Articles

Antibacterial Nicotinamide Adenine Dinucleotide Synthetase Inhibitors: Amide- and Ether-Linked Tethered Dimers with α-Amino Acid End Groups

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Tethered dimers incorporating natural α-amino acid end groups were synthesized, including examples in which the previously reported esterase-sensitive ester linker was replaced with more stable amide or ether linkers. These compounds remained effective both as inhibitors of NAD synthetase and as potent antibacterial agents for Gram-positive strains. Studies on nonspecific effects, including detergent properties and promiscuous inhibition, suggested little contribution to observed activities.

Introduction

The need for development of new antibacterial agents has become a priority of great significance. One factor receiving major attention is the potential for use of infectious bacteria as weapons in biowarfare or bioterrorism,[1−4] including those engineered to be resistant against existing drugs. And the natural emergence of antibiotic-resistant bacteria, due in part to continuing overuse of antibiotics, continues to increase[5,6] such that the majority of *Staphylococcus aureus* strains are now resistant to methicillin or other antibiotics. Further, *Enterococci* have developed alarming resistance to vancomycin, once considered an antibiotic of "last resort". In spite of these threats, the introduction of new antibacterial drugs for clinical use has dramatically decreased.

In an effort to identify new antibacterial compounds that act against novel targets, we have pursued inhibitors of the enzyme nicotinamide adenine dinucleotide (NAD[a]) synthetase. NAD synthetase belongs to the amidotransferase family[7] and catalyzes the last step in the biosynthesis of NAD, transforming nicotinic acid adenine dinucleotide (NaAD) into the amide product NAD via a two-step process[8] involving mixed anhydride derivatization of the carboxylate, using ATP, followed by reaction with ammonia (in procaryotes) to provide the amide. The inhibition of bacterial NAD synthetase appeared likely to provide antibacterial actions since NAD plays an important role in energy metabolism and numerous biochemical transformations such as DNA repair, DNA recombination, and protein-ADP ribosylation.[9] Additionally, this enzyme is required for the outgrowth of spore-forming bacteria into the vegetative cell,[10] and its inhibition may thus block both spore germination/outgrowth and vegetative growth for the spore-forming *Bacillus anthracis*.

We utilized the protein crystal structure of *Bacillus subtilis* NAD synthetase in complex with the natural substrates to guide the initial design of potential inhibitors.[11] As a first approach, we targeted the NaAD binding subsite with the goal of obtaining inhibitors that were chemically simpler than NaAD. We, thus, based early libraries on simple tethered dimers containing aromatic end groups and a polymethylene linker of varying length. This approach[12,13] resulted in low micromolar inhibitors of *B. subtilis* NAD synthetase that also exhibited potent antibacterial actions. These early tethered dimers contained a substituted indole at one end and an aromatic group containing a positively charged N at the other end connected by a polymethylene linker. SAR studies incorporating substituted phenols in the place of indole also yielded active compounds,[14] and the best example contained a 4-benzyloxy-substituted phenol at one end and a *N*,*N*,*N*-trimethylammonium phenyl acetate group at the other end of an 8-carbon polymethylene linker (**1**, Figure 1). To further define SAR, here we describe studies involving substitutions at (1) the ammonium end and (2) the esterase-sensitive ester linker. Further, we evaluate possible nonspecific enzyme inhibition actions of the tethered dimers, including detergent properties and promiscuous behavior.

Results and Discussion

Substitutions at the Ammonium End. (a) α-Amino Acids. We first proposed to incorporate several *N*,*N*,*N*-trimethylammonium derivatives of natural amino acids in place of the *N*,*N*,*N*-trimethylammonium phenyl acetate end group of compound **1**. Because previous SAR studies revealed that the presence of an aromatic ring near the ammonium group is favorable, we selected natural α-amino acids containing an aromatic group, namely, phenylalanine, tyrosine, and tryptophan (targets **2a**−**2c** in Figure 1).

The syntheses of **2a**−**2c** are summarized in Scheme 1. As shown, the anion of commercially available 4-benzyloxyphenol **3** was alkylated with 8-bromo-1-octanol to afford alcohol **4**. Intermediate **4** was esterified with the appropriate Boc-protected amino acids in the presence of EDAC to give the esters **5a**−**c**.

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[a] Abbreviations: ADH, alcohol dehydrogenase; ATP, adenosine triphosphate; BOG, β-(*n*-octyl)-D-glucopyranoside; CMC, critical micellar concentration; CFU, colony forming unit; HEPPS, 3-[4-(2-hydroxyethyl)-1-piperazinyl]propanesulfonic acid; MIC, minimum inhibitory concentration; NaAD, nicotinic acid adenine dinucleotide; NAD, β-nicotinamide adenine dinucleotide; NADH, β-nicotinamide adenine dinucleotide, reduced form.

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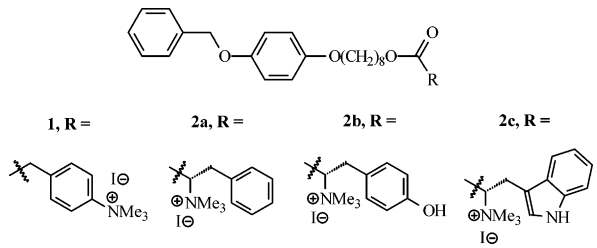


Figure 1.

The protecting groups were removed using TFA to give the free amines **6a**−**c**, which were reacted with iodomethane to provide the quaternary ammonium salts **2a**−**c**.

The IC_{50} values of **2a**−**c** for the inhibition of purified *B. subtilis* NAD synthetase are given in Table 1. Compounds **2a**−**c** are all effective enzyme inhibitors as compared to compound **1**. Compounds **2a** and **2b** were further tested against different strains of Gram-positive and Gram-negative bacteria, and their MIC (minimum inhibitory concentration) values were determined. For comparison purposes, identical MIC determinations were performed with rifampin, methicillin, ampicillin, and ciprofloxacin. The results are given in Table 1.

As shown, compounds **2a** and **2b** are potent inhibitors of the growth of Gram-positive bacteria but are inactive against Gram-negative bacteria (e.g., *Pseudomonas*). They are similar in effectiveness to commercial antibiotics. Of particular interest is the observation that methicillin-resistant strains of *S. aureus* also remain susceptible.

All tethered dimer inhibitors that we have described so far contain an ester linkage. We have observed (unpublished results) that these esters are susceptible to plasma esterases. To circumvent this problem, we proposed a common strategy of changing the ester to a more stable amide or ether functionality. Thus, the syntheses of amide- or ether-linked compounds **11a**−**d** (Figure 2) was next pursued. The procedure is described in Scheme 2. As shown, for the amide linkers, 4-benzyloxyphenol (**3**) was alkylated with *N*-(8-bromooctyl) phthalimide and NaH to give phthalimide **7**. The phthalimide group was removed by treatment with hydrazine to provide amine **8** as its hydrochloride salt. Amine **8** was converted to the intermediate amides **9a**,**b** by treatment with (L)-*N*-(*tert*-butoxycarbonyl)phenylalanine or (L)-*N*-(*tert*-butoxycarbonyl)phenylglycine, respectively, in CH_2Cl_2 in the presence of EDAC and DMAP.

For the ether linkers, intermediate alcohol **4** (Scheme 1) was converted to the triflate using triflic anhydride, and the product, in one pot, was converted to ethers **9c**,**d** by treatment with (L)-*N*-(*tert*-butoxycarbonyl)phenylalaninol or (L)-*N*-(*tert*-butoxycarbonyl)phenylglycinol in the presence of NaH.

The final amide and ether targets **11a**−**d** were prepared by removal of the Boc group from **9a**−**d** using TFA to afford amines **10a**−**d**. The reaction of amines **10a**−**d** with iodomethane gave the final quaternary ammonium products **11a**−**d**.

Compounds **11a**−**d** were evaluated as inhibitors of *B. subtilis* NAD synthetase, and the IC_{50} values are given in the Table 1. As shown, compounds **11a**−**d** all effectively inhibit the enzyme. Compounds **11a** and **11b** are the amide- and ether-linked analogs of parent ester **2a**, and this structural change had little effect on activity. Also, shortening of the amino acid end to phenylglycine (amide **11c** and ether **11d**) similarly had little effect, revealing that the amide and ether linkages provide tethered dimers with comparable activity to the parent esters. Further, as found for **2a**, compounds **11a**−**d** were effective inhibitors of the growth of Gram-positive bacteria but were inactive against the Gram-negative *Pseudomonas aeruginosa*.

(b) Guanidines. The structures of the above compounds contain a permanent positive charge, which is unfavorable for membrane permeability and oral bioavailability of potential drugs. Thus, we next proposed compounds **13a**−**d** (Figure 3), which are analogs of **11a**−**d** but contain a highly basic guanidinium group in place of the trimethylammonium group. Note that the guanidinium group does not contain a permanent positive charge.

The syntheses of guanidine analogs **13a**−**d** are shown in Scheme 3. Thus, amines **10a**−**d** were treated with 1,3-bis(Boc)-*S*-methylisothiourea in the presence of $HgCl_2$ to give protected guanidines **12a**−**d**. Removal of the Boc groups using TFA followed by treatment with 1 N HCl afforded the hydrochloride salts of guanidines **13a**−**d**.

Compounds **13a**−**d** were evaluated as inhibitors of *B. subtilis* NAD synthetase and as antibacterial agents. As shown in Table 1, IC_{50} and MIC values again remained similar to the earlier tethered dimers discussed above. However, it is important to note that the *N*,*N*-dimethyl (tertiary amine) analogs of **1**, **2a**−**2c**, and **11a**−**11d** are ineffective either as inhibitors of NAD synthetase (up to 200 μM) or as antibacterial agents (MIC > 50 μg/mL; data not shown). Thus, either a permanent positive charge, or a positive charge generated from a strongly basic functionality, appears to be a structural requirement for activity in this series.

