Asian Journal of Chemistry; Vol. 35, No. 10 (2023), 2527-2536

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2023.29067

Facile Synthesis of Substituted 2-Styrylnaphthyridine and its Derivatives *via* sp^3 C-H Functionalization under Mild Conditions and their Antimicrobial Activity

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Received: 21 August 2023; *Accepted*: 5 September 2023; *Published online*: 28 September 2023; AJC-21406

A simple, metal free strategy is described for the synthesis of substituted 2-styryl-1,8-naphthyridines and pyrazole, imidazopyridine based styryl conjugates under basic mild conditions (piperidine in ethanol) at 70 ºC. The reaction progressed *via* sp^3 C-H functionalization of substituted methyl-1,8-naphthyridines with various aromatic, heteroaromatic aldehyde substrates by Knoevenagel condensation to provides functionalized pyrazole, imidazopyridine based styryl-1,8-naphthyridines in good to excellent yields (85-95%) at impressive reaction time. This approach involves a common organocatalyst, cheap starting materials and shorter reaction times. An extensive variability of substrates was tolerated well to afford the desired products. Furtherly, all the synthesized derivatives were tested for their biological activity, *i.e.*, antibacterial and antifungal. In tested series, compounds **3c**, **3d**, **3e**, **3i**, **3k**, **3l**, **4c**, **4d** and **4f** established excellent inhibition zone of activity against standard drugs.

Keywords: 1,8-Naphthyridines, Knoevenagel condensation, Ogranocatalyst, Antibacterial, Antifungal.

INTRODUCTION

1,8-Naphthyridines are significant class of heterocyclics and has related to quinolines (antimalarial: cincona alkaloids) class. The naphthyridine framework exists in a number of natural and biological properties and its structural core units representing focus on wide spectrum of biological activities such as diuretic [1], antibacterial agent [2], anti-inflammatory [3], antihypertensive [4], antiplatelet activity [5], anticancer [6], HIV-I inhibitor [7], anticonvulsant [8] and anti-Alzheimer [9]. In addition, its derivatives have been chosen as the ideal building blocks for recognition of carbohydrates [10]. The 2-amino-1,8-naphthyridines exhibit fluorescence properties and show promise in the identification and analysis of many chemical and biological entities, for example, fluorogenic 2-amino-1,8-naphthyridine derivatives which is well known for the ability to detect the pathogenic bacteria in agar-based cell culture [11] and 1,8-naphthyridine derivatives served as tripodal receptor [12]. The subsidiary molecules of 1,8-naphthyridines are 1,6-naphthyridines also exhibit the anticancer activity [13]. Promisingly, these motifs widely used in diagnostics and treatment of several human diseases, in agriculture and in photophysical applications [14].

Furthermore, different 2-phenyl-1,8-naphthyridines have been showed high affinity towards adenosine receptor A1 up to the sub-nanomolar range with good selectivity between the adenosine receptors A1/A2a and A1/A3 [15,16]. Various arylated naphthyridines helped as non-competitive metabotropic glutamate receptor 5 (mGluR5) antagonists, which are promising agents against pain and disorders related to the central nervous system, including anxiety and Parkinson's disease [17]. Derivatives of 1,8-naphthyridine exhibit potent antitumor [18], neurotoxic [19], neuroprotective [20] and cardiac [21] activities. In addition, they also represent interesting building blocks for non-covalent assemblies in supramolecular chemistry [22]. Naphthyridines have been employed as receptor molecules to study of biologically relevant species, such as guanine [23], monosaccharides [24] and guanosine triphosphate [25].

In previous studies, numerous synthetic approaches have been reported for the synthesis of substituted 2-styryl-1,8-naphthyridine derivatives. These strategies have been explored under diverse reaction conditions and methods. Zhu *et al.* [26] synthesized styryl-1,8-naphthyridine derivatives by reacting 1,8-naphthyridine, DMSO and benzaldehyde under $NaOBu^t$, followed by Lewie's acid *via* direct α-methylation approach. Moreover, styryl-1,8-naphthyridine scaffolds were achieved by the coupling of 2-aminonicotinaldehyde, substituted (*E*)-benzylidene acetones in the presence organocatalysts such as water + AcOH (1 mol%) and KOH + EtOH [27,28]. Zhang *et al.* [29] also reported the synthesis of 1,8-naphthyridine styryls *via* dehydrogenative coupling of 2-methyl-1,2,3,4-tetrahydro-1,8-naphthyridine and benzaldehyde using cobalt nanocatalyst. However, almost all of these methods suffer from one or the other drawbacks such as requirement of non readily available precursors, need of rare compounds, use of expensive catalysts, multistep sequence, harsh reaction conditions, prolonged reaction times and low product yield. The search for emerging eco-friendly synthetic approaches using greener conditions has suffered challenging since the last few decades. Inspite of significant enhancement in this field, the development of new synthetic methods is required for the synthesis of titled compounds *via* Knoevenagel condensation of 2-methyl-1,8-naphthyridine in a green, facile and metal-free method leftovers highly desirable. The aforementioned synthetic strategies highlight certain drawbacks. In order to address these concerns, it is imperative to investigate a metal-free synthetic approach that is both simple and efficient for the synthesis of the aforementioned compounds. This alternative strategy offers several advantages, including the utilization of a less expensive catalyst (piperidine), a more environmentally friendly solvent, milder reaction conditions, cost-effectiveness, enhanced safety, non-toxicity, eco-friendliness, a straightforward procedure and the absence of metal catalysts. Additionally, the starting materials required for this approach are readily accessible. Considering the significant biological activity of substituted 1,8-naphthyridine, the constraints associated with previously reported approaches and the lack of accessible synthetic pathways for the desired compounds, an innovative synthetic route for the synthesis of 2-styryl-1,8-naphthyridine derivatives is developed under mild basic conditions (specifically piperidine in ethanol) in a grinner manner.

EXPERIMENTAL

All the starting materials are purchased from SRL, Sigma-Aldrich, Spectrochem and SD-Fine were utilized without further purification. The ^1H and ^{13}C NMR spectra were recorded by Bruker 400 MHz spectrometer using $CDCl_3$ & DMSO-d_6 solvents (reported in δ ppm). UV-visible and fluorescent spectra were recorded using Perkin-Elmer spectrophotometer. The melting points were recorded using Stuart melting point apparatus and are uncorrected. The cyclic voltammetry spectra were recorded by CH Instruments CHI660D Electrochemical Workstation.

