SUPPLEMENTAL MATERIAL

S1. Chemical synthesis of SMC-3176.

General considerations: All of the solvents and reagents used were obtained commercially and used as such unless noted otherwise. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions at 300 K using a Brucker Ultrashield 300 MHz instrument or a Brucker Ultrashield 400 MHz instrument. ^{13}C NMR spectra were recorded in DMSO-d_6 solutions at 300 K and 126 MHz using a Brucker DRX-500 500 MHz instrument with a QNP cryoprobe or at 101 MHz using a Brucker Ultrashield 400 MHz instrument or at 75.5 MHz using a Brucker Ultrashield 300 MHz instrument. Chemical shifts are reported as parts per million relative to TMS (0.00) for ^{1}H and ^{13}C NMR. High-resolution mass spectra (HRMS) were obtained using a hybrid quadrupole time-of-flight mass spectrometer (microTOFq II, Bruker Daltonics) in ESI^+ mode. Silica gel chromatographies were performed on an ISCO Combiflash Companion Instruments using ISCO RediSep Flash Cartridges (particle size: 35-70 microns) or Silicycle SiliaSep Flash Cartridges (particle size: 40-63 microns). When not indicated, compound intermediates and reagents were purchased from chemical supply houses. The final compound was determined to be greater than 95% pure via analysis by reverse phase UPLC-MS (retention times, RT, in min) with a Waters Acquity UPLC instrument with DAD and ELSD and a UPLC HSS T3, 2.1 × 30 mm, 1.8 μm column and a gradient of 2 to 98% acetonitrile in water with 0.1% formic acid over 2.0 min at 1 mL/min. Injection volume was 1 μL and the column temperature was 30 °C. Detection was based on electrospray ionization (ESI) in positive and negative polarity using Waters SQD mass spectrometer (Milford, MA, USA), diode-array UV detector from 210 to 400 nm, and evaporative light scattering detector.

2-(4,5-*bis*(Benzyloxy)piconiloyl)-*N*-(3-(methylthio)propyl)hydrazinecarboxamide: In a 2-L glass round bottom flask, 5-(4,5-*bis*(benzyloxy)pyridin-2-yl)-1,3,4-oxadiazol-2(3*H*)-one (Flanagan ME *et al*. *ACS Med Chem Lett* 2011; 2: 385-390.) (50 g, 134 mmol) was suspended in anhydrous THF (1L). To the suspension was added 3-(methylthio)propan-1-amine (14.8 g, 140 mmol) in a single portion. The reaction suspension was heated to reflux for 4 h. The reaction mixture was cooled to room temperature and then filtered through a sintered glass funnel. The filter cake was washed with THF and then dried to a constant weight. Isolation gave 51g of the title compound in 79% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.55 - 1.71 (m, 2 H) 1.97 - 2.07 (m, 3 H) 2.38 - 2.47 (m, 2 H) 2.98 - 3.14 (m, 2 H) 3.24 - 3.37 (m, 1 H) 5.27 - 5.40 (m, 4 H) 6.35 - 6.48 (m, 1 H) 7.26 - 7.53 (m, 10 H) 7.62 - 7.73 (m, 1 H) 7.73 - 7.89 (m, 1 H) 8.08 - 8.44 (m, 1 H) 9.52 - 10.06 (m, 1 H).

ESI-MS m/z: 481 $[M + H]^+$.

3-(4,5-*bis*(Benzyloxy)pyridin-2-yl)-4-(3-(methylthio)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one: In a 1-L glass round bottom flask, KOH (60 g, 1069 mmol) was dissolved in water (600 mL). To the warm basic solution was added 2-(4,5-bis(benzyloxy)picolinoyl)-*N*-(3-(methylthio)propyl)hydrazinecarboxamide (51.4 g, 107 mmol). The suspension was heated to 100 °C for 20 h. The reaction mixture was transferred to a 4-L Erlenmeyer flask. The reaction mixture was diluted with water (1.5 L) and acidified (pH = 2-3) with conc. HCl (~80 mL). The suspension was filtered through Watman paper and the cake washed with water (2 L). The solids were dried under vacuum for 2 h. Excess water was removed by slurrying the solids in minimal acetone and filtering. The first crop was then dried in a vacuum oven at 60 °C until a constant weight was achieved. The mother liquor from the acetone slurry was

concentrated to 1/3 the volume and a second crop was isolated as described above. The two crops were combined to yield 43.6 g of the title compound in 88% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.74 - 1.89 (m, 2 H) 1.92 - 2.02 (m, 3 H) 2.36 - 2.47 (m, 2 H) 4.02 - 4.18 (m, 2 H) 5.23 - 5.37 (m, 4 H) 7.27 - 7.51 (m, 10 H) 7.54 - 7.67 (m, 1 H) 8.24 - 8.41 (m, 1 H) 11.89 - 12.10 (m, 1 H).

