In Vitro Antibacterial Activity of Modithromycin, a Novel 6,11-Bridged Bicyclolide, against Respiratory Pathogens, Including Macrolide-Resistant Gram-Positive Cocci[▽]

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The *in vitro* activities of modithromycin against Gram-positive and -negative respiratory pathogens, including macrolide-resistant cocci with different resistance mechanisms, were compared with those of other macrolide and ketolide agents. MICs were determined by the broth microdilution method. All 595 test strains used in this study were isolated from Japanese medical facilities. The *erm* (ribosome methylase) and/or *mef* (efflux pump) gene, which correlated with resistance to erythromycin as well as clarithromycin and azithromycin, was found in 81.8%, 21.3%, and 23.2% of *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and methicillin-susceptible *Staphylococcus aureus* (MSSA) strains, respectively. Modithromycin showed MIC$_{90}$s of 0.125 μg/ml against these three cocci, including macrolide-resistant strains. In particular, the MIC of modithromycin against *ermB*-carrying *S. pyogenes* was ≥32-fold lower than that of telithromycin. The activities of modithromycin as well as telithromycin were little affected by the presence of *mefA* or *mefE* in both streptococci. Against Gram-negative pathogens, modithromycin showed MIC$_{90}$s of 0.5, 8, and 0.031 μg/ml against *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Legionella* spp., respectively. The MICs of modithromycin against *M. catarrhalis* and *H. influenzae* were higher than those of telithromycin and azithromycin. However, modithromycin showed the most potent anti-*Legionella* activity among the macrolide and ketolide agents tested. These results suggested that the bicyclolide agent modithromycin is a novel class of macrolides with improved antibacterial activity against Gram-positive cocci, including telithromycin-resistant streptococci and intracellular Gram-negative bacteria of the *Legionella* species.

Macrolides such as clarithromycin and azithromycin are antimicrobial agents for the treatment of mild to moderate community-acquired pneumonia and are clinically useful for pediatric and penicillin-allergic patients (2, 19). However, the rate of macrolide resistance among Gram-positive cocci, particularly *Streptococcus pneumoniae*, has been increasing throughout the world (12, 16). Therefore, the choice of these agents for use in empirical treatment has become complicated. In addition, although the ketolide agent telithromycin was shown to be active even against macrolide-resistant clinical strains of *S. pneumoniae*, the emergence of high-level telithromycin-resistant strains has also been reported recently (1, 10, 29).

Target site modifications and active efflux pumps are known to be the predominant macrolide resistance mechanisms in streptococci and staphylococci (17, 27, 28). As for the target site modification, some methylase enzymes encoded by the *erm* genes induce dimethylation of an adenine residue in domain V, the peptidyltransferase site, of a 23S ribosomal subunit, which results in reduced binding affinity to macrolide, lincosamide (clindamycin), and streptogramin B (MLS$_B$) antibiotics. The

erm-induced resistance can be classified into inducible and constitutive phenotypes. The efflux pumps encoded by the *mef* and *msr* genes have been found in clinical strains of streptococci and staphylococci, respectively (17, 28). The strains carrying *mef* genes are resistant to low or moderate levels of 14- and 15-membered macrolides but are not resistant to 16-membered macrolides, clindamycin, streptogramin B, or the ketolide telithromycin. On the other hand, the Msr efflux pumps encoded by *msr* genes confer resistance to 14- and 15-membered macrolides and streptogramin B and also, in some cases, to clindamycin and telithromycin (24). In addition, mutations in L4 or L22 ribosomal proteins, either alone or in combination with the presence of *erm* genes or 23S rRNA mutations, have been reported to confer reduced susceptibility to macrolides and, to a lesser extent, telithromycin in streptococci (1, 28, 29).

Modithromycin (EDP-420, EP-013420, S-013420), a novel 6,11-bridged bicyclolide, was designed and synthesized by Enanta Pharmaceuticals, Inc., to potentiate the antibacterial activity against Gram-positive and -negative respiratory pathogens (Fig. 1) (28). In this study, we examined the *in vitro* activity of modithromycin against clinical strains of Gram-positive cocci, including macrolide-resistant strains with different macrolide resistance mechanisms, and Gram-negative organisms, including intracellular pathogens.

