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One-Pot Three Component Synthesis of Highly Functionalized Novel 1,8-Naphthyridine Derivatives from Substituted 2-Aminopyridines, Aldehydes and Malononitrile

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Protocol for one-pot three component cascade synthesis was planned to achieve the highly functionalized novel 1,8-naphthyridine derivatives from readily available starting material. Substituted aldehydes and malononitrile were refluxed in THF followed by the addition of substituted 2-aminopyridine to obtain highly functionalized novel 1-8-naphthyridine **(12a-12x)**, in good to excellent yields**.** The structures of the newly synthesized 1,8-naphthyridine derivatives have been established on the basis of analytical (C, H, N) and spectroscopic (^{1}H NMR and ^{13}C NMR) data. These fully functionalized heterocycles would be employed as versatile synthons for further chemical transformation and eventually, screened for biological studies.

Keywords: Amino acid, Ultrasound, Aqueous media, Cavitation.

INTRODUCTION

The 1,8-naphthyridine derivatives posses a prominent place in the field of medicinal chemistry [1], as the presence of two nitrogen atom in the aromatic ring make appropriate linkage sites through hydrogen bonding with microbes. Hydrogen bonding is very effective in the medicinal area as antibacterial [2], anti-inflammatory [3], antihypertensive [4] and anticancer activities [5].

Considerable attention have been attracted due to the presence of its skeleton in number of naturally occurring organic compounds like vosaroxin (**1**), having a range of biological activities [6,7]. Nalidixic acid (**2**) used mainly for the treatment of urinary area infections with Gram-negative pathogens because of possessing strong antibacterial activity [8]. In addition, antimicrobial activity [9] of gemifloxacin (**3**) have established many year ago whereas 1,8-Naphthyridine series of (E)- and (Z)-O-(diethylamino)ethyl oximes (**4**) is known potential drugs for local anaesthesia [10] and 1-(2-fluorobenzyl)-3-(2-tolyl)-1,8-naphthyridin-2(1H)-one (**5**) is used for the treatment of Alzheimer's disease [11].

2-Amino-N-hydroxy-1,8-naphthyridine-3-carboxamidine (**6**, Fig. 1) possesses herbicidal properties and used for the discriminatory control of weeds in barley, wheat, maize, sorghum and rice crops [12]. These naturally occurring compounds (**1-6**) provoked to investigate a new series of naphthyridine derivatives having close resemblance with above said medicinally important luxuries. As a part of our ongoing research [13-15], we wish to report a series of 1,8-naphthyridine derivatives synthesized through three component one-pot reaction of aldehydes, malononitrile and substituted 2-aminopyridines.

EXPERIMENTAL

All chemicals and solvents were purchased from Aldrich, Fluka and Merck-Schuchatdt. Arylidine derivatives were synthesized through the standard procedure. Melting points were determined on cover slips by using a Fisher-Johns melting point apparatus and are uncorrected. Elemental (C, H, N) analyses were performed on a Leco CHNS-9320 (USA) elemental analyzer and were in full agreement with the proposed structures within ± 0.4 % of the theoretical limits, except where noted otherwise. Infrared (IR) spectra (KBr discs) were run on Shimadzu Prestige-21 FT-IR spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in DMSO-d_6 on Bruker (Rhenistetten-Forchheim, Germany) AM 300 spectrometer, operating at 300 MHz and using TMS as an internal standard. The chemical shifts (δ) are reported in ppm and coupling constants (Hz). ^{13}C NMR spectra were recorded at 300 MHz with the same internal standard. The progress of the reaction and purity of the products were checked on TLC plates coated with Merck silica gel 60 GF_{254} and the spots were

