Das Filtrat wurde i. Vak. zur Trockne eingeengt und der feste Rückstand 2× mit je 2 ml Ether gewaschen. Der Rückstand (16 mg bei **1a**, 7 mg bei **1b**) wurde durch IR-spektroskopischen Vergleich mit einer authentischen Probe [7] als **2** identifiziert.

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Synthesis and *in vitro* antibacterial activity of *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadiazole-2-yl] piperazinyl quinolone derivatives

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Fluoroquinolones are a group of synthetic antibacterial agents structurally related to nalidixic acid. They exhibite a broad antibacterial spectrum both to Gram-positive and Gram-negative bacteria [1]. During recent years much attention has been devoted to the synthesis of new 4-quinolone-3-carboxylic acids and to their antibacterial activity [2–3]. Further advances in quinolone development are likely to provide better compounds for clinical use [4].

Quinolones exert antibacterial activity primarily by inhibiting bacterial DNA gyrase. A ternary complex of drug, enzyme, and DNA blocks progress of the replication fork [5]. The inhibition of DNA gyrase and cell permeability of the quinolones are greatly influenced by the nature of the C-7 substituent on the standard structure of 4-quinolone-3-carboxylic acids [6]. In addition, substitution of bulky functional groups are permitted at the C-7 position [7].

We previously reported the synthesis of a series of *N*-(2-aryl-2-oxoethyl) piperazinyl quinolones and related compounds, with significant antibacterial activity against some Gram-positive and Gram negative organisms [8, 9].

According to data from the literature that some 2,5-disubstituted-1,3,4-thiadiazole derivatives [10–12] and 5-nitro-2-furyl analogues (e.g. nitrofurantoin) [13] have antibacterial activity, we designed and synthesized a new series of N-substituted piperazinyl quinolones with certain structural modifications containing a 2-(5-nitro-2-furyl)-1,3,4-thiadiazole moiety **(3a–c)** as potential new antibacterial agents.

The intermediate 2-chloro-5-(5-nitro-2-furyl)-1,3,4-thiadiazole (**1**) was prepared from 5-nitrofurfurylidene diacetate according to a previously described procedure [14]. Reaction of compound **1** with piperazinyl quinolones **2a–c** in dimethylformamide at 90 °C afforded compounds **3a–c** in high yields (Scheme).

The antibacterial activity of **3a–c** was investigated *in vitro* in side-by-side comparison with norfloxacin, ciprofloxacin and enoxacin, against some Gram-positive and Gram-negative bacteria using a conventional agar dilution procedure. The results are summarized in the Table.

The antibacterial data revealed that compounds **3a–c** had a strong and better activity against Gram-positive organisms than the reference quinolones such as ciprofloxacin, norfloxacin and enoxacin. However, all three compounds were nearly inactive against Gram negative bacteria. This is in contrast to the good antibacterial activity of quinolones and 5-nitrofuran derivatives (e.g. nitrofurntion) [13] against Gram negative bacteria such as *E. coli*. However,

Scheme

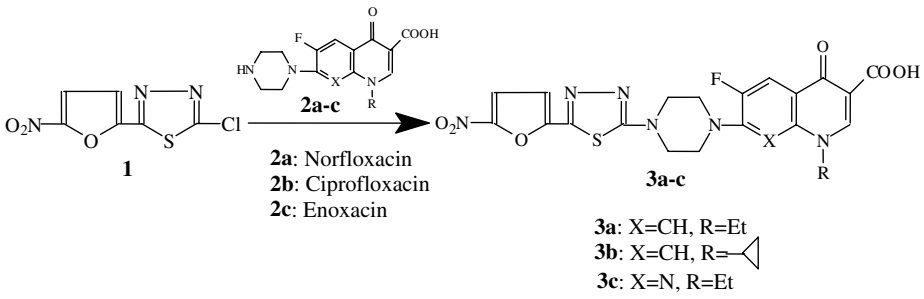

Table: ***In vitro*** **antibacterial activity of 3a–c and standard quinolones (MIC μg/ml)**

