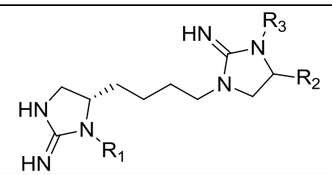
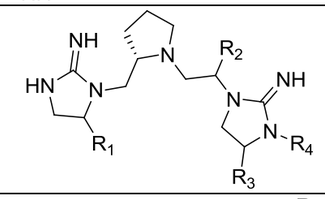
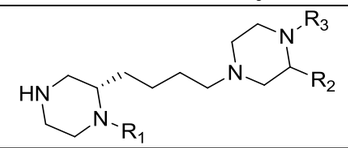
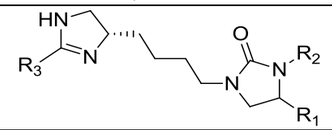
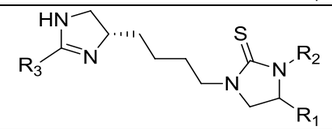
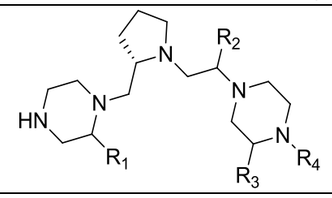
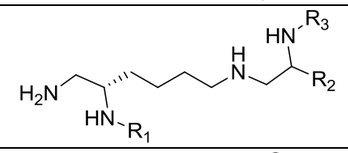
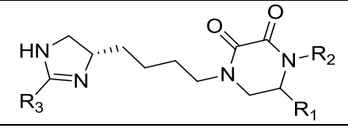
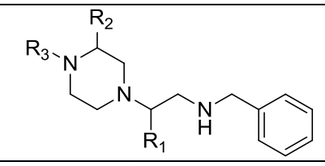
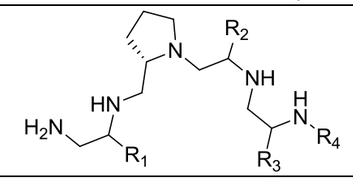
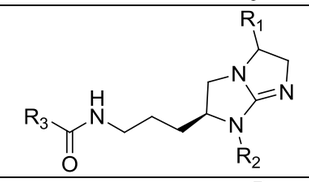
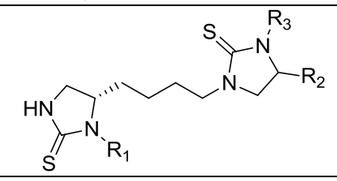
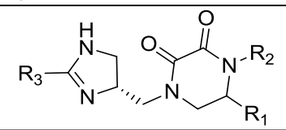
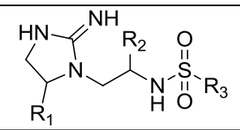
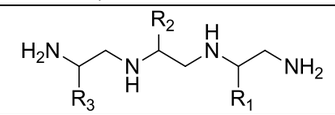
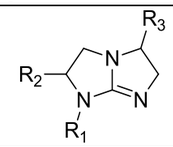
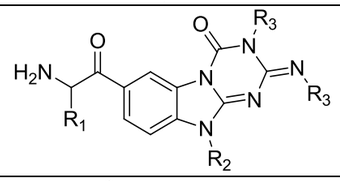
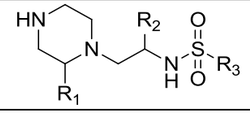
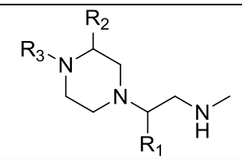
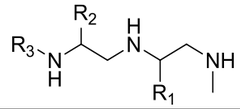
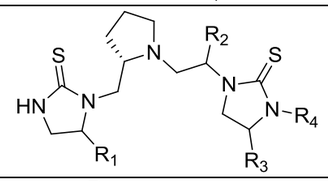
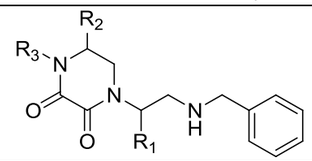
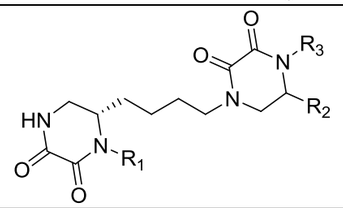
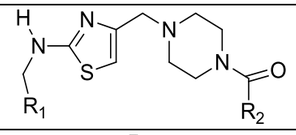
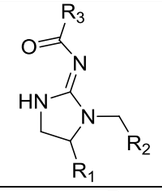
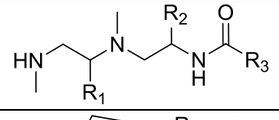
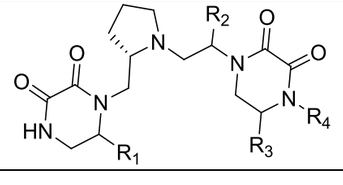
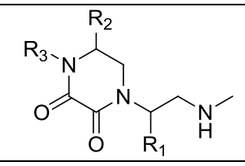
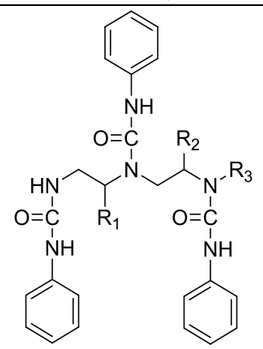
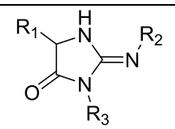
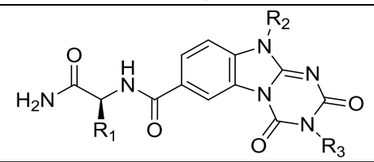
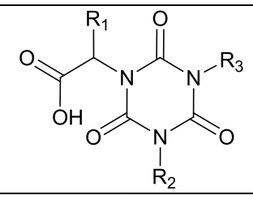
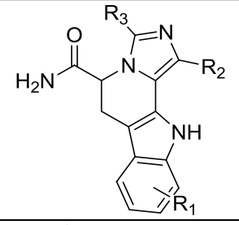
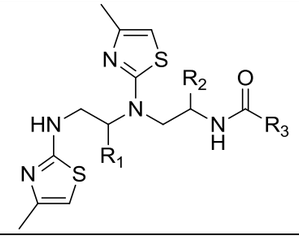
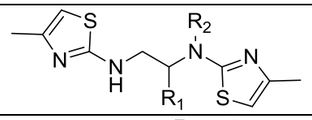
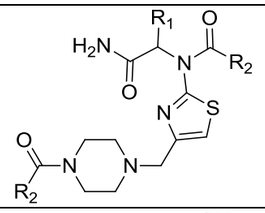
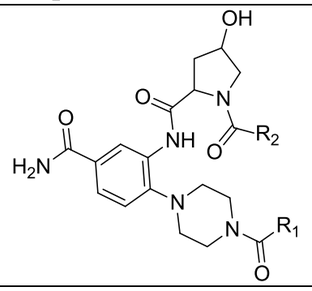
Supplemental Table S1. Chemical composition of the synthetic scaffold ranking library. "ID" corresponds to the numbers used in Figure 1 and throughout the manuscript. "# of samples" is the number of samples comprised in corresponding positional scanning library for a given scaffold. "Total #" is the total number of compounds in a given scaffold ranking sample. "ESKAPE" are the antimicrobial activity values used to generate the stacked scored bars in Figure 1, score of 20 = 5μM activity, 10 = 10μM, 4 = 25μM, 2 = 50μM, 1 = 100μM, 0 = no activity at any dose tested. The table is presented in the same order as Figure 1 in the manuscript; scaffolds that showed no activity against any of the pathogens were not included in Figure 1.

	# of samples	Total #	Structure of Core Scaffold	E	S	K	A	P	E
2157	110	45,864		20	20	0	20	10	20
1955	120	738,192		1	20	0	10	0	1
2160	110	45,864		1	20	0	10	0	1
1319	116	56,610		4	20	0	4	0	0
1276	116	56,610		4	20	0	2	0	0
1954	120	738,192		4	10	0	10	0	1
2161	110	45,864		1	10	2	2	1	2
1275	116	56,610		2	10	0	4	0	0

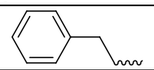
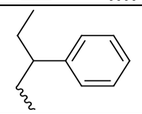
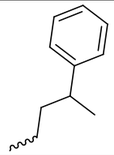
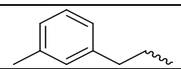
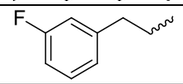
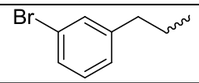
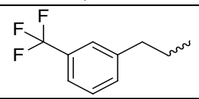
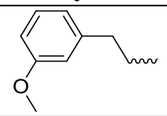
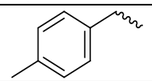
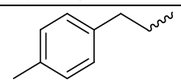
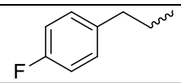
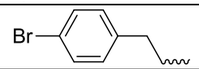
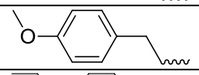
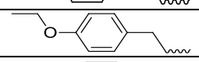
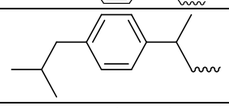
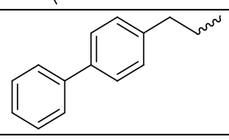
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1952	120	738,192		1	10	1	2	1	1
882	125	72,283		0	10	0	0	0	0
2159	110	45,864		2	4	0	4	0	0
1324	116	56,610		1	4	0	1	0	0
2048	83	17,340		1	4	0	1	0	0
1456	174	195,112		0	4	0	1	0	0
2123	142	102,459		0	4	0	1	0	0
1509	319	13,398		0	4	0	0	0	0
2049	83	17,340		0	4	0	0	0	0

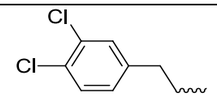
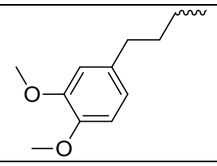
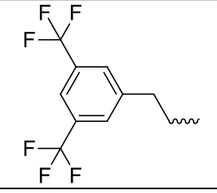
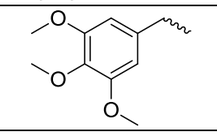
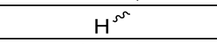
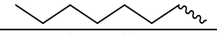
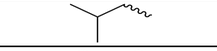
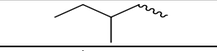
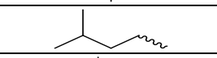
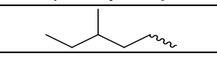
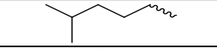
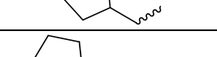
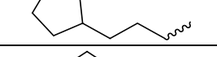
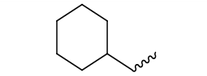
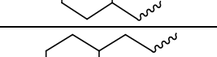
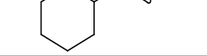
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1662	96	31,320		0	2	0	0	0	0
2158	110	45,864		0	2	0	0	0	0
2057	94	3,249		1	1	0	0	0	0
1295	107	45,288		0	1	0	0	0	0
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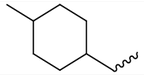
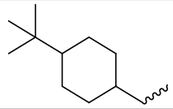
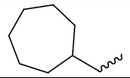
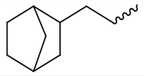
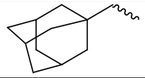
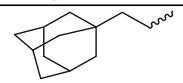
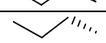
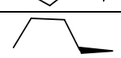
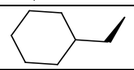
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1387	400	16,000		0	0	0	0	0	0
1409	400	10,800		0	0	0	0	0	0
1978	128	38,250		0	0	0	0	0	0
2017	156	134,560		0	0	0	0	0	0

