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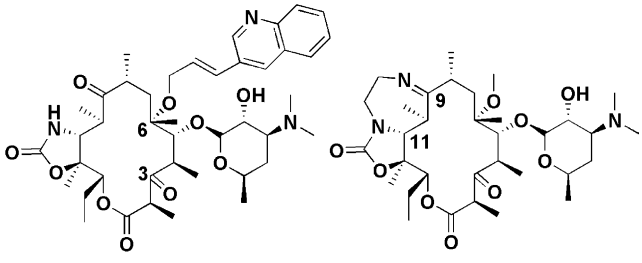
Abstract—A novel series of 6-*O*-arylpropargyl diazalides was synthesized and evaluated for their antibacterial activity. Members of this series exhibited potent activity against erythromycin-resistant respiratory tract pathogens.

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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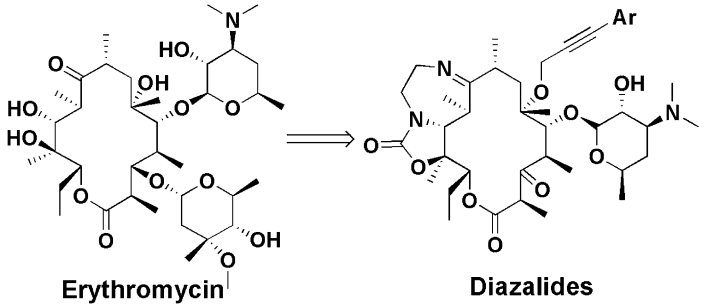
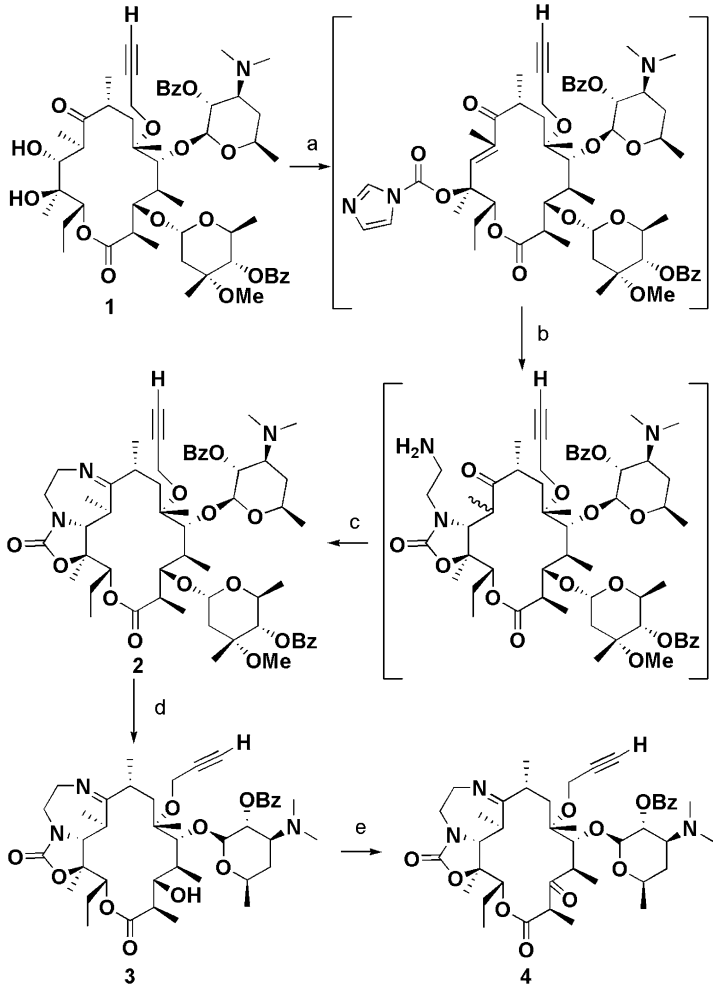


Figure 1. Synthetic modifications required for the construction of 6-*O*-arylpropargyl diazalides from erythromycin.

