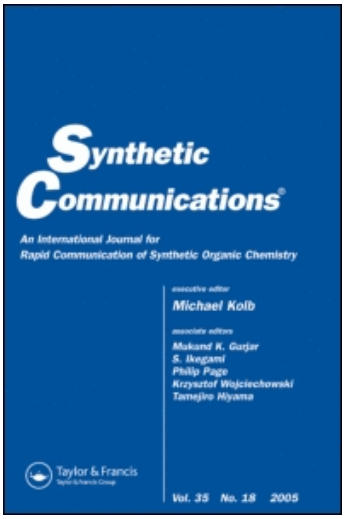

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Synthesis of Some 2-Aryl- and 2,3-Diaryl-quinolin-4-carboxylic Acid Derivatives

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SYNTHESIS OF SOME 2-ARYL- AND 2,3-DIARYL-QUINOLIN-4-CARBOXYLIC ACID DERIVATIVES

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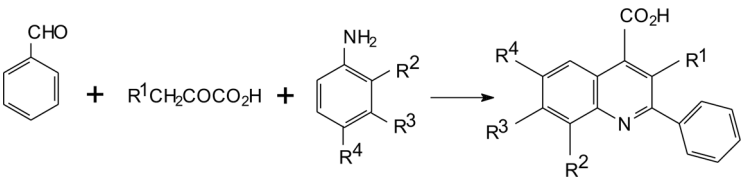
GRAPHICAL ABSTRACT



Abstract *Eighteen 2-aryl- and 2,3-diaryl-quinolin-4-carboxlic acid derivatives were synthesized. Basically, the synthetic design of these compounds arose from the appropriate disconnections of the target compounds, which revealed pyruvic acid, aromatic amine, and benzaldehyde or phenyl pyruvic acid, aromatic amine, and benzaldehyde as possible logical precursors for 2-aryl- and 2,3-aryl-quinolin-4-carboxylic acids respectively. The purity and identities of the synthesized compounds were elucidated through chromatographic and spectroscopic techniques (ultraviolet, infrared, mass,* ^{1}H *NMR, and* ^{13}C *NMR). The prepared derivatives were screened for their antibacterial activity against the standard bacterial organisms* B. subtilis, S. aureus, E. coli, *and* P. vulgaris. *2,3-Diphenyl-6-sulfanilamido-quinolin-4-carboxylic acid showed the highest activity against the four tested organisms.*

Keywords Antibacterial activity; heterocycles; quinolin-4-carboxylic acids; spectroscopy; total synthesis

INTRODUCTION

Quinolines are a group of compounds associated with different biological activities, such as antiplatelet,[1] antibacterial, antimalarial, and antinuclear inhibitors of immunodeficiency virus.[2] Some derivatives of quinoline-4-carboxylic acid elicited profound changes in the morphology of typical tips of *Botrytis cinerea*.[3]

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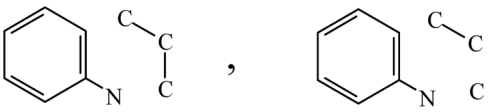
A series of 7-substituted-6-fluoro-1-fluoromethyl 4-oxo-4H-(1,3) thiazeto (3,2-a) quinoline-3-carboxylic acid derivatives showed excellent in vitro and in vivo antibacterial activity.[4] 4-(Phenylamino)quinoline-3-carboxamides were evaluated for antisecretory activity against histamine-induced gastric acid secretion in rats. Most of the compounds inhibited this activity.[5] The 2-phenylquinoline-4-carboxamide has been found to possess moderate affinity for human neurokinin-3 receptor, and thiazoloquinolone derivatives were highly cytotoxic against mammalian cells. The thiazetoquinolone derivatives were less cytotoxic than the thiazoloquinolone derivatives.[6]

The present work aimed at synthesizing certain substituted 2-aryl-and 2,3-diaryl-quinolin-4-carboxylic acids. The design of these compounds included the insertion of certain types of substituents in the homocyclic ring. These substituents should be to some extent bioisosters to each others. The work aimed to screen the compounds for antimicrobial activities.

