N-Hydroxy-3-phenyl-2-propenamides as Novel Inhibitors of Human Histone Deacetylase with in Vivo Antitumor Activity: Discovery of (2*E*)-*N*-Hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1*H*-indol-3-yl)ethyl]amino]methyl]-phenyl]-2-propenamide (NVP-LAQ824)

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A series of *N*-hydroxy-3-phenyl-2-propenamides were prepared as novel inhibitors of human histone deacetylase (HDAC). These compounds were potent enzyme inhibitors, having IC_{50}s < 400 nM in a partially purified enzyme assay. However, potency in cell growth inhibition assays ranged over 2 orders of magnitude in two human carcinoma cell lines. Selected compounds having cellular IC_{50} < 750 nM were tested for maximum tolerated dose (MTD) and for efficacy in the HCT116 human colon tumor xenograft assay. Four compounds having an MTD ≥ 100 mg/kg were selected for dose−response studies in the HCT116 xenograft model. One compound, **9** (NVP-LAQ824), had significant dose-related activity in the HCT116 colon and A549 lung tumor models, high MTD, and low gross toxicity. On the basis, in part, of these properties, **9** has entered human clinical trials in 2002.

Introduction

Histone acetylation is one major regulator of gene expression which may act by changing the accessibility of transcription factors to DNA.[1] Cell specific patterns of gene expression dependent on histone acetylation result from a balance of the competing activities of two classes of enzymes, the histone acetyl transferases[2,3] and the histone deacetylases (HDACs).[4,5] Perturbations of this balance have been linked to cancer,[6,7] and inhibition of HDAC has been shown to have antiproliferative effects on tumor cell lines, resulting in considerable interest in this field. Several HDAC inhibitors (HDAIs) are in clinical trials as anticancer agents, including SAHA (**1**), FK-228 (**2**), and MS-275 (**3**, Chart 1).[8−12]

We initiated a program to discover novel HDAIs as anticancer agents and, in undertaking the development of a new class of inhibitors, set the following minimum requirements to select compounds for in vivo evaluation: Novel structural type, enzyme potency < 500 nM, and cellular potency < 750 nM. On the basis of the known HDAIs trichostatin A[13] (TSA, **4**), dimethylaminobenzamidylcaprylic hydroxamate[14,15] (DBCH, **5**), and trapoxin B[16] (TpxB, **6**), we, and others,[17,18] have proposed a generalized HDAI structure as A−B−C **4** (Chart 1), where C is a Zn^{2+} ligand, B is a spacer, and A is a specificity element. A synthetic chemistry effort was initiated based on this general HDAI structure in parallel with a high throughput screen (HTS) of the Novartis compound archive. Several structural classes identified from these efforts were examined as leads. The most promising compound, **8** (NVP-LAK974), was obtained from the HTS. While this compound met our basic structural and in vitro requirements, it had poor efficacy in the HCT116 human colon tumor xenograft model. We, therefore, instituted a systematic structural exploration of *N*-hydroxy-3-phenyl-2-propenamides with the goal of synthesizing a novel, well tolerated, efficacious compound with acceptable pharmaceutical properties. Our efforts have led to the discovery of **9** (NVP-LAQ824), a potent HDAI and antitumor agent currently undergoing human clinical trials against both solid tumors and leukemia.

Chemistry

The synthesis of the majority of compounds was accomplished by reductive amination of methyl 4-formylcinnamate (**10**)[19] with either primary or secondary amines using $NaBH_3CN$ (Method A) or $NaBH(OAc)_3$ (Method B, Scheme 1) to afford secondary amines **11** or tertiary amines **12**. The aminoesters **11** and **12** were converted to the corresponding hydroxamic acids **13** and **14** by one of three methods: reaction with aqueous hydroxylamine in the presence of NaOH (Method C), treatment with a solution of hydroxylamine in methanol (Method D), or by adding methanolic NaOMe to a mixture of the ester and hydroxylamine hydrochloride in MeOH (Method E). Tertiary amine hydroxamates **14** were prepared by reacting secondary amine **11** or **13** with an alkyl halide or by reductive amination of **11** or **13** with an aldehyde or ketone.

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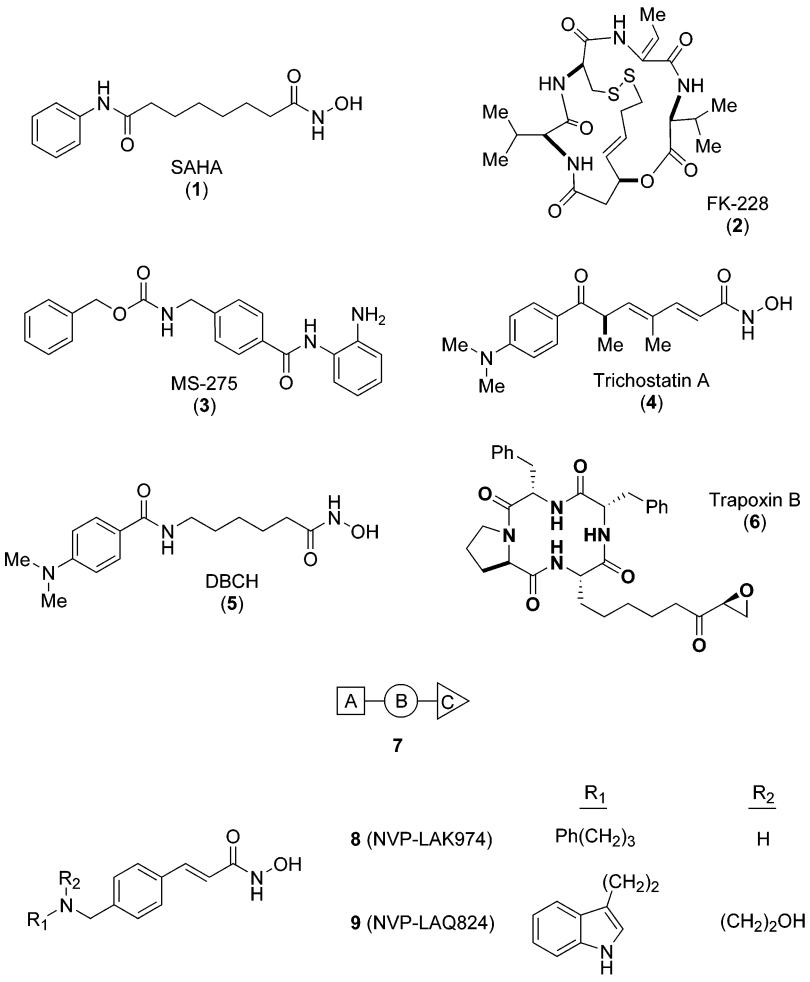
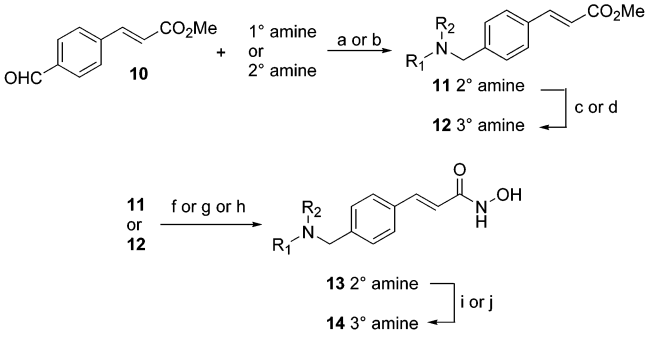
Chart 1

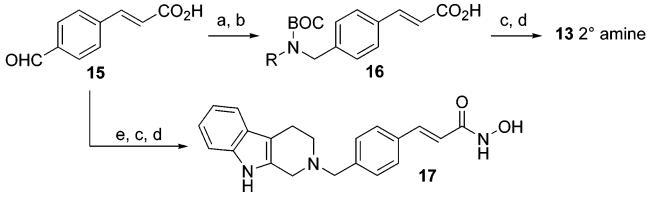


Scheme 1[a]



[a] Reagents: (a) $NaBH(CN)_3$, MeOH, HOAc (optional) (Method A); (b) $NaBH(OAc)_3$, THF or dichloroethane (DCE), HOAc (optional) (Method B); (c) alkyl halide, base; (d) aldehyde or ketone, Method A or Method B; (e) $HONH_2$ (aq), NaOH (aq) (Method C); (f) MeOH/$HONH_2$ (anhydrous, Method D); (g) NaOMe, $HONH_3Cl$, MeOH (Method E); (i) alkyl halide, amine base; (j) aldehyde or ketone, Method A.

Scheme 2[a]



[a] Reagents: (a) primary amine, Method A; (b) $(BOC)_2O$, Et_3N, MeOH; (c) Tr-ONH_2, EDCI, HOBT, 1-methylmorpholine (NMM), DMF; (d) 5% H_2O/TFA; (e) 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole, Method A.

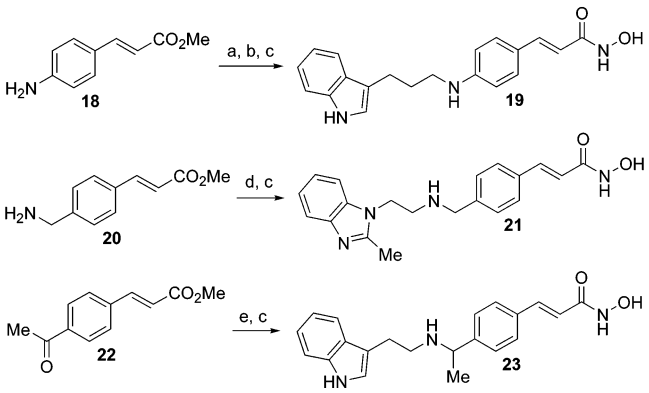
Reductive amination of 4-formylcinnamic acid (**15**) with a primary amine followed by BOC protection of the resulting amino acid afforded acid **16** (Scheme 2). EDCI-mediated coupling of **16** with *O*-tritylhydroxylamine followed by acidic deprotection provided hydroxamic acid **13**. The tricyclic derivative **17** was prepared in a similar fashion.

Methyl 4-aminocinnamate (**18**)[20] was acylated with 3-indolepropionic acid (Scheme 3). The resulting amide was treated with $NaBH_4$/HOAc[21] followed by hydroxylamine to afford **19**. Alkylation of aminoester **20** with 1-(2-bromoethyl)benzimidazole and subsequent treatment with hydroxylamine afforded hydroxamate **21**. Reductive amination of methyl 4-acetylcinnamate (**22**) with tryptamine followed by hydroxylamine treatment afforded **23**.

In Vitro Biology

Compounds were profiled using partially purified HDAC enzyme obtained from H1299 human lung carcinoma cell lysates[22] and in antiproliferative assays using HCT116 human colon and H1299 human lung carcinoma cells.[23] Most of the compounds tested have enzyme IC_{50} values below 100 nM, but no clear structure−activity relationship (SAR) could be proposed. Larger differences are observed in the cellular IC_{50}s, with values ranging from 6 to 600 nM for HCT116

Scheme 3[a]



[a] Reagents: (a) 1*H*-3-indolepropanoic acid, *i*-BuOC(O)Cl, NMM, THF; (b) $NaBH_4$/HOAc, THF; (c) Method C; (d) 1-(2-bromoethyl)-benzimidazole, DIEA, DMSO; (e) tryptamine, Method A.

growth inhibition and from 30 to 2900 nM in H1299 growth inhibition, and some trends regarding structure and activity are observed. Possible reasons for the lack of correlation between enzyme potency and cellular potency and for large differences in cellular potency between homologous compounds may be due to differences in cellular uptake of the compounds or to isoform specificity of the compounds. Profiling of these compounds in individual HDAC isoforms is in progress.

Cellular potency in homologous series tended to be better for compounds with even numbers of atoms between the basic N of the benzylic amine and the terminal moiety. For example, **13g** and **13i**, having two and four methylene groups between the basic N and the indole, respectively, are between 2- and 5-fold more potent in H1299 growth inhibition and 3- and 5-fold more potent in HCT116 growth inhibition than **13q** and **13u**, having three and one methylene groups between the basic N and the indole, respectively (Table 1). More dramatically, there is a loss of 11- and 16-fold in H1299 and HCT116 potency, respectively, when going from two methylenes in **13b** to three in **13r**. However, this not the case for the 2-substituted indoles **13l**, having a 2-methylene spacer, and **13p**, having a 1-methylene spacer, where no change in HCT116 inhibition and a minor 1.7-fold difference in H1299 potency was observed.

For the secondary amines, methyl substitution of the benzylic carbon, **23** (Table 3), or the chain carbon α to the benzylamine *N*, **13h** (Table 1), had no effect on enzyme or cellular activity relative to the unsubstituted analogue **13g**. There is no effect on enzyme or HCT116 potency in either enantiomer of hydroxymethyl compounds **13n** and **13o**, compared to **13g**, and only a minor 2-fold loss of H1299 potency. Substitution of the indole *N* with a methyl group resulted in improved cellular potency, with **13c** being 2- to 3-fold more potent than **13g**. However, the *N*-cyclopropylmethyl indole **13e** was not significantly better than **13g**, being only 1.6-fold more potent in H1299 potency, and equipotent in HCT116 potency. Substitution of the 5-position of the indole had variable effects on cellular potency. The 5-benzyloxy derivative **13a** is 6-fold more potent than **13g** in H1299 growth inhibition, but equal to **13g** in HCT116 growth inhibition. The 5-fluoro derivative **13f** and the 5-methoxy compound **13m** are equipotent to **13g** in both cell lines. The benzimidazole **21** is 7-fold less potent in cell growth inhibition than the indole **13g**, while **13t** is 3-fold less potent and **13s** is 2- to 3-fold less potent than **8**, suggesting that polarity in this region is detrimental to cellular activity.

A series of tertiary amine analogues of the indole-containing inhibitors were prepared, along with a small number of analogues of our lead compound, **8**, and an analogue of **13j** (Table 2). Of the compounds prepared, no clear SAR was deduced for enzyme inhibition or cell growth inhibition.

In the indole series, aliphatic, relatively nonpolar amine substitution generally resulted in compounds having increased cellular potency. Thus, **14a** is 13- and 5-fold more potent than **13g** in H1299 and HCT116 cell growth inhibition, respectively, the *N*-cyclohexyl derivative **14b** is 10- to 12-fold more potent than **13g**, and the *N*-tetrahydropyranyl derivative **14c** is 10- to 15-fold more potent than **13g** in cell growth inhibition (Table 2). The *N*-hydroxethyl analogue **9** is ca. 3-fold more potent in each cell line than **13g**, but the bis-hydroxy derivative **14h** is 16-fold less potent in each cell line than **13g**.

Aryl substitution of the amine N results in reduced cellular potency. The benzylamine **14g** is 5- and 4-fold less potent than **13g** in H1299 and HCT116 growth inhibition, respectively. A similar loss of potency is observed in the 2- and 3-pyridyl derivatives of **8**, **14i**, and **14f**.

Conformationally restricted indole derivatives **14j** and **17** were prepared. The potency of **14j** (Table 3) is essentially equal to the 3-methylene spacer acyclic analogue **13q** (Table 1), while the potency of **17** (Table 3) is similar to that of the 2-substituted indole **13u** (Table 1), and quite different from the 3-substituted indole **13g** (Table 1).

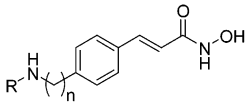
For comparison, we also tested **1**, **3**, **4**, and **6** in our in vitro assays. Enzyme and cell growth inhibition for **4** and **6** are below 100 nM, in the range of our most potent HDAIs. The enzyme IC_{50} of 194 nM for **1** is within the range observed for our HDAIs, but the cell growth inhibition is between 241- to 2.5-fold less potent in H1299 growth inhibition and 321- to 2.6-fold less potent in HCT116 growth inhibition than our compounds.

In our hands, **3** does not inhibit HDAC enzyme activity, while the reported IC_{50} for **3** is 2 μM[24] and 4.8 μM.[25] One possible explanation for this discrepancy is the source of the enzyme. Saito[24] and Suzuki[25] used HDACs isolated from K562 human erythroleukemia cells while we used HDACs isolated from H1299 human lung carcinoma cells. Alternatively, the substrates used, nuclear histones isolated from K562 cells vs the histone H4 N-terminus 24mer peptide, may affect the activity observed with the differing enzyme preparations. Focusing on cellular activity, **3** is between 227- to 2.4-fold less potent in H1299 growth inhibition and 111-fold less potent to equipotent at HCT116 growth inhibition than our HDAIs.