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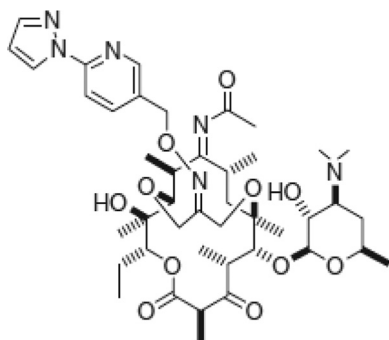
FIG. 1. Chemical structure of modithromycin (EDP-420, EP-013420, S-013420).

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MATERIALS AND METHODS

Antimicrobial agents. Modithromycin and telithromycin were kindly supplied from Shionogi & Co., Ltd. (Osaka, Japan). Clarithromycin, azithromycin, erythromycin, and clindamycin were purchased from U.S. Pharmacopeia (Rockville, MD). Levofloxacin was kindly supplied from Daiichi Sankyo Co., Ltd. (Tokyo, Japan). The solvent for modithromycin was 1 M acetate buffer (pH 4.5).

Bacteria. A total of 534 clinical strains, including *S. pneumoniae* (148 strains), *Streptococcus pyogenes* (94 strains), methicillin-susceptible *Staphylococcus aureus* (MSSA; 99 strains), *Haemophilus influenzae* (93 strains), and *Moraxella catarrhalis* (100 strains), were isolated at Toho University Omori Hospital in 2006. Sixty-one clinical strains of *Legionella* spp., including *Legionella pneumophila* (56 strains), *Legionella longbeachae* (2 strains), *Legionella sainthelensi* (1 strain), *Legionella micdadei* (1 strain), and an unidentified *Legionella* species (1 strain), were collected from 34 Japanese medical facilities from 1994 to 2006.

Determination of MICs. MICs were determined by the broth microdilution method recommended by the Clinical and Laboratory Standards Institute (CLSI) (7). Cation-adjusted Mueller-Hinton broth (Difco) was used for MSSA and *M. catarrhalis*. For streptococci, cation-adjusted Mueller-Hinton broth supplemented with 5% lysed horse blood was used. For *H. influenzae*, Haemophilus test medium (Nissui Pharmaceutical Co., Ltd., Japan) was used. For *Legionella* spp., *N*-(2-acetamido)-2-aminoethanesulfonic acid-buffered yeast extract broth supplemented with 0.1% α-ketoglutarate, 0.04% L-cysteine, and 0.025% iron(III) diphosphate (final pH, 6.9) was used (22, 26). After inoculation of the bacteria into the broth medium containing serial dilutions of the antimicrobial agents in a 96-well microplate (inoculum, approximately 5×10^5 CFU/ml), incubation was performed for 20 h at 35°C for all organisms except *Legionella* species. For *Legionella* spp., incubation was performed for 67 h at 35°C. The MIC was defined as the lowest concentration of antimicrobial agent which inhibited visible growth of bacteria. Interpretation of MICs as susceptible, intermediate resistant, or resistant was determined on the basis of the CLSI breakpoints (8).

Determination of macrolide-resistant genotypes and phenotypes. Macrolide resistance genes were detected by using a conventional PCR protocol. For streptococci, three sets of primers for *ermB*, *ermTR*, and *mefA* (*mefE*) were used (13, 15). For MSSA, four sets of primers for *ermA*, *ermB*, *ermC*, and *msrA* (*msrB*) were used (21, 23). Among erythromycin-resistant strains of MSSA carrying the *erm* genes, the strains resistant to clindamycin were judged to have the constitutive resistance phenotype of methylase expression. Other erythromycin-resistant *erm*-carrying MSSA and *ermTR*-carrying streptococci, which were susceptible to clindamycin, were judged to have the inducible resistance phenotype of methylase expression because a D-shaped inhibition zone around the clindamycin disk was observed by the double-disk diffusion test on Todd-Hewitt agar with clindamycin and erythromycin disks (17).