DISCUSSION

Chemistry

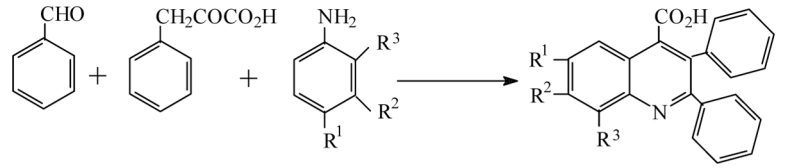
The synthetic design in this work depends on the appropriate retrosynthetic analysis, through disconnection or functional group interchange (FGI) and functional group removal strategies. The total synthesis of any of the quinolines in this work can be simply linked to benzaldehyde as starting material. The retrosynthetic analysis of quinoline derivatives exemplifies two important overall strategies by which the heterocyclic ring can be constructed, as indicated by (I) and (II):



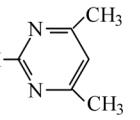
I II

2-Phenylquinolin-4-carboxylic acid derivatives were prepared by the Doebner reaction, through the condensation of benzaldehyde, aniline, and pyruvic acid in absolute ethanol. Similarly, 2,3-diphenylquinolin-4-carboxylic acid derivatives were prepared through the condensation of a primary aromatic amines with phenylpyruvic acid and benzaldehyde (Schemes 1 and 2). Quinolin-4-carboxylic acids were obtained through a modified Pfitzinger approach involving the condensation of a ketone with an isatin derivative.[7] A synthesis of quinolin-4-carboxylic acid derivatives has been reported by the reaction of 2-methoxy acrylates or acylamides with N-arylbenzaldimines.[8]

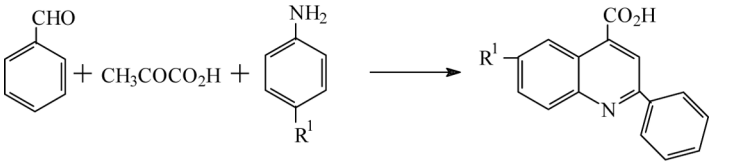
The methyl ester derivatives, compounds **14** and **15**, were prepared through direct esterification of compounds **13** and **1** respectively. Compound **1** on treatment with slight excess of thionyl chloride at room temperature followed by addition of the required amine furnished the carboxamide compounds (**16**–**18**) (Scheme 3).



1 , R^1=H R^2= H R^3= H
2 , R^1=H R^2= H R^3= CH_3
3 , R^1= CH_3 R^2= H R^3= H
4 , R^1=H R^2= CH_3 R^3= H
5 , R^1= SO_2NH_2 R^2= H R^3= H
6 , R^1= NO_2 R^2= H R^3= H
7 , R^1= CO_2H R^2= H R^3= H
8 , R^3= H R^2= H R^1= $-SO_2NH-$

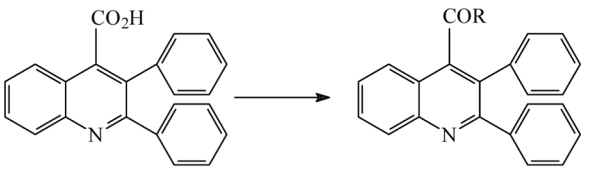


Scheme 1. Chemical structures of substituted 2,3-diaryl-quinolin-4-carboxylic acids.



9 , R^1= CH_3
10 , R^1= SO_2NH_2
11 , R^1= NO_2
12 , R^1= CO_2H
13 , R^1=H

Scheme 2. Chemical structures of substituted 2-aryl-quinolin-4-carboxylic acids.



15 , R = OCH_3
16 , R = NH_2
17 , R = NHC_6H_5
18 , R = $NHCH_3$

Scheme 3. Chemical structures of 2,3-diarylquinoline-4-carboxy derivatives.

Antibacterial Activity

As revealed by the results (Table 1), compounds **3, 6, 15, 17**, and **18** were inactive against *S. aureus* while compounds **6, 8, 10, 11**, and **15** were inactive against *P. vulgaris*. All the tested compounds were active against *B. subtilis* and *E. coli*. Compound **5** showed the highest activity against the four tested organisms. The most

Table 1. Antibacterial activity of the compounds tested

Compound (1 mg/ml)	Mean inhibition zone diameter (mm)			
	B. subtilis	*S. aureus*	*E. coli*	*P. vulgaris*
2	17	17	15	20
3	15	—	15	19.5
5	23.5	22.5	19.5	20
6	16	—	16	—
8	20	—	16.5	—
9	20.5	18.5	19.5	20
10	21	15	18	—
11	18.5	14.5	16	—
15	20	—	15	—
17	14.5	—	16.5	24.5
18	21	—	17	22.5
Ampicillin in PRG (125 μg/ml)	11	34	14	00
Ampicillin in PRG (250 μg/ml)	12	36	15	00
Ampicillin in PRG (500 μg/ml)	13	41	19	00

