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Novel Piperidinyloxy Oxazolidinone Antibacterial Agents. Diversification of the *N*-Substituent

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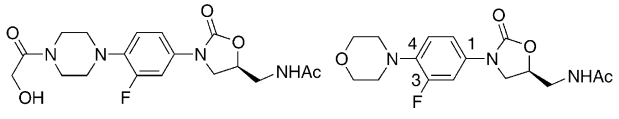
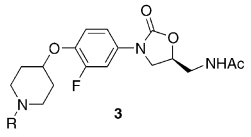
Abstract—Oxazolidinone antibacterial agents, where the morpholino group of linezolid was replaced with an *N*-substituted piperidinyloxy moiety, were synthesized and shown to be active against a variety of resistant and susceptible Gram-positive organisms. The functionality attached to the piperidine nitrogen was varied extensively to determine the SAR for this series. One of the most potent compounds, **11**, showed in vivo efficacy upon subcutaneous administration in a *Staphylococcus aureus* Smith murine systemic infection.

Introduction

New classes of antibacterial agents with novel mechanisms of action are urgently needed to combat the increase in multidrug resistant infections. Recent reports indicate that in 1998, at least 21% of all nosocomial enterococcal infections in US hospitals were due to vancomycin-resistant enterococci (VRE).[1] The oxazolidinones, a new class of totally synthetic antibacterial agents, are active against a variety of clinically important susceptible and resistant Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), VRE, and penicillin-resistant *Streptococcus pneumoniae* (PRSP). Scientists at DuPont originally discovered this class of agents in the late 1980's.[2] However, development of DuP-721, the drug candidate that emerged from these initial studies, was discontinued following Phase I clinical trials. Subsequently, researchers at Pharmacia and Upjohn identified two clinical candidates, eperezolid (**1**) and linezolid (**2**).[3] Linezolid is currently marketed for the treatment of multidrug resistant Gram-positive infections such as nosocomial and community-acquired pneumonia and skin infections.



eperezolid (**1**) linezolid (**2**)



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The oxazolidinone class of antibacterial agents selectively binds to the 23S RNA component of the 50S ribosomal subunit, inhibiting protein synthesis at an early phase of translation.[4] Due to its unique mechanism of action, it is believed that there will be a lack of cross-resistance with other classes of protein synthesis inhibitors.[5]

Several SAR studies of the oxazolidinones have demonstrated a high tolerance for structural variation at the 4-position of the phenyl ring, while the oxazolidinone ring is essential for activity.[6] Based on these reports, we have developed a series of oxazolidinone antibacterial agents **3** where the morpholine moiety of linezolid was replaced with a 4-piperidinyloxy group with various functionalities appended to the nitrogen.

Previous studies from these laboratories have examined the effect of ring size and fluorine substitution on in

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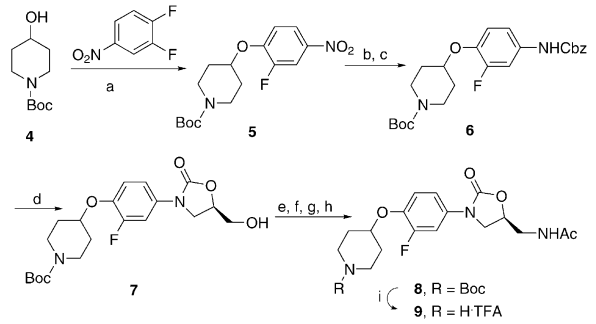
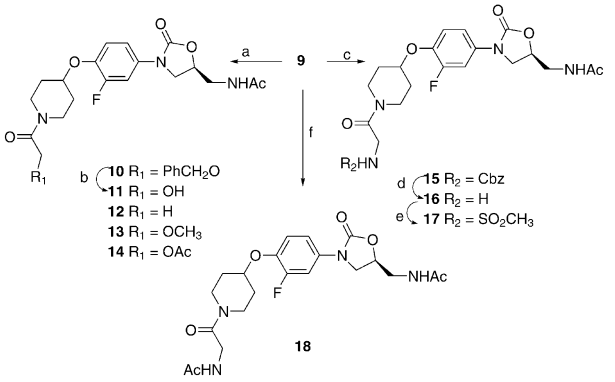


Scheme 1. Reagents: (a) KO*t*Bu, THF, 89%; (b) HCO_2NH_4, Pd/C, MeOH, 99%; (c) Cbz–Cl, $NaHCO_3$, acetone, water, 89%; (d) (i) *n*BuLi, THF, −78 °C; (ii) (*R*)-glycidyl butyrate, 72%; (e) Ms–Cl, TEA, CH_2Cl_2, 0 °C; (f) NaN_3, DMF, 75 °C, 92%; (g) (i) PPh_3, THF; (ii) water, reflux; (h) Ac_2O, pyridine, EtOAc, 85%; (i) TFA, CH_2Cl_2, 98%.



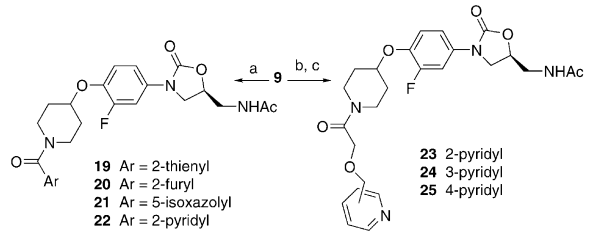
Scheme 2. Reagents: (a) (i) TEA, CH_2Cl_2; (ii) $R_1CH_2C(O)Cl$; (b) HCO_2NH_4, Pd/C, MeOH; (c) (i) TEA, CH_2Cl_2; (ii) $CbzNHCH_2C(O)F$; (d) H_2, Pd/C, MeOH, 50 psi; (e) CH_3SO_2Cl, TEA, CH_2Cl_2; (f) (i) TEA, CH_2Cl_2; (ii) acetylglycine, EDCI.

vitro activity.[7] It was reported that fluorine substitution increases potency and the six-membered 4-piperidinyloxy ring was optimal. This paper describes efforts to increase the in vitro activity by diversification of the nitrogen substituent. In addition, several of the more potent compounds were studied in vivo.

