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Synthesis and antimicrobial evaluation of substituted benzimidazolyl fluoroquinolones under conventional and microwave irradiation conditions

Abstract: New ciprofloxacin analogs **3a–i** were prepared using a conventional methodology and with the help of a microwave irradiation technique. The structures of the synthesized compounds were established on the basis of spectral and analytical data. The antimicrobial activities of newly synthesized compounds were evaluated against a number of microorganisms by using ciprofloxacin as reference. Many of the evaluated compounds exhibit remarkable activities against Gram positive organisms such as *Staphylococcus aureus, Streptococci, Bacillus* spp., Gram negative organisms such as *Escherichia coli, Klebsiella Pneumoniae, Pseudomonas aeruginosa, Salmonella* spp., *Salmonella typhi* and antifungal activity against *Candida albicans*. Among these, compounds **3a, 3b** and **3i** exhibit excellent antibacterial activity and products **3c** and **3f** show very good antifungal activity.

Keywords: antimicrobial activity; fluoroquinolones; microwave irradiation; 5-substituted 2-piperidino-1*H*-benzo[*d*]imidazole pharmacophore.

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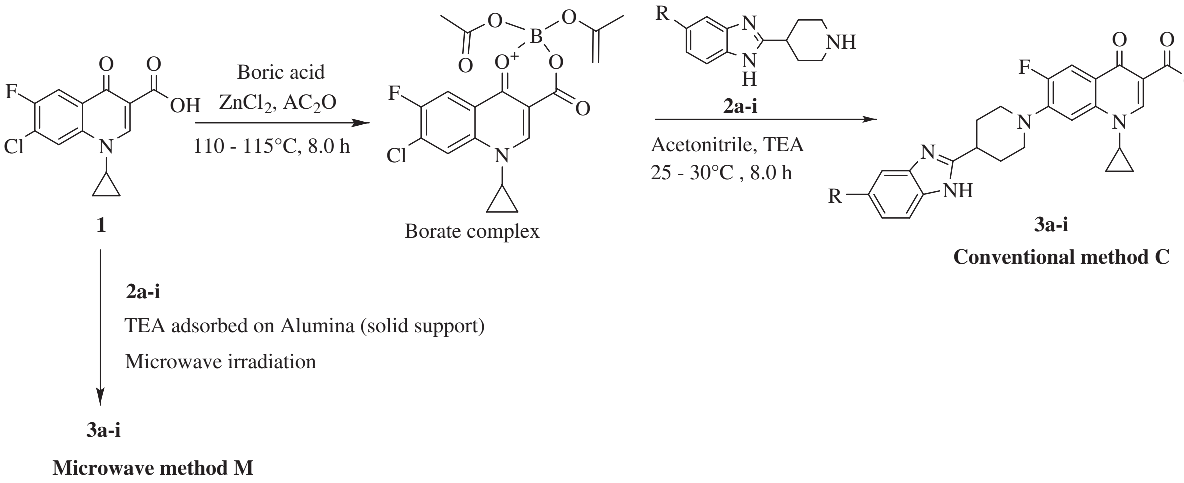
Introduction

Fluoroquinolones have gained importance due to their potent antibacterial activity against wide varieties of Gram positive and Gram negative bacteria with minimum toxic side effects (Renau et al., 1995, 1996; Mascellino et al., 1998). Fluoroquinolones are broad-spectrum antibiotics (Hooper, 1998). They exhibit various pharmacological properties such as antimicrobial (Hurst et al., 2002), anti-inflammatory (Espinosa and Muñoz de la Peña, 2005), analgesic (Bar-Oz et al., 2003) and antiviral activities (Masahiko et al., 1999). Fluoroquinolones have also been incorporated in a wide variety of therapeutically interesting antibacterial drugs such as ciprofloxacin, levofloxacin and moxifloxacin. By contrast, heterocyclic compounds substituted with benzimidazoles are a promising class of bioactive compounds that exhibit a wide range of medicinal uses. These include anticancer (Meena, 2012), antimicrobial (Parmender et al., 2011), antiviral (Barbara et al., 2004) and antifungal (John et al., 1998) activity. A survey of the literature indicates that substitution and chemical manipulation at position 7 of fluoroquinolone ring system provides potent antibacterial agents with enhanced biological activities. The pharmacological importance of both fluoroquinolones and 4-benzimidazolylpiperazino moiety prompted us to synthesize a series of novel fluoroquinolone derivatives containing a substituted benzimidazole moiety. Herein, we report facile synthesis of compounds **3a–I** employing conventional and microwave methods.

