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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Microwave-irradiated synthesis and antimicrobial activity of 2-phenyl-7-substitutedalkyl/arylaminoquinoline-4-carboxylic acid derivatives

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Abstract This report focuses on the synthesis of 2-phenyl-7-substitutedquinoline-4-carboxylic acid derivatives through both conventional and microwave-irradiated methods. Intermediate 7-chloro-2-phenyl-quinoline-4-carboxylic acid was synthesized by condensation and cyclization of benzaldehyde, pyruvic acid, and *m*-chloroaniline in the presence of absolute ethanol and further substituted with aromatic, aliphatic, and alicyclic amines to obtain the desired 2-phenyl-7-substitutedaryl/alkylamino-quinoline-4-carboxylic acid derivatives under the influence of microwave irradiation, with output power ranging from 160 to 480 W, yield ranging from 90% to 95%, and a shorter reaction time than with the conventional method. All the synthesized compounds were screened for in vitro antimicrobial activity against six gram-positive and four gram-negative organisms. All synthesized compounds are active against a broad spectrum of microorganisms, with prominent results for *Streptococcus pyrogenes* and *Pseudomonas aeruginosa*. Compounds **7c** and **7h** showed a minimum inhibitory concentration of less than 10 μg.

Keywords Doebner reaction · In vitro antimicrobial activity · MIC · Microwave irradiation · Quinoline-4-carboxylic acid

Introduction

In past few years, the use of microwave irradiation for both the organic reaction and synthesis of pharmaceutical compounds is rapidly increasing due to the short duration of reaction and high yield with purity (Mitra *et al*., 1999). Use of the domestic microwave oven is now a well-established procedure for microwave-induced organic

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reaction enhancement (MORE) chemistry (Bose *et al.*, 1990, 1991). The lack of a wide spectrum of biologic data is an important obstacle preventing efficient molecular design.

Quinoline derivatives are known to exhibit a variety of biologic effects (Musiol *et al.*, 2007). A novel and highly convergent synthesis leading to 2-phenyl-quinolines has already been developed (Yan *et al.*, 2005).

Quinoline-4-carboxylic acids and their salts are useful as immunosuppressive agents, as neurokinin receptor antagonists, as a mosquito repellant, and as antiviral agents, to name a few (Batt *et al.*, 1996; Belenkaya *et al.*, 1981; Carling *et al.*, 2006; Gualtieri *et al.*, 1973). The antimicrobial activity of quinoline-4-carboxylic acid derivatives against gram-positive and gram-negative organisms is reported (Dinakaran *et al.*, 2008; Metwally *et al.*, 2006; Strigacova *et al.* 2000). Newer quinoline-4-carboxylic acid derivatives also have been synthesized by the microwave-irradiated method (Duvelleroy *et al.*, 2005; Ivachtchenko *et al.*, 2004; Tu *et al.*, 2006).

This report describes the microwave-irradiated synthesis and in vitro antimicrobial activity of 2-phenyl-7-substitutedaryl/alkylamino-quinoline-4-carboxylic acid derivatives for the first time.

