Available online at www.sciencedirect.com
SCIENCE DIRECT®
Il Farmaco 58 (2003) 1023–1028
IL FARMACO
www.elsevier.com/locate/farmac

Synthesis and in vitro antibacterial activity of some *N*-(5-aryl-1,3,4-thiadiazole-2-yl)piperazinyl quinolone derivatives

Alireza Foroumadi *, Fatemeh Soltani, Mohammad Hasan Moshafi, Rogheeyeh Ashraf-Askari

Department of Medicinal Chemistry, Faculty of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran

Received 4 April 2003; accepted 15 July 2003

Abstract

A series of *N*-[5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole-2-yl] and *N*-[5-(nitrophenyl)-1,3,4-thiadiazole-2-yl] piperazinyl quinolone derivatives (**5a**–**c** and **5d**–**l**) were synthesized and evaluated for in vitro antibacterial activity against some Gram-positive and Gram-negative bacteria. The antibacterial data revealed that all nitroimidazole derivatives (**5a**–**c**) showed interesting activity against tested Gram-positive bacteria (minimum inhibitory concentration, MIC = 0.008–0.03 μg/ml) while they did not show good activity against Gram-negative organisms. Despite the significant activity of nitroimidazole series, all nitrophenyl analogues (**5d**–**l**) were inactive against both Gram-positive and Gram-negative bacteria. Among all of the tested compounds, **5a** (ciprofloxacin derivative in nitroimidazole series) exhibited excellent activity against *Staphylococcus aureus* and *Staphylococcus epidermidis* (MIC = 0.008 μg/ml).

Keywords: Antibacterial activity; *N*-Piperazinyl quinolones; Minimum inhibitory concentration

1. Introduction

Fluoroquinolones have a useful role in the treatment of many bacterial infectious [1]. They exert their antibacterial activity primarily by inhibiting bacterial enzymes, DNA gyrase and topoisomerase IV [2].

In recent years much attention has been devoted to the synthesis of new quinolones and to testing these agents for antibacterial activity [3,4]. The rapid growth in the quinolone research changed the whole face of the previous SAR concepts. Structure modification at all positions of the quinolone nucleus, except the 4-oxo group, have successfully led to the discovery of potent antimicrobial agents [5]. In addition, a position on the quinolone molecule, where substitutions of bulky functional groups are permitted, is at C-7 [6].

Recently, we reported the synthesis and antibacterial activity of *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadiazole-2-yl]piperazinyl quinolones which had significant activity against some Gram-positive bacteria [7].

Considering the fact that 2,5-disubstituted-1,3,4-thiadiazole derivatives [8,9] and 5-nitro-2-imidazolyl analogues (e.g. metronidazole) [10,11] have antibacterial activity, a new series of *N*-substituted piperazinyl quinolones carrying a 5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole moiety (**5a**–**c**) were designed and synthesized as potential antibacterial agents. Also, as a continuation of this research, we have synthesized and evaluated some *N*-[5-(nitrophenyl)-1,3,4-thiadiazol-2-yl]piperazinyl quinolones (**5d**–**l**) for their antibacterial activity.

2. Experimental

2.1. Chemistry

Melting points were taken on Electrothermal IA-9100 Capillary apparatus and are uncorrected. The IR spectra were obtain on Shimadzu 470 spectrophotometer (potassium bromide disks). ^{1}H NMR spectrum

* Corresponding author.
E-mail address: aforoumadi@yahoo.com (A. Foroumadi).

0014-827X/03/$ - see front matter
doi:10.1016/S0014-827X(03)00191-5

was recorded on a Bruker DRX-500 Avance instrument. Chemical shifts are reported in parts per million (δ) relative to tetramethyl silane as an internal standard.

