J = 17 Hz, CH_2), 2.19 (d, 1H, J = 16 Hz, CH_2)*, 2.21 (d, 1H, J = 16 Hz, CH_2), 2.31 (d, 1H, J = 18 Hz, CH_2)*, 2.59 (d, 1H, J = 17 Hz, CH_2), 2.74 (d, 1H, J = 18 Hz, CH_2), 2.93 (d, 1H, J = 17 Hz, CH_2)*, 5.25 (s, 1H, CH), 5.29 (s, 1H, CH)*, 5.82 (s, 2H, NH_2), 5.82 (s, 2H, NH_2)*, 5.92 (s, 2H, NH_2)*, 6.17 (s, 2H, NH_2), 6.62 (d, 2H, J = 8 Hz, C_6H_5)*, 6.76 (t, 1H, J = 7 Hz, C_6H_5)*, 6.89 (t, 1H, J = 7 Hz, C_6H_5), 6.95 (d,

2H, J=8 Hz, C_6H_5), 7.13–7.36 (m, 2H, C_6H_5)*, 7.13–7.36 (m, 2H, C_6H_5), 7.13–7.36 (m, 3H, C_6H_4), 7.13–7.36 (m, 3H, C_6H_4)*, 7.47 (dd, 1H, J=8 Hz, J=1.6 Hz, C_6H_4)*, 7.54 (d, 1H, J=7 Hz, C_6H_4), 8.19 (s, 1H, NH), 8.59 (s, 1H, NH)*; IR: 3383, 3312 (NH_2), 3205 (NH), 2190 (CN), 1630 (C=O); MS: *m/z* (%) 484 $[M]^+$ (5). Anal. Calcd for $C_{27}H_{25}ClN_6O$: C, 66.87; H, 5.20; N, 17.33. Found: C, 66.74; H, 5.09; N, 17.47.

2,4-Diamino-8,8-dimethyl-6-oxo-10-(phenylamino)-5-(p-tolyl)-5,6,7,8,9,10-hexahydrobenzo[*b*][1,8]naphthyridine-3-carbonitrile (2i) This compound was obtained in 70% yield (0.33 g) as a pale yellow solid; mp 234–235°C (dec); ^{1}H NMR: δ 0.77 (s, 3H, CH_3)*, 0.80 (s, 3H, CH_3), 0.93 (s, 3H, CH_3)*, 0.99 (s, 3H, CH_3), 1.96 (d, 1H, J=16 Hz, CH_2)*, 2.09 (d, 1H, J=16 Hz, CH_2), 2.20 (s, 3H, CH_3)*, 2.23 (s, 3H, CH_3), 2.24 (d, 1H, J=16 Hz, CH_2), 2.28 (d, 1H, J=18 Hz, CH_2)*, 2.48 (d, 1H, J=18 Hz, CH_2), 2.52 (d, 1H, J=18 Hz, CH_2)*, 2.64 (d, 1H, J=18 Hz, CH_2), 2.88 (d, 1H, J=18 Hz, CH_2)*, 5.10 (s, 1H, CH)*, 5.24 (s, 1H, CH), 5.79 (s, 2H, NH_2)*, 6.10 (s, 2H, NH_2), 6.11 (s, 2H, NH_2)*, 6.22 (s, 2H, NH_2), 6.56 (d, 2H, J=8 Hz, C_6H_5)*, 6.74–6.76 (m, 2H, C_6H_5), 6.74–6.76 (m, 1H, C_6H_5)*, 6.82 (t, 1H, J=7 Hz, C_6H_5), 6.98 (d, 2H, J=8 Hz, C_6H_4), 7.02 (d, 2H, J=8 Hz, C_6H_4)*, 7.13–7.19 (m, 2H, C_6H_5), 7.13–7.19 (m, 2H, C_6H_5)*, 7.13–7.19 (m, 1H, C_6H_4), 7.23 (d, 1H, J=8 Hz, C_6H_4)*, 8.21 (s, 1H, NH), 8.61 (s, 1H, NH)*; IR: 3494, 3302 (NH_2), 3234 (NH), 2200 (CN), 1660 cm^{-1} (C=O); MS: *m/z* (%) 464 $[M]^+$ (10), 373 $[M–91]^+$ (43), 282 $[M–182]^+$ (67), 93 $[M–371]^+$ (100). Anal. Calcd for $C_{28}H_{28}N_6O$: C, 72.39; H, 6.08; N, 18.09. Found: C, 72.56; H, 5.99; N, 18.23.

2,4-Diamino-8,8-dimethyl-5-(3-nitrophenyl)-6-oxo-10-(phenylamino)-5,6,7,8,9,10-hexahydrobenzo[*b*][1,8]naphthyridine-3-carbonitrile (2j) This compound was obtained in 87% yield (0.43 g) as a pale yellow solid; mp 231–232°C (dec); ^{1}H NMR: δ 0.75 (s, 3H, CH_3)*, 0.77 (s, 3H, CH_3), 0.94 (s, 3H, CH_3)*, 1.00 (s, 3H, CH_3), 1.98 (d, 1H, J=16.6 Hz, CH_2)*, 2.10 (d, 1H, J=16 Hz, CH_2), 2.24 (d, 1H, J=16 Hz, CH_2)*, 2.27 (d, 1H, J=16 Hz, CH_2), 2.31 (d, 1H, J=18 Hz, CH_2)*, 2.52 (d, 1H, J=18 Hz, CH_2), 2.69 (d, 1H, J=18 Hz, CH_2), 2.91 (d, 1H, J=18 Hz, CH_2)*, 5.40 (s, 1H, CH)*, 5.48 (s, 1H, CH), 5.92 (s, 2H, NH_2)*, 6.20 (s, 2H, NH_2), 6.39 (s, 2H, NH_2)*, 6.47 (s, 2H, NH_2), 6.59 (d, 2H, J=8 Hz, C_6H_5)*, 6.74–6.80 (m, 1H, C_6H_5)*, 6.74–6.80 (m, 2H, C_6H_5), 6.84 (t, 1H, J=7 Hz, C_6H_5), 7.15–7.20 (m, 2H, C_6H_5), 7.15–7.20 (m, 2H, C_6H_5)*, 7.52 (t, 1H, J=8 Hz, C_6H_4)*, 7.56 (t, 1H, J=8 Hz, C_6H_4), 7.75 (dt, 1H, J=8 Hz, J=1 Hz, C_6H_4)*, 7.80 (dt, 1H, J=8 Hz, J=1 Hz, C_6H_4), 7.99 (ddd, 1H, J=8 Hz, J=2 Hz, J=1 Hz, C_6H_4)*, 8.04 (ddd, 1H, J=8 Hz, J=2 Hz, J=1 Hz, C_6H_4), 8.17 (t, 1H, J=2 Hz, C_6H_4), 8.26 (s, 1H, NH), 8.33 (t, 1H, J=2 Hz, C_6H_4)*, 8.66 (s, 1H, NH)*; IR: 3492, 3316 (NH_2), 3238 (NH), 2198 (CN), 1660 cm^{-1} (C=O); MS: *m/z* (%) 495 $[M]^+$ (17), 373 $[M–122]^+$ (74), 93 $[M–402]^+$ (100). Anal. Calcd for $C_{27}H_{25}N_7O_3$: C, 65.44; H, 5.09; N, 19.79. Found: C, 65.30; H, 5.00; N, 19.87.

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