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Conventional and Microwave-Assisted Synthesis of Quinolone Carboxylic Acid Derivatives[1]

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Abstract—Various antibacterial fluoroquinolone compounds are synthesized by the direct amination of 7-halo-6-fluoroquinolone-3-carboxylic acids with a variety of piperazine derivatives and (4aR,7aR)-octahydro-1*H*-pyrrolo[3,4-*b*]pyridine using microwave under different reaction conditions. Solvent free high yield microwave synthesis of antibacterial fluoroquinolone compounds is convenient, rapid and environmentally friendly method.

Keywords: synthesis, rapid amination, antibacterial fluoroquinolone compounds, microwave irradiation, solvent free reaction, enrofloxacin

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INTRODUCTION

Fluoroquinolones compose the class of synthetic antibacterial agents widely used for treatment of infectious diseases [1, 2]. These compounds exhibit high activity against gram-negative and comparatively moderate activity against gram-positive bacteria. Mechanism of their action is based on inhibition of an enzyme essential for bacterial DNA replication called DNA gyrase [3]. Some fluoroquinolones demonstrate anticancer and anti-HIV activities [4–6].

Unfortunately fluoroquinolones exhibited some characteristic side effects. Therefore structure modifica-tion of the fluoroquinolone skeleton became an objective of synthesis of their new efficient derivatives for prevention of hospital-acquired infections induced by fluroquinolone-resistant pathogens [7–9] and other sides of biological activity [10–13].

Herein we present a facile and high yield synthesis of fluoroquinolone antibacterials by two-component condensation of a variety amines and some 7-halo-6-fluoro-quinolone-3-carboxylic acids under microwave irradiation.

RESULTS AND DISCUSSION

Fluoroquinolones were prepared by the direct amination of 7-halo-6-fluoroquinolone-3-carboxylic acids **1a–1d** with (4aR,7aR)-octahydro-1*H*-pyrrolo[3,4-*b*]-pyridine and piperazine derivatives **2a–2d** under heating in an oil bath or microwave irradiation (Scheme 1). Synthesis of enrofloxacin **3c** by the two-component reaction of the acid **1a** (1 mmol) and *N*-ethyl piperazine **2c** (1.5 mmol) was selected as a model process for optimization of the reaction conditions (Tables 1 and 2). On the basis of accumulated data microwave irradiation under solvent-free condition demonstrated the highest efficiency.

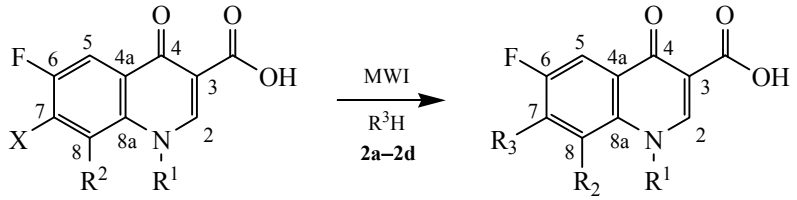
According to the above data reactions of **1a–1d** with a range of amines **2a–2d** under the optimized conditions were carried out. Condensation of **1a–1d** and **2a–2d** gave the products **3** in high yields over relatively short reaction time under microwave irradiation. Purity of all products was higher than 93% (HPLC). Melting points of the products **3** were close to those reported earlier [14–21] and their structures were confirmed by FT-IR, ^{1}H and ^{13}C NMR spectra.

EXPERIMENTAL

All analytical grade chemicals were obtained from Sigma-Aldrich and used without further purification. Melting points were determined on a Stuart SMP3 melting point apparatus. FT-IR spectra were recorded for KBr disks on a Tensor 27 Bruker spectrophoto-meter. ^{1}H NMR spectra were measured on a Bruker 300 spectrometers (DMSO-d_6). Microwave irradiation was carried out in a MicroSYNTH, Milestone srl reactor, 800 W.

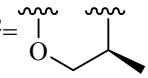
[1] The text was submitted by the authors in English.

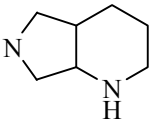
Scheme 1. Microwave-assisted synthesis of antibacterial fluoroquinolones.



