ISSN 1070-3632, Russian Journal of General Chemistry, 2018, Vol. 88, No. 4, pp. 780–788. © Pleiades Publishing, Ltd., 2018.

An Efficient Microwave-Assisted Synthesis of Novel 2-{4-[(3-Aryl-1,8-naphthyridin-2-yl)amino]phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-diones and Their Antimicrobial Activity[1]

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Received November 15, 2017

Abstract—The Buchwald–Hartwig amination reaction between 2-chloro-3-aryl-1,8-naphthyridines and 2-(4-aminophenyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione in the presence of the catalytic system $Pd(PPh_3)_4$ and the base KO-*t*-Bu in toluene was studied. The reaction was initiated by microwave irradiation. Highly efficient synthesis has been developed for 2-{4-[(3-aryl-1,8-naphthyridin-2-yl)amino]phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-diones. Structures of the synthesized compounds were evaluated by IR, ^1H and ^{13}C NMR spectroscopy. All products were tested for antimicrobial activity against *Escheria coli, Bacillus subtilis, Klebsiella pneumoniae,* and *Staphylococcus aureus*.

Keywords: Antimicrobial activity, C–N bond formation, microwave irradiation, molecular docking, 1,8-naphthyridine, $Pd(PPh_3)_4$ catalyst

DOI: 10.1134/S1070363218040242

INTRODUCTION

1,8-Naphthyridine derivatives isolated from natural sources demonstrated various biological activities [1–3]. Nalidixic acid, for example, possesses robust antibacterial activity and is used mostly against gram negative pathogens of urinary tract infections [4]. Vosaroxin is a naphthyridine analog of the anticancer quinolones [5]. Gemifloxacin is an antimicrobial and antibacterial agent [6]. Also, 1,8-naphthyridines and their dimer derivatives have been studied in host-guest and self-assembling systems [7] (Fig. 1).

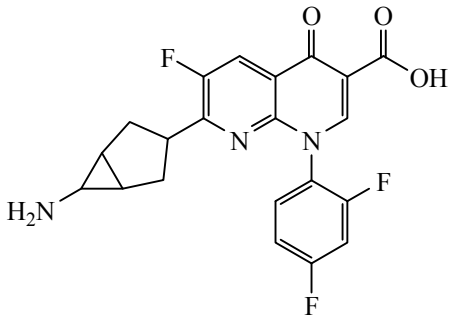
The rising interest in synthesis of 1,8-naphthyridines [8] was initiated by their biological activities including antitumor [9], anti-inflammatory [10, 11], anticonvulsant [12], and antihypertensive [13, 14]. Some 1,8-naphthyridine mixtures have been patented as efficient agrochemicals [15, 16]. Palladium catalyzed coupling of aryl halides with amine nucleophiles in the presence of stoichiometric amounts of a base was reported in 1955 [17]. This was developed further later on [18, 19].

Microwave-assisted organic synthesis is now a well-established procedure in organic synthesis [20–22]. In such procedures solvents with higher dielectric constants are superheated and the reactions proceed rapidly. In view of the above information and as a development of our earlier studies of microwave-assisted processes with 1,8-naphthyridine derivatives [23], we report herein a new efficient procedure for the synthesis of 2-{4-[(3-aryl-1,8-naphthyridin-2-yl)amino]-phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-diones (**9a–9h**) (Scheme 1).

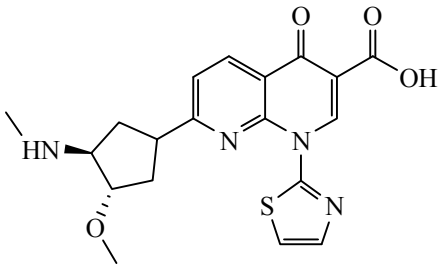
RESULTS AND DISCUSSION

Condensation of 2-aminonicotinaldehyde (**1**) with 2-phenylacetonitrile (**2**) in the presence of piperidine without a solvent at room temperature resulted in formation of 2-amino-1,8-naphthyridines (**3**), which was converted into 1,8-naphthyridine-2(1*H*)-ones (**4**) by the reaction with $NaNO_2$. Refluxing of compounds **4** with $POCl_3$ afforded 2-chloro-1,8-naphthyridines (**5**) [24]. Condensation of benzene-1,4-diamine (**6**) with benzo[*de*]isochromene-1,3-dione (**7**) in the presence of methanol upon refluxing afforded 2-(4-aminophenyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**8**) [25].

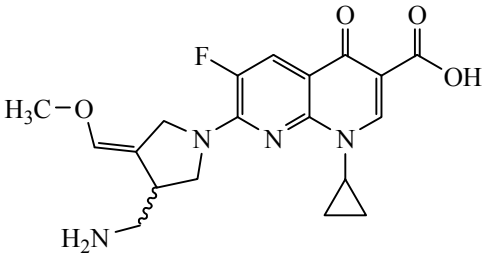
[1] The text was submitted by the authors in English.



