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Syntheses and biological studies of novel spiropiperazinyl oxazolidinone antibacterial agents using a spirocyclic diene derived acylnitroso Diels–Alder reaction

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ABSTRACT

Several novel oxazolidinone antibiotics with a spiropiperazinyl substituent at the 4′-position of the phenyl ring were synthesized through nitroso Diels–Alder chemistry and the in vitro antibacterial activities were evaluated against various Gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*, *Enterococcus faecalis*), Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) and mycobacteria (*Mycobacterium vaccae*, *Mycobacterium tuberculosis*). Analogs (**8a** and **12**) were active against selected drug resistant microbes, like methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) and had no mammalian toxicity in a Hep-2 cellular assay (CC_{50} >100 μM).

1. Introduction

The rate of antimicrobial resistance has increased dramatically in the past few decades due to the misuse and overuse of antibiotics.[1,2] Infections caused by resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and penicillin-resistant *Streptococcus pneumoniae* (PRSP) are often extremely difficult to treat. Therefore, efforts towards the discovery of new antibiotics are of great significance.

The oxazolidinones are a class of wholly synthetic, orally active antibiotics that has excellent activity against a variety of susceptible and resistant Gram-positive bacteria.[3–6] Targeting bacterial protein synthesis, this class of compounds possesses a unique mode of action by preventing binding of the aminoacyl-tRNA to the A site of the ribosome.[7,8] This unique activity indicates the potential for oxazolidinones to have low cross-resistance with existing protein synthesis inhibitors.[9–11] To date, linezolid (Zyvox™, Fig. 1) is the only oxazolidinone that has been approved for clinical use for the treatment of pneumonia and skin infections due to drug resistant Gram-positive bacteria such as MRSA, VRE and PRSP.[3,12,13] Unfortunately, though in only a few cases, resistance against linezolid was observed not long after it was put into use.[14–17] The development of resistance encourages the design, syntheses, studies and hopefully development of novel oxazolidinone derivatives.

Extensive structure–activity relationships have been established for oxazolidinone derivatives (Fig. 1).[3] The *S*-configuration at the C-5 position of the oxazolidinone ring is necessary and the acetamide is good for antibacterial activity. Meanwhile, electron-donating nitrogen substituents at the 4′-position of the phenyl ring are well tolerated and often improve the overall safety profile.[4–6,18] For example, a number of linezolid derivatives with pyrroloaryl,[19] azabicyclic[20–23] and cyanomethylpiperidinyl[24,25] *N*-substituents have been reported and some display improved properties relative to the parent drug.[26]

Nitroso Diels–Alder (NDA) chemistry has been used as a remarkably efficient method for derivatization of complex diene-containing natural products by direct incorporation of a 1,4-amino-oxo group (Scheme 1).[27–30] This provides opportunities for Modular Enhancement of Nature's Diversity (MEND).[31,32] NDA adducts derived from cyclopentadiene and other dienes are also synthetically valuable precursors for many biologically interesting molecules, such as carbocyclic nucleosides[33–36] and natural product analogs.[37,38] Herein we report the synthesis and biological activity evaluation of novel oxazolidinone derivatives with various

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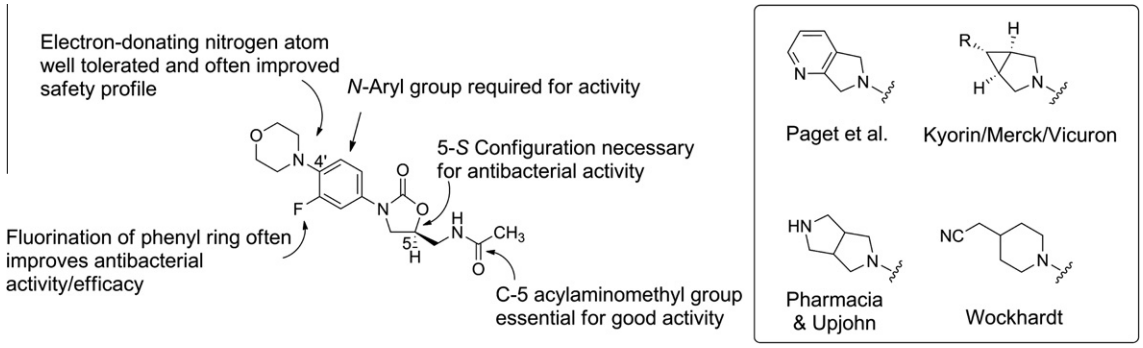
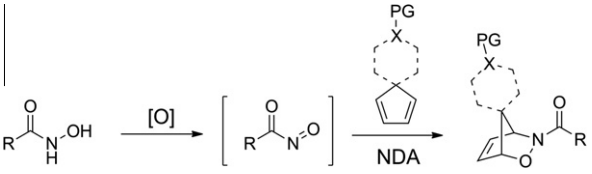


Figure 1. Structure–activity relationships of linezolid and several examples of different *N*-substituents at the 4′-position of the phenyl ring.



Scheme 1. Acyl-nitroso Diels–Alder (NDA) reaction.

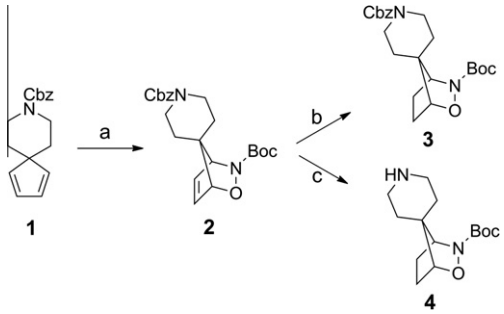
spiropiperazinyl substituents using acyl-nitroso Diels–Alder (NDA) reactions.

2. Results and discussion

2.1. Chemistry

The spirocyclic diene **1** was prepared from cyclopentadienyl anion and *N*-Cbz-*bis*-(2-chloro-ethyl) amine, as reported previously.[34] Diene **1** was reacted with the nitroso species generated from Boc-protected hydroxylamine by in situ oxidation with sodium periodate, providing spirocycloadduct **2** in 61% yield.[39] To remove the Cbz protecting group, **2** was treated with a catalytic amount of 10% palladium on carbon and hydrogen gas (1 atm). However, a selective reduction of the alkene occurred to give compound **3** in 93% yield while leaving the Cbz group intact. The reason for the selectivity was proposed to be the steric effect of the bulky Boc group during the hydrogenolysis process. Increasing hydrogen gas to 50 psi and changing the catalyst to palladium hydroxide (20% palladium on carbon) simultaneously reduced the alkene and removed the Cbz protecting group, producing compound **4** in 91% yield for further reactions (Scheme 2).