2.2. Synthesis of compounds **5a–l**

2.2.1. 1-Cyclopropyl-6-fluoro-7-{4-[5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-3-quinoline carboxylic acid (**5a**)

A mixture of compound **3a** (246 mg, 1 mmol), ciprofloxacin (331 mg, 1 mmol) and sodium bicarbonate (84 mg, 1 mmol) in dimethylformamide (DMF) (5 ml) was heated under reflux at 90 °C for 6 h. The solvent was removed under reduced pressure. Water was added to the residue, the solids were filtered, washed with H_2O and crystallized from DMF giving 448 mg of **5a** in 83% yield, m.p. 307–310 °C (dec.). IR (KBr) ν_{max}: 1715, 1619 (C=O) and 1523, 1366/cm (NO_2). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.70 (s, 1H, H2-quinoline), 8.2 (s, 1H, H4-imidazole), 7.97 (d, 1H, H5-quinoline, $J = 13$ Hz), 7.66 (d, 1H, H8-quinoline, $J = 7$ Hz), 4.35 (s, 3H, CH_3), 3.88–3.84 (m, 4H, piperazine), 3.60–3.53 (m, 5H, 4H, piperazine and 1H, CH), 1.34–1.20 ppm (m, 4H, cyclopropyl).

2.2.2. 1-Ethyl-6-fluoro-7-{4-[5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-3-quinoline carboxylic acid (**5b**)

A mixture of compound **3a** (246 mg, 1 mmol), norfloxacin (319 mg, 1 mmol) and sodium bicarbonate (84 mg, 1 mmol) in DMF (5 ml) was heated under reflux at 90 °C for 6 h. The solvent was removed under reduced pressure. Water was added to the residue, the solids were filtered, washed with H_2O and crystallized from DMF giving 370 mg of **5b** in 70% yield, m.p. 302–304 °C (dec.). IR (KBr) ν_{max}: 1720, 1625 (C=O) and 1520, 1330/cm (NO_2). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.98 (s, 1H, H2-quinoline), 8.2 (s, 1H, H4-imidazole), 8.16 (d, 1H, H5-quinoline, $J = 13$ Hz), 7.27 (d, 1H, H8-quinoline, $J = 7$ Hz), 4.64–4.59 (m, 2H, CH_2), 4.35 (s, 3H, CH_3), 3.85–3.81 (m, 4H, piperazine), 3.61–3.56 (m, 4H, piperazine), 1.44 ppm (t, 3H, CH_3, $J = 7$ Hz).

2.2.3. 1-Ethyl-6-fluoro-7-{4-[5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**5c**)

A mixture of compound **3a** (246 mg, 1 mmol), enoxacin (320 mg, 1 mmol) and sodium bicarbonate (84 mg, 1 mmol) in DMF (5 ml) was heated under reflux at 90 °C for 6 h. The solvent was removed under reduced pressure. Water was added to the residue, the solids were filtered, washed with H_2O and crystallized from DMF giving 444 mg of **5c** in 84% yield, m.p. 315–316 °C (dec.). IR (KBr) ν_{max}: 1715, 1625 (C=O) and 1523, 1363/cm (NO_2). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.01 (s, 1H, H2-quinolone), 8.17 (d, 1H, H5-quinolone, $J = 13.3$ Hz), 8.24 (s, 1H, H4-imidazole), 4.55 (q, 2H, CH_2, $J = 7.1$ Hz), 4.35 (s, 3H, CH_3), 4.07–4.05 (m, 4H, CH_2, piperazine), 3.85–3.83 (m, 4H, CH_2, piperazine), 1.43 ppm (t, 3H, CH_3, $J = 7.1$ Hz).

2.2.4. 1-Cyclopropyl-6-fluoro-7-{4-[5-(2-nitrophenyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-3-quinoline carboxylic acid (**5d**)

This compound was prepared as described for **5a** in 69% yield. Reaction time: 8 h, temperature: 120 °C, m.p. 289–290 °C (dec.) (DMF). IR (KBr) ν_{max}: 1728, 1628 (C=O) and 1591, 1337/cm (NO_2). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.68 (s, 1H, H2-quinoline), 8.01 (d, 1H, phenyl, $J = 8$ Hz) 7.96 (d, 1H, H5-quinoline, $J = 13.0$ Hz), 7.85–7.79 (m, 2H, phenyl), 7.78–7.74 (m, 1H, phenyl), 7.65 (d, 1H, H8-quinoline, $J = 7.2$ Hz), 3.87–3.78 (m, 5H, 4H, piperazine and 1H, CH), 3.57–3.53 (m, 4H, piperazine), 1.36–1.20 ppm (m, 4H, cyclopropyl).

