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Design, synthesis, and antibacterial activities of novel 3,6-bicyclolide oximes: Length optimization and zero carbon linker oximes

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ABSTRACT

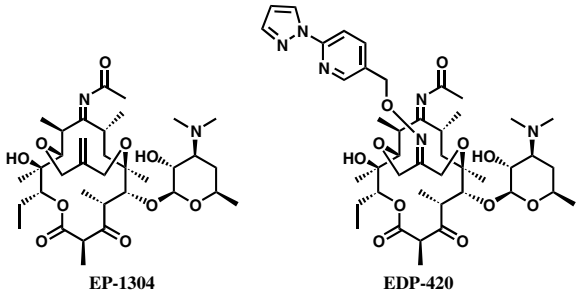
We designed and synthesized a series of novel 3,6-bicyclolide oximes, possessing linkers of varying lengths to the secondary binding site. The *E* isomers exhibited excellent antibacterial profiles against a broad spectrum of resistant pathogens.

The development of novel, effective, and safe antibacterial agents is urgently needed to control infectious disease caused by antibiotic-resistant bacteria. Macrolide antibiotics are an important class of therapeutic agents against bacterial infections.[1] However, the extensive clinical use of macrolide antibiotics has resulted in an increasing MLS_B-resistance in respiratory pathogens. In our laboratories, we have been pursuing new generations of macrolides. Recently, EP-1304,[2] a 6,11-bicyclolide core, was discovered. Subsequent chemistry efforts based on this core structure resulted in EDP-420 (EP-013420),[3] our first-in-class bicyclolide antibiotic clinical candidate, currently in phase II clinical trial for the treatment of community acquired pneumonia. In continuation of our efforts, we have designed and synthesized 3,6-bicyclolide oxime derivatives possessing linkers of varying lengths attached to the secondary aromatic binding motifs[4] (see Fig. 1).

The synthesis of 3,6-bicyclolide oxime is outlined in Scheme 1. Key intermediate 11,12-carbamate 3,6-bicyclolide **2** was prepared from **1** in 85% yield in a three-step one-pot fashion. The following Osmium tetraoxide and sodium periodate mediated olefin cleavage provided diketone compound **3** in 94% yield. The acid catalyzed oxime formation was carried out using diketone **3** and hydroxylamine **4a–4f** in an aqueous alcoholic media at room temperature. Oxime formation at C-9 ketone was not observed under these reaction conditions. The resulting oximes **5a–5f** were usually about 3 to 1 *E*/*Z* mixtures, which underwent 2′-deacetylation to give **6a–6f** as mixtures in similar *E*/*Z* ratios. The final desired 3,6-bicyclolide *E*-oximes **7a–7f** were isolated by either crystallization or preparative reverse-phase HPLC chromatography.[5]

The structure of ketolide **7b** was confirmed by the X-ray crystallography (Fig. 2).

The 3,6-bicyclolides **7a–7f** and the reference compound, erythromycin A, were tested against a panel of representative respiratory pathogens. Various macrolide- and multidrug-resistant isolates were included in the panel in order to identify potent analogues that could overcome macrolide resistance. *Staphylococcus aureus* 29213, *Streptococcus pyogenes* 19615, and *Streptococcus pneumoniae* 49619 are erythromycin-susceptible strains. *Staphylococcus aureus* 27660 is an inducibly MLSB-resistant strain encoded by an *ermA* gene. *Staphylococcus aureus* 33591 is an MRSA. *Streptococcus pyogenes* 2912 is constitutive MLS_B-resistant strain encoded



EP-1304 EDP-420

Figure 1. Structure of 6,11-bicyclolide EP-1304 and EDP-420.

