# An Exceedingly Mild, Green Synthesis of Substituted *N*-3-diaryl-1,8-naphthyridin-2-amine Derivatives and Their Antimicrobial Activity

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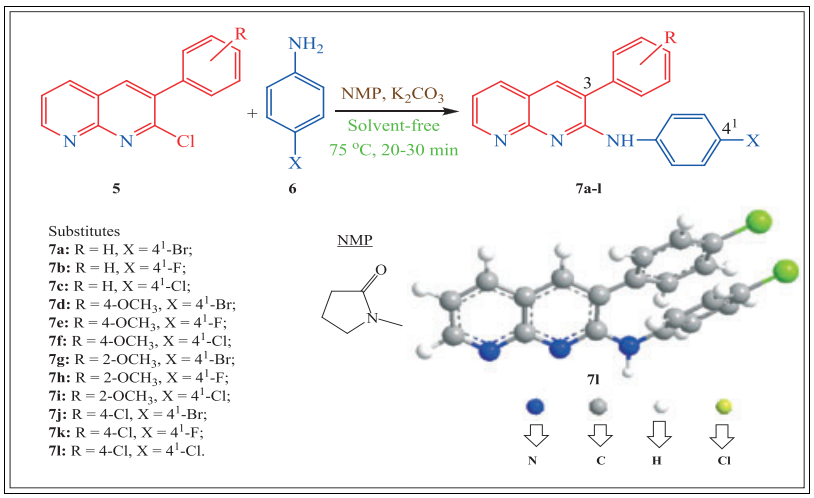


An exceedingly and highly efficient procedure has been described for the synthesis of substituted *N*-3-diaryl-1,8-naphthyridin-2-amines by the reaction of 2-chloro-3-aryl-1,8-naphthyridines with various anilines in the presence of *N*-methyl-2-pyrrolidone and $K_2CO_3$ under thermal green solvent-free conditions. The significant features of this green reaction include very good yields in purity, simple experimental, short reaction time, easy workability, and avoidance of toxic solvents. All synthesized compounds have been evaluated for their antibacterial activity.

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## INTRODUCTION

In recent years, research on derivatives of 1,8-naphthyridines represents an significant class of organic molecules that attract the interest of medicinal chemists because of their extremely wide spectrum of bio-organic/chemical/medicinal/pharmaceutical and biological importance [1–4] as well as their use as important binding units in the molecular plan of synthetic receptors [5]. 1,8-naphthyridine derivatives attract the interest of much biological importance, such as anti-tumor [6–8], anti-mycobacterial [9], anti-allergic [10,11], antibacterial [12–14], anti-inflammatory [15], anti-hypertensive [16], anti-HIV [17] and local anesthetic [18]. Gemifloxacin has both antimicrobial and antibacterial activities [2]. Some of new 1,8-naphthyridine derivatives including benzo [1,8] naphthyridine have recently been patented as growth regulators, nemathocides, herbicides, insecticides, and fungicides of new generation [19–21]. Some of the biologically potent 1,8-naphthyridines derivatives are shown in Figure 1.

Nowadays, increasingly attractive to researchers due to developing and interest has been focused on solvent-free conditions [22,23]. The field of solvent-free organic fusion admiration to experimental processes and covers all branches of organic chemistry. Resulting yields are remarkably high starting from stoichiometric amount of reactants, especially in the case of solid–solid reactions. Moreover, the advantage of green synthesis, interesting properties like simple procedures, the process is environmentally natural, efficient workup procedures, hazards, low costs, simplicity, reaction times can be dramatically shortened and minimization of energy consumption. It is now known that many chemical conversions example formation of C–N that was reported to require solid supports with catalytic activity [24,25]. It has been exposed that with neat reaction, solvents can be boiled above their boiling points, and it may be explained that it is this form of superheated, and the reactions take place rapidly, which leads to observed rate improvements for many reactions; these would be especially significant during industrial manufacture [26]. In green chemistry, as previously mentioned [27], the solvents are to be used as the source of solid-state grinding, and they must couple it successfully with eco-friendly synthetic processes. In this paper, we would like to report a fast, practical, and facile