Results and discussion

Synthesis

7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**1**) was allowed to react with boric acid and acetic anhydride in the presence of a catalytic amount of zinc chloride to yield an unstable borate complex. Hence, a solution of the complex in acetonitrile was immediately treated with 5-substituted 2-piperidino-1*H*-benzo[*d*] imidazoles **2a–i** (Guruswamy and Arul, 2011) in the presence of triethylamine to give products **3a–i** with acceptable yield and quality (Scheme 1). To avoid the use of acetic anhydride and the synthesis of unstable borate complex, the same compounds were alternatively synthesized using a microwave irradiation technique in the presence of a catalytic amount of



3a: R = H; **3b**: R = CH_3; **3c**: R = F; **3d**: R = Cl; **3e**: R = Br; **3f**: R = CF_3; **3g**: R = CN; **3h**: R = NH_2; **3i**: R = OCH_3.

Scheme 1 Synthesis of compound **3a–i** by conventional method C and microwave method M.

triethylamine adsorbed on alumina solid support. The microwave assisted method gave surprisingly excellent yields (72–90%) of products **3a–i**. The compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral techniques.

Biological activity

All compounds **3a–i** were screened for their antibacterial activity *in vitro* against three Gram positive organisms, namely *Staphylococcus aureus, Streptococci* and *Bacillus* spp., five Gram negative organisms including *Escherichia coli, Klebsiella Pneumoniae, Pseudomonas aeruginosa, Salmonella* spp. and *Salmonella typhi*, and antifungal activity against *Candida albicans* by using ciprofloxacin as reference. Biological activities of these compounds were tested using the agar well diffusion method. Bacteria inoculums (2–8 h old) containing approximately 105–110 colony forming units (CFU/mL) were spared on the surface in agar with the help of sterile cotton swab. A solution of the test compound in DMSO (4 mg/mL) was added to the wells. The plate was incubated immediately at 38°C for 24 h. Antibacterial activity was determined by measuring the diameter of zones showing complete inhibition (mm). The results are shown in Table 1.

S. no.	Compound	Zone of inhibition in mm								
		Gram positive sp.			Gram negative sp.					Fungus sp.
		Sa	*St*	*Bs*	*Ec*	*Kp*	*Pa*	*Ss*	*S*	*Ca*
1	**3a**	18	22	24	–	27	52	32	33	36
2	**3b**	22	32	40	24	23	44	16	23	31
3	**3c**	7	9	38	27	30	41	38	35	33
4	**3d**	10	14	19	12	28	35	29	30	28
5	**3e**	18	17.5	18	23	19	14	41.5	43	12
6	**3f**	12	28	20	24	17	14	45	29	36
7	**3g**	26	12	32	22	19	29	34	30	18
8	**3h**	39	34	27.5	29	22	28	37	40	18
9	**3i**	19	16	30	27	33.5	48	33	29	–
10	**Ciprofloxacin(reference)**	8	15	18	13	32	35	28	30	12

Table 1 Antimicrobial activity of compounds **3a–i**.
Sa, Staphylococcus aureus; St, Streptococci; Bs, Bacillus spp.; *Ec, Escherichia coli; Kp, Klebsiella pneumoniae; Pa, Pseudomonas aeruginosa; Ss, Salmonella* spp.; *S, Salmonella typhi; Ca, Candida albicans*.

