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Synthesis and structure–activity relationships of novel 9-oxime acylides with improved bactericidal activity

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ABSTRACT

9-Oxime acylides have different SAR and binding modes from 9-oxime ketolides. An aminopyridyl or carbamoylpyridyl group anchored at the end of the 9-oxime 2-propargyl group is beneficial for antimicrobial activity. Both the 2-pyridyl and 3-pyridyl groups derived from 3-OH have stacking interactions with the base pair G2505/C2610 (*Escherichia coli* numbering) of the bacterial rRNA. Compounds **3** presented characteristic features that belong to bactericidal agents when used against constitutive-*erm* resistant *Staphylococcus aureus*, susceptible and *mef*-encoded *Streptococcus pneumoniae*, inducible-*erm* resistant *Streptococcus pyogenes*, and *Moraxella catarrhalis*. A docking model indicated that the carbamoylpyridyl group of **3h** may hydrogen bond to G2061 in addition to π–π stacking over the adenine of A2062 that proved to gate the tunnel for the egress of the nascent peptide. This study suggests that the 9-oxime acylides possess a bactericidal mechanism that is different from the traditional near-complete inhibition of protein synthesis. These studies provide a foundation for the rational design of macrolide antibiotics.

1. Introduction

The bacterial protein synthesis inhibitor erythromycin is a 14-membered macrolide (Fig. 1) that has been prescribed against upper and lower respiratory tract infections for more than 60 years. Nowadays, macrolide resistance is increasingly prevalent among clinical isolates. In the presence of erythromycin or its derivatives such as clarithromycin and azithromycin (Fig. 1), resistance caused by macrolide efflux (named *mef*) or erythromycin ribosomal methylation (named *erm*) are observed. Cladinose attached at the 3-O position is believed to be responsible for induction of erythromycin-resistance.[1]

To combat the resistance, a new scaffold named ketolide appeared with a 3-keto group, instead of the original cladinose, plus a spacer anchored with an aryl group. Further study indicated the additional sidechains play vital roles in fighting against the *erm*-encoded resistant bacteria whose ribosomal A2058Ec nucleotides (*Escherichia coli* numbering) are mono- or dimethylated. For example, telithromycin,[2,3] solithromycin,[4] and K-1804[5] were verified to interact with a new target A752Ec, and the extra binding affinity helps the ketolides regain antimicrobial activity. Thus far, telithromycin has been marketed, and solithromycin, cethromycin,[6] modithromycin[7] and PF-02487881[8] are in clinical trials (Figs. 1 and 2). However, ketolides have several deficiencies. First, ketolides induce *erm* resistance [9] by a new pathway named ribosomal frameshifting.[10] Second, the liver damage caused by the lead ketolide, telithromycin, resulted in the removal of two of the three indications by the U.S. FDA, and the experts stated that the future use of ketolides may be limited by the issue of hepatotoxicity unless the etiology can be clarified.[11,12] Third, ketolides are generally inactive against constitutively resistant *erm*-containing *Staphylococcus aureus*. Thus, there remains an acute need for safe and effective macrolides that are not limited by bacterial resistance.

Acylides, an early non-ketolide chemotype with potent activity versus resistant strains, were invented by Taisho. Pyridyl acetyl groups replaced the original cladinose (Fig. 3).[13,14] Later, new acylides were reported with an additional sidechain at the 6-OH,[15] and the 11-N,[16–18] respectively. Unlike ketolides, the binding mode of the acylides is unclear. We previously reported that the sidechains of 3-quinoly-2-*E*-propenyl and 4-isoquinoly-2-propargyl groups were optimal for 9-oxime ketolides and the resulting ketolides showed activity comparable to telithromycin.[19,20] But the antibacterial activity dropped off steeply when these sidechains were installed on 9-oxime acylides, as illustrated in Figure 4.[21] This phenomenon suggested that 9-oxime acylides probably have a different binding mode from 9-oxime ketolides and an in-depth study of the structure–activity relationships was required.

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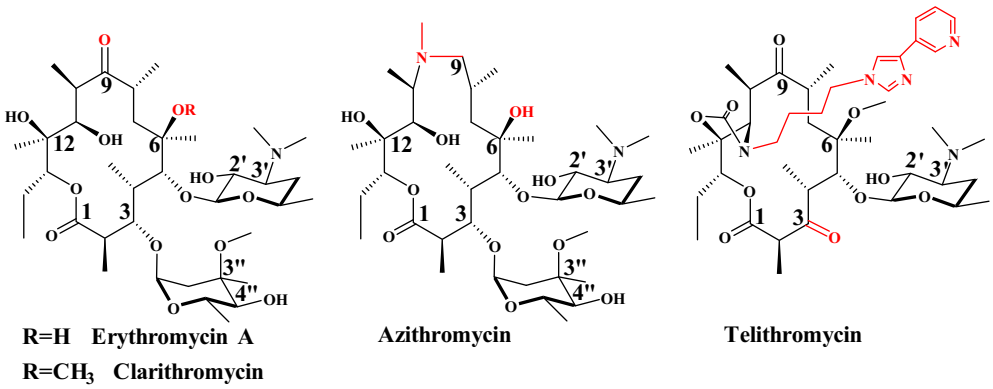

Figure 1. The marketed 1st, 2nd, and 3rd generation erythromycins.