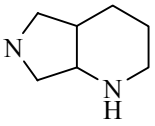
1a–1d **3a–3k**

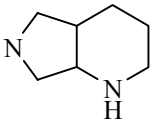
1: X = Cl, R^1 = cyclopropyl, R^2 = H (**a**), X = F, R^1 = cyclopropyl, R^2 = OCH_3 (**b**), X = F, R^1 = R^2= $CH(CH_3)CH_2O$ (**c**),

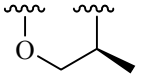
X = F, R^1 = R^2=  (**d**).

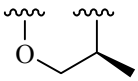
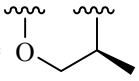
2: R^3 = piperazinyl (**a**), R^3 = 4-methylpiperazin-1-yl (**b**), R^3 = 4-ethylpiperazin-1-yl (**c**), R^3 =  (**d**).

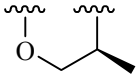
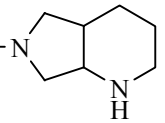
3: R^1 = cyclopropyl, R^2 = H, R^3 = piperazinyl (**a**), R^1 = cyclopropyl, R^2 = H, R^3 = 4-methylpiperazin-1-yl (**b**),

R^1 = cyclopropyl, R^2 = H, R^3 = 4-ethylpiperazin-1-yl (**c**), R^1 = cyclopropyl, R^2 =H, R^3 =  (**d**),

R^1 = cyclopropyl, R^2 = OCH_3, R^3 =  (**e**), R^1 = R^2 = $CH(CH_3)CH_2O$ R^3 = piperazinyl (**f**),

R^1 = R^2 = $CH(CH_3)CH_2O$, R^3 = 4-methylpiperazin-1-yl (**g**), R^1 = R^2 =  , R^3 = piperazinyl (**h**), R^1 = R^2 =

 , R^3 = 4-methylpiperazin-1-yl (**i**), R^1 = R^2 =  ,

R^3 = 4-ethylpiperazin-1-yl (**j**), R^1 = R^2 =  , R^3 =  (**k**).

Typical experimental procedure. A mixture of 6-chloro-4-cyclopropyl-7-fluoro-1-oxo-1,4-dihydronaphthalene-2-carboxylic acid **1a** (1 g, 3.5 mmol) with *N*-ethylpiperazine **2c** (0.6 g, 5.25mmol) was loaded in a small flask fitted with a micro condenser, placed in the microwave reactor and irradiated for 25 min at 150°C under solvent free conditions. The reaction progress was monitored by TLC. Upon completion of the process, addition of hot absolute ethanol (10 mL) to the reaction mixture was followed by filtration. The filtrate was concentrated and stored at room temperature for precipitation. The solid was filtered off and recrystallized from absolute ethanol to give compound **3c**.

1-Cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (3a). Yield 90%, mp 256–258°C (255–257°C [15]). FT-IR spectrum, ν, cm^{-1}: 3533, 3335, 3033, 2912, 1705, 1623, 1494, 1447, 1383, 1271, 1144, 1024, 804. ^{1}H NMR spectrum, δ, ppm: 1.15–1.20 m (2H, CH_2), 1.30–1.35 m (2H, CH_2), 2.90 t (*J* = 6.0 Hz, 4H, $2CH_2$), 3.22 t (*J* = 6.0 Hz, 4H, $2CH_2$), 3.75–3.85 m (1H, CH), 7.47 d (*J* = 9.0 Hz, 1H, C^8H), 7.75 d (*J* = 15.0 Hz, 1H, C^5H), 8.58 s (1H, C^2H). ^{13}C NMR spectrum, δ, ppm: 7.9, 36.2, 45.8, 51.1, 106.9, 107.1, 111.4, 118.7, 139.6, 146.1, 148.2, 154.0, 165.6, 176.6.

