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Novel monobactams utilizing a siderophore uptake mechanism for the treatment of gram-negative infections

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ABSTRACT

Novel siderophore-linked monobactams with in vitro and in vivo anti-microbial activity against MDR Gram-negative pathogens are described.

Multidrug resistance (MDR) to antibacterial agents, particularly among Gram-negative pathogens, represents a serious and growing threat to human health.[1] Simultaneously, we are approaching a crisis with regard to the development of new antibiotics, so continued research in the area is desperately needed.[1,2] We recently disclosed a series of novel antibacterial compounds incorporating a monocarbam nucleus conjugated to a siderophore moiety, including MC-1 (**1**, Fig. 1) and its 4-methyl analog (**2**).[3] Other researchers have also recently described compelling work in the area of siderophore-conjugated β-lactams, most particularly with BAL19764[4] and BAL30072[5] (**3**). Herein, we report additional efforts targeting MDR Gram-negative pathogens with a series of novel siderophore-conjugated monobactams, represented generically by **4**. This work has culminated in the identification of numerous analogs with potent MIC_{90} values against three clinically important pathogens, *Pseudomonas aeruginosa* (*P. aer.*), *Klebsiella pneumoniae* (*K. pneumo.*), and *Escherichia coli* (*E. coli*).

Gram-negative microorganisms have evolved a series of resistance mechanisms which limit the utility of currently available therapies.[6] These mechanisms include barriers to drug penetration, active efflux of compounds via a plethora of transporters, and enzymes such as β−lactamases which catalyze the degradation of certain therapies. New medicines capable of overcoming or circumventing these resistance mechanisms will prove useful in the treatment of infections from MDR pathogens.[7] Bacteria rely on the acquisition of certain nutrients from the host in order to survive and have developed specialized mechanisms to facilitate these processes. Among the most intriguing are mechanisms for iron acquisition,[8] in which bacteria manufacture and secrete iron

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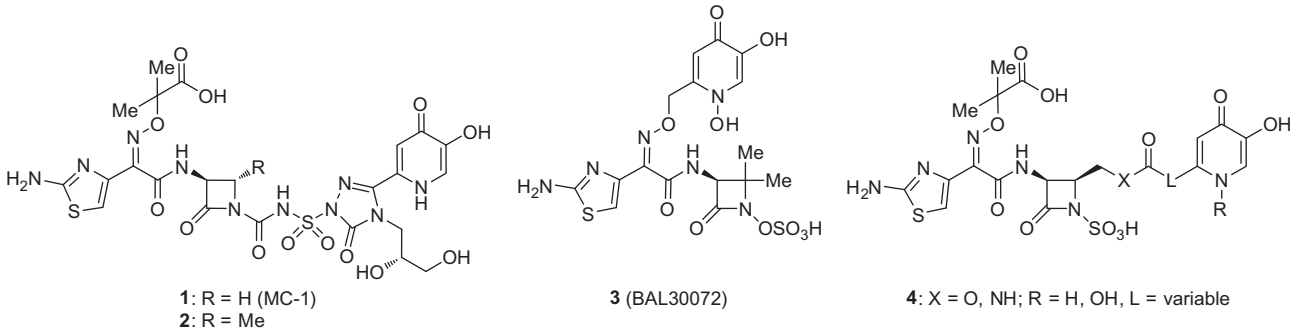


Figure 1. Siderophore-conjugated monocyclic β-lactams.

chelators known as siderophores.[8,9] The organisms then utilize specialized transport systems for the reuptake of these siderophores and subsequently utilize the acquired iron. Conjugation of siderophore mimics to drugs such as β-lactams enables active delivery of the antibacterial moiety to the bacteria by exploiting the siderophore transport system, effectively a 'Trojan Horse' approach.[10,11]

Our efforts with monocarbams such as **1** capitalized effectively on this strategy to deliver highly potent agents with promising Gram-negative spectrum,[3] remarkable stability to β-lactamases,[12] and in vivo efficacy in murine models of infection. One potential limitation of monocarbams such as **1**, however, is their sensitivity to aqueous hydrolysis. This issue is not unique to monocarbams. For example, the carbapenem meropenem exhibited similar stability issues in our hands.[3] The enhanced stability shown by compounds such as the 4-methyl analog **2**[3] led us to consider investigation of siderophore linkage to the 4-position of the β-lactam. Structural biology efforts (*vide infra*) also suggested an opportunity for productive exploration of SAR via this strategy, and we sought to develop robust synthetic chemistry that would facilitate this understanding. In this light, our interest was piqued by earlier work from Magerlein, who demonstrated that catechol-containing esters such as **5** and **6** (Fig. 2) possessed both in vitro and in vivo activity against the key pathogens of interest.[13,14]