ESI-MS m/z: 463 $[M + H]^+$.

3-(4,5-*bis*(Benzyloxy)pyridin-2-yl)-4-(3-(methanesulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (6b): In a 1-L glass round bottom flask, 3-(4,5-*bis*(benzyloxy)pyridin-2-yl)-4-(3-(methylthio)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (43.6 g, 94.2 mmol) was suspended in dichloromethane (1 L). The reaction slurry was cooled to 0 °C. In a 250 mL beaker, a dichloromethane suspension (250 mL) containing 3-chlorobenzoperoxoic acid (48.8 g, 283 mmol) was prepared. The suspension was added to the reaction mixture in portions so as to not let the internal temperature rise above 10 °C. Reaction mixture was concentrated to dryness by rotary evaporation. The solids were triturated in acetone and then filtered, washed and dried *in vacuo*. Isolation gave 40 g of the title compound in 86% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.98 - 2.16 (m, 2 H) 2.87 - 3.00 (m, 3 H) 3.05 - 3.19 (m, 2 H) 4.10 - 4.23 (m, 2 H) 5.21 - 5.38 (m, 4 H) 7.28 - 7.49 (m, 10 H) 7.57 - 7.71 (m, 1 H) 8.23 - 8.44 (m, 1 H) 11.98 - 12.15 (m, 1 H).

ESI-MS m/z: 495 $[M + H]^+$.

***tert*-Butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-*bis*(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** In an oven dried flask, 3-(4,5-

bis(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-one (22.2 g, 45.1 mmol) was suspended in THF (200 mL). *N*-Methyl-*N*-trimethylsilyltrifluoroacetamide (11.2 mL, 60.0 mmol) was added and the reaction was allowed to stir at room temperature for 1 h. After this time the reaction was concentrated *in vacuo* and then allowed to dry under high vacuum for 1 h to afford the silyl intermediate, which was confirmed by NMR. In a separate oven dried flask, *tert*-butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (Flanagan ME *et al*. *ACS Med Chem Lett* 2011; 2: 385-390.) (15.3 g, 30.0 mmol) was dissolved in dichloromethane (100 mL) and cooled to 0 °C in an ice bath. A dichloromethane solution (10 mL) containing chlorosulfonyl isocyanate (2.61 mL, 30.0 mmol) was then added slowly to the reaction mixture via syringe and the resultant solution was allowed to stir at that temperature for 10 min. The dry silyl intermediate was slurried in dichloromethane (100 mL) and cooled to 0 °C. The solution containing the isocyanate intermediate was then added dropwise to the slurry of silyl intermediate via an addition funnel. The reaction was complete after 90 min. The reaction was quenched with MeOH (25 mL) and then concentrated by rotary evaporation. The crude reaction mixture was triturated in acetone and the solids removed by filtration. The mother liquor was concentrated and then purified by silica gel flash column chromatography (0-100% EtOAc in hexanes). Isolation gave 18.6 g of the title compound in 56% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 - 1.59 (m, 30 H) 2.02 - 2.17 (m, 2 H) 2.87 - 3.01 (m, 3 H) 3.03 - 3.23 (m, 2 H) 3.84 (qd, *J*=6.15, 2.64 Hz, 1 H) 4.09 - 4.24 (m, 2 H) 4.47 (dd, *J*=8.16, 2.89 Hz, 1 H) 5.23 - 5.37 (m, 4 H) 7.19 - 7.28 (m, 1 H) 7.29 - 7.53 (m, 10 H) 7.56 - 7.70 (m, 1 H) 8.26 - 8.52 (m, 1 H) 8.94-9.16 (m, 1 H) 11.81 (br. s., 1 H) 13.74 (br. s., 1 H). ESI-MS m/z: 1112 $[M + H]^+$.

***tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate:** In an oven dried flask, *tert*-butyl 2-(((*Z*)-(2-(((2*S*,3*S*)-1-(((3-(4,5-*bis*(benzyloxy)pyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (18.6 g, 16.7 mmol) was suspended in EtOH (400 mL). The solution was evacuated and back-filled with argon. Palladium black (100 mg, 0.94 mmol) was added using caution, keeping a stream of argon flowing into the flask to keep the surrounding inert. The suspension was stirred vigorously under a balloon pressure of hydrogen for 5 h. Celite was added and the reaction mixture was filtered. The mother liquor was concentrated to dryness by rotary evaporation. The crude reaction mixture was purified by reverse phase column chromatography (C18, 5-95% MeCN/H_2O w/ 0.1% TFA). The fractions were collected and concentrated. Once the acetonitrile was removed, the product began to precipitate from solution. The suspension was extracted with EtOAc (200 mL x 2). Brine was added to aid in the separation. The organic phases were dried over Na_2SO_4, filtered and concentrated to dryness. Isolation gave 10.3 g of the title compound in 66% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 - 1.50 (m, 34 H) 2.00 - 2.10 (m, 2 H) 2.90 - 2.99 (m, 4 H) 3.06 - 3.19 (m, 2 H) 3.74 - 3.87 (m, 1 H) 4.07 - 4.16 (m, 2 H) 4.40 - 4.54 (m, 1 H) 7.05 - 7.34 (m, 1 H) 7.34 - 7.56 (m, 1 H) 7.89 - 8.26 (m, 1 H) 8.79 - 9.16 (m, 2 H) 11.68 - 11.90 (m, 1 H).

ESI-MS m/z: 931 $[M + H]^+$.

2-(((*Z*)-(1-(2-Aminothiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoic acid (7b): *tert*-Butyl 2-(((*Z*)-(1-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)-2-(((2*S*,3*S*)-1-(((3-(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-4-(3-(methylsulfonyl)propyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)sulfonyl)carbamoyl)-2-methyl-4-oxoazetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropanoate (10.3 g, 11.1 mmol) was dissolved in 100 mL of a 50% v/v dichloromethane solution containing TFA and the reaction was allowed to stir at room temperature for 30 min. The reaction was concentrated to dryness and azeotropically removed excess TFA by rotary evaporation. The crude reaction mixture was purified by reverse phase column chromatography (C18, 5-95% MeCN/H_2O w/ 0.1% TFA). Fractions were collected, acetronitrile removed by rotary evaporation, froze and then lyophilized. Isolation gave 5.38 grams of the title compound in 63% yield.

UPLC RT = 0.51 min, MS (ES) MH^+ 775.2 for $C_{25}H_{30}N_{10}O_{13}S_3$

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.39 - 1.44 (m, 2 H) 1.46 (d, *J*=2.51 Hz, 6 H) 1.96 - 2.08 (m, 2 H) 2.91 - 2.98 (m, 3 H) 3.06 - 3.16 (m, 2 H) 3.73 - 3.83 (m, 1 H) 4.11 (t, *J*=6.65 Hz, 2 H) 4.48 (dd, *J*=8.16, 2.89 Hz, 1 H) 6.83 - 6.93 (m, 1 H) 7.37 - 7.41 (m, 1 H) 8.03 (s, 1 H) 9.13 (d, *J*=8.28 Hz, 1 H).

HRMS (ES+) Calcd for $C_{25}H_{31}N_{10}O_{13}S_3$ $[M + H]^+$ 775.1189; Found 775.1229.

S2. Whole-genome sequencing. Total DNA was extracted using the Promega Maxwell 16 instrument and Maxwell 16 Cell DNA Purification kit following the recommended procedure (Promega, Madison, WI). DNA samples were diluted to 0.3 ng/μL and 5 μL was used for library generation using the Nextera XT DNA sample preparation kit and Nextera XT index primers (Illumina, Inc., San Diego, CA). Sufficient samples were diluted to 600 μL to provide a 15-20 pmol multiplexed library, and sequenced on an Illumina MiSeq V2 instrument as 2×150 paired-end reads. Assembly and analysis was performed off-instrument using CLCBio Genomics Workbench v6.5 (Cambridge, MA). Fastq files were trimmed for quality and minimum length (50 bp) and reads were *de novo* assembled at high stringency (length fraction = 0.9; similarity fraction = 0.99) using default mismatch/insertion/deletion costs. Detection of SNPs / indels was accomplished by mapping reads to a parent reference assembly using the same parameters. Quality based SNPs were detected at a minimum frequency of >80% with a minimum of 10-fold coverage using default criteria. Samples were sequenced to 25-50 fold genome coverage.

