

Letter

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Structure-Activity Relationship for the Oxadiazole Class of Antibacterials

Marc A. Boudreau[†], Derong Ding[†], Jayda E. Meisel[†], Jeshina Janardhanan[†], Edward Spink[†], Zhihong Peng[†], Yuanyuan Qian[†], Takao Yamaguchi[†], Sebastian A. Testero[†], Peter I. O'Daniel[†], Erika Leemans[†], Elena Lastochkin[†], Wei Song[†], Valerie A. Schroeder[‡], William R. Wolter[‡], Mark A. Suckow[‡], Shahriar Mobashery^{†*}, and Mayland Chang^{†*}

[†]Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN 46556

[‡]Freimann Life Sciences Center and Department of Biological Sciences, University of Notre Dame, Notre Dame, IN 46556

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ABSTRACT: A structure-activity relationship (SAR) for the oxadiazole class of antibacterials was evaluated by syntheses of 72 analogs and determination of the minimal-inhibitory concentrations (MICs) against the ESKAPE panel of bacteria. Selected compounds were further evaluated for *in vitro* toxicity, plasma protein binding, pharmacokinetics (PK), and a mouse model of methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Oxadiazole **72c** showed potent *in vitro* antibacterial activity, exhibits low clearance, a high volume of distribution, 41% oral bioavailability, and shows efficacy in mouse models of MRSA infection.

Antibiotics have been called miracle drugs. Not only have they saved millions of lives in treatment of infections, they have also made possible other medical interventions such as surgery, dialysis, and organ transplantation. The availability of antibiotics has contributed to the increase in life expectancy in the United States from 59.7 years in 1930 to 78.8 years in 2010.¹ Notwithstanding, emergence of resistance to any antibiotic is inevitable, threatening viability of any given class of such agents. Among Gram-positive bacteria, resistant *Staphylococcus aureus* and Enterococci pose the biggest threat.² *S. aureus* is a leading cause of health-related infections. Every year in the United States more than 80,000 severe methicillin-resistant *S. aureus* (MRSA) infections occur, resulting in 11,285 annual deaths.³ Enterococci cause infections, including endocarditis, urinary-tract infections, and wound infections. Over 66,000 Enterococcus infections are reported every year in the United States, of which 20,000 are vancomycin-resistant Enterococcus (VRE), resulting in 1,300 deaths.³ The limited pipeline of new antibiotics has exacerbated the antibiotic-resistance crisis.

The oxadiazoles are a newly discovered class of non- β -lactam antibiotics targeting cell-wall biosynthesis.⁴ These antibiotics show potent bactericidal activity against difficult-to-treat Gram-positive bacteria, including MRSA and VRE. They do not have Gram-negative antibacterial activity. Our initial studies into this class of antibiotics produced lead compounds **1** – **3**, of which **2** and **3** exhibit 100% oral bioavailability and *in vivo* efficacy.⁴ Further studies on compound **2** suggested inhibition of the penicillin-binding proteins (PBPs) of *S. aureus*, which are responsible for bacterial cell-wall biosynthesis.⁴

With a view to explore the structural space of this class of antibiotics, we recently reported a structure-activity relationship (SAR) of the oxadiazoles against *S. aureus*⁵ with a focus on modifications in ring A. We found that 4-phenol, 4-chloropyrazole, or 5-indole substitutions were generally favored at this position (**1**, **2**, and **4**–**8**; Figure 1). These compounds exhibit minimal-inhibitory concentration (MIC) values against *S. aureus* ranging from 0.5 to 4 μ g/mL. Furthermore, antibiotic **8** gave excellent efficacy in MRSA-infected mice comparable to results obtained with linezolid, the gold standard, and exhibited oral bioavailability and low toxicity.^{5–6}

We report herein the synthesis and SAR results against *S. aureus* of 72 synthetic oxadiazoles with modifications in ring D (see Figure 1 for ring designations). To enable a comparison to our previously reported active compounds, we have limited our discussion in this report to compounds with the aforementioned ring A modifications. The SAR was established by initial screening of the synthetic derivatives against the ESKAPE panel of bacteria. This panel is comprised of *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter sp.*, and *Escherichia coli*. These bacteria account for the majority of problematic human infections.⁷ Selected compounds were further evaluated for *in vitro* toxicity, plasma protein binding, pharmacokinetics (PK), and in mouse models of MRSA infection.