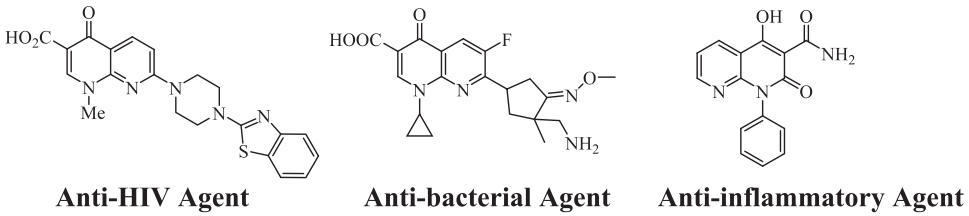



**Figure 1.** Biologically potent of 1,8-naphthyridines derivatives.

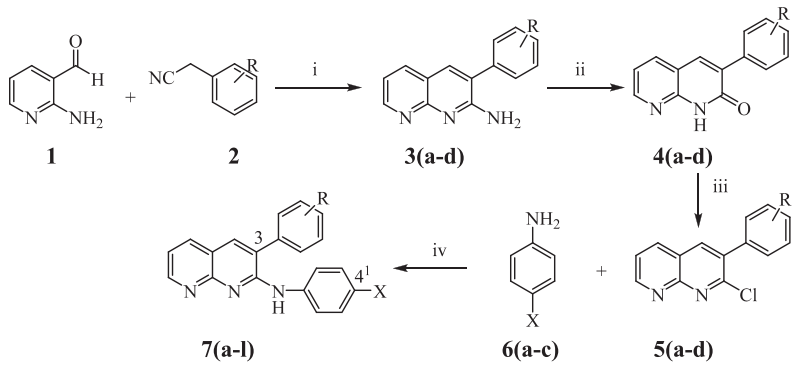
protocol for the creation of substituted *N*-3-diaryl-1,8-naphthyridin-2-amine derivatives under thermal green solvent-free conditions (Scheme 1).

## RESULTS AND DISCUSSION

In continuation of our exploration for new catalysts [28–30] convenient herein, we wish to report an exceedingly, mildly, and highly efficient procedure for the synthesis of several substituted aryl at the *N* and C-3 position of the 1,8-naphthyridine ring; compounds are profiled in Scheme 1. Condensation of 2-aminonicotinaldehyde **1** with 2-phenyl acetonitrile **2** in the presence of 10% potassium hydroxide (KOH) without any solvent under microwave irradiation (MWI) afforded 2-amino-1,8-naphthyridines **3**, which is converted into 1,8-naphthyridine-2(1*H*)-ones **4** by the reaction with $NaNO_2$. Treatment of compounds **4** with $POCl_3$ under MWI yielded 2-chloro-1,8-naphthyridines **5** was prepared following the literature procedure [31]. The reactions proceed efficiently in excellent yields at ambient pressure within few minutes. A remarkable influence of the nucleophilic substitution of chlorine at position 2 in 3-aryl-2-chloro-1,8-naphthyridine substituents by different substituents in all three cases anilines (X = F, Cl, Br) outcome of this reaction to produce *N*-3-diaryl-1,8-naphthyridin-2-amines. To detect the effect of substituents on 2-chloro-3-aryl-1,8-naphthyridines on the reaction, *o*-methoxyphenyl-1,8-naphthyridine and *p*-methoxyphenyl-1,8-naphthyridine (bearing electron-donating methoxyl groups) and *p*-chlorophenyl-1,8-naphthyridine (containing electron-withdrawing chloride) were chosen as the substrates. The results are listed in Table 1.

In this research, 2-chloro-3-aryl-1,8-naphthyridines (**5a–d**) used as a suitable intermediate for the synthesis of

**Scheme 1.** Synthetic route for the synthesis of *N*-3-diaryl-1,8-naphthyridin-2-amine derivatives.




**3/4/5a:** R = H;
**3/4/5b:** R = 4-$OCH_3$;
**3/4/5c:** R = 2-OCH3;
**3/4/5d:** R = 4-Cl;
**6a:** X = Br;
**6b:** X = F;
**6c:** X = Cl.

