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Synthesis and In-vitro Antibacterial Activity of New *N*-Substituted Piperazinyl Quinolones

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Abstract

A series of *N*-[2-(2-furyl)-2-oxoethyl], *N*-[2-hydroxyimino-2-(2-furyl)ethyl], *N*-[2-(2-furyl)-2-methoxyiminoethyl] and *N*-[2-(2-furyl)-2-phenylmethoxyiminoethyl] piperazinyl quinolones were synthesized and evaluated for in-vitro antibacterial activity.

Compounds with a 2-(2-furyl)-2-oxoethyl group attached to the piperazine ring had similar antibacterial activity to the reference drugs, norfloxacin and ciprofloxacin, against staphylococci, but significantly decreased activity against Gram-negative bacteria. If the hydrogen of oxime was replaced with a methyl or benzyl group, in-vitro antibacterial activity decreased against Gram-negative bacteria, but activity was similar against staphylococci.

Generally, ciprofloxacin derivatives were more active than norfloxacin derivatives.

The introduction of fluoroquinolones, such as ciprofloxacin and ofloxacin, has been the most important advance in the discovery of new antimicrobial agents in the past decade. These agents are attractive because of their bioavailability after oral administration and relatively few side-effects. They are primarily used for the treatment of infections caused by Gram-negative bacteria. Promising new fluoroquinolones are being developed that have a broader spectrum of antimicrobial activity including, in some cases, effectiveness against Gram-positive and anaerobic infections (Mandell & Petri 1996).

The compounds currently available for clinical use are 4-quinolones containing a carboxylic acid moiety in the 3 position of the basic structure. The newer fluoroquinolones also contain a fluorine substituent at the 6 position, and many of these compounds contain a piperazine moiety at the 7 position. The inhibition of DNA gyrase and cell permeability of the quinolones are greatly influenced by the nature of the C-7 substituent (Domagala et al 1986). In addition, substitution of bulky functional groups is permitted at the C-7 position (Shen et al 1989). The synthesis of a series of compounds having an oxime and a substituted oxime attached to the pyrrolidine and piperidine rings at the C-7 position of quinolone, which showed selective activity against Gram-positive organisms, has been reported (Cooper et al 1992). We previously reported the synthesis of a series of *N*-(2-oxyimino-2-phenylethyl)piperazinyl quinolone derivatives, with significant antibacterial activity against some Gram-positive and Gram-negative organisms (Foroumadi et al 1997).

Here we report a new series of *N*-substituted piperazinyl quinolone derivatives with certain structural modifications containing a 2-furyl moiety, as potential antibacterial agents.

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Material and Methods

Chemical procedures

Reaction of hydroxylamine hydrochloride, *O*-methylhydroxylamine hydrochloride or *O*-benzylhydroxylamine hydrochloride with α-bromo-2-acetylfuran (**3**) in methanol at room temperature afforded compounds **5a**, **5b** and **7**, respectively (Schumann et al 1964; Schaefer & Mangold 1982). Reaction of quinolones **1**, **2** with α-bromo-2-acetylfuran (**3**) or α-bromo-2-acetylfuran oximes (**5a**–**b** and **7**) without protection of the 3-carboxylic acid of quinolones (Kondo et al 1986) in the presence of sodium bicarbonate in dimethylformamide (DMF) at room temperature yielded ketones **4a**–**b** and oximes **6a**–**d** and **8a**–**b**, respectively (Figure 1). The compounds were characterized by ^{1}H NMR, IR spectroscopy and microanalysis. The purity of

