Green Synthesis of Fused Imidazo[1,2-a][1,8]naphthyridine Derivatives Catalyzed by DABCO under Solvent-Free Solid-State Conditions and Their Biological Evaluation

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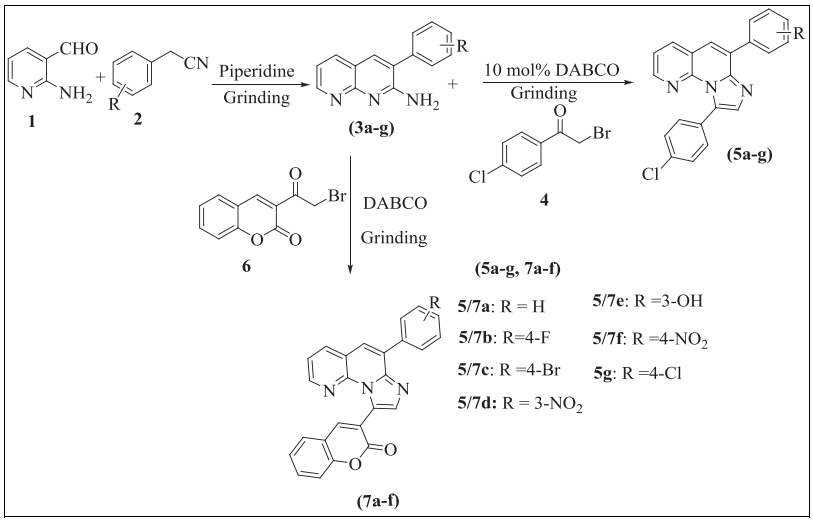

An efficient and eco-friendly methodology has been developed for the construction of fused imidazo[1,2-a][1,8]naphthyridine derivatives in the presence of 1,4-diazabicyclo[2.2.2]octane, and involving various substituted heterocyclic amines with phenacyl bromide under solvent-free solid-state condition obtained the corresponding compounds (**5a–g**, **7a–f**) in short reaction time with high yield which is the important features of this protocol. All newly synthesized products were evaluated for their antibacterial and fungal activities. All these compounds displayed good antibacterial and antifungal activity. In predominantly, compounds **7e**, **7d**, and **5d** demonstrate the highest antibacterial and antifungal activities. Furthermore, *in silico* molecular docking studies results were well complemented to the antimicrobial activity.

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INTRODUCTION

Nitrogen atom containing heterocyclic compounds play key role in the field of medicinal chemistry [1]. Among these heterocyclic compounds 1,8-naphthyridine derivatives possess broad range of useful biological properties establish in therapeutic and medicinal research. 1,8-Naphthyridine scaffolds possess broad spectrum of beneficial pharmacological activities that include anti-inflammatory [2], anti-HIV [3], antimicrobial [4], and antitumor activities [5]. 1,8-Naphthyridine derivatives have also exhibited potential applications in neurological disorders such as Alzheimer's disease [6]. In addition, they possess activities such as antimalarial [7], anti-allergic [8], and antituberculosis activities [9]. Some of the biologically potent 1,8-naphthyridine derivatives are shown in Figure 1.

In recent years, development of organic reactions in the solvent-free solid-state grinding method has been attracting to the synthetic organic researchers and medicinal chemists. Meanwhile, solid-state reactions without using harmful solvent are of great interest especially in relation to environmental concerns today and have unique advantages on high purity of the products, cost-effectiveness, reduction in pollution, environmentally benign procedure, and simplicity in handling make this protocol "green" and eco-friendly [10–13]. Nowadays, much attention has been directed towards the development of green chemical processes as the environmentally sustainable methods, chemicals, and reagents [14,15]. In continuation of our previous studies on the development of eco-friendly methodologies [16–18], we have developed a simple, convenient, and environmentally benign synthesis of fused imidazo[1,2-a][1,8]naphthyridine derivatives. To the best of

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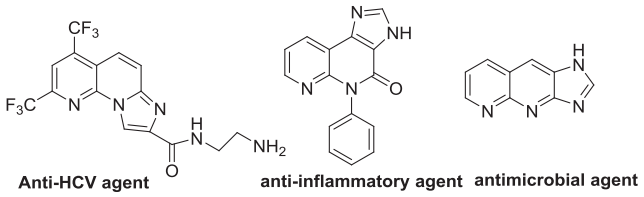


Figure 1. Some of the biologically active 1,8-naphthyridines.

