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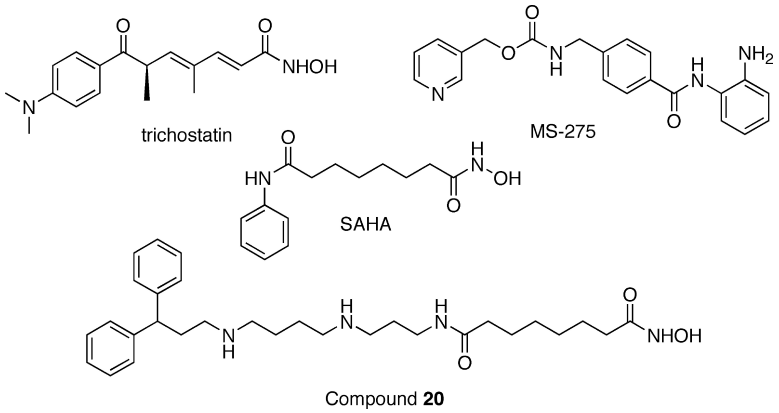

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Alkyl-Substituted Polyaminohydroxamic Acids: A Novel Class of Targeted Histone Deacetylase Inhibitors

Sheeba Varghese,[†] Deepak Gupta,[†] Tiffany Baran,[†] Anchalee Jiemjit,[§] Steven D. Gore,[§] Robert A. Casero, Jr.,[§] and Patrick M. Woster[†,*]

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The reversible acetylation of histones is critical for regulation of eukaryotic gene expression. The histone deacetylase inhibitors trichostatin (TSA, **1**), MS-275 (**2**) and suberoylanilide hydroxamic acid (SAHA, **3**) arrest growth in transformed cells and in human tumor xenografts. However, **1**−**3** suffer from lack of specificity among the various HDAC isoforms, prompting us to design and synthesize polyaminohydroxamic acid (PAHA) derivatives **6**−**21**. We felt that PAHAs would be selectively directed to chromatin and associated histones by the positively charged polyamine side chain. At 1 μM, compounds **12**, **15** and **20** inhibited HDAC by 74.86, 59.99 and 73.85%, respectively. Although **20** was a less potent HDAC inhibitor than **1**, it was more potent than **2**, more effective as an initiator of histone hyperacetylation, and significantly more effective than **2** at re-expressing $p21^{Waf1}$ in ML-1 leukemia cells. On the basis of these results, PAHAs **6**−**21** represent an important new chemical class of HDAC inhibitors.

Introduction

The reversible acetylation of histones, mediated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), plays a critical role in chromatin architecture and hence in regulation of gene expression.[1,2] Acetylation of cationic lysine tails in nucleosome-associated histones neutralizes charge and promotes relaxation of chromatin, leading to transcriptional activation. Conversely, deacetylation of these lysine residues promotes formation of condensed chromatin, and transcription is repressed. In some tumor cell types, excessive hypocetylation of histones results in the underexpression of growth regulatory factors such as the cyclin dependent kinase inhibitor $p21^{Waf1}$ and thus contributes to the development of cancer.[1,2] Histone hyperacetylation caused by HDAC inhibitors such as trichostatin (TSA, **1**), MS-275 (**2**) and SAHA (**3**) (Figure 1) can cause growth arrest in a wide range of transformed cells and can inhibit the growth of human tumor xenografts.[1−4] Cyclic peptide HDAC inhibitors such as apicidin, depsipeptide, trapoxin and CHAPs have also shown promising activity in cell culture and in vivo. Current structure/activity studies involving analogues of **1**−**3** have focused largely on modifications to the aromatic ring moiety and the aliphatic linker region present in these molecules.[4] Although they are effective both in vitro and in vivo, HDAC inhibitors typified by **1**−**3** suffer from lack of specificity among the various forms of HDAC, including deacetylases that target nonhistone proteins. Further, compounds **1** and **2** (and to some degree **3**) produce side effects through activity in noncancerous cells. Thus, it would be desirable to identify potent HDAC inhibitors that restore the expression of normal tumor suppressor factors without producing significant dose-limiting toxicity.[5] To address these problems, we designed and synthesized a series of polyaminohydroxamic acid (PAHA) derivatives that incorporate structural features of the polyamines spermidine and spermine (**4** and **5**, respectively, Figure 1) and the hydroxamic acid moiety commonly found in active HDAC inhibitor molecules such as **1** and **3**. This strategy was developed based on the observation that polyamine analogues can exert antitumor effects by virtue of their high affinity for DNA.[6−9] We postulated that these compounds could enter cells using the

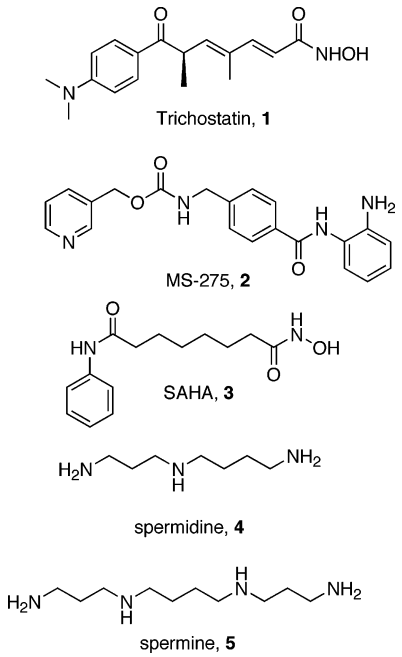

Figure 1. Structures of trichostatin, MS-275, SAHA, spermidine and spermine.

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[†] Wayne State University.
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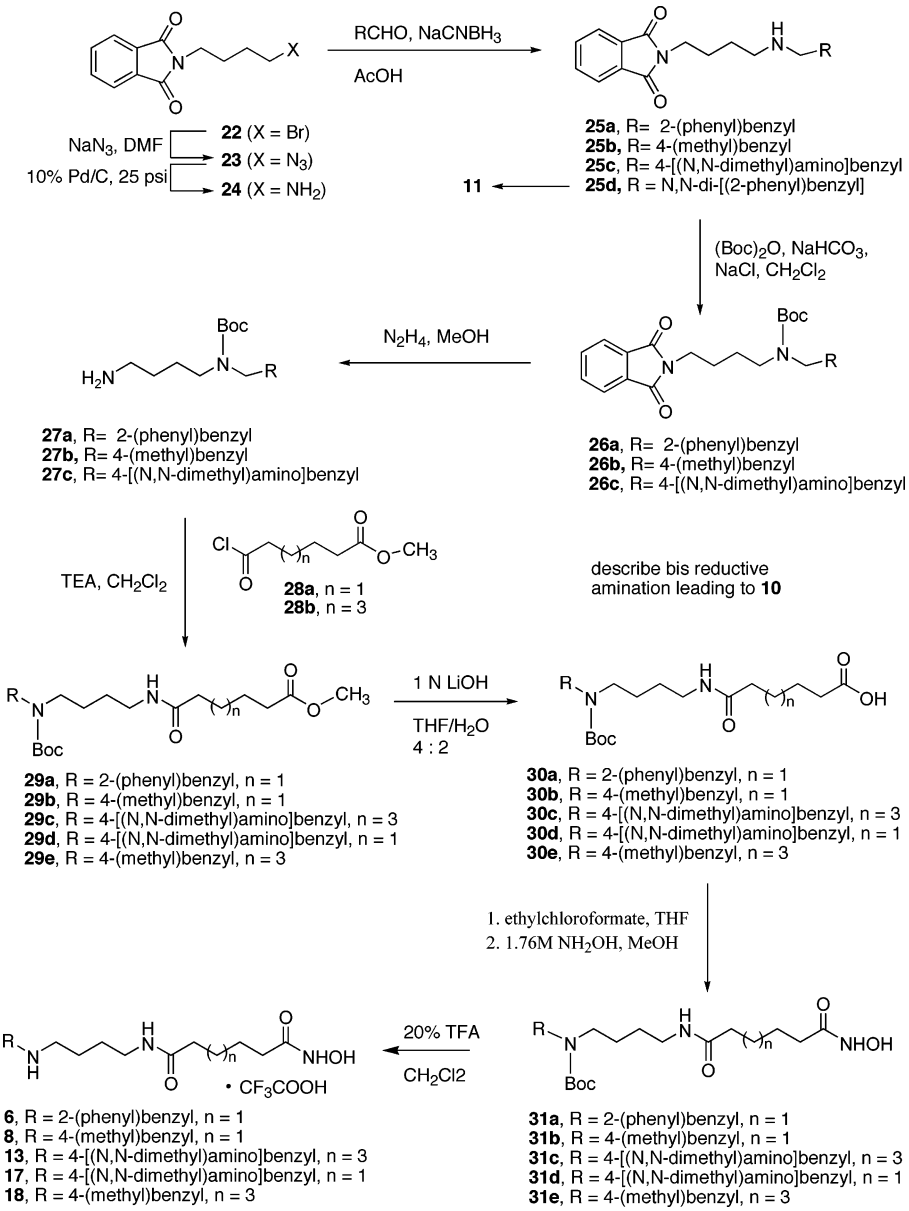
Scheme 1

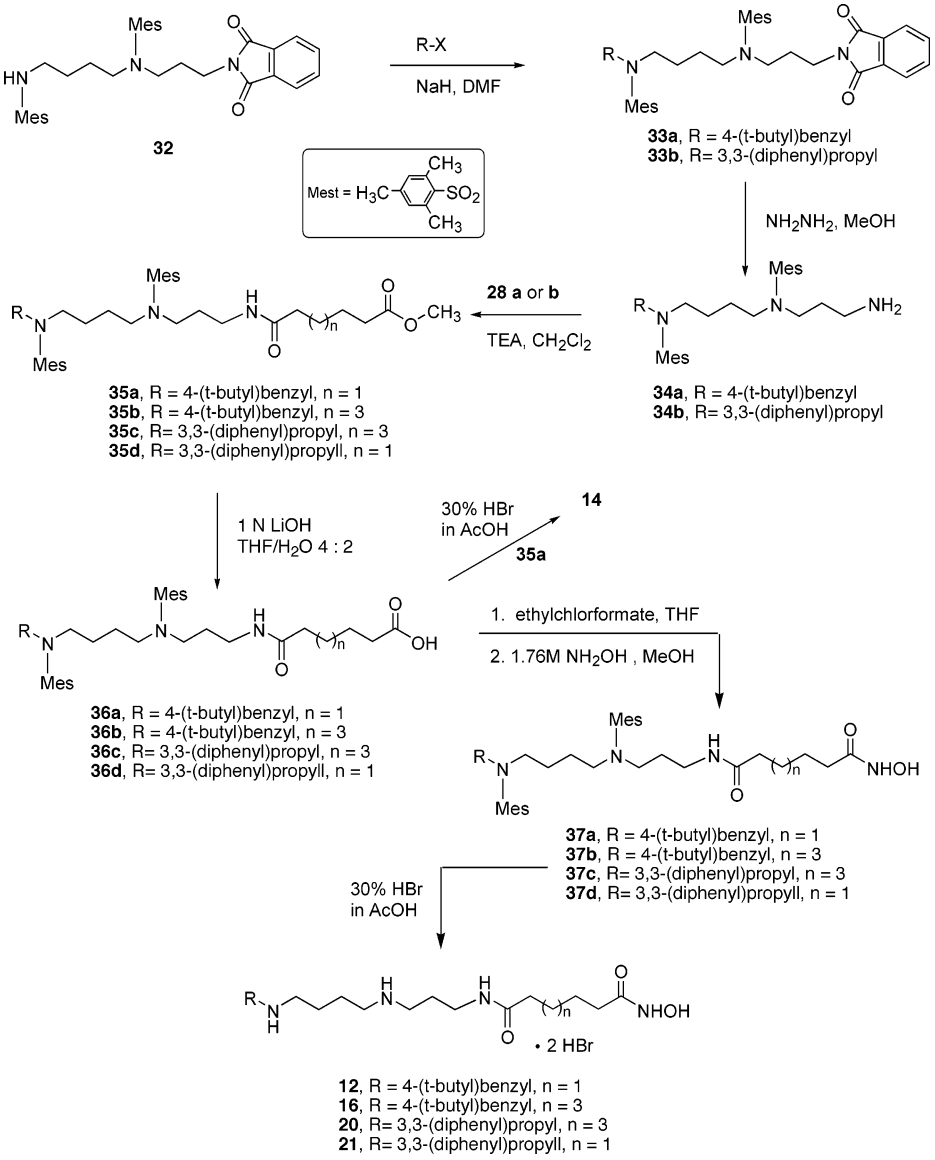


polyamine cellular transport system,[6,10] and could be selectively directed to DNA and associated histones, by virtue of the positively charged polyamine portion of the structure. In addition, it has been shown that histone deacetylases differ in primary sequence at specific residues in the rim region outside the lysine binding site.[3] Therefore, it may be possible to produce isoform specific inhibitors for individual HDACs by altering the polyamine chain composition and the terminal alkyl group on that chain. Using these design criteria, we successfully identified three lead compounds from a library consisting of only 16 analogues.

Chemistry

Depending on structure, one of 5 synthetic routes was used to produce compounds **6**−**21**, as outlined in Schemes 1−5. The structures and molecular weights of analogues **6**−**21** are summarized in Table 1. The synthesis of compounds **6**, **8**, **11**, **13**, **17** and **18** is shown in Scheme 1. Commercially available *N*-(3-bromobutyl)phthalimide **22** was first converted to the corresponding azide **23** (NaN_3, DMF),[11] which was immediately reduced to the corresponding amine **24** by catalytic hydrogenation (10% Pd/C, 25 psi).[12] The desired aralkyl group was then added by reductive amination[13] of the appropriate aldehyde ($NaCNBH_3$, AcOH) to afford the phthalimide-protected diamines **25a**−**c**. The secondary amine was then N-Boc protected ($(Boc)_2O$, $NaHCO_3$, NaCl)[14] to provide **26a**−**c**, followed by removal of the phthalimide (methanolic NH_2NH_2)[15] to give **27a**−**c**. The free primary amine was then coupled to acid chloride **28a** (n=1) or **28b** (n = 3), yielding **29a**−**e**.[13,16] The methyl ester in **29a**−**e** was cleaved (1N LiOH),[11] resulting in the free acids **30a**−**e**, and these intermediates were then converted to hydroxamic acids **31a**−**e** in a two step process[17] involving formation of an activated mixed anhydride (ethylchloroformate, THF) followed by addition of hydroxylamine (1.76 M NH_2OH in MeOH). Removal of the N-Boc protecting group (20% TFAA in CH_2Cl_2)[14] then afforded compounds **6**, **8**, **13**, **17** and **18** as trifuoroacetate salts. During the reductive amination step, one of the isolated products was tertiary amine **25d**,

Scheme 2



which resulted from addition of two equivalents of 2-(phenyl)benzaldehyde. Elaboration of this intermediate as described above resulted in the formation of target analogue **11**.

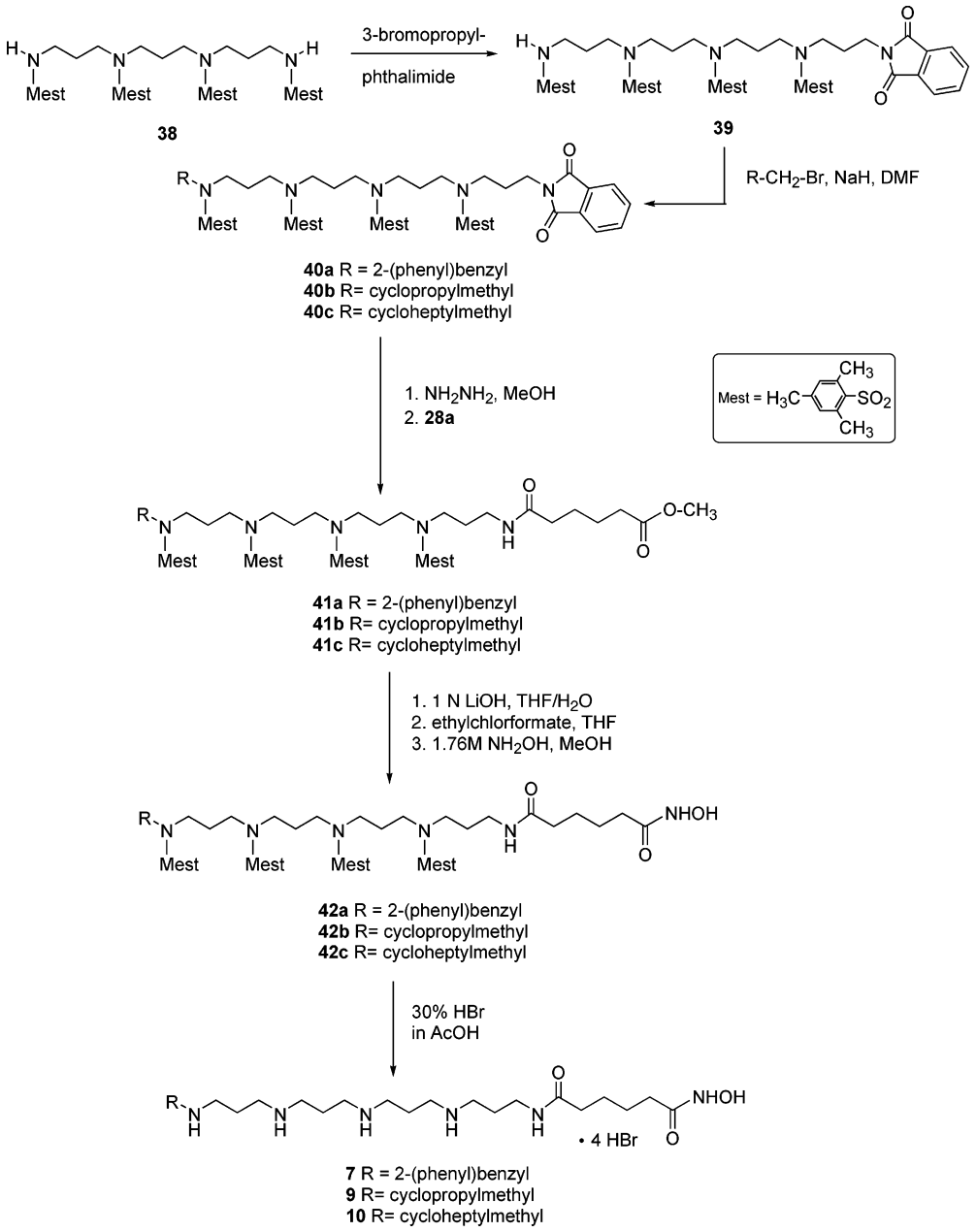
The synthetic route used to produce target analogues **12**, **16**, **20** and **22** is outlined in Scheme 2. The previously described dimesitylated phthalimide **32**[18] was monoalkylated with a suitable aralkyl halide (NaH, DMF)[19] to produce **33a**-**b**. Subsequent removal of the phthalimide (methanolic NH_2NH_2)[15] provided the free amines **34a**−**b**. Coupling with **28a** or **28b** as described above afforded intermediates **35a**−**d**, followed by ester cleavage (1 N LiOH)[11] to give **36a**−**d**. These intermediates were then converted to the corresponding hydroxamic acids **37a**−**d** as described above,[17] and removal of the mesityl protecting groups (30% HBr in AcOH)[20,21] afforded target compounds **12**, **16**, **20** and **21** as dihydrobromide salts. Direct deprotection of carboxylic acid **36a** (30% HBr in AcOH)[20,21] produced target compound **14**.

