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Microwave Assisted Stereoselective Synthesis and Antibacterial Activity of New Fluoroquinolinyl-β-lactam Derivatives

Mazaahir Kidwai[1,*], **Pooja Sapra**[1], **Kumar R. Bhushan**[1], **Rajendra K. Saxena**[2], **Rani Gupta**[2], and **Meena Singh**[2]

[1] Department of Chemistry, University of Delhi, Delhi-110007, India
[2] Department of Microbiology, University of Delhi, New Delhi-110021, India

Summary. A series of quinoline ring substituted N-(3-chloro-2-(2-fluoro-quinolin-3-yl)-4-oxo-azetidin-1-yl)-octanamides were synthesized from chloroacetyl chloride, octanoic acid, (2-fluoro-quinolin-3-yl-methylene)-hydrazides, and triethylamine using microwave irradiation as well as conventional heating. The reaction time can be brought down from hours to minutes with improved yields using microwave irradiation compared to conventional heating. The compounds were tested for their *in vitro* antibacterial activity against 2253-*Corynebacterium rubrum*, 2340-*Enterobacter*, 2491-*Erwinia herbicola*, K_{12}-*E. coli*, and 2873-*Z. mobilis*. and found to possess activities comparable with or superior to the standard drug ampicillin.

Keywords. β-Lactam; Microwaves; Quinoline derivatives; Antibiotics; Spectroscopy.

Mikrowellenassistierte stereoselektive Synthese und antibakterielle Aktivität von neuen Fluorchinolyl-β-lactamderivaten

Zusammenfassung. Eine Reihe von am Chinolinring substituierten N-(3-Chlor-2-(2-fluorchinolin-3-yl)-4-oxo-azetidin-1-yl)-octanamiden wurden durch Erhitzen der entsprechenden Octansäurehydrazide mit Mikrowellen oder auf konventionelle Weise dargestellt. Die Reaktionszeit wurde durch die Anwendung von Mikrowellen von Stunden auf Minuten reduziert, wobei die Ausbeuten höher lagen. Die Verbindungen wurden auf ihre *in vitro*-antibakterielle Aktivität gegen 2253-*Corynebacterium rubrum*, 2340-*Enterobacter*, 2491-*Erwinia herbicola*, K_{12}-*E. coli* und 2873-*Z. mobilis* getestet. Dabei wurde gefunden, daß ihre Aktivität vergleichbar bzw. besser als jene des Standardwirkstoffs Ampicillin ist.

Introduction

β-Lactam antibiotics continue to play an important role in antibacterial therapy due to their high efficiency and extremely safe toxicological profile. Apart from their potent antibacterial activity [1] they are also known to possess antifungal [2], antiparkinsonian [3] and antitumor [4] activities. Thus they are agents of choice for

* Corresponding author

microbial infectious diseases in the current therapeutic index [5]. Tremendous efforts have been made for the synthesis and structural modification of the β-lactam nucleus to increase antimicrobial activity and pharmacokinetic performance [6]. Fluorinated quinoline derivatives [7, 8] are also pharmacologically important. Recently, the MORE (microwave induced organic reaction enhancement) technique has become famous in synthetic chemistry as a convenient, safe, and rapid methodology [9, 10]. In continuation of our work on microwave assisted synthesis [11, 12] of bioactive heterocycles [13, 14] it was thought worthwhile to develop a rapid synthesis of a new series of *trans*-β-lactams [15] and to screen the products for antibacterial activity. Moreover, a comparative study in terms of yield and reaction time is also reported using conventional heating.

Results and Discussion

Synthesis

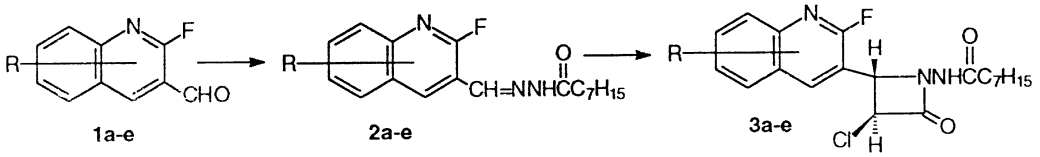
2-Fluoro-3-formyl substituted quinolines **1a–e** [11] gave the corresponding hydrazones **2a–e** upon condensation with octanoic acid hydrazide in ethanol. These hydrazones react with chloroacetyl chloride and triethylamine in a microwave oven as well as under conventional heating to afford the corresponding β-lactams **3a–e**. Microwave irradiation reduces the reaction time from hours to minutes with improved yields compared to conventional heating (Table 1).