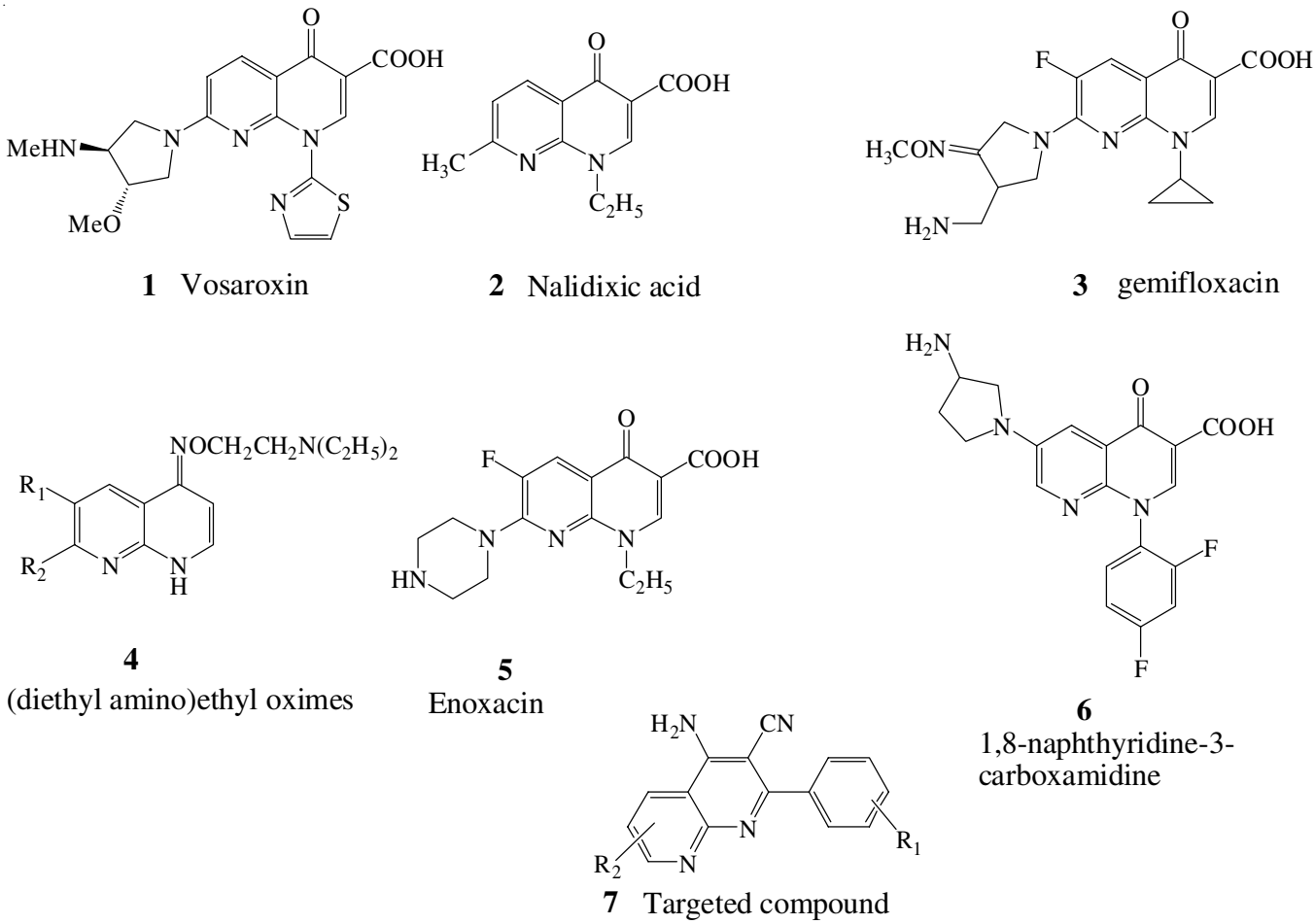


Fig. 1. Some medicinal important naturally occurring 1,8-naphthyridine derivatives (**1-6**) and targeted compounds (**7**)

visualized under ultraviolet light at 254 and 366 nm and/or spraying with iodine vapours.

General procedure of the preparation of substituted 1,8-naphthyridines (12a-12t): The solution of malononitrile (0.01 mol) and appropriate aldehyde (0.01 mol) in dry THF (20 mL) was refluxed for 0.5 h in presences of trace of pyridine as base. The appropriate 2-aminopyridine (0.01 mol) dissolved in 5 mL of THF was added when TLC showed the complete formation of arylidine intermediate and reaction mixture was further refluxed for 3 h with continuous stirring. The reaction was monitored by TLC during the course of the reaction. The reaction mixture was cooled to room temperature and coloured precipitates formed during refluxing were filtered, washed with methanol and dried to furnish the desire 1,8-naphthyridines derivatives pure enough for further characterization.

4-Amino-2-phenyl-1,8-naphthyridine-3-carbonitrile (12a): Yield 85 % as yellow solid; m.p.: 192-194 °C; IR (KBr, ν_{max}, cm^{-1}): 3311, 3285 (NH stretching), 2196 (CN), 1637 (C=N), 1620 (C=C), 1514, 1475, 1272, 767, 752, 688; ^{1}H NMR (300 MHz, DMSO-d_6); δ, ppm, 4.78 (broad s, 2H, NH_2), 7.39 (m, 3H), 7.56 (t, *J* = 6.4 Hz, 1H), 7.66 (d, *J* = 6.3 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 9.26 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 84.91, 107.12, 112.43, 122.65, 24.93, 125.43, 128.13, 130.27, 133.76, 135.51, 139.28, 148.43, 153.83, 156.46, 161.24. Anal. calcd. (%) for $C_{15}H_{10}N_4$: C, 73.16; H, 4.09; N, 22.75. Found (%): C, 73.11; H, 4.08; N, 22.73.

4-Amino-2-(2-chloro-phenyl)-[1,8]naphthyridine-3-carbonitrile (12b): Yield 78 % as yellow colour product m.p.: 220-222 °C; IR (KBr, ν_{max}, cm^{-1}): 3321, 3276 (NH stretching), 2905 (C-H stretching), 2854, 2231 (CN), 1691 (C=N), 1589 (C=C), 1527, 1491, 1505, 1235, 1057, 879, 746; ^{1}H NMR (300 MHz, DMSO-d_6); δ, ppm, 4.72 (broad s, 2H, NH_2), 6.94 (dd, *J* = 8.2 & 1.3 Hz, 1H), 7.25 (m, 2H), 7.49 (t *J* = 6.5 Hz, 1H), 7.57 (d, *J* = 6.4 Hz, 1H), 7.79 (dd, *J* = 8.3 & 1.4 Hz, 1H), 9.01 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 88.14, 111.24, 113.32, 122.54, 124.76, 127.48, 128.26, 128.97, 132.71, 133.51, 134.92, 146.23, 158.54, 159.34, 160.73. Anal. calcd. (%) for $C_{15}H_9N_4Cl$: C, 64.18; H, 3.23; N, 19.96. Found (%): C, 64.14; H, 3.22; N, 19.95.