Synthesis of (*E*)-2-chloro-7-styryl-1,8-naphthyridine (3b): To a solution of 2-chloro-7-methyl-1,8-naphthyridine (**1b**) (1 equiv.) in ethanol, was added piperidine (1 equiv.) and stirred the reaction mass for 10 min at room temperature followed by the addition of benzaldehyde (1 equiv.) (**2b**) to the reaction mixture and raised the temperature up to 70 ºC and continued the stirring for 7 h. After completion of the reaction (progress of the reaction was monitored by TLC), the reaction mass was warmed to room temperature and diluted with cold water and the organic layer was extracted with ethyl acetate, washed with brine solution and dried over sodium sulphate. Further, the organic layer was minimized by vacuum (under condensed pressure) to get sticky crude mass (**Scheme-I**). The pure form of desired compound **3b** was isolated by column chromatography (EtOAc 10% in *n*-hexane (1:10 v/v) as solvent system).

(*E*)-2-Chloro-7-styryl-1,8-naphthyridine (3b): White solid, m.p.: 150-152 ºC, 92% yield. ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.53 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 8.17-7.90 (m, 4H), 7.87-7.74 (m, 2H), 7.73-7.57 (m, 2H), 7.26 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 159.7, 155.6, 152.6, 146.6, 141.9, 138.8, 136.2, 135.3, 134.9, 133.6, 129.7, 128.6, 123.4, 120.5; HRMS (ESI, *m/z*): calcd. for $C_{16}H_{11}ClN_2H^+$ 267.0684, found 267.0680.

(*E*)-2-Chloro-7-(4-methoxystyryl)-1,8-naphthyridine (3c): Pale yellow solid, m.p.: 163-165 ºC, 86% yield. IR (KBr, ν_{max}, cm^{-1}): 3040, 1588, 1510, 1360, 1150, 850. ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.05 (d, *J* = 16.0 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 16.2 Hz, 1H), 7.60-7.53 (m, 2H), 7.42-7.24 (m, 4H), 7.16-7.13 (m, 1H), 5.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 159.0, 154.3, 152.1, 146.7, 135.1, 134.6, 131.9, 131.1, 128.9, 128.5, 127.7, 122.7, 122.1, 114.7; HRMS (ESI, *m/z*): calcd. for $C_{17}H_{14}ClN_2OH^+$ 297.0789, found 297.0789.

(*E*)-2-Chloro-7-(3,4-dimethoxystyryl)-1,8-naphthyridine (3d): Yellow solid, m.p.: 178-180 ºC, 85% yield. IR (KBr, ν_{max}, cm^{-1}): 3040, 2850, 1581, 1502, 1360, 1176, 836. ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 15.8 Hz, 1H), 8.19-8.04 (m, 2H), 7.99-7.83 (m, 2H), 7.72 (s, 1H), 7.48-7.25 (m, 2H), 7.00 (d, *J* = 7.8 Hz, 1H), 4.04 (d, *J* = 8.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 157.1, 150.4, 148.2, 145.6, 137.2, 134.8, 132.4, 130.4, 129.0, 127.7, 125.9, 122.2, 121.6, 117.3, 111.3, 56.2, 56.1; HRMS (ESI, *m/z*): calcd. for $C_{18}H_{15}ClN_2O_2H^+$ 327.0895, found 327.0890.

(*E*)-4-(2-(7-Chloro-1,8-naphthyridin-2-yl)vinyl)phenol (3e): Yellow solid, m.p.: 171-173 ºC, 88% yield. IR (KBr, ν_{max}, cm^{-1}): 3440, 3150, 1585, 1514, 1335, 1122, 846. ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 12.44 (s, 4H), 8.05 (d, *J* = 16.2 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 16.4 Hz, 1H), 7.60-7.53 (m, 3H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.35-7.24 (m, 3H), 5.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 159.0, 154.3, 152.1, 146.7, 135.1, 134.7, 131.9, 131.1, 128.9, 128.5, 127.7, 122.7, 122.1, 114.7; HRMS (ESI, *m/z*): calcd. for $C_{16}H_{11}ClN_2OH^+$ 283.0633, found 283.0630.

(*E*)-2-Chloro-7-(2-nitrostyryl)-1,8-naphthyridine (3f): Yellow solid, m.p.: 182-184 ºC, 95% yield. IR (KBr, ν_{max}, cm^{-1}): 3040, 1552, 1488, 1346, 1161, 855. ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.61 (d, *J* = 16.2 Hz, 1H), 8.31-8.01 (m, 4H), 7.96-7.73 (m, 1H), 7.45 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$

+ DMSO-d_6): δ 160.8, 155.8, 149.5, 145.44, 137.9, 135.2, 133.6, 132.4, 130.1, 129.8, 128.6, 126.5, 124.1, 123.7, 121.6, 120.5; HRMS (ESI, *m/z*): calcd. for $C_{16}H_{10}ClN_3O_2H^+$ 312.0534, found 312.0530.

(*E*)-2-Chloro-7-(4-nitrostyryl)-1,8-naphthyridine (3g): Yellow solid, m.p.: 201-203 ºC, 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.42 (d, *J* = 16.0 Hz, 1H), 8.35-7.91 (m, 5H), 7.83 (d, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 16.0 Hz, 1H), 7.18 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 160.1, 157.9, 152.2, 149.2, 143.2, 140.4, 138.0, 135.9, 133.5, 128.8, 127.8, 124.8, 122.3, 121.9; HRMS (ESI, *m/z*): calcd. for $C_{16}H_{10}ClN_3O_2H^+$ 312.0534, found 312.0531.

(*E*)-2-Chloro-7-(4-chlorostyryl)-1,8-naphthyridine (3h): Yellow solid, m.p.: 179-182 ºC, 90% yield. IR (KBr, ν_{max}, cm^{-1}): 3082, 1566, 1488, 1322, 1156, 836, 865. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.10 (d, *J* = 16.0 Hz, 1H), 7.90-7.68 (m, 5H), 7.57 (d, *J* = 10.0 Hz, 1H), 7.45 (d, *J* = 6.8 Hz, 1H), 7.38-7.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 159.2, 156.5, 150.2, 142.4, 138.6, 136.1, 134.1, 131.1, 130.7, 130.3, 129.7, 126.7, 123.3, 121.7; HRMS (ESI, *m/z*): calcd. for $C_{16}H_{10}C_{l2}N_2H^+$ 301.0294, found 301.0294.

(*E*)-2-Chloro-7-(4-bromostyryl)-1,8-naphthyridine (3i): Yellow solid, m.p.: 220-222 ºC, 92% yield. IR (KBr, ν_{max}, cm^{-1}): 3090, 2850, 1581, 1486, 1360, 1176, 836. 675. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.24 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 16.8 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.82-7.75 (m, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.36-7.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 161.0, 159.9, 156.3, 150.1, 141.6, 139.5, 137.1, 133.9, 133.1, 131.7, 130.5, 129.7, 124.1, 121.5; HRMS (ESI, *m/z*): calcd. for $C_{16}H_{10}BrClN_2H_2^+$ 345.9867, found 345.9855.