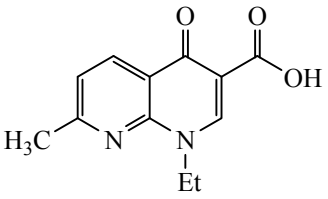
Trovafloxacin



Vosaroxin

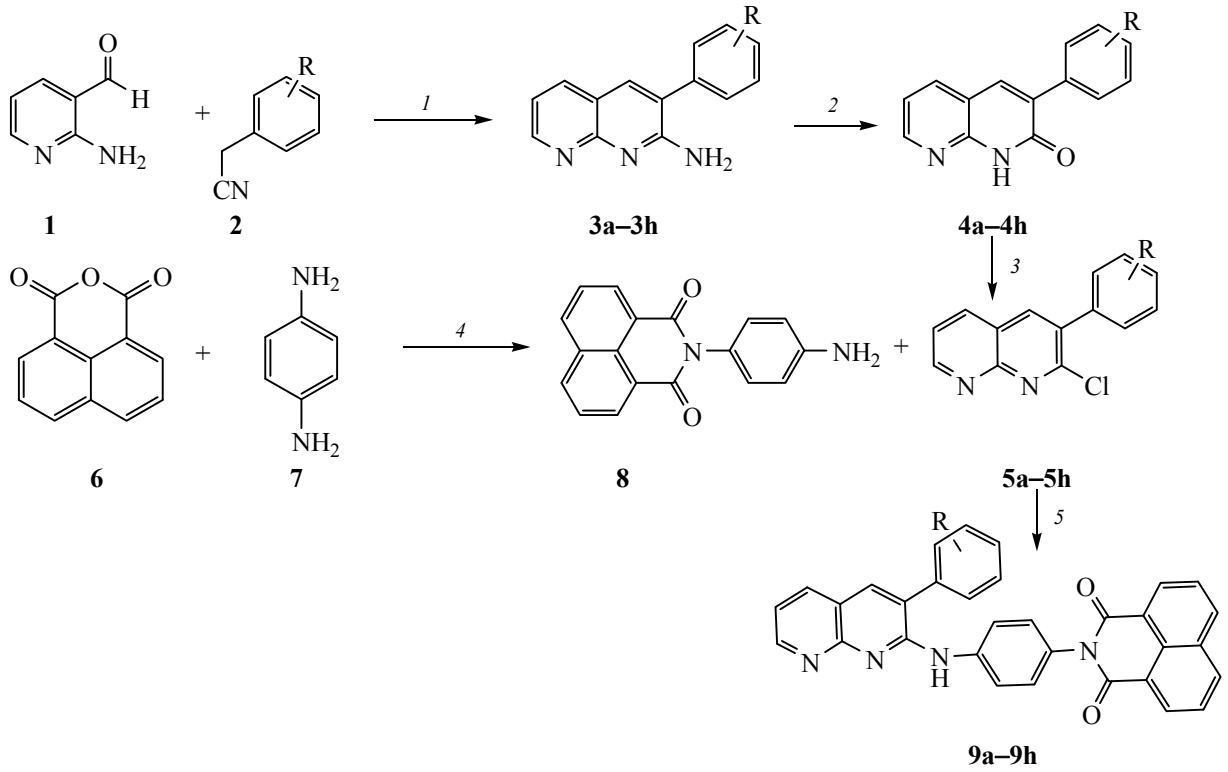


Gemifloxacin



Nalidixic Acid

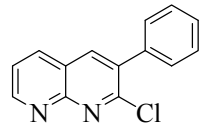
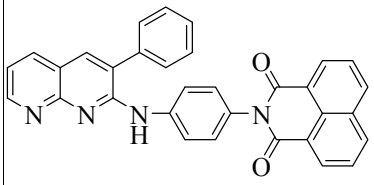
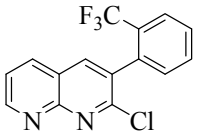
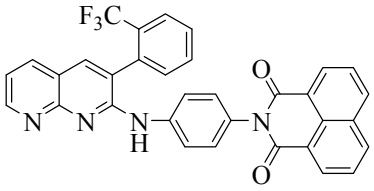
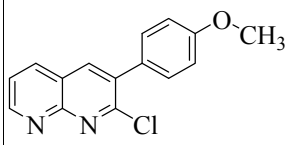
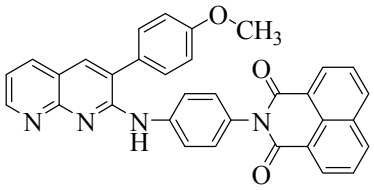
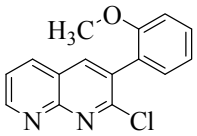
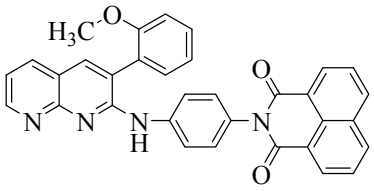
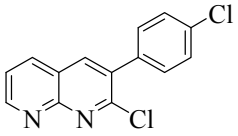
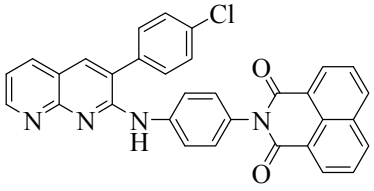
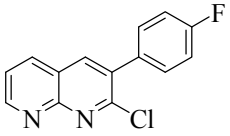
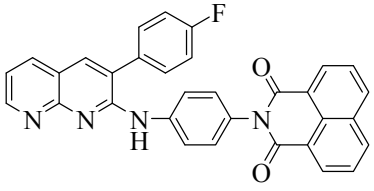
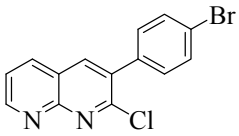