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



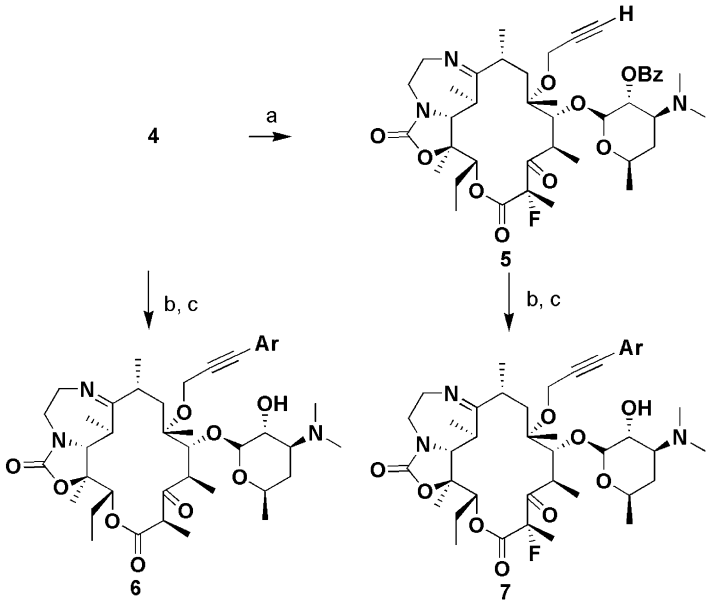
Scheme 1. Reagents and conditions: (a) CDI, DBU, DMAP, THF/DMF (3:1); (b) ethylene diamine, CH_3CN/H_2O (10:1); (c) AcOH, toluene, 59% for (a)–(c); (d) 2 N HCl, $EtOH/H_2O$ (1:1), 55 °C, 2 days, 82%; (e) NCS, DMS, NEt_3, CH_2Cl_2, 75%.

oxidation of the resulting C-3 hydroxy compound **3** furnished the 6-*O*-propargyl diazalide **4** which served as a key intermediate for the following derivatizations.

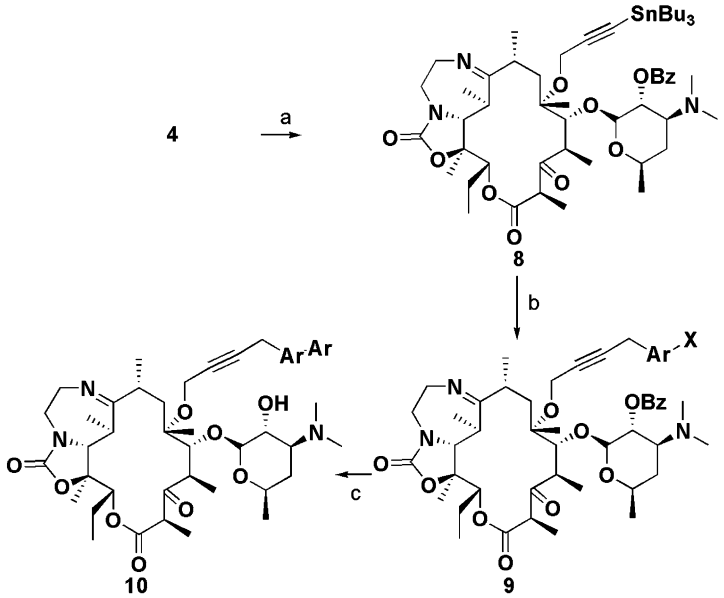
The 2-fluoro-6-*O*-propargyl diazalide **5**, another key intermediate, was prepared by reacting compound **4** with NaH and $(PhSO_2)_2NF$.[6] Treatment of compound **4** or **5** with a variety of aryl halides under the Sonogashira coupling conditions led to coupling products in good to excellent yields. Finally hydrolysis of the 2′-*O*-protecting group by heating in methanol provided the desired 6-*O*-arylpropargyl diazalides **6** and **7** (Scheme 2).

The methylene homologues of compounds **6** were prepared through an alkynylstannane **8** which was prepared according to a published procedure.[4b] Reaction of **4** with tributyltin ethoxide provided a stable intermediate **8** that was purified by chromatography. Coupling of **8** with an arylmethyl halide catalyzed by a palladium catalyst provided **9**, which was converted into the desired diazalide homologues **10** under Stille coupling conditions followed by debenzoylation (Scheme 3).

The antibacterial activity of the 6-*O*-arylpropargyl diazalides and their homologues was measured as the

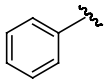
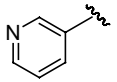
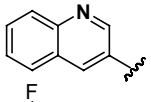
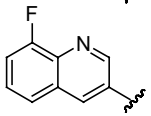
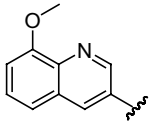
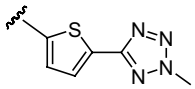
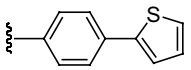
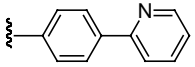
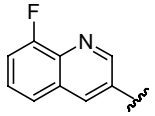


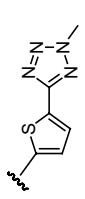
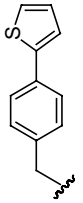
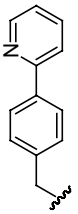
Scheme 2. Reagents and conditions: (a) NaH, $(PhSO_2)_2NF$, DMF, 0 °C, 40%; (b) Sonogashira coupling (A) ArBr, Pd_2dba_3, DPPE, CuI, NEt_3/CH_3CN or (B) ArBr, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3/CH_3CN; (c) MeOH, reflux, 40–80% for two steps.