Chemicals and Condition

i) KOH

ii) $NaNO_2$

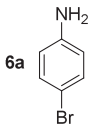
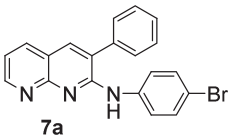
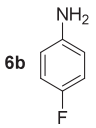
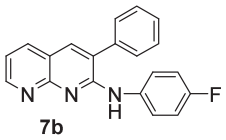
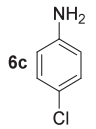
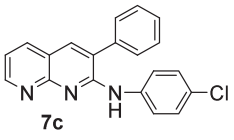
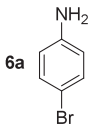
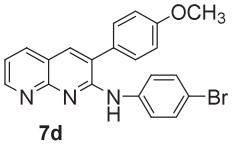
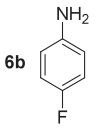
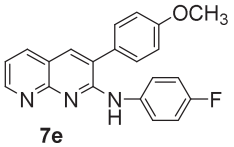
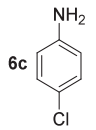
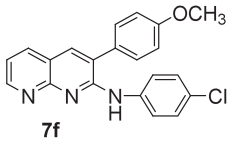
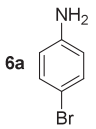
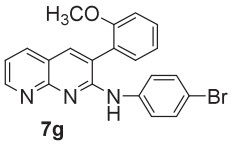
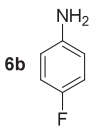
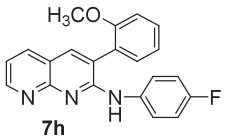
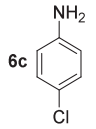
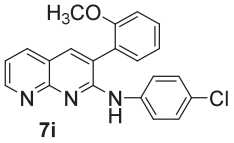
iii) $POCl_3$

iv) NMP, $K_2CO_3$,
Solvent-free, 75 $^oC$, 20-30 min

Substitutes
**7a:** R = H, X = $4^1$-Br (86%);
**7b:** R = H, X = $4^1$-F (88%);
**7c:** R = H, X = $4^1$-Cl (84%);
**7d:** R = 4-$OCH_3$, X = $4^1$-Br (90%);
**7e:** R = 4-$OCH_3$, X = $4^1$-F (92%);
**7f:** R = 4-$OCH_3$, X = $4^1$-Cl (88);
**7g:** R = 2-$OCH_3$, X = $4^1$-Br (85%);
**7h:** R = 2-$OCH_3$, X = $4^1$-F (91%);
**7i:** R = 2-$OCH_3$, X = $4^1$-Cl (84%);
**7j:** R = 4-Cl, X = $4^1$-Br (92%);
**7k:** R = 4-Cl, X = $4^1$-F (88%);
**7l:** R = 4-Cl, X = $4^1$-Cl (91%).

**Table 1**

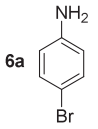
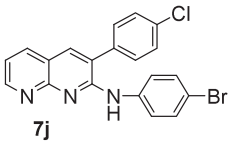
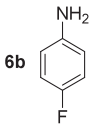
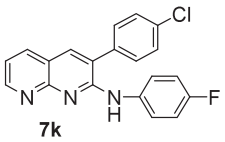
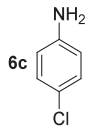
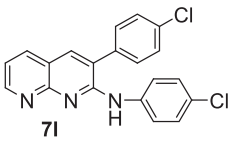
Synthesis of *N*-3-diaryl-1,8-naphthyridin-2-amine derivatives (**7a**–**l**).

| Entry | Amine | Product[a] | Time (min) | Yield (%)[b] | Mp (°C) |
|---|---|---|---|---|---|
| 1 |  **6a** |  **7a** | 25 | 86 | 196–198 |
| 2 |  **6b** |  **7b** | 20 | 88 | 220–222 |
| 3 |  **6c** |  **7c** | 25 | 84 | 233–235 |
| 4 |  **6a** |  **7d** | 30 | 90 | 250–252 |
| 5 |  **6b** |  **7e** | 30 | 92 | 268–270 |
| 6 |  **6c** |  **7f** | 25 | 88 | 232–234 |
| 7 |  **6a** |  **7g** | 20 | 85 | 208–210 |
| 8 |  **6b** |  **7h** | 25 | 91 | 225–227 |
| 9 |  **6c** |  **7i** | 25 | 84 | 201–202 |

(*Continues*)

**Table 1**

(*Continued*)

| Entry | Amine | Product[a] | Time (min) | Yield (%)[b] | Mp (°C) |
|---|---|---|---|---|---|
| 10 |  **6a** |  **7j** | 20 | 92 | 260–262 |
| 11 |  **6b** |  **7k** | 25 | 88 | 244–246 |
| 12 |  **6c** |  **7l** | 20 | 91 | 230–232 |