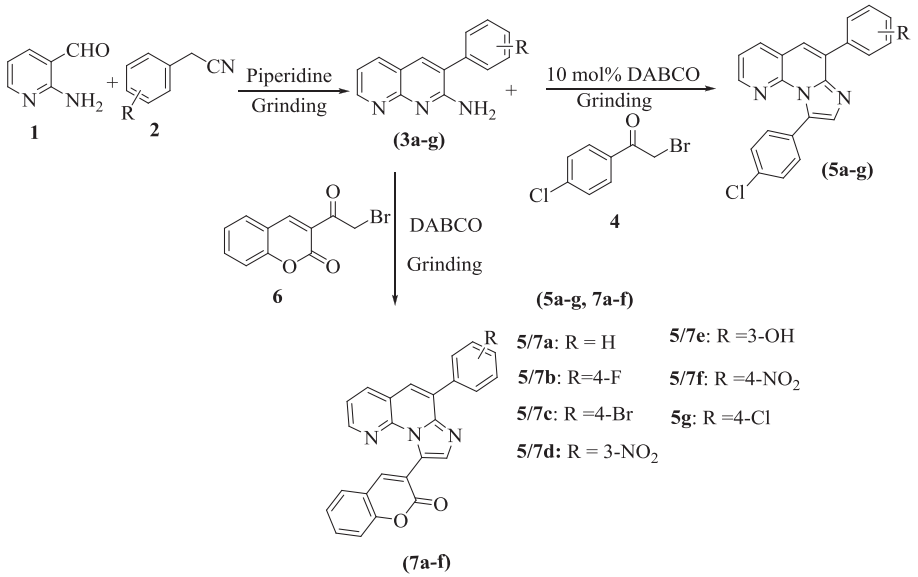
our knowledge, there is no grinding method that has been reported in the literature for the construction of fused imidazo[1,2-a][1,8]naphthyridine scaffolds utilizing, 4-diazabicyclo[2.2.2]octane (DABCO) as catalyst under solvent-free solid-state conditions.

RESULTS AND DISCUSSION

A representation for the construction of fused imidazo[1,2-a][1,8]naphthyridine derivatives (**5a–g, 7a–f**) catalyzed by DABCO under solvent-free solid-state condition is exposed in Scheme 1.

Solid-state reactions transpired competently and more selectively than the solution phase reactions [19]. The present work, grinding method is eco-friendly, requires no special apparatus and non-hazardous solvents. Rate accelerations can be described because of the conversion of mechanical energy (kinetic energy applied due to grinding) into heat energy, which becomes the driving force for improved activation of molecules. The kinetic energy provided during grinding can have various effects on a crystalline solid [20–22] which exclusively is a kind of "stirring." To develop an eco-friendly green methodology, we have synthesized novel fused imidazo[1,2-a][1,8]naphthyridine scaffolds using under the solvent-free grinding method by involving 2-aminonicotinaldehyde **1** on condensation with phenylacetonitrile **2** in the presence of piperidine obtained corresponding compound 2-amino-1,8-naphthyridines **3** at room temperature according to the literature procedure [23], and then 2-amino-1,8-naphthyridines reacted with 2-bromo-1-(4-chlorophenyl) ethan-1-one **4** in the presence of DABCO (10 mol %) 11.2 mg in water (5 mL) interestingly furnished corresponding 9-(4-chlorophenyl)-6-phenylimidazo[1,2-a][1,8]naphthyridine derivatives (**5a–g**) with good yields, and then the same reaction carried out 3-(2-bromoacetyl)-2H–chromen-2-one **6** instead of 2-bromo-1-(4-chlorophenyl)ethan-1-one obtained 3-(6-phenylimidazo[1,2-a][1,8]naphthyridin-9-yl)-2H–chromen-2-one derivatives (**7a–f**) with good yields in short reaction time. The reaction is facile and efficient and is devoid of any side products. The route is environmentally benign. The experimental procedure is simple and avoids sophistication.

Scheme 1. Synthesis of novel fused imidazo[1,2-a][1,8]naphthyridine scaffolds under solvent-free solid-state condition.



EXPERIMENTAL

Materials and chemicals. All the solvents and chemicals were purchased from Aldrich/ Merck and used without further purification. Melting points were determined in open capillaries using Buchi melting point apparatus and are uncorrected. The progress of the reactions and purity of the compounds were monitored by thin layer chromatography (TLC) with F254 silica-gel precoated aluminum sheets using hexane/ethyl acetate (7/3) as eluent. Infrared (IR) spectra were recorded on Perkin-Elmer 100S spectrophotometer (PerkinElmer, Inc. Waltham, MA) using KBr pellet. NMR spectra were recorded on Bruker 400 MHz spectrometer (Bruker, Bengaluru, Karnataka, India) using hexadeuterated dimethyl sulfoxide (DMSO-d_6) as solvent and tetramethylsilane as an internal standard. Mass spectra (electrospray ionization) were recorded on a Jeol JMSD-300 spectrometer (Jeol, India). Elemental analyses were performed on a Carlo Erba EA 1108 automatic elemental analyzer (Carrer Filadors, Sabadell, Barcelona, Spain).

