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Alumina-Supported Synthesis of Antibacterial Quinolines using Microwaves

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Abstract—7-(5′-Alkyl-1′,3′,4′-thiadiazol/oxadiazol-2′-ylthio)-6-fluoro-2,4-dimethylquinolines and 3-formyl-2-(2′-hydroxy-1′,4′-naphthoquinon-3′-yl)-4-methyl/6-methyl/7-methyl/8-methylquinolines have been synthesised by the reaction of 5-alkyl-1,3,4-thiadiazol/oxadiazol-2-thiols with 7-chloro-6-fluoro-2,4-dimethylquinoline and by the reaction of 2-hydroxy-1,4-naphthoquinone with 2-chloro-3-formyl-4-methyl/6-methyl/7-methyl/8-methylquinolines respectively on basic alumina using microwaves, the reaction time has been brought down from hours to seconds with improved yield as compared to conventional heating. The compounds were tested for their in vitro antibacterial activity. All compounds showed promising antibacterial activity. The best activity was observed by compounds **3a** and **3f**.

Introduction

Quinolines and their derivatives have been associated with various biological activities. Compounds containing quinoline moiety have shown good amoebicidal,[1] bactericidal,[2] fungicidal[3] and antimalarial[4] activities. Highly active antimalarial drugs plasmaquin,[5] chloroquin and primaquin[6] are well known in the market. 1,3,4-Thiadiazoles/oxadiazoles are pharmacologically[7] important. 1,4-Naphthoquinone is also associated with diverse biological activities.[8,9] Reactions on solid support[10,11] without using solvent in a domestic microwave oven[12,13] are currently in use for synthetic chemists to develop an eco-friendly technique.[14] Keeping in view the utility of microwave irradiation (MWI) and pharmacological importance of the above-mentioned heterocycles, we report herein the synthesis of quinoline derivatives in dry media using MWI in order to develop an economical, rapid and safe method devoid of solvent usage and to screen them for bactericidal activity.

Keywords: quinoline; drymedia; basic alumina; microwaves; solid support.
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Results and Discussion

Chemistry

7-Chloro-6-fluoro-2,4-dimethylquinoline **2** was synthesised via cyclisation of 4-(3-chloro-4-fluoroanilino)pent-3-en-2-one **1** (mixture) by adsorption on acidic alumina using MWI for 210 s as evidenced by the disappearance of the C=O band at 1685 cm^{-1} in IR spectra. Substitution of chlorine in 7-chloro-6-fluoro-2,4-dimethylquinoline (2-chloro-3-formyl methylquinolines)[15] with mercapto substituted-1,3,4-thiadiazoles/oxadiazoles (2-hydroxy-1,4-naphthoquinone) was achieved by adsorption of 7-chloro-6-fluoro-2,4-dimethylquinoline (2-chloro-3-formyl methylquinolines) and thiadiazoles/oxadiazoles[16] (2-hydroxy-1,4-naphthoquinone) on basic alumina using MWI for 120–180 s furnishing 7-(5′-alkyl-1′,3′,4′-thiadiazol/oxadiazol-2′-ylthio)-6-fluoro-2,4-dimethylquinolines [3-formyl- 2-(2′-hydroxy-1′,4′-naphthoquinon-3′-yl)-4-methyl/6-methyl/7-methyl/8-methylquinolines]. The structure of compounds **3a–f** (Scheme 1) were evidenced by the disappearance of signal for SH proton in ^1H NMR spectrum at δ 11–12, band in IR spectrum at 2570 cm^{-1} and appearance of band at 1525–1580 cm^{-1} due to C=N. The structure of compounds **5a–e** (Scheme 2) were confirmed by disappearance of signal in ^1H NMR spectrum at δ 7.0 due to C_3 proton and appearance of multiplet at δ 7.25–8.32 due to aromatic protons.

