Synthesis and Antitumor Activity of Ester-Modified Analogues of Bengamide B

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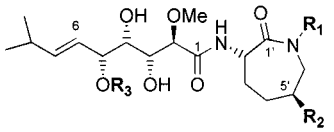
Bengamide B, a novel sponge-derived marine natural product with broad spectrum antitumor activity, was not suitable for further preclinical development because of its difficult synthesis and very poor water solubility. Bengamide B produced a 31% T/C at its solubility-limited maximum intravenous dose of 33 μmol/kg in MDA-MB-435 breast carcinoma implanted subcutaneously as a xenograft in nude mice. Compound **8a**, a bengamide B analogue with three structural changes (*t*-Bu alkene substituent, unsubstituted lactam nitrogen, and inverted lactam 5′-myristoyloxy group), was as potent as bengamide B in vitro and more efficacious than bengamide B in vivo. A series of ester-modified analogues based on **8a** were synthesized and tested in vitro and in vivo (MDA-MB-435). The cyclohexyl- and phenethyl-substituted esters, **8c** and **8g**, respectively, had in vitro and in vivo activities similar to that of **8a** and enhanced water solubility (ca. 1 mg/mL). Consequently, **8c** and **8g** were tested in the MDA-MB-435 xenograft model at 100 μmol/kg and produced 29% and 57% tumor regression, respectively.

Introduction

The bengamides comprise a family of marine natural products first isolated by Crews et al. from *Jaspis* sponges indigenous to the coral reefs that surround the Fiji islands.[1] These fused ketide−amino acid derivatives are potent antiproliferative agents against both transformed and nontransformed cells.[2] Bengamide B was evaluated in the NCI 60 cell line screening panel and found to have a unique profile compared to that of standard antitumor agents.[3] Fluorescence-activated cell sorting (FACS) analyses of transformed and nontransformed cells treated with bengamides revealed arrest at both G1 and G2/M phases of the cell cycle.[2b] Additional experiments including Western blot analysis of key cell cycle regulators and FACS analysis of synchronized cells suggested that the G1 arrest occurs at the G1/S restriction point. Interestingly, cells that are arrested in the G2/M phase of the cell cycle do not seem to be inhibited during nuclear division but rather during cytokinesis.[2b] The intracellular target of the bengamides is under investigation.

The bengamides may be categorized into two structural classes: (1) hydroxylysine-derived (e.g., bengamides A, B, and Z) and (2) lysine-derived (e.g., bengamides E, F, and P). The structures and antiproliferative activities (MDA-MB-435 breast carcinoma, IC_{50} values) of six representative bengamides are given in Table 1. Hydroxylysine-derived bengamides that bear a myristate ester (bengamides A and B) are ca. 100-fold more potent than nonmyristate-containing bengamide Z and all of the lysine-derived bengamides. Bengamide P is >500-fold less potent than bengamides A and B despite the presence of a myristate ester on the allylic hydroxy position. Thus, from this limited SAR data it appears that the presence of a lipophilic ester on the caprolactam is essential for in vitro potency and that lactam N-substitution by a methyl group has no effect on in vitro potency.

Table 1. Structures and MDA-MB-435 Human Breast Carcinoma in Vitro Activity of Selected Bengamides



bengamide	R_1	R_2	R_3	IC_{50} [a] (μM)
A (**1**)	H	$O_2C(CH_2)_{12}CH_3$	H	0.001 ± 0.0006
B (**2**)	Me	$O_2C(CH_2)_{12}CH_3$	H	0.0024 ± 0.0008
E (**3**)	H	H	H	3.3 ± 1.2
F (**4**)	Me	H	H	2.9 ± 2.9
P (**5**)	H	H	$O_2C(CH_2)_{12}CH_3$	1.2 ± 7.9
Z (**6**)	Me	OH	H	2.9 ± 1.5

[a] IC_{50} values are the concentrations corresponding to 50% growth inhibition (see Experimental Section for a detailed description of the assay).

Sufficient amounts of bengamides B, E, and Z were isolated from a supply of crude sponge extract to test against MDA-MB-435 breast carcinoma cells grown as xenografts in nude mice. Bengamide B was the most potent of the three (Table 2)[2a]. However, the differences in potency were small compared to the potency differences observed in the MDA-MB-435 in vitro assay. The poor water solubility of bengamide B limited intravenous administration to a maximum dose of 20 mg/kg. All three bengamides achieved a significant inhibition of tumor growth at doses that caused little or no loss in body weight.