effective compounds, **5, 8**, and **10**, contain a sulfanilamido moiety in position 6 of the quinoline ring system. Replacement of this group by methyl, nitro, or carboxyl groups decreases activity. It seems that the phenyl group at position 3 is not essential for activity when comparing the pairs of compounds with the same substituents: **3, 9**; **5, 10**, and **6, 11**. Conversion of the carboxyl group into ester and amide functionalities results, in improved activity against *P. vulgaris*. The greater activity of compound **5** compared to compound **10** may be attributed to the large, rigid character that the additional phenyl group in **5** confers on the molecule. Such molecules can be inserted into membranes and induce permeability changes leading to leakage out of the cellular membrane. On the other hand, the greater activity in the other compounds cannot be explained in terms of cellular differences. It is more likely due to interaction of the molecules with some intercellular target. The presence of the powerful electron-withdrawing group (-SONH-) alters the nature of the compound to promote binding to the target.[9]

EXPERIMENTAL

All chemicals and reagents were general purpose reagent grade and were used without further purification. Melting points were uncorrected. Elemental analyses for CHNS were within +0.3%. Infrared (IR) analysis was carried out using IR satellite Fourier transfrom (FT)–IR spectrometer (Mattson). Ultraviolet/visible (UV/vis) spectrometry was carried out using an UV/vis spectrophotometer (Jenway model 6505). Mass spectra analysis was carried out using a GC/MS instrument (GP 5050A Shimadzu GC-17A). ^{1}H and ^{13}C NMR analysis were carried out using a Jeol ECP 400-MHZ instrument and a Jeol JNMFX 100-MHz instrument. Thin-layer chromatography (TLC) was carried out with silica-gel 60 GF_{254} (Merck, Germany) precoated plates, and different mobile phases were attempted.

Preparation of 2,3-Diarylquinoline-4-carboxylic Acids (1–8)

A mixture of benzaldehyde (0.6 g, 0.5 ml, 0.236 mol), phenyl pyruvic acid (0.5 g, 0.25 mol), and absolute ethanol (5 ml) was stirred at room temperature. A solution of the required aromatic amine (0.248 mol) in absolute ethanol (2.0 ml) was added slowly with shaking. The mixture was refluxed on a water bath for 3 h and allowed to stand overnight. The crude product was filtered, washed with a little ether, and recrystallized from ethanol.

Selected Data

2,3-Diphenyl quinoline-4-carboxylic acid (1, $C_{22}H_{15}NO_2$). Yield = 62%; mp = 245–146 °C; ^{1}H NMR ppm, δ = 7.65–7.75 (4, m), 10.64 (1, s), 7.03–7.18 (5, m), 7.28–7.38 (5, m); ^{13}C NMR ppm, δ = 129.0, 128.8, 132.2, 139.2, 138.2, 129.2, 137.5, 166.0, 138.1, 143.6, 122.4, 123.1, 125.1, 127.9, 127.3, 128.3, 128.0; IR (KBr): ν = 1670, 1615, 1470, 1400, 1570, 1170, 1210, 730, 700, 3400–2600, 1280 cm^{-1}; UV-vis (ethanol) λ_{max} = 210, 220 nm; MS (70 eV): molecular formula, m/z (% relative abundance): $C_{22}H_{15}NO_2$, 325, 280, 207 (33), 179 (74), 89 (4), 77 (31), 51 (12).

8-Methyl-2,3-diphenyl quinoline-4-carboxylic acid (2, $C_{23}H_{17}NO_2$). Yield = 78%; mp = 280–282 °C; ^{1}H NMR ppm, δ = 2.51 (3, d), 7.94–8.00 (3, m), 10.67 (1, s), 7.10–7.30 (5, m), 7.43–7.64 (5, m); ^{13}C NMR ppm, δ = 129.1, 129.0, 132.0, 138.5, 138.3, 129.8, 131.3, 167.8, 133.4, 147.4, 122.0, 122.6, 126.1, 127.3, 127.5, 128.7, 129.0, 21.9; IR (KBr): ν = 1700, 1490, 1420, 1620, 1320, 1210, 3200, 740, 680, 3400–2600, 1280 cm^{-1}; UV-vis (ethanol) λ_{max} = 255 nm; MS (70 eV): molecular formula, m/z (% relative abundance): $C_{23}H_{17}NO_2$, 339, 294 (1), 263 (8), 220 (10), 193 (4), 179 (100), 89 (38), 77 (79), 51 (53).

