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Synthesis and antimicrobial activity of symmetrical two-tailed dendritic tricarboxylato amphiphiles

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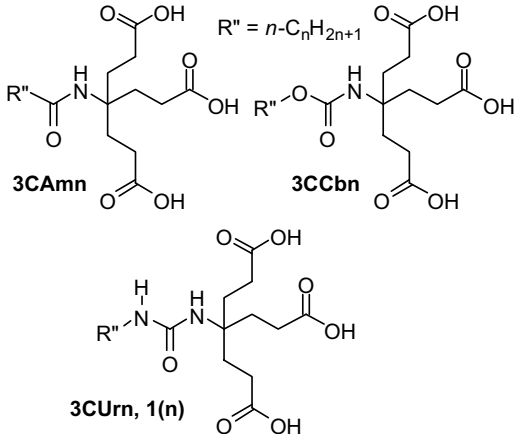
Abstract—Two series of water-soluble, symmetrical two-tailed homologous dendritic amphiphiles—$R_2NCONHC((CH_2)_2COOH)_3$, **2**(**n**,**n**), and $R_2CHNHCONHC((CH_2)_2COOH)_3$, **3**(**n**,**n**), where R = *n*-C_nH_{2n+1}—were synthesized and compared to $R''NHCONHC((CH_2)_2COOH)_3$, **1**(**n**), R″ = *n*-C_nH_{2n+1}, to determine whether antimicrobial activity was influenced by total or individual alkyl chain lengths, and whether antimicrobial activity depends on hydrophobicity or tail topology (one or two). In a broad screen of 11 microorganisms, **2**(**n**,**n**) and **3**(**n**,**n**) generally displayed higher minimal inhibitory concentrations (MICs) than **1**(**n**) against growth as measured by broth microdilution assays. Chain-length specificity was observed against *Candida albicans* as **1**(**16**), **2**(**8**,**8**), and **3**(**8**,**8**) showed the lowest MIC in their respective series. The one case where two-tailed compounds displayed the lowest MICs—**3**(**10**,**10**), 15 μM; **3**(**11**,**11**), 7.2 μM; and **3**(**12**,**12**), 6.9 μM—was against *Cryptococcus neoformans*.

1. Introduction

Studies[1,2] of homologous fatty acid carboxylates as germicides date back to the 1920s and 1930s. Over the years, measuring microbial susceptibility to long-chain fatty acids has involved dissolving the fatty acid in an organic solvent, typically alcohols and DMSO, then diluting it in an aqueous broth. Natural saturated fatty acids have low solubilities in aqueous solutions.[3] As such, uncertainties in measurements of antimicrobial activities arise because the precise concentration of fatty acid available to the microorganism is unknown. To overcome this uncertainty and to probe the structure–activity of the hydrocarbon moiety of an amphiphile, highly hydrophobic headgroups are needed to enable solubility in water.

Our recent report[4] describes the selective antimicrobial activity of one-tailed, long-chain, water-soluble, dendritic tricarboxylato amphiphiles against a broad spectrum of microorganisms. Very long fatty chains, up to 22 carbon atoms, are included in these one-tailed amphiphiles—**3CAmn**, **3CCbn**, **3CUrn** (**1**(**n**)), where **3C** = three carboxyl groups, **Am** = amido linker, **Ur** = ureido linker, **Cb** = carbamato linker, and **n** = the number of carbons in the fatty chain. These amphiphiles with the Newkome-type first-generation dendron[5] as a headgroup have >20,000 μM solubility in aqueous triethanolamine for the longest chains.[4] As a result of the relatively high solubility of these amphiphiles with very hydrophobic chains, one can probe the inherent chain-length specificities of antimicrobial activities without resorting to organic solvents, suspensions, or emulsions to deliver the agent.



Keywords: Dendritic amphiphiles; Antimicrobial activity; Hydrophobicity, Structure–activity study.
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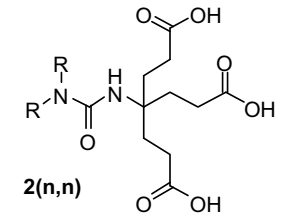
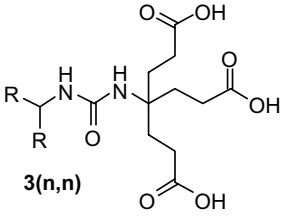
To further understand the characteristics that determine antimicrobial activity, we examine how hydrophobicity and tail topology (one or two) affect antimicrobial activity. The two series, **2**(**n**,**n**) and **3**(**n**,**n**), of two-tailed amphiphiles correspond with the **1**(**n**) series of one-tailed amphiphiles; the total carbon number ($2 \times \mathbf{n}$) equals that of the **1**(**n**) series. The **2**(**n**,**n**) series, where '**n**' represents the number of carbons in a tail, has two tails attached to the distal nitrogen (from the headgroup) of the ureido linker. The **3**(**n**,**n**) series, where '**n**' represents the number of carbons in a tail, has a single carbon separating the ureido linker and the two symmetrical tails. In other words, a long tail is connected to the distal nitrogen on the ureido linker via the middle carbon atom of a long chain (R_2CH–).



R = *n*-C_nH_{2n+1}



The objective is to understand how the tail topology (one or two) affects antimicrobial activity and to discover new leads for affordable anti-infectives. Here, we describe the synthesis of two homologous series of symmetrical two-tailed dendritic amphiphiles. Because of the similarity of the total number of carbon atoms in the two tails, the different series have similar hydrophobicities (e.g., $\log D$).[6] By comparing antimicrobial activities as the minimal inhibitory concentrations (MICs) against a broad spectrum of microorganisms, the similarities and differences among **3**(**n**,**n**), **2**(**n**,**n**), and **1**(**n**) can be identified. We anticipate that these series can serve as probes of membrane structure and function, and that the pattern of antimicrobial activity will enable designing more active antimicrobial amphiphiles. Further, highly active amphiphiles can then lead to identification of novel targets for antimicrobial activity.

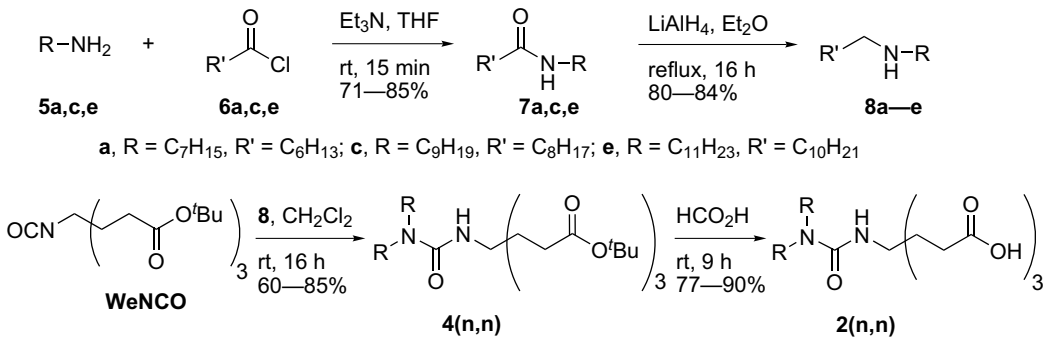
2. Chemistry

2.1. Synthesis of *2*(*n*,*n*)

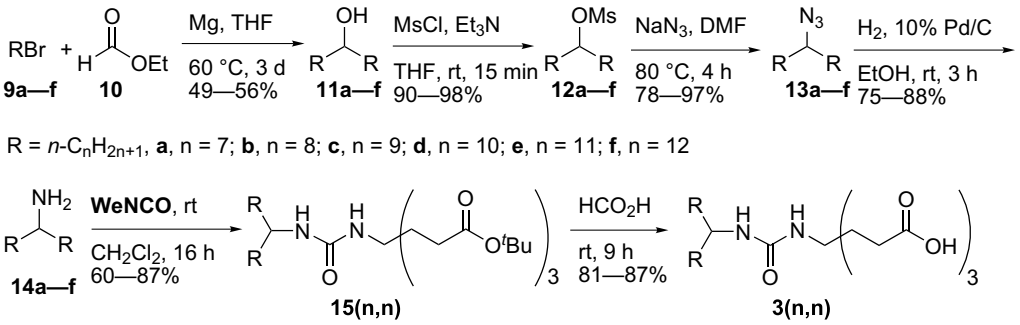
Based on the reaction of **WeNCO** and piperidine,[7] we expected acyclic secondary amines to react readily with **WeNCO** to form **4**(**n**,**n**) (Scheme 1). The even-numbered symmetrical dialkylamines (**8b**,**d**) are readily available; the odd-numbered compounds (**8a**,**c**,**e**) required synthesis. Our procedure followed that of Nagase et al.,[8] who synthesized secondary amines **8** by treating *N*-alkylalkanamides **7** with lithium aluminum hydride. More recently, Djedovič et al.[9] reported syntheses of symmetrical *N*-alkylalkanamines **8** with a similar procedure. Condensing **5a**,**c**,**e** and **6a**,**c**,**e** gave **7a**,**c**,**e**, which were isolated by flash column chromatography. Reduction of **7a**,**c**,**e** produced **8a**,**c**,**e**, which were used as isolated along with commercial **8b**,**d** for the reaction with **WeNCO** to give **4**(**n**,**n**). Flash column chromatography of crude products gave purified homologues, which were fully characterized. Formolysis of the tri-*tert*-butyl esters gave **2**(**n**,**n**) in high yields of recrystallized products.

2.2. Synthesis of 3(n,n)

The synthesis began with Grignard reactions of 1-bromoalkanes **9a**–**f** and ethyl formate **10** to form dialkylcarbinols **11a**–**f** following a recent synthesis[10] of **11f** (Scheme 2). After recrystallization, the known products were identified by comparison with melting points[11–14] and the ^{1}H NMR spectrum[10] of **11f** with appropriate adjustment for integration of the methylenes for each homologue. The rapid reactions of **11a**–**f** with mesyl chloride gave **12a**–**f** as clean products as judged by ^{1}H NMR spectra in comparison with the spectrum[15] of the known **12**(n = 16) making adjustments for each homologue. Based on a procedure[16] for a smaller analogue, **12a**–**f** reacted with sodium azide in hot DMF to produce **13a**–**f** after flash column chromatography. As these compounds were unknown and stable, full characterization ensued. Reductions of **13a**–**f** to **14a**–**f**



Scheme 1. Synthesis of **2**(**n**,**n**).