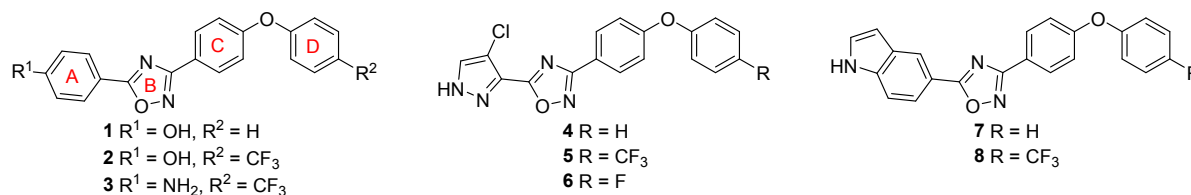
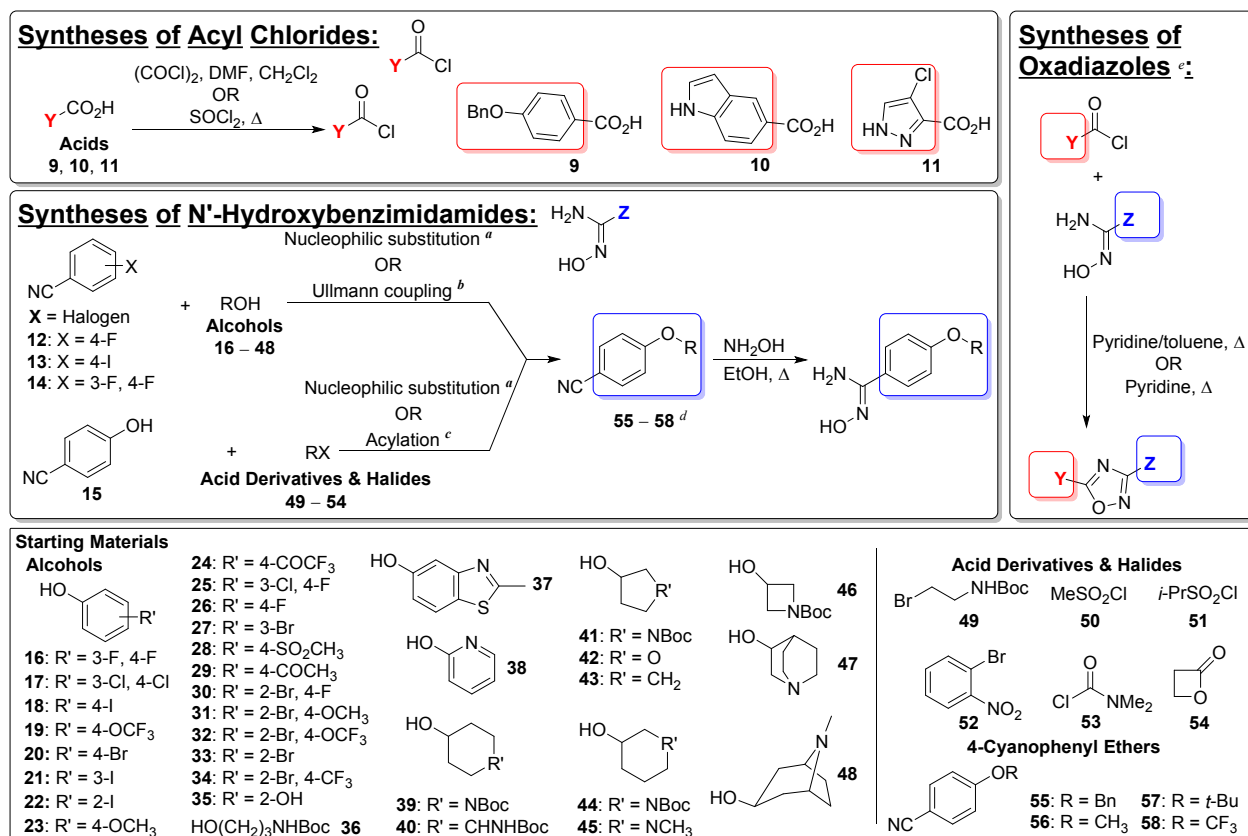