6-Methyl-2,3-diphenyl quinoline-4-carboxylic acid (3, $C_{23}H_{17}NO_2$). Yield = 63%; mp = 145–146 °C; ^{1}H NMR ppm, δ = 2.50 (3, s), 7.50–7.73 (3, m), 10.58 (1, s), 7.06–7.24 (5, m), 7.27–7.35 (5, m); ^{13}C NMR ppm, δ = 129.1, 134.3, 134.9, 143.7, 138.2, 132.3, 135.9, 165.8, 136.7, 149.3, 121.5, 122.5, 122.8, 127.7, 128.3, 128.8, 129.0, 129.1, 21.2; IR (KBr): ν = 1700, 1610, 1450, 1580, 1320, 1210, 3020, 780, 700, 3400–2600, 1250 cm^{-1}; UV-vis (ethanol) λ_{max} = 205, 265 nm; MS (70 eV): molecular formula, m/z (% relative abundance): $C_{23}H_{17}NO_2$, 339, 263 (4), 219 (1), 194 (100), 179 (3), 89 (14), 77 (9), 51 (13).

7-Methyl-2,3-diphenyl quinoline-4-carboxylic acid (4, $C_{23}H_{17}NO_2$). Yield = 84%; mp = 185–186 °C; ^{1}H NMR ppm, δ = 2.24 (3, s), 7.42–7.73 (3, m), 10.58 (1, s), 7.06–7.20 (5, m), 7.28–7.37 (5, m); ^{13}C NMR ppm, δ = 128.9, 128.7, 137.4, 132.2, 138.0, 129.0, 138.2, 165.9, 138.4, 143.6, 119.6, 123.0, 123.1, 125.8, 127.7, 127.9, 128.3, 128.4, 21.7; IR (KBr) ν = 1680, 1600, 1450, 1420, 1500, 1300, 1100, 850, 780, 700, 3400–2600, 1200 cm^{-1}; UV-vis (ethanol) λ_{max} = 210, 265 nm; MS (70 eV): molecular formula, m/z (% relative abundance): $C_{23}H_{17}NO_2$, 339, 322, 294, 263, 218, 194 (5), 179 (100), 89 (9), 77 (12), 51 (2).

6-Sulfanilamido-2,3-diphenyl quinoline-4-carboxylic acid (5, $C_{22}H_{16}O_4N_2S$). Yield = 64%; mp = 212–214; ^{1}H NMR ppm, δ = 6.64 (2, s), 7.71–7.98 (3, m), 10.03 (1, s), 7.08–7.22 (5, m), 7.27–7.47 (5, m); ^{13}C NMR ppm, δ = 131.9, 133.4,

136.2, 141.7, 129.2, 128.9, 136.2, 166.7, 137.5, 143.2, 121.6, 121.8, 124.0, 126.9, 127.9, 128.9, 129.2, 129.5; IR (KBr): $\nu = 1690$, 1480, 1450, 1580, 1160, 880, 820, 760, 3400–2600, 1200, 3400, 3300, 1410, 1370, 1150, 1600 cm^{-1}; UV-vis (ethanol) $\lambda_{max} = 205$, 265 nm; MS (70 eV): molecular formula, m/z (% relative abundance): $C_{22}H_{16}O_4N_2S$, 404, 327 (35), 282 (3), 260 (100), 179 (61), 89 (10), 77 (29), 51 (12).

6-Nitro-2,3-diphenyl quinoline-4-carboxylic acid (6, $C_{22}H_{14}N_2O_4$). Yield = 57%; mp = 145–147 °C; ^{1}H NMR ppm, $\delta = 7.72$–8.20 (3, m), 10.28 (1, s), 7.09–7.23 (5, m), 7.31–7.50 (5, m); ^{13}C NMR ppm, $\delta = 128.6$, 128.2, 129.1, 156.0, 143.3, 143.0, 166.3, 141.4, 143.3, 121.2, 121.7, 125.0, 126.9, 127.2, 128.0, 128.2, 129.0; IR (KBr): $\nu = 1690$, 1500, 1400, 1490, 1180, 1160, 820, 780, 3400–2600, 1200, 1520, 1350 cm^{-1}; UV-vis (ethanol) $\lambda_{max} =$ nm; 220, 265 MS (70 eV): molecular formula, m/z (% relative abundance): $C_{22}H_{14}N_2O_4$, 370, 353, 325, 294, 278, 223 (3), 179 (100), 89 (5), 77 (10), 51 (5).