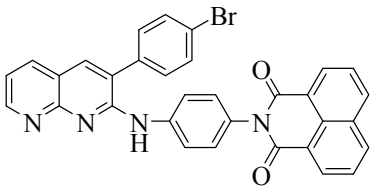
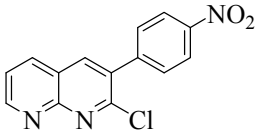
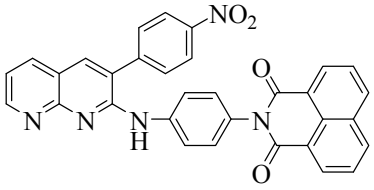
Fig. 1. Chemical structure of the some active 1,8-naphthyridines.



Scheme 1. Synthesis pathway of the compounds **3a–3h** to **9a–9h**.

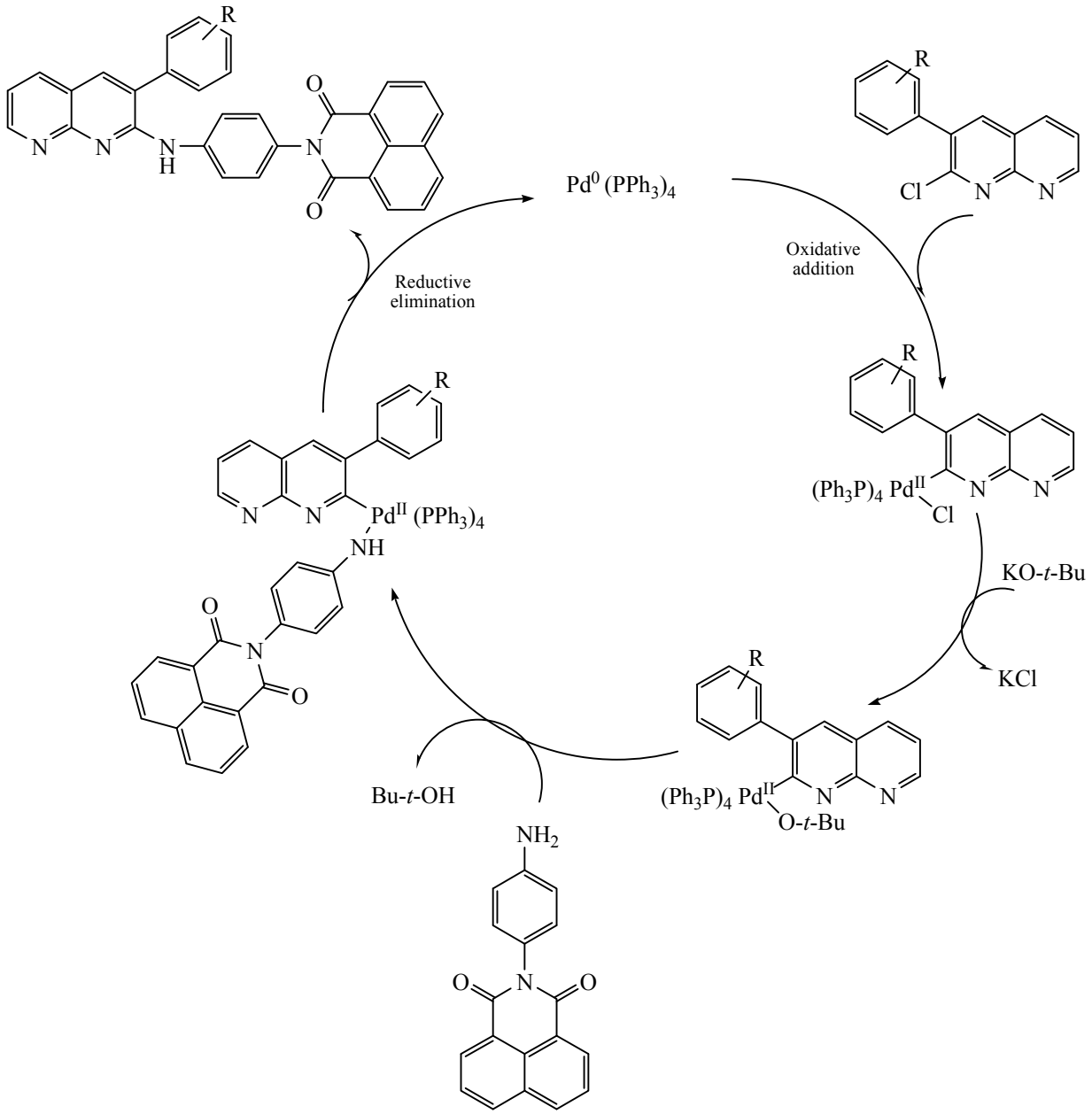
R = H (**3a–5a, 9a**); *o*-CF_3 (**3b–5b, 9b**); *p*-OCH_3 (**3c–5c, 9c**); *o*-OCH_3 (**3d–5d, 9d**); *p*-Cl (**3e–5e, 9e**); *p*-F (**3f–5f, 9f**); *p*-Br (**3g–5g, 9g**); *p*-NO_2 (**3h–5h, 9h**). Reagents and conditions: (*1*) piperidine, (*2*) $NaNO_2$, room temperature to reflux; (*3*) $POCl_3$; (*4*) MeOH, reflux; (*5*) $Pd(PPh_3)_4$, KO-*tert*-Bu, toluene, microwave.

