Design, Synthesis, and Antimicrobial Activity of 6-O-Substituted Ketolides Active against Resistant Respiratory Tract Pathogens

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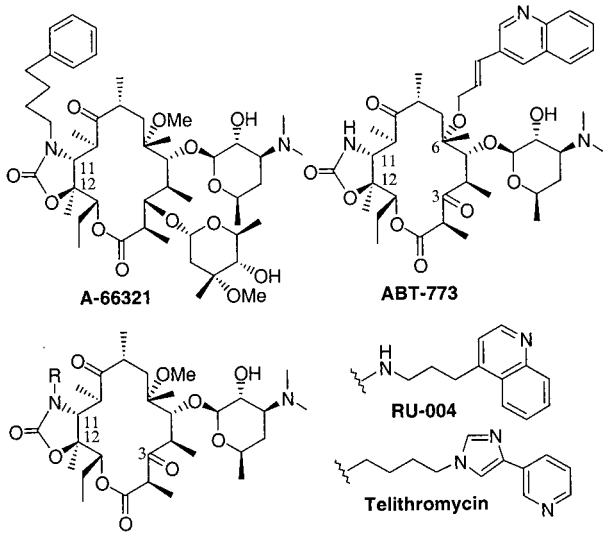
Introduction. Bacterial resistance to antibiotic treatment has become a global health problem at the turn of the millennium.[1] Resistance occurs not only in hospitals[2] but also in certain community-acquired pathogens, particularly among the major respiratory tract pathogens.[3] A 1997 multicenter surveillance study in the United States and Canada indicated that 43.8% of *Streptococcus pneumoniae* clinical isolates were intermediately or highly resistant to penicillin, a steady increase since the 1980s when only 3.8% of isolates were reported to be resistant to the same drug.[4] These penicillin-resistant *S. pneumoniae* isolates also showed multiple resistance to other β-lactams, chloramphenicol, sulfonamides, tetracyclines, and macrolides. The same study revealed that in 1997, 33.5% of *Haemophilus influenzae* and 92.2% of *Moraxella catarrhalis* clinical isolates were found to be β-lactamase positive.[5] ABT-773 is a member of a new generation of macrolide antibiotics which effectively addresses the drug-resistance problems associated with the treatment of respiratory tract infections.

The first macrolide, erythromycin, was introduced in the 1950s as a safe and effective agent. It is widely prescribed to patients with allergic reactions to penicillin. The major problem associated with erythromycin is its acid instability, leading to the formation of a 6,9-hemiketal and consequential degradation products which are directly responsible for its poor pharmacokinetic profile and gastrointestinal (GI) side effects.[6] To address these problems, new macrolides such as clarithromycin and azithromycin were introduced in late 1980s. These agents effectively prevent the formation of 6,9-hemiketal degradation products, resulting in improved pharmacokinetics and better GI tolerability.[7] The recent development of macrolide resistance among respiratory tract pathogens has, however, spurred further research aimed at the discovery of a next generation macrolide which can address the resistance issue and other deficiencies of current agents.[8] In 1995, a novel series of macrolides, known as ketolides, was introduced. These compounds exhibited excellent activity against several types of macrolide-resistant organisms.[9] In this communication, we wish to report the design, synthesis, and antibacterial activity of ABT-773, a novel ketolide having potent activity against multidrug-resistant respiratory tract pathogens and excellent in vivo efficacy in experimental animal infection models. A full account of this work with a detailed study of the synthesis, structure−activity relationships, mechanism of action, and pharmacokinetic profiles will be published at a future date.



Design Rationale. Structural modification of existing antibiotics remains one of the most effective approaches for overcoming bacterial resistance.[10] We focused our efforts on the modification of erythromycin, a safe and effective macrolide antibiotic with a well-defined mechanism of action and resistance mechanism.[11] Several earlier series of macrolides have made important contributions to our drug design strategy. In 1989, a series of aryl-substituted 11,12-cyclic carbamate macrolides, exemplified by A-66321, was reported by Abbott Laboratories. Several analogues of this series exhibited moderate activity against *S. pyogenes* with inducible and constitutive types of macrolides−lincosamides−streptogramin B (MLS_B) resistance.[12] In 1995, a series of aryl-substituted 11,12-cyclic carbamate ketolides, exemplified by RU-004, was reported by Hoechst Marion Roussel, which possessed potent activity against MLS_B-resistant *S. pneumoniae* and improved activity against *H. influenzae*.[9] Telithromycin, a close analogue of RU-004, is currently under clinical development by Hoechst-Marion-Roussel.[13] Also in 1995, Taisho reported a tricyclic ketolide series, exemplified by TE-802, which demonstrated activity against some erythromycin-resistant organisms.[14] Both RU-004 and TE-802 showed excellent acid stability due to the removal of the acid-labile cladinose group. The structure−activity relationships (SARs) of these macrolide derivatives led us to believe that the aryl groups attached to the lactone ring are essential for overcoming MLS_B resistance, while the 3-keto group is important for overcoming efflux resistance.