[a]Reaction conditions: 2-chloro-3-aryl-1,8-naphthyridine (**5**,1 mmol), *p*-fluoro or *p*-chloro, or *p*-bromoanilines (**6**, 1 mmol), *N*-methyl-2-pyrrolidone (10 mmol), $K_2CO_3$ (3.5 mmol), 75°C, neat conditions.
[b]Isolated yields after purification.

target compounds. *N*,3-diaryl-1,8-naphthyridin-2-amines (**7a**–**l**) were synthesized an exceeding method by 2-chloro-3-aryl-1,8-naphthyridines (**5a**–**d**) with various p-amino phenyl halides at the ratio of 1:1 in the presence of dry N-methyl2-pyrrolidone (NMP), and $K_2CO_3$ under green/ solvent-free conditions, the progress of the reaction was monitored by TLC. The experimental procedure is very simple and completed in 20–30 min (Table 1). The reaction is very rapid, good yields (84–92%), and the products were obtained with a high degree of purity by this procedure. This displayed that NMP acts as an active catalyst in this reaction. Furthermore, the solvent-free reaction has many advantages: low costs, reduced pollution, and simplicity in process and handing.

In a typical experimental procedure, equimolar quantities of 2-chloro-3-phenyl-1,8-naphthyridine **5a**, *p*-bromoaniline in NMP, and $K_2CO_3$ were added to the mixture, heated to 75°C for 25 min under neat condition. The precipitated product was filtered. After usual workup *N*-(4-bromophenyl)-3-phenyl-1,8-naphthyridin-2-amine **7a** was obtained in 86% yield. The reaction is of general applicability different compounds (**5b**–**d**) and (**6b**–**c**) to substituted *N*-3-diaryl-1,8-naphthyridin-2-amine compounds (**7b**–**l**) were synthesized, and recrystallized in methanol for more purification.

Structures **7a**–**l** was established by elemental analysis and spectral data. For example, the molecular weight for *N*-(4-bromophenyl)-3-(4-methoxyphenyl)-1,8-naphthyridin-2-amine (**7d**, $C_{21}H_{16}BrN_3O$) was determined as 406 (M + H) by LC–MS–MS. Its IR spectrum shows an absorption at 3167 $cm^{-1}$ for NH group, 1138 $cm^{-1}$ for $OCH_3$ group, and 705 $cm^{-1}$ for C–Br group. Its $^1H$ nuclear magnetic resonance (NMR) spectrum exhibited a singlet at δ 12.30 ppm for NH group and aromatic hydrogen group range between δ 7.02 and 8.51 ppm. The methoxyl hydrogen (singlet) resonated at 3.81 ppm was also detected clearly.

## EXPERIMENTAL

**Materials and methods.** All the materials and reactants were used as purchased from Aldrich Chemical Company and were used without further purification. The purity of the compounds was checked by TLC silica gel plates (60 F-254, Merck KGaA64271 Darmstadt, Germany) with hexane: ethyl acetate as eluent, and spots were visualized in iodine vapor. All the melting points were determined in open capillary tubes using Cintex apparatus (Cintex Industrial Corporation, Mumbai, India) and were uncorrected. IR spectra were distinguished on a Perkin Elmer FTIR spectrophotometer (Waltham, MA) using KBr pellets. The $^1H$ NMR spectra were recorded on Varian Gemini 400 MHz instrument (Palo Alto, CA) using TMS as an internal standard in DMSO-$d_6$. Chemical shifts are expressed in parts per million. Microanalyses were performed on a Carlo-Erba model EA1108 analytical unit (Carlo Erba Manasquan, NJ).

***General procedure for the synthesis of 3-phenyl-1,8-naphthyridin-2-amines (3a–d).*** A mixture of 2-aminonicotinaldehyde **1** (1 mmol, 122.12 mg) and aryl acetonitrile **2** (1 mmol) in 10% KOH (five drops) was exposed to MWI at 400 W intermittently at 30 s intervals for 2.5–3.0 min. On completion of reaction, as monitored by TLC, the reaction mixture was cooled and treated with chilled water. The solid that precipitated was filtered, washed with water, and recrystallized from ethanol to give compound (**3a–d**) with good yields.