Analogs were tested for minimum inhibitory concentrations (MICs) using a panel of organisms, including both drug-susceptible strains (*P.aer*. 1091-05 is representative) and recent MDR clinical isolates (*P. aer*. 1042-06 is representative). Particularly promising analogs were also evaluated using broader panels of organisms in order to determine MIC_{90} values,[15] (concentration at which visible growth of 90 percent of the strains is inhibited). Screening of **6** in the initial panel revealed sufficiently compelling potency to justify additional work but also revealed poor activity against recent clinical isolates of *P.aer* (Table 1).

Table 1
Minimum inhibitory concentrations (MICs) for sample organisms

Compound	MIC *P. aer.* 1091-05[a] (μg/mL)	MIC *P. aer.* 1042-06[b] (μg/mL)
Aztreonam	2–4	32–64
6	0.5	32
7	1	16
8	1	32
9	0.125	0.5
13	0.25	0.25
14	4	4
15	0.5	1
16	8	32

[a] 1091-05 (UC12120) is a penicillin-resistant, quinolone-sensitive strain courtesy of Bronson Methodist Hospital, Kalamazoo, MI.
[b] 1042-06 is a β-lactam- and quinolone-resistant, polymyxin B-sensitive skin/soft tissue isolate courtesy of the British Society for Antimicrobial Chemotherapy (BSAC).

In some instances, isobutyric acid-substitution of the oxime in place of the acetic acid moiety found in **6** (i.e., $-C(CH_3)_2-$ vs $-CH_2-$) can provide enhanced anti-*Pseudomonal* activity.[16] Compound **7** (Fig. 2) incorporates this strategy but failed to demonstrate any meaningful improvements (Table 1).[17] Catechol derivatives have also been shown to undergo metabolism via catechol O-methyltransferase,[18,19] a liability which can hinder optimization of their pharmacokinetic properties. However, 3-hydroxypyridin-4(1*H*)-one (henceforward referred to as pyridone for simplicity) moieties appear to circumvent this undesired metabolic pathway[18,20] and have been employed successfully as siderophore mimics in compounds such as **1**, U-78608,[21] and pirazmonam (SQ-83,360).[20] Work with cephalosporins also demonstrated the feasibility of

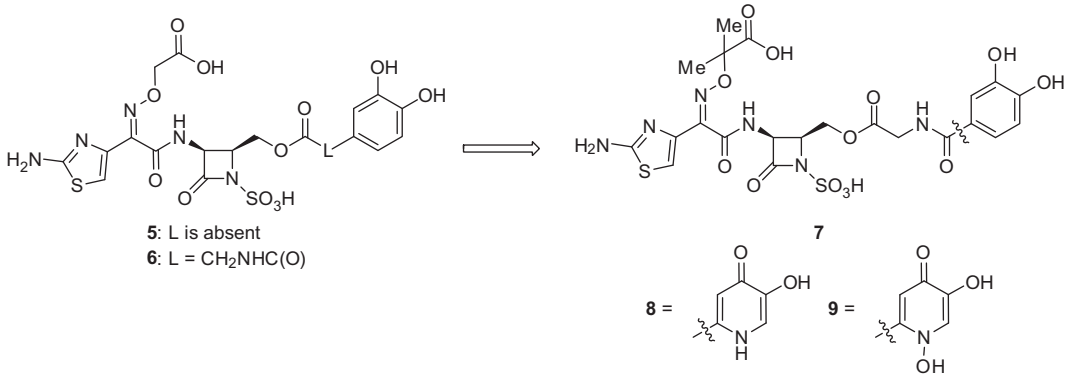


Figure 2. Examples of precedented and novel siderophore-conjugated monobactams.

1,3-dihydroxypyridones (henceforth *N*-hydroxypyridones),[22] and this siderophore mimic has also been employed with BAL19764[4] and BAL30072[5] (**3**). Consequently, we prepared analogs **8** and **9**. Whereas **8** demonstrated comparable activity, while the MICs for **9** represented a surprising breakthrough.