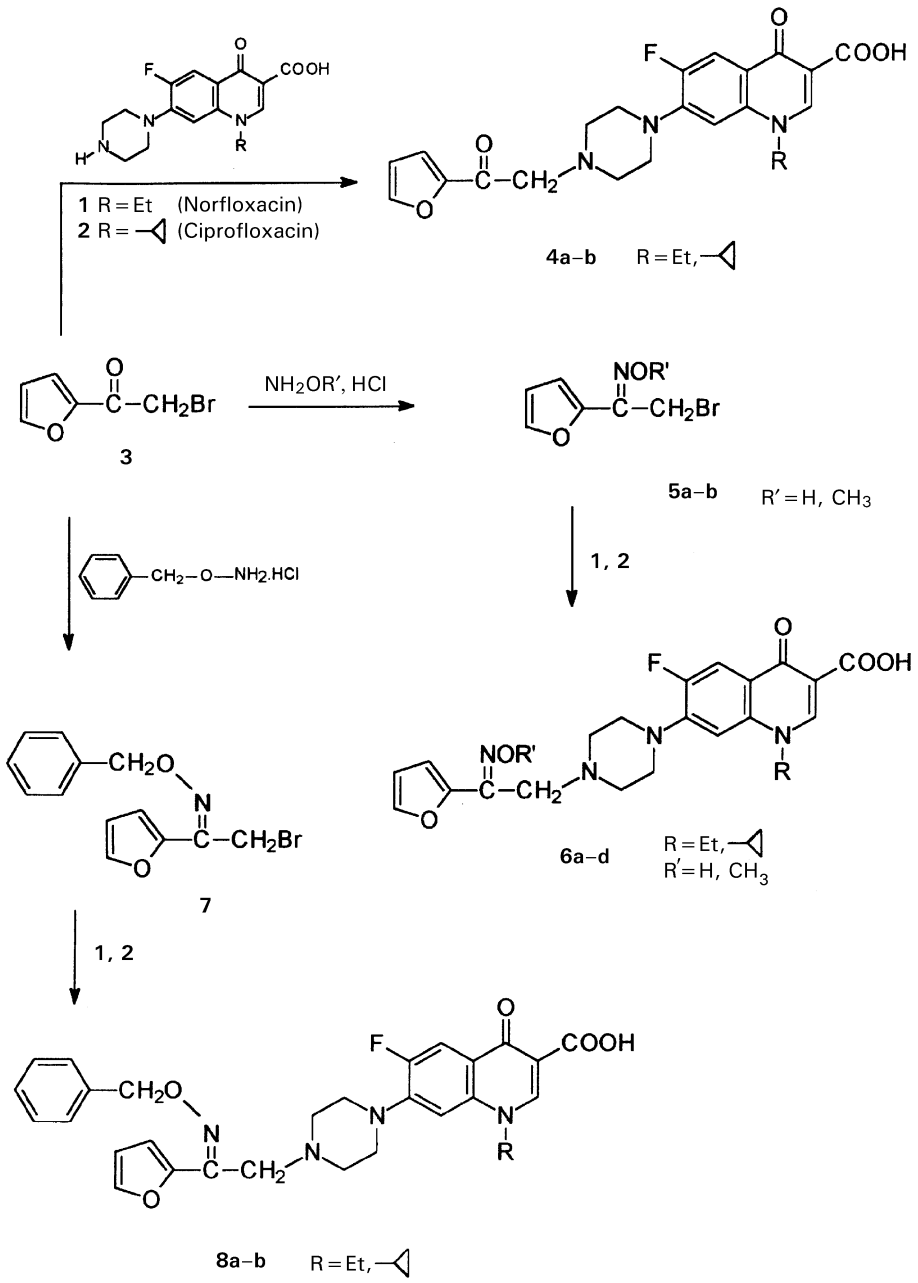

Figure 1. Synthesis of *N*-substituted piperazinyl quinolones.

all products was determined by thin-layer chromatography using several solvent systems of different polarity. Reaction times and physical properties of the products are listed in Table 1.

In-vitro antibacterial activity

The in-vitro antibacterial activity of the test compounds was investigated in side-by-side comparison with norfloxacin and ciprofloxacin, against Gram-positive (*Staphylococcus aureus* and *Staphylococcus epidermidis*) and Gram-negative (*Escherichia coli*, *Kelebsiella pneumoniae* and *Enterobacter cloacae*) bacteria using conventional agar dilution procedures (Baron & Finegold 1990).

Twofold serial dilutions of the test compounds and reference drugs were prepared in Muller–Hinton agar. Drugs (6·4 mg) were dissolved in dimethylsulphoxide (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, 0·5, 0·25, 0·13, 0·06, 0·03 and 0·015 $\mu g\,mL^{-1}$. Petri dishes were inoculated with $1-5 \times 10^4$ colony forming units and incubated at 37°C for 18 h. The minimum

Table 1. Physical properties of *N*-substituted piperazinyl quinolones.

