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Microwave Assisted Synthesis and Antibacterial Activity of New Quinolone Derivatives

Mazaahir Kidwai[1,*], **Preeti Misra**[1], **Rajesh Kumar**[1], **Rajendra K. Saxena**[2], **Rani Gupta**[2], and **Sapna Bradoo**[2]

[1] Department of Chemistry, University of Delhi, Delhi 110007, India
[2] Department of Microbiology, University of Delhi, South Campus, Delhi 110021, India

Summary. A series of novel 6-fluoro-7-(5-alkyl-1,3,4-thiadiazol/oxadiazol-2-ylsulfanyl)-4-quinolone-3-carboxylic acids were synthesized using microwave irradiation. The compounds were tested for their *in vitro* antibacterial activity. All compounds containing the 1,3,4-thiadiazole/oxadiazole moiety at position 7 showed promising antibacterial activity.

Keywords. Microwave irradiation; Quinolones; Antibacterial activity.

Mikrowellenunterstützte Synthese und antibakterielle Aktivität von neuen Chinolonderivaten

Zusammenfassung. Einige neue 6-Fluoro-7-(5-alkyl-1,3,4-thiadiazol/oxadiazol-2-sulfanyl)-4-chinolon-3-carbonsäuren wurden unter Bestrahlung mit Mikrowellen synthetisiert. Die Verbindungen wurden hinsichtlich ihrer antibakteriellen Aktivität *in vitro* untersucht. Sämtliche Verbindungen mit 7-ständigen 1,3,4-Thiadiazol/Oxadiazol-Einheiten zeigten vielversprechende Aktivität.

Introduction

In recent years, three quinolones [1] (ciprofloxacin [2], ofloxacin [3], and norfloxacin [4]) have become commercially available. Quinolones inhibit the replication of DNA [5] by inhibition of the DNA gyrase. The latter is probably a metalloenzyme and interacts with the DNA molecule *via* an intermediate (iron complex) that carries the quinolone drug. It has been reported that quinolone antibacterial agents do not bind to the gyrase subunit, but rather to DNA, and the mechanism of action is based on drug DNA complex formation [6–7]. Quinolones act as bidentate chelating agents.

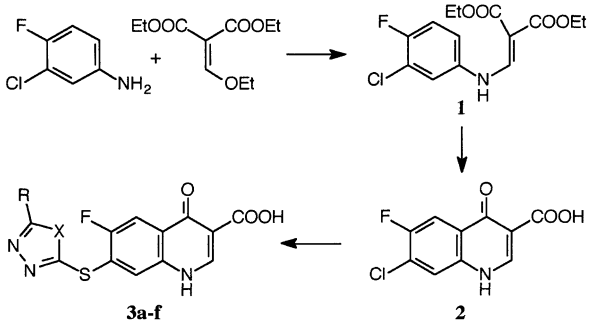
Quinolone derivatives have been associated with antibacterial [8], antimicrobial [9], and antistaphylococcal [10] activities. Thiadiazoles and oxadiazoles are pharmacologically important [11]. Keeping in view the importance of MORE (Microwave induced Organic Reaction Enhancement [12–17] chemistry and the biological importance of the above mentioned moieties, it was thought worthwhile to develop a method for the rapid synthesis of 6-fluoro-7-(5-alkyl-1,3,4-thiadiazol/oxadiazol-2-ylsulfanyl)-4-quinolone-3-carboxylic acids and to screen them for bactericidal activity.

* Corresponding author

Results and Discussion

To our knowledge, this is the first report on quinolone synthesis in which microwave technique has been used and thiadiazole/oxadiazole rings are incorporated.

Diethyl-3-chloro-4-fluoroanilinomethylene malonate (**1**) was synthesized by condensation of 3-chloro-4-fluoroaniline with diethylethoxymethylene malonate. Cyclization of **1** in *PPA* under microwave irradiation for 3 min yielded the cyclized ester which upon alkaline hydrolysis afforded **2** as evidenced by the disappearance of the ester group signals in the ^{1}H NMR spectrum at $\delta = 1.5$ and 4.2 ppm. Formal nucleophilic substitution of the chlorine in **2** with mercapto substituted 1,3,4-thiadiazoles/oxadiazoles was achieved under microwave irradiation for 4–5 min furnishing **3a–f** (Scheme 1). The structures of the compounds were confirmed by their analytical and spectroscopic data given in the experimental part.