Scheme 2. Synthesis of **3**(**n**,**n**).

by catalytic hydrogenation proceeded to clean product as judged by ^{1}H NMR spectra in comparison with the spectrum[17] of the known **14c** making adjustments for each homologue. The amines **14a**–**f** reacted with **WeNCO** to produce **15**(**n**,**n**), which were purified by flash column chromatography and recrystallized. Formolysis of the tri-*tert*-butyl esters gave **3**(**n**,**n**), which were recrystallized.

2.3. Aqueous solubility

Following our previous method,[4] all members of both **2**(**n**,**n**) and **3**(**n**,**n**) dissolved readily in a solution of triethanolamine/water [~5% (wt/vol)]; the final solution contained ⩾9:1 molar equivalents of triethanolamine:**2**(**n**,**n**) or **3**(**n**,**n**). Choosing the counterions for the ionized carboxyls followed from a study[18] of *N*-lauroyl-L-glutamate in water; the triethanolammonium salt dissolved to a much greater concentration than did the potassium salt. As chain length affects the pK_a of fatty acids because of aggregation,[19] we explored several conditions to achieve the maximum solubility in aqueous solutions while maintaining the minimum equivalents of triethanolamine (pK_a 7.76).[20] Stock solutions (12.5 mg/mL) for all homologues were prepared by simply vortexing the tricarboxylic acid in the aqueous triethanolamine solution. Final stock concentrations ranged from 19,500 to 25,700 μM depending on the formula weight of the homologue. Stock solutions of the amphiphiles in aqueous triethanolamine had a pH of 8–9.

3. Microbiology

3.1. Antimicrobial results

The three series of dendritic tricarboxylato amphiphiles did not display a uniform pattern of activity against the broad spectrum of microorganisms tested, but displayed amphiphile-series-, species-, or chain-length-specific patterns. Although the MIC values obtained were not in the range of 1 μM or lower, a few MICs were below 10 μM (Table 1).

Cryptococcus neoformans was unique among the microorganisms tested by virtue of its susceptibility to members of both series of two-tailed amphiphiles and the one-tailed tricarboxylato dendritic amphiphiles (Table 1). *Mycobacterium smegmatis*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Saccharomyces cerevisiae* were distinguished from the other microorganisms by their susceptibility to all 5 members of the **1**(**n**) series tested. (Although the three bacteria have an outer membrane, *S. cerevisiae* and the remaining microorganisms lack an outer membrane, so that is apparently not the common cellular structure responsible for susceptibility.)

Lactobacillus plantarum, *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *Micrococcus luteus*, and *Aspergillus niger* were simply not inhibited to any degree by the compounds (Table 1). Lack of antimicrobial activity against *L. plantarum* is advantageous because lactobacilli, members of the skin microflora (e.g., vagina), provide some protection to acquisition of infections (e.g., sexually transmitted pathogens).[21]

These results with long chains contrasted with those studies[22,23] that have shown that medium chain free fatty acids (C_8–C_{12}) exhibit the highest antibiotic activity against a variety of mycobacteria, including *M. smegmatis*. *C. neoformans* was unique by its susceptibility to all 5 members of the **3**(**n**,**n**) series (Table 1). With the exception of *C. neoformans* (e.g., **2**(**10**,**10**)), the panel of microorganisms, including the other pathogenic yeast *Candida albicans*, were resistant to the **2**(**n**,**n**) series (Table 1).

Amphiphile-series specificity is shown when a particular series of amphiphiles—**1**(**n**), **2**(**n**,**n**) or **3**(**n**,**n**)—is specifically active against a tested microorganism. Amphiphile-series-specific antimicrobial activities were displayed by the **1**(**n**) series against *E. coli*, *K. pneumoniae*, *M. smegmatis*, and *S. cerevisiae* (Table 1). Members of the **1**(**n**) series were significantly more active against those microorganisms than the corresponding members of the **2**(**n**,**n**) and **3**(**n**,**n**) series. The one exception to that statement was activity against *S. cerevisiae* by **2**(**8**,**8**) (MIC = 380 μM) and **1**(**16**) (MIC = 550 μM); **2**(**8**,**8**) showed incomplete inhibition but **1**(**16**) showed complete inhibition.

Species specificity was displayed when a particular microbial species is uniquely susceptible to a particular amphiphile. The **1**(**n**) homologues were active against the two Gram-negative bacteria, the mycobacterium and *S. cerevisiae*, they were not active against Gram-positive bacteria, the pathogenic yeast, and the filamentous fungus (Table 1). Two-tailed amphiphiles were only active against the yeast, but not the bacteria,

Table 1. MICs of tricarboxylato amphiphiles against bacteria, yeasts, and fungus[a]

Amphiphile	MIC (μM)										
	E. coli	*K. pneumoniae*	*L. plantarum*	*S. aureus*	MRSA	*M. luteus*	*M. smegmatis*	*S. cerevisiae*	*C. albicans*	*C. neoformans*	*A. niger*
1(14)[b]	290	290[a]	6400[a]	6400[a]	6400[a]	>13,000	580[a]	580	1600[a]	1600[a]	6400
1(16)[b]	140	280[a]	6100[a]	760[a]	6100[a]	>12,000	140[a]	550	47[a]	47[a]	3000
1(18)[b]	130	260[a]	1400[a]	1400[a]	720[a]	>12,000	33[a]	130	1400[a]	90[a]	1400
1(20)[b]	62	250[a]	1400[a]	1400[a]	1400[a]	>11,000	62[a]	120	2700[a]	2700[a]	680
1(22)[b]	120	470[a]	950[a]	1300	1300[a]	>10,000	120[a]	30	2600[a]	5200[a]	5200
2(7,7)	3200[a]	>1200	6400[a]	>13,000	3200[a]	6400[a]	3200[a]	800[a]	1600[a]	1200[a]	800[a]
2(8,8)	760[a]	>1100	1500[a]	>12,000	3000[a]	3000[a]	1500[a]	380[a]	190[a]	550[a]	380[a]
2(9,9)	1400[a]	>1000	12,000[a]	>12,000	12,000[a]	12,000[a]	1400[a]	720[a]	>12,000	260[a]	5800[a]
2(10,10)	2700[a]	>1000	11,000[a]	>11,000	11,000[a]	11,000[a]	680[a]	2700[a]	>11,000	62[a]	11,000[a]
2(11,11)	2600[a]	>950	10,000[a]	>10,000	10,000[a]	10,000[a]	650[a]	5200[a]	>10,000	>950	10,000[a]
3(7,7)	3100[a]	>12,000	6200[a]	>12,000	>12,000	>12,000	3100[a]	6200[a]	3100[a]	1100[a]	6200
3(8,8)	1500[a]	>12,000	5900[a]	>12,000	>12,000	>12,000	1500[a]	3000[a]	740[a]	270[a]	5900
3(9,9)	350[a]	>11,000	5600[a]	>11,000	>11,000	>11,000	350[a]	2800[a]	>11,000	64[a]	2800
3(10,10)	2700[a]	>11,000	5300[a]	>11,000	>11,000	>11,000	330[a]	2700[a]	>11,000	15[a]	11,000
3(11,11)	2500	>10,000	10,000[a]	>10,000	>10,000	>10,000	640[a]	1300[a]	>10,000	7.2[a]	10,000
3(12,12)	2400	>9800	9800[a]	>9800	>9800	>9800	1200[a]	610[a]	>9800	6.9[a]	9800

[a] Incomplete inhibition.
[b] MIC data from Ref. 1.

mycobacterium, or filamentous fungus. For the yeasts tested, some homologues of the **2(n,n)** series had antimicrobial activity against both *C. albicans* and *C. neoformans*, while all but one of the **3(n,n)** amphiphile series had strong antimicrobial activity against *C. neoformans*.

As only particular members of the homologous series with specific chain length show distinct activities, these amphiphiles also displayed another type of specificity, namely chain-length specificity. Chain-length specificity was displayed when amphiphiles in a homologous series with a particular chain length are exceptionally active compared to those with other chain lengths. Chain-length specificity was displayed by members of the **1(n)** series against *M. smegmatis*, *S. cerevisiae*, *C. albicans*, and *C. neoformans*, by those of the **2(n,n)** series against *C. albicans* and *C. neoformans*, and by those of the **3(n,n)** series against *C. neoformans* (Table 1).

In the **1(n)** series, the MIC of **1(16)** against both *C. albicans* and *C. neoformans* was 47 μM, the MIC of **1(18)** against *M. smegmatis* was 33 μM, and the MIC of **1(22)** against *S. cerevisiae* was 30 μM. This chain-length specificity was not found in the **1(n)** series against the rest of the microorganisms tested and the homologues of **1(n)** were not particularly active against those microorganisms. Among the two-tailed amphiphiles, the three homologues **3(10,10)**, **3(11,11)**, and **3(12,12)** showed unique and promising MICs of 15 μM, 7.2 μM, and 6.9 μM, respectively, against *C. neoformans*.

Chain-length specificity was particularly demonstrated by **2(8,8)** against *C. albicans* (MIC = 190 μM) and **2(10,10)** against *C. neoformans* (MIC = 62 μM) (Table 1). As the strain of *C. albicans* was grown at 37 °C, it had low cell surface hydrophobicity,[24] which likely contributed to relative resistance of the cells to amphiphiles.