In Vivo Biology

Selected compounds meeting the in vitro requirements discussed above were tested for maximum tolerated dose (MTD), defined as the highest dose that

Table 1. HDAC Enzyme and Cell Growth Inhibition Data for Secondary Amines



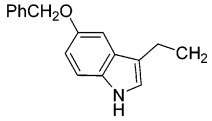
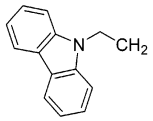
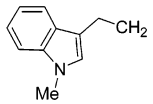
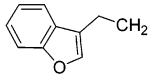
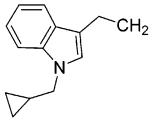
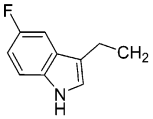
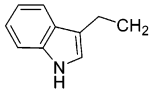
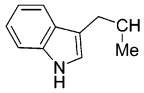
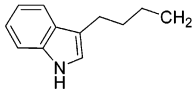
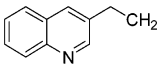
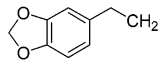
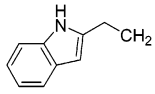
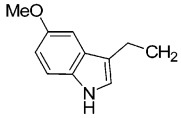
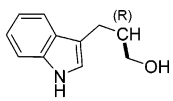
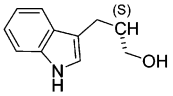
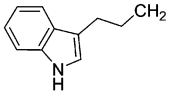
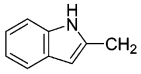
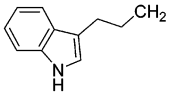
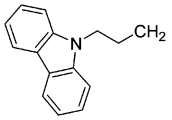
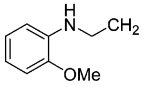
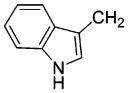
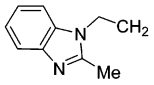
Cpd	R	n	IC_{50} (nM) Enzyme[a]	H1299[b]	HCT116[b]
13a		1	30 ± 2	65	40
13b		1	66 ± 12	100	10
13c		1	23 ± 12	170	10
13d		1	16 ± 4	180	30
13e		1	84 ± 41	250	30
13f		1	14 ± 2	310	30
13g		1	63 ± 10	400	30
13h		1	24 ± 5	410	20
13i		1	37 ± 15	480	30
13j		1	67 ± 6	500	40
13k		1	30 ± 13	500	50
13l		1	46 ± 3	540	40
13m		1	14 ± 1	580	30
13n		1	40 ± 8	750	40

Table 1 (Continued)

Cpd	R	n	IC_{50} (nM) Enzyme[a]	H1299[b]	HCT116[b]
8	$Ph(CH_2)_3$	1	150 ± 94	800	50
13o		1	27 ± 3	810	50
19		0	262 ± 97	820	480
13p		1	51 ± 11	940	50
13q		1	53 ± 52	1000	100
13r		1	79 ± 23	1100	160
13s	Ph-O-CH_2CH_2	1	69 ± 3	1530	160
13t		1	111 ± 103	2160	170
13u		1	59 ± 4	2200	160
21		1	38 ± 2	2750	200

[a] Values are mean ± standard deviation (SD) of a minimum of three separate experiments. [b] Values are the mean of two triplicate experiments.

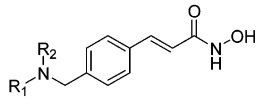
resulted in no deaths when the compound was administered once daily (qd) intravenously (iv) for five consecutive days, up to a maximum of 200 mg/kg/day to a group of four athymic mice. Compounds were administered as the lactate salt using 10% DMSO in 5% dextrose/water (D5W) as the vehicle. MTDs ranged from 10 mg/kg for **13b** to > 200 mg/kg for **9** (Table 4).

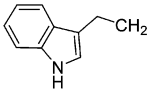
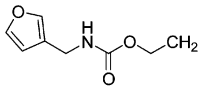
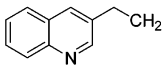
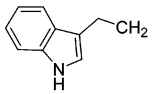
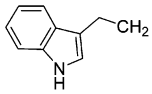
Following MTD determination, the compounds were tested for efficacy in athymic mice bearing HCT116 subcutaneous tumor xenografts at the compound's MTD, or a maximum of 100 mg/kg, iv qd, 5×/week for 10 or 15 total doses. Athymic mice were implanted subcutaneously with a suspension of ≈10^6 HCT116 human colon carcinoma cells. After tumors had reached approximately 100 mm^3, the animals were sorted into groups of eight balanced with respect to the mean and range of tumor volume and treatment started. Results are reported as % T/C, the ratio of the change in tumor volume of treated animals to the change in tumor volume of control animals. Statistical significance was determined using a one-tailed Student's *t*-test and physiologic relevance was defined to be T/C ≤ 50%. Maximal efficacy was 9% T/C, tumor regressions were not observed and body weight change ranged from +3.1 to −9.4%.

Potency in vitro did not correlate with efficacy, illustrated by **13a**, the most potent secondary amine in vitro, which had modest efficacy and **13b**, the next most potent, which had no efficacy at its MTD. Compounds having indole groups had the best efficacy and tolerability. Substituents on the indole had some effect on toxicity, with indole *N*-cyclopropylmethyl derivative **13e** having the lowest MTD and least efficacy. Comparing **13g** and **9**, addition of the hydroxyethyl group improved tolerability while maintaining efficacy. For the quinolyl compounds **13j** and **14e**, a smaller increase in tolerability was observed for the hydroxyethyl derivative, but this was insufficient to achieve an efficacious dose.

On the basis of their MTD and efficacy in the screening study, **9**, **13f**, **13g**, and **13m** were chosen for dose−response studies in the HCT116 xenograft model, with 5-fluorouracil used as a positive control. Compounds were administered iv as the lactate salt in 10% DMSO/D5W 5×/week for 15 total doses. The positive

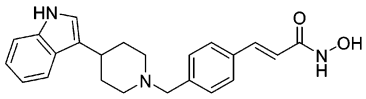
Table 2. HDAC Enzyme and Cell Growth Inhibition Data for Tertiary Amines



Cpd	R_1	R_2	IC_{50} (nM) Enzyme[a]	H1299[b]	HCT116[b]
14a		*i*-propyl	23 ± 6	30	6
14b	"	cyclohexyl	20 ± 12	40	17
14c	"	tetrahydropyran-4-yl	10 ± 1	40	6
9	"	CH_2CH_2OH	32 ± 18	150	10
14d	"		370 ± 95	180	15
14e		CH_2CH_2OH	24 ± 15	530	40
14f	$Ph(CH_2)_3$	3-pyridylmethyl	164 ± 130	1700	420
14g		$PhCH_2$	85 ± 16	2060	120
14h			52 ± 1	2500	160
14i	$Ph(CH_2)_3$	2-pyridylmethyl	278 ± 126	2740	740

[a] Values are mean ± standard deviation (SD) of a minimum of three separate experiments. [b] Values are the mean of two triplicate experiments.

Table 3. HDAC Enzyme and Cell Growth Inhibition Data for Miscellaneous *N*-Hydroxy-3-phenyl-2-propenamides, Trichostatin A and Trapoxin B

Cpd	Structure	IC_{50} (nM) Enzyme[a]	H1299[b]	HCT116[b]
23		23 ± 12	480	15
14j		53 ± 7	900	110
17		118 ± 39	2900	430
SAHA (**1**)		194 ± 68	7240	1930
MS-275 (**3**)		>10000	6820	670
TSA (**4**)		26 ± 10	100	13
TpxB (**6**)		< 5	4	2

[a] Values are mean ± standard deviation (SD) of a minimum of three separate experiments. [b] Values are the mean of two triplicate experiments.

control, 5-fluorouracil, was administered in 1% DMSO/0.9% saline at 100 mg/kg iv 1×/week for three total doses.

Each compound caused statistically significant growth inhibition for all doses tested and a good dose−response was observed (Figures 1−4). For **9**, T/C ranged from 55%

Table 4. Efficacy, MTD and Body Weight Change of Selected HDAIs Administered to Athymic Mice Bearing HCT116 Human Colon Carcinoma Xenografts[a]

compd[b]	dose (mg/kg)	% *T/C*	MTD	Δ% body weight
8	45[c]	86	45	−3.1 ± 0.41
9	100[c]	12[d]	>200	−0.9 ± 0.42
13a	50[e]	45[d]	50	−3.0 ± 0.96
13b	10[c]	85	10	−3.7 ± 0.32
13c	75[c]	15[d]	75	−3.2 ± 0.41
13d	50[f]	49[g]	50	+0.5 ±0.65
13e	20[c]	81	20	−0.9 ± 0.81
13f	100[c]	16[d]	100	−6.7 ± 0.28
13g	100[c]	17[d]	100	−9.4 ± 0.41
13j	30[c]	77	30	−5.4 ± 0.37
13m	100[c]	9[d]	100	−7.4 ± 0.39
14a	25[c]	29[d]	25	−4.1 ± 2.7
14c	40[e]	32[d]	40	+0.1 ± 1.4
14e	50[e]	78	50	+3.1 ± 1.3

[a] Eight mice per group. [b] Administered qd 5×/week. [c] 15 doses. [d] $p < 0.01$. [e] 10 doses. [f] The study was terminated on day 22 postimplant after the sixth dose, because of the six deaths in the treatment group. %*T*/*C* was calculated on day 22 predose. [g] $p < 0.05$.

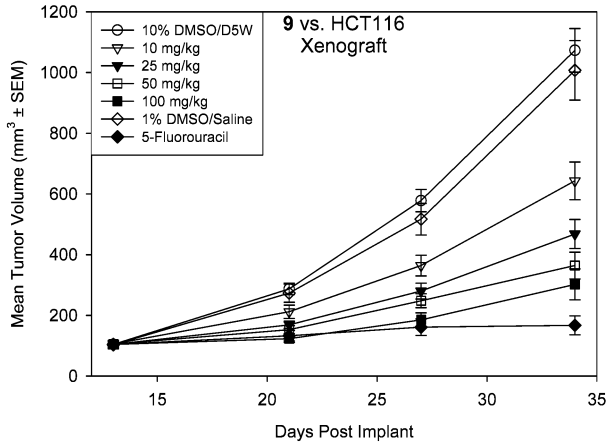


Figure 1. Growth curves of HCT116 human colon tumor xenografts, expressed as mean tumor volume ± standard error of the mean (SEM), after treatment with **9**, 10% DMSO/D5W, 5-fluorouracil, and 1% DMSO/0.9% saline. Treatment started 13 days postimplant when tumors were ≈100 mm^3. **9** was administered as the lactate salt in 10% DMSO/D5W qd iv 5 days/week for 15 total doses. 5-Fluorouracil was administered at 100 mg/kg in 1% DMSO/0.9% saline 1 day/week for three total doses. For all treatment groups, at all measurements, $p < 0.01$ compared to vehicle controls using a one-tailed Student's *t*-test.

to 20%, body weights at the end of the study were equal to or greater than the weights at the start of dosing and no deaths occurred in any group. Efficacy for **13f** ranged from 40% T/C to 8% T/C, no treatment-related deaths occurred and a dose-independent 1.7% to 7.5% body weight loss was observed (Table 5). For **13g**, T/C ranged from 56% to 13%, with no deaths and a dose-independent body weight loss from 7% to 10.2%. Results for **13m** were similar to those of **13g**, with T/C from 64 to 22%, no deaths and a dose dependent 4.6% to 12.0% body weight loss.

Of the four compounds, **9** was of most interest, since, in the HCT116 dose−response study, animals treated with **9** exhibited the least gross toxicity as measured by weight loss, its MTD was >200 mg/kg and it was 2- to 3-fold more potent in cell growth inhibition than the other compounds. Therefore, we tested the efficacy of **9** in a second xenograft model and chose the slower

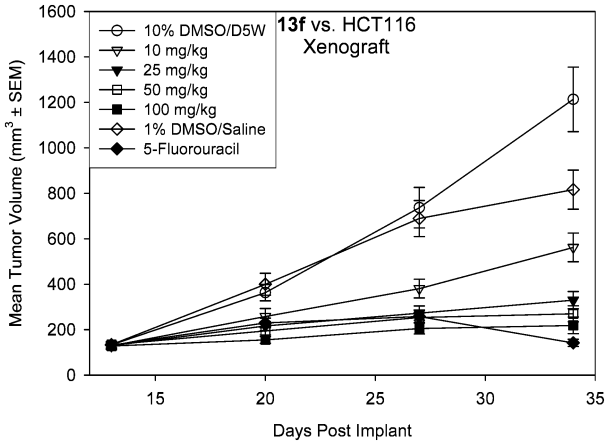


Figure 2. Growth curves of HCT116 human colon tumor xenografts, expressed as mean tumor volume ± standard error of the mean (SEM), after treatment with **13f**, 10% DMSO/D5W, 5-fluorouracil, and 1% DMSO/0.9% saline. Treatment started 13 days postimplant when tumors were ≈100 mm^3. **13f** was administered as the lactate salt in 10% DMSO/D5W qd iv 5 days/week for 15 total doses. 5-Fluorouracil was administered at 100 mg/kg in 1% DMSO/0.9% saline 1 day/week for three total doses. For all treatment groups, at all measurements, $p < 0.01$ compared to vehicle controls using a one-tailed Student's *t*-test.

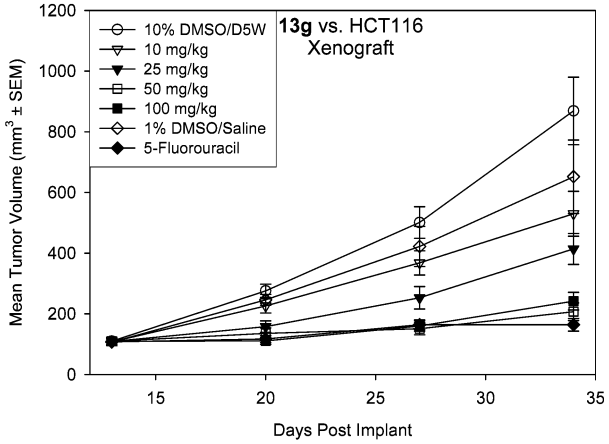


Figure 3. Growth curves of HCT116 human colon tumor xenografts, expressed as mean tumor volume ± standard error of the mean (SEM), after treatment with **13g**, 10% DMSO/D5W, 5-fluorouracil, and 1% DMSO/0.9% saline. Treatment started 13 days postimplant when tumors were ≈100 mm^3. **13g** was administered as the lactate salt in 10% DMSO/D5W qd iv 5 days/week for 15 total doses. 5-Fluorouracil was administered at 100 mg/kg in 1% DMSO/0.9% saline 1 day/week for three total doses. For all treatment groups, except 10 mg/kg **13g**, $p < 0.01$ at all measurements, using a one-tailed Student's *t*-test; $p < 0.05$ at all measurements for **13g** at 10 mg/kg.

growing A549 human lung carcinoma cell line (monolayer growth inhibition $IC_{50} = 30$ nM in this cell line). Athymic mice were implanted subcutaneously with a suspension of ≈10^7 A549 human lung carcinoma cells, tumors were permitted to grow to approximately 100 mm^3, the animals were sorted into groups of eight, balanced with respect to the mean and range of tumor volume, and treatment started. Drug was administered as the lactate salt using the same doses, vehicle, and schedule as in the HCT116 xenograft study. Mitomycin C, the positive control, was administered intraperitoneally (ip) in 10% DMSO/D5W at 2 mg/kg 3×/week for

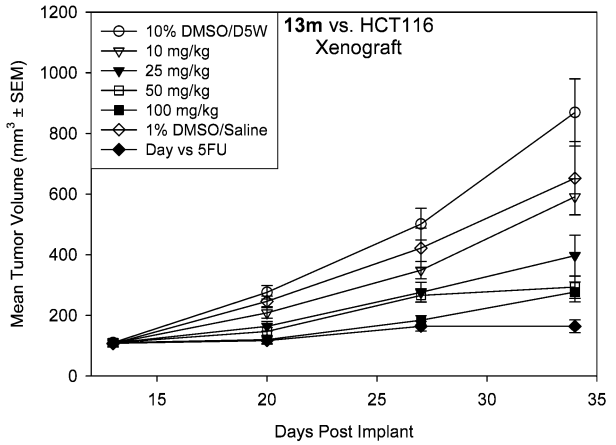


Figure 4. Growth curves of HCT116 human colon tumor xenografts, expressed as mean tumor volume ± standard error of the mean (SEM), after treatment with **13m**, 10% DMSO/D5W, 5-fluorouracil, and 1% DMSO/0.9% saline. Treatment started 13 days postimplant when tumors were ≈100 mm^3. **13m** was administered as the lactate salt in 10% DMSO/D5W qd iv 5 days/week for 15 total doses. 5-Fluorouracil was administered at 100 mg/kg in 1% DMSO/0.9% saline 1 day/week for three total doses. For all treatment groups, except 10 mg/kg **13m**, $p < 0.01$ at all measurements, using a one-tailed Student's *t*-test; $p < 0.05$ at all measurements for **13m** at 10 mg/kg.