S3. Preparation of CDMHB media. CDMHB was prepared as previously described (Tomaras AP *et al*. *Antimicrob Agents Chemother* 2013; 57: 4197-4207.) to a large batch scale. 180 g Chelex 100 resin (Bio-Rad, Hercules, CA) was mixed vigorously in 900 mL MHB at room temperature for 6 h then transferred to 15,000 molecular weight cut-off Spectra/Por dialysis tubing (Spectrum Laboratories, Rancho Dominguez, CA) in 120 mL aliquots, after which the 10× MHB slurry was dialyzed against 8 liters of distilled, deionized water with stirring at 4 °C for 16 h. Following dialysis, tubing and slurries were discarded, and magnesium sulfate and calcium chloride were added back to media to achieve final concentrations of 2 and 0.2 mM, respectively. The completed CDMHB was mixed by inversion, filter-sterilized, and then stored at 4 °C until use.

S4. Construction of isogenic Δ*piuC* mutant. The Δ*piuC* isolate was constructed at AstraZeneca using ASN516. PCR was used to fuse three PCR products (upstream *piuC*, downstream *piuC*, and gentamycin-resistant gene (*aacC1*) along with the FRT sites into one product. This product was cloned into the TOPO vector (K4500-01, Invitrogen, CA) and transformed into *E. coli* TOP10 cells (C4040-10, Invitrogen, CA). After selection on 15 μg/mL gentamycin, a positive clone (pAN136) was confirmed by Sanger sequencing. The plasmid pAN136 was electroporated into ASN516 and selected for clones where the open reading frame of *piuC* was replaced by *aacC1* using 15 μg/mL gentamycin. Replacement of *piuC* with the *aacC1* gene was further confirmed by PCR and sequencing. The *aacC1* gene was then excised from the chromosome by introduction of the pFLP3 plasmid followed by subsequent cure of the plasmid using 10% sucrose. The final unmarked deletion mutant construct (Δ*piuC*) was confirmed by WGS (Illumina MiSeq, San Diego, CA).

Table of isolates, plasmids, and primers used for construction of Δ*piuC*

	Description[a]	Reference
Isolates		
PAO1	Wild-type, ATCC15692	American Type Culture Collection
ASN516	PAO1 containing pAN131	This study
Plasmids		
pAN131	λ Red genes and *sacB* cloned into pUCP18	This study
pAN136	508 bp of upstream region and 528 bp of downstream region of *piuC* flanking on either side of the gentamycin resistant gene with FRT sites cloned into TOPO vector	This study
pFLP3	Plasmid expressing Flp recombinase	Choi KH, Gaynor JB, White KG, Lopez C, Bosio CM, Karkhoff-Schweizer RR, Schweizer HP. 2005. A Tn7-based broad-range bacterial cloning and expression system. Nat Methods 2:443-448.
Primers		
piuC-Up-F	CAGTGTCCTTGATCACCTGC	This study

piuC-Up-R	CGCTGTGCAAGGGCGAATTCCTGTCCACGAAGGCGAAATG	This study
piuC-Dn-F	GAGCATGCATCTAGAGGGCCCATGCGCCACCTGCTGCTTC	This study
piuC- Dn-R	CGATACCAGTGCGCAGCTTG	This study
piuC-out-F	GTTGAAGCCACGGATGAATG	This study
piuC- out-R	CTGAACTGGCCGCGAAAATC	This study
piuC-in-F	CAACCTGCAACTGCCGCAGG	This study
piuC- in-R	CTGGTCCATTTCGAATAGCAG	This study
TOPO 3'	GTAAAACGACGGCCAGTG	This study
TOPO 5'	CAGGAAACAGCTATGACC	This study

[a] For primers, description denotes the primer sequence from 5' to 3'

S5. Genotypes of key *P. aeruginosa* isolates. (White field indicates gene is identical to PAO1 or the listed reference allele sequence. Gray field indicates gene is absent. Bolded text indicates predicted loss-of-function alteration.)