All compounds **3a–i** were also screened for their antifungal activity *in vitro* against *Candida albicans* and the results were compared with the activity of ciprofloxacin (Table 1). The methodology was similar to that described above.

Conclusion

Compounds **3a–i** were synthesized by green and environmentally benign methodology with the help of a microwave irradiation technique and tested for biological activity. Compounds, **3a, 3b** and **3i** exhibit excellent antibacterial activity and **3c** and **3f** show very good antifungal activity.

Experimental section

Melting points are not corrected. Thin layer chromatography (TLC) was carried out on aluminum sheets coated with silica gel 60 F254 (Merck). IR spectra were recorded on a Perkin-Elmer-1700 spectrophotometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were taken in DMSO-d_6 at 300 MHz and 75 MHz, respectively. Electrospray ionization mass spectra (ES-MS) were recorded on an Avarian 300-MS spectrometer. Microwave reactions were performed using a MARS 240/50 instrument, model no. 907510.

Procedure for adsorption of triethylamine on alumina (Al_2O_3)

A mixture of diethyl ether (200.0 mL), triethylamine (50.0 g) and alumina (50.0 g) was stirred for 30 min at 25–30°C. Then diethyl ether was removed under a reduced pressure and the residue was additionally kept under a reduced pressure at 55–60°C to give 71.3 g of free flowing solid with a 27% triethylamine content.

General preparation of compounds 3a–i

Conventional method C A mixture of acetic anhydride (25.0 mL), zinc chloride (0.125 g, 5 mol%) and boric acid (1.36 g, 22.1 mmol) was stirred at room temperature for 15 min. Then, compound **1** (5.0 g, 17.75 mmol) was added and the mixture was stirred and heated to 110–115°C for 8 h. After cooling to 50–60°C the excess of acetic anhydride was removed under a reduced pressure. The resultant borate complex was immediately dissolved in acetonitrile (25.0 mL) and the solution was treated with compound **2a–i** (26.5 mmol) and triethylamine (53.1 mmol). The mixture was stirred at room temperature for 8 h, as monitored by TLC, then poured into crushed ice and treated with diluted hydrochloric acid to pH below 2.0. The precipitated product **3a–i** was filtered, washed with water, dried and crystallized from methanol.

Microwave method M A mixture of compounds **1** (2.5 g, 8.8 mmol) and **2a–i** (10.6 mmol) was treated with triethylamine adsorbed on alumina (10 mol%) and transferred into a microwave vial. The vial was sealed and placed in a microwave oven. The reaction was run at 100°C for 5 min. For the entire experiment, the power setting was held at 100 W. The mixture was cooled to room temperature and subjected to silica gel column chromatography eluting with methanol/dichloromethane (90:10). Product **3a–i** was crystallized from methanol.

7-(4-(1*H*-Benzo[*d*]imidazol-2-yl)piperidino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3a) Off-white powder; yield 74% (method C) and 86% (method M); mp 266–268°C (dec); IR: 3319, 3046, 1719, 1622, 1517, 1461, 1393, 1231, 1057 cm^{-1}; ^{1}H NMR: δ 14.93 (s, 1H, exchangeable with D_2O), 8.66 (s, 1H), 7.90 (m, 1H), 7.78 (m, 2H), 7.62 (m, 1H), 7.51 (m, 2H), 5.74 (s, 1H), 3.56 (m, 3H), 3.49 (m, 1H), 3.13 (m, 2H), 2.30 (m, 2H), 2.12 (m, 2H), 1.26 (m, 2H), 1.20 (m, 2H); ^{13}C NMR: δ 179.4, 168.2, 147.0, 146.6, 145.9, 143.5, 142.5, 139.9, 137.6, 125.0, 124.0, 119.0, 117.4, 115.2, 114.2, 110.3, 103.0, 51.7, 50.7, 37.0, 36.6, 30.9, 29.3, 5.8, 5.6; MS: m/z 447.1 [M]$^+$. Anal. Calcd for $C_{25}H_{23}FN_4O_3$: C, 67.25; H, 5.19; N, 12.55. Found: C, 67.08; H, 4.99; N, 12.35.