2,3-Diphenyl quinoline-4,6-dicarboxylic acid (7, $C_{23}H_{15}NO_4$). Yield = 61%; mp = 272–273 °C; ^{1}H NMR ppm, $\delta = 12.82$ (1, s), 7.71–7.92 (3, m), 10.72 (1, s), 7.07–7.24 (5, m), 7.30–7.42 (5, m); ^{13}C NMR ppm, $\delta = 130.5$, 131.9, 137.8, 131.9, 130.5, 128.8, 131.8, 166.3, 141.4, 143.3, 121.2, 124.0, 126.9, 127.9, 128.2, 128.6, 128.8, 129.1, 167.3; IR (KBr): $\nu = 1700$, 1690, 1600, 1580, 1520, 1290, 1180, 3180, 820, 780, 3300, 1220 cm^{-1}; UV-vis (ethanol) $\lambda_{max} = 205$, 265 nm; MS (70 eV): molecular formula, m/z (% relative abundance): $C_{23}H_{15}O_4N$, 369, 324, 291, 249, 224 (2), 179 (100), 89 (4), 77 (12), 51 (7).

6-(4,6-Dimethyl pyrimid-2-yl sulfanilamido)-2,3-diphenyl quinoline-4-carboxylic acid (8, $C_{28}H_{22}O_4N_4S$). Yield = 68%; mp 110–112 °C; ^{1}H NMR ppm, $\delta = 3.37$ (3, s), 2.50 (3, s), 7.88–8.0 (1, s), 7.61–7.72 (3, m), 10.02 (1, s), 7.03–7.24 (5, m), 7.30–7.42 (5, m); ^{13}C NMR ppm, $\delta = 129.5$, 129.7, 130.1, 133.4, 129.8, 129.9, 135.2, 167.9, 136.7, 143.2, 126.9, 127.96, 128.1, 128.3, 128.8, 128.5, 129.0, 129.5; IR (KBr): $\nu = 1700$, 1600, 1500, 1520, 1200, 1200, 3060, 750, 700, 3370, 1280, 3300, 1350, 1160, 1600 cm^{-1}; UV-vis (ethanol) $\lambda_{max} = 210$, 220 nm; MS (70 eV): molecular formula, m/z (% relative abundance): $C_{28}H_{22}O_4N_4S$, 518, 372 (7), 179 (14), 89 (4), 77 (65), 51 (30).

Preparation of 2-Arylquinoline-4-carboxylic Acids (9–13)

A mixture of benzaldehyde (0.6 g, 0.5 ml, 0.236 mol), freshly distilled pyruvic acid (1 ml, 0.25 mol), and absolute ethanol (5 ml) were stirred at room temperature. A solution of the required aromatic amine (0.248 mol) in absolute ethanol (5 ml) was added slowly with shaking. The mixture was refluxed on a water bath for 3 h and allowed to stand overnight. The crude product was filtered, washed with a little ether, and recrystallized from ethanol.

Selected Data

6-Methyl-2-phenyl quinoline-4-carboxylic acid (9, $C_{17}H_{13}NO_2$). Yield = 66%; mp = 190–192 °C; ^{1}H NMR ppm, $\delta = 7.96$ (1, s), 2.56 (3, s), 8.27 (1, d), 8.57 (1, d), 13.97 (1, s), 8.40 (1, s), 7.50–7.60 (5, m); ^{13}C NMR ppm, $\delta = 129.2$, 140.7,

149.3, 130.4, 130.5, 129.5, 156.2, 168.3, 138.6, 156.3, 118.8, 122.1, 125.6, 127.7; IR (KBr): $\nu = 1700$, 1600, 1420, 1540, 1230, 1200, 2910, 890, 720, 3450, 1340, 1030 cm^{-1}; UV-vis (ethanol) $\lambda_{max} = 205$, 265 nm; MS (70 eV): molecular formula, m/z (% relative abundance): $C_{17}H_{13}NO_2$, 263 (100), 219 (68), 204 (23), 190 (4), 176 (1), 89 (13), 77 (7), 51 (4).

6-Sulfanilamido-2-phenyl quinoline-4-carboxylic acid (10, $C_{16}H_{12}N_2O_4S$). Yield = 77%; mp = 244–245 °C; ^{1}H NMR ppm, $\delta = 7.85$ (1, d), 7.76 (1, d), 7.27 (1, s), 7.83 (1, s), 7.30–7.45 (5, m); ^{13}C NMR 137.7, 135.7, 127.6, 145.4, 167.1, 140.3, 140.0, 113.8, 116.5, 121.5, 126.3; IR (KBr): $\nu = 1700$, 1600, 1480, 1530, 1100, 820, 750, 3400–2600, 1330, 1170, 1380, 1160, 1620, 3270, 3250 cm^{-1}; UV-vis (ethanol) $\lambda_{max} = 210$, 265 nm; MS (70 eV): molecular formula, m/z (% relative abundance): $C_{16}H_{12}N_2O_4S$, 328, 311, 285, 205, 172 (82), 156 (100), 92 (66), 89 (1), 77 (5), 51 (6).

