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Design, synthesis and structure–activity relationships of 6-*O*-arylpropargyl diazalides with potent activity against multidrug-resistant *Streptococcus pneumoniae*

Hong Yong,*,† Yu Gui Gu, Richard F. Clark, Thomas Marron, Zhenkun Ma, Niru Soni, Gregory G. Stone, Angela M. Nilius, Kennan Marsh and Stevan W. Djuric

Infectious Disease Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60044, USA

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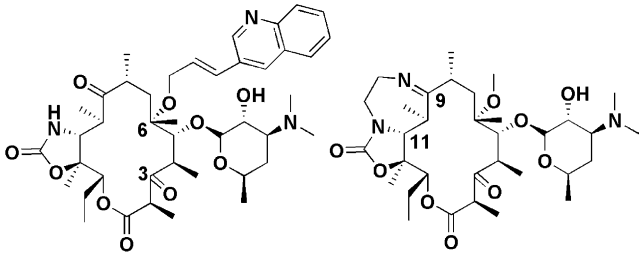
Abstract—A novel series of 6-*O*-arylpropargyl diazalides was synthesized and evaluated for their antibacterial activity. Members of this series exhibited potent activity against erythromycin-resistant respiratory tract pathogens.

Streptococcus pneumoniae is a critical pathogen causing community-acquired respiratory tract infections (RTIs). Currently, a high percentage of clinical isolates of this important pathogen are resistant to β-lactams, macrolides, quinolones and other commonly used antibiotics.[1] In order to identify a safe and effective agent to combat infections caused by multidrug-resistant *S. pneumoniae* (MRSP), we have designed and synthesized a series of novel tricyclic ketolides, named diazalides. Members of this series exhibit potent activity against MRSP and improved pharmacological profiles.

Previous work in this laboratory illustrated that introduction of an arylalkyl group to the 6-*O* position of the ketolide skeleton provides a series of compounds with improved activity against MRSP.[2] These compounds are exemplified by cethromycin (ABT-773), a potent ketolide that is currently in late stage clinical development. Our structure–activity relationship (SAR) analysis suggested that the improved activity against drug resistant organisms was likely due to an anchor effect of the aryl group that provides additional interactions with the molecular target, the bacterial ribosome.[3] Studies have also indicated that the linker group between the 6-*O* position of the macrolide skeleton and the aryl group play a significant role for the activity against resistant strains. A propargyl or allyl linker appears to be optimal.[4] In addition, a series of tricyclic ketolides, exemplified by TE-802, has been reported by Taisho scientists.[5] The analogues are characterized by a diaza bridge linking the C-9 and the C-11 positions of the macrolide ring and are therefore called 'diazalides'. These diazalides exhibit improved acid stability, longer in vivo half-life and increased tissue penetration. To take advantage of the potency profile of the 6-*O*-arylpropargyl ketolide series and the pharmacological profile of the diazalide series, we designed a new series of analogues (Fig. 1) that combines the structural characteristics of both 6-*O*-arylpropargyl ketolide and the Taisho diazalides.



The synthesis of these target molecules requires three major modifications to erythromycin as highlighted in

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* Corresponding author. Tel.: +1 847 938 6939; fax: +1 847 938 1674; e-mail: hong.yong@abbott.com
† At present address: Abbott Laboratories, D47H, AP10-3, 100 Abbott Park Road, Abbott Park, IL 60064-6112, USA.