1-Cyclopropyl-6-fluoro-7-(4-(5-methyl-1*H*-benzo[*d*]imidazole-2-yl)piperidino)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3b) Off-white powder; yield 65% (method C) and 80% (method M); mp 236–238°C (dec); IR: 3315, 3086, 1726, 1612, 1519, 1455, 1389, 1221, 1047 cm^{-1}; ^{1}H NMR: δ 14.93 (s, 1H exchangeable with D_2O), 8.66 (s, 1H), 7.90 (m, 1H), 7.78 (m, 2H), 7.62 (m, 1H), 7.51 (m, 1H), 5.74 (s, 1H), 3.56 (m, 3H), 3.49 (m, 1H), 3.13 (m, 2H), 2.30 (m, 2H), 2.12 (m, 2H), 2.10 (m, 3H), 1.26 (m, 2H), 1.20 (m, 2H); ^{13}C NMR: δ 179.4, 168.2, 147.0, 146.6, 145.9, 143.5, 142.5, 139.9, 137.6, 125.0, 124.0, 119.0, 117.4, 115.2, 114.2, 110.3, 103.0, 51.7, 50.7, 37.0, 36.6, 30.9, 29.3, 24.8, 5.8, 5.6; MS: m/z 461.3 [M]$^+$. Anal. Calcd for $C_{25}H_{25}FN_4O_3$: C, 67.68; H, 5.39; N, 12.38. Found: C, 67.81; H, 5.47; N, 12.17.

1-Cyclopropyl-6-fluoro-7-(4-(5-fluoro-1*H*-benzo[*d*]imidazol-2-yl)piperidino)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3c) Off-white powder; yield 72% (method C) and 86% (method M); mp 246–249°C (dec); IR: 3320, 3026, 1718, 1620, 1515, 1465, 1397, 1235, 1059 cm^{-1}; ^{1}H NMR: δ 14.67 (s, 1H, exchangeable with D_2O), 8.69 (s, 1H), 7.72 (m, 1H), 7.65 (m, 2H), 7.59 (m, 1H), 7.48 (m, 1H), 5.44 (s, 1H), 3.78, (m, 3H), 3.49 (m, 1H), 3.19 (m, 2H), 2.31 (m, 2H), 2.17 (m, 2H), 1.36 (m, 2H), 1.25 (m, 2H); ^{13}C NMR: δ 176.2, 165.2, 149.0, 147.6, 146.9, 145.5, 144.5, 142.9, 140.6, 129.0, 127.0, 125.0, 117.4, 116.2, 114.2, 113.3, 108.0, 55.7, 52.7, 40.0, 39.6, 37.9, 27.5, 8.8, 8.6; MS: m/z 465.1 [M]$^+$. Anal. Calcd for $C_{25}H_{22}F_2N_4O_3$: C, 64.65; H, 4.77; N, 12.06. Found: C, 64.28; H, 4.99; N, 12.35.

7-(4-(5-Chloro-1*H*-benzo[*d*]imidazol-2-yl)piperidino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3d) Off-white powder; yield 72% (method C) and 78% (method M); mp 232–235°C (dec); IR: 3240, 3196, 1738, 1620, 1565, 1470, 1377, 1255, 1099 cm^{-1}; ^{1}H NMR: δ 14.77 (s, 1H, exchangeable with D_2O), 8.61 (s, 1H), 7.92 (m, 1H), 7.85 (m, 2H), 7.69 (m, 1H), 7.58 (m, 1H), 5.64 (s, 1H), 3.58 (m, 3H), 3.51 (m, 1H), 3.10 (m, 2H), 2.33 (m, 2H), 2.15 (m, 2H), 1.28 (m, 2H), 1.23 (m, 2H); ^{13}C NMR: δ 178.4, 167.2, 145.0, 148.6, 145.9, 144.5, 143.5, 140.9, 139.6, 127.0, 125.0, 121.0, 119.4, 117.2, 115.2, 112.3, 106.0, 53.7, 51.7, 39.0, 37.6, 30.9, 29.5, 6.8, 6.6; MS: m/z 481.2 [M]$^+$. Anal. Calcd for $C_{25}H_{22}ClFN_4O_3$: C, 62.44; H, 4.61; N, 11.65. Found: C, 62.28; H, 4.59; N, 12.01.