4-Amino-2-(3-chloro-phenyl)-[1,8]naphthyridine-3-carbonitrile (12c): Yield 74 % as yellow colour product m.p.: 205-207 °C; IR (KBr, ν_{max}, cm^{-1}): 3371, 3245 (NH), 2954, 2823, 2215 (CN), 1698 (C=N), 1645 (C=C), 1573, 1467, 1465, 1315, 987; ^{1}H NMR (300 MHz, DMSO-d_6); δ, ppm, 4.87 (broad s, 2H, NH_2), 7.10 (dd, *J* = 8.2 & 1.6 Hz, 1H), 7.28 (t, *J* = 8.4 Hz, 1H), 7.54-7.69 (m, 3H), 7.74 (s, 1H), 7.82 (dd, *J* = 8.3 & 1.4Hz, 1H), 9.16 (dd, *J* = 6.5 & 1.1 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 86.47, 110.52, 115.31, 124.67, 127.31, 128.43, 130.37, 132.76, 133.58, 137.92, 148.63, 155.83, 158.66, 159.61, 161.76. Anal. calcd. (%) for $C_{15}H_9N_4Cl$: C, 64.18; H, 3.23; N, 19.96. Found (%): C, 64.15; H, 3.22; N, 19.94.

4-Amino-2-(4-chlorophenyl)-1,8-naphthyridine-3-carbonitrile (12d): Yield 76.4 % as yellow colour product m.p.: 210-212 °C; IR (KBr, ν_{max}, cm^{-1}): 3311, 3286 (NH), 2916, 2844, 2204 (CN), 1651 (C=N), 1620 (C=C), 1517, 1494, 1265, 1087, 920, 758; ^{1}H NMR (300 MHz, DMSO-d_6); δ, ppm, 4.71 (broad s, 2H, NH_2), 7.06 (d, *J* = 8.1 Hz, 2H), 7.31 (t, *J* = 6.2 Hz, 1H), 7.50 (d, *J* = 6.3 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 9.16 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 87.39, 112.22, 116.34, 122.54, 126.33, 129.23, 130.37, 133.58, 134.92, 145.23, 155.83, 158.61, 160.76. Anal. calcd. (%) for $C_{15}H_9N_4Cl$: C, 64.18; H, 3.23; N, 19.96. Found (%): C, 64.16; H, 3.23; N, 19.95.

4-Amino-2-(3-nitro-phenyl)-[1,8]naphthyridine-3-carbonitrile (12e): Yield 79 % as yellow colour product m.p.: 196-199 °C; IR (KBr, ν_{max}, cm^{-1}): 3385, 3223 (NH), 2914, 2833, 2215 (CN), 1675 (C=N), 1643 (C=C), 1573 (N-O), 1465, 1461, 1311, 977; ^{1}H NMR (300 MHz, DMSO-d_6); δ, ppm, 4.85 (broad s, 2H, NH_2), 7.41 (t, *J* = 6.2 Hz, 1H), 7.52 (t, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 6.4 Hz, 1H), 8.07 (dd, *J* = 8.5 & 1.9 Hz, 1H), 8.23 (dd, *J* = 8.6 & 1.9 Hz, 1H), 9.19 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 87.52, 110.15, 115.13, 124.41, 124.73, 125.13, 128.35, 129.73, 132.54, 134.58, 138.86, 149.34, 157.31, 158.61, 160.76. Anal. calcd. (%) for $C_{15}H_9N_5O_2$: C, 61.85; H, 3.11; N, 24.04. Found (%): C, 61.82; H, 3.10; N, 24.02.

4-Amino-2-(4-nitro-phenyl)-[1,8]naphthyridine-3-carbonitrile (12f): Yield 75 % as yellow colour product m.p.: 178-182 °C; IR (KBr, ν_{max}, cm^{-1}): 3382, 3289 (NH), 2936, 2824, 2212 (CN), 1672 (C=N), 1631 (C=C), 1517, 1454, 1395 (NO_2), 1215, 987; ^{1}H NMR (300 MHz, DMSO-d_6); δ, ppm, 4.29 (broad s, 2H, NH_2), 7.40 (t, *J* = 6.3 Hz, 1H), 7.58 (d, *J* = 6.2 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 8.23 (d, *J* = 8.4 Hz, 2H), 9.27 (d, *J* = 6.3 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 87.95, 111.62, 115.31, 123.74, 127.31, 128.43, 129.37, 133.58, 146.92, 155.83, 158.65, 160.61, 163.12. Anal. calcd. (%) for $C_{15}H_9N_5O_2$: C, 61.85; H, 3.11; N, 24.04. Found (%): C, 61.81; H, 3.11; N, 24.01.