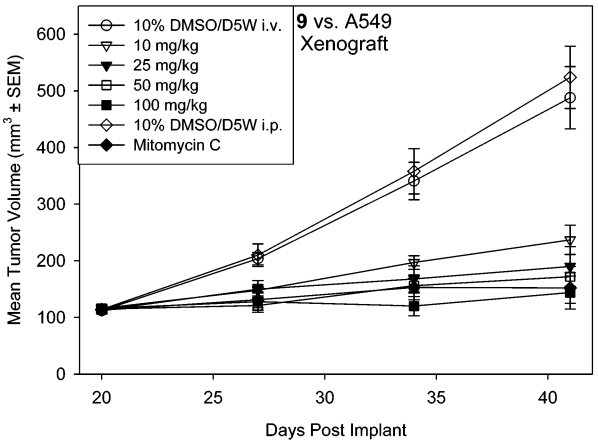


Figure 5. Growth curves of A549 human lung tumor xenografts, expressed as mean tumor volume ± standard error of the mean (SEM), after treatment with **9**, 10% DMSO/D5W (ip), mitomycin C and 10% DMSO/D5W (ip). Treatment started 20 days post implant when tumors were ≈ 100 mm^3. **9** was administered in 10% DMSO/D5W qd iv 5 days/week for 15 total doses. Mitomycin C was administered at 2 mg/kg in 10% DMSO/D5W ip 3×/week for nine total doses. For all treatment groups at all measurements, $p < 0.01$ using a one-tailed Student's *t*-test.

Table 5. Dose−Response of **9**, **13f**, **13g**, and **13m** in the HCT116 Human Colon Carcinoma Xenograft Study[a]

compd[b]	dose (mg/kg)	% *T/C*	body weight change (%)	dead/total
9	10	55[c]	2.7 ± 0.50	0/8
	25	38[c]	0.0 ± 0.49	0/8
	50	27[c]	2.3 ± 0.33	0/8
	100	20[c]	1.4 ± 0.33	0/8
13f	10	40[c]	−6.4 ± 0.39	0/8
	25	19[c]	−6.6 ± 0.81	0/8
	50	13[c]	−1.7 ± 0.40	0/8
	100	8[c]	−7.5 ± 0.34	0/8
13g	10	56[d]	−10.2 ± 0.47	0/8
	25	40[c]	−7.0 ± 0.21	0/8
	50	13[c]	−7.3 ± 0.31	0/8
	100	17[c]	−9.4 ± 0.41	0/8
13m	10	64[d]	−4.6 ± 0.46	0/8
	25	38[c]	−5.5 ± 0.14	0/8
	50	24[c]	−8.1 ± 0.61	0/8
	100	22[c]	−12.0 ± 0.51	0/8

[a] Eight mice per group. [b] Administered as the lactate salt qd 5×/week for 15 total doses. [c] $p < 0.01$ using a one-tailed Student's *t*-test. [d] $p < 0.05$ using a one-tailed Student's *t*-test.

nine total doses. As in the HCT116 study, an excellent dose−response was observed, with statistically significant tumor growth inhibition observed at all measurements for all doses of **9** ($p < 0.01$, Figure 5). The T/C ranged from 32% to 7%, body weight change ranged from −0.9% to +1.3% (Table 6), and no deaths were observed.

Table 6. Dose−Response of **9** in the A549 Human Lung Carcinoma Xenograft Study[a]

dose[b] (mg/kg)	% *T/C*	body weight change (%)	dead/total
10	32[c]	1.3 ± 0.31	0/8
25	20[c]	−0.9 ± 0.32	0/8
50	15[c]	−0.4 ± 0.34	0/8
100	7[c]	0.4 ± 0.29	0/8

[a] Eight mice per group. [b] Administered as the lactate salt qd 5×/week for 15 total doses. [c] $p < 0.01$ using a one-tailed Student's *t*-test.

Summary

Based on the lead compound from a HTS of the Novartis compound archive for novel inhibitors of HDAC, a series of *N*-hydroxy-3-phenyl-2-propenamides were prepared. These compounds were all potent inhibitors of partially purified HDAC isolated from H1299 cellular lysates, with IC_{50}s < 400 nM. Their potency in cell growth inhibition ranged over 2 orders of magnitude in both H1299 and HCT116 cells. Selected compounds were screened for efficacy at their MTD or a maximum of 100 mg/kg, as the lactate salt, in athymic mice using the subcutaneous HCT116 human colon carcinoma xenograft model. Four compounds, **9**, **13f**, **13g**, and **13m**, were selected for dose−response studies in the HCT116 xenograft model, and good responses were observed for each compound. One compound, **9**, was 2- to 3-fold more potent in cell growth inhibition, had a greater MTD and caused the least gross toxicity in the HCT116 xenograft dose−response study. Thus, **9** was selected for testing in the A549 human lung carcinoma xenograft model, where a good dose−response was observed with minimal body weight loss. Compared to **1**, which is currently in clinical trials, **9** is 6-fold more potent at HDAC inhibition, 48-fold more potent at H1299 cell growth inhibition, and 193-fold more potent at HCT116 cell growth inhibition. Compared to **3**, also in clinical trials, **9** is 45-fold more potent at H1299 cell growth inhibition and 67-fold more potent at HCT116 cell growth inhibition. On the basis, in part, of these properties, **9** has entered clinical trials as a novel anticancer agent.

Experimental Section

All chemicals were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed with silica (Merck EM9385, 230−400 mesh). Preparative reverse phase HPLC (RPHPLC) was done using a C-18 column with a gradient of MeCN in H_2O containing 0.1% TFA as the eluent. Analytical RPHPLC was

done using a Rainin Dynamax HPLC equipped with a PDA detector using the following columns and systems: a Waters Symmetry Shield 4.6 × 250 mm C-18 column (5 μM particle size), linear gradient from 10% to 100% MeCN/(H_2O + 0.1% TFA), flow rate = 1.5 mL/min (System 1) or linear gradient from 10% to 100% MeOH/(H_2O + 0.1% TFA), flow rate = 1.5 mL/min (System 2); Waters XTerra 4.6 × 250 mm C-18 column (5 μM particle size), linear gradient from 10% to 70% MeCN/(H_2O + 0.1% TFA), flow rate = 1.5 mL/min (System 3) or linear gradient from 10% to 70% MeOH/(H_2O + 0.1% TFA), flow rate = 1.0 mL/min (System 4). ^{1}H and ^{13}C NMR spectra were recorded at 500 or 300 and at 125 or 75 MHz, respectively. Proton and carbon chemical shifts are expressed in ppm relative to internal tetramethylsilane, and coupling constants (*J*) are expressed in hertz. High-resolution MS was carried out using a Micromass model LCT TDF/MS. Cells were obtained from American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852. Elemental analyses were performed by Robertson Microanalytical Laboratories, Madison, NJ. Lactic acid (1 N) was purchased from Alfa and was used as received.

Method A. Reductive Amination Using $NaBH_3CN$. $NaBH_3CN$ (1.2−2 equiv) was added in portions to a MeOH solution of an aldehyde or ketone and a primary or secondary amine. In some cases, 1 equiv of HOAc was added to the mixture before the addition of $NaBH_3CN$. After the reaction was complete, the volume was reduced by half, this mixture extracted with EtOAc or CH_2Cl_2, and the extracts were washed with sat. $NaHCO_3$ and brine. The organic solution was dried and evaporated and the residue purified by chromatography, trituration, or crystallization.

Method B. Reductive Amination Using $NaBH(OAc)_3$. $NaBH(OAc)_3$ (1−1.5 equiv) was added in portions to a solution of an aldehyde or ketone and a primary or secondary amine in dichlororethane (DCE) or THF. In some cases, 1 equiv of HOAc was added to the mixture before the addition of $NaBH(OAc)_3$. After the reaction was complete, the mixture was diluted with sat. $NaHCO_3$ and extracted with EtOAc or CH_2Cl_2, and the extracts were washed with brine. The organic solution was dried and evaporated and the residue purified by chromatography, trituration or crystallization.

Method C. Hydroxamate Formation Using Aqueous NH_2OH. To a solution of methyl ester in MeOH or EtOH at 0 °C was added $HONH_2$ (50% aq. solution, 10−15 equiv) followed by 1 M NaOH (7−10 equiv). The mixture was stirred at 0 °C for 2−4 h, warmed to room temperature, and stirred until the reaction was complete (TLC). Acidification with 1 M HCl to pH 7−8 (pH paper) resulted in product precipitation. The precipitate was filtered, analyzed by RPHPLC, and purified by preparative RPHPLC if necessary.

Method D. Hydroxamate Formation Using Methanolic NH_2OH. A stock solution of NH_2OH was prepared by adding a solution of KOH (12.9 g (87%), 0.2 mol) in MeOH (100 mL) to a solution of NH_2OH·HCl (13.9 g, 0.2 mol) in MeOH (200 mL). After 15 min, the mixture was filtered, the filter cake washed with a minimum of MeOH, and the filtrate volume reduced to approximately 75 mL. The mixture was filtered and the volume adjusted to 100 mL with MeOH. The resulting 2 M solution was stored under N_2 at −20 °C for up to 2 weeks. **Caution: The 2 M NH_2OH solution decomposes at room temperature. NH_2OH is explosive when dry. Use proper precautions!** The ester (1 equiv) was added to 2 M NH_2OH in MeOH (10 equiv) at 0 °C, followed by a solution of KOH (1.1−1.5 equiv). The ice bath was removed and the mixture monitored by TLC. When the reaction was complete, a small amount of dry ice was added to the mixture and the mixture evaporated to dryness. The residue was purified by RPHPLC to give the product.

Method E. Hydroxamate Formation Using NH_2OH·HCl and NaOMe. To a mixture of 1 equiv of methyl ester and 7−10 equiv of NH_2OH·HCl in MeOH was added 10−12 equiv of ∼3.0 M NaOMe/MeOH (freshly prepared). The reaction was monitored by TLC, and additional NH_2OH·HCl and ∼3.0 M NaOMe/MeOH were added if necessary. The mixture was acidified to pH ∼ 6 (pH paper) with HOAc or 1 M HCl and diluted with EtOAc or CH_2Cl_2. The mixture was washed with sat. $NaHCO_3$ and brine, dried, and evaporated and the residue purified by crystallization, trituration, or preparative RPHPLC.

General Procedure for Neutralization of Trifluoroacetate Salts. Trifluoroacetate salts of compounds obtained after HPLC purification were neutralized by dissolving the salt in CH_2Cl_2 or EtOAc and washing the solution with sat. $NaHCO_3$ followed by brine. The solution was dried and evaporated to afford the free base.

***N*-Hydroxy-3-[4-[[[3-phenylpropyl]amino]methyl]phenyl]-(2*E*)-2-propenamide 8.** Following Method A, 3-phenylpropylamine (6.76 g, 50.0 mmol), **15** (8.81 g, 50.0), and $NaBH_3CN$ were reacted in MeOH containing 1 equiv of HOAc to provide 3-[4-[[[3-phenylpropyl]amino]methyl]phenyl]-(2*E*)-2-propenoic acid which precipitated from the reaction mixture. The precipitate was filtered, washed with MeOH, and suspended in 50% H_2O/dioxane. Et_3N (7.0 mL, 5.08 g, 50.2 mmol) and $(BOC)_2O$ (10.9 g, 49.9 mmol) were added, and the mixture was stirred for 2 h and extracted with EtOAc. The combined extracts were washed with brine, dried, and evaporated to give an oil which was purified by flash chromatography to afford 3-(4-[(*tert*-butoxycarbonyl)(3-phenylpropyl)amino]methyl]phenyl)-(2*E*)-2-propenoic acid (11.6 g, 59%): ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 1.86 (s, 2H), 2.60 (m, 2H), 3.23 (m, 2H), 4.47 (s, 2H), 6.47 (d, 15.8 Hz, 1H), 7.24 (m, 7H), 7.53 (d, 7.9 Hz, 2H), 7.80 (d, 16.2 Hz, 1H); *m*/*z* 396 (MH^+). The acid (11.6 g, 29.3 mmol), *O*-tritylhydroxylamine (9.7 g, 35.3 mmol), EDCI·HCl (6.8 g, 35.3 mmol), HOBT·H_2O (6.0 g, 44.1 mmol) and 1-methylmorpholine (NMM) were dissolved in DMF, and the mixture was stirred. After 16 h, the mixture was diluted with EtOAc and washed with H_2O and the organic solution dried ($MgSO_4$) and evaporated to dryness. Purification of the residue by flash chromatography provided (3-phenylpropyl)-[4-((*E*)-2-trityloxycarbamoylvinyl)benzyl]carbamic acid *tert*-butyl ester (7.8 g, 40%): ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), 1.84 (s, 2H), 2.60 (m, 2H), 3.24 (m, 2H), 4.42 (m, 2H), 6.11 (d, 15.8 Hz, 1H), 7.20 (m, 5H), 7.34 (m, 15H), 7.48 (m, 5H); *m*/*z* 653 (MH^+). The *O*-tritylhydroxamate (7.8 g, 11.9 mmol) was treated with 5% H_2O/TFA for 2 h, the mixture evaporated to dryness and the residue purified by RPHPLC to afford **8** as the TFA salt which was neutralized and treated with 1 equiv of lactic acid to provide **8** as the lactate salt (2.23 g, 46%): retention time System 3 = 16.63 min, retention time System 4 = 29.84 min; ^{1}H NMR (CD_3OD) δ 1.36 (d, 6.8 Hz, 5H, lactate), 2.02 (m, 2H), 2.71 (t, 7.5 Hz, 2H), 3.04 (m, 2H), 4.11 (q, 6.9 Hz, 1.75H, lactate), 4.19 (s, 2H), 6.51 (d, 15.8 Hz, 1H), 7.26 (m, 5H), 7.56 (m, 5H); ^{13}C NMR (CD_3OD) δ 19.72, 27.53, 32.19, 50.47, 67.03, 118.55, 126.07, 128.01, 128.04, 128.28, 130.10, 132.68, 136.10, 139.00, 164.46, 178.63; *m*/*z* 312 (MH^+); HRMS (MH^+) calcd for $C_{19}H_{23}N_2O_2$, 311.1760, found 311.1754; Anal. ($C_{19}H_{22}N_2O_2$·1.75$C_3H_6O_3$·0.65H_2O), C 60.56%, H 6.29%, N 6.19%.

(2*E*)-*N*-Hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1*H*-indol-3-yl)ethyl]amino]methyl]phenyl]-2-propenamide 9. A mixture of (2*E*)-3-[4-[[[2-(1*H*-indol-3-yl)ethyl]amino]methyl]phenyl]-2-propenoic acid methyl ester (20.00 g, 59.81 mmol), 2-bromoethanol (21.5 mL, 37.9 g, 303 mmol), and K_2CO_3 in MeCN was heated at 60 °C for 18 h, cooled, and filtered and the filtrate evaporated. The residue was purified by flash chromatography to afford (2*E*)-3-[4-([(2-hydroxyethyl)-[2-(1*H*-indol-3-yl)ethyl]amino]methyl)phenyl]-2-propenoic acid methyl ester (13.97 g, 62%): *m*/*z* 379 (MH^+). Following Method C, the ester (13.90 g, 36.73 mmol) was converted to the hydroxamate which was treated with 1 equiv of lactic acid to provide **9** as the lactate salt (7.44 g, 53%): ^{1}H NMR (DMSO-d_6) δ 1.24 (d, 6.8 Hz, 3H, lactate), 2.67 (t, 6.4 Hz, 2H), 2.77 (dd, 9.6, 4.71 Hz, 2H), 2.87 (m, 2H), 3.54 (t, 6.4 Hz, 2H), 3.76 (s, 2H), 4.04 (q, 6.9 Hz, 1H, lactate), 6.46 (d, 15.8 Hz, 1H), 6.91 (t, 7.5 Hz, 1H), 7.04 (t, 7.5 Hz, 1H), 7.10 (d, 1.9 Hz, 1H), 7.37 (m, 5H), 7.50 (m, 2H), 10.75 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.88, 22.85, 55.14, 56.15, 58.45, 59.55, 66.19, 111.70, 112.76, 118.44, 118.57, 118.89, 121.16, 122.86, 127.57, 127.67, 129.61, 133.82,

136.57, 138.55, 141.67, 163.20, 176.73; *m/z* 380 (MH^+); Anal. ($C_{22}H_{25}N_3O_3 \cdot C_3H_6O_3 \cdot H_2O$) C, H, N, mp 100−103 °C.