General procedure for the synthesis of 3-phenyl-1,8-naphthyridin-2-amines (3a–g). To take compound 2-amino-nicotinaldehyde **1** (1 mmol, 122.12 mg), aryl acetonitrile **2** (1 mmol) and added catalytic amount of piperidine were ground in a mortar pestle and interestingly obtained the desired product (**3a–g)** with good yields. After completion of the reaction (monitored by the TLC), the reaction mixture was poured into cold water. The product, which separated, was filtered, washed with water, and purified by recrystallization from methanol to obtain the pure products.

General procedure for the synthesis of 9-(4-chlorophenyl)-6-phenyl imidazo[1,2-a][1,8]naphthyridine derivatives (5a–g). To take compound 3-phenyl-1,8-naphthyridin-2-amine **3** (1 mmol), 2-bromo-1-(4-chlorophenyl)ethan-1-one **4** (1 mmol) and added catalyst DABCO 10 mol % (11.2 mg) in water (5 mL) were ground in a mortar and pestle for the specified time indicated in Table 1. After completion of the reaction (monitored by the TLC), the reaction mixture was poured into cold water. The solid found was filtered, washed with water, recrystallized from methanol, and obtained analytically pure products.

General procedure for the synthesis of 3-(6-phenyl imidazo[1,2-a][1,8]naphthyridin-9-yl)-2*H*-chromen-2-one derivatives (7a–f). The mixture of the appropriate 3-phenyl-1,8-naphthyridin-2-amine **3** (1 mmol), 3-(2-bromoacetyl)-2H–chromen-2-one **6** (1 mmol), and added DABCO (10 mol %) (11.2 mg) in water (5 mL) was ground by mortar and pestle. On completion of the reaction (monitored by TLC), the mixture was poured into ice cold water, and then the resulting solid product was filtered, washed with water, and purified by recrystallization from methanol to furnish corresponding compounds (**7a–f**).

Table 1

Synthesis of fused imidazo[1,2-a][1,8]naphthyridine derivatives (**5a–g**, **7a–f**) under solvent-free solid-state conditions.

Entry	Analog	Time (min)	Yield[a] (%)	Melting points (°C)
1	**5a**	4	87	273
2	**5b**	5	90	252
3	**5c**	6	88	295
4	**5d**	4	86	246
5	**5e**	6	85	287
6	**5f**	5	83	304
7	**5g**	5	91	312
8	**7a**	6	87	291
9	**7b**	5	89	317
10	**7c**	4	85	249
11	**7d**	5	87	281
12	**7e**	4	89	325
13	**7f**	4	84	329

[a]Isolated yields after purification.

9-(4-chlorophenyl)-6-phenyl imidazo[1,2-a][1,8] naphthyridine (5a). Brown solid; IR (KBr) (λ_{max}, cm^{-1}): 1658 (C═C), 1606, (C═N), 833 (C-Cl); ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm: 8.83 (s, 1H), 8.02 (d, 2H, J = 7.2 Hz), 7.76 (d, 2H, J = 7.2 Hz), 7.94 (m, 5H), 6.87 (m, 4H); ^{13}C NMR (400 MHz; DMSO-d_6), δ, ppm: 148.9, 147.2 (2C), 143.5, 142.1 (2C), 141.8, 140.1, 138.6, 136.3, 135.4, 133.6, 132.2, 130.6 (2C), 129.7 (2C), 128.2, 126.4, 125.8, 118.6; *Anal*. Calcd for $C_{22}H_{14}ClN_3C$ (355): C, 74.26; H, 3.97; N, 11.81; Found: C, 74.49; H, 4.12; N, 11.73.

9-(4-chlorophenyl)-6-(4-fluorophenyl) imidazo[1,2-a][1,8] naphthyridine (5b). White compound; IR (KBr) (λ_{max}, cm^{-1}): 1663 (C═C), 1604, (C═N), 829 (C─Cl); ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm: 8.97 (s, 1H), 8.37 (d, 2H, J = 7.2 Hz), 7.86 (d, 2H, J = 7.2 Hz), 7.36–7.21 (m, 4H), 7.08 (m, 2H), 6.49 (m, 3H); ^{13}C NMR (400 MHz; DMSO-d_6), δ, ppm: 148.6, 147.1, 142.9 (2C), 141.6, 140.5, 139.2, 138.4, 136.1, 135.8, 133.4, 130.8 (2C), 129.4, 128.7, 125.9, 125.2, 119.7; *Anal*. Calcd for $C_{22}H_{13}ClFN_3$ (373): C, 70.69; H, 3.51; N, 11.24; Found: C, 70.83; H, 3.26; N, 11.38.