(*E*)-2-Chloro-7-(4-methylstyryl)-1,8-naphthyridine (3j): White solid, m.p.: 210-212 ºC, 86% yield. IR (KBr, ν_{max}, cm^{-1}): 3060, 2980, 1565, 1468, 1342, 1129, 860. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.99 (d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 15.8 Hz, 1H), 7.48-7.34 (m, 4H), 7.27- 7.24 (m, 2H), 7.16 (d, *J* = 7.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 160.9, 155.4, 152.7, 148.5, 140.9, 135.9, 134.1, 133.2, 132.5, 130.1, 128.2, 125.2, 123.7, 120.55, 24.5; HRMS (ESI, *m/z*): calcd. for $C_{17}H_{13}ClN_2H^+$ 281.0840, found 281.0835.

(*E*)-2-Chloro-7-(2,4-dichlorostyryl)-1,8-naphthyridine (3k): Yellow solid, m.p.: 188-190 ºC, 93% yield. IR (KBr, ν_{max}, cm^{-1}): 3070, 1562, 1450, 1355, 1163, 866. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.48 (d, *J* = 16.2 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.76 (dd, *J* = 16.4, 8.2 Hz, 2H), 7.66-7.51 (m, 2H), 7.41 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 160.0, 155.3, 150.3, 139.5, 136.1, 135.7, 132.9, 132.1, 131.2, 129.5, 128.7, 127.1, 126.1, 123.7, 122.9 120.8; HRMS (ESI, *m/z*): calcd. for $C_{16}H_9C_{l3}N_2H^+$ 334.9904, found 334.9904.

(*E*)-2-Chloro-7-(2-(furan-2-yl)vinyl)-1,8-naphthyridine (3l): Yellow solid, m.p.: 192-194 ºC, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 15.8 Hz, 1H), 7.65 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.52-7.49 (m, 2H), 7.37 (dt, *J* = 5.2, 2.4 Hz, 1H), 7.20 (d, *J* = 15.8 Hz, 1H), 6.58 (d, *J* = 3.8 Hz, 1H), 6.47 (dd, *J* = 4.2, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 152.6, 150.9, 146.3, 143.3, 134.9, 131.2, 129.2, 128.3, 125.1, 123.6, 121.7, 112.3, 111.9; HRMS (ESI, *m/z*): calcd. for $C_{14}H_9ClN_2OH^+$ 257.0476; found 257.0470.

(*E*)-2-Chloro-7-(2-(naphthalen-2-yl)vinyl)-1,8-naphthyridine (3m): Yellow solid, m.p.: 210-212 ºC, 91% yield. IR (KBr, ν_{max}, cm^{-1}): 3060, 1562, 1468, 1352, 1162, 854. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.77 (d, *J* = 16.2 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.3 Hz, 4H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.52– 7.34 (m, 5H), 7.27 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 161.2, 156.2, 149.9, 141.1, 138.6, 133.9, 132.9, 131.4, 131.3, 130.5, 130.0, 129.5, 129.2, 128.9, 128.6, 126.6, 124.6, 124.1, 123.2, 121.7; HRMS (ESI, *m/z*): calcd. for $C_{18}H_{16}ClN_2O_2H^+$ 327.0895, found 327.0890.

(*E*)-2-(2-(2-Phenylimidazo[1,2-*a*]pyridin-3-yl)vinyl)-1,8-naphthyridine (4a): Yellow solid, m.p.: 171-169 ºC, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (dd, *J* = 7.8, 1.6 Hz, 1H), 8.37 (dd, *J* = 7.8, 1.6 Hz, 1H), 8.22 (dt, *J* = 8.0, 2.2 Hz, 1H), 8.14 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.72 (d, *J* = 16.0 Hz, 1H), 7.60 (dd, *J* = 4.8, 2.8 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.49-7.38 (m, 5H), 7.33 (d, *J* = 15.2 Hz, 1H), 7.24 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.86 (dd, *J* = 7.5, 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 156.6, 155.3, 153.6, 146.8, 140.9, 139.1, 137.8, 136.3, 133.5, 132.9, 132.5, 132.1, 131.6, 130.2, 128.7, 127.7, 123.7, 120.8, 117.2, 115.7, 115.0; HRMS (ESI, *m/z*): calcd. for $C_{23}H_{16}N_4H^+$ 349.1448, found 349.1448.

(*E*)-2-Chloro-7-(2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)vinyl)-1,8-naphthyridine (4b): Yellow solid, m.p.: 188-190 ºC, 90% yield. IR (KBr, ν_{max}, cm^{-1}): 3089, 2863, 1565, 1486, 1386, 1157, 854. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.51 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.44 (dd, *J* = 7.4, 2.0 Hz, 1H), 8.24 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.84-7.76 (m, 3H), 7.71 (d, *J* = 16.2 Hz, 1H), 7.63-7.50 (m, 4H), 7.46-7.40 (m, 1H), 7.37-7.29 (m, 2H), 6.96 (td, *J* = 8.2, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 155.6, 153.8, 146.1, 144.7, 141.2, 140.4, 139.5, 138.1, 134.6, 131.0, 130.1, 129.4, 128.8, 128.0, 127.3, 124.0, 122.8, 121.1, 119.2, 115.9, 114.4; HRMS (ESI, *m/z*): calcd. for $C_{23}H_{15}ClN_4H^+$ 383.1058, found 383.1058.

(*E*)-2-(2-(2-(4-Bromophenyl)imidazo[1,2-*a*]pyridin-3-yl)vinyl)-7-chloro-1,8-naphthyridine (4c): Yellow solid, m.p.: 178-180 ºC, 86% yield. IR (KBr, ν_{max}, cm^{-1}): 3080, 1535, 1478, 1386, 1148, 853, 680. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.33 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.13 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.71 (d, *J* = 6.8 Hz, 1H), 7.63-7.54 (m, 5H), 7.51-7.43 (m, 2H), 7.23 (dd, *J* = 8.0, 1.89 Hz, 1H), 7.17 (d, *J* = 15.8 Hz, 1H), 6.85 (td, *J* = 7.8, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 154.7, 152.2, 147.1, 142.5, 136.2, 135.4, 134.3, 132.3, 131.8, 130.1, 128.5, 128.3, 127.1, 126.3, 125.1, 123.8, 123.4, 122.1, 120.4, 116.7, 115.2; HRMS (ESI, *m/z*): calcd. for $C_{23}H_{15}BrClN_4H_2^+$ 462.0241, found 462.0230.

(*E*)-2-(2-(2-(3-Bromophenyl)imidazo[1,2-*a*]pyridin-3-yl)vinyl)-7-chloro-1,8-naphthyridine (4d): Greenish yellow solid, m.p.: 210-212 ºC, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.33 (dd, *J* = 8.0, 1.8 Hz, 1H), 8.13 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.88 (t, *J* = 1.8 Hz, 1H), 7.75-7.64 (m, 2H), 7.60 (d, *J* = 16.2 Hz, 1H), 7.52-7.42 (m, 3H), 7.34-7.21 (m, 2H), 7.17 (d, *J* = 16.2 Hz, 1H), 6.85 (td, *J* = 7.8,

1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 155.3, 153.8, 146.2, 143.8, 140.5, 139.3, 138.1, 136.1, 135.6, 134.3, 132.9, 132.0, 131.0, 129.9, 129.5, 128.7, 126.7, 125.9, 123.1, 122.9, 120.8, 116.8, 115.7; HRMS (ESI, *m/z*): calcd. for $C_{23}H_{15}BrClN_4H_2^+$ 462.0241, found 462.0230.