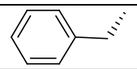
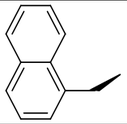
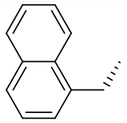
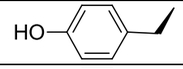
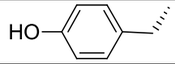
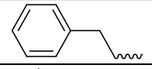
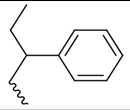
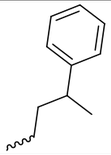
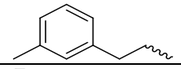
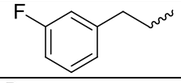
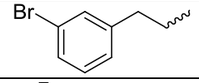
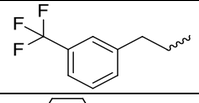
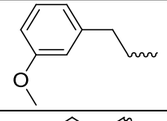
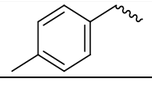
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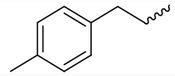
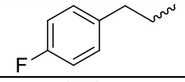
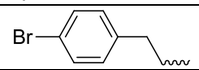
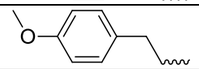
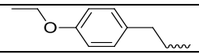
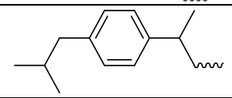
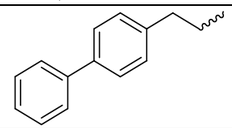
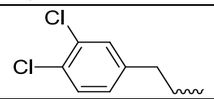
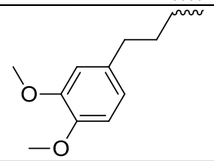
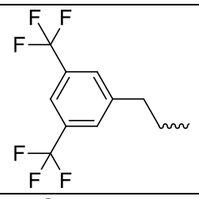
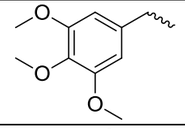
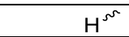
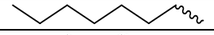
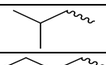
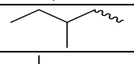
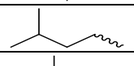
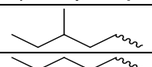
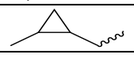
Supplemental Table S2. Deconvolving the 2157 library. The 2157 scaffold ranking mixture was systematically synthesized into a positional scanning library containing 110 samples that were fixed at either the R_1 (42 samples), R_2 (26 samples) or R_3 (42 samples) positions.

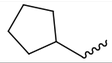
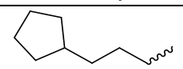
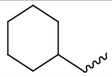
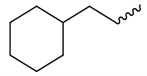
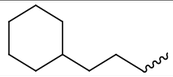
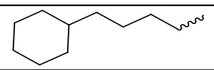
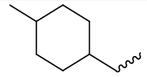
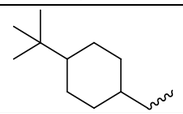
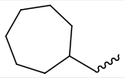
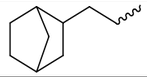
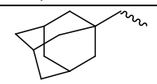
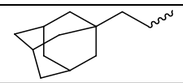
Sample #	Figure 2 Code	Incorporated Functionality	R1	R2	R3
2157.001	1		phenylethyl	X	X
2157.002	2		2-phenylbutyl	X	X
2157.003	3		3-phenylbutyl	X	X
2157.004	4		*m*-tolylethyl	X	X
2157.005	5		2-(3-fluoro-phenyl)-ethyl	X	X
2157.006	6		2-(3-bromo-phenyl)-ethyl	X	X
2157.007	7		2-(3-trifluoromethyl-phenyl)-ethyl	X	X
2157.008	8		2-(3-methoxy-phenyl)-ethyl	X	X
2157.009	9		4-methyl-benzyl	X	X
2157.010	10		*p*-tolylethyl	X	X
2157.011	11		2-(4-fluoro-phenyl)-ethyl	X	X
2157.012	12		2-(4-bromo-phenyl)-ethyl	X	X
2157.013	13		2-(4-methoxy-phenyl)-ethyl	X	X
2157.014	14		2-(4-ethoxy-phenyl)-ethyl	X	X
2157.015	15		2-(4-Isobutyl-phenyl)-propyl	X	X
2157.016	16		2-Biphenyl-4-yl-ethyl	X	X

2157.017	17		3,4-dichlorophenethyl	X	X
2157.018	18		3-(3,4-dimethoxy-phenyl)-propyl	X	X
2157.019	19		2-(3,5-bis-trifluoromethyl-phenyl)-ethyl	X	X
2157.020	20		3,4,5-trimethoxy-benzyl	X	X
2157.021	21		hydrogen	X	X
2157.022	22		butyl	X	X
2157.023	23		heptyl	X	X
2157.024	24		isobutyl	X	X
2157.025	25		2-methylbutyl	X	X
2157.026	26		3-methylbutyl	X	X
2157.027	27		3-methylpentyl	X	X
2157.028	28		4-methylpentyl	X	X
2157.029	29		2-methylcyclopropyl-methyl	X	X
2157.030	30		cyclobutyl-methyl	X	X
2157.031	31		cyclopently-methyl	X	X
2157.032	32		3-cyclopentyl-propyl	X	X
2157.033	33		cyclohexyl-methyl	X	X
2157.034	34		cyclohexyl-ethyl	X	X
2157.035	35		cyclohexyl-propyl	X	X
2157.036	36		cyclohexyl-butyl	X	X

2157.037	37		4-methyl-1-cyclohexyl-methyl	X	X
2157.038	38		4-*tert*-butyl-cyclohexyl-methyl	X	X
2157.039	39		cycloheptyl-methyl	X	X
2157.040	40		2-Bicyclo[2.2.1]hept-2-yl-ethyl	X	X
2157.041	41		adamantan-1-yl-methyl	X	X
2157.042	42		adamantan-1-yl-ethyl	X	X
2157.043	a		X	hydrogen	X
2157.044	b		X	S-methyl	X
2157.045	c		X	R-methyl	X
2157.046	d		X	S-propyl	X
2157.047	e		X	R-propyl	X
2157.048	f		X	S-butyl	X
2157.049	g		X	R-butyl	X
2157.050	h		X	S-isopropyl	X
2157.051	i		X	R-isopropyl	X
2157.052	j		X	S-2-butyl	X
2157.053	k		X	R-2-butyl	X
2157.054	l		X	S-isobutyl	X
2157.055	m		X	R-isobutyl	X
2157.056	n		X	S-cyclohexylmethyl	X
2157.057	o		X	R-cyclohexylmethyl	X
2157.058	p		X	R-hydroxymethyl	X
2157.059	q		X	S-hydroxymethyl	X
2157.060	r		X	(R,R)-1-hydroxyethyl	X
2157.061	s		X	(S,S)-1-hydroxyethyl	X

2157.062	t		X	S-phenyl	X
2157.063	u		X	S-benzyl	X
2157.064	v		X	R-benzyl	X
2157.065	w		X	S-2-naphthylmethyl	X
2157.066	x		X	R-2-naphthylmethyl	X
2157.067	y		X	S-4-hydroxybenzyl	X
2157.068	z		X	R-4-hydroxybenzyl	X
2157.069	1		X	X	phenethyl
2157.070	2		X	X	2-phenylbutyl
2157.071	3		X	X	3-phenylbutyl
2157.072	4		X	X	*m*-tolylethyl
2157.073	5		X	X	2-(3-fluoro-phenyl)-ethyl
2157.074	6		X	X	2-(3-bromo-phenyl)-ethyl
2157.075	7		X	X	2-(3-trifluoromethyl-phenyl)-ethyl
2157.076	8		X	X	2-(3-methoxy-phenyl)-ethyl
2157.077	9		X	X	4-methyl-benzyl

2157.078	10		X	X	*p*-tolylethyl
2157.079	11		X	X	2-(4-fluoro-phenyl)-ethyl
2157.080	12		X	X	2-(4-bromo-phenyl)-ethyl
2157.081	13		X	X	2-(4-methoxy-phenyl)-ethyl
2157.082	14		X	X	2-(4-ethoxy-phenyl)-ethyl
2157.083	15		X	X	2-(4-Isobutyl-phenyl)-propyl
2157.084	16		X	X	2-Biphenyl-4-yl-ethyl
2157.085	17		X	X	3,4-dichlorophenethyl
2157.086	18		X	X	3-(3,4-dimethoxy-phenyl)-propyl
2157.087	19		X	X	2-(3,5-bis-trifluoromethyl-phenyl)-ethyl
2157.088	20		X	X	3,4,5-trimethoxy-benzyl
2157.089	21		X	X	hydrogen
2157.090	22		X	X	butyl
2157.091	23		X	X	heptyl
2157.092	24		X	X	isobutyl
2157.093	25		X	X	2-methylbutyl
2157.094	26		X	X	3-methylbutyl
2157.095	27		X	X	3-methylpentyl
2157.096	28		X	X	4-methylpentyl
2157.097	29		X	X	2-methylcyclopropyl-methyl

2157.098	30		X	X	cyclobutyl-methyl
2157.099	31		X	X	cyclopently-methyl
2157.100	32		X	X	3-cyclopentyl-propyl
2157.101	33		X	X	cyclohexyl-methyl
2157.102	34		X	X	cyclohexyl-ethyl
2157.103	35		X	X	cyclohexyl-propyl
2157.104	36		X	X	cyclohexyl-butyl
2157.105	37		X	X	4-methyl-1-cyclohexyl-methyl
2157.106	38		X	X	4-*tert*-butyl-cyclohexyl-methyl
2157.107	39		X	X	cycloheptyl-methyl
2157.108	40		X	X	2-Bicyclo[2.2.1]hept-2-yl-ethyl
2157.109	41		X	X	adamantan-1-yl-methyl
2157.110	42		X	X	adamantan-1-yl-ethyl

Supplemental Table S3. Minimal inhibitory concentrations of the deconvolved 2157 libraries against the ESKAPE pathogens. Derivation of the functional groups for each compound can be found by referencing supplemental table S2. Compounds marked with an asterisk (*) denote those used to synthesize the 27 new agents in Supplemental Table S4 (1-27).