4-Amino-2-(4-hydroxy-3-methoxyphenyl)-1,8-naphthyridine-3-carbonitrile (12g): Yield 79.8 % as dark yellow precipitates m.p.: 116-118 °C; IR (KBr, ν_{max}, cm^{-1}): 3550(OH), 3315, 3209 (NH stretching), 2214 (CN), 1566 (C=C), 1506, 1456, 1294, 1242, 1128, 1024, 767, 622, 594; ^{1}H NMR (300 MHz, DMSO-d_6); δ, ppm, 3.60 (s, 3H, CH_3), 4.68 (broad s, 2H, NH_2), 6.08 (broad s, 1H, OH), 6.59 (d, *J* = 8.4 Hz, 1H), 7.25 (s, 1H), 7.41 (t, *J* = 6.4 Hz, 1H), 7.59 (d, *J* = 6.5 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 8.97 (d, *J* = 6.4 Hz, 1H),; ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 87.34, 112.89, 115.37, 121.74, 124.67, 127.31, 128.43, 130.37, 133.76, 136.98, 137.92, 148.63, 154.66, 159.61, 160.16. Anal. calcd. (%) for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found (%): C, 65.70; H, 4.13; N, 19.13.

4-Amino-6-chloro-2-phenyl-[1,8]naphthyridine-3-carbonitrile (12h): Yield 83 % as yellow solid; m.p.: 198-201 °C; IR (KBr, ν_{max}, cm^{-1}): 3341, 3278 (NH stretching), 2176 (CN), 1654 (C=N), 1629 (C=C), 1514, 1475, 1272, 767, 752, 688; ^{1}H NMR (300 MHz, DMSO-d_6); δ, ppm, 4.92 (broad s, 2H, NH_2), 7.20-7.36 (m, 3H), 7.53 (s, 1H), 7.79 (d, *J* = 7.6Hz, 2H), 8.27 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 86.57, 109.23, 113.78, 122.14, 125.67, 127.72, 133.76, 134.54, 141.92, 149.56, 152.83, 155.43, 160.53. Anal. calcd. (%) for $C_{15}H_9N_4Cl$: C, 64.18; H, 3.23; N, 19.96. Found (%): C, 64.12; H, 3.22; N, 19.95.

4-Amino-6-chloro-2-(2-chloro-phenyl)[1,8]naphthyridine-3-carbonitrile (12i): Yield 79 % as pale yellow solid; m.p.: 205-207 °C; IR (KBr, ν_{max}, cm^{-1}): 3323, 3254 (NH stretching), 2216 (CN), 1642 (C=N), 1623 (C=C), 1521, 1515, 1254, 787, 762, 638; ^{1}H NMR (300 MHz, DMSO-d_6); δ, ppm, 4.72 (broad s, 2H, NH_2), 6.84 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.56-7.72 (m, 2H), 7.89 (d, *J* = 7.9 Hz, 1H), 8.12 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 89.37, 110.12, 114.31, 123.24, 125.17, 126.09, 127.45, 129.77, 131.21, 133.76, 135.58, 137.65, 148.63, 156.87, 158.89. Anal. calcd. (%) for $C_{15}H_8N_4Cl_2$: C, 57.17; H, 2.56; N, 17.78. Found (%): C, 57.14; H, 2.55; N, 17.75.

4-Amino-2-(3-bromophenyl)-6-chloro-[1,8]naphthyridine-3-carbonitrile (12j): Yield 72 % (0.04g) as reddish solid m.p.: 75-77 °C; Solubility (soluble in chloroform, DMSO); IR (KBr, ν_{max}, cm^{-1}): 3461 (NH_2), 3296 (NH), 2229 (CN), 1625 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 4.55 (s, 2H, NH2), 6.49 (d, *J* = 8.7, 1H), 7.39-7.47 (m, 2H), 7.73-7.78 (m, 1H), 7.91 (d, *J* = 7.8, 1H), 7.98 (t, *J* = 1.5 Hz 1H), 8.02 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 84.62, 109.87, 112.04, 113.21, 120.93, 123.66, 128.65, 131.11, 132.53, 133.49, 137.30, 138.00, 145.89, 156.73, 158.16. Anal. calcd. (%) for $C_{15}H_8N_4BrCl$: C, 50.10; H, 2.24; N, 15.58. Found (%): C, 50.06, H, 2.23; N, 15.53.

4-Amino-2-(4-chlorophenyl)-6-chloro-[1,8]naphthyridine-3-carbonitrile (12k): Yield 74 % (0.03g) as brown colour precipitates m.p.: 120-122 °C; Solubility (soluble in chloroform, DMSO); IR (KBr, ν_{max}, cm^{-1}): 3461 (NH_2), 3303 (NH), 2229 (CN), 1625 (C=N) ; ^{1}H NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 4.59 (s, 2H, NH_2), 6.47 (d, *J* = 8.7 Hz, 1H), 7.39 (d, *J* = 7.2, 1H), 7.52 (d, *J* = 8.1, 1H), 7.75 (s, 1H), 7.85 (d, *J* = 8.1, 1H), 8.01 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 83.26, 109.58, 112.38, 113.49, 120.90, 129.25, 130.09, 131.87, 137.68, 141.18, 146.22, 156.79, 158.38. Anal. calcd. (%) for $C_{15}H_8N_4Cl_2$: C, 57.17; H, 2.56; N, 17.78. Found (%): C, 57.15; H, 2.56; N, 17.76.