***General procedure for the synthesis of 3-phenyl-1,8-naphthyridin-2(1H)-one (4a–d).*** To a cold solution of **3** (1 mmol) in 2 M HCl (25 ml) was added $NaNO_2$ solution (1 mmol in 25 ml water) and the reaction mixture was stirred at room temperature for 0.5 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice-cold water. The solid thus obtained was filtered, washed with water, and recrystallized from ethanol to afford (**4a–d**) with good yields.

***General procedure for the synthesis of 2-chloro-3-phenyl-1,8-naphthyridine (5a–d).*** A solution of **4** (1 mmol) in $POCl_3$ (15 mL) was exposed to MWI at 200 W intermittently at 30 s intervals for 2.0–2.5 min. After the reaction mixture was cooled to room temperature, the resulting reaction mixture was dissolved in cold $H_2O$ (2 × 75 mL) and saturated $NaHCO_3$. The organic phase was dried and evaporated to dryness. The crude product was filtered, washed with water, and recrystallized from *n*-pentane to furnish **5a**–**d**.

***General procedure for the synthesis of N-3-diaryl-1,8-naphthyridin-2-amines (7a–l).*** A mixture of 2-chloro-3-aryl-1,8-naphthyridine (1 mmol, 5a–d), p-amino phenyl halides (1 mmol, 6a–c), 10 mmol of dry NMP and $K_2CO_3$ (3.5 mmol) under solvent-free conditions at 75°C for 20–30 min. During this time, the progress of the reaction was followed by the TLC test (Table 1). When the reaction was completed, cooled to room temperature and poured into a mixture of ethyl acetate. The solid separated out was filtered, washed with water, and recrystallized from methanol to furnish **7a**–**l** with good yields.

**Spectral data of representative compounds.** ***N-(4-bromophenyl)-3-phenyl-1,8-naphthyridin-2-amine (7a).*** Pale-yellow solid; yield 3.24 g; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3313, 3170, 3026, 1546, 1325, 694; $^1H$ NMR (400 MHz, DMSO-$d_6$, ppm): δ 7.28 (1H, dd, *J* = 7.7, 4.7 Hz, ArH), 7.36–7.53 (5H, m, ArH), 7.69–7.80 (3H, m, ArH), 8.13 (1H, s, ArH), 8.17 (2H, dd, *J* = 7.7, 1.6 Hz, ArH), 8.52 (1H, dd, *J* = 4.7, 1.7 Hz, ArH), 12.35 (1H, s, NH); MS [EI, m/z(%)]: 375 ($M^+$); *Anal*. Calcd for $C_{20}H_{14}BrN_3$: C, 63.84; H, 3.75; N, 11.17; found: C, 63.90; H, 3.70; N, 11.00%.

***N-(4-fluorophenyl)-3-phenyl-1,8-naphthyridin-2-amine (7b).*** White solid; yield 2.77 g; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3273, 3167, 3030, 1508, 1278, 1155; $^1H$ NMR (400 MHz, DMSO-$d_6$, ppm): δ 7.24–7.35 (5H, m, ArH), 7.76–7.85 (3H, m, ArH), 8.10–8.20 (3H, m, ArH), 8.50–8.59 (2H, m, ArH), 12.40 (1H, s, NH); MS [EI, m/z(%)]: 315 $(M + H)^+$; *Anal*. Calcd for $C_{20}H_{14}FN_3$: C, 76.18; H, 4.48; N, 13.33; found: C, 76.01; H, 4.42; N, 13.22%.

***N-(4-chlorophenyl)-3-phenyl-1,8-naphthyridin-2-amine (7c).*** Half-white solid; yield 2.78 g; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3235, 3130, 1510, 1311, 1214; $^1H$ NMR (400 MHz, DMSO-$d_6$, ppm): δ 7.25–7.33 (2H, m, ArH), 7.37–7.48 (4H, m, ArH), 7.70–7.80 (3H, m, ArH), 8.09–8.19 (3H, m, ArH), 8.48–8.54 (1H, m, ArH), 12.35 (1H, s, NH); MS [EI, m/z(%)]: 331 $(M + H)^+$; *Anal*. Calcd for $C_{20}H_{14}ClN_3$: C, 72.40; H, 4.25; N, 12.66; found: C, 72.51; H, 4.40; N, 12.42%.

