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# Antibacterial Activity of Naphthyridone Derivatives Containing 8-Alkoxyimino-1,6-dizaspiro[3,4]octane Scaffolds

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We report herein *in vitro* antibacterial activity of a series of novel naphthyridone derivatives containing 8-alkoxyimino-1,6-dizaspiro-[3.4]octane scaffolds, the position isomers of the side chain at the C-7 position of zabofloxacin. Our results revealed that the target compounds were generally less active than the reference against the tested Gram-positive and Gram-negative strains with few exceptions, but compounds **1-5** and **7** showed good activity against MSSA and *P. aeruginosa* (MICs: 0.25-1 μg/mL). Especially, compounds **3** and **7** (MICs: 0.25 μg/mL) were found to be 4 times more potent than or comparable to levofloxacin against *P. aeruginosa*, the important conditioned pathogen on hospital infection. Simple structure-activity relationship was also discussed in this paper.

**Keywords: Naphthyridone derivatives, 8-Alkoxyimino-1,6-dizaspiro[3.4]octane Scaffolds, Antibacterial activity.**

## INTRODUCTION

Quinolones, exert their effect by inhibition of two type II bacterial topoisomerase enzymes, DNA gyrase (topoisomerase II) and topoisomerase IV[1,2], have been used to treat various diseases including respiratory tract infections, urinary tract infections, sexually transmitted diseases, gastrointestinal and abdominal infections, skin and soft tissue infections and infections of the bone and joints[3].

Structure-activity relationship (SAR) studies of quinolone antibacterial agents have revealed that the C-7 position is the most adaptable site for chemical modification and this area greatly influences their potency, spectrum and safety[4,5]. More interestingly, previous work on piperidinyl quinolones suggested the importance of the relative positions of substituent groups on the C-7 side chain with respect to biological activity. For example, 7-(4-alkoxyimino-3-aminopiperidin-yl)quinolones might have completely different activity compared to their position isomers containing a 3-alkoxyimino-4/5-aminopiperidine moiety at the C-7 position[6-8].

## EXPERIMENTAL

Zabofloxacin (DW224a, Fig. 1), a novel naphthyridone agent containing an oxime-functionalized spirocycle scaffold as the C-7 substituent, showed excellent activity against Gram-positive resistant bacteria, associated with very low toxicity and favorable pharmacokinetic profiles[9]. Therefore, we have designed and synthesized a series of novel naphthyridone derivatives having 8-alkoxyimino-1,6-dizaspiro[3.4]octane scaffolds **1-9** (Fig. 1), the position isomers of the side chain at the C-7 position of zabofloxacin[10]. Their *in vitro* antibacterial activity against representative strains and structure-activity relationship were studied in this paper.

## RESULTS AND DISCUSSION

The target compounds **1-9** were synthesized according to our previous work[10] and evaluated for their *in vitro* antibacterial activity against representative Gram-positive and Gram-negative strains using standard techniques[11]. Minimum inhibitory concentration (MIC) is defined as the concentration of the compound required to give complete inhibition of bacterial growth and MICs of the synthesized compounds along with the reference drug levofloxacin (LVFX) for comparison are reported in Table-1. These data suggested that *in vitro* antibacterial activity of the target compounds was less than the reference against all of the tested Gram-positive and Gram-negative strains with few exceptions. Nevertheless, compounds **1-5** and **7** showed good activity against four strains of