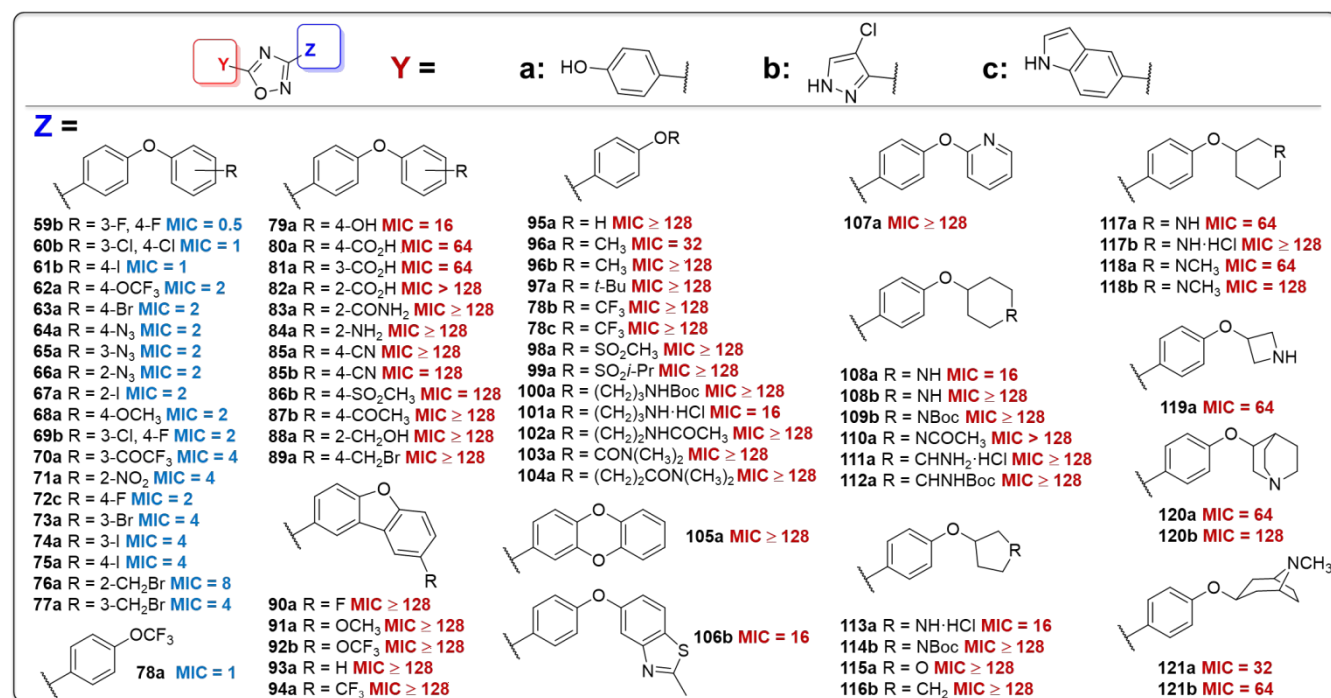