R1	*E*	*S*	*K*	*A*	*P*	*E*	R2	*E*	*S*	*K*	*A*	*P*	*E*	R3	*E*	*S*	*K*	*A*	*P*	*E*
2157.001	○	○	◖	○	○	●	2157.043	◖	○	○	○	○	○	2157.069	◔	○	◖	○	○	○
2157.002	●	◖	●	◔	○	◔	2157.044	◖	○	○	○	○	○	2157.070	●	●	○	○	○	○
2157.003	●	●	●	◔	○	◔	2157.045	◖	○	○	○	○	○	2157.071	●	●	●	◖	○	◖
2157.004	●	◖	◖	◔	○	○	2157.046	●	○	◖	●	○	○	2157.072	●	●	●	◔	○	◖
2157.005	◔	◖	◖	◖	○	○	2157.047	●	●	●	○	○	○	2157.073	●	●	◔	◖	○	○
2157.006	●	●	●	●	◖	◖	2157.048*	●	●	●	●	◖	●	2157.074	●	●	◔	●	◖	◖
2157.007*	●	●	●	●	◖	●	2157.049	●	●	●	●	◖	●	2157.075	●	●	●	●	○	◖
2157.008	◔	○	●	◖	○	○	2157.050	●	○	◖	◖	○	○	2157.076	●	◖	◖	◖	○	◖
2157.009	○	◖	○	○	○	○	2157.051	●	◖	◖	○	○	○	2157.077	●	◖	◔	◖	○	◖
2157.010	●	●	◔	●	◖	◖	2157.052	●	●	●	●	○	○	2157.078	◖	●	◖	○	○	○
2157.011	●	●	●	●	◖	◖	2157.053	●	●	●	●	○	◖	2157.079	◖	○	◔	○	○	○
2157.012	●	○	◔	●	◖	◖	2157.054	●	●	●	●	○	●	2157.080	●	●	◔	●	◖	◖
2157.013	●	●	◔	○	○	○	2157.055	●	●	●	●	○	●	2157.081	◖	○	◖	○	○	○
2157.014	●	●	◔	○	○	○	2157.056*	◔	●	●	●	◔	●	2157.082	●	●	◖	●	○	○
2157.015	◖	●	●	○	○	○	2157.057	●	●	●	●	◖	◖	2157.083	●	●	●	●	◖	●
2157.016	●	●	●	●	◖	●	2157.058	◖	○	○	○	○	○	2157.084*	●	●	●	●	○	●
2157.017	●	●	●	◖	○	●	2157.059	◖	○	◖	○	○	○	2157.085	●	●	●	●	◖	◔
2157.018	◖	○	○	○	○	○	2157.060	○	○	○	○	○	○	2157.086	◔	●	○	○	○	○
2157.019	●	●	●	●	○	●	2157.061	◖	○	◔	○	○	○	2157.087	●	●	●	●	◖	●
2157.020	◖	○	○	○	○	○	2157.062	●	○	●	●	○	◖	2157.088	○	○	○	○	○	○
2157.021	●	○	○	○	○	○	2157.063	◖	○	●	●	○	◖	2157.089	○	○	○	○	○	○
2157.022	◖	○	○	○	○	○	2157.064	●	○	●	●	○	●	2157.090	◖	○	○	○	○	○
2157.023	●	○	●	●	○	○	2157.065	●	●	●	●	◔	●	2157.091*	●	●	●	●	◖	●
2157.024	◖	○	○	○	○	○	2157.066*	●	●	●	●	◔	●	2157.092	○	●	○	○	○	○
2157.025	●	○	◖	●	○	○	2157.067	●	○	◖	○	○	○	2157.093	◖	○	○	○	○	○
2157.026	◖	○	○	○	○	○	2157.068	◖	○	○	○	○	○	2157.094	◖	○	◖	○	○	○
2157.027	●	●	◖	◖	○	○	KEY							2157.095	◔	○	◖	○	○	○
2157.028	◔	○	◖	○	○	○								2157.096	◔	○	◔	○	○	○
2157.029	◖	○	○	○	○	○	● ≤ 5 µM							2157.097	◖	○	◖	○	○	○
2157.030	◖	○	○	○	○	○								2157.098	◖	○	○	○	○	○
2157.031	◔	○	○	○	○	○								2157.099	◖	○	◔	○	○	○
2157.032	●	○	●	●	○	◖								2157.100	●	●	●	●	◖	●
2157.033	◖	○	○	○	○	○	◔ 5 - 10 µM							2157.101	●	●	◖	●	○	○
2157.034	●	●	◔	●	○	◖								2157.102	●	●	◔	●	◖	◖
2157.035	●	●	●	●	◖	◖								2157.103	●	●	●	●	◖	○
2157.036*	●	●	●	●	○	●								2157.104*	●	●	●	●	◔	●
2157.037	●	○	◖	●	○	○	◖ 10 -25 µM							2157.105	●	●	◖	●	○	◔
2157.038	●	●	●	◖	◔	●								2157.106	●	●	●	●	◔	●
2157.039	●	●	●	○	○	◖								2157.107	◔	●	◖	○	○	○
2157.040	●	●	●	●	◖	◔								2157.108	●	●	●	●	◖	◔
2157.041	●	●	●	●	◖	●	○ >25 µM							2157.109	◔	●	●	●	◖	◔
2157.042*	●	●	●	●	◔	●								2157.110	●	●	●	●	◖	●

Supplemental Table S4a. Chemical composition of individually synthesized bis-cyclic guanidines. Shown are the functional groups attached at each diversity position on the individual bis-cyclic guanidines, the molecular formulas, the calculate [M+H]+ “MH+ calc.”, the MS (ESI) m/z [M+H]+ “MH+ found,” the retention time in minutes “RT min,” the UV % purity “UV purity %”, the physicochemical properties, and the stacked score “Total” for each compound. (Supplemental Table S4b shows the details on the stacked scores and Table S4c shows the full structure for all 54 compounds). The RT min and UV purity % were determined from analyzing the 214nm spectrum of compounds run under conditions described in the section “LCMS analysis of crude material” in the Materials and Methods.

ID	R1	R2	R3	Molecular Formula	MH+ calc.	MH+ found	RT min.	UV Purity %	MW	AlogP	HBA	HBD	RB	PSA	Total
1	2-(3-trifluoromethyl-phenyl)-ethyl	S-butyl	heptyl	$C_{30}H_{49}F_3N_6$	551.40	551.20	4.458	82.7	550.75	7.41	6	3	18	69.45	163
2	2-(3-trifluoromethyl-phenyl)-ethyl	S-butyl	cyclohexyl-butyl	$C_{33}H_{53}F_3N_6$	591.43	591.45	4.582	84.9	590.81	8.20	6	3	17	69.45	173
3	2-(3-trifluoromethyl-phenyl)-ethyl	S-butyl	2-Biphenyl-4-yl-ethyl	$C_{37}H_{47}F_3N_6$	633.38	633.30	4.512	84.6	632.80	8.13	6	3	16	69.45	148
4	2-(3-trifluoromethyl-phenyl)-ethyl	R-2-naphthylmethyl	heptyl	$C_{37}H_{49}F_3N_6$	635.40	635.30	4.557	84.6	634.82	8.44	6	3	17	69.45	127
5	2-(3-trifluoromethyl-phenyl)-ethyl	R-2-naphthylmethyl	cyclohexyl-butyl	$C_{40}H_{53}F_3N_6$	675.43	675.30	4.721	88.4	674.88	9.23	6	3	16	69.45	109
6	2-(3-trifluoromethyl-phenyl)-ethyl	R-2-naphthylmethyl	2-Biphenyl-4-yl-ethyl	$C_{44}H_{47}F_3N_6$	717.38	717.30	4.597	87.4	716.88	9.16	6	3	15	69.45	94
7	2-(3-trifluoromethyl-phenyl)-ethyl	S-cyclohexylmethyl	heptyl	$C_{33}H_{53}F_3N_6$	591.43	591.35	4.632	83.8	590.81	8.20	6	3	17	69.45	156
8	2-(3-trifluoromethyl-phenyl)-ethyl	S-cyclohexylmethyl	cyclohexyl-butyl	$C_{36}H_{57}F_3N_6$	631.46	631.40	4.813	89.5	630.87	8.99	6	3	16	69.45	115
9	2-(3-trifluoromethyl-phenyl)-ethyl	S-cyclohexylmethyl	2-Biphenyl-4-yl-ethyl	$C_{40}H_{51}F_3N_6$	673.41	673.25	4.651	92.6	672.87	8.93	6	3	15	69.45	130
10	cyclohexyl-butyl	S-butyl	heptyl	$C_{31}H_{60}N_6$	517.49	517.35	4.647	80.9	516.85	8.05	6	3	19	69.45	140
11	cyclohexyl-butyl	S-butyl	cyclohexyl-butyl	$C_{34}H_{64}N_6$	557.52	557.35	4.832	80.3	556.91	8.84	6	3	18	69.45	155
12	cyclohexyl-butyl	S-butyl	2-Biphenyl-4-yl-ethyl	$C_{38}H_{58}N_6$	599.47	599.40	4.629	88.4	598.91	8.78	6	3	17	69.45	107.5
13	cyclohexyl-butyl	R-2-naphthylmethyl	heptyl	$C_{38}H_{60}N_6$	601.49	601.40	4.759	85.0	600.92	9.08	6	3	18	69.45	125
14	cyclohexyl-butyl	R-2-naphthylmethyl	cyclohexyl-butyl	$C_{41}H_{64}N_6$	641.52	641.45	4.898	84.2	640.99	9.87	6	3	17	69.45	94
15	cyclohexyl-butyl	R-2-naphthylmethyl	2-Biphenyl-4-yl-ethyl	$C_{45}H_{58}N_6$	683.47	683.40	4.747	84.4	682.98	9.80	6	3	16	69.45	68
16	cyclohexyl-butyl	S-cyclohexylmethyl	heptyl	$C_{34}H_{64}N_6$	557.52	557.35	4.841	86.9	556.91	8.84	6	3	18	69.45	151
17	cyclohexyl-butyl	S-cyclohexylmethyl	cyclohexyl-butyl	$C_{37}H_{68}N_6$	597.55	597.40	5.028	84.6	596.98	9.64	6	3	17	69.45	120
18	cyclohexyl-butyl	S-cyclohexylmethyl	2-Biphenyl-4-yl-ethyl	$C_{41}H_{62}N_6$	639.50	639.40	4.832	89.5	638.97	9.57	6	3	16	69.45	120
19	adamantan-1-yl-ethyl	S-butyl	heptyl	$C_{33}H_{60}N_6$	541.49	541.30	4.644	84.4	540.87	7.36	6	3	17	69.45	156
20	adamantan-1-yl-ethyl	S-butyl	cyclohexyl-butyl	$C_{36}H_{64}N_6$	581.52	581.45	4.797	84.4	580.93	8.15	6	3	16	69.45	160
21	adamantan-1-yl-ethyl	S-butyl	2-Biphenyl-4-yl-ethyl	$C_{40}H_{58}N_6$	623.47	623.40	4.649	87.4	622.93	8.08	6	3	15	69.45	123
22	adamantan-1-yl-ethyl	R-2-naphthylmethyl	heptyl	$C_{40}H_{60}N_6$	625.49	625.40	4.717	82.7	624.94	8.38	6	3	16	69.45	135
23	adamantan-1-yl-ethyl	R-2-naphthylmethyl	cyclohexyl-butyl	$C_{43}H_{64}N_6$	665.52	665.45	4.898	83.5	665.01	9.18	6	3	15	69.45	29
24	adamantan-1-yl-ethyl	R-2-naphthylmethyl	2-Biphenyl-4-yl-ethyl	$C_{47}H_{58}N_6$	707.47	707.40	4.747	84.4	707.00	9.11	6	3	14	69.45	14
25	adamantan-1-yl-ethyl	S-cyclohexylmethyl	heptyl	$C_{36}H_{64}N_6$	581.52	581.40	4.810	84.7	580.93	8.15	6	3	16	69.45	160
26	adamantan-1-yl-ethyl	S-cyclohexylmethyl	cyclohexyl-butyl	$C_{39}H_{68}N_6$	621.55	621.45	5.002	87.6	621.00	8.94	6	3	15	69.45	120
27	adamantan-1-yl-ethyl	S-cyclohexylmethyl	2-Biphenyl-4-yl-ethyl	$C_{43}H_{62}N_6$	663.50	663.45	4.791	92.6	662.99	8.87	6	3	14	69.45	84
28	heptyl	hydrogen	hydrogen	$C_{17}H_{34}N_6$	323.28	323.05	3.450	86.1	322.49	2.54	6	4	11	78.24	0