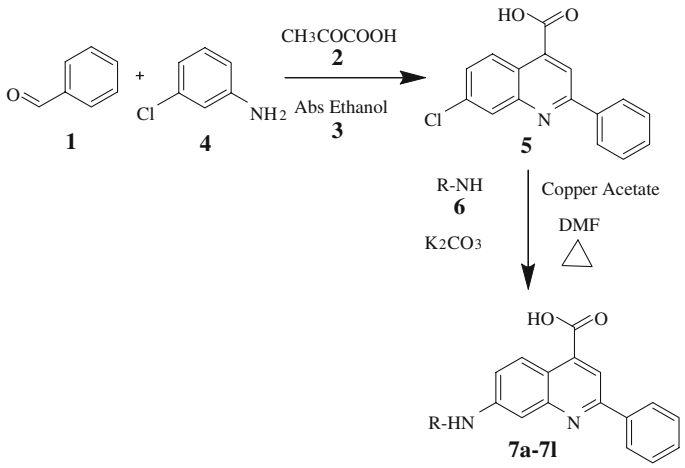
Materials and methods

Chemistry

The synthesis of 2-phenyl-7-substitutedaryl/alkylamino-quinoline-4-carboxylic acid follows the doebner pyruvic acid synthesis (Atwell *et al.*, 1989). In the presence of benzaldehyde **1**, pyruvic acid **2**, and absolute ethanol **3**, *m*-chloroaniline **4** condensed and cyclized to form intermediate 7-chloro-2-phenyl-quinoline-4-carboxylic acid **5** after 5–6 h of heating in a steam bath. This intermediate moiety was further substituted with different aromatic, aliphatic, or alicyclic amines **6** to synthesize the final product, 2-phenyl-7-substitutedaryl/alkylamino-quinoline-4-carboxylic acid (**7a**–**7l**), in presence of potassium carbonate, copper acetate, and *N*,*N*-dimethyl formamide (Koga *et al.*, 1980; Wolf *et al.*, 2006) after it had been heated on heating metal for 4–5 h (Scheme 1).

The aforementioned conventional synthesis has three major disadvantages, namely, a longer reaction time, a large amount of required solvents that are not eco-friendly, and poor yield. Hence, we report the rapid synthesis of 2-phenyl-7-substitutedaryl/alkylamino-quinoline-4-carboxylic acid derivatives under microwave irradiation in a domestic microwave oven in the absence of solvent. The output power range varies from 160 to 480 W, and the reaction time varies from 30 to 200 s for a 90% to 95% yield.

The comparison of the results from both the conventional and microwave-irradiated methods are summarized in Table 1. The time required for completion of the reaction under the influence of microwave irradiation is drastically shorter than with the conventional method. The yield of the microwave-irradiated reaction also is greater than with the conventional method. Reactions performed in such conditions are faster and cleaner due to less thermal decomposition of products. All



Scheme 1 Synthesis of 2-phenyl-7-substitutedaryl/alkylamino-quinoline-4-carboxylic acid: R–NH=**7a**: $–NH–C_6H_4–CH_3$, **7b**: $–NH–C_6H_4–NO_2$, **7c**: $–NH–C_6H_5$, **7d**: piperazine, **7e**: $–NH–C_6H_4–SO_2NH_2$, **7f**: $–NH–CO–NH_2$, **7g**: $–NH–CS–NH_2$, **7h**: 2-aminothiazole, **7i**: $–NH–C_6H_4–OCH_3$, **7j**: $–NH–CH_2–$COOH, **7k**: 4-amino-1,2,4-triazole, **7l**: 4-aminopyridine

Table 1 Comparison of the conventional method and the microwave-irradiated method

Compound no.	Molecular formula	Conventional method		Microwave-irradiated method		
		Time (h)	Yield (%)	Time (s)	Output (W)	Yield (%)
5	$C_{16}H_{10}O_2NCl$	6	72	60	160	95
7a	$C_{23}H_{18}O_2N_2$	4.5	65	160	320	93
7b	$C_{22}H_{15}O_4N_3$	4.5	60	120	160	95
7c	$C_{22}H_{16}O_2N_2$	4	55	60	480	94
7d	$C_{20}H_{19}O_2N_3$	4	58	60	320	91
7e	$C_{22}H_{17}O_4N_3S$	5	75	60	320	95
7f	$C_{17}H_{13}O_3N_3$	5	60	60	320	92
7g	$C_{17}H_{13}O_2N_3S$	5	61	100	160	94
7h	$C_{19}H_{13}O_2N_3S$	4.5	62	35	320	93
7i	$C_{23}H_{18}O_3N_2$	5	54	50	320	91
7j	$C_{18}H_{13}O_4N_2$	4.5	67	160	320	93
7k	$C_{18}H_{13}O_2N_5$	5	53	130	320	91
7l	$C_{21}H_{15}O_2N_3$	5	61	90	160	91

the synthesized derivatives were characterized by FT-IR, ^{1}H NMR, and mass and elemental analysis.