Compound **5** was prepared in 85% yield by an S_NAr reaction of **4** with 3,4-difluoronitrobenzene in the presence of Hünig's base. The nitro group was reduced with 10% palladium on carbon and hydrogen gas (1 atm) to give amine **6** in 95% yield. The amine was then protected with a Cbz group to generate intermediate **7** in 90% yield. The oxazolidinone ring was constructed according to precedent by treatment of **7** with *n*-butyl lithium and *R*-glycidyl butyrate sequentially at −78 °C, producing alcohol derivative **8a** in 85% yield with defined stereochemistry at the C-5 position.[40] An ester derivative **8b** was also formed in 5% yield in the same reaction. It was easily and quantitatively converted to **8a** by treatment with sodium hydroxide. The hydroxyl group of **8a** was converted to mesylate **9** in 90% yield. Sodium azide displacement of the mesylate provided compound **10** in 74% yield (Scheme 3).

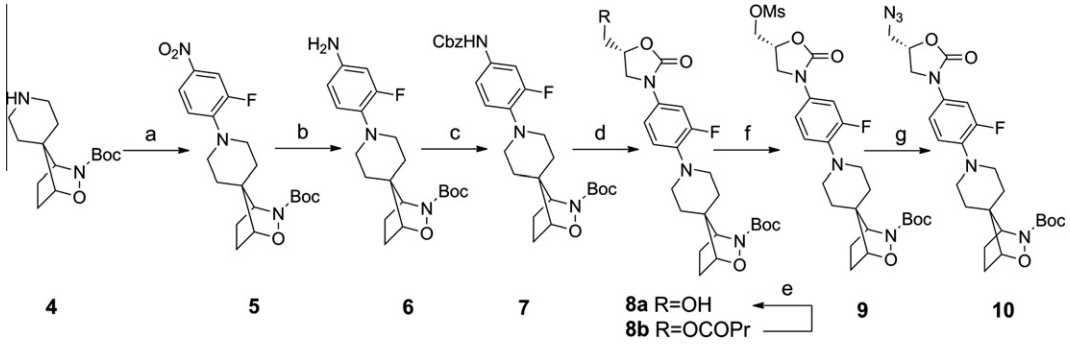


Scheme 2. Reagents: (a) $NaIO_4$, BocNHOH, H_2O/MeOH, rt, 8 h, 61%; (b) H_2 (1 atm), 10% Pd/C, MeOH, rt, 8 h, 93%; (c) H_2 (50 psi), $Pd(OH)_2$, MeOH, rt, 8 h, 91%.

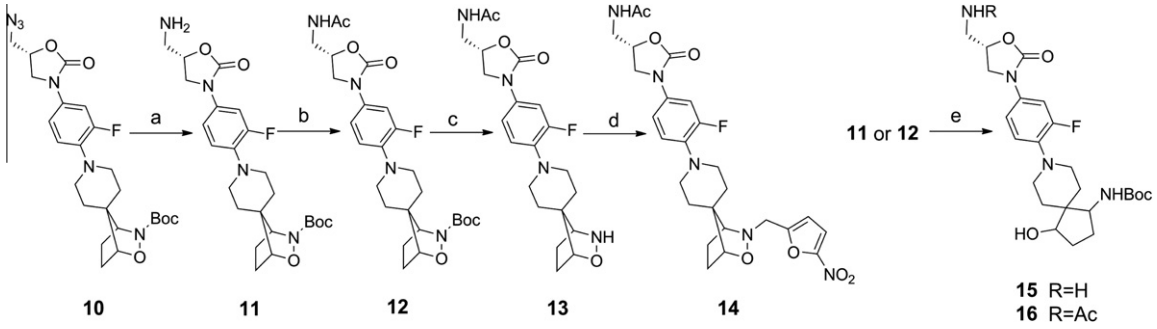
Exposure of **10** to hydrogen over palladium on carbon produced the corresponding amine **11** in 95% yield. Acetylation then afforded linezolid analog **12** in 70% yield. Compound **12** can serve as a common intermediate for various modifications on the spiropiperazine moiety without cleaving the N–O bond, which retains the rigidity of the molecule. For example, after removal of the *N*-Boc protecting group of **12** with trifluoroacetic acid, reductive amination can be done as shown by incorporation of a nitrofuranyl substituent in moderate yield. Nitrofuranyl was chosen because of its structural similarity of **14** to the dual action antimicrobial agent RBx-7644 reported by the Ranbaxy Laboratories.[41] Cleavage of the N–O bond in the spiropiperazine moiety was anticipated to produce more flexible derivatives as the restriction of ring conformation would be eliminated. Indeed, molybdenum hexacarbonyl-mediated bond cleavage[42] of compounds **11** and **12** provided the ring opened derivatives **15** and **16** in 64% and 80% yields, respectively (Scheme 4).

3. Biological activity

Compounds **8a**, **11**, **12** and **16** were initially screened for antibiotic activity against representative Gram-positive and Gram-negative bacteria as well as *Mycobacterium vaccae* using agar diffusion assays (Table 1). Compounds **8a** and **12** displayed in vitro antibacterial activities comparable to linezolid. Both showed good activity against all Gram-positive organisms tested including drug-resistant strains such as *Staphylococcus aureus* 134/93 (MRSA) and *Enterococcus faecalis* 1528 (VRE) as indicated by the large zones of inhibition they induced. *Mycobacterium vaccae* is a non-pathogenic model organism for *Mycobacterium tuberculosis*, the causative agent of tuberculosis. Although less active than linezolid, all compounds showed moderate to good activities against *Mycobacterium vaccae*, suggesting their potential in anti-tuberculosis agent development. Interestingly, compound **16** derived from reduction of the N–O bond showed decreased activity compared to its parent cycloadduct **12**. Similar phenomena were observed in studies of C-5 side chain modification of linezolid through nitroso Diels–Alder chemistry.[43] None of the compounds tested in this study



Scheme 3. Reagents: (a) 3,4-difluoronitrobenzene, DIPEA, CH_3CN, rt, 8 h, 85%; (b) H_2, 10% Pd/C, MeOH, rt, 1 h, 95%; (c) Cbz-Cl, $NaHCO_3$, 0 °C to rt, 2 h, 90%; (d) (*R*)-(−)-glycidyl butyrate, *n*-BuLi, THF, −78 °C to rt, 2 h, 85%; (e) NaOH, H_2O/THF, rt, 100%; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 90%; (g) NaN_3, DMSO, 75 °C, 8 h, 74%.