6-(4-bromophenyl)-9-(4-chlorophenyl) imidazo[1,2-a][1,8] naphthyridine (5c). White compound; IR (KBr) (λ_{max}, cm^{-1}): 1648 (C═C), 1602, (C═N), 839 (C─Cl); ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm: 8.73 (s, 1H), 8.21 (d, 2H, J = 7.8 Hz), 7.96 (d, 2H, J = 7.2 Hz), 7.38–7.97 (m, 8H); ^{13}C NMR (400 MHz; DMSO-d_6), δ, ppm: 148.9, 147.5, 145.1 (2C), 144.6, 143.2, 138.6, 137.3, 136.4 (2C), 134.7, 133.9, 132.4, 131.2, 128.5, 127.8, 126.2, 125.6 (2C), 121.6, 116.8; *Anal*. Calcd for $C_{22}H_{13}BrClN_3$ (434): C, 60.78; H, 3.01; N, 9.67; Found: C, 60.53; H, 3.17; N, 9.74.

9-(4-chlorophenyl)-6-(3-nitrophenyl) imidazo[1,2-a][1,8] naphthyridine (5d). Brown compound; IR (KBr) (λ_{max}, cm^{-1}): 1652 (C═C), 1608, (C═N), 841 (C─Cl); ^{1}H

NMR (400 MHz; DMSO-d_6), δ, ppm: 8.62 (s, 1H), 8.51 (d, 2H, J = 7.6 Hz), 8.32 (d, 2H, J = 7.2 Hz), 7.96 (m, 5H), 7.38–7.97 (m, 3H); ^{13}C NMR (400 MHz; DMSO-d_6), δ, ppm: 149.3, 148.7, 146.3 (2C), 144.8, 142.5, 139.1, 138.8, 135.6, 134.3 (2C), 133.4, 132.6, 129.3, 128.4, 127.3, 126.7, 125.9, 122.2, 118.5; *Anal*. Calcd for $C_{22}H_{13}ClN_4O_2C$ (400): C, 65.93; H, 3.27; N, 13.98; Found: C, 65.67; H, 3.41; N, 13.76.

3-(9-(4-chlorophenyl)imidazo[1,2-a][1,8]naphthyridin-6-yl) phenol (5e). Pale yellow compound; IR (KBr) (λ_{max}, cm^{-1}): 1656 (C═C), 1608, (C═N), 833 (C─Cl); ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm: 9.87 (s, 1H), 8.19 (d, 2H, J = 7.2 Hz), 7.98 (m, 6H), 7.83 (d, 2H, J = 7.2 Hz), 6.95 (m, 3H); ^{13}C NMR (400 MHz; DMSO-d_6), δ, ppm: 144.9, 143.7, 142.6, 140.3, 139.7, 138.5, 136.8 (2C), 134.6, 133.6, 132.3 (2C), 129.5, 128.3, 127.4, 126.9, 125.3 (2C), 120.7, 114.8; *Anal*. Calcd for $C_{22}H_{14}ClN_3O$ (371.82): C, 71.07; H, 3.80; N, 11.30; Found: C, 71.23; H, 3.96; N, 11.54.

9-(4-chlorophenyl)-6-(4-nitrophenyl) imidazo[1,2-a][1,8] naphthyridine (5f). White compound; IR (KBr) (λ_{max}, cm^{-1}): 1653 (C═C), 1609, (C═N), 837 (C─Cl); ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm: 8.83 (m, 3H), 8.27 (s, 1H), 7.96 (m, 3H), 7.83 (d, 2H), 7.32–7.27 (m, 3H), 6.72 (s, 1H); ^{13}C NMR (400 MHz; DMSO-d_6), δ, ppm: 149.6, 148.3, 147.5, 145.2, 143.5 (2C), 140.7, 139.6, 137.4, 136.3, 134.4, 132.2 (2C), 129.8, 129.2, 128.4, 127.6, 125.3, 123.6, 119.7; *Anal*. Calcd for $C_{22}H_{13}ClN_4O_2$ (400.82): C, 65.93; H, 3.27; N, 13.98; Found: C, 65.82; H, 3.46; N, 13.86.