***N-(4-bromophenyl)-3-(4-methoxyphenyl)-1,8-naphthyridin-2-amine (7d).*** Yellow solid; yield 3.65 g; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3167, 1510, 1421, 1138, 705; $^1H$ NMR (400 MHz, DMSO-$d_6$, ppm): δ 3.81 (3H, s, $ArOCH_3$), 7.02 (2H, d, *J* = 9.0 Hz, ArH), 7.22–7.30 (3H, m, ArH), 7.70–7.79 (3H, m, ArH), 7.90 (1H, d, *J* = 2.2 Hz, ArH), 8.08 (1H, s, ArH), 8.51 (2H, s, ArH), 12.30 (1H, s, NH); MS [EI, m/z(%)]: 406 $(M + H)^+$; *Anal*. Calcd for $C_{21}H_{16}BrN_3O$: C, 62.08; H, 3.97; N, 10.34; found: C, 62.20; H, 3.80; N, 10.30%.

***N-(4-fluorophenyl)-3-(4-methoxyphenyl)-1,8-naphthyridin-2-amine (7e).*** Gray solid; yield 3.17 g; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3207, 1519, 1415, 1181, 891; $^1H$ NMR (400 MHz, DMSO-$d_6$, ppm): δ 3.81 (3H, s, $ArOCH_3$), 6.96–7.05 (3H, m, ArH), 7.15 (2H, s, ArH), 7.38–7.47 (3H, m, ArH), 8.10 (2H, s, ArH), 8.43–8.52 (2H, m, ArH), 12.33 (1H, s, NH); MS [EI, m/z(%)]: 345 $(M + H)^+$; *Anal*. Calcd for $C_{21}H_{16}FN_3O$: C, 73.03; H, 4.67; N, 12.17; found: C, 73.10; H, 4.71; N, 12.33%.

***N-(4-chlorophenyl)-3-(4-methoxyphenyl)-1,8-naphthyridin-2-amine (7f).*** Colorless solid; yield 3.18 g; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3309, 1520, 1154, 1021, 751; $^1H$ NMR (400 MHz, DMSO-$d_6$, ppm): δ 3.81 (3H, s, $ArOCH_3$), 7.05 (2H, d, *J* = 8.5 Hz, ArH), 7.20–7.27 (2H, m, ArH), 7.50 (1H, s, ArH), 7.72–7.80 (3H, m, ArH), 8.19–8.25 (1H, m, ArH), 8.64 (1H, s, ArH), 8.71 (2H, s, ArH), 12.38 (1H, s, NH); MS [EI, m/z(%)]: 362 $(M + H)^+$; *Anal*. Calcd for $C_{21}H_{16}ClN_3O$: C, 69.71; H, 4.46; N, 11.61; found: C, 69.87; H, 4.56; N, 11.55%.

***N-(4-bromophenyl)-3-(2-methoxyphenyl)-1,8-naphthyridin-2-amine (7g).*** Pale-yellow solid; yield 3.46 g; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3360, 3028, 1508, 1136, 692; $^1H$ NMR (400 MHz, DMSO-$d_6$, ppm): δ 3.80 (3H, s, $ArOCH_3$), 7.01 (2H, d, *J* = 8.0 Hz, ArH), 7.22–7.27 (2H, m, ArH), 7.46–7.58 (1H, m, ArH), 7.73 (2H, d, *J* = 9.0 Hz, ArH), 7.90 (1H, s, ArH), 8.08 (1H, s, ArH), 8.12–8.17 (1H, m, ArH), 8.51 (2H, s, ArH), 12.30 (1H, s, NH); MS [EI, m/z(%)]: 406 $(M + H)^+$; *Anal*. Calcd for $C_{21}H_{16}BrN_3O$: C, 62.08; H, 3.97; N, 10.34; found: C, 62.21; H, 3.83; N, 10.23%.

***N-(4-fluorophenyl)-3-(2-methoxyphenyl)-1,8-naphthyridin-2-amine (7h).*** Gray solid; yield 3.14 g; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3320, 1581, 1056, 996; $^1H$ NMR (400 MHz, DMSO-$d_6$, ppm): δ 3.80 (3H, s, $ArOCH_3$), 7.28 (2H, dd, *J* = 7.7, 4.8 Hz, ArH), 7.44–7.56 (3H, m, ArH), 7.78

(3H, t, $J$ = 2.3 Hz, ArH), 8.09–8.26 (3H, m, ArH), 8.53 (1H, dd, $J$ = 4.7, 1.6 Hz, ArH), 12.41 (1H, s, NH); MS [EI, m/z(%)]: 345 $(M + H)^+$; *Anal*. Calcd for $C_{21}H_{16}FN_3O$: C, 73.03; H, 4.67; N, 12.17; found: C, 73.20; H, 4.82; N, 12.33%.