3.2. Comparing hydrophobicity and antimicrobial activity

Partitioning of these amphiphiles into both outer and cytoplasmic membranes should be a major contributor to their antimicrobial activity. From simple approximations of hydrophobicity, the distribution coefficient increases with increasing alkyl chain length. Calculations[6] of log D at pH 7.4 give values that range from −5.1 for **1(14)** to −1.9 for **1(22)** in increments of 0.8 for each additional $–CH_2–CH_2–$ unit, from −5.2 for **2(7,7)** to −2.0 for **2(11,11)** in increments of 0.8 for each additional $–CH_2–$ in each chain, and from −5.0 for **3(7,7)** to −1.0 for **3(12,12)** in increments of 0.8 for an additional $–CH_2–$ in each chain. Because of the multiple ionization states of the headgroup, log D is the appropriate choice. These calculations suggest that the triheaded amphiphiles are substantially more likely to favor being in a hydrophilic phase than in a hydrophobic phase.

Comparing log D versus MIC for each member of the three series reveals the similarities with respect to the antimicrobial activity against *C. albicans* (Fig. 1).

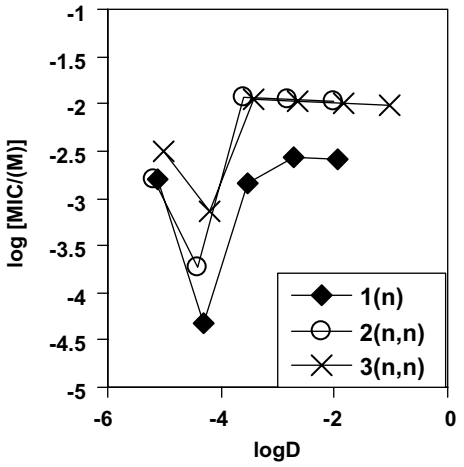


Figure 1. Relationship between MIC and log D for *C. albicans*. Error bars (not shown for clarity) are ±0.3. Lines connecting the symbols are eye guides.

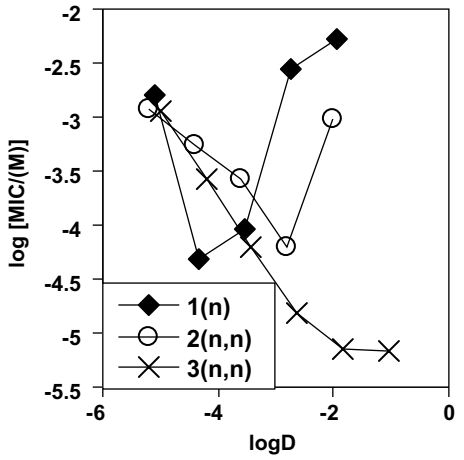


Figure 2. Relationship between MIC and log D for *C. neoformans*. Error bars (not shown for clarity) are ±0.3. Lines connecting the symbols are eye guides.

All series show a similar pattern of activity against *C. albicans*, a microorganism that shows chain-length specificity. In this comparison, one can see that the log D predicts activity, but it is not the only property of the amphiphile that contributes to the antimicrobial activity. As the one-tail amphiphile **1(16)** has better activity than **2(8,8)** and **3(8,8)**, tail topology also contributes.

Comparing log D versus MIC for each member of the three series reveals significant differences with respect to the antimicrobial activity against *C. neoformans* (Fig. 2). For *C. neoformans*, there is no similarity in the patterns among the three series; log D does not predict activity. Amphiphiles **1(16)**, **2(10,10)**, and **3(12,12)** are the most active members of the respective series. Clearly, the **3(n,n)** series is the best among these three series. The trend in the plot of the **3(n,n)** series suggests that longer homologues should be tested to see whether **3(12,12)** is the best in the series.

4. Conclusions

4.1. Comparison with prior work

Many compounds containing two symmetrical alkyl chains bonded to a nitrogen atom have been synthesized and studied for their antibacterial and antifungal activity. To our knowledge, none of these compounds have anionic headgroups as reported in this study. In these previous studies, the compounds are in the neutral[25,26] or charged form.[27–30] The charged forms involve quaternary ammonium with chloride counterions,[27–29] or intercalation complexes[30] with montmorillonite or saponite. In a study[27] of antibacterial properties against *S. aureus*, several homologous tertiary amines quaternize cross-linked chloromethyl polystyrenes; antibacterial efficiency increases as the alkyl chain length increases.

Unlike compounds containing a nitrogen atom directly bonded to two symmetrical fatty chains, there are only few studies on compounds containing a nitrogen atom bonded to a swallowtail, a long fatty chain bonded through the middle carbon atom. These compounds have been synthesized and investigated for antibacterial[31,32] and antifungal[31] activity. These compounds have cationic[31,32] and neutral[31] headgroups.

4.2. Summary and mechanistic speculation

In our study, amphiphiles with two tails are less active than the amphiphiles with one tail. However, two results worth further investigation emerge from this study. The first result is the good activity of **3(11,11)** and **3(12,12)** against *C. neoformans*. It will be interesting to measure the antimicrobial activity of longer homologues of **3(n,n)**. The second result is the chain-length specificity for activity against *C. albicans* by **1(16)**, **2(8,8)**, and **3(8,8)**. For the most part, long one-tailed amphiphiles were more antimicrobial than two-tailed amphiphiles with the same total chain length. As two-tailed amphiphiles had moderate antimicrobial activity, longer chain two-tailed amphiphiles may have even higher antimicrobial activities compared to the long one-tailed amphiphiles. Accordingly, measurement of the activity of the odd-numbered chain homologues and those with unsymmetrical tails is planned. Further, substitutions in the chain might lead to more active antifungal agents as evidenced by recent studies of synthetic fatty acids.[33–36]

Although the mechanism of action of these amphiphiles remains to be determined, we expect that these amphiphiles exert their antimicrobial activity by interacting with the cell membranes or cell walls or both. Excluding detergency (disrupting cell walls and solubilizing membranes), these amphiphiles can inactivate microorganisms by several mechanisms: (1) as monomers, changing fluidity and porosity of membranes; (2) as monomers, altering membrane-associated pathways (e.g., cell signaling); (3) as monomers, changing the flow of constituents and nutrients between a cell and a medium; and (4) as monomers, inhibiting membrane-associated enzymes or enzymes involved in fatty acid synthesis.

As our recent study[37] of the antimycobacterial activity of **1**(**n**) reveals, the MIC (and possibly the mechanism of action) depends on the number of colonies in the inoculum. Studies are planned to measure this inoculum effect with **2**(**n**,**n**) and **3**(**n**,**n**) against selected microorganisms.

5. Experimental

5.1. General chemical procedures

Chemicals were obtained from Aldrich, Acros, Lancaster, and TCI; they were used without further purification. Solvents were reagent grade or HPLC grade; they were used as received unless otherwise specified. THF was distilled from sodium/benzophenone ketyl. WeNCO was prepared as described[38] with a shorter reaction time—15 min. Analytical thin layer chromatography was performed on polyester-coated silica gel 60 Å strips and detected by treating with 10% ethanolic phosphomolybdic acid reagent (20 wt. % solution in ethanol) followed by heating. Flash column chromatography was carried out on silica gel (60 Å); samples were loaded as concentrated solutions in the solvent system needed; column diameter × height ($1^3/_4 \times 6$ in), eluted samples varied between ~2.00 and 4.00 g, flow rate (~1.5–2 in/min) was controlled by air pressure. Solutions were concentrated by rotary evaporation. Melting ranges were determined in open capillary tubes and are uncorrected. NMR spectra were recorded at 400 and 100 MHz for ^{1}H and ^{13}C, respectively, and reported in ppm relative to the known solvent residual peak. Resonances were reported in the order of chemical shift (δ), followed by the splitting pattern, and the number of protons. Abbreviations used in the splitting pattern were as follows: s = singlet, d = doublet, t = triplet, quin = quintet, m = multiplet, and b = broad. IR spectra were recorded on neat samples with an FTIR equipped with a diamond ATR system and reported in cm^{-1}. HRMS data were obtained on a dual-sector mass spectrometer in FAB mode with 2-nitrobenzyl alcohol as the proton donor. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

5.2. General procedures for *N*-alkylalkanamide (7a,c,e)

An alkan-1-amine **5** (13.0 mmol) and Et_3N (15.6 mmol) were combined, dissolved in dry THF (38 mL), and stirred in the ice bath. An acid chloride **6** (14.3 mmol) was added dropwise to the solution, which was maintained at 2.5 ± 1.0 °C. After the addition, the ice bath was removed, and the reaction mixture was stirred for another 15 min at rt. The resulting reaction mixture was washed successively with HCl (1 M, 7.5 mL), saturated aqueous $NaHCO_3$ (12 mL), and water (12 mL). The organic layer was dried with Na_2SO_4 and concentrated to dryness to give a white solid, which was purified by flash column chromatography to give a pure white solid, which gave a single spot on TLC with 2% MeOH in CH_2Cl_2 (R_f = 0.23–0.31).

5.2.1. *N*-Heptylheptanamide (7a). The general procedure described above afforded a white solid (2.50 g, 85%); mp 45.0–45.7 °C (lit.[9] mp 44–46 °C); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.35 (bm, 14H), 1.50 (m, 2H), 1.62 (m, 2H), 2.17 (t, 2H), 3.24 (m, 2H), 5.69 (bs, 1H) (lit. 250 MHz,[39] 300 MHz[9]); ^{13}C NMR ($CDCl_3$) δ 14.19, 14.20, 22.69, 22.75, 26.0, 27.1, 29.15, 29.17, 29.9, 31.7, 31.9, 37.1, 39.7, 173.3 (lit.[9] 75 MHz); IR 3287, 2955, 2921, 2851, 1640, 1555, 1467 (lit.[39] neat); HRMS: for $C_{14}H_{30}NO$ $[M+H]^+$ calcd 228.2327, found 228.2328.