	R	*X*		*R*	*X*
3a	CH_3	S	**3d**	CH_3	O
3b	C_9H_{19}	S	**3e**	C_9H_{19}	O
3c	$C_{11}H_{23}$	S	**3f**	$C_{11}H_{23}$	O

Table 1. Antibacterial activity of compounds **3a–f**

Organism	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	Norfloxacin
2253-*Corynebacterium rubrum* NCL	+++	+	+++	++++	+++	+++	++++
2281-*Klebsiella aerogens* NCL	+	−	−	+++	++	+	++++
2491-*Erwinia herbicola* NCL	++	+	++	+++	+++	+++	+++
2715-*Bacillus lichenformis* NCL	+	+	++	++	+	−	++++
2323-*Bacillus coagulans* NCL	+	−	+	+	++	++	+++
K_{12}-*E. coli*	++	+	+	+++	++	++	++++
2689-*Bacillus lichenformis* NCL	+++	+	−	++	+++	++	+++

−: No measurable activity; +: 3–9 mm; ++: 10–12 mm; +++: 13–16 mm; ++++: 17–21 mm

Compounds **3a–f** were tested (Table 1) for their *in vitro* antibacterial activity against 6 bacterial strains by the cup-plate agar diffusion method [18]. They were dissolved in *DMF* at a concentration of 50 μg/ml. All compounds were found active against *Corynebacterium rubrum*, *Escherichia coli*, and *Erwinia herbicola*. Compounds with a 1,3,4-oxadiazole ring at position 7 possess better antibacterial activity than those with a 1,3,4-thiadiazole ring. Among all synthesized quinolones, **3d** provided the best antibacterial activity and compared well with the activities of norfloxacin. **3a**, **3e**, and **3f** also possess promising antibacterial activity.

Experimental

Melting points were taken on an electrothermal apparatus and are uncorrected. IR spectra were recorded on a 1710 Perkin Elmer FTIR spectrophotometer using KBr discs. ^{1}H NMR spectra were recorded on a FTNMR Hitachi R-600 spectrometer operating at 90 MHz using *TMS* as internal standard (δ in ppm). Elemental analysis data agreed satisfactorily with the calculated ones. A Padmini Essentia microwave oven, Model Brownie, at 2450 MHz was used. For TLC analysis, silica gel coated Al plates (Merck) were used.

Diethyl-3-chloro-4-fluoroanilinomethylene malonate (**1**; $C_{14}H_{15}O_4$ NClF)

A stirred mixture containing an equimolar ratio of 3-chloro-4-fluoro aniline and diethylethoxymethylene malonate was heated at 120–140°C until the evolution of ethanol ceased. The disappearance of aniline was confirmed by TLC using petrol ether:$CHCl_3$:acetone (80:15:5) as eluent. The yield was almost quantitative, and the crude product (oil) was pure enough for the next step.

Yield: 91%; IR (KBr): 3320 (N-H), 1725 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ): 1.3 (t, 6H, $2CH_2CH_3$), 4.1 (q, 4H, $2CH_2CH_3$), 7.0–7.3 (m, 3H, Ar-H), 9.1 (br, 1H, NH), 9.4 (s, 1H, C_2-H) ppm; MS: *m/z* calculated for $C_{14}H_{15}O_4$ NClF (M^+) 315.18, found 315.03.

7-Chloro-6-fluoro-4-quinolone-3-carboxylic acid (**2**; $C_{10}H_5O_3$ NClF)

A mixture containing 1.5 g **1** and 7 ml polyphosphoric acid (*PPA*) was subjected to microwave irradiation (MWI) for 3 min. The reaction was monitored by TLC using petrol ether:ethylacetate (9:1) as eluent. The resulting mixture was alkalized with an excess of NaOH and subjected to MWI for 4–5 min. The resulting solution was neutralized with 10% HCl to adjust the *pH* value to 4 and extracted with ethyl acetate. After drying over Na_2SO_4, the extract was evaporated to dryness. **2** was isolated as slightly yellow crystalline product.

Yield: 78%; m.p.: >300°C; IR (KBr): 3400 (N–H), 1700 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ): 8.7 (d, 1H, $J = 9$ Hz, C_5-H), 9.0 (d, 1H, $J = 5$ Hz, C_8-H), 9.6 (s, 1H, C_2-H), 9.2 (br, 1H, NH) ppm; MS: *m/z* calculated for $C_{10}H_5O_3$ NClF (M^+) 241.51, found 241.43.

General procedure for the preparation of 6-fluoro-7-(5-alkyl-1,3,4-thiadiazol/oxadiazol-2-ylsulfanyl)-4-quinolone-3-carboxylic acids (**3a–f**)

A mixture of **2** (0.05 mol), 1, 3, 4-thiadiazole/oxadiazole (0.05 mol), and 4 g K_2CO_3 in 5 ml *DMF* was subjected to MWI for 4–5 min. The inorganic salt was filtered off, and the resulting filtrate was poured into an excess of ice cold water (100 ml) and extracted with ethyl acetate. The organic layer was washed with water (2×50 ml), dried over Na_2SO_4, and evaporated to afford the corresponding products which were recrystallized from *DMF*–EtOH.