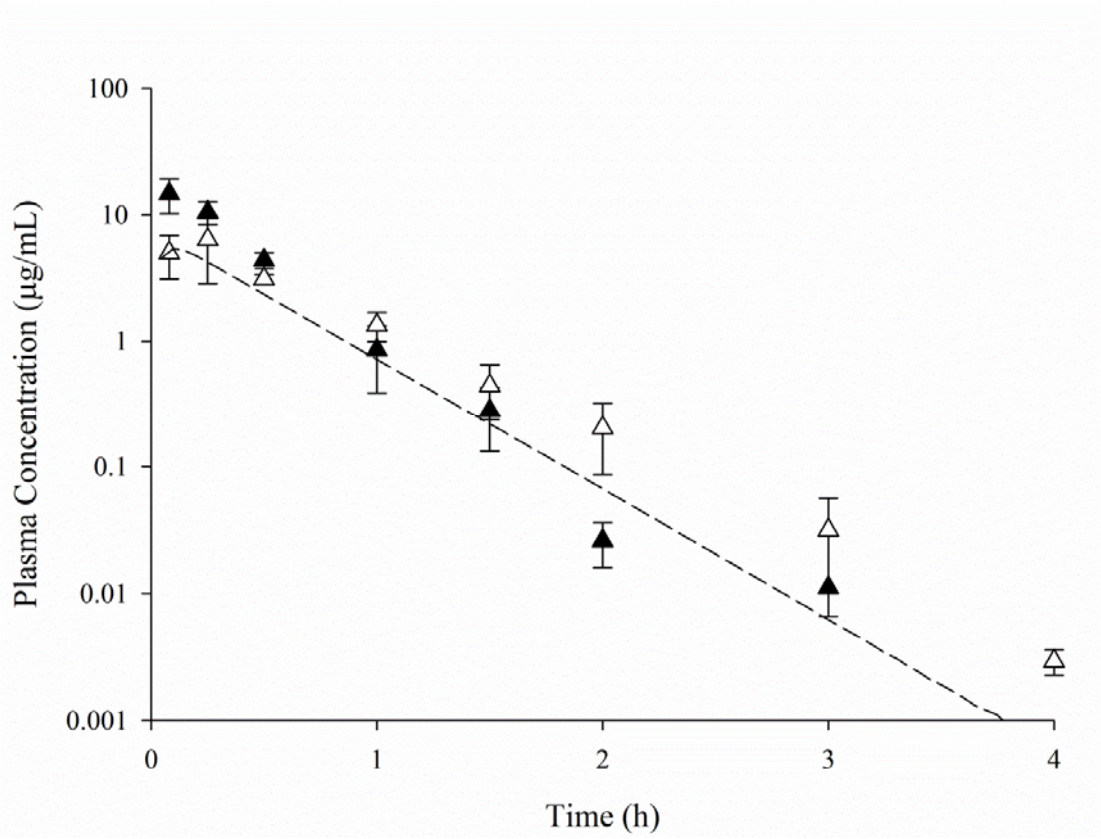
Isolate	Acquired β-lactamase	AmpC	AmpD	AmpR	DacB	OprD (PAO1)[a]	OprD (LES B58)	PiuA (PAO1)[a]
ARC545 (PAO1)	None							
ARC3483	None	ampC::GentR [L37], del[PoxB(PA5514)]						
ARC3502	VIM-1	G27D, A97V, T105A, V205L, G391A	V50G, G148A	G283E, M288R		**Y283fs**		
ARC3506	VEB-1, OXA-10	G27D, A97V, T105A, V205L, G391A	G148A,	G283E, M288R		**A406fs**		
ARC3514	KPC-2	G27D, T105A, V205L, V356I, G391A		G283E, M288R	G287S	**W277***		Q34H, P79L
ARC4659	None	P7S, T105A, V205L, G391A	E68D, G148A	E114A, S179T, G283E, M288R				
AZ 8-18	None	G27D, T105A, V205L, G391A		E114A, G283E, M288R		**N52fs**		
AZ 32-13	None	F19L, R79Q, T105A, V205L, G391A		A51T, E114A, M288R				Q34H
JJ 4-36	None	R79Q, T105A, P274L			A394P			Q34H
JJ 5-35	None	T105A, L176R	A136V,				**L238fs**	
JJ 8-16	None	R79Q, T105A, R235H	G148A, **E163***, S175L		A474T			
JJ 11-54	None	R79Q, T105A	C110R, G148A					Q34H, T674N

