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Microwave Activated Solid Support Synthesis of New Antibacterial Quinolones

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Summary. A novel synthesis of 6-fluoro-7-(5-aryl-1,3,4-thiadiazol/oxadiazol-2-yl-sulfanyl)-4-quinolone-3-carboxylic acids from 7-chloro-6-fluoro-4-quinolone-3-carboxylic acid and 5-substituted 1,3,4-thiadiazoles/oxadiazoles on basic alumina under microwave activation is described. All compounds were screened for their *in vitro* antibacterial activity against *B. lichenformis*, 2689, *K. aerogens* 2281, *S. typhimurium* 2501, *E. herbicola* 2491, and *P. vulgaris* 2027 and found to possess activities comparable to that of the standard drug norfloxacin.

Keywords. Quinolones; Solid support; Microwave irradiation; Antibacterial activity.

Introduction

Microwave heating techniques for solventless organic reactions have been developed very recently by *Villemin* [1] and *Mingos* [2] who have used inorganic oxides (alumina, silica) and acidic clays (montmorillonite K10 or KSF) as carriers [3]. The strategy of microwave activated synthesis on solid inorganic supports [4–5] seems to be the most efficient technology. Acidic or basic solid mineral oxides such as silica gel, alumina, *etc*. act both as catalysts and supports [6]. Moreover, we have coupled this technique with microwave activation, thus achieving more effective reactions than by the use of conventional methods for dry organic reactions [4–6] combined with the advantages of clean products and short reaction times [7–8].

The broad application spectrum and *in vivo* efficiency of quinolone antibacterials [9], thiadiazoles [10], and oxadiazoles [11] have generated much enthusiasm in the medical community and prompted extensive research in the pharmaceutical industry as well. Substituted quinolones have been prepared by nucleophilic substitution reactions using heterocyclic groups like piperazinyl, pyrrole, *etc*. under basic conditions [12]. These methods are very expensive, require long reaction times, and are characterized by difficult work-up procedures resulting in low yields.

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Keeping in view the importance of quinolones and the advantages of solvent-free microwave induced reactions [13, 14], it was thought worthwhile to synthesize the thiadiazolyl/oxadiazolyl substituted quinolones **3a–j** using the above technique.

Results and Discussion

Syntheses

Diethyl-3-chloro-4-fluoro anilinomethylene malonate (**1**) was synthesized from the corresponding chlorofluoroaniline and methylene malonate within 6–7 h using conventional heating [15], whereas under microwave irradiation (MWI) the reaction was completed within 40 s. Cyclization of **1** to the quinolone **2** was carried out using acidic alumina, thus circumventing the use of polyphosphoric acid as has been reported earlier [15]. The reaction of **2** with mercapto substituted 1,3,4-thiadiazoles/oxadiazoles **3a–j** [16] on basic alumina under MWI for 60–90 s furnished the substituted carboxylic acids **4a–j** within 60–90 s, without the need to use bases like NaOH or K_2CO_3. The yields were significantly better than for the conventional methods [17] (Table 1).

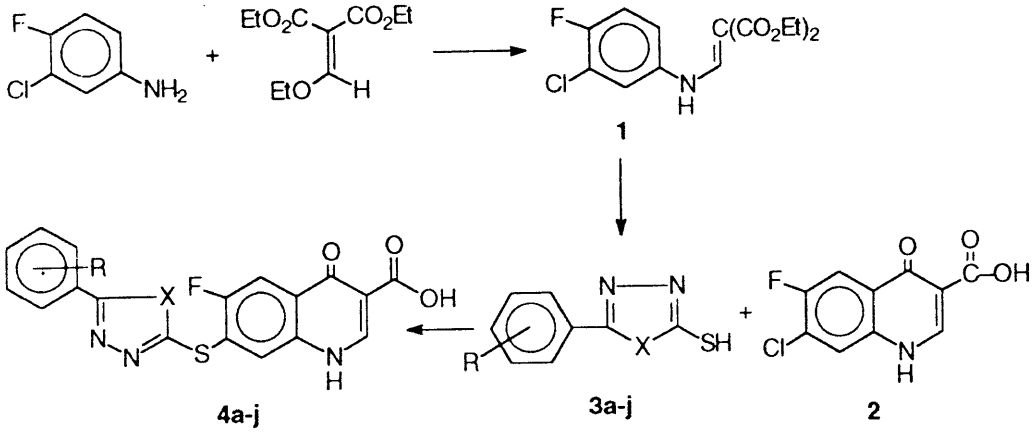
The formation of compounds **4a–j** was evidenced by the disappearance of the band due to the -SH moiety of the thiadiazoles/oxadiazoles at 2550 cm^{-1} and the appearance of the C=N band of the thiadiazole ring at 1575 cm^{-1} in the IR spectra. In the ^1H NMR spectra, the signal for the -SH protons at $\delta = 11.1$ ppm was missing and thus confirmed the condensation of two moieties.