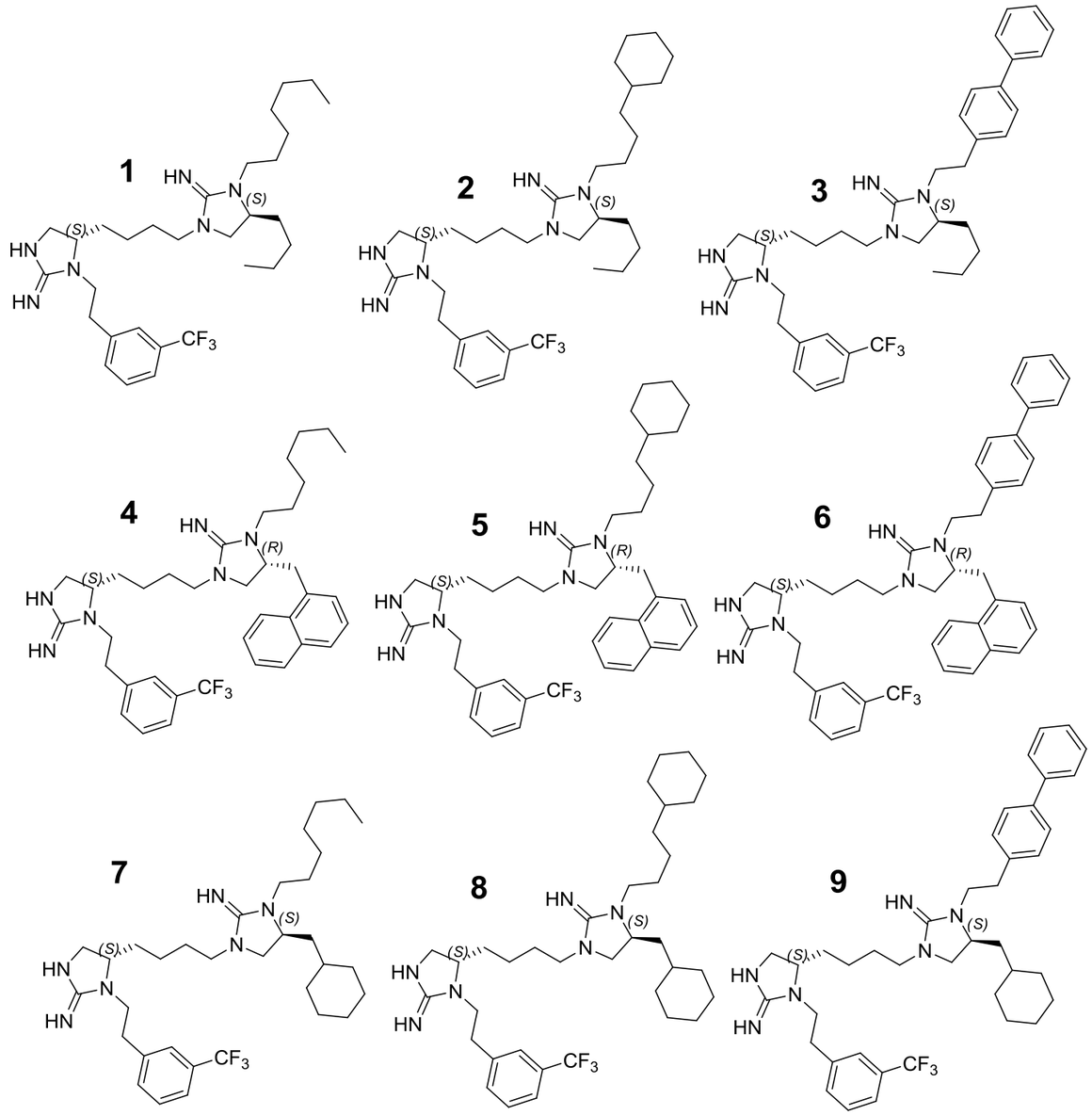
29	heptyl	hydrogen	m-tolylethyl	$C_{26}H_{44}N_6$	441.36	441.15	4.008	86.0	440.67	5.14	6	3	14	69.45	4
30	heptyl	hydrogen	2-methylbutyl	$C_{22}H_{44}N_6$	393.36	393.10	3.956	80.5	392.63	4.39	6	3	14	69.45	0
31	heptyl	S-2-butyl	hydrogen	$C_{21}H_{42}N_6$	379.35	379.10	3.884	87.7	378.60	4.22	6	4	13	78.24	4
32	heptyl	S-2-butyl	m-tolylethyl	$C_{30}H_{52}N_6$	497.43	497.25	4.299	82.8	496.77	6.81	6	3	16	69.45	51
33	heptyl	S-2-butyl	2-methylbutyl	$C_{26}H_{52}N_6$	449.43	449.25	4.211	81.2	448.73	6.07	6	3	16	69.45	4
34	heptyl	R-propyl	hydrogen	$C_{20}H_{40}N_6$	365.33	365.10	3.801	85.9	364.57	3.90	6	4	13	78.24	4
35	heptyl	R-propyl	m-tolylethyl	$C_{29}H_{50}N_6$	483.41	483.20	4.256	80.5	482.75	6.50	6	3	16	69.45	22
36	heptyl	R-propyl	2-methylbutyl	$C_{25}H_{50}N_6$	435.41	435.20	4.158	84.6	434.70	5.75	6	3	16	69.45	4
37	cyclohexyl-methyl	hydrogen	hydrogen	$C_{17}H_{32}N_6$	321.27	321.05	3.195	87.8	320.48	2.03	6	4	7	78.24	0
38	cyclohexyl-methyl	hydrogen	m-tolylethyl	$C_{26}H_{42}N_6$	439.35	439.15	3.848	87.0	438.65	4.63	6	3	10	69.45	4
39	cyclohexyl-methyl	hydrogen	2-methylbutyl	$C_{22}H_{42}N_6$	391.35	391.10	3.688	93.9	390.61	3.89	6	3	10	69.45	0
40	cyclohexyl-methyl	S-2-butyl	hydrogen	$C_{21}H_{40}N_6$	377.33	377.10	3.687	87.1	376.58	3.71	6	4	9	78.24	0
41	cyclohexyl-methyl	S-2-butyl	m-tolylethyl	$C_{30}H_{50}N_6$	495.41	495.20	4.182	84.0	494.76	6.31	6	3	12	69.45	4
42	cyclohexyl-methyl	S-2-butyl	2-methylbutyl	$C_{26}H_{50}N_6$	447.41	447.25	4.080	84.6	446.72	5.56	6	3	12	69.45	4
43	cyclohexyl-methyl	R-propyl	hydrogen	$C_{20}H_{38}N_6$	363.32	363.05	3.584	90.3	362.56	3.39	6	4	9	78.24	0
44	cyclohexyl-methyl	R-propyl	m-tolylethyl	$C_{29}H_{48}N_6$	481.39	481.25	4.125	89.5	480.73	5.99	6	3	12	69.45	4
45	cyclohexyl-methyl	R-propyl	2-methylbutyl	$C_{25}H_{48}N_6$	433.39	433.20	4.006	80.7	432.69	5.24	6	3	12	69.45	4
46	4-Methyl-1-cyclohexyl-methyl	hydrogen	hydrogen	$C_{18}H_{34}N_6$	335.28	335.10	3.379	87.8	334.50	2.28	6	4	7	78.24	0
47	4-Methyl-1-cyclohexyl-methyl	hydrogen	m-tolylethyl	$C_{27}H_{44}N_6$	453.36	453.15	3.969	89.4	452.68	4.88	6	3	10	69.45	4
48	4-Methyl-1-cyclohexyl-methyl	hydrogen	2-methylbutyl	$C_{23}H_{44}N_6$	404.36	405.15	3.820	98.5	404.64	4.14	6	3	10	69.45	0
49	4-Methyl-1-cyclohexyl-methyl	S-2-butyl	hydrogen	$C_{22}H_{42}N_6$	391.35	391.10	3.812	81.4	390.61	3.96	6	4	9	78.24	4
50	4-Methyl-1-cyclohexyl-methyl	S-2-butyl	m-tolylethyl	$C_{31}H_{52}N_6$	509.43	509.25	4.261	84.6	508.78	6.56	6	3	12	69.45	24
51	4-Methyl-1-cyclohexyl-methyl	S-2-butyl	2-methylbutyl	$C_{27}H_{52}N_6$	461.43	461.25	4.163	89.5	460.74	5.81	6	3	12	69.45	4
52	4-Methyl-1-cyclohexyl-methyl	R-propyl	hydrogen	$C_{21}H_{40}N_6$	377.33	377.10	3.730	86.1	376.58	3.64	6	4	9	78.24	4
53	4-Methyl-1-cyclohexyl-methyl	R-propyl	m-tolylethyl	$C_{30}H_{50}N_6$	495.41	495.25	4.214	88.2	494.76	6.24	6	3	12	69.45	4
54	4-Methyl-1-cyclohexyl-methyl	R-propyl	2-methylbutyl	$C_{26}H_{50}N_6$	447.41	447.20	4.112	91.0	446.72	5.50	6	3	12	69.45	4

Supplemental Table S4b. MIC data for Individual Compounds. Shown in columns 2 through 7 are the doses where a compound showed activity against a given pathogen. Columns 8 through 13 show the "stacked score" activity, 100/MIC, for each compound against a given pathogen. Column 14 is the total stacked score value used in Figures 3 and 5 of the paper. To distinguish *E. faecium* from *E. cloacae* in ESKAPE, the latter organism is denoted in red in the above table.

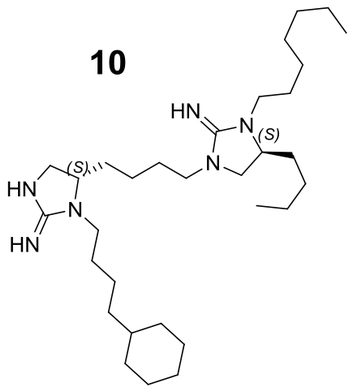
ID	25 ug/ml	10 ug/ml	5 ug/ml	4 ug/ml	3 ug/ml	2 ug/ml	E	S	K	A	P	E	Total
1	ESKAPE	ESKAPE	ESKAPE	SK	SK	S	20	50	33	20	20	20	163
2	ESKAPE	ESKAPE	ESKAPE	ESAP	ES	E	50	33	20	25	25	20	173
3	ESKAPE	ESKAPE	ESKAPE	ESKA	S	-	25	33	25	25	20	20	148
4	ESKAPE	ESKAE	ESKAE	ESA	E	-	33	25	20	25	4	20	127
5	ESKAPE	ESKAE	ESKAE	K	-	-	20	20	25	20	4	20	109
6	ESKAPE	ESKAE	SKAE	-	-	-	10	20	20	20	4	20	94
7	ESKAPE	ESKAPE	ESKAPE	ESAP	ES	-	33	33	20	25	25	20	156
8	ESKAPE	ESKAPE	EKAPE	P	-	-	20	10	20	20	25	20	115
9	ESKAPE	ESKAPE	ESKAPE	EP	-	-	25	20	20	20	25	20	130
10	ESKAPE	ESKAPE	ESKAPE	ESAP	-	-	25	25	20	25	25	20	140
11	ESKAPE	ESKAPE	ESAPE	EA	E	E	50	20	20	25	20	20	155
12	ESKAPE	ESKAPE	ESKAE	A	-	-	20	20	20	25	2.5	20	107.5
13	ESKAPE	ESKAE	ESKAE	P	-	-	20	20	20	20	25	20	125
14	ESKAPE	ESKAE	SKAE	-	-	-	10	20	20	20	4	20	94
15	ESKAPE	ESKE	SE	-	-	-	10	20	10	4	4	20	68
16	ESKAPE	ESKAPE	ESKAPE	EAP	EA	-	33	20	20	33	25	20	151
17	ESKAPE	ESKAPE	ESKAPE	-	-	-	20	20	20	20	20	20	120
18	ESKAPE	ESKAPE	ESKAPE	-	-	-	20	20	20	20	20	20	120
19	ESKAPE	ESKAPE	ESKAPE	ESAP	ES	-	33	33	20	25	25	20	156
20	ESKAPE	ESKAPE	ESKAPE	EAP	E	E	50	20	20	25	25	20	160
21	ESKAPE	ESKAPE	ESKAPE	EA	E	-	33	20	20	25	5	20	123
22	ESKAPE	ESKAE	ESKAE	EAP	-	-	25	20	20	25	25	20	135
23	ESE	S	S	S	-	-	4	25	0	0	0	0	29
24	ES	S	-	-	-	-	4	10	0	0	0	0	14
25	ESKAPE	ESKAPE	ESKAPE	EAP	E	E	50	20	20	25	25	20	160
26	ESKAPE	ESKAPE	ESKAPE	-	-	-	20	20	20	20	20	20	120
27	ESKAPE	ESKPE	SKP	-	-	-	10	20	20	4	20	10	84
28	-	-	-	-	-	-	0	0	0	0	0	0	0
29	S	-	-	-	-	-	0	4	0	0	0	0	4