Scheme 4. Reagents: (a) H_2, 10% Pd/C, MeOH, rt, 8 h, 95%. (b) AcCl, pyridine, CH_2Cl_2, 0 °C to rt, 70%; (c) TFA, CH_2Cl_2, rt, 2 h, 95%; (d) 5-nitrofuraldehyde, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, HOAc, rt, 2 h, 53%; (e) $Mo(CO)_6$, $NaBH_4$, CH_3CN/H_2O, 60 °C, 6 h, 64% (for **15**), 80% (for **16**).

Table 1
Antimicrobial activity in the agar diffusion assay (diameter of inhibition zone, measured in mm)

Compds	Gram-positive bacteria				Gram-negative bacteria			
	Bacillus subtilis	*Staphylococcus aureus*		*Enterococcus faecalis*	*Escherichia coli*	*Pseudomonas aeruginosa*		*Mycobacterium vaccae*
	ATCC 6633	SG 511	134/93 (MRSA)	1528 (VRE)	SG 458	SG 137	K799/61	IMET 10670
Linezolid[a]	31/35P	27/36P	NT	NT	NT	NT	10P	42
8a	23.5/28A/30p	22	24	22	0	0	0	30p
11	12	10/13A	14A	14P	10	0	A	18/25P
12	25/27A	18/22p	25	23	0	0	0	24/37p
16	14/19A	16p	14/18A	15/18p	0	0	0	13p

p, partially clear inhibition zone/colonies in the inhibition zone; P, unclear inhibition zone/many colonies in the inhibition zone; A, indication of growth inhibition; NT, not tested; Exactly 50 μL of a 2.0 mM solution of each compound dissolved in 1:9 DMSO/MeOH was filled in 9 mm wells in agar media (Standard I Nutrient Agar, Serva or Mueller Hinton II Agar, Becton, Dickinson and Company). Inhibition zones read after incubation at 37 °C for 24 h.

[a] Linezolid data from Ref.[43]

displayed any noticeable significant activity against several Gram-negative indicator strains including *E. coli* and *P. aeruginosa*.

Cycloadducts **8a** and **12**, the two most active compounds in the agar diffusion assay, were subjected to further assays to determine their minimum inhibitory concentrations (MIC). Although both showed inferior antibacterial activity relative to linezolid,[44] compound **12** has one dilution lower (better) MIC values against MSSA and MRSA than did compound **8a** (Table 2), consistent with the expected advantage of having an acetamide on the C-5 side chain. To further assess their potential, the effect of protein binding on the activity was assessed by adding 50% mouse or human serum to the MIC assays, and calculating the fold shift in MIC values. Comparing to **8a** which is relatively inactive in serum, compound **12** exhibited only 2 and 4-fold MIC shift in mouse and human

Table 2
MIC determination (μg mL^{-1}) of methicillin-susceptible (MS) and resistant (MR) *Staphylococcus aureus*, assessment of protein binding, and toxicity (μM) of spiropiperazinyl compounds

Compds	Mol. Wt.	MSSA	MRSA	MRSA +50% mouse serum	Fold shift mouse	MRSA +50% human serum	Fold shift human	Hep2 toxicity (CC_{50} μM)
8a	477.53	>64	32	>64	>2×	>64	>2×	>100
12	518.58	64	16	32	2×	64	4×	>100

Abbreviations: ATCC, American Type Culture Collection; MSSA, methicillin-susceptible *Staphylococcus aureus* ATCC 29213; MRSA, methicillin-resistant *Staphylococcus aureus* ATCC 700699; CC_{50} is defined as the concentration of drug that results in toxicity to 50% of the cells compared with untreated control cells.

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serum, respectively, demonstrating that the spiropiperazinyl substituent at 4′-position of the phenyl ring of linezolid does not significantly change its stability or protein binding property in plasma. Potential mammalian toxicity was preliminarily assessed by screening the compounds against the Hep2 cancer cell line. Both compounds **8a** and **12** did not show toxicity against the mammalian cell line.

Additionally, since linezolid and its thiomorpholine analog (PNU-100480)[45] are under consideration as potential antitubercular treatments, we decided to evaluate a set of compounds (**5**–**9**, **12** and **16**) against replicating *M. tuberculosis* $H_{37}Rv$ in two different media, GAS[46] and GAST[47] (Table 3). The analogs lacking the oxazolidinone core (**5**, **6**, and **7**) all were inactive (>128 μM). The incorporation of this moiety in compounds (**8a**, **8b**, **9**, **12**, and **16**) produced a range of antitubercular activity (MICs of 97, 19, 118, 24, >128 μM, respectively in the GAS medium). As expected compound **12**, the one most similar to linezolid, had one of the lowest MIC values at 24 μM. Interestingly, compound **8b** also had potency similar to that of compound **12** at 19 μM despite missing the *N*-acyl moiety thought to be essential for antibacterial activity. Compound **16** derived from reduction of the N–O bond was inactive (>128 μM), in sharp contrast to its parent cycloadduct **12** (24 μM). This trend correlated to the observation in the agar diffusion assay against *M. vaccae* in which compound **16** gave only a small and unclear inhibition zone. Linezolid is reported to have excellent antitubercular potency[45] (MIC range of 0.125–1 μg mL^{-1}) which was substantiated by our *Mtb* assay where it showed an MIC of 0.4 μM (0.135 μg mL^{-1}) in the GAST medium and superior to our spiropiperazinyl analogs.

4. Conclusion

In conclusion, novel oxazolidinone antibiotics with a spiropiperazinyl substituent at the 4′-position of the phenyl ring were synthesized through nitroso Diels–Alder chemistry. The Gram-positive antibacterial activities of some of the compounds indicate that the diverse functionalities were well tolerated at phenyl 4′-position. The syntheses further exemplify the practicability of nitroso Diels–Alder chemistry as a powerful synthetic tool for the creation of unique structural and functional diversity.

5. Experimental

5.1. General

All reactions were carried out under argon by using standard techniques. All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel plates visualized under UV light, iodine or $KMnO_4$ staining. Silica gel column chromatography was performed using Sorbent Technologies silica gel 60 (32–63 μm). NMR spectra were recorded on a Varian Unity-plus 300 MHz spectrometer, Varian Inova 500 MHz spectrometer, or Varian 600 MHz spectrometer at ambient temperature. Benzyl 8-azaspiro[4.5]deca-1,3-diene-8-carboxylate (**1**) and 1′-benzyl 3-*tert*-butyl 2-oxa-3-azaspiro[bicyclo[2.2.1]hept[5]ene-7,4′-piperidine]-1′,3-dicarboxylate (**2**) were prepared according to published procedures.[39]

Table 3
Activity of various compounds against replicating *Mtb* $H_{37}Rv$ in various media (μM)

Compds	Mol. Wt.	MIC (μM) against *Mtb* $H_{37}Rv$ in medium:	
		GAS	GAST
5	407.44	>128	>128
6	377.45	>128	>128
7	511.59	>128	>128
8a	477.53	97	>128
8b	561.64	19.2	29.2
9	555.62	118	67.4
12	518.58	24.4	22
16	520.59	>128	>128
Linezolid	337.35	NT	0.40

MIC = Minimum Inhibitory Concentration required to inhibit the growth of 90% of organisms; NT = Not tested; GAS = Glycerol-alanine-salts media; GAST = Iron deficient glycerol-alanine-salts with Tween 80 media. Values reported are the average of three individual measurements.