Bengamide B was not a candidate for further preclinical development because of limited supply (via sponge extraction or total synthesis) and poor water solubility (0.002 mg/mL at pH 6.8). Although an improved total synthesis of bengamide B compared to

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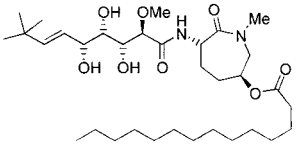
Table 2. MDA-MB-435 Human Breast Carcinoma in Vivo Activity of **2**, **3**, and **6**[a]

bengamide	dose (μmol/kg)	% T/C	Δ% body weight	dead/ total
B (**2**)	10	45**	0.5	0/8
	33 (20 mg/kg)	31**	−2.3	0/8
E (**3**)	28	62	8.4	0/8
	84	62	7.1	0/8
	279	19**	6.7	0/8
Z (**6**)	26	42**	9.5	0/8
	52	41**	0.8	0/8

[a] In vivo antitumor data for compounds **2**, **3**, and **6** in Table 2 were compiled from separate studies. ** indicates $p < 0.01$ (see Experimental Section for a detailed description).



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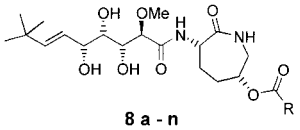


8 a - n

Compound	R	Compound	R
8a	$(CH_2)_{12}CH_3$	**8i**	CH_2-(N)
8b	c-pentyl	**8j**	CH_2CH_2-(N)
8c	c-hexyl	**8k**	-(C$_6$H$_5$)
8d	c-heptyl	**8l**	-(C$_6$H$_5$)-C_5H_{11}
8e	CH_2-c-hexyl	**8m**	-(C$_6$H$_5$)-$C_{10}H_{21}$
8f	CH_2Ph	**8n**	-(C$_6$H$_5$)-O-$C_{10}H_{21}$
8g	CH_2CH_2Ph		
8h	*trans*-CH=CHPh		

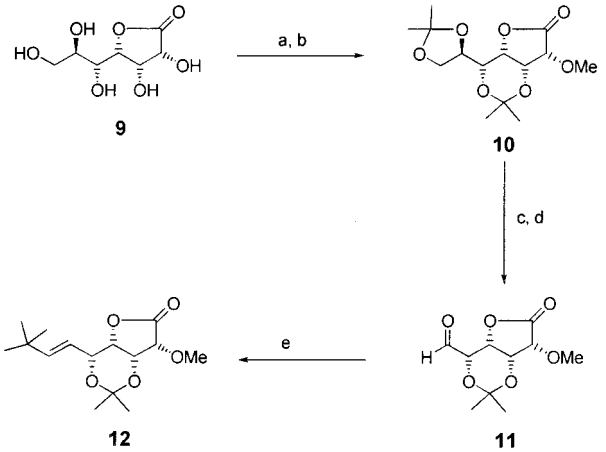
Figure 1. Structures of bengamide B analogues.

previous literature reports (>30 steps) was recently developed in our laboratories, the synthesis still requires 14 total steps and suffers from a low-yield olefination reaction.[4] The design and synthesis of bengamide B analogues were initiated as a means to address the synthetic feasibility and water solubility issues. The first hurdle was to prepare analogues using shorter and higher yielding synthetic routes with in vivo efficacy equal to or greater than that of bengamide B. Three modifications to the structure of bengamide B were made: (1) removal of the lactam *N*-methyl group (i.e., bengamide A), (2) replacement of the *i*-Pr alkene substituent by a *t*-Bu group (compound **7**), and (3) inversion of the caprolactam ester-bearing hydroxy group (compound **8a**). Once it was established that these structural changes were well tolerated, a focused SAR study based on substitution of the myristate group with fewer lipophilic ester moieties was performed (Figure 1).

Chemistry

The general strategy for the preparation of bengamide analogues is based on the improved syntheses of bengamides B and E developed in our laboratories.[4] The synthesis of each analogue utilizes lactone **12** and a substituted aminocaprolactam intermediate (**15**, **18**, or **20**), which are joined via an amide coupling reaction. The synthesis of lactone **12** is outlined in Scheme 1. An acetone solution of α-D-glucoheptonic γ-lactone (**9**) was treated with catalytic I_2 to give a bis(acetonide) that was subsequently methylated with Ag_2O and methyl iodide

Scheme 1. Synthesis of Lactone Intermediate[a]