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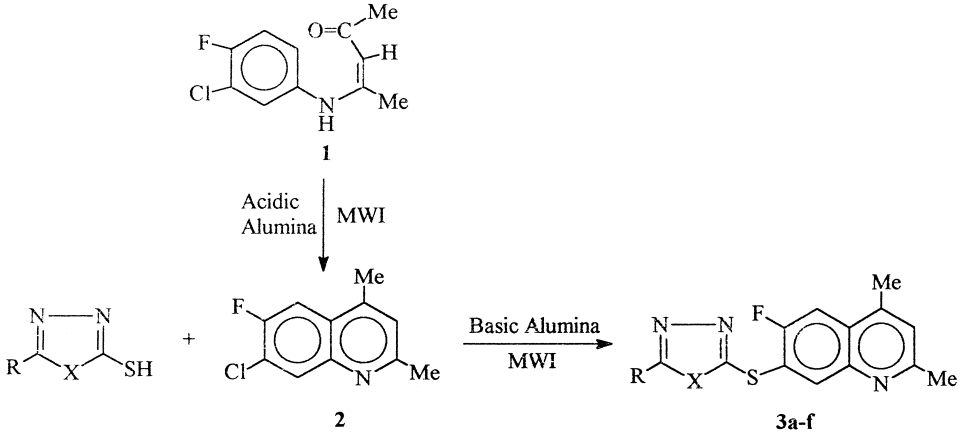
Antibacterial Activity

Compounds **3a–f** and **5a–e** were tested (Table 2) for their in vitro antibacterial activity against five bacterial strains by the cup-plate agar diffusion method.[17] Compounds were dissolved in phosphate buffer at concentration of 50 μg/mL. Among all synthesised quinolines, **3a** and **3f** provided the best antibacterial activity and compared well with the activities of norfloxacin. Compounds **3c**, **3d**, **5a**, **5b** and **5d** also possess promising antibacterial activity. All compounds were found active against *Klebsiella aerogens* and *Escherichia coli*.

This is the first report on the reactions of quinolines on a solid support using MWI in which thiadiazole/oxadiazole/1,4-naphthoquinone rings are incorporated. In short, the salient feature of our approach is coupling microwaves with solvent free technique keeping modernisation and simplification of classical procedure, avoiding volatile and toxic organic solvents, corrosive mineral acids which make it a clean, efficient and cheap technology to obtain various useful heterocyclic compounds for organic synthesis. The results shown in Table 1 demonstrate the versatility of the process as considerable reaction rate enhancement has been observed by bringing down the reaction time from hours to seconds with improved yield as compared to conventional heating.[18]

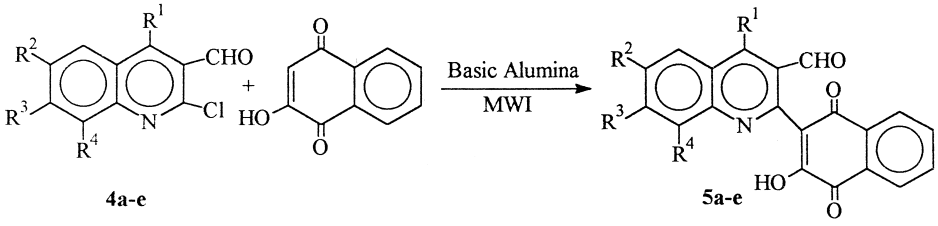
Experimental

Melting points (mp) were determined using a Thomas Hoover melting point apparatus and are uncorrected. IR (KBr, cm^{-1}) spectra were obtained on a Perkin–Elmer FTIR-1710 spectrophotometer. ^1H NMR spectra were recorded at 90 MHz on a Perkin–Elmer R-32 spectrometer using TMS as internal standard (chemical shifts in δ, ppm). Elemental analyses were performed on a Heraeus CHN-Rapid Analyser. EI mass spectra were



	R	X
3a	C_7H_{15}	O
3b	C_7H_{15}	S
3c	C_9H_{19}	O
3d	C_9H_{19}	S
3e	$C_{11}H_{23}$	O
3f	$C_{11}H_{23}$	S

Scheme 1.



