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Synthesis and antibacterial evaluation of novel 11-O-carbamoyl clarithromycin ketolides

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ABSTRACT

A series of novel 11-O-carbamoyl clarithromycin ketolides were designed, synthesized and evaluated for their *in vitro* antibacterial activity. The results showed that the majority of the target compounds displayed improved activity compared with references against erythromycin-resistant *S. pneumoniae* A22072 expressing the *mef* gene, *S. pneumoniae* B1 expressing the *erm* gene and *S. pneumoniae* AB11 expressing the *mef* and *erm* genes. In particular, compounds **9**, **18**, **19** and **22** showed the most potent activity against erythromycin-resistant *S. pneumoniae* A22072 with the MIC values of 0.5 μg/mL. Furthermore, compounds **11**, **18**, **19**, **24** and **29** were also found to exhibit favorable antibacterial activity against erythromycin-susceptible *S. pyogenes* with the MIC values of 0.125–1 μg/mL, and moderate activity against erythromycin-susceptible *S. aureus* ATCC25923 and *B. subtilis* ATCC9372.

Macrolide antibiotics are weak basic and lipophilic compounds produced by *Streptomycetes*, the activity of which stems from macrolide ring, a large lactone ring to which one or more deoxy sugars, usually cladinose or desosamine, are attached.[1] They have been proved to be safe and effective for use in treating upper and lower respiratory tract infections.[2] Preventing the protein synthesis of bacteria by binding to the entrance of the peptide exit tunnel of the large subunit (50S) of bacterial ribosome is the mechanism of macrolide antibiotics.[3] Erythromycin A (EMA), which belongs to the first-generation macrolides, readily degrades under acidic conditions leading to the loss of antibacterial activity and the generation of gastrointestinal side effects.[4] Clarithromycin (CAM) and azithromycin (AZM) (Fig. 1), the representatives of the second-generation macrolides, have better acid-stability in the stomach and more excellent bioavailability, as well as fewer gastrointestinal side effects.

However, the growth of drug-resistant bacteria appears rapidly due to the abuse of macrolide antibiotics, thus making the effectiveness of macrolide antibiotics be severely limited.[5] The macrolide-resistant pathogens are mainly divided into two genotypes: the *erm* gene-mediated base-specific mono- or di-methylation of 23S ribosomal RNA, and the *mef* gene-mediated membrane protein efflux pump that can export the macrolides outside of the cells.[6] Therefore, it's urgent to develop novel macrolide antibiotics against resistant pathogens. An X-ray cocrystal structure research reveals that 3-O-cladinose is not a necessary moiety for antibacterial activity,[7] and modification at the C-3 position results in enhanced activity against efflux resistance.[8] Consequently, in the late of 1990s, the third-generation macrolides known as ketolides[1] and acylides[9] (Fig. 1) were designed to settle the resistance.

Mounts of investigations have been carried out on the chemical modifications of 14-membered macrolides to effectively cope with bacterial resistance over the past years. Compound EP-1553 (Fig. 1), bearing an arylalkyl group at the C-11 position of its skeleton, exhibited good activity against macrolide-resistant bacteria.[10] We also reported a 15-membered macrolide azithromycin derivative A (Fig. 1), which was modified at the C-11 and C-4″ positions, and showed remarkably improved anti-resistant activity compared to CAM and AZM.[11] Besides, the ketolide telithromycin was not only less prone to induce bacterial resistance than other macrolide antibiotics, but also displayed good pharmacokinetic parameters *in vivo*, as well as high therapeutic efficacy in mice that infected with respiratory pathogens.[12]

On the basis of the consideration detailed above, we designed and synthesized a series of novel 11-O-carbamoyl clarithromycin ketolides to prevent the *erm*- or *mef*-mediated bacterial resistance and broaden their antibacterial spectra. To our knowledge, the 11-O-carbamoyl clarithromycin ketolides were first investigated by our group. On the one hand, 3-keto group avoided the induction of bacterial resistance due to removal of the 3-O-cladinose. On the other hand, the 11-O-arylalkylcarbamoyl side chain was