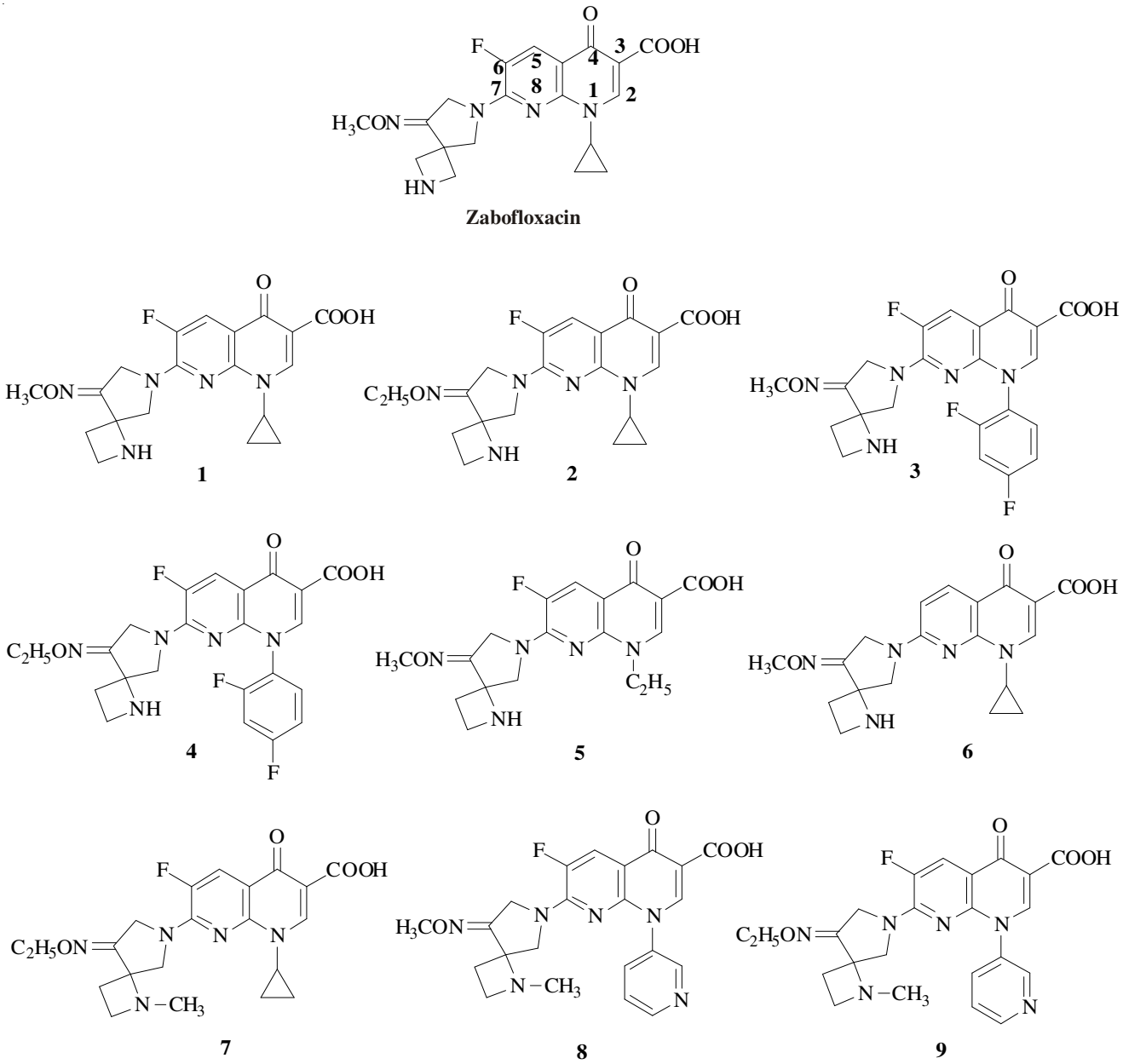


Fig. 1. Chemical structures of zabofloxacin and its derivatives

methicillin-sensitive *Staphylococcus aureus* (MSSA) (MICs: 0.25-1 μg/mL) and two strains of *Pseudomonas aeruginosa* (MICs: 0.25-0.5 μg/mL). Among of them, compounds **3** and **7** (MICs: 0.25 μg/mL) were found to be 4 times more potent than or comparable to LVFX against *P. aeruginosa*, the important conditioned pathogen on hospital infection.

The structure-activity relationship activity revealed that: (1) for N-1 position with the same C-7 substituent, cyclopropyl > 2,4-difluorobenzyl ≈ ethyl; (2) 6-fluoro naphthyridones > 6-hydrogen analogs; (3) introduction of *N*-methyl group at C-7 position decreased their activity against Gram-positive strains (**2** *vs* **7**), but appeared no effect for their activity against Gram-negative strains.