7-(4-(5-Bromo-1*H*-benzo[*d*]imidazol-2-yl)piperidino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3e) Light brown powder; yield 54% (method C) and 67% (method M); mp 217–218°C (dec); IR: 3319, 3046, 1719, 1622, 1517, 1461, 1393, 1231, 1057 cm^{-1}; ^{1}H NMR: δ 14.93 (s, 1H, exchangeable with D_2O), 8.86 (s, 1H), 7.97–7.92 (m, 1H), 7.81–7.79 (m, 1H), 7.72–7.75 (m, 1H), 7.60–7.64 (m, 2H), 5.84 (s, 1H), 3.56–3.92, (m, 3H), 3.52–3.59 (m, 1H), 3.23–3.19 (m, 2H), 2.97–2.89 (m, 2H), 2.32–2.29 (m, 2H), 1.29–1.35 (m, 2H), 1.22–1.27 (m, 2H); ^{13}C NMR: δ 176.2, 165.2, 149.0, 147.6, 146.9, 145.5, 144.5, 142.9, 140.6, 129.0, 127.0, 125.0, 117.4, 116.2, 114.2, 113.3, 108.0, 55.7, 52.7, 40.0, 39.6, 37.9, 27.5, 8.8, 8.6; MS: m/z 525.1 [M]$^+$. Anal. Calcd for $C_{25}H_{22}BrFN_4O_3$: C, 57.15; H, 4.22; N, 10.66. Found: C, 57.28; H, 4.59; N, 10.01.

1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(5-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)piperidino)-1,4-dihydroquinoline-3-carboxylic acid (3f) Light brown powder; yield 58% (method C) and 69% (method M); mp 202–205°C (dec); IR: 3319, 3046, 1719, 1622, 1517, 1461, 1393, 1231, 1057 cm^{-1}; ^{1}H NMR: δ 14.93 (s, 1H, exchangeable with D_2O), 8.66 (s, 1H), 7.92 (m, 1H), 7.78 (m, 1H), 7.62 (m, 1H), 7.51 (m, 2H), 5.74 (s, 1H), 3.56, (m, 3H), 3.49 (m, 1H), 3.13 (m, 2H), 2.30 (m, 2H), 2.12 (m, 2H), 1.26 (m, 2H), 1.20 (m, 2H); ^{13}C NMR: δ 176.2, 165.2, 149.0, 147.6, 146.9, 145.5, 144.5, 142.9, 140.6, 129.0, 127.0, 125.0, 120, 117.4, 116.2, 114.2, 113.3, 108.0, 55.7, 52.7, 40.0, 39.6, 37.9, 27.5, 8.8, 8.6; MS: m/z 515.1 [M]$^+$. Anal. Calcd for $C_{26}H_{22}F_4N_4O_3$: C, 60.70; H, 4.31; N, 10.89. Found: C, 59.98; H, 4.68; N, 11.01.

