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Original article

Synthesis and antibacterial activity of nitroaryl thiadiazole–gatifloxacin hybrids

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ABSTRACT

A number of gatifloxacin analogues containing a nitroaryl-1,3,4-thiadiazole moiety attached to the piperazine ring at C-7 position were prepared and evaluated as antibacterial agents against a panel of Gram-positive and Gram-negative bacteria. Among synthesized compounds, nitrofuran analog **6a** exhibited more potent inhibitory activity against Gram-positive bacteria including *Staphylococcus epidermidis* (MIC = 0.0078 μg/mL), *Bacillus subtilis* (MIC = 0.0039 μg/mL), *Enterococcus faecalis* (MIC = 0.125 μg/mL) and *Micrococcus luteus* (MIC = 0.125 μg/mL), with respect to other synthesized compounds and reference drug gatifloxacin. The target compounds were also assessed for their cytotoxic activity against normal mouse fibroblast (NIH/3T3) cells using MTT assay. The results indicated that these compounds exhibit antibacterial activity at non-cytotoxic concentrations.

1. Introduction

During recent years much attention has been devoted to the synthesis of new fluoroquinolones and to their antibacterial activity. Antibacterial resistance is now well documented for many pathogens, and studies with a variety of bacteria indicate that resistance can develop within just a few years. Resistance against many members of fluoroquinolones, particularly older ones, such as ciprofloxacin **1**, is increasing. Further advances in quinolone field are likely to provide better compounds capable of dealing with the resistant strains [1–3].

The inhibition of DNA gyrase or DNA topoisomerase IV 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. In addition, the substitution of bulky groups is permitted at the C-7 position [4–6]. Furthermore, it has been proposed that for Gram-positive organisms, increasing molecular mass and bulkiness of a substituent at the C-7 position are not barriers to penetration. With these in mind, previously several hybrids of 5-(nitroaryl)-1,3,4-thiadiazoles and different quinolones including ciprofloxacin **1**, norfloxacin **2**, enoxacin **3** and levofloxacin **4** have been synthesized with enhanced antibacterial activity against some Gram-positive organisms compared to the parent quinolones [7,8]. Gatifloxacin **5**, is a novel extended-spectrum fluoroquinolone (fourth-generation) with improved Gram-positive and anaerobe coverage compared with older agents such as ciprofloxacin **1** [9]. However, dysglycemia has been noted as the life-threatening adverse effect of gatifloxacin, which led to its withdrawal from the market in the United States in 2006 [10]. Thus, there exists continuous need for novel gatifloxacin derivatives, with better activity profile and tolerability, to overcome the limitations of gatifloxacin.

In continuing our efforts to find new quinolone–nitroarylthiadiazole hybrids, herein we report the synthesis and antibacterial activity of gatifloxacin hybrids **6** carrying a 5-(nitroaryl)-1,3,4-thiadiazol-2-yl group (Fig. 1).

2. Results and discussion

Our synthetic route to target compounds **6a–f** is presented in Fig. 2. The requisite 2-chloro-5-(nitroaryl)-1,3,4-thiadiazole **7a–f**,

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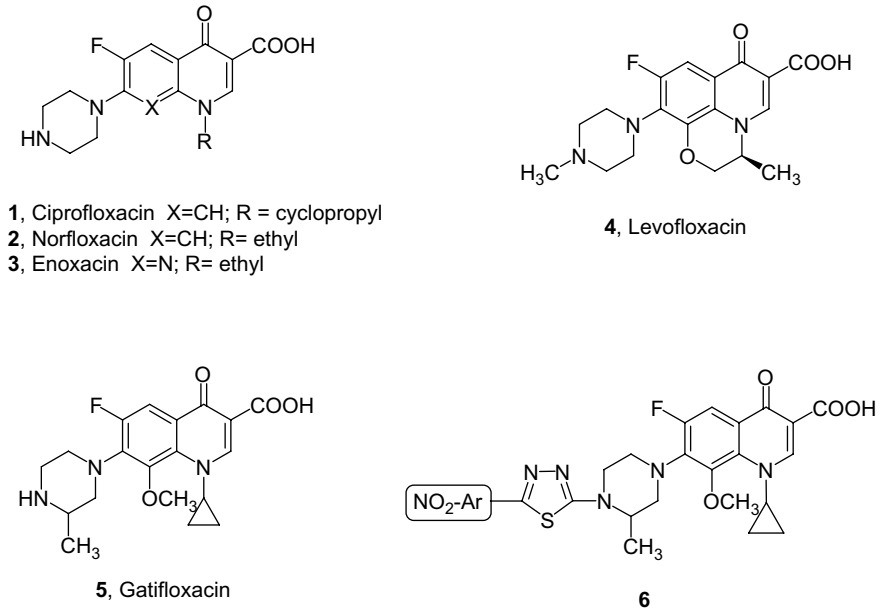

Fig. 1. Chemical structures of some piperazinyl quinolones and target compounds nitroaryl thiadiazole–gatifloxacin hybrids **6**.

was prepared according to the previously described method [7,8]. Reaction of gatifloxacin **5**, with 2-chloro-5-(nitroaryl)-1,3,4-thiadiazole **7a–f**, in DMF in the presence of $NaHCO_3$ at 85–90 °C, gave compounds **6a–f** (Table 1) [11,12].

