Synthesis and Structure−Activity Relationship Studies of Highly Potent Novel Oxazolidinone Antibacterials

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Novel antibacterial biaryl oxazolidinones bearing an aza-, an oxa-, or a thiabicyclo[3.1.0]hex-6-yl ring system were synthesized, and their in vitro antibacterial activity and structure−activity relationships (SAR) were evaluated. Most of the synthesized biaryl bicyclo[3.1.0]hex-6-yl oxazolidinones showed good antibacterial activity against the Gram-positive and -negative bacteria tested. Regarding SAR trends among the C-ring subtypes, the pyridyl ring was preferable to the phenyl ring. The results showed that the structural variety of the C-ring has a greater impact on antibacterial activity than that of the B-ring. A cyano group at the D-ring C-6 position plays an important role in the highly potent antibacterial activity.

Introduction

Worldwide spread of drug-resistant bacteria is now a critical problem in global health. Of particular importance are severe infections caused by drug-resistant Gram-positive and RTI[a] (respiratory tract infection) causative Gram-negative bacteria in hospital and community care. Linezolid (**1**) (Scheme 1), the first and only oxazolidinone, belongs to a new class of synthetic antibacterial drugs and is available for intravenous or oral treatment of Gram-positive infections caused by bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant *Enterococcus faecalis* (VRE).[1] However, **1** displays modest activity against RTI-causative Gram-negative bacteria such as *Haemophilus influenzae*, and resistance against **1** has already been observed in Gram-positive bacteria such as *S. aureus*[2] and *Enterococcus faecium*.[3−7] Therefore, significant efforts have been made by many research groups to improve the potency and antibacterial spectrum of this new drug.[8]

During the course of our initial efforts to develop novel oxazolidinones, we designed and synthesized azabicyclo-[3.1.0]hexane derivatives such as **2** (Scheme 1).[9] We found that a cyano group at the C-6 position of the azabicyclo[3.1.0]hex-3-yl ring system greatly enhanced the antibacterial activity. Although compound **2** showed superior antibacterial activity against Gram-positive bacteria compared with **1**, compound **2** showed only modest activity against *H. influenzae* (data not shown). We next synthesized and evaluated azabicyclo[3.1.0]hex-6-yl derivatives **3** as a positional isomer of **2**.[10] Although **3** possessed good antibacterial activity comparable to that of **1**, it was still insufficient in meeting our criteria. Finally, we focused on the biaryl oxazolidinones **4** bearing the azabicyclo[3.1.0]hex-6-yl ring system to enhance antibacterial activity (Scheme 1). As we anticipated, on the basis of the reports on pyridylphenyl oxazolidinones,[11,12] **4** inserted an aryl ring between the B-ring and D-ring of **3** and thus was expected to possess enhanced antibacterial activity. We also targeted the oxa- and thiabicyclo-[3.1.0]hex-6-yl ring system in this investigation by replacing a bicyclo[3.1.0]hexane ring with an aryl ring from the C-3 position to the C-6 position. We herein report our attempts to develop novel, potentially improved antibacterial biaryl oxazolidinones bearing a bicyclo[3.1.0]hex-6-yl ring moiety.

Chemistry

The synthesis of the biaryl oxazolidinones bearing a bicyclo[3.1.0]hex-6-yl ring is outlined in Scheme 2. We employed the cyclopropane ring formation by way of 1,2-cyclic sulfate reported by Sharpless[13] to construct the 6-aryl-6-cyanobicyclo[3.1.0]hexane ring system. Thus, S_NAr reaction of 2,5-dibromopyridine (**5**) with *tert*-butyl cyanoacetate afforded **6**. Removal of a *tert*-butoxycarbonyl group of **6** by using montmorillonite KSF clay[14] cleanly provided pyridylacetonitrile **7a**[15] (Scheme 3).