6-Fluoro-7-(5-methyl-1,3,4-thiadiazol-2-ylsulfanyl)-4-quinolone-3-carboxylic acid
(**3a**; $C_{13}H_8O_3N_3FS_2$)

Yield: 50%; m.p.: >300°C; IR (KBr): 1680 (C=O), 1580 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.7 (s, 3H, CH_3), 8.65 (d, 1H, $J = 9$ Hz, C_5-H), 9.13 (d, 1H, $J = 5$ Hz, C_8-H), 9.62 (s, 1H, C_2-H), 9.27 (br, 1H, NH) ppm; MS: *m/z* calculated for $C_{13}H_8O_3N_3FS_2$ (M^+) 337.12, found 337.02.

6-Fluoro-7-(5-nonyl-1,3,4-thiadiazol-2-ylsulfanyl)-4-quinolone-3-carboxylic acid
(**3b**; $C_{21}H_{24}O_3N_3FS_2$)

Yield: 72%; m.p.: 278°C; IR (KBr): 1685 (C=O), 1575 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.88 (t, 3H, 9′CH_3), 1.27 (m, 12H, 6CH_2), 1.6 (m, 2H, 2′CH_2), 2.34 (t, 2H, 1′ CH_2), 8.67 (d, 1H, $J = 9$ Hz, C_5-H), 9.15 (d, 1H, $J = 5$ Hz, C_8-H), 9.65 (s, 1H, C_2-H), 9.25 (br, 1H, NH) ppm; MS: *m/z* calculated for $C_{21}H_{24}O_3N_3FS_2$ (M^+) 449.29, found 449.14.

6-Fluoro-7-(5-undecyl-1,3,4-thiadiazol-2-ylsulfanyl)-4-quinolone-3-carboxylic acid
(**3c**; $C_{23}H_{28}O_3N_3FS_2$)

Yield: 67%; m.p.: 290°C; IR (KBr): 1680 (C=O), 1575 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.88 (t, 3H, 11′CH_3), 1.26 (m, 16H, 8CH_2), 1.62 (m, 2H, 2′CH_2), 2.34 (t, 2H, 1′CH_2), 8.63 (d, 1H, $J = 9$ Hz, C_5-H), 9.10 (d, 1H, $J = 5$ Hz, C_8-H), 9.58 (s, 1H, C_2-H), 9.20 (br, 1H, NH) ppm; MS: *m/z* calculated for $C_{23}H_{28}O_3N_3FS_2$ (M^+) 477.31, found 477.18.

6-Fluoro-7-(5-methyl-1,3,4-oxadiazol-2-ylsulfanyl)-4-quinolone-3-carboxylic acid
(**3d**; $C_{13}H_8O_4N_3FS$)

Yield: 58%; m.p.: >300°C; IR (KBr): 1675 (C=O), 1530 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.76 (s, 3H, CH_3), 8.70 (d, 1H, $J = 9$ Hz, C_5-H), 9.10 (d, 1H, $J = 5$ Hz, C_8-H), 9.76 (s, 1H, C_2-H), 9.32 (br, 1H, NH) ppm; MS: *m/z* calculated for $C_{13}H_8O_4N_3FS$ (M^+) 321.14, found 321.03.

6-Fluoro-7-(5-nonyl-1,3,4-oxadiazol-2-ylsulfanyl)-4-quinolone-3-carboxylic acid
(**3e**; $C_{21}H_{24}O_4N_3FS$)

Yield: 69%; m.p.: 280°C; IR (KBr): 1680 (C=O), 1525 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.89 (t, 3H, 9′CH_3), 1.26 (m, 12H, 6CH_2), 1.62 (m, 2H, 2′CH_2), 2.34 (t, 2H, 1′CH_2), 8.67 (d, 1H, $J = 9$ Hz, C_5-H), 9.15 (d, 1H, $J = 5$ Hz, C_8-H), 9.65 (s, 1H, C_2-H), 9.27 (br, 1H, NH) ppm; MS: *m/z* calculated for $C_{21}H_{24}O_4N_3FS$ (M^+) 433.22, found 433.20.

6-Fluoro-7-(5-undecyl-1,3,4-oxadiazol-2-ylsulfanyl)-4-quinolone-3-carboxylic acid
(**3f**; $C_{23}H_{28}O_4N_3FS$)

Yield: 63%; m.p.: 286°C; IR (KBr): 1685 (C=O), 1520 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.88 (t, 3H, 11′-CH_3), 1.25 (m, 16H, 8CH_2), 1.6 (m, 2H, 2′-CH_2), 2.34 (t, 2H, 1′-CH_2), 8.65 (d, 1H, $J = 9$ Hz, C_5-H), 9.15 (d, 1H, $J = 5$ Hz, C_8-H), 9.60 (s, 1H, C_2-H), 9.27 (br, 1H, NH) ppm; MS: *m*/z calculated for $C_{23}H_{28}O_4N_3FS$ (M^+) 461.24, found 461.10.

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