***N*-Hydroxy-3-[4-[[[2-[5-(phenylmethoxy)-1*H*-indol-3-yl]-ethyl]amino]methyl]phenyl]-(2*E*)-2-propenamide 13a.** Following Method B, 5-benzyloxytryptamine (7.2 g, 27.0 mmol), **10** (5.35 g, 28.1 mmol), and $NaBH(OAc)_3$ (1.4 equiv) were reacted in DCE to afford 9.8 g (82%) of 3-[4-[[[2-[5-(phenylmethoxy)-1*H*-indol-3-yl]ethyl]amino]methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester: ^{1}H NMR (DMSO-d_6) δ 2.78 (m, 4H), 3.72 (s, 3H), 3.77 (s, 2H), 5.04 (s, 2H), 6.58 (d, 16.2 Hz, 1H), 6.79 (dd, 8.9, 2.5 Hz, 1H), 7.08 (dd, 6.0, 2.3 Hz, 2H), 7.23 (d, 9.0 Hz, 1H), 7.36 (m, 5H), 7.46 (m, 2H), 7.64 (m, 3H), 10.65 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 25.97, 49.82, 51.81, 52.93, 70.22, 102.19, 111.97, 112.36, 112.79, 117.37, 123.74, 128.04, 128.71, 131.96, 132.67, 138.20, 144.44, 144.89, 152.27, 167.14; *m/z* 441 (MH^+); Anal. ($C_{28}H_{28}N_2O_3$) C, H, N. Following Method C, the ester (1.53 g, 3.47 mmol) was converted to the hydroxamate (0.75 g, 50%) which was treated with 1 equiv of lactic acid to provide **13a** as the lactate salt: ^{1}H NMR (DMSO-d_6) δ 1.35 (d, 6.78 Hz, 3 H, lactate), 3.14 (br s, 2H), 3.31 (m, 4H), 4.10 (q, 6.78 Hz, 1H, lactate), 5.05 (s, 2H) 6.50 (d, 15.8 Hz, 1H), 6.88 (d, 8.7 Hz, 1H), 7.12 (m, 2H), 7.32 (m, 5H), 7.46 (m, 5H), 7.59 (m 2H); ^{13}C NMR (DMSO-d_6) δ 21.66 (lactate), 23.81, 51.20, 69.05 (lactate), 72.56, 103.34, 110.39, 113.74, 114.16, 120.31, 125.54, 128.85, 129.91, 129.89, 131.94, 134.20, 134.47, 137.83, 139.70, 140.86, 154.76, 166.30, 180.87 (lactate); *m/z* 442 (MH^+); Anal. ($C_{27}H_{27}N_3O_3 \cdot C_3H_6O_3$) C, H, N.

3-[4-[[[2-(9*H*-Carbazol-9-yl)ethyl]amino]methyl]phenyl]-*N*-hydroxy-(2*E*)-2-propenamide 13b. Following Method B, 9*H*-carbazole-9-ethanamine hydrobromide[26] (919 mg, 3.16 mmol), 1.4 equiv of Et_3N, **10** (500 mg, 2.63 mmol), and $NaBH(OAc)_3$ (1.4 equiv) were reacted in DCE to afford 555 mg (47%) of 3-[4-[[[2-(9*H*-carbazol-9-yl)amino]methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester: ^{1}H NMR (DMSO-d_6) δ 2.90 (t, 6.6 Hz, 2H), 3.72 (s, 5H), 4.48 (t, 6.6 Hz, 2H), 6.59 (d, 15.8 Hz, 1H), 7.19 (t, 7.0 Hz, 2H), 7.29 (d, 8.3 Hz, 2H), 7.44 (t, 7.7 Hz, 2H), 7.62 (m, 5H), 8.14 (d 7.9, 2H); ^{13}C NMR (DMSO-d_6) δ 43.00, 47.54, 51.38, 52.73, 109.72, 117.47, 119.03, 120.59, 122.42, 125.97, 128.60, 128.71, 132.77, 140.55, 143.85, 144.84, 176.14; *m/z* 385 (MH^+). Following Method E, the ester (405 mg, 1.05 mmol) was converted to the hydroxamate which was purified by RPHPLC to afford **13b** as the TFA salt which was neutralized and treated with 1 equiv of lactic acid to provide **13b** as the lactate salt (190 mg, 40%): retention time System 3 = 16.82 min, retention time System 4 = 28.11 min; ^{1}H NMR (DMSO-d_6) δ 1.26 (d, 6.8 Hz, 3H lactate), 3.26 (br s, 2H), 4.04 (q, 6.8 Hz, 1H lactate), 4.12 (br s, 1H), 4.67 (m, 1H), 6.52 (d, 15.8 Hz, 1H), 7.23 (t, 7.35 Hz, 2H), 7.48 (m 5H), 7.62 (m 4H), 8.16 (d, 7.9 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 20.91 (lactate), 45.65, 51.02, 66.21 (lactate), 109.49, 119.56, 120.78, 122.72, 126.24, 128.02, 130.31, 135.30, 138.06, 140.27, 162.94, 176.86 (lactate); *m/z* 386 (MH^+); HRMS (MH^+) calcd for $C_{24}H_{24}N_3O_2$, 386.1892, found 386.1869; mp 169.5−185.4 °C; Anal. ($C_{24}H_{23}N_3O_2 \cdot C_3H_6O_3 \cdot 0.7TFA \cdot 0.7H_2O$) C, H, N.

***N*-Hydroxy-3-[4-[[[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenamide 13c.** Following Method A, 1-methyl-1*H*-indole-3-ethanamine[27] (320 mg, 1.84 mmol), **10** (350 mg, 1.84 mmol), HOAc (1 equiv), and $NaBH_3CN$ (1.5 equiv) were reacted in MeOH to afford 3-[4-[[[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester (159 mg, 25%): ^{1}H NMR ($CDCl_3$) δ 2.97 (t, 3.4 Hz, 4H), 3.74 (s, 3H), 3.80 (s, 3H), 3.82 (s, 2H), 6.41 (d, 15.8 Hz, 1H), 6.87 (s, 1H), 7.09 (t, 6.8 Hz, 1H), 7.22 (m, 1H), 7.29 (m, 3H), 7.45 (m 2H), 7.59 (d, 7.9 Hz, 1H), 7.67 (d, 15.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.04, 33.01, 49.92, 52.08, 53.89, 109.61, 112.68, 117.71, 119.13, 119.39, 122.02, 127.21, 128.54, 129.00, 133.48, 137.51, 145.07, 167.93; *m/z* 349 (MH^+). Following Method C, the ester (132 mg, 0.379 mmol) was converted to the hydroxamate which was purified by RPHPLC. The resulting TFA salt was neutralized to give **13c** (28 mg, 21%): retention time System 3 = 13.06 min, retention time System 4 = 22.56 min; ^{1}H NMR (DMSO-d_6) δ 2.80 (m, 4H), 3.37 (br s, 3H), 3.72 (s, 3H), 3.76 (s, 2H), 6.45 (d, 15.8 Hz, 1H), 6.99 (t, 7.2 Hz, 1H), 7.13 (m, 2H), 7.45 (m, 7H); ^{13}C NMR (DMSO-d_6) δ 25.7, 32.58, 49.95, 52.95, 109.88, 112.33, 118.58, 118.91, 121.34, 127.38, 127.69, 127.96, 128.80, 133.52, 136.97, 138.52, 143.09, 163.17; *m/z* 350 (MH^+); HRMS (MH^+) calcd for $C_{21}H_{24}N_3O_2$, 350.1869, found 350.1876; mp 115.2−118.1 °C; Anal. ($C_{21}H_{23}N_3O_2 \cdot 0.1H_2O \cdot 0.3TFA$) C, H, N.

3-[4-[[[2-(3-Benzofuranyl)ethyl]amino]methyl]phenyl]-*N*-hydroxy-(2*E*)-2-propenamide 13d. Following Method B, 3-benzofuranethanamine[28] (1.10 g, 6.84 mmol), **10** (1.30 g, 6.84 mmol), and $NaBH(OAc)_3$ (1.1 equiv) were reacted in THF to afford 900 mg (39%) of 3-[4-[[[2-(3-benzofuranyl)ethyl]amino]-methyl]phenyl]-(2*E*)-2-propenic acid methyl ester: ^{1}H NMR ($CDCl_3$) δ 2.93 (m, 4H), 3.80, (s, 3H), 3.83 (s, 2H), 6.41(d, 16.2 Hz, 1H), 7.27 (m, 4H), 7.45 (m, 4H), 7.54 (d, 7.5 Hz, 1H), 7.68 (d, 16.2 Hz, 1H); *m/z* 336 (MH^+). Following Method E, the ester (840 mg, 2.51 mmol) was converted to the hydroxamate which was purified by RPHPLC to afford **13d** as the TFA salt, which was neutralized and treated with 1 equiv of lactic acid to provide **13d** as the lactate salt (588 mg, 55%): ^{1}H NMR (CD_3OD) δ 1.33 (d, 6.8 Hz, 3H, lactate), 3.13 (m, 2H), 3.36 (m, 2H), 4.07 (q, 6.8 Hz, 1H, lactate), 4.24 (s, 2H), 6.51 (d, 15.8 Hz, 1H), 7.29 (m, 2H), 7.54 (m, 7H), 7.68 (s, 1H); ^{13}C NMR (CD_3OD) δ 21.81 (lactate), 22.23, 52.43, 69.36 (lactate), 112.92, 117.15, 120.75, 124.26, 126.24, 128.94, 129.83, 131.89, 135.13, 137.73, 140.91, 144.30, 157.38, 166.33, 181.53 (lactate); *m/z* 337 (MH^+); Anal. ($C_{20}H_{20}N_2O_3 \cdot C_3H_6O_3 \cdot 0.5H_2O$) C, H, N.

3-[4-[[[2-(1-Cyclopropylmethyl-1*H*-indol-3-yl)ethyl]amino]methyl]phenyl]-*N*-hydroxy-(2*E*)-2-propenamide 13e. Following Method B, 1-(cyclopropylmethyl)-1*H*-indole-3-ethanamine[29] (954 mg, 4.45 mmol), **10** (799 mg, 4.20 mmol), and $NaBH(OAc)_3$ (1.5 equiv) were reacted in DCE to afford 911 mg (47%) of 3-[4-[[[2-(1-cyclopropylmethyl-1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester: ^{1}H NMR ($CDCl_3$) δ 0.34 (q, 5.2 Hz, 2H), 0.60 (m, 2H), 0.88 (m, 1H), 2.99 (m, 4H), 3.48 (s, 1H), 3.80 (s, 3H), 3.82 (s, 2H), 3.92 (d, 6.8 Hz, 2H), 6.41 (d, 15.8 Hz, 1H), 7.07 (m 2H), 7.27 (m, 4H), 7.45 (d, 8.3 Hz, 2H), 7.59 (d, 7.2 Hz, 1H), 7.67 (d, 15.8 Hz, 1H), *m/z* 389 (MH^+). Following Method D, the ester (875 mg, 2.25 mmol) was converted to the hydroxamate which was purified by RPHPLC to afford **13e** as the TFA salt which was neutralized and treated with 1 equiv of lactic acid to provide **13e** as the lactate salt (525 mg, 48%): retention time System 3 = 16.63 min, retention time System 4 = 29.84 min; ^{1}H NMR (CD_3OD) δ 0.38 (t, 5.3 Hz, 2H), 0.57 (m, 2H), 1.25 (m, 1H), 1.35 (d, 7.2 Hz, 3.6H, lactate), 2.14 (m, 2H), 3.35 (m, 2H), 4.00 (d, 6.8 Hz, 2H), 4.12 (q, 6.9 Hz, 1.2H, lactate), 4.24 (s, 2H), 6.52 (d, 15.5 Hz, 1H), 7.05 (t, 7.0 Hz, 1H), 7.18 (t, 7.7 Hz, 1H), 7.22 (s, 1H), 7.41 (d, 8.3 Hz, 1H), 7.56 (m, 6H); ^{13}C NMR (CD_3OD) δ 4.80, 12.82, 21.52 (lactate), 23.69, 51.73, 52.22, 68.81 (lactate), 110.08, 11.28, 119.67, 120.36, 120.56, 123.27, 127.81, 129.86, 131.95, 140.85, 166.45; *m/z* 390 (MH^+); HRMS (MH^+) calcd for $C_{24}H_{28}N_3O_2$, 390.2182, found 390.2205; Anal. ($C_{24}H_{27}N_3O_2 \cdot 1.2C_3H_6O_3 \cdot 0.15H_2O \cdot 0.45TFA$) C, H, N.

3-[4-[[[2-(5-Fluoro-1*H*-indol-3-yl)ethyl]amino]methyl]-phenyl]-*N*-hydroxy-(2*E*)-2-propenamide 13f. Following Method B, 5-fluorotryptamine (8.30 g, 46.6 mmol), **10** (8.85 g, 46.6 mmol), and $NaBH(OAc)_3$ (1.1 equiv) were reacted in THF to afford 10.9 g (67%) of 3-[4-[[[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester: *m/z* 353 (MH^+). Following Method D, the ester was converted to the hydroxamate which was purified by RPHPLC. Neutralization of the resulting TFA salt afforded **13f** (7.90 g, 72%): ^{1}H NMR (DMSO-d_6) δ 2.96 (m, 4H), 3.18 (s, 2H), 6.50 (d, 15.8 Hz, 1H), 6.91 (dt, 9.2, 2.6 Hz, 1H), 7.31 (m, 3H), 7.47 (m, 3H), 7.57 (m, 2H), 11.02 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.85, 48.51, 51.43, 103.16, 103.47, 109.33, 109.68, 111.62, 112.72, 119.59, 125.58, 127.68, 127.91, 129.86, 133.31, 134.69, 138.29, 155.54, 158.61, 163.11; *m/z* 354 (MH^+); Anal. ($C_{20}H_{20}FN_3O_2 \cdot H_2O$) C, H, N.

***N*-Hydroxy-3-[4-[[[2-(1*H*-indol-3-yl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenamide 13g.** Following Method B, tryptamine (1.78 g, 11.1 mmol), **10** (2.00 g, 10.5 mmol), $NaBH(OAc)_3$ (1.5 equiv), and HOAc (1 equiv) were reacted in DCE to give 3-[4-[[[2-(1*H*-indol-3-yl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester (2.20 g, 63%): ^{1}H NMR

($CDCl_3$) δ 2.91 (m, 4H), 3.72 (s, 3H), 3.74 (s, 2H), 6.33 (d, 16.2 Hz, 1H), 6.92 (d, 2.6 Hz, 1H) 7.03 (dt, 7.5, 1.1 Hz, 1H) 7.11 (dt, 7.6, 1.3 Hz, 1H) 7.19 (m, 2H) 7.26 (d, 7.9 Hz, 1H) 7.36 (m, 2H) 7.53 (d, 7.9 Hz, 1H) 7.59 (d, 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.23, 49.80, 52.17, 53.97, 77.09, 77.51, 77.94, 111.63, 114.27, 117.69, 119.34, 119.72, 122.48, 127.86, 128.60, 128.99, 133.44, 136.85, 143.50, 145.18, 168.04; *m/z* 335 (MH^+). Following Method C, the ester (7.50 g, 22.5 mmol) was converted to the hydroxamate (7.23 g, 96%), which was treated with 1 M lactic acid to provide **13g** as the lactate salt: ^{1}H NMR (DMSO-d_6) δ 1.21 (d, 6.8 Hz, 3H, lactate), 2.95 (s, 4H), 3.90 (q, 6.9 Hz, 1H, lactate), 3.95 (s, 2H), 6.48 (d, 15.8 Hz, 1H), 6.97 (t, 7.4 Hz, 1H), 7.06 (t, 7.0 Hz, 1H), 7.34 (d, 7.9 Hz, 1H), 7.48 (m, 6H), 10.86 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.23 (lactate), 24.35, 48.84, 51.67, 66.61 (lactate), 111.72, 111.78, 118.61, 119.39, 121.33, 123.18, 127.43, 127.81, 129.59, 134.37, 136.63, 138.29, 163.03, 177.46 (lactate); *m/z* 336 (MH^+); Anal. ($C_{20}H_{21}N_3O_2 \cdot C_3H_6O_3 \cdot 0.5H_2O$) C, H, N.