6-(3-chlorophenyl)-9-(4-chlorophenyl) imidazo[1,2-a][1,8] naphthyridine (5g). Yellow compound; IR (KBr) (λ_{max}, cm^{-1}): 1655 (C═C), 1607, (C═N), 842 (C─Cl); ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm: 8.58 (s, 1H), 8.34 (d, 2H, J = 7.2 Hz), 8.13 (s, 1H), 7.96 (d, 2H, J = 7.2 Hz), 7.38–7.97 (m, 7H); ^{13}C NMR (400 MHz; DMSO-d_6), δ, ppm: 148.7, 147.5 (2C), 146.5, 145.7 (2C), 144.5, 142.7, 139.5, 138.2, 136.4, 135.1 (2C), 131.7, 129.4, 128.8, 127.9, 126.6, 125.4, 122.7 (2C), 118.5; *Anal*. Calcd for $C_{22}H_{13}Cl_2N_3$ (390.27): C, 67.71; H, 3.36; N, 10.77; Found: C, 67.59; H, 3.45; N, 10.83.

3-(6-phenyl imidazo[1,2-a][1,8]naphthyridin-9-yl)-2H-chromen-2-one (7a). Pale yellow compound; IR (KBr) (λ_{max}, cm^{-1}): 1720 (lactone, C═O), 1680 (C═C), 1224 (C─O─C); ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm: 9.17 (s, 1H), 8.47 (m, 4H), 7.51 (d, 2H, J = 7.2 Hz), 7.27.05 (m, 5H), 6.98 (d, 2H, J = 6.8 Hz), 6.04 (s, 1H); ^{13}C NMR (400 MHz; DMSO-d_6), δ, ppm: 161.9, 153.4 (2C), 148.3, 146.5, 143.6, 138.7 (2C), 136.3, 133.5 (2C), 129.8, 129.5 (2C), 127.8, 127.5, 119.6, 116.5, 115.9; Anal. Calcd for $C_{25}H_{15}N_3O_2$ (389.41): C, 77.11; H, 3.88; N, 10.79; Found: C, 77.26; H, 3.97; N, 10.68.

3-(6-(4-fluorophenyl) imidazo[1,2-a][1,8]naphthyridin-9-yl)-2H-chromen-2-one (7b). White compound; IR (KBr) (λ_{max}, cm^{-1}): 1724 (lactone, C═O), 1676 (C═C), 1223 (C─O─C); ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm: 8.91 (s, 1H), 8.27 (d, 2H, J = 7.2 Hz), 7.96–7.82 (m, 6H), 7.72 (m, 5H); ^{13}C NMR (400 MHz; DMSO-d_6), δ, ppm: 161.2, 154.2, 148.6, 147.2, 143.7 (2C), 139.4, 137.2, 134.3, 129.6, 129.2 (2C), 127.9, 127.5, 120.4 (2C), 117.5, 116.3; *Anal*. Calcd for $C_{25}H_{14}FN_3O_2$ (407.40): C, 73.70; H, 3.46; N, 10.31; Found: C, 73.57; H, 3.62; N, 10.49.

3-(6-(4-bromophenyl) imidazo[1,2-a][1,8]naphthyridin-9-yl)-2H-chromen-2-one (7c). Brown compound; IR (KBr) (λ_{max}, cm^{-1}): 1722 (lactone, C=O), 1678 (C=C), 1221 (C–O–C); ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm: 8.58 (s, 1H), 8.26 (m, 4H), 7.96 (d, 2H, J = 7.2 Hz), 7.89–7.56 (m, 7H); ^{13}C NMR (400 MHz; DMSO-d_6), δ, ppm: 160.3, 153.7, 149.3, 147.4 (2C), 141.7, 139.7, 135.4 (2C), 132.9, 129.2 (2C), 129.0, 127.5, 121.6 (2C), 117.3, 116.5; *Anal*. Calcd for $C_{25}H_{14}BrN_3O_2$ (468.31): C, 64.12; H, 3.01; N, 8.97; Found: C, 64.06; H, 3.23; N, 8.82.

3-(6-(3-nitrophenyl) imidazo[1,2-a][1,8]naphthyridin-9-yl)-2H-chromen-2-one (7d). Light brown compound; IR (KBr) (λ_{max}, cm^{-1}): 1723 (lactone, C═O), 1672 (C═C), 1220 (C─O─C); ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm: 8.69 (s, 1H), 8.36 (d, J = 7.2 Hz, 2H), 7.94 (m, 6H), 7.21 (d, J = 6.8 Hz, 2H), 7.18–7.06 (m, 3H); ^{13}C NMR (400 MHz; DMSO-d_6), δ, ppm: 161.2, 153.5, 149.1, 147.6, 142.4 (2C), 139.6, 136.7, 135.6 (2C), 129.4, 129.0 (2C), 128.9, 127.6, 119.2 (2C), 117.4, 115.1; *Anal*. Calcd for $C_{25}H_{14}N_4O_4$ (434.41): C, 69.12; H, 3.25; N, 12.90; Found: C, 69.34; H, 3.14; N, 12.76.