30	-	-	-	-	-	-	0	0	0	0	0	0	0
31	S	-	-	-	-	-	0	4	0	0	0	0	4
32	ESAP	ES	S	S	S	-	10	33	0	4	4	0	51
33	S	-	-	-	-	-	0	4	0	0	0	0	4
34	S	-	-	-	-	-	0	4	0	0	0	0	4
35	ESAP	S	-	-	-	-	4	10	0	4	4	0	22
36	S	-	-	-	-	-	0	4	0	0	0	0	4
37	-	-	-	-	-	-	0	0	0	0	0	0	0
38	S	-	-	-	-	-	0	4	0	0	0	0	4
39	-	-	-	-	-	-	0	0	0	0	0	0	0
40	-	-	-	-	-	-	0	0	0	0	0	0	0
41	S	-	-	-	-	-	0	4	0	0	0	0	4
42	S	-	-	-	-	-	0	4	0	0	0	0	4
43	-	-	-	-	-	-	0	0	0	0	0	0	0
44	S	-	-	-	-	-	0	4	0	0	0	0	4
45	S	-	-	-	-	-	0	4	0	0	0	0	4
46	-	-	-	-	-	-	0	0	0	0	0	0	0
47	S	-	-	-	-	-	0	4	0	0	0	0	4
48	-	-	-	-	-	-	0	0	0	0	0	0	0
49	S	-	-	-	-	-	0	4	0	0	0	0	4
50	ESA	ES	-	-	-	-	10	10	0	4	0	0	24
51	S	-	-	-	-	-	0	4	0	0	0	0	4
52	S	-	-	-	-	-	0	4	0	0	0	0	4
53	S	-	-	-	-	-	0	4	0	0	0	0	4
54	S	-	-	-	-	-	0	4	0	0	0	0	4

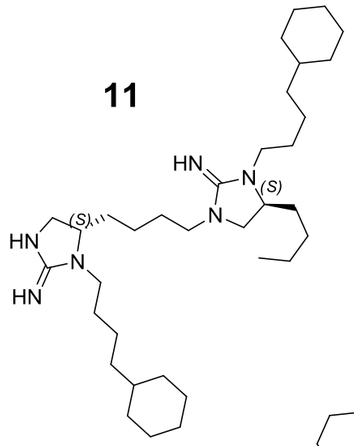
Supplemental Table S4c. Structures of individually synthesized bis-cyclic guanidines.



