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LETTER

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Discovery of 4″-Ether Linked Azithromycin-Quinolone Hybrid Series: Influence of the Central Linker on the Antibacterial Activity

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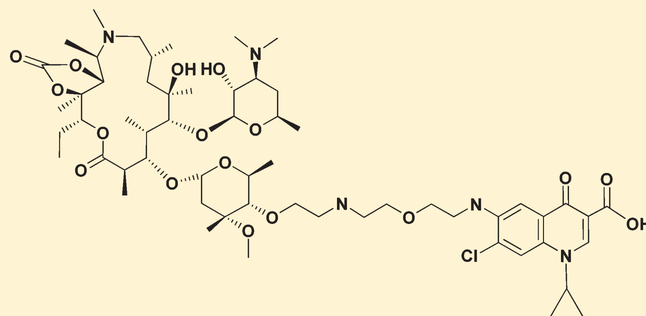
Supporting Information

ABSTRACT: A series of novel C-4″-substituted azithromycins was synthesized and evaluated for *in vitro* antibacterial activity against a panel of representative erythromycin-susceptible and macrolide-lincosamide-streptogramin (MLS) resistant pathogens. In summary, azithromycin and quinolone substructures merged in a mutually SAR-compatible design gave rise to a new class of antimicrobials with an improved spectrum and potency over azithromycin. Prototypical analogues **7f** and **8f** display an improved potency versus azithromycin against Gram-positive and fastidious Gram-negative pathogens. In particular, these new leads maintain activity against MLS-resistant strains of *Streptococcus pneumoniae* and *Streptococcus pyogenes*. In addition, they represent an improvement over telithromycin (**1**) and cethromycin (**2**) against the fastidious Gram-negative pathogen *Haemophilus influenzae*.



KEYWORDS: Macrolide antibiotics, C-4″-substituted azithromycins, quinolones, macrolide resistance

The development of bacterial resistance to currently available antibacterial agents is a growing global health problem.[1] A number of solutions to the problem of bacterial resistance are possible. The most common approach is to continue modifying existing classes of antibacterial agents to provide new analogues with improved attributes. As a result of this approach, numerous macrolide analogues have been synthesized over the years.[2,3] Most recently, a few major classes of 14-membered macrolides stand out with regard to their proven activity against resistant bacteria. One of the most prominent members of a relatively new family of macrolide antibacterial agents, the ketolides, is telithromycin (**1**, Figure 1).[4]

Compound **1** is the only commercialized macrolide antibiotic active against resistant pathogens. It has also been proven that the C-11,C-12 cyclic carbamate present in telithromycin and cethromycin (**2**, ABT-773)[5] can be replaced by a properly functionalized C-11,C-12 α-amino lactone ring. This type of modification led to a novel lead series exemplified by the prototype ketolide antibiotic GW773546X (**3**) (Figure 1).[6] The ketolide series is not necessarily the only class of macrolides that can effectively address the resistance problems. Numerous other design concepts have come forward in response to the growing need for new macrolide antibiotics with improved antibacterial activity against resistant pathogens. In an effort to change the status of ketolides as the "future of macrolides",[7] a rather extensive line of studies were directed toward tethering of quinolone subunits onto the macrolide scaffold.[8,9] These workers synthesized numerous C-4″-substituted macrolides tethered to a quinolone-3-carboxylic acid substructure by a wide variety of different linkers. However, most of these derivatives were connected to C-4″ position of the cladinose sugar through an ester bond which is known to be easily hydrolyzed by a variety of bacterial enzymes. In addition, very little effort on C-4″ ether linked macrolides has yet been reported.[10]

At present, besides cethromycin[11] and a few other ketolides,[12−14] C-4″ substituted azithromycins are probably one of the most advanced series of macrolides with respect to their potent and broad-spectrum antibacterial activity against all key respiratory pathogens.[15]

The 15-membered ring macrolide antibiotics—for example, azithromycin[16]—are an important series within the macrolide class of antibiotics, since they offer some advantages over 14-membered macrolides derived from erythromycin A. These advantages include better gastrointestinal tolerance, safety profile, and pharmacokinetics coupled with activity against Gram-negative pathogens. However, in contrast to 14-membered macrolides, the structure−activity relationships of their corresponding 15-membered analogues have been much less explored. In this study, we report the synthesis of numerous C-4″ side chain modified analogues of azithromycin and azithromycin 11,12-cyclic carbonate and their antibacterial activity against some key macrolide-lincosamide-streptogramin (MLS) resistant pathogens.