To develop new macrolides with activity against such resistance, we sought to incorporate two key structural features into the molecules: an aryl group appropriately attached to the lactone ring and a keto group at the C-3 position. Both crystal and solution conformations of A-66321 and RU-004 indicated that the aryl groups in

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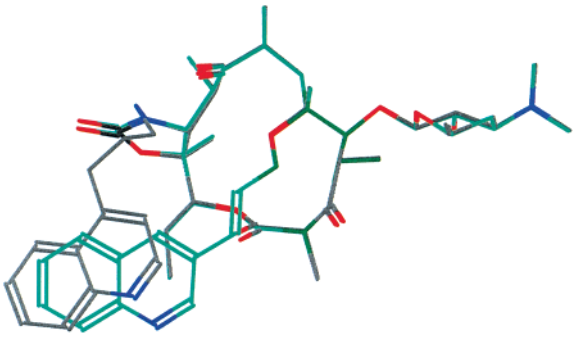


Figure 1. Superimposed minimized solution conformations of ABT-773 (green) and RU-004 (black).

these molecules were positioned on the top, hydrophilic face of the macrolide ring, where the majority of oxygen-containing groups are localized.[15] Since the C-6 hydroxy group of erythromycin is also located on the hydrophilic face of the macrolide ring, we felt that this position represented an ideal point for aryl group attachment. Our conformational analysis indicated that an aryl group tethered to the 6-O position would position itself in a similar spatial area with the aryl groups in A-66321 and RU-004. This relationship can be better illustrated by the superimposed conformations of ABT-773 and RU-004 (Figure 1).

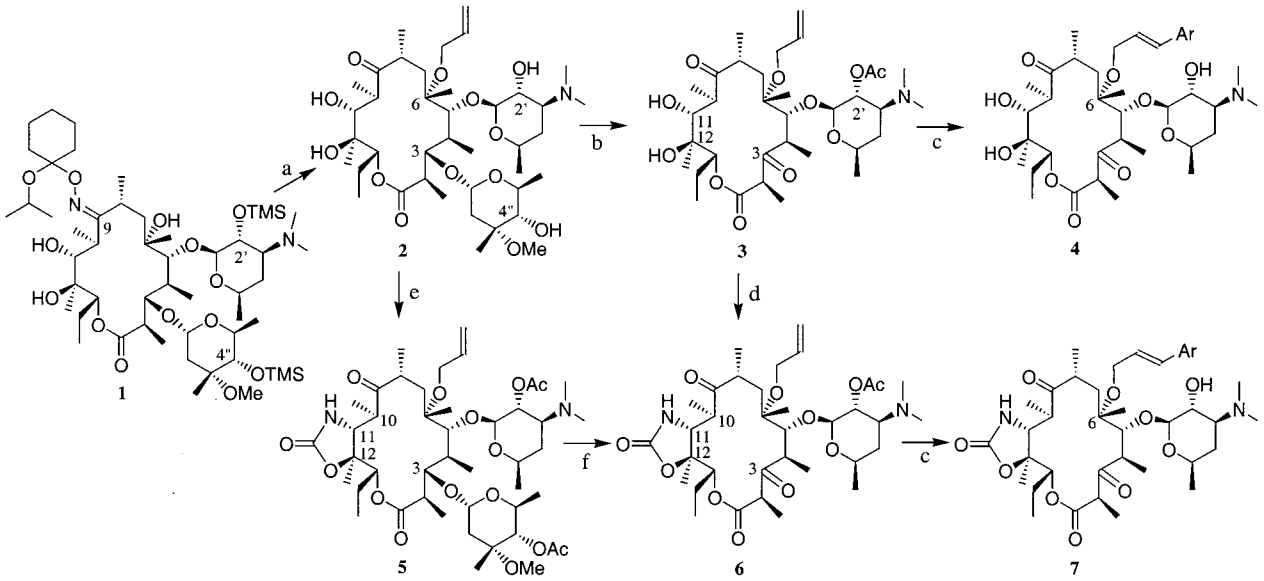
Synthesis. The introduction of a versatile functional group at the sterically hindered C-6 hydroxy position became our first synthetic challenge. Previously, a methyl group had been successfully introduced at this position leading to the discovery of clarithromycin. However, attempts to introduce alkyl groups other than a methyl group proved to be impractical due to steric hindrance.[16] We decided to take a more convergent approach by introducing an allyl group followed by further derivatization.