Pharmacological results

B. lichenformis, *K. aerogenes*, *S. typhimurium*, *E. herbicola*, and *P. vulgaries* were used to determine the antibacterial activity by the cup diffusion method [18]. Compounds were dissolved in *DMF* at a concentration of 50 µg/cm^3. All compounds were found to be active; however, only compounds **4f**, **4h**, and **4i** showed promising antibacterial activity. Norfloxacin was used as the standard drug (Table 2).

Table 1. Comparison of reaction times and yields for the transformation **3a–j** → **4a–j**

	Solution phase (conv.) yield/% / time/h	Solution Phase (MWI) yield/% / time/min	Solid Phase (MWI) yield/% / time/s
4a	60/12	72/4	90/60
4b	62/13	70/4	94/70
4c	59/10	73/5	92/65
4d	60/14	72/3	90/90
4e	65/16	73/5	93/80
4f	62/13	74/4	96/60
4g	63/11	72/4	90/80
4h	63/9	76/4	94/85
4i	63/15	78/5	92/90
4j	65/10	73/5	96/75



	X	*R*		*X*	*R*
4a	S	H	**4f**	O	H
4b	S	4-Cl	**4g**	O	4Cl
4c	S	2-Cl	**4h**	O	2-Cl
4d	S	4-NO_2	**4i**	O	4-NO_2
4e	S	4-CN	**4j**	O	4-CN

Scheme 1

Table 2. *In vitro* antibacterial activity of compounds **4a–j**; +: 3–9 mm, ++: 10–12 mm, +++: 13–16 mm, ++++: 17–21 mm

	B. lichenformis 2689	*K. aerogenes* 2281	*S. typhimurium* 2501	*E. herbicola* 2490	*P. vulgaris* 2027
4a	+	++	+	+	++
4b	++	+	++	+	+
4c	+	+	++	+	+
4d	++	++	+	++	+
4e	++	+	+	+	+
4f	++	++	++	++	++
4g	+	+	+	+	+
4h	++	++	++	++	++
4i	++	++	++	++	++
4j	++	+	+	++	+
Norfloxacin	+++	++++	+++	+++	+++

Experimental

Melting points were determined by means of a Thomas Hoover melting point apparatus and are uncorrected. IR spectra (KBr pellets) were recorded on a Perkin-Elmer spectrophotometer model 599. ^{1}H NMR were recorded on a Perkin-Elmer R-32 (90 MHz) instrument using *TMS* as internal standard. Elemental analyses were performed by means of a Heraeus CHN rapid analyser; their results agreed satisfactorily with the calculated values. A Padmini Essentia Microwave oven (Model

Brownie; 2450 MHz, 560 W) was used. For TLC analysis, silica gel coated Al plates (Merck) were employed.

Diethyl-3-chloro-4-fluoroanilino-methylene malonate (**1**)

A mixture of 0.01 mol 3-chloro-4-fluoro-aniline and 0.01 mol diethyl ethoxy methylenemalonate was mixed in an 250 cm^3 *Erlenmeyer* flask and subjected to MWI for 40 s. The formation of the product was confirmed by TLC. The crude product (oil) was pure enough for the next step. A yield of 96% was obtained.