7-(4-(5-Cyano-1*H*-benzo[*d*]imidazol-2-yl)piperidino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3g) Off-white powder; yield 54% (method C) and 63% (method M); mp 236–238°C (dec); IR: 3359, 3089, 2200, 1721, 1629, 1527, 1469, 1373, 1251, 1077 cm^{-1}; ^{1}H NMR: δ 14.93 (s, 1H, exchangeable with D_2O), 8.66 (s, 1H), 7.90–7.94 (m, 1H), 7.78–7.81 (m, 1H), 7.62–7.65 (m, 1H), 7.51–7.54 (m, 2H), 5.74 (s, 1H), 3.56–3.92, (m, 3H), 3.49–3.53 (m, 1H), 3.13–3.20 (m, 2H), 2.30–2.34 (m, 2H), 2.12–2.20 (m, 2H), 1.26–1.33 (m, 2H), 1.20–1.25 (m, 2H); ^{13}C NMR: δ 16.2, 165.2, 149.0, 147.6, 146.9, 145.5, 144.5, 142.9, 140.6, 129.0, 127.0, 125.0, 117.4, 116.2, 114.2, 113.3, 118, 108.0, 55.7, 52.7, 40.0, 39.6, 37.9, 27.5, 8.8, 8.6; MS: m/z 472.1 [M]$^+$. Anal. Calcd for $C_{26}H_{22}FN_5O_3$: C, 66.23; H, 4.70; N, 14.85. Found: C, 66.48; H, 4.68; N, 14.01.

7-(4-(5-Amino-1*H*-benzo[*d*]imidazol-2-yl)piperidino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3h) Pale yellow powder; yield 63% (method C) and 52% (method M); mp 278–281°C (dec); IR: 3349, 3079, 1816, 1723, 1635, 1527, 1469, 1373, 1251, 1077 cm^{-1}; ^{1}H NMR: δ 14.93 (s, 1H, exchangeable with D_2O), 8.66 (s, 1H), 7.90 (m, 1H), 7.78 (m, 1H), 7.62 (m, 1H), 7.51 (m, 2H), 5.91 (m, 1H), 5.74 (s, 1H), 3.94 (s, 2H), 3.56 (m, 2H), 3.49 (m, 1H), 3.13 (m, 2H), 2.30 (m, 2H), 2.12 (m, 2H), 1.26 (m, 2H), 1.20 (m, 2H); ^{13}C NMR: δ 16.2, 165.2, 149.0, 147.6, 146.9, 145.5, 144.5, 142.9, 140.6, 129.0, 127.0, 125.0, 117.4, 116.2, 114.2, 113.3, 118, 108.0, 55.7, 52.7, 40.0, 39.6, 37.9, 27.5, 8.8, 8.6; MS: m/z 462.1 [M]$^+$. Anal. Calcd for $C_{25}H_{24}FN_5O_3$: C, 64.95; H, 3.92; N, 14.88. Found: C, 65.07; H, 5.04; N, 15.18.

1-Cyclopropyl-6-fluoro-7-(4-(5-methoxy-1*H*-benzo[d]imidazol-2-yl)piperidino)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3i) Off-white powder; yield 71% (method C) and 85% (method M); mp 277–280°C (dec); IR: 3349, 3079, 1816, 1723, 1635, 1527, 1469, 1373, 1251, 1077 cm^{-1}; ^{1}H NMR: δ 14.93 (s, 1H, exchangeable with D_2O), 8.66 (s, 1H), 7.90–7.94 (m, 1H), 7.78–7.81 (m, 1H), 7.62–7.65 (m, 1H), 7.51–7.54 (m, 2H), 5.74 (s, 1H), 3.56–3.92, (m, 3H), 3.49–3.53 (m, 1H), 3.33 (s, 3H), 3.13–3.20 (m, 2H), 2.30–2.34 (m, 2H), 2.12–2.20 (m, 2H), 1.26–1.33 (m, 2H), 1.20–1.25 (m, 2H); ^{13}C NMR: δ 176.2, 165.2, 149.0, 147.6, 146.9, 145.5, 144.5, 142.9, 140.6, 129.0, 127.0, 125.0, 120, 117.4, 116.2, 114.2, 113.3, 108.0, 55.7, 52.7, 40.0, 39.6, 37.9, 27.5, 8.8, 8.6; MS: m/z 477.1 [M]$^+$. Anal. Calcd for $C_{26}H_{25}FN_4O_4$: C, 65.54; H, 5.29; N, 11.76. Found: C, 65.18; H, 4.98; N, 11.01.

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