Isolate	PiuA (LES B58)	PiuC	PirA	PirR	FecI	PvdA (PAO1)[a]	PvdA (M18)	PvdS	FpvA (Type I - PAO1)[a]	FpvA (Type IIa - AF537095)
ARC545 (PAO1)										
ARC3483										
ARC3502	Q96K, T411I, V577A	R201H	S20N, T235I	G52A			T431A, A432P	V180L, H182N		
ARC3506	Q96K, T411I, V577A	R201H	S20N, T235I	G52A			T431A, A432P	V180L, H182N		
ARC3514		R201H		G52A			T431A, A432P	V180L, H182N		T32A, L483S
ARC4659	Q96K, V577A, V726I	R201H	Y2S	G52A			V203A, T431A, A432P	V180L, H182N		A3T, T32A, L483S
AZ 8-18	Q96K, V577A, V726I	R201H	D608G	G52A	A55V	T431A, A432P			I24M, V46I	
AZ 32-13				G52A, E69D	T143A		T431A, A432P	V180L, H182N		T32A, L483S
JJ 4-36		G139A								
JJ 5-35	Q96K, V577A	V104I					T431A, A432P	V180L, T181A, H182N		
JJ 8-16	Q96K, V577A	V104I						V180L, T181A, H182N		
JJ 11-54		G139A	A370T			T431A, A432P				

Isolate	FpvA (Type IIa' - ARC3506)	FpvA (Type IIb - AF540993)	FpvA (Type III - AF537094)	p*fecI*	p*pvdS*
ARC545 (PAO1)					
ARC3483					
ARC3502					'+50 del[T] - outside *fur*-boxes, +48 [A>C]
ARC3506					'+50 del[T] - outside *fur*-boxes, +48 [A>C]
ARC3514					
ARC4659				GTG → ATG start codon	'+50 del[T] - outside *fur*-boxes, +48 [A>C]
AZ 8-18					+96 (*fur*-box I) G>T
AZ 32-13					+50 del[T] - outside *fur*-boxes, +48 [A>C]
JJ 4-36					
JJ 5-35	A86P, F400F, F408L, L552F				
JJ 8-16	A86P, F400F, F408L, L552F				
JJ 11-54			A32V, N51D, V93L, A516G		

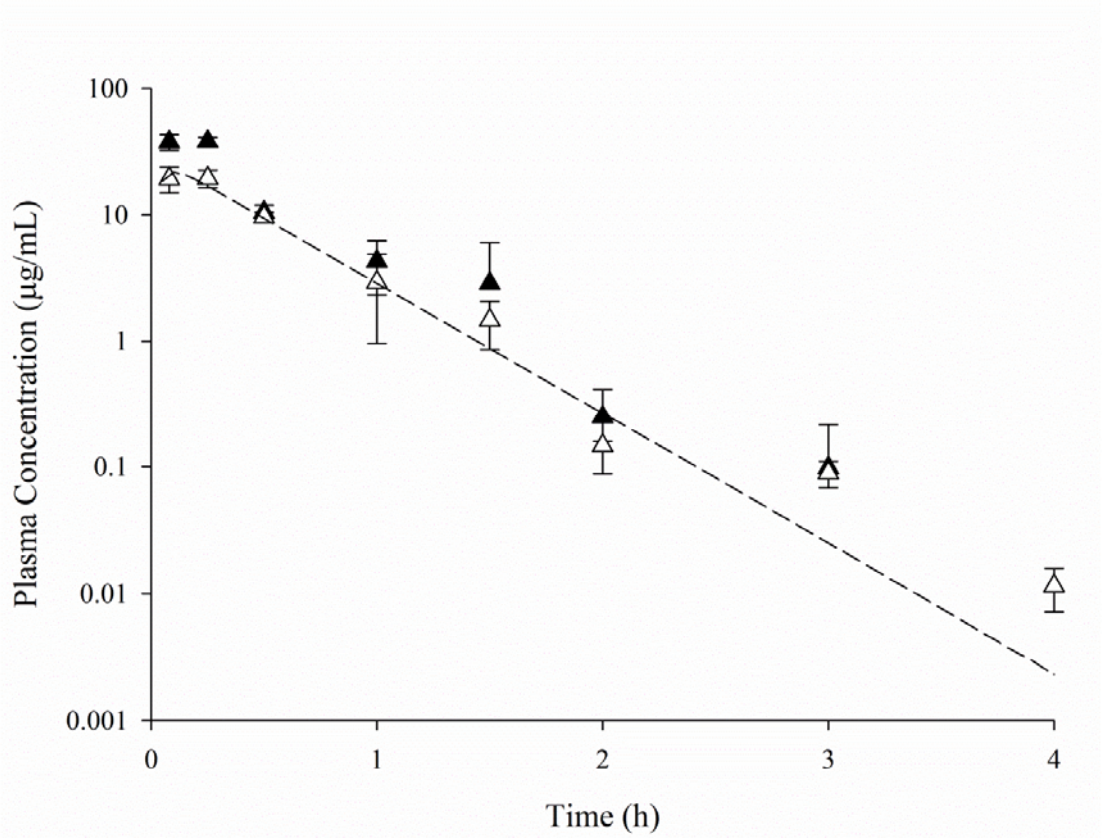
[a] Due to inter-isolate heterogeneity, protein sequences for OprD, PiuA, PvdA, and FpvA were split into subtypes in order to simplify annotations. PAO1 isolate sequence is one archetype and other archetype isolate sequences used for comparison are listed in column headings.