5.2. Synthesis

5.2.1. 1′-Benzyl 3-*tert*-butyl 2-oxa-3-azaspiro[bicyclo[2.2.1]heptane-7,4′-piperidine]-1′,3-dicarboxylate (3)

Compound **2** (1.5 g, 3.7 mmol) was dissolved in 10 mL of methanol in a 25-mL round-bottomed flask under argon. 10% Pd on carbon (0.2 g) was added and the flask was flushed with H_2 gas and left to stir under a hydrogen atmosphere (balloon) for 8 h. After purging with argon, the mixture was filtered and concentrated in vacuo to give compound **3** (1.4 g, 90%) as a light yellow oil: IR (neat, cm^{-1}): 2927, 1698, 1432; ^1H NMR (600 MHz, $CDCl_3$) δ 7.29–7.37 (m, 5H), 5.12 (s, 2H), 4.19–4.28 (m, 2H), 3.41–3.56 (m, 4H), 1.80–2.00 (m, 4H), 1.56–1.75 (m, 4H), 1.47 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 136.6, 128.4, 127.9, 127.8, 82.7, 81.8, 67.0, 63.4, 62.2, 41.9, 28.1, 27.6, 26.6; HRMS (FAB) calcd for $C_{22}H_{30}N_2O_5$ $(M)^{+\cdot}$: 402.2155; found 402.2165.

5.2.2. *tert*-Butyl 2-oxa-3-azaspiro[bicyclo[2.2.1]heptane-7,4′-piperidine]-3-carboxylate (4)

Compound **2** (1.0 g, 2.5 mmol) was dissolved in 15 mL of methanol in a 250-mL Parr bottle under argon. $Pd(OH)_2$ (20% Pd on carbon, 0.2 g) was added and the bottle was flushed with H_2 gas. The flask was shaken under 50 psi hydrogen using a Parr shaker at room temperature for 8 h. After purging with argon, the mixture was filtered and concentrated in vacuo to give compound **4** (0.61 g, 90%) as a light yellow oil: IR (neat, cm^{-1}): 3485, 2978, 1697, 1368; ^1H NMR (500 MHz, $CDCl_3$) δ 4.12–4.45 (m, 2H), 3.20–3.35 (m, 4H), 1.86–2.10 (m, 8H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 82.4, 81.4, 63.6, 61.7, 42.4, 42.3, 28.2, 27.4, 26.3, 25.2, 23.8; HRMS (FAB) calcd for $C_{14}H_{25}N_2O_3$ $(M+H)^+$: 269.1865; found, 269.1871.

5.2.3. *tert*-Butyl 1′-(2-fluoro-4-nitrophenyl)-2-oxa-3-azaspiro[bicyclo[2.2.1]heptane-7,4′-piperidine]-3-carboxylate (5)

A 10-mL oven-dried, round-bottomed flask was charged with compound **4** (0.35 g, 1.3 mmol), 3,4-difluoronitrobenzene (0.25 mL, 2.0 mmol) and DIPEA (0.45 mL, 2.6 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 18 h and quenched by adding 1 N HCl (4 mL). The solution was extracted with ethyl acetate (5 mL × 3) and the combined organic layers were washed sequentially with sat. $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column (hexanes:ethyl acetate = 3:1) to give compound **5** (0.45 g, 85%) as a yellow oil: IR (neat, cm^{-1}): 2974, 1699, 1517; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.9, 2.6 Hz, 1H), 7.90 (dd, J = 13.1, 2.6 Hz, 1H), 6.92 (t, J = 8.8 Hz, 1H), 4.10–4.34 (m, 2H), 3.22–3.38 (m, 4H), 1.82–2.01 (m, 8H), 1.58 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 152.0, 145.6, 140.4, 121.0, 117.2, 112.6, 112.4, 83.2, 82.0, 64.0, 62.4, 48.5, 48.4, 28.3, 27.6, 26.6;

HRMS (FAB) calcd for $C_{20}H_{25}FN_3O_5$ $(M-H)^+$: 406.1778; found 406.1787.

5.2.4. *tert*-Butyl 1′-(4-amino-2-fluorophenyl)-2-oxa-3-aza spiro [bicyclo[2.2.1]heptane-7,4′-piperidine]-3-carboxylate (6)

Compound **5** (0.30 g, 0.74 mmol) was dissolved in 4 mL of methanol in a 10-mL round-bottomed flask under argon. 10% Pd on carbon (30 mg) was added and the flask was flushed with H_2 gas and left to stir under a hydrogen atmosphere (balloon) for 4 h. After purging with argon, the mixture was filtered and concentrated in vacuo to give compound **6** (0.27 g, 95%) as a viscous oil: IR (neat, cm^{-1}): 2924, 1701, 1513; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.54 (m, 1H), 6.58–6.72 (m, 2H), 4.10–4.42 (m, 2H), 3.20–3.40 (m, 4H), 1.82–2.20 (m, 8H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.7, 155.1, 135.9, 132.3, 122.8, 113.8, 105.9, 82.3, 54.7, 51.4, 50.3, 46.1, 45.1, 41.1, 34.6, 28.2; HRMS (FAB) calcd for $C_{20}H_{28}FN_3O_3$ $(M)^{+\cdot}$: 377.2115; found 377.2118.