Compound **9** was prepared according to Scheme 1. Acid **10** was reacted with ethyl glycine to give the corresponding amide. Saponification and oxidation of the pyridine with urea hydrogen peroxide (UHP) and trifluoroacetic anhydride provided acid **11**, contaminated with a lesser amount of the unoxidized pyridine. Esterification with the known alcohol **12**,[23] sulfonation[24] and global deprotection with BCl_3 afforded the targeted compound in modest yield. Similar chemistry was employed for related analogs.

Having demonstrated potent antimicrobial activity for **9**, we sought to evaluate progress against two principal design objectives, aqueous stability and utilization of the iron-uptake pathway for bacterial entry. The aqueous stability profile for **9** was similar to the 4-methylated monocarbam **2** and thus helped build our confidence in this strategy (Fig. 3). A mutant organism of *K. pneumo.* with an abrogated TonB[25] system (required for providing the energy for siderophore active uptake) showed substantially poorer MIC values relative to the wild-type strain (unpublished results). A similar observation was made with a strain of *P. aer.* which carried a mutated piuA, a TonB-dependent gene.[26] These results clearly demonstrate a dependence on the siderophore uptake pathway. Profiling **9** against small panels of organisms revealed very

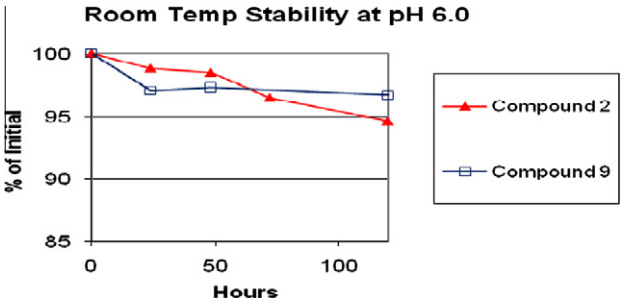
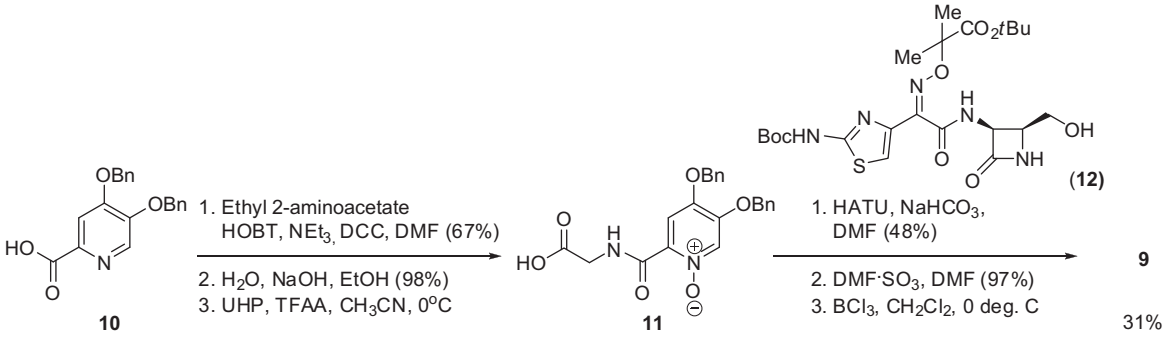
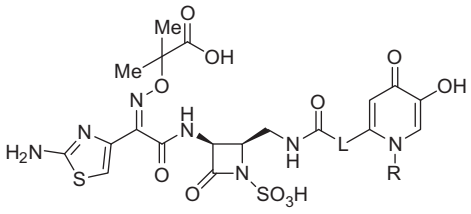


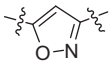
Figure 3. Aqueous stability data at room temperature for compounds **2** and **9**.

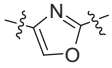


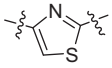
Scheme 1. Synthesis of ester analog **9**.

Table 2
MIC and MIC_{90} data for selected compounds



L =  R = OH (**14**) R = H (**16**)

L =  R = OH (**15**) R = H (**17**)

L =  R = H (**18**)

L = absent R = OH (**19**) R = H (**21**)