Cyclic sulfate **11** prepared from *cis*-3,4-dihydroxypyrrolidine **8**[16] easily reacted with **7a** under basic conditions to give azabicyclo[3.1.0]hexane **14a** as the sole product (Scheme 4). The stereochemistry of **14a** was determined unambiguously by a NOESY experiment. This stereoselective cyclization of **7a** and **11** probably proceeded because of the steric hindrance between a pyrrolidine ring and a pyridine ring. A stereoselective cyclization that proceeded in a similar manner was previously reported.[17] For replacement of the pyridine C-ring with a benzene ring, use of phenylacetonitriles **7b−d** as the starting material in place of **7a** resulted in the bicyclo[3.1.0]hexanes **14b−d**. In the case of the synthesis of oxa- and thiabicyclo-[3.1.0]hexanes **15** and **16**, *cis*-3,4-dihydroxytetrahydrofuran (**9**)[18] and *cis*-3,4-dihydroxytetrahydrothiophene (**10**)[19] were used instead of **8**. The synthesis of *cis*-tetrahydrothiophen-3,4-cyclic sulfate (**13**) was achieved by the reaction of **10** and sulfuryl chloride (Scheme 4).

With the desired aza-, oxa-, and thiabicyclo[3.1.0]hexanes **14a−d**, **15**, and **16** in hand, the stage was set to carry out the Pd-coupling reaction with oxazolidinones **21c** or **22a**,**b** (Schemes 5 and 6). Indeed, the coupling reaction of **14−16** with **21c** or **22a**,**b** derived from **17**[20] or **21a**,**b**[21] proceeded smoothly to the desired biaryl oxazolidinones **23−28**, **35−46** carrying a 1,2,3-triazole ring moiety at the A-ring C-5 position. Removal of a *tert*-butoxycarbonyl (Boc) group of **23−28** under acidic conditions afforded **29−34**. Oxidation of a sulfur atom of **38−40** by

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[a] Abbreviations: RTI, respiratory tract infection; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PRSP, penicillin-resistant *Streptococcus pneumoniae*; PSSP, penicillin-susceptible *Streptococcus pneumoniae*; VRE, vancomycin-resistant *Enterococcus faecalis*; MIC, minimum inhibitory concentration; SAR, structure−activity relationships.

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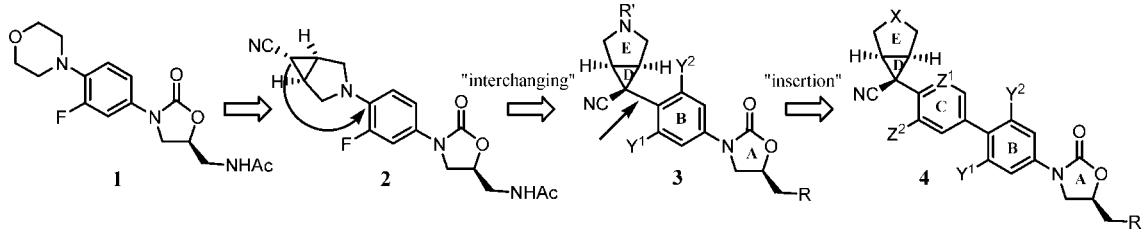
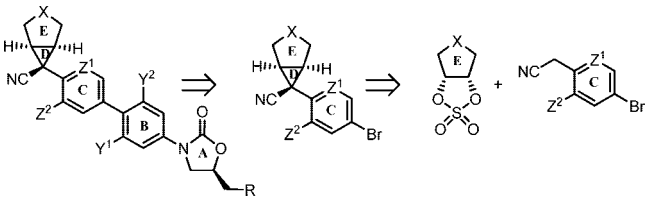
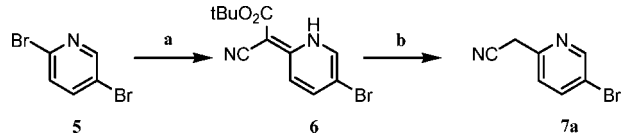
Scheme 1



Scheme 2

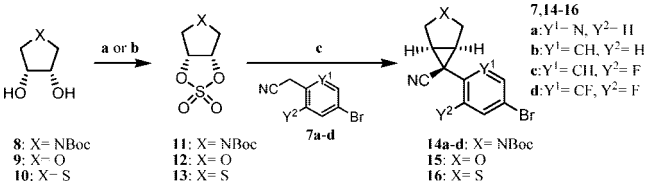


Scheme 3[a]



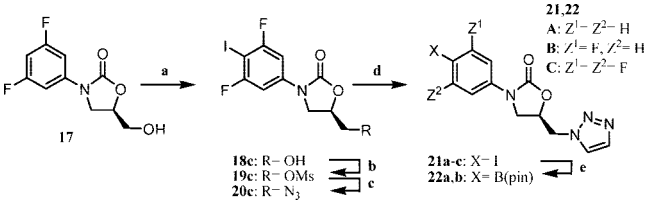
[a] Reagents: (a) *tert*-butyl cyanoacetate, NaH, 88%; (b) KSF clay, 72%.