Figure 1. Structures of oxadiazoles active against *S. aureus***Figure 2.** General synthetic routes to access the 1,2,4-oxadiazoles, and the starting materials used for variations within ring D. ^aNucleophilic substitution: NaH/K₂CO₃, DMSO/DMF, 60 – 100 °C, overnight; ^bUllmann coupling: CuI, Cs₂CO₃, *N,N*-dimethylglycine·HCl, 1,4-dioxane, 90 °C, 2 – 5 h; ^cAcylation: anhydrous pyridine, 0 °C to rt, 4 – 6 h; ^dOutliers like dibenzo[*b,d*]furan and dibenzo[*b,e*][1,4]dioxine are not listed for simplicity of the graph. Compounds **55 – 58** are 4-cyanophenyl ethers purchased commercially; ^eAdditional modifications are listed in Supporting Information.**Figure 3.** Antibacterial activities of the synthetic 1,2,4-oxadiazole derivatives with modifications of ring D. The MIC values (in μg/mL) measured for *S. aureus* ATCC 29213, with MIC of active compounds denoted in blue (MIC ≤ 8 μg/mL) and inactive ones in red (MIC > 8 μg/mL).

The general synthetic routes to the oxadiazoles have been described previously.⁴⁻⁵ The same approach was used to access the analogs reported herein, except our focus was on modification of ring D, which necessitated diversification of the structures at the stage of the diphenyl ether construction. This was achieved either by direct nucleophilic substitution and Ullmann coupling reactions of nitriles **12–14** or direct nucleophilic substitution and acylation of 4-hydroxybenzonitrile **15** (Figure 2). In many cases, ring D variations could be introduced by using commercially available substituted phenols (**16–48**), carboxylic acid derivatives (**50, 51, 53** and **54**) or halides (**49** and **52**). The substituents of several of these analogs could be used as synthetic handles for further elaboration, the reactions of which are described in the Supporting Information. In some cases where ring D was replaced by non-annular substituents, the requisite ethers were purchased (**55–58**).

We established the SAR for the oxadiazoles by screening them for antibacterial activity against the aforementioned ESKAPE panel of bacteria. The analogs reported herein show activity against Gram-positive bacteria. We specifically focused our attention on the analogs that exhibited activity against *S. aureus* (Figure 3).

In general, hydrophobic substituents, and especially halogens, were well-tolerated in ring D. Addition of an extra fluorine (**59b**) or chlorine (**69b**) at the 3-position retained activity in the 4-chloropyrazole series, as did substitution by two chlorines at these same positions (**60b**). Replacement of the fluorine by an iodine, either at position 4 (**61b, 75a**), position 3 (**74a**), or position 2 (**67a**) also retained activity overall. The same trend was observed with introduction of a bromine atom at position 4 (**63a**) or position 3 (**73a**). Introduction of a trifluoromethoxy or methoxy group at position 4 of the ring (**62a, 68a**) also retained activity, as did the presence of a 3-trifluoromethyl ketone substituent (**70a**). An azide group at any position of the ring also maintained a favorable MIC against *S. aureus* (**64a, 65a, 66a**). Interestingly, a benzylic bromide at position 2 (**76a**) or position 3 (**77a**) of the ring did not result in a noticeable increase in MIC, but introduction of this substituent at position 4 (**89a**) completely abolished activity.

We also explored the effect of tethering rings C and D at their respective 2-positions to form a dibenzofuran, and we found that the resulting compounds where ring A was a phenol were inactive when ring D was unsubstituted (**93a**) or substituted with a 4-trifluoromethyl group (**94a**), 4-fluoro (**90a**), 4-methoxy (**91a**), or 4-trifluoromethoxy (**92b**). Likewise, expanding the furan portion with a heteroatom to form dibenzodioxine **105a** resulted in loss of activity.

Replacing ring D with linear alkyl substituents resulted in only one active compound, the trifluoromethoxy derivative **78a**, which contains a phenol for ring A. However, changing ring A to a 4-chloropyrazole (**78b**) or an indole (**78c**) resulted in loss of activity. The reasons for this are not clear at present. Other alkyl substituents introduced as surrogates for ring D, such as methyl (**96a, 96b**) and *tert*-butyl (**97a**) gave compounds with poor activity, as did sulfonates (**98a, 99a**), alkylcarbamates (**100a**) and amines (**101a**), and amides (**102a, 103a, 104a**).

We observed that introducing partially or fully saturated systems at ring D gave compounds with good activity in a few cases. Introduction of a nitrogen atom to give 3-pyrrolidines **113a** and **114b**, or of an oxygen atom to give 3-tetrahydrofuran **115a**, decreased or abolished the activity. As a general trend, introduction of hydrogen-bond-donating substituents at ring D resulted in compounds with decreased antimicrobial activity

against *S. aureus*. Thus, the 4-phenol derivative **79a** was only modestly active (MIC = 16 µg/mL), and 2-benzyl alcohol **88a** exhibited no activity. Similarly, benzoic acid derivatives **80a, 81a**, and **82a** were either poorly active or inactive, and 2-carboxamide **83a** and 2-aniline **84a** were inactive. Introduction of polar substituents onto an aliphatic system also resulted in compounds with no activity, as observed with 4-aminocyclohexane derivatives **111a**, and **112a**. Electron-withdrawing substituents introduced onto ring D also resulted in compounds with no activity, as evidenced by 4-benzonitriles **85a** and **85b**, as well as 4-methylsulfonate **86b** and 4-acetate **87b**. One exception is 2-nitro derivative **71a**, which had an MIC of 4 µg/mL against *S. aureus*.