Ethyl-7-chloro-6-fluoro-4-quinolone-3-carboxylic acid (**2**)

Acidic alumina [19] (18 g) was added to a solution of 0.01 mol **1** in 10 cm^3 CH_2Cl_2 at room temperature. The reactants were thoroughly mixed, and the material was dried on air and placed in an alumina bath [20] inside the domestic microwave oven at 560 W for 60–90 s. Progress of the reaction was monitored by TLC at an interval of 30 s. After cooling the mixture to room temperature, the solid was extracted with 4×10 cm^2 CH_2Cl_2, and the solvent was recovered under vacuum to yield 82% **2**.

6-Fluoro-7-(5-aryl-1,3,4-thiadiazol/oxadiazol-2-ylsulfanyl)-4-quinolone-3-carboxylic acids (**4a–j**); *general procedure*

5-Aryl-1,3,4-thiadiazole/oxadiazole-2-thiols **3a–j** (0.01 mol) and 0.01 mol ethyl carboxylate (**2**) were adsorbed separately on basic alumina [21]. Both adsorbed materials were mixed intimately and irradiated in the microwave oven for 60–90 s. After completion of the reaction the mixture was cooled, and the product was extracted with 4×10 cm^3 CH_2Cl_2. Recovering the solvent under reduced pressure afforded the products **4a–j** which were recrystallized from EtOH/CH_2Cl_2. For details on yields, see Table 1.

6-Fluoro-7-(5-phenyl-1,3,4-thiadiazol-2-yl-sulfanyl)-4-quinolone-3-carboxylic acid (**4a**; $C_{18}H_{10}N_3O_3S_2F$)

M.p.: 230–232°C. ^{1}H NMR ($CDCl_3$+*DMSO*-d_6, δ, 90 MHz): 7.4–7.8 (m, 5H, Ar-H), 8.65 (d, 1H, $J = 9$ Hz, C_5-H), 9.15 (d, 1H, $J = 9$ Hz, C_8-H), 9.28 (brs, 1H, NH), 9.70 (s, 1H, C_2-H) ppm.

6-Fluoro-7-(5-(4′-chlorophenyl)-1,3,4-thiadiazol-2-yl-sulfanyl)-4-quinolone-3-carboxylic acid (**4b**; $C_{18}H_9N_3O_3S_2FCl$)

M.p.: 225–227°C; ^{1}H NMR ($CDCl_3$+*DMSO*-d_6, δ, 90 MHz): 7.6–7.8 (m, 4H, Ar-H), 8.73 (d, 1H, $J = 9$ Hz, C_5-H), 9.10 (d, 1H, $J = 5$ Hz, C_8-H), 9.25 (brs, 1H, NH), 9.69 (s, 1H, C_2-H) ppm.

6-Fluoro-7-(5-(2′-chlorophenyl)-1,3,4-thiadiazol-2-yl-sulfanyl)-4-quinolone-3-carboxylic acid (**4c**; $C_{18}H_9N_3O_3S_2FCl$)

M.p.: 232–233°C; ^{1}H NMR ($CDCl_3$+*DMSO*-d_6, δ, 90 MHz): 7.5–7.8 (m, 4H, Ar-H), 8.66 (d, 1H, $J = 9$ Hz, C_5-H), 9.12 (d, 1H, $J = 5$ Hz, C_8-H), 9.25 (brs, 1H, NH), 9.69 (s, 1H, C_2-H) ppm.

6-Fluoro-7-(5-(3′-nitrophenyl)-1,3,4-thiadiazol-2-yl-sulfanyl)-4-quinolone-3-carboxylic acid (**4d**; $C_{18}H_9N_3O_3S_2FCl$)

M.p.: 225–227°C; ^{1}H NMR ($CDCl_3$+*DMSO*-d_6, δ, 90 MHz): 7.5–7.9 (m, 4H, Ar-H), 8.72 (d, 1H, $J = 9$ Hz, C_5-H), 9.13 (d, 1H, $J = 9$ Hz, C_8-H), 9.25 (brs, 1H, NH), 9.72 (s, 1H, C_2-H) ppm.