As indicated in Scheme 1, 6-*O*-allylerythromycin (**2**) was synthesized in an analogous fashion to the preparation of 6-*O*-methylerythromycin (clarithromycin).[17] Erythromycin was first protected as 9-ketaloxime 2′,4″-bis(trimethylsilyl)erythromycin (**1**). Treatment of **1** with allyl bromide and potassium hydroxide (KOH), in a mixture of dimethyl sulfoxide (DMSO) and tetrahydrofuran (THF), provided a low conversion of starting material. We soon realized that the low conversion was due to a competing reaction between allyl bromide and KOH. Potassium *tert*-butoxide (KOBu^t), a sterically hindered base, was thus employed to minimize the undesired side reaction. This modification brought the reaction to more than 90% conversion.[18] Sequential deprotection of the trimethylsilyl (TMS) and ketal groups followed by deoximation provided 6-*O*-allylerythromycin (**2**) in 31% overall yield from erythromycin.

The 3-keto group was introduced in three steps from 6-*O*-allylerythromycin,[19] beginning with the acidic hydrolysis of the cladinose sugar. The 2′-OH was then protected as an acetyl ester. Finally, Corey−Kim oxidation[20] of the 3-OH provided the 6-*O*-allyl ketolide **3** in 77% overall yield from **2**. Introduction of an aryl group to the allyl side chain of **3** was achieved by utilizing a Heck coupling reaction.[21] Under optimized conditions ($Pd(OAc)_2$/P(*o*-tolyl)$_3$/Et_3N/CH_3CN), various *trans*-6-*O*-arylallyl ketolides **4** were obtained in good yields after deprotection (Scheme 1).[22]

Conversion of **3** to the corresponding 11,12-cyclic carbamate **6** was achieved in two steps, proceeding through an acylimidazole intermediate **8** (Scheme 2). Thus, when **3** was treated with lithium hydride (LiH) in the presence of *N*,*N*-carbonyldiimidazole (CDI) for a period of 7 days, **8** was obtained in good yield. This transformation has been known to proceed through a 11,12-cyclic carbonate intermediate.[23] Base-catalyzed elimination at the 10,11-position, followed by acylation of the free 12-OH, provided acylimidazole **8**. Subsequent reaction of **8** with aqueous ammonia provided **6** as the

Scheme 1[a]



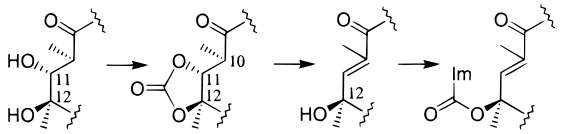
[a] Conditions: (a) (1) allyl bromide, KOBu^t, DMSO−THF, (2) HOAc, H_2O−CH_3CN, (3) $NaHSO_3$/HCO_2H, EtOH−H_2O, 33% in 3 steps; (b) (1) HCl, EtOH, (2) Ac_2O, Et_3N, CH_2Cl_2, (3) NCS, Me_2S, Et_3N, CH_2Cl_2, 77% in 3 steps; (c) (1) Ar-X, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, CH_3CN, (2) MeOH, 60−85% in 2 steps; (d) (1) LiH, CDI, THF, (2) aq NH_3 (28%), CH_3CN−THF, 60% in 2 steps; (e) (1) Ac_2O, Et_3N, DMAP, CH_2Cl_2, (2) $NaN(TMS)_2$, CDI, THF−DMF, (3) aq NH_3 (28%), CH_3CN−THF, 78% in 3 steps; (f) (1) HCl, EtOH, (2) NCS, Me_2S, Et_3N, CH_2Cl_2, 80% in 2 steps.

Table 1. In Vitro Antibacterial Activity of Selected Compounds (MIC, μg/mL)

	compound (Ar group)							
strain	**4a** (H)	**4b** (Ph)	**4c** (3-quinolyl)	**7a** (H)	**7b** (Ph)	**7c** (3-quinolyl)	Teli	Ery
S. aureus ATCC 6538P	12.5	1.56	0.2	0.78	0.1	0.05	0.1	0.2
S. aureus A 5177	50	1.56	0.2	1.56	0.1	0.05	0.1	6.2
S. aureus A 5278	>100	>100	>100	>100	>100	>100	>100	>100
S. pyogenes EES 61	–	0.25	0.2	0.25	0.03	0.004	0.004	0.06
S. pyogenes 930	>128	64	100	>64	64	1	8	>128
S. pyogenes PIU 2548	32	2	0.1	2	0.25	0.125	2	32
S. pneumoniae ATCC 6303	4	0.25	0.03	0.5	0.03	0.004	0.004	0.06
S. pneumoniae 5737	>128	64	16	>64	64	0.25	8	>128
S. pneumoniae 5649	8	2	0.25	0.25	0.25	0.25	0.5	16
H. influenzae DILL	>128	128	16	64	4	2	2	8

major product and its 10-epimer as a minor product in a 2:1 ratio.