2.2.5. 1-Ethyl-6-fluoro-7-{4-[5-(2-nitrophenyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-3-quinoline carboxylic acid (**5e**)

This compound was prepared as described for **5b** in 73% yield, reaction time: 12 h, temperature: 90 °C, m.p. 284–286 °C (dec.) (DMF). IR (KBr) ν_{max}: 1712, 1628 (C=O) and 1532, 1352/cm (NO_2). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.98 (s, 1H, H2-quinoline), 8.03 (d, 1H, phenyl, $J = 7.9$ Hz), 7.99 (d, 1H, H5-quinoline, $J = 13.0$ Hz), 7.84–7.75 (m, 3H, phenyl), 7.29 (d, 1H, H8-quinoline, $J = 7.0$ Hz), 4.64–4.60 (m, 2H, CH_2), 3.80–3.76 (m, 4H, piperazine), 3.58–3.53 (m, 4H, piperazine), 1.45 ppm (t, 3H, CH_3, $J = 7.0$ Hz).

2.2.6. 1-Ethyl-6-fluoro-7-{4-[5-(2-nitrophenyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**5f**)

This compound was prepared as described for **5c** in 80% yield, reaction time: 12 h, temperature: 120 °C, m.p. 285–287 °C (dec.) (DMF). IR (KBr) ν_{max}: 1715, 1628 (C=O), 1523, 1372/cm (NO_2). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.01 (s, 1H, H2-quinoline), 8.16 (d, 1H, H5-quinoline, $J = 13.2$ Hz), 8.02 (d, 1H, phenyl, $J = 7.9$ Hz), 7.88–7.84 (m, 1H, phenyl), 7.83–7.81 (m, 2H, phenyl), 4.55 (q, 2H, CH_2, $J = 7.0$ Hz), 4.07–4.05 (m, 4H, piperazine), 3.79–3.77 (m, 4H, piperazine), 1.42 ppm (t, 3H, CH_3, $J = 7.0$ Hz).

2.2.7. 1-Cyclopropyl-6-fluoro-7-{4-[5-(3-nitrophenyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-3-quinoline carboxylic acid (**5g**)

This compound was prepared as described for **5a** in 69% yield, reaction time: 10 h, temperature: 120 °C, m.p. 303–305 °C (dec.) (DMF). IR (KBr) ν_{max}: 1712, 1628 (C=O) and 1523, 1372/cm (NO_2). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.70 (s, 1H, H2-quinoline), 8.58–8.55 (m, 1H, phenyl), 8.33–8.30 (m, 1H, phenyl), 8.25–8.23 (m,

1H, phenyl), 7.98 (d, 1H, H5-quinoline, $J = 13.0$ Hz), 7.82 (t, 1H, phenyl, $J = 8.12$ Hz), 7.66 (d, 1H, H8-quinoline, $J = 7$ Hz), 3.87–3.81 (m, 5H, 4H, piperazine and 1H, CH), 3.58–3.53 (m, 4H, piperazine), 1.25–1.15 ppm (m, 4H, cyclopropyl).

2.2.8. 1-Ethyl-6-fluoro-7-{4-[5-(3-nitrophenyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-3-quinoline carboxylic acid (**5h**)

This compound was prepared as described for **5b** in 82% yield, reaction time: 24 h, temperature: 90 °C, m.p. 307–309 °C (dec.) (DMF). IR (KBr) ν_{max}: 1728, 1620 (C=O) and 1591, 1335/cm (NO_2). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.95 (s, 1H, H2-quinoline), 8.57–8.55 (m, 1H, phenyl), 8.33–8.30 (m, 1H, phenyl), 8.25–8.22 (m, 1H, phenyl), 7.99 (d, 1H, H5-quinoline, $J = 12.8$ Hz), 7.82 (t, 1H, phenyl, $J = 8$ Hz), 7.28 (d, 1H, H8-quinoline, $J = 7.1$ Hz), 4.65–4.55 (m, 2H, CH_2), 3.85–3.80 (m, 4H, piperazine), 3. 57–3.52 (m, 4H, piperazine), 1.44 ppm (t, 3H, CH_3, $J = 6.9$ Hz).