Scheme 3. Reagents and conditions: (a) Bu_3SnOEt, 110 °C, 80%; (b) X-$ArCH_2X'$, $Pd(PPh_3)_4$, toluene, 64%; (c) (i) $ArSnBu_3$, $Pd(PPh_3)_4$, toluene, (ii) MeOH, reflux, 30–50%.

Table 1. Antibacterial activity of 6-*O*-arylpropargyl diazalides and homologues (MIC, μg/mL)

Compds	Ar	MIC (μg/mL)[a]							
		S. aureus 6538P	*S. aureus* A5177	*S. pyogene* EES61	*S. pyogene* 930	*S. pneumoniae* ATCC6303	*S. pneumoniae* 5979	*S. pneumoniae* 5649	*H. influenzae* GYR1435
Ery[b]		0.39	6.2	0.03	>128	0.06	>128	16	8
ABT-773		0.05	0.05	<0.005	1	0.03	16	0.25	2
TE-802		0.1	0.1	0.06	>128	0.06	>128	1	4
6a		0.2	0.2	0.06	64	0.03	>128	0.5	8
6b		0.2	0.2	0.03	64	0.03	>128	1	2
6c		0.1	0.1	0.03	64	0.03	>128	0.25	4
6d		0.1	0.1	0.015	1	⩽0.004	2	0.25	2
6e		0.06	0.1	⩽0.008	0.5	0.004	4	0.25	2
6f		0.25	0.06	⩽0.008	4	⩽0.008	8	0.06	2
6g		0.5	0.125	⩽0.008	2	⩽0.008	0.003	0.06	4
6h		0.5	0.03	⩽0.008	4	⩽0.008	⩽0.008	⩽0.008	2
6i		0.25	0.03	⩽0.008	8	⩽0.008	⩽0.008	⩽0.008	1
7e		0.25	0.125	⩽0.008	0.25	⩽0.008	0.125	0.125	4

7g		0.5	0.125	⩽0.008	2	⩽0.008	0.125	0.25	4
10h		1	0.5	⩽0.008	0.5	0.015	0.125	0.25	8
10i		0.25	0.25	⩽0.008	0.5	⩽0.008	0.03	0.06	2

[a] Minimum inhibitory concentrations.
[b] Erythromycin A.

minimum concentration inhibiting visible bacterial growth (MIC) by using National Committee for Clinical Laboratories Standard.[7] A panel of erythromycin-susceptible and resistant strains were selected to assess the spectrums of antibacterial activity. The strains are *Staphylococcus aureus* 6538P (erythromycin-susceptible strain), *S. aureus* A5177 (erythromycin-resistant strain bearing an inducible erm (A) gene), *Streptococcus pyogenes* EES61 (erythromycin-susceptible strain), *S. pyogenes* 930 (erythromycin-resistant strain bearing a constitutive erm (B) gene), *S. pneumoniae* ATCC 6303 (erythromycin-susceptible strain), *S. pneumoniae* 5979 (MLS_B resistant strain bearing an erm (B) gene), *S. pneumoniae* 5649 (efflux-resistant strain bearing a mef (E) gene) and *Haemophilus influenzae* GYR1435 (erythromycin-susceptible strain).

The potency of our 6-*O*-arylpropargyl diazalides is summarized in Table 1. It is apparent that the current series is highly potent against both erythromycin-susceptible and resistant Gram-positive organisms. The compounds of the current series are also active against *H. influenzae*, an important Gram-negative respiratory pathogen. Introduction of the 2-fluoro group has no significant effects on the antibacterial potency as illustrated by compounds **7e** and **g** compared to the corresponding non-fluorinated analogues **6e** and **g**. The structure of the aryl group plays a significant role for activity against both susceptible and resistant strains as illustrated by **6a**–**i**. Compounds with a fused bicyclic aryl group (**6d**–**f**) or biaryl group (**6g**–**i**) gave the best activity, particularly against the erythromycin-resistant organisms. Compounds **10h** and **i** (homologues of **6h** and **i**) demonstrated further improved activity against *S. pyogenes* 930.

Another excellent feature of this class of compounds is their desirable pharmacokinetic (PK) profile. They generally possess long half-life ($t_{1/2}$) and high volume of distribution (V_β)[8]. For example, compound **6g** has $t_{1/2}$ of 13.9 h and V_β of 30.9 L/kg after iv dosing in dog (1 mg/kg), while its $t_{1/2}$ reaches 20.6 h after oral dosing. The oral bioavailability (F) is 57.4%. In the in vivo efficacy study, the ED_{50}[9] of compound **6g** against *S. pneumoniae* 6303 in the mouse protection test model[10] is 8 mg/kg.

In conclusion, we have designed and synthesized a series of 6-*O*-arylpropargyl diazalides and the methylene homologues. These compounds demonstrated potent antibacterial activity against both erythromycin-susceptible and resistant *S. pneumoniae* and other important respiratory pathogens. They also showed good PK profile and potent in vivo efficacy. This series of compounds represent an important development in the macrolide/ketolide area and warrant further investigation.

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