Scheme 2



Alternatively, **6** was obtained through another route starting from **2**. After protection of the 2′- and 4″-OH groups, the diacetate was converted to the acylimidazole intermediate **8** (Scheme 2), which was further reacted with aqueous ammonia to give **5** in 78% overall yield from **2**. In this case the reaction was more selective, producing less than 10% of the 10-epimer of **5**. Subsequent hydrolysis of the C-3 cladinose and Corey−Kim oxidation[20] of the resulting 3-OH compound provided **6** in 80% yield over two steps. Finally, aryl groups were introduced to **6** under Heck coupling conditions[21] as stated above to give, after deprotection, *trans*-6-*O*-arylallyl ketolides **7** in excellent yields.

In Vitro Antibacterial Activity. The 6-O-substituted ketolides and the reference agents telithromycin and erythromycin were tested against a panel of representative respiratory pathogens selected from the Abbott clinical culture collection. Various macrolide- and multidrug-resistant isolates were included in these tests in order to identify potent analogues that could overcome macrolide resistance. *Staphylococcus aureus* ATCC 6538P, *Streptococcus pyogenes* EES 61, and *Streptococcus pneumoniae* ATCC 6303 are erythromycin-susceptible strains. *S. aureus* A 5177 is an inducibly MLS_B-resistant strain encoded by an *ermA* gene. *S. aureus* A 5278 is a constitutively MLS_B-resistant strain also encoded by an *ermA* gene. *S. pyogenes* 930 and *S. pneumoniae* 5737 are MLS_B-resistant strains encoded by *ermB* gene. *S. pyogenes* PIU 2548 and *S. pneumoniae* 5649 are efflux-resistant strains encoded by *mefA* and *mefE* genes, respectively. *Haemophilus influenzae* DILL is an ampicillin-resistant strain with a β-lactamase-positive determinant. The in vitro antibacterial activities are reported as minimum inhibitory concentrations (MICs), which were determined by the agar dilution method as recommended by the National Committee for Clinical Laboratory Standards. The in vitro antibacterial activities of a selected group of 6-O-substituted ketolides and reference compounds are shown in Table 1.

The 6-*O*-allyl ketolide **4a** showed weak antibacterial activity. However, the corresponding 6-*O*-phenylallyl analogue **4b** and the 6-*O*-quinolylallyl analogue **4c** exhibited significantly improved activity. A similar trend was observed when an aryl group was introduced to the 6-*O*-allyl-11,12-carbamate ketolide **7a**. Compounds **7b** and **7c** showed much better antibacterial activity than **7a** against both susceptible and resistant organisms. The structures of the aryl groups in these analogues also had profound effects on the antibacterial activities. The quinolyl analogues (**4c** and **7c**), for example, demonstrated further improved activity when compared to their phenyl counterparts (**4b** and **7b**). In addition, the 11,12-cyclic carbamate group was an important contributor to the antibacterial activity. Compounds **7a**, **7b,** and **7c** exhibited more than 10-fold improved activity as compared to the corresponding 11,-12-diols **4a**, **4b,** and **4c**.

Compound **7c** was designated as ABT-773 and is currently under clinical studies. Compared with erythromycin, ABT-773 exhibited significantly improved activity against erythromycin-susceptible strains. It showed excellent activity against both inducible and efflux-resistant organisms, while erythromycin was only weakly active. It also exhibited potent activity against MLS_B-resistant *S. pyogenes* and *S. pneumoniae* which were highly resistant to erythromycin. In addition, it showed 4-fold improvement in MIC against ampicillin-resistant *H. influenzae*. Compared with reference ketolide telithromycin, ABT-773 demonstrated improved activity against both efflux- and MLS_B-resistant bacteria. However, none of the new ketolides, including ABT-773 and telithromycin, showed any activity against MLS_B constitutively resistant *S. aureus*.