Results and discussion

All the synthesized compounds were screened for their antimicrobial activity against six gram-positive microbial organisms and four gram-negative microbial

organisms by the agar well-diffusion method. A minimum inhibitory concentration (MIC) study was performed by the agar-dilution method (Butler *et al*., 2007; Goksu *et al*., 2005). A 10-μg/well concentration of all the synthesized compounds was evaluated.

The results of the antimicrobial activity with respect to zone of inhibition in millimeters are shown in Table 2. All the compounds showed good results for a wide range of microbial organisms, indicating broad-spectrum efficacy of the designed series. Specifically, compounds **7b**, **7c**, **7f**, **7g**, and **7h** showed promising results for all microbial organisms compared with the standard drugs ofloxacin and gentamicin. Compounds **7c** and **7h** showed good activity against *Streptococcus pyrogenes* and *Pseudomonas aeruginosa.* The MICs of these two compounds are summarized in Table 3.

Table 2 Antimicrobial activity of standard and synthesized compounds against gram-positive and gram-negative organisms (zone of inhibition diameter in millimeters)

Compound no.	Concentration in μg/well[a]	S.A.	B.S.	B.C.	B.P.	S.P.	K.P.	E.C.	E.F.	P.A.	P.O.
5	10	–	5	4	8	4	3	7	7	2	6
7a	10	5	6	6	9	7	3	8	9	3	8
7b	10	7	5	9	11	2	–	12	3	–	8
7c	10	8	9	10	5	7	5	10	9	4	12
7d	10	4	2	5	5	7	6	10	7	4	11
7e	10	9	5	5	2	5	–	8	5	4	11
7f	10	9	9	10	6	9	6	7	6	9	9
7g	10	9	–	5	3	5	–	5	9	12	7
7h	10	10	9	13	12	13	5	7	12	15	13
7i	10	2	4	4	3	5	3	3	8	8	5
7j	10	–	–	4	2	5	5	2	7	4	8
7k	10	2	–	3	2	–	4	3	3	–	4
7l	10	3	5	5	6	–	4	4	7	5	4
Ofloxacin	10	16	17	16	17	17	19	17	16	16	17
Gentamicin	10	16	19	17	17	17	16	16	18	19	19

S.A., *Staphylococcus aureus*; B.S., *Bacillus subtilis*; B.C., *Bacillus cereus*; B.P., *Bacillus pumilus*; S.P., *Streptococcus pyrogenes*; K.P., *Klebsiella pneumoniae*; E.C., *Escherichia coli*; E.F., *Enterococcus faecalis*; P.A., *Pseudomonas aeruginosa*; P.O., *Pseudomonas oleovorans*; –, no zone of inhibition

[a] Vehicle DMSO (as control) produced no zone of inhibition

Table 3 Minimum inhibitory concentrations (MICs in μg)

Comp. no.	S.P.	P.A.
7c	7	9
7h	5	3

Comp., compound; S.P., *Streptococcus pyrogenes*; P.A., *Pseudomonas aeruginosa*

Structure–activity relationship study

The agar well-diffusion method was used to evaluate the antimicrobial activity of synthesized derivatives, and the agar-dilution method was used for the MIC study. The results of antimicrobial activity showed that incorporation of the substituted alkyl/arylamino group at **C-7** of quinoline-4-carboxylic acid has a comparative effect on the various six gram-positive and four gram-negative microbial organisms. The concentration of compounds used for the current study was 10 μg/well, and effectiveness was evaluated by measuring the zone of inhibition in millimeters.