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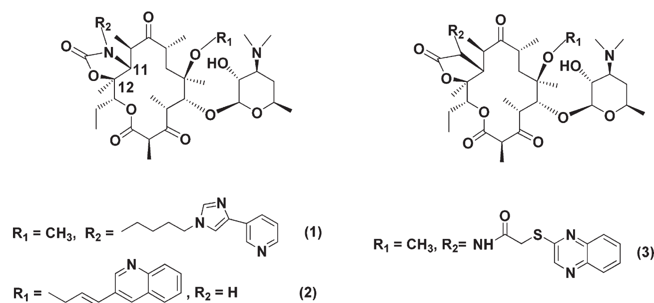


Figure 1. Representative examples of ketolides derived from 14-membered macrolides.

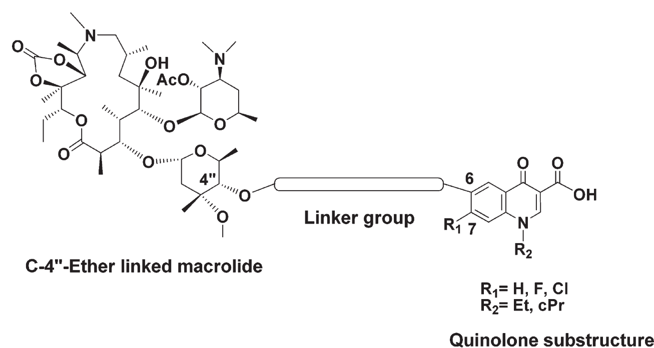
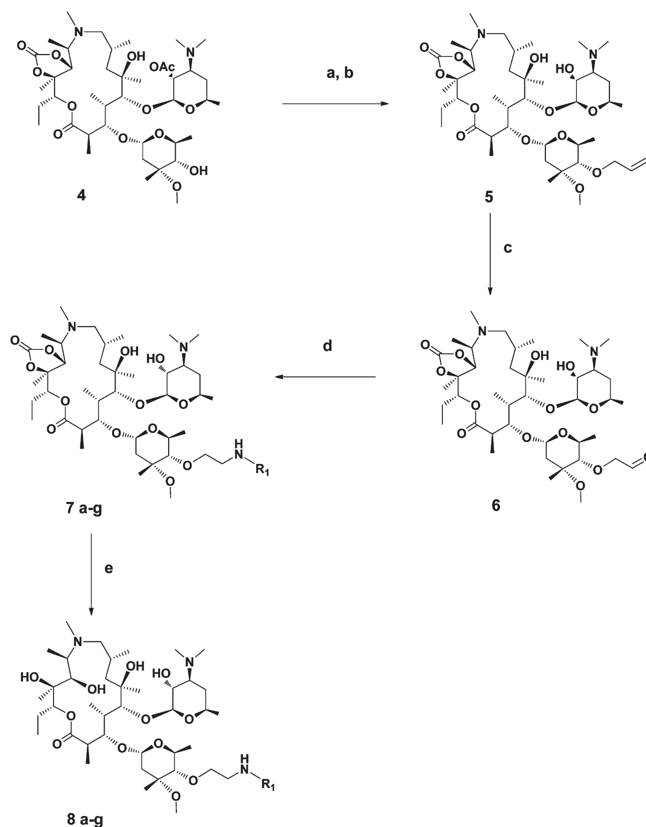


Figure 2. Design of novel C-4″-ether linked macrolides tethered to the quinolone subunit by different linker groups.