S6. Plasma concentration-time profile of SMC-3176 following single 6.25 mg/kg dose in the neutropenic thigh-infected mouse



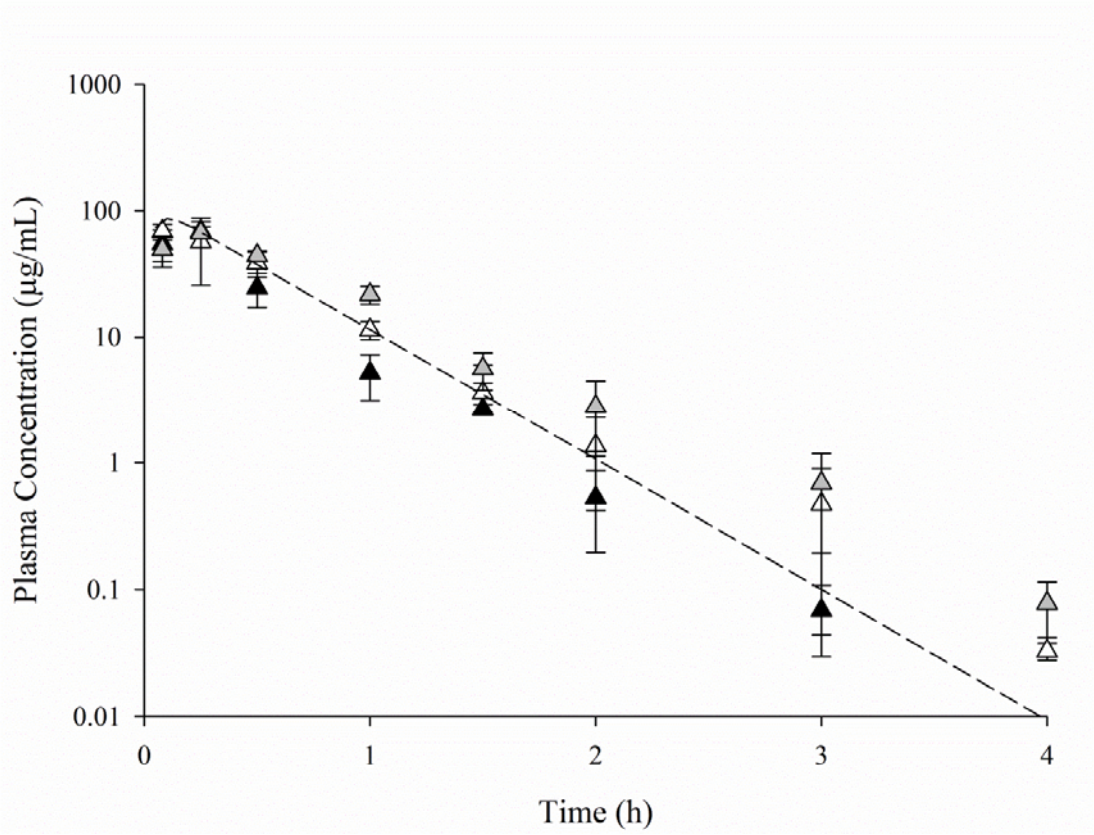
Each symbol represents mean value ± SD from at least three data points in two separate studies.