Structure

Compounds **2a–e** were characterized by a singlet at $\delta = 8.40$–8.60 ppm (-N=CH proton) in their ^{1}H NMR spectra. The IR band of compounds **3a–e** at 1720–1735 cm^{-1} is characteristic of the β-lactam carbonyl group. The stereochemistry of the β-lactam rings was elucidated by their ^{1}H NMR spectroscopic data which exhibited two doublets ($J = 1.8$–2.1 Hz) for the hydrogen atoms at C-3 and C-4. Their coupling constant confirmed the *trans* stereochemistry of the β-lactams [15]. In addition, the structures of the compounds were confirmed by their analytical and spectroscopic data given in the experimental part. The reaction pathway is depicted in Scheme 1.

Table 1. Comparison of synthesis conditions and yields for **3a–e**

	Reaction time / min		Yield (%)	
	Method A	Method B	Method A	Method B
3a	360	6.5	55	70
3b	300	6	62	76
3c	360	5.5	60	78
3d	480	7.5	58	72
3e	360	7	60	75



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a 4-Me
b 4-H
c 6-Me
d 7-Me
e 8-Me

Scheme 1

Table 2. *In vitro* antibacterial activity of **3a–e** and ampicillin

Organism	3a	3b	3c	3d	3e	Ampicillin
2491-*Erwinia herbicola*	++	++++	+	−	−	++++
2253-*Corynebacterium rubrum*	+++	+++	++	+	++	++++
2340-*Enterobacter*	+++	++++	−	++	+++	+++
K_{12}-*E. coli*	++	++	+	++	+	+++
2873-*Z. Mobilis*	++	+++	+	+	++	++++

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

Antibacterial activity

Compounds **3a–e** were tested for their *in vitro* antibacterial activity against 5 bacterial strains by the cup-plate agar diffusion method [16] (Table 2). The compounds were dissolved in *DMF* at a concentration of 50 μg/ml. All compounds were found to be active against *Corynebacterium rubrum*, *Escherichia coli*, and *Z. Mobilis*. Among all synthesized β-lactams, **3b** provided the best antibacterial activity and compared well with the activities of ampicillin which was used as reference drug. Compounds containing a methyl substituent at position 4 show better antibacterial activity than those containing the methyl substituent at any other position. **3a** and **3e** also possess promising antibacterial activity.

Experimental

Melting points were taken on a Electrothermal apparatus and are uncorrected. IR spectra (KBr pellets) were recorded on a 1710 Perkin-Elmer FTIR spectrophotometer. ^{1}H NMR spectra ($CDCl_3$) were measured on an FTNMR Hitachi R-600 spectrometer (90 MHz) using *TMS* as internal standard. Elemental analysis were performed by means of a Heracus CHN-Rapid analyzer; the results (C, H, N) were found to be in good agreement with the calculated values. A Padmini Essentia Microwave oven, Model Brownie, at 2450 MHz (5–7 W) was employed for microwave irradiation.

General procedure for the preparation of **2a–e**

Octanoic acid hydrazide (0.49 g, 0.01 mol) and 0.01 mol 2-fluoro-3-formyl-substituted quinoline **1a–e** were dissolved in 15 cm^3 ethanol in a round bottomed flask. The reaction mixture was stirred in

an ice bath for 20–23 h. The solid obtained was filtered, washed with cold ethanol, dried, and recrystallized from ethanol to give the substituted hydrazones **2a–e**.

Octanoic acid (2-fluoro-4-methyl-quinolin-3-yl-methylene)-hydrazide (**2a**; $C_{19}H_{24}N_3OF$)

Yield: 90%; m.p.: 116–118°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 0.9 (t, 3H, 7-CH_3), 1.28 (m, 8H, 4×CH_2), 1.63 (m, 2H, 2-CH_2), 2.36 (t, 2H, 1-CH_2), 3.0 (s, 3H, 4′-CH_3), 7.3–8.4 (m, 4H, Ar-H), 8.5 (s, 1H, CH=N), 8.65 (br s, 1H, NH) ppm; IR (KBr): $\nu = 1650$ (C=O), 3200 (NH) cm^{-1}.