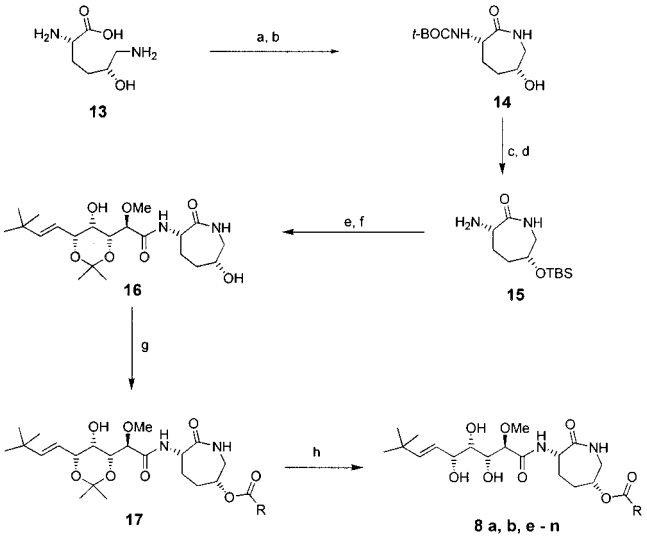
[a] Reagents: (a) acetone, cat. I_2 (86%); (b) MeI, Ag_2O (82%); (c) HOAc (68%); (d) $NaIO_4$, MeOH (85%); (e) $(CH_3)_3CCHI_2$, $CrCl_2$, THF, DMF (63%).

to give the methyl ether **10**.[5] Selective removal of the 1,2-acetonide in the presence of the 1,3-acetonide was accomplished by the treatment of bis(acetonide) **10** with acetic acid.[6] The desired vicinal diol was then converted to aldehyde **11** via oxidative cleavage with $NaIO_4$. Aldehyde **11** was then olefinated with the low-valent organochromium species generated in situ from 1,1-diiodoneopentane (prepared in two steps from pivaldehyde[7]) and $Cr(II)Cl_2$ to produce the desired *E*-olefin in 63% yield after flash column chromatography.[8] A small, variable amount (up to 10%) of the *Z*-olefin was also produced during the reaction. The yield and selectivity of this reaction were significantly improved compared to those of the analogous reaction with 1,1-diiodoisobutane used to prepare bengamides B and E (39% yield of a 3:1 mixture of *E*- to *Z*-isomers).[4]

Bengamide analogues **8a**,**b**,**e**−**n** were prepared using the synthetic route outlined in Scheme 2. Cyclization of (5*R*)-5-hydroxy-L-lysine (**13**) followed by *N*-Boc carbamoylation of the free amine was performed in one pot using standard peptide synthesis conditions (58% yield for two steps).[4] The secondary alcohol **14** was protected as the corresponding TBS ether using TBSCl and DMAP (78% yield). Treatment with TMSI removed the *t*-BOC protecting group to give the amine **15** in 96% yield. Amine **15** was coupled with lactone **12** in a minimal amount of 2-propanol and DIEA stirred at reflux (42% yield). The resulting amide was treated with TBAF to remove the TBS protecting group to give alcohol **16** (91% yield). Esterification of **16** with either an acid chloride (using Et_3N and DMAP) or a carboxylic acid in the presence of EDCI and DMAP produced the acetonide-protected analogues **17**. Hydrolysis of the acetonide using TFA/H_2O/THF furnished the desired target compound. This synthesis permits stockpiling of the late intermediate **16** so that analogues can be quickly assembled in two steps, as required.

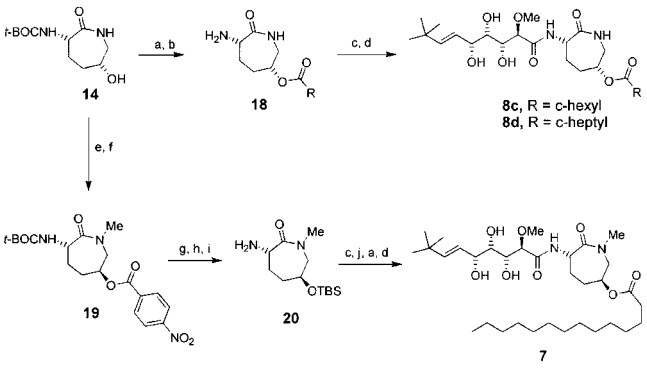
An alternative synthesis that eliminates the TBS protection/deprotection steps was used in the syntheses of analogues **8c** and **8d** (Scheme 3). Rather than protect the caprolactam hydroxy group as a TBS ether, intermediate **14** was acylated directly, then treated with TFA to remove the *t*-BOC protecting group to give ester **18**. The aminocaprolactam was coupled with lactone **12**,

Scheme 2. Syntheses of Bengamide B Analogues **8a**,**b**,**e**−**n**[a]



[a] Reagents: (a) EDCI, HOBT, DMF; (b) $(Boc)_2O$ (58% for two steps); (c) TBSCl, imidazole, DMF (78%); (d) TMSI, CH_2Cl_2, −78 °C (96%); (e) **12**, *i*-PrOH, DIEA, reflux (42%); (f) TBAF, THF (91%); (g) RC(O)Cl, Et_3N, DMAP, CH_2Cl_2 or RCO_2H, EDCI, DMAP, CH_2Cl_2; (h) TFA, THF, H_2O.