1-Cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

Table 1. Optimization of synthesis of enrofloxacin **3c** under conventional heating

Solvent	*T*, °C	Time, h	Yield, %
Methanol	30	12	68
Methanol	45	12	73
Methanol	55	11	74
Methanol	Reflux	10	81
Ethanol	30	11	76
Ethanol	50	10	85
Ethanol	60	10	85
Ethanol	Reflux	10	88
Butanol	50	9	73
Butanol	75	8	81
Butanol	90	8	89
Butanol	Reflux	6	90
Water	40	10	73
Water	55	10	75
Water	70	10	80
Water	Reflux	9	85
DMSO	50	7	73
DMSO	80	7	82
DMSO	120	6	85
DMSO	Reflux	5	91
Solvent free	80	6	26
Solvent free	120	5	43
Solvent free	150	5	63

(3b). Yield 89%, mp 247–249°C (248–250°C [14]). FT-IR spectrum, ν, cm^{-1}: 3428, 3093, 2935, 1729, 1626, 1507, 1469, 1378, 1299, 1142, 1007, 885. ^{1}H NMR spectrum, δ, ppm: 1.17 s (2H, CH_2), 1.32 d (*J* = 9.0 Hz, 2H, CH_2), 2.23 s (3H, NCH_3), 2.20–2.35 m (4H, $2CH_2$), 3.00–3.10 m (4H, $2CH_2$), 3.75–3.85 m (1H, CH), 7.47 d (*J* = 6.0 Hz, 1H, C^8H), 7.75 d (*J* = 12.0 Hz, 1H, C^5H), 8.62 s (1H, C^2H). ^{13}C NMR spectrum, δ, ppm: 8.0, 31.2, 36.3, 45.9, 49.4, 106.0, 107.1, 111.0, 118.0, 139.6, 146.1, 148.3, 151.0, 166.3, 176.7.

1-Cyclopropyl-7-(4-ethylpiperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3c). Yield 93%, mp 214–217°C (219–221°C [14]). FT-IR spectrum, ν, cm^{-1}: 3533, 3335, 3033, 2912, 1738, 1627, 1470, 1381, 1337, 1254, 1154, 1022, 803. ^{1}H NMR spectrum, δ, ppm: 1.05 t (*J* = 7.0 Hz, 3H, CH_3), 1.10–1.35 m (4H, $2CH_2$), 2.42 q (*J* = 6.0 Hz, 2H, NCH_2), 2.50–2.60 m (8H, $4CH_2$, overlapped with solvent), 3.75–3.85 m (1H, CH), 7.55 d (*J* = 6.0 Hz, 1H, C^8H), 7.88 d (*J* = 15.0 Hz, 1H, C^5H), 8.65 s (1H, C^2H), 15.23 br.s (1H, COOH). ^{13}C NMR spectrum, δ, ppm: 8.0, 12.4, 36.2, 40.7, 49.8–52.4, 106.5, 107.1, 111.3, 118.8, 139.5, 145.5, 148.1, 155.0, 166.3, 176.5.

Table 2. Solvents effect under microwave irradiation in synthesis of enrofloxacin **3c**

Solvent	Time, min	Isolated yield, %
Methanol	35	84
Ethanol	35	87
Butanol	25	88
CH_2Cl_2	40	77
$CHCl_3$	37	82
DMSO	25	89
Water	40	85
Solvent free	25	93

1-Cyclopropyl-6-fluoro-7-{hexahydro-1*H*-pyrrolo-[3,4-*b*]pyridin-6(2*H*)-yl}-4-oxo-1,4 dihydroquinoline-3-carboxylic acid (3d). Yield 84%, mp 257–259°C (256–258°C [16]). FT-IR spectrum, ν, cm^{-1}: 3504, 3308, 3076, 2938, 1719, 1629, 1549, 1509, 1412, 1336, 1180, 1108, 888. ^{1}H NMR spectrum, δ, ppm: 1.10–1.35, 1.55–1.70, 2.50–2.60, 3.30, 3.33–3.55, 3.63–3.75, 6.91, 7.65, 8.49.