Chemistry

The synthesis of key intermediate **9** is outlined in Scheme 1. A nucleophilic aromatic substitution reaction between Boc-protected 4-hydroxypiperidine (**4**) and 3,4-difluoronitrobenzene afforded the nitroaromatic derivative **5**. Reduction of the nitro group followed by protection of the resulting aniline gave Cbz derivative **6**. The oxazolidinone ring was assembled in one step by reaction of the anion of **6** with (*R*)-glycidyl butyrate to afford alcohol **7**.[3] Standard functional group manipulations yielded Boc-protected acetamide **8** in several steps. The Boc group was removed by treatment with trifluoroacetic acid in methylene chloride to provide intermediate **9** as the TFA salt in excellent overall yield.

Amine **9** was derivatized as shown in Schemes 2 and 3. Acylation with a variety of acid chlorides proceeded



Scheme 3. Reagents: (a) (i) TEA, CH_2Cl_2; (ii) ArC(O)Cl; (b) (i) TEA, CH_2Cl_2; (ii) $ClCH_2C(O)Cl$; (c) pyridylmethanol, NaH, THF.

smoothly to afford amides **10** and **12–14**. α-Hydroxyacetamide **11** was obtained by deprotection of α-benzyloxyacetamide **10**. Sulfonamide **17** was prepared via glycinamide **16**. Acetamide **18** was synthesized directly by coupling of **9** with acetylglycine (Scheme 2).

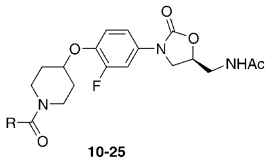
Reaction of **9** with heteroaryl acid chlorides afforded amides **19–22** in good yield. Pyridino analogues **23–25** of α-benzyloxy acetamide **10** were synthesized in two steps. Amine **9** was converted to the α-chloroacetamide followed by reaction with the sodium alkoxide of the appropriate pyridinylmethanol regioisomer (Scheme 3).

Results and Discussion

The oxazolidinone analogues synthesized were tested for in vitro antibacterial activity against a panel of susceptible and resistant Gram-positive and Gram-negative organisms. None of these compounds exhibited any activity against Gram-negative organisms such as *Escherichia coli* K-12 wild type strain or an *E. coli* strain OC 2530 that is hypersensitive to antimicrobial agents due to a defective outer membrane when tested at concentrations as high as 32 μg/mL. Data for select Gram-positive organisms are reported as a minimum inhibitory concentration (MIC) expressed in μg/mL (Table 1). Compounds were tested in broth as well as in the presence of 50% mouse serum against *Staphylococcus aureus* Smith (OC4172) to give an indication of serum protein binding. If the MIC is increased at least 4-fold in the presence of serum the compound may be binding to serum proteins or is inactivated by components of the serum. As a result, there may no longer be a sufficient concentration of free drug in the serum to inhibit the growth of bacteria effectively in vivo.

The initial compounds screened were the α-benzyloxyacetamide **10** and the α-hydroxyacetamide **11**, the direct analogues of eperezolid (**1**). These compounds showed measurable in vitro antibacterial activity against a range of susceptible as well as resistant Gram-positive organisms, such as MRSA and VRE. Since these compounds were 2- to 4-fold less potent than linezolid (**2**), modification of the hydroxyl group was investigated as a possible means to increase potency. Examination of the MIC values for compounds **10–14** relative to linezolid, indicate that the hydroxyl may be functioning as a hydrogen bond donor since des-hydroxyl analogue **12**, methylated analogue **13**, and the acetylated derivative **14** are 2-fold less potent than **11**. In addition, the phenyl group of **10** is important since this compound is 2- to

Table 1. In vitro antibacterial activity (MIC, μg/mL)



10-25

Compd	R	*S. aureus* OC 4172	*S. aureus* with serum[a]	*MRSA* OC 2878	*E. faecium* (VRE) OC 3312	*E. faecalis* ATCC 29212
10	CH_2OCH_2Ph	4	16	2	4	4
11	CH_2OH	4	4	4	8	8
12	CH_3	8	16	8	16	16
13	CH_2OCH_3	8	16	8	16	16
14	CH_2OAc	8	16	8	16	16
15	CH_2NHCbz	8	32	8	8	8
16	CH_2NH_2	32	32	32	32	32
17	$CH_2NHSO_2CH_3$	8	16	16	16	16
18	CH_2NHAc	8	16	16	64	32
19	2-Thienyl	8	16	4	8	8
20	2-Furyl	16	32	8	8	16
21	5-Isoxazolyl	8	16	4	8	8
22	2-Pyridyl	8	16	8	16	16
23	CH_2OCH_2-(2-pyridyl)	32	16	16	32	32
24	CH_2OCH_2-(3-pyridyl)	16	16	16	8	16
25	CH_2OCH_2-(4-pyridyl)	8	16	8	8	16
2	—	2	2	2	2	2

[a]In the presence of 50% mouse serum.

4-fold more potent than the methylated analogue **13**. However, benzyloxy analogue **10** exhibits an increase in MIC in the presence of mouse serum indicating either binding to or inactivation by serum proteins, whereas hydroxy acetamide **11** does not exhibit this behavior. This is most likely due to the increased lipophilicity of the benzyloxy moiety relative to the hydroxyl.