(*E*)-2-Chloro-7-(2-(1,3-diphenyl-1*H*-pyrazol-4-yl)-vinyl)-1,8-naphthyridine (4e): White solid, m.p.: 192-194 ºC, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 6.8, 1H), 8.40 (dd, *J* = 7.6, 2.0 Hz, 1H), 8.17-8.09 (m, 3H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.68-7.58 (m, 4H), 7.54-7.39 (m, 6H), 7.36-7.30 (m, 2H), 7.18 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 155.2, 151.9, 143.6, 141.8, 139.5, 136.6, 134.2, 132.5, 131.7, 130.4, 129.4, 128.7, 128.3, 127.3, 126.8, 123.3, 122.9, 119.8, 118.8, 116.7; HRMS (ESI, *m/z*): calcd. for $C_{25}H_{17}ClN_4H^+$ 409.1215, found 409.1215.

(*E*)-2-(2-(1-(4-Bromophenyl)-3-phenyl-1*H*-pyrazol-4-yl)vinyl)-7-chloro-1,8-naphthyridine (4f): Greenish yellow solid, m.p.: 196-198 ºC, 89% yield. IR (KBr, ν_{max}, cm^{-1}): 3070, 1525, 1465, 1380, 1136, 865, 629. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (dd, *J* = 8.0, 1.8 Hz, 1H), 8.35 (s, 1H), 8.15 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.76-7.69 (m, 3H), 7.66-7.51 (m, 6H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.33 (dd, *J* = 5.8, 3.4 Hz, 1H), 6.96 (d, *J* = 16.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 150.2, 146.02, 143.0, 139.6, 137.2, 136.2, 135.4, 134.7, 134.3, 132.7, 131.6, 130.3, 129.2, 128.8, 128.5, 126.9, 126.0, 122.8, 120.6, 117.7; HRMS (ESI, *m/z*): calcd. for $C_{23}H_{16}BrClN_4H^+$ 462.0241, found 462.0230.

(*E*)-3-(2-(7-Chloro-1,8-naphthyridin-2-yl)vinyl)-4*H*-chromen-4-one (4g): Pale yellow solid, m.p.: 161-163 ºC, 81% yield. IR (KBr, ν_{max}, cm^{-1}): 3085, 1685, 1525, 1465, 1380, 1198, 868. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.40 (dd, *J* = 7.8, 2.0 Hz, 1H), 8.13 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.74-7.66 (m, 2H), 7.55 (m, 2H), 7.30-7.06 (m, 2H), 7.09-6.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 178.6, 155.2, 152.9, 147.3, 144.5, 139.5, 137.6, 134.4, 132.8, 131.9, 130.4, 129.4, 128.2, 127.6, 125.6, 123.1, 122.2, 120.1, 115.4; HRMS (ESI, *m/z*): calcd. for $C_{19}H_{11}ClN_2O_2H^+$ 335.0582, found 335.0580.

Biological activity: Gram-positive strains *viz.* Methcillin-resistant *Staphylococcus aureus* (MRSA, NCTC 13616), *Mycobacterium tuberculosis* (ATCC 25177), *Bacillus subtilis* (ATCC 6633), *Bacillus cereus* (ATCC 14579) and Gram-negative strains *viz. Pseudomonas aeruginosa* (ATCC 27853), *Klebsiella pneumoniae* (ATCC 43816), *Escherichia coli* (ATCC 8739), *Proteus vulgaris* (ATCC 13315) were procured from American type culture collection (ATCC), USA. The methcillin-resistant *Staphylococcus aureus* was purchased from culture collections, UK. Fungal strains *Microsporum canis* (ATCC-36299), *Microsporum gypseum* (ATCC-24102), *Epidermophyton floccosum* (ATCC-15694) were collected from the Department of Biotechnology, Kakatiya University, Warangal, India. All microbial strains stored at - 80 ºC were streaked on Luria-Bertani (LB) agar plates (Hi-media Lab., Mumbai, India) and incubated at 37 ºC for 20-24 h. A few isolated colonies were selected from each plate and suspended in 5 mL of LB broth in a sterile culture vessel. The vessel was plugged with cotton and incubated with gentle shaking (140 rpm) at 37 ºC for 20 h.

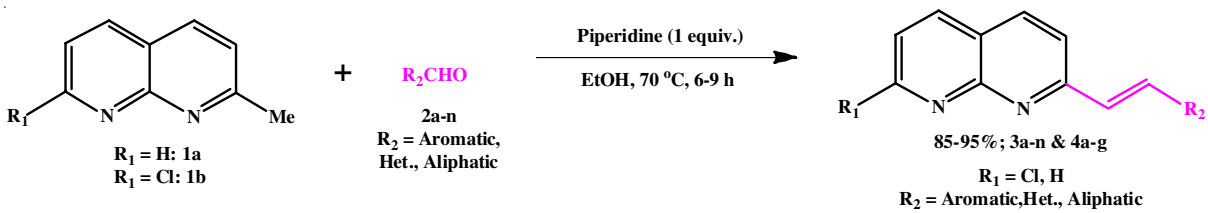
Preparation of inoculums: Following the protocol of the Kirby-Bauer disk diffusion assay, four to five well-isolated colonies of the same morphological type were picked with an inoculating loop, transferred into 5 mL of nutrient broth and incubated at 37 ºC for 24 h until a slight visible turbidity appeared. The turbidity of the actively growing broth cultures was then adjusted with broth to a density equivalent to that of 0.5 McFarland standard and the resulting suspensions were used as the initial inocula in the assay