The synthesis of compounds **7**, **9** and **10** is shown in Scheme 3. Tetramesitylnorspermine **38**[18,19] was monoalkylated (1.1 equiv of *N*-(3-bromobutyl)phthalimide **22**, NaH, DMF)[18,19] to give **39**, followed by a second alkylation[22] with the appropriate alkyl- or aralky halide (NaH, DMF) to provide **40a**−**c**. Removal of the phthalimide (methanolic NH_2NH_2)[15] followed by coupling to acid chloride **28a** as described above then yielded the fully protected intermediates **41a**−**c**. Conversion of the ester in **41a**−**c** was then accomplished in three steps as described above,[11,17] resulting in hydroxamates **42a**−**c**. Deprotection (30% HBr in AcOH)[20,21] then afforded compounds **7**, **9** and **10** as tetrahydrobromide salts.

The synthesis of compound **19** is outlined in Scheme 4. Phthalimide **24** was converted to intermediate **25c** by reductive amination (4-dimethylaminobenzaldehyde, $NaCNBH_3$, AcOH),[13] followed by coupling to acid chloride **28b** as described above[13,16] to provide compound **43**. Removal of the phthalimide (methanolic NH_2NH_2)[15] followed by N-Boc protection[14] afforded **44**, and subsequent conversion of the ester to the corresponding hydroxamate as described above[11,17] produced **45**. Removal of the N-Boc group (20% TFAA in in CH_2Cl_2)[14] then afforded the desired **19** as the trifluoroacetate salt.

The synthesis of analogue **15** is described in Scheme 5. Removal of the phthalimide[15] from compound **32** and

Scheme 3



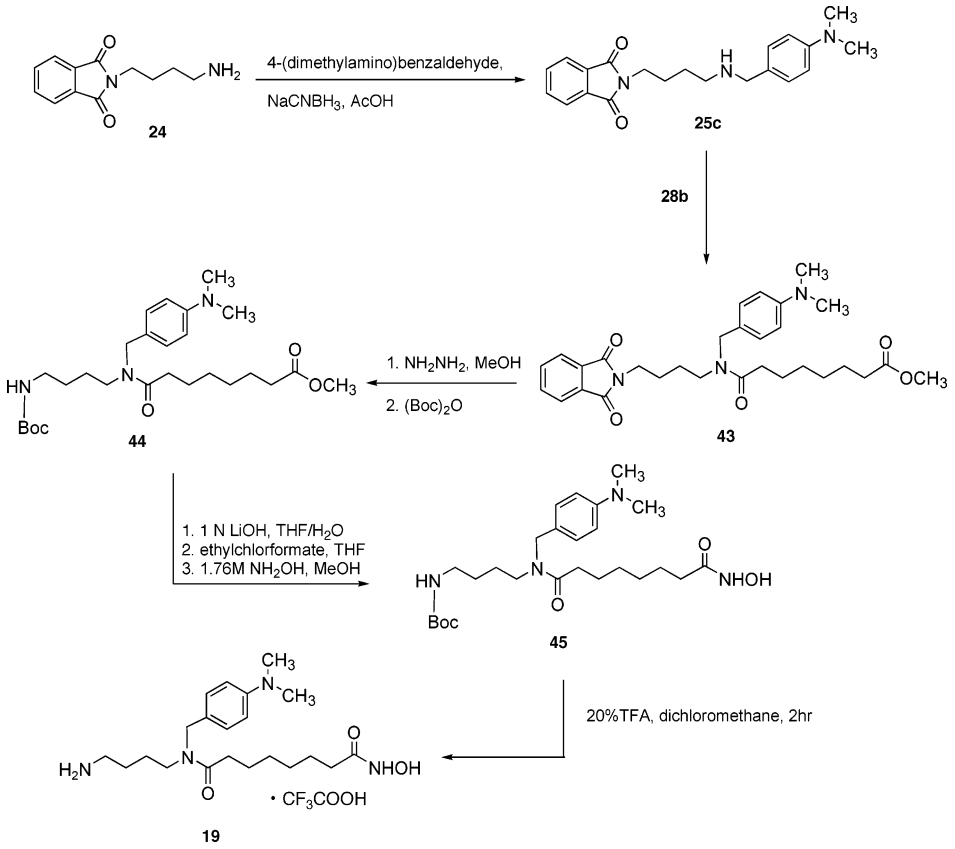
reductive amination (4-dimethylaminobenzaldehyde, $NaCNBH_3$, AcOH)[13] resulted in **46**, which was then coupled to acid chloride **28a**[13,16] to afford intermediate **47**. The ester was converted to the corresponding hydroxamic acid **48** as described above,[17] and then removal of the mesityl protecting groups (30% HBr in AcOH)[20,21] resulted in the formation of analogue **15** as the dihydrobromide salt.

Biological Evaluation

Compounds **6**−**21** were evaluated for their ability to inhibit isolated HDAC at 1 μM in a commercially available assay (Fluor de Lys Assay System, Biomol International LP, Plymouth Meeting, PA), employing 1 μM **1** and **2** as positive controls. The results of these studies are summarized in Table 1. Three of these analogues, compounds **12**, **15** and **20**, reduced HDAC activity by 74.86, 59.99 and 73.85%, respectively, and as such were selected for more extensive studies. These three compounds were subjected to a dose response analysis using the same commercial assay kit, and varying the concentration of inhibitor between 0.5 and 1000 nM, with **1** as a positive control. As shown in Figure 2, compounds **12**, **15** and **20** were essentially equipotent over the concentration range tested (IC_{50} = 400 nM). Compounds **12**, **15** and **20** act as potent inhibitors of HDAC that are significantly less effective than **1**, but more effective than **2**[4] in this isolated enzyme assay system.

The most potent inhibitor of isolated HDAC, compound **20**, was next evaluated in a series of cell proliferation studies in the ML-1 human myelocytic leukemia cell line. The results of these studies are outlined in Figure 3. Compound **20**, as well as the positive controls **1** and **2**, were compared at concentrations between 0.1 and 100 μM, and cell viability was determined in the ML-1 cultured cell preparation at 3 and 7 days (Figure 3) by direct cell count. Significant

Scheme 4



Scheme 5

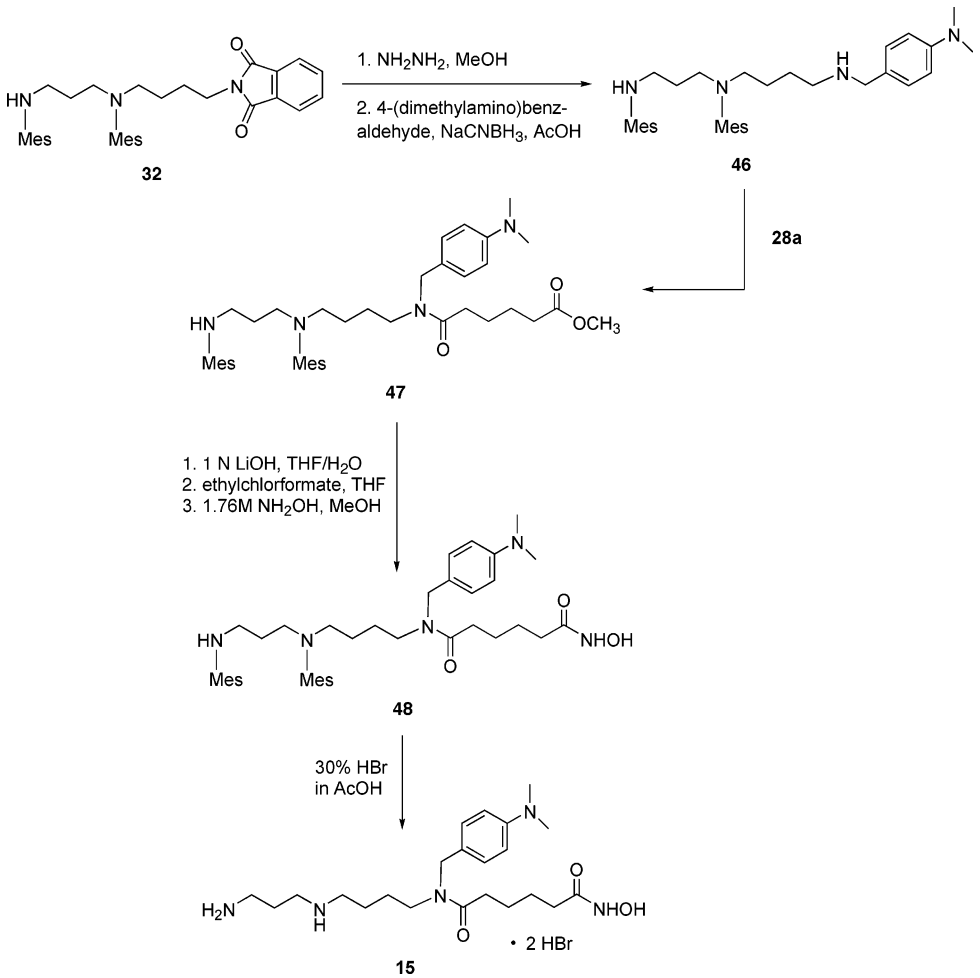
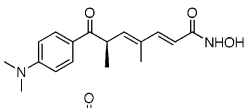
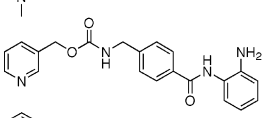
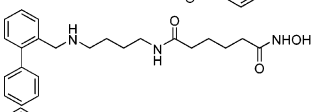
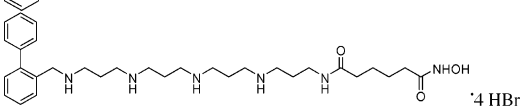
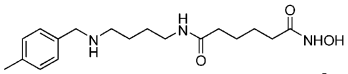
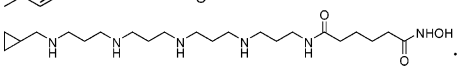
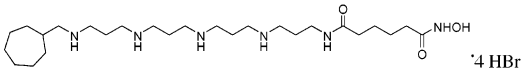
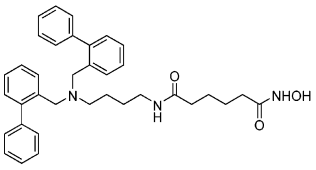
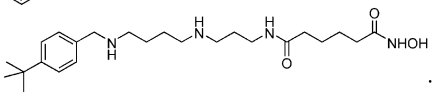
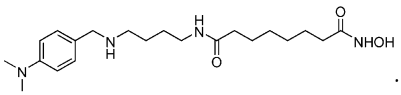
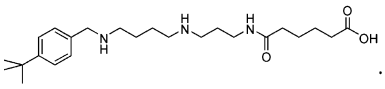
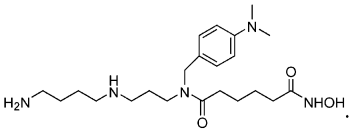
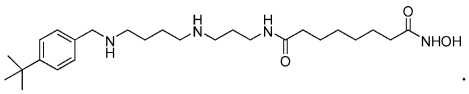
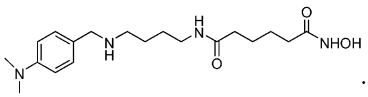
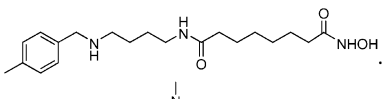
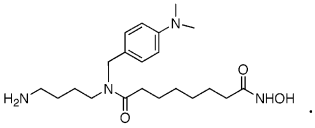
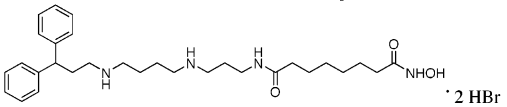
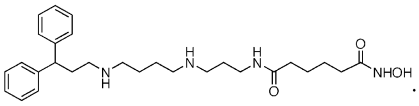


Table 1. Comparison of the in Vitro Inhibitory Activity of **1**, **2** and **6**−**20** at 1 μM Concentration Using an Isolated HDAC Assay Kit

Structure	No.	Empirical Formula	MW	HDAC activity remaining
	**1**	$C_{17}H_{22}NO_3$	288.35	0% (control)
	**2**	$C_{21}H_{20}N_4O_3$	376.41	0% (control)
	**6**	$C_{23}H_{31}N_3O_3$	397.51	83.66
 ·4 HBr	**7**	$C_{31}H_{54}N_6O_3Br_4$	1004.01	ND (insolb)
	**8**	$C_{18}H_{29}N_3O_3$	335.44	55.83
 · 4 HBr	**9**	$C_{22}H_{50}N_6O_3Br_4$	766.29	ND (insolb)
 ·4 HBr	**10**	$C_{26}H_{58}N_6O_3Br_4$	822.39	58.97
	**11**	$C_{36}H_{41}N_3O_3$	563.73	96.26
 · 2 HBr	**12**	$C_{24}H_{44}N_4O_3Br_2$	596.44	25.14
 · CF_3COOH	**13**	$C_{23}H_{37}N_4O_5F_3$	508.56	66.11
 · 2 HBr	**14**	$C_{24}H_{43}N_3O_3Br_2$	581.42	98.52
 · 2 HBr	**15**	$C_{22}H_{41}N_5O_3Br_2$	583.40	40.01
 · 2 HBr	**16**	$C_{26}H_{47}N_3O_3Br_2$	609.48	50.64
 · CF_3COOH	**17**	$C_{21}H_{33}N_4O_5F_3$	478.51	89.68
 · CF_3COOH	**18**	$C_{22}H_{34}N_3O_5F_3$	477.52	46.80
 · CF_3COOH	**19**	$C_{23}H_{37}N_4O_5F_3$	544.56	84.40
 · 2 HBr	**20**	$C_{30}H_{48}N_4O_3Br_2$	672.51	26.15
 · 2 HBr	**21**	$C_{28}H_{44}N_4O_3Br_2$	644.46	80.25

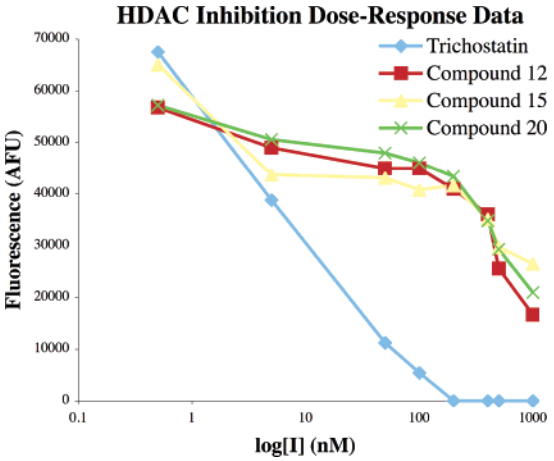


Figure 2. In vitro dose−response for inhibition of HDAC caused by trichostatin and PAHAs **12**, **15** and **20**. The enzyme preparation was exposed to a concentration range of each inhibitor as described in the Experimental section. Each data point is the average of three determinations that in each case differed by 3% or less.