6-Fluoro-7-(5-(4′-cyanophenyl)-1,3,4-thiadiazol-2-yl-sulfanyl)-4-quinolone-3-carboxylic acid (**4e**; $C_{19}H_9N_4O_3S_2F$)

M.p.: 280–282°C; ^{1}H NMR ($CDCl_3$+*DMSO*-d_6, δ, 90 MHz): 7.7–8.0 (m, 4H, Ar-H), 8.75 (d, 1H, $J = 9$ Hz, C_5-H), 9.12 (d, 1H, $J = 5$ Hz, C_8-H), 9.25 (brs, 1H, NH), 9.69 (s, 1H, C_2-H) ppm.

6-Fluoro-7-(5-phenyl-1,3,4-oxadiazol-2-yl-sulfanyl)-4-quinolone-3-carboxylic acid (**4f**; $C_{18}H_{10}N_3O_4SF$)

M.p.: 225–227°C; ^{1}H NMR ($CDCl_3$+*DMSO*-d_6, δ, 90 MHz): 7.6–7.9 (m, 4H, Ar-H), 8.67 (d, 1H, $J = 9$ Hz, C_5-H), 9.15 (d, 1H, $J = 5$ Hz, C_8-H), 9.25 (brs, 1H, NH), 9.65 (s, 1H, C_2-H) ppm.

6-Fluoro-7-(5-(4′-chlorophenyl)-1,3,4-oxadiazol-2-yl-sulfanyl)-4-quinolone-3-carboxylic acid (**4g**; $C_{18}H_{10}N_3O_4SF$)

M.p.: 280–282°C; ^{1}H NMR ($CDCl_3$+*DMSO*-d_6, δ, 90 MHz): 7.7–8.0 (m, 4H, Ar-H), 8.75 (d, 1H, $J = 9$ Hz, C_5-H), 9.12 (d, 1H, $J = 5$ Hz, C_8-H), 9.27 (brs, 1H, NH), 9.66 (s, 1H, C_2-H) ppm.

6-Fluoro-7-(5-(2′-chlorophenyl)-1,3,4-oxadiazol-2-yl-sulfanyl)-4-quinolone-3-carboxylic acid (**4h**; $C_{18}H_{10}N_3O_4SF$)

M.p.: 285–287°C; ^{1}H NMR ($CDCl_3$+*DMSO*-d_6, δ, 90 MHz): 7.6–7.9 (m, 4H, Ar-H), 8.69 (d, 1H, $J = 9$ Hz, C_5-H), 9.15 (d, 1H, $J = 9$ Hz, C_8-H), 9.27 (brs, 1H, NH), 9.69 (s, 1H, C_2-H) ppm.

6-Fluoro-7-(5-(3′-nitrophenyl)-1,3,4-oxadiazol-2-yl-sulfanyl)-4-quinolone-3-carboxylic acid (**4i**; $C_{18}H_9N_4O_6SF$)

M.p.: 220–222°C; ^{1}H NMR ($CDCl_3$+*DMSO*-d_6, δ, 90 MHz): 7.7–8.1 (m, 4H, Ar-H), 8.69 (d, 1H, $J = 9$ Hz, C_5-H), 9.15 (d, 1H, $J = 9$ Hz, C_8-H), 9.30 (brs, 1H, NH), 9.80 (s, 1H, C_2-H) ppm.

6-Fluoro-7-(5-(4′-cyanophenyl)-1,3,4-oxadiazol-2-yl-sulfanyl)-4-quinolone-3-carboxylic acid (**4j**; $C_{18}H_9N_4O_6SF$)

M.p.: 289–291°C; ^{1}H NMR ($CDCl_3$+*DMSO*-d_6, δ, 90 MHz): 7.7–8.2 (m, 4H, Ar-H), 8.70 (d, 1H, $J = 9$ Hz, C_5-H), 9.16 (d, 1H, $J = 9$ Hz, C_8-H), 9.25 (brs, 1H, NH), 9.65 (s, 1H, C_2-H) ppm.

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