***N*-Hydroxy-3-[4-[[[2-(1*H*-indol-3-yl)-1-methylethyl]amino]methyl]phenyl]-(2*E*)-2-propenamide 13h.** Following Method A, α-methyltryptamine (770 mg, 4.42 mmol), **10** (700 mg, 3.68 mmol), and $NaBH_3CN$ were reacted in MeOH to afford 3-[4-[[[2-(1*H*-indol-3-yl)-1-methylethyl]amino]methyl]-phenyl]-(2*E*)-2-propenoic acid methyl ester (620 mg, 48%): ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 6.0 Hz, 3H), 2.64 (m, 1H), 2.98 (m, 2H), 3.72 (s, 3H), 3.89 (m 2H), 6.62 (d, 15.8 Hz, 1H) 6.93 (t, 7.5 Hz, 1H) 7.05 (t, 7.5 Hz, 1H) 7.13 (d, 1.9 Hz, 1H) 7.39 (m, 4H) 7.65 (m, 3H), 10.82 (s, 1H); *m/z* 349 (MH^+). Following Method C, the ester (620 mg, 1.78 mmol) was converted to the hydroxamate and purified by RPHPLC which, after neutralization, afforded **13h** (200 mg, 32%): ^{1}H NMR (DMSO-d_6) δ 1.00 (d, 6.0 Hz, 3H), 2.62 (m, 1H), 2.92 (m, 2H), 3.86 (m, 2H), 6.43 (d, 15.8 Hz, 1H), 6.93 (td, 7.4, 0.9 Hz, 1H), 7.04 (td, 7.4, 0.9 Hz, 1H), 7.13 (d, 1.9 Hz, 1H), 7.41 (m, 7H), 10.82 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.29, 32.55, 50.31, 53.15, 111.71, 112.01, 118.51, 118.80, 121.15, 123.69, 127.67, 127.89, 128.86, 133.63, 136.60, 138.54, 163.17; *m/z* 350 (MH^+); Anal. ($C_{21}H_{23}N_3O_2 \cdot 1.5H_2O$) C, H, N.

***N*-Hydroxy-3-[4-[[[4-(1*H*-indol-3-yl)butyl]amino]methyl]phenyl]-(2*E*)-2-propenamide 13i.** Following Method A, 1*H*-indole-3-butanamine[30] (1.91 g, 10.1 mmol), **10** (1.59 g, 8.37 mmol), and $NaBH_3CN$ were reacted in MeOH to afford 3-[4-[[[4-(1*H*-indol-3-yl)butyl]amino]methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester (2.61 g, 86%) which was used without further purification: *m/z* 363 (MH^+). Following Method C, the ester (898 mg, 2.48 mmol) was converted to the hydroxamate and purified by RPHPLC which, after neutralization, afforded **13i** (160 mg, 18%): ^{1}H NMR (DMSO-d_6) δ 1.51 (m, 3H), 1.67 (m, 2H), 2.54 (m, 2H), 2.66 (t, 7.4 Hz, 2H), 3.70 (s, 2H), 6.43 (d, 15.8 Hz, 1H), 6.94 (t, 7.4 Hz, 1H), 7.05 (m, 2H), 7.42 (m, 7H), 10.72 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 24.52, 27.65, 29.18, 48.43, 52.51, 111.19, 114.50, 117.93, 118.24, 120.65, 122.01, 127.12, 127.22, 128.38, 133.07, 136.19, 138.11, 162.69; *m/z* 364 (MH^+); Anal. ($C_{22}H_{25}N_3O_2 \cdot 0.25H_2O$) C, H, N.

***N*-Hydroxy-3-[4-[[[2-(3-quinolinyl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenamide 13j.** To a solution of 3-quinolineacetonitrile (2.30 g, 13.7 mmol) in 5% TFA/MeOH was added 10% Pd/C 1.0 g, 0.94 mmol), and the mixture was shaken under H_2 (Paar apparatus). After 3 h the mixture was filtered through Celite, and the filtrate was evaporated to give 3-quinolinethaneamine which was used immediately in the next reaction. Following Method B, 3-quinolinethaneamine, **10** (2.49 g, 13.1 mmol), and $NaBH(OAc)_3$ (1 equiv) were reacted in DCE containing 1 equiv of HOAc to afford 3-[4-[[[2-(3-quinolinyl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester (2.96 g, 78%): retention time System 1 = 5.35 min, retention time System 2 = 7.62 min; ^{1}H NMR ($CDCl_3$) δ 3.01 (s, 4H), 3.81 (s, 3H), 3.84 (s, 2H), 6.42 (d, 16.2 Hz, 1H), 7.29 (s, 1H), 7.32 (s, 1H), 7.45 (s, 1H), 7.48 (s, 1H), 7.53 (t, 6.8 Hz, 1H), 7.67 (m, 2H), 7.76 (d, 8.3 Hz, 1H), 7.95 (d, 2.3 Hz, 1H), 8.09 (d, 8.3 Hz, 1H), 8.81 (d, 2.3 Hz, 1H); *m/z* 347 (MH^+). Following Method D, the ester (2.89 g, 8.35 mmol) was converted to the hydroxamate which was purified by RPHPLC to afford **13j** (2.75 g, 57%): ^{1}H NMR (CD_3OD) δ 3.39 (m, 7.91 Hz, 2H), 3.53 (m, 2H), 4.31 (s, 2H), 6.51 (d, 15.82 Hz, 1H), 7.58 (m, 5H), 7.83 (t, 7.72 Hz, 1H), 7.99 (m, 1H), 8.14 (dd, 7.72, 5.46 Hz, 2H), 8.73 (s, 1H), 9.03 (d, 1.88 Hz, 1H); *m/z* 348 (MH^+); HRMS (MH^+) calcd for $C_{21}H_{22}N_3O_2$, 348.1712, found 348.1696; Anal. ($C_{21}H_{21}N_3O_2 \cdot 1.5\ C_3H_6O_3 \cdot H_2O$), Calcd: C 61.19%, H 6.44%, N 8.39%; Found: C 60.71%, H 6.00%, N 8.30%.

3-[4-[[[2-(1,3-Benzodioxol-5-yl)ethyl]amino]methyl]-phenyl]-*N*-hydroxy-(2*E*)-2-propenamide 13k. Following Method B, 1,3-benzodioxole-5-ethanamine (806 mg, 4.89 mmol), **10** (774 mg, 4.07 mmol), and $NaBH(OAc)_3$ (1.4 equiv) were reacted to afford 3-[4-[[[2-(1,3-benzodioxol-5-yl)ethyl]amino]-methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester (650 mg, 47%) which was used without further purification: *m/z* 340 (MH^+). Following Method C, the ester (640 mg, 1.89 mmol) was converted to **13k** (391 mg, 61%): ^{1}H NMR (DMSO-d_6) δ 2.64 (m, 4H), 3.70 (s, 2H), 5.93 (s, 2H), 6.42 (d, 15.9 Hz, 1H), 6.63 (dd, 7.9, 1.53 Hz, 1H), 6.78 (m, 2H), 7.32 (d, 8.2 Hz, 2H), 7.42 (d, 15.6 Hz, 1H), 7.47 (d, 7.9 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 35.46, 50.57, 52.48, 100.56, 108.00, 109.01, 118.35, 121.34, 127.30, 128.41, 133.14, 134.25, 138.17, 142.57, 145.26, 147.09, 162.78; *m/z* 341 (MH^+); Anal. ($C_{19}H_{20}N_2O_4$) C, H, N.

***N*-Hydroxy-3-[4-[[[2-(1*H*-indol-2-yl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenamide 13l.** Following Method B, 1*H*-indole-2-ethanamine[31] (100 mg, 0.63 mmol), **10** (118 mg, 0.62 mmol), and $NaBH(OAc)_3$ (1.1 equiv) were reacted in THF to afford 3-[4-[[[2-(1*H*-indol-2-yl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester (131 mg, 27%): ^{1}H NMR (DMSO-d_6) δ 2.90 (s, 4H), 3.72 (s, 3H), 3.84 (s, 2H), 6.15 (s, 1H), 6.62 (d, 16.2 Hz, 1H), 6.95 (m, 2H), 7.27 (d, 7.9 Hz, 1H), 7.40 (dd, 7.7, 3.6 Hz, 3H), 7.67 (m, 3H), 10.91 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.01, 27.84, 47.91, 51.37, 52.00, 98.60, 110.57, 117.24, 118.51, 119.02, 120.01, 128.23, 128.64, 132.62, 135.87, 137.84, 144.30, 166.65, 171.94; *m/z* 335 (MH^+). Following Method C, the ester was converted to **13l** (65 mg, 53%): ^{1}H NMR (DMSO-d_6) δ 2.83 (m, 4H), 3.75 (s, 2H), 6.13 (s, 1H), 6.43 (d, 15.8 Hz, 1H), 6.94 (m, 2H), 7.37 (m, 8H), 10.89 (s, 1H); ^{13}C NMR (DMSO-d_6) 28.87, 48.77, 52.88, 98.92, 110.99, 118.75, 118.91, 119.41, 120.36, 127.70, 128.69, 128.82, 133.55, 136.30, 138.56, 138.86, 142.93, 163.17; *m/z* 336 (MH^+); Anal. ($C_{20}H_{21}N_3O_2 \cdot 0.5H_2O$) C, H, N.

***N*-Hydroxy-3-[4-[[[2-[5-methoxy-1*H*-indol-3-yl]ethyl]-amino]methyl]phenyl]-(2*E*)-2-propenamide 13m.** Following Method B, 5-methoxytryptamine (15.0 g, 78.8 mmol), **10** (19.0 g, 78.8 mmol), and $NaBH(OAc)_3$ (1.4 equiv) were reacted in THF (250 mL) containing $CaSO_4$ (10.9 g) to afford 14.5 g (46%) of 3-[4-[[[2-[5-methoxy-1*H*-indol-3-yl]ethyl]amino]methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester hydrochloride: *m/z* 365 (MH^+). Following Method C, the hydrochloride (14.4 g, 35.9 mmol) was converted to the hydroxamate (13.0 g, 98%) which was treated with 1 equiv of lactic acid to provide **13m** as the lactate salt: ^{1}H NMR (DMSO-d_6) δ 1.21 (d, 6.8 Hz, 3H, lactate), 3.74 (s, 3H), 3.89 (q, 7.0 Hz, 1H, lactate), 3.98 (s, 2H), 6.49 (d, 15.8 Hz, 1H), 6.71 (dd, 8.8, 2.4 Hz, 1H), 6.98 (d, 2.3 Hz, 1H), 7.12 (d, 1.9 Hz, 1H), 7.23 (d, 9.0 Hz, 1H), 7.45 (m, 3H), 7.55 (m, 2H), 10.71 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 18.86, 21.66 (lactate), 46.00, 48.91, 53.24, 64.28 (lactate), 97.96, 108.81, 109.02, 109.97, 117.01, 121.42, 125.22, 125.34, 127.23, 129.29, 132.01, 135.75, 136.41, 150.88, 160.53, 175.31 (lactate); *m/z* 366 (MH^+); Anal. ($C_{21}H_{23}N_3O_3 \cdot C_3H_6O_3$) C, H, N.

***N*-Hydroxy-3-[4-[[[(1*R*)-2-hydroxy-1-(1*H*-indol-3-ylmethyl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenamide 13n.** Following Method A, D-tryptophanol (1.0 g, 5.3 mmol), **10** (1.0 g, 5.3 mmol), and $NaBH_3CN$ (10 equiv) were reacted in MeOH to afford 3-[4-[[[(1R)-2-hydroxy-1-(1*H*-indol-3-ylmethyl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester (1.4 g, 75%): ^{1}H NMR (DMSO-d_6) δ 2.79 (m, 3H), 3.33 (m, 2H), 3.72 (s, 3H), 3.85 (s, 2H), 6.60 (d, 15.8 Hz, 1H), 6.92 (t, 7.0 Hz, 1H), 7.04 (t, 7.0 Hz, 1H), 7.12 (d, 2.3 Hz, 1H), 7.33 (t, 7.9 Hz, 3H), 7.43 (d, 7.9 Hz, 1H), 7.64 (m, 3H), 10.80 (s, 1H); *m/z* 365 (MH^+). Following Method C, the ester (1.0 g, 2.7 mmol) was converted to **13n** (250 mg, 25%): ^{1}H NMR (CD_3OD) δ 2.88 (m, 2H), 3.00 (m, 1H), 3.57 (m, 2H), 3.85 (s, 2H), 6.42 (d, 15.8 Hz, 1H), 6.93 (t, 7.5 Hz, 1H), 7.08 (m, 2H), 7.17 (d, 7.9 Hz, 2H), 7.33 (d, 8.3 Hz, 1H), 7.41 (m, Hz, 3H), 7.52 (d,

15.8 Hz, 1H); ^{13}C NMR (CD_3OD) δ 28.50, 52.20, 60.19, 65.04, 112.72, 112.76, 118.66, 119.86, 120.10, 122.86, 124.69, 129.17, 129.28, 130.35, 135.54, 141.74, 142.82, 166.77; *m/z* 366 (MH^+); Anal. ($C_{21}H_{23}N_3O_3 \cdot H_2O$) C, H, N.

***N*-Hydroxy-3-[4-[[[(1*S*)-2-hydroxy-1-(1*H*-indol-3-ylmethyl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenamide 13o.** Following Method A, L-tryptophanol (700 mg, 3.7 mmol), **10** (800 mg, 4.2 mmol), and $NaBHCN_3$ (8 equiv) were reacted in MeOH to afford 3-[4-[[[(1S)-2-hydroxy-1-(1*H*-indol-3-ylmethyl)-ethyl]amino]methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester (710 mg, 58%): ^{1}H NMR (DMSO-d_6) δ 2.78 (m, 3H), 3.35 (m, 2H), 3.72 (s, 3H), 3.86 (s, 2H), 6.61 (d, 16.2 Hz, 1H), 6.92 (t, 6.8 Hz, 1H), 7.04 (t, 7.0 Hz, 1H), 7.33 (m, 3H), 7.44 (d, 7.9 Hz, 1H), 7.64 (m, 3H), 10.80 (s, 1H), *m/z* 365 (MH^+). Following Method C, the ester (710 mg, 1.9 mmol) was converted to **13o** (220 mg, 32%): ^{1}H NMR (DMSO-d_6) δ 2.77 (m, 3H), 3.34 (m, 2H), 3.83 (s, 2H), 6.42 (d, 15.8 Hz, 1H), 6.92 (t, 7.4 Hz, 1H), 7.04 (t, 7.5 Hz, 1H), 7.11 (s, 1H), 7.32 (d, 7.5 Hz, 3H), 7.43 (m, 4H), 10.78 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.22, 50.74, 59.54, 63.33, 111.66, 111.94, 118.47, 118.73, 118.80, 121.13, 123.74, 127.65, 127.93, 128.75, 133.50, 136.57, 138.57, 163.18; *m/z* 365 (MH^+); Anal. ($C_{21}H_{23}N_3O_3 \cdot 0.1H_2O$) C, H, N.

(2*E*)-*N*-Hydroxy-3-[4-[[(1*H*-indol-2-ylmethyl)amino]-methyl]phenyl]-2-propenamide 13p. Following Method A, 1*H*-indole-2-methanamine[32] (600 mg, 3.75 mmol), **10** (700 mg, 3.75 mmol), and $NaBH_3CN$ (2 equiv) were reacted in MeOH to afford (2*E*)-3-[4-[[(1*H*-indol-2-ylmethyl)amino]methyl]phenyl]-2-propenoic acid methyl ester (500 mg, 42%): ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 3.83 (s, 2H), 3.98 (s, 2H), 6.35 (s, 1H), 6.44 (d, 16.20 Hz, 1H), 7.13 (m, 2H), 7.35 (m, 3H), 7.53 (m, 3H), 7.69 (d, 15.83 Hz, 1H), 8.52 (s, 1H). Following Method C, the ester was converted to the hydroxamate and purified by RPHPLC which, after neutralization, afforded **13p** (350 mg, 64%): ^{1}H NMR (DMSO-d_6) δ 3.74 (s, 2H), 3.82 (s, 2H), 6.28 (s, 1H), 6.93 (m, 1H), 7.01 (t, 6.8 Hz, 1H), 7.32 (d, 7.9 Hz, 1H), 7.46 (m, 6H), 9.03 (s, 1H), 10.72 (br. s, 1H), 10.94 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 45.86, 52.11, 99.71, 111.31, 118.83, 118.99, 119.80, 120.74, 127.73, 128.39, 128.93, 133.67, 136.52, 138.57, 138.93, 142.49, 163.18; *m/z* 322 (MH^+); Anal. ($C_{19}H_{19}N_3O_2 \cdot H_2O$) C, H, N.