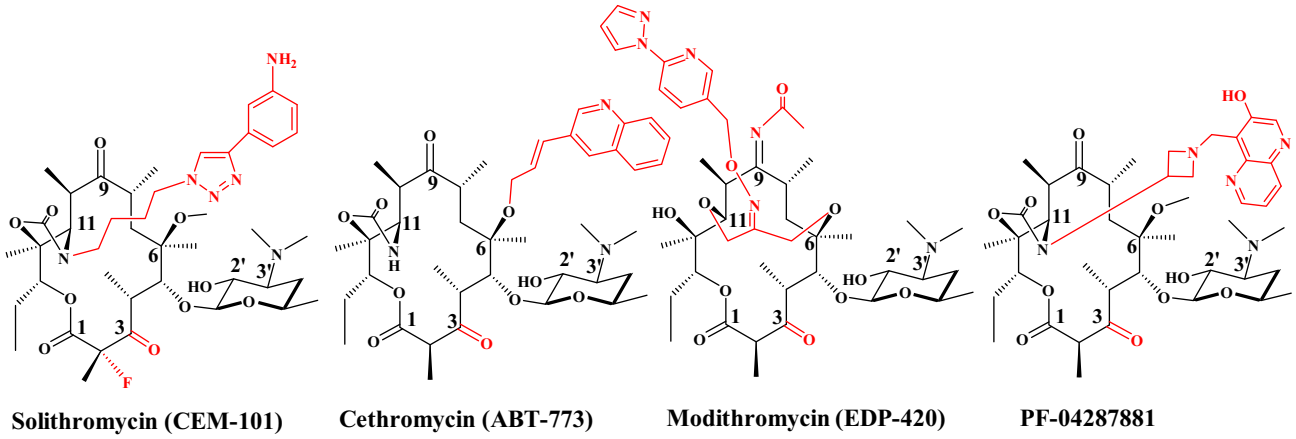

Figure 2. The ketolides in clinical trials.

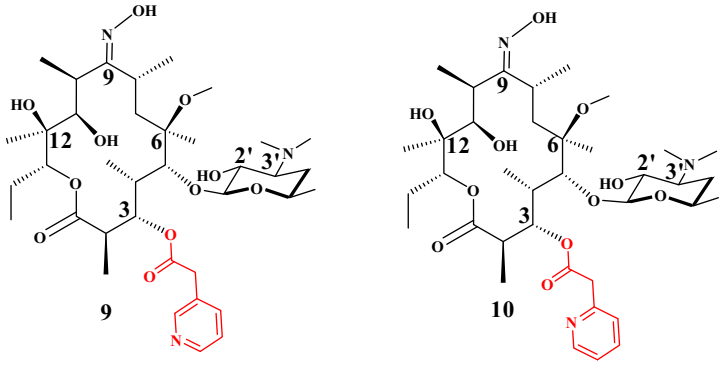

Figure 3. The acylides invented by Taisho.

Erythromycin is a complete inhibitor of protein synthesis so erythromycins are long viewed as being bacteriostatic agents. Little attention has been paid to the bactericidal activity.[22–25] Recent research indicated that in comparison to erythromycin, ketolides allow continued synthesis of far more proteins, and blocking the expression of only a part of the proteome is believed to be more fatal to the cell.[26] Nevertheless, erythromycins' bactericidal structure–activity relationships have not been completely mapped.[27] Herein, we propose a potential binding mode of the acylides and revisit the 9-oxime acylides. Meanwhile, new 9-oxime acylides with high bactericidal activity are presented to offer a valuable tool for clarifying the details of the selective release mode of nascent proteins, which challenges the traditional view in this field.[26,28]

2. Chemistry

Target compounds **3**, **7** and **8** were designed and prepared for biological assay, as illustrated in Schemes 1–4. Compounds **1** and **5** were obtained according to the reported procedure in seven steps from commercially available erythromycin 9-oxime.[19,20] Next, Sonogashira reaction with **1** (or Heck reaction with **5**) led to compounds **2** (or **6**). The introduction of a 2-pyridyl acetyl group to the 3-OH of **2** (or **6**) followed by methanolysis of the 2′-acetate produced the corresponding compounds **3a**–**3e** (or **7a**–**7e**), as illustrated in Scheme 1 (or Scheme 3). The amino groups on the heteroaryl groups of **2b**–**2d** and **6b**–**6d** were vulnerable to acylation by excess 2-pyridyl acetic acid. As a result, **3b**–**3d** and **7b**–**7d** were