Table 1. Synthesized C–N bond formations of C^3 substituted 1,8-naphthyridine ring (**9a–9h**)

Comp. no.	2-Chloro-3-aryl-1,8-naphthyridines	Product no.	Product **9**[a]	Time, min	Yield[b], %
5a		**9a**		4.5	82
5b		**9b**		4.0	80
5c		**9c**		4.5	76
5d		**9d**		4.0	69
5e		**9e**		4.0	81
5f		**9f**		3.5	80
5g		**9g**		3.5	69
5h		**9h**		4.0	78

[a] IR, ^1H, ^{13}C NMR, and MS spectra were proven with the assigned structures of all new compounds. [b] Isolated yield after work up.

Scheme 2. Proposed mechanism of preparation of 2-{4-[(3-aryl-1,8-naphthyridin-2-yl)amino]phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-diones (**9a–9h**).



R = H (**9a**), *o*-CF_3 (**9b**), *p*-OCH_3 (**9c**), *o*-OCH_3 (**9d**), *p*-Cl (**9e**), *p*-F (**9f**), *p*-Br (**9g**), *p*-NO_2 (**9h**).

Treatment of the latter with 2-chloro-3-aryl-1,8-naphthyridines (**5a–5h**) in the presence of a catalytic system tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] and KO-*t*-Bu in toluene under MWI at 200 W, gave the corresponding 2-{4-[(3-aryl-1,8-naphthyridin-2-yl)-amino]phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-diones (**9a–9h**) of high purity in high yields (69–82%) within short reaction time (3.5–4.5 min) (Table 1). Structures of compounds **9** were elucidated from IR, ^1H, and ^{13}C NMR, and mass spectra.

The plausible mechanism of formation of compounds **9a–9h** (Scheme 2) starts with oxidative addition of tetrakis(triphenylphosphine) palladium(0) species to 2-chloro-3-aryl-1,8-naphthyridines **5a–5h** leading to the intermediate organopalladium(II) species.

Table 2. Antimicrobial activity data of the synthesized compounds **9a–9h**

Compound no.	Concentration, μg/disc	Inhibition zone, mm			
		gram(+ve) bacteria		gram(–ve) bacteria	
		Staphylococcus aureus	*Bacillus subtilis*	*Klebsiella pneumoniae*	*Escheria coli*
9a	100	15	20	11	30
	200	20	22	13	31
9b	100	20	35	16	19
	200	25	40	20	21
9c	100	22	15	16	15
	200	25	19	20	18
9d	100	28	25	17	16
	200	31	28	20	21
9e	100	18	15	15	11
	200	20	18	18	14
9f	100	16	22	20	28
	200	18	25	21	30
9g	100	11	16	33	20
	200	16	18	35	22
9h	100	28	31	12	15
	200	32	32	15	18
Chloramphenicol	100	35	38	42	40
	200	39	41	45	44

Alternatively, the same process under conventional conditions of heating to 90°C in a water bath completed in 10 h gave compound **9a** with the yield only 42%.