5.2.2. *N*-Nonylnonanamide (7c). The general procedure described above afforded a white solid (3.05 g, 83%); mp 62.7–63.39 °C (lit.[40] mp 52–55 °C); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.20–1.35 (bm, 22H), 1.48 (m, 2H), 1.62 (m, 2H), 2.15 (t, 2H), 3.25 (m, 2H), 5.36 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.66, 22.68, 25.9, 26.9, 29.18, 29.25, 29.32, 29.35, 29.5, 29.7, 31.84, 31.87, 37.0, 39.5, 173.03; IR 3287, 2955, 2918, 2849, 1638, 1551, 1467; HRMS: for $C_{18}H_{38}NO$ $[M+H]^+$ calcd 284.2953, found 284.2940.

5.2.3. *N*-Undecylundecanamide (7e). The general procedure described above afforded a white solid (3.12 g, 71%); mp 73.9–74.7 °C (lit.[41] mp 73 °C); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.35 (bm, 32H), 1.49 (m, 2H), 1.62 (m, 2H), 2.15 (t, 2H), 3.24 (m, 2H), 5.36 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.1, 27.2, 29.53, 29.54, 29.59, 29.73, 29.77, 29.79, 29.80, 29.9, 32.1, 37.2, 39.7, 173.3; IR 3312, 2953, 2914, 2849, 1634, 1544, 1471 (lit.[42] bands); HRMS: for $C_{22}H_{46}NO$ $[M+H]^+$ calcd 340.3579, found 340.3584.

5.3. General procedures for *N*-alkylalkan-1-amine (8a,c,e)

An *N*-alkylalkanamide **7** (9.58 mmol) was added slowly to a stirred suspension of $LiAlH_4$ (574 mg, 14.7 mmol) in Et_2O (50 mL). Addition took place in an ice–salt bath, while the temperature was maintained at 0.0 ± 1.0 °C. After the addition, the reaction mixture was warmed to rt and then heated to reflux. After being refluxed overnight, the resulting reaction mixture was cooled to rt. Successive addition of water (2 mL), NaOH (10 M, 2.5 mL), and water (4 mL) yields a sticky white solid. The organic layer was decanted, and the sticky white solid was washed once with Et_2O (10 mL). The organic layers were combined, dried with Na_2SO_4, and concentrated to give clear liquids (n = 7, 9), and a white solid (n = 11) in 80–85% yield. Each resulting *N*-alkylalkan-1-amine (**8a**,**c**,**e**) was used for the next step without further purification.

5.3.1. *N*-Heptylheptan-1-amine (8a). The general procedure described above afforded a clear liquid (1.72 g, 84%) (lit.[9] mp 30–31 °C); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.35 (bm, 16H), 1.48 (m, 4H), 2.58 (t, 4H) (lit. 60 MHz,[43] 300 MHz[9]); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.8, 27.6, 29.5, 30.4, 32.0, 50.4 (lit.[9] 75 MHz); IR 2955, 2922, 2853, 1457, 1377, 1129 (lit.[43] neat); HRMS: for $C_{14}H_{32}N$ $[M+H]^+$ calcd 214.2535, found 214.2538.

5.3.2. *N*-Nonylnonan-1-amine (8c). The general procedure described above afforded a clear liquid (2.14 g,

83%) (lit.[40] 37–39 °C); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.35 (bm, 24H), 1.47 (m, 4H), 2.58 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 27.7, 29.5, 29.79, 29.82, 30.5, 32.1, 50.4; IR 2954, 2921, 2852, 1466, 1377, 1130; HRMS: for $C_{18}H_{40}N$ $[M+H]^+$ calcd 270.3161, found 270.3148.

5.3.3. *N*-Undecylundecan-1-amine (8e). The general procedure described above afforded a white solid (2.50 g, 80%); mp 47.5–48.3 °C (lit.[44] 51.5–52.5 °C); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.35 (bm, 32H), 1.47 (m, 4H), 2.58 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 27.7, 29.6, 29.8, 30.5, 32.1, 50.4; IR 2955, 2913, 2827, 1469, 1375, 1127; HRMS: for $C_{22}H_{48}N$ $[M+H]^+$ calcd 326.3787, found 326.3775.

5.4. General procedures for two-tailed tri-*tert*-butyl esters, 4(n,n)

A dialkylamine **8** (4.95 mmol) was added slowly to a solution of **WeNCO** (4.71 mmol) in CH_2Cl_2 (20 mL). The resulting transparent solution was stirred at rt. After stirring overnight, the solution was concentrated to leave a crude white solid. The crude solid was purified by flash column chromatography with 5:1 (v/v) hexane:EtOAc to give a white solid (60–85%), which gave a single spot on TLC (hexane/EtOAc, 5:1, $R_f = 0.18$–0.25).

5.4.1. Di-*tert*-butyl 4-(2-*tert*-butoxycarbonylethyl)-4-(3,3-diheptylureido)heptanedioate, 4(7,7). The general procedure described above afforded a white solid (2.44 g, 79%); mp 53.5–54.1 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.35 (bm, 16H), 1.43 (bs, 27H), 1.51 (m, 4H), 1.96 (m, 6H), 2.22 (m, 6H), 3.12 (m, 4H), 4.56(s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 27.0, 28.0, 28.7, 29.1, 29.9, 30.6, 31.8, 47.2, 56.6, 80.3, 156.1, 173.1; IR 3368, 2925, 1733, 1725, 1615, 1365, 1143; HRMS: for $C_{37}H_{71}N_2O_7$ $[M+H]^+$ calcd 655.5261, found 655.5242. Anal. Calcd for $C_{37}H_{70}N_2O_7$: C, 67.85; H, 10.77; N, 4.28. Found: C, 67.89; H, 10.84; N, 4.30.

5.4.2. Di-*tert*-butyl 4-(2-*tert*-butoxycarbonylethyl)-4-(3,3-dioctylureido)heptanedioate, 4(8,8). The general procedure described above afforded a white solid (1.93 g, 60%); mp 56.8–57.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 6H), 1.20–1.35 (bm, 20H), 1.43 (s, 27H), 1.50 (m, 4H), 1.96 (m, 6H), 2.21 (m, 6H), 3.11 (m, 4H), 4.55 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 27.0, 28.1, 28.7, 29.27, 29.44, 29.9, 30.6, 31.8, 47.3, 56.6, 80.4, 156.1, 173.2; IR 3366, 2923, 1732, 1724, 1615, 1365, 1144; HRMS: for $C_{39}H_{75}N_2O_7$ $[M+H]^+$ calcd 638.5574, found 638.5540. Anal. Calcd for $C_{39}H_{74}N_2O_7$: C, 68.58; H, 10.92; N, 4.10. Found: C, 68.55; H, 11.07; N, 4.10.

5.4.3. Di-*tert*-butyl 4-(2-*tert*-butoxycarbonylethyl)-4-(3,3-dinonylureido)heptanedioate, 4(9,9). The general procedure described above afforded a white solid (2.34 g, 70%); mp 62.6–63.4 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.35 (bm, 24H), 1.44 (bs, 27H), 1.51 (bm, 4H), 1.97 (m, 6H), 2.22 (m, 6H), 3.12 (m, 4H), 4.57 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 27.0, 28.1, 28.7, 29.2, 29.49, 29.58, 29.9, 30.6, 31.8, 47.3, 56.6, 80.4, 156.1, 173.15; IR 3377, 2922, 1732, 1725, 1617, 1365, 1144; HRMS: for $C_{41}H_{79}N_2O_7$ $[M+H]^+$ calcd 711.5887, found 711.5893. Anal. Calcd for $C_{41}H_{78}N_2O_7$: C, 69.25; H, 11.06; N, 3.94. Found: C, 69.34; H, 11.27; N, 3.96.

5.4.4. Di-*tert*-butyl 4-(2-*tert*-butoxycarbonylethyl)-4-(3,3-didecylureido)heptanedioate, 4(10,10). The general procedure described above afforded a white solid (2.96 g, 85%); mp 49.7–50.4 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.35 (bs, 28H), 1.43 (s, 27H), 1.50 (m, 4H), 1.96 (m, 6H), 2.21 (m, 6H), 3.11 (m, 4H), 4.55 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 27.0, 28.1, 28.7, 29.3, 29.49, 29.55, 29.63, 29.9, 30.6, 31.9, 47.3, 56.6, 80.4, 156.1, 173.2; IR 3389, 2925, 1729, 1719, 1618, 1365, 1143; HRMS: for $C_{43}H_{83}N_2O_7$ $[M+H]^+$ calcd 739.6200, found 739.6213. Anal. Calcd for $C_{43}H_{82}N_2O_7$: C, 69.88; H, 11.18; N, 3.79. Found: C, 70.02; H, 11.41; N, 3.80.

5.4.5. Di-*tert*-butyl 4-(2-*tert*-butoxycarbonylethyl)-4-(3,3-diundecylureido)heptanedioate, 4(11,11). The general procedure described above afforded a white solid (2.64 g, 73%); mp 42.9–43.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.35 (bm, 32H), 1.43 (bs, 27H), 1.50 (bm, 4H), 1.96 (m, 6H), 2.21 (m, 6H), 3.11 (m, 4H), 4.56(s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.65, 27.03, 28.1, 28.7, 29.3, 29.49, 29.59, 29.62, 29.9, 30.6, 31.9, 47.3, 56.6, 80.35, 156.1, 173.1; IR 3372, 2923, 1734, 1725, 1616, 1365, 1143; HRMS: for $C_{45}H_{87}N_2O_7$ $[M+H]^+$ calcd 767.6513, found 767.6498. Anal. Calcd for $C_{45}H_{86}N_2O_7$: C, 70.45; H, 11.30; N, 3.65. Found: C, 70.45; H, 11.46; N, 3.71.

5.5. General procedures for two-tailed triacids, 2(n,n)

A tri-*tert*-butyl ester **4(n,n)** (3.33 mmol) was dissolved in 99% HCOOH so that its concentration was 0.1 M. The mixture might need to be warmed slightly to get all the **4(n,n)** to dissolve. Once dissolved to give a clear colorless solution, the solution was stirred at rt. After 9 h, the resulting milky white solution was concentrated. The white solid was recrystallized from EtOAc to yield a white solid (77–90%).