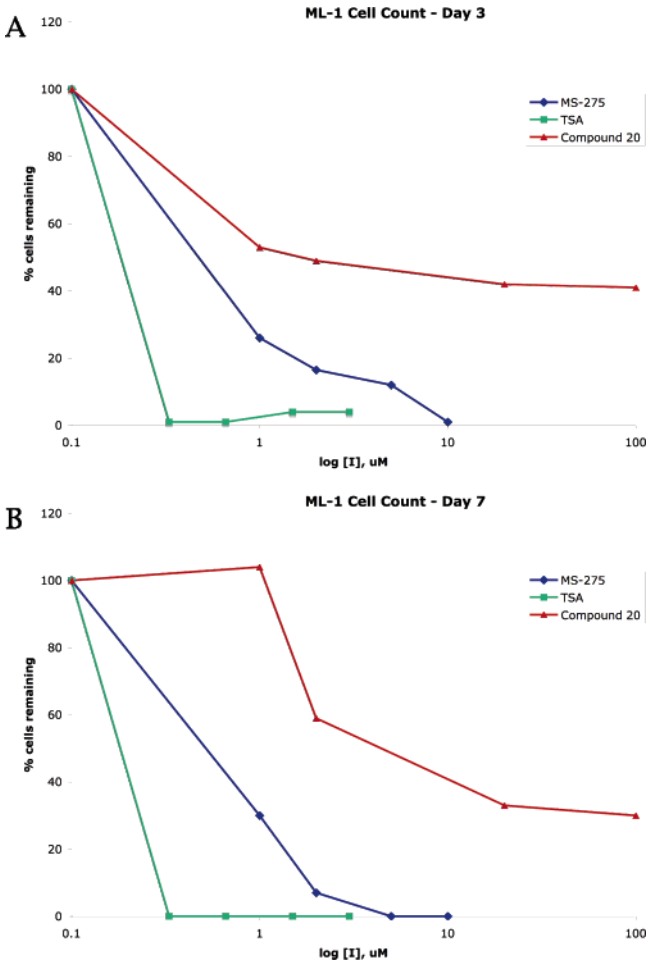


Figure 3. Toxicity of **1**, **2** and compound **20** to ML-1 myelocytic leukemia cells in culture. Cells were exposed to a range of concentrations of the inhibitor, and cell viability was determined by direct cell count. Panel A: 3 days of treatment; Panel B: 7 days of treatment. Each data point is the result of three separate determinations that in each case differed by 3% or less.

toxicity was noted in the presence of **1** and **2**, with IC_{50} values less than 10 μM in all cases. By contrast, compound **20** produced significantly lower cell toxicity

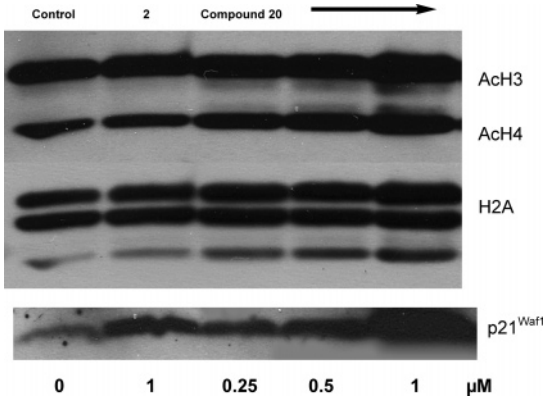


Figure 4. Acetylation of histone H3 and H4 and expression of $p21^{WAF1/CIP1}$ in ML-1 cells. ML-1 cells were incubated for 24 h with compound **20** prior to Western blot analysis. Compound **2** was used as a positive control.

than **1** and **2**, especially at concentrations greater than 10 μM. These effects were similar when cell viability was monitored at either day 3 or 7. Comparable results were obtained in a separate set of experiments where cell proliferation was measured by a standard MTT assay procedure (data not shown).

Compound **20** was also compared to the HDAC inhibitor **2** (IC_{50} = 4.8 μM)[4] for the ability to promote hyperacetylation of histones H3 and H4 in the ML-1 cell line, as shown in Figure 4. At 1 μM, compound **20** produced higher levels of acetylated H3 and H4 than **2** after 24 h, as determined by Western blot analysis. Histone H2a levels were also determined as an internal standard, and the levels of this protein did not change in the presence of **2** or **20**. Re-expression of the cyclin dependent kinase inhibitor $p21^{Waf1}$ was also determined in the presence of **2** and **20**, and **20** was found to be significantly more effective at promoting the re-expression of this protein. Taken together, the data shown in Figures 2-4 suggest that **20** produces more dramatic effects on ML-1 histone acetylation than **2**, even though it is only a marginally more potent HDAC inhibitor in the in vitro enzyme assay.

Discussion

Well characterized HDAC inhibitors such as **1**−**3** and related analogues typically contain three structural features that are thought to be required for optimal activity: an aromatic cap group, an aliphatic chain and a metal binding functional group (Figure 5). Based on molecular modeling studies involving the histone deacetylase-like protein (HDLP), these molecules are thought to bind in a pocket in the enzyme active site that includes a channel region flanked by a zinc ion on one end, and a region that binds the cap group on the other end.[2] In this model, the aromatic group and aliphatic chain of the inhibitor are buried in the enzyme pocket in such a way that the metal binding moiety coordinates the zinc ion that is required for activity. For these reasons, compounds such as **1**−**3** do not inhibit Class III HDACs, since they do not require zinc for activity. As was mentioned above, the development of additional HDAC inhibitors has focused on modifications to the aliphatic linker group and the aromatic moiety. Somewhat less attention has been paid to the metal binding group, which is typically a hydroxamic acid. We rea-

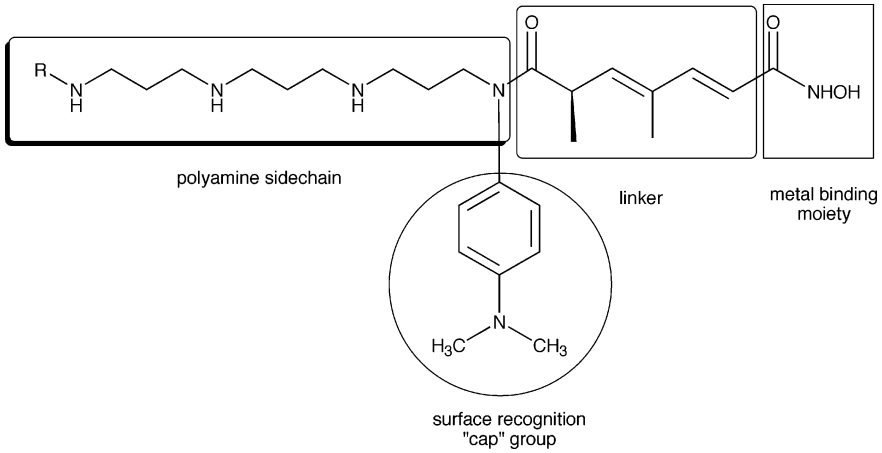


Figure 5. Refined structural design model for polyaminohydroxamate HDAC inhibitors.

soned that this model could be expanded by the addition of a polyamine chain to the structural model for active HDAC inhibitors, as shown in Figure 5. It was hypothesized that the polyamine portion would impart beneficial effects on activity, including cellular import of the molecule by the polyamine transport system, improved nuclear localization of the analogue, enhanced affinity of compounds for chromatin, and the potential to interfere with the association of HDACs with histone proteins. These suppositions were in part supported by data showing that the polyamines spermidine and spermine are known to inhibit yeast HDAC,[23] although it is unclear whether this is a direct inhibition at the active site or some other effect such as inhibition of HDAC binding to chromatin. It has also been shown that the amino acid residues that interact with **1** in the binding region of HDLP are highly conserved in the individual HDAC isoforms. However, the amino acids in the surrounding rim area are less conserved.[3] We further hypothesized that the polyamine tail shown in Figure 5 would be available to bind to amino acids in this rim area, and that variations in charge, carbon chain length and the nature of the R group could be used to develop isoform-specific inhibitors. Using these parameters for the design of novel HDAC inhibitors, we were able to successfully identify three lead compounds from a library of only 16 analogues. Preliminary biological data suggests that some of our suppositions could be true, but additional experiments now being conducted (transport studies, DNA binding analysis, cell cycle studies, determination of activity against individual HDAC isoforms and molecular modeling) will be necessary to demonstrate the precise mechanism of these analogues. Although **20** is more potent with respect to inducing $p21^{Waf1}$ re-expression, it demonstrates less overt growth inhibition in ML-1 cells in vitro than either **1** or **2**. This feature may be therapeutically exploitable in that the re-expression of previously inactivated growth regulatory genes without overt cytotoxicity may restore more normal growth control to transformed cells, thus making them less tumorigenic and potentially more susceptible to combination treatment with other cytotoxic agents. This possibility is currently being examined experimentally.

Preliminary examination of the structure/activity correlations for compounds **6**−**21** reveals interesting trends that will be studied through the synthesis of additional analogues. It is of interest to note that of the three most active analogues (**12**, **15** and **20**), only compound **15** has a traditional cap group. Compounds **12** and **20** do contain aromatic groups at the terminal nitrogens of their polyamine chains, but they are unlikely to be positioned in the aromatic binding region of HDAC due to their distance from the hydroxamic acid moiety. This indicates that the polyamine portion of the chain may in part be responsible for the activity of these analogues, since each molecule contains two nitrogens that are charged at physiological pH. Not surprisingly, conversion of the hydroxamic acid moiety in **12** to a carboxyl group (as in **14**) essentially abolished inhibitory activity. When the linker region of **12** was expanded from four to six carbons to produce **16**, inhibitory activity was reduced by nearly 35%. By contrast, compound **20**, with a six-carbon linker region, was nearly 4 times as active as an HDAC inhibitor as **21**, which has a four-carbon linker region. Compounds with either one or four protonated nitrogens in the polyamine segment were generally only moderately active. These SAR correlations are preliminary, and additional data from an expanded series of analogues is required to generate a more substantive pharmacophore. The synthesis of additional analogues and more extensive biological evaluation procedures are currently underway in our laboratories, and will be published in a subsequent manuscript.

Experimental Section

All reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI), Sigma Chemical Co. or Acros Chemical (Chicago, IL) and were used without further purification except as noted below. Pyridine was dried by passing it through an aluminum oxide column and then stored over KOH. Triethylamine was distilled from potassium hydroxide and stored in a nitrogen atmosphere. Methanol was distilled from magnesium and iodine under a nitrogen atmosphere and stored over molecular sieves. Methylene chloride was distilled fron phosphorus pentoxide and chloroform was distilled from calcium sulfate. Tetrahydrofuran was purified by distillation from sodium and benzophenone. Dimethylformamide was dried by distillation from anhydrous calcium sulfate and was stored under nitrogen. Preparative scale chromatographic procedures were carried out using E. Merck silica gel 60, 230−440 mesh. Thin-layer chromatography was conducted on Merck precoated silica gel 60 F-254. Ion exchange chromatography was conducted on Dowex 1 × 8−200 anion-exchange resin. Compounds **32** (Scheme 2) and **38** (Scheme 3) were synthesized as previously described.

All ^{1}H and ^{13}C NMR spectra were recorded on a General Electric QE-300 or a Varian Mercury 400 MHz spectrometer, and all chemical shifts are reported as δ values referenced to TMS or DSS. Infrared spectra were recorded on a Nicolet 5DXB FT-IR spectrophotometer and are referenced to polystyrene. In all cases, ^{1}H NMR, ^{13}C NMR, and IR spectra were consistent with assigned structures. Melting points were recorded on a Thomas-Hoover Capillary melting point apparatus and are uncorrected. Mass spectra were recorded on a Kratos MS 80 RFA (EI and CI) or Kratos MS 50 TC (FAB) mass spectrometers. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN, and were within 0.4% of calculated values.

***N*-[4-(Azido)butyl]phthalimide (23).** A 1.0 g portion of *N*-[4-(bromo)butyl]phthalimide **22** (0.0035 mol) was dissolved in 10 mL of DMF, and to this solution was added 0.290 g (0.0044 mol) of sodium azide. The reaction was then allowed to stir for 5 h under nitrogen, after which the reaction mixture was concentrated in vacuo to yield a white semisolid. The semisolid was dissolved in water and extracted with three 50 mL portions of ethyl acetate, the combined organic layers were dried over anhydrous magnesium sulfate and filtered, and the solvent was removed to afford **23** (0.760 g, 88%) as a white amorphous powder. This preparation was used in the next reaction without further purification. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.6−1.68 (m, 2H), 1.74−1.82 (m, 2H), 3.3 (t, J = 7.2 Hz, 2H), 3.7 (t, J = 7.2 Hz, 2H), 7.71−7.73 (m, 2H), 7.83−7.86 (m, 2H). ^{13}C NMR(400 MHz $CDCl_3$) δ 26.1, 28.6, 44.02, 53.6, 127.4, 128.0, 132.34, 134.12, 168.52, 171.0.

***N*-[4-(Amino)butyl]phthalimide (24).** Compound **23** (0.760 g, 0.0031 mol) was dissolved in 50 mL of ethanol along with 0.100 g of 10% Pd/C, and the suspension was hydrogenated at 25psi for 12 h. The reaction mixture was then filtered, and the filtrate was concentrated in vacuo to yield **24** as an amorphous white solid (0.620 g, 92%) that was of sufficient purity to use in the next reaction. ^{1}H NMR (400 MHz CD3OD) δ 1.6−1.8 (m, 4H), 2.9 (t, J = 7.2 Hz, 2H), 3.7 (t, J = 7.6 Hz, 2H), 7.9 (m, 4H). ^{13}C NMR (400 MHz $CDCl_3$) δ 26.1, 33.8, 44.0, 46.4, 127.4, 128.0, 132.23, 134.12, 168.25, 171.0

***N*-{4-[(*N*,*N*-Dimethylamino)benzyl]butyl}phthalimide (25c).** A 0.589 g portion of **24** (0.0027 mol) was dissolved in 20 mL of dichloroethane, and to this solution *N*,*N*-dimethylaminobenzaldehyde (0.477 g, 0.0032 mol) was added along with 0.186 g (0.0031 mol) of acetic acid. The reaction was allowed to stir at room temperature for 20 min. after which time sodium cyanoborohydride (0.220 g, 0.0035 mol) was dissolved in 3 mL of methanol and added to the reaction, which was then allowed to stir for an additional 12 h. The reaction mixture was concentrated on a rotary evaporator, and the resulting yellow oil was dissolved in water and extracted with three 50 mL portions of chloroform. The organic layers were combined, washed with brine, and then dried over anhydrous magnesium sulfate. The solution was filtered and concentrated in vacuo to give crude **25a** as a cloudy yellow oil. The crude compound was purified using column chromatography (hexane: ethyl acetate 1:3 followed by ethyl acetate:methanol 2:1), to yield **25a** as a clear yellow oil (0.810 g, 85.4%). ^{1}H NMR (400 MHz $CDCl_3$) δ 1.55 (q, J = 7.2 Hz, 2H), 1.72 (q, J = 7.2 Hz, 2H), 2.65 (t, J = 7.6 2H), 2.92 (s, 6H), 3.69 (s, 2H), 3.71 (t, J =7.2 Hz,2H), 6.7 (d,2H), 7.1 (d, 2H),7.68−7.71 (m, 2H), 7.81−7.83 (m,2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 24.35, 25.35, 40.9, 50.06, 112.85, 127.4, 128.0, 128.6, 132.34, 134.12, 150.0, 168.52, 169.0.

***N*-{4-[4-(Methyl)benzylamino]butyl}phthalimide (25b)**. Compound **25b** was synthesized from **24** and 4-methylbenzaldehyde according to the procedure used to synthesize **25c** in 73.2% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (q, J = 7.2 Hz, 2H), 1.70 (q, J = 7.2 Hz, 2H), 2.31(s, 3H), 2.62 (t, J = 7.6 2H), 6H), 3.68 (s, 2H), 3.70 (t, J = 7.2 Hz,2H), 6.7 (d,2H), 7.1 (d, 2H),7.68−7.71 (m, 2H), 7.81−7.83 (m,2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 25.52, 26.19, 37.85, 46.02, 53.65, 60.61, 123.41, 127.36, 127.95, 129.33, 132.34, 134.12, 136.92, 168.59.

***N*-{4-[2-(Phenyl)benzylamino]butyl}phthalimide (25a)**. Compound **25a** was synthesized from **24** and 2-(phenyl)-benzaldehyde according to the procedure used to synthesize **25c** in 75% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.42 (q, J = 7.6 Hz, 2H), 1.59 (q, J = 7.2 Hz, 2H), 2.54 (t, J = 7.2 Hz, 2H), 3.59 (t, J = 7.2 Hz, 2H), 3.84 (s, 2H), 7.19−7.45 (complex m, 9H), 7.77−7.81 (m, 4H). ^{13}C NMR (400 MHz $CDCl_3$) δ 25.52, 26.18, 37.8, 47.15, 48.07, 123.38, 126.98, 127.34, 127.86, 128.461,129.37, 139.06, 132.35, 134.10, 141.0, 146.9, 168.50

1-*N*-{4-[(*N*,*N*-Dimethyl)amino]benzyl}-1-*N*-[(*tert*-butyloxy)carbonyl]-4-phthalimidobutylamine (26c). A 0.800 g portion of **25c** (0.0023 mol) was dissolved in 20 mL of dichloromethane, and the reaction mixture was cooled to 0 °C. To this mixture was added an aqueous solution of sodium bicarbonate (0.220 g, 0.0027 mol) and sodium chloride (0.160 g, 0.0027 mol), and the reaction was allowed to stir at 0 °C for 30 min. Di-*tert*-butyl dicarbonate (0.596 g, 0.0027 mol) was dissolved in 5 mL of dichloromethane, and the solution was slowly added to the reaction. The mixture was allowed to stir at 0 °C for an additional 10 min and warmed to room temperature, followed by reflux for 12 h. The reaction mixture was cooled and extracted with three 25 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of saturated sodium bicarbonate and 50 mL of saturated sodium chloride solution and then dried over anhydrous magnesium sulfate. The mixture was then filtered, and the solvent was removed in vacuo to yield crude **26c**. The crude compound was purified on a silica gel column eluted with hexane:ethyl acetate (4:3) and then ethyl acetate (100%), to yield compound **26c** as a clear yellow oil (0.950 g, 91.5%). ^{1}H NMR (400 MHz $CDCl_3$) δ 1.4 (s, 9H), 1.51−1.61 (broad m, 4H), 2.89 (s, 6H), 3.1−3.18 (broad m, 2H), 3.65 (t, 2H), 4.3 (s, 2H), 6.65 (d, J = 6.4 Hz, 2H), 7.09 (broad s, 2H), 7.68−7.71 (m, 2H), 7.81−7.83 (m, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 25.52, 26.19, 28.66, 37.85, 46.02, 53.65, 60.61, 79.82 123.41,127.36, 127.95, 129.33, 132.34,134.12, 136.92, 168.59. IR (cm^{-1}) 3410.2, 2942.8, 1651.8, 1555.8, 1532.2, 1460.12, 1105.32.