Compound	MIC *P. aer.* 1091–05 (μg/mL)	MIC *P. aer.* 1042–06 (μg/mL)	*P. aer.* MIC_{90} (n = 51) (μg/mL)	*K. pneumo.* MIC_{90} (n = 11) (μg/mL)	*E. coli.* MIC_{90} (n = 11) (μg/mL)	*A. bau.* MIC_{90} (n = 11) (μg/mL)
Meropenem	0.5	NT	>64	32	0.06	64
1	0.125*	0.5	0.5*	8*	2*	>64*
3	1	8	4	>64	16	64
9	0.125	0.5	2	32	1	>64
13	0.25	0.25	1	2	0.125	>64
19	0.125–0.5	0.125	0.25	16	1	>64
20	0.125	0.5	0.5	16	4	16
21	1	0.5	1	32	1	>64
22	0.25	0.5	1	8	1	32
23	1	2	2	4	1	>64
24	0.5	0.5	2	2	0.5	16
25	8	>64	ND	ND	ND	ND
26	0.125	0.5	1	8	1	>64

* Data for **1** from literature using larger panel of organisms.[3]

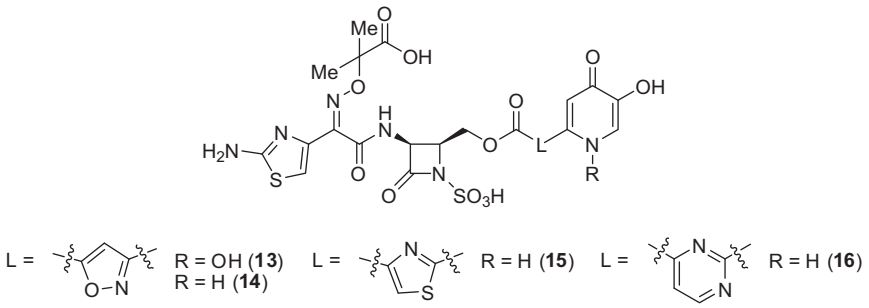
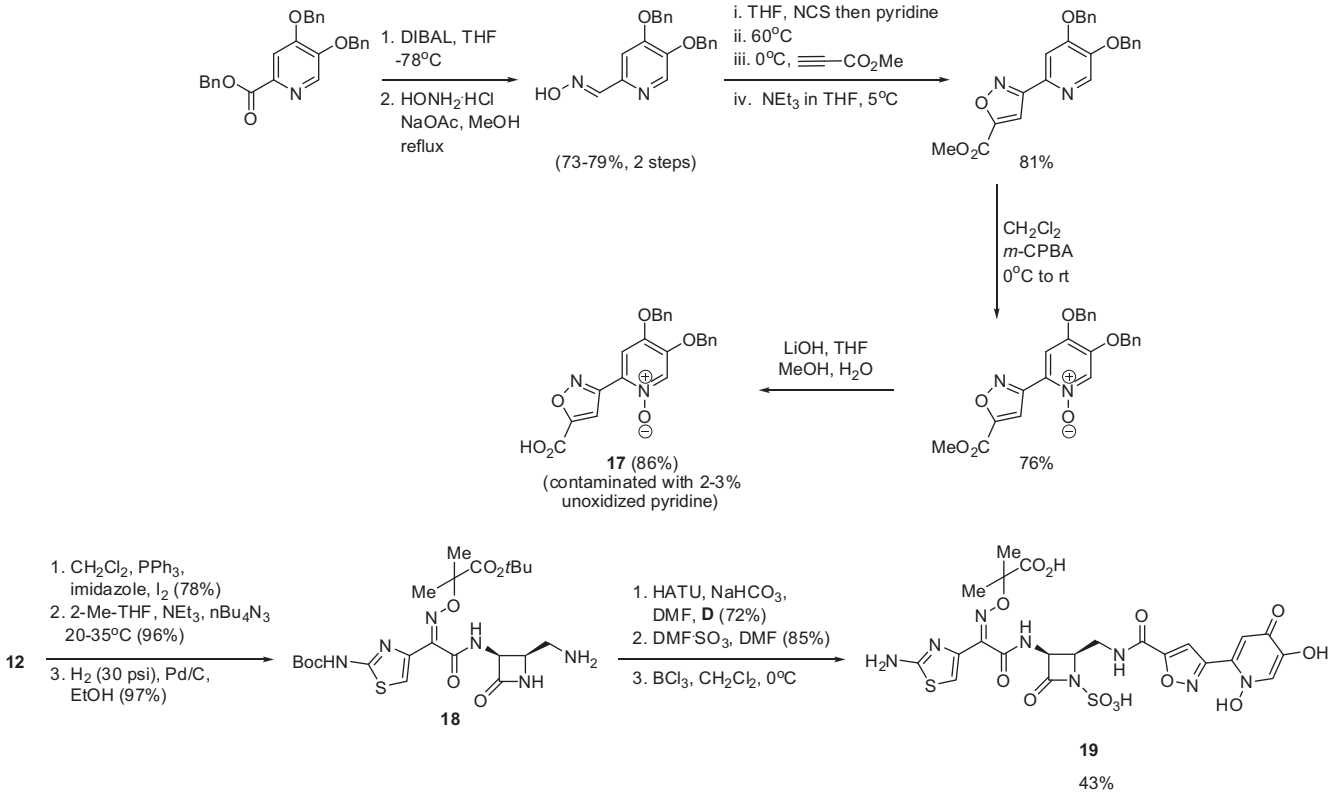


Figure 4. Heteroaromatic ester-linked siderophore-conjugated monobactams.