Replacement of the phenyl ring at position D with heteroaromatic systems was also detrimental to activity. Thus, benzothiazole derivative **106b** was modestly active (MIC = 16 µg/mL), while pyridine derivative **107a** was inactive (MIC >128 µg/mL). We observed a similar trend with heteroaliphatic ring systems, such as 4-piperidines (**108a, 108b, 109b, 110a**), 3-piperidines (**117a, 117b, 118a, 118b**), 3-azetidines (**119a**), as well as the pyrrolidines and tetrahydrofuran discussed above. Finally, we introduced more complex aliphatic amine-containing ring systems, giving quinuclidine derivatives **120a** and **120b** and tropine derivatives **121a** and **121b**, however, these exhibited poor activity against *S. aureus* (MIC ≥32 µg/mL).

Compounds **59b, 60b, 61b, 62a, 69b, 78a**, and **72c** were selected and further evaluated for *in vitro* toxicity using the XTT assay with HepG2 cells and hemolysis of red blood cells (Table 1). Compound **78a**, in which the ring D was replaced with trifluoromethoxy caused 16% hemolysis at a concentration of 64 µg/mL; no further studies were done with this compound. Plasma protein binding was between 90% to 99%. Although high, it is within the range for 43% of the 1500 most frequently prescribed drugs,⁸ including many antibiotics on the market such as daptomycin, oxacillin, teicoplanin, rifampicin, and clindamycin.⁹⁻¹² Compounds **59b, 60b, 61b, 62a**, and **69b** showed >1% hemolysis or < 35 for the ratio of XTT/MIC and were not studied further.

Table 1. *In vitro* evaluation of oxadiazoles

	MIC µg/mL	Human plasma protein binding %	XTT IC ₅₀ (µg/mL)	Hemolysis %
8a	2	98.2 ± 3.2	75.7 ± 7.3	<1
59b	0.5	98.9 ± 1.6	17.7 ± 1.0	1.3
60b	1	97.8 ± 0.3	17.2 ± 1.0	1.8
61b	1	90.5 ± 0.3	30.7 ± 0.8	3.1
62a	2	99.8 ± 0.1	16.9 ± 0.9	2.1
69b	2	91.2 ± 0.6	21.0 ± 0.9	2.9
78a	1	ND	84.9 ± 0.9	16
72c	1	98.8 ± 0.7	37.0 ± 0.9	<1

^aData from Spink *et al.*, reproduced for comparison

Compound **72c** was evaluated in a broader panel of Gram-positive bacteria and compared to the previous lead oxadiazole **8** and the standards vancomycin and linezolid (Table 2). Oxadiazole **72c** showed better activity against MRSA strains

NRS70, VRS1, and VRS2, and *S. haemolyticus*, *B. cereus*, *B. licheniformis*, and *E. faecalis* ATCC 29212 than oxadiazole **8**.

Table 2. Activity of oxadiazoles against Gram-positive organisms. MIC in $\mu\text{g/mL}$.