3-(6-(3-hydroxyphenyl) imidazo[1,2-a][1,8]naphthyridin-9-yl)-2H-chromen-2-one (7e). Light brown compound; IR (KBr) (λ_{max}, cm^{-1}): 3336 (OH), 1724 (lactone, C═O), 1602 (C═N), 1205 (C─O─C); ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm: 9.34 (s, 1H), 8.87 (d, 2H, J = 7.2 Hz), 8.15 (m, 3H), 7.96 (m, 4H), 7.21–7.09 (m, 4H); ^{13}C NMR (400 MHz; DMSO-d_6), δ, ppm: 160.4, 153.2, 148.9 (2C), 147.4, 141.3 (2C), 139.7, 138.2, 136.2, 129.4 (2C), 128.9, 128.8 (2C), 128.1, 118.6, 117.3, 116.8; *Anal*. Calcd for $C_{25}H_{15}N_3O_3$ (405.41): C, 74.07; H, 3.73; N, 10.36; Found: C, 74.26; H, 3.56; N, 10.48.

3-(6-(4-nitrophenyl) imidazo[1,2-a][1,8]naphthyridin-9-yl)-2H-chromen-2-one (7f). Brown compound; IR (KBr) (λ_{max}, cm^{-1}): 1724 (lactone, C═O), 1671 (C═C), 1222 (C─O─C); ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm: 9.06 (s, 1H), 8.47 (m, 3H), 8.06 (m, 5H), 7.87 (d, 2H, J = 7.2 Hz), 7.31–7.23 (m, 3H); ^{13}C NMR (400 MHz; DMSO-d_6), δ, ppm: 161.4, 152.4, 147.5, 147.6 (2C), 141.3, 139.7, 137.4, 134.7 (2C), 129.3, 128.7, 128.3 (2C), 127.6, 117.6, 116.4, 116.4; *Anal*. Calcd for $C_{25}H_{14}N_4O_4$ (434.41): C, 69.12; H, 3.25; N, 12.90; Found: C, 69.26; H, 3.17; N, 12.76.

Biological evaluation (antimicrobial activity).

Antibacterial activity. All the newly synthesized compounds (**5a–g**, **7a–f**) were evaluated for their *in vitro*

antibacterial activity against the Gram-positive bacteria *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli* at three different concentrations using standard reference drug Penicillin. The activity was determined by agar well diffusion technique according to the literature procedure [24]. These entire compounds demonstrate good inhibition activity. Especially, compounds **7e**, **7d**, and **5d** demonstrated high antibacterial activity against all the tested strains as shown in Table 2.

Antifungal activity. All these synthesized compounds (**5a–g**, **7a–f**) were evaluated for their antifungal activity against the two pathogenic fungal strains *Aspergillus niger* and *Candida metapsilosis* utilizing standard reference drug Griseofulvin. The activity was resolved by using the disc diffusion technique [25]. All these compounds shown good inhibition activity against the tested pathogenic fungal strains among them products **5c**, **7c**, and **7f** showed appreciable activity while the compounds **7e**, **7d**, and **5d** exhibited excellent antifungal activity shown in Table 2.

Table 2

Antimicrobial evaluation data of the novel imidazo[1,2-a][1,8]naphthyridines.

	Zone of inhibition of compounds (**5a–g**, **7a–f**) in (mm)											
	Bacterial strains						Fungal strains					
	Staphylococcus aureus (Conc. in μg/mL)			*Escherichia coli* (Conc. in μg/mL)			*Aspergillus niger* (Conc. in μg/mL)			*Candida metapsilosis* (Conc. in μg/mL)		
Compounds	**10**	**25**	**35**	**10**	**25**	**35**	**10**	**26**	**35**	**10**	**26**	**35**
5a	6	16	26	7	18	25	6	20	25	5	19	27
5b	5	17	23	6	19	26	7	19	24	7	16	26
5c	4	16	22	5	17	25	6	17	26	6	19	25
5d	**8**	**19**	**29**	**8**	**20**	**30**	**7**	**20**	**29**	**7**	**21**	**28**
5e	8	8	11	6	9	10	8	10	12	7	18	26
5f	5	14	24	6	19	26	5	18	26	6	18	21
5g	7	16	20	6	17	27	6	17	25	5	15	23
7a	7	18	31	8	2	32	8	17	28	7	15	25
7b	5	16	23	6	17	21	5	15	23	6	16	24
7c	6	18	31	8	2	32	8	17	28	7	15	26
7d	**8**	**19**	**31**	**8**	**2**	**32**	**8**	**17**	**28**	**7**	**20**	**29**
7e	**9**	**20**	**33**	**8**	**21**	**33**	**9**	**21**	**30**	**8**	**22**	**31**
7f	6	19	28	7	19	26	6	17	25	7	17	27
Penicillin	**9**	**24**	**34**	**9**	**25**	**34**	-	-	-	-	-	-
Griseofulvin	-	-	-	-	-	-	**10**	**24**	**33**	**10**	**23**	**34**

Compounds that show more activity are shown in bold font.