RESULTS AND DISCUSSION

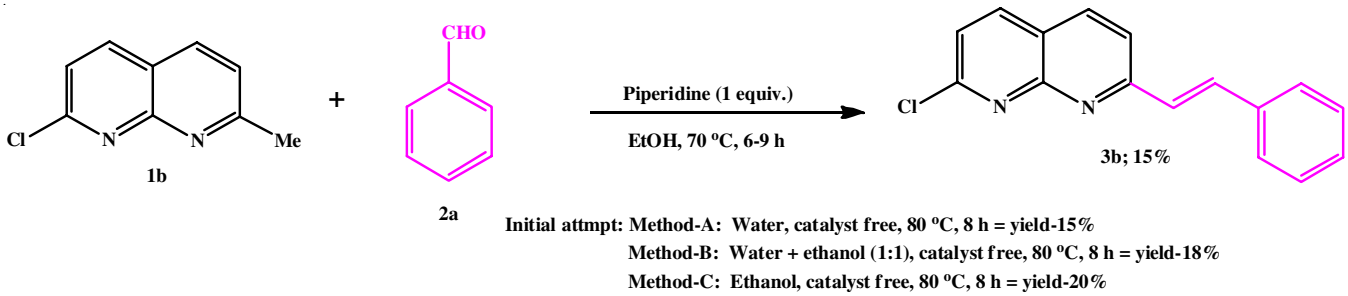
Considering, the above biological importance, in this present study, a novel efficient, simple, metal-free method is explored for the synthesis of substituted 2-styrylnaphthyridine and its derivatives with biologically useful pyrazole, imazo-pyridine and chromene based styryl scaffolds are reported piperidine catalyzed reaction of substituted methyl-1,8-naphthyridines and various aromatic and heteroaromatic aldehyde substrates *via* sp^3-C-H functionalization using Knoevenagel condensation reactions under ethanolic medium at 70 ºC for 6-9 h in good to excellent yields (85-95%) as shown in **Scheme-I**.

In present work, an initial attempt was made using 2-chloro-7-methyl-1,8-naphthyridine **1b** (1 equiv.) with benzaldehyde **2a** (1 equiv.) at reflux condition (80 ºC) under catalyst free, aqueous medium (on water synthesis) for 8 h to produce a resultant titled compound with a very poor yield 15%. And also tested above reaction at mixture of solvents water + EtOH (1:1) and ethanol under catalyst free condition to furnished desire the compound with poor yields, *i.e.* 18% and 20%, respectively as shown in **Scheme-II**.

A variety of organic and inorganic catalysts, *e.g.* Lewis acids and amino acids, as well as solvents (EtOH, MeOH, DCM, MeCN, H_2O), reaction temperatures and other experimental factors were examined in order to improve the yield of the titled compound (Table-1). The above reaction further analyzed in DIPEA in various solvents such as ethanol and water medium at 80 ºC to generate lesser yields (up to 30 %) in pro-longer time (maximum 12 h). The poor yields and the prolonged reaction progress time and low yields were not encouraging. Based on the above tested reaction, later our attempts were shifted to



Scheme-I: Synthetic route of substituted 2-styrylnaphthyridine derivatives



Scheme-II: Initial attempt of the synthesis of (*E*)-2-chloro-7-styryl-1,8-naphthyridine (**3b**)

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS FOR THE SYNTHESIS OF COMPOUND **3b**[a]

Entry	Catalyst[b]	Solvent	Temp. (°C)	Time (h)	Yield[c] (%)
1	DIPEA	EtOH	70	10	30
2	DIPEA	H_2O	90	8	20
3	DIPA	EtOH	80	7	30
4	DMAP	THF	65	8	Trace
5	Pyridine	DCM	Reflux	8	Trace
6	Pyrrolidine	DCM	Reflux	7	20
7	Piperidine	EtOH	70	7	92
8	Piperidine	MeOH	70	7	60
9	Piperidine	H_2O	70	7	50
10	Piperidine	DCM	70	7	45
11	$NHEt_2$	EtOH	70	8	30
12	$NHEt_2$	MeCH	70	8	Trace
13	NEt_3	EtOH	70	8	60
14	NEt_3	Toluene	70	8	45
15	NEt_3	EtOH	70	8	50
16	NaOH	EtOH	70	8	Trace
17	KOH	EtOH	70	8	Trace
18	K_2CO_3	EtOH	70	10	18
19	$SnCl_2$	EtOH	70	10	ND
20	$SnCl_4$	EtOH	70	12	30
21	$ZnCl_2$	EtOH	70	10	15
22	HCl	EtOH	70	12	Trace
23	*p*-TSA	EtOH	70	10	Trace
24	CSA	DCM	Reflux	10	15
25	Gycine	EtOH	70	8	10
26	L-Proline	EtOH	70	8	ND

[a]Reaction conditions: Reactions were optimized at **1b** (1 eqviv.), **2a** (1 eqviv.), Catalyst[b]: Piperidine (1 eqviv.) 5 mL of EtOH at 70 °C. (ND: Not detected), Yield[c]: Isolated yields.

screen the reaction conditions with various organic and inorganic bases (*i.e.*, DIPA, DMAP, pyridine, pyrrolidine, triethylamine, diethylamine, piperidine, NaOH, KOH and K_2CO_3 in various protic and aprotic polar solvents) to furnish medium to good yields (Table-1) with an impressive reaction time of 7-12 h.

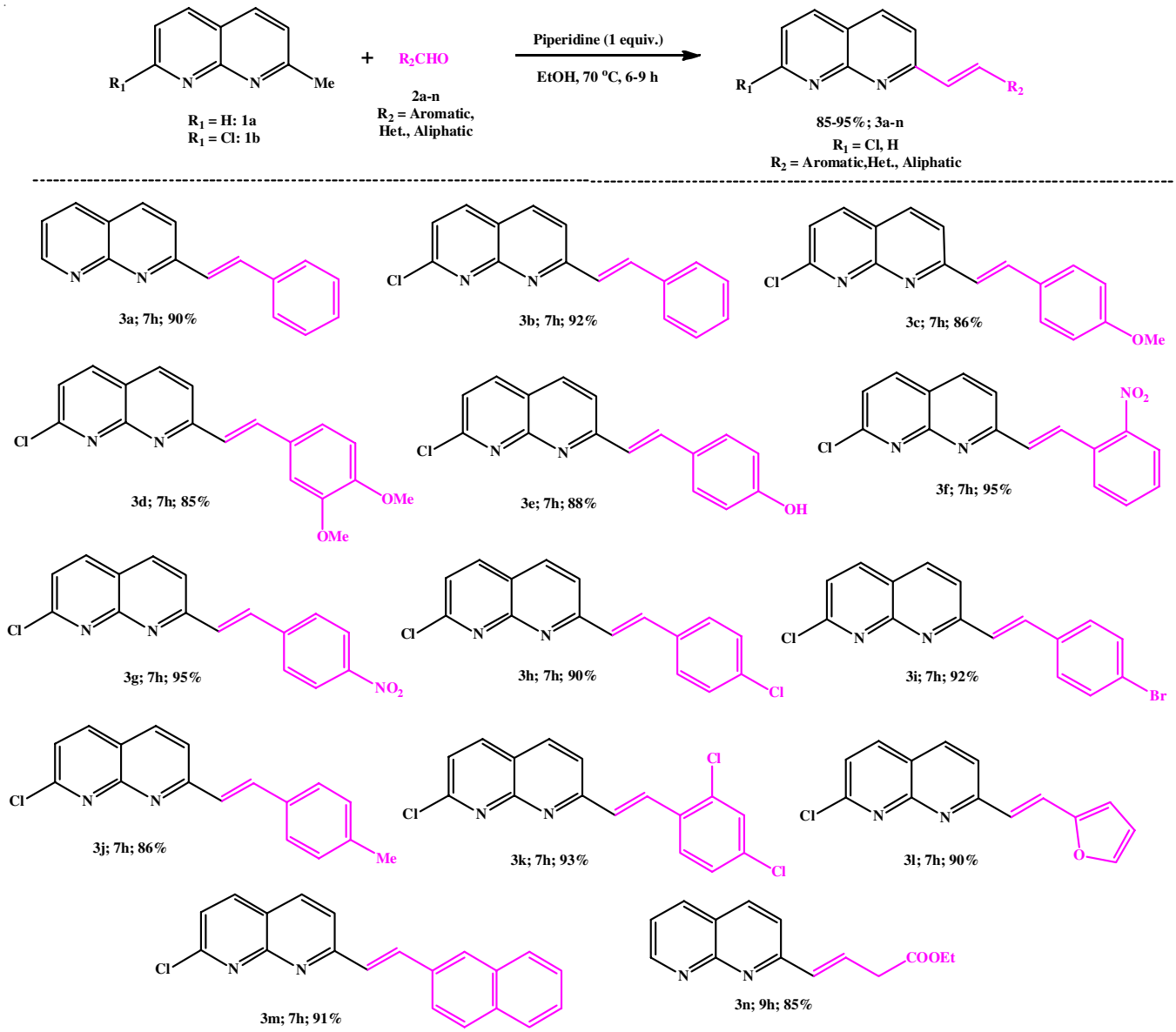
Considering the above results, among the screened catalysts, the suitable condition using piperidine (1 equiv.) in ethanol at 70 ºC for 7 h (entry-7, Table-1) is considered as a successful optimized reaction condition for the above successive reaction to giving the desired product in 92% yield (entry-7, Table-1).