Studies on Nonspecific Detergent Effects and Promiscuous Inhibition. Compounds **1**, **2a**−**2c**, **11a**−**11d**, **and 13a**−**13d** all display remarkably similar activities as both NAD synthetase inhibitors and antibacterial agents. While indeed these compounds are structurally very similar, this observation raised concerns regarding possible nonspecific actions that may cause the observed biological activities. Specifically, we considered the possibility that tethered dimers containing positively charged end groups may act through a (a) nonspecific detergent effect and/or (b) may show promiscuous behavior. Thus, we pursued studies to better understand the mechanism of enzyme inhibition by these compounds.

(a) Detergent Effects. Given the structural resemblance of our best inhibitors to detergents, it was of particular interest to determine if structurally similar (thus possessing similar detergent properties) compounds would reveal significant differences in enzyme activity. As we reported earlier,[14] different positional isomers, assumed to have nearly identical detergent properties, sometimes exhibited very different enzyme inhibition activities. This observation suggested that specific interactions give rise to enzyme inhibition, as opposed to nonspecific detergent or surfactant properties, although detergent properties at that time were not directly measured. To further support this conclusion, we have measured the CMC (critical micelle concentration) values of three of the most active tethered dimer inhibitors (**1**, **2a**, and **11a**), which all have IC_{50} values in the low micromolar range. CMC values were determined by two different experimental methods, one using solubilization of a colored dye[15] and the second using fluorescence[16] to detect micelle formation. The measured CMC values by these two methods, compared to those for known detergents, are shown in Table 2. As illustrated, while these compounds are obviously good detergents, the CMC values are at least 10-fold greater than the IC_{50} values. These results suggest that detergent properties of these compounds are not primarily responsible for their enzyme inhibition activity.

(b) Promiscuous Inhibition. "Promiscuous inhibitors" have recently been described as compounds that nonspecifically inhibit a variety of enzymes through the formation of aggregates

Scheme 1

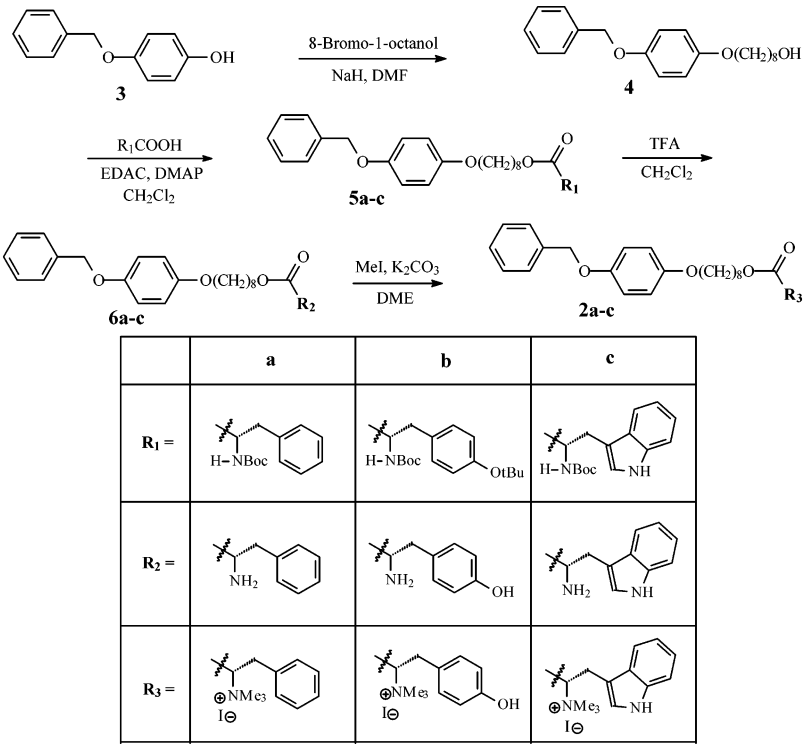
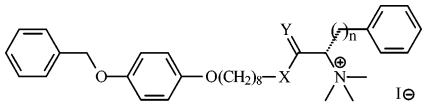


Table 1. Inhibition of *B. Subtilis* NAD Synthetase (IC_{50}, μM), and Antibacterial Activities (MIC, μM) for Tethered Dimers.

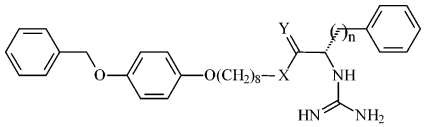
		MIC (μM)			
cmpd	IC_{50} (μM)	*Bacillus subtilis* ATCC# 14289	*Staphylococcus aureus* ATCC# 29213	*Staphylococcus aureus* (MRSA[a]) ATCC# 33591	*Pseudomonas aeruginosa* ATCC# 27853
1	41 ± 8.5	2	9.4	6.2	>50
2a	22 ± 2.4	0.78	0.78	0.78	>50
2b	53 ± 9.5	1.56	[b]	3.13	[b]
2c	19 ± 2.1	[b]	[b]	[b]	[b]
11a	40 ± 4.5	0.39	0.78	0.78	>50
11b	21 ± 1.2	0.39	0.78	1.56	>50
11c	45 ± 0.8	1.56		1.56	[b]
11d	38 ± 6.1	0.78	[b]	3.13	[b]
13a	12 ± 1.8	3.13	[b]	1.56	[b]
13b	11 ± 2.2	3.13	[b]	0.78	[b]
13c	19 ± 0.6	1.56	[b]	1.56	[b]
13d	11 ± 1.1	3.13	[b]	0.78	[b]
doxycycline		1.56	1.56	>30	[b]
ampicillin		0.2	[b]	>50	[b]
ciprofloxacin		0.5	[b]	0.5	[b]
rifampin		1.5	[b]	[b]	[b]
methicillin		[b]	1	32	[b]

[a] MRSA = methicillin-resistant *Staphylococcus aureus*. [b] Data not available.



11a, X = NH, Y = O, n = 1
11b, X = O,Y = H,H, n = 1
11c, X = NH, Y = O, n = 0
11d, X = O,Y = H,H, n = 0

Figure 2.



13a, X = NH, Y = O, n = 1
13b, X = O, Y = H,H, n = 1
13c, X = NH, Y = O, n = 0
13d, X = O, Y = H,H, n = 0

Figure 3.

that are hypothesized to bind and inactivate enzyme.[17−19] The inhibition of promiscuous inhibitors can be greatly diminished by the addition of a detergent such as Triton X-100. We proposed to evaluate the promiscuous behavior of the tethered dimers **2a** and **11a** by observing the effect of added detergent on the inhibition of NAD synthetase and on a second enzyme, alcohol dehydrogenase (ADH; used as a reporter enzyme in the NADS assay). We selected Triton X-100 as the added detergent, because it has been shown to diminish the inhibitory activities of some known promiscuous inhibitors at concentrations as low as 0.001%, and most promiscuous inhibitors are reported to lose inhibition in the presence of 0.01% Triton X-100.[18] The latter

Table 2. CMC Values of Selected Inhibitors

	CMC (mM)	
cmpd	ink	fluorescence
2a	0.35	0.14
11a	0.45	0.65
CTAB	0.8 (0.9[a])	
BOG	21 (19[a])	
SDS		7.5 (7.8[a])
TTABr		4.3 (3.5[b])

[a] Literature value.[15] [b] Literature value.[16]

Table 3. Effect of Added Triton X-100 on the Inhibition of NAD Synthetase

	IC_{50} (μM)		
cmpd	0% Triton X-100	0.001% Triton X-100	0.01% Triton X-100
2a	16.0 ± 0.7	16.5 ± 0.7	37.0 ± 0.7
11a	27.0 ± 2.8	27.8 ± 1.1	104.5 ± 3.5
clotrimazole	>1500	no inhibition	no inhibition

Table 4. Effect of Added Triton X-100 on the Inhibition of ADH.

	IC_{50} (μM)		
cmpd	0% Triton X-100	0.001% Triton X-100	0.01% Triton X-100
2a	27.0 ± 2.8	69.0 ± 15.6	265.5 ± 6.4
11a	>1500	>1500	>1500
clotrimazole	96.5 ± 16.3	no inhibition	no inhibition

concentration has little effect on enzyme activity or inhibition by conventional inhibitors. We also included a reported[18] classical promiscuous inhibitor, clotrimazole, which has been shown to be a strong aggregator.

As shown in Table 3, the two tethered dimer NAD synthetase inhibitors behaved similarly in the inhibition assay as the % Triton X-100 increased from 0 to 0.01%. The IC_{50} values did not increase with added 0.001% Triton X-100 but increased somewhat as the detergent concentration was increased to 0.01%. However, in all cases, the increase in IC_{50} was no more than 4-fold, which is significantly less dramatic than typically observed for strong aggregators. Interestingly, clotrimazole was not an inhibitor of NAD synthetase, suggesting this enzyme may be less sensitive to promiscuous inhibitors.

The results for inhibition of ADH are summarized in Table 4. As shown, tethered dimer **11a** did not inhibit up to the highest concentration tested. However, dimer **2a** was a significant inhibitor of ADH, suggesting promiscuous behavior on this enzyme. This was further supported by the 10-fold increase in IC_{50} in the presence of 0.01% Triton X-100. Further, the promiscuous inhibitor clotrimazole was, unlike the result with NADS, an effective inhibitor of ADH (IC_{50} = 96 μM), and this inhibition disappeared at the lowest detergent concentration (0.001%), which is characteristic of promiscuous inhibitors. Thus, **2a** appears to exhibit moderate promiscuous behavior on ADH, although not as strongly as that seen for clotrimazole's inhibition of ADH. It is important to note that, while **2a** inhibits ADH in this promiscuous inhibition experiment, much higher concentrations of ADH and ethanol were used in the NAD synthetase assay, and **2a** did not inhibit ADH when evaluated under these conditions.

In conclusion, dimers **2a** and **11a** do not exhibit promiscuous behavior with NAD synthetase. Further, these compounds inhibit NAD synthetase at concentrations well below their CMC values. The results emphasize that, while contributions to the inhibition of NAD synthetase from nonspecific behavior are possible for some tethered dimer inhibitors, these selected examples (and likely others) appear to exhibit classical behavior. Further, while the present and earlier studies are consistent with NAD synthetase inhibition as the target for antibacterial actions, other unexplored mechanisms of action remain as possibilities.