## Conclusion

In summary, a series of novel naphthyridone derivatives containing 8-alkoxyimino-1,6-dizaspiro[3.4]octane scaffolds were evaluated for their *in vitro* antibacterial activity against representative strains. Although most of the target compounds were generally less active than the reference against the tested Gram-positive and Gram-negative strains, compounds **1-5** and **7** showed good activity against MSSA and *P. aeruginosa*. Among of them, compounds **3** and **7** (MICs: 0.25 μg/mL) were found to be 4 times more potent than or comparable to LVFX against *P. aeruginosa*.

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TABLE-1
*IN VITRO* ANTIBACTERIAL ACTIVITY OF COMPOUNDS **1-9** AGAINST GRAM-POSITIVE AND GRAM-NEGATIVE STRAINS

| Strains | MIC (μg/mL) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | LVFX |
| S.a. | 0.25 | 0.25 | 0.25 | 2 | 0.5 | 0.25 | 0.5 | 2 | 2 | 0.125 |
| MRSA1* | 64 | 32 | 32 | 64 | 128 | 32 | >128 | >128 | >128 | 32 |
| MRSA2* | 64 | 32 | 32 | 128 | 128 | 32 | >128 | >128 | >128 | 32 |
| MRSA3* | 32 | 32 | 32 | 128 | 64 | 32 | >128 | >128 | >128 | 16 |
| MSSA1* | 0.25 | 0.25 | 0.25 | 0.5 | 0.5 | 1 | 0.5 | 4 | 4 | 0.125 |
| MSSA2* | 0.5 | 0.5 | 1 | 0.5 | 0.5 | 4 | 1 | 8 | 8 | 0.5 |
| MSSA3* | 0.5 | 0.25 | 0.25 | 0.5 | 0.5 | 4 | 0.5 | 2 | 2 | 0.25 |
| MRSE1* | 32 | 64 | 16 | 64 | 128 | >128 | >128 | >128 | >128 | 8 |
| MRSE2* | 4 | 2 | 8 | 8 | 16 | 128 | 16 | >128 | >128 | 4 |
| MSSE1* | 64 | 64 | 64 | 64 | 128 | 128 | >128 | >128 | >128 | 128 |
| MSSE2* | 8 | 16 | 16 | 16 | 64 | 128 | 4 | >128 | >128 | 4 |
| MSSE3* | 8 | 16 | 8 | 16 | 64 | 128 | 4 | >128 | >128 | 4 |
| MSSE4* | 64 | 64 | 64 | 64 | 128 | 128 | >128 | >128 | >128 | 128 |
| E.fa.1 | 32 | 32 | 8 | 16 | 64 | 128 | >128 | 64 | >128 | 8 |
| E.fa.2 | 32 | 64 | 64 | 128 | 128 | 128 | >128 | >128 | >128 | 64 |
| E.f3.1 | 32 | 64 | 32 | 32 | 128 | 128 | >128 | 128 | 128 | 16 |
| E.fm.1 | 32 | 64 | 32 | 64 | 64 | 64 | >128 | >128 | >128 | 32 |
| E.fm.2 | 32 | 2 | 2 | 4 | 8 | 64 | >128 | 32 | 64 | 2 |
| E.fm.3 | 32 | 64 | 32 | 64 | 64 | 64 | >128 | >128 | >128 | 32 |
| S.p. 1* | 16 | 16 | 16 | 16 | 8 | 32 | 32 | 32 | 64 | 16 |
| S.p. 2* | 4 | 4 | 8 | 2 | 4 | 32 | 4 | 16 | 64 | 1 |
| S.p. 3* | 32 | 32 | 64 | 64 | 64 | 64 | >128 | >128 | >128 | 32 |
| S.p. 4* | 2 | 2 | 1 | 2 | 8 | 32 | 4 | 32 | 32 | 1 |
| S.p. 5* | 0.125 | 0.25 | 1 | 2 | 0.5 | 1 | 2 | 16 | 32 | 0.06 |
| E.co. | 0.06 | 0.25 | 0.5 | 1 | 0.5 | 0.5 | 2 | 8 | 16 | 0.008 |
| E.co.1 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | 4 |
| E.co.2 | 16 | 4 | 16 | 16 | 8 | 8 | 16 | 32 | 128 | 0.25 |
| E.co.3 | 32 | >128 | 64 | >128 | 128 | 128 | >128 | >128 | >128 | 4 |
| E.co.2* | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | 16 |
| E.co.3* | 128 | 128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | 8 |
| E.co.4* | 8 | 16 | 32 | 64 | 32 | 32 | >128 | >128 | >128 | 1 |
| K.p.1 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | 32 |
| K.p.2 | 16 | 4 | 8 | 16 | 8 | 8 | 16 | 32 | 128 | 1 |
| K.p.4 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | 32 |
| K.p.1* | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | 4 |
| K.p.2* | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | 8 |
| K.p.3* | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | >128 | 8 |
| P.a.1* | 0.5 | 0.5 | 0.25 | 0.5 | 0.5 | 2 | 0.25 | 2 | 2 | 0.25 |
| P.a.2* | 0.5 | 0.5 | 0.25 | 0.5 | 0.5 | 2 | 0.25 | 2 | 2 | 1 |