5a	$R^1 = R^2 = R^3 = R^4 = H$
5b	$R^1 = R^2 = R^3 = H$; $R^4 = Me$
5c	$R^1 = R^2 = R^4 = H$; $R^3 = Me$
5d	$R^1 = R^3 = R^4 = H$; $R^2 = Me$
5e	$R^2 = R^3 = R^4 = H$; $R^1 = Me$

Scheme 2.

Table 1. Physical data of compounds **3a–f** and **5a–e**

Compound no.	Conventional heating Time (h)/yield (%)	MWI Time (s)/yield (%)
3a	4/79	150/94
3b	6/76	150/96
3c	4/78	135/95
3d	5/80	180/98
3e	6/75	165/94
3f	7/76	180/96
5a	4/80	120/95
5b	5/77	135/95
5c	6/70	165/96
5d	5/71	120/94
5e	4/82	150/98

Table 2. Antibacterial activity[a] of quinoline derivatives[a]

Compound no.	BL[b]	KA[c]	EC[d]	EH[e]	CR[f]
3a	+ +	+ + +	+ + + +	+ +	+ + + +
3b	–[g]	+ +	+	–	+ + +
3c	–	+ + +	+ + +[j]	+ + +	–
3d	–	+[h]	+ + +	+ + +	+ +[i]
3e	–	+ +	+	+ + +	+
3f	+ +	+ + +	+ + +[k]	+ +	+ + + +
5a	+ + +	+ +	+ + +	–	+ +
5b	+ +	+ + +	+ +	–	+ + + +
5c	+ + +	+	+	–	+ + + +
5d	+ +	+ +	+ + +	–	+ + +
5e	–	+ + +	+ +	–	–
Norfloxacin	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +

[a]Data are zones of inhibition (mm).
[b]BL, *Bacillus lichenformis*-2715.
[c]KA, *Klebsiella aerogens*-2281.
[d]EC, *Escherichia coli*-K_{12}.
[e]EH, *Erwinia herbicola*-2491.
[f]CR, *Corynbacterium rubrum*-2253.
[g]– = No measurable activity.
[h]+ = 3–9 mm.
[i]+ + = 10–12 mm.
[j]+ + + = 13–16 mm.
[k]+ + + + = 17–21 mm.

recorded on a JEOLJHS-DX 303 mass spectrometer. For microwave irradiation a Padmini Essentia domestic microwave oven, Model Brownie (2450 MHz) was used.

General procedure for the preparation of 7-chloro-6-fluoro-2,4-dimethylquinoline (2)

Acidic alumina (20 g) was added to the solution of compound **1** (2.27 g, 10 mmol) dissolved in CH_2Cl_2 (10 mL) at room temperature. The reaction mixture was thoroughly mixed and the adsorbed material was dried in air (beaker) and placed in an alumina bath[19] inside the microwave oven for 210 s. Upon completion of the reaction, the mixture was cooled and then product was extracted into CH_2Cl_2 (3×15 mL). The solvent was removed under reduced pressure and the residue was purified by crystallisation from CH_3OH to give product identified as **2** (1.95 g, 94%).

2. Mp 66–68 °C. ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, 4-CH_3), 2.43 (s, 3H, 2-CH_3), 6.91 (s, 1H, 3-H), 7.50 (d, 1H, J = 9 Hz, 5-H), 8.12 (d, IH, J = 5 Hz, 8-H). MS m/z (%) 207/(209). Anal. calcd for $C_{11}H_9NFCl$: C, 63.15; H, 4.30; N, 6.69. Found: C, 63.12; H, 4.28; N, 6.70.

General procedure for the preparation of 7-(5′-alkyl-1′,3′,4′-thiadiazol/oxadiazol-2′-ylthio)-6-fluoro-2,4-dimethylquinolines (3a–f)

Basic alumina (40 g) was added to the solution of thiadiazole/oxadiazole (10 mmol) and quinoline **2** (2.09 g, 10 mmol) in CH_2Cl_2 (10 mL) at room temperature. The reaction mixture was mixed and the adsorbed material was dried, placed in an alumina bath inside the microwave oven and then irradiated for 120–180 s. On completion of the reaction, the mixture was worked up as described above and crystallised from EtOH:$CHCl_3$ (3:1).