5.5.1. 4-(2-Carboxyethyl)-4-(3,3-diheptylureido)heptanedioic acid, 2(7,7). The general procedure described above afforded a white solid (1.46 g, 90%); mp 125.3–125.9 °C; ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 6H), 1.10–1.30 (bm, 16H), 1.38 (m, 4H), 1.81 (m, 6H), 2.09 (m, 6H), 3.09 (m, 4H), 5.07 (s, 1H), 12.00 (bs, 3H); ^{13}C NMR (DMSO-d_6) δ 14.4, 22.5, 26.7, 28.5, 28.7, 29.0, 30.2, 31.7, 46.3, 56.4, 156.3, 175.1; IR 2926, 1735, 1701, 1590, 1527, 1285, 1174; HRMS: for $C_{25}H_{47}N_2O_7$ $[M+H]^+$ calcd 487.3383 found 487.3391. Anal. Calcd for $C_{25}H_{46}N_2O_7$: C, 61.70; H, 9.53; N, 5.76. Found: C, 61.61; H, 9.50; N, 5.75.

5.5.2. 4-(2-Carboxyethyl)-4-(3,3-dioctylureido)heptanedioic acid, 2(8,8). The general procedure described above afforded a white solid (1.47 g, 86%); mp 120.4–120.8 °C; ^{1}H NMR (DMSO-d_6) δ 0.80 (t, 6H), 1.10–1.30 (bm, 20H), 1.38 (m, 4H), 1.81 (m, 6H), 2.08 (m,

6H), 3.09 (m, 4H), 5.06 (s, 1H), 12.00 (bs, 3H); ^{13}C NMR (DMSO-d_6) δ 13.9, 22.0, 26.2, 28.0, 28.2, 28.7, 28.8, 29.7, 31.2, 45.8, 55.9, 155.9, 174.7; IR 2921, 1713, 1694, 1607, 1533, 1293, 1175; HRMS: for $C_{27}H_{51}N_2O_7$ $[M+H]^+$ calcd 515.3702, found 515.3696. Anal. Calcd for $C_{27}H_{50}N_2O_7$: C, 63.01; H, 9.79; N, 5.40. Found: C, 62.98; H, 9.79; N, 5.40.

5.5.3. 4-(2-Carboxyethyl)-4-(3,3-dinonylureido)heptanedioic acid, 2(9,9). The general procedure described above afforded a white solid (1.59 g, 88%); mp 121.3–121.7 °C; ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 6H), 1.10–1.30 (bm, 24H), 1.38 (m, 4H), 1.82 (m, 6H), 2.09 (m, 6H), 3.09 (m, 4H), 5.07 (s, 1H), 11.98 (bs, 3H); ^{13}C NMR (DMSO-d_6) δ 14.6, 22.8, 27.0, 28.7, 29.0, 29.3, 29.58, 29.66, 30.4, 32.0, 46.6, 56.6, 156.6, 175.4; IR 3446, 2919, 1712, 1694, 1608, 1534, 1293, 1175; HRMS: for $C_{29}H_{55}N_2O_7$ $[M+H]^+$ calcd 543.4009, found 543.3997. Anal. Calcd for $C_{29}H_{54}N_2O_7$: C, 64.18; H, 10.03; N, 5.16. Found: C, 63.93; H, 10.02; N, 5.15.

5.5.4. 4-(2-Carboxyethyl)-4-(3,3-didecylureido)heptanedioic acid, 2(10,10). The general procedure described above afforded a white solid (1.63 g, 88%); mp 120.9–121.2 °C. ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 6H), 1.10–1.30 (bm, 28H), 1.37 (m, 4H), 1.81 (m, 6H), 2.08 (m, 6H), 3.09 (m, 4H), 5.08 (s, 1H), 11.99 (bs, 3H); ^{13}C NMR (DMSO-d_6) δ 14.4, 22.5, 26.7, 28.5, 28.7, 29.1, 29.32, 29.40, 29.46, 30.2, 31.7, 46.3, 56.4, 156.3, 175.2; IR 2919, 1712, 1694, 1608, 1534, 1293, 1175; HRMS: for $C_{31}H_{59}N_2O_7$ $[M+H]^+$ calcd 571.4322, found 571.4315. Anal. Calcd for $C_{31}H_{58}N_2O_7$: C, 65.23; H, 10.24; N, 4.91. Found: C, 65.33; H, 10.34; N, 4.93.

5.5.5. 4-(2-Carboxyethyl)-4-(3,3-diundecylureido)heptanedioic acid, 2(11,11). The general procedure described above afforded a white solid (1.53 g, 77%); mp 121.4–122.1 °C; ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 6H), 1.10–1.30 (bm, 32H), 1.38 (m, 4H), 1.81 (m, 6H), 2.08 (m, 6H), 3.09 (m, 4H), 5.07 (s, 1H), 12.00 (bs, 3H); ^{13}C NMR (DMSO-d_6) δ 14.4, 22.6, 26.7, 28.5, 28.7, 29.17, 29.33, 29.46, 30.2, 31.8, 46.4, 56.4, 156.3, 175.2; IR 2917, 1713, 1694, 1608, 1535, 1295, 1185; HRMS: for $C_{33}H_{63}N_2O_7$ $[M+H]^+$ calcd 599.4635, found 599.4620. Anal. Calcd for $C_{33}H_{62}N_2O_7$: C, 66.19; H, 10.44; N, 4.68. Found: C, 66.17; H, 10.40; N, 4.69.

5.6. General procedure for the preparation of dialkylcarbinols (11a–f)

To a three-necked round-bottomed flask containing Mg turnings (2.34 g, 100 mmol) were added several chips of I_2. After the flask was flushed with N_2, the mixture was stirred for a couple of minutes until I_2 sublimed. THF (12 mL) was added, following a solution of bromoalkane **9** (48.1 mmol) in THF (36 mL) in a dropwise (1 drop/3 s) manner through a dropping funnel. Then, **10** (1.43 g, 19.0 mmol) in dry THF (24 mL) was added at the same rate through a dropping funnel. The reaction mixture was stirred and heated (65–70 °C). Monitoring the reaction with TLC showed that 3 d were needed to achieve the best yields. The reaction mixture was diluted with THF (36 mL), followed by successive addition of MeOH (4 mL) and saturated NH_4Cl (30 mL). The organic layer was separated and washed with saturated NaCl (65 mL). The organic layer was dried and concentrated to give a light yellow solid, which was recrystallized from EtOAc to give a pure white solid (**11**) in moderate yield (49–56%); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.50 (bm, 24–44Hs), 3.58 (bm, 1H) (lit.[10] 200 MHz, **11f**); **11a** mp 53.5–54.3 °C (lit.[12] 52–52.6 °C); **11b** 61.7–62.2 °C (lit.[12] 60.8–61.2 °C); **11c** 67.0–67.4 °C (lit.[13] 65.9–66.1 °C); **11d** 71.1–72.0 °C (lit.[14] 71.3–72.5 °C); **11e** 76.8–77.6 °C (lit.[12] 75.5–75.7 °C); **11f** 80.2–81.0 °C (lit.[11] 79.5–80.5 °C).

5.7. General procedure for the preparation of bis(alkyl)methyl mesylates (12a–f)

To a solution of **11** (8.96 mmol) and Et_3N (9.86 mmol) in THF (59 mL) was added MsCl (25.7 mmol) dropwise through a syringe at rt. In the middle of the addition, the clear solution became cloudy. After the addition, the reaction mixture was stirred for another 15 min. The resulting suspension was filtered; the filtrate was washed successively with water (8 mL) and saturated aqueous NaCl (2 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated to give a light yellow liquid (**12**) in 90–98% yield. The product was used for the next step without further purification; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.50 (bm, 24–44Hs), 1.60–1.75 (m, 4H), 3.00 (s, 3H), 4.70 (quin, 1H) (lit.[15] 200 MHz, **9**, R = n-$C_{16}H_{33}$).

5.8. General procedures for bis(alkyl)azidomethanes (13a–f)

To a stirred solution of **12** (7.41 mmol) in DMF (49 mL) at rt was slowly added NaN_3 (36.3 mmol). The suspension was heated to 85 °C for 4 h. After the resulting yellow solution was cooled to rt, hexane (98 mL) and water (16 mL) were added. The organic layer was separated and washed successively with saturated $NaHCO_3$ (8 mL) and saturated NaCl (8 mL). The organic layer was dried with Na_2SO_4 and concentrated to give a colorless oil, which was purified by flash column chromatography with hexane to give a pure colorless oil (**13a–e**) or a white solid (**13f**), which gave a single spot on TLC with hexane (R_f = 0.41), in 78–97% yield.

5.8.1. 8-Azidopentadecane (13a). The general procedure described above afforded a colorless liquid (1.46 g, 78%); ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.20–1.53 (bm, 24H), 3.22 (quin, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.4, 29.4, 29.6, 32.0, 34.6, 63.4; IR 2924, 2855, 2093; HRMS: for $C_{15}H_{32}N_3$ $[M+H]^+$ calcd 254.2596, found 254.2597. Anal. Calcd for $C_{15}H_{31}N_3$: C, 71.09; H, 12.33; N, 16.58. Found: C, 71.16; H, 12.44; N, 16.44.

5.8.2. 9-Azidoheptadecane (13b). The general procedure described above afforded a colorless liquid (1.73 g, 83%); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.53 (bm, 28H), 3.22 (quin, 1H); ^{13}C NMR ($CDCl_3$) δ14.3, 22.9, 26.4, 29.5, 29.68, 29.70, 32.1, 34.6, 63.4; IR 2923, 2854, 2091; HRMS: for $C_{17}H_{36}N_3$ $[M+H]^+$ calcd 254.2848, found 254.2847. Anal. Calcd for $C_{17}H_{35}N_3$:

C, 72.54; H, 12.53; N, 14.93. Found: C, 72.83; H, 12.68; N, 14.86.