1-*N*-[4-(Methyl)benzyl]-1-*N*-[(*tert*-butyloxy)carbonyl]-4-phthalimidobutylamine (26b). Compound **26b** was synthesized from **25b** according to the procedure used to synthesize **25c** in 92% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.44 (s, 9H), 1.53−1.63 (m, 4H), 2.30 (s, 3H), 3.14−3.22 (broad d, 2H), 3.66 (t, J = 7.2 Hz, 2H), 4.36 (s, 2H), 7.09 (s, 2H), 7.71 (m, 2H), 7.84 (m, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 24.64, 26.19, 28.71, 39.03, 40.92, 51.77, 60.61, 79.82 112.85, 123.41,127.36, 127.95, 129.33, 132.34,134.12, 136.92, 150.66, 156.17. IR (cm^{-1}) 2962.5, 2942.8, 1768.7, 1710.3, 1684.3, 1619.4, 1487.2, 1365.4, 1301.4.

1-*N*-[2-(Phenyl)benzyl]-1-*N*-[(*tert*-butyloxy)carbonyl]-4-phthalimidobutylamine (26a). Compound **26a** was synthesized from **25a** according to the procedure used to synthesize **25c** in 90.2% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.38−1.42 (m, 11H), 1.52 (m, 2H), 2.96 (broad s 1H), 3.09 (broad s 1H), 3.56 (broad s, 2H), 4.34 (s, 1H), 4.43 (s, 1H), 7.18 (d, J = 7.6 Hz,1H), 7.21−7.4 (m,8H),7.70−7.77 (m, 2H), 7.8−7.83(m, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 25.52, 26.18, 27.63, 28.62, 37.8, 47.15, 48.07, 79.83, 85.4123.38, 126.98, 127.34, 127.86, 128.461,129.37, 139.06, 132.35, 134.10, 141.0, 146.9, 168.50.

1-*N*-{4-[(*N*,*N*-Dimethyl)amino]benzyl}-1-*N*-[(*tert*-butyloxy)carbonyl]-4-aminobutylamine (27c). A 0.90 g (0.0019 mol) portion of **26c** was dissolved in 10 mL of methanol, and 0.191 g (0.0059 mol) of hydrazine was added dropwise with stirring. The reaction was allowed to reflux under nitrogen for 12 h, and then the reaction mixture was concentrated in vacuo to yield a white semisolid. This solid was dissolved in 50 mL of 4.0 N ammonium hydroxide and extracted with three 50 mL portions of chloroform. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo, to yield **27c** (0.560 g, 88.3%) as a white amorphous solid. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.37 (broad m, 2H), 1.45 (s, 9H), 1.47 (m, 2H), 2.6 (t, J = 7.2 Hz, 2H), 2.92 (s, 6H), 3.09 (broad m, 2H), 4.3 (s, 2H), 6.6 (d, 2H), 7.1 (m, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 26.19, 28.66, 37.85, 46.02, 53.65, 60.61, 79.82 123.41, 112.85, 127.36, 127.95, 168.59. IR (cm^{-1}) 3365.8, 2974.8, 2929.7, 1689.8, 1570.5, 1467.0, 1310.1, 1168.6.

1-*N*-[4-(Methyl)benzyl]-1-*N*-[(*tert*-butyloxy)carbonyl]-4-aminobutylamine (27b). Compound **27b** was synthesized from **26b** according to the procedure used to synthesize **27c** in 82.8% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.38 (m, 2H), 1.44−1.48 (m, 11H), 2.32 (s, 3H), 2.66 (t, J = 6.8 Hz, 2H), 3.11−3.19 (broad m, 2H), 4.38 (s, 2H), 7.11 (s, 4H). ^{13}C NMR (400 MHz $CDCl_3$) δ 25.39, 28.67, 31.22, 42.13, 46.36.49.68, 50.13, 79.69, 115.28, 127.33, 127,92, 129.33, 135.67, 138.90. IR (cm^{-1}) 3360.6, 2975.8, 2929.3, 1690.8, 1514.9, 1410.6, 1365.3, 1245.0.

1-*N*-[2-(Phenyl)benzyl]-1-*N*-[(*tert*-butyloxy)carbonyl]-4-aminobutylamine (27a). Compound **27a** was synthesized from **26a** according to the procedure used to synthesize **27c** in 78.6% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.24−1.31(m, 4H), 1.461(s, 9H), 2.56(m, 2H), 2.95(broad s, 1H), 3.08(bs, 1H), 4.35-(s, 1H), 4.45(s, 1H), 7.31−7.41(m, 9H) ^{13}C NMR (400 MHz $CDCl_3$) δ 25.32, 25.38, 28.56, 28.63, 31.08, 42.06, 46.19, 46.63, 48.05, 79.72, 126.97, 127.36, 127.85, 128.45, 129.36, 130.12, 141.06 IR (cm^{-1}) 3372.9, 2929.4, 1683.0, 1569.4, 1514.2, 1473.2, 1198.7.

5-{4-[*N*-(*tert*-Butyloxy)carbonyl]-4-[*N*,*N*-(dimethylamino)-benzyl]amino}butylcarbamoylpentanoic Acid Methyl Ester (29d). A 0.500 g (0.0051 mol) portion of **27c** was dissolved in 15 mL of dichloromethane, and the reaction mixture was cooled to 0 °C. Two to three drops of triethylamine was then added to the solution, and the reaction was allowed to stir for 15 min. The acid chloride **28a** (0.333 g, 0.0019 mol) was slowly added to the reaction mixture, which was allowed to stir at 0 °C for 15 min, then heated to room temperature and allowed to stir for an additional 8 h. The solvent was removed in vacuo, and the residue was dissolved in water and extracted with three 50 mL portions of chloroform. The organic layers were combined and washed with 50 mL of saturated sodium bicarbonate and 50 mL of saturated sodium chloride and then dried over magnesium sulfate. Filtration and removal of the solvent in vacuo then afforded crude **29d**. Purification on silica gel (hexane:EtOAc 1:3) then gave pure **29d** (0.580 g, 80.2%) as a clear yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.2 (m, 4H), 1.4 (s, 9H), 1.5 (m, 4H), 2.11 (t, J = 7.2 Hz, 2H), 2.28 (t, J = 7.6 Hz, 2H), 2.93 (s, 6H), 3.22 (m, 4H), 3.6 (s, 3H), 4.3 (s, 2H), 6.6 (d, J = 8.4 Hz, 2H), 7.1 (m, 2H).^{13}C NMR (400 MHz $CDCl_3$) δ 24.64, 25.35, 26.32, 28.71, 33.89, 34.01, 36.41, 39.30, 40.92, 45.57, 50.06, 51.77, 79.72, 112.84, 128.66, 150.06, 156.17, 172.93, 174.21 IR (cm^{-1}) 3416.2, 2942.7, 1736.2, 1651.9, 1554.6, 1522.2, 1256.8.

7-{4-[(*tert*-Butyloxy)carbonyl]-[4-(methyl)benzyl]-amino}butylcarbamoylheptanoic Acid Methyl Ester (29e). Compound **29e** was synthesized from **27b** and **28b** according to the procedure used to synthesize **29d** in 64.8% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.33 (m, 4H), 1.46 (broad s, 13H), 1.62 (m, 4H), 2.14 (m, 2H), 2.29 (m, 2H), 2.39 (s, 3H), 3.22 (m, 4H), 3.66 (s, 3H), 4.37 (s, 2H), 7.12 (s, 4H). ^{13}C NMR (400 MHz $CDCl_3$) TM 24.94, 25.55, 25.77, 26.46, 28.66, 28.99, 29.08, 34.17, 36.85, 39.23, 46.04, 49.85, 50.4, 51.66, 80.01, 127.41,-127.94, 129.36, 135.55, 137.00, 156.13, 173.30, 174.41. IR (cm^{-1}) 3607.4, 3328.7, 2936.2, 2858.4, 1738.6, 1691.8, 1652.0, 1548.6, 1509.1.

7-{4-[(*tert*-Butyloxy)carbonyl]-4-[*N*,*N*-(dimethylamino)-benzyl]amino}butylcarbamoylheptanoic Acid Methyl Ester (29c). Compound **29c** was synthesized from **27c** and **28b** according to the procedure used to synthesize **29d** in 76.5% yield. ^{1}H NMR ($CDCl_3$) δ 1.40−1.59 (m, 13H), 1.60 (m, 8H), 2.11 (m, 2H), 2.3 (m, 2H), 2.95 (s, 6H), 3.20 (m, 4H), 3.66 (s, 3H), 4.23 (s, 2H), 6.69 (d,J = 8 Hz, 2H), 7.11(broad s, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 24.64, 25.35, 26.32, 28.25, 28.64, 28.71, 29.07, 33.89, 35.98, 36.88, 40.01, 41.13, 46.57, 50.07, 51.92, 80.02, 128.66, 129.50, 150.06, 156.17, 172.93, 174.21. IR (cm^{-1}) 3437.5, 2956.6, 1739.3, 1651.0, 1550.6, 1522.2, 1256.8.

5-{4-[(*tert*-Butyloxy)carbonyl]-[4-(methyl)benzyl]-amino}butylcarbamoylpentanoic Acid Methyl Ester (29b). Compound **29b** was synthesized from **27b** and **28a** according to the procedure used to synthesize **29d** in 70.7% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.44 (broad s, 13H), 1.60 (m, 4H), 2.14 (m, 2H), 2.29 (m, 2H), 2.4 (s, 3H), 3.22 (m, 4H), 3.67 (s, 3H), 4.33 (s, 2H), 7.12 (s, 4H). ^{13}C NMR (400 MHz $CDCl_3$) δ 25.77, 26.46, 28.99, 29.08, 34.17, 36.85, 39.23, 46.04, 49.85, 50.4, 51.66, 80.01, 127.41,127.94, 129.36, 135.55, 137.00, 156.13, 173.30, 174.41. IR (cm^{-1}) 3338.4, 3318.9, 2936.2, 2858.4, 1736.2, 1690.8, 1651.9, 1548.1, 1509.1.

5-{4-[(*tert*-Butyloxy)carbonyl]-[2-(phenyl)benzyl]-amino}butylcarbamoyl}pentanoic Acid Methyl Ester (29a). Compound **29a** was synthesized from **27a** and **28a** according to the procedure used to synthesize **29d** in 62.4% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.23−1.48 (m,13H), 1.62−1.71 (m, 4H), 2.15 (m, 2H), 2.31−2.38 (m, 2H), 2.96 (s, 1H), 3.08 (m, 4H), 3.64 (s, 3H), 4.35 (s, 1H), 4.43 (s, 1H), 6.26 (s, 1H), 7.20−7.42 (m, 9H). ^{13}C NMR (400 MHz $CDCl_3$) δ 24.86, 28.33, 36.502, 39.35, 46.12, 47.14, 48.15, 51.73, 51.78, 60.60, 79.97, 126.76, 126.92, 127.41, 127.59, 127.85, 128.49, 129.31, 130.15, 172.93, 173.48, 174.13, 175.72. IR (cm^{-1}) 3304.9, 2921.0, 1722.3, 1671.4, 1651.9., 1551.6, 1158.9.

5-{4-[*N*-(*tert*-Butyloxy)carbonyl]-4-[*N*,*N*-(dimethylamino)-benzyl]amino}butylcarbamoylpentanoic Acid (30d). A 0.500 g (0.0011 mol) portion of **29d** was dissolved in 6 mL of tetrahydrofuran:water (4:2) and cooled to 0 °C, and 6 mL of 1.0 N LiOH was added to the mixture by dropwise addition. The solution was warmed to room temperature and allowed to stir for 16 h, during which time the reaction was monitored by TLC. The mixture was again cooled to 0 °C, neutralized by the dropwise addition of 2.0 N HCl, and extracted with three 50 mL portions of ethyl acetate. The ethyl acetate layers were combined, washed with brine, and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo yielded compound **30d** as a cloudy yellow oil (0.375 g, 75.8%) of sufficient purity to be used in the next reaction without further purification. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.2 (m, 4H), 1.4 (s, 9H), 1.5 (m, 4H), 2.11 (t, J = 7.2 Hz, 2H), 2.28 (t, J = 7.2 Hz, 2H), 2.93 (s, 6H), 3.22 (m, 4H), 4.3 (s, 2H), 6.6 (d, J = 8.8 Hz, 2H), 7.1 (m, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 21.29, 24.57, 25.20, 26.35, 28.72, 29.64, 29.92, 36.19, 39.26, 40.99, 45.76, 50.09, 60.65, 80.01, 113.01, 128.68, 150.09, 171.45, 172.28. IR (cm^{-1}) 3325.4, 2929.7, 2858.4, 1716.8, 1658.4, 1613. 0, 1554.6, 1486.8, 1006.0.

7-{4-[*N*-(*tert*-Butyloxy)carbonyl]-4-[4-(methyl)benzyl]-amino}butylcarbamoylheptanoic Acid (30e). Compound **30e** was synthesized from **29e** according to the procedure used to synthesize **30d** in 72.7% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.18 (m, 6H), 1.39 (bs, 12H), 1.53 (m, 4H), 2.10 (m, 2H), 2.2 (m, 2H), 2.26 (s, 3H), 3.14 (m, 4H), 4.30 (s, 2H), 7.05 (s, 4H) ^{13}C NMR (400 MHz $CDCl_3$) δ, 21.93, 24.93, 25.70, 26.44, 28.62, 28.87, 29.01, 31.07, 36.6, 39.26, 46.05, 49.73, 50.35, 60.58, 64.53, 80.09, 127.34, 127.85, 129.33, 135.45, 136.93, 156.1, 171.38, 173.91. IR (cm^{-1}) 3326.9, 2932.8, 2863.1, 1730.5, 1691.0, 1644.1, 1661.8, 1555.3, 1464.62, 1366.05, 1244.7, 1168.19, 1036.0, 729.15 (cm^{-1})

7-{4-[*N*-(*tert*-Butyloxy)carbonyl]-4-[*N*,*N*-(dimethylamino)-benzyl]amino}butylcarbamoylheptanoic Acid (30c). Compound **30c** was synthesized from **29c** according to the procedure used to synthesize **30d** in 72.3% yield. ^{1}HNMR (400 MHz $CDCl_3$) δ 1.35−1.44 (m, 17H), 1.63 (m, 4H), 2.2 (m, 4H), 2.32 (m, 2H), 2.93 (s, 6H), 3.16 (m, 4H), 4.29 (s, 2H), 6.69 (d, J = 8.8 Hz, 2H), 7.11 (m, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 14.34, 21.19, 21.93, 24.93, 25.46, 25.76, 26.43, 28.60, 28.88, 29.01, 31.07, 36.6, 39.26, 46.05, 49.73, 50.35, 60.58, 64.53, 80.09, 127.34, 127.85, 129.33, 135.45, 136.93, 156.1, 171.38, 173.91. IR (cm^{-1}) 3348.2, 2929.7, 1718.3, 2658.4, 1616.4, 1555.6, 1478.8, 1398.1, 1110.7.

5-{4-[(*tert*-Butyloxy)carbonyl]-[4-(methyl)benzyl]-amino}butylcarbamoylpentanoic Acid Methyl Ester (30b). Compound **30b** was synthesized from **29b** according to the procedure used to synthesize **30d** in 70.9% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.2(m, 4H), 1.40 (broad s, 9H), 1.53 (m, 4H), 2.10 (m, 2H), 2.2 (m, 2H), 2.30 (s, 3H), 3.20 (m, 4H), 4.32 (s, 2H), 7.05 (s, 4H). ^{13}C NMR (400 MHz $CDCl_3$) δ 25.70, 26.44, 28.62, 28.87, 29.01, 31.07, 36.6, 39.26, 46.05, 49.73, 50.35, 60.58, 64.53, 80.09, 127.34, 127.85, 129.33, 135.45, 136.93,

156.1, 171.38, 173.91. IR (cm^{-1}) 3326.4, 2934.4, 2863.1, 1729.7, 1691.7, 1645.4, 1664.8, 1555.3, 1464.6, 1421.1, 1168.2, 1136.0, 732.4.

5-{4-[(*tert*-Butyloxy)carbonyl]-[2-(phenyl)benzyl]-amino}butylcarbamoyl}pentanoic Acid Methyl Ester (30a). Compound **30a** was synthesized from **29a** according to the procedure used to synthesize **30d** in 86.1% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.30−1.43 (m,13H),1.54 (m,4H), 2.11−2.27 (m,4H), 2.93−3.05 (m,4H), 4.36(d, J = 32 Hz, 2H), 7.20−7.38 (m,9H). ^{13}C NMR (400 MHz $CDCl_3$) δ 21.29, 25.58, 26.54, 28.56, 29.68, 29.92, 30.54, 30.85, 36.26, 39.32, 46.38, 47.24, 48.27, 60.64, 64.60, 80.10, 125.75, 126.77, 127.05, 127.44, 127.85, 128.53, 129.3, 130.18, 135.51, 135.83, 140.97, 141.56, 156.03, 173.62. IR (cm^{-1}) 3304.9, 2921.0, 1730.0, 1671.4, 1651.9, 1551.6, 1158.9.