We have been involved in a program dedicated to the preparation of a large number of macrolide compounds using solution-phase chemistry. The driving force for all these synthetic endeavors lay primarily in the biological profile of the macrolide analogues and their potential as antiinfective agents. In our previous work,[17] we have synthesized a range of 15-membered 8a- and 9a-azahomoerythromycin analogues, which has provided us with the information toward an understanding of the essential structural features needed for antibacterial activity. In particular, within the 8a-azahomoerythromycin series, some compounds incorporating a ketolide combined with quinolone pharmacophore substructures showed potent activity against a variety of erythromycin-susceptible and MLS-resistant Gram-positive pathogens as well as fastidious Gram-negative pathogens.[18] These studies have highlighted the importance of a quinolone substructure to the overall antibacterial activity and demonstrated that the quinolone moiety attached to the 8a-azaketolide core is a basic requirement for potent antibacterial activity.

Mindful of previous results, we felt that further investigation of structure−activity relationships within the macrolide-quinolone class of compounds could lead to substantial improvements of antibacterial activity. This led us to consider the azithromycin scaffold as a suitable platform for further derivatization because of its excellent pharmacokinetic profile and ease of chemical transformation of key moieties on the scaffold. Our strategy was to attach the quinolone pharmacophore to a cladinose moiety that is remote from the macrocyclic ring and, therefore, more susceptible to such transformation than the ring itself. Basically, it was anticipated that the regioselectively protected azithromycin could be used as starting material to produce a number of analogues substituted at the C-4″ position of the L-cladinose sugar as shown in Figure 2.

Scheme 1. Synthesis of C-4″-Ether Linked Macrolides by Reductive Amination of the Key Intermediate 6 with Selected Amines (Chart *1*)[a]



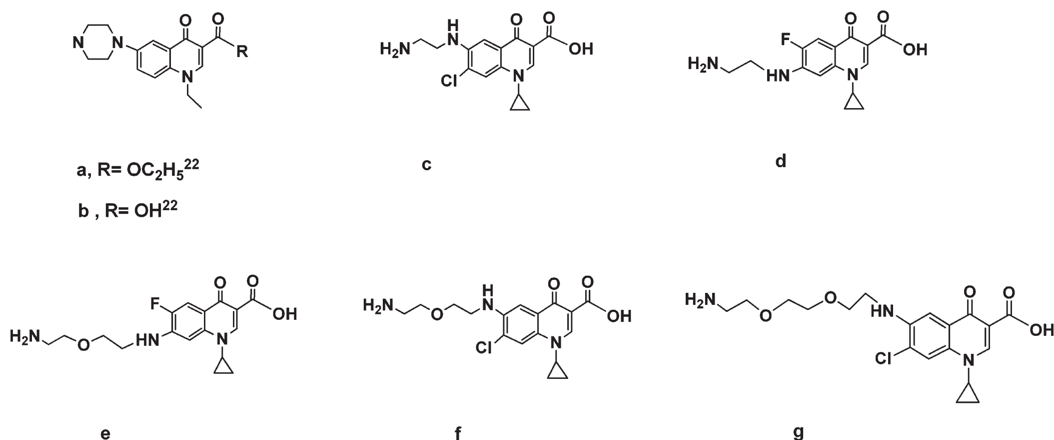
[a] Reagents and conditions: (a) allyl-*tert*-butylcarbonate, $Pd(Ph_3P)_4$, THF, reflux, 3 h; (b) MeOH, rt, 20 h; (c) OsO_4, $NaIO_4$, THF, rt, 3 h; (d) R_1NH_2, $NaBH_3CN$ or $NaBH(OAc)_3$, AcOH, MeOH, rt, 3 h; or HCO_2H, EtOAc, reflux, 5 h; (e) LiOH, THF/H_2O, rt, 12 h.