5.8.3. 10-Azidononadecane (13c). The general procedure described above afforded a colorless liquid (2.11 g, 92%); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.54 (bm, 32H), 3.22 (quin, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.4, 29.5, 29.65, 29.72, 32.1, 34.6, 63.3; IR 2922, 2853, 2093; HRMS: for $C_{19}H_{40}N_3$ $[M+H]^+$ calcd 282.3161, found 282.3149. Anal. Calcd for $C_{19}H_{39}N_3$: C, 73.73; H, 12.70; N, 13.57. Found: C, 73.91; H, 12.77; N, 13.42.

5.8.4. 11-Azidohenicosane (13d). The general procedure described above afforded a colorless liquid (2.47 g, 97%); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 6H), 1.24–1.55 (bm, 36H), 3.22 (quin, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.3, 29.5, 29.65, 29.71, 29.76, 29.78, 32.1, 34.6, 63.4; IR 2922, 2853, 2093; HRMS: for $C_{21}H_{44}N_3$ $[M+H]^+$ calcd 310.3474, found 310.3467. Anal. Calcd for $C_{21}H_{43}N_3$: C, 74.71; H, 12.84; N, 12.45. Found: C, 74.86; H, 12.98; N, 12.44.

5.8.5. 12-Azidotricosane (13e). The general procedure described above afforded a colorless liquid (2.28 g, 84%); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 6H), 1.20–1.54 (bm, 40H), 3.23 (quin, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.4, 29.6, 29.7, 29.75, 29.78, 29.85, 29.86, 32.1, 34.6, 63.4; IR 2921, 2852, 2094; HRMS: for $C_{23}H_{48}N_3$ $[M+H]^+$ calcd 338.3787, found 338.3794. Anal. Calcd for $C_{23}H_{47}N_3$: C, 75.55; H, 12.96; N, 11.49. Found: C, 75.78; H, 13.10; N, 11.49.

5.8.6. 13-Azidopentacosane (13f). The general procedure described above afforded a white solid (2.63 g, 90%); mp 36.8–37.4 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.26–1.52 (bm, 44H), 3.22 (quin, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.4, 29.6, 29.67, 29.75, 29.8, 29.86, 29.88, 32.1, 34.6, 63.4; IR 2913, 2848, 2085; HRMS: for $C_{25}H_{52}N_3$ $[M+H]^+$ calcd 366.4100, found 366.4090. Anal. Calcd for $C_{25}H_{51}N_3$: C, 72.67; H, 13.06; N, 10.67. Found: C, 76.35; H, 13.14; N, 10.63.

5.9. General procedures for bis(alkyl)methanamines (14a–f)

To a solution of **13** (7.03 mmol) in hexane (35 mL) was added 10% Pd/C (3% weight of azidoalkane). The resulting solution was shaken and hydrogenated under 62 psi at rt for 3 h. After sitting overnight, the resulting solution was filtered. The filtrate was concentrated to give a colorless liquid (**14a**–**d**) or a white solid (**14e**,**f**) in 75–88% yield. The product was used in the next step without purification.

5.9.1. Pentadecan-8-amine (14a). The general procedure described above afforded a colorless liquid (1.22 g, 76%); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.45 (bm, 26H; 2Hs exchange with D_2O), 2.67 (bm, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.8, 26.4, 29.5, 30.0, 32.0, 38.4, 51.40; IR 2955, 2921, 2852, 1464, 767.

5.9.2. Heptadecan-9-amine (14b). The general procedure described above afforded a colorless liquid (1.35 g, 75%); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.45 (bm, 30H), 2.67 (bm, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.4, 29.5, 29.8, 30.0, 32.1, 38.2, 51.4; R 2955, 2921, 2852, 1464, 800.

5.9.3. Nonadecan-10-amine (14c). The general procedure described above afforded a colorless liquid (1.67 g, 84%); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.45 (bm, 34H; 2Hs exchange with D_2O), 2.68 (bm, 1H) (lit.[17] 500 MHz); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.4, 29.5, 29.8, 29.9, 30.0, 32.1, 38.4, 51.4; IR 2955, 2921, 2852, 1464, 797 (lit.[17] KBr pellet).

5.9.4. Henicosan-11-amine (14d). The general procedure described above afforded a colorless liquid (1.93 g, 88%); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.45 (bm, 38H; 2Hs exchange with D_2O), 2.67 (bm, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.4, 29.5, 29.83, 29.85, 29.87, 30.0, 32.1, 38.3, 51.4; IR 2955, 2920, 2852, 1464, 792.

5.9.5. Tricosan-12-amine (14e). The general procedure described above afforded a white solid (1.93 g, 81%); mp 65.5–66.4 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.13 (s, 2H), 1.20–1.45 (bm, 42H; 2Hs exchange with D_2O), 2.67 (bm, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.4, 29.6, 29.86, 29.89, 30.1, 32.1, 33.3, 51.4; IR 2953, 2913, 2848, 1468, 720.

5.9.6. Pentacosan-13-amine (14f). The general procedure described above afforded a white solid (2.15 g, 86%); mp 79.7–80.4 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.45 (bm, 46H; 2Hs exchange with D_2O), 2.67 (bm, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.4, 29.6, 29.87, 29.89, 29.91, 30.1, 32.1, 38.4, 51.4; IR 2952, 2914, 2848, 1467, 720.

5.10. General procedures for swallowtail tri-*tert*-butyl esters, 15(n,n)

An amine **14** (4.95 mmol) was added slowly to a solution of **WeNCO** (4.71 mmol) in CH_2Cl_2 (20 mL). The resulting transparent solution was stirred at rt. After stirring overnight, the solution was concentrated to afford a crude white solid. This crude product was purified by flash column chromatography to give a white solid, which gave a single spot on TLC (hexane/EtOAc, 5:1, R_f = 0.17–0.30). The isolated solid was then recrystallized from CH_3CN (60–87%).

5.10.1. Di-*tert*-butyl 4-(2-*tert*-butoxycarbonylethyl)-4-[3-(1-heptyloctyl)ureido]heptanedioate, 15(7,7). The general procedure described above afforded a white solid (1.89 g, 60%); mp 109.0–109.8 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.35 (bm, 22H), 1.43 (bs, 29H), 1.94 (m, 6H), 2.23 (m, 6H), 3.52 (bm, 1H), 3.76 (d, 1H), 4.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 25.8, 28.0, 29.2, 29.6, 29.8, 30.6, 31.8, 35.7, 50.2, 56.4, 80.4, 156.4, 173.0; IR 3329, 2922, 2852, 1726, 1650, 1151; HRMS: for $C_{38}H_{73}N_2O_7$ $[M+H]^+$ calcd 669.5418, found 669.5419. Anal. Calcd for $C_{38}H_{72}N_2O_7$: C, 68.22; H, 10.85; N, 4.19. Found: C, 67.96; H, 10.91; N, 4.26.

5.10.2. Di-*tert*-butyl 4-(2-*tert*-butoxycarbonylethyl)-4-[3-(1-octylnonyl)ureido]heptanedioate, 15(8,8). The general procedure described above afforded a white solid (2.30 g, 70%); mp 108.5–109.3 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.35 (bm, 26H), 1.43 (bs, 29H), 1.94 (m, 6H), 2.23 (m, 6H), 3.51 (bm, 1H), 3.75 (d, 1H), 4.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 25.8, 28.0, 29.2, 29.5, 29.7, 29.8, 30.6, 31.8, 35.7, 50.2, 56.4, 80.4, 156.4, 173.0; IR 3317, 2925, 2855, 1730, 1630, 1147; HRMS: for $C_{40}H_{77}N_2O_7$ $[M+H]^+$ calcd 697.5731, found 697.5731. Anal. Calcd for $C_{40}H_{76}N_2O_7$: C, 68.92; H, 10.99; N, 4.02. Found: C, 69.06; H, 11.17; N, 4.06.

5.10.3. Di-*tert*-butyl 4-(2-*tert*-butoxycarbonylethyl)-4-[3-(1-nonyldecyl)ureido]heptanedioate, 15(9,9). The general procedure described above afforded a white solid (2.90 g, 85%); mp 89.6–90.3 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.40 (bm, 30H), 1.43 (bs, 29H), 1.93 (m, 6H), 2.23 (m, 6H), 3.51 (bm, 1H), 3.76 (d, 1H), 4.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 25.9, 28.0, 29.3, 29.55, 29.56, 29.7, 29.9, 30.7, 31.8, 35.7, 50.2, 56.4, 80.4, 156.4, 173.0; IR 3328, 2922, 2852, 1726, 1651, 1148; HRMS: for $C_{42}H_{81}N_2O_7$ $[M+H]^+$ calcd 725.6044, found 725.6028. Anal. Calcd for $C_{42}H_{80}N_2O_7$: C, 69.57; H, 11.12; N, 3.86. Found: C, 69.60; H, 11.22; N, 3.85.

5.10.4. Di-*tert*-butyl 4-(2-*tert*-butoxycarbonylethyl)-4-[3-(1-decylundecyl)ureido]heptandioate, 15(10,10). The general procedure described above afforded a white solid (2.73 g, 77%); mp 87.0–87.6 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.40 (bm, 34H), 1.44 (bs, 29H), 1.93 (m, 6H), 2.23 (m, 6H), 3.52 (bm, 1H), 3.86 (d, 1H), 4.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 25.9, 28.02, 28.04, 29.3, 29.57, 29.61, 29.68, 29.9, 30.6, 31.9, 35.7, 50.2, 56.4, 80.4, 156.4, 173.0; IR 3376, 2919, 2850, 1730, 1675, 1146; HRMS: for $C_{44}H_{85}N_2O_7$ $[M+H]^+$ calcd 753.6357, found 753.6376. Anal. Calcd for $C_{44}H_{84}N_2O_7$: C, 70.17; H, 11.24; N, 3.72. Found: C, 69.89; H, 11.33; N, 3.70.