Scheme 4[a]



[a] Reagents: (a) (i) $SOCl_2$, Et_3N, (ii) $RuCl_3$, $NaIO_4$, 97% (for **11**), 84% (for **12**); (b) SO_2Cl_2, Et_3N, 54% (for **13**); (c) NaH, 88% (for **14a**), 58% (for **14b**), 87% (for **14c**), 41% (for **14d**), 71% (for **15**), 12% (for **16**).

Scheme 5[a]

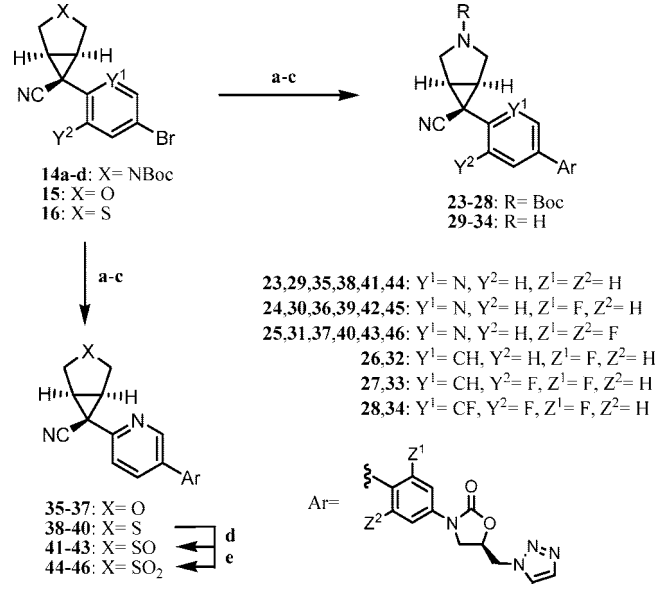


[a] Reagents: (a) ICl, 62%; (b) MsCl, Et_3N; (c) NaN_3, 99% (two steps); (d) 2,5-norbornadiene, 94%; (e) bis(pinacolato)diboron, AcOK, [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride, 73% (for **22a**), 79% (for **22b**).

using *m*-chloroperbenzoic acid gave sulfoxides **41**−**43** or sulfones **44**−**46**, respectively. Because of the low water solubility of the oxa- and thiabicyclo biaryl oxazolidinones **35**−**46**, synthetic efforts were focused on the synthesis of the azabicyclo biaryl oxazolidinone derivatives, particularly **30**.

To estimate the impact of a cyano group at the D-ring C-6 position on antibacterial activity, the cyano group of **30** was replaced with other substituents, such as an aminomethyl, a carbamoyl, or an amino group (Scheme 7). Alkaline hydrolysis of **14a** provided the carbamoyl derivative **47**. Hofmann rearrangement of **47** using lead(IV) acetate and subsequent addition of *tert*-butanol to the isocyanate intermediate gave the carbamate **48**. Each of **47** and **48** were subjected to the coupling reaction

Scheme 6[a]