6-Nitro-2-phenyl quinoline-4-carboxylic acid (11, $C_{16}H_{10}N_2O_4$). Yield = 62%; mp = 165–167 °C; ^{1}H NMR ppm, $\delta = 7.23$ (1, d), 7.41 (1, d), 8.14 (1, s), 9.38 (1, s), 8.13 (1, s), 7.43–7.48 (5, m); ^{13}C NMR ppm, $\delta = 127.4$, 126.0, 127.9, 140.4, 136.8, 127.5, 129.4, 170.4, 129.6, 148.7, 116.5, 121.2, 121.8, 125.1; IR (KBr): $\nu = 1770$, 1670, 1520, 1200, 1130, 750, 700, 3350, 1330, 1150, 1520, 1320 cm^{-1}; UV-vis (ethanol) $\lambda_{max} = 205$, 265 nm; MS (70 eV): molecular formula, m/z (% relative abundance): $C_{16}H_{10}N_2O_4$, 294, 277, 251 (100), 205 (52), 137 (3), 105 (21), 91 (3), 179 (6), 89 (6), 77 (19), 51 (10).

2-Phenyl quinoline-4,6-dicarboxylic acid (12, $C_{17}H_{11}NO_4$). Yield = 68%; mp = 304–306 °C (lit. 305 °C[10]); ^{1}H NMR ppm, $\delta = 7.70$ (1, d), 7.89 (1, d), 10.01 (1, s), 7.89 (1, s), 12.89 (1, s), 8.30 (1, s), 7.40–7.60 (5, m); ^{13}C NMR ppm, $\delta = 129.5$, 130.0, 130.6, 141.4, 129.7, 129.6, 131.4, 167.3, 131.5, 146.6, 116.4, 120.9, 123.4, 127.3, 167.7; IR (KBr): $\nu = 1700$, 1600, 1420, 1540, 1190, 1220, 850, 780, 3320, 1380, 1120 cm^{-1}; UV-vis (ethanol) $\lambda_{max} = 205$, 255 nm; MS (70 eV): molecular formula, m/z (% relative abundance): $C_{17}H_{11}NO_4$, 293 (100), 276 (7), 249 (61), 204 (37), 220 (5), 176 (7), 89 (12), 77 (13), 51 (9).

2-Phenyl quinoline-4-carboxylic acid (13, $C_{16}H_{11}NO_2$). Yield = 51%; mp = 209–210; ^{1}H NMR $\delta = 8.67$ (1, d), 8.13–8.35 (3, m), 14.02 (1, s), 8.47 (1, s), 7.53–7.90 (5, m); ^{13}C NMR ppm, $\delta = 138.2$, 130.2, 130.5, 130.8, 129.5, 128.3, 138.2, 168.2, 138.5, 148.9, 119.7, 127.8, 124.1, 125.9; IR (KBr): $\nu = 1680$, 1600, 1230, 1210, 2820, 760, 720, 1350 cm^{-1}; UV-vis (ethanol) $\lambda_{max} = 205$, 265 nm; MS (70 eV): molecular formula, m/z (% relative abundance): $C_{16}H_{11}NO_2$, 249 (100), 232, 204 (81), 176 (10), 88 (5), 77 (4), 51 (13).

Preparation of Methyl-2-phenylquinoline-4-carboxylate (14, $C_{17}H_{13}NO_2$) and Methyl-2,3-diphenylquinoline-4-carboxylate (15, $C_{23}H_{17}NO_2$)

2-Phenylquinoline-4-carboxylic acid (**13**) or 2,3-diphenylquinoline-4-carboxylic acid (**1**) (0.3 mol), methanol (10 ml), and concentrated sulfuric acid (1 ml) were refluxed for 2 h and cooled to room temperature. Sodium carbonate solution was added to the mixture and left to stand for 1 h. Pale yellow crystals were collected and washed with distilled water. Compound **14**: Yield = 50%; mp = 58–59 °C;

