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Research paper

Synthesis, antimycobacterial and antibacterial activity of fluoroquinolone derivatives containing an 3-alkoxyimino-4-(cyclopropylanimo)methylpyrrolidine moiety

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ABSTRACT

A series of novel fluoroquinolone derivatives containing an 3-alkoxyimino-4-(cyclopropylanimo)methylpyrrolidine moiety were designed, synthesized and evaluated for their biological activity. Our results revealed that **19b2** shows good activity against MTB H37Rv ATCC 27294 (MIC: <0.25 μg/mL) and MDR-MTB 6133 clinical isolate (MIC: 0.11 μg/mL). Most of them have potent potency against Gram-positive strains, although they are generally poor active against Gram-negative strains. Especially, compounds **22b1** and **23a3** (MICs: <0.008–8 μg/mL) were found to 2–128 times more potent than ciprofloxacin and levofloxacin against all of the tested Gram-positive strains including quinolone-resistant MRSA, MRSE, *Enterococcus faecium* and *Enterococcus faecalis*.

1. Introduction

Fluoroquinolones (FQs) represent an extremely successful family of antibiotics that have a broad spectrum of antibacterial activity and relatively few side effects [1]. Targeting two type II bacterial topoisomerase enzymes, DNA gyrase and topoisomerase IV, FQs are used mainly to fight community-acquired and serious hospital-acquired infections [2]. Among of them, ciprofloxacin (CPFX), ofloxacin and levofloxacin (LVFX) are frequently used for the treatment of tuberculosis (TB) including multi-drug resistant TB (MDR-TB) as components of second-line regiments [3]. Two C-8 methoxy FQs gatifloxacin (GTFX) and moxifloxacin (MXFX), currently in Phase III clinical trials [4], show particularly strong in vitro and in vivo activity against *Mycobacterium tuberculosis* (MTB) and MDR-MTB [5,6].

However, FQ resistance increases in almost all Gram-negative and Gram-positive species as well as MTB, due mainly to the high level of use and to some degree of abuse [7,8]. The ideal strategy to such challenges is to find novel agents that inhibit new targets in pathogens, but it now remains extremely difficult. A more practical approach is to modify the structures of existing antibacterial agents to increase potency and to overcome resistance [9].

From the chemical structural point of view, FQs consist of a 4-quinolone/naphthyridone-3-carboxylic acid core and a secondary amino group attached to the C-7 position of the heterocyclic core (Fig. 1). CPFX, GTFX, LVFX and gemifloxacin (GMFX) represent the most common cores of important FQs on the market. Some new FQs, such as sitafloxacin (STFX), delafloxacin (DLFX) and AM-1954 have novel cores which are different from the traditional ones. On the other hand, the basic substituent at C-7 position, playing an important role in the antibacterial potency, spectrum and safety of FQs [10], is recognized as the most adaptable site for chemical change, and the presence of five- or six-membered nitrogen heterocycle including pyrrolidine, piperazine and piperidine at this position is particularly structural feature of FQs [11].

Recently, methyloxime-functionalized pyrrolidines as novel C-7 substituents have attracted great attention and led to the discovery

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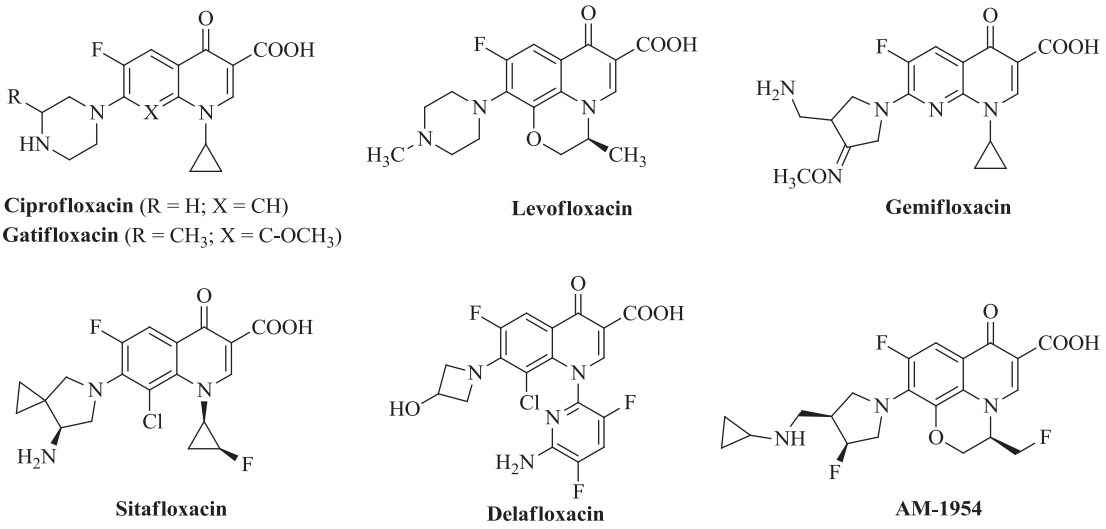