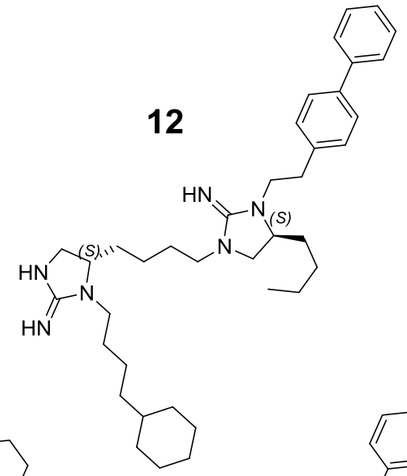
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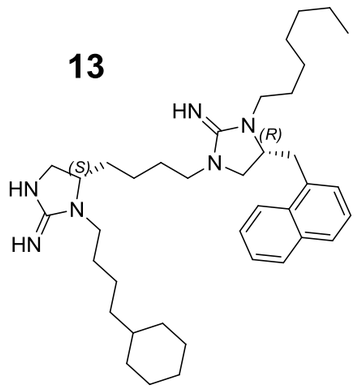
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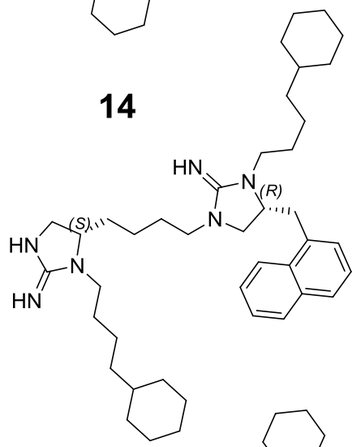
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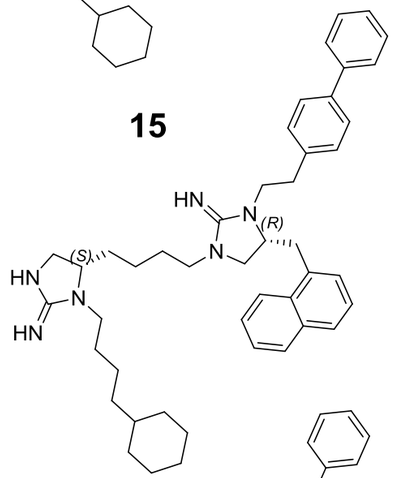
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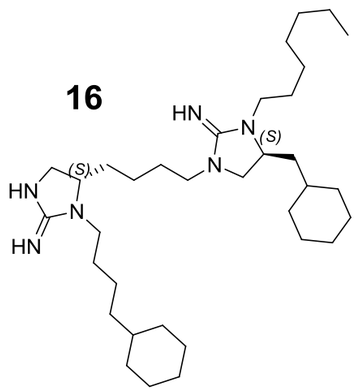
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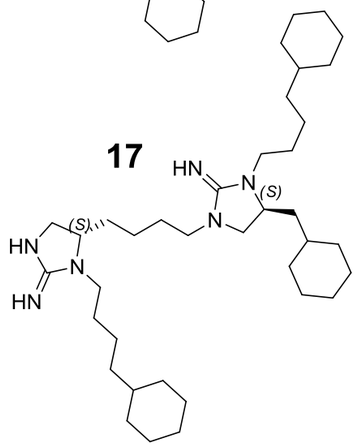
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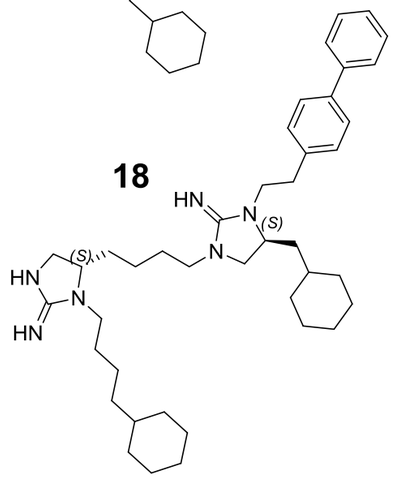
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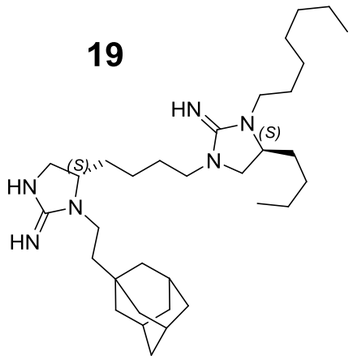
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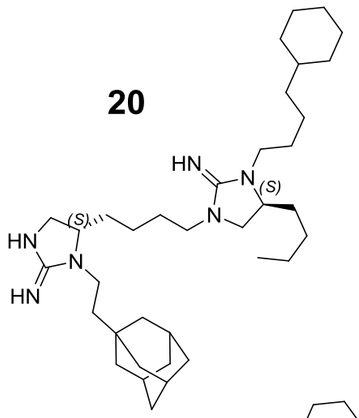
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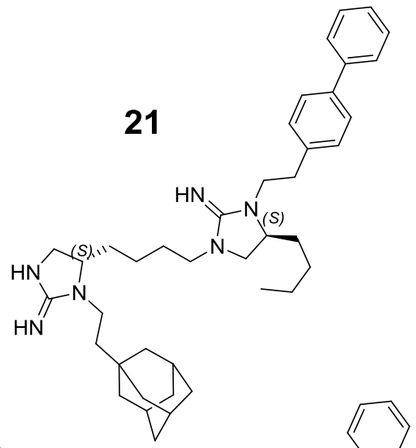
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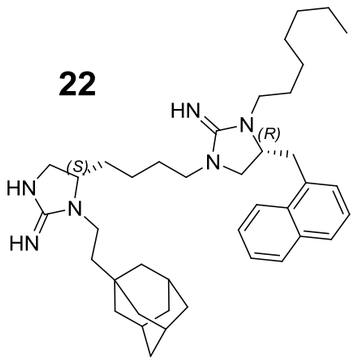
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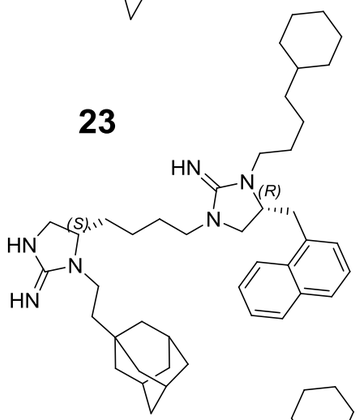
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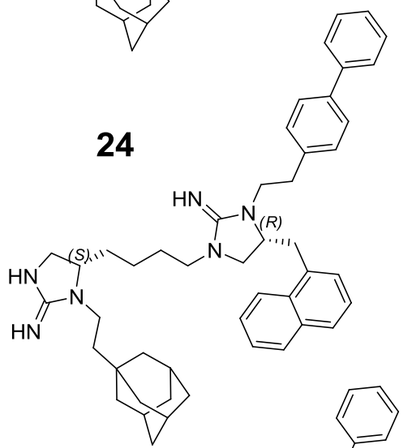
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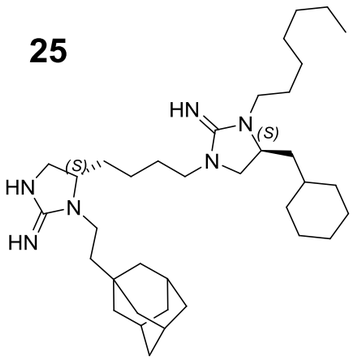
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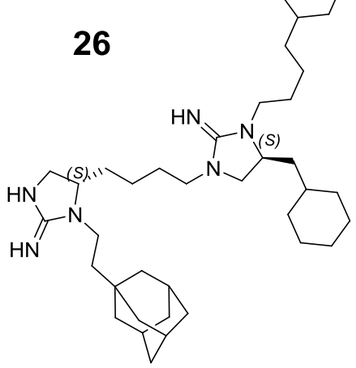
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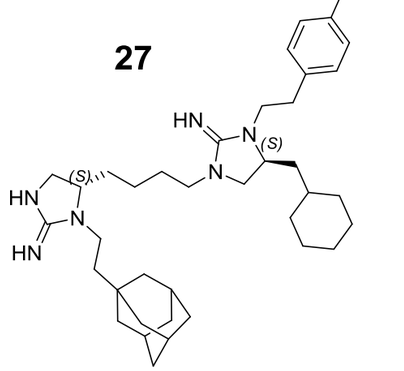
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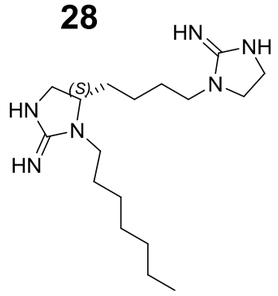
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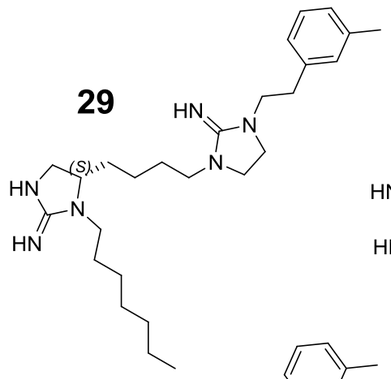
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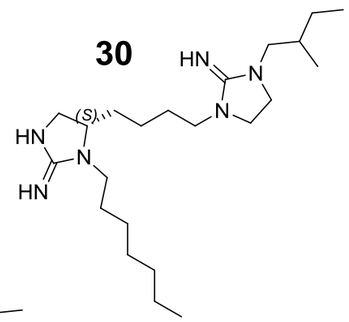
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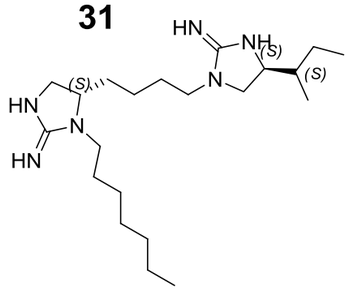
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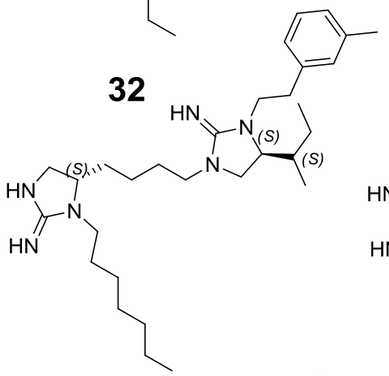
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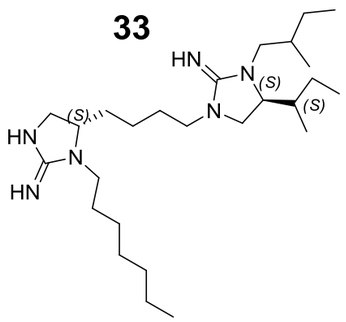
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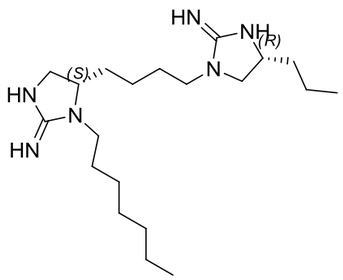
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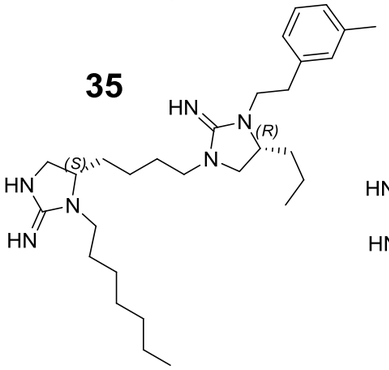
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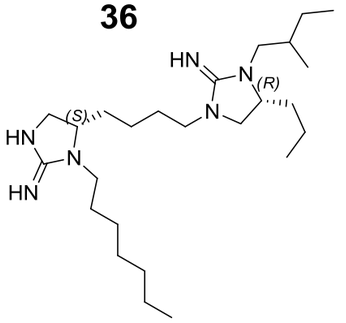
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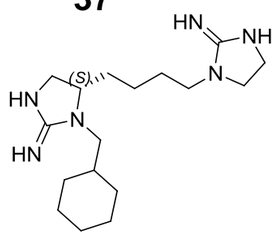
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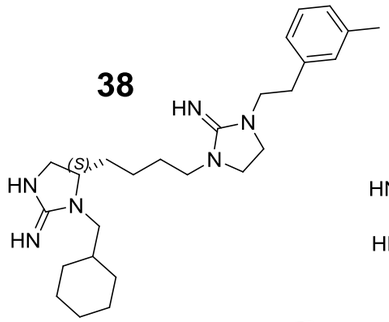
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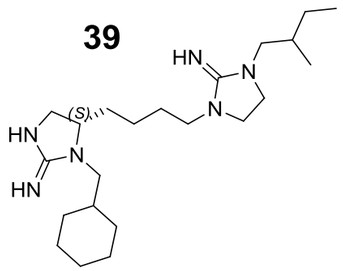
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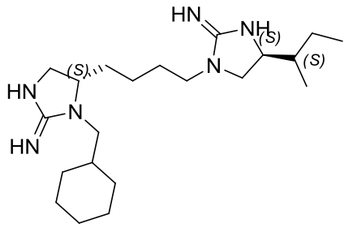
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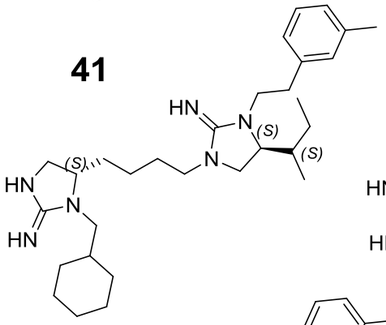
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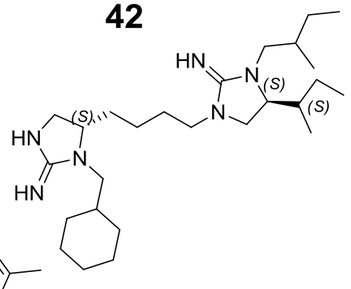
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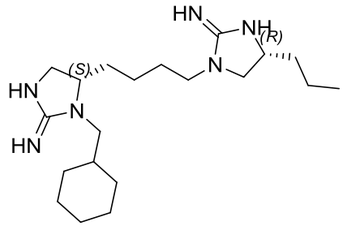
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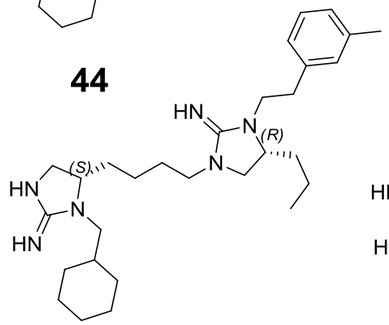
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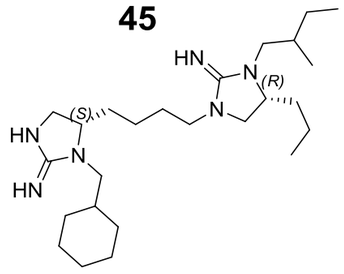
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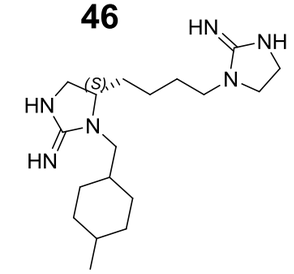
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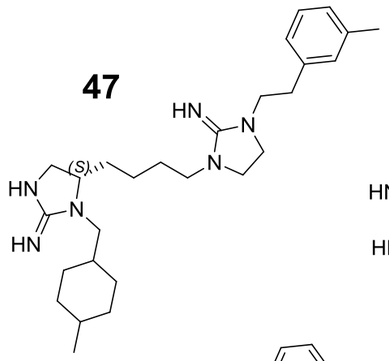
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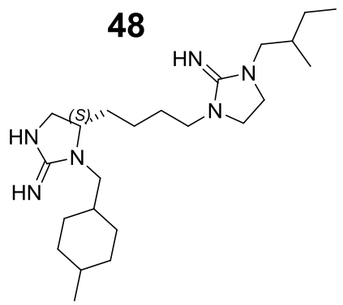
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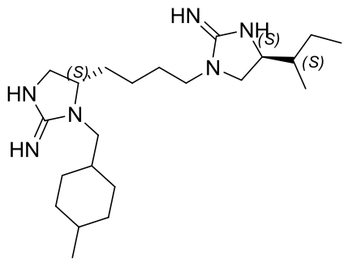
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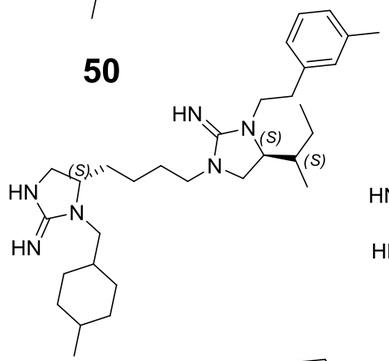
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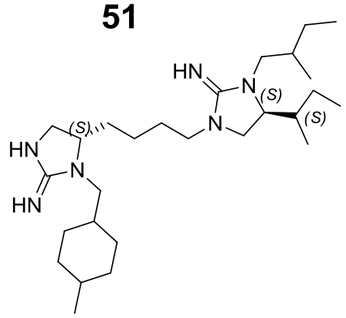
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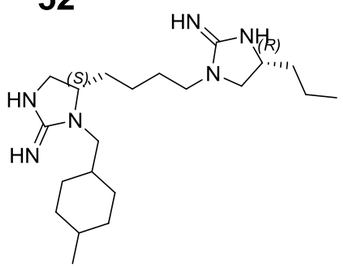
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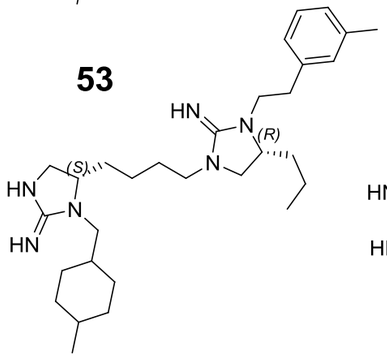
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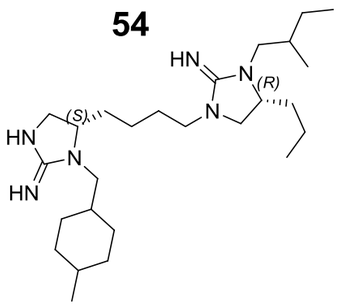
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Supplemental Table S5. Minimal inhibitory concentrations of lead bis-cyclic guanidine against the entire panel of ESKAPE pathogens. MIC values were determined for each of the 5 lead agents against the entire collection of ESKAPE pathogens. Strain information is included in supplemental table S6.