Experimental Section

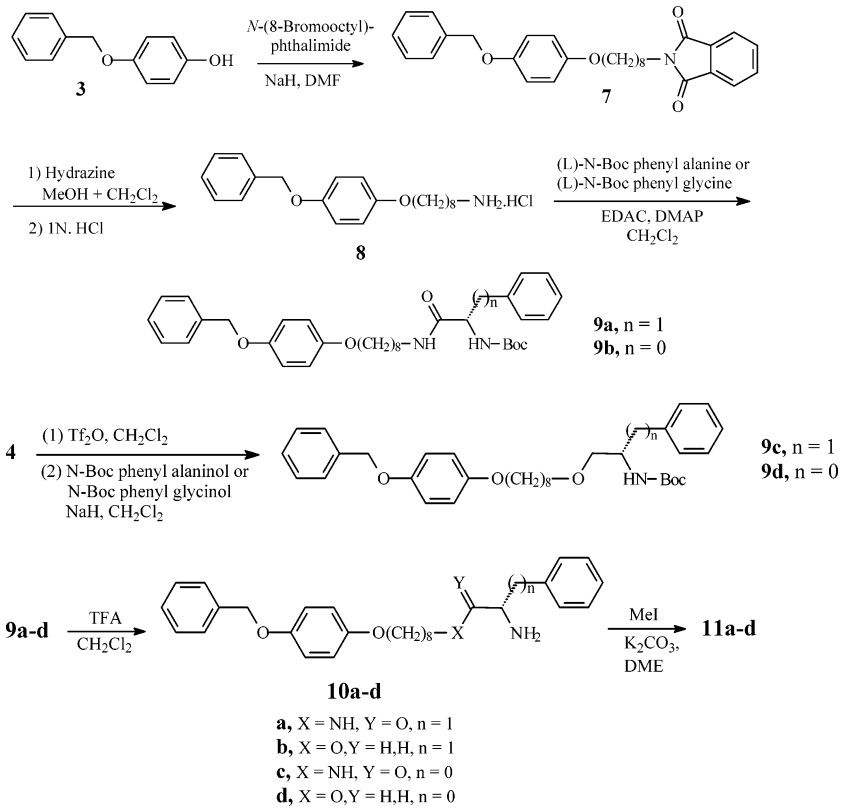
Enzyme Assays. High-Throughput Assay for NAD Synthetase Inhibition. NAD synthetase from *Bacillus subtilis* was overexpressed and purified as previously described.[12] We also previously reported[12] the detailed procedure for high-throughput inhibition assays. Briefly, this coupled assay monitors the production of NAD in the enzyme reaction through its conversion to NADH in the presence of ethanol and ADH from bakers' yeast (Sigma). The assay system at pH 8.5 contained 58.5 mM HEPPS buffer, 18.5 mM NH_4Cl, 19.5 mM KCl, 9.75 mM $MgCl_2$, 1% (v/v) EtOH, 0.1 mM NaAD, 0.3% BOG, 40 μg/mL ADH, 2.0 μg/mL NAD synthetase, 0.2 mM ATP, and inhibitor at several concentrations (with 2.5% (v/v) final DMSO concentration). The enzyme inhibition assay was carried out in 96-well microtiter plates with a total reaction volume of 200 μL. Two detection methods were simultaneously employed: UV absorbance at 340 nm and fluorescence emission at 460 nm, both resulting from the NADH produced in the reaction. OD was read on a SpectraMax Pro microplate reader (Molecular Devices), and fluorescence was read on a PolarStar microplate reader (BMG-LabTechnologies). After initiation by adding 25 μL of ATP solution, the reaction was allowed to proceed for 10 min and stopped by adding 50 μL of 6 M guanidine·HCl. The IC_{50} value was determined by plotting the percentage inhibition versus compound concentration.

Inhibition Assay for NAD Synthetase with Added Triton X-100. The fluorescence-based assays were carried out in opaque 96-well assay plates using a PolarStar Optima fluorescence plate reader from BMG LabTech. The final reaction volume was 200 μL in each well and contained the same components as described above for the high-throughput assay, except the 0.3% BOG was omitted. Additionally, 0 to 0.01% Triton X-100 was added along with inhibitors **2a**, **11a**, and clotrimazole at various concentrations. The assay was initiated by adding 0.2 mM ATP. The production of NADH was monitored by fluorescence at an emission wavelength of 460 nm (excitation wavelength was 355 nm) as a function of time. The linear part of the kinetic curve was used to calculate the initial reaction rate, V_o. Percentage inhibition was calculated based on the difference in V_o with and without the inhibitors. The IC_{50} value was determined by plotting the percentage inhibition versus the inhibitor concentration. Each point on the IC_{50} curve was an average of three measurements. The final IC_{50} values were averages from two sets of experiments.

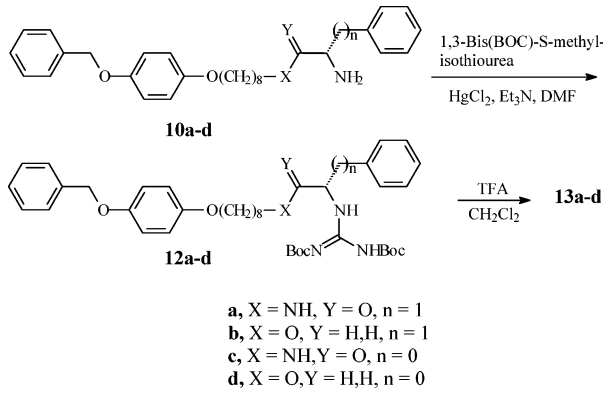
Inhibition Assay for ADH with Added Triton X-100. The reaction mixture contained 60 mM HEPPS, pH 8.5, 0.5 mM NH_4Cl, 20 mM KCl, 10 mM $MgCl_2$, 60 mM ethanol, 2.5 μg/mL yeast ADH, 2.5% (v/v) DMSO, 0 to 0.01% Triton X-100, and inhibitors **2a**, **11a**, or clotrimazole at various concentrations. The assay was initiated by adding 0.75 mM β-NAD and stopped by the addition of 1.2 M guanidine·HCl after 2 min. The production of NADH was measured by fluorescence at an emission wavelength of 460 nm (excitation wavelength is 355 nm). Endpoint values were calculated by subtracting fluorescence of the mixture before adding β-NAD from fluorescence after adding guanidine·HCl. The percent inhibition was calculated based on the difference in endpoint values with inhibitor and without inhibitor. Each point on the IC_{50} curve was an average of three measurements. The final IC_{50} values were averages from two sets of experiments.

Dimer **2a** was also evaluated for inhibition against ADH in a separate set of experiments that used the same conditions as the NAD synthetase coupled assay. The reaction mixtures consisted of the same buffering components as the promiscuous study, along with 0.3% BOG, 40 μg/mL ADH, 1% ethanol, and three different concentrations of β-NAD (0.75 mM, 0.1 mM, and 0.01 mM). The kinetic curves of the reactions were monitored by fluorescence after initiation of the reaction by adding β-NAD. The reaction reached

Scheme 2



Scheme 3



at least 60% completion before the first point of the curve could be read (within 15 s) and reached a plateau within 1 min, regardless of the β-NAD concentration. Dimer **2a** did not show any inhibition in this study.

Antibacterial Assays. The detailed procedure was previously reported.[12] As before, MICs were determined by MicroBioTest, Inc., of Sterling, VA. Briefly, bacteria were subcultured from stock cultures onto the appropriate agar and incubated overnight at 37 ± 2 °C in ambient air. The overnight cultures were inoculated into 3 mL of the appropriate broth, and each suspension was adjusted to contain approximately 5×10^8 CFU/mL. Starting at 50 μg/mL inhibitor, doubling dilutions were created for a total of 10 tubes (in duplicate), and each tube was then inoculated with the challenge microorganism broth (0.01 mL). The tubes were incubated at 37 ± 2 °C for 20 h. The MIC was defined as the lowest concentration of test substance that completely inhibited visible growth of the microorganism. Controls were included for viability, sterility, and reproducible MIC values for known antibiotics.

Synthetic Chemistry. General. Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded with Brucker Vector-22 and Bomen MB-104 instruments. All ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 300 MHz spectrometer using TMS as internal standard. The values of chemical shifts (δ) are given in ppm and coupling constants (J) are given in Hz. Elemental analyses were performed by Atlantic Microlab, Norcross, Georgia, and the results indicated by symbols for the elements were within ±0.4% of theoretical values. Reactions were monitored by TLC (Whatmann, silica gel, UV254, 25 μm plates), and flash column chromatography utilized "Baker" silica gel (40 μm) in the solvent systems indicated. Anhydrous solvents used for reactions were purchased in Sure-Seal bottles from Aldrich Chemical Co. Other reagents were purchased from Aldrich, Lancaster, or Acros chemical companies and used as received.

8-(4-Benzyloxyphenoxy)octan-1-ol (4). To a solution of 4-benzyloxyphenol **3** (5.0 g, 25 mmol) in anhydrous DMF (40 mL), NaH (0.83 g, 28 mmol) was added and the mixture was stirred at room temperature for 30 min. A solution of 8-bromo-1-octanol (4.7 mL, 27 mmol) in anhydrous DMF (20 mL) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with saturated NH_4Cl (50 mL) and extracted with EtOAc (3×80 mL). The combined EtOAc extracts were washed with water (3×80 mL) and brine (1×80 mL) and dried over Na_2SO_4. The drying agent was removed by filtration and the filtrate was evaporated under vacuum to afford the crude product, which crystallized upon the addition of hexanes. This was filtered, washed with hexanes, and dried to obtain pure **4** (6.6 g, 80%): mp 94−95 °C; ^{1}H NMR ($CDCl_3$) δ 1.28−1.51 (m, 8H), 1.51−1.63 (m, 3H), 1.69−1.81 (m, 2H), 3.62 (t, 2H, J = 6.58 Hz), 3.88 (t, 2H, J = 6.52 Hz), 5.00 (s, 2H), 6.82 (d, 2H, J = 9.09 Hz), 6.89 (d, 2H, J = 9.21 Hz), 7.26−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.6, 25.9, 29.3, 32.6, 62.9, 68.5, 70.6, 115.3, 115.7, 127.4, 127.8, 128.4, 137.2, 152.7, 153.4; IR (KBr) 3303 cm^{-1}; MS (ES) m/z 329 (M + H); Anal. ($C_{21}H_{28}O_3$) C, H.