5.10.5. Di-*tert*-butyl 4-(2-*tert*-butoxycarbonylethyl)-4-[3-(1-undecyldodecyl)ureido]heptanedioate, 15(11,11). The general procedure described above afforded a white solid (3.16 g, 86%); mp 92.9–93.8 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.20–1.40 (bm, 38H), 1.44 (bs, 29H), 1.94 (m, 6H), 2.24 (m, 6H), 3.52 (bm, 1H), 3.83 (m, 1H), 4.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 25.9, 28.0, 29.3, 29.58, 29.60, 29.7, 29.9, 30.7, 31.9, 35.7, 50.2, 56.4, 80.4, 156.4, 173.0; IR 3374, 2920, 2850, 1722, 1676, 1148; HRMS: for $C_{46}H_{89}N_2O_7$ $[M+H]^+$ calcd 781.6670, found 781.6657. Anal. Calcd for $C_{46}H_{88}N_2O_7$: C, 70.72; H, 11.35; N, 3.59. Found: C, 70.49; H, 11.37; N, 3.67.

5.10.6. Di-*tert*-butyl 4-(2-*tert*-butoxycarbonylethyl)-4-[3-(1-dodecyltridecyl)ureido]heptanedioate, 15(12,12). The general procedure described above afforded a white solid (3.49 g, 87%); mp 73.8–74.3 °C; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 6H), 1.20–1.40 (bm, 42H), 1.44 (bs, 29H), 1.94 (m, 6H), 2.24 (m, 6H), 3.51 (bm, 1H), 3.80 (d, 1H), 4.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.9, 28.0, 29.3, 29.61, 29.63, 29.66, 29.70, 29.85, 30.6, 31.9, 35.7, 50.2, 56.4, 80.4, 156.4, 173.1; IR 3319, 2917, 2851, 1730, 1654, 1147; HRMS: for $C_{48}H_{93}N_2O_7$ $[M+H]^+$ calcd 809.6983, found 809.7014. Anal. Calcd for $C_{48}H_{92}N_2O_7$: C, 71.24; H, 11.46; N, 3.46. Found: C, 71.43; H, 11.58; N, 3.50.

5.11. General procedures for swallowtail triacids, 3(n,n)

A tri-*tert*-butyl ester **15(n,n)** (3.00 mmol) was dissolved in 99% HCOOH so that the concentration was 0.1 M. Some mixtures needed warming to completely dissolve **15(n,n)**. Once dissolved to give a clear colorless solution, the mixture was stirred at rt. After stirring for 9 h, the resulting milky white solution was concentrated. The white solid was recrystallized from EtOAc to yield a white solid (77–90%).

5.11.1. 4-(2-Carboxyethyl)-4-[3-(1-heptyloctyl)ureido]heptanedioic acid, 3(7,7). The general procedure described above afforded a white solid (1.28 g, 85%); mp 168.5–169.2 °C; ^{1}H NMR (CD_3OD) δ 0.89 (t, 6H), 1.20–1.40 (bm, 24H), 1.44 (m, 2H), 1.95 (m, 6H), 2.28 (m, 6H), 3.55 (bm, 1H); ^{13}C NMR (DMSO-d_6) δ 14.4, 22.5, 25.8, 28.6, 29.2, 29.4, 30.5, 31.7, 35.8, 48.3, 55.4, 157.4, 175.0; IR 3405, 2924, 2855, 1732, 1700 1585; HRMS: for $C_{26}H_{49}N_2O_7$ $[M+H]^+$ calcd 501.3540, found 501.3562. Anal. Calcd for $C_{26}H_{48}N_2O_7$: C, 62.37; H, 9.66; N, 5.60. Found: C, 62.28; H, 9.57; N 5.52.

5.11.2. 4-(2-Carboxyethyl)-4-[3-(1-octylnonyl)ureido]heptanedioic acid, 3(8,8). The general procedure described above afforded a white solid (1.36 g, 86%); mp 164.3–165.1 °C; ^{1}H NMR (CD_3OD) δ 0.89 (t, 6H), 1.20–1.40 (bm, 28H), 1.44 (m, 2H), 1.95 (m, 6H), 2.28 (m, 6H), 3.54 (bm, 1H); ^{13}C NMR (DMSO-d_6) δ 14.7, 22.8, 26.1, 28.8, 29.4, 29.69, 29.73, 30.8, 31.9, 36.0, 48.5, 55.6, 157.6, 175.2; IR 3404, 2921, 2852, 1730, 1699, 1556; HRMS: for $C_{28}H_{53}N_2O_7$ $[M+H]^+$ calcd 529.3853, found 529.3837. Anal. Calcd for $C_{28}H_{52}N_2O_7$: C, 63.61; H, 9.91; N, 5.30. Found: C, 63.65; H, 9.94; N 5.20.

5.11.3. 4-(2-Carboxyethyl)-4-[3-(1-nonyldecyl)ureido]heptanedioic acid, 3(9,9). The general procedure described above afforded a white solid (1.39 g 83%); mp 165.1–165.7 °C; ^{1}H NMR (CD_3OD) δ 0.86 (t, 6H), 1.20–1.35 (bm, 30H), 1.41 (m, 2H), 1.92 (m, 6H), 2.25 (m, 6H), 3.51 (bm, 1H); ^{13}C NMR (DMSO-d_6) δ 14.4, 22.5, 25.8, 28.6, 29.1, 29.36, 29.43, 30.5, 31.7, 35.7, 48.3, 55.4, 157.3, 174.9; IR 3405, 2921, 2852, 1730, 1699, 1554; HRMS: for $C_{30}H_{57}N_2O_7$ $[M+H]^+$ calcd 557.4166, found 557.4172. Anal. Calcd for $C_{30}H_{56}N_2O_7$: C, 64.72; H, 10.14; N, 5.03. Found: C, 64.73; H, 10.20; N 5.01.

5.11.4. 4-(2-Carboxyethyl)-4-[3-(1-decylundecyl)ureido]heptanedioic acid, 3(10,10). The general procedure described above afforded a white solid (1.42 g, 81%); mp 162.8–163.5 °C; ^{1}H NMR (CD_3OD) δ 0.86 (t, 6H), 1.20–1.35 (bm, 34H), 1.41 (m, 2H), 1.87 (t, 6H), 2.25 (t, 6H), 3.51 (bm, 1H); ^{13}C NMR (DMSO-d_6) δ 14.4, 22.5, 25.8, 28.5, 29.1, 29.41, 29.43, 30.5, 31.7, 35.6,

48.3, 55.4, 157.3, 174.9; IR 3404, 2921, 2852, 1731, 1699, 1557; HRMS: for $C_{32}H_{61}N_2O_7$ $[M+H]^+$ calcd 585.4479, found 585.4501. Anal. Calcd for $C_{32}H_{60}N_2O_7$: C, 65.72; H, 10.34; N, 4.79. Found: C, 65.52; H, 10.31; N 4.78.

5.11.5. 4-(2-Carboxyethyl)-4-[3-(1-undecyldodecyl)ureido]heptanedioic acid, 3(11,11). The general procedure described above afforded a white solid (1.56 g, 85%); mp 164.6–165.1 °C; ^{1}H NMR (CD_3OD) δ 0.86 (t, 6H), 1.20–1.35 (bm, 38H), 1.41 (m, 2H), 1.92 (m, 6H), 2.25 (m, 6H), 3.51 (bm, 1H); ^{13}C NMR (DMSO-d_6) δ 14.4, 22.5, 25.7, 28.5, 29.1, 29.41, 29.44, 30.5, 31.7, 35.6, 48.2, 55.3, 157.3, 174.9; IR 3404, 2921, 2852, 1732, 1699, 1557; HRMS: for $C_{34}H_{65}N_2O_7$ $[M+H]^+$ calcd 613.4792, found 613.4792. Anal. Calcd for $C_{34}H_{64}N_2O_7$: C, 66.63; H, 10.53; N, 4.57. Found: C, 66.77; H, 10.64; N 4.56.

5.11.6. 4-(2-Carboxyethyl)-4-[3-(1-dodecyltridecyl)ureido]heptanedioic acid, 3(12,12). The general procedure described above afforded a white solid (1.67 g, 87%); mp 163.3–163.9 °C; ^{1}H NMR (CD_3OD) δ 0.86 (t, 6H), 1.20–1.35 (bm, 42H), 1.41 (m, 2H), 1.95 (m, 6H), 2.25 (m, 6H), 3.51 (bm, 1H); ^{13}C NMR (DMSO-d_6) δ 14.6, 22.8, 26.0, 28.8, 29.4, 29.67, 29.71, 29.75, 30.8, 32.0, 35.9, 48.5, 55.6, 157.6, 175.2; IR 3403, 2920, 2851, 1731, 1700, 1559; HRMS: for $C_{36}H_{69}N_2O_7$ $[M+H]^+$ calcd 641.5105, found 641.5095. Anal. Calcd for $C_{36}H_{68}N_2O_7$: C, 67.46; H, 10.69; N, 4.37. Found: C, 67.31; H, 10.62, N 4.34.