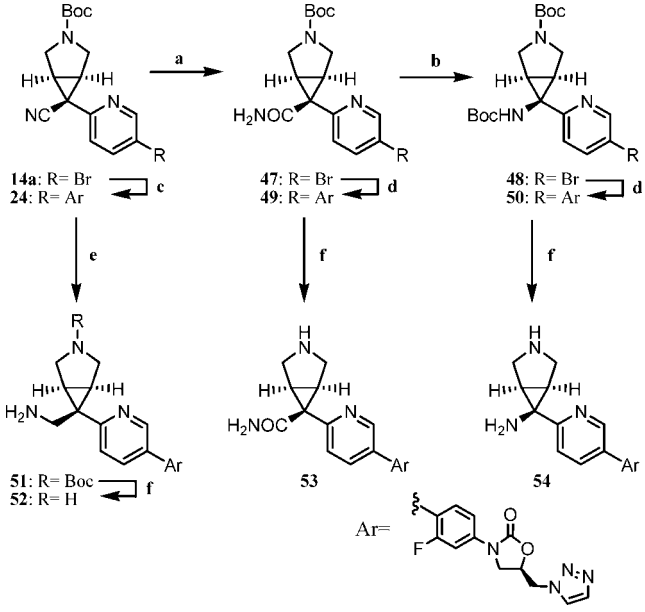
[a] Reagents: (a) ArB(pin) (**22a** or **22b**), $(Ph_3P)4Pd$, 2 M Na_2CO_3, 78% (for **23**), 56% (for **24**), 72% (for **26**), 75% (for **27**), 93% (for **28**), 71% (for **35**), 79% (for **36**), 64% (for **38**), 79% (for **39**); (b) (i) ArI (**21c**), bis(pinacolato)diboron, AcOK, [1,1′-bis(diphenylphosphino)ferrocene]-palladium(II) dichloride, (ii) $(Ph_3P)4Pd$, 2 M Na_2CO_3, 29% (two steps for **25**), 37% (two steps for **37**), 19% (two steps for **40**); (c) 4 M HCl−dioxane, 94% (for **29**), 63% (for **30**), 92% (for **31**), 98% (for **32**), 88% (for **33**), 88% (for **34**); (d) mCPBA (1.4 equiv), 95% (for **41**), 91% (for **42**), 90% (for **43**); (e) mCPBA (3 equiv), 76% (for **44**), 96% (for **45**), 96% (for **46**).

with **22b** and removal of a Boc group to afford **53** and **54**, respectively. Reduction of the cyano group of **24** by sodium borohydride/cobalt(II) chloride and subsequent deprotection of a Boc group successfully provided the aminomethyl derivative **52**.

We next attempted to synthesize the C-5 derivatives at the A-ring, such as amide or isoxazole derivatives, by acylation or Mitsunobu reaction (Scheme 8). Many C-5 substituents have been well examined on various oxazolidinone antibacterials by other research groups.[8] The C-5 substituents examined here were selected from among the C-5 substituents previously reported to be good replacement for the triazole moiety. Acylation of amine **56d** derived from **55b** by acid chloride or anhydride easily provided the amides **58**−**61**. Acetamide **57** was prepared by the Pd-coupling reaction of **14a** and **55a**. The thiocarbonyl derivatives **62** and **63** were prepared from **56d** by employing thiocarbonyl transfer and isothiocyanate formation. The isoxazole derivatives **64** and **65** were cleanly provided by way of Mitsunobu reaction of alcohol **56a** with *N*-Boc-aminoisoxazole or hydroxyisoxazole.

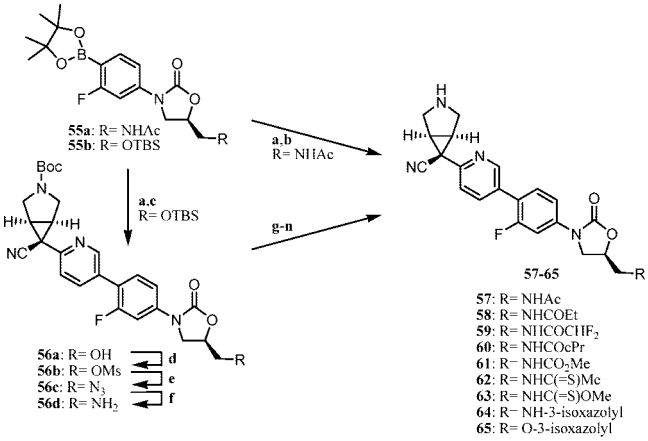
Finally, **30** served as a starting material for further modifications at a nitrogen atom of the E-ring, such as by acylation, alkylation, or S_NAr reaction, to provide azabicyclo[3.1.0]hexane

Scheme 7[a]



[a] Reagents: (a) 25% NaOH, 92%; (b) lead tetraacetate, *tert*-BuOH, 58%; (c) see Scheme 5; (d) **22b**, $(Ph_3P)_4Pd$, 2 M Na_2CO_3, 41% (for **49**), 48% (for **50**); (e) $NaBH_4$, $CoCl_2 \cdot 6H_2O$, 56%; (f) 4 M HCl−dioxane, 96% (for **52**), 68% (for **53**), 96% (for **54**).