8-(4-Benzyloxyphenoxy)-1-octyl 2-(*N*-*tert*-Butoxycarbonyl-amino)-3-phenylpropionate (5a). To a solution of alcohol **4** (0.328 g, 1.00 mmol) in anhydrous CH_2Cl_2 (20 mL), *N*-Boc-phenylalanine (0.318 g, 1.20 mmol), EDAC (0.229 g, 1.12 mmol), and DMAP (0.012 g, 0.10 mmol) were added and the mixture was stirred at room temperature for 3 h. This was diluted with 10 mL of CH_2Cl_2

and washed with 1 M $NaHCO_3$ (3 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL) and dried over Na_2SO_4. The drying agent was removed by filtration and the filtrate was evaporated under vacuum to afford the crude product, which was purified by flash column chromatography on silica gel (2 × 10 cm; $CHCl_3$ eluent) to afford pure **5a** (0.495 g, 86.1%): ^{1}H NMR ($CDCl_3$) δ 1.25−1.44 (m, 8H), 1.41 (s, 9H), 1.51−1.65 (m, 2H), 1.69−1.78 (m, 2H), 2.98−3.10 (m, 2H), 3.89 (t, 2H, J = 6.5 Hz), 4.10 (t, 2H, J = 6.5 Hz), 4.51−4.62 (m, 1H), 4.97 (bs, 1H, NH), 5.01 (s, 2H), 6.82 (d, 2H, J = 9.2 Hz), 6.90 (d, 2H, J = 9.2 Hz), 7.10−7.45 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.7, 25.9, 28.2, 28.4, 29.1, 29.2, 29.3, 38.4, 54.4, 65.4, 68.4, 70.6, 79.8, 115.3, 115.7, 126.9, 127.4, 127.8, 128.4, 128.5, 129.2, 136.0, 137.2, 152.8, 153.4, 155.0, 171.9; MS (ES) m/z 576 (M + H); Anal. ($C_{35}H_{45}NO_6$) C, H, N.

8-(4-Benzyloxyphenoxy)-1-octyl 2-(*N*-*tert*-Butoxycarbonylamino)-3-(4-*tert*-butoxyphenyl)propionate (5b). Compound **5b** (0.66 g, 100%) was prepared using a procedure similar to that for **5a**: ^{1}H NMR ($CDCl_3$) δ 1.25−1.45 (m, 8H), 1.31 (s, 9H), 1.41 (s, 9H), 1.46−1.63 (m, 2H), 1.70−1.79 (m, 2H), 2.94−3.08 (m, 2H), 3.88 (t, 2H, J = 6.5 Hz), 4.01−4.11 (m, 2H), 4.50−4.58 (m, 1H), 4.97 (br s, 1H, NH), 4.99 (s, 2H), 6.81 (d, 2H, J = 9.2 Hz), 6.89 (d, 2H, J = 9.2 Hz), 6.90 (d, 2H, J = 8.4 Hz), 7.02 (d, 2H, J = 8.4 Hz), 7.27−7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.6, 25.9, 28.2, 28.3, 28.7, 29.0, 29.1, 29.2, 37.7, 54.4, 65.3, 68.3, 70.5, 78.2, 79.7, 115.2, 115.6, 124.0, 127.3, 127.7, 128.4, 129.6, 130.8, 137.2, 152.7, 153.3, 154.2, 155.0, 171.9; MS (ES) m/z 648 (M + H).

8-(4-Benzyloxyphenoxy)-1-octyl 2-(*N*-*tert*-Butoxycarbonylamino)-3-(1*H*-indol-3-yl)propionate (5c). Compound **5c** (0.52 g, 84.1%) was prepared using a procedure similar to that for **5a**: ^{1}H NMR ($CDCl_3$) δ 1.18−1.48 (m, 10H), 1.42 (s, 9H), 1.48−1.60 (s, 2H), 1.74 (p, 2H, J = 6.5 Hz), 3.27 (d, 2H, J = 5.43 Hz), 3.89 (t, 2H, J = 6.5 Hz), 3.99−4.06 (m, 2H), 4.59−4.66 (m, 1H), 5.00 (s, 2H), 5.09 (br d, 1H, NH, J = 7.7 Hz), 6.82 (d, 2H, J = 9.1 Hz), 6.90 (d, 2H, J = 9.1 Hz), 6.95 (s, 1H), 7.07−7.56 (m, 9H), 8.23 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 25.6, 25.9, 28.1, 28.3, 28.4, 29.0, 29.1, 29.3, 54.2, 65.4, 68.5, 70.6, 79.7, 110.1, 111.1, 115.3, 115.7, 118.7, 119.4, 122.1, 122.7, 127.4, 127.6, 127.8, 128.5, 136.1, 137.2, 152.8, 153.4, 155.2, 172.4; MS (ES) m/z 615 (M + H).

8-(4-Benzyloxyphenoxy)-1-octyl 2-Amino-3-phenylpropionate (6a). To a solution of the ester **5a** (0.38 g, 0.66 mmol) in CH_2Cl_2 (2 mL), a mixture of TFA (2 mL) and CH_2Cl_2 (2 mL) was added dropwise and the solution was stirred at room temperature for 30 min. The solvent and TFA were completely removed under vacuum and the residue was dissolved in CH_2Cl_2 (20 mL). This solution was washed with 1 M Na_2CO_3 (3 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL) and dried over Na_2SO_4. The drying agent was removed by filtration and the filtrate was evaporated in vacuo to afford the crude product, which was purified by flash column chromatography on silica gel (2 × 10 cm) using MeOH/$CHCl_3$ eluent (1:19) to afford pure **6a** (0.26 g, 83%): ^{1}H NMR ($CDCl_3$) δ 1.25−1.39 (m, 6H), 1.39−1.51 (m, 4H), 1.51−1.64 (m, 2H, NH_2), 1.73 (p, 2H, J = 6.5 Hz), 2.85 (dd, 1H, J_1 = 13.5 Hz, J_2 = 7.8 Hz), 3.05 (dd, 1H, J_1 = 13.5 Hz, J_2 = 5.5 Hz), 3.70 (dd, 1H, J_1 = 7.8 Hz, J_2 = 5.5 Hz); 3.86 (t, 2H, J = 6.5 Hz), 4.07 (t, 2H, J = 6.5 Hz); 4.98 (s, 2H), 6.80 (d, 2H, J = 9.2 Hz), 6.88 (d, 2H, J = 9.2 Hz), 7.16−7.41 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.6, 25.8, 28.3, 28.9, 29.0, 29.1, 41.0, 55.6, 64.8, 68.2, 70.4, 115.1, 115.5, 126.6, 127.2, 127.6, 128.3(2C), 129.1(2C), 137.1, 152.6, 153.2, 174.9; MS (ES) m/z 476 (M + H); Anal. ($C_{30}H_{37}NO_4$) C, H, N.

8-(4-Benzyloxyphenoxy)-1-octyl 2-Amino-3-(4-hydroxyphenyl)propionate (6b). Compound **6b** (0.31 g, 100%) was prepared using a procedure similar to that for **6a**: ^{1}H NMR ($CDCl_3$) δ 1.27−1.50 (m, 8H), 1.58−1.69 (m, 2H), 1.74 (p, 2H, J = 6.5 Hz), 2.81 (dd, 1H, J_1 = 13.7 Hz, J_2 = 7.6 Hz), 3.02 (dd, 1H, J_1 = 13.7 Hz, J_2 = 5.2 Hz), 3.61 (br s, 2H, NH_2), 3.70 (dd, 1H, J_1 = 7.6 Hz, J_2 = 2 Hz), 3.89 (t, 2H, J = 6.5 Hz), 4.10 (t, 2H, J = 6.5 Hz), 4.99 (s, 2H), 6.65 (d, 2H, J = 8.5 Hz), 6.82 (d, 2H, J = 9.2 Hz), 6.89 (d, 2H, J = 9.2 Hz), 6.98 (d, 2H, J = 8.5 Hz), 7.25−743 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.7, 25.9, 28.4, 29.0, 29.1, 29.2, 39.7, 55.4, 65.3, 68.5, 70.6, 115.3, 115.6, 115.7, 127.4, 127.6, 127.8, 128.4, 130.2, 137.1, 152.7, 153.3, 155.4, 174.8; MS (ES) m/z 492 (M + H); Anal. ($C_{30}H_{37}NO_5$) C, H, N.

8-(4-Benzyloxyphenoxy)-1-octyl 2-Amino-3-(1*H*-indol-3-yl)propionate (6c). Compound **6c** (0.25 g, 74.6%) was prepared using a procedure similar to that for **6a**: ^{1}H NMR ($CDCl_3$) δ 1.19−1.44 (m, 10H), 1.44−1.62 (m 2H), 1.63−1.80 (m, 2H), 1.96 (br s, 2H, NH_2), 3.01 (dd, 1H, J_1 = 14.2 Hz, J_2 = 7.6 Hz), 3.25 (dd, 1H, J_1 = 14.2 Hz, J_2 = 4.6 Hz), 3.75−3.83 (m, 1H), 3.85 (t, 2H, J = 5.3 Hz), 4.06 (t, 2H, J = 6.2 Hz), 4.94 (s, 2H), 8.79 (d, 2H, J = 9.1 Hz), 6.87 (d, 2H, J = 9.1 Hz), 6.89 (s, 1H), 7.05−7.39 (m, 8H), 7.58 (d, 1H, J = 7.6 Hz), 8.71 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 25.5, 25.7, 28.2, 28.9, 29.0, 29.1, 30.7, 54.8, 64.9, 68.2, 70.4, 110.5, 111.1, 115.1, 115.5, 118.4, 119.1, 121.7, 122.9, 127.24, 127.29, 127.6, 128.3, 136.1, 137.1, 152.6, 153.2, 175.2; MS (ES) m/z 515 (M + H); Anal. ($C_{32}H_{38}N_2O_4$) C, H, N.