Scheme 2. Enabling synthetic chemistry for amide analogs such as **19**.

potent preliminary MIC_{90} values against both *P.aer.* and *E. coli* with somewhat weaker activity against *K. pneumo.* and no notable potency against *Acinetobacter baumannii* (Table 2). Compound **9** also displayed favorable human protein binding (Fu = 0.57) and low clearance in the rat after IV dosing (8.9 ml/min/kg). With this information in hand, we sought to further optimize the properties of compound **9**, for example by improving upon the *K. pneumo.* activity.

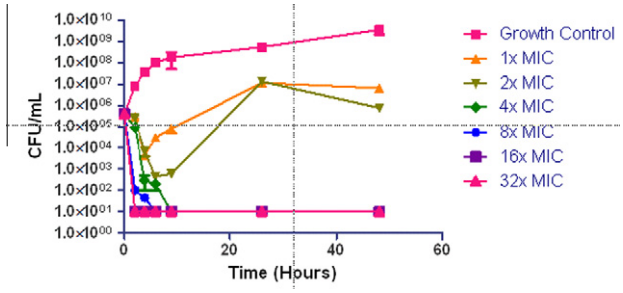


Figure 5. Static time kill experiment with compound **19**.

Polar heteroaromatic rings have previously been utilized successfully as linkers between β-lactams and siderophore mimics.[27] Replacement of the glycine linker in **9** with an isoxazole as in **13** (Fig. 4) greatly improved the *K. pneumo.* MIC_{90} while preserving the broader Gram-negative spectrum. Consistent with our previous experience, the analogous pyridone analog **14** displayed substantially reduced potency. Replacement of the isoxazole in **14** with a thiazole (**15**) resulted in intermediate activity, whereas replacement with a pyrimidine (**16**) was highly deleterious. These efforts established both the viability of the series and the ability to modulate attributes such as antimicrobial potency using different linker motifs.

Despite its compelling Gram-negative spectrum, compound **13** contains a potentially labile ester moiety and showed suboptimal pharmacokinetic properties (*vide infra*). Given our concerns around metabolic stability, we also prepared analogs containing an amide

linkage in place of the ester. The requisite 4-aminomethyl-substituted β-lactam intermediate **18** could be accessed from alcohol **12** via the corresponding azide as depicted in Scheme 2.

The amide series yielded a number of highly compelling analogs. The isoxazole **19** (Scheme 2) proved more potent than ester **13** against *P. aer.*, showed acceptable *E. coli* activity, and provided somewhat diminished *K. pneumo.* potency (Table 2). A static concentration time kill experiment with *P. aer.* 1091-05 demonstrated extremely rapid killing (Fig. 5).

Our group has previously reported X-ray crystallographic data of the covalent complex of **1** and its primary biological target in *P. aer.*, penicillin binding protein 3 (PBP3).[28] Biochemical assays also showed **19** to be a potent inhibitor of PBP3 (data not shown), and we aimed to better understand its binding mode through structural studies. Comparing the crystal structures of **1** and **19** with PBP3, one notes substantial overlap of the homologous portions of the analogs (Fig. 6). In addition, despite their differing points of attachment to the β−lactam nucleus, the siderophore moieties are located in roughly similar positions. The linker moieties adopt substantially different conformations in this relatively large pocket, providing additional justification for continued analog work in this series.

Other 5-membered heteroaryl analogs such as oxazole **20** (Table 2) also showed promise. In addition, we prepared pyridone analogs (**21** and **22**). Somewhat surprisingly, these compounds demonstrated roughly similar activity to their N–OH series comparators (**19** and **20**, respectively). A thiazole (**23**) also showed promise. The simple amide **24** showed excellent spectrum and demonstrated moderate activity against *A. baumannii*. In contrast, the enantiomer of **24** (i.e., **25**) showed greatly diminished activity, consistent with literature precedent regarding the importance of the stereochemistry at C3 of the lactam.[29] The pyridone analog (**26**) of N-hydroxypyridone **24** lacked appreciable MICs against *A. bau.* and also showed reduced *K. pneumo.* activity.