2.2.9. 1-Ethyl-6-fluoro-7-{4-[5-(3-nitrophenyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**5i**)

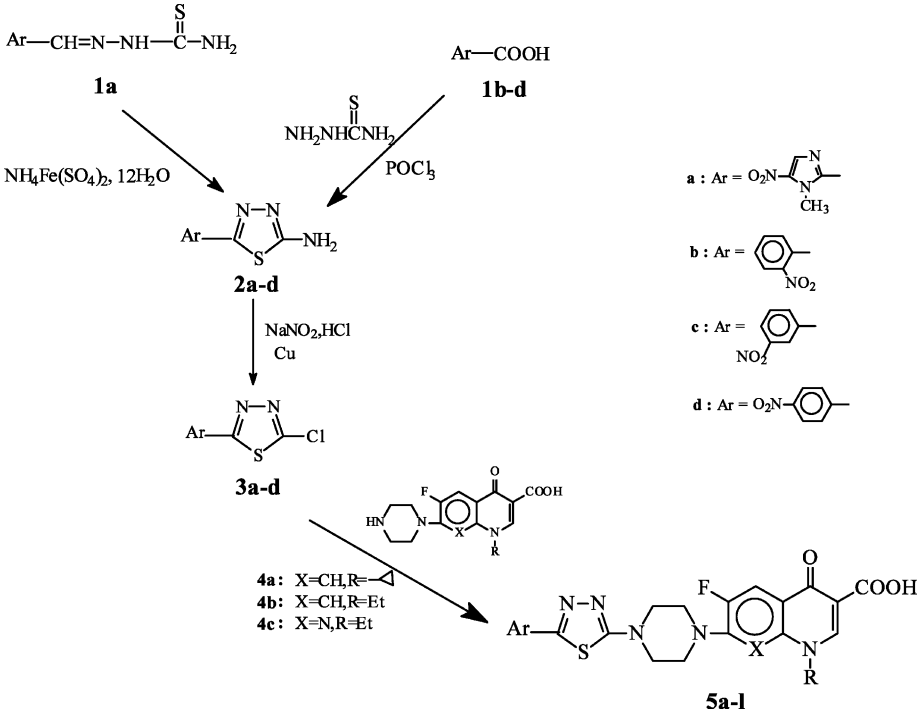
This compound was prepared as described for **5c** in 74% yield, reaction time: 8 h, temperature: 95 °C, m.p. 328–330 °C (dec.) (DMF). IR (KBr) ν_{max}: 1720, 1625 (C=O) and 1536, 1365/cm (NO_2). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.01 (s, 1H, H2-quinoline), 8.58–8.55 (m, 1H, phenyl), 8.33–8.30 (m, 1H, phenyl), 8.25–8.22 (m, 1H, phenyl), 8.17 (d, 1H, H5-quinoline, $J = 13.2$ Hz), 7.82 (t, 1H, phenyl, $J = 8.0$ Hz), 4.55 (q, 2H, CH_2, $J = 7.0$ Hz), 4.07–4.05 (m, 4H, piperazine), 3.84–3.82 (m, 4H, piperazine), 1.43 ppm (t, 3H, CH_3, $J = 7.0$ Hz).