We were particularly interested in C-4″-ether linked macrolides, since it is known that they are more stable than the corresponding ester compounds toward a range of enzymes that cause ester bond cleavage. In order to selectively alkylate the hydroxyl group at the C-4″-position, a regioselective protection strategy had to be employed. This approach involved the selective alkylation of the C-4″ hydroxyl group using an activated alkylating agent, such as allyl-*tert*-butyl carbonate. Thus, azithromycin was first protected as its 2′-O-acetyl-11,12-cyclic carbonate derivative **4** according to a modified literature procedure (Scheme 1).[19]

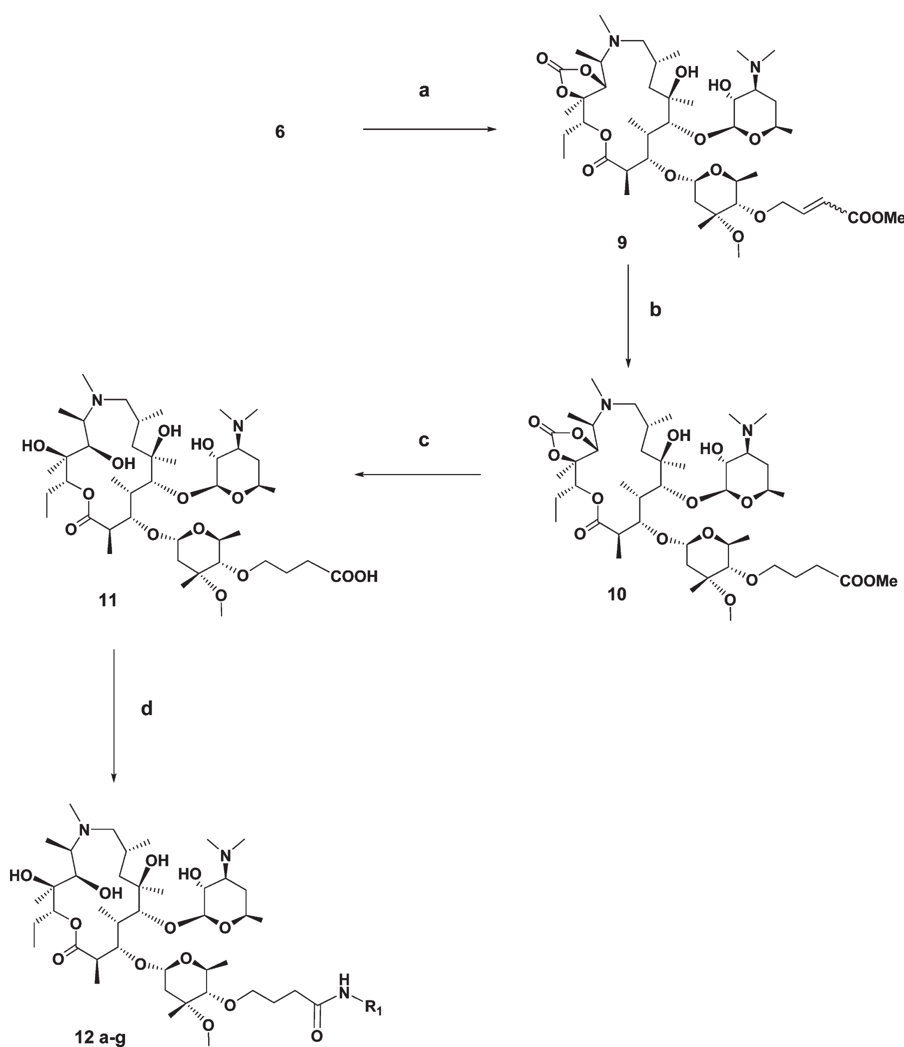
Selective allylation with allyl-*tert*-butyl carbonate in the presence of a catalytic amount of $Pd(Ph_3P)_4$ followed by deprotection of the C-2′ acetyl group gave the expected 4″-O-allyl azithromycin 11,12-cyclic carbonate **5** in 70% isolated yield. The 4″-O-allyl azithromycin was further converted to the corresponding aldehyde **6** by one-pot oxidative cleavage of *in situ* formed *cis*-diol with OsO_4/sodium periodate reagent.[20]