4-Amino-6-chloro-2-(3-nitro-phenyl)-[1,8]naphthyridine-3-carbonitrile (12l): Yield 75 % as reddish solid; m.p.: 223-225 °C; IR (KBr, ν_{max}, cm^{-1}): 3392, 3284 (NH stretching), 2243 (CN), 1645 (C=N), 1617 (C=C), 1531, 1552, 1211, 756, 742, 658; ^{1}H NMR (300 MHz, DMSO-d_6); δ, ppm, 4.74 (broad s, 2H, NH_2), 7.42 (t, *J* = 8.3 Hz 1H), 7.89 (dd, *J* = 8.4 & 1.6 Hz, 1H), 7.96 (s, 1H), 8.13 (s, 1H), 8.37 (dd, *J* = 8.4 & 1.4 Hz, 1H), 8.63 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 85.69, 113.42, 119.21, 121.34, 124.17, 128.13, 129.35, 131.56, 132.58, 134.92, 148.73, 151.83, 156.66, 158.61, 162.76. Anal. calcd. (%) for $C_{15}H_8N_5ClO_2$: C, 55.31; H, 2.48; N, 21.50. Found (%): C, 55.26; H, 2.47; N, 21.47.

4-Amino-6-chloro-2-(4-nitro-phenyl)-[1,8]naphthyridine-3-carbonitrile (12m): Yield 76 % as reddish solid; m.p.: 245-247 °C; IR (KBr, ν_{max}, cm^{-1}): 3413, 3344 (NH stretching), 2256 (CN), 1667 (C=N), 1626 (C=C), 1532, 1561, 1253, 776, 767, 691; ^{1}H NMR (300 MHz, DMSO-d_6); δ, ppm, 4.64 (broad s, 2H, NH_2), 7.52 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 2H), 8.03 (s, 1H), 8.39 (d, *J* = 7.6 Hz, 2H), ; ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 86.27, 118.21, 121.14, 122.67, 127.13, 129.35,

131.58, 135.92, 148.63, 150.83, 157.66, 158.61, 161.76. Anal. calcd. (%) for $C_{15}H_8N_5ClO_2$: C, 55.30; H, 2.46; N, 21.51;.

4-Amino-5-methyl-2-phenyl-[1,8]naphthyridine-3-carbonitrile (12n): Yield 79.2 % as light yellow solid m.p.: 91-94 °C; Solubility (soluble in chloroform, DMSO); IR (KBr, ν_{max}, cm^{-1}): 3367 (NH_2), 3219 (NH), 2251 (CN), 1636 (C=N), 1539, 1274, 975, 786; ^{1}H NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 2.53 (s, 3H, CH_3), 7.26 (t, *J* = 7.7 Hz, 2H), 7.39 (s, 2H, NH_2), 7.51 (t, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.9Hz, 2H), 8.09 (d, *J* = 7.5 Hz, 1H), 9.26 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 23.42, 87.52, 112.21, 120.14, 122.75, 126.01, 128.13, 129.37, 130.46, 139.63, 151.94, 152.66, 153.61, 161.71; Anal. calcd. (%) for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.52. Found (%): C, 73.80; H, 4.64; N, 21.50.

4-Amino-2-(2-chloro-phenyl)-5-methyl-[1,8]naphthyridine-3-carbonitrile (12o): Yield 83 % as reddish brown solid m.p.: 85-87 °C; Solubility (soluble in chloroform, DMSO); IR (KBr, ν_{max}, cm^{-1}): 3325 (NH_2), 3291 (NH stretching), 2219 (CN), 1643 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 2.31 (s, 3H, CH_3), 7.16 (d, *J* = 7.2 Hz, 1H), 7.29-7.35 (m, 3H, NH_2), 7.52 (t, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.90Hz, 1H), 8.01 (d, *J* = 7.4 Hz, 1H), 9.26 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 21.39, 82.56, 114.14, 119.32, 122.77, 125.21, 127.59, 128.35, 130.36, 132.58, 133.92, 138.63, 151.65, 152.86, 153.64, 160.16. Anal. calcd. (%) for $C_{16}H_{11}N_4Cl$: C, 65.20; H, 3.76; N, 19.01. Found (%): C, 65.16; H, 3.75; N, 19.00.