Abbreviations: *S.a.*, *Staphylococcus aureus* ATCC259223; MRSA1, methicillin-resistant *Staphylococcus aureus* 10-11; MRSA2, methicillin-resistant *Staphylococcus aureus* 10-13; MRSA3, methicillin-resistant *Staphylococcus aureus* 10-15; MSSA1, methicillin-sensitive *Staphylococcus aureus* 10-11; MSSA2, methicillin-sensitive *Staphylococcus aureus* 10-13; MSSA3, methicillin-sensitive *Staphylococcus aureus* 10-14; MRSE1, methicillin-resistant *Staphylococcus epidermidis* 10-10; MRSE2, methicillin-resistant *Staphylococcus epidermidis* 10-13; MSSE1, methicillin-sensitive *Staphylococcus epidermidis* 10-11; MSSE2, methicillin-sensitive *Staphylococcus epidermidis* 10-13; MSSE3, methicillin-sensitive *Staphylococcus epidermidis* 10-14; MSSE4, methicillin-sensitive *Staphylococcus epidermidis* 10-15; E.fa.1, *Enterococcus faecalis* 10-5; E.fa.2, *Enterococcus faecalis* 10-6; E.fa.3, *Enterococcus faecalis* 10-7; *E.fm.*1, *Enterococcus faecium* 10-5; *E.fm.*2, *Enterococcus faecium* 10-6; *E.fm.*3, *Enterococcus faecium* 10-9; *S.p.*1, *Streptococcus pneumoniae* 10-1; *S.p.*2, *Streptococcus pneumoniae* 10-2; *S.p.*3, *Streptococcus pneumoniae* 10-4; *S.p.*4, *Streptococcus pneumoniae* 10-5; *S.p.*5, *Streptococcus pneumoniae* 10-6; *E.co.*, *Escherichia coli* ATCC25922; *E.co.*1, *Escherichia coli* 10-1; *E.co.*2, *Escherichia coli* 10-2; *E.co.*3, *Escherichia coli* 10-3; *E.co.*4, *Escherichia coli* 10-4; *K.*p.1, *Klebsiella pneumoniae* 10-1; *K.*p.2, *Klebsiella pneumoniae* 10-2; *K.*p.3, *Klebsiella pneumoniae* 10-3; *K.*p.4, *Klebsiella pneumoniae* 10-4; *P.a.*1, *Pseudomonas aeruginosa* 10-9; *P.a.*2, *Pseudomonas aeruginosa* 10-18; *, extended spectrum beta-lactamases (ESBLs)-producing; LVFX, levofloxacin


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