Having identified a number of highly potent analogs as measured by in vitro activity, we sought additional means to prioritize them for future study. Pharmacokinetic assessments in rat were carried out using an intravenous dose of 1 mg/kg (Table 3). Likewise, the protein binding was evaluated using rat and human plasma. Using these values to calculate unbound clearance in rat, it appeared that the *N*-hydroxypyridone analogs in general provided superior pharmacokinetic properties (**20** vs **22** and **24** vs **26**). Amide **19** also showed substantially reduced clearance versus ester **13**.

Selected compounds were also evaluated for efficacy using a murine infection model of pneumonia with *P. aer.* 1091-05 (Table 4). ED_{50} values were determined on the basis of reductions in lung colony forming unit (CFU) counts over the course of the study. As a general rule, efficacy correlated well with intrinsic clearance in this model, suggesting a reasonable linkage between pharmacokinetic properties and efficacy. Compound **24** proved to be an exception, as it under performed in vivo. Preliminary studies using static time

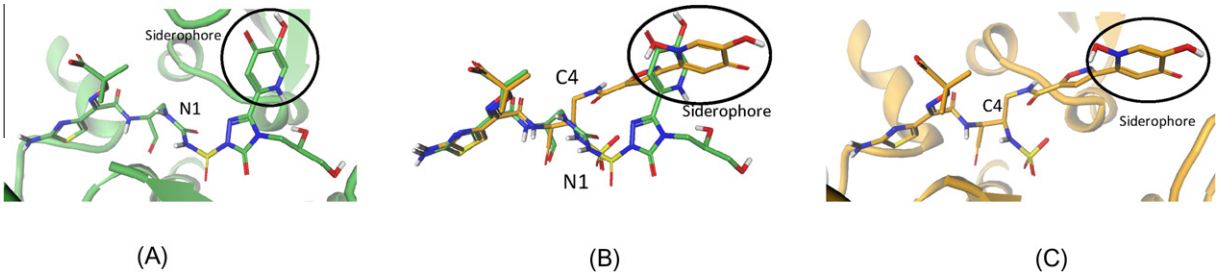


Figure 6. Crystal structure of *Pseudomonas aeuroginosa* PBP3 with monocarbam **1** (green) and monobactam **19** (orange). PBP3 backbone is shown in a ribbon representation for reference. (A) **1** (open form) complexed with *Pseudomonas aeuroginosa* PBP3, (B) Overlay of bound conformations (ligands only) of **1** (green) and **19** (orange), (C) **19** (open form) complexed with *Pseudomonas aeuroginosa* PBP3. (PDB deposition numbers: compound **1** (3PBT), compound **19** (4FSF)).

Table 3
Pharmacokinetic and protein binding data for selected compounds

Compound	Human plasma protein binding (Fu)	Rat plasma protein binding (Fu)	Rat plasma Cl (mL/min/kg)	
			Total	Unbound
9	0.57	0.36	8.9	24.7
13	0.32	0.24	34.7	144.6
19	0.46	0.33	8.1	24.5
20	0.80	0.25	9.1	36.4
21	0.31	0.26	15.7	60.4
22	0.30	0.073	8.8	120.5
23	0.08	0.03	19.6	653.3
24	0.44	0.58	8.0	13.8
26	0.54	0.66	46.6	70.6

Table 4
Murine pharmacokinetics and in vivo efficacy results for selected analogs

Compound	Mouse plasma protein binding (Fu)	Mouse Cl (ml/min/kg)	Mouse Cl,int[a] (ml/min/kg)	ED_{50} (mg/kg/dose)
19	0.65	34.7	86.97	73.6
20	0.99	21.9	29.29	34.7
22	0.42	34.7	134.60	>100
24	0.80	30.6	58.06	>100

[a] total plasma clearance corrected for protein binding and mouse blood flow.

kills (data not shown) suggest that this result may be due to a greater propensity to elicit resistance.

In summary, we have presented a synthetically enabled series of siderophore-conjugated monobactams with excellent in vitro activity against MDR Gram-negative pathogens. Certain analogs also possess favorable pharmacokinetic and in vivo efficacy properties. Additional efforts toward the optimization of this series will be communicated in due course.

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