Isolate	1 [MIC µM]	2 [MIC µM]	7 [MIC µM]	16 [MIC µM]	19 [MIC µM]
E. faecium					
1451	2.0	2.0	2.0	2.0	2.0
1406	2.0	2.0	2.0	2.0	2.0
1407	2.0	2.0	2.0	2.0	2.0
1432	2.0	2.0	2.0	2.0	2.0
1438	2.0	2.0	2.0	2.0	2.0
1439	2.0	2.0	2.0	2.0	2.0
1443	2.0	2.0	2.0	2.0	2.0
1444	2.0	2.0	2.0	2.0	2.0
1449	2.0	2.0	2.0	2.0	2.0
1450	2.0	2.0	2.0	2.0	2.0
S. aureus					
1043	2.0	2.0	2.0	2.0	2.0
1049	2.0	2.0	2.0	2.0	2.0
626	2.0	2.0	2.0	2.0	2.0
690	2.0	2.0	2.0	2.0	2.0
693	2.0	2.0	2.0	2.0	2.0
635	2.0	2.0	2.0	2.0	2.0
648	2.0	2.0	2.0	2.0	2.0
715	2.0	2.0	2.0	2.0	2.0
728	2.0	2.0	2.0	2.0	2.0
542	2.0	2.0	2.0	2.0	2.0
834	2.0	2.0	2.0	2.0	2.0
K. pneumoniae					
1411	2.0	2.0	2.0	2.0	2.0
1433	2.0	2.0	2.0	2.0	2.0
1434	5.0	3.0	5.0	5.0	5.0
1440	2.0	5.0	3.0	3.0	3.0
1441	2.0	2.0	2.0	2.0	2.0
1408	2.0	2.0	2.0	2.0	2.0
1409	3.0	3.0	3.0	3.0	3.0
1410	3.0	2.0	2.0	3.0	3.0
1412	5.0	2.0	2.0	3.0	3.0
1413	3.0	2.0	2.0	3.0	3.0
A. baumannii					
1403	2.0	2.0	2.0	2.0	2.0

1643	2.0	2.0	2.0	2.0	2.0
1644	2.0	2.0	2.0	2.0	2.0
1647	2.0	2.0	2.0	2.0	2.0
1648	2.0	2.0	2.0	2.0	2.0
1649	2.0	2.0	2.0	2.0	2.0
1650	2.0	2.0	2.0	2.0	2.0
1651	2.0	2.0	2.0	2.0	2.0
1653	2.0	2.0	2.0	2.0	2.0
1654	2.0	2.0	2.0	2.0	2.0
P. aeruginosa					
1414	5.0	3.0	3.0	3.0	5.0
1415	5.0	3.0	3.0	3.0	5.0
1416	5.0	2.0	2.0	2.0	3.0
1417	5.0	3.0	3.0	3.0	3.0
1418	7.0	7.0	7.0	7.0	7.0
1419	5.0	3.0	3.0	3.0	3.0
1420	5.0	3.0	5.0	3.0	5.0
1421	5.0	3.0	2.0	3.0	5.0
1422	5.0	3.0	5.0	3.0	5.0
1423	2.0	2.0	2.0	2.0	2.0
E. cloacae					
1404	2.0	2.0	2.0	2.0	2.0
1405	5.0	2.0	2.0	2.0	2.0
1430	3.0	2.0	2.0	2.0	3.0
1431	5.0	2.0	2.0	2.0	2.0
1445	3.0	2.0	2.0	2.0	3.0
1446	7.0	7.0	5.0	5.0	5.0
1447	5.0	3.0	2.0	2.0	2.0
1448	3.0	3.0	2.0	2.0	2.0
1454	3.0	2.0	2.0	2.0	2.0
1455	2.0	2.0	2.0	2.0	2.0

Supplemental Table S6. Clinical ESKAPE strains used in this study. The clinical strain set used in this study is detailed, alongside drug resistances/sensitivities, provenance and patient site of isolation. **R** denotes known resistances to given compounds, and **S** refers to any sensitivity determined.

* = Isolates used for library screening, positional scanning screening, MBC, MBEC and resistance assays.
# = Isolate used for the murine model of infection.

Strain name	Identifying Features	Provenance	References
E. faecium			
1451	**R**=Gentamycin, Penicillin G, Tetracycline, Daptomycin **S**=Vancomycin, Linezolid	Moffitt Cancer Center Urine	This Study
1406	**R**= Penicillin G, Tetracycline, Daptomycin, Vancomycin, Linezolid **S**=Gentamycin	Moffitt Cancer Center VRE Screen	This Study
1407	**R**= Gentamycin, Penicillin G, Tetracycline, Daptomycin, Vancomycin, Linezolid	Moffitt Cancer Center Urine	This Study
1432	**R**= Gentamycin, Penicillin G, Tetracycline, Daptomycin, Vancomycin **S**=Linezolid	Moffitt Cancer Center Urine	This Study
1438	**R**= Gentamycin, Penicillin G, Tetracycline, Daptomycin, Vancomycin, Linezolid	Moffitt Cancer Center VRE Screen	This Study
1439	**R**= Gentamycin, Penicillin G, Tetracycline, Daptomycin, Vancomycin, Linezolid	Moffitt Cancer Center VRE Screen	This Study
1443	**R**= Gentamycin, Penicillin G, Tetracycline, Daptomycin, Vancomycin, Linezolid	Moffitt Cancer Center VRE Screen	This Study
1444	**R**= Gentamycin, Penicillin G, Tetracycline, Daptomycin, Vancomycin **S**=Linezolid	Moffitt Cancer Center Tissue	This Study
1449*	**R**= Gentamycin, Penicillin G, Tetracycline, Daptomycin, Vancomycin, Linezolid	Moffitt Cancer Center Rectum	This Study
1450	**R**= Gentamycin, Penicillin G, Tetracycline, Daptomycin, Vancomycin, Linezolid	Moffitt Cancer Center Rectum	This Study
S. aureus			
1043	R= Ampicillin, Azithromycin, Cethromycin, Erythromycin, Penicillin S= Gentamycin, Oxacillin, Sulfamethoxazole, Rifampin, Tetracycline	University of Washington Medical Center (WA-UW-04-008) Sputum	This Study
1049	R= Ampicillin, Azithromycin, Cethromycin, Erythromycin, Penicillin S= Gentamycin, Oxacillin, Sulfamethoxazole, Rifampin, Tetracycline	University of Washington Medical Center (WA-UW-04-014) Buttock skin	This Study

626	R= Ampicillin, Azithromycin, Chloramphenicol, Clindamycin, Cethromycin, Erythromycin, Penicillin S= Gentamycin, Oxacillin, Sulfamethoxazole, Rifampin, Tetracycline	Tampa General Hospital Nose-Throat	This Study
690	R= Ampicillin, Azithromycin, Chloramphenicol, Cethromycin, Erythromycin, Penicillin S= Gentamycin, Oxacillin, Sulfamethoxazole, Rifampin, Tetracycline	Tampa General Hospital (FL-TGH-04-056) Nose	This Study
693	R= Ampicillin, Azithromycin, Chloramphenicol, Cethromycin, Erythromycin, Penicillin S= Gentamycin, Oxacillin, Sulfamethoxazole, Rifampin, Tetracycline	Tampa General Hospital (FL-TGH-04-059) Nasal	This Study
635*	R= Ampicillin, Azithromycin, Chloramphenicol, Clindamycin, Cethromycin, Erythromycin, Penicillin S= Gentamycin, Oxacillin, Sulfamethoxazole, Rifampin, Tetracycline	Tampa General Hospital (FL-TGH-03-021-B) Blood	Carroll et al. (2013)
648	R= Ampicillin, Chloramphenicol, Penicillin, Gentamycin, Tetracycline S= Oxacillin, Sulfamethoxazole, Rifampin, Tetracycline, Erythromycin	Tampa General Hospital Blood	This Study
715	R= Ampicillin, Azithromycin, Cethromycin, Erythromycin, Penicillin, Chloramphenicol S= Gentamycin, Oxacillin, Sulfamethoxazole, Rifampin, Tetracycline	Tampa General Hospital Feces	This Study
728	R= Ampicillin, Azithromycin, Cethromycin, Erythromycin, Penicillin S= Gentamycin, Oxacillin, Sulfamethoxazole, Rifampin, Tetracycline	Tampa General Hospital (FL-TGH-04-086-B) Blood	This Study
542	R= Ampicillin, Azithromycin, Cethromycin, Erythromycin, Penicillin S= Gentamycin, Oxacillin, Sulfamethoxazole, Rifampin, Tetracycline	Harborview Medical Center WA (WA-HMC-03-47436) Blood	This Study
FPR 3757[#]	R= β lactams, erythromycin, clindamycin, tetracycline, ciprofloxacin, mupirocin, doxycycline S= trimethoprim-sulfamethoxazole		Diep et al. (2006)
K. pneumoniae			
1411	**R**=Tetracycline, Ciprofloxacin, Ampicillin **S**= Chloramphenicol, Gentamycin, Imepenem	Moffitt Cancer Center Stool	This Study
1433*	**R**=Tetracycline, Ciprofloxacin, Ampicillin, Imepenem **S**= Chloramphenicol, Gentamycin	Moffitt Cancer Center Urine	This Study

1434	**R**=Tetracycline, Ciprofloxacin, Ampicillin, Imepenem **S**= Chloramphenicol, Gentamycin	Moffitt Cancer Center Urine	This Study
1440	**R**=Tetracycline, Gentamycin, Ciprofloxacin, Ampicillin, Imepenem **S**= Chloramphenicol	Moffitt Cancer Center Urine	This Study
1441	**R**=Tetracycline, Gentamycin, Ciprofloxacin, Ampicillin, Imepenem **S**= Chloramphenicol	Moffitt Cancer Center Fluid	This Study
1408	**R**=Tetracycline, Gentamycin, Ciprofloxacin, Ampicillin **S**= Chloramphenicol, Imepenem	Moffitt Cancer Center Respiratory	This Study
1409	**R**=Tetracycline, Gentamycin, Ciprofloxacin, Ampicillin **S**= Chloramphenicol, Imepenem	Moffitt Cancer Center Wound	This Study
1410	**R**=Tetracycline, Gentamycin, Ciprofloxacin, Ampicillin **S**= Chloramphenicol, Imepenem	Moffitt Cancer Center Blood	This Study
1412	**R**=Tetracycline, Gentamycin, Ciprofloxacin, Ampicillin **S**= Chloramphenicol, Imepenem	Moffitt Cancer Center Blood	This Study
1413	**R**=Tetracycline, Gentamycin, Ciprofloxacin, Ampicillin **S**= Chloramphenicol, Imepenem	Moffitt Cancer Center Blood	This Study