Hydroxyl mimics **15**–**18** were investigated next. As is evident from the data, a basic functionality is detrimental to activity since amine **16** exhibits a significant loss in potency. The sulfonamide **17** and acetamide **18** also are several-fold less potent than hydroxy acetamide **11**. The highly lipophilic Cbz derivative **15** displays a 4-fold increase in MIC in the presence of serum, thus indicating possible protein binding.

A 5-isoxazolyl amide has been reported to be a rigid bioisostere for the hydroxyacetamide functionality of eperezolid (**1**).[8] To this end, heteroaryl amides **19**–**22** were synthesized. In general, replacement of the benzyloxy acetamide with heteroaryl amides led to less potent compounds. 2-Thienyl amide **19** and 5-isoxazolyl amide **21** were the most potent analogues in this series. Not unexpectedly, the 2-pyridyl substitution was better than the regiosiomeric pyridine analogues (data not shown) since this placement of the nitrogen more closely mimics the α-hydroxyacetyl moiety.

Since benzyloxyacetamide **10** had a favorable susceptibility profile except for the increased MIC in the presence of serum, attention was focused on the preparation of analogues that would minimize this interaction. The regioisomeric pyridyl analogues **23**–**25** exhibited reduced serum protein binding, however, these compounds were less potent than the parent compound **10**.

Compounds **10** and **11** were screened against an expanded panel of Gram-positive organisms as well as *Haemophilus influenzae*, a Gram-negative respiratory pathogen. Benzyloxyacetamide **10** exhibited a MIC range of 1–8 μg/mL against a panel of 26 isolates of penicillin-susceptible and penicillin-resistant *S. pneumoniae*, while hydroxyacetamide **11** had a MIC range of 0.5–4 μg/mL against the same organisms. Linezolid had a range of 0.12–1 μg/mL. Neither of the piperidinyloxy compounds **10** nor **11** was active against *H. influenzae* at concentrations as high as 32 μg/mL, whereas linezolid was active against some strains (MIC range 4–32 μg/mL).

Compounds **10** and **11**, administered subcutaneously in a *S. aureus* Smith murine systemic infection model, had ED_{50} values of 48 and 13 mg/kg/day, respectively. The ED_{50} for linezolid was 2.7 mg/kg/day. The poor in vivo activity of **10** compared to **11** is most likely due to a combination of serum protein binding and poor solubility in the vehicle (40% hydroxypropyl-β-cyclodextrin) utilized for the study.

In conclusion, a series of piperidinyloxy oxazolidinone antibacterial agents was discovered with in vitro activity against a variety of clinically relevant susceptible as well as resistant (MRSA, VRE, and PRSP) Gram-positive organisms. Diverse functional groups are tolerated on the piperidinyloxy nitrogen; however, bulky substituents resulted in a loss of activity. Two of the most potent compounds, **10** and **11**, were active against a larger panel of bacterial pathogens, but had MIC values >32 μg/mL against *H. influenzae*. α-Hydroxyacetamide **11**

showed in vivo efficacy upon subcutaneous administration in a *S. aureus* Smith murine systemic infection model.

Experimental

General

Proton (^{1}H NMR) magnetic resonance spectra were recorded on a Bruker Avance 300 instrument in deuteriochloroform unless noted otherwise. Mass spectra were recorded on a HP1100 LC/MSD with an ESI source and single quad analyzer. Column chromatography was performed with EM Silica Gel 60. Melting points were determined on a Thomas Hoover Mel-Temp apparatus and are uncorrected. The term 'dried' refers to the use of anhydrous magnesium sulfate.

1-[*N*-(*t*-Butoxycarbonyl)piperidinyl-4-oxy]-2-fluoro-4-nitrobenzene (5). To a solution *N*-(*t*-butoxycarbonyl)-4-piperidinol (740 mg; 3.7 mmol) in dry THF (10 mL) at 0 °C was added dropwise KO*t*Bu (1 M in THF; 4.0 mL; 4.0 mmol). After stirring at 0 °C for 0.5 h, 3,4-difluoronitrobenzene (0.40 mL; 3.6 mmol) was added and the reaction warmed to room temperature and stirred overnight. The reaction was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with H_2O, dried and the solvent evaporated. The solid was triturated with cold hexanes to afford 1.1 g (89%) of **5** as a pale yellow solid; mp 88–90 °C. ^{1}H NMR δ 7.98–8.06 (m, 2H), 7.05 (t, J = 8.5 Hz, 1H), 4.67 (septet, J = 3.5 Hz, 1H), 3.66–3.75 (m, 2H), 3.37–3.45 (m, 2H), 1.94–2.05 (m, 2H), 1.80–1.89 (m, 2H), 1.61 (s, 9H). MS $[M+Na]^+$ 364. Anal. calcd for $C_{16}H_{21}FN_2O_5$: C, 56.46; H, 6.22; N, 8.23. Found: C, 56.48; H, 6.22; N, 8.02.

2-Fluoro-1-{*N*-(*t*-butoxycarbonyl)piperidinyl-4-oxy}-4-(phenylmethoxycarbonylamino)benzene (6). To nitrobenzene **5** (1.78 g, 5.23 mmol) in MeOH (100 mL) was added ammonium formate (1.05 g; 16.6 mmol) and 10% Pd/C (70 mg) and the reaction heated at reflux under N_2 for 2 h. The reaction was filtered through a pad of Celite and the filtrate evaporated to afford the aniline as a gold oil. To crude aniline (5.23 mmol) in 2:1 acetone/H_2O (150 mL) at 0 °C was added $NaHCO_3$ (1.03 g; 12.3 mmol) and benzylchloroformate (0.90 mL; 6.30 mmol). After stirring at room temperature for 6 h, the volatiles were evaporated, the residue diluted with H_2O (300 mL) and extracted with Et_2O (3×150 mL). The combined organic layers were washed with H_2O, dried and the solvent evaporated. Chromatography (20% EtOAc/hexanes) afforded 2.06 g (89%) of **6** as a yellow, waxy solid, mp 101–103 °C. ^{1}H NMR δ 7.31–7.44 (m, 6H), 6.93–7.06 (m, 2H), 6.60 (br s, 1H), 5.19 (s, 2H), 4.35–4.49 (m, 1H), 3.74–3.87 (m, 2H), 3.22–3.39 (m, 2H), 1.81–2.07 (m, 2H), 1.62–1.79 (m, 2H), 1.48 (s, 9H). MS$[M+Na]^+$ 467. Anal. calcd for $C_{24}H_{29}FN_2O_5$: C, 64.85; H, 6.56; N, 6.30. Found: C, 64.62; H, 6.57; N, 6.19.