2.2.10. 1-Cyclopropyl-6-fluoro-7-{4-[5-(4-nitrophenyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-3-quinoline carboxylic acid (**5j**)

This compound was prepared as described for **5a** in 86% yield, reaction time: 12 h, temperature: 110 °C, m.p. 335–336 °C (dec.) (DMF). IR (KBr) ν_{max}: 1720, 1625 (C=O) and 1535, 1365/cm (NO_2). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.70 (s, 1H, H2-quinoline), 8.35 (d, 2H, phenyl, $J = 8.5$ Hz), 8.09 (d, 2H, phenyl, $J = 8.5$ Hz), 7.98 (d, 1H, H5-quinoline, $J = 13.5$ Hz), 7.66 (d, 1H, H8-quinoline, $J = 7.0$ Hz), 3.87–3.84 (m, 4H, piperazine), 3.59–3.54 (m, 5H, 4H, piperazine and 1H, CH), 1.36–1.20 ppm (m, 4H, cyclopropyl).

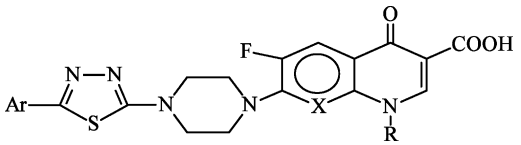
2.2.11. 1-Ethyl-6-fluoro-7-{4-[5-(4-nitrophenyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-3-quinoline carboxylic acid (**5k**)

This compound was prepared as described for **5b** in 93% yield, reaction time: 12 h, temperature: 120 °C, m.p. (dec.) 345–347 °C (DMF). IR (KBr) ν_{max}: 1715, 1623 (C=O) and 1536, 1350/cm (NO_2). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.98 (s, 1H, H2-quinoline), 8.35 (d, 2H, phenyl, $J = 8.86$ Hz), 8.09 (d, 2H, phenyl, $J = 8.86$ Hz), 7.99 (d, 1H, H5-quinoline, $J = 13.1$ Hz), 7.29 (d, 1H, H8-quinoline, $J = 6.9$ Hz), 4.62 (q, 2H, CH_2, $J = 7.0$ Hz), 3.85–4.82 (m, 4H, piperazine), 3.62–3.58 (m, 4H, piperazine), 1.45 ppm (t, 3H, CH_3, $J = 7.0$ Hz).



Scheme 1. Synthesis of some *N*-piperazinyl quinolones **5a**–**l**.

Table 1
In vitro antibacterial activity of *N*-substituted piperazinyl quinolones **5a**–**l** expressed as the MIC



Compound	Ar	X	R	MIC (μg/ml)					
				E. coli ATCC8739	*K. pneumoniae ATCC10031*	*P. aeruginosa ATCC9027*	*B. subtilis PTCC1023*	*S. aureus ATCC6538P*	*S. epidermidis ATCC12228*
5a	1-methyl-5-nitro-2-imidazolyl	CH	Cpr [a]	2	> 64	> 64	0.015	0.008	0.008
5b	1-methyl-5-nitro-2-imidazolyl	CH	Et	2	32	> 64	0.015	0.03	0.015
5c	1-methyl-5-nitro-2-imidazolyl	N	Et	32	> 64	> 64	0.03	0.015	0.015
5d	2-nitrophenyl	CH	Cpr	16	16	64	16	16	8
5e	2-nitrophenyl	CH	Et	32	64	> 64	32	> 64	> 64
5f	2-nitrophenyl	N	Et	32	32	> 64	64	32	8
5g	3-nitrophenyl	CH	Cpr	32	64	> 64	32	64	16
5h	3-nitrophenyl	CH	Et	32	> 64	> 64	32	> 64	> 64
5I	3-nitrophenyl	N	Et	32	64	> 64	16	> 64	64
5j	4-nitrophenyl	CH	Cpr	32	32	32	> 64	32	32
5k	4-nitrophenyl	CH	Et	32	64	> 64	> 64	> 64	> 64
5l	4-nitrophenyl	N	Et	64	> 64	> 64	> 64	> 64	> 64
Ciprofloxacin				0.06	0.06	0.5	0.008	0.5	0.25
Norfloxacin				0.25	0.25	4	0.06	1	1
Enoxacin				0.13	0.25	4	0.13	0.5	0.5

[a] Cyclopropyl.