S7. Plasma concentration-time profile of SMC-3176 following single 25 mg/kg dose in the neutropenic thigh-infected mouse



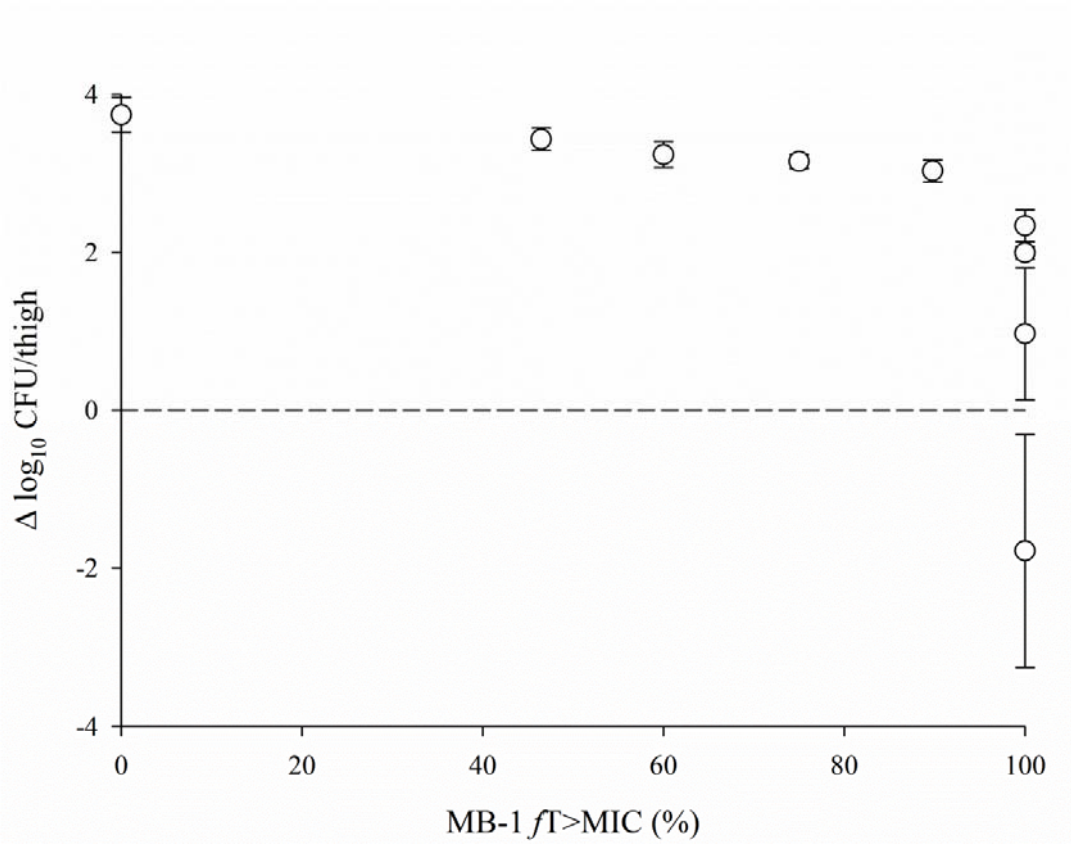
Each symbol represents mean value ± SD from at least three data points in two separate studies.

S8. Plasma concentration-time profile of SMC-3176 following single 100 mg/kg dose in the neutropenic thigh-infected mouse



Each symbol represents mean value ± SD from at least three data points in three separate studies.

S9. Lack of correlation between *f*T>MIC and *in vivo* response for MB-1 against *P. aeruginosa* JJ 4-36 (CDMHB MIC=0.25) in the neutropenic mouse thigh model (dose-ranging approach)



Each symbol represents mean value ± SD from six data points.