RESULTS

Antibacterial activity of modithromycin against clinical strains. The activities of modithromycin and the reference

antimicrobial agents against clinical strains are shown in Table 1. The MIC_{90} of modithromycin was 0.125 µg/ml against *S. pneumoniae*, which was comparable to that of telithromycin. On the other hand, against *S. pneumoniae*, clarithromycin and azithromycin showed MIC_{50}s of 32 and >64 µg/ml, respectively. Modithromycin showed a MIC_{90} of 0.125 µg/ml against *S. pyogenes*, which was 4-fold lower than that of telithromycin and 64-fold lower than the MIC_{90}s of clarithromycin and azithromycin. Modithromycin inhibited the growth of all strains of these streptococci at a concentration of 0.5 µg/ml, whereas telithromycin did so at a concentration of 8 µg/ml. Against MSSA, the activity of modithromycin was comparable to that of telithromycin, with a MIC_{90} of 0.125 µg/ml, although some strains showed high-level resistance to modithromycin and telithromycin, with MICs of >64 µg/ml. However, modithromycin was much more active against MSSA than clarithromycin and azithromycin, which showed MIC_{90}s of >64 µg/ml. Compared to levofloxacin, the MIC_{90}s of modithromycin were 4- to 16-fold lower against these Gram-positive cocci.

Against *M. catarrhalis* and *H. influenzae*, modithromycin showed MIC_{90}s of 0.5 and 8 µg/ml, respectively, which were higher than those of telithromycin and azithromycin but comparable to the MIC_{90} of clarithromycin. On the other hand, modithromycin showed the most potent anti-*Legionella* activity, with a MIC_{90} of 0.031 µg/ml. The MIC_{90} of modithromycin was 4- and 32-fold lower than the MIC_{90} of telithromycin and azithromycin, respectively, and was comparable to that of levofloxacin.

Evaluation of macrolide-resistant genotypes and phenotypes in clinical strains of Gram-positive cocci. The determination of macrolide-resistant genotypes in Gram-positive cocci was performed by conventional PCR to evaluate the differences in the activities between modithromycin and the other macrolide/ketolide agents tested. Among the 148 clinical strains of *S. pneumoniae*, the *ermB* and *mefE* genes were found in 56.8% and 30.4%, respectively (including 5.4% of the strains carrying both genes), whereas *ermTR* was not detected in any strain. Among the 94 clinical strains of *S. pyogenes*, the *ermB*, *ermTR*, and *mefA* genes were found in 4.3%, 2.1%, and 14.9%, respectively. Among the 99 clinical strains of MSSA, the *ermA*, *ermB*, and *ermC* genes were found in 17.1%, 1.0%, and 5.1%, respectively, but in none of the strains carrying the *msrA* (*msrB*) gene.

All of these *erm*-carrying cocci were resistant to erythromycin (MICs, ≥ 1 µg/ml for streptococci and ≥ 8 µg/ml for MSSA, according to the CLSI breakpoints). Among the *erm*-carrying strains, 2 out of 2 *ermTR*-carrying *S. pyogenes* strains, 13 out of 17 *ermA*-carrying MSSA strains, and 5 out of 5 *ermC*-carrying MSSA strains were identified as being of the inducible resistance phenotype, because they were susceptible to clindamycin and showed a D-shaped inhibition zone in the double-disk diffusion test (Tables 2 to 4). All other *erm*-carrying strains showed resistance to clindamycin. None of the erythromycin-susceptible strains of streptococci and MSSA possessed any of these macrolide resistance genes, but it was interesting that one of the erythromycin-susceptible MSSA strains showed reduced susceptibility to clindamycin, with a MIC of 8 µg/ml.

Comparison of susceptibilities of various macrolide-resistant strains of Gram-positive cocci. All the *erm* gene-carrying strains of *S. pneumoniae* and *S. pyogenes* showed intermediate

TABLE 1. Antibacterial activities of modithromycin and reference antimicrobial agents against clinical
strains of Gram-positive and -negative organisms