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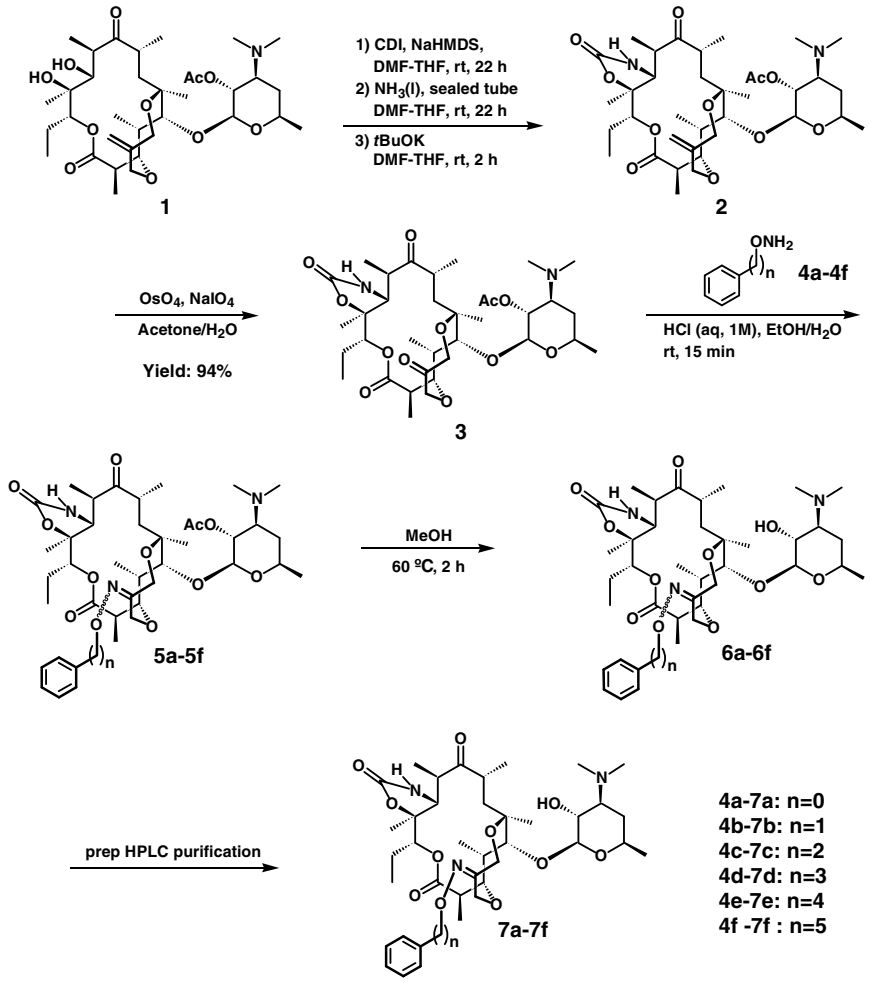


Scheme 1. Synthesis of 3,6-bicyclolide oximes.

by an *ermA* gene, and *S. pneumoniae* 700906 is resistant strain encoded by an *erm* gene. *Streptococcus pyogenes* 1323 and *S. pneumoniae* 7701 are efflux-resistant strains encoded by *mefA* genes. *Haemophilus influenzae* 33929 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 utilizing the broth-microdilution method as per CLSI standards. The in vitro antibacterial activities of 3,6-bicyclolides **7a–7f** and reference compound are shown in Table 1.

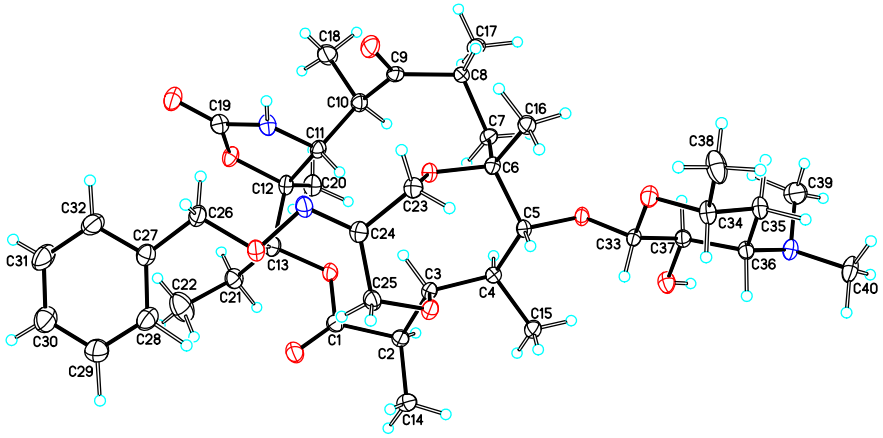
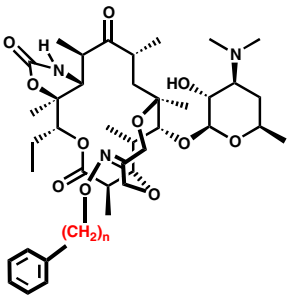