Antibacterial activity. All synthesized compounds **9a–9h** were screened for their antimicrobial activities against *Bacillus subtilis, Staphylococcus aureus* (Gram +ve) and *Escheria coli, Klebsiella pneumoniae* (Gram –ve) at 100 and 200 μg/disc concentration using chloramphenicol as a reference drug. The accumulated data demonstrated high activity of the products (Table 2). The compounds **9c** and **9d** containing the electron-donating substituents in phenyl ring (*p*-OCH_3, *o*-OCH_3), exhibited maximum zones of inhibition close to that of chloramphenicol. All other compounds with substituent R = Cl, F, Br in the phenyl ring were of moderate antibacterial activity. Among all products the compound **9b** exhibited the highest antimicrobial activity against *Bacillus subtilis* at a concentration of 20 0 μg/disc.

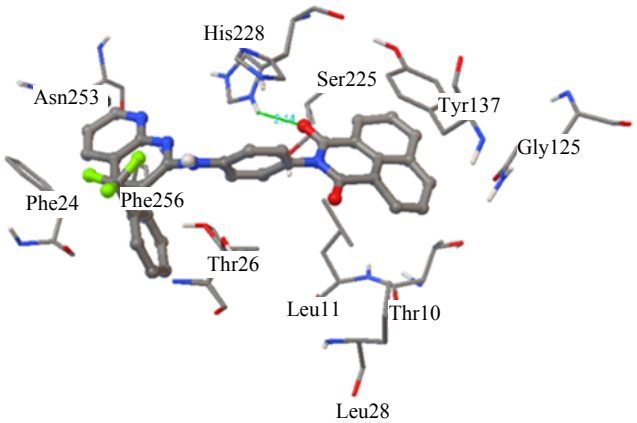


Fig. 2. Molecular docking interactions of 2-{4-[(3-(2-trifluoromethyl)phenyl)-1,8-naphthyridin-2-yl)amino]-phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**9b**).

Molecular modeling. In this study, the synthesized ligands have been identified as potent antibacterial inhibitors. AutoDock4.2 uses binding free energy assessment to assign the best binding conformation. Experimental activities and predicted by Lamarckian Genetic Algorithm dockings values for selected compounds are summarized in Table 3. With only one exception the molecules demonstrated interactions and

Table 3. Molecular docking interactions and their binding energy of **9b**, **9d**, and **9f**

Ligand no.	Interacting amino acids	Interacting residue	Grid *x, y, z* coordinates	Binding energy Δ*G*, kcal/mol	Dissociation constant *K*, nM
9b	His228	O–HD1	20.204, 26.232, –0.054	–9.12	207.68
9d	–	–	20.204, 26.232, –0.054	–9.32	146.66
9f	–	–	20.204, 26.232, –0.054	–11.06	7.85

low free energy values, indicating substantial thermodynamic interactions.

Docking of the synthesized compounds into the binding site of a 4M7X and estimating the binding affinity of the complex was significant for the structure based drug design process. The structural interactions between PDB and 3 inhibitors were docked separately. (*x, y, z*) Coordinates of PDB were selected by using SPDBV. The amino acid residues present in the binding pockets were Thr99, Gly9, Gly125, Gly121, Thr10, Lys13, Leu11, and Ser225 (Fig. 2).

EXPERIMENTAL

All reagents were used as purchased from Aldrich Chemical Company. Melting points were measured in open capillary tubes on a Cintex apparatus and were uncorrected. Purity of compounds was tested by TLC using ethyl acetate : *n*-hexane (2 : 8) as an eluent. IR spectra were recorded on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer using KBr discs. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ or DMSO-d_6 media on a Varian Gemini 400 MHz or 101 MHz spectrometer using TMS as an internal standard. Mass spectra were measured on a Jeol JMSD-300 spectrometer. Microanalysis was performed on a Carlo-Erba model EA1108 analytical unit. Irradiation was carried out in a domestic microwave oven.

The Buchwald–Hartwig amination coupling, synthesis of 2-{4-[(3-aryl-1,8-naphthyridin-2-yl)amino]-phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-diones (9a–9h). Mixture of a compound **5a–5h** (1.0 mmol) with 2-(4-aminophenyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione **8** (0.288 g, 1.0 mmol), KO-*t*-Bu (0.170 g, 1.5 mmol), and $[Pd^0(PPh_3)_4]$ (0.578 g, 0.5 mmol) in toluene (5 mL) was subjected to microwave irradiation at 200 W intermittently at 30 s intervals for a certain time (3.5–4.5 min, Table 1). After completion of the reaction, as indicated by TLC, the mixture was poured into cool water. The precipitated solid was collected, washed with *n*-hexane, dried, and recrystallized from methanol (3 mL) to give the target compound **9a–9h**.