Organism (no. of strains)	Test agent	MIC (µg/ml)		
		Range	50%	90%
Gram-positive organisms				
Streptococcus pneumoniae (148)	Modithromycin	≤0.063–0.5	≤0.063	0.125
	Telithromycin	≤0.063–2	≤0.063	0.125
	Clarithromycin	≤0.063–>64	32	>64
	Azithromycin	≤0.063–>64	>64	>64
	Erythromycin	≤0.063–>64	>64	>64
	Levofloxacin	0.5–1	0.5	1
Streptococcus pyogenes (94)	Modithromycin	≤0.063–0.25	≤0.063	0.125
	Telithromycin	≤0.063–8	≤0.063	0.5
	Clarithromycin	≤0.063–>64	≤0.063	8
	Azithromycin	≤0.063–>64	≤0.063	8
	Erythromycin	≤0.063–>64	≤0.063	16
	Levofloxacin	0.25–2	0.5	2
MSSA (99)	Modithromycin	≤0.063–>64	0.125	0.125
	Telithromycin	≤0.063–>64	≤0.063	0.125
	Clarithromycin	≤0.063–>64	0.25	>64
	Azithromycin	0.25–>64	0.5	>64
	Erythromycin	0.125–>64	0.25	>64
	Levofloxacin	≤0.063–16	0.25	0.5
Gram-negative organisms				
Moraxella catarrhalis (100)	Modithromycin	≤0.063–1	0.25	0.5
	Telithromycin	≤0.063–0.25	0.125	0.25
	Clarithromycin	≤0.063–0.5	0.125	0.25
	Azithromycin	≤0.063–0.125	≤0.063	≤0.063
	Erythromycin	≤0.063–1	0.125	0.5
	Levofloxacin	≤0.063–1	≤0.063	≤0.063
Haemophilus influenzae (93)	Modithromycin	1–16	4	8
	Telithromycin	0.5–4	1	2
	Clarithromycin	2–32	4	16
	Azithromycin	0.125–4	1	2
	Erythromycin	1–16	4	8
	Levofloxacin	≤0.063	≤0.063	≤0.063
Legionella pneumophila (56) and other *Legionella* spp. (5)	Modithromycin	0.016–0.25	0.031	0.031
	Telithromycin	0.031–0.25	0.125	0.125
	Clarithromycin	0.016–0.125	0.031	0.063
	Azithromycin	0.063–2	0.125	1
	Erythromycin	0.125–2	0.25	1
	Levofloxacin	0.016–0.063	0.031	0.031

resistance or resistance to clarithromycin and azithromycin. However, modithromycin showed MICs of ≤0.5 µg/ml against both *erm*-carrying streptococci (Tables 2 and 3). Although telithromycin showed potent activity against almost all the *ermB*-carrying *S. pneumoniae* strains, one of the strains, which showed susceptibility to modithromycin with a MIC of 0.25 µg/ml, had intermediate resistance to telithromycin, with a

MIC of 2 µg/ml. In addition, the *ermB*-carrying *S. pyogenes* strains were not susceptible to telithromycin, with MICs of 4 to 8 µg/ml; therefore, the activity of modithromycin was 32-fold or more potent than that of telithromycin against these strains. On the other hand, the activities of modithromycin and telithromycin were little affected by the presence of the Mef efflux pumps, encoded by *mefA* or *mefE*, in both streptococci,

TABLE 2. Comparison of susceptibilities of various macrolide-resistant strains of *S. pneumoniae*

Test agent	None (*n* = 27)		*ermB* (*n* = 76)		*mefE* (*n* = 37)		*ermB* + *mefE* (*n* = 8)	
	MIC range (µg/ml)	% I and R[a]	MIC range (µg/ml)	% I and R	MIC range (µg/ml)	% I and R	MIC range (µg/ml)	% I and R
Modithromycin	≤0.063	NC	≤0.063–0.5	NC	≤0.063–0.5	NC	0.125–0.5	NC
Telithromycin	≤0.063	0	≤0.063–2	1.3	≤0.063–0.5	0	≤0.063–0.5	0
Clarithromycin	≤0.063	0	1–>64	100	0.25–8	91.9	>64	100
Azithromycin	≤0.063–0.25	0	4–>64	100	0.25–8	86.5	>64	100
Clindamycin	≤0.063	0	2–>64	100	≤0.063	0	64–>64	100

[a] The percentages of intermediate–resistant (I) and resistant (R) strains are shown. The CLSI breakpoint criteria are as follows: telithromycin, 2 and ≥4 µg/ml; clarithromycin, 0.5 and ≥1 µg/ml; azithromycin, 1 and ≥2 µg/ml; clindamycin, 0.5 and ≥1 µg/ml. NC, not calculated (the breakpoints of modithromycin have not been determined).