Octanoic acid (2-fluoro-quinolin-3-yl-methylene)-hydrazide (**2b**; $C_{18}H_{22}N_3OF$)

Yield: 85%; m.p.: 110–112°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 0.89 (t, 3H, 7-CH_3), 1.28 (m, 8H, 4×CH_2), 1.63 (m, 2H, 2-CH_2),2.34 (t, 2H, 1-CH_2), 7.3–8.5 (m, 5H, Ar-H), 8.6 (s, 1H, CH=N), 8.8 (br s, 1H, NH) ppm; IR (KBr): $\nu = 1655$ (C=O), 3219 (NH) cm^{-1}.

Octanoic acid (2-fluoro-6-methyl-quinolin-3-yl-methylene)-hydrazide (**2c**; $C_{19}H_{24}N_3OF$)

Yield: 89%; m.p.: 122–124°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 0.9 (t, 3H, 7-CH_3), 1.26 (m, 8H, 4×CH_2), 1.62 (m, 2H, 2-CH_2), 2.36 (t, 2H, 1-CH_2), 2.8 (t, 3H, 6′-CH_3), 1.2–8.4 (m, 4H, Ar-H), 8.55 (s, 1H, CH=N), 8.7 (br s, 1H, NH) ppm; IR (KBr): $\nu = 1655$ (C=O), 3200 (NH) cm^{-1}.

Octanoic acid (2-fluoro-7-methyl-quinolin-3-yl-methylene)-hydrazide (**2d**; $C_{19}H_{24}N_3OF$)

Yield: 92%; m.p.: 113–115°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 0.88 (t, 3H, 7-CH_3), 1.28 (m, 8H, 4×CH_2), 1.63 (m, 2H, 2-CH_2), 2.35 (t, 2H, 1-CH_2), 2.7 (t, 3H, 7′-CH_3), 7.1–8.3 (m, 4H, Ar-H), 8.42 (s, 1H, CH=N), 8.50 (br s, 1H, NH) ppm; IR (KBr): $\nu = 1662$ (C=O), 3216 (NH) cm^{-1}.

Octanoic acid (2-fluoro-8-methyl-quinolin-3-yl-methylene)-hydrazide (**2e**; $C_{19}H_{24}N_3OF$)

Yield: 90%; m.p.: 127–129°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 0.9 (t, 3H, 7-CH_3), 1.25 (m, 8H, 4×CH_2), 1.63 (m, 2H, 2-CH_2), 2.36 (t, 2H, 1-CH_2), 2.8 (t, 3H, 8′-CH_3), 7.2–8.4 (m, 4H, Ar-H), 8.55 (s, 1H, CH=N), 8.7 (br s, 1H, NH) ppm; IR (KBr): $\nu = 1657$ (C=O), 3220 (NH) cm^{-1}.

General procedure for the preparation of **3a–e**

Method A: Chloroacetyl chloride (1.15 g, 0.05 mol) dissolved in 10 cm^3 CH_2Cl_2 was added dropwise at room temperature to a stirred solution of 0.01 mol hydrazone **2a–e** and 0.95 g triethylamine (0.03 mol) in 10 cm^3 anhydrous CH_2Cl_2. After stirring for 5–8 h the solvent was removed under reduced pressure, diethyl ether was added to the residue, and the precipitate was filtered off. The filtrate was concentrated, and the residue was purified by column chromatography using $CHCl_3$/EtOAC (1:1) as eluent.

Method B: A mixture of 0.01 mol hydrazone **2a–e**, 1.15 g chloroacetyl chloride (0.05 mol), and 0.95 g triethylamine (0.03 mol) dissolved in 20 cm^3 CH_2Cl_2 was put in an erlenmeyer flask (500 ml) and heated in the microwave oven for 5–8 min [17]. Subsequently, the mixture was worked up similarly as described above. For the yield, see Table 1.