(2*E*)-*N*-Hydroxy-3-[4-[[[3-(1*H*-indol-3-yl)propyl]amino]-methyl]phenyl]-2-propenamide 13q. Following Method B, 1*H*-indole-3-propanamine (1.23 g, 7.1 mmol), **10** (1.48 g, 7.8 mmol), and $NaBH(OAc)_3$ (1.4 equiv) were reacted in DCE to afford (2*E*)-3-[4-[[[3-(1*H*-indol-3-yl)propyl]amino]methyl]phenyl]-2-propenoic acid methyl ester (0.99 g, 40%): ^{1}H NMR (CD_3-OD) δ 1.92 (m, 2H), 2.62 (t, 7.4 Hz, 2H), 2.77 (t, 7.4 Hz, 2H), 3.68 (s, 2H), 3.77 (s, 3H), 6.49 (d, 15.8 Hz, 1H), 7.02 (m, 3H), 7.28 (m, 3H), 7.51 (m, 3H), 7.66 (d, 16.2 Hz, 1 H); *m/z* 349 (MH^+). Following Method D, the ester (0.95 g, 2.73 mmol) was converted to the hydroxamate **13q** which was purified by RPHPLC and converted to the lactate salt (405 mg, 34%): ^{1}H NMR (CD_3OD) δ 1.32 (d, 6.8 Hz, 3.9H, lactate), 2.11 (m, 2 H), 2.86 (t, 7.0 Hz, 2H), 3.03 (m, 2H), 4.02 (q, 6.8 Hz, 1.3H, lactate), 4.13 (s, 2H), 6.49 (d, 15.8 Hz, 1H), 7.05 (m, 3H), 7.33 (d, 7.9 Hz, 1H), 7.42 (d, 7.9 Hz, 2H), 7.53 (m, 3H); ^{13}C NMR (CD_3OD) δ 21.64, 23.24, 27.98, 51.74, 69.36, 112.42, 114.28, 119.26, 119.74, 119.81, 122.50, 123.36, 128.49, 129.39, 131.55, 134.33, 137.28, 138.33, 140.53, 165.95, 181.94; *m/z* 350 (MH^+); Anal. ($C_{21}H_{23}N_3O_2 \cdot 1.3C_3H_6O_3 \cdot H_2O$), C, H, N.

(2*E*)-3-[4-[(3-Carbazol-9-ylpropylamino)methyl]-phenyl]-*N*-hydroxy-2-propenamide 13r. Following the procedure described for the preparation of **8**, 9*H*-carbazole-9-propanamine (2.80 g, 12.5 mmol), and **15** (2.42 g, 13.8 mmol) was converted to **13r**: ^{1}H NMR (CD_3OD) δ 1.39 (d, 7.2 Hz, 4.8H, lactate), 2.31 (m, 2H), 3.01 (m, 2H), 4.12 (s, 2H), 4.21 (q, 6.9 Hz, 1.6H, lactate), 4.55 (t, 6.4 Hz, 2H), 6.50 (d, 16.2 Hz, 1H), 7.25 (t, 7.4 Hz, 2H), 7.33 (d, 7.9 Hz, 2H), 7.52 (m, 7H), 8.11 (d, 7.5 Hz, 2H); ^{13}C NMR (CD_3OD) δ 21.27 (lactate), 27.34, 40.92, 46.57, 52.06, 68.30 (lactate), 110.15, 120.32, 120.78, 121.75, 124.73, 127.43, 129.79, 131.85, 133.89, 137.86, 140.79, 141.96, 166.26, 179.33 (lactate); *m/z* 400 (MH^+); Anal. ($C_{25}H_{25}N_3O_2 \cdot$ 1.6 $C_3H_6O_3 \cdot H_2O$), Calcd: C 61.75%, H 6.71%, N 7.25%; Found: C 61.44%, H 6.21%, N 7.41%.

(2*E*)-*N*-Hydroxy-3-[4-[(2-phenoxyethylamino)methyl]-phenyl]-2-propenamide 13s. Following the procedure described for the preparation of **8**, 2-phenoxyethylamine (4.12 g, 30.0 mmol) and **10** (5.82 g, 33.0 mmol) was converted to **13s**: ^{1}H NMR (CD_3OD) δ 1.37 (d, 6.8 Hz, 3.75H), 3.5 (m, 2H), 4.13 (q, 6.9 Hz, 1.25H), 4.31 (m, 2H), 4.34 (s, 2H), 6.55 (d, 15.8 Hz, 1H), 7.01 (m, 3H), 7.32 (m, 2H), 7.62 (m, 5H); ^{13}C NMR (CD_3OD) δ 20.43 (lactate), 46.85, 51.28, 63.70 (lactate), 114.88, 119.07, 121.97, 128.67, 129.90, 130.90, 133.53, 136.63, 139.71, 158.62, 165.13, 179.59 (lactate); *m/z* 313 (MH^+); Anal. ($C_{18}H_{20}N_2O_3 \cdot$1.25 $C_3H_6O_3 \cdot$1.75H_2O), Calcd: C 57.23%, H 6.84%, N 6.14%; Found: C 57.20%, H 5.99%, N 5.93%.

(2*E*)-*N*-Hydroxy-3-[4-[[[2-[(2-methoxyphenyl)amino]-ethyl]amino]methyl]phenyl]-2-propenamide 13t. Following Method B, *N*-(2-methoxyphenyl)-1,2-ethanediamine[33] (770 mg, 4.6 mmol), **10** (1.05 g, 5.5 mmol), and $NaBH(OAc)_3$ (1.5 equiv) were reacted in MeOH to afford (2*E*)-3-(4-[[2-(2-methoxyphenylamino)ethylamino]methyl]phenyl)-2-propenoic acid methyl ester (2.2 g) which was used directly in the next step. Following Method C, the crude ester obtained in the previous reaction (412 mg) was converted to **13t** and purified by RPHPLC (214 mg): ^{1}H NMR (DMSO-d_6) δ 3.12 (t, 6.03 Hz, 2H), 3.41 (t, 6.22 Hz, 2H), 3.77 (s, 3H), 4.22 (s, 2H), 6.58 (m, 3H), 6.80 (m, 2H), 7.50 (m, 3H), 7.63 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 45.86, 50.12, 55.60, 109.55, 110.35, 116.66, 120.45, 121.39, 128.04, 130.85, 133.39, 135.85, 137.56, 147.01, 158.90; *m/z* 342 ((MH^+); Anal. ($C_{19}H_{23}N_3O_3 \cdot$1.6TFA$\cdot$1.3H_2O) C, H.

(2*E*)-*N*-Hydroxy-3-[4-[[(1*H*-indol-3-ylmethyl)amino]-methyl]phenyl]-2-propenamide 13u. Following Method A, 1*H*-indole-3-methanamine (2.60 g, 17.6 mmol), **10** (3.30 g, 17.6 mmol), HOAc (1 equiv), and $NaBHCN_3$ (1.5 equiv) were reacted in MeOH to afford (2*E*)-3-(4-[[(1*H*-indol-3-ylmethyl)amino]-methyl]phenyl)propenoic acid methyl ester (950 mg, 17%); ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 3.87 (s, 2H), 4.00 (s, 2H), 6.41 (d, 15.8 Hz, 1H), 7.13 (m, 2H), 7.21 (m, 1H), 7.36 (m, 3H), 7.48 (m, 2H), 7.63 (m, 2H), 8.19 (s, 1H), *m/z* 321 (MH^+). Following Method C, the ester (925 mg, 2.89 mmol) was converted to the hydroxamate and purified by RPHPLC which, after neutralization, afforded **13u** (231 mg, 25%): ^{1}H NMR (DMSO-d_6) δ 3.75 (s, 2H), 3.83 (s, 2H), 6.44 (d, 15.8 Hz, 3H), 6.97 (t, 7.00 Hz, 1H), 7.06 (m, 1H), 7.23 (d, 2.64 Hz, 1H), 7.46 (m, 7H), 10.86 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 43.67, 51.96, 111.23, 113.42, 118.15, 118.21, 118.72, 120.83, 123.34, 126.88, 127.23, 128.37, 133.01, 136.26, 138.15, 142.69, 162.72; *m/z* 322 (MH^+); Anal. ($C_{19}H_{19}N_3O_2 \cdot H_2O$) C, H, N.

(2*E*)-*N*-Hydroxy-3-[4-[[[2-(1*H*-indol-3-yl)ethyl](1-methylethyl)amino]methyl]phenyl]-2-propenamide 14a. A solution of (2*E*)-3-[4-[[[2-(1*H*-indol-3-yl)ethyl]amino]methyl]-phenyl]-2-propenoic acid methyl ester (500 mg, 1.50 mmol), 2-iodopropane (1.01 g, 5.9 mmol), and DIEA (1.50 mL, 1.11 g, 8.61 mmol) in MeCN was heated to 50 °C. After 48 h, the solution was evaporated and the residue purified by flash chromatography to afford (2*E*)-3-[4-([[2-(1*H*-indol-3-yl)ethyl]-(1-methylethyl)amino]methyl)phenyl]-2-propenoic acid methyl ester (455 mg, 80%): ^{1}H NMR (DMSO-d_6) δ 1.01 (d, 6.4 Hz, 6H), 2.66 (m, 2H), 2.75 (m, 2H), 3.66 (s, 2H), 3.73 (s, 3H), 6.61 (d, 15.8 Hz, 1H), 6.89 (t, 7.9 Hz, 1H), 7.02 (t, 8.1 Hz, 1H), 7.07 (d, 2.3 Hz, 1H), 7.30 (d, 8.7 Hz, 2H), 7.42 (d, 8.3 Hz, 2H), 7.66 (m, 3.96 Hz, 3H), 10.74 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 17.96, 20.69, 50.57, 51.36, 53.26, 59.68, 111.21, 117.95, 118.04, 120.65, 122.37, 127.09, 128.14, 128.64, 136.07, 144.48, 166.70; *m/z* 377 (MH^+). Following Method C, the ester (420 mg, 1.12 mmol) was converted to the hydroxamate which was purified by RPHPLC to afford **14a** (325 mg, 59%): retention time System 3 = 8.07 min, retention time System 4 = 25.12 min; ^{1}H NMR (DMSO-d_6) δ 1.36 (d, 6.8 Hz, 3H), 1.39 (d, 6.8 Hz, 3H), 3.09 (m, 3H), 3.35 (m, 1H), 3.71 (m, 1H), 4.45 (m, 2H), 6.57 (d, 15.8 Hz, 1H), 6.95 (t, 7.4 Hz, 1H), 7.08 (t, 7.2 Hz, 1H), 7.21 (d, 1.9 Hz, 1H), 7.33 (m, 2H), 7.62 (m, 5H), 9.50 (s, 1H), 11.00 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 16.58, 21.06, 49.90, 53.39, 55.15, 109.31, 112.00, 118.28, 118.88, 120.82, 121.60, 126.92, 128.27, 132.00, 132.15, 136.31, 136.58, 158.78, 159.24, 162.86; *m/z* 377 (MH^+); HRMS (MH^+) calcd for $C_{23}H_{28}N_3O_2$, 378.2182,

found 378.2207; Anal. ($C_{23}H_{27}N_3O_2$·2 TFA·0.25H_2O) Calcd: C 53.16%, H 4.87%, N 6.89%; Found: C 52.76%, H 4.88%, N 7.32%.

(2*E*)-3-[4-[[Cyclohexyl[2-(1*H*-indol-3-yl)ethyl]amino]-methyl]phenyl]-*N*-hydroxy-2-propenamide 14b. Following Method A, a mixture of **13g** (500 mg, 1.49 mmol), cyclohexanone (0.32 mL, 303 mg, 3.09 mmol), and $NaBH_3CN$ (4.3 equiv) in MeOH was heated at reflux. After 4 h, the reaction was cooled, diluted with EtOAc, and washed with sat. $NaHCO_3$ and brine. The organic solution was dried and evaporated, and the residue was purified by RPHPLC to afford **14b** (484 mg, 50%): ^{1}H NMR (DMSO-d_6) δ 1.23 (m, 3H), 1.62 (m, 3H), 1.83 (m, 2H), 2.10 (m, 2H), 3.14 (m, 5H), 4.38 (m, 1H), 4.56 (m, 1H), 6.55 (d, 15.8 Hz, 2H), 6.94 (t, 7.0 Hz, 2H), 7.07 (t, 7.0 Hz, 1H), 7.28 (m, 3H), 7.50 (d, 15.8 Hz, 1H), 7.67 (m, 4H), 9.36 (s, 1H), 10.97 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.70, 24.53, 25.86, 26.10, 49.97, 62.41, 108.79, 111.53, 117.82, 118.41, 120.35, 121.16, 123.35, 126.40, 127.85, 131.58, 131.72, 135.88, 136.09; *m*/*z* 418 (MH^+); Anal. ($C_{26}H_{31}N_3O_2$·1.75TFA) C, H, N.

(2*E*)-*N*-Hydroxy-3-[4-[[[2-(1*H*-indol-3-yl)ethyl](tetrahydro-2*H*-pyran-4-yl)amino]methyl]phenyl]-2-propenamide 14c. Following Method B, (2*E*)-3-[4-[[[2-(1*H*-indol-3-yl)ethyl]amino]methyl]phenyl]-2-propenoic acid methyl ester (1.02 g, 3.06 mmol), tetrahydro-4*H*-pyran-4-one (0.32 mL, 346 mg, 3.45 mmol) and $NaBH(OAc)_3$ (1.5 equiv) were reacted to afford (*E*)-3-(4-[[[2-(1*H*-indol-3-yl)ethyl](tetrahydro-2*H*-pyran-4-yl)amino]methyl]phenyl)-2-propenoic acid methyl ester (612 mg, 48%): ^{1}H NMR ($CDCl_3$) δ 1.68 (m, 4H), 2.82 (m, 4H), 3.34 (m, 2H), 3.76 (s, 2H), 3.81 (s, 3H), 4.02 (m, 2H), 6.43 (d, 15.83 Hz, 1H), 6.92 (d, 2.26 Hz, 1H), 7.05 (t, 6.97 Hz, 1H), 7.16 (t, 6.97 Hz, 1H), 7.39 (m, 6H), 7.70 (d, 15.83 Hz, 1H), 7.96 (s, 1H). Following Method C, the ester (319 mg, 0.763 mmol) was converted to the hydroxamate **14c** which was purified by RPHPLC and converted to the lactate salt (375 mg, 47%): ^{1}H NMR (CD_3OD) δ 1.35 (d, 6.8 Hz, 3.9H, lactate), 1.84 (m, 4H), 2.96 (m, 2H), 3.12 (m, 2H), 3.38 (m, 3H), 4.08 (m, 5H), 6.51 (d, 15.8 Hz, 1H), 6.92 (t, 7.5 Hz, 1H), 7.06 (m, 2H), 7.24 (d, 7.9 Hz, 1H), 7.31 (d, 8.3 Hz, 1H), 7.55 (m, 5H); ^{13}C NMR (CD_3OD) δ 21.17, 24.01, 29.78, 51.82, 55.36, 60.24, 68.16, 68.48, 112.22, 112.44, 119.07, 119.78, 122.52, 123.69, 128.38, 129.25, 131.56, 136.42, 138.19, 141.02, 166.22, 180.06; *m*/*z* 420 (MH^+); Anal. ($C_{25}H_{29}N_3O_3$·1.3$C_3H_6O_3$) C, H, N.