This compound served as the key intermediate for the preparation of other analogues (Scheme 1). Reductive amination[21] of **6** with C-6 and C-7 substituted quinolones (Chart 1) using sodium cyanoborohydride, sodium triacetoxyborohydride, or formic acid afforded the desired products **7a**−**g** in good yields. Deprotection of cyclic carbonates **7a**−**g** with LiOH in aqueous

Chart 1. Quinolones Used as the R_1 Substituents in Reductive Amination of 6 and HBTU Coupling of 11



Scheme 2. Synthesis of C-4″-Ether Linked Macrolides by HBTU-Mediated Coupling of Carboxylic Acid 11 with Selected Amines (Chart *1*)[a]



[a] Reagents and conditions: (a) allyl-*tert*-butylcarbonate, $Pd(Ph_3P)_4$, THF, reflux, 3 h; (b) MeOH, rt, 20 h; (c) OsO_4, $NaIO_4$, THF, rt, 3 h; (d) R_1NH_2, $NaBH_3CN$ or $NaBH(OAc)_3$, AcOH, MeOH, rt, 3 h; or HCO_2H, EtOAc, reflux, 5 h; (e) LiOH, THF/H_2O, rt, 12 h.

THF finally gave azithromycin derivatives **8a**−**g**, which were purified by column chromatography. The quinolones **a** and **b** were prepared by modified literature methods[22] as designated. The synthesis of amines **c**−**g** was effected by heating of a mixture

Table 1. In Vitro Antibacterial Activity of C-4″-Ether Linked Macrolides against Selected Pathogens[a,b]

	S. aureus				*S. pneumoniae*			*S. pyogenes*					
compd	Ery-S	iMLS	cMLS	M	Ery-S	cMLS	M	Ery-S	iMLS	cMLS	M	*M. cat.*[c]	*H. inf.*[d]
7a	0.5	64	>64	8	≤0.125	64	≤0.125	≤0.125	1	64	16	0.25	1
7b	1	16	32	2	≤0.125	32	≤0.125	0.25	4	32	4	4	2
7c	2	64	>64	4	≤0.125	64	≤0.125	≤0.125	0.5	2	0.5	0.25	2
7d	4	64	>64	4	≤0.125	64	0.25	≤0.125	0.25	8	4	0.5	4
7e	8	64	>64	64	≤0.125	16	≤0.125	≤0.125	1	32	4	0.5	4
7f	≤0.125	0.25	32	0.25	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	0.5	≤0.125	≤0.125	0.5
7g	2	64	32	2	≤0.125	64	≤0.125	≤0.125	≤0.125	1	0.5	0.5	1
8b	2	64	64	4	≤0.125	64	≤0.125	≤0.125	0.25	64	0.5	4	8
8c	4	64	>64	8	≤0.125	64	0.25	≤0.125	1	16	8	0.5	2
8d	2	64	64	2	≤0.125	32	≤0.125	≤0.125	≤0.125	1	1	1	4
8e	8	64	>64	8	≤0.125	2	≤0.125	≤0.125	≤0.125	2	1	8	8
8f	≤0.125	0.25	64	0.5	≤0.125	0.25	≤0.125	≤0.125	≤0.125	1	0.125	0.125	0.5
8g	4	64	32	1	≤0.125	64	≤0.125	≤0.125	≤0.125	2	2	1	4
12c	4	32	64	4	0.5	0.5	≤0.125	≤0.125	0.25	2	2	4	8
12d	8	8	64	16	1	1	4	1	1	16	16	2	8
12e	16	64	64	32	0.5	8	0.25	0.25	0.25	4	2	8	16
12f	2	64	64	8	≤0.125	4	0.25	≤0.125	≤0.125	2	1	4	4
12g	16	64	64	8	≤0.125	64	0.25	0.25	0.5	4	1	2	8
1	≤0.125	0.5	>64	0.25	≤0.125	≤0.125	0.5	≤0.125	≤0.125	4	0.25	≤0.125	1
2	≤0.125	0.25	>64	0.25	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	1	≤0.125	≤0.125	1
Azi	1	>64	>64	>64	≤0.125	>64	4	≤0.125	8	>64	1	0.25	1
Cipro	0.125	≤0.125	16	≤0.125	≤0.125	0.25	0.25	2	0.25	0.5	≤0.125	0.125	≤0.125