Compared with **C-7**–substituted compounds, 7-chloro-2-phenylquinoline-4-carboxylic acid (**5**) showed less activity, indicating the effectiveness of the alkyl/arylamino substitution at the **C-7** position to inhibit the growth of microorganisms. Compound **7h** (2-aminothiazole substitution at the **C-7** position) exhibited the most potent antimicrobial activity among all the synthesized compounds in this series. It showed the highest antimicrobial activity on *P. aeruginosa*. Compound **7h** also showed moderate activity against *Bacillus cereus*, *Bacillus pumilus, S. pyrogenes, Enterococcus faecalis,* and *Pseudomonas oleovorans,* indicating wide-spectrum antimicrobial activity. It possessed the least antimicrobial activity against *Klebsiella pneumoniae*. Substitution with 4-nitrophenylamino (**7b**), phenylamino (**7c**), ureido (**7f**), and thioureido (**7g**) at the **C-7** position showed promising results against a wide range of microbial organisms. Compounds with 4-amino-1,2,4-triazole substitution (**7k**) and 4-aminopyridine substitution (**7l**) at **C-7** showed the least effect on the growth of microorganisms, indicating less effectiveness of these compounds. The MICs of compounds **7h** and **7c** were carried out on *P. aeruginosa* and *S. pyrogenes* by the agar-dilution method. Compound **7h** showed MICs of 3 and 5 μg, respectively, whereas **7c** showed MICs of 9 and 4 μg, respectively.

These findings indicate that substitution at the **C-7** position is essential to enhance the antimicrobial activity of a given series of quinoline-4-carboxylic acid derivatives.

Conclusion

In summary, we have demonstrated a practical application for the microwave-enhanced synthesis of 2-phenyl-7-substitutedaryl/alkylaminoquinoline-4-carboxylic acids. Spectacular results have been obtained, clearly indicating the potentialities and advantages of this new technique compared with conventional methods. All the synthesized compounds showed good antimicrobial activity against various organisms, indicating a wide spectrum of antimicrobial activity. The structure–activity relationship (SAR) study demonstrated the comparative activity of compounds 2-aminothiazole substitution (**7h**) and aniline substitution (**7c**) against all microorganisms. The SAR study also showed that substitution on **C-7** is essential to obtain the desired antimicrobial activity. The MIC of both **7h** and **7c** is less than 10 μg, which showed the effectiveness of these compounds. The synthesized series

of quinoline-4-carboxylic acids can be developed further to show their best use in various infectious disease conditions.

Experimental approach

General

Melting points were taken in the open capillary on an electrically heated metal block and are uncorrected. The FT-IR spectra were recorded on a Jasco FT-IR 6100 spectrometer. The ^{1}H NMR spectra were recorded in a BRUKER DPX-200 spectrometer operation at 200 MHz in dimethyl sulphoxide (DMSO d6) with tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on a Waters Micromass Q-Tof Micro. An elemental analysis was performed on a Perkin Elmer 2400 series II. The reactions were carried out in a domestic microwave oven (KenStar OM 20 DGQ, KenStar Kitchen Appliances India Ltd., Aurangabad, India). The compounds of the current invention were synthesized using the methods described in the following sections.

Conventional method (Scheme 1)

*Synthesis of 7-chloro-2-phenyl-quinoline-4-carboxylic acid (**5**)*

An equi-mole quantity of the starting materials was taken and reacted. Benzaldehyde **1** (0.01 mole, 1.06 g) and pyruvic acid **2** (0.01 mole, 0.88 g, 0.70 mL) were dissolved in 20 mL of absolute ethanol **3** and refluxed over a steam bath with a calcium chloride guard tube. As the solution started boiling, *m*-chloroaniline **4** (0.01 mole, 1.27 g) dissolved in 20 mL of absolute ethanol was added drop-wise and continued refluxing for 5–6 h. The refluxing was stopped, and the solution was kept overnight at room temperature. Solids precipitated from the solution were filtered, washed with small quantity of ether, and dried. The intermediate 7-chloro-2-phenyl-quinoline-4-carboxylic acid **5** was recrystallized with absolute ethanol, and the melting point was reported.