(*R*)-[3-[3-Fluoro-4-{*N*-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]-methanol (7). To Cbz derivative **6** (1.73 g; 3.89 mmol) in dry THF (25 mL) at −78 °C, was added 2.5M *n*-BuLi (2.0 mL; 5.0 mmol) and the reaction stirred for 1 h. (*R*)-Glycidyl butyrate (0.71 mL; 5.01 mmol) was added via syringe and the reaction warmed to room temperature and stirred overnight. The reaction was carefully poured into satd NH_4Cl (150 mL) and extracted with EtOAc (3×100 mL). The combined organic layers were washed with H_2O, dried and the solvent evaporated. Chromatography (60% EtOAc/hexanes) gave 1.15 g (72%) of alcohol **7** as a white solid; mp 110–111 °C. ^{1}H NMR δ 7.47 (dd, J = 12.8, 3.0 Hz, 1H), 7.15 (dt, J = 8.8, 1.4 Hz, 1H), 7.00 (t, J = 8.8 Hz, 1H), 4.73–4.83 (m, 1H), 4.38–4.46 (m, 1H), 3.90–4.01 (m, 3H), 3.68–3.80 (m, 3H), 3.25–3.46 (m, 2H), 2.37 (br s, 1H), 1.84–2.01 (m, 2H), 1.71–1.80 (m, 2H), 1.48 (s, 9H). MS $[M+Na]^+$ 433.5. Anal. calcd for $C_{20}H_{27}FN_2O_6$: C, 58.53; H, 6.63; N, 6.83. Found: C, 58.27; H, 6.59; N, 6.61.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (8). To alcohol **7** (2.13 g; 5.20 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added triethylamine (1.5 mL; 5.27 mmol) and methanesulfonyl chloride (0.78 mL; 10.0 mmol). After stirring for 3 h at 0 °C, the reaction was poured into H_2O (75 mL) and extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with H_2O, dried and the solvent evaporated to yield 2.54 g (99%) of mesylate as a cream solid; mp 127–129 °C, MS $[M+H-Boc]^+$ 389.2. To a solution of mesylate (5.20 mmol) in DMF (70 mL) was added sodium azide (1.22 g; 18.8 mmol) and the reaction heated at 75 °C overnight. The reaction was poured into H_2O (300 mL) and extracted with EtOAc (3×200 mL). The combined organic layers were washed with H_2O (3×200 mL), dried and the solvent evaporated to yield 2.07 g (92%) of azide as a beige solid. ^{1}H NMR δ 7.46 (dd, J = 12.9, 2.7 Hz, 1H), 7.14 (dt, J = 8.9, 1.4 Hz, 1H), 7.01 (t, J = 8.9 Hz, 1H), 4.71–4.83 (m, 1H), 4.34–4.43 (m, 1H), 4.05 (t, J = 8.9 Hz, 1H), 3.83 (dd, J = 8.9, 6.2 Hz, 1H), 3.77–3.88 (m, 2H), 3.71 (dd, J = 13.2, 4.6 Hz, 1H), 3.59 (dd, J = 13.2, 4.3 Hz, 1H), 3.23–3.38 (m, 2H), 1.85–2.00 (m, 2H), 1.71–1.81 (m, 2H), 1.47 (s, 9H).

To a solution of azide (4.78 mmol) in dry THF (9 mL) was added triphenylphosphine (1.51 g, 5.75 mmol) and the reaction stirred for 3 h at room temperature. H_2O (4.5 mL) was added and the reaction heated at 60 °C for 4 h. The volatiles were evaporated and the residue azeotroped with benzene (2×20 mL) to yield the crude amine. To a solution of this crude amine in EtOAc (100 mL) was added acetic anhydride (0.58 mL; 6.15 mmol) and pyridine (1.2 mL; 14.8 mmol), and the reaction stirred at room temperature overnight. The reaction mixture was poured into H_2O (250 mL) and extracted with EtOAc (3×150 mL). The combined organic layers were dried and the solvent removed. Chromatography (100% EtOAc to 5% MeOH/EtOAc) yielded 1.85 g (85%) of acetamide **8** as a white solid; mp 179–180 °C. ^{1}H NMR δ 7.47 (dd J = 12.8, 2.4 Hz, 1H), 7.09 (dt, J = 8.9 Hz, 1.4 Hz, 1H), 7.01 (t, J = 8.9 Hz, 1H), 6.05 (br t, J = 6.0 Hz, 1H), 4.71–4.85 (m, 1H), 4.33–4.46 (m, 1H), 4.00 (t, J = 9.0 Hz, 1H), 3.51–3.85 (m, 5H), 3.23–3.39 (m, 2H), 2.08 (s, 3H), 1.62–1.98 (m, 4H), 1.50 (s, 9H).

MS $[M+Na]^+$ 474. Anal. calcd for $C_{22}H_{30}FN_3O_6$: C, 58.53; H, 6.70; N, 9.31. Found: C, 58.56; H, 6.84; N, 9.02.