After, fruitfully optimizing successive reaction (optimal) condition (entry-7, Table-1) it was continued to test the catalyst (piperidine) reactivity with substituted methyl-1,8-naphthyridine (**1a/1b**) and various aromatic and heteroaromatic aldehyde substrates **2a-n** under the optimal conditions (entry-7) to synthesize corresponding substituted styryl-1,8-naphthyridine scaffolds (**3a-n**) *via* sp^3 C-H activation followed by dehydration reactions with good to excellent yields (85-95%) in practical reaction time 6-9 h (**Scheme-III**). Predominantly, aldehyde substrates with electron deficient groups (*e.g.* NO_2) on the aromatic ring providing with excellent yields were observed as compared to the electron rich groups (*e.g.* 3,4-diOMe).

Furthermore, a test reaction on a gram scale, specifically up to 10 g was conducted to produce the desired product (**3b**). By employing various reaction conditions, we were able to achieve a yield of 88% within a time frame of 7 h. This observation suggests that when scaling up the production process, there is a slight reduction in the yield of the desired product (**3b**) compared to smaller scale batches (100 mg).

As a result, the obtained favourable results and the recognition of the biological significance of substituted styryl-1,8-naphthyridine scaffolds (**3a-l**) have prompted us to pursue further. In this regard, we have undertaken the sp^3 C-H activation of substituted methyl-1,8-naphthyridine (**1a/1b**) as a means to achieve this goal. Interestingly, next the same synthetic strategy and optimal conditions extended to 2-phenylimidazo[1,2-*a*]-pyridine-3-carbaldehydes, substituted 1,3-diphenyl-[1*H*]-pyrazole-4-carbaldehydes and 4-oxo-[4*H*]-chromene-3-carbaldehyde instead of simple aromatic and heteroaromatic aldehyde substrates. Whereas, molecule *i.e.* substituted 2-methyl-1,8-naphthyridines (**1a/1b**) reacted with substituted imidazopyridine, pyrazole chromene based heteroaromatic aldehyde substrates (**2a-g**) to provides corresponding imidazo-pyridine, pyrazole, chromene based styryl derivatives (**4a-g**) in moderate to good yields 70-90% in moderate reaction time 6-9 h (**Scheme-IV**). It is worth to mention that heteroaromatic aldehyde compounds containing an electron-withdrawing group (3-Br) exhibited lower yields (80%) compared to substrates without a functional group. Comparatively, the simple aromatic aldehyde substrates show better yields than heteroaromatic aldehydes and these reactions are proceeded *via* the C-H functionalization followed dehydration.

Proposed mechanism: A possible reaction mechanism for the synthesis of compound **3b** is represented in Fig. 1. In this mechanism, imine-enamine tautomerism involves *via* C-H functionalization intermolecular aldol reaction followed by dehydration. It is assumed that the methyl group of methyl-1,8-naphthyridine can undergo imine-enamine type tautomerism (A). Initially piperidine undergoes a proton abstraction