Table 3

Phosphoinositide-dependent protein kinase-1 (PDK-1) molecular interactions.

Ligand	Receptor and its atoms involved in interactions (PDK-1)	Interacting atoms	H-bond distance in (A°)	Docking energy (Kcal/Mol)
5c	ALA259-O	12 NH2	3.13	−86.202
	LYS257-O	18 NH2	2.99	
5d	ARG204-NH1	30 O	**2.63**	−79.507
	ALA259-O	13 NH2	3.00	
	VAL229-NH	28 NH2	3.30	
7c	LYS257-O	18 NH2	2.97	−74.806
	ALA259-O	18 NH2	3.25	
	ARG196-NH1	1O	3.07	
7d	ILE202-NH	12 0	**1.59**	−78.019
	ALA259-O	18 NH2	3.09	
7e	LYS257-O	18 NH2	2.95	−71.133
	ALA259-O	18 NH2	3.15	
	PHE142HE2	36O	**1.46**	
7f	LEU230-NH	9 O	2.81	−82.583
	LYS257-O	18 NH2	2.88	
	ALA259-O	18 NH2	3.31	

Compounds that show more activity are shown in bold font.

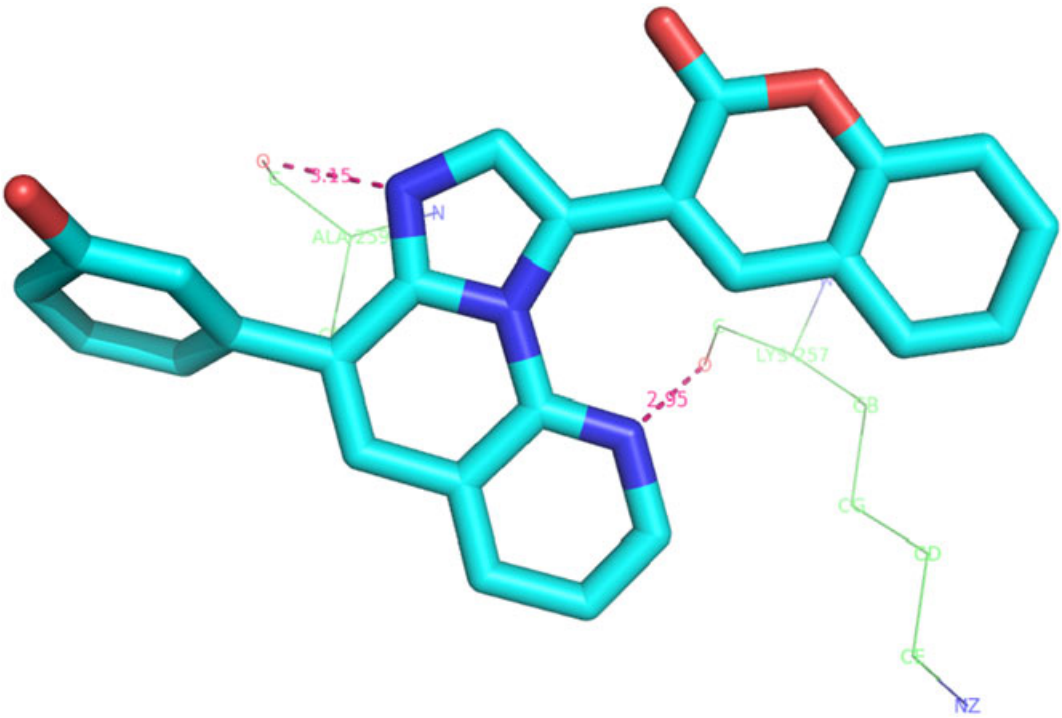


Figure 2. Binding mode of the phosphoinositide-dependent protein kinase-1 and **7e** molecule. [Color figure can be viewed at wileyonlinelibrary.com]