(2-Furanylmethyl)carbamic Acid 2-[[[4-[(1*E*)-3-(Hydroxyamino)-3-oxo-1-propenyl]phenyl]methyl][2-(1*H*-indol-3-yl)ethyl]amino]ethyl Ester 14d. To a stirred slurry of THF (50 mL), ice (50 g), K_2CO_3 (4.25 g, 30.7 mmol), and 2-furanmethanamine (2.8 g, 25.7 mmol) was added 2-bromoethyl chloroformate (3.60 mL, 5.29 g, 28.2 mmol). After 4 h, the mixture was acidified (1 M HCl), NaCl was added, and the solution was extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered, and evaporated to afford furan-2-ylmethylcarbamic acid 2-bromoethyl ester which was used without further purification. A solution of the bromide (469 mg, 1.80 mmol), (2*E*)-3-[4-[[[2-(1*H*-indol-3-yl)ethyl]amino]-methyl]phenyl]-2-propenoic acid methyl ester (517 mg, 1.55 mmol), and DIEA (0.33 mL, 1.89 mmol) in DMSO (5 mL) was heated to 60 °C. After 6 h, the reaction was diluted with H_2O and extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. The resulting residue was purified by column chromatography to afford (2*E*)-3-[4-([[2-(furan-2-ylmethylcarbamoyloxy)ethyl]-[2-(1*H*-indol-3-yl)ethyl]amino]methyl)phenyl]-2-propenic acid methyl ester (428 mg, 55%): ^{1}H NMR (CD_3OD) δ 2.81 (m, 4H), 2.91 (m, 2H), 3.74 (s, 2H), 3.77 (d, 4.5 Hz, 3H), 4.18 (t, 5.7 Hz, 2H), 4.24 (s, 2H), 6.20 (d, 3.0 Hz, 1H), 6.30 (m, 1H), 6.48 (d, 16.2 Hz, 1H), 6.90 (t, 7.0 Hz, 1H), 6.98 (s, 1H), 7.04 (t, 7.0 Hz, 1H), 7.29 (d, 8.3 Hz, 1H), 7.36 (m, 4H), 7.48 (m, 2H), 7.67 (d, 15.8 Hz, 1H); ^{13}C NMR (CD_3OD) δ 24.33, 38.70, 52.21, 53.96, 56.32, 59.78, 64.11, 107.79, 111.36, 112.19, 114.25, 118.07, 119.39, 119.44, 122.19, 123.23, 128.86, 129.22, 130.69, 134.46, 138.15, 143.24, 143.94, 146.31, 153.83, 169.30; *m*/*z* 502 (MH^+). Following Method D, the ester (420 mg, 0.837 mmol) was converted to the hydroxamate which was purified by RPHPLC to give **14d** (230 mg, 55%): ^{1}H NMR (CD_3OD) δ 3.23 (m, 2H), 3.51 (m, 2H), 3.62 (s, 2H), 4.24 (s, 2H), 4.46 (br s, 4H), 6.23 (d, 3.0 Hz, 1H), 6.32 (m, 1H), 6.53 (d, 15.8 Hz, 1H), 6.94 (t, 7.4 Hz, 1H), 7.10 (m, 2H), 7.35 (m, 3H), 7.47 (m, 2H), 7.57 (m, 3H); ^{13}C NMR (CD_3OD) δ 21.85, 39.18, 54.91, 55.37, 59.33, 61.00, 108.64, 109.65, 111.82, 113.07, 119.26, 120.65, 123.32, 124.96, 128.25, 130.04, 132.29, 133.06, 138.48, 138.76, 140.70, 143.85, 153.55, 158.68; *m*/*z* 503 (MH^+); Anal. ($C_{28}H_{30}N_4O_5$·1.5TFA) C, H, F, N.

(2*E*)-*N*-Hydroxy-3-[4-[[(2-hydroxyethyl)[2-(3-quinolinyl)-ethyl]amino]methyl]phenyl]-2-propenamide 14e. A solution of 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (1.67 mL, 10.6 mmol), 3-[4-[[[2-(3-quinolinyl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenoic acid methyl ester (2.63 g, 7.60 mmol), and DIEA (2.00 mL, 11.4 mmol) in DMSO (25 mL) was heated to 60 °C for 17 h. The cooled mixture was diluted with H_2O and extracted with EtOAc. The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography to afford (2*E*)-3-[4-([(2-quinolin-3-ylethyl)-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]amino]methyl)-phenyl]-2-propenic acid methyl ester (1.36 g, 38%): *m*/*z* 475 (MH^+). Following Method C, the ester (1.31 g, 2.76 mmol) was converted to the hydroxamate which was purified by RPHPLC to afford **14e** as the TFA salt which was neutralized and treated with 1 M lactic acid to provide **14e** as the lactate salt (1.01 g, 76%): ^{1}H NMR (DMSO-d_6) δ 1.23 (d, 6.8 Hz, 3H, lactate), 2.62 (t, 6.2 Hz, 2H), 2.81 (t, 6.8 Hz, 2H), 2.95 (t, 6.8 Hz, 2H), 3.48 (t, 6.2 Hz, 2H), 3.71 (s, 2H), 3.99 (t, 6.8 Hz, 1H), 6.44 (d, 15.8 Hz, 1H), 7.25 (d, 7.9 Hz, 2H), 7.41 (m, 3H), 7.57 (t, 7.4 Hz, 1H), 7.70 (t, 7.4 Hz, 1H), 7.87 (d, 7.9 Hz, 1H), 8.00 (d, 8.3 Hz, 1H), 8.09 (s, 1H), 8.77 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.00, 30.37, 48.97, 55.60, 55.95, 58.39, 59.61, 66.37, 118.90, 126.81, 127.57, 127.90, 128.09, 128.99, 129.39, 133.70, 134.02, 134.74, 138.45, 141.71, 146.63, 152.58, 163.16, 177.01; *m*/*z* 392 (MH^+); Anal. ($C_{23}H_{25}N_3O_3$·$C_3H_6O_3$·2.5H_2O) C, H, N, mp 68.2−74.8 °C.

(2*E*)-*N*-Hydroxy-3-(4-[[(3-phenylpropyl)pyridin-3-yl-methylamino]methyl]phenyl)-2-propenamide 14f. Following Method A, 2-pyridinecarboxaldehyde (1.18 g, 11.0 mmol), (2*E*)-3-[4-[(3-phenyl-propylamino)-methyl]-phenyl]-2-propenoic acid methyl ester (3.09 g, 10.0 mmol), HOAc (1 equiv), and $NaBH_3CN$ (1.1 equiv) were reacted in MeOH to afford (2*E*)-3-(4-[[(3-phenylpropyl)pyridin-3-ylmethylamino]-methyl]phenyl)-2-propenoic acid methyl ester (3.76 g, 94%): ^{1}H NMR ($CDCl_3$) δ 1.87 (m, 2H), 2.52 (t, 7.2 Hz, 2H), 2.60 (m, 2H), 3.60 (s, 2H), 3.61 (s, 2H), 3.84 (s, 3H), 6.46 (d, 15.8 Hz, 1H), 7.20 (m, 6H), 7.39 (d, 8.3 Hz, 2H), 7.50 (d, 8.3 Hz, 2H), 7.72 (m, 2H), 8.52 (dd, 4.7, 1.7 Hz, 1H), 8.59 (d, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.24, 33.85, 52.16, 56.12, 58.49, 77.69, 117.83, 123.78, 126.21, 128.55, 128.74, 129.72, 133.72, 136.91, 142.47, 145.05, 148.98, 150.69, 167.95; *m*/*z* 401; (MH^+). Following Method D, the ester (3.70 g, 9.20 mmol) was converted to the hydroxamate which was purified by RPHPLC to afford **14f** as the TFA salt which was neutralized and treated with 1 M lactic acid to provide **14f** as the lactate salt (3.34 g, 73%): ^{1}H NMR (CD_3OD) δ 1.40 (d, 6.8 Hz, 4.5H, lactate), 1.88 (m, 2H), 2.57 (q, 6.9 Hz, 4H), 3.74 (m, 4H), 4.23 (q, 6.9 Hz, 1.5H, lactate), 6.49 (d, 15.8 Hz, 1H), 7.14 (m, 5H), 7.41 (m, 3H), 7.56 (m, 3H), 7.84 (d, 7.8 Hz, 1H), 8.46 (d, 4.1 Hz, 1H), 8.52 (s, 1H); ^{13}C NMR (CD_3OD) δ 21.21, 29.79, 34.63, 54.31, 57.00, 59.58, 68.16, 118.83, 125.65, 127.25, 129.34, 129.77, 131.30, 135.94, 136.67, 139.76, 141.69, 141.76, 143.46, 149.27, 151.03, 166.75, 179.04; *m*/*z* 402 (MH^+); Anal. ($C_{25}H_{27}N_3O_2$·1.5$C_3H_6O_3$·0.2H_2O) C, H, N.

(2*E*)-*N*-Hydroxy-3-[4-[[[2-(1H-indol-3-yl)ethyl](phenylmethyl)amino]methyl]phenyl]-2-propenamide 14g. Following Method B, *N*-benzyltryptamine (2.05 g, 8.20 mmol), **10** (1.49 g, 7.83 mmol), HOAc (1 equiv), and $NaBH(OAc)_3$ were reacted in DCE to afford (2*E*)-3-[4-([benzyl-[2-(1*H*-indol-3-yl)-ethyl]amino]methyl)phenyl]-2-propenoic acid methyl ester (1.48 g, 45%): ^{1}H NMR ($CDCl_3$) δ 2.80 (m, 2H), 2.97 (m, 2H), 3.67 (s, 2H), 3.69 (s, 2H), 3.80 (s, 3H), 6.41 (d, 16.2 Hz, 1H), 6.89 (d, 2.3 Hz, 1H), 7.01 (t, 7.3 Hz, 1H), 7.15 (t, 7.5 Hz, 1H), 7.32 (m, 11H), 7.68 (d, 16.2 Hz, 1H), 7.90 (s, 1H); *m*/*z* 425 (MH^+). Following Method D, the ester (1.45 g, 3.42 mmol) was

converted to the hydroxamate which was purified by RPHPLC to afford **14g** as the TFA salt which was neutralized and treated with 1 M lactic acid to provide **14g** as the lactate salt (649 mg, 40%): ^{1}H NMR (CD_3OD) δ 1.37 (d, 6.8 Hz, 4.8H, lactate), 3.19 (m, 2H), 3.31 (m, 2H), 4.21 (q, 6.8 Hz, 1.6H, lactate), 4.44 (m, 4H), 6.54 (d, 15.8 Hz, 1H), 6.90 (t, 7.5 Hz, 1H), 7.11 (m, 3H), 7.33 (d, 7.9 Hz, 1H), 7.50 (s, 8H), 7.64 (m, 2H); ^{13}C NMR (CD_3OD) δ 20.79, 21.59, 53.50, 58.45, 58.97, 67.68, 109.91, 112.63, 118.83, 120.11, 120.25, 122.84, 124.14, 129.63, 130.57, 132.20, 132.68, 137.93, 138.31, 140.41, 178.47; *m*/*z* 426 (MH^+); Anal. ($C_{25}H_{27}N_3O_2 \cdot 1.6\ C_3H_6O_3 \cdot 4H_2O$); Calcd: C 59.52%, H 7.01%, N 6.55%; Found C 59.91%, H 5.48%, N 6.22%.

(2*E*)-*N*-Hydroxy-3-[4-[[[2-hydroxy-1-(hydroxymethyl)-ethyl][2-(1*H*-indol-3-yl)ethyl]amino]methyl]phenyl]-2-propenamide 14h. Following Method A, 1,3-dihydroxyacetone dimer (4.2 g, 23 mmol), (2*E*)-3-[4-[[[2-(1*H*-indol-3-yl)ethyl]amino]methyl]phenyl]-2-propenoic acid methyl ester (1.5 g, 4.5 mmol), and $NaBH_3CN$ (3 equiv) were reacted in MeOH to afford (2*E*)-3-[4-([(2-hydroxy-1-hydroxymethylethyl)-[2-(1*H*-indol-3-yl)ethyl]amino]methyl)phenyl]-2-propenoic acid methyl ester (920 mg, 50%): *m*/*z* 409 (MH^+). Following Method C, the ester (900 mg, 2.21 mmol) was converted to the hydroxamate which was purified by RPHPLC and neutralized to afford **14h** (370 mg, 41%): retention time System 3 = 10.22 min, retention time System 4 = 22.27 min; ^{1}H NMR (CD_3OD) δ 2.87 (m, 2H), 2.99 (m, 2H), 3.62 (m, 4H), 3.90 (s, 2H), 6.43 (d, 15.8 Hz, 1H), 6.96 (m, 3H), 7.30 (m, 4H), 7.42 (m, 2H), 7.53 (d, 16.2 Hz, 1H); ^{13}C NMR (CD_3OD) δ 21.83, 31.37, 52.72, 56.01, 60.93, 64.23, 112.72, 114.11, 118.32, 119.76, 119.96, 122.73, 123.94, 126.60, 129.05, 129.19, 131.00, 135.50, 138.61, 141.75, 166.74; *m*/*z* 410 (MH^+); HRMS (MH^+) calcd for $C_{23}H_{28}N_3O_4$, 410.2080, found 410.2107; Anal. ($C_{23}H_{27}N_3O_4 \cdot 0.65CH_2Cl_2 \cdot 0.25$THF) C, H, N.

(2*E*)-*N*-Hydroxy-3-(4-[[(3-phenylpropyl)-pyridin-2-yl-methylamino]methyl]phenyl)-2-propenamide 14i. Following Method B, 2-pyridinecarboxaldehyde (1.33 g, 12.4 mmol), (2*E*)-3-[4-[(3-phenylpropylamino)methyl]phenyl]-2-propenoic acid methyl ester (3.51 g, 11.3 mmol), and $NaBH(OAc)_3$ (1.5 equiv) were reacted in DCE to afford (2*E*)-3-(4-[[(3-phenylpropyl)pyridin-2-ylmethylamino]methyl]phenyl)-2-propenoic acid methyl ester (2.72 g, 60%): ^{1}H NMR ($CDCl_3$) δ 1.85 (m, 2H), 2.57 (m, 4H), 3.65 (s, 2H), 3.78 (s, 2H), 3.80 (s, 3H), 6.42 (d, 16.2 Hz, 1H), 7.17 (m, 6H), 7.42 (m, 4H), 7.55 (d, 7.9 Hz, 1H), 7.68 (m, 2H), 8.54 (d, 4.1 Hz, 1 H), *m*/*z* 401 (MH^+). Following Method E, the ester (1.29 g, 3.22 mmol) was converted to the hydroxamate which was purified by RPHPLC to afford **14i** as the TFA salt which was neutralized and treated with 1 equiv of lactic acid to provide **14i** as the lactate salt (1.5 g, 83%): retention time System 3 = 4.72 min, retention time System 4 = 25.32 min; ^{1}H NMR (DMSO-d_6) δ 1.24 (d, 7.2 Hz, 4.5H, lactate), 1.77 (m, 2H), 2.44 (t, 6.8 Hz, 2H), 2.52 (m, 2H), 3.61 (s, 2H), 3.68 (s, 2H), 4.05 (q, 7.0 Hz, 1.5H lactate), 6.45 (d, 15.8 Hz, 1H), 7.17 (m, 6H), 7.48 (m, 6H), 7.77 (m, 1H), 8.48 (d, 4.1 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 20.42 (lactate), 28.37, 32.69, 52.68, 57.59, 59.49, 65.70 (lactate), 118.46, 121.99, 122.53, 125.48, 127.32, 128.07, 128.15, 129.10, 133.40, 136.43, 140.90, 141.91, 148.59, 159.45, 176.28 (lactate); *m*/*z* 402 (MH^+); HRMS (MH^+) calcd for $C_{25}H_{27}N_3O_2$, 402.2182, found 402.2199; Anal. ($C_{25}H_{27}N_3O_2 \cdot 1.5\ C_3H_6O_3 \cdot 3H_2O \cdot 0.75$ TFA$\cdot$ 0.75 THF) C, H, N.