(*S*)-*N*-[3-[3-Fluoro-4-{piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide trifluoroacetate (9). To a solution of protected acetamide **8** (1.94 g; 4.30 mmol) in CH_2Cl_2 (225 mL) was added trifluoroacetic acid (2.5 mL; 32.50 mmol) and the reaction stirred at room temperature for 6 h. The volatiles were evaporated to yield a viscous oil (98%). ^{1}H NMR (DMSO-d_6) δ 9.50 (br s, 1H), 9.27 (br s, 1H), 8.21 (t, $J=5.8$ Hz, 1H), 7.54 (dd, $J=12.0$, 2.3 Hz, 1H), 7.06–7.11 (m, 2H), 4.74–4.79 (m, 1H), 4.49–4.58 (m, 1H), 4.05 (t, $J=8.9$ Hz, 1H), 3.80 (dd, $J=8.9$, 6.5 Hz, 1H), 3.51–3.62 (m, 2H), 3.27–3.33 (m, 2H), 3.18–3.23 (m, 2H), 2.04–2.15 (m, 4H), 1.95 (s, 3H). MS $[M+Na]^+$ 374.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(benzyloxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (10). To a suspension of **9** (1.50 mmol) in CH_2Cl_2 (50 mL) was added NEt_3 (0.60 mL, 4.3 mmol) and benzyloxyacetyl chloride (0.25 mL, 1.58 mmol). After stirring for 18 h, the reaction was poured into H_2O (75 mL) and extracted with CH_2Cl_2 (4×50 mL). The combined organic layers were dried and evaporated. Chromatography (5% MeOH/EtOAc) afforded **10** as a white glass (86%). ^{1}H NMR δ 7.47 (dd, $J=12.9$, 2.5 Hz, 1H), 7.21–7.45 (m, 6H), 6.98 (t, $J=8.8$ Hz, 1H), 6.24 (br t, $J=6.1$ Hz, 1H), 4.74–4.87 (m, 1H), 4.61 (s, 2H), 4.48–4.53 (m, 1H), 4.20 (s, 2H), 4.02 (t, $J=9.0$ Hz, 1H), 3.62–3.87 (m, 6H), 3.47–3.52 (m, 1H), 2.02 (s, 3H), 1.81–1.98 (m, 4H). MS $[M+Na]^+$ 522. Anal. calcd for $C_{26}H_{30}FN_3O_6$: C, 62.52; H, 6.05; N, 8.41. Found: C, 62.38; H, 6.08; N, 8.42.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(α-hydroxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (11). To a solution of **10** (540 mg, 1.08 mmol) in MeOH (50 mL) was added ammonium formate (503 mg) and a catalytic amount of 10% Pd/C, and the reaction was heated at reflux overnight. Then the reaction was filtered through a pad of Celite and the solvent removed under reduced pressure. Chromatography (2–10% MeOH/CH_2Cl_2) afforded **11** as a hygroscopic white glass (93%), mp 71–75 °C. ^{1}H NMR δ 7.49 (dd, $J=12.9$, 2.6 Hz, 1H), 7.09 (dd, $J=8.9$, 1.6 Hz, 1H), 7.00 (t, $J=8.9$ Hz, 1H), 6.18 (br t, $J=6.1$ Hz, 1H), 4.75–4.83 (m, 1H), 4.51 (q, $J=4.6$ Hz, 1H), 4.19 (s, 2H), 4.02 (t, $J=9.0$ Hz, 1H), 3.51–3.86 (m, 7H), 3.20 (dt, $J=13.7$, 5.2 Hz, 1H), 2.03 (s, 3H), 1.80–1.95 (m, 4H). MS $[M+Na]^+$ 432. Anal. calcd for $C_{19}H_{24}FN_3O_6$: C, 55.74; H, 5.91; N, 10.26. Found: C, 55.85; H, 5.86; N, 10.13.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(acetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (12). This was prepared according to the procedure for **10** utilizing acetyl chloride instead of benzyloxyacetyl chloride. The title compound was isolated as a hygroscopic glass (46%). ^{1}H NMR δ 7.47 (dd, $J=12.9$, 2.2 Hz, 1H), 7.02–7.09 (m, 2H), 6.97 (br t, $J=8.8$ Hz, 1H), 4.75–4.79 (m, 1H), 4.44–4.48 (m, 1H), 4.03 (t, $J=9.0$ Hz, 1H), 3.61–3.87 (m, 6H), 3.38–3.49 (m, 1H), 2.12 (s, 3H), 2.02 (s, 3H), 1.80–1.90 (m, 4H). MS $[M+H]+$ 394. Anal. calcd $C_{19}H_{24}FN_3O_5/1.5H_2O$: C, 54.28; H, 6.47; N, 9.99. Found: C, 54.36; H, 6.16; N, 10.17.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(methoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide (13). This was prepared according to the procedure for **10** utilizing methoxyacetyl chloride instead of benzyloxyacetyl chloride. Chromatography (2.5–10% MeOH/CH_2Cl_2) afforded 101 mg (32%) of **13** as a beige foam. ^{1}H NMR δ 7.48 (dd, $J=12.9$, 2.5 Hz, 1H), 7.09–7.12 (m, 1H), 7.00 (t, $J=8.8$ Hz, 1H), 6.00 (br t, 1H), 4.67–4.72 (m, 1H), 4.40–4.43 (m, 1H), 4.13 (s, 2H), 4.03 (t, $J=8.9$ Hz, 1H), 3.52–3.86 (m, 6H), 3.44 (s, 3H), 3.40–3.43 (m, 1H), 2.03 (s, 3H), 1.72–1.96 (m, 4H). MS $[M+Na]^+$ 446. Anal. calcd for $C_{20}H_{26}FN_3O_6$: C, 56.73; H, 6.19; N, 9.92. Found: C, 57.05; H, 6.21; N, 9.55.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(acetoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (14). This was prepared according to the procedure for **10** utilizing acetoxyacetyl chloride instead of benzyloxyacetyl chloride. Chromatography using 10% MeOH/CH_2Cl_2 afforded **14** as a pale beige solid (53%); mp 146–147.5 °C. ^{1}H NMR δ 7.48 (dd, $J=12.9$, 2.4 Hz, 1H), 7.06–7.12 (m, 1H), 7.00 (t, $J=8.9$ Hz, 1H), 6.08 (br t, $J=5.8$ Hz, 1H), 4.68–4.81 (m, 3H), 4.46–4.51 (m, 1H), 4.03 (t, $J=9.0$ Hz, 1H), 3.61–3.78 (m, 6H), 3.30–3.35 (m, 1H), 2.19 (s, 3H), 2.02 (s, 3H), 1.80–1.91 (m, 4H). MS $[M+H]^+$ 452. Anal. calcd for $C_{21}H_{26}FN_3O_7$: C, 55.81; H, 5.81; N, 9.31. Found: C, 55.55; H, 5.71; N, 9.28.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(α-phenylmethoxycarbonylamino-acetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide (15). To a solution of **9** (266 mg, 0.76 mmol) in CH_2Cl_2 (15 mL) was added NEt_3 (0.2 mL) and *N*-phenylmethoxycarbonylglycine acid fluoride (188 mg, 0.89 mmol) and the reaction was stirred at room temperature for 1.5 h. Then the reaction was poured into sat. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2. The combined organic layers were dried and the solvent evaporated to afford 375 mg (91%) of crude **15**. ^{1}H NMR δ 7.48 (dd, $J=12.9$, 2.4 Hz, 1H), 7.37–7.44 (m, 5H), 7.09–7.12 (m, 1H), 7.00 (t, $J=8.9$ Hz, 1H), 6.21–6.25 (m, 1H), 5.87 (br t, $J=5.9$ Hz, 1H), 5.15 (s, 2H), 4.70–4.75 (m, 1H), 4.48–4.52 (m, 1H), 3.97–4.11 (m, 3H), 3.62–3.86 (m, 6H), 3.27–3.33 (m, 1H), 2.10 (s, 3H), 1.80–1.89 (m, 4H). MS $[M+Na]^+$ 465. Anal. calcd for $C_{27}H_{31}FN_4O_7/0.25CH_2Cl_2$: C, 58.05; H, 5.63; N, 9.94. Found: C, 58.35; H, 5.75; N, 9.59.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(α-aminoacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (16). A solution of **15** (340 mg, 0.62 mmol) in EtOH (30 mL) was treated with 10% Pd/C (36 mg), followed by hydrogenation at 50 psi overnight. The suspension was filtered through Celite and the filtrate evaporated to afford crude amine. Trituration of the crude solid with $CHCl_3$ yielded **16** as a beige glass (73%); mp 142–146 °C. ^{1}H NMR (DMSO-d_6) δ 8.29 (br t, $J=5.8$ Hz, 1H), 7.53 (dd, $J=13.0$, 2.5 Hz, 1H), 7.17–7.32 (m, 2H), 4.68–4.80 (m, 1H), 4.52–4.73 (m, 1H), 4.10 (t, $J=9.1$