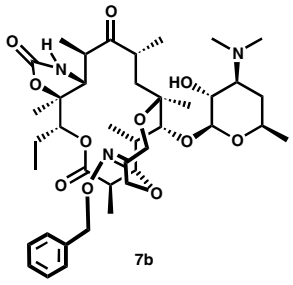
Figure 2. X-ray single crystal structure of 3,6-bicyclolide **7b**.

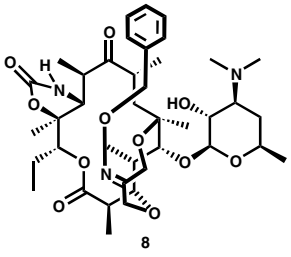
Table 1
In vitro antibacterial activities of 3,6-bicyclolide oximes—length optimization



Organism		MIC (μg/ml)						
		7a (n = 0)	**7b** (n = 1)	**7c** (n = 2)	**7d** (n = 3)	**7e** (n = 4)	**7f** (n = 5)	Ery A
S. aureus 29213	Ery S	⩽0.06	⩽0.06	0.125	0.125	0.25	0.25	0.5
S. aureus 27660	MLS Ri	⩽0.06	⩽0.06	0.125	0.125	0.25	0.25	>64
S. aureus 33591	MRSA	>64	>64	>64	>64	64	>64	>64
S. pneumoniae 49619	Ery S	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06
S. pneumoniae 7701	Ery R-mef	⩽0.06	⩽0.06	⩽0.06	⩽0.06	0.125	0.125	4
S. pneumoniae 700906	Ery R-erm	32	>64	16	4	4	8	>64
S. pyogenes 19615	Ery S	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06	0.015
S. pyogenes 1323	Ery R-mef	⩽0.06	0.125	0.125	⩽0.06	0.25	0.125	16
S. pyogenes 2912	Ery R-erm	4	4	8	8	16	8	>64
H. influenzae 33929	Amp R	1	2	2	2	4	4	4
H. influenzae	Amp S	2	2	2	2	8	4	4
M. catarrhalis		⩽0.06	⩽0.06	⩽0.06	0.125	0.25	0.25	0.13

Table 2
In vitro antibacterial activities of 3,6-bicyclolide oximes—*E*/*Z* isomer comparison





Organism		MIC (μg/ml)	
		7b	**8**
S. aureus 29213	Ery S	⩽0.06	0.5
S. aureus 27660	MLS Ri	⩽0.06	0.5
S. aureus 33591	MRSA	>64	>64
S. pneumoniae 49619	Ery S	⩽0.06	⩽0.06
S. pneumoniae 7701	Ery R-mef	⩽0.06	0.125
S. pneumoniae 700906	Ery R-erm	>64	>64
S. pyogenes 19615	Ery S	⩽0.06	⩽0.06
S. pyogenes 1323	Ery R-mef	0.125	0.25
S. pyogenes 2912	Ery R-erm	4	64
H. influenzae 33929	Amp R	2	16
H. influenzae	Amp S	2	8
M. catarrhalis		⩽0.06	0.125