Organism	72c	8	vancomycin	linezolid
<i>S. aureus</i> ATCC 29213 ^a	1 – 2	4	1	2
<i>S. aureus</i> ATCC 27660 ^b	2 – 4	4	2	1
<i>S. aureus</i> N315 (NRS70) ^b	1	2	1	1
<i>S. aureus</i> NRS100 (COL) ^b	2	2	2	1
<i>S. aureus</i> NRS119 ^c	1 – 2	2	1	32
<i>S. aureus</i> NRS120 ^c	2	2	1	32
<i>S. aureus</i> VRS1 ^d	1	2	64	1
<i>S. aureus</i> VRS2 ^e	1	2	32	1
<i>S. epidermidis</i> ATCC 35547	1	2	4	0.5
<i>S. haemolyticus</i> ATCC 29970	2	4 – 8	4	1
<i>B. cereus</i> ATCC 13061	4	16	1	0.5
<i>B. licheniformis</i> ATCC 12759	2	8	0.5	0.5
<i>E. faecalis</i> ATCC 29212 ^a	4	8	2	1
<i>E. faecalis</i> 201 (Van S) ^f	4	4	1	1
<i>E. faecalis</i> 99 (Van R) ^g	4	4	128	1
<i>E. faecium</i> 119-39A (Van S) ^f	1	1	0.5	1
<i>E. faecium</i> 106 (Van R) ^g	1	2	128	1
<i>E. faecium</i> NCTC 7171	1	2	0.5	1

^aA quality-control strain to monitor accuracy of MIC testing; ^b*mecA* positive, resistant to methicillin, oxacillin, and tetracycline; susceptible to vancomycin and linezolid; ^c*mecA* positive, resistant to ciprofloxacin, gentamicin, oxacillin, penicillin, and linezolid; ^dvancomycin-resistant MRSA (*vanA*) clinical isolate from Michigan; ^evancomycin-resistant MRSA (*vanA*) clinical isolate from Pennsylvania; ^fvancomycin-susceptible clinical isolate; ^gvancomycin-resistant clinical isolate.

A PK study was conducted with **72c** after intravenous (iv) and oral (po) administration (Figure 4). Oxadiazole **72c** had low clearance of 7.8 mL/min/kg, a large volume of distribution of 14.2 L/kg, and a long terminal half-life of 21.1 h after iv administration (Table 3). Maximum concentration of 1.0 $\mu\text{g/mL}$ was achieved at 2.5 h and oral bioavailability was 41%. Systemic exposure and oral bioavailability for **72c** were generally lower than the corresponding parameters for oxadiazole **8**. In addition, the half-life for distribution after iv administration for oxadiazole **8** was shorter than that for **72c**.

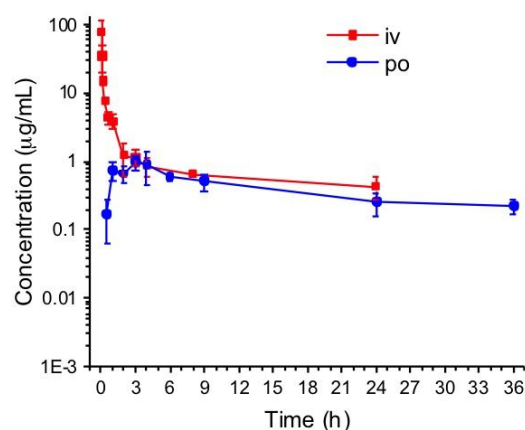


Figure 4. Pharmacokinetics of **72c** after single iv and po administration at 20 mg/kg to mice (n=3 mice per time point).

Table 3. Pharmacokinetic parameters of **72c** in mice

	72c	8 ^a
Dose 20 mg/kg iv		
AUC _{0–last}	1790	3140
($\mu\text{M}\cdot\text{min/mL}$)		
AUC _{0–∞} ($\mu\text{M}\cdot\text{min/mL}$)	2570	3520
CL (mL/min/kg)	7.8	5.7
V _d (L/kg)	14.2	4.7
t _{1/2} dist (h)	0.4	0.009
t _{1/2} elim (h)	21.1	9.6
Dose 20 mg/kg po		
AUC _{0–last}	718	3060
($\mu\text{M}\cdot\text{min/mL}$)		
AUC _{0–∞} ($\mu\text{M}\cdot\text{min/mL}$)	1040	4060
C _{max} ($\mu\text{g/mL}$)	1.0	2.3
T _{max} (h)	2.5	6
t _{1/2} abs (h)	1.3	0.8
t _{1/2} dist (h)	6.2	15.9
t _{1/2} elim (h)	17.0	18.6
F (%)	41	97