*2.2.12. 1-Ethyl-6-fluoro-7-{4-[5-(4-nitrophenyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**5l**)*

This compound was prepared as described for **5c** in 95% yield, reaction time: 10 h, temperature: 120 °C, m.p. 342–346 °C (dec.) (DMF). IR (KBr) ν_{max}: 1721, 1630 (C=O) and 1536, 1357/cm (NO_2). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.01 (s, 1H, H2-quinoline), 8.34 (d, 2H, phenyl, $J = 8.6$ Hz), 8.17 (d, 1H, H5-quinoline, $J = 13.3$ Hz), 8.08 (d, 2H, phenyl, $J = 8.6$ Hz), 4.55 (q, 2H, CH_2, $J = 7.1$ Hz), 4.08–4.05 (m, 4H, piperazine), 3.84–3.82 (m, 4H, piperazine), 1.43 ppm (t, 3H, CH_3, $J = 7.1$ Hz).

2.3. Biological assay

The in vitro antibacterial activity of the tested compounds was investigated in side-by-side comparison with ciprofloxacin, norfloxacin and enoxacin against Gram-negative (*Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus* and *Staphylococcus epidermidis* and *Bacillus subtilis*) bacteria using conventional agar dilution procedures [12].

Twofold serial dilutions of the tested compounds and reference drugs were prepared in Muller–Hinton agar. Drugs (6.4 mg) were dissolved in dimethylsulfoxide (DMSO, 1 ml) and the solution was diluted with distilled water (9 ml). Further progressive double dilutions with melted Muller–Hinton agar were performed to obtain the required concentrations of 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.13, 0.06, 0.03, 0.015, 0.008 and 0.004 μg/ml. Petri dishes were inoculated with $1–5 \times 10^4$ colony forming units and incubated at 37 °C for 18 h. The minimum inhibitory concentration (MIC) was the lowest concentration of the tested compound and yielded no visible growth on the plate. To ensure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with DMSO at the same dilutions as used in the experiments.

3. Results and discussion

A series of *N*-[5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole-2-yl] and *N*-[5-(nitrophenyl)-1,3,4-thiadiazole-2-yl] piperazinyl quinolone derivatives (**5a**–**c** and **5d**–**l**) were synthesized according to Scheme 1. The 2-amino-5-aryl-1,3,4-thiadiazoles (**2a**–**d**) were obtained from 1-methyl-5-nitroimidazolecarboxaldehyde thiosemicarbazone (**1a**) by refluxing in aqueous ammonium ferric sulfate solution [13], or by direct cyclization of an arylcarboxylic acid (**1b**–**d**) and thiosemicarbazide in phosphorous oxychloride [14]. Diazothiazation of amines **2** in hydrochloric acid in the presence of copper powder gave 2-chloro-5-aryl-1,3,4-thiadiazoles **3a**–**d** [13]. Reaction of the latter with piperazinyl quinolones (**4a**–**c**) in DMF afforded compounds **5a**–**l** (Scheme 1).

The antibacterial activity of **5a**–**l** was assessed in side-by-side comparison with ciprofloxacin, norfloxacin and enoxacin against some Gram-positive and Gram-negative bacteria using conventional agar dilution procedure, and the results are summarized in Table 1. The antibacterial data indicated that the nitroimidazole derivatives had significant activity against tested Gram-positive organisms (MIC = 0.008–0.03 μg/ml) in comparison to the reference drugs, but they did not show good activity against Gram-negative bacteria (Table 1). In contrast to the good activity of nitroimidazole analogues, all isomeric nitrophenyl derivatives showed negligible activity against both Gram-positive and Gram-negative bacteria.

The MIC values of tested derivatives indicated that ciprofloxacin analogue in nitroimidazole series (**5a**) was the most active compound against *S. aureus* and *S. epidermidis* (MIC = 0.008 μg/ml).

In addition **5a** in comparison to ciprofloxacin was 62 times more potent against *S. aureus* and 31 times more potent against *S. epidermidis*.