^{1}H NMR ppm, δ = 8.18–8.57 (4, m), 4.02 (3, s), 8.48 (1, s), 7.50–7.87 (5, m); ^{13}C NMR ppm, δ = 128.6, 130.4, 130.7, 130.9, 148.9, 129.6, 156.9, 166.9, 138.3, 136.1, 119.9, 123.7, 125.7, 127.8, 53.5; IR (KBr): ν = 1720, 1570, 1450, 1420, 1530, 1190, 1230, 1320, 2960, 780, 690 cm^{-1}; UV-vis (ethanol) λ_{max} = 215, 265 nm; MS (70 eV): molecular formula, *m/z* (% relative abundance): $C_{17}H_{13}NO_2$, 263 (29), 232 (3), 205 (72), 176 (8), 89 (5), 77 (8), 51 (14). Compound **15**: Yield = 33%; mp = 215–216 °C; ^{1}H NMR ppm, δ = 8.16–8.57 (4, m), 4.02 (3, s), 7.53–7.88 (10, m); ^{13}C NMR ppm, δ = 130.0, 130.4, 130.6, 130.9, 131.0, 136.8, 156.3, 166.8, 138.2, 148.8, 119.9, 123.6, 125.6, 126.0, 127.7, 128.5, 129.5, 129.9, 53.5; IR (KBr): ν = 1720, 1570, 1450, 1530, 1120, 1230, 1320, 2960, 780, 690 cm^{-1}; UV-vis (ethanol) λ_{max} = 255 nm; MS (70 eV): molecular formula, *m/z* (% relative abundance): $C_{23}H_{17}NO_2$, 339, 205 (97), 263 (100), 176 (8), 88 (4), 75 (5), 51 (9).

Preparation of 2,3-Diarylquinoline-4-carboxamide (16–18)

A mixture of 2,3-diphenylquinoline-4-carboxylic acid (**1**) (1.0 g, 0.003 mol), chloroform (25 ml), and thionyl chloride (0.004 mol) were placed. The mixture was stirred by magnetic stirrer for 30 min. The required amine (0.004 mol) was added immediately with continuous stirring. Clear crystals occurred.The product was allowed to stand for several hours, filtered, and dried in air.

Selected Data

2,3-Diarylquinoline-4-carboxamide (16, $C_{22}H_{16}N_2O$). Yield = 55%; mp = 240–242 °C; ^{1}H NMR ppm, δ = 7.64–7.74 (4, m), 6.54 (2, s), 7.03–7.19 (5, m), 7.27–7.38 (5, m); ^{13}C NMR ppm, δ = 130.0, 128.7, 129.0, 129.1, 132.1, 131.8, 137.4, 165.9, 138.1, 143.5, 122.4, 123.0, 125.0, 126.3, 127.8, 127.8, 128.2, 128.4; IR (KBr): ν = 1680, 1600, 1430, 1510, 1200, 1220, 3050, 790, 700, 1320, 3200 cm^{-1}; UV-vis (ethanol) λ_{max} = 215, 260 nm; MS (70 eV): molecular formula, *m/z* (% relative abundance): $C_{22}H_{16}N_2O$, 324, 282 (2), 207 (43), 179 (100), 89 (6), 77 (36), 51 (10).

N-Phenyl-2,3-diarylquinoline-4-carboxamide (17, $C_{28}H_{20}N_2O$). Yield = 75%; mp = 185–186 °C; ^{1}H NMR ppm, δ = 7.46–7.50 (4, m), 6.55 (1, s), 7.38–7.40 (5, m), 7.15–7.18 (5, m), 7.27–7.31 (5, m); IR (KBr): ν = 1770, 1600, 1470, 1520, 1500, 1100, 1190, 2900, 740, 1320, 3200, 1570 cm^{-1}; UV-vis (ethanol) λ_{max} = 205, 265 nm; MS (70 eV): molecular formula, *m/z* (% relative abundance): $C_{28}H_{20}N_2O$, 400, 282 (4), 207 (47), 179 (100), 89 (4), 77 (25), 51 (10).

N-Methyl-2,3-diarylquinoline-4-carboxamide (18, $C_{23}H_{18}N_2O$). Yield = 66%; mp = 240–242 °C; ^{1}H NMR ppm, δ = 7.66–7.84 (4, m), 6.19 (1, s), 2.39 (3, s), 7.02–7.17 (5, m), 7.23–7.39 (5, m); ^{13}C NMR ppm, δ = 129.6, 128.2, 128.3, 128.6, 128.8, 135.0, 135.5, 169.7, 138.3, 140.6, 122.0, 124.2, 124.5, 126.4, 127.7, 128.1, 128.2, 25.81; IR (KBr): ν = 1680, 1600, 1450, 1500, 1260, 1170, 3060, 760, 690, 1380, 3060 cm^{-1}; UV-vis (ethanol) λ_{max} = 205, 265 nm; MS (70 eV): molecular formula, *m/z* (% relative abundance): $C_{23}H_{18}N_2O$, 338, 282 (4), 207 (29), 179 (100), 89 (2), 77 (16), 51 (6).