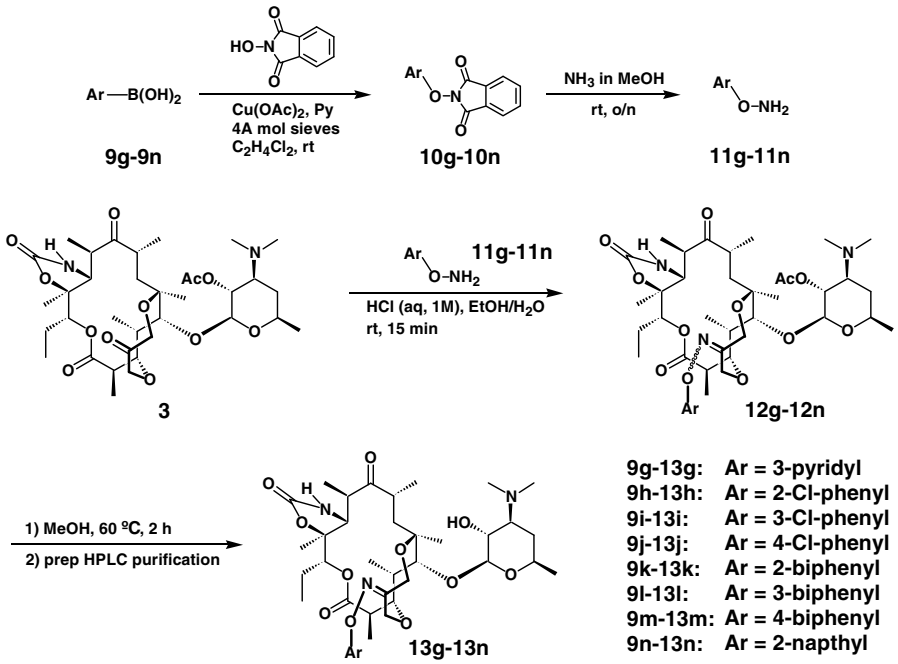
The undesired *Z*-oxime isomer **8** was isolated and subjected to in vitro antibacterial test together with the corresponding *E*-oxime isomer **7b** (Table 2). This direct comparison clearly showed that the *E*-oxime was much more potent than the *Z*-oxime.

All 3,6-bicyclolide oximes **7a–7f** showed good antibacterial activities against the susceptible strains, *mef* resistant strains, as well as *H. influenzae* strains. These results strongly suggested that each of the 3,6-bicyclolide oximes are good templates for further modifications.

To overcome *S. pneumoniae* and *S. pyogenes erm* resistant strains, zero carbon linker 3,6-bicyclolide oximes **13g–13n** were synthesized as shown in Scheme 2. Boronic acids **9g–9n** were reacted with *N*-hydroxyl phthalimide via copper (II) acetate-catalyzed coupling condition to give **10g–10n**.[6] Treating **10g–10n** with ammonia in methanol provided zero carbon linker *O*-hydroxylamine **11g–11n**. Oxime formation reactions from diketone **3** and **11g–11n** were carried out in a similar fashion as previously described to give 3,6-bicyclolide *E*/*Z* oxime mixtures **12g–12n**. Finally, 2′-deacetylation followed by preparative reverse-phase chromatography provided the desired zero carbon 3,6-bicyclolide *E*-oximes **13g–13n** (see Table 3).

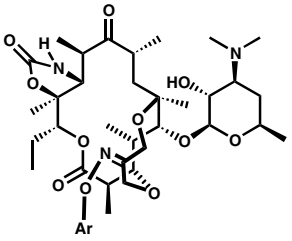
Compared to its phenyl analog, 3-pyridyl oxime **13g** showed slight antibacterial improvement against *S. pneumoniae erm* and *Haemophilus influenzae*. Among the three chlorophenyl derivatives **13h**, **13i**, and **13j**, the *meta*-substituted oxime **13i** showed the most potent antibacterial profile against the resistant strains. Furthermore, the three biphenyl analogs **13k**, **13l**, and **13m** appeared to give similar antibacterial activity pattern. *Meta*-biphenyl oxime **13l** gave the most balanced antibacterial profile and it even exhibited good potency against *S. aureus* resistance strain MRSA. These zero carbon 3,6-bicyclolides represent a novel and promising macrolide series.

In conclusion, we designed and synthesized a series of novel 3,6-bicyclolide oximes, possessing linkers of varying lengths to the secondary binding site. Further modifications of zero carbon linker 3,6-bicyclolide oximes improved antibacterial activities against a broad panel of macrolide-resistant bacterial strains. Good overall antibacterial activities of 3,6-bicyclolide oximes warrant further efforts on this novel class of antibiotics.



Scheme 2. Synthesis of zero carbon linker 3,6-bicyclolide oximes.