5.2.5. *tert*-Butyl 1′-(4-(benzyloxycarbonylamino)-2-fluorophe nyl)-2-oxa-3-azaspiro[bicyclo[2.2.1]heptane-7,4′-piperidine]-3-carboxylate (7)

A 10-mL oven-dried, round-bottomed flask was charged with compound **6** (0.38 g, 1.0 mmol), sodium bicarbonate (92 mg, 1.1 mmol) in a mixture of THF–H_2O 1:1 (4 mL). After the solution was cooled to 0 °C, benzylchloroformate (0.18 mL, 1.1 mmol) was added and the mixture was stirred at the same temperature for 1 h. The reaction was quenched by adding 1 N HCl (4 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed sequentially with sat. $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column (hexanes:ethyl acetate = 3:1) to give **7** (0.46 g, 90%) as a colorless oil: IR (neat, cm^{-1}): 2936, 1704, 1516; ^1H NMR (600 MHz, $CDCl_3$) δ 7.28–7.40 (m, 5H), 6.94–7.00 (m, 1H), 6.86–6.89 (m, 1H), 6.72–6.76 (m, 1H), 5.19 (s, 2H), 4.08–4.33 (m, 2H), 2.88–3.08 (m, 4H), 1.76–1.98 (m, 8H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 157.1, 153.9, 153.3, 135.9, 133.4, 128.6, 128.4, 128.3, 119.2, 114.3, 107.5, 83.2, 81.6, 66.8, 64.1, 62.5, 49.4, 28.6, 28.0, 27.5, 26.8; HRMS (FAB) calcd for $C_{28}H_{34}FN_3O_5$ $(M)^{+\cdot}$, 511.2482; found 511.2473.

5.2.6. 1′-(2-Fluoro-4-((*R*)-5-(hydroxymethyl)-2-oxooxazolidin-3-yl)phenyl)-2-oxa-3-azaspiro[bicyclo[2.2.1]heptane-7,4′-piperidine]-3-carboxylate (8a) and *tert*-butyl 1′-(4-((R)-5-(butyrylo xymethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-2-oxa-3-azas piro[bicyclo[2.2.1]heptane-7,4′-piperidine]-3-carboxylate (8b)

Compound **7** (0.41 g, 0.80 mmol) was dissolved in 4 mL of anhydrous tetrahydrofuran in a 10-mL oven-dried, round-bottomed flask. The solution was cooled to −78 °C using dry ice-acetone bath and *n*-butyl lithium (1.6 M in hexane, 1.0 mL, 1.6 mmol) was added. After stirred at that temperature for 15 min, the solution was treated with (*R*)-glycidyl butyrate (0.15 mL, 1.0 mmol) and slowly warmed to 25 °C. After stirred for additional 2 h, the reaction mixture was quenched with sat. NH_4Cl (3 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column (hexanes:ethyl acetate = 1:1) to give **8a** (0.32 g, 85%) and **8b** (22 mg, 5%) as light yellow oils. **8a**: IR (neat, cm^{-1}): 3421 (br), 2968, 2360, 1732, 1516; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 14.2 Hz, 1H), 7.09 (m, 1H), 6.94 (m, 1H), 4.70–4.78 (m, 1H), 4.10–4.32 (m, 2H), 4.08 (m, 2H), 3.93–4.01 (m, 3H), 3.72–3.80 (m, 1H), 2.92–3.14 (m, 4H), 1.74–2.00 (m, 8H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 154.6, 154.5, 136.6, 133.1, 119.3, 113.8, 107.4, 83.3, 81.9, 72.8, 64.3, 62.7, 49.4, 46.4, 28.8, 28.2, 28.0, 27.1; HRMS (FAB) calcd for $C_{24}H_{32}FN_3O_6$ $(M)^{+\cdot}$: 477.2275; found 477.2293; **8b**: IR (neat, cm^{-1}): 2966, 1715, 1517; ^1H NMR (600 MHz, $CDCl_3$) δ 7.42 (dd, J = 14.0, 2.4 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 9.1 Hz, 1H), 4.85 (m, 1H), 4.38 (dd, J = 12.3, 3.8 Hz, 1H), 4.26–4.34 (m, 3H), 3.78 (dd, J = 8.8, 6.2 Hz, 1H), 3.00–3.12 (m, 4H), 2.32 (t, J = 7.6 Hz, 2H), 1.80–2.00 (m, 8H), 1.62–1.67 (m, 2H), 1.50 (s, 9H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.2, 156.4, 154.8, 154.0, 136.9, 136.8, 133.0, 119.4, 113.8, 107.5, 105.2, 81.7, 70.0. 63.8, 49.7, 47.2, 35.8, 28.3, 18.3, 13.6. Ester **8b** can be converted to **8a** by the following procedure: A 10-mL oven-dried, round-bottomed flask was charged with compound **8b** (66 mg, 0.12 mmol) and sodium hydroxide (40 mg, 1.0 mmol) in a mixture of THF-H_2O 1:1 (4 mL). After stirred at room temperature for 1 h, the solution was neutralized with 1 N HCl and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed sequentially with sat. $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give **8a** in quantitative yield.

5.2.7. *tert*-Butyl 1′-(2-fluoro-4-((*R*)-5-((methylsulfonyloxy) methyl)-2-oxooxazolidin-3-yl)phenyl)-2-oxa-3-azaspiro [bicyclo[2.2.1]heptane-7,4′-piperidine]-3-carboxylate (9)

Compound **8a** (0.37 g, 0.78 mmol) was dissolved in 4 mL of dichloromethane in a 10-mL round-bottomed flask. Methyl sulfonyl chloride (0.10 mL, 1.2 mmol) and triethylamine (0.20 mL, 1.2 mmol) were added and the mixture was stirred at room temperature for 18 h. The solution was neutralized with 1 N HCl and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed sequentially with sat. $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column (hexanes:ethyl acetate = 1:1) to give **9** (0.39 g, 90%) as a light yellow oil: IR (neat, cm^{-1}): 2975, 2360, 1752, 1517, 1356; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (dd, J = 14.0, 2.4 Hz, 1H), 7.07–7.13 (m, 1H), 6.95 (t, J = 9.0 Hz, 1H), 4.88–4.96 (m, 1H), 4.50 (dd, J = 11.7, 3.7 Hz, 1H), 4.41 (dd, J = 11.7, 4.2 Hz, 1H), 4.08–4.36 (m, 3H), 3.91 (dd, J = 9.1, 6.1 Hz, 1H), 3.00–3.12 (m, 7H), 1.76–2.00 (m, 8H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 154.5, 153.6, 137.0, 132.4, 119.4, 114.0, 107.6, 83.0, 81.8, 69.4, 68.1, 63.9, 62.3, 49.4, 46.6, 37.8, 28.7, 28.5, 27.9, 26.8; HRMS (FAB) calcd for $C_{25}H_{34}FN_3O_8S$ $(M)^{+\cdot}$: 555.2051; found 555.2036.