In Vivo Efficacy. The in vivo efficacies of ABT-773 and reference compounds azithromycin and telithromycin were assessed by mouse protection tests and rat lung infection models. In the mouse protection tests, the mice were inoculated intravenously with a 100-fold LD_{50} of representative organisms. Test compounds were administered by oral gavage at 1 and 5 h post-inoculation. Mortality rates of the mice were monitored for a period of 7 days post-inoculation with a 100% mortality rate for untreated controls. The efficacy of each compound, based on the survival rates over a dose range, was reported as the drug dose resulting in a survival of 50% of treated mice over the duration of the trial (ED_{50}). In the rat lung infection models, the rats were intratracheally inoculated with 0.5 mL of a bacteria suspension in 5% gastric hog mucin containing log 10^6−10^8 cfu. Test compounds were administered by peroral gavage once

Table 2. In Vivo Efficacy of Selected Compounds in the Mouse Protection Tests (ED_{50}, mg/kg)

	S. aureus 10649[a]		*S. pneumoniae* 6303[a]		*S. pyogenes* C203[a]	
compd	MIC (μg/mL)	ED_{50} (95% CL)	MIC (μg/mL)	ED_{50} (95% CL)	MIC (μg/mL)	ED_{50} (95% CL)
ABT-773	0.05	10.4 (7−15)	0.004	12.5 (10−16)	0.002	2.5 (2−4)
Teli	0.1	12.5 (8−20)	0.004	34.1 (21−57)	–	–
Azi	0.78	24.8 (18−37)	0.12	18.8 (10−34)	0.06	6.1 (4−9)

[a] *S. aureus* 10649, *S. pyogenes* C203, and *S. pneumoniae* 6303 are erythromycin-susceptible strains. CL, confidence limits.

Table 3. In Vivo Efficacy of Selected Compounds in Rat Lung Infection Models (ED_{50}, mg/kg/day)

	S. pneumoniae 6303[a]		*S. pneumoniae* 5649[a]		*S. pneumoniae* 6396[a]	
compd	MIC (μg/mL)	ED_{50} (95% CL)	MIC (μg/mL)	ED_{50} (95% CL)	MIC (μg/mL)	ED_{50} (95% CL)
ABT-773	0.004	<0.63	0.25	7.0 (6.9−7.1)	0.015	1.6 (1.3−2.2)
Teli	0.004	2.3 (2.1−2.5)	0.5	25.8 (9.3−72)	0.125	26.7 (21−34)
Azi	0.12	6.0 (3.8−9.6)	16	78.7 (62−99)	>128	>100

[a] *S. pneumoniae* 6303 is an erythromycin-susceptible strain, *S. pneumoniae* 5649 is an efflux-resistant strain, and *S. pneumoniae* 6396 is a MLS_B-resistant strain. CL, confidence limits.

daily, days 1−3, starting 18 h post-inoculation. Lung bacterial burden was assessed from serial dilution plating of lung tissue homogenates on day 4. The ED_{50} to yield a 2 log reduction in bacteria count compared to vehicle-treated infected controls was calculated from the group means using linear regression. The efficacy of ABT-773 and reference compounds is shown in Tables 2 and 3.

In the mouse protection tests ABT-773 demonstrated improved efficacy against macrolide-susceptible strains as compared to reference macrolide azithromycin and reference ketolide telithromycin. In the rat lung infection models, ABT-773 exhibited superior efficacy against various *S. pneumoniae* strains. ABT-773 showed substantially better efficacy than both telithromycin and azithromycin against a macrolide-susceptible strain, *S. pneumoniae* 6303. Against infections caused by an efflux-resistant strain, *S. pneumoniae* 5649, ABT-773 exhibited a 3-fold improvement in efficacy over telithromycin and a 10-fold improvement over azithromycin. Against infections caused by an MLS_B-resistant strain, *S. pneumoniae* 6396, ABT-773 demonstrated excellent efficacy, while telithromycin showed weaker efficacy and azithromycin gave no efficacy under a 100 mg/kg/day dose.

Conclusion. A novel series of 6-O-substituted ketolides having activity against both MLS_B- and efflux-resistant bacteria was designed and synthesized. SAR studies led to the discovery of a potent antibacterial agent, ABT-773. ABT-773 exhibited excellent activities against all the key respiratory tract pathogens, including those resistant to macrolides and other antibiotics. It was highly active against the two major types of resistance: MLS_B resistance encoded by *erm* genes and efflux resistance encoded by *mef* genes. ABT-773 demonstrated excellent efficacies against various infections in experimental animal models. It showed improved efficacy against infections caused by macrolide-susceptible bacteria as compared to reference macrolide azithromycin and reference ketolide telithromycin. ABT-773 provided excellent efficacy against infections caused by macrolide-resistant bacteria, while telithromycin showed weaker efficacy and azithromycin showed weaker or no efficacy against such infections.

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