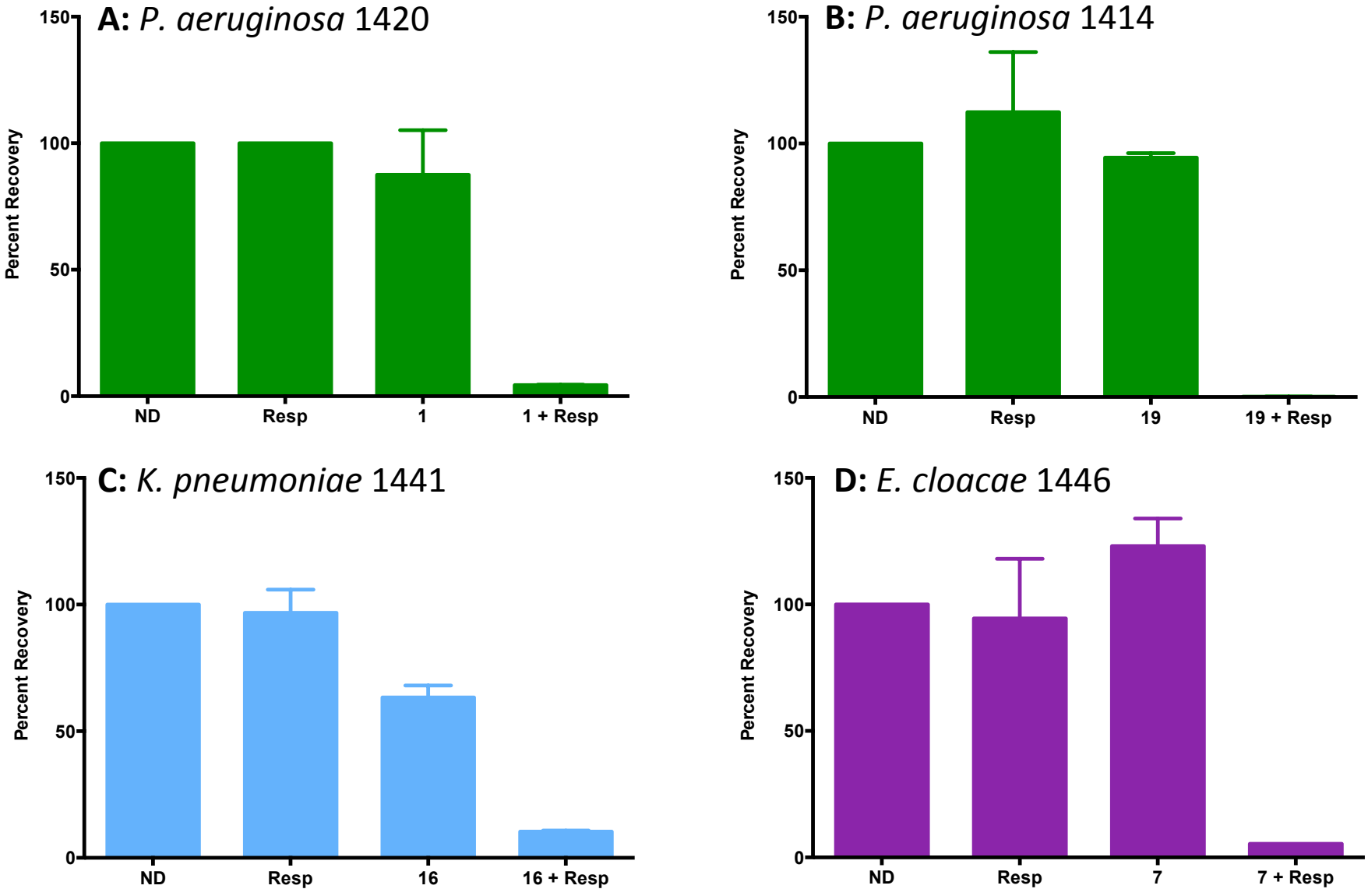
A. baumannii

1403*	**R**= Ampicillin, Ciprofloaxacin, Gentamycin, Polymyxin B, Trimethoprim, Sulfamethoxazole **S**= Rifampin, Chloramphenicol, Tetracycline, Imepenem	Moffitt Cancer Center Urine	This Study
1643	**R**=Ampicillin, Amikacin, Amp-Sulbactam, Aztreonam, Cefepime, Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Chloramphenicol, Gentamycin, Piperacillin, Timentin, Tobramycin, Trimethoprim, Sulfamethoxazole, Levofloxacin **S**= Imepenem, Meropenem, Polymyxin B, Rifampin	University of Nebraska Medical Center (2006) Sputum PFGE A: 510	Jacobs et al. (2010)
1644	**R**= Ampicillin, Chloramphenicol, Ciprofloxacin **S**= Gentamycin, Polymyxin B, Rifampin, Tetracycline	ATCC (1968) Blood PFGE C: 17904	Jacobs et al. (2010)
1647	**R**= Gentamycin, Polymyxin B, Ampicillin, Tetracycline, Ciprofloxacin, Chloramphenicol, Sulfamethoxazole	ATCC (1951) Fetal meningitis PFGE E: 17978	Jacobs et al. (2010)

	S= Rifampin		
1648	**R**= Ampicillin, Aztreonam, Chloramphenicol, Ciprofloxacin, Cefotaxime, **S**= Amikacin, Amp-Sulbactam, Cefepime, Ceftriaxone, Gentamycin, Piperacillin, Timentin, Tobramycin, Trimethoprim, Sulfamethoxazole, Levofloxacin, Polymyxin B, Rifampin, Tetracycline	CDC (TX; 1998) Endotracheal tube PFGE F: 983701	Jacobs et al. (2010)
1649	**R**= Ampicillin, Aztreonam, Cefotaxime, Sulfamethoxazole, Ceftriaxone, Tetracycline **S**= Amikacin, Amp-Sulbactam, Cefepime, , Gentamycin, Piperacillin, Timentin, Tobramycin, Trimethoprim, Levofloxacin, Polymyxin B, Rifampin, Ciprofloxacin, Chloramphenicol	CDC (TX; 1998) Sputum PFGE G: 983702	Jacobs et al. (2010)
1650	**R**= Ampicillin, Aztreonam, Sulfamethoxazole, Tetracycline, Chloramphenicol **S**= Amikacin, Amp-Sulbactam, Cefepime, , Gentamycin, Piperacillin, Timentin, Tobramycin, Trimethoprim, Levofloxacin, Polymyxin B, Rifampin, Ciprofloxacin, Cefotaxime, Ceftriaxone	CDC (TX; 1998) Tracheal aspirate PFGE H: 983705	Jacobs et al. (2010)
1651	**R**= Ampicillin, Aztreonam, Sulfamethoxazole, Chloramphenicol **S**= Amikacin, Amp-Sulbactam, Cefepime, , Gentamycin, Piperacillin, Timentin, Tobramycin, Trimethoprim, Levofloxacin, Polymyxin B, Rifampin, Ciprofloxacin, Cefotaxime, Ceftriaxone, Tetracycline	CDC (TX; 1998) Cerebrospinal fluid PFGE I: 983709	Jacobs et al. (2010)
1653	**R**=Ampicillin, Amikacin, Amp-Sulbactam, Aztreonam, Cefepime, Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Gentamycin, Piperacillin, Timentin, Tobramycin, Trimethoprim, Sulfamethoxazole **S**= Imepenem, Meropenem, Polymyxin B, Rifampin, Levofloxacin	CDC (IN; 2001) Blood PFGE K: 011205	Jacobs et al. (2010)
1654	**R**=Ampicillin, Amikacin, Amp-Sulbactam, Aztreonam, Cefepime, Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Gentamycin, Piperacillin, Tobramycin, Trimethoprim, Sulfamethoxazole, Levofloxacin **S**= Imepenem, Meropenem, Polymyxin B, Rifampin, Timentin, Chloramphenicol, Tetracycline	CDC (KY; 2007) Unknown PFGE L: 070954	Jacobs et al. (2010)
P. aeruginosa			
1414	**R**= Ampicillin, Polymyxin B, Gentamycin, Chloramphenicol, Imepenem, Ciprofloxacin **S**= Tetracycline	Moffitt Cancer Center Fluid	This Study
1415	**R**= Ampicillin, Polymyxin B, Gentamycin, Chloramphenicol, Imepenem, Ciprofloxacin	Moffitt Cancer Center Fluid	This Study

	S= Tetracycline		
1416	**R**= Ampicillin, Polymyxin B, Gentamycin, Chloramphenicol, Imepenem **S**= Ciprofloxacin, Tetracycline	Moffitt Cancer Center Fluid	This Study
1417	**R**= Ampicillin, Polymyxin B, Gentamycin, Chloramphenicol, Imepenem **S**= Ciprofloxacin, Tetracycline	Moffitt Cancer Center Wound	This Study
1418	**R**= Ampicillin, Polymyxin B, Gentamycin, Chloramphenicol, Imepenem, Ciprofloxacin, Tetracycline	Moffitt Cancer Center Respiratory	This Study
1419	**R**= Ampicillin, Polymyxin B, Gentamycin, Chloramphenicol, Imepenem, Ciprofloxacin **S**= Tetracycline	Moffitt Cancer Center Respiratory	This Study
1420	**R**= Ampicillin, Polymyxin B, Gentamycin, Chloramphenicol, Imepenem, Ciprofloxacin **S**= Tetracycline	Moffitt Cancer Center Urine	This Study
1421	**R**= Ampicillin, Polymyxin B, Gentamycin, Chloramphenicol, Imepenem, Ciprofloxacin **S**= Tetracycline	Moffitt Cancer Center Respiratory	This Study
1422	**R**= Ampicillin, Polymyxin B, Gentamycin, Chloramphenicol, Imepenem, Ciprofloxacin **S**= Tetracycline	Moffitt Cancer Center Fluid	This Study
1423*	**R**= Ampicillin, Polymyxin B, Gentamycin, Chloramphenicol, Imepenem, Ciprofloxacin, Tetracycline	Moffitt Cancer Center Urine	This Study
E. cloacae			
1404	**R**= Ampicillin, Chloamphenicol, Imepenem, Gentamycin, Polymyxin B, Ciprofloxacin **S**= Tetracycline	Moffitt Cancer Center Urine	This Study
1405	**R**= Ampicillin, Chloamphenicol, Imepenem, Gentamycin, Polymyxin B, Ciprofloxacin, Tetracycline	Moffitt Cancer Center Wound	This Study
1430	**R**= Ampicillin, Chloamphenicol, Imepenem, Gentamycin **S**= Polymyxin B, Ciprofloxacin, Tetracycline	Moffitt Cancer Center Blood	This Study
1431	**R**= Ampicillin, Chloamphenicol, Imepenem, Gentamycin, Polymyxin B, Ciprofloxacin **S**= Tetracycline	Moffitt Cancer Center Urine	This Study
1445	**R**= Ampicillin, Chloamphenicol, Imepenem,	Moffitt Cancer Center	This Study

	Gentamycin, Polymyxin B, Ciprofloxacin **S**= Tetracycline	Sputum	
1446	**R**= Ampicillin, Chloamphenicol, Imepenem, Gentamycin, Polymyxin B, Ciprofloxacin **S**= Tetracycline	Moffitt Cancer Center Urine	This Study
1447	**R**= Ampicillin, Chloamphenicol, Imepenem, Gentamycin, Polymyxin B, Ciprofloxacin, Tetracycline	Moffitt Cancer Center Urine	This Study
1448	**R**= Ampicillin, Chloamphenicol, Imepenem, Gentamycin, Polymyxin B, Ciprofloxacin, Tetracycline	Moffitt Cancer Center Urine	This Study
1454*	**R**= Ampicillin, Chloamphenicol, Imepenem, Gentamycin, Polymyxin B, Ciprofloxacin, Tetracycline	Moffitt Cancer Center Urine	This Study
1455	**R**= Ampicillin, Chloamphenicol, Imepenem, Gentamycin, Polymyxin B, Ciprofloxacin, Tetracycline	Moffitt Cancer Center Urine	This Study



Supplemental Figure S1. Bacterial efflux accounts for variations in MIC of front runner agents between individual isolates. Bacterial cell recovery (CFU/mL) was assessed by comparison to no drug (ND) controls, using either lead agent alone, reserpine alone, or in combination. **A:** Lead agent **1** was tested at 2 μM against *P. aeruginosa* strain 1420 with or without 100 μM reserpine. **B:** As in A, but using lead agent **19** and *P. aeruginosa* strain 1414. **C:** As in A, but using lead agent **16** and *K. pneumoniae* strain 1441. **D:** As in A, but using lead agent **7** and *E. cloacae* strain 1446.