1-Cyclopropyl-6-fluoro-7-{hexahydro-1*H*-pyrrolo-[3,4-*b*]pyridin-6(2*H*)-yl}-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (3e). Yield 83%, mp 240–243°C (238–242°C [20]). FT-IR spectrum, ν, cm^{-1}: 3529, 3470, 3033, 2929, 1708, 1624, 1517, 1457, 1353, 1324, 1186, 1047, 805. ^{1}H NMR spectrum, δ, ppm: 0.81–1.25 m (4H, $2CH_2$), 1.63–1.85 m (4H, $2CH_2$), 2.60–2.70 m (2H, CH_2), 3.10–3.20 m (1H, CH), 3.37 s (3H, OCH_3), 3.60–3.65 m (1H, CH), 3.70–3.80 m (1H, CH), 3.82 –3.97 m (2H, CH_2), 4.04–4.19 m (2H, CH_2), 7.63 d.d (*J* = 12.0, 3.0 Hz, 1H, C^5H), 8.64 s (1H, C^2H), 15.15 br.s (COOH). ^{13}C NMR spectrum, δ, ppm: 8.8, 17.2, 20.9, 34.6, 39.1, 41.1, 41.8, 54.4, 62.3, 106.8, 117.6, 134.9, 137.1, 140.6, 150.8, 151.7, 154.0, 166.3, 176.4.

9-Fluoro-3-methyl-7-oxo-10-(piperazin-1-yl)-3,7-dihydro-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid (3f). Yield 91%, mp 263–265°C (257–260°C

[19]). FT-IR spectrum, ν, cm^{-1}: 3255, 3092, 2968, 1723, 1573, 1454, 1392, 1254, 1023, 1011, 805. ^1H NMR spectrum, δ, ppm: 1.44 d (J = 6.0 Hz, 3H, CH_3), 2.80–2.85 m (4H, $2CH_2$), 3.18–3.25 m (4H, $2CH_2$, overlapped with solvent), 4.37 d (J = 12.0 Hz, 1H, CH_2, diastereotopic proton), 4.58 d (J = 12.0 Hz, 1H, CH_2, diastereotopic proton), 4.85–4.95 m (1H, CH), 7.51 d.d (J = 12.0, 6.0 Hz, 1H, C^5H), 8.91 s (1H, C^2H). ^{13}C NMR spectrum, δ, ppm: 18.4, 46.6, 52.0, 55.2, 68.4, 103.6, 107.1, 120.0, 125.2, 132.3, 140.5, 146.5, 154.0, 166.5, 176.7.

9-Fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-3,7-dihydro-2*H*-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (3g). Yield 83%, mp 248–252°C (250–257°C [19]). FT-IR spectrum, ν, cm^{-1}: 3419, 3335, 3043, 2968, 1714, 1622, 1523, 1469, 1371, 1255, 1146, 1056, 804. ^1H NMR spectrum, δ, ppm: 1.44 d (J = 9.0 Hz, 3H, CH_3), 2.22 s (3H, NCH_3), 2.35–2.50 m (4H, $2CH_2$), 3.20–3.40 m (4H, $2CH_2$), 4.35 d.d (J = 12.0, 3.0 Hz, 1H, CH_2, diastereotopic proton), 4.59 d.d (J = 12.0, 3.0, 1H, CH_2, diastereotopic proton), 4.85–4.98 m (1H, CH), 7.52 d (J = 12.0 Hz, 1H, C^5H), 8.95 s (1H, C^2H), 15.17 br.s (1H, COOH). ^{13}C NMR spectrum, δ, ppm: 18.4, 46.5, 50.5, 55.2, 55.7, 68.4, 103.5, 107.0, 119.8, 125.2, 132.5, 140.5, 146.5, 154.2, 166.5, 176.7.

(*S*)-9-Fluoro-3-methyl-7-oxo-10-(piperazin-1-yl)-3,7dihydro-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid (3h). Yield 87%, mp 257–260°C (263–265°C [21]). FT-IR spectrum, ν, cm^{-1}: 3255, 3092, 2968, 1723, 1573, 1454, 1392, 1254, 1023, 1011, 805. ^1H NMR spectrum, δ, ppm: 1.45 d (J = 6.0 Hz, 3H, CH_3), 2.75–2.85 m (4H, $2CH_2$), 3.15–3.25 m (4H, $2CH_2$, overlapped with solvent), 4.30–4.40 m (1H, CH_2, diastereotopic proton), 4.52–4.62 m (1H, CH_2, diastereotopic proton), 4.85–4.95 m (1H, CH), 7.51 d (J = 12.0 Hz, 1H, C^5H), 8.92 s (1H, C^2H). ^{13}C NMR spectrum, δ, ppm: 18.4, 45.8, 51.0, 55.2, 68.5, 103.6, 107.2, 120.2, 125.2, 132.3, 140.5, 146.5, 154.2, 166.5, 176.7.