[a] Minimum inhibitory concentration (MIC) values are given in μg/mL. [b] All compounds were also tested against Cipro-resistant *S. aureus* strain. MICs were ≥64 for all except **7f**: 32 μg/mL. [c] *M. catarrhalis*. [d] *H. influenzae*. Ery-S, erythromycin-susceptible strains; iMLS, inducible resistance to MLS antibiotics; cMLS, constitutive MLS resistance; M, efflux mediated macrolide resistance; Azi, azithromycin; Cipro, ciprofloxacin.

of fluoro- and chloro-quinolone-3-carboxylic acid derivatives at the positions C-6 and C-7 with commercially available diamines, followed by column chromatography of the formed regioisomers.

Additionally, we focused on the effects of modification of the linker-quinolone group connection moiety and linker length on antibacterial activity. From 4″-*O*-(2-oxo-ethyl)azithromycin 11,12-cyclic carbonate (**6**), another series of azithromycin analogues was prepared through the carboxylic acid intermediate **11**, as outlined in Scheme 2.

Wittig reaction of aldehyde **6** with (carbomethoxymethylene)triphenylphosphorane in refluxing benzene generated a mixture of α,β-unsaturated esters **9** highly enriched in the *E* isomer (*E*/*Z* = 95/5). Catalytic hydrogenation of **9** with 10 mol % Pd on carbon in methanol at room temperature afforded aliphatic ester **10**, which was used in the next step without further purification. LiOH-induced hydrolysis of the ester group in **10** resulted at the same time in deprotection of C-11,12 cyclic carbonate and the formation of 4″-O-azithromycin carboxylic acid **11**, a key intermediate for further transformation. HBTU coupling of **11** with C-6-amino- and C-7-amino-substituted quinolone-3-carboxylic acids (Chart 1) was thus employed. The reaction proceeded smoothly to afford the corresponding azithromycin analogues in 60−90% isolated yield.

The antibacterial activity of the C-4″substituted azithromycins was tested against a panel of representative pathogens selected from the Pliva Research Institute culture collection. The *in vitro* antibacterial activities are reported as minimum inhibitory concentrations (MICs) that were determined by the agar microdilution method according to NCCLS standards.[23] Table 1 shows the *in vitro* activity of the azithromycin analogues and the reference compounds, azithromycin, telithromycin (**1**), cethromycin (**2**), and ciprofloxacin.

In general, the azalides were poorly active against a constitutively MLS-resistant strain of *Staphylococcus aureus* (MICs 32 to >64 μg/mL). In contrast to ketolides,[17] most of these compounds were also poorly active against inducibly resistant *S. aureus* strains. The most interesting feature of these new compounds was their effectiveness against efflux resistant staphylococci and pneumococci as well as the activity of selected analogues against constitutively MLS-resistant pneumococci.