4-Amino-2-(3-chloro-phenyl)-5-methyl-[1,8]naphthyridine-3-carbonitrile (12p): Yield 80.5 % as brown solid m.p.: 112-115 °C; Solubility (soluble in chloroform, DMSO); IR (KBr, ν_{max}, cm^{-1}): 3332 (NH_2), 3189 (NH), 2216 (CN), 1643 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 2.45 (s, 3H, CH_3), 7.26 (d, *J* = 7.2 Hz, 1H), 7.29-7.35 (m, 3H, NH_2), 7.67 (d, *J* = 7.9 Hz, 1H), 8.12 (s, 1H), 8.06 (d, *J* = 7.2 Hz, 1H), 9.10 (d, *J* = 7.1 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 23.71, 89.98, 117.21, 119.56, 123.47, 125.31, 127.13, 129.35, 130.34, 131.58, 135.92, 138.63, 151.91, 152.56, 153.41, 161.36. Anal. calcd. (%) for $C_{16}H_{11}N_4Cl$: C, 65.20; H, 3.76; N, 19.01. Found (%): C, 65.15; H, 3.75; N, 18.98

4-Amino-2-(4-chloro-phenyl)-5-methyl-[1,8]naphthyridine-3-carbonitrile (12q): Yield 82 % as reddish brown solid m.p.: 89-92 °C; Solubility (soluble in chloroform, DMSO); IR (KBr, ν_{max}, cm^{-1}): 3375 (NH_2), 3254 (NH stretching), 2232 (CN), 1612 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 2.46 (s, 3H, CH_3), 7.34 (d, *J* = 7.2 Hz, 2H), 7.39 (s, 2H, NH_2), 7.57 (d, *J* = 7.8 Hz, 2H), 8.01 (d, *J* = 7.2 Hz, 1H), 9.16 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 22.31, 85.51, 115.14, 119.32, 127.81, 128.91, 131.32, 133.38, 153.92, 138.63, 149.65, 152.86, 155.69, 161.16. Anal. calcd. (%) for $C_{16}H_{11}N_4Cl$: C, 65.20; H, 3.76; N, 19.01. Found (%): C, 65.18; H, 3.76; N, 18.99.

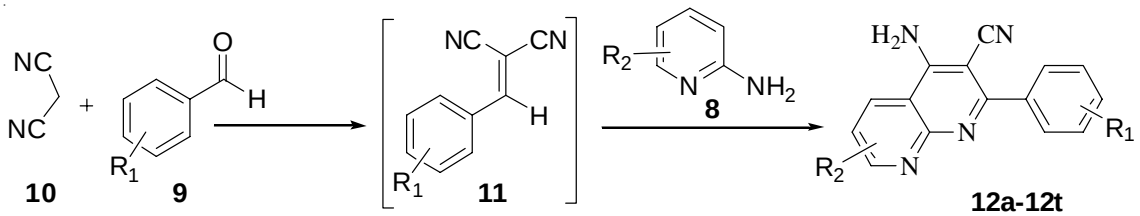
4-Amino-5-methyl-2-(3-nitro-phenyl)-[1,8]naphthyridine-3-carbonitrile (12r): Yield 78 % as brown solid m.p.: 243-245 °C; Solubility (soluble in chloroform, DMSO); IR (KBr, ν_{max}, cm^{-1}): 3432 (NH_2), 3289 (NH), 2196 (CN), 1643 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 2.42 (s, 3H, CH_3), 7.39 (m, 2H, NH_2), 7. 52 (d, *J* = 7.2 Hz, 1H), 7.73 (t, *J* = 7.9 Hz, 1H), 7.96 (dd, *J* = 7.8 & 1.2 Hz, 1H), 8.19 (dd, *J* = 7.8 & 1.2 Hz, 1H), 8.73 (s, 1H), 9.24 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 23.71, 89.98, 127.29, 129.56, 133.47, 135.81, 137.13, 139.35, 140.34, 141.58, 145.92, 148.63, 151.91, 154.56, 156.41, 162.36. Anal. calcd. (%) for $C_{16}H_{11}N_5O_2$: C, 62.95; H, 3.63; N, 22.94. Found (%): C, 62.92; H, 3.62; N, 22.93.

4-Amino-5-methyl-2-(4-nitro-phenyl)-[1,8]naphthyridine-3-carbonitrile (12s): Yield 76 % as reddish brown solid m.p.: 213-215 °C; Solubility (soluble in chloroform, DMSO); IR (KBr, ν_{max}, cm^{-1}): 3435 (NH_2), 3354 (NH stretching), 2256 (CN), 1676 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 2.61 (s, 3H, CH_3), 7.54 (d, *J* = 7.2 Hz, 2H), 7.63 (s, 2H, NH_2), 7.89 (d, *J* = 7.8 Hz, 2H), 8.12 (d, *J* = 7.5 Hz, 1H), 9.29 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 25.12, 83.52, 116.14, 125.85, 127.87, 129.97, 132.32, 135.38, 136.92, 138.63, 149.78, 153.86, 155.08, 161.66. Anal. calcd. (%) for $C_{16}H_{11}N_5O_2$: C, 62.95; H, 3.63; N, 22.94. Found (%): C, 62.93; H, 3.63; N, 22.92.