8-(4-Benzyloxyphenoxy)-1-octyl 2-(*N*,*N*,*N*-Trimethylammonium)-3-phenylpropionate, Iodide (2a). To a solution of the amine **6a** (0.150 g, 0.315 mmol) in DME (5 mL) was added K_2CO_3 (0.260 g, 1.88 mmol) followed by iodomethane (0.200 mL, 3.21 mmol) and the mixture was stirred at room temperature for 12 h. Precipitation of the product quaternary ammonium salt occurred. The precipitate was dissolved by the addition of CH_2Cl_2 (20 mL), and K_2CO_3 was removed by filtration through celite-521. The filtrate was concentrated and the product was precipitated by the addition of hexanes. The precipitated product was filtered, washed on the filter with cold EtOAc, and dried to obtain pure **2a** (0.114 g, 58.6%): ^{1}H NMR ($CDCl_3$) δ 0.91−1.02 (m, 2H), 1.11−1.45 (m, 9H), 1.68−1.79 (m, 2H), 3.12 (t, 1H, J = 12.1 Hz), 3.62−3.65 (m, 1H), 3.69 (s, 9H), 3.89 (t, 2H, J = 6.6 Hz), 3.91 (t, 2H, J = 6.8 Hz), 4.71 (dd, 1H, J_1 = 12.1 Hz, J_2 = 4.2 Hz), 5.00 (s, 2H), 6.82 (d, 2H, J = 9.2 Hz), 6.90 (d, 2H, J = 9.2 Hz), 7.24−7.44 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.2, 25.8, 27.7, 28.8, 28.9, 29.2, 33.3, 53.1, 66.9, 68.4, 70.6, 75.5, 115.2, 115.7, 127.4, 127.7, 128.0, 128.4, 129.0, 129.6, 131.8, 137.2, 152.7, 153.3, 166.6; MS (ES) m/z 518 (M^+); Anal. ($C_{33}H_{44}INO_4$) C, H, N.

8-(4-Benzyloxyphenoxy)-1-octyl 2-(*N*,*N*,*N*-Trimethylammonium)-3-(4-hydroxyphenyl)propionate, Iodide (2b). Compound **2b** (0.105 g, 60.0%) was prepared using a procedure similar to that for **2a**: ^{1}H NMR ($CDCl_3$) δ 1.01−1.46 (m, 10H), 1.71 (p, 2H, J = 6.8 Hz), 2.97 (t, 1H, J = 12.1 Hz), 3.45 (s, 9H), 3.46−3.55 (m, 1H), 3.85−4.00 (m, 4H), 4.55−4.59 (m, 1H), 4.97 (s, 2H), 6.81 (d, 2H, J = 9.2 Hz), 6.88 (d, 2H, J = 9.2 Hz), 6.95 (d, 2H, J = 8.2 Hz), 7.07 (d, 2H, J = 8.2 Hz), 7.26−7.41 9 m, 5H), 7.50 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 25.2, 25.8, 27.8, 28.8, 28.9, 29.1, 32.5, 53.1, 66.9, 68.5, 70.5, 75.5, 115.3, 115.6, 116.1, 122.9, 127.3, 127.7, 128.4, 130.7, 137.1, 152.7, 153.1, 156.2, 166.5; MS (ES) m/z 534 (M^+); Anal. ($C_{33}H_{44}INO_5$) C, H, N.

8-(4-Benzyloxyphenoxy)-1-octyl 2-(*N*,*N*,*N*-Trimethylammonium)-3-(1*H*-indol-3-yl)propionate, Iodide (2c). Compound **2c** (0.135 g, 67.6%) was prepared using a procedure similar to that for **2a**: ^{1}H NMR ($CDCl_3$) δ 0.75−0.90 (m, 2H), 0.99−1.19 (m, 6H), 1.31−1.41 (m, 2H), 1.70 (p, 2H, J = 7.02 Hz), 3.23−3.33 (m, 1H), 3.41 (s, 9H), 3.55−3.65 (m, 1H), 3.72−3.81 (m, 2H), 3.88 (t, 2H, J = 6.5 Hz), 4.46−4.53 (m, 1H), 4.99 9s, 2H), 6.82 (d, 2H, J = 9.1 Hz), 8.90 (d, 2H, J = 9.1 Hz), 7.04−7.16 (m, 2H), 7.27−7.48 (m, 7H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.4, 25.0, 25.8, 27.5, 28.7, 28.9, 29.2, 52.9, 67.0, 68.5, 70.5, 75.1, 105.2, 111.8, 115.3, 115.7, 118.0, 119.7, 122.1, 124.8, 126.4, 127.4, 127.8, 128.4, 135.8, 137.1, 152.7, 153.3, 167.1; MS (ES) m/z 557 (M^+); Anal. ($C_{35}H_{45}IN_2O_4 \cdot 0.25H_2O$) C, H, N.

***N*-[8-(4-Benzyloxyphenoxy)-1-octyl] Phthalimide (7).** To a solution of phenol **3** (8.00 g, 40.0 mmol) in anhydrous DMF (100 mL) under nitrogen, NaH (1.92 g, 60% in mineral oil, 48.0 mmol) was added and the mixture was stirred at room temperature for 30 min. A solution of *N*-(8-bromooctyl)phthalimide (14.9 g, 44.0 mmol) in DMF (30 mL) was added dropwise over 5 min and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated NH_4Cl (150 mL) and extracted with EtOAc (3 × 150 mL). The organic layers were combined, washed with 1 N NaOH (2 × 150 mL), water (3 × 150 mL), and brine (1 × 150 mL), and dried over Na_2SO_4. The drying

agent was removed by filtration and the filtrate was evaporated in vacuo to afford the crude product, which crystallized upon the addition of hexanes. This was filtered, dried, and recrystallized from methanol to afford the pure **7** (14.6 g, 79.8%): mp 72−73 °C; ^{1}H NMR ($CDCl_3$) δ 1.25−1.50 (m, 8H), 1.65−1.79 (m, 4H), 3.67 (t, 2H, J = 7.4 Hz), 3.88 (t, 2H, J = 6.5 Hz), 5.00 (s, 2H), 6.82 (d, 2H, J = 9.1 Hz), 6.89 (d, 2H, J = 9.1 Hz), 7.25−7.45 (m, 5H), 7.67−7.72 (m, 2H), 7.81−7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.7, 28.5, 29.0, 29.1, 29.2, 37.9, 68.4, 70.6, 115.3, 115.7, 123.1, 127.4, 127.8, 128.4, 132.1, 133.8, 137.3, 152.7, 153.4, 168.4; IR (neat) 2929 cm^{-1}; MS (ES) m/z 458 (M + H); Anal. ($C_{29}H_{31}NO_4$) C, H, N.

8-(4-Benzyloxyphenoxy)-1-octylamine, Hydrochloride (8). To a solution of phthalimide **7** (14.0 g, 30.6 mmol) in a mixture of CH_2Cl_2 (175 mL) and MeOH (175 mL), hydrazine (5.88 g, 183.8 mmol) was added dropwise and the mixture was stirred at room temperature under N_2 for 12 h. A white precipitate of the byproduct was filtered, the filtrate was evaporated in vacuo, and the residue was taken up in a $CHCl_3$/EtOAc (1:1) mixture (150 mL). More precipitation of the byproduct occurred and it was again filtered. The filtrate was evaporated under vacuum and the residue obtained was dissolved in $CHCl_3$ (200 mL). This was washed with water (2 × 100 mL) and brine (1 × 100 mL) and concentrated under vacuum to a volume of 50 mL. HCl (1 N) was added dropwise with stirring until the pH was ∼2. The white amine hydrochloride precipitated and was filtered, washed on the filter with ice cold water, EtOAc, and ether, and dried to obtain pure **8** (8.50 g, 76.4%): mp 185−186 °C; ^{1}H NMR (DMSO-d_6) δ 1.22−1.44 (m, 8H), 1.48−1.61 (m, 2H), 1.66 (p, 2H, J = 6.6 Hz), 2.67−2.81 (m, 2H), 2.69−2.78 (m, 2H), 3.86 (t, 2H, J = 6.6 Hz), 5.02 (s, 2H), 6.83 (d, 2H, J = 9.1 Hz), 6.91 (d, 2H, J = 9.1 Hz), 7.28−7.45 (m, 5H), 7.98 (br s, 3H, NH_3); ^{13}C NMR (DMSO-d_6) δ 25.5, 25.8, 26.9, 28.5 (2C), 28.6, 28.7, 67.7, 69.6, 115.2, 115.6, 127.6, 127.7, 128.4, 137.3, 152.2, 152.8; IR (neat) 3440 cm^{-1}; MS (ES) m/z 328 (M^+); Anal. ($C_{21}H_{30}ClNO_2$) C, H, N.

***N*-[8-(4-Benzyloxyphenoxy)-1-octyl]-2-(*N*-*tert*-butoxycarbonylamino)-3-phenylpropionamide (9a).** To a solution of amine hydrochloride **8** (0.363 g, 1.00 mmol) in CH_2Cl_2 (10 mL), Et_3N (0.160 mL, 1.20 mmol) was added and the mixture was stirred at room temperature for 5 min. Then *N*-(Boc)phenylalanine (0.397 g, 1.50 mmol), EDAC (0.286 g, 1.50 mmol), and DMAP (0.012 g, 0.10 mmol) were added and stirred at room temperature for 12 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with 1 M $NaHCO_3$ (3 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL), and dried over Na_2SO_4. The drying agent was removed by filtration and the filtrate was evaporated under vacuum to afford the crude product, which was purified by flash column chromatography on silica gel (2 × 10 cm) using MeOH/$CHCl_3$ (1:19) eluent to afford pure **9a** (0.410 g, 71.4%): ^{1}H NMR ($CDCl_3$) δ 1.11−1.49 (m, 10H), 1.40 (s, 9H), 1.67−1.77 (m, 2H), 2.95−3.18 (m, 4H), 3.88 (t, 2H, J = 6.4 Hz), 4.19−4.32 (m, 1H), 5.00 (s, 2H), 5.12 (br s, 1H, NH), 5.74 (br s, 1H, NH), 6.81 (d, 2H, J = 9.2 Hz), 6.90 (d, 2H, J = 9.2 Hz), 7.15−7.43 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.4, 27.1, 28.7, 29.5 (2C), 29.6, 29.7, 29.8, 39.1, 30.8, 68.9, 71.1, 80.5, 115.7, 116.2, 127.3, 127.8, 128.2, 128.9, 129.1, 129.7, 136.0, 137.7, 153.2, 153.8, 155.5, 171.2; MS (ES) m/z 575 (M + H); Anal. ($C_{35}H_{46}N_2O_5$) C, H, N.