2-{4-[(3-Phenyl-1,8-naphthyridin-2-yl)amino]-phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (9a). Gray solid, yield 82%, mp 222–224°C. FT-IR spectrum, ν, cm^{-1}: 3523, 3028, 3307, 1604, 1516, 1354. ^{1}H NMR spectrum, δ, ppm: 10.12 s (1H), 8.54–8.48 m (5H), 8.17 d (*J* = 7.7 Hz, 1H), 8.13 s (1H), 7.91 t (*J* = 7.7 Hz, 2H), 7.77–7.67 m (4H), 7.50–7.37 m (3H), 7.33–7.24 m (3H). ^{13}C NMR spectrum, δ, ppm: 168.4 (2C), 163.7, 161.8, 150.2, 149.2, 139.0 (2C), 136.4 (2C), 135.7, 134.3, 132.6, 131.4, 130.7, 129.2 (2C), 128.7 (2C), 128.0, 127.9 (2C), 127.7 (2C), 127.2 (2C), 122.5 (2C), 119.2, 118.4 (2C), 114.6. MS (EI, *m/z*, %): 493 $[M + H]^+$. Found, %: C 77.85; H 4.08; N 11.18. $C_{32}H_{20}N_4O_2$. Calculated, %: C 78.03; H 4.09; N 11.38.

2-{4-[(3-(2-Trifluoromethylphenyl)-1,8-naphthyridin-2-yl)amino]phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (9b). Colorless solid, yield 80%, mp 250–252°C. FT-IR spectrum, ν, cm^{-1}: 3309, 1705, 1656, 1519, 1234, 1111. ^{1}H NMR spectrum, δ, ppm: 10.13 s (1H), 8.51 s (5H), 8.16 s (1H), 8.01–7.58 m (8H), 7.48 s (1H), 7.30 s (3H). ^{13}C NMR spectrum, δ, ppm: 163.7 (2C), 161.8, 150.7, 150.6, 149.6, 139.0, 137.3 (2C), 136.6, 135.5, 134.4 (2C), 133.1, 132.6, 132.1, 131.4, 130.7, 129.2 (2C), 128.6, 127.7, 127.2 (4C), 122.6 (2C), 119.2, 118.8, 118.5 (2C), 113.9. MS (EI, *m/z*, %): 561 $[M + H]^+$. Found, %: C 70.51; H 3.16; N 9.85. $C_{33}H_{19}F_3N_4O_2$. Calculated, %: C 70.71; H 3.42; N 10.00.

2-{4-[(3-(4-Methoxyphenyl)-1,8-naphthyridin-2-yl)amino]phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (9c). Yellow solid, yield 76%, mp 201–203°C. FT-IR spectrum, ν, cm^{-1}: 3523, 3309, 1703, 1658, 1232, 1109. ^{1}H NMR spectrum, δ, ppm: 12.29 s (1H), 8.54–8.48 m (2H), 8.21–8.13 m (4H), 8.08 s (1H), 7.90 d (*J* = 2.2 Hz, 1H), 7.79–7.70 m (4H), 7.30– 7.22 m (4H), 7.02 d (*J* = 9.0 Hz, 2H), 3.81 s (3H). ^{13}C NMR spectrum, δ, ppm: 163.7, 158.0 (2C), 155.7, 153.8, 151.4, 144.2, 141.9, 141.5, 139.0 (2C), 134.4, 131.4, 130.7, 129.4 (2C), 129.3 (2C), 129.2, 127.8, 129.2, 127.8, 127.2 (2C), 122.5 (2C), 120.0, 119.2, 117.3 (2C), 115.0, 114.2 (2C), 57.1. MS (EI, *m/z*, %): 523

[M + H]$^+$. Found, %: C 76.05; H 4.43; N 11.02. $C_{33}H_{22}N_4O_3$. Calculated, %: C 75.85; H 4.24; N 10.72.

2-{4-[(3-(2-Methoxyphenyl)-1,8-naphthyridin-2-yl)amino]phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (9d). Gray solid, yield 69%, mp 200–202°C. FT-IR spectrum, ν, cm^{-1}: 3522, 3307, 1639, 1182, 1026. ^{1}H NMR spectrum, δ, ppm: 10.67 s (1H), 8.69–8.60 m (3H), 8.27 t (J = 7.2 Hz, 1H), 7.98–7.92 m (2H), 7.84–7.76 m (4H), 7.73 d (J = 8.7 Hz, 3H), 7.24–7.19 m (1H), 7.09 d (J = 8.5 Hz, 1H), 7.03–6.97 m (2H), 6.83 d (J = 8.5 Hz, 1H), 3.87 s (3H). ^{13}C NMR spectrum, δ, ppm: 163.8 (2C), 163.7, 150.1, 149.8, 139.0, 136.4 (2C), 136.1, 135.9, 135.0, 134.3, 134.2, 131.4, 130.7, 130.6, 129.9, 129.4 (2C), 129.2, 128.7 (2C), 127.2 (2C), 122.6, 122.5 (2C), 119.2 (2C), 118.3, 114.7, 113.4, 56.1. MS (EI, *m/z*, %): 523 [M + H]$^+$. Found, %: C 76.15; H 4.54; N 11.00. $C_{33}H_{22}N_4O_3$. Calculated, %: C 75.85; H 4.24; N 10.72.