Hz, 1H), 3.92 (s, 2H), 3.71–3.75 (m, 1H), 3.38–3.62 (m, 6H), 1.88 (s, 3H), 1.75–1.87 (m, 4H). MS $[M+H]^+$ 409. Anal. calcd for $C_{19}H_{25}FN_4O_5/0.65CHCl_3$: C, 48.56; H, 5.32; N, 11.53. Found: C, 48.68; H, 5.42; N, 11.21.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(α-methylsulfonylaminoacetyl)-piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (17). To a solution of **16** (340 mg, 0.62 mmol) in CH_2Cl_2 (30 mL) was added NEt_3 (0.23 mL) and methanesulfonyl chloride (0.07 mL, 0.90 mmol) and the reaction stirred at room temperature for 18 h. The reaction was poured into sat. $NaHCO_3$ (50 mL), extracted with CH_2Cl_2, washed with H_2O, dried and the solvent removed. Chromatography (5% MeOH/CH_2Cl_2) yielded 109 mg (32%) of **17** as a white foam; mp 78–82 °C. ^{1}H NMR δ 7.49 (dd, $J=13.0$, 2.6 Hz, 1H), 7.07–7.10 (m, 1H), 7.00 (t, $J=8.8$ Hz, 1H), 5.94 (br s, 1H), 5.34 (br s, 1H), 4.75–4.82 (m, 1H), 4.43–4.52 (m, 1H), 3.99–4.06 (m, 3H), 3.61–3.78 (m, 6H), 3.38–3.41 (m, 1H), 2.98 (s, 3H), 2.03 (s, 3H), 1.85–1.93 (m, 4H). MS $[M+H]^+$ 487. Anal. calcd for $C_{20}H_{27}FN_4O_7S/0.1H_2O$: C, 49.19; H, 5.61; N, 11.47. Found: C, 48.98; H, 5.39; N, 11.09.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(α-*N*-acetylaminoacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (18). To a solution of *N*-acetylglycine (74 mg, 0.63 mmol) in CH_2Cl_2 (10 mL) was added EDCI (125 mg, 0.65 mmol) and the reaction stirred at room temperature for 2 h. Then a solution of **9** (304 mg, 0.65 mmol) and NEt_3 (0.15 mL, 1.07 mmol) in CH_2Cl_2 (10 mL) was added and the reaction stirred at room temperature for 3 h. The reaction was poured into H_2O (10 mL) and extracted with CH_2Cl_2. The combined organic layers were dried and the solvent evaporated to yield the crude product. Chromatography (5% MeOH/CH_2Cl_2) yielded 161 mg (57%) of **18** as a white foam; mp 66–68 °C. ^{1}H NMR δ 7.47 (dd, $J=13.0$, 2.6 Hz, 1H), 7.08–7.10 (m, 1H), 6.99 (t, $J=8.8$ Hz, 1H), 6.61 (br s, 1H), 5.98 (br t, $J=6.0$ Hz, 1H), 4.71–4.79 (m, 1H), 4.49–4.52 (m, 1H), 4.06–4.15 (m, 2H), 4.03 (t, $J=9.0$ Hz, 1H), 3.58–3.78 (m, 6H), 3.36–3.45 (m, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 1.84–1.90 (m, 4H). MS $[M+H]^+$ 451. Anal. calcd for $C_{21}H_{27}FN_4O_6/0.3CH_2Cl_2$: C, 53.75; H, 5.85; N, 11.77. Found: C, 53.85; H, 5.96; N, 11.62.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(2-thienylcarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (19). This was prepared according to the procedure for **10** utilizing thiophene-2-carbonyl chloride instead of benzyloxyacetyl chloride. Pure **19** was isolated as a beige foam (63%); mp 48–51 °C. ^{1}H NMR δ 7.44–7.51 (m, 2H), 7.28–7.31 (m, 1H), 6.98–7.07 (m, 3H), 6.11 (br t, $J=6.0$ Hz, 1H), 4.74–4.79 (m, 1H), 4.49–4.53 (m, 1H), 4.03 (t, $J=9.0$ Hz, 1H), 3.56–3.95 (m, 6H), 2.88–3.09 (m, 1H), 2.03 (s, 3H), 1.86–1.97 (m, 4H). MS $[M+H]^+$ 462. Anal. calcd for $C_{22}H_{24}FN_3O_5S$: C, 57.26; H, 5.24; N, 9.10. Found: C, 57.23; H, 5.24; N, 8.78.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(2-furoyl)piperdinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (20). This was prepared according to the procedure for **10** utilizing 2-furoyl chloride instead of benzyloxyacetyl chloride. Trituration with warm ether afforded **20** as a white solid (81%); mp 134–136 °C. ^{1}H NMR δ 7.45–7.51 (m, 2H), 6.98–7.09 (m, 3H), 6.48 (dd, $J=3.5$, 1.8 Hz, 1H), 6.20 (t, $J=6.1$ Hz, 1H), 4.74–4.82 (m, 1H), 4.50–4.55 (m, 1H), 4.03 (t, $J=8.9$ Hz, 1H), 3.57–3.94 (m, 7H), 2.03 (s, 3H), 1.82–1.93 (m, 4H). MS $[M+H]^+$ 446. Anal. calcd for $C_{22}H_{24}FN_3O_6$: C, 59.32; H, 5.43; N, 9.42. Found: C, 59.17; H, 5.29; N, 9.35.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(5-isoxazolylcarbonyl)piperdinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (21). This was prepared according to the procedure for **10** utilizing isoxazole-5-carbonyl chloride instead of benzyloxyacetyl chloride. Chromatography with 5% MeOH/CH_2Cl_2 afforded **21** as a white foam (65%). ^{1}H NMR δ 8.31 (d, $J=1.8$ Hz, 1H), 7.49 (dd, $J=12.9$, 2.6 Hz, 1H), 7.08–7.12 (m, 1H), 7.01 (t, $J=8.8$ Hz, 1H), 6.77 (d, $J=1.8$ Hz, 1H), 6.04 (t, $J=6.0$ Hz, 1H), 4.73–4.81 (m, 1H), 4.52–4.57 (m, 1H), 4.03 (t, $J=9.0$ Hz, 1H), 3.56–3.95 (m, 7H), 2.03 (s, 3H), 1.75–2.00 (m, 4H). MS $[M+H]^+$ 447. Anal. calcd for $C_{21}H_{23}FN_4O_6$: C, 56.50; H, 5.19; N, 12.55. Found: C, 56.13; H, 5.05; N, 12.61.