Compound	*S. aureus* ATCC 6538P	*S. epidermidis* ATCC 12228	*S. faecalis* [d]PTCC 1237	*B. subtilis* [d]PTCC 1023	*E. coli* ATCC 8739	*K. pneumoniae* ATCC 10031	*E. cloacae* [d]PTCC 1003	*P. aeruginosa* ATCC 9027
3a[a]	0.03	0.015	2	0.03	64	>64	64	>64
3b[b]	0.015	0.008	0.5	0.004	64	64	32	>64
3c[c]	0.015	0.015	0.25	0.008	>64	64	32	>64
Norfloxacin	1	0.5	1	0.06	0.125	0.25	0.125	4
Ciprofloxacin	0.5	0.25	0.5	0.015	0.03	0.06	0.03	1
Enoxacin	1	0.5	2	0.125	0.125	0.5	0.25	4

[a] Norfloxacin analogue; [b] Ciprofloxacin analogue; [c] Enoxacin analogue, [d]PTCC: Persian Type Culture collection

it is known that the nature of the functional group at the C-7 position of the quinolone ring system has strong influence on the spectrum and extent of antibacterial activity *in vitro* [15]. Furthermore, the C-7 substituents were proposed as the domain that intract with the enzyme for further strengthening drug binding.

According to the data presented in the Table, substitution of 2-(5-nitro-2-furyl)-1,3,4-thiadiazole to the piperazine ring of the quinolones resulted in a new series of quinolones with potent and selective antibacterial activity against Gram positive bacteria. All the three derivatives **3a–c** demostrated a 33-fold improvement in activity over the reference drugs against *S. aureus* and *S. epidermidis.*

Experimental

1. Chemistry

The 2-chloro-5-(5-nitro-2-furyl)-1,3,4-thiadiazole (**1**) was prepared according to the previously described procedure [14].

1.1. 1-Ethyl-6-fluoro-7-{4-[5-(5-nitro-2-furyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-3-quinolone carboxylic acid (**3a**)

A mixture of compound **1** (231 mg, 1 mmol), norfloxacin (319 mg, 1 mmol) and sodium bicarbonate (84 mg, 1 mmol) in DMF (5 ml) was heated under reflux in 90 °C for 6 h. The solvent was removed under reduced pressure. To the residue H_2O was added (10 ml) and the precipitate was filtered, washed with H_2O and crystallized from DMF giving 437 mg of **3a** in 85% yield, m.p. 300–301 °C. IR (KBr) ν_{max}: 1715, 1621 (C=O) and 1530, 1355 cm^{-1} (NO_2). ^1H NMR (DMSO-d6, 80 MHz) δ: 8.75 (s, 1 H, H_2-quinolone), 7.98 (d, 1 H, H_5-quinolone, J = 13 Hz), 7.67 (d, 1 H, furyl, J = 4 Hz), 7.27 (d, 1 H, furyl, J = 4 Hz), 7.10 (d, 1 H, H_8-quinolone, J = 7 Hz), 4.50 (q, 2 H, CH_2, J = 7 Hz), 3.97–3.70 (m, 4 H, CH_2-piperazine), 3.70–3.45 (m, 4 H, CH_2-piperazine) and 1.49 ppm (t, 3 H, CH_3, J = 7 Hz).

1.2. 1-Cyclopropyl-6-fluoro-7-{4-[5-(5-nitro-2-furyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-3-quinolone caroxylic acid (**3b**)

This compound was prepared as described for **3a** in 83% yield, m.p. 288–289 °C (DMF).

1.3. 1-Ethyl-6-fluoro-7-{4-[5-(5-nitro-2-furyl)-1,3,4-thiadiazole-2-yl]-1-piperazinyl}-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**3c**)

This compound was prepared as described for **3a** in 91% yield, m.p. 318–319 °C (DMF).

Spectroscopic values are given for only compound **3a**, since those of their analogues are similar.

2. Antibacterial activity

MICs of all compounds and reference drugs were determined using a conventional agar dilution procedure. Twofold serial dilution of the test compounds and reference drugs were prepared in Müller-Hinton agar. Drugs (6.4 mg) were dissolved in DMSO and the solution was diluted with distilled water (9 ml), further progressive double-dilutions with melted Müller-Hinton agar were performed to obtain the required concentration ranging from 64 to 0.002 μg/ml.

Petri dishes were inoculated with $1–5 \times 10^4$ colony forming units and incubated at 37 °C for 18 h. The MIC was the lowest concentration of the test compound that 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 used in the experiments.

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