Fig. 1. Structures of some fluoroquinolones.

of new FQs (GMFX, zabofloxacin and DW286) [12–14]. In our previous works, some FQs containing oxime-functionalized azetidines, pyrrolidines or piperidines were found to have considerable biological activity [1,15–18]. These studies suggest the importance of the oxime functional group with respect to biological activity and pharmacokinetic profiles of FQs. Therefore, we intended to apply this modification strategy to the C-7 substituent of AM-1954 (Fig. 1) which has good in vitro activity against MDR-Gram-positive organisms [19]. More specifically, introduction of an oxime group of GMFX (and an alkyl group) instead of the fluorine atom on the pyrrolidine ring of AM-1954 develops 3-alkoxyimino-4-(cyclopropylanimo)methylpyrrolidine and 3-alkoxyimino-4-(cyclopropylanimo)methylpyrrolidine (Fig. 2) as new side chains at the 7-position of FQs. A series of novel FQ derivatives were designed and synthesized by condensation of the side chains with the traditional and new FQ cores. Our primary objective was to optimize the potency of these compounds against clinically important pathogens (especially Gram-positive ones) and MTB including MDR-MTB. A preliminary structure-activity relationship (SAR) study was also explored to facilitate the further development of FQs.

2. Results and discussion

2.1. Chemistry

Detailed synthetic pathways to pyrrolidine derivatives **11a**,**b** and target compounds **19**–**25** are depicted in Schemes 1 and 2, respectively. Reduction of readily available pyrrolidones (**1a**,**b**) [20,21] with $NaBH_4$ in methanol gave alcohols (**2a**,**b**), which upon hydroxyl protection by treatment with 3,4-dihydro-2H-pyran (DHP) in the presence of 4-methylbenzenesulfonic acid (p-TsOH) yielded esters (**3a**,**b**). Aldehydes (**5a**,**b**) were prepared via reduction of the esters **3a**,**b** with $LiAlH_4$ in tetrahydrofuran (THF) and then oxidation of the resulting alcohols (**4a**,**b**) with Dess-Martin Periodinane (DMP). Condensation of **5a**,**b** and cyclopropanamine produced secondary amines (**6a**,**b**), which were protected by treatment with di-tert-butyl dicarbonate (Boc_2O) and then deprotection of the hydroxyl groups gave the desired bis-Boc-protected amino alcohols (**8a**,**b**). Oxidation of compounds **8a**,**b** by DMP afforded the corresponding ketones (**9a**,**b**), on which the oxime function groups were introduced via condensation with alkoxylamines to yield amines (**10a**,**b**). The bis-Boc-protecting groups of **10a**,**b** were removed by pumping hydrogen chloride gas in methylene chloride to afford the pyrrolidine derivative dihydrochlorides (**11a**,**b**) (Scheme 1).

Finally, the target compounds **19**–**25** were obtained by coupling the new pyrrolidine derivatives **11a**,**b** with various compounds containing quinolone and naphthyridone cores according to well-established literature procedures (Scheme 2) [22]. In the case of naphthyridones **19**–**21**, direct condensation of **11a**,**b** with **12**–**14** was performed in the presence of triethylamine. However for quinolones **22**–**25**, boric chelates **15**–**18** were required to increase reactivity. All of the synthetic compounds were well characterized through the spectral characteristics.

2.2. Anti-MTB activity

Fifteen of the target compounds were selected initially for evaluation their in vitro activity against MTB H37Rv ATCC 27294 (MTB-1) using the Microplate Alamar Blue Assay (MABA) [23,24]. The minimum inhibitory concentration (MIC) is defined as the lowest concentration effecting a reduction in fluorescence of ≥90% relative to the mean of replicate bacterium-only controls and MICs of these compounds along with isoniazid (INH) and rifampicin (RFP) for comparison are presented in Table 1. The data reveal that

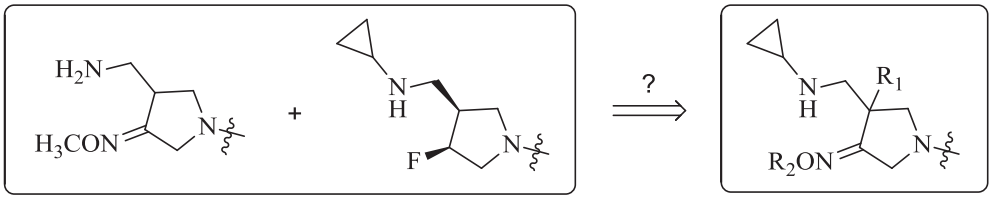

Fig. 2. Design of the new pyrrolidyl side chains.