***N-(4-chlorophenyl)-3-(2-methoxyphenyl)-1,8-naphthyridin-2-amine (7i).*** Cream solid; yield 3.02 g (84%); IR (KBr, $\nu_{max}$, $cm^{-1}$): 3358, 3028, 1508, 1423, 1060, 775; $^1H$ NMR (400 MHz, DMSO-$d_6$, ppm): δ 3.80 (3H, s, $ArOCH_3$), 7.04 (3H, d, $J$ = 11.5 Hz, ArH), 7.51 (1H, d, $J$ = 20.5 Hz, ArH), 7.70–7.81 (3H, m, ArH), 7.90 (1H, s, ArH), 8.08 (1H, s, ArH), 8.17 (3H, d, $J$ = 11.5 Hz, ArH), 12.30 (1H, s, NH); MS [EI, m/z(%)]: 362 $(M + H)^+$; *Anal*. Calcd for $C_{21}H_{16}ClN_3O$: C, 69.71; H, 4.46; N, 11.61; found: C, 69.80; H, 4.55; N, 11.35%.

***N-(4-bromophenyl)-3-(4-chlorophenyl)-1,8-naphthyridin-2-amine (7j).*** Pale-yellow solid; yield 3.77 g; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3358, 3030, 1487, 1274, 767, 732; $^1H$ NMR (400 MHz, DMSO-$d_6$, ppm): δ 7.28 (2H, d, $J$ = 1.9 Hz, ArH), 7.52 (3H, d, $J$ = 8.6 Hz, ArH), 7.80 (3H, d, $J$ = 4.6 Hz, ArH), 8.11–8.24 (3H, m, ArH), 8.54 (1H, d, $J$ = 9.7 Hz, ArH), 12.41 (1H, s, NH); MS [EI, m/z(%)]: 410 $(M + H)^+$; *Anal*. Calcd for $C_{20}H_{13}BrClN_3$: C, 58.49; H, 3.19; N, 10.23; found: C, 58.53; H, 3.32; N, 10.12%.

***3-(4-chlorophenyl)-N-(4-fluorophenyl)-1,8-naphthyridin-2-amine (7k).*** White solid; yield 3.08 g; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3356, 3030, 1510, 1278, 1157, 738; $^1H$ NMR (400 MHz, DMSO-$d_6$, ppm): δ 7.28 (2H, dd, $J$ = 7.7, 4.8 Hz, ArH), 7.50–7.55 (3H, m, ArH), 7.77–7.82 (3H, m, ArH), 8.17 (1H, d, $J$ = 1.6 Hz, ArH), 8.19 (2H, s, ArH), 8.53 (1H, dd, $J$ = 4.7, 1.7 Hz, ArH), 12.41 (1H, s, NH); MS [EI, m/z(%)]: 350 $(M + H)^+$; *Anal*. Calcd for $C_{20}H_{13}ClFN_3$: C, 68.67; H, 3.75; N, 12.01; found: C, 68.73; H, 3.82; N, 12.12%.

***N-3-bis (4-chlorophenyl)-1,8-naphthyridin-2-amine (7l).*** Colorless solid; yield 3.33 g; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3356, 3030, 1489, 1222, 767, 731; $^1H$ NMR (400 MHz, DMSO-$d_6$, ppm): δ 7.24–7.35 (4H, m, ArH), 7.73–7.87 (3H, m, ArH), 8.08–8.23 (3H, m, ArH), 8.48–8.60 (2H, m, ArH), 12.39 (1H, s, NH); MS [EI, m/z(%)]: 366 $(M + H)^+$; *Anal*. Calcd for $C_{20}H_{13}Cl_2N_3$: C, 65.59; H, 3.58; N, 11.47; found: C, 65.49; H, 3.52; N, 11.51%.

**Antibacterial activity.** The title compounds as potentially useful compounds with possible biological activities. The compounds **7a–l** were protected for their antibacterial activity against *Bacillus subtilis* (Gram-positive) and *Escherichia coli* (Gram-negative) by filter paper disc technique [32] at 400 and 600 μg/disc concentrations. Streptomycin antibiotic was used as standard for the antibacterial activity, under similar conditions. The results of the antibacterial screening are given in Table 2.