4-Amino-2-(3-bromophenyl)-5-methyl-[1,8]naphthyridine-3-carbonitrile (12t): Yield 82 % (0.54 g) as yellow solid m.p.: 97-99 °C; Solubility (soluble in chloroform, DMSO); IR (KBr, ν_{max}, cm^{-1}): 3311 (NH_2), 3089 (NH), 2196 (CN), 1652 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 2.53 (s, 3H, CH_3), 7.06 (d, *J* = 7.2 Hz, 1H), 7.29-7.42 (m, 3H, NH_2), 7.65 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 7.4 Hz, 1H), 8.09 (s, 1H), 9.26 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$-d_6); δ, ppm, 21.72, 85.52, 117.21, 119.14, 122.77, 125.01, 127.13, 128.35, 130.06, 131.58, 133.92, 138.63, 150.93, 152.66, 153.61, 161.76. Anal. calcd. (%) for $C_{16}H_{11}N_4Br$: C, 56.66; H, 3.27; N, 16.52. Found (%): C, 56.61; H, 3.26; N, 16.50.

RESULTS AND DISCUSSION

To synthesize the novel 1,8-naphthyridine derivatives, 2-aminopyridine (**8**), aromatic aldehyde (**9**) and malanonitriles (**10**) were first chosen to examine the scope of reaction (**Scheme-I**) in various polar and non-polar solvents to obtain



R_1= H, 2-Chloro, 3-Chloro, 4-Chloro, 3-bromo, 3-Nitro, 4-Nitro
R_2= H, 5-Chloro, 4-Methyl

Scheme-I: Cascade synthesis of fused ring heterocycles

the targeted compounds (**12a**) and THF was found to be the best choice with respect to the product yield (Table-1, entry 3). Different acids and bases were also used as catalyst to check their effect on product yield and pyridine was found to be the most suitable catalyst for the said synthesis (Table-1, entry 6). Arylidines formation as an intermediate **(11)** act as *bis*-electrophilic which reacted further with 2-aminopyridine, a *bis*-nucleophile, through condensation followed by cyclization to form desired 1,8-naphthyridine derivatives (**12a-12t**).

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS AND EFFECT OF DIFFERENT CATALYSTS TO GET FUSED RING HETEROCYCLES (**12a-12t**)

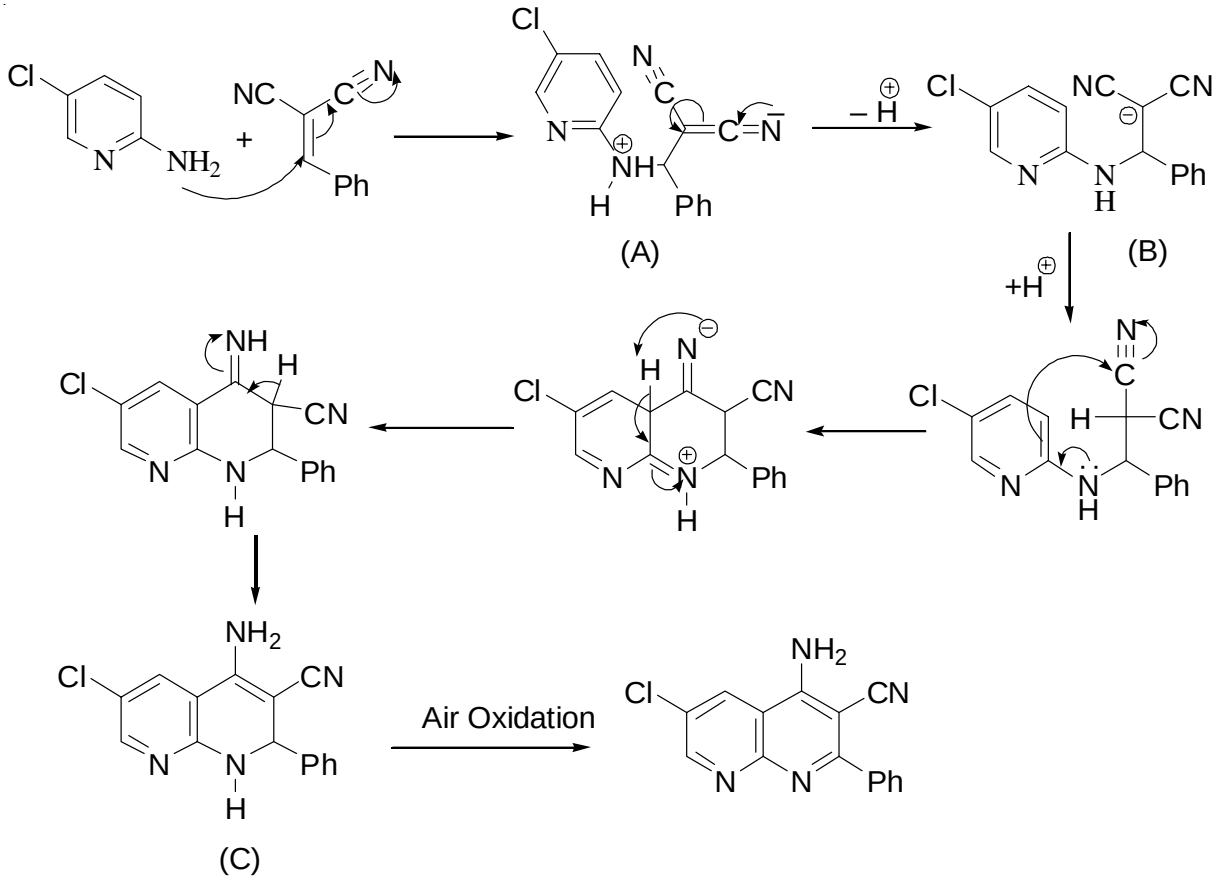
Entry	Reaction solvents	Catalysts	Reaction conditions	Yield (%)
1	Ethanol	–	Reflux, 3 h	52
2	Methanol	–	Reflux, 3 h	48
3	THF	–	Reflux, 3 h	76
4	Chloroform	–	Reflux, 3 h	63
5	DMSO	–	Reflux, 3 h	40
6	**THF**	**Pyridine**	**Reflux, 6 h**	**85**
7	THF	AcOH	Reflux, 3 h	35
8	THF	$ZnCl_2$	Reflux, 3 h	42
9	THF	$AlCl_3$	Reflux, 3 h	40
10	THF	Lead acetate	Reflux, 3 h	32
11	THF	NEt_3	Reflux, 3 h	80
12	THF	HCl	Reflux, 3 h	22