***N*-[8-(4-Benzyloxyphenoxy)-1-octyl]-2-(*N′*-*tert*-butoxycarbonylamino)-2-phenylacetamide (9b).** Compound **9b** (0.41 g, 73%) was prepared using a procedure similar to that for **9a**: ^{1}H NMR ($CDCl_3$) δ 1.07−1.29 (m, 6H), 1.29−1.47 (m, 4H), 1.40 (s, 9H), 1.70 (p, 2H, J = 6.5 Hz), 3.02−3.26 (m, 2H), 3.85 (t, 2H, J = 6.5 Hz), 4.98 (s, 2H), 5.14−5.39 (m, 1H), 5.87−6.14 (m, 1H), 6.37 (br s, 1H, NH), 6.80 (d, 2H, J = 9.2 Hz), 6.89 (d, 2H, J = 9.2 Hz), 7.24−7.43 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.7, 26.4, 28.1, 28.9, 29.0, 29.2 (2C), 39.5, 58.1, 68.2, 70.4, 79.7, 115.2, 115.6, 126.9, 127.3, 127.7, 127.9, 128.3, 128.7, 137.1, 138.5, 152.6, 153.2, 155.1, 170.0; IR (neat) 3365, 3318, 1686, 1654 cm^{-1}; MS (ES) 561 (M + H); Anal. ($C_{34}H_{44}N_2O_5$) C, H, N.

1-(4-Benzyloxyphenoxy)-8[2-(*N*-*tert*-butoxycarbonylamino)-3-phenyl-1-propyloxy]octane (9c). To a solution of alcohol **4** (1.00 g, 3.04 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added 2,6-lutidine (0.460 mL, 3.95 mmol) followed by triflic anhydride (0.620 mL, 3.68 mmol). The addition was carried out slowly while maintaining the temperature of the reaction at 0 °C. After stirring at 0 °C for 15 min, the reaction mixture was washed with water (2 × 20 mL) and brine (1 × 20 mL) and dried over Na_2SO_4. After removal of the drying agent, solvent was completely removed to obtain the product triflate. This was dried at high vacuum for 15 min and used without further purification for the next step. The crude triflate was then dissolved in CH_2Cl_2 (10 mL) and added over 10 min to a solution of *N*-Boc phenylalaninol (1.53 g, 6.09 mmol) and NaH (0.305 g, 60% in mineral oil, 7.62 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction bubbled vigorously. It was stirred for 5 min and then 18-crown-6 (0.081 g, 0.31 mmol) was added. The reaction mixture was stirred at room temperature for another 30 min. The reaction was then carefully quenched with water (20 mL) and the organic layer was separated. The organic layer was washed with water (2 × 20 mL) and brine (1 × 20 mL) and dried over Na_2SO_4. The drying agent was filtered and the solvent was completely removed under vacuum to obtain the crude product. It was purified by silica flash column chromatography (4 × 20 cm) using EtOAc/hexanes (1:9) as eluent to afford pure **9c** (4.50 g, 67.5%): ^{1}H NMR ($CDCl_3$) δ 1.28−1.36 (m, 6H), 1.41 (s, 9H), 1.43−1.51 (m, 2H), 1.51−1.64 (m, 2H), 1.69−1.81 (m, 2H), 2.75−2.94 (m, 2H), 3.23−3.32 (m, 2H), 3.32−3.45 (m, 2H), 3.88 (t, 2H, J = 6.5 Hz), 3.88−3.96 (m, 1H), 4.88 (br d, 1H, J = 8.04 Hz, NH), 4.98 (s, 2H), 6.81 (d, 2H, J = 9.2 Hz), 6.89 (d, 2H, J = 9.2 Hz), 7.15−7.43 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.1, 28.3 (2C), 29.2, 29.3, 29.5, 37.7, 51.5, 68.4, 70.2, 70.5, 71.1, 79.1, 115.2, 115.6, 126.1, 127.3, 127.7, 128.2, 128.4, 129.3, 137.2, 138.2, 152.7, 153.3, 155.2; IR (neat) 3373, 1685 cm^{-1}; MS (ES) 562 (M + H); Anal. ($C_{35}H_{47}NO_5$) C, H, N.

1-(4-Benzyloxyphenoxy)-8[2-(*N*-*tert*-butoxycarbonylamino)-2-phenyl-1-ethyloxy]octane (9d). Compound **9d** (0.411 g, 75%) was prepared using a procedure similar to that for **9c**: ^{1}H NMR ($CDCl_3$) δ 1.23−1.35 (m, 8H), 1.41 (s, 9H), 1.48−1.61 (m, 2H), 1.74 (p, 2H, J = 6.6 Hz), 3.31−3.49 (m, 2H), 3.49−3.69 (m, 2H), 3.88 (t, 2H, J = 6.6 Hz), 4.79 (br s, 1H), 5.01 (s, 2H), 5.26 (br s, 1H), 6.82 (d, 2H, J = 9.2 Hz), 6.90 (d, 2H, J = 9.2 Hz), 7.19−7.45 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.9 (2C), 28.3 (2C), 29.3 (2C), 29.4, 54.0, 68.4, 70.6, 71.2, 73.5, 79.4, 115.3, 115.7, 126.6, 127.1, 127.4, 127.8, 128.3, 128.5(2C), 137.2, 152.7, 153.4, 155.4; IR (neat) 3382, 1687 cm^{-1}; MS (ES) 548 (M + H); Anal. ($C_{34}H_{45}NO_5$) C, H, N.

***N*-[8-(4-Benzyloxyphenoxy)-1-octyl]-2-amino-3-phenylpropionamide (10a).** To a solution of amide **9a** (0.400 g, 0.696 mmol) in CH_2Cl_2 (2 mL) was added a mixture of TFA (2 mL) and CH_2Cl_2 (2 mL), dropwise, and the mixture was stirred at room temperature for 30 min. The solvent and TFA were completely removed under vacuum, and the residue was dissolved in CH_2Cl_2 (20 mL). The solution was washed with 1 M Na_2CO_3 (3 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL) and dried over Na_2SO_4. The drying agent was removed by filtration and the filtrate was evaporated in vacuo to afford the crude product, which was purified by flash column chromatography on silica gel (2 × 10 cm) using MeOH/$CHCl_3$ (1:19) eluent to afford pure **10a** (0.310 g, 93.8%): ^{1}H NMR ($CDCl_3$) δ 1.23−1.61 (m, 14H including NH_2), 1.74 (p, 2H, J = 6.5 Hz), 2.69 (dd, 1H, J_1 = 13.6 Hz, J_2 = 9.3 Hz), 3.19−3.29 (m, 3H), 3.58 (dd, 1H, J_1 = 9.3 Hz, J_2 = 4.1 Hz), 3.89 (t, 2H, J = 6.5 Hz), 5.00 (s, 2H), 6.82 (d, 2H, J = 9.2 Hz), 6.89 (d, 2H, J = 9.2 Hz), 7.18−7.44 (m, 10H); ^{13}CNMR ($CDCl_3$) δ 25.9, 26.8, 29.1, 29.2, 29.3, 29.5, 39.0, 41.1, 56.4, 68.4, 70.6, 115.3, 115.7, 126.7, 127.4, 127.8, 128.4, 128.6, 129.2, 137.2, 137.7, 152.7, 153.4, 173.9; MS (ES) m/z 475 (M + H); Anal. ($C_{30}H_{38}N_2O_3$) C, H, N.

1-(4-Benzyloxyphenoxy)-8-(2-amino-3-phenyl-1-propyloxy)-octane (10b). Compound **10b** (0.31 g, 94.3%) was prepared using a procedure similar to that for **10a**: ^{1}H NMR ($CDCl_3$) δ 1.28−1.50 (m, 8H), 1.50−1.64 (m, 2H), 1.73 (p, 2H, J = 6.3 Hz), 2.47−2.61 (m, 1H), 2.71−2.78 (m, 1H), 3.15−3.27 (m, 2H), 3.33−3.48 (m, 3H), 3.85 (t, 2H, J = 6.3 Hz), 4.96 (s, 2H), 6.79 (d, 2H, J =

9.1 Hz), 6.87 (d, 2H, J = 9.1 Hz), 7.15−7.42 (m, 10H); ^{13}CNMR ($CDCl_3$) δ 25.8, 25.9, 29.1(2C), 29.2, 29.5, 40.6, 52.2, 68.3, 70.4, 71.1, 75.2, 115.1, 115.5, 126.1, 127.2, 127.6, 128.2, 128.3, 129.1, 137.1, 138.8, 152.6, 153.3; MS (ES) m/z 462 (M + H); Anal. ($C_{30}H_{39}NO_3$) C, H, N.

***N*-[8-(4-Benzyloxyphenoxy)-1-octyl]-2-amino-2-phenylacetamide (10c).** Compound **10c** (0.41 g, 73.2%) was prepared using a procedure similar to that for **10a**: ^{1}H NMR ($CDCl_3$) δ 1.23−1.35 (m, 6H), 1.35−1.54 (m, 4H), 1.73 (p, 2H, J = 6.5 Hz), 1.83 (br s, 2H, NH_2), 3.24 (q, 2H, 7.1 Hz), 3.88 (t, 2H, J = 6.5 Hz), 4.49 (s, 1H), 5.01 (s, 2H), 6.82 (d, 2H, J = 9.2 Hz), 6.90 (d, 2H, J = 9.2 Hz), 7.06 (br s, 1H, NH), 7.26−7.44 (m, 10H); ^{13}CNMR ($CDCl_3$) δ 25.8, 26.7, 29.1, 29.2, 29.3, 29.5, 39.1, 59.8, 68.4, 70.6, 115.3, 115.7, 126.8, 127.4, 127.8, 127.9, 127.4, 128.7, 137.2, 141.1, 152.7, 153.3, 172.7; IR (neat) 3294, 1640 cm^{-1}; MS (ES) 461 (M + H); Anal. ($C_{29}H_{36}N_2O_3$) C, H, N.