5.2.8. *tert*-Butyl 1′-(4-((*R*)-5-(azidomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-2-oxa-3-azaspiro[bicyclo[2.2.1]heptane-7, 4′-piperidine]-3-carboxylate (10)

A 10-mL oven-dried, round-bottomed flask was charged with compound **9** (0.28 g, 0.5 mmol) and sodium azide (65 mg, 1.0 mmol) in anhydrous dimethylsulfoxide (4 mL). The solution was stirred at 80 °C for 8 h. After the reaction mixture was cooled to room temperature, water (4 mL) was added. The mixture was extracted with ethyl acetate (5 mL × 5). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column (hexanes:ethyl acetate = 1:1) to give **10** (0.19 g, 74%) as a yellow oil: IR (neat, cm^{-1}): 2921, 2105, 1717, 1514; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, J = 14.2, 2.4 Hz, 1H), 7.10–7.14 (m, 1H), 6.95 (t, J = 9.0 Hz, 1H), 4.76–4.81 (m, 1H), 4.10–4.34 (m, 2H), 4.04 (dd, J = 8.8, 8.8 Hz, 1H), 3.82 (dd, J = 8.8, 6.2 Hz, 1H), 3.70 (dd, J = 13.2, 4.6 Hz, 1H), 3.58 (dd, J = 13.2, 4.6 Hz, 1H), 2.94–3.12 (m, 4H), 1.82–2.00 (m, 8H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 154.8, 154.0, 137.1, 133.1, 119.6, 114.0, 107.7, 83.3, 82.0, 70.7, 64.2, 53.2, 49.6, 47.9, 28.8, 28.5, 27.9, 27.1.

5.2.9. *tert*-Butyl 1′-(4-((*S*)-5-(aminomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-2-oxa-3-azaspiro[bicyclo[2.2.1]heptane-7,4′-piperidine]-3-carboxylate (11)

Compound **10** (0.14 g, 0.28 mmol) was dissolved in 4 mL of methanol in a 10-mL round-bottomed flask under argon. 10% Pd on carbon (15 mg) was added and the flask was flushed with H_2 gas and left to stir under a hydrogen atmosphere (balloon) for 8 h. After purging with argon, the mixture was filtered and concentrated in vacuo to give compound **11** (0.13 g, 95%) as a viscous oil: IR (neat, cm^{-1}): 2980, 1515; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, J = 14.2, 2.4 Hz, 1H), 7.10–7.16 (m, 1H), 6.95 (dd, J = 9.1, 9.0 Hz, 1H), 4.65–4.83 (m, 1H), 4.10–4.34 (m, 2H), 4.00–4.04 (m, 1H), 3.81–3.84 (m, 1H), 2.89–3.14 (m, 6H), 1.80–2.00 (m, 8H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 154.6, 136.6, 133.3, 119.3, 113.4, 107.4, 107.2, 83.3, 81.8, 73.7, 71.9, 64.2, 62.6, 54.5, 49.5, 47.8, 44.9, 36.4, 28.8, 28.5, 27.9, 27.1; HRMS (FAB) calcd for $C_{24}H_{33}FN_4O_5$ $(M)^{+\cdot}$: 476.2435; found 476.2449.

5.2.10. *tert*-Butyl 1′-(4-((*S*)-5-(acetamidomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-2-oxa-3-azaspiro[bicyclo[2.2.1]heptane-7,4′-piperidine]-3-carboxylate (12)

Compound **11** (0.11 g, 0.23 mmol) was dissolved in 4 mL of dichloromethane in a 10-mL round-bottomed flask. Acetic anhydride (0.08 mL, 0.80 mmol) and triethylamine (0.11 mL, 0.80 mmol) were added and the mixture was stirred at room temperature for 2 h. After neutralized with 1 N HCl, the mixture was extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed sequentially with sat. $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column (100% ethyl acetate) to give **12** (84 mg, 70%) as a colorless oil: IR (neat, cm^{-1}): 2922, 1749, 1516; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, J = 14.2, 2.4 Hz, 1H), 7.04–7.09 (m, 1H), 6.93 (dd, J = 9.1, 9.0 Hz, 1H), 6.30 (t, J = 6.0 Hz 1H), 4.75–4.80 (m, 1H), 4.10–4.32 (m, 2H), 4.02 (d, J = 9.0, 9.0 Hz, 1H), 3.74–3.77 (m, 1H), 3.67–3.72 (m, 1H), 3.58–3.64 (m, 1H), 2.93–3.11 (m, 4H), 2.02 (s, 3H), 1.79–1.99 (m, 8H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 156.5, 154.5, 154.3, 136.8, 133.0, 119.3, 113.8, 107.4, 83.3, 81.8, 71.8, 64.2, 62.6, 49.4, 47.6, 41.9, 28.7, 28.5, 27.9, 27.1, 23.3; HRMS (FAB) calcd for $C_{26}H_{35}FN_4O_6$ $(M)^{+\cdot}$: 518.2541; found 518.2518.

5.2.11. *N*-(((5*S*)-3-(3-fluoro-4-(3-((5-nitrofuran-2-yl)methyl)-2-oxa-3-azaspiro[bicyclo[2.2.1]heptane-7,4′-piperidine]-1′-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (13)

Compound **12** (20 mg, 0.04 mmol) was dissolved in 3 mL of dichloromethane in a 10-mL round-bottomed flask. Trifluoroacetic acid (0.5 mL) was added and the mixture was stirred at room temperature for 1 h. The solution was concentrated under reduced pressure to give the cyclic hydroxylamine which is used without further purification: IR (neat, cm^{-1}): 2980, 1644, 1419; ^1H NMR (300 MHz, CD_3OD) δ 7.50 (dd, J = 14.6, 2.5 Hz, 1H), 7.08–7.21 (m, 2H), 4.74–4.83 (m, 2H), 4.24–4.27 (m, 1H), 4.12 (dd, J = 9.2, 9.1 Hz, 1H), 3.77–3.82 (m, 1H), 3.54–3.58 (m, 2H), 3.01–3.22 (m, 4H), 1.90–2.25 (m, 11H); HRMS (FAB) calcd for $C_{21}H_{28}FN_4O_4$ $(M+H)^+$, 419.2095; found, 419.2086.