3a. Mp 79–81 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 8 Hz, 7′-CH_3), 1.28 (m, 8H, 4×CH_2), 1.62 (m, 2H, 2′-CH_2), 2.36 (t, 2H, J = 7 Hz, 1′-CH_2) 2.52 (s, 3H, 4-CH_3), 2.62 (s, 3H, 2-CH_3), 6.99 (s, 1H, 3-H), 7.91 (d, IH, J = 9 Hz, 5-H), 8.10 (d, 1H, J = 5 Hz, 8-H). IR (KBr cm^{-1}) 1526 (C=N). Anal. calcd for $C_{20}H_{24}N_3SOF$: C, 64.31; H, 4.28; N, 6.70. Found: C, 64.34; H, 4.30; N, 6.69.

3b. Mp 55–57 °C. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 8 Hz, 7′-CH_3), 1.28 (m, 8H, 4×CH_2), 1.61 (m, 2H, 2′-CH_2), 2.37 (t, 2H, J = 7 Hz, 1′-CH_2), 2.49 (s, 3H, 4-CH_3), 2.60 (s, 3H, 2-CH_3). 6.97 (s, 1H, 3-H), 7.71 (d, 1H, J = 9 Hz, 5-H), 8.11 (d, 1H, J = 5 Hz, 8-H). IR (KBr cm^{-1}) 1575 (C = N). Anal. calcd for $C_{20}H_{24}N_3S_2F$: C, 61.69; H, 6.16; N, 10.77. Found: C, 61.67; H, 6.18; N, 10.81.

3c. Mp 48–50 °C. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J = 8 Hz, 9′-CH_3), 1.29 (m, 12H, 6×CH_2), 1.62 (m, 2H, 2′-CH_2), 2.41 (t, 2H, J = 7 Hz, 1′-CH_2), 2.46 (s, 3H, 4-CH_3), 2.59 (s, 3H, 2-CH_3), 6.98 (s, 1H, 3-H), 7.80 (d, 1H, J = 9 Hz, 5-H), 8.10 (d, 1H, J = 5 Hz, 8-H). IR (KBr cm^{-1}) 1528 (C=N). Anal. calcd for $C_{22}H_{28}N_3SOF$: C, 65.83; H, 6.98; N, 10.47. Found: C, 65.85; H, 6.95; N, 10.50.

3d. Mp 50–52 °C. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 8 Hz, 9′-CH_3), 1.25 (m, 12H, 6×CH_2), 1.62 (m, 2H, 2′-CH_2), 2.35 (t, 2H, J = 7 Hz, 1′-CH_2), 2.47 (s, 3H, 4-CH_3), 2.58 (s, 3H, 2-CH_3), 6.98 (s, 1H, 3-H), 7.61 (d, 1H, J = 9 Hz, 5-H), 8.15 (d, IH, J = 5 Hz, 8-H). IR (KBr cm^{-1}) 1573 (C = N). Anal. calcd for $C_{22}H_{28}N_3S_2F$: C, 63.30; H, 6.71; N, 10.07. Found: C, 63.27; H, 6.73; N, 10.09.

3e. Mp 86–88 °C. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 8 Hz, 11′-CH_3), 1.27 (m, 16H, 8×CH_2), 1.73 (m, 2H, 2′-CH_2), 2.51 (t, 2H, J = 7 Hz, 1′-CH_2), 2.45 (s, 3H, 4-CH_3), 2.60 (s, 3H, 2-CH_3), 6.99 (s, 1H, 3-H), 7.81 (d, 1H, J = 9 Hz, 5-H), 8.14 (d, 1H, J = 5 Hz, 8-H). IR (KBr cm^{-1}) 1530 (C=N). Anal. calcd for $C_{24}H_{32}N_3SOF$: C, 67.13; H, 7.45; N, 9.79. Found: C, 67.11; H, 7.40; N, 9.75.