(*S*)-*N*-[3-[3-Fluoro-4-{*N*-(2-pyridoyl)piperidinyl-4-oxy}-phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide (22). This was prepared according to the procedure for **10** utilizing picolinoyl chloride instead of benzyloxyacetyl chloride. Isolated as an off-white solid, 190 mg (69%); mp 55–58 °C. ^{1}H NMR δ 8.59 (d, $J=4.8$ Hz, 1H), 7.81 (t, $J=7.5$ Hz, 1H), 7.64 (d, $J=7.5$ Hz, 1H), 7.48 (dd, $J=12.9$, 2.5 Hz, 1H), 7.35 (dd, $J=7.1$, 5.5 Hz, 1H), 7.06–7.11 (m, 1H), 7.01 (t, $J=8.8$ Hz, 1H), 6.02 (br t, 1H), 4.72–4.77 (m, 1H), 4.50–4.55 (m, 1H), 4.03 (t, $J=8.8$ Hz, 1H), 3.50–3.99 (m, 7H), 2.03 (s, 3H), 1.80–1.98 (m, 4H). MS $[M+H]^+$ 457. Anal. calcd for $C_{23}H_{25}FN_4O_5/0.2CH_2Cl_2$: C, 58.86; H, 5.41; N, 11.83. Found: C, 59.03; H, 5.59; N, 11.47.