2-{4-[(3-(4-Chlorophenyl)-1,8-naphthyridin-2-yl)-amino]phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (9e). Gray solid, yield 81%, mp 229–231°C. FT-IR spectrum, ν, cm^{-1}: 3601, 3309, 1662, 1587, 1429, 775, 702. ^{1}H NMR spectrum, δ, ppm: 10.77 s (1H), 8.68–8.63 m (2H), 8.28 d (J = 8.7 Hz, 1H), 7.97 d (J = 7.7 Hz, 1H), 7.85–7.82 m (2H), 7.79 d (J = 8.0 Hz, 1H), 7.71 d (J = 8.5 Hz, 4H), 7.44 d (J = 8.5 Hz, 3H), 7.30–7.27 m (2H), 7.25–7.21 m (2H). ^{13}C NMR spectrum, δ, ppm: 168.4 (2C), 163.7, 161.6, 150.4, 149.8, 146.2, 141.4, 139.0, 136.7 (2C), 136.6 (2C), 134.3, 132.7, 131.4, 130.7, 130.5 (2C), 129.2 (2C), 128.0 (2C), 127.7, 127.2 (2C), 122.5 (2C), 119.2, 118.5 (2C), 114.5. MS (EI, *m/z*, %): 527 [M + H]$^+$. Found C 73.16; H 3.82; N 10.95. $C_{32}H_{19}ClN_4O_2$. Calculated, %: C 72.93; H 3.63; N 10.63.

2-{4-[(3-(4-Fluorophenyl)-1,8-naphthyridin-2-yl)-amino]phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (9f). Light yellow solid, yield 80%, mp 238–240°C. FT-IR spectrum, ν, cm^{-1}: 3523, 3307, 1665, 1232. ^{1}H NMR spectrum, δ, ppm: 10.38 s (1H), 8.68–8.61 m (3H), 8.31–8.25 m (2H), 7.98–7.94 m (1H), 7.84–7.69 m (8H), 7.25–7.21 m (1H), 7.12–7.19 m (3H). ^{13}C NMR spectrum, δ, ppm: 163.7 (2C), 156.2, 155.3, 154.6, 152.6, 151.6, 150.8, 149.5, 146.6, 145.1, 142.9, 139.0 (2C), 136.6 (2C), 136.4 (2C), 134.3, 130.9, 130.7 (2C), 129.2 (2C), 127.7, 127.2 (2C), 122.6 (2C), 119.2 (2C), 114.7. MS (EI, *m/z*, %): 511 [M + H]$^+$. Found, %: C 75.38; H 3.90; N 11.22. $C_{32}H_{19}FN_4O_2$. Calculated, %: C 75.28; H 3.75; N 10.97.

2-{4-[(3-(4-Bromophenyl)-1,8-naphthyridin-2-yl)-amino]phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (9g). Pale yellow solid, yield 69%, mp 218–220°C. FT-IR spectrum, ν, cm^{-1}: 3522, 3030, 1660, 1587, 831, 777. ^{1}H NMR spectrum, δ, ppm): 10.41 s (1H), 8.65 d (J = 7.7 Hz, 3H), 8.28 t (J = 7.7 Hz, 2H), 7.96 d (J = 9.0 Hz, 1H), 7.76–7.85 m (3H), 7.71 d (J = 8.2 Hz, 1H), 7.56–7.67 m (4H), 7.51 d (J = 10.7 Hz, 1H), 7.38 d (J = 8.0 Hz, 1H), 7.08 d (J = 8.2 Hz, 1H), 6.83 d (J = 8.5 Hz, 1H). ^{13}C NMR spectrum, δ, ppm): 163.7 (2C), 150.5, 149.2, 136.7 (2C), 136.6 (2C), 134.3, 131.4, 131.0, 130.9, 130.8 (2C), 130.7, 130.6 (2C), 129.2, 129.1 (2C), 127.2, 122.7 (2C), 122.5 (2C), 121.4, 120.7, 119.2, 118.5 (2C), 114.5, 113.9. MS (EI, *m/z*, %): 571 [M + H]$^+$. Found, %: C 67.51; H 3.43; N 10.02. $C_{32}H_{19}BrN_4O_2$. Calculated, %: C 67.26; H 3.35; N 9.80.