Antibacterial Activity

The standard microbiological two-layer agar diffusion technique was adopted with some modification. Nutrient agar (Oxoid), which was used as the culture medium, was reconstituted, sterilized at 121 °C for 15 min, and distributed in 15-ml aliquots into sterile Petri dishes and allowed to set forming the base layer. The organisms (*B. subtilis*, *S. aureus*, *E. coli*, and *P. vulgaris*) were grown in nutrient broth (Oxoid) at 37 °C for 18 h. Each bacterial culture was used to introduce to inoculate the agar media. The inoculated medium (1×108 cell per ml) was distributed in 10-ml portions onto the surface of the base layer evenly. Five cups $\times$ 5 mm in diameter were cut out using sterile cork borer. Each solution (0.2 ml, 1 mg/ml) of the test compound in propylene glycol (PRG) was added to these cups and allowed to diffuse at room temperature. The plates were incubated at 37 °C for 18 h. The mean diameters of the inhibition zones were tabulated in Table 1.

REFERENCES

1. Ko, T. C.; Hour, M. J.; Leien, J. Synthesis of 4-alkoxy-2-phnoel aniline derivatives as potent antiplatelet agents. *Bio. Org. Med. Chem. Lett.* **2001**, *11*, 279–282.
2. Baba, M.; Makino, T.; Kimura, Y.; Ikeuchi, T.; Sakaguchi, T.; Okamoto, T. Potent and selective inhibition of human immunodeficiency virus type I transcription by piperazinyloroquinoline derivatives. *Antimicrob. Agents Chemother.* **1997**, *41*, 1250–1255.
3. Strigacova, J.; Hudecova, D.; Varecka, L.; Lasikova, A.; Vegh, D. Some biological properties of new quinoline-4-carboxylic acid derivatives. *Folia Microbiol. (Praha)* **2000**, *45*, 305–309.
4. Matsuoka, M.; Seowa, J.; Amimoto, I.; Masdui, Y.; Tomii, Y.; Kitano, M.; Kise, M. Synthesis and antibacterial activity of novel 7-substituted-6-fluro-1-fluoromethyl-4-oxo-44-[1,3-thiazeto[3,2-a]-quinoline-3-carboxylic derivatives. *Chem. Pharm. Bull.* **1999**, *47*, 1765–1773.
5. Uchida, M.; Matsubara, J.; Ohtani, T.; Morita, S.; Yamasaki, K. Synthesis of 4-(phenyl-amino)-quinoline-3-carboxamides as a novel class of gastric H+/k+-ATpase inhibitors. *Chem. Pharm. Bull.* **1995**, *43*, 693–698.
6. Ozaki, M.; Segawa, J.; Kitano, M.; Tomii, Y.; Honmuura, T.; Matsuda, M.; Kise, M.; Nishino, T. Structure–antibacterial activity and cytotoxicity relationships of thiazo-10 and thiazetoquinoline derivatives. *Biol. Pharm. Bull.* **1996**, *19*, 1457–1462.
7. Lackey, K.; Sternbach, D. D. Synthesis of substituted quinoline-4-carboxylic acids. *Synthesis* **1993**, 993–997.
8. Duvelleroy, D.; Perrio, C.; Parisel, O.; Lasne, M. C. Rapid synthesis of quinoline-4-carboxylic acid derivatives from aryl imines and 2-substituted acrylates or acryl amides under indium(III) chloride and microwave activation: Scope and limitations of the reaction. *Org. Biomol. Chem.* **2005**, *3*, 3794–3804.
9. Waring, M. J.; Hadda, T. B.; Kotchevar, A. T.; Ramdani, A.; Touzani, R.; Elkadiri, S.; Hakkou, A.; Bouakka, M.; Ellis, T. 2,3-Bifunctionalized quinoxalines: Synthesis, DNA interactions, and evaluation of anticancer, antituberculosis, and antifungal activity. *Molecules* **2007**, *7*, 641–656.
10. Di Fonzo, M.; Saracini, C. 2-Phenyl-quinoline-4-6-dicarboxylic acid. *Farmaco Sci.* **1956**, *11*, 221–227.