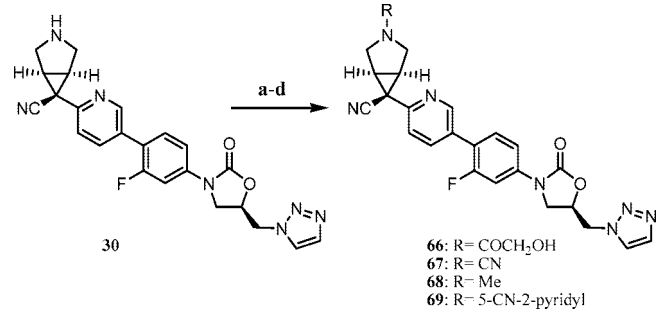
Scheme 8[a]



[a] Reagents: (a) **14a**, $(Ph_3P)_4Pd$, 2 M Na_2CO_3, 71% (for **57**), 81% (for **56a**); (b) 4 M HCl−dioxane, 73% (for **57**); (c) TBAF, 93%; (d) MsCl, Et_3N; (e) NaN_3, 90% (two steps); (f) (i) Ph_3P, (ii) H_2O, 80% (two steps); (g) (i) propionyl chloride, Et_3N, 91% (from **56d**), (ii) reagents (b), 68% (for **58**); (h) (i) difluoroacetic anhydride, Et_3N, 74% (from **56d**), (ii) reagents (b), 76% (for **59**); (i) cyclopropanecarboxylic acid, 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride, 76% (from **56d**), (ii) reagents (b), 83% (for **60**); (j) methyl chloroformate, Et_3N, 24% (from **56d**), (ii) reagents (b), 74% (for **61**); (k) ethyl dithioacetate, Et_3N, 73% (from **56d**), (ii) TFA, 73% (for **62**); (l) (i) CS_2, Et_3N, 77%, (ii) NaOMe, 74%, (iii) TFA, 62% (for **63**); (m) (i) 3-*N*-Boc-aminoisoxazole, tetramethylazodicarboxamide, Bu_3P, 86% (from **56a**), (ii) reagents (b), 87% (for **64**); (n) (i) 3-hydroxyisoxazole, diisopropyl azodicarboxylate, Ph_3P, 95% (from **56a**), (ii) reagents (b), 86% (for **65**).

derivatives **66**−**69** (Scheme 9). Acylation of **30** with acetoxyacetyl chloride and subsequent methanolysis of an acetyl group gave the *N*-hydroxyacetyl derivative **66**. Electrophilic cyanation of **30** with cyanogen bromide in the presence of sodium acetate provided the *N*-cyano derivative **67**. Reductive methylation of **30** with formaldehyde and sodium triacetoxyborohydride afforded the *N*-methyl derivative **68**. S_NAr reaction of **30** with

Scheme 9[a]



[a] Reagents: (a) (i) acetoxyacetyl chloride, Et_3N, 95%, (ii) K_2CO_3, MeOH, 58% (for **66**); (b) BrCN, AcONa, 44% (for **67**); (c) 35% HCHO, $NaBH(OAc)_3$, 73% (for **68**); (d) 2-Br-5-CN-pyridine, diisopropylethylamine, 52% (for **69**).

Table 1. In Vitro Antibacterial Activity of Biaryl Oxazolidinones **29**−**46**

						MIC (μg/mL)[a]					
compd	X	Y^1	Y^2	Z^1	Z^2	MSSA	MRSA	PSSP	PRSP	VRE	HI
29	NH	N	H	H	H	0.125	0.125	0.125	0.125	0.25	2
30		N	H	F	H	0.06	0.06	0.06	0.06	0.125	2
31		N	H	F	F	0.125	0.125	0.125	0.125	0.25	4
32		CH	H	F	H	0.125	0.06	0.125	0.06	0.25	4
33		CH	F	F	H	0.25	0.125	0.25	0.25	0.25	16
34		CF	F	F	H	0.5	0.5	1	1	0.25	>128
35	O	N	H	H	H	0.06	0.06	0.125	0.125	0.25	4
36				F	H	0.06	0.06	0.06	0.06	0.25	2
37				F	F	0.06	0.06	0.25	0.125	0.25	4
38	S	N	H	H	H	0.06	0.06	0.125	0.06	0.25	8
39				F	H	0.06	0.06	0.125	0.06	0.25	>2
40				F	F	0.06	0.06	0.25	0.25	0.5	>16
41	SO	N	H	H	H	0.125	0.125	0.125	0.125	0.25	8
42				F	H	0.06	0.06	0.06	0.06	0.125	4
43				F	F	0.06	0.06	0.125	0.125	0.125	8
44	SO_2	N	H	H	H	0.06	0.06	0.06	0.06	0.125	4
45				F	H	0.06	0.125	0.125	0.06	0.06	4
46				F	F	0.06	0.06	0.06	0.06	0.125	4
1						1	1	1	1	2	16