5-{4-[*N*-(*tert*-Butyloxy)carbonyl]-4-[*N*,*N*-(dimethylamino)-benzyl]amino}butylcarbamoyl-pentanohydroxamic Acid (31d). Ethyl chlorformate (0.086 g, 0.0008 mol) and triethylamine (0.08 g, 0.0008 mmol) were added to the solution of **30d** (0.300 g, 0.0007 mol) in 5 mL of THF, and the mixture was cooled to 0 °C. The reaction was allowed to stir for 20 min, after which time it was filtered and added to 20 mL of freshly prepared 1.76 M hydroxylamine in methanol. The reaction was stirred at room temperature for 30 min, filtered and concentrated in vacuo to yield the crude **31d**. Purification on silica gel (ethyl acetate:methanol 4:2) then afforded pure **31d** (0.252 g, 77.5%) as a dark yellow oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.2 (m, 4H), 1.4 (s, 9H), 1.5 (m, 4H), 2.15 (broad s, 4H), 2.93 (s, 6H), 3.22 (m, 4H), 3.6 (s, 3H), 4.3 (s, 2H), 6.6 (d, J = 8.0 Hz, 2H), 7.1 (m, 2H), 7.8 (broad s, NHO*H*). ^{13}C NMR (400 MHz $CDCl_3$) δ 21.2, 23.11, 25.71, 28.72, 31.51, 39.45, 40.91, 41.08, 45.79, 112.86, 1125.73, 126.25, 128.37, 128.62, 132.28, 150.12, 156.13. IR (cm^{-1}) 3396.8, 2929.7, 1638.9, 1610.2,1554.6, 1450.8, 1405.4.

7-{4-[*N*-(*tert*-Butyloxy)carbonyl]-4-[4-(methyl)benzyl]-amino}butylcarbamoylheptanohydroxamic Acid (31e). Compound **31e** was synthesized from **30e** according to the procedure used to synthesize **31d** in 78.0% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.24−1.31 (m, 4H), 1.43−1.6 (m, 13H), 2.16 (m, 2H), 2.32 (s, 3H), 3.18 (m, 4H), 4.35 (s, 2H), 7.11 (s, 4H). ^{13}C NMR (400 MHz $CDCl_3$) δ 20.07, 23.29, 25.29, 25.46, 25.57, 26.38, 28.53, 28.61, 32.45, 35.71, 38.24, 46.88, 50.92, 80.01, 117,7, 128.33, 129.64, 129.74, 139.67, 156.22, 174.0.38. IR (cm^{-1}) 3221.6, 2929.7, 2858.4, 1671.4, 1638.9, 1554.6, 1450.8, 1190.1, 1150.8, 1110.9.

7-{4-[*N*-(*tert*-Butyloxy)carbonyl]-4-[*N*,*N*-(dimethylamino)-benzyl]amino}butylcarbamoyl-heptanohydroxamic Acid (31c). Compound **31c** was synthesized from **30c** according to the procedure used to synthesize **31d** in 75.7% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.24 (m, 4H), 1.44(m, 15H), 1.52 (m, 2H), 2.1 (m, 4H), 2.90 (s, 6H), 3.14 (m, 4H), 4.26 (s, 2H), 6.65 (d, J = 7.6 Hz, 2H), 7.08 (broad s, 1H). ^{13}C NMR (400 MHz $CDCl_3$) δ 21.34, 22.43, 23.11, 25.71, 28.72, 31.51, 39.45, 40.91, 41.08, 45.79, 112.86, 1125.73, 126.25, 128.37, 128.62, 132.28, 150.12, 156.13. IR (cm^{-1}) 3385.7, 2932.4, 1632.4, 1622.0.0, 1554.6, 1460.7, 1425.1, 1304.2.

5-{4-[*N*-(*tert*-Butyloxy)carbonyl]-4-[4-(methyl)benzyl]-amino}butylcarbamoylpentanohydroxamic Acid (31b). Compound **31b** was synthesized from **30b** according to the procedure used to synthesize **31d** in 80.9% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.24−1.31 (m, 4H), 1.43 (m, 9H), 2.18 (m, 4H), 2.32 (s, 3H), 3.18 (m, 4H), 4.32 (s, 2H), 7.11 (s, 4H). ^{13}C NMR (400 MHz $CDCl_3$) δ 25.31, 25.06, 26.38, 28.53, 28.61, 32.45, 35.71, 38.24, 46.88, 50.92, 80.24, 127.37, 127.9, 129.64, 129.74, 137.67, 156.33, 174.21. IR (cm^{-1}) 3267.0, 2929.7, 2858.4, 1651.9, 1548.1, 1463.8, 1418.4.

5-{4-[(*tert*-Butyloxy)carbonyl]-4-[2-(phenyl)benzyl]-amino}butylcarbamoyl}pentanohydroxamic Acid (31a). Compound **31a** was synthesized from **30a** according to the procedure used to synthesize **31d** in 80.6% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.25−1.42(m,15H), 1.56 (m,2H),1.99−2.26 (m,-4H),2.94−3.05(m,4H), 4.36(d, J = 31.2 Hz, 2H),7.21−7.40(m,-9H) ^{13}C NMR (400 MHz $CDCl_3$) δ 25.04, 25.49, 26.47, 28.57, 29.92, 32.24, 35.91, 39.98, 46.5, 48.32, 80.24, 126.8, 125.08, 127.47, 127.88, 128.55, 129.3, 130.2, 135.74, 140.95, 141.58, 156.18, 174.09. IR (cm^{-1}) 3260.5, 2975.1, 2929.7, 1664.9, 1651.9, 1554.6.

5-{4-[4-*N*,*N*-(Dimethyl)aminobenzyl]amino}butyl-carbamoylpentanohydroxamic Acid (17). Compound **31d** (0.140 g, 0.0003 mol) was dissolved in 5 mL of 20% trifluoroacetic acid in dichloromethane, and the reaction was allowed to stir at room temperature for 8 h. The solvent was then removed in vacuo, and the residue was taken up in 25 mL of chloroform and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent afforded crude **17** (0.110 g, 76.7%) as a buff colored solid. An analytical sample of **17** was prepared by recrystallization from aqueous ethanol. ^{1}H NMR (400 MHz CD_3OD) δ 1.2 (m, 4H), 1.5 (m, 4H), 2.15 (t, J = 7.2 Hz, 2H), 2.19 (t, J = 7.2 Hz, 2H), 2.93 (s, 6H), 3.22 (m, 4H), 4.03 (s, 2H), 6.7(d, J = 8.0 Hz, 2H), 7.3 (m, 2H). ^{13}C NMR (400 MHz CD_3OD) δ 23.28, 24.35, 26.31, 131.63, 161.58. IR (cm^{-1}) 2988.1, 1671.4, 1554.6, 1444.3, 1203.8, 1165.9. Anal. for $C_{21}H_{33}F_3N_4O_5$: C, H, N.

7-{4-[4-(Methyl)benzyl]aminobutyl}carbamoylheptano-hydroxamic Acid (18). Compound **18** was synthesized from **31e** according to the procedure used to synthesize **17** in 71.6% yield. An analytical sample of **18** was prepared by recrystallization from aqueous ethanol. ^{1}H NMR (400 MHz CD_3OD) δ 1.23−1.43 (m, 4H), 1.59−1.6 (m, 8H), 2.07−2.17 (m, 4H), 2.35 (s, 3H), 2.86 (t, J = 7.2 Hz, 2H), 3.03 (m, 2H), 3.19 (m, 2H), 4.14 (s, 2H), 7.26 (d, J = 6.4, 2H), 7.37 (d, J = 6.8 Hz, 2H), 8.06 (broad s, N*H*CO), 9.93(broad s, NHO*H*). ^{13}C NMR (400 MHz CD_3OD) δ 23.3, 25.4, 25.7, 26.44, 28.54, 28.62, 32.43, 35.68, 38.27, 50.82, 117.70, 128.33, 129.64, 129.8, 139.7, 160.41, 175.21 IR (cm^{-1}) 3226.6, 2929.7, 2853.4, 1671.4, 1640.3, 1551.0, 1444.7, 1209.8, 1163.8. Anal. for $C_{22}H_{34}F_3N_3O_5$: C, H, N.

7-{4-[4-*N*,*N*-(Dimethylamino)benzyl]aminobutyl}-carbamoylheptanohydroxamic Acid (13). Compound **13** was synthesized from **31c** according to the procedure used to synthesize **17** in 72.1% yield. An analytical sample of **13** was prepared by recrystallization from aqueous ethanol. ^{1}H NMR (400 MHz CD_3OD) δ 1.62 (m, 8H), 1.74 (m, 2H), 2.12 (t, J = 6.8 Hz, 2H), 2.21 (t, J = 6.8 Hz, 2H), 3.06 (m, 2H), 3.15 (s, 6H), 3.21 (m, 2H), 4.20 (s, 2H), 7.36 (broad s, 2H), 7.58 (broad s, 2H). ^{13}C NMR (400 MHz CD_3OD) δ 26.86, 26.9,28.12, 29.01, 29.2, 29.47, 30.13, 30.35, 36.19, 43.09, 46.58, 44.4, 57.0, 112.8, 112.9, 129.32, 129.4, 168.56, 174.23 IR (cm^{-1}) 2982.2, 1671.4, 1556.1, 1445.3, 1203.8, 1168.4. Anal. for $C_{23}H_{37}F_3N_4O_5$: C, H, N.

5-{4-[4-(Methyl)benzyl]aminobutyl}carbamoylpentano-hydroxamic Acid (8). Compound **8** was synthesized from **31b** according to the procedure used to synthesize **17** in 72.9% yield. An analytical sample of **8** was prepared by recrystallization from aqueous ethanol. ^{1}H NMR (400 MHz CD_3OD) δ 1.23−1.43 (m, 4H), 1.6 (m, 4H), 2.0−2.1 (m, 4H), 2.35 (s, 3H), 2.86 (t, J = 7.2 Hz, 2H), 3.02 (m, 2H), 3.20 (m, 2H), 4.23 (s, 2H), 7.24 (d, J = 6.4, 2H), 7.35 (d, J = 6.8 Hz, 2H). ^{13}C NMR (400 MHz CD_3OD) δ 26.04, 28.63, 28.54, 34.86, 36.12, 38,99, 51.32, 118.48, 128.33, 129.64, 129.8, 139.7, 160.14, 175.21. IR (cm^{-1}) 3221.6, 2929.7, 2858.4, 1781.6, 1671.4, 1638,9, 1554.6, 1450.8, 1190.1, 1150.8, 1110.9. Anal. for $C_{20}H_{30}F_3N_3O_5$: C, H, N.

5-{4-[2-(Phenyl)benzyl]aminobutyl}carbamoylpentano-hydroxamic Acid (6). Compound **6** was synthesized from **31a** according to the procedure used to synthesize **17** in 87% yield. An analytical sample of **6** was prepared by recrystallization from aqueous ethanol. ^{1}H NMR (400 MHz CD_3OD) δ 1.53(m,-4H),1.60(m,4H),2.10(m,2H),2.18(m,2H),2.82(t, J = 8 Hz, 2H),3.11 (t, J = 6.4 Hz, 2H),4.22 (s,2H),7.35(d, J = 7.2 Hz, 3H), 7.36−7.50(m,5H), 7.66(d, J = 2.8 Hz, 1H) ^{13}C NMR (400 MHz CD_3OD) δ 22.92, 24.9, 25.25, 25.47, 26.2, 32.11, 35.45, 38.10, 47.02, 127.82, 128.31, 1128.70, 128.96, 129.29, 129.47, 130.73, 139.95, 143.27, 155.38, 171.12, 174.79. IR (cm^{-1}) 3723.51, 2923.24, 2851.89, 1671.35, 1561.08, 1431.35, 1176.6, 1112.7. Anal. for $C_{25}H_{32}F_3N_3O_5$: C, H, N.

1-Phthalimido-4-{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}-8-{*N*-[4-(*tert*-butyl)benzyl]-*N*-[2,4,6-(trimethyl)-

benzenesulfonyl]}amino-4-azaoctane (33a). Sodium hydride 60% oil dispersion (equivalent to 0.027 g, 0.0011 mol of NaH was dissolved in 1 mL of dimethylformamide under nitrogen, and the reaction was cooled to 0 °C. Compound **32** (0.500 g, 0.0010 mol) was dissolved in 4 mL of dimethylformamide and added dropwise to the reaction mixture, which was allowed to stir for 30 min. A 0.250 g portion (0.0011 mol) of 4-*tert*-butylbenzyl bromide was dissolved in 2 mL of dimethylformamide and added to the reaction slowly via syringe. The reaction was stirred for 12 h, the solvent was removed in vacuo and the residue was dissolved in water and extracted with three 50 mL portions of ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and filtered, and the solvent was removed to yield crude **33a**. Purification of the crude material on silica gel (hexane:ethyl acetate 4: 3) then afforded pure **33a** as a fluffy white solid (0.619 g, 71.6%). ^{1}H NMR (400 mHz $CDCl_3$) δ 1.25 (s, 9H) 1.4 (m, 2H), 1.61 (m,2H), 1.72 (m, 2H), 2.24 (s, 6H), 2.62 (s, 6H), 2.62 (s, 6H), 3.04−3.06 (t, J = 6.4 Hz, 4H), 3.18 (t, J = 7.2 Hz, 2H), 4.17 (s,2H), 6.95 (s, 2H), 7.23 (d, J = 6.8 Hz, 2H), 7.73 (m, 2H), 7.83−7.85 (m, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 21.19, 23.06, 24.32, 24.49, 24.66, 25.29, 25.39, 25.95, 27.11, 28.70, 31.52, 33.78, 33.87, 36.28, 36.40, 36.47, 43.52, 43.64, 51.76, 51.89, 132.15, 132.30, 132.34, 133.18, 140.15, 140.27, 142.92, 173.24, 174.02, 174.17, 178.84.

1-Phthalimido-4-{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}-8-{*N*-[3,3-(diphenyl)propyl]-*N*-[2,4,6-(trimethyl)-benzenesulfonyl]}amino-4-azaoctane (33b). Compound **33b** was synthesized from **32** and 3,3-diphenylpropyl chloride using the procedure described for the synthesis of **33a** in 60.3% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.40 (m, 4H), 1.69 (q, J = 7.2 Hz, 2H), 2.08 (q, J = 8 Hz, 2H), 2.3 (s, 3H), 2.44 (s, 3H), 2.51 (d, J = 11.2 Hz, 12H), 3.03 (t, J = 8 Hz, 2H), 3.09 (t, J = 8 Hz, 1H), 3.16 (m, 4H), 3.46 (t, J = 6.8 Hz, 2H), 3.73 (t, J = 8 Hz, 1H), 6.76 (s, 2H), 6.90 (s, 2H), 7.03 (d, J = 7.6 Hz, 2H), 7.12−7.27 (m, 7H), 7.68 (m, 2H), 7.8 (m, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 14.43, 21.18, 21.20, 21.29, 22.96, 22.99, 24.85, 24.90, 26.74, 32.98, 35.43, 44.37, 44.42, 45.40, 45.44, 48.96, 60.62, 123.40, 126.59, 127.76, 128.78, 132.13, 132.18, 132.19, 133.09, 133.4, 134.23, 140.18, 140.35, 142.49, 142.66, 143.99, 168.25. IR (cm^{-1}) 3059.5, 3020.5, 2936.2, 1768.7, 1716.8, 1600.0, 1561.1, 1450.8, 1139.5.

1-Amino-4-{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}-8-{*N*-[4-(*tert*-butyl)benzyl]-*N*-[2,4,6-(trimethyl)benzenesulfonyl]}amino-4-azaoctane (34a). Compound **34a** was prepared from **33a** using the procedure described for the synthesis of **27c** in 70.8% yield. ^{1}H NMR ($CDCl_3$) δ 1.28(s,9H) 1.4 (m, 2H), 1.61 (m,2H), 1.56 (m, 2H), 2.24 (s, 6H), 2.51 (s, 6H), 2.57 (s,-6H), 2.62 (q, J = 6.8 Hz, 2H), 3.08 (t, J = 7.2 2H), 3.24 (t, J = 7.6 Hz, 2H), 3.49 (t, J = 7.2 Hz, 2H), 4.2 (s,2H), 6.81 (s, 2H), 6.95 (m, 6H), 7.23 (d, J = 6.8 Hz, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 21.11, 21.48, 21.79, 22.5, 22.8, 25.42, 26.87, 28.43, 28.48, 31.74, 32.59, 40.08, 46.77, 46.81, 125.12, 128.2, 136.44, 145.1, 145.64.

1-Amino-4-{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}-8-{*N*-[3,3-(diphenyl)propyl]-*N*-[2,4,6-(trimethyl)benzenesulfonyl]}amino-4-azaoctane (34b). Compound **34b** was prepared from **33b** using the procedure described for the synthesis of **27c** in 78.5% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.37 (m, 4H), 1.58 (q, J = 7.2 Hz, 2H), 2.04 (m, 2H), 2.28 (s, 3H), 2.31 (s, 3H), 2.46 (s, 6H), 2.57 (s, 6H), 2.97 (t, J = 8 Hz, 2H), 3.10 (t, J = 4.8 Hz, 2H), 3.17 (m, 4H), 3.48 (t, J = 7.2 Hz, 1H), 3.7 (q, J = 5.6 Hz, 2H), 6.9 (d, J = 3.2 Hz, 4H), 7.01 (d, J = 6.8 Hz, 4H), 7.12−7.23 (m, 5H). ^{13}C NMR (400 MHz $CDCl_3$) δ 14.40, 14.99, 15.84, 21.14, 21.19, 21.26, 22.91, 23.05, 24.66, 25.33, 25.44, 29.90, 31.02, 39.31, 41.28, 42.45, 43.20, 44.63, 45.14, 45.46, 48.90, 52.04, 55.64, 60.06, 64.29, 126.60, 127.67, 128.76, 129.46, 132.18, 133.35, 133.40, 140.22, 140.29, 142.51, 142.60, 143.89, 149.41 IR (cm^{-1}) 3364.3, 3027.0, 2936.2, 2871.4, 1600.0, 1561.1, 1314.6, 1139.5.