Compound	X	R	Mp (°C)	Yield (%)	Crystallization solvent	Reaction time (h)
4a	O	Ethyl	212–213	64	EtOH	24
4b	O	Cyclopropyl	180–181	60	EtOH	24
6a	NOH	Ethyl	219–221	36	$CHCl_3$–EtOH	48
6b	NOH	Cyclopropyl	227–228	44	$CHCl_3$–EtOH	72
6c	$NOCH_3$	Ethyl	223–224	63	EtOH	48
6d	$NOCH_3$	Cyclopropyl	214–215	52	EtOH	120
8a	$NOCH_2C_6H_5$	Ethyl	141–142	38	EtOH	120
8b	$NOCH_2C_6H_5$	Cyclopropyl	131–132	28	EtOH	120

inhibitory concentration (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 dimethylsulphoxide at the same dilutions used in the experiments.

Results and Discussion

Compounds **4a**–**b**, **6a**–**d** and **8a**–**b** were evaluated for in-vitro antibacterial activity against Gram-positive and Gram-negative bacteria. Activity was determined by conventional agar dilution techniques and the results are summarized in Table 2. Data for norfloxacin (**1**) and ciprofloxacin (**2**) were included for comparison.

The nature of the functional group at the 7 position of the quinolone ring system is known to influence the range and extent of in-vitro antibacterial activity. We previously reported a series of quinolones having *N*-phenacyl, *N*-(2-phenyl-2-hydroxyiminoethyl) and *N*-(2-phenyl-2-phenylmethoxyiminoethyl)piperazine attached to the 7 position which showed significant antibacterial activity against some Gram-positive and Gram-negative bacteria. In this study a series of *N*-[2-(2-furyl)-2-oxoethyl], *N*-[2-hydroxyimino-2-(2-furyl) ethyl], *N*-[2-(2-furyl)-2-methoxyiminoethyl] and *N*-[2-(2-furyl)-2-phenylmethoxyiminoethyl] piperazinyl quinolones (**4a**–**b**, **6a**–**b**, **6c**–**d** and **8a**–**b**; Figure 1) were synthesized and evaluated for in-vitro antibacterial activity. Compounds having a 2-(2-furyl)-2-oxoethyl group attached to the piperazine ring (**4a** and **4b**) showed similar antibacterial activity to norfloxacin and ciprofloxacin against both Gram-positive and Gram-negative bacteria. The oximes, **6a** and **6b**, were more potent than norfloxacin and ciprofloxacin against staphylococci, however, a significant decrease in potency was observed against Gram-negative bacteria. If the hydrogen of the oxime is replaced by a methyl group (**6c** and **6d**), in-vitro antibacterial activity was decreased against Gram-negative bacteria but activity was similar against staphylococci. The same results were observed when the hydrogen of the oxime was replaced with a benzyl group (**8a** and **8b**). These oximes had greater potency than previously reported (Foroumadi et al 1997). Generally, ciprofloxacin derivatives were more active than norfloxacin derivatives.

Table 2. In-vitro antibacterial activity of piperazinyl quinolones expressed as the minimum inhibitory concentration (MIC).

Compound	MIC ($\mu g\,mL^{-1}$)				
	S. aureus ATCC 6538p	*S. epidermidis* ATCC 12228	*E. coli* ATCC 8739	*K. pneumoniae* ATCC 10031	*E. cloacae* PTCC 1003
4a	1	0·5	0·06	0·25	0·13
4b	0·5	0·25	0·03	0·03	0·03
6a	0·5	0·25	4	8	4
6b	0·13	0·13	1	2	1
6c	1	0·5	8	8	8
6d	0·25	0·25	0·5	2	1
8a	1	1	4	8	8
8b	0·13	0·25	0·5	2	1
Norfloxacin	1	1	0·25	0·25	0·13
Ciprofloxacin	0·25	0·25	0·06	0·06	0·03

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