[a] Organisms selected for inclusion in the table: MSSA, methicillin-sensitive *S. aureus* Smith; MRSA, methicillin-resistant *S. aureus* TK7; PSSP, penicillin-susceptible *S. pneumoniae* IID553; PRSP, penicillin-resistant *S. pneumoniae* PR44; VRE, vancomycin-resistant *E. faecium* A2280; HI, *H. influenzae* IID983.

2-bromo-5-cyanopyridine proceeded to give the *N*-pyridyl derivative **69**.

Results and Discussion

The synthesized aza-, oxa-, and thiabicyclic biaryl oxazolidinone derivatives were evaluated for their antibacterial activity against a panel of Gram-positive and -negative bacteria. The in vitro antibacterial activity was assessed by minimum inhibitory concentration (MIC) values utilizing the agar dilution method.

As shown in Table 1, highly potent antibacterial activity of the synthesized biaryl oxazolidinones and interesting trends in the structure−activity relationships (SAR) were observed. Among the C-ring subtypes, the pyridyl analogue **30** was more potent than the phenyl analogues **32**−**34**. In the B-ring subtypes, the monofluorophenyl moiety was superior to the phenyl and difluorophenyl moieties for the azabicyclo[3.1.0]hexane derivatives (**30** vs **29** and **31**). Structural modification of the C-ring had a greater impact on antibacterial activity than that of the B-ring. In the azabicyclo[3.1.0]hexane types, these B-ring and C-ring SAR trends held for both the Gram-positive and -negative bacteria examined. Among the phenyl analogues **32**−**34**, antibacterial activity except for that against VRE was cleanly

Table 2. In Vitro Antibacterial Activity of Biaryl Oxazolidinones **30**, **52**−**54**: D-Ring Cyano Group

		MIC (μg/mL)[a]					
compd	R	MSSA	MRSA	PSSP	PRSP	VRE	HI
30	CN	0.06	0.06	0.06	0.06	0.125	2
52	CH_2NH_2	4	4	4	8	16	128
53	$CONH_2$	2	2	1	0.5	4	NT
54	NH_2	1	2	0.5	0.5	2	32

[a] Organisms selected for inclusion in the table: MSSA, methicillin-sensitive *S. aureus* Smith; MRSA, methicillin-resistant *S. aureus* TK7; PSSP, penicillin-susceptible *S. pneumoniae* IID553; PRSP, penicillin-resistant *S. pneumoniae* PR44; VRE, vancomycin-resistant *E. faecium* A2280; HI, *H. influenzae* IID983.

Table 3. In Vitro Antibacterial Activity of Biaryl Oxazolidinones **57**−**65**: A-Ring C-5 Substituents

		MIC (μg/mL)[a]					
compd	R	MSSA	MRSA	PSSP	PRSP	VRE	HI
57	NHCOMe	0.125	0.125	0.125	0.06	0.25	4
58	NHCOEt	0.25	0.25	0.25	0.125	0.25	8
59	$NHCOCHF_2$	0.125	0.125	0.06	0.06	0.25	2
60	NHCOcPr	0.5	0.25	0.25	0.25	0.5	8
61	$NHCO_2Me$	0.125	0.125	0.125	0.125	0.125	4
62	NHC(=S)OMe	0.06	0.03	0.06	0.03	0.06	2
63	NHC(=S)Me	0.03	0.03	0.03	0.03	0.06	0.5
64	O-3-isoxazolyl	0.125	0.125	0.25	0.25	0.5	>16
65	NH-3-isoxazolyl	0.06	0.06	0.125	0.06	0.125	4

[a] Organisms selected for inclusion in the table: MSSA, methicillin-sensitive *S. aureus* Smith; MRSA, methicillin-resistant *S. aureus* TK7; PSSP, penicillin-susceptible *S. pneumoniae* IID553; PRSP, penicillin-resistant *S. pneumoniae* PR44; VRE, vancomycin-resistant *E. faecium* A2280; HI, *H. influenzae* IID983.