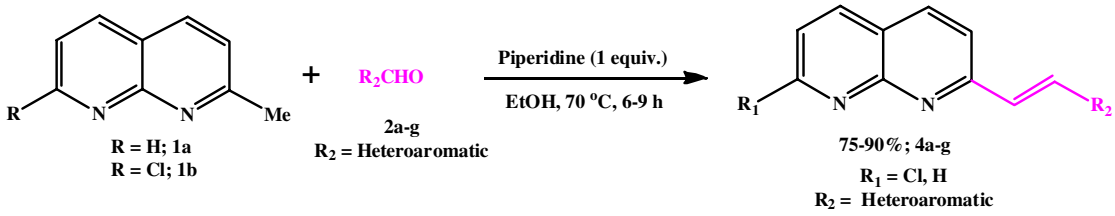


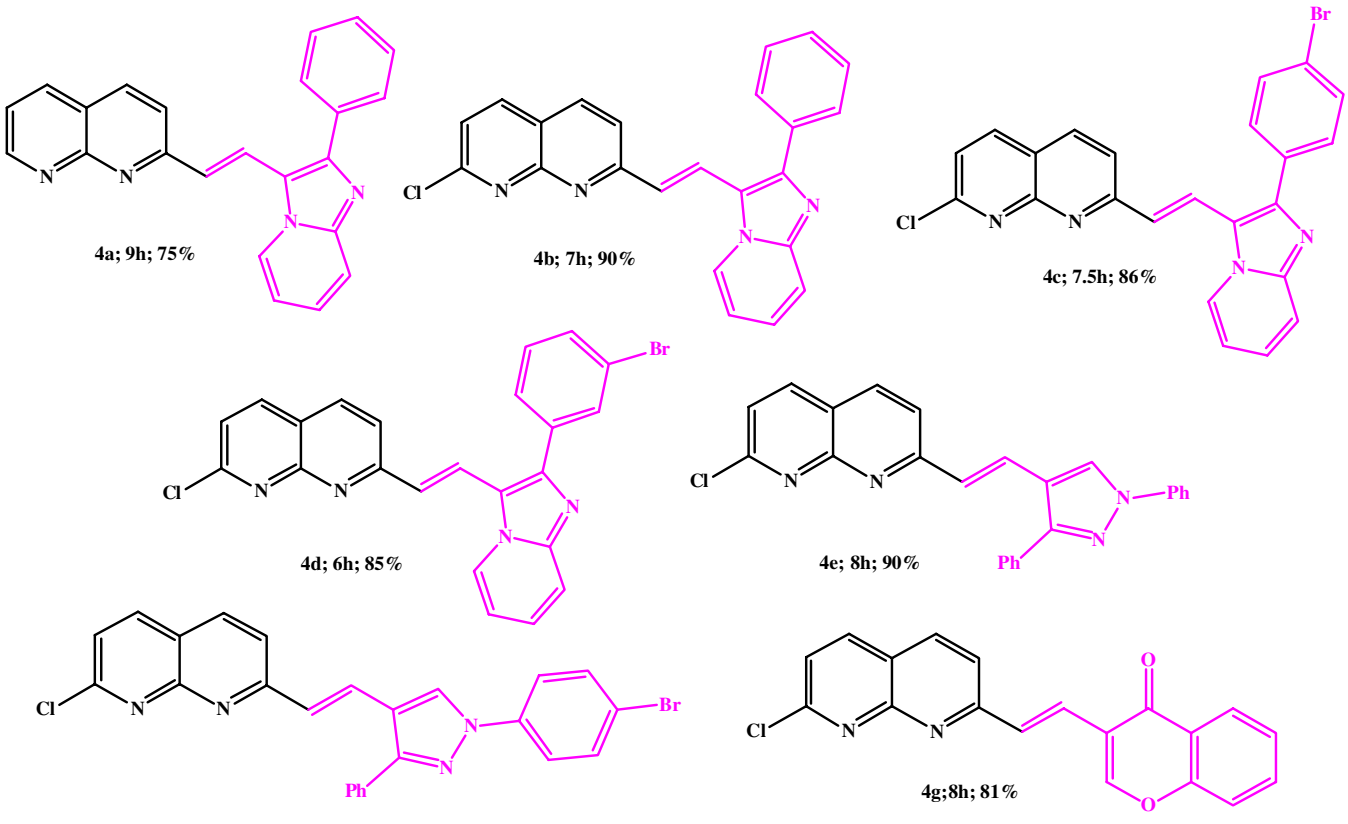
Scheme-III: Substrate scope of substituted substrate scope of substituted styryl-1,8-naphthyridine scaffolds

takes place on enamine part, after that the nucleophile (enamine) attacked on the electrophilic site of aldehyde (B), which further continue to intermolecular aldol reaction and followed by dehydration to generate desire product **3b**.

Biological studies

Antimicrobial activity of 2-styrylnaphthyridines (3a-n and 4a-g): Antibacterial activity of the synthesized compounds **3a-3n** and **4a-4g** were further tested for its antibacterial activity using the Kirby-Bauer disk diffusion assay [30]. All the synthesized compounds (**3a-n** and **4a-g**) presented a reasonable to admirable inhibition activity of the tested Gram-positive and Gram-negative strains at two concentrations, *i.e.* at 75 and 100 µg/mL with compared to that of the positive control, gentamycin sulfate as shown in Table-2. Compounds **3c**, **3d**, **3e**, **3i**, **3k**, **3l**, **4c**, **4d** and **4f** demonstrated an excellent inhibition zone of activity against *Mycobacterium tuberculosis*, methicillin-resistant *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumonia* and *Proteus vulgaris*. Among the tested molecules, compounds **3e**, **3i** and **3l** shows best zone of inhibition activity values at 34, 34, 32 mm (higher values then standard drug indicated impressive antimicrobial activity) in *Pseudomonas aeruginosa* strain against standard zentamicin drug (31 mm) at 100 µg/mL concentration and inhibition activity values at 32 nm, 32 nm, 31 mm at 75 µg/mL concentration at same strain in Gram-negative bacteria (Table-2) with comparison to Gram-negative bacteria strains. However, compounds **3e**, **3i** and **3l** showed good antimicrobial activities due to presence of hydroxy donating, bromo groups on the benzene ring and furan conjugates with naphthyridine, which enhanced the zone of inhibition antimicrobial activity and similarly **3c**, **3d**, **3k**, **4c**, **4d** and **4f** also displaying good zone of antimicrobial activity values against standard zentamicin drug (Table-2). Therefore, the antibacterial activity of the series **4a-g**, compounds **4c**, **4d** and **4f** demonstrating moderate to good zone of inhibition activity





Scheme-IV: Substrate scope of substituted pyrazole, imidazopyridine based styryl-1,8-naphthyridine scaffolds

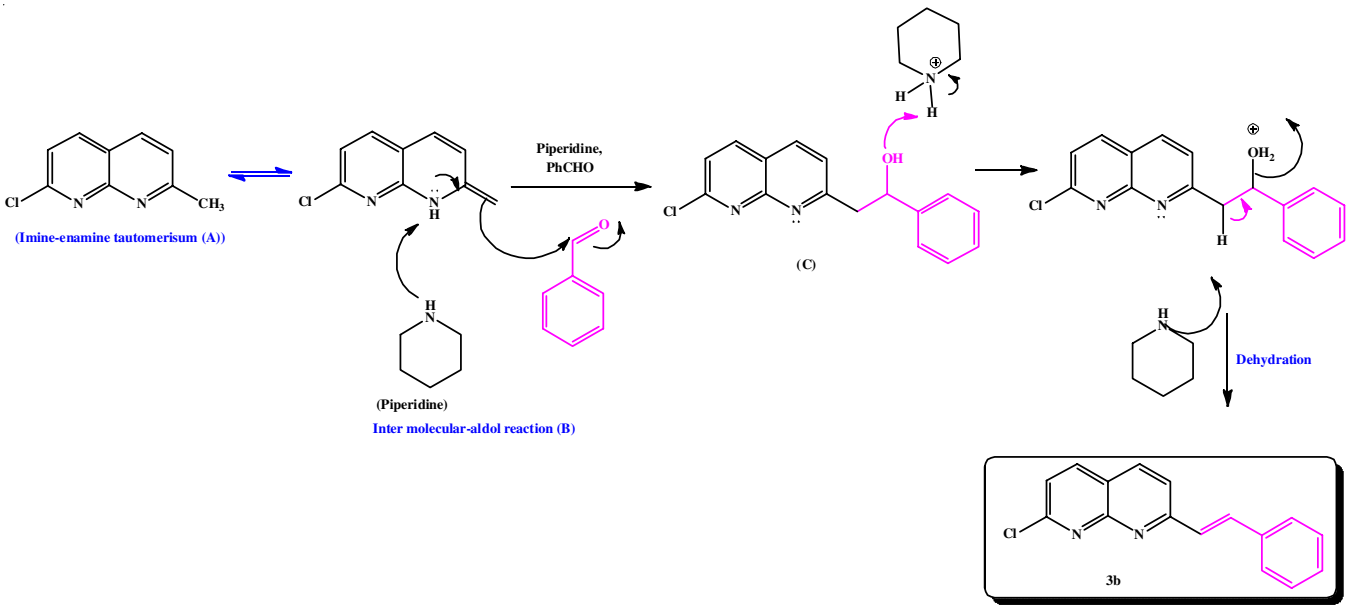


Fig. 1. Possible mechanism for the synthesized compound **3b**

TABLE-2
ANTIBACTERIAL ACTIVITY DATA OF THE SYNTHESIZED COMPOUNDS (**3a-n** AND **4a-g**)