N-(3-Chloro-2-(2-fluoro-4-methyl-quinolin-3-yl)-4-oxo-azetidin-1-yl)-octanamide (**3a**; $C_{21}H_{25}N_3O_2FCl$)

M.p.: 65–67°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 1.1 (t, 2H, 7″-CH_3), 1.3 (m, 8H, 4×CH_2), 1.8 (m, 2H, 2″-CH_2), 2.4 (t, 2H, 1″-CH_2), 3.0 (s, 3H, 4′-CH_3), 4.0 (d, 1H, $J = 2.0$ Hz, 4-CH), 4.9 (d, 1H,

$J = 2.0$ Hz, 3-CH), 7.3–8.5 (m, 4H, Ar-H), 9.6 (br s, 1H, NH) ppm; IR (KBr): $\nu = 1732$ (C=O), 3374 (NH) cm^{-1}.

N-(3-chloro-2-(2-fluoro-quinolin-3-yl)-4-oxo-azetidin-1-yl)-octanamide (**3b**; $C_{20}H_{23}N_3O_2FCl$)

M.p.: 60–62°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 1.2 (t, 3H, 7″-CH_3), 1.3 (m, 8H, 4×CH_2), 1.8 (m, 2H, 2″-CH_2), 2.3 (t, 2H, 1″-CH_2), 4.1 (d, 1H, $J = 2.1$ Hz, 4-CH), 5.0 (d, 1H, $J = 2.1$ Hz, 3-CH), 7.5–8.6 (m, 5H, Ar-H), 9.5 (1H, br s, NH) ppm; IR (KBr): $\nu = 1729$ (C=O), 3380 (NH) cm^{-1}.

N-(3-Chloro-2-(2-fluoro-6-methyl-quinolin-3-yl)-4-oxo-azetidin-1-yl)-octanamide (**3c**; $C_{21}H_{25}N_3O_2FCl$)

M.p.: 64–66°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 1.0 (t, 3H, 7″-CH_3), 1.2 (m, 8H, 4×CH_2), 1.9 (m, 2H, 2″-CH_2), 2.4 (t, 2H, 1″-CH_2), 2.9 (s, 3H, 6′-CH_3), 4.0 (d, 1H, $J = 1.8$ Hz, 4-CH), 5.1 (d, 1H, $J = 1.8$ Hz, 3-CH), 7.4–8.5 (m, 4H, Ar-H), 9.6 (1H, br s, NH) ppm; IR (KBr): $\nu = 1730$ (C=O), 3375 (NH) cm^{-1}.

N-(3-Chloro-2-(2-fluoro-7-methyl-quinolin-3-yl)-4-oxo-azetidin-1-yl)-octanamide (**3d**; $C_{21}H_{25}N_3O_2FCl$)

M.p.: 62–64°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 1.1 (t, 3H, 7″-CH_3), 1.3 (m, 8H, 4×CH_2), 1.8 (m, 2H, 2″-CH_2), 2.3 (t, 2H, 1″-CH_2), 2.7 (s, 3H, 7′-CH_3), 4.1 (d, 1H, $J = 2.0$ Hz, 4-CH), 5.1 (d, 1H, $J = 2.0$ Hz, 3-CH), 7.5–8.5 (m, 4H, Ar-H), 9.5 (1H, br s, NH) ppm; IR (KBr): $\nu = 1731$ (C=O), 3370 (NH) cm^{-1}.

N-(3-Chloro-2-(2-fluoro-8-methyl-quinolin-3-yl)-4-oxo-azetidin-1-yl)-octanamide (**3e**; $C_{21}H_{25}N_3O_2FCl$)

M.p.: 64–66°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 1.2 (t, 3H, 7″-CH_3), 1.2 (m, 8H, 4×CH_2), 1.8 (m, 2H, 2″-CH_2), 2.3 (t, 2H, 1″-CH_2), 2.9 (s, 3H, 8′-CH_3), 4.1 (d, 1H, $J = 1.9$ Hz, 4-CH), 5.1 (d, 1H, $J = 1.9$ Hz, 3-CH), 7.3–8.5 (m, 4H, Ar-H), 9.5 (br s, 1H, NH) ppm; IR (KBr): $\nu = 1730$ (C=O), 3365 (NH) cm^{-1}.

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