Compounds **6a–f**, were tested *in vitro* by the conventional agar dilution method against a panel of microorganisms including *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 4940, *Streptococcus pneumonia* ATCC 1240, *Bacillus subtilis* ATCC 6051, *Enterococcus faecalis* NCTC 6013, *Micrococcus luteus* ATCC 1110, *Escherichia coli* ATCC 25922, *Salmonella typhi* ATCC 19430, *Shigella flexneri* NCTC 8516, *Klebsiella pneumonia* ATCC 10031, *Serratia marcescens* PTCC 1111 and *Pseudomonas aeruginosa* ATCC 27853 [13]. The minimum inhibitory concentration values (MICs) were determined by comparison to the parent quinolone, gatifloxacin **5** as reference drug (Table 2).

The MIC values of compounds **6a–f** against *Staphylococcus* strain indicated that some compounds possess a comparable or better activity with respect to gatifloxacin. Compound **6c**, exhibited the most potent inhibitory activity against *S. aureus* (MIC = 0.0313 μg/mL), and compound **6a** showed the most inhibitory activity against *S. epidemidis* (MIC = 0.0078 μg/mL), which were two and eightfold more potent than their parent quinolone (gatifloxacin **5**), respectively. The MIC values of compounds **6a–f** against *S. pneumonia* indicated that 4-nitrophenyl analog **6f** showed the most potent activity (MIC = 0.0625 μg/mL). Its activity was fourfold more than that of gatifloxacin. In addition, compounds **6a**, **b** and **d** exhibited potent activity (MIC = 0.25 μg/mL) comparable to gatifloxacin. Furthermore, the data obtained indicate that all compounds have more or equal inhibitory activity against *B. subtilis* (MIC = 0.0039–0.5 μg/mL), in comparison to reference drug (MIC = 0.5 μg/mL), with the exception of **6e** (MIC = 32 μg/mL). Most tested compounds had respectable *in vitro* activity against *E. faecalis*, but were less active than reference drug, with the exception of **6a** (MIC = 0.125 μg/mL), which was fourfold more potent than gatifloxacin. Compounds **6a**, **d** and **f** possessed a comparable or better activity against *M. luteus* (MIC = 0.125–1 μg/mL), with respect to gatifloxacin (MIC = 1 μg/mL).

Generally, compounds **6a–d** and **f** showed moderate to good activity against Gram-negatives including *E. coli*, *S. typhi*, *S. flexneri*, *K. pneumoniae* and *S. marcescens* but were less active than reference drug, with the exception of **6c** for *K. pneumoniae* (MIC = 0.5 μg/mL). In contrast, all the synthesized compounds did not show significant activity against another Gram-negative bacteria, *P. aeruginosa* (MICs >64).

Among synthesized compounds, nitrofuran analog **6a** exhibited the most potent inhibitory activity against Gram-positive bacteria including *S. epidermidis* (MIC = 0.0078 μg/mL), *B. subtilis* (MIC = 0.0039 μg/mL), *E. faecalis* (MIC = 0.125 μg/mL) and *M. luteus* (MIC = 0.125 μg/mL), with respect to other synthesized compounds and reference drug. Its inhibitory activity against *E. coli* (MIC = 1 μg/mL) and *S. pneumonia* (MIC = 0.25 μg/mL) was equal to reference drug gatifloxacin.

The *in vitro* cytotoxic activity of the test compounds **6a–f** against normal mouse fibroblast cell line (NIH/3T3) was investigated using

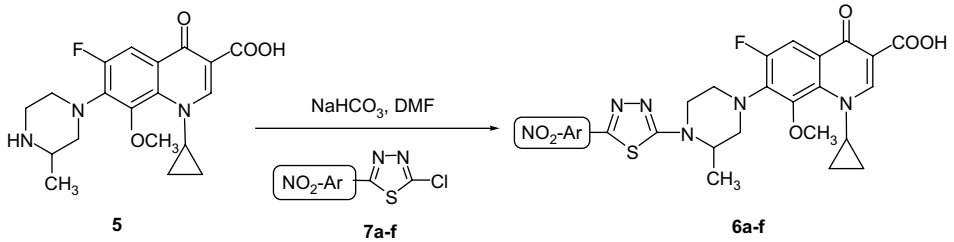

Fig. 2. Synthetic route to target compounds **6a–f**.