(*S*)-*N*-[3-Fluoro-[4-{*N*-(pyridin-2-ylmethoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (23). This was prepared via the α-chloroacetamide. (*S*)-*N*-[3-[4-{*N*-(Chloroacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide, prepared according to the procedure of **10**, was isolated as a viscous oil. To NaH (60% in oil; 117 mg; 2.93 mmol) in anhydrous THF (5 mL) at 0 °C, was added dropwise pyridine-2-methanol (0.24 mL, 2.47 mmol) in THF (5 mL). After stirring for 15 min, chloroacetamide (523 mg, 1.22 mmol) in anh THF (5 mL) was added in one portion. The reaction was warmed to room temperature and stirred for 72 h. The reaction was poured into water (50 mL) and extracted CH_2Cl_2 (3×75 mL). The combined organic layers were dried and evaporated. Purification by chromatography (5% MeOH/CH_2Cl_2) yielded 403 mg (59%) of **23** as a yellow semi-solid. ^{1}H NMR δ 8.54 (d, $J=4.2$ Hz, 1H), 7.72 (t, $J=7.7$ Hz, 1H), 7.45–7.49 (m, 2H), 7.21 (t, $J=6.1$ Hz, 1H), 7.07–7.10 (m, 1H), 7.00 (t, $J=8.8$ Hz, 1H), 6.01 (br t, $J=5.8$ Hz, 1H), 4.75–4.78 (m, 1H), 4.73 (s, 2H), 4.44–4.48 (m, 1H), 4.31 (s, 2H), 4.02 (t, $J=8.9$ Hz, 1H), 3.58–3.79 (m, 6H), 3.42–3.45 (m, 1H), 2.03 (s, 3H), 1.85–1.90 (m, 4H). MS $[M+H]^+$ 501. Anal. calcd for $C_{25}H_{29}FN_4O_6/0.7CH_2Cl_2$: C, 55.12; H, 5.47; N, 10.01. Found: C, 55.17; H, 5.67; N, 10.21.

(*S*)-*N*-[3-Fluoro-[4-{*N*-(pyridin-3-ylmethoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (24). This was prepared according to the procedure for **23** utilizing pyridine-3-methanol instead of pyridine-2-methanol. Chromatography with 3% MeOH/CH_2Cl_2 afforded **24** as a clear glass (43%). ^{1}H NMR δ 8.56–8.60 (m, 2H), 7.73 (d, J = 7.8 Hz, 1H), 7.47 (dd, J = 13.0, 2.6 Hz, 1H), 7.30 (dd, J = 7.8, 5.1 Hz, 1H), 7.08 (dd, J = 8.9, 1.6 Hz, 1H), 6.99 (t, J = 8.9 Hz, 1H), 6.02 (t, J = 6.2 Hz, 1H), 4.70–4.78 (m, 1H), 4.64 (s, 2H), 4.43–4.47 (m, 1H), 4.24 (s, 2H), 4.02 (t, J = 8.9 Hz, 1H), 3.57–3.78 (m, 6H), 3.35–3.45 (m, 1H), 2.02 (s, 3H), 1.80–1.96 (m, 4H). MS $[M+H]^+$ 501. Anal. calcd for $C_{25}H_{29}FN_4O_6/0.25CH_2Cl_2$: C, 58.13; H, 5.70; N, 10.74. Found: C, 58.24; H, 5.73; N, 11.04.

(*S*)-*N*-[3-Fluoro[4-{*N*-(pyridin-4-ylmethoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (25). This was prepared according to the procedure for **23** utilizing pyridine-4-methanol instead of pyridine-2-methanol. Chromatography using 5% MeOH/CH_2Cl_2, afforded **25** as a white foam (63%). ^{1}H NMR ($CDCl_3$) δ 8.59 (d, J = 5.9 Hz, 2H), 7.47 (dd, J = 12.9, 2.6 Hz, 1H), 7.28 (d, J = 5.9 Hz, 2H), 7.07–7.11 (m, 1H), 6.99 (t, J = 8.8 Hz, 1H), 5.91–5.94 (m, 1H), 4.72–4.79 (m, 1H), 4.65 (s, 2H), 4.45–4.49 (m, 1H), 4.26 (s, 2H), 4.02 (t, J = 8.9 Hz, 1H), 3.40–3.78 (m, 7H), 2.02 (s, 3H), 1.85–1.95 (m, 4H). MS $[M+H]^+$ 501. Anal. calcd for $C_{25}H_{29}FN_4O_6/0.25CH_2Cl_2$: C, 58.13; H, 5.70; N, 10.74. Found: C, 57.92; H, 5.61; N, 10.96.

Bacterial strains

A set of nine strains was used as the primary screening panel: *S. aureus* OC 4172 (Smith strain) and ATCC 29213, are methicillin susceptible; OC 2878 and OC 3726 (COL strain) are methicillin resistant (MRSA); *E. faecalis* ATCC 29212 and *E. faecium* OC 3312 are susceptible and resistant to vancomycin, respectively; *E. coli* OC 2605 (strain KL16) and OC 2530 (LPS-defective); *Pseudomonas aeruginosa* ATCC 27853. Other strains used herein were clinical isolates from the Johnson and Johnson Pharmaceutical Research and Development, LLC culture collection.

Microbiological methods

Broth microdilution MIC (lowest concentration of compound inhibiting visible growth) determinations were performed according to National Committee for Clinical Laboratory Standards methods.[9]

Mouse protection assay

In vivo efficacy was assessed in a murine septicemia model of infection caused by *S. aureus* Smith. Female Swiss–Webster mice were infected ip with approximately 6×10^5 CFU/mL of the challenging strain. Protecting compounds were administered subcutaneously in 40% hydroxypropyl-β-cyclodextrin at 1 and 3 h after infection. The dose allowing survival of 50% of the animals (ED_{50}) was calculated using the Logistic routine of the SAS suite of statistical programs.

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