1-(4-Benzyloxyphenoxy)-8-(2-amino-2-phenyl-1-ethyloxy)octane (10d). Compound **10d** (0.21 g, 85.2%) was prepared using a procedure similar to that for **10a**: ^{1}H NMR ($CDCl_3$) δ 1.26−1.38 (m, 6H), 1.38−1.49 (m, 2H), 1.51−1.64 (m, 2H), 1.74 (p, 2H, J = 6.5 Hz), 1.92 (br s, 2H, NH_2), 3.31−3.57 (m, 4H), 3.88 (t, 2H, J = 6.5 Hz), 4.19 (dd, 1H, J_1 = 8.9 Hz, J_2 = 3.6 Hz), 4.99 (s, 2H), 6.82 (d, 2H, J = 9.2 Hz), 6.89 (d, 2H, J = 9.2 Hz), 7.21−7.44 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.1, 29.3 (2C), 29.4, 29.6, 55.4, 68.4, 70.6, 71.2, 115.3, 115.7, 126.7, 127.3, 127.4, 127.8, 128.3, 128.4, 137.2, 142.4, 152.7, 153.4; IR (neat) 3314−3162 cm^{-1}; MS (ES) 448 (M + H).

***N*-[8-(4-Benzyloxyphenoxy)-1-octyl]-2-(*N*,*N*,*N*-trimethylammonium)-3-phenylpropionamide, Iodide (11a).** To a solution of the amine **10a** (0.15 g, 0.32 mmol) in DME (5 mL) were added K_2CO_3 (0.270 g, 1.95 mmol) and iodomethane (0.20 mL, 3.2 mmol), and the mixture was stirred at room temperature for 12 h. Precipitation of the product quaternary ammonium salt occurred, and it was dissolved by the addition of CH_2Cl_2 (20 mL). K_2CO_3 was removed by filtration through celite-521. The filtrate was concentrated and the product was precipitated upon the addition of hexanes. This was filtered, washed on the filter with EtOAc, and dried to obtain pure **11a** (0.13 g, 66%): ^{1}H NMR ($CDCl_3$) δ 0.93−1.07 (m, 2H), 1.10−1.45 (m, 8H), 1.71 (p, 2H J = 6.5 Hz), 2.85−2.95 (m, 2H), 3.06−3.34 (m, 3H), 3.48 (s, 9H), 3.87 (t, 2H, J = 6.5 Hz), 4.99 (s, 2H), 5.59 (dd, 1H, J_1 = 11.5 Hz, J_2 = 4.1 Hz), 6.82 (d, 2H, J = 9.0 Hz), 6.89 (d, 2H, J = 9.0 Hz), 7.22−7.45 (m, 10H), 7.72 (t, 1H, J = 5.8 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 25.8, 26.3, 28.2, 28.8, 28.9, 29.1, 32.8, 39.2, 52.6, 68.3, 70.5, 72.9, 115.2, 115.6, 127.3, 127.7, 128.4 (2C), 128.8, 129.6, 132.2, 137.1, 152.6, 153.3, 164.5; MS (ES) m/z 517 (M^+); Anal. ($C_{33}H_{45}IN_2O_3$) C, H, N.

1-(4-Benzyloxyphenoxy)-8-(2-*N*,*N*,*N*-trimethylammonium-3-phenyl-1-propyloxy)octane, Iodide (11b). Compound **11b** (0.13 g, 60%) was prepared using a procedure similar to that for **11a**: ^{1}H NMR ($CDCl_3$) δ 1.28−1.50 (m, 8H), 1.50−1.62 (m, 2H), 1.72−1.81 (m, 2H), 3.05−3.42 (m, 5H), 3.57 (s, 9H), 3.84−3.88 (m, 1H), 3.90 (t, 2H, J = 6.5 Hz), 4.26−4.35 (m, 1H), 5.01 (s, 2H), 6.82 (d, 2H, J = 9.2 Hz), 6.90 (d, 2H, J = 9.2 Hz), 7.21−7.43 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.0, 29.1, 29.20, 29.23, 29.3, 31.3, 53.4, 65.1, 68.3, 70.5, 71.7, 73.8, 115.2, 115.6, 127.3, 127.5, 127.7, 128.4, 129.0, 129.4, 134.7, 137.1, 152.7, 153.3; IR (neat) 2931, 2856 cm^{-1}; MS (ES) 504 (M^+); Anal. ($C_{33}H_{46}INO_3$) C, H, N.

***N*-[8-(4-Benzyloxyphenoxy)-1-octyl]-2-(*N*,*N*,*N*-trimethylammonium)-2-phenylacetamide, Iodide (11c).** Compound **11c** (0.114 g, 58.1%) was prepared using a procedure similar to that for **11a**: ^{1}H NMR ($CDCl_3$) δ 1.19−1.31 (m, 6H), 1.31−1.44 (m, 2H), 1.44−1.60 (m, 2H), 1.63−1.76 (m, 2H), 3.17−3.32 (m, 2H), 3.38 (s, 9H), 3.85 (t, 2H, J = 6.5 Hz), 4.99 (s, 2H), 6.70 (s, 1H), 6.80 (d, 2H, J = 9.1 Hz), 6.88 (d, 2H, J = 9.1 Hz), 7.26−7.56 (m, 8H), 7.85−7.94 (m, 3H, including NH); ^{13}C NMR ($CDCl_3$) δ 25.5, 26.4, 28.4, 28.6, 28.8, 28.9, 39.4, 51.8, 68.1, 70.3, 73.2, 115.0, 115.4, 126.6, 127.1, 127.5, 128.2, 129.0, 131.2, 131.8, 136.9, 152.4, 153.1, 164.6; IR (neat) 3223, 1679 cm^{-1}; MS (ES) m/z 503 (M^+); Anal. ($C_{32}H_{43}IN_2O_3\cdot 0.5CHCl_3$) C, H, N.

1-(4-Benzyloxyphenoxy)-8-(2-*N*,*N*,*N*-trimethylammonium-2-phenyl-1-ethyloxy)octane, Iodide (11d). Compound **11d** (0.11 g, 78.1%) was prepared using a procedure similar to that for **11a**: ^{1}H NMR ($CDCl_3$) δ 1.31−1.51 (m, 8H), 1.57−1.69 (m, 2H), 1.69−1.82 (m, 2H), 3.46 (s, 9H), 3.37−3.63 (m, 2H), 3.90 (t, 2H, J = 6.5 Hz), 4.06−4.14 (m, 1H), 4.20−4.25 (m, 1H), 5.01 (s, 2H), 5.44 (t, 1H, J = 3.9 Hz), 6.82 (d, 2H, J = 9.1 Hz), 6.91 (d, 2H, J = 9.1 Hz), 7.27−7.53 (m, 8H), 7.73−7.79 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.1, 29.1 (2C), 29.2, 29.3, 53.1, 68.3, 69.5, 70.5, 72.1, 74.5, 115.3, 115.7, 127.3, 127.7, 128.4, 129.2, 130.8, 131.2 (2C), 137.1, 152.7, 153.3; IR (neat) 2934, 2858 cm^{-1}; MS (ES) m/z 490 (M^+); Anal. ($C_{32}H_{44}INO_3\cdot 0.5H_2O$) C, H, N.

***N*-[8-(4-Benzyloxyphenoxy)-1-octyl]-2-(*N*′,*N*″-bis-*tert*-butoxycarbonylguanidino)-3-phenylpropionamide (12a).** To a solution of amine **10a** (6.00 g, 12.6 mmol) in anhydrous DMF (60 mL) were added 1,3-bis(Boc)-2-methyl-2-thiopseudourea (3.67 g, 12.6 mmol) and Et_3N (6.8 mL, 51 mmol), and the mixture was stirred at room temperature for 5 min. $HgCl_2$ (3.77 g, 13.9 mmol) was added and formation of a white precipitate occurred almost instantly. The mixture was stirred at room temperature for 30 min. It was diluted with EtOAc (200 mL), filtered through celite-521 to remove the precipitate, and the filter was washed with EtOAc (100 mL). The filtrate was washed with 1 N NaOH (3 × 100 mL), water (2 × 100 mL), and brine (100 mL). Removal of solvent from the dried (Na_2SO_4) extract gave the crude product, which was purified by flash silica chromatography (7 × 20 cm) using EtOAc/hexanes (1:4) as eluent to afford **12a** as a colorless oil (8.21 g, 90.5%): ^{1}H NMR ($CDCl_3$) δ 1.15−1.45 (m, 10H), 1.47 (s, 18H), 1.65−1.77 (m, 2H), 3.07−3.18 (m, 4H), 3.87 (t, 2H, J = 6.5 Hz), 4.67 (q, 2H, J = 7.2 Hz), 4.99 (s, 2H), 6.41 (t, 1H, NH, J = 5.5 Hz), 6.81 (d, 2H, J = 9.2 Hz), 6.89 (d, 2H, J = 9.2 Hz), 7.19−7.44 (m, 10H), 8.81 (d, 1H, J = 7.2 Hz), 11.31 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 25.8, 26.5, 27.8, 28.1, 29.0 (2C), 29.1, 29.2, 37.5, 39.2, 55.7, 68.3, 70.5, 79.1, 83.3, 115.2, 115.6, 126.7, 127.3, 127.7, 128.3, 128.4, 129.3, 136.7, 137.1, 152.5, 152.6, 153.3, 155.6, 162.8, 169.9; MS (ES) m/z 717 (M + H); Anal. ($C_{41}H_{56}N_4O_7$) C, H, N.