*Synthesis of 2-phenyl-7-substitutedaryl/alkylamino-quinoline-4-carboxylic acids (**7a–7l**)*

The compound **5** (0.01 mole, 2.83 g) was dissolved in 20 mL of *N*,*N*-dimethyl formamide. Anhydrous potassium carbonate (0.02 mole, 2.7 g), copper acetate (0.01 mole, 1.82 g), and substituted amine **6** (0.01 mole) were added. The mixture was refluxed on the heating metal for 4–5 h. After completion of refluxing, the solution was added to crushed ice and stirred well. The solids were separated out, filtered, and dried. The solid 2- phenyl-7-substitutedaryl/alkylamino-quinoline-4-carboxylic acids (**7a–7l**) were purified with acetic acid–sodium hydroxide solution. The melting points were reported.

Microwave-irradiated method

*Synthesis of 7-chloro-2-phenyl-quinoline-4-carboxylic acid (**5**)*

Benzaldehyde **1** (0.01 mole, 1.06 g) and pyruvic acid **2** (0.01 mole, 0.88 g, 0.70 ml) were taken in a closed vessel and irradiated for 30 s at 160 W of output power. Next, *m*-chloroaniline **4** (0.01 mole, 1.27 g) was added, and they again were put into an oven for 30 s at 160 W of output power. The yellow colored residue was dissolved in absolute ethanol, filtered, washed with a small quantity of ether, and dried. The intermediate 7-chloro-2-phenyl-quinoline-4- carboxylic acid **5** was recrystallized with absolute ethanol, and the melting point was reported.

*Synthesis of 2-phenyl-7-substitutedaryl/alkylamino-quinoline-4-carboxylic acids (**7a–7l**)*

To the compound **5** (0.01 mole, 2.83 g), anhydrous potassium carbonate (0.02 mole, 2.7 g), copper acetate (0.01 mole, 1.82 g), and substituted amine **6** (0.01 mole) were added. The mixture was irradiated for 30 to 200 s at 160 to 480 W of output power. After completion of irradiation, the resulting mixture was added to crushed ice and stirred well. The solids were separated out, filtered, and dried. The solid 2-phenyl-7-substituted aryl/alkylamino-quinoline-4-carboxylic acids **7a–7l** were purified with acetic acid–sodium hydroxide solution. The melting points were reported.

*7-Chloro-2-phenyl-quinoline-4-carboxylic acid (**5**)* M.p. 182–184°C. IR (KBr): *v*: 3280 (OH), 1720 (C=O), 1610 (C=N), 1585 cm^{-1} (C=C). ^1H NMR (DMSO-d6): δ 7.1–7.8 (8 H, m, Ar–H), 8.5 (1 H, s, 3-H), 10.63 (1H, s, –COOH). MS (ESI): *m*/*z* 284.1 ($M^+ + 2$). Anal. Calcd for $C_{16}H_{10}O_2NCl$: C, 67.74; H, 3.55; N, 4.94. Found: C, 67.70; H, 3.60; N, 4.92.

*2-Phenyl-7-(p-tolylamino)quinoline-4-carboxylic acid (**7a**)* M.p. 165–167°C. IR (KBr): *v*: 3350 (NH), 3310 (OH), 1705(C=O), 1610 (C=N), 1580 cm^{-1} (C=C). ^1H NMR (DMSO-d6) δ: 2.5 (3 H, s, $–CH_3$), 7.1–7.7 (12 H, m, Ar–H), 8.2 (1 H, s, 3-H), 9.1 (1 H, s, –NH–), 10.55 (1 H, s, –COOH). MS (ESI): *m*/*z* 353.3 (M^+). Anal. Calcd for $C_{23}H_{18}O_2N_2$: C, 77.95; H, 5.12; N, 7.90. Found: C, 77.90; H, 5.15; N, 7.94.