In vitro antibacterial evaluation indicated that the nitroimidazole derivatives **5a**–**c** possess similar antibacterial profiles as compared to their nitrofuran counterparts [7].

Acknowledgements

This research was partially supported by the Research Council of Medical Sciences University of Kerman, Iran.

References

[1] M.T. Mascellino, S. Farinelli, F. Iegri, E. Iona, C. De Simone, Antimicrobial activity of fluoroquinolones and other antibiotics on 1116 clinical gram-positive and gram-negative isolates, Drug. Exp. Clin. Res. 24 (1998) 139–151.
[2] D.C Hooper, Mechanisms of action of antimicrobials: focus on fluoroquinolones, Clin. Infect. Dis. 32 (2001) S9–S15.
[3] K.C. Fang, Y.L. Chen, J.Y. Sheu, T.C. Wang, C.C. Tzeng, Synthesis, antibacterial and cytotoxic evaluation of certain 7-substituted norfloxacin derivatives, J. Med. Chem. 43 (2000) 3809–3812.
[4] C.S. Cooper, M.D. Tufano, P.K. Donner, D.T. Chu, The synthesis and in vitro antibacterial activity of conformationally restricted quinolone antibacterial agents, Bioorg. Med. Chem. 4 (1996) 1307–1315.
[5] D.C. Hooper, J.S. Wolfson, Quinolone Antimicrobial Agents, second ed., American Society for Microbiology, Washington, DC, 1993, pp. 3–15.
[6] L.L. Shen, L.A. Mitscher, P.N. Sharma, T.J. O' Donell, D.W.T. Chu, C.S. Cooper, T. Rosen, A.G. Pernet, Mechanism of inhibition of DNA gyrase by quinolone antibacterials, Biochemistry 28 (1989) 3886–3894.

[7] A. Foroumadi, R. Ashraf-Askari, M.H. Moshafi, S. Emami, A. Zeynali, Synthesis and in vitro antibacterial activity of *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadiazole-2-yl]piperazinyl quinolone derivatives, Pharmazie 58 (2003) 432–433.
[8] F.A. Ashour, N.S. Habib, M. Taibbi, S. Dine, A. Dine, Synthesis of 1,3,4-thiadiazoles,imidazo[2,1-*b*]1,3,4-thiadiazoles and thiadiazolo[3,2-*a*]pyrimidines derived from benzimidazole as potential antimicrobial agents, Farmaco 45 (1990) 134–139.
[9] S. Rollas, S. Karakus, B.B. Durgun, M. Kiraz, H. Erdeniz, Synthesis and antimicrobial activity of some 1,4-disubstituted thiosemicarbazide and 2,5-disubstituted 1,3,4-thiadiazole derivatives, Farmaco 51 (1996) 811–814.
[10] C.D. Freeman, N.E. Klutman, K.C. Lamp, Metronidazole a therapeutic review and update, Drugs 54 (1997) 679–708.
[11] A.H. Lau, N.P. Lam, S.C. Piscitelli, L. Wilkes, L.H. Danziger, Clinical pharmacokinetics of metronidazole and other nitroimidazole anti-infectives, Clin. Pharmacokinet. 23 (1992) 328–364.
[12] E.J. Baron, S.M. Finegold, Bailey & Scott's Diagnostic Microbiology, eighth ed., The C.V. Mosby Company, 1990, pp. 171–194.
[13] A. Foroumadi, M. Daneshtalab, A. Shafiee, Synthesis and in vitro antifungal activity of 2-aryl-5-phenylsulfonyl-1,3,4-thiadiazole derivatives, Arzneim. Forsch. Drug Res. 49 (1999) 1035–1038.
[14] I. Lalezari, A. Shafiee, Selenium heterocycles. IV. Synthesis of 2-amino-1,3,4-selenadiazole and 2-substituted-6-phenylimidazo[2,1-*b*]-1,3,4-selenadiazoles, J. Heterocyclic Chem. 8 (1971) 835–837.