TABLE 3. Comparison of susceptibilities of various macrolide-resistant strains of _S. pyogenes_

Test agent	None (_n_ = 74)		_ermTR_ (_n_ = 2)		_ermB_ (_n_ = 4)		_mefA_ (_n_ = 14)	
	MIC range (μg/ml)	% I and R[a]	MIC range (μg/ml)	% I and R	MIC range (μg/ml)	% I and R	MIC range (μg/ml)	% I and R
Modithromycin	≤0.063	NC	≤0.063	NC	≤0.063–0.25	NC	≤0.063–0.25	NC
Telithromycin	≤0.063	NC	≤0.063	NC	4–8	NC	≤0.063–0.5	NC
Clarithromycin	≤0.063	0	0.5–1	100	>64	100	0.5–8	100
Azithromycin	≤0.063–1.25	0	4–8	100	>64	100	2–8	100
Clindamycin	≤0.063	0	≤0.063	0	16–>64	100	≤0.063	0

[a] The percentages of intermediate-resistant (I) and resistant (R) strains are shown. The CLSI breakpoint criteria are as follows: clarithromycin, 0.5 and ≥1 μg/ml; azithromycin, 1 and ≥2 μg/ml; clindamycin, 0.5 and ≥1 μg/ml. NC, not calculated (the breakpoints of modithromycin and telithromycin have not been determined).

while it caused intermediate resistance or resistance to clarithromycin and azithromycin. Modithromycin as well as telithromycin and clindamycin had potent activity against MSSA with the inducible resistance phenotype of _ermA_ and _ermC_, while clarithromycin and azithromycin did not (Table 4). However, MSSA with the constitutive resistance phenotype of _ermA_ and _ermB_ showed high-level resistance to modithromycin and telithromycin as well as other macrolide agents and clindamycin.

DISCUSSION

During the last few decades, the incidence of clinical strains of macrolide-resistant Gram-positive cocci has been increasing worldwide. The prevalence rate of resistant organisms varies considerably among countries, presumably because the use of these antimicrobial agents also varies among countries (3, 4, 5, 6). In the PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) study, clinical strains of _S. pneumoniae_ resistant to erythromycin accounted for 24.2% of _S. pneumoniae_ strains in the United Kingdom, 34.7% in the United States, 53.1% in France, 81.9% in Japan, and 97.6% in Taiwan (11). In the present study, approximately 80% of _S. pneumoniae_ strains collected from a Japanese medical facility had the macrolide resistance genes of _ermB_ and/or _mefE_ and showed resistance to macrolide agents, such as clarithromycin and azithromycin. The frequency of the resistant strains was similar to the results of a previous surveillance study in Japan (14). All of the macrolide-resistant streptococci in this study had one or more genes that have been reported to cause resistance to macrolide agents, so there seemed to be no resistant strains with unknown mechanisms of

resistance. The predominant resistance genotype in _S. pneumoniae_ strains was _ermB_ rather than _mefE_ in this study. It has also been reported that _ermB_ is the most predominant resistance genotype among clinical strains in Japan and most European countries (12, 14). We did not observe the _msr_ gene, which is plasmid mediated, in any of the MSSA strains tested in this study. This observation was consistent with the previous report on _msr_ being prevalent in coagulase-negative staphylococci, such as _Staphylococcus epidermidis_ and _Staphylococcus haemolyticus_ (17, 18, 21). One erythromycin-susceptible MSSA strain showed resistance to clindamycin, with an MIC of 8 μg/ml. Because no cross-resistance between clindamycin and the macrolide agents tested was observed, clindamycin resistance mechanisms such as those involving the _mph_ and _lnu_ genes, encoding a lincosamide inactivator, may exist in this MSSA isolate (17).

To overcome the macrolide resistance mechanisms, including target site modification and active efflux, the ketolide antimicrobial agent telithromycin was developed (20, 28). Telithromycin has unique structural features, such as an additional aromatic side chain, which enhances the affinity of binding to the ribosomal domain II as well as domain V, and the C-3 ketone, due to removal of the cladinose sugar responsible for the inducibility of macrolide resistance and the possibility of macrolide recognition by the _mef_ efflux pump. A novel bicyclolide, modithromycin, which has a unique 6,11-bridged ether ring and aromatic side chain, in addition to the C-3 ketone, was also designed to improve the antibacterial activity against macrolide-resistant organisms (28). Our results revealed that modithromycin has excellent antibacterial activity against all clinical strains of _S. pneumoniae_, including

TABLE 4. Comparison of susceptibilities of various macrolide-resistant strains of MSSA