The agar diffusion method was used for antibacterial activity was evaluated by measuring the diameter of the zones of inhibition against the tested bacteria. The test organisms were subcultured on lysogeny broth. Take 1 μ of Luria Bertani (LB broth powder) and dissolve in 10 ml of distilled water in a test tube and autoclaved at 15-lb pressures for 15 min and cool. Then add 400 and 600 μg/disc of bacterial culture to the broth in laminar air flow and stored at 4°C in the refrigerator. For bacterial assay, nutrient agar (40 g/mL) was used for developing surface colony growth. Stock solution of each compound was prepared at a concentration of 1 μ/mL. The diameter of the inhibition zone in millimeter was measured, and the activity index was also calculated. About 100 μL of 400 and 600 μg/disc concentrations of compounds were

**Table 2**

Antibacterial activity screening data of the synthesized compounds **7a**–**l**.

| | Inhibition zone (in mm) against | | | |
|---|---|---|---|---|
| | *Escherichia coli* at | | *Bacillus subtilis* at | |
| Compound | 400 μg/disc | 600 μg/disc | 400 μg/disc | 600 μg/disc |
| **7a** | 6.5 | 7.5 | 4.0 | 5.0 |
| **7b** | 6.0 | 7.0 | 4.0 | 5.0 |
| **7c** | 6.5 | 7.5 | 5.0 | 6.0 |
| **7d** | 10.0 | 11.0 | 7.0 | 8.0 |
| **7e** | 8.0 | 9.5 | 6.0 | 7.0 |
| **7f** | **11.0** | **12.0** | 6.5 | 7.5 |
| **7g** | 7.5 | 8.5 | 5.0 | 6.0 |
| **7h** | 6.5 | 7.5 | 5.5 | 6.0 |
| **7i** | 7.5 | 6.0 | 4.0 | 5.5 |
| **7j** | 8.0 | 9.0 | 5.5 | 6.5 |
| **7k** | 7.5 | 8.0 | 5.0 | 6.0 |
| **7l** | 10.5 | 11.5 | **8.0** | **8.5** |
| Streptomycin | 13.0 | 15.0 | 10.0 | 12.0 |

The results for **7f** and **7l** are highest antibacterial activity compared with **7a–e** and **7g–k**.
Bold values shows more activity compared to other antibacterial compounds.

added by sterile pipette into the wells and allowed to diffuse at room temperature for 3 h. Control experiments (positive and negative) comprising inoculums without compounds were set up. The plates were incubated at 37°C for 15–22 h for bacterial pathogens. For each replicates, the readings were taken in three different fixed directions, and the values were recorded.

The activity of the synthesized compounds depends upon the nature and position of the substituent at the phenyl moiety. The presence of certain flouro-substituted, chloro-substituted, and bromo-substituted aryl group diminishes the activity of the compounds. On the other hand, certain substituents especially methoxyl and chloro groups when attached to phenyl ring augment the antibacterial activity remarkably. In the case of *E. coli*, the compound **7f** is showing maximum antimicrobial activity against gram-negative bacteria, and **7d** and **7l** are nearest to standard drug, whereas the compound **7l** is showing equipotent antimicrobial activity with streptomycin drug in the case of *B. subtilis*. We report herein the first structure–activity relationship of this class of antimicrobial by systematically varying the *N*-(4-bromophenyl)-3-(4-methoxyphenyl)-1,8-naphthyridin-2-amine (**7d**) and *N*-(4-bromophenyl)-3-(2-methoxyphenyl)-1,8-naphthyridin-2-amine (**7g**). When methoxyl was a phenyl ring, para-substitution was found to be superior to ortho-substitution. While the electron-donating of substituents position 4-methoxyphenyl compound (**7d**) was well tolerated, but 2-methoxyphenyl (**7g**) was not. All the compounds are showing good to moderate antibacterial activity.

## CONCLUSIONS

In conclusion, a mild and highly efficient method has been developed for the synthesis of novel *N*-substituted 1,8-naphthyridin-2-amines. Moreover, in solvent-free conditions make syntheses good to excellent yields, obviously reduce pollution, easy work-up, short reaction time, simpler and excellent purities of the products. The antibacterial activity of synthesized compounds **7d**, **7f**, and **7l** exhibits uppermost activity to that of streptomycin towards *E. coli*.

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## SUPPORTING INFORMATION

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