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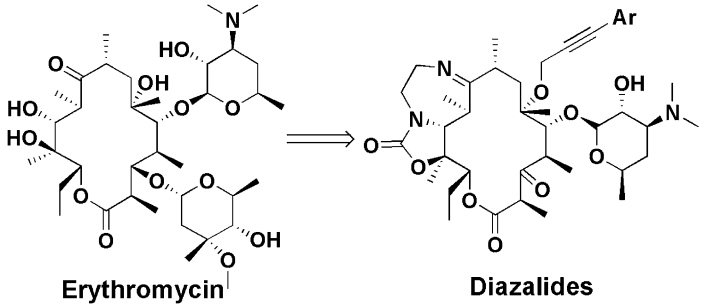
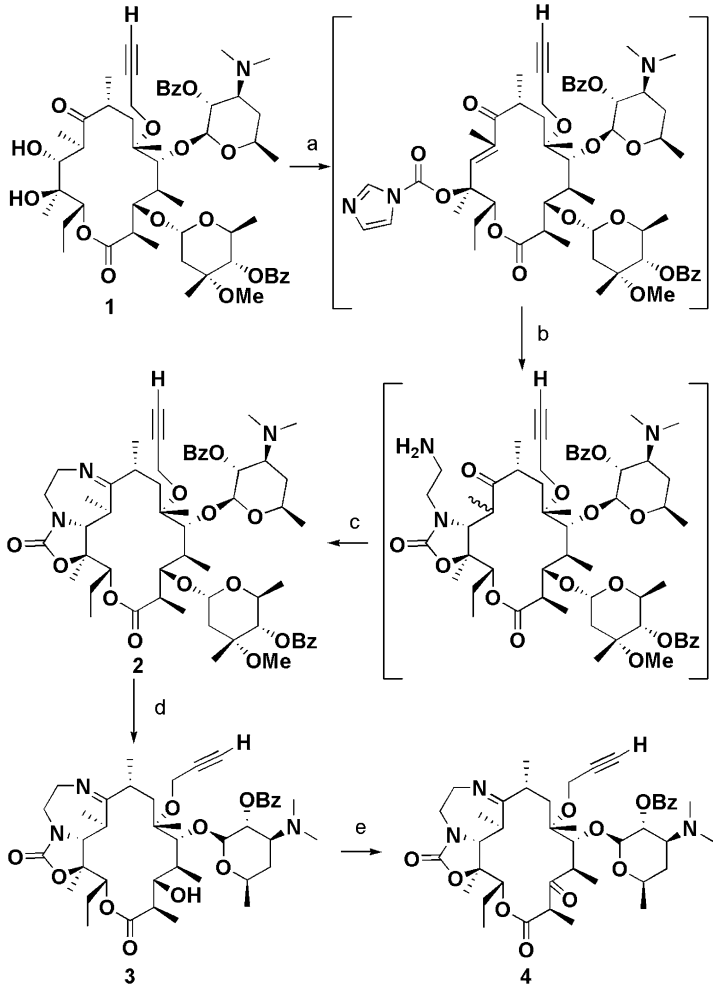


Figure 1. Synthetic modifications required for the construction of 6-*O*-arylpropargyl diazalides from erythromycin.

Figure 1: (1) installation of a keto group to the C-3 position; (2) construction of a C-9 to C-11 diaza bridge group and (3) introduction of a C-6 substitution.

Our synthesis (Scheme 1) started from 6-*O*-propargyl-2′-*O*-benzoyl-4″-*O*-benzoylerythromycin **1**, which was prepared according to a published procedure.[4] As discussed earlier, the 6-*O*-propargyl group was strategically introduced before the C-3 keto and the C-9/C-11 bridge to prevent undesirable side reactions.[3] Reaction of **1** with CDI in the presence of DBU and DMAP led to the corresponding acylimidazolide. Subsequent reaction of the acylimidazolide with ethylenediamine provided the cyclic carbamate as a mixture of C-10 diastereomers. The carbamate intermediate was then treated with acetic acid which induced the epimerization of the C-10 chiral centre and facilitated cyclization of the terminal amino group onto the C-9 keto group to form the tricyclic skeleton **2**. Hydrolysis of the cladinose sugar at the C-3 position under acidic conditions followed by Corey–Kim



Scheme 1. Reagents and conditions: (a) CDI, DBU, DMAP, THF/DMF (3:1); (b) ethylene diamine, CH_3CN/H_2O (10:1); (c) AcOH, toluene, 59% for (a)–(c); (d) 2 N HCl, $EtOH/H_2O$ (1:1), 55 °C, 2 days, 82%; (e) NCS, DMS, NEt_3, CH_2Cl_2, 75%.