Test agent	None (_n_ = 76)		_ermA_ (i)[a] (_n_ = 13)		_ermA_ (c)[b] (_n_ = 4)		_ermB_ (c) (_n_ = 1)		_ermC_ (i) (_n_ = 5)	
	MIC range (μg/ml)	% I and R[c]	MIC range (μg/ml)	% I and R	MIC range (μg/ml)	% I and R	MIC range (μg/ml)	% I and R	MIC range (μg/ml)	% I and R
Modithromycin	≤0.063–0.125	NC	≤0.063–0.125	NC	16–>64	NC	>64	NC	0.125	NC
Telithromycin	≤0.063–0.125	0	≤0.063–0.125	0	>64	100	>64	100	≤0.063–0.125	0
Clarithromycin	≤0.063–0.25	0	64–>64	100	>64	100	>64	100	>64	100
Azithromycin	0.25–1	0	>64	100	>64	100	>64	100	>64	100
Clindamycin	≤0.063–8	1.3	≤0.063–0.125	0	>64	100	>64	100	≤0.063–0.25	0

[a] i, inducible resistance phenotype.
[b] c, constitutive resistance phenotype.
[c] The percentages of intermediate-resistant (I) and resistant (R) strains are shown. The CLSI breakpoint criteria are as follows: telithromycin, 2 and ≥4 μg/ml; clarithromycin, 4 and ≥8 μg/ml; azithromycin, 4 and ≥8 μg/ml; clindamycin, 1 to 2 and ≥4 μg/ml. NC, not calculated (the breakpoints of modithromycin have not been determined).

macrolide-resistant *ermB*- and/or *mefE*-carrying strains. In addition, modithromycin was also active against one *ermB*-carrying strain which showed intermediate resistance to telithromycin, with an MIC of 2 μg/ml. The telithromycin resistance mechanism of this strain has not been revealed yet; however, it has been reported that specific mutations of 23S rRNA, ribosomal protein, or the *ermB* upstream region cause intermediate or high-level resistance to telithromycin in *S. pneumoniae* (1, 17, 28). Modithromycin also showed activity against both *ermB*- and *ermTR*-carrying *S. pyogenes* strains. In particular, modithromycin was 32- to >64-fold more active than telithromycin against *ermB*-carrying strains. Douthwaite et al. have reported that the telithromycin resistance in *S. pyogenes* correlates with the degree of rRNA dimethylation by Erm (9). These findings demonstrated that the bicyclolide nucleus and aromatic side chain of modithromycin would contribute to the increased affinity for the dimethylated ribosome of streptococci, including telithromycin-resistant strains. Unlike the Erm phenotype in streptococci, except for ErmTR, the expression of the Erm phenotype can be determined to be inducible or constitutive in *S. aureus* by the inducibility test using erythromycin and clindamycin (17, 27). Against the *ermA*-, *ermB*-, or *ermC*-carrying MSSA strains, clarithromycin and azithromycin were inactive regardless of the inducible or constitutive resistance phenotypes. Modithromycin, as well as telithromycin and clindamycin, was active against *ermA*- and *ermC*-carrying strains with the inducible resistance phenotype but was not active against *ermA*- and *ermB*-carrying strains with the constitutive resistance phenotype. Although it is not fully understood why the activity of modithromycin against *ermB*-carrying strains differed between streptococci and MSSA, we speculate that possible reasons may be differences in the degree of rRNA dimethylation or in the ribosomal region of modithromycin binding.

Our results also revealed the potent antibacterial activity of modithromycin against Gram-negative respiratory pathogens, such as *M. catarrhalis*, *H. influenzae*, and *Legionella* species. In particular, the anti-*Legionella* activity of modithromycin was more potent than the activities of the other macrolide and ketolide agents tested and comparable to that of levofloxacin. *Legionella* is a facultative intracellular pathogen that causes life-threatening pneumonia. Therefore, efficient penetration of the antimicrobial agents into cells at the site of infection is required for therapeutic efficacy against this pathogen. We have already evaluated the *in vivo* efficacy of modithromycin in a murine model of *L. pneumophila* pneumonia and found it to be excellent (25), indicating that modithromycin seemed to have preferable pharmacokinetic features for efficacy, in addition to its potent *in vitro* activity.

In summary, the novel bicyclolide modithromycin was shown to possess a broad spectrum of *in vitro* activity against both Gram-positive and -negative pathogens that cause respiratory tract infections. In particular, modithromycin was shown to have advantages over currently available macrolide and ketolide agents because it has potent activity against the clinically important macrolide-resistant Gram-positive cocci that have spread worldwide and Gram-negative intracellular bacteria of the genus *Legionella*.

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