In order to expand the scope of reaction, the reaction of malononitrile (**10**), substituted benzaldehyde (**9**) and substituted 2-aminopyridines (**8**) were examined under our optimized reaction conditions using THF as solvent and catalytic quantity of pyridine. The reaction resulted in the formation of fused ring heterocycles (**12a-12t**) in good to excellent yields and results are summarized in Table-2.

TABLE-2
REACTIONS OF AMINOPYRIDINES WITH ARYLIDINES AND MALONONITRILE

S. No.	R_1	R_2	Product	Yield %[a]
1	H	H	**12a**	85.0
2	2-Chloro	H	**12b**	78.0
3	3-Chloro	H	**12c**	74.0
4	4-Chloro	H	**12d**	76.4
5	3-Nitro	H	**12e**	79.0
6	4-Nitro	H	**12f**	75.0
7	4-Hydroxy-3-methoxy	H	**12g**	79.8
8	H	5-Chloro	**12h**	83.0
9	2-Chloro	5-Chloro	**12i**	79.0
10	3-Bromo	5-Chloro	**12j**	72.0
11	4-Chloro	5-Chloro	**12k**	74.0
12	3-Nitro	5-Chloro	**12l**	75.0
13	4-Nitro	5-Chloro	**12m**	76.0
14	H	4-Methyl	**12n**	79.0
15	2-Chloro	4-Methyl	**12o**	83.0
16	3-Chloro	4-Methyl	**12p**	80.5
17	4-Chloro	4-Methyl	**12q**	82.0
18	3-Nitro	4-Methyl	**12r**	78.0
19	4-Nitro	4-Methyl	**12s**	76.4
20	3-Bromo	4-Methyl	**12t**	82.0

[a]Isolated yield.



Scheme-II: Plausible mechanism of the reaction

The structure of the synthesized 1,8-naphthyridine derivatives **(12a-12t)** was established on the bases of spectroscopic (IR, ^{1}H NMR and ^{13}C NMR) and analytical (CHN-analysis) data. The IR data of 1,8-naphthyridine derivatives **(12a-12t)** showed three prominent absorption at about 3300, 2200 and 1650 cm^{-1} due to presences of NH, C≡N and C=N respectively. The ^{1}H NMR spectra of **12a**-**12m** showed absorption for two protons of NH_2-group at about 4-5 ppm whereas the spectra of **12n** to **12t** the same NH_2 protons appeared at about 7 ppm indicated the difference of substitution at position-6 and position-5 of naphthyridine derivatives **(12a-12t)**, respectively. The other ^{1}H NMR absorptions and ^{13}C NMR signals were exactly according to the purposed structure of the said substituted 1,8-naphthyridines.

The plausible reaction mechanism of one-pot three component domino reaction to form fused ring heterocyclic 1,8-naphthyridine derivatives is depicted in **Scheme-II**. Reaction is initiated with the Knoevenagel condensation of malononitrile and aldehyde in presence of pyridine as base to form respective arylidine intermediate with the loss of water molecule. The 2-aminopyridine would act as *bis*-nucleophile and arylidine intermediate would undergo aza-Michael addition reaction followed by intramolecular cyclization to construct six member ring of naphthyridine nucleus (c). The air-oxidation of naphthyridine nucleus offered the highly substituted 1,8-naphthyridine derivatives.

Conclusion

One-pot three component synthetic method has been developed for the preparation of highly substituted 1,8-naphthyridine derivatives **12a-12t** employing 2-aminopyridines as *bis*-nucleophile, malononitrile and substituted aldehydes. The newly synthesized 1,8-naphthyridine derivatives **12a-12t** resembles closely with the naturally occurring molecules (Fig. 1, compounds **1-6**) and contain a number of tunable functional groups for further manipulation to develop valuable precursors for the medicinally active compounds.

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