5.12. Microbial strains, culture conditions, and preparations of inocula for susceptibility testing

Strains of *E. coli* strain C (ATCC # 13706), *K. pneumoniae* (ATCC # 4352), *L. plantarum* (ATCC # 14917), *S. aureus* (ATCC # 6538), and *M. smegmatis* (ATCC # 607) were obtained from the American Type Culture Collection. A methicillin-resistant isolate of *S. aureus* (MRSA) was obtained from the Microbiology Laboratory, Danville Community Hospital (Virginia), and *S. cerevisiae*, *C. albicans*, *C. neoformans*, *A. niger*, and *M. luteus* strains were obtained from the Virginia Tech Microbiology teaching culture collection. Colonies of *E. coli*, *K. pneumoniae*, *S. aureus*, MRSA, *M. luteus*, *S. cerevisiae*, *C. albicans*, and *C. neoformans* were grown on 1/10-strength Brain Heart Infusion Broth (BBL Microbiology Systems, Cockeysville, MD) containing 0.2% (wt/vol) sucrose (BHIB + S) and 1.5% (wt/vol) agar. *L. plantarum* was grown on 1/4-strength Tryptic Soy Broth (TSB, BBL Microbiology Systems, Cockeysville, MD) containing 0.2% glucose (TSB + G) and 1.5% (wt/vol) agar. *M. smegmatis* was grown on Middlebrook 7H10 agar (BBL Microbiology Systems, Cockeysville, MD) and *A. niger* on Potato Dextrose Agar (PDA, BBL Microbiology Systems, Cockeysville, MD). Streaked plates were incubated at 37 °C for 3–7 days, except for that of *A. niger*, which was incubated in the dark at 30 °C. A single colony for each microbe except *A. niger* was used to inoculate 5 mL of 1/10-strength BHIB + S (*E. coli*, *K. pneumoniae*, *M. luteus*, *S. aureus*, and MRSA), TSB (*L. plantarum*), Middlebrook 7H9 broth (*M. smegmatis*), or Yeast Extract Peptone Maltose broth (*S. cerevisiae*, *C. albicans*, and *C. neoformans*) and incubated at 37 °C (*S. cerevisiae* and *M. luteus* at 30 °C) for 4–7 days. After growth, the resulting broth cultures were diluted with buffered saline gelatin [BSG, gelatin (0.1 g/L), NaCl (8.5 g/L), KH_2PO_4 (0.3 g/L), Na_2HPO_4 (0.6 g/L)] to equal the turbidity of a No. 1 McFarland Standard. To check for viability and contamination, broth cultures were streaked on Plate Count Agar (BBL Microbiology Systems, Cockeysville, MD); the plates were incubated at 37 °C for 3–4 days, except those for *M. luteus* and *S. cerevisiae* which were incubated at 30 °C. Spores of *A. niger* were scraped from the surface of PDA and suspended in 5 mL of 1/10-strength BHIB + S and that suspension transferred to a sterile test tube. The turbidity was adjusted to a No. 1 McFarland Standard by dilution with BSG. To check for viability and contamination, those spore suspensions were streaked on PDA and incubated at 37 °C for 3–4 days.

5.13. Quality assurance

For the work reported here, all cultures and suspensions that were used as inocula were uncontaminated and the colonies had the expected morphologies. All viable, uncontaminated inocula were stored up to 14 days at 4 °C until used without any differences in susceptibility to antimicrobial compounds.

5.14. Measurement of MIC

Stock solutions (12,500 mg/L) for all homologues were easily prepared by simply vortexing the tricarboxylic acid in the aqueous triethanolamine solution. Final stock concentrations ranged from 19,500 to 25,700 μM depending on the formula weight of the homologue.

MICs of compounds dissolved in aqueous triethanolamine were measured by broth microdilution in 96-well microtiter plates.[4] Preliminary experiments demonstrated that 4% (wt/vol) triethanolamine/water did not inhibit the growth of any microorganism tested. A two-fold dilution series of the compounds was prepared in 96-well microtiter plates in a 50 μL volume of 1/10-strength BHIB + S and the dilution series was inoculated with 50 μL of each cell suspension. For *E. coli* and *K. pneumoniae*, the volumes of the medium and the inoculum were doubled. The resulting inoculated dilution series were incubated at 30 °C (37 °C for *E. coli* and *K. pneumoniae*) and growth, as turbidity, scored visually and recorded on the fourth day (the seventh day for *E. coli* and *K. pneumoniae*). The MIC of each compound was measured in triplicate and was defined as the lowest concentration of drug resulting in a prominent visible decrease in turbidity (incomplete; i.e., $\geqslant$50%) or an absence of visible turbidity (complete) compared to the drug-free control. In many cases (identified in Table 1 by superscript[a]), inhibition was incomplete.

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References and notes

1. Bayliss, M. *J. Bacteriol.* **1936**, *31*, 489.
2. Walker, J. E. *J. Infect. Dis.* **1924**, *35*, 557.
3. Vorum, H.; Brodersen, R.; Kragh–Hansen, U.; Pedersen, A. O. *Biochim. Biophys. Acta* **1992**, *1126*, 135.
4. Williams, A. A.; Sugandhi, E. W.; Macri, R. V.; Falkinham, J. O., III; Gandour, R. D. *J. Antimicrob. Chemother.* **2007**, *59*, 451.
5. Newkome, G. R.; Behera, R. K.; Moorefield, C. N.; Baker, G. R. *J. Org. Chem.* **1991**, *56*, 7162.
6. Csizmadia, F. Log*P* and log*D* calculator <http://intro.bio.umb.edu/111-112/OLLM/111F98/newclogp.html>, accessed November 15, 2006.
7. Newkome, G. R.; Weis, C. D.; Moorefield, C. N.; Fronczek, F. R. *Tetrahedron Lett.* **1997**, *38*, 7053.
8. Nagase, A.; Kuwahara, Y.; Tominaga, Y.; Sugawara, R. *Agric. Biol. Chem.* **1983**, *47*, 53.
9. Djedovič, N.; Ferdani, R.; Harder, E.; Pajewska, J.; Pajewski, R.; Weber, M. E.; Schlesinger, P. H.; Gokel, G. W. *New J. Chem.* **2005**, *29*, 291.
10. Boal, A. K.; Das, K.; Gray, M.; Rotello, V. M. *Chem. Mater.* **2002**, *14*, 2628.
11. Baykut, F. *Rev. Fac. Sci. Univ. Istanbul.* **1954**, *19*, 121.
12. Breusch, F. L.; Sokullu, S. *Chem. Ber.* **1953**, *86*, 678.
13. Meakins, R. J.; Sack, R. A. *Aust. J. Sci. Res.* **1951**, *4A*, 213.
14. Overmars, F. J. J.; Engberts, J. B. F. N.; Weringa, W. D. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 293.
15. Meekel, A. A. P.; Wagenaar, A.; Šmisterová, J.; Kroeze, J. E.; Haadsma, P.; Bosgraaf, B.; Stuart, M. C. A.; Brisson, A.; Ruiters, M. H. J.; Hoekstra, D.; Engberts, J. B. F. N. *Eur. J. Org. Chem.* **2000**, *2000*, 665.
16. Malanga, C.; Mannucci, S.; Lardicci, L. *J. Chem. Res. Synop.* **2000**, *6*, 701.
17. Wescott, L. D.; Mattern, D. L. *J. Org. Chem.* **2003**, *68*, 10058.
18. Kaneko, D.; Olsson, U.; Sakamoto, K. *Langmuir* **2002**, *18*, 4699.
19. Kanicky, J. R.; Shah, D. O. *Langmuir* **2003**, *19*, 2034.
20. Bates, R. G.; Allen, G. F. *J. Res. Natl. Bur. Stand. (US)* **1960**, *64A*, 343.
21. Boris, S.; Barbes, C. *Microbes Infect.* **2000**, *2*, 543.
22. Kondo, E.; Kanai, K. *Jpn. J. Med. Sci. Biol.* **1972**, *25*, 1.
23. Seidel, V.; Taylor, P. W. *Int. J. Antimicrob. Agents* **2004**, *23*, 613.
24. Masuoka, J.; Hazen, K. C. *Glycobiology* **1999**, *9*, 1281.
25. Genco, C. A.; Maloy, W. L.; Kari, U. P.; Motley, M. *Int. J. Antimicrob. Agents* **2003**, *21*, 75.
26. Quinn, F. R.; Driscoll, J. S.; Hansch, C. *J. Med. Chem.* **1975**, *18*, 332.
27. Jiang, S.; Wang, L.; Yu, H.; Chen, Y. *React. Funct. Polym.* **2005**, *62*, 209.
28. Langsrud, S.; Sundheim, G.; Borgmann-Strahsen, R. *J. Appl. Microbiol.* **2003**, *95*, 874.
29. Walsh, S. E.; Maillard, J.-Y.; Russell, A. D.; Catrenich, C. E.; Charbonneau, D. L.; Bartolo, R. G. *J. Appl. Microbiol.* **2003**, *94*, 240.
30. Oya, A.; Funato, Y.; Sugiyama, K. *J. Mater. Sci.* **1994**, *29*, 11.
31. Cox, J. M.; Marsden, J. H. E.; Elmore, N.; Shephard, M. C.; Burrell, R. A. US Patent 4146716, 1979, 17 pp
32. Grier, N.; Dybas, R. A.; Strelitz, R. A.; Witzel, B. E.; Dulaney, E. L. *J. Pharm. Sci.* **1982**, *71*, 365.
33. Carballeira, N. M.; Ortiz, D.; Parang, K.; Sardari, S. *Arch. Pharm.* **2004**, *337*, 152.
34. Carballeira, N. M.; O'Neill, R.; Parang, K. *Chem. Phys. Lipids* **2005**, *136*, 47.
35. Carballeira, N. M.; Sanabria, D.; Parang, K. *Arch. Pharm.* **2005**, *338*, 441.
36. Carballeira, N. M.; Sanabria, D.; Cruz, C.; Parang, K.; Wan, B. J.; Franzblau, S. *Lipids* **2006**, *41*, 507.
37. Sugandhi, E. W.; Macri, R. V.; Kite, B. L.; Williams, A. A.; Slebodnick, C.; Falkinham, J. O., III; Esker, A. R.; Gandour, R. D. *J. Med. Chem.* **2007**, *50*, doi:10.1021/jm061240d. Available online 9 March 2007.
38. Newkome, G. R.; Weis, C. D.; Childs, B. J. *Des. Monomers Polym.* **1998**, *1*, 3.
39. Troyanskii, E. I.; Ioffe, V. A.; Mizintsev, V. V.; Nikishin, G. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1984**, *8*, 1814.
40. Gall, R.; Bosies, E. Germany Patent DE 3623397 A1, 1988, 12 pp
41. Froger, C.; Parisot, A. *Compt. Rend.* **1954**, *238*, 1589.
42. Yoshioka, Y.; Tashiro, K. *J. Phys. Chem. B* **2003**, *107*, 11835.
43. Rao, H. S. P.; Bharathi, B. *Indian J. Chem. B* **2002**, *41*, 1072.
44. Wright, J. B.; Elderfield, R. C. *J. Org. Chem.* **1946**, *11*, 111.