15-{*N*-[2,4,6-(Trimethyl)benzenesulfonyl-*N*-[(4-*tert*-butyl)benzyl]}amino-11-[*N*-2,4,6-(trimethyl)benzenesulfonyl]-6-oxo-7,11-diazapentadecanoic Acid Methyl Ester (35a). Compound **35a** was synthesized from **34a** and **27a** using the method described for the synthesis of **29c** in 72.3% yield. ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H) 1.34 (m, 4H), 1.61 (m, 4H), 1.72 (m, 2H), 2.11 (t, J = 7.2 Hz, 2H), 2.24 (m, 8H), 2.51 (s, 6H), 2.62 (s, 8H), 3.08 (m, 2H), 3.24 (m, 2H), 3.6 (t, 3H), 4.13 (s,2H), 6.90 (broad s, 2H), 7.22 (broad s, 2H), 7.28 (d, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 14.35, 14.41, 21.19, 21.27, 22.87, 23.11, 23.12, 24.17, 24.46, 24.68, 25.29, 27.12, 31.50, 31.8, 33.91, 34.72, 36.34, 36.38, 43.29, 44.57, 45.12, 48.93, 51.75, 60.61, 125.74, 128.38, 132.28, 132.30, 132.56, 133.36, 133.39, 140.25, 140.29, 142.80, 151.11, 172.95, 174.11 IR (cm^{-1}) 3387.9, 2952.2, 1738.3, 1655.3, 1603.5, 1541.2, 1458.2.

17-{*N*-[2,4,6-(Trimethyl)benzenesulfonyl-*N*-[(4-*tert*-butyl)benzyl]}amino-13-[*N*-2,4,6-(trimethyl)benzenesulfonyl]-8-oxo-7,11-diazaheptadecanoic Acid Methyl Ester (35b). Compound **35b** was synthesized from **34a** and **27b** using the method described for the synthesis of **29c** in 78.3% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.28 (s, 9H), 1.32−1.36 (m, 8H), 1.58−1.7 (m, 8H), 2.09 (t,J = 2.8 Hz, 2H), 2.30 (m, 8H), 2.58 (d, J = 9.2 Hz, 12H), 3.03 (m, 4H), 3.20 (q, J = 6.8 Hz, 6H), 3.6 (s, 3H), 4.12 (s, 2H), 5.979 (t, J = 5.6 Hz, 1H), 6.90 (d, J = 8.4 Hz, 2H), 6.96 (s, 4H), 7.27 (d, J = 1.2 Hz, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 21.19, 23.12, 24.17, 24.46, 24.74, 24.93, 24.97, 25.74, 27.09, 28.89, 28.95, 29.02, 29.10, 31.51, 34.06, 34.2, 34.73, 36.36, 36.76, 43.29, 44.58, 45.13, 48.95, 21.70, 51.72, 125.74, 128.37, 132.28, 132.55, 133.36, 133.39, 140.25, 140.31, 142.81, 151.13, 173.66, 174.45, 178.43. IR (cm^{-1}) 2929.7, 2864.9, 1736.2, 1645.4, 1600.0, 1554.6, 1314.6, 1139.5.

17-{*N*-[2,4,6-(Trimethyl)benzenesulfonyl-*N*-[3,3-(diphenyl)propyl]}amino-13-[*N*-2,4,6-(trimethyl)-benzenesulfonyl]-8-oxo-7,11-diazaheptadecanoic Acid Methyl Ester (35c). Compound **35c** was synthesized from **34b** and **27b** using the method described for the synthesis of **29c** in 75.1% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.25−1.39 (m, 8H), 1.55−1.69 (m, 6H), 2.05 (q, J = 8 Hz, 2H), 2.07 (m, 2H), 2.28 (m, 2H), 2.32 (m, J = 8 Hz, 8H), 2.45 (s, 6H), 2.57 (s, 6H), 2.93 (t, J = 7.6 Hz, 2H), 3.10 (t, J = 7.6 Hz, 2H), 3.15−3.22 (m, 6H), 3.65 (s, 3H), 3.69 (t, J = 8 Hz, 1H), 5.84 (t, 1H), 6.91 (d, J = 9.6 Hz, 2H), 6.98 (d, J = 7.2 Hz, 4H), 7.14−7.20 (m, 5H). ^{13}C NMR (400 MHz $CDCl_3$) δ 14.42, 21.17, 21.20, 21.29, 22.93, 23.10, 24.47, 24.72, 24.98, 25.73, 27.13, 29.04, 29.12, 32.75, 34.20, 36.35, 36.74, 43.32, 44.09, 45.14, 45.29, 48.87, 51.69, 60.29, 126.65, 127.65, 128.79, 132.24, 132.31, 133.36, 140.25, 142.61, 142.79, 143.82, 173.42, 174.42 IR (cm^{-1}) 2936.2, 2851.9, 1736.2, 1671.4, 1638.9, 1593.5, 1146.0.

15-{*N*-[2,4,6-(Trimethyl)benzenesulfonyl-*N*-[3,3-(diphenyl)propyl]}amino-11-[*N*-2,4,6-(trimethyl)-benzenesulfonyl]-6-oxo-7,11-diazapentadecanoic Acid Methyl Ester (35d). Compound **35d** was synthesized from **34b** and **27a** using the method described for the synthesis of **29c** in 72.6% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.32−1.39 (m, 4H), 1.58−1.60 (m, 4H), 1.68 (q, J = 6.8 Hz, 4H), 1.99 (q, J = 8 Hz, 2H), 2.10 (t, J = 6.8 Hz, 2H), 2.28−2.35 (d, J = 9.2 Hz, 8H), 2.45 (s, 6H), 2.57 (s, 6H), 2.93 (t, J = 8 Hz, 2H), 3.09 (t, J = 9.6 Hz, 2H), 3.15−3.22 (m, 6H), 3.65 (m, 4H), 5.94 (s. 1H), 6.91 (d, J = 9.6 Hz, 4H), 6.93 (d, J = 6.8 Hz, 4H), 7.12−7.22 (m, 5H). ^{13}C NMR (400 MHz $CDCl_3$) δ 14.41, 21.16, 21.19, 21.83, 22.92, 23.09, 24.46, 24.66, 24.71, 25.28, 27.14, 32.74, 33.91, 36.31, 36.42, 43.34, 44.08, 45.14, 45.28, 48.86, 51.75, 60.62, 126.64, 127.64, 128.79, 132.25, 132.31, 133.36, 140.23, 142.62, 142.81, 143.82, 172.96, 174.12. IR (cm^{-1}) 3370.8, 2929.7, 1736.2, 1671.4, 1651.9, 1600.0, 1541.6.

15-{*N*-[2,4,6-(Trimethyl)benzenesulfonyl-*N*-[(4-*tert*-butyl)benzyl]}amino-11-[*N*-2,4,6-(trimethyl)benzenesulfonyl]-6-oxo-7,11-diazapentadecanoic Acid (36a). Compound **36a** was synthesized from **35a** using the method described for the synthesis of **30d** in 70.6% yield. ^{1}H NMR ($CDCl_3$) δ 1.28 (s,9H) 1.34 (m, 4H), 1.61 (m,4H), 1.72 (m, 2H), 2.11 (t, J = 8.0 Hz, 2H), 2.24 (m, 8H), 2.51 (s, 6H), 2.62 (s,-8H), 3.08 (m, 2H), 3.24 (m, 2H), 4.13 (s, 2H), 6.90 (broad s, 2H), 7.22 (broad s, 2H), 7.28 (d, J = 6.8 Hz, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 14.41, 21.27, 23.11, 14.71, 24.46, 24.11, 27.09, 28.97, 29.11, 30.89, 31.50, 34.35, 34.67, 36.54, 36.26, 43.22, 44.05, 45.61, 48.69, 60.46, 64.76, 125.17, 128.53, 132.72,

132.73, 132.15, 133.73, 140.12, 140.43, 142.43, 142.88, 151.81, 171.34, 173.28 IR (cm^{-1}) 3377.3, 2929.7, 1723.2, 1645.4, 1600.0, 1548.1.

17-{*N*-[2,4,6-(Trimethyl)benzenesulfonyl-*N*-[(4-*tert*-butyl)benzyl]}amino-13-[*N*-2,4,6-(trimethyl)benzenesulfonyl]-8-oxo-7,11-diazaheptadecanoic Acid (36b). Compound **36b** was synthesized from **35b** using the method described for the synthesis of **30d** in 80.0% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.27 (s,9H), 1.32 (m, 8H), 1.56−1.62 (m, 4H), 1.68 (t, J = 7.6 Hz, 2H), 2.30 (d, J = 5.6 Hz, 8H), 2.57 (d, J = 10 Hz, 2H), 3.01 (m, 4H), 3.02−3.23 (m, 4H), 4.12 (s, 2H), 6.05 (s,1H), 6.90 (d, J = 8 Hz, 2H), 6.95 (d, J = 3.2 Hz, 4H), 7.25 (d, J = 8.4 Hz, 2H).^{13}C NMR (400 MHz $CDCl_3$) δ 13.92, 14.41, 19.34, 21.19, 21.27, 23.11, 23.12, 24.17, 24.46, 24.81, 25.68, 27.09, 28.91, 28.99, 29.67, 29.91, 30.83, 31.51, 34.37, 34.72, 36.42, 36.69, 43.32, 44.58, 45.13, 48.94, 60.64, 64.60, 125.74, 128.38, 132.28, 132.31, 132.56, 133.37, 140.25, 140.34, 142.81, 151.11, 171.45, 173.81 IR (cm^{-1}) 3370.9, 2929.7, 1723.2, 1645.4, 1600.0, 1549.2.

17-{*N*-[2,4,6-(Trimethyl)benzenesulfonyl-*N*-[3,3-(diphenyl)propyl]}amino-13-[*N*-2,4,6-(trimethyl)-benzenesulfonyl]-8-oxo-7,11-diazaheptadecanoic Acid (36c). Compound **36c** was synthesized from **35c** using the method described for the synthesis of **30d** in 72.8% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.25−1.43 (m, 8H), 1.58−1.67 (m, 6H), 1.97−2.08 (m, 4H), 2.27 (d, J = 14 Hz, 8H), 2.44 (s, 6H), 2.56 (s, 6H), 2.93 (t, J = 8 Hz, 2H), 3.08 (t, J = 7.6 Hz, 2H), 3.19 (m, 6H), 3.66 (t, J = 7.6 Hz, 1H), 6.00 (t, 1H), 6.92 (d, J = 7.6 Hz, 4H), 6.98 (d, J 7.2 Hz, 4H), 7.12−7.20 (m, 5H). ^{13}C NMR (400 MHz $CDCl_3$) δ 14.42, 21.17, 21.20, 21.29, 22.93, 23.01, 24.46, 24.72, 24.82, 25.68, 27.10, 28.91, 28.98, 29.65, 29.92, 30.53, 32.74, 34.45, 36.46, 36.66, 38.74, 43.35, 44.09, 45.13, 45.29, 45.78, 48.86, 60.66, 125.74, 126.65, 127.65, 128.80, 132.32, 133.33, 133.36, 140.24, 142.63, 142.82, 143.83, 171.48, 173.85. IR (cm^{-1}) 3367.2, 2931.4, 172.0, 1645.0, 1593.1, 1541.0.

15-{*N*-[2,4,6-(Trimethyl)benzenesulfonyl-*N*-[3,3-(diphenyl)propyl]}amino-11-[*N*-2,4,6-(trimethyl)-benzenesulfonyl]-6-oxo-7,11-diazapentadecanoic Acid (36d). Compound **36d** was synthesized from **35d** using the method described for the synthesis of **30d** in 80% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.41 (m, 4H), 1.43−1.68 (m, 6H), 1.99 (m, 2H), 2.11 (t, J = 6.8 Hz, 2H), 2.27 (d, J = 17.2 Hz, 6H), 2.44 (s, 6H), 2.58 (s, 6H), 2.93 (t, J = 8 Hz, 2H), 3.09 (t, J = 6.8 Hz, 2H), 3.20 (m, 6H), 3.66 (t, J = 7.6 Hz, 1H), 6.08 (s, 1H), 6.93 (d, J = 8 Hz, 4H), 6.98 (d, J = 6.8 Hz, 4H), 7.12−7.21 (m, 5H). ^{13}C NMR (400 MHz $CDCl_3$) δ 14.40, 21.16, 21.19, 21.27, 22.92, 23.08, 24.45, 24.71, 25.14, 27.098, 29.91, 32.72, 33.78, 36.22, 36.54, 43.42, 44.06, 45.18, 45.28, 48.84, 60.64, 126.64, 127.63, 128.78, 132.26, 132.31, 133.30, 140.24, 142.65, 142.81, 143.81, 171.45, 173.37, 177.76. IR (cm^{-1}) 3364.3, 2936.2, 1723.2, 1710.3, 1632.4, 1600.0, 1314.6, 1152.4.

15-{*N*-[2,4,6-(Trimethyl)benzenesulfonyl-*N*-[(4-*tert*-butyl)benzyl]}amino-11-[*N*-2,4,6-(trimethyl)benzenesulfonyl]-6-oxo-7,11-diazapentadecanohydroxamic Acid (37a). Compound **37a** was synthesized from **36a** according to the method described for the synthesis of **31d** in 76.6% yield. ^{1}H NMR ($CDCl_3$) δ 1.27 (broad s, 13H), 1.61 (m, 4H), 2.16 (broad s, 2H), 2.3 (m, 8H), 2.54 (s, 6H), 2.62 (s, 8H), 2.99 (m, 4H), 3.24 (m, 4H), 4.11 (s, 2H), 6.87 (d, J = 6.8 Hz,2H), 6.95 (s, 4H) 7.28 (d, J = 7.2 Hz, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 21.18, 23.10, 24.14, 24.40, 24.88, 27.28, 31.50, 34.71, 35.88, 36.83, 43.52, 44.58, 45.15, 48.89, 50.89, 125.72, 128.37, 132.30, 132.52, 133.23, 133.30, 140.23, 140.28, 142.85, 151.09, 174.16. IR (cm^{-1}) 3340.5, 2936.2, 2858.4, 1716.8, 1644.5, 1600.0, 1544.2, 1457.3.

17-{*N*-[2,4,6-(Trimethyl)benzenesulfonyl-*N*-[(4-*tert*-butyl)benzyl]}amino-13-[*N*-2,4,6-(trimethyl)benzenesulfonyl]-8-oxo-7,11-diazaheptadecanohydroxamic Acid (37b). Compound **37b** was synthesized from **36b** using the method described for the synthesis of **31d** in 65.9% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.27 (s, 9H), 1.31 (m, 8H), 1.61−1.69 (m, 4H), 2.1 (m, 3H), 2.29−2.31 (m, s, 7H), 2.58 (d, J = 7.6 Hz, 12H), 3.02 (m, 4H), 3.23 (m, 4H), 4.10 (s, 2H), 6.88 (d, J 7.6 Hz, 2H), 6.96 (s, 4H), 7.24 (s, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 20.97, 21.21, 23.12, 24.18, 24.46, 31.51, 34.74, 44.59, 45.21, 48.91, 125.71, 128.31, 132.34, 132.4, 132.5, 133.3, 140.26, 140.21, 142.88, 151.15, 174.12. IR (cm^{-1}) 3247.6, 2936.2, 2858.4, 1716.8, 1646.4, 1606.5, 1541.6, 1457.3.

17-{*N*-[2,4,6-(Trimethyl)benzenesulfonyl-*N*-[3,3-(diphenyl)propyl]}amino-13-[*N*-2,4,6-(trimethyl)-benzenesulfonyl]-8-oxo-7,11-diazaheptadecanohydroxamic Acid (37c). Compound **37c** was synthesized from **36c** using the method described for the synthesis of **31d** in 75.8% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.24−1.39 (m, 8H), 1.54−1.68 (m, 6H), 2.10 (m, 4H), 2.24 (s, 4H), 2.30 (s, 4H), 2.43 (s, 6H), 2.54 (s, 6H), 2.9 (m, 2H), 3.03 (m, 2H), 3.21 (m, 6H), 3.66 (t, 1H), 6.90 (s, 4H), 6.97 (d, J = 6.4 Hz, 4H), 7.13−7.19 (m, 6H). ^{13}C NMR (400 MHz $CDCl_3$) δ 14.42, 21.21, 22.92, 23.10, 24.37, 24.70, 32.74, 43.42, 44.11, 45.31, 48.83, 60.65, 126.62, 127.66, 128.78, 132.26, 132.34, 133.33, 140.19, 140.24, 142.62, 142.81, 143.86, 171.45, 174.80. IR (cm^{-1}) 3254.1, 2929.7, 2858.4, 1651.9, 1632.4, 1606.5, 1554.6.