5.2.12. *N*-(((5*S*)-3-(3-fluoro-4-(3-((5-nitrofuran-2-yl)methyl)-2-oxa-3-azaspiro[bicyclo[2.2.1]heptane-7,4′-piperidine]-1′-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (14)

Compound **13** (84 mg, 0.2 mmol) and 5-nitrofuraldehyde (84 mg, 0.6 mmol) were dissolved in 4 mL of 1,2-dichloroethane in a 10-mL round-bottomed flask. After stirred at room temperature for 15 min, the solution was treated with sodium triacetoxyborohydride (0.12 g, 0.6 mmol) and acetic acid (0.05 mL). The reaction was stirred at room temperature for 2 h and quenched with 5 mL of sat. $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (5 mL × 3). The combined organic layers were sequentially washed with sat. $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column (100% ethyl acetate) to give **14** (58 mg, 53%) as a colorless oil: IR (neat, cm^{-1}): 2929, 1674, 1517; ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 (dd, J = 14.1, 2.6 Hz, 1H), 7.30 (d, J = 3.5 Hz, 1H), 7.07–7.10 (m, 1H), 6.95 (dd, J = 9.1, 9.1 Hz, 1H), 6.55 (d, 1H, J = 3.5 Hz), 5.9 (t, J = 6.2 Hz, 1H), 4.75–4.79 (m, 1H), 4.22 (d, 1H, J = 15.6 Hz), 4.07 (s, 1H), 4.03 (t, J = 9.1 Hz, 1H), 3.99 (d, J = 15.6 Hz, 1H), 3.70–3.76 (m, 2H), 3.58–3.63 (m, 1H), 3.37 (s, 1H), 2.96–3.17 (m, 4H), 2.16–2.27 (m, 4H), 2.03 (s, 3H), 1.85–1.99 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 156.5, 154.2, 112.9, 111.1, 88.9, 80.6, 71.8, 53.2, 49.6, 47.6, 42.0, 29.1, 28.9, 23.2; HRMS (FAB) calcd for $C_{26}H_{30}FN_5O_7$ $(M)^{+\cdot}$: 543.2129; found 543.2115.

5.2.13. *tert*-Butyl 8-(4-((*S*)-5-(aminomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-4-hydroxy-8-azaspiro[4.5]decan-1-ylcarbamate (15)

Compound **11** (0.12 g, 0.25 mmol) was dissolved in a mixture of 3 mL of acetonitrile and 1 mL of water in a 10-mL oven-dried, round-bottomed flask. Molybdenumhexacarbonyl (20 mg, 0.07 mmol) and sodium borohydride (15 mg, 0.50 mmol) were added to the solution in the indicated order. The mixture was stirred at 60 °C for 6 h. After the reaction mixture cooled to room temperature, all the solvent was removed under reduced pressure, and the residue was purified by chromatography on a silica gel column (ethyl acetate: MeOH = 10:1) to give compound **15** (76 mg, 64%) as a colorless oil: IR (neat, cm^{-1}): 3487, 2927, 1747, 1616; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 14.1, 1.9 Hz, 1H), 6.98–7.06 (m, 1H), 6.86–6.96 (m, 1H), 5.46–5.54 (m, 1H), 4.58–4.76 (m, 1H), 3.92–4.06 (m, 3H), 3.73–3.79 (m, 1H), 2.84–3.12 (m, 6H), 2.14–2.32 (m, 4H), 1.66–2.00 (m, 6H), 1.40 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 155.5, 154.5, 153.7, 137.0, 132.7, 119.1, 113.6, 107.2, 106.9, 80.0, 78.8, 77.4, 73.7, 55.3, 48.2, 47.6, 44.8, 33.2, 31.1, 30.5, 28.3, 27.2; HRMS (FAB) calcd for $C_{24}H_{35}FN_4O_5$ $(M)^{+\cdot}$: 478.2591; found 478.2592.

5.2.14. *tert*-Butyl 8-(4-((*S*)-5-(acetamidomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-4-hydroxy-8-azaspiro[4.5]decan-1-ylcarbamate (16)

Compound **12** (21 mg, 0.04 mmol) was dissolved in a mixture of 3 mL of acetonitrile and 1 mL of water in a 10-mL round-bottomed flask. Molybdenumhexacarbonyl (5 mg, 0.02 mmol) and sodium borohydride (5 mg, 0.16 mmol) were added to the solution in the indicated order. The mixture was stirred at 60 °C for 6 h. After the reaction mixture cooled to room temperature, all the solvent was removed under reduced pressure, and the residue was purified by chromatography on a silica gel column (hexanes:ethyl acetate = 1:1) to give compound **16** (16 mg, 80%) as a colorless oil: IR (neat, cm^{-1}): 3331 (br), 2962, 1686, 1518; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 14.2 Hz, 1H), 6.90–7.04 (m, 2H), 6.32–6.38 (m, 1H), 5.38–5.48 (m, 1H), 4.72–4.81 (m, 1H), 3.96–4.10 (m, 3H), 3.56–3.76 (m, 3H), 2.86–3.16 (m, 4H), 1.72–2.08 (m, 11H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 157.0, 155.5, 154.4, 153.8, 149.9, 137.3, 132.4, 129.7, 128.7, 126.9, 126.2, 119.4, 113.8, 107.4, 80.2, 78.9, 77.4, 71.8, 55.6, 48.5, 47.9, 47.7, 42.2, 33.6, 31.4, 30.8, 30.1, 28.7, 27.4, 23.2; HRMS (FAB) calcd for $C_{26}H_{37}FN_4O_6$ $(M)^{+\cdot}$, 520.2697; found 520.2697.