reduced with an increase of the number of fluorine substitutions. In particular, **34**, which carries three fluorine atoms on the B-ring and C-ring, showed drastically reduced antibacterial activity against *H. influenzae*, probably because of its increased hydrophobicity. Regarding the SAR trends for heteroatoms on the E-ring, the oxothia- and dioxothia-bicyclic biaryl oxazolidinones **41**−**43** and **44**−**46** showed highly potent activity against VRE. Our results suggested that the hydrophobicity of the heteroatoms on the E-ring have a particularly pronounced impact on the anti-*H. influenzae* activity.

As shown in Table 2, the antibacterial activity of the aminomethyl, carbamoyl, and amino derivatives **52**−**54** was dramatically reduced by replacement of a cyano group. Among the C-6 derivatives examined, **54**, which carries a basic primary amino substituent instead of the cyano group, showed 8- to 32-fold less activity. The antibacterial activity of **52**, which possesses a more basic and bulky aminomethyl substituent at the C-6 position, was even less than that of **54**. A carbamoyl group in **53**, which is a more hydrophilic and bulky substituent than a cyano group, is also not preferable to the cyano group in **30** in terms of achieving a strong antibacterial activity. At the D-ring C-6 position of **30**, the cyano group plays an important role in the highly potent antibacterial activity.

As shown in Table 3, although the thiocarbonyl derivatives **62** and **63** showed more potent activity than **30**, the other C-5 substituted derivatives **57**−**61**, **64**, and **65** showed 2- to 8-fold less activity than **30**. The hydrophobicity of the C-5 substituents thus had a greater impact on antibacterial activity than the steric bulk of the C-5 substituents (**57** vs **58** vs **60**, **58** vs **61**).

The acylated or alkylated analogues **66**−**69** prepared by modification at the nitrogen atom of the E-ring of **30** resulted in comparable or 2-fold higher MICs than **30** (Table 4). In particular, the *N*-cyano derivative **67** showed more potent activity against VRE than **30**. Although the modifications examined at the nitrogen atom of **30** were well tolerated, the resulting N-substituted compounds **66**−**69** possessed poor solubility for intravenous administration.

Table 4. In Vitro Antibacterial Activity of Biaryl Oxazolidinones **66**−**69**: E-Ring N-3 Substituents

		MIC (μg/mL)[a]					
compd	R	MSSA	MRSA	PSSP	PRSP	VRE	HI
66	$COCH_2OH$	0.06	0.06	0.06	0.06	0.125	4
67	CN	0.06	0.06	0.06	0.06	0.06	2
68	Me	0.06	0.06	0.06	0.06	0.25	4
69	5-CN-2-pyridyl	0.06	0.06	0.125	0.06	0.125	>2

[a] Organisms selected for inclusion in the table: MSSA, methicillin-sensitive *S. aureus* Smith; MRSA, methicillin-resistant *S. aureus* TK7; PSSP, penicillin-susceptible *S. pneumoniae* IID553; PRSP, penicillin-resistant *S. pneumoniae* PR44; VRE, vancomycin-resistant *E. faecium* A2280; HI, *H. influenzae* IID983.

Conclusions

We have succeeded in the design, synthesis, and SAR analysis of novel biaryl oxazolidinones bearing a bicyclo[3.1.0]hex-6-yl ring moiety. Most of the synthesized biaryl bicyclo[3.1.0]hex-6-yl oxazolidinones showed higher antibacterial activity against the tested Gram-positive drug-resistant bacteria MRSA, PRSP, and VRE and the RTI-causative Gram-negative bacteria *H. influenzae* compared with **1**. Among the synthesized biaryl bicyclo[3.1.0]hex-6-yl oxazolidinones, **30** was selected for further evaluation. Further study of **30** demonstrated its excellent antibacterial activity against drug-resistant clinical isolates such as MRSA and VRE and against typical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*,[22] its low resistance potential,[23] and its intravenous and orally active in vivo efficacy in the linezolid-resistant MRSA mouse infection model[24] of **30**. We have selected **30** (AM-7359) as a candidate for further evaluation in clinical trials.

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Supporting Information Available: Experimental details, elemental analysis results for new compounds, and NOESY spectra of **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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