15-{*N*-[2,4,6-(Trimethyl)benzenesulfonyl-*N*-[3,3-(diphenyl)propyl]}amino-11-[*N*-2,4,6-(trimethyl)-benzenesulfonyl]-6-oxo-7,11-diazapentadecanohydroxamic Acid (37d). Compound **37d** was synthesized from **36d** using the method described for the synthesis of **31d** in 70.2% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.39 (m, 4H), 1.59−1.68 (m, 6H), 2.01 (m, 4H), 2.20 (s, 3H), 2.25 (s, 3H), 2.43 (s, 6H), 2.54 (s, 6H), 2.91 (m, 2H), 3.05 (m, 2H), 3.17 (m, 6H), 3.64 (t, J = 7.6 Hz, 1H), 6.90 (s, 4H), 6.98 (d, J = 7.2 Hz, 2H), 7.12−7.26 (m, 5H). ^{13}C NMR (400 MHz $CDCl_3$) δ 14.42, 21.20, 21.29, 22.97, 23.08, 24.68, 29.93, 32.71, 44.08, 45.30, 48.83, 52.55, 60.64, 126.64, 127.65, 128.79, 132.27, 133.31, 140.23, 142.67, 143.83, 162.23, 171.44. IR (cm^{-1}) 3340.5, 1638.9, 1606.6, 1535.1, 1444.3, 1308.1.

15-*N*-[(4-*tert*-Butyl)benzyl]amino-6-oxo-7,11-diazapentadecanohydroxamic Acid dihydrobromide (12). A 4.71 g portion of phenol (0.050 mol) was dissolved in 50 mL of 30% HBr in acetic acid in a stoppered flask, and to this mixture was added a solution of **37a** (0.300 g, 0.0004 mol) in 20 mL of ethyl acetate in three portions over a period of 3 h After the addition was complete, the reaction mixture was stirred for an additional 15 h at room temperature, then cooled to 0 °C, and diluted with 100 mL of water. The aqueous phase was washed with two 100 mL portions of ethyl acetate before being lyophylized to give the crude product as yellow solid. This crude product was washed with methanol and filtered to yield the tetrahydrobromide salt of **12** (0.186 g, 77.8%) as an off white solid. An analytical sample of **12** was prepared by recrystallization from aqueous ethanol. ^{1}H NMR (D_2O) δ 1.20 (s, 9H), 1.42 (m, 4H) 1.61 (m, 4H), 2.01 (m,2H), 2.13 (m, 2H), 2.99 (m, 9H), 3.12 (m, 2H), 4.06 (s, 2H), 7.26 (d, J = 6.4 Hz, 2H), 7.24 (d, J = 6.4 Hz 2H). ^{13}C NMR (400 MHz D_2O) δ 22.85, 22.92, 22.98, 23.81, 24.06, 24.52, 24.78, 25.77, 30.55, 32.13, 34.26, 35.42, 36.06, 38.93, 45.21, 46.20, 47.00, 47.08, 50.73, 126.44, 127.83, 129.94, 130.13, 153.57, 173.06, 177.18. IR (cm^{-1}) 3419.0, 2952.2, 1696.8, 1686.5, 1634.6, 1603.5, 1551.6. Anal. for $C_{24}H_{44}Br_2N_4O_3$: C, H, N.

17-*N*-[(4-*tert*-Butyl)benzyl]amino-8-oxo-7,11-diazaheptadecanohydroxamic Acid dihydrobromide (16). Compound **16** was synthesized from **37b** using the method described for the synthesis of **12** in 78.4% yield. An analytical sample of **16** was prepared by recrystallization from aqueous ethanol. ^{1}H NMR (400 MHz D_2O) 1.15−1.28 (m, 13H), 1.62 (m, 4H), 1.74 (m, 2H), 1.99 (m, 2H), 2.10 (m, 2H), 2.91 (m, 8H), 3.14 (m, 2H), 4.07 (d, J = 10.08 Hz, 2H), 7.29 (t, J = 8 Hz, 2H), 7.42 (t, J = 9.6 Hz, 2H). ^{13}C NMR (400 MHz D_2O) δ 22.84, 24.48, 25.23, 25.77, 27.76, 27.91, 30.54, 32.38, 35.70, 36.00, 45.19, 46.16, 47.00, 50.71, 126.44, 127.83,129.94, 130.13, 153.44, 173.41, 177.85. IR (cm^{-1}) 3240.5, 2936.2, 1682.2, 1645.4, 1603.2, 1541.6, 1457.3. Anal. for $C_{26}H_{48}Br_2N_4O_3$: C, H, N.

17-*N*-[4-(3,3-Diphenyl)propyl]amino-8-oxo-7,11-diazaheptadecanohydroxamic Acid dihydrobromide (20). Compound **20** was synthesized from **37c** using the method described for the synthesis of **12** in 75.7% yield. An analytical

sample of **20** was prepared by recrystallization from aqueous ethanol. ^{1}H NMR (400 MHz D_2O) δ 1.07 (m, 4H), 1.39 (m, 4H), 1.53 (m, 4H), 1.68 (m, 2H), 1.96 (m, 2H), 2.06 (m, 2H), 2.30 (m, 2H), 2.83 (m, 8H), 3.09 (m, 2H), 3.94 (m, 1H), 7.11 (m,-1H), 7.22 (m, 8H). ^{13}C NMR (400 MHz D_2O) δ 20.61, 22.76, 22.86, 24.84, 22.86, 24.84, 25.20, 25.75, 27.73, 27.89, 30.85, 32.33, 35.65, 35.93, 45.12, 45.43, 46.75, 46.94, 48.08, 61.82, 63.38, 127.15, 127.58, 129.18, 143.64, 173.58, 177.85 IR (cm^{-1}) 3390.3, 2923.2, 2845.4, 1658.4, 1632.4, 1554.6, 1444.3. Anal. for $C_{30}H_{48}Br_2N_4O_3$: C, H, N.

15-*N*-[4-(3,3-diphenyl)propyl]amino-6-oxo-7,11-diazapentadecanohydroxamic Acid dihydrobromide (21). Compound **21** was synthesized from **37d** using the method described for the synthesis of **12** in 70.1% yield**.** An analytical sample of **21** was prepared by recrystallization from aqueous ethanol. ^{1}H NMR (400 MHz D_2O) δ 1.07 (m, 4H), 1.39 (m, 4H), 1.53 (m, 4H), 1.68 (m, 2H), 1.97 (m, 2H), 2.06 (m, 2H), 2.30 (m, 2H), 2.83 (m, 8H), 3.01 (m, 2H), 3.94 (m, 2H), 7.11 (m, 1H), 7.22 (m, 8H). ^{13}C NMR (400 MHz D_2O) δ 22.8, 22.89, 24.51, 24.78, 25.79, 30.89, 35.42, 36.02, 45.12, 45.18, 46.49, 46.72, 46.81, 46.97, 48.13, 127.18, 127.18, 127.62, 129.22, 143.68, 177.23. IR (cm^{-1}) 3383.8, 2903.8, 1658.4, 1632.4, 1561.1, 1444.3. Anal. for $C_{28}H_{44}Br_2N_4O_3$: C, H, N.

1-(Phthalimido)-4,8,12-tris{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}-15-*N*-[2,4,6-trimethylbenzenesulfonyl)-amino]-4,8,12-triazapentadecane (39). Compound **39** was synthesized from **38** using the procedure described for the synthesis of **33a** in 65.7% yield. ^{1}H NMR ($CDCl_3$) δ 1.22 (m, 4H), 1.33−1.44 (m, 2H), 1.61−1.72 (m, 2H), 2.22 (s, 12H), 2.53 (s, 12H), 2.58 (s, 12H), 2.8 (q, 2H), 2.95 (m, 8H), 3.2 (t, J = 7.2 Hz, 2H), 6.99 (d, J = 6.8 Hz, 8H), 7.73 (m, 2H), 7.83−7.85 (m, 2H).

1-(Phthalimido)-4,8,12-tris{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}- 15-{*N*-[2,4,6-(trimethyl)benzenesulfonyl]-*N*-[2-(phenyl)benzyl]}amino-4,8,12-triazapentadecane (40a).

1-(Phthalimido)-4,8,12-tris{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}- 15-{*N*-[2,4,6-(trimethyl)benzenesulfonyl]-*N*-[(cyclopropyl)methyl]}amino-4,8,12-triazapentadecane (40b).

1-(Phthalimido)-4,8,12-tris{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}-15-{*N*-[2,4,6-(trimethyl)benzenesulfonyl]-*N*-[(cycloheptyl)methyl]}amino-4,8,12-triazapentadecane (40c).

Compounds **40a**−**c** were synthesized from **39** and the appropriate alkyl halide using the method described for the synthesis of **33a**.

Compound **40a** (65% yield). ^{1}H NMR (400 MHz $CDCl_3$) δ 1.08 (m, 2H), 1.48(m, 2H), 1.62(m, 4H), 2.21(m, 12H), 2.43(s, 6H), 2.46(s, 6H), 2.52(m, 14H), 2.64(t, J = 6.8 Hz, 2H), 2.75(t, J = 7.2 Hz, 2H), 2.91−3.07(m, 8H), 3.42(t, J = 6.8 Hz, 2H), 4.27(s, 2H), 6.77(s, 2H), 6.85(s, 2H), 6.91(s, 2H), 6.94(s, 2H), 7.16(m, 3H), 7.26(m, 3H), 7.38(m, 3H), 7.72(m, 2H), 7.80(m, 2H).

Compound **40b** (73% yield). ^{1}H NMR ($CDCl_3$) δ 0.02 (m, 2H), 0.45 (dd, J = 8 Hz, 5.2 Hz, 2H), 0.75 (m, 1H), 1.66 (m, 8H), 2.18 (s, 2H), 2.25 (s, 2H), 2.30 (s, 8H), 2.48 (s, 6H), 2.56 (s, 18H), 2.91 (d, J = 6.8 Hz, 2H), 3.01 (m, 12H), 3.15 (t, J = 7.2 Hz, 2H), 3.44(t, J = 6.8 Hz, 2H), 6.79 (s, 2H), 6.94 (s, 6H), 7.76 (m, 2H), 7.82 (m, 2H).

Compound **40c** (72.2% yield). ^{1}H NMR (400 MHz $CDCl_3$) δ 0.77 (m,2H),1.22 (m, 8H), 1.33−1.44(m, 6H), 1.61−1.72 (m, 6H), 2.22 (s, 12H), 2.53 (s, 12H), 2.58 (s,12H),2.7 (d, J = 6.8 Hz, 2H) 2.8 (q, J = 6.6 Hz, 2H),2.95 (m, 12H), 3.2 (t, J = 7.2 Hz, 2H), 6.99 (d, J = 7.6 Hz, 8H), 7.73 (m, 2H), 7.83−7.85 (m, 2H).

11,15,19-Tris{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}-22-{*N*-[2,4,6-trimethylbenzenesulfonyl)]-*N*-[2-(phenyl)-benzyl]amino}-6-oxo-7,11,15,19-tetraazadocosanoic Acid Methyl Ester (41a).

11,15,19-Tris{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}-22-{*N*-[2,4,6-trimethylbenzenesulfonyl)]-*N*-[(cyclopropyl)-methyl]amino}-6-oxo-7,11,15,19-tetraazadocosanoic Acid Methyl Ester (41b).

11,15,19-Tris{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}-22-{*N*-[2,4,6-trimethylbenzenesulfonyl)]-*N*-[2-(cycloheptyl)-methyl]amino}-6-oxo-7,11,15,19-tetraazadocosanoic Acid Methyl Ester (41c).

Compounds **41a**−**c** were synthesized from **40a-c** and **28a** in two steps using the methods described for the synthesis of **27a** and **29a**.

Compound **41a** (70% yield). ^{1}H NMR ($CDCl_3$) δ 1.08 (m, 2H), 1.48 (m, 2H), 1.43−1.79 (m, 8H), 2.05 (m, 2H), 2.21−2.39 (m, 14H), 2.53 (m, 28H), 2.77 (t, J = 7.2 Hz, 2H), 2.98 (m, 8H), 3.12 (m, 4H), 3.61 (s, 3H), 4.19 (s, 2H), 6.91 (s, 2H), 6.94 (m, 6H), 7.13 (m, 4H), 7.24 (m, 3H), 7.35 (m, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 21.18, 22.98, 23.02, 23.05, 23.08, 24.26, 24.68, 25.11, 25.28, 25.41, 25.78, 27.13, 33.91, 34.02, 36.25, 42.75, 43.25, 43.28, 46.18, 51.75, 109.99, 127.69, 127.78, 128.98, 128.65, 129.19, 129.46, 130.29, 132.18, 132.29, 132.34, 132.85, 133.06, 140.06, 140.26, 140.44, 142.46, 142.80, 142.89, 142.95, 172.45, 174.32. IR (cm^{-1}) 3336.0, 2931.4, 1740.5, 1655.3, 1582.7.

Compound **41b** (74% yield). ^{1}H NMR ($CDCl_3$) δ 0.01 (m, 2H), 0.46 (m, 2H), 0.75 (m, 1H), 1.58 (m, 12H), 2.01 (m, 2H), 2.32 (s, 12H), 2.43 (m, 2H), 2.68 (s, 24H), 2.92 (d, J = 6.8 Hz, 2H), 3.06 (m, 10H), 3.18 (m, 4H), 3.78 (s, 3H), 6.98 (m, 8H). IR (cm^{-1}) 3383.7, 1742.7, 1664.8, 1606.4, 1561.0.

Compound **41c** (70.2% yield). ^{1}H NMR ($CDCl_3$) δ 0.77 (m, 2H), 1.22 (m, 2H), 1.33−1.44 (m, 8H), 1.61−1.78 (m, 12H), 2.1 (t, 2H), 2.22 (m, 14H), 2.53 (s, 12H), 2.58 (s, 14H), 2.75 (d, J = 6.8 Hz, 2H), 2.9−3.01 (m, 12H), 3.14−3.18 (m, 4H), 3.67 (s,-3H), 6.88−6.94 (m, 8H). ^{13}C NMR (400 MHz $CDCl_3$) δ 21.19, 23.06, 24.32, 24.49, 24.66, 25.29, 25.39, 25.95, 27.11, 28.70, 31.52, 33.78, 33.87, 36.28, 36.40, 36.47, 43.45, 43.52, 43.64, 51.76, 51.89, 132.15, 132.30, 132.34, 133.18, 140.15, 140.27, 142.95, 173.24, 174.02, 174.17, 178.84.

11,15,19-Tris{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}-22-{*N*-[2,4,6-trimethylbenzenesulfonyl)]-*N*-[2-(phenyl)benzyl]amino}-6-oxo-7,11,15,19-tetraazadocosanohydroxamic Acid (42a).

11,15,19-Tris{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}-22-{*N*-[2,4,6-trimethylbenzenesulfonyl)]-*N*-[(cyclopropyl)-methyl]amino}-6-oxo-7,11,15,19-tetraazadocosanohydroxamic Acid (42b).

11,15,19-Tris{*N*-[2,4,6-(trimethyl)benzenesulfonyl]}-22-{*N*-[2,4,6-trimethylbenzenesulfonyl)]-*N*-[2-(cycloheptyl)-methyl]amino}-6-oxo-7,11,15,19-tetraazadocosanohydroxamic Acid (42c).

Compounds **42a**−**c** were synthesized from **41a**−**c** in two steps using the methods described for the synthesis of **30a** and **31a**.

Compound **42a (**62.6% yield). ^{1}H NMR ($CDCl_3$) δ 1.41−1.79 (m, 12H), 2.13 (m, 2H), 2.21−2.38 (m, 14H), 2.40−2.59 (m, 28H), 2.78(t, J = 7.2 Hz, 2H), 2.98(m, 6H), 3.18(m, 2H), 4.20-(s, 2H), 6.88(s, 2H),6.96(m, 6H), 7.15−7.43(m, 9H) ^{13}C NMR (400 MHz $CDCl_3$) δ 14.42, 21.13, 21.18, 21.21, 21.28, 23.02, 23.09, 24.15, 24.40, 27.61, 31.61, 39.57, 42.39, 43.25, 43.82, 45.24, 46.15, 51.71, 60.61, 110.12, 127.66, 127.77, 127.99, 128.64, 129.19, 129.48, 130.27, 132.14, 132.33, 133.08, 133.31, 134.19, 139.11, 140.03, 140.17, 140.29, 140.45, 142.12, 142.46, 142.62, 142.83, 142.93, 168.21, 174.13 IR (cm^{-1}) 3407.6, 2910.1, 2765.4, 1664.7, 1644.9, 1603.6, 1447.84.

Compound **42b** (60.9% yield). ^{1}H NMR ($CDCl_3$) δ 0.01 (m, 2H), 0.5 (m, 2H), 0.72 (m, 1H), 1.73 (m, 12H), 2.29 (m, 2H), 2.30 (m, 2H), 2.41 (s, 12H), 2.65 (s, 24H), 2.88 (d, J = 6.8 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H), 3.10 (m, 8H), 3.21 (t, J = 7.2 Hz, 2H), 3.28 (m, 4H), 7.06 (s, 8H). ^{13}C NMR (400 MHz $CDCl_3$) δ 5.05, 11.08, 17.20, 18.02, 18.96, 19.05, 19.09, 20.71, 21.30, 21.55, 25.94, 31.74, 32.63, 46.13, 128.21, 128.31, 128.35, 128.96, 129.07, 129.21, 136.29, 138.75, 139.0, 150.92, 169.62, 172.23. IR (cm^{-1}) 3312.0, 2904.4, 1658.2, 1645.4, 1605.8, 1540.9.