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References and notes

1. Spellberg, B.; Guidos, R.; Gilbert, D.; Bradley, J.; Boucher, H. W.; Scheld, W. M.; Bartlett, J. G.; Edwards, J., Jr. *Clin. Infect. Dis.* **2008**, *46*, 155.
2. Boucher, H. W.; Talbot, G. H.; Bradley, J. S.; Edwards, J. E.; Gilbert, D.; Rice, L. B.; Scheld, M.; Spellberg, B.; Bartlett, J. *Clin. Infect. Dis.* **2009**, *48*, 1.
3. Barbachyn, M. R.; Ford, C. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2010.
4. Gravestock, M. B. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 469.
5. Hutchinson, D. K. *Expert Opin. Ther. Pat.* **2004**, *14*, 1309.
6. Renslo, A. R.; Luehr, G. W.; Gordeev, M. F. *Bioorg. Med. Chem.* **2006**, *14*, 4227.
7. Ippolito, J. A.; Kanyo, Z. F.; Wang, D. P.; Franceschi, F. J.; Moore, P. B.; Steitz, T. A.; Duffy, E. M. *J. Med. Chem.* **2008**, *51*, 3353.
8. Leach, K. L.; Swaney, S. M.; Colca, J. R.; McDonald, W. G.; Blinn, J. R.; Thomasco, L. M.; Gadwood, R. C.; Shinabarger, D.; Xiong, L.; Mankin, A. S. *Mol. Cell* **2007**, *26*, 393.
9. Barry, A. L. *Antimicrob. Agents Chemother.* **1988**, *32*, 150.
10. Neu, H. C.; Novelli, A.; Saha, G.; Chin, N. X. *Antimicrob. Agents Chemother.* **1988**, *32*, 580.
11. Slee, A. M.; Wuonola, M. A.; McRipley, R. J.; Zajac, I.; Zawada, M. J.; Bartholomew, P. T.; Gregory, W. A.; Forbes, M. *Antimicrob. Agents Chemother.* **1987**, *31*, 1791.
12. Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673.
13. Brickner, S. J.; Barbachyn, M. R.; Hutchinson, D. K.; Manninen, P. R. *J. Med. Chem.* **1981**, *2008*, 51.
14. Tsiodras, S.; Gold, H. S.; Sakoulas, G.; Eliopoulos, G. M.; Wennersten, C.; Venkataraman, L.; Moellering, R. C.; Ferraro, M. J. *Lancet* **2001**, *358*, 207.
15. Gonzales, R. D.; Schreckenberger, P. C.; Graham, M. B.; Kelkar, S.; DenBesten, K.; Quinn, J. P. *Lancet* **2001**, *357*, 1179.
16. Auckland, C.; Teare, L.; Cooke, F.; Kaufmann, M. E.; Warner, M.; Jones, G.; Bamford, K.; Ayles, H.; Johnson, A. P. *J. Antimicrob. Chemother.* **2002**, *50*, 743.
17. Seedat, J.; Zick, G.; Klare, I.; Konstabel, C.; Weiler, N.; Sahly, H. *Antimicrob. Agents Chemother.* **2006**, *50*, 4217.
18. Hutchinson, D. K. *Curr. Top. Med. Chem.* **2003**, *3*, 1021.
19. Paget, S. D.; Foleno, B. D.; Boggs, C. M.; Goldschmidt, R. M.; Hlasta, D. J.; Weidner-Wells, M. A.; Werblood, H. M.; Wira, E.; Bush, K.; Macielag, M. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4173.
20. Fukuda, Y. H.; Hammond, M. L. U. S. Patent 6,897,230, 2005.
21. Renslo, A. R.; Jaishankar, P.; Venkatachalam, R.; Hackbarth, C.; Lopez, S.; Patel, D. V.; Gordeev, M. F. *J. Med. Chem.* **2005**, *48*, 5009.
22. Gordeev, M. F.; Renslo, A.; Patel, D. V. U. S. Patent 6,875,784, 2005.
23. Barbachyn, M. R.; Brickner, S. J.; Hutchinson, D. K. U. S. Patent 6,090,820, 2000.
24. Patel, M. V.; Deshpande, P. K.; Sindkhedkar, M. D.; Gupte, S. V.; Chugh, Y.; Shetty, N.; Shukla, M. C.; Yeole, R. D.; De Souza, N. J. U. S. Patent Application 2004/0063954, 2004.
25. Chugh, Y.; Shetty, N.; Deshpande, P. K.; Sindkhedkar, M. D.; Jafri, M. D.; Yeole, R. D.; Shukla, M. C.; Gupte, S. V.; Patel, M. V.; De Souza, N. J. U. S. Patent Application 2004/0235900, 2004.
26. Prasad, J. V. *Curr. Opin. Microbiol.* **2007**, *10*, 454.
27. Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1 (Stereoselective Heterocyclic Synthesis I).
28. Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317.
29. Yamamoto, H.; Momiyama, N. *Chem. Commun. (Cambridge, U. K.)* **2005**, 3514.
30. Bodnar, B. S.; Miller, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5629.
31. Li, F. Z.; Yang, B. Y.; Miller, M. J.; Zajicek, J.; Noll, B. C.; Möllmann, U.; Dahse, H. M.; Miller, P. A. *Org. Lett.* **2007**, *9*, 2923.
32. Krchnak, V.; Waring, K. R.; Noll, B. C.; Möllmann, U.; Dahse, H. M.; Miller, M. J. *J. Org. Chem.* **2008**, *73*, 4559.
33. Ji, C.; Miller, M. J. *Tetrahedron Lett.* **2010**, *51*, 3789.
34. Lin, W. M.; Gupta, A.; Kirn, K. H.; Mendel, D.; Miller, M. J. *Org. Lett.* **2009**, *11*, 449.
35. Li, F. Z.; Brogan, J. B.; Gage, J. L.; Zhang, D. Y.; Miller, M. J. *J. Org. Chem.* **2004**, *69*, 4538.
36. Kim, K. H.; Miller, M. J. *Tetrahedron Lett.* **2003**, *44*, 4571.
37. Li, F. Z.; Miller, M. J. *J. Org. Chem.* **2006**, *71*, 5221.
38. Li, F. Z.; Warshakoon, N. C.; Miller, M. J. *J. Org. Chem.* **2004**, *69*, 8836.
39. Lin, W. M.; Virga, K. G.; Kim, K. H.; Zajicek, J.; Mendel, D.; Miller, M. J. *J. Org. Chem.* **2009**, *74*, 5941.
40. Tucker, J. A.; Allwine, D. A.; Grega, K. C.; Barbachyn, M. R.; Klock, J. L.; Adamski, J. L.; Brickner, S. J.; Hutchinson, D. K.; Ford, C. W.; Zurenko, G. E.; Conradi, R. A.; Burton, P. S.; Jensen, R. M. *J. Med. Chem.* **1998**, *41*, 3727.
41. Das, B.; Rudra, S.; Yadav, A.; Ray, A.; Rao, A.; Srinivas, A.; Soni, A.; Saini, S.; Shukla, S.; Pandya, M.; Bhateja, P.; Malhotra, S.; Mathur, T.; Arora, S. K.; Rattan, A.; Mehta, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4261.
42. Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; Desarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351.
43. Yan, S. S.; Miller, M. J.; Wencewicz, T. A.; Möllmann, U. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1302.
44. Typical MIC values of linezolid against MSSA and MRSA are 1–2 and 0.5–2 mg mL-1, respectively. See Phillips, O. A.; Udo, E. E.; Ali, A. A. M.; Samuel, S. M. *Eur. J. Med. Chem.* **2007**, *42*, 214.
45. Williams, K. N.; Stover, C. K.; Zhu, T.; Tasneen, R.; Tyagi, S.; Grosset, J. H.; Nuermberger, E. *Antimicrob. Agents Chemother.* **2009**, *53*, 1314.
46. Collins, L. A.; Franzblau, S. G. *Antimicrob. Agents Chemother.* **1997**, *41*, 1004.
47. Cho, S. H.; Warit, S.; Wan, B.; Hwang, C. H.; Pauli, G. F.; Franzblau, S. G. *Antimicrob. Agents Chemother.* **2007**, *51*, 1380.