3f. Mp 73–75 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 8 Hz, 11′-CH_3), 1.26 (m, 16H, 8×CH_2), 1.65 (m, 2H,

2′-CH_2), 2.43 (t, 2H, $J=7$ Hz, 1′-CH_2), 2.45 (s, 3H, 4-CH_3), 2.60 (s, 3H, 6-CH_3), 7.10 (s, 1H, 3-H), 8.02 (d, 1H, $J=9$ Hz, 5-H), 8.20 (d, 1H, $J=5$ Hz, 8-H). IR (KBr cm^{-1}) 1580 (C=N). Anal. calcd for $C_{24}H_{32}N_3S_2F$: C, 64.71, H, 7.19; N, 9.43. Found: C, 64.69; H, 7.21; N, 9.45.

General procedure for the preparation of 3-formyl-2-(2′-hydroxy-1′,4′-naphthoquinon-3′-yl)-4-methyl/6-methyl/7-methyl/8-methylquinolines (5a–e)

Basic alumina (40 g) was added to the solution of 2-hydroxy-1,4-naphthoquinone (1.68 g, 10 mmol) and quinoline **4a–e** (10 mmol) in CH_2Cl_2 (10 mL) at room temperature. The reaction mixture was mixed and the adsorbed material was dried, placed in an alumina bath inside the microwave oven and then irradiated for 2–3 min. On completion of the reaction, the mixture was worked up as described above and crystallised from C_2H_5OH.

5a. Mp 120–122 °C. ^{1}H NMR (DMSO-d_6 + $CDCl_3$) δ 5.10 (s, 1H, OH), 7.25–8.32 (m, 10H, Ar-H), 10.45 (s, 1H, CHO). MS *m*/*z* (%) 331/(329). Anal. calcd for $C_{20}H_{11}NO_4$: C, 72.94; H, 3.34, N, 4.25. Found: C, 72.91; H, 3.31; N, 4.22.

5b. Mp 74–76 °C. ^{1}H NMR (DMSO-d_6 + $CDCl_3$) δ 2.72 (s, 3H 8-CH_3), 5.20 (s, 1H, OH), 7.30–8.41 (m, 9H, Ar-H), 10.40 (s, 1H, CHO). MS *m*/*z* (%) 345/(343). Anal. calcd for $C_{21}H_{13}NO_4$: C, 73.48; H, 3.79; N, 4.08. Found: C, 73.45, H, 3.77; N, 4.05.

5c. Mp 92–94 °C. ^{1}H NMR (DMSO-d_6 + $CDCl_3$) δ 2.63 (s, 3H, 7-CH), 5.15 (s, 1H, OH), 7.25–8.35 (m, 9H, Ar-H), 10.39 (s, 1H, CHO). MS m/z (%) 343/(343). Anal. calcd for $C_{21}H_{13}NO_4$: C, 73.48; H, 3.79; N, 4.08. Found: C, 73.42; H, 3.76, N, 4.05.

5d. Mp 122–124 °C. ^{1}H NMR (DMSO-d_6 + $CDCl_3$) δ 2.56 (s, 3H, 6-CH_3), 5.10 (s, 1H, OH), 7.26–8.32 (m, 9H, Ar-H), 10.43 (s, 1H, CHO). MS *m*/*z* (%) 343/(343). Anal. calcd for $C_{21}H_{13}NO_4$: C, 73.48; H, 3.79; N, 4.08. Found: C, 73.46; H, 3.77; N, 4.06.

5e. Mp 73–75 °C. ^{1}H NMR (DMSO-d_6 + $CDC1_3$) δ 2.62 (s, 3H 4-CH_3), 5.15 (s, 1H OH), 7.25–8.37 (m, 9H, Ar-H), 10.40 (s, 1H, CHO). MS *m*/*z* (%) 344/(343). Anal. calcd for $C_{21}H_{13}NO_4$: C, 73.48; H, 3.79; N, 4.08. Found: C, 73.45; H, 3.77; N, 4.05.

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