2-{4-[(3-(4-Nitrophenyl)-1,8-naphthyridin-2-yl) amino]phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (9h). Brownish yellow solid, yield 78%, mp 240–242°C. FT-IR spectrum, ν, cm^{-1}: 3522, 3359, 1701, 1664, 1512, 1406, 1352. ^{1}H NMR spectrum, δ, ppm: 10.12 s (1H), 8.61– 8.45 m (6H), 8.38–8.29 m (1H), 8.25–8.15 m (1H), 8.06 d (J = 8.7 Hz, 1H), 7.91 t (J = 7.7 Hz, 3H), 7.70 d (J = 8.7 Hz, 3H), 7.29 d (J = 8.7 Hz, 3H). ^{13}C NMR spectrum, δ, ppm: 168.4 (2C), 163.7, 156.6, 154.9, 150.3, 139.0 (2C), 136.2 (2C), 135.4, 134.7, 134.3, 130.7, 130.5 (2C), 129.2 (2C), 128.6 (2C), 127.7, 127.2 (2C), 122.5, 121.3 (2C), 121.0, 119.2, 116.6 (2C), 114.7, 113.8. MS (EI, *m/z*, %): 538 [M + H]$^+$. Found, %: C 71.85; H 3.72; N 13.26. $C_{32}H_{19}N_5O_4$. Calculated, %: C 71.50; H 3.56; N 13.03.

Antimicrobial assay. Screening of antimicrobial activity was carried out by the agar well diffusion method. The tested organisms were sub cultured on LB Broth (Lennox) Powder. LB Broth (Lennox) Powder (1 μL) was dissolved in 10 mL of distilled water in a test tube and autoclaved at 15 pound pressure for 15 min and cooled. Bacterial culture (10 μL) was added to the broth in laminar air flow and stored at 4°C in a refrigerator to maintain the stock.

A modified Murray (1995) antimicrobial susceptibility was tested on solid media in petri plates. For bacterial assay nutrient agar (40 gm/L) was used for developing surface colony growth. The suspension culture for bacterial cells growth was carried out by preparing 2% LB Broth (Lennox) Powder (w/v). All media prepared were sterilized by autoclaving the media at 121°C for 20 min. Wells (10 mm diameter ca

2 cm) were made in each of these plates using a sterile cork borer. Stock solution of each compound was prepared at a concentration of 1 μL/mL. About 100 μL of different concentrations of compounds were added by sterile pipette into the wells and allowed to diffuse at room temperature for 2 h. Control experiments (positive and negative) comprising inoculums without compounds were set up. The plates were incubated at 37°C for 18–24 h for bacterial pathogens. The diameter of the inhibition zone (mm) was measured and the activity index was also calculated. The experiments were carried out in triplicates and the average values were recorded. The minimum inhibitory concentration was defined as the lowest one.

Molecular docking The ligands were sketched in Sybyl6.7 and saved in .mol2 format. All sketched molecules were converted to energy minimized 3D structures by using Gasteiger-Huckel charges for in silico protein–ligand docking using AutoDock Tools [26]. Each molecule was docked separately. Initially the molecule was loaded; torsions were set and saved in PDBQT format. All heteroatoms were removed from the 4M7X.PDB (Staphylococcus aureus Type II pantothenate kinase in complex with a pantothenate analog), to make complex receptor free of any ligand before docking. The PDB was also saved in PDBQT format. All calculations for protein-ligand flexible docking were performed using the Lamarckian Genetic Algorithm (LGA) method [27]. A grid box with the dimensions of *x* 20.204, *y* 26.232 and *z* –0.054 Å, with a default grid spacing of 0.375 Å was used. The conformation with the lowest docked energy was chosen. The interactions of 4M7X protein and ligand conformations, including hydrogen bonds and the bond lengths, were analyzed.

Molecular docking study was performed by using AUTODOCK 4.2, which was a suite of automated docking tools and used to predict the affinity, activity, binding orientation of ligand with the target protein and to analyze best conformations, the protein with all 3 compounds were loaded individually into ADT and evaluated ten finest conformations. In the present study we focused mainly on the binding energy, hydrogen bonds, and distance between the protein and ligand.

CONCLUSIONS

In summary, we have synthesized 2-{4-[(3-aryl-1,8-naphthyridin-2-yl)amino]phenyl}-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-diones (**9a–9h**) by using the green method MW heating, which is more efficient than the classical conditions. We determined that compounds **9a–9h** demonstrated *in vitro* antimicrobial potency. Molecular docking study was carried out.

ACKNOWLEDGMENTS

The authors are thankful to the Directors, CFRD-OU, IICT, Hyderabad for providing IR, ^{1}H, and ^{13}C NMR, and mass spectral and analytical data. One of the author (B. Sakram) expresses thanks to the University Grant Commission, New-Delhi, India, for the financial support.

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