Molecular docking studies. Crystal structure of phosphoinositide-dependent protein kinase-1 (PDK-1) was obtained from the protein data bank (3H9O) [26] and imported into Discovery studio 2.5. Crystallized water molecules were removed, and polar hydrogen was added to the complex structure, and 3H9O was applied CHARM force field, and minimizations were performed until the average root mean square deviation of the non-hydrogen atoms reached 0.3 A°. A grid (10 × 10 × 10 A°) was generated around the centroid of the phosphoinositide within 4 Å. Furthermore, we identified the binding sites in the structure, and these are used for docking using the ligand fit module provided by acceleries, and obtained results were scrutinized based on the highest dock score and number of H-bond interactions. All these ligands were docked in Ligand fit module and molecular interactions of docking complex of PDK-1, and these ligands interactions showed were listed in the Table 3. In docking interactions, **5c** structures two hydrogen bonds with ALA259 and LYS257 with 3.13 and 2.99 A° bond lengths, respectively; the binding site residue, ALA259

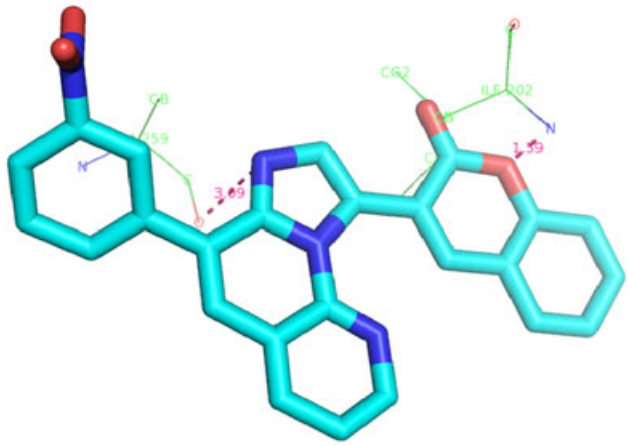


Figure 3. Binding mode of phosphoinositide-dependent protein kinase-1 and **7d** molecule. [Color figure can be viewed at wileyonlinelibrary.com]

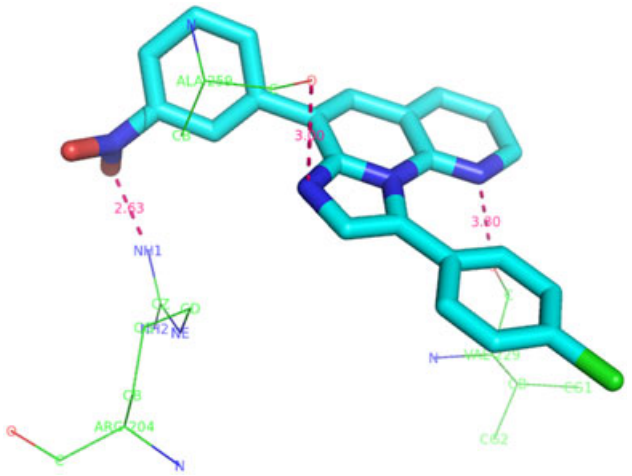


Figure 4. Molecular docking interactions of phosphoinositide-dependent protein kinase-1 with our synthesized molecule **5d.** [Color figure can be viewed at wileyonlinelibrary.com]

and LYS257 of PDK-1, was involved in π–π interaction with all ligands. **7d** structures ILE202 and ALA259 with 1.59 and 3.09 A^o, respectively, **7f** structures three hydrogen bonds with LEU230, LYS257, and ALA259 with 2.81, 2.88, and 3.31 A^o, respectively, and **7e** structures two hydrogen bonds with LYS257 and ALA259 with 2.95 and 3.15 A^o, respectively. All these compounds shown better molecular bonding interactions. Among them **5c**, **5d**, **5g**, **7d**,**7e**, **7f** involved in intermolecular hydrogen bonding with low distance and Vander Waal contacts. Among the all compounds (**5a–g**, **7a–f**), the most active **7e**, **7d**, and **5d** interacting receptors are exposed in Figures 2, 3, and 4.

CONCLUSIONS

In conclusion, we have developed an efficient, convenient, environmentally friendly, economically viable, high yielding, and cleaner methodology for the construction of fused imidazo[1,2-a][1,8]naphthyridine derivatives using DABCO catalyst ground by mortar pestle. The significant advantages of this procedure are operational simplicity, short reaction times, and excellent purity of the products. Further, we found that the solid state reactions proceed much faster and more efficiently than the solution phase reactions, probably because the solid state reaction is a very high concentration reaction. The antimicrobial activity of the synthesized compounds was assessed against pathogenic bacterial and fungal strains and compounds **7e**, **7d**, and **5d** exhibited the highest activity. Moreover, *in silico* molecular docking studies results have proved that strong binding affinity and more H-bonds interaction.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.