Compound **42c** (75.9% yield). ^{1}H NMR ($CDCl_3$) δ 0.77 (m, 4H), 1.33−1.44 (m, 8H), 1.61−1.78 (m, 12H), 2.15−2.27 (m, 4H), 2.22 (s, 12H), 2.53 (s, 12H), 2.58 (s,12H), 2.66 (d, J = 7.2 Hz, 2H), 2.9−3.01 (m, 12H), 3.14−3.18 (m, 4H), 6.92−6.98 (m, 8H).^{13}C NMR (400 MHz $CDCl_3$) δ 14.42, 21.19, 21.29, 23.02,

23.06, 24.72, 24.88, 25.36, 25.94, 28.71, 36.44, 43.38,43.56, 60.64, 64.60, 132.15, 132.34, 132.98, 133.10, 133.33, 133.97, 140.14, 140.26, 142.70, 142.97, 171.44, 173.82.

22-{*N*-[2-(Phenyl)benzyl]amino}-6-oxo-7,11,15,19-tetraazadocosanohydroxamic Acid (7). Compound **7** was synthesized from **42a** using the method described for the synthesis of **12** in 68% yield. ^{1}H NMR (D_2O) δ 1.48 (m, 4H), 1.79 (m, 4H), 1.98 (m, 4H), 2.15 (m, 2H), 2.23 (m, 2H), 2.75 (t, J = 8.0 Hz, 2H), 2.8−3.05 (m, 12H), 3.12 (t, J = 6.4 Hz, 2H), 4.16 (s, 2H), 7.24−7.44 (m, 9H). ^{13}C NMR (400 MHz D_2O) δ 22.42, 22.76, 22.83, 23.75, 23.81, 24.83, 25.77, 33.42, 33.51, 35.47, 36.06, 43.92, 44.62, 44.67, 45.44, 48.23, 115.47, 120.78, 128.05, 128.21, 128.67, 129.10, 129.56, 129.90, 130.08, 130.12, 130.97, 139.53, 142.81, 177.23, 178.65. IR (cm^{-1}) 3419.0, 3045.5, 2910.6, 1688.5, 1651.3, 1603.4. Anal. for $C_{31}H_{54}Br_4N_6O_3$: C, H, N.

22-{*N*-[(Cyclopropyl)methyl]amino}-6-oxo-7,11,15,19-tetraazadocosanohydroxamic Acid (9). Compound **9** was synthesized from **42b** using the method described for the synthesis of **12** in 65% yield. ^{1}H NMR (D_2O) δ 0.22 (m, 2H), 0.54 (m, 2H), 0.91 (m, 1H), 1.45(m, 5H), 1.75 (q, J = 6.8 Hz, 3H), 1.98 (m, 4H), 2.13 (t, J = 6.8 Hz, 2H) 2.25(t, J = 7.2 Hz, 2H), 2.83 (d, J = 7.6 Hz, 2H), 2.93 (t, J = 7.6 Hz, 2H), 3.05 (m, 12H), 3.14 (t, J = 7.2 Hz, 2H). IR (cm^{-1}) 3312.1, 2931.4, 1655.3, 1645.4, 1593.0. Anal. for $C_{22}H_{50}Br_4N_6O_3$: C, H, N.

22-{*N*-[2-(Cycloheptyl)methyl]amino}-6-oxo-7,11,15,19-tetraazadocosanohydroxamic Acid (10). Compound **10** was synthesized from **42c** using the method described for the synthesis of **12**

in 70.4% yield ^{1}H NMR (D_2O) δ 1.08−1.16 (m, 4H), 1.28−1.58(m, 14H), 1.73−1.78 (m, 2H), 1.93−2.07 (m, 6H), 2.78 (d, J = 8.8 Hz, 2H), 2.93 (t, J = 7.2 Hz, 2H) 2.96−3.01 (m, 12H), 3.12−3.16 (t, J = 6.8 Hz, 2H).^{13}C NMR (400 MHz D_2O) δ 22.66, 22.79, 24.52, 24.76, 25.42, 25.81, 27.95, 31.25, 32.12, 35.42, 36.01, 36.30, 173.11, 177.26 IR (cm^{-1}) 3408.7, 2910.7, 2848.4, 1665.7, 1644.0, 1447.8. Anal. for $C_{26}H_{58}Br_4N_6O_3$: C, H, N.

7-{4-[(Phthalimido)amino]butyl}-{*N*-[4-*N*,*N*-(dimethyl)-aminobenzyl]carbamoyl}heptanoic Acid Methyl Ester (43). Compound **43** was synthesized from **25c** and **28b** using the procedure described for the synthesis of **29c** in 72.6% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.24−1.35 (m, 4H), 1.61−1.64 (m, 8H), 2.26−2.36 (m, 4H), 2.92 (d, J = 8.8 Hz, 6H), 3.20 (t, J = 7.2 Hz, 1H), 3.36 (t, J = 6.8 Hz, 1H), 3.65−3.71 (m, 5H), 4.42 (s, 1H), 4.48 (s, 1H), 6.65 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.69−7.75 (m, 2H), 7.80−7.86 (m, 2H). ^{13}C NMR (400 MHz $CDCl_3$) δ 24.82, 24.99, 25.56, 26.21, 28.92, 28.97, 29.20, 29.29, 33.24, 33.40, 34.19, 37.57, 37.86, 40.81, 40.86, 45.39, 46.23, 47.62, 50.79, 51.65, 112.84, 113.00, 123.37, 123.50, 124.50, 125.84, 127.47, 129.46, 132.19, 134.08, 134.26, 150.11, 150.21, 168.57, 173.08, 174.45 IR (cm^{-1}) 3461.6, 2936.2, 2858.4, 1742.7, 1768.7, 1710.3, 1638.9, 1613.0, 1515.7.

7-{4-[*N*-(*tert*-Butyloxycarbonyl)amino]butyl}-{*N*-[4-*N*,*N*-(dimethyl)aminobenzyl]carbamoyl}heptanoic Acid (44). Compound **44** was synthesized from **43** in three steps using the procedures described for the synthesis of **27b** (phthalimide cleavage) and **26c** (N-Boc protection) and **31c** in 70.2% overall yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.25 (m, 2H), 1.30 (m, 2H), 1.39 (s, 12H), 1.47 (m, 2H), 1.58 (m, 4H), 2.15 (m, 2H), 2.29 (m, 2H), 2.86 (d, J = 7.2, 6H), 3.03 (m, 2H), 3.11 (t, J = 7.6, 1H), 3.26 (t, J = 7.2 Hz, 1H), 4.35 (s, 1H), 4.42 (s, 1H), 4.85 (s, 1H), 6.60 (d, J = 8.8 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H). ^{13}C NMR (400 MHz $CDCl_3$) δ 14.32, 21.24, 24.24, 25.28, 25.36, 25.86, 27.54, 28.36, 28.62, 28.95, 33.30, 33.94, 40.25, 40.39, 40.84, 40.89, 45.56, 46.47, 47.63, 50.77, 60.60, 81.44, 112.90, 113.09, 124.51, 127.49, 129.38, 150.08, 150.25, 156.30, 171.42, 173.24, 173.32, 173.70. IR (cm^{-1}) 3280.0, 2975.1, 2929.7, 2864.9, 1690.8, 1619.5, 1522.2.

7-{4-[*N*-(*tert*-Butyloxycarbonyl)amino]butyl}-{*N*-[4-*N*,*N*-(dimethyl)aminobenzyl]carbamoyl}heptano-hydroxamic Acid (45). Compound **45** was synthesized from **44** using the procedure described for the synthesis of **31c** in 74.4% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.31 (m, 4H), 1.37 (m, 4H), 1.64 (m, 4h), 2.29−2.36 (m, 4H), 2.94 (d, J = 8.4 Hz, 6H), 3.09 (m, 2H), 3.27 (t, J = 7.2 Hz, 1H), 3.32 (t, J = 8.6 Hz, 1H), 4.41 (s, 1H), 4.48 (s, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 7.1 (d, J = 8.8 Hz, 1H), 8.22 (d, J = 8.8 Hz, NH). ^{13}C NMR (400 MHz $CDCl_3$) δ 25.00, 25.26, 25.35, 25.88, 27.60, 28.37, 28.64, 28.92, 29.90, 33.00, 33.27, 34.01, 40.28, 40.44, 40.87, 40.91, 45.58, 46.47, 47.65, 50.79, 81.63, 112.89, 113.10, 124.55, 127.50, 129.44, 150.12, 150.27, 155.91, 156.27, 173.19, 173.67, 174.97. IR (cm^{-1}) 3267.0, 2975.1, 2936.2, 2864.9, 1684.3, 1677.8, 1619.5, 1509.2, 1450.8.

7-{[4-(Amino)butyl]-*N*-[4-(dimethylaminobenzyl)-carbamoyl]}heptanohydroxamic Acid (19). synthesized from **32** according to the procedure mentioned for **13** in 90.9% yield. ^{1}H NMR (400 MHz CD_3OD) δ 1.31−1.40 (m, 4H), 1.64 (m, 8H), 2.26−2.36 (m, 2H), 2.38 (t, J = 4.8 Hz, 1H), 2.49 (t, J = 4.8 Hz, 1H), 2.94 (m, 2H), 3.29 (s, 6H), 3.39 (m, 2H), 4.65 (s, 1H), 4.73 (s, 1H), 7.45 (t, J = 7.2 Hz, 2H), 7.62 (d, J = 6 Hz, 1H), 7.67 (d, J = 5.6 Hz, 1H). ^{13}C NMR (400 MHz CD_3-OD) δ 24.14, 24.59, 24.72, 24.77, 24.97, 25.13, 25.42, 28.62, 28.68, 28.78, 32.52, 32.86, 39.11, 50.33, 114.58, 117.45, 120.59, 120.94, 128.400, 129.46, 139.73, 140.57, 141.98, 160.22, 173.05, 174.63, 175.03. IR (cm^{-1}) 2936.2, 1671.4, 1626.0, 1515.7, 1463.8, 1424.8. Anal. for $C_{23}H_{37}F_3N_4O_5$: C, H, N.

1-*N*-[2,4,6-(Trimethyl)benzenesulfonyl]amino-4-*N*-[2,4,6-(trimethyl)benzenesulfonyl]-8-*N*-{4-[*N*,*N*-(dimethyl)-benzyl]amino}-4-azaoctane (46). Compound **46** was synthesized in two steps from **32** using the procedure described for the syntheses of **27c** and **25c** in 77.3% overall yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.35 (q, J = 7.6 Hz, 2H), 1.47 (q, J = 6.8 Hz, 2H), 1.57 (q, J = 6.8 Hz, 2H), 2.28 (d, J = 2.8 Hz, 6H), 2.51−2.59 (m, 14H), 2.78 (t, J = 6.8 Hz, 2H), 3.13 (t, J = 7.6 Hz, 2H), 3.17 (t, J = 7.6 Hz, 2H), 6.93 (d, J = 10 Hz, 4H). ^{13}C NMR (400 MHz $CDCl_3$) δ 14.21,19.08, 22.47, 25.6, 26.22, 27.46, 32.41, 40.12, 40.1, 43.88, 46.18, 127.44, 128.14, 136.25, 137.49, 141.58, 142.33.

5-[(4-*N*,*N*-(Dimethylamino)benzyl)−(4-{(2,4,6-trimethyl-benzenesulfonyl)-[3-(2,4,6-trimethyl-benzenesulfonyl-amino)propyl]amino}butyl)carbamoyl]pentanoic Acid Methyl Ester (47). Compound **47** was synthesized from **46** and **28a** using the procedure described for the synthesis of **29d** in 81.6% yield. ^{1}H NMR (400 MHz $CDCl_3$) δ 1.26 (m, 2H), 1.63 (m, 2H), 1.68 (m, 6H), 2.29 (m, 2H), 2.32 (m, 6H), 2.36 (m, 2H), 2.52 (m, 6H), 2.62 (m, 6H), 2.79 (m, 2H), 2.92 (s, 6H), 3.01−3.13 (m, 6H), 3.67 (s, 3H), 4.29 (s, 1H), 4.35 (s, 1H), 6.68 (d, J = 8.4 Hz, 2H), 6.88−6.95 (m, 6H). IR (cm^{-1}) 3409.7, 2923.2, 1736.8, 1664.8, 1619.4, 1528.6.

5-[(4-*N*,*N*-(Dimethylamino)benzyl)−(4-{(2,4,6-trimethyl-benzenesulfonyl)-[3-(2,4,6-trimethyl-benzenesulfonylamino)propyl]amino}butyl)carbamoyl]pentano-hydroxamic Acid (48). Compound **48** was synthesized in two steps from **47** using the procedures described for the syntheses of **30d** and **31d** in 66.2% overall yield. ^{1}H NMR (400 MHz D_2O) δ 1.40 (m, 4H), 1.50 (m, 2H) 1.63 (m, 4H) 1.80 (m, 1H), 1.98 (m, 1H), 2.07 (m, 1H), 2.31 (m, 1H), 2.71 (m, 1H), 2.90−2.93 (m, 8H), 3.14 (d, J = 4.4 Hz, 6H), 3.38 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H). IR (cm^{-1}) 3398.3, 2941.8, 2683.2, 1613.0, 1522.2, 1470.3, 1184.9, 990.3.

5-[(4-*N*,*N*-(Dimethylamino)benzyl)−(4-{(2,4,6-trimethyl-benzenesulfonyl)-[3-(2,4,6-trimethyl-benzenesulfonylamino)propyl]amino}butyl)carbamoyl]pentano-hydroxamic Acid (15). Compound **15** was synthesized in two steps from **48** using the procedure described for the synthesis of **12** in 82.2% yield. ^{1}H NMR (400 MHz D_2O) δ 1.14 (s, 9H), 1.43 (m, 4H), 1.59 (m, 4H), 1.72 (q, J = 7.6 Hz, 2H), 2.11 (t, J = 6.4 Hz, 2H), 2.32 (t, J = 7.2 Hz, 2H), 2.85−2.94 (m, 6H), 3.12 (t, J = 6.4 Hz, 2H), 4.05 (s, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 1.6 Hz, 2H). ^{13}C NMR (400 MHz D_2O) δ 22.83, 22.96, 23.80, 24.05, 24.84, 25.77, 30.53, 33.49, 34.26, 35.43, 36.02, 45.17, 46.15, 46.97, 50.17, 126.44, 127.81, 129.92, 153.57, 177.28, 178.68. IR (cm^{-1}) 3396.8, 2929.7, 1677.8, 1606.5, 1424.9.

Histone Deacetylase Activity Assay. Compounds **6**−**21** were evaluated for their ability to inhibit isolated HDAC in a

commercially available assay (Fluor de Lys Assay System, Biomol International LP, Plymouth Meeting, PA), employing **1** and **2** as positive controls. The reaction mixture contains a HeLa cell nuclear extract and a commercial substrate containing acetylated lysine side chains. The substrate and extract are incubated in the presence of the appropriate concentration of the inhibitor. Deacetylation of the substrate followed by mixing with mixing with the provided developer generates a fluorophore, and comparison of inhibited vs control relative fluorescence using a standard plate reader was employed to determine percent HDAC activity remaining. All determinations were carried out in triplicate, and reported values are the average of these determinations, which in no case varied by more than 3%.

Cell Lines and Drug Treatment. ML-1 cells were maintained in RPMI medium supplemented with 10% fetal calf serum, 0.1 mg/mL gentamicin, and 2 mM L-glutamine. 3×10^5 cells/ml were treated with **1** (Wako Pure Chemicals, Richmond, VA), **2** (Mitsui Pharmaceuticals, Chiba, Japan) and the desired test compound for the concentration and time indicated in the figure legend.

Histone Preparation. Histones were prepared by a modification of a previously described method.[24] Cells were washed in 2 mL of HBSS and disrupted by 1 mL of ice-cold lysis buffer A (10 mM Tris pH 7.6, 5 mM butyric acid, 1% Triton X-100, 1 mM $MgCl_2$, and 1 mM PMSF). Nuclei were collected by centrifugation at 14 000 rpm for 15 min. The pellet was resuspended once with 250 μL of ice-cold lysis buffer B (10 mM Tris pH 7.6, 0.25 M Sucrose, 3 mM $CaCl_2$, and 5 mM butyric acid). Sulfuric acid was added to a concentration of 0.4 N, and the tubes were incubated at 4 °C for overnight. Debris was pelleted by centrifugation, and the supernatant was collected. Histones were precipitated by addition of 10 vol of acetone and incubated at −20 °C overnight. Pellets were collected by centrifugation, briefly dried under vacuum, and resuspended in ddH_2O.

$p21^{WAF1/Cip1}$ Expression Analysis. ML-1 cells after treatment were lysed in RIPA lysis buffer containing an EDTA-free protease inhibitor cocktail, at 4 °C for 30 min. Lysate was clarified by centrifugation at 14 000 rpm for 15 min. The resulting supernatant was used for analysis. The total protein content was determined by a bicinchoninic acid (BCA) assay kit (Pierce, Rockford, IL), and the absorbance of the solution was measured using a spectrophotometer at a wavelength of 570 nm. Absorbance was converted to protein content using an albumin standard curve.

The proteins (10 μg for histone or 30 μg for $p21^{Waf1}$) were separated by 15% SDS PAGE and visualized by Western blot analysis using the following antibodies against interesting proteins: antibodies for acetylhistone H3 (06-599) (diluted 1:1000), acetylhistone H4 (06-866) (diluted 1:500), and histone H2A (07-146) (diluted 1:1000) were from Upstate Biotechnologies, $p21^{Waf1}$ (556431) (diluted 1:500) from BD Pharmigen, and β-actin (ON365) (diluted 1:1000) from Oncogene Research Products. The immunoreactive proteins were detected using ECL western blotting analysis system (Amersham Biosciences, Piscataway, NJ). Cell proliferation was quantified by the MTT assay according to the supplied protocol (Promega, Madison, WI).

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