1-(4-Benzyloxyphenoxy)-8-(2-*N*,*N*′-bis-*tert*-butoxycarbonylguanidino)-3-phenyl-1-propyloxy)octane (12b). Compound **12b** (0.218 g, 92.8%) was prepared using a procedure similar to that for **12a**: ^{1}H NMR ($CDCl_3$) δ 1.27−1.43 (m, 8H), 1.47 (s, 9H), 1.50 (s, 9H), 1.53−1.67 (m, 2H), 1.74 (p, 2H, J = 6.5 Hz), 2.83−3.02 (m, 2H), 3.25−3.35 (m, 2H), 3.39 (t, 2H, J = 6.2 Hz), 3.87 (t, 2H, J = 6.5 Hz), 4.41−4.54 (m, 1H), 4.98 (s, 2H), 6.81 (d, 2H, J = 9.2 Hz), 6.88 (d, 2H, J = 9.2 Hz), 7.15−7.43 (m, 10H), 8.66 (d, 1H, J = 8.3 Hz, NH), 11.5 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.0, 27.9, 28.2, 29.2, 29.3, 29.4, 29.5, 37.2, 51.4, 68.3, 69.4, 70.4, 71.1, 78.7, 82.6, 115.2, 115.6, 126.2, 127.3, 127.7, 128.1, 128.3, 129.5, 137.1, 137.9, 152.6, 152.8, 153.3, 155.5, 163.6; MS (ES) m/z 704 (M + H); Anal. ($C_{41}H_{57}N_3O_7$) C, H, N.

***N*-[8-(4-Benzyloxyphenoxy)-1-octyl]-2-(*N*′,*N*″-bis-*tert*-butoxycarbonylguanidino)-2-phenylacetamide (12c).** Compound **12c** (0.113 g, 82.7%) was prepared using a procedure similar to that for **12a**: ^{1}H NMR ($CDCl_3$) δ 1.16−1.45 (m, 10H), 1.47 (s, 9H), 1.48 (s, 9H), 1.66−1.78 (m, 2H), 3.10−3.34 (m, 2H), 3.88 (t, 2H, J = 6.5 Hz), 5.01 (s, 2H), 5.61 (d, 1H, J = 7.1 Hz), 5.90 (t, 1H, J = 5.5 Hz), 6.82 (d, 2H, J = 9.2 Hz), 6.89 (d, 2H, J = 9.2 Hz), 7.27−7.47 (m, 10H), 9.38 (d, 1H, J = 7.1 Hz), 11.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.5, 27.9, 28.2, 29.1, 29.2, 29.3 (2C), 39.7, 58.0, 68.4, 70.6, 115.3, 115.7, 127.4, 127.5, 127.8, 128.3, 128.4, 128.8, 137.2, 137.3, 152.6, 152.7, 153.4, 155.2, 163.1, 169.4; IR (neat) 3314, 3245, 3162, 1653, 161 cm^{-1}; MS (ES) m/z 703 (M + H); Anal. ($C_{40}H_{54}N_4O_7$) C, H, N.

1-(4-Benzyloxyphenoxy)-8-(2-*N*,*N*′-bis-*tert*-butoxycarbonylguanidino-2-phenyl-1-ethyloxy)octane (12d). Compound **12d** (0.16 g, 79%) was prepared using a procedure similar to that for **12a**: ^{1}H NMR ($CDCl_3$) δ 1.19−1.37 (m, 8H), 1.37−1.60 (m, 2H), 1.45 (s, 9H), 1.49 (s, 9H), 1.73 (p, 2H, J = 6.6 Hz), 3.32−3.48 (m, 2H), 3.61−3.75 (m, 2H), 3.87 (t, 2H, J = 6.6 Hz), 4.99 (s, 2H), 5.42−5.51 (m, 1H), 6.81 (d, 2H, J = 9.2 Hz), 6.88 (d, 2H, J = 9.2 Hz), 7.19−7.44 (m, 11H), 9.13 (d, 1H, J = 8.5 Hz), 11.55 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.8, 25.9, 27.9, 28.2, 29.2, 29.4,

53.2, 68.3, 70.5, 70.8, 71.3, 73.2, 78.9, 82.8, 115.2, 115.6, 126.8, 127.1, 127.3, 127.7, 128.2, 128.4, 137.2, 139.7, 152.7, 152.9, 153.3, 155.6, 163.5; IR (neat) 3325, 3279 cm^{-1}; MS (ES) *m*/*z* 690 (M + H); Anal. ($C_{40}H_{55}N_3O_7$) C, H, N.

***N*-[8-(4-Benzyloxyphenoxy)-1-octyl]-2-guanidino-3-phenylpropionamide (13a).** To a solution of compound **12a** (8.21 g, 11.4 mmol) in anhydrous CH_2Cl_2 (50 mL), a solution of TFA (50 mL) in anhydrous CH_2Cl_2 (50 mL) was added dropwise and the mixture stirred at room temperature under N_2 for 3 h. The solvent and TFA were completely removed under vacuum. The residue was dissolved in CH_2Cl_2 (100 mL), washed with saturated Na_2CO_3 (3 × 50 mL), water (2 × 50 mL), and brine (50 mL), and dried over Na_2SO_4. After filtering, the solvent was completely removed to obtain the crude product. It was purified by column chromatography over Si gel (7 × 20 cm) using MeOH/$CHCl_3$ (1:19) as eluent to afford the guanidine **13a** (4.60 g, 78.2%). Guanidine **13a** was dissolved in MeOH (50 mL), 2 N HCl (10 mL) was added, and the mixture was stirred for 3 h. The solvent and water were completely removed under vacuum, and the residue was coevaporated with anhydrous benzene (3 × 50 mL) to remove the last traces of water. Finally, hexanes were added and the suspension was stirred and filtered to obtain the hydrochloride salt of guanidine **13a** (4.10 g, 82.9%): ^{1}H NMR (MeOD-d_4) δ 1.19−1.51 (m, 10H), 1.65−1.77 (m, 2H), 2.93−3.25 (m, 4H), 3.89 (t, 2H, J = 6.2 Hz), 4.31 (t, 1H, J = 8.7 Hz), 4.99 (s, 2H), 6.80 (d, 2H, J = 9.2 Hz), 7.89 (d, 2H, J = 9.2 Hz), 7.19−7.42 (m, 10H); MS (ES) *m*/*z* 517 (M + H); Anal. ($C_{31}H_{41}ClN_4O_3 \cdot 0.5H_2O$) C, H, N.

1-(4-Benzyloxyphenoxy)-8-(2-guanidino-3-phenyl-1-propyloxy)-octane (13b). Compound **13b** (0.082 g, 72%) was prepared using a procedure similar to that for **13a**: ^{1}H NMR ($CDCl_3$) δ 1.17−1.45 (m, 8H), 1.45−1.61 (m, 2H), 1.72 (p, 2H, J = 6.5 Hz), 2.73−2.87 (m, 1H), 2.87−3.04 (m, 1H), 3.25−3.43 (m, 3H), 3.43−3.56 (m, 1H), 3.65−3.80 (m, 1H), 3.85 (t, 2H, J = 6.5 Hz), 4.97 (s, 2H), 6.81 (d, 2H, J = 9.2 Hz), 6.87 (d, 2H, J = 9.2 Hz), 6.90−7.16 (m, 1H, NH), 7.16−7.49 (m, 12H including NH_2), 8.09 (d, 1H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 25.6, 25.7, 29.0 (2C), 29.1 (2C), 37.1, 55.1, 68.2, 70.3, 70.1, 73.9, 115.1, 115.5, 126.8, 127.2, 127.6, 128.2, 128.5, 128.8, 136.4, 137.1, 152.5, 153.2, 158.7; IR (neat) 3329, 3259, 3155, 1668 cm^{-1}; MS (ES) 504 (M + H); Anal. ($C_{33}H_{42}F_3N_3O_5$) (analyzed as TFA salt) C, H, N.

***N*-[8-(4-Benzyloxyphenoxy)-1-octyl]-2-guanidino-2-phenylacetamide (13c).** Compound **13c** (0.101 g, 88.4%) was prepared using a procedure similar to that for **13a**: ^{1}H NMR ($CDCl_3$) δ 0.98−1.46 (m, 10H), 1.55−1.75 (m, 2H), 2.75−3.21 (m, 2H), 3.81 (t, 2H, J = 6.4 Hz), 4.95 (s, 2H), 5.93 (br s, 1H, NH), 6.77 (d, 2H, J = 9.1 Hz), 6.85 (d, 2H, J = 9.1 Hz), 7.13−7.42 (m, 10H), 7.42−7.56 (m, 2H, NH_2), 7.97 (br s 1H, NH), 8.32 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.6, 28.7, 29.1, 29.2, 29.3, 29.6, 40.0, 68.4, 70.5, 115.3, 115.7, 126.6, 127.4, 127.8, 128.4, 128.8, 129.1, 135.7, 137.2, 152.7, 153.3, 156.7, 169.6; IR (neat) 3314, 3245, 3162, 1653, 1611 cm^{-1}; MS (ES) *m*/*z* 503 (M + H); Anal. ($C_{30}H_{39}ClN_4O_3$) C, H, N.

1-(4-Benzyloxyphenoxy)-8-(2-guanidino-2-phenyl-1-ethyloxy)-octane (13d). Compound **13d** (0.078 g, 87.9%) was prepared using a procedure similar to that for **13a**: ^{1}H NMR ($CDCl_3$) δ 1.21−1.49 (m, 8H), 1.49−1.62 (m, 2H), 1.73 (p, 2H, J = 6.6 Hz), 3.34−3.5 (m, 2H), 3.54−3.68 (m, 2H), 3.88 (t, 2H, J = 6.5 Hz), 4.45−4.57 (m, 1H), 4.99 (s, 2H), 6.82 (d, 2H, J = 9.1 Hz), 6.89 (d, 2H, J = 9.1 Hz), 7.27−7.45 (m, 10H), 7.45−7.80 (br s, 3H), NH, NH_2), 8.32 (d, 1H, J = 5.6 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 25.8, 25.9, 29.23, 29.26, 29.3, 57.8, 68.4, 70.5, 71.8, 75.3, 115.3, 115.7, 126.7, 127.4, 127.8, 128.4, 128.7, 129.1, 136.1, 137.2, 152.7, 153.4, 158.7; IR (neat) 3318, 3261, 3147, 1664 cm^{-1}; MS (ES) 490 (M + H); Anal. ($C_{30}H_{40}ClN_3O_3 \cdot 0.5H_2O$) C, H, N.

Supporting Information Available: A table of elemental combustion analyses data for all new compounds described in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

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