^aData from Spink *et al.*, reproduced for comparison

Oxadiazole **72c** was evaluated in the mouse peritonitis MRSA model of infection. The compound showed efficacy, with half of the mice surviving after two 20 mg/kg doses of the compound given iv at 30 min and 7.5 h after infection. Compound **72c** was further evaluated in a mouse neutropenic thigh MRSA infection model using linezolid-sensitive (NRS70) and linezolid-resistant (NRS119) MRSA strains (Figure 5). The efficacy of **72c** after a single oral dose at 40 mg/kg was comparable to that of compound **8**, with 1.1-log and 1.5-log reduction in bacterial count compared to vehicle in the NRS70

and NRS119 strains, respectively. In the NRS119 study, bacterial counts after treatment with **72c** and **8** were significantly lower ($p < 0.05$) than in the linezolid group. Drug concentrations at 48 h after a single oral 40 mg/kg dose of compound **8** were $7.6 \pm 2.3 \mu\text{g/g}$ and $6.0 \pm 1.2 \mu\text{g/g}$ in the NRS70 and NRS119 uninfected thighs, respectively (Table S5), which corresponded to 3- to 4-fold above MIC. Likewise, levels of compound **72c** were $5.8 \pm 1.4 \mu\text{g/g}$ and $6.4 \pm 1.3 \mu\text{g/g}$ in the NRS70 and NRS119 uninfected thighs, respectively (Table S5), 6-fold above MIC. The levels of linezolid had dropped significantly and could not be quantified in the uninfected thighs. In summary, **72c** showed potent *in vitro* activity against MRSA, oral bioavailability, and efficacy in mouse models of MRSA infection.

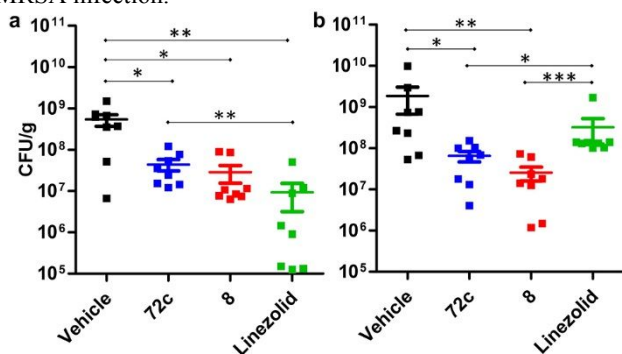


Figure 5. Efficacy of **72c** in a mouse neutropenic thigh MRSA infection model using (a) NRS70 (linezolid-sensitive) and (b) NRS119 (linezolid-resistant). Mice ($n = 8$ per group) were made neutropenic by administration of cyclophosphamide. Bacteria (10^5 cfu) were injected intramuscularly into the right thigh. A single 40 mg/kg oral dose of vehicle, **72c**, **8**, or linezolid was given 1 h after infection. The thighs were harvested 48 h after infection, homogenized, and plated for colony counts. Mean \pm SEM, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ by Mann-Whitney U test two-paired.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and experimental are supplied as Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

* Shahriar Mobashery (mobashery@nd.edu) or Mayland Chang (mchang@nd.edu)

Author Contributions

MAB, DD, ES, TY, SAT, PIO, and EL synthesized compounds. YQ conducted some of the MS and NMR work and helped in preparing the manuscript. JEM, ZP, and WS conducted plasma protein binding and PK. JEM determined drug concentrations in plasma and thighs in the mouse neutropenic thigh infection study. JJ conducted the mouse peritonitis and mouse neutropenic thigh infection studies and MIC against Gram-positive organisms. E. Lastochkin conducted MIC against the ESKAPE organisms and *in vitro* cytotoxicity. VAS, WRW, and MAS conducted the in-life portion of mouse peritonitis and PK studies. SM and MC designed the studies and wrote the manuscript, with contributions of all authors. All authors have given approval to the final version of the manuscript.

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ABBREVIATIONS

AUC, area-under-the curve; iv, intravenous; MIC, minimal-inhibitory concentration; MRSA, methicillin resistant *Staphylococcus aureus*; PK, pharmacokinetics; po, per os; SAR, structure-activity relationship; VRE, vancomycin-resistant Enterococci.

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