The compounds generally maintained good activity against erythromycin-susceptible strains of *S. pyogenes* and *S. pneumoniae* as well as MLS inducibly and constitutively resistant strains of *S. pyogenes*. The compounds most active against constitutively resistant streptococcal strains (**7f**, **8f**, **12c**) are linked through the C-6 position of the quinolone nucleus and the C-4″-position of azithromycin or azithromycin 11,12-cyclic carbonate by a spacer of eight or nine atoms in length. In a similar fashion, antibacterial results show a linker-length-dependent activity which peaked with compound **7f**, a macrolide analogue having a nine carbon-heteroatom linker separating the quinolone ring from the C-4″ ether oxygen on the cladinose ring. Compounds **7c** and **7d**, analogues having shorter carbon−heteroatom linkers than those of **7f**, show a reduction in antibacterial activity with the decrease in linker length. Compound **7g**, the analogue with the longest carbon−heteroatom linker in the series herein disclosed, also shows a reduction in activity in comparison to **7f**. The MIC values of the C-6 linked quinolones **7c** and **7f** were

in general 2−256-fold better than that of the C-7 linked analogues **7d** and **7e**, respectively, against most of the strains tested. In addition, the structure of the linker connecting the macrolide and quinolone pharmacophores appears to be critical for antibacterial activity. Amide-linked quinolone analogues **12c**−**g** were generally not as active as macrolides **8b**−**g**, incorporating quinolone substructures linked via an amine group.

A few compounds exhibited noteworthy levels of activity against *H. influenzae* and constitutively resistant *S. pyogenes*. In particular, **7f** and **8f** were more potent then azithromycin and telithromycin against *H. influenzae* B 0529 strain (MICs of 0.5 μg/mL for both compounds, Table 1; see also Table 2 in the Supporting Information for time-kill studies) and cMLS *S. pyogenes* (MICs of 0.5 and 1 μg/mL, respectively).

Among the various 4′′-ether linked azithromycin-quinolone hybrids, compound **7f** exhibited the most potent and balanced activity against both susceptible and resistant bacteria. In contrast, azithromycin showed either weak or no activity against the resistant organisms. These results clearly indicated that the introduction of a quinolone substituted side chain onto the macrolide scaffold was the key factor for overcoming constitutive resistance. Design of the C-4′′ tether connecting the quinolone and azithromycin therefore appears critical for potent antibacterial activity.

In order to gain further insight into the mode of action of hybrids, we measured for **7f** and **8f** the inhibition of protein synthesis in an in vitro transcription/translation assay and the inhibition of the enzymes that are targeted by the quinolones, DNA gyrase, and topoisomerase IV (Table 3, Supporting Information). The activities observed in the in vitro protein assay show that the macrolones are strong inhibitors of protein synthesis with potencies comparable to that of telithromycin, demonstrating their macrolide MOA. Furthermore, the macrolones **7f** and **8f** were essentially devoid of DNA gyrase and Topo IV inhibitory activity, clearly indicating that the dual mode of action is not operative for these compounds. It is also important to note that all analogues were inactive against the ciprofloxacin-resistant *S. aureus* strain and that the quinolones **a**−**g** were inactive against all bacterial pathogens tested (Table 4, Supporting Information).

In summary, a novel series of azithromycin derivatives with potent activity against key respiratory pathogens, including those resistant to macrolide antibiotics, has been identified. These compounds are characterized by having a quinolyl moiety tethered to the C-4′′-position of the azithromycin skeleton through an ether bond. Extensive structural modification of the quinolone substituted side chain led to the discovery of several promising compounds with potent activity against both erythromycin-susceptible and MLS-constitutively resistant organisms. These studies demonstrate a great sensitivity of antibacterial activity toward structural changes of the side chain. These studies also reveal a promising potential for further systematic modification to fine-tune the biological properties of future analogues within the same C-4′′-ether linked series. As a result of extensive structural modification, macrolides **7f** and **8f** were identified as potential lead candidates for further evaluation.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectral data, antibacterial data for selected new compounds, and activity of **7f** and **8f** as inhibitors of DNA gyrase, Topo IV, and bacterial protein synthesis. This material is available free of charge via the Internet at http://pubs.acs.org.

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ABBREVIATIONS

MLS, macrolide-lincosamide-streptogramin antibiotics; HBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; DIPEA, diisopropylethylamine; SAR, structure−activity relationships; MOA, mode of action; Topo IV, topoisomerase IV.

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