(2*E*)-*N*-Hydroxy-3-[4-[[4-(1*H*-indol-3-yl)-1-piperidinyl]-methyl]phenyl]-2-propenamide 14j. Following Method B, 3-(piperidin-4-yl)-1*H*-indole (2.00 g, 10 mmol), **10** (1.90 g, 10 mmol), and $NaBH(OAc)_3$ (1 equiv) were reacted in DCE to afford (2*E*)-3-[4-[4-(1*H*-indol-3-yl)piperidin-1-ylmethyl]phenyl]-2-propenoic acid methyl ester (2.90 g, 77%): ^{1}H NMR ($CDCl_3$) δ 1.90 (m, 2H), 2.07 (m, 3H), 2.24 (t, 11.1 Hz, 2H), 2.88 (m, 1H), 3.06 (d, 11.3 Hz, 2H), 3.64 (s, 2H), 3.84 (s, 3H), 6.47 (d, 16.2 Hz, 1H), 7.00 (d, 1.9 Hz, 1H), 7.13 (m, 1H), 7.21 (m, 1H), 7.40 (m, 3H), 7.54 (m, 2H), 7.71 (m, 2H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 33.36, 33.83, 52.15, 54.81, 63.57, 111.63, 117.78, 119.52, 120.09, 122.35, 127.09, 128.48, 130.18, 133.67, 136.79, 145.16, 167.99; *m*/*z* 375 (MH^+). Following Method C, the ester (1.87 g, 4.99 mmol) was converted to hydroxamate **14j** (1.66 g, 88%): ^{1}H NMR (DMSO-d_6) δ 1.70 (m, 2H), 1.92 (m, 2H), 2.13 (t, 10.7 Hz, 2H), 2.75 (m, 1H), 2.91 (d, 11.3 Hz, 2H), 3.53 (s, 2H), 6.45 (d, 15.8 Hz, 1H), 6.94 (m, 1H), 7.04 (m, 1H), 7.09 (d, 2.3 Hz, 1H), 7.35 (m, 3H), 7.45 (d, 15.8 Hz, 1H), 7.53 (m, 3H), 10.77 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 32.76, 32.97, 53.73, 62.15, 111.32, 117.94, 118.46, 119.51, 120.40, 120.69, 126.22, 127.26, 129.21, 133.37, 136.26, 138.07, 140.32, 162.68; *m*/*z* 376 (MH^+); Anal. ($C_{23}H_{25}N_3O_3 \cdot 0.4H_2O$) C, H, N.

(2*E*)-*N*-Hydroxy-3-[4-[(1,3,4,9-tetrahydro-2*H*-pyrido-[3,4-b]indol-2-yl)methyl]phenyl]-2-propenamide 17. Following the procedure described for the preparation of **8**, 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (5.01 g, 29.1 mmol) and **12** (5.74 g, 32.6 mmol) were converted to **17**: ^{1}H NMR (CD_3OD) δ 2.97 (t, 5.6 Hz, 2H, lactate), 3.24 (t, 5.8 Hz, 2H), 3.99 (s, 2H), 4.14 (m, 3H), 6.54 (d, 16.2 Hz, 1H), 7.06 (m, 2H), 7.31 (d, 7.9 Hz, 1H), 7.44 (d, 7.5 Hz, 1H), 7.59 (m, 5 H); ^{13}C NMR (CD_3OD) δ 21.49 (lactate), 21.62, 51.26, 52.50, 62.17, 68.78 (lactate), 107.96, 112.44, 119.11, 120.48, 122.93, 129.57, 132.31, 138.56, 141.31, 166.59, 180.51; *m*/*z* 348 (MH^+); Anal. ($C_{21}H_{21}N_3O_2 \cdot C_3H_6O_3$) C, H, N.

(2*E*)-*N*-Hydroxy-3-[4-[[3-(1*H*-indol-3-yl)propyl]amino]-phenyl]-2-propenamide 19. To a solution of 1*H*-indole-3-propanoic acid (5.00 g, 26.4 mmol) and *i*-BuOCCl (3.50 mL, 3.65 g, 26.7 mmol) in THF was added NMM (5.90 mL, 5.43 g, 53.6 mmol). After 2 h, **18** hydrochloride (5.65 g, 26.4 mmol) was added and the mixture stirred overnight. The reaction mixture was diluted with EtOAc and washed with 1 M HCl, 1 M NaOH, and brine. The organic extract was dried ($MgSO_4$), filtered and the filtrate evaporated to give an oil which was dissolved in EtOAc. Hexane addition afforded (2*E*)-3-[4-(3-1*H*-Indol-3-ylpropionylamino)phenyl]-2-propenoic acid methyl ester as a solid which, after filtration, was used without purification in the next step (5.65 g, 61%): *m*/*z* 439 (MH^+). A solution of HOAc (8.62 g, 144 mmol) in 25 mL of THF was added dropwise to a suspension of $NaBH_4$ (5.43 g, 144 mmol) in 100 mL of THF. After 2 h, a solution of the amide (5.04 g, 14.5 mmol) in 50 mL of THF was added to the $NaBH_4$/HOAc mixture. After 3 h, the reaction mixture was slowly poured into brine (250 mL) and the mixture stirred overnight. The mixture was extracted with EtOAc, and the extracts were washed with water and brine, dried, and evaporated. The residue was purified (flash chromatography) to an oil which was dissolved in 4 M HCl/dioxane. The dioxane solution was diluted with Et_2O to give a precipitate which was filtered and dried to provide (2*E*)-3-[4-[3-(1*H*-indol-3-yl)propylamino]phenyl]-2-propenoic acid methyl ester hydrochloride (2.48 g, 51%): ^{1}H NMR (DMSO-d_6) δ 2.00 (m, 2H), 2.79 (t, 7.5 Hz, 2H), 3.21 (t, 7.4 Hz, 2H), 3.70 (s, 3H), 6.45 (d, 15.8 Hz, 1H), 6.96 (t, 7.4 Hz, 1H), 7.06 (m, 2H), 7.15 (s, 1H), 7.34 (d, 7.9 Hz, 1H), 7.57 (m, 4H), 9.91 (br s, 2H), 10.85 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.40, 28.31, 46.07, 51.61, 111.76, 113.94, 118.50, 118.65, 121.25, 122.70, 127.44, 130.35, 136.70, 144.84, 167.37; *m*/*z* 335 (MH^+); mp 187−190 °C; Anal. ($C_{21}H_{22}N_2O_2 \cdot$HCl) C, H, N, Cl. Following Method C, the amine hydrochloride (1.51 g, 4.07 g) was converted to **19**, which precipitated from the reaction mixture upon neutralization. The free base was treated with HCl/dioxane as described above to give **19** as the HCl salt (519 mg, 34%): retention time System 3 = 15.51 min, retention time System 4 = 26.63 min; ^{1}H NMR (DMSO-d_6) δ 2.01 (m, 2H), 2.79 (t, 7.35 Hz, 2H), 3.23 (m, 2H), 6.38 (d, 15.5 Hz, 1H), 6.96 (t, 7.4 Hz, 1H), 7.06 (t, 7.4 Hz, 1H), 7.15 (m, 3H), 7.34 (d, 7.9 Hz, 1H), 7.40 (d, 15.8 Hz, 1H), 7.51 (m, 3H), 10.84 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.33, 27.98, 47.14, 111.77, 113.83, 118.53, 118.64, 121.27, 122.73, 127.41, 129.27, 136.70, 138.25, 163.44; *m*/*z* 336 (MH^+); HRMS (MH^+) calcd for $C_{20}H_{22}N_3O_2$, 336.1712, found 336.1725; mp 148−149 °C decomp.; Anal. ($C_{20}H_{21}N_3O_2 \cdot$ HCl$\cdot 0.15Et_2O \cdot 0.4H_2O$) C, H, N, Cl.

(2*E*)-*N*-Hydroxy-3-[4-[[[2-(2-methyl-1*H*-benzimidazol-1-yl)ethyl]amino]methyl]phenyl]-2-propenamide 21. A mixture of 1-(2-bromoethyl)-2-methyl-1*H*-benzimidazole[34] (2.93 g, 12.3 mmol), **20** hydrochloride (2.79 g, 12.3 mmol), and DIEA (4.3 mL, 24.7 mmol) in DMSO (50 mL) was heated to 50 °C for 72 h, cooled, diluted with sat. $NaHCO_3$ (aq.), and extracted

with EtOAc. The combined extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was purifed (flash chromatography) to give an oil. This was dissolved in MeOH and treated with 4.0 M HCl/dioxane and the solution diluted with Et_2O to afford (2*E*)-3-[4-[[[2-(2-methyl-1*H*-benzimidazol-1-yl)ethyl]amino]methyl]phenyl]-2-propenoic acid methyl ester hydrochloride (438 mg, 9%): ^{1}H NMR (DMSO-d_6) δ 2.93 (s, 3H), 3.46 (s, 2H), 3.73 (s, 3H), 4.21 (s, 2H), 4.94 (t, 6.22 Hz, 2H), 6.71 (d, 16.20 Hz, 1H), 7.57 (m, 2H), 7.67 (m, 3H), 7.78 (m, 3H), 8.14 (m, 1H), 10.37 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 12.13, 40.81, 44.41, 49.74, 51.46, 112.59, 113.87, 118.55, 125.25, 125.74, 128.38, 130.18, 130.57, 131.62, 133.89, 134.40, 143.70, 152.40, 166.50; *m*/*z* 350 (MH^+); mp 175−179 °C. Following Method C, the ester hydrochloride (386 mg, 1.00 mmol) was converted to the hydroxamate and triturated with Et_2O to afford **21** (46 mg, 13%): retention time System 3 = 3.01 min, retention time System 4 = 18.96 min; ^{1}H NMR (DMSO-d_6) δ 2.54 (s, 3H), 2.83 (t, 6.03 Hz, 2H), 3.35 (s, 2H), 3.70 (s, 2H), 4.24 (t, 6.41 Hz, 2H), 6.41 (d, 15.82 Hz, 1H), 7.13 (m, 2H), 7.26 (d, 7.91 Hz, 2H), 7.47 (m, 5H), 10.73 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 12.26 41.89, 46.17, 50.81, 108.39, 116.67, 117.02, 119.56, 119.79, 125.87, 126.85, 131.80, 133.83, 136.70, 140.93, 150.60; *m*/*z* 351 (MH^+), HRMS (MH^+) calcd for $C_{20}H_{23}N_4O_2$, 351.1821, found 351.1850; mp 147−152 °C decomp.; Anal. ($C_{20}H_{22}N_4O_2 \cdot 0.2Et_2O \cdot 0.4H_2O$), C, H, N.

***N*-Hydroxy-3-[4-[1-[[2-(1*H*-indol-3-yl)ethyl]amino]ethyl]phenyl]-(2*E*)-2-propenamide 23.** Following Method A, tryptamine (680 mg, 4.25 mmol), **22** (702 mg, 3.44 mmol), and $NaBH_3CN$ were reacted in MeOH to afford 3-[4-[1-[[2-(1*H*-indol-3-yl)ethyl]amino]ethyl]phenyl]-(2*E*)-2-propenoic acid methyl ester: ^{1}H NMR ($CDCl_3$) δ 1.42 (d, 6.8 Hz, 3H), 2.92 (m, 4H), 3.81 (s, 3H), 3.91 (q, 6.4 Hz, 1H), 6.39 (d, 15.8 Hz, 1H), 7.07 (m, 2H), 7.19 (td, 7.5, 1.1 Hz, 1H), 7.27 (m, 2H), 7.37 (ddd, 8.1, 1.1, 0.9 Hz, 1H), 7.46 (m, 3H), 7.64 (d, 15.8 Hz, 1H), 8.06 (s, 1H); *m*/*z* 349 (MH^+). Following Method C, the ester (460 mg, 1.61 mmol) was converted to the hydroxamate and purified by RPHPLC which, after neutralization, afforded **23** (223 mg, 40%): ^{1}H NMR (DMSO-d_6) δ 1.26 (d, 6.4 Hz, 3H), 2.71 (m, 4H), 3.84 (m, 6.8 Hz, 1H), 6.43 (d, 15.8 Hz, 1H), 6.92 (t, 7.4 Hz, 1H), 7.05 (m, 2H), 7.40 (m, 7H), 10.76 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.77, 25.18, 47.76, 57.05, 111.24, 112.18, 118.01, 118.12, 118.35, 120.74, 122.43, 127.07, 127.11, 127.41, 133.32, 136.12, 138.08, 162.71; *m*/*z* 350 (MH^+); Anal. ($C_{21}H_{23}N_3O_2 \cdot H_2O$) C, H, N.

HDAC Enzyme Assay. HDAC was partially purified from H1299 human non small cell lung carcinoma cells. Cells were grown to 70−80% confluence in RPMI media in the presence of 10% fetal calf serum, harvested, and lysed using sonication. The lysate was centrifuged at 23 420 × g for 10−15 min and the supernatant applied to a Hiload 26/10 High Performance Q-sepharose column (Amersham Pharmacia Biotech), previously equilibrated with a Buffer A (20mM Tris pH8, 0.1 mM EDTA, 10 mM NH_4Cl_2, 1 mM β-mercaptoethanol, 5% glycerol, 2 μg/mL aprotinin, 1 μg/mL leupeptin, and 400 mM phenyl methyl sulfonyl fluoride (PMSF)) and eluted with a linear gradient of 0−500 mM NaCl in Buffer A at a flow rate of 2.5 mL/min. Four milliliter fractions were collected, and each was titrated for HDAC activity using a modification of the published procedure[35] to determine the optimal amount needed to obtain a signal-to-noise ratio of at least 5:1. The substrate used is a peptide of amino acid sequence SGRGKGGKGLGKGGAKRHRKVLRD, corresponding to the 24 N-terminal amino acids of human histone H4, biotinylated at the N-terminus and peracetylated with ^{3}H-acetate at each lysine residue. The substrate is diluted in 10 μL of Buffer B (100 mM Tris pH 8.0, 2 mM EDTA), added to the enzyme mixture, and incubated at 37 °C for 1.5 h. The reaction is stopped by the addition of 20 μL of 0.5 N HCl/0.08 M HOAc and extracted with TBME, and an aliquot of the organic layer is added to Opti-Phase Supermix liquid scintillation cocktail (Wallac). The mixture was read on a 1450 MicroBeta Trilux liquid scintillation and luminescence counter (Wallac) with a color/chemical quench and dpm correction and the data corrected for background luminescence.

Monolayer Growth Inhibition Assay. All incubations were performed at 37 °C. The effect of the HDAIs on monolayer cell proliferation was measured using an adaptation of a published procedure.[23] Cells were plated in 96-well plates at initial densities of between 1000 and 3000 cells/well and incubated at 37 °C. After 24 h, test compounds were added to test wells, vehicle added to vehicle control (VC) wells and initial growth control wells (IGC) received 10 μL 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium, inner salt (MTS) mixture (prepared on day of use at a ratio of 10 μL of a 0.92 mg/mL solution of phenazine methosulfate (PMS) to a 190 μL of a 2 mg/mL solution of MTS), the plate was incubated for 4 h at 37 °C, and the OD_{490} of IGC wells was measured on a Molecular Devices Thermomax at 490 nm using the Softmax program to determine initial cell density values. The plates were further incubated for 72 h at 37 °C, 10 μL/well of MTS mixture was added to the test and VC wells, and the OD_{490} was measured. OD_{490} values for wells containing cells were corrected for media absorbance. The following formulas were used to calculate percent growth: If $X > T_0$, % growth = $100 \times ((X - T_0)/(GC - T_0))$, if $X < T_0$, % growth = $100 \times (X - T_0)/T_0$; where T_0 = IGC well OD_{490} − background, GC = VC well OD_{490} − background, X = compound-treated well OD_{490} − background.

Efficacy Experiments. The studies were performed using outbred athymic (nu/nu) female mice ("Hsd:Athymic Nude-nu" from Harlan Sprague Dawley, Indianapolis, IN). Mice were anesthetized with Metofane (Mallinckrodt Veterinary, Inc., Mundelein, IL), and a cell suspension (100 μL), containing either ≈10^6 HCT116 cells or ≈10^7 A549 cells, was injected subcutaneously into the right axillary (lateral) region of each animal. Tumors were allowed to grow until a volume of ≈100 mm^3 was achieved. At this point, mice bearing tumors with acceptable morphology and size were sorted into groups of eight for the study. The sorting process produced groups balanced with respect to mean and range of tumor size. Solid compound, as the lactate salt, was dissolved in pure DMSO to create a stock solution. This solution was diluted with D5W just prior to dosing so the final DMSO concentration was 10% and the compound remained in solution. Positive-control animals in the HCT116 xenograft studies received 5-fluorouracil formulated in 0.9% w/v saline and dosed iv at 100 mg/kg 1×/week for three doses. Positive-control animals in the A549 xenograft studies received mitomycin C formulated in 10% DMSO/D5W and dosed ip 3×/week for nine doses. Tumors were measured, and individual animal body weights were recorded once weekly. Antitumor activity is expressed as % *T*/*C*, the ratio of the change in tumor volume of treated animals to the change in tumor volume of vehicle control animals.

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