Table 3
In vitro antibacterial activities of 3,6-bicyclolide oximes—length optimization



Organism		MIC (μg/ml)									
		7a	**13g**	**13h**	**13i**	**13j**	**13k**	**13l**	**13m**	**13n**	Ery A
	Ar=	Ph	3-Pyridyl	2-Cl-Ph	3-Cl-Ph	4-Cl-Ph	2-Ph-Ph	3-Ph-Ph	4-Ph-Ph	2-Napthyl	
S. aureus 29213	Ery S	⩽0.06	0.125	⩽0.06	⩽0.06	⩽0.06	0.5	0.125	0.5	0.25	0.5
S. aureus 27660	MLS Ri	⩽0.06	0.125	⩽0.06	⩽0.06	⩽0.06	0.5	0.125	0.5	0.25	>64
S. aureus 33591	MRSA	>64	>64	64	32	>64	16	4	16	32	>64
S. pneumoniae 49619	Ery S	⩽0.06	0.125	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06
S. pneumoniae 7701	Ery R-mef	⩽0.06	0.125	⩽0.06	⩽0.06	⩽0.06	0.5	⩽0.06	0.125	0.125	4
S. pneumoniae 700906	Ery R-erm	32	16	32	8	16	16	2	0.25	0.5	>64
S. pyogenes 19615	Ery S	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06	0.015
S. pyogenes 1323	Ery R-mef	⩽0.06	0.25	⩽0.06	⩽0.06	⩽0.06	0.5	0.125	0.25	0.125	16
S. pyogenes 2912	Ery R-erm	4	4	4	1	2	16	4	2	2	>64
H. influenzae 33929	Amp R	1	1	2	2	4	8	4	8	8	4
H. influenzae	Amp S	2	1	2	2	4	8	4	8	4	4
M. catarrhalis		⩽0.06	⩽0.06	⩽0.06	⩽0.06	⩽0.06	0.5	0.125	1	0.25	0.13

Acknowledgment

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References and notes

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5. Synthesis of 3,6-bicyclolide **7b** and **8**: To a solution of *O*-benzyl-hydroxylamine (18 mg, 0.15 mmol, 1.5 equiv) and 1.0 M aqueous hydrochloric acid (0.2 ml, 0.2 mmol, 2.1 equiv) in ethanol (0.25 ml) was added a solution of bridged ketone **3** (67 mg, 0.10 mmol) in acetonitrile (0.25 ml) dropwise at room temperature. After stirring for 15 min at room temperature the mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with EtOAc twice.

The combined organic extracts were washed with brine, dried, filtered, and concentrated in vacuo to give an *E*/*Z* oxime mixture **5b** as a tan foam. MS (ESI): *m*/*z* 802.15 [M+H].

The above residue was dissolved in methanol (1 ml) and stirred at room temperature for 21 h. The reaction mixture was in vacuo to give *E*/*Z* (2:1 ratio by HPLC) oxime mixture **6b** as a tan foam. MS (ESI): *m*/*z* 760.10 [M+H].

The above residue was purified by HPLC to afford the desired *E*-oxime **7b** and *Z*-oxime **8**.

Compound **7b** : ^{13}C NMR ($CDCl_3$) δ 217.0, 177.6, 158.0, 157.8, 137.9, 128.6, 128.2, 128.1, 104.8, 84.5, 80.8, 80.5, 79.2, 76.8, 76.5, 70.6, 69.6, 66.3, 66.1, 61.0, 58.3, 44.4, 44.2, 43.0, 40.6, 39.0, 37.4, 23.0, 21.5, 21.4, 19.9, 13.9, 13.5, 11.6, 11.4, 11.0 ppm.

Compound **8**: ^{13}C NMR ($CDCl_3$) δ 217.1, 177.3, 158.5, 157.7, 137.7, 128.6, 128.5, 128.1, 103.4, 84.4, 82.3, 81.0, 80.9, 76.6, 76.3, 73.1, 70.0, 68.2, 67.2, 58.6, 44.4, 44.1, 43.3, 41.4, 40.5, 39.5, 37.3, 32.0, 22.6, 21.7, 21.0, 20.1, 14.1, 13.4, 12.3, 11.3, 11.1 ppm.

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