*7-(4-Nitrophenylamino)-2-phenylquinoline-4-carboxylic acid (**7b**)* M.p. 170–172°C. IR (KBr): *v*: 3350 (NH), 3240 (OH), 1720 (C=O), 1620 (C=N), 1605 (C=C), 1535 cm^{-1} (NO_2). ^1H NMR (DMSO-d6) δ: 7.2–7.9 (12 H, m, Ar–H), 8.9 (1 H, s, 3–H), 9.3 (1 H, s, –NH–), 11.42 (1 H, s, –COOH). MS (ESI): *m*/*z* 384.1 (M^+). Anal. Calcd for $C_{22}H_{15}O_4N_3$: C, 68.57; H, 3.92; N, 10.90. Found: C, 68.60; H, 3.95; N, 10.94.

*2-Phenyl-7-(phenylamino)quinoline-4-carboxylic acid (**7c**)* M.p. 155–157°C. IR (KBr): *v*: 3300 (NH), 3250 (OH), 1725 (C=O), 1625 (C=N), 1595 cm^{-1} (C=C). ^1H

NMR (DMSO-d6) δ: 7.1–7.9 (13 H, m, Ar–H), 8.2 (1 H, s, 3-H), 9.20 (1 H, s, –NH–), 10.40 (1 H, s, –COOH). MS (ESI): *m/z* 341.2 (M^++1). Anal. Calcd for $C_{22}H_{16}O_2N_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.66; H, 4.76; N, 8.20.

*2-Phenyl-7-(piperazin-1-yl)quinoline-4-carboxylic acid (**7d**)* M.p. 168–170°C. IR (KBr): *v*: 3320 (NH), 3230 (OH), 1715 (C=O), 1625 (C=N), 1575 cm^{-1} (C=C). ^{1}H NMR (DMSO-d6) δ: 3.25–3.4 (8 H, m, piperazine-H), 3.8 (1 H, m, piperazine-NH), 7.2–7.9 (8 H, m, Ar–H), 8.3 (1 H, s, 3-H), 11.25 (1 H, s, –COOH). MS (ESI): m/z 332.2 (M^+). Anal. Calcd for $C_{20}H_{19}O_2N_3$: C, 72.05; H, 5.74; N, 12.60. Found: C, 72.02; H, 5.77; N, 12.55.

*2-Phenyl-7-(4-sulfamoylphenylamino)quinoline-4-carboxylic acid (**7e**)* M.p. 172–174°C. IR (KBr): *v*: 3310 (NH), 3250 (OH), 1720 (C=O), 1615 (C=N), 1595 (C=C), 3350, 3340, 1355 cm^{-1} (SO_2NH_2). ^{1}H NMR (DMSO-d6) δ: 2.5 (2 H, s, –SO_2NH_2), 7.1–7.8 (12 H, m, Ar–H), 8.7 (1 H, s, 3-H), 9.4 (1 H, s, –NH–), 11.90 (1 H, s, –COOH). MS (ESI): *m/z* 419.3 (M^+). Anal. Calcd for $C_{22}H_{17}O_4N_3S$: C, 63.00; H, 4.09; N, 10.02. Found: C, 63.03; H, 4.10; N, 10.03.

*2-Phenyl-7-ureidoquinoline-4-carboxylic acid (**7f**)* M.p. 170–172°C. IR (KBr): *v*: 3330 (NH), 3170 (OH), 1705 (C=O), 1570 (C=N), 1555 cm^{-1} (C=C). ^{1}H NMR (DMSO-d6) δ: 7.1–7.9 (8 H, m, Ar–H), 8.3 (1 H, s, 3-H), 8.7 (2 H, s, –NH_2), 9.1 (1 H, s, –NH–), 10.90 (1 H, s, –COOH). MS (ESI): *m/z* 307.3 (M^+). Anal. Calcd for $C_{17}H_{13}O_3N_3$: C, 67.44; H, 4.26; N, 13.67. Found: C, 67.50; H, 4.30; N, 13.61.