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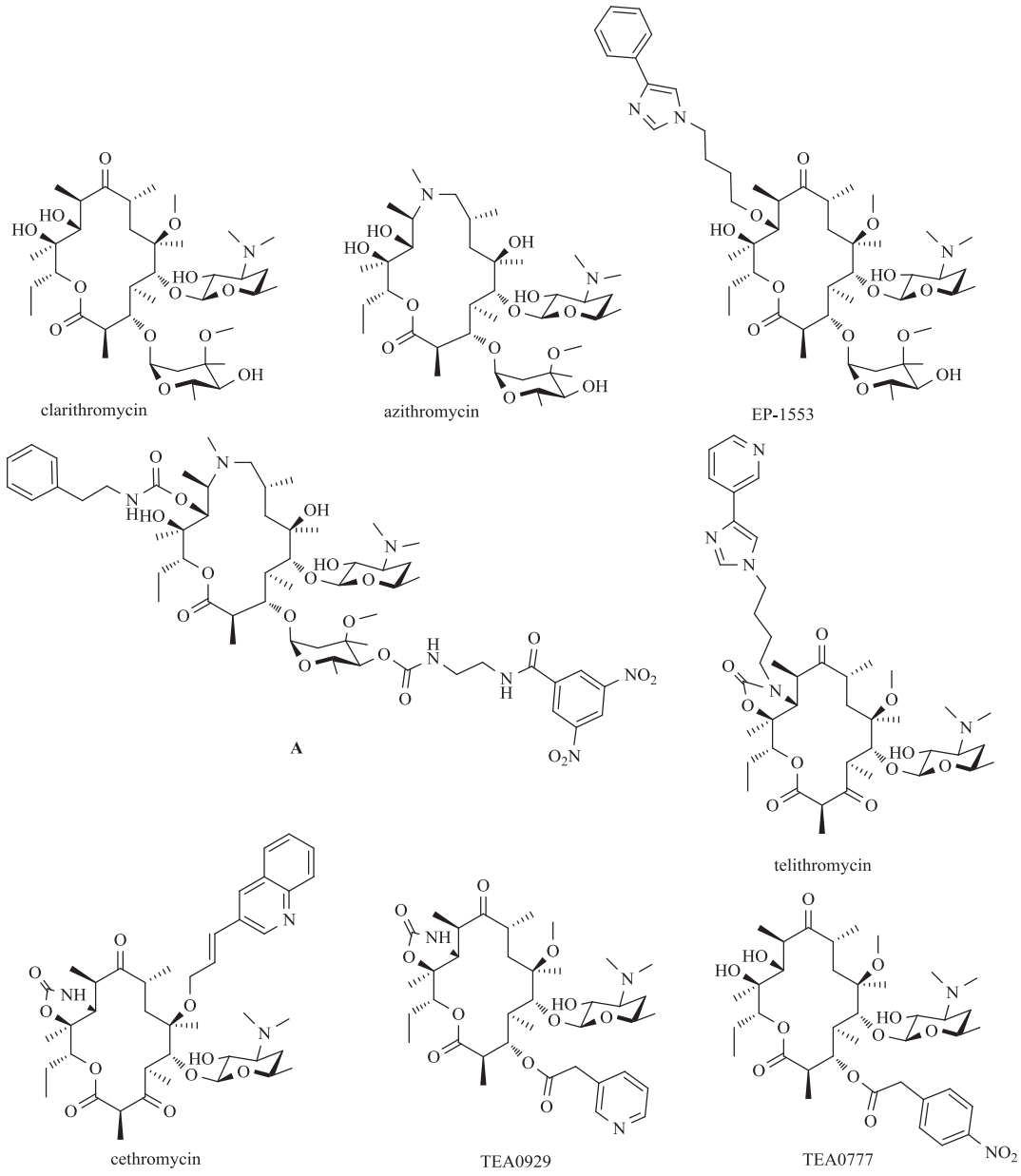
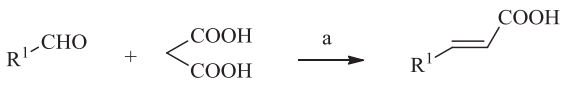


Fig. 1. The structures of clarithromycin, azithromycin, EP-1553, **A**, ketolides and acylides.

beneficial to bind with A752 in domain II through additional forces such as hydrogen bonding, π-stacking or van der Waals interactions to improve the antibacterial activity.

The general synthetic method for the acrylic acids is shown in Scheme 1. The reaction of different aldehydes with malonic acid gave corresponding acrylic acids (**A1-A11**) in the presence of pyridine and piperidine.

The synthetic method for 11-O-aralkylcarbamoyl-3-O-descladinosyl-3-oxo-clarithromycin derivatives is shown in Scheme 2. Clarithromycin was used as the starting material for the synthesis



A1	R^1= phenyl	**A5**	R^1= 4-nitrophenyl	**A9**	R^1= 2,4-dichlorophenyl
A2	R^1= 4-fluorophenyl	**A6**	R^1= 4-methylphenyl	**A10**	R^1= naphthyl
A3	R^1= 4-chlorophenyl	**A7**	R^1= 4-hydroxyphenyl	**A11**	R^1= furyl
A4	R^1= 4-bromophenyl	**A8**	R^1= 2-chlorophenyl		

Scheme 1. Synthesis of acrylic acids. Reagents and conditions: a) pyridine, piperidine, reflux, 43–86%.