(*S*)-9-Fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-3,7-dihydro-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid (3i). Yield 89%, mp 223–225°C (225–226°C [17]). FT-IR spectrum, ν, cm^{-1}: 3251, 3079, 2973, 1721, 1539, 1517, 1439, 1394, 1289, 1087, 1004, 801. ^1H NMR spectrum, δ, ppm: 1.44 d (J = 6.0 Hz, 3H, CH_3), 2.22 s (3H, NCH_3), 2.35–2.50 m (4H, $2CH_2$), 3.20–3.30 m (4H, $2CH_2$), 4.36 d.d (J = 12.0, 3.0 Hz, 1H, CH_2, diastereotopic proton), 4.59 d.d (J = 12.0, 3.0 Hz, 1H, CH_2, diastereotopic proton), 4.85–4.95 m (1H, CH), 7.48 d (J = 12.0 Hz, 1H, C^5H), 8.94 s (1H, C^2H), 15.15 br.s (1H, COOH). ^{13}C NMR spectrum, δ, ppm: 18.4, 46.5, 50.5, 55.2, 55.7, 68.4, 103.8, 107, 120, 125.2, 132.3, 140.4, 146.5, 154.2, 166.5, 176.7.

(*S*)-10-(4-Ethylpiperazin-1-yl)-9-fluoro-3-methyl-7-oxo-3,7-dihydro-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid (3j). Yield 91%, mp 225–228°C (229–230°C [18]). FT-IR spectrum, ν, cm^{-1}: 3432, 3042, 2975, 1714, 1623, 1529, 1478, 1306, 1243, 1200, 1010, 743. ^1H NMR spectrum, δ, ppm: 1.05 t (J = 6.0 Hz, 3H, CH_3), 1.45 d (J = 9.0 Hz, 3H, CH_3), 2.35–2.40 m (2H, CH_2, overlapped with solvent), 2.40–2.60 m (4H, $2CH_2$), 3.15–3.20 m (4H, $2CH_2$), 4.37 d (J = 12.0 Hz, 1H, CH_2, diastereotopic proton), 4.57 d (J = 9.0 Hz, 1H, CH_2, diastereotopic proton), 4.91 d (1H, J = 6.0 Hz, CH), 7.56 d (J = 12.0 Hz, 1H, C^5H), 8.94 s (1H, C^2H). ^{13}C NMR spectrum, δ, ppm: 12.2, 18.4, 46.5, 50.5, 53.4, 55.3, 68.5, 103.0, 107.0, 125.2, 126.8, 132.3, 140.0, 146.7, 154.0, 166.5, 176.6.

(3*S*)-9-Fluoro-10-{hexahydro-1*H*-pyrrolo[3,4-*b*]-pyridin-6(2*H*)-yl}-3-methyl-7-oxo-3,7-dihydro-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid (3k). Yield 89%, mp 264–268°C (265–268°C [16]). FT-IR spectrum, ν, cm^{-1}: 3319, 3044, 2932, 1719, 1622, 1527, 1472, 1357, 1191, 1087, 1045, 862. ^1H NMR spectrum, δ, ppm: 1.30–1.70 m (4H, $2CH_2$), 1.45 d (J = 6.0 Hz, 3H, CH_3), 2.10–2.20 m (1H, CH), 2.80–2.90 m (1H, CH), 3.15–3.40 m (4H, $2CH_2$), 4.00–4.15 m (2H, CH_2), 4.23 d (J = 12.0 Hz, 1H, CH_2, diastereotopic proton), 4.59 d (J = 12.0 Hz, 1H, CH_2, diastereotopic proton), 4.80–4.92 m (1H, CH), 7.47 d (J = 15 Hz, 1H, C^5H), 8.85 s (1H, C^2H).

CONCLUSIONS

A facile high yield synthesis of fluoroquinolone antibacterial agents by direct amination of 7-halo-6-fluoroquinolone-3-carboxylic acids with amines under microwave irradiation is developed. Presence of a solvent is essential for oil bath heating but under microwave irradiation it shows the adverse effect.

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