*2-Phenyl-7-thioureidoquinoline-4-carboxylic acid (**7g**)* M.p. 160–162°C. IR (KBr): *v*: 3230 (NH), 3200 (OH), 1715 (C=O), 1620 (C=N), 1590 (C=C), 1180 cm^{-1} (C=S). ^{1}H NMR (DMSO-d6) δ: 7.1–7.7 (8 H, m, Ar–H), 7.9 (2 H, s, –NH_2), 8.7 (1 H, s, 3-H), 10.2 (1 H, s, –NH–), 11.90 (1 H, s, –COOH). MS (ESI): *m/z* 325.3 (M^+ + 2). Anal. Calcd for $C_{17}H_{13}O_2N_3S$: C, 63.14; H, 4.05; N, 12.99. Found: C, 63.11; H, 4.02; N, 12.98.

*2-Phenyl-7-(thiazol-2-ylamino)quinoline-4-carboxylic acid (**7h**)* M.p. 158–160°C. IR (KBr): *v*: 3250 (NH), 3200 (OH), 1713 (C=O), 1605 (C=N), 1595 cm^{-1} (C=C). ^{1}H NMR (DMSO-d6) δ: 6.59 (1 H, d, 5H of thiazole), 7.1 (1 H, d, 4H of thiazole), 7.4–7.8 (8 H, m, Ar–H), 8.4 (1 H, s, 3-H), 10.2 (1 H, s, –NH), 10.32 (1 H, s, –COOH). MS (ESI): *m/z* 350 (M^+ + 3). Anal. Calcd for $C_{19}H_{13}O_2N_3S$: C, 65.69; H, 3.77; N, 12.10. Found: C, 65.67; H, 3.79; N, 12.13.

*7-(4-Methoxyphenylamino)-2-phenylquinoline-4-carboxylic acid (**7i**)* M.p. 146–148°C. IR (KBr): *v*: 3300 (NH), 3160 (OH), 1715 (C=O), 1610 (C=N), 1590 cm^{-1} (C=C). ^{1}H NMR (DMSO-d6) δ: 3.4 (3 H, s, –OCH_3), 7.1–7.7 (12 H, m, Ar–H), 8.3 (1 H, s, 3-H), 9.4 (1 H, s, –NH), 10.81 (1 H, s, –COOH). MS (ESI): *m/z* 373 (M^+ +3). Anal. Calcd for $C_{23}H_{18}O_3N_2$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.60; H, 4.94; N, 7.54.

*7-(Carboxymethylamino)-2-phenylquinoline-4-carboxylic acid (**7j**)* M.p. 153–155°C. IR (KBr): *v*: 3320 (NH), 3280 (OH), 1715 (C=O), 1620 (C=N), 1590 cm^{-1} (C=C). ^1H NMR (DMSO-d6) δ: 3.4 (2 H, d, $–CH_2$), 6.6 (1 H, s, –NH), 7.1–7.7 (8 H, m, Ar–H), 8.2 (1 H, s, 3-H), 11.86 (1 H, s, –COOH). MS (ESI): *m/z* 325.2 (M^++2). Anal. Calcd for $C_{18}H_{13}O_4N_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.09; H, 4.40; N, 8.70.

*7-(4H-1,2,4-triazol-4-ylamino)-2-phenylquinoline-4-carboxylic acid (**7k**)* M.p. 140–143°C. IR (KBr): *v*: 3300 (NH), 3210 (OH), 1705 (C=O), 1610 (C=N), 1575 cm^{-1} (C=C). ^1H NMR (DMSO-d6) δ: 7.1–7.4 (8 H, m, Ar–H), 8.1 (1 H, s, 3-H), 8.35 (2 H, s, 3 and 5-H of triazole), 9.1 (1 H, s, –NH–), 12.50 (1 H, s, –COOH). MS (ESI): *m/z* 331.2 (M^+). Anal. Calcd for $C_{18}H_{13}O_2N_5$: C, 69.25; H, 3.95; N, 21.14. Found: C, 69.29; H, 3.90; N, 21.10.