Compd.	Conc. (µg/mL)	Zone of inhibition (mm)							
		Gram-positive bacteria				Gram negative bacteria			
		M. tuberculosis	MRSA	*B. subtilis*	*B. cereus*	*P. aeruginosa*	*K. pneumonia*	*E. coli*	*P. vulgaris*
3a	75	12	11	16	11	11	11	12	10
	100	16	13	18	12	13	16	14	16
3b	75	11	15	NA	08	08	14	12	11
	100	16	18	NA	09	09	18	16	16
3c	75	28	27	26	25	30	27	24	25
	100	29	32	28	27	32	31	28	27
3d	75	27	26	26	24	28	29	23	27
	100	30	28	31	28	33	27	26	30
3e	75	25	26	21	25	32	25	28	24
	100	31	27	24	29	34	27	31	28
3f	75	11	14	17	14	18	16	12	09
	100	15	19	18	17	20	17	15	10
3g	75	14	14	12	14	12	15	07	14
	100	21	20	14	16	15	18	10	15
3h	75	14	16	11	17	16	19	15	16
	100	17	19	14	19	17	21	17	19
3i	75	25	25	29	26	32	24	22	25
	100	32	28	33	30	34	28	26	31
3j	75	11	12	11	14	13	12	13	15
	100	13	16	15	17	16	14	16	18
3k	75	29	26	25	24	29	25	24	27
	100	30	29	28	26	34	30	26	29
8l	75	27	27	25	28	31	26	24	27
	100	30	31	28	30	32	28	27	29
3m	75	16	14	14	11	12	18	09	11
	100	18	17	21	17	16	12	10	14
3n	75	13	10	15	14	11	10	09	16
	100	15	13	19	17	18	12	14	20
4a	75	11	11	12	13	12	09	11	14
	100	15	13	15	16	18	15	14	16
4b	75	12	11	10	11	08	06	07	11
	100	14	16	12	13	14	10	09	16
4c	75	27	29	28	24	31	26	27	29
	100	29	31	32	30	32	28	29	30
4d	75	29	30	29	28	26	28	31	27
	100	36	33	32	33	28	30	33	34
4e	75	10	11	13	13	09	11	08	15
	100	13	15	19	17	12	13	11	17
4f	75	28	29	28	27	28	26	29	28
	100	30	31	33	29	34	27	31	29
4g	75	08	09	11	10	08	06	07	10
	100	10	12	15	13	14	09	05	14
Zentamicin	75	29	31	30	31	28	27	31	29
	100	32	33	33	34	31	30	33	31

NA = No activity

(Table-2) due to naphthyridine ring conjugates with pyridoimadazole, pyrazole moiety with bromo groups.

Antifungal activity: The antifungal activity of the synthesized compounds **3a-n** and **4a-g** at 75 and 100 µg/mL concentrations against three dermatophytes, *i.e. Microsporum canis*, *Microsporum gypseum* and *Epidermophyton floccosum*. Among all the screened derivatives, it was found that compounds **3c**, **3d**, **3e**, **3i**, **3k**, **3l**, **4c**, **4d** and **4f** shows good zone of inhibition against the tested fungal strains with compared to standard drug nystatin. Amongst the tested compounds with fungal strains, compound **3e** at *Microsporum gypseum* strain displayed very impressive zone of inhibition values 27/32 mm (at 75/100 µg/mL) against standard drug nystatin (20/24 mm). Whereas *M. gypseum* and *M. canis* strains also shown an impressive antifungal activity of compounds **3c**, **3d**, **3i**, **3k**, **3l**, **4c**, **4d** and **4f** (Table-3).

Conclusion

A facile, metal free strategy is described for the synthesis of novel class of substituted 2-styryl-1,8-naphthyridines and pyrazole, imidazopyridine based styryl conjugates under basic mild conditions (piperidine in ethanol) at 70 ºC . The reaction

TABLE-3
ANTIFUNGAL ACTIVITY OF THE SYNTHESIZED 2-STYRYLNAPHTHYRIDINE COMPOUNDS (**3a-n** AND **4a-g**)

Compd.	Conc. (µg/mL)	Zone of inhibition (mm)		
		M. canis	*M. gypseum*	*E. floccosum*
3a	75	10	12	07
	100	13	15	12
3b	75	12	10	08
	100	15	14	10
3c	75	30	25	24
	100	32	29	27
3d	75	26	24	22
	100	29	29	25
3e	75	24	27	24
	100	30	32	26
3f	75	11	08	11
	100	14	10	12
3g	75	10	11	08
	100	14	13	10
3h	75	12	10	11
	100	15	14	15
3i	75	26	31	25
	100	28	33	30
3j	75	11	09	10
	100	15	13	15
3k	75	25	26	08
	100	30	28	10
3l	75	26	26	22
	100	29	31	25
3m	75	11	09	10
	100	13	15	13
3n	75	12	11	15
	100	16	14	18
4a	75	08	09	10
	100	15	11	13
4b	75	09	08	12
	100	12	11	15
4c	75	25	22	19
	100	28	25	20
4d	75	28	26	19
	100	30	29	22
4e	75	10	12	08
	100	12	15	10
4f	75	24	19	19
	100	29	25	23
4g	75	11	09	09
	100	15	13	14
Nystatin	75	25	20	20
	100	28	24	23

progressed *via* sp^3 C-H functionalization of substituted methyl-1,8-naphthyridines with various aromatic, heteroaromatic aldehyde substrates *via* Knoevenagel condensation to provide functionalized pyrazole, imidazopyridine based styryl-1,8-naphthyridines in good to excellent yields (85-95%). This approach involves a common organocatalyst, low cost starting materials and shorter reaction times. An extensive variability of substrates was tolerated well to afford the desired products. All the synthesized derivatives were tested for their biological activity *i.e.*, antibacterial and antifungal. Among the synthesized compounds, compounds **3c**, **3d**, **3e**, **3i**, **3k**, **3l**, **4c**, **4d** and **4f** established excellent inhibition zone of activity against standard drugs. Nine compounds of substituted styryl-1,8-naphthyridines, containing the electron donating methoxy, hydroxy, chloro and bromo groups proved significant antibacterial and antifungal activity against the tested dermatophyte fungi and microbial strains, respectively.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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