*2-Phenyl-7-(pyridin-4-ylamino)quinoline-4-carboxylic acid (**7l**)* M.p. 163–165°C. IR (KBr): *v*: 3350 (NH), 3260 (OH), 1725 (C=O), 1610 (C=N), 1570 cm^{-1} (C=C). ^1H NMR (DMSO-d6) δ: 7.0–7.5 (10 H, m, Ar–H; 3 and 5-H of pyridine), 8.1 (1 H, s, 3-H), 8.4 (2 H, s, 2 and 6-H of pyridine), 9.3 (1 H, s, –NH–), 11.91 (1 H, s, –COOH). MS (ESI): *m/z* 342.2 (M^+). Anal. Calcd for $C_{21}H_{15}O_2N_3$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.92; H, 4.40; N, 12.30.

Biologic activity

In vitro antimicrobial studies

All the synthesized compounds were screened by the agar well-diffusion method for their antimicrobial activity, and MIC study was carried out by the agar-dilution method. The bacterial strains were procured from the Microbial Type Culture Collection & Gene Bank (Chandigarh, India). The antimicrobial activity of the synthesized compounds was screened against the following bacterial strains: six gram-positive microbial organisms (*Staphylococcus aureus* [MTCC 737], *Bacillus subtilis* [MTCC 2397], *B. cereus* [MTCC 430], *B. pumilus* [MTCC 1640], *S. pyrogenes* [MTCC 442], *K. pneumoniae* [MTCC 109]) and four gram-negative microbial organisms (*Eschericnia coli* [MTCC 1652], *E. faecalis* [MTCC 439], *P. aeruginosa* [MTCC 741], *P. oleovorans* [MTCC 617]). For all the synthesized compounds, a 10-μg/well concentration in DMSO was evaluated for antimicrobial activity. Nutrient agar and broth media were used for the preparation of the stock cultures and subcultures of all the microorganisms. Nutrient agar medium (M00-500G) and nutrient broth medium (M002-500G) were purchased from HI MEDIA Lab Ltd. (Mumbai, India). Freshly prepared nutrient agar medium was used during each experimental procedure.

The melted nutrient agar medium was poured into sterilized petri dishes to a uniform depth and allowed to solidify under aseptic conditions. The bacterial suspension, prepared from a subculture of bacterial strains, then was streaked over

the medium surface using a sterile cotton swab to ensure confluent growth of organism. The wells, each 6 mm in diameter, were made by a sterile cork borer in the petri dish. The sample solutions of test compounds and the standard drugs were loaded separately into each well with the help of a micropipette. Inoculated plates were incubated in a biochemical oxygen demand (BOD) incubator at 37 ± 1°C for 24 h. The zone of inhibition diameter produced by each compound was measured in millimeters using the Antibiotic Zone Reader (Kshitij Innovations, Ambala Cant, India). The results for the synthesized compounds were screened against the standard drugs ofloxacin and gentamycin, with DMSO as a vehicle.

The agar-dilution method was used to determine the MIC of the synthesized compounds. The test compounds were dissolved in DMSO and further diluted with nutrient broth medium to make the final concentration of 10–100 μg/mL. Then, 1 mL of the solution so obtained was added to 10 mL of melted agar medium at a temperature of 40–50°C. The melted agar medium was added to the sterile petri dish and allowed to solidify. All the petri dishes loaded with the test compounds were inoculated with a loopful of a bacterial suspension on the surface of the solidified agar. The petri dishes were incubated at 37 ± 1°C for 24 h, after which the MICs were recorded by visual observation. The MIC was taken as the highest dilution (least concentration) of the test compound showing no detectable growth.

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