Scheme 3. Synthesis of **7**, **8c**, and **8d**[a]



[a] Reagents: (a) RCOCl, Et_3N, CH_2Cl_2 or RCO_2H, EDCI, DMAP, CH_2Cl_2; (b) TFA, CH_2Cl_2; (c) **12**, *i*-PrOH, reflux; (d) TFA/THF, H_2O; (e) DEAD, PPh_3, *p*-nitrobenzoic acid (78%); (f) MeI, NaHMDS (79%); (g) LiOH; (h) TBSCl, imidazole, DMF; (i) TMSI, CH_2Cl_2 (55% for three steps); (j) TBAF, THF (66%).

then treated with TFA, as before, to give the desired analogues. It was also found that the amide coupling step proceeded in higher yield without DIEA. To prepare bengamide B analogue **7**, an inversion reaction was required (Scheme 3). 5′-Hydroxylactam **14** was converted to the corresponding *p*-NO_2-benzoate ester using Mitsunobu conditions.[9] Subsequent N-methylation with NaHMDS/MeI provided lactam **19**. Hydrolysis of the ester with LiOH, TBS protection, and TMSI-mediated *t*-BOC removal provided aminocaprolactam **20**. Condensation of **20** with lactone **12**, TBAF desilylation, myristylation, and acetonide hydrolysis were then employed to complete the synthesis of the *t*-Bu bengamide B analogue **7**.

Results and Discussion

Bengamide B analogues were first examined for antiproliferative activity against MDA-MB-435 human breast carcinoma cells grown in monolayers. The analogues were then administered intravenously at 10 and 33 μmol/kg doses to nude mice bearing subcutaneously implanted MDA-MB-435 xenografts. The 33 μmol/kg dose is equivalent to the solubility-limiting 20 mg/kg dose of bengamide B. The first bengamide analogues prepared were intended to improve synthetic feasibility through incorporation of minor structural changes. The first modification was simple replacement of the *i*-Pr group alkene substituent with a *t*-Bu group. The substitution of *i*-Pr with *t*-Bu in the Takai−Utimoto olefination reaction improved the yield and selectivity dramatically.[8] Compound **7**, the corresponding *t*-Bu analogue of bengamide B, and bengamide B (**2**) were equipotent in vitro and had similar % T/C values in vivo (Table 3). Since the presence of the caprolactam *N*-methyl group did not affect the antitumor activity between closely related bengamides (A and B or E and F; see Table 1), it was expected that this change could be made freely on all bengamide analogues. Syntheses of the hydroxylysine-derived bengamides (A, B, and Z) required that the 5′-OH group, originating from commercially available (5*R*)-5-hydroxy-L-lysine, needed to be inverted. (5*S*)-5-Hydroxy-L-lysine was not readily available. To test whether the *S*-configuration at the 5′-hydroxy position was essential for antitumor activity, compound **8a** was prepared. **8a** was one of the most potent bengamide B analogues tested in this series in vitro and halted the tumor's growth in vivo (% T/C value was ∼0) at the same dose for which bengamide B produced a 31% T/C value. When the yield is significantly increased in the olefination step (Scheme 1) and

Table 3. In Vitro and in Vivo Activity of **7** and **8a**−**n** against MDA-MB-435 Human Breast Carcinoma[a]

compound	IC_{50} (μM) av ± SEM	dose (μmol/kg)	% T/C	Δ% body weight	dead/ total
7	0.01 ± 0.01	10	58*	6.1	0/8
		33	46**	6.4	0/8
8a	<0.01	10	41**	7.4	0/8
		33	4**	5.7	0/8
8b	0.13 ± 0.01	10	67	7.6	0/8
		33	13**	3.0	0/8
8c	0.04 ± 0.00	10	58**	10.5	0/8
		33	7**	3.5	0/8
		100	29% reg**	−2.6	0/8
8d	0.02 ± 0.01	10	39**	10.1	0/8
		33	28**	8.4	0/8
8e	0.06 ± 0.00	10	47**	4.6	0/8
		33	34**	3.5	0/8
8f	0.26 ± 0.04	10	72	10.6	0/8
		33	43**	3.9	0/8
8g	0.01 ± 0.01	10	53**	6.0	0/8
		33	12**	5.3	0/8
		100	58% reg**	−3.1	0/8
8h	0.02 ± 0.00	10	64**	7.4	0/8
		33	63**	7.5	0/8
8i	5.85 ± 0.01	10	69	6.4	0/8
		33	82	6.8	0/8
8j	0.46 ± 0.04	10	92	10.1	0/8
		33	44**	3.0	0/8
8k	0.37 ± 0.01	10	93	5.5	0/8
		33	80	5.6	0/8
8l	0.02 ± 0.01	10	111	6.0	0/8
		33	91	2.6	0/8
8m	0.03 ± 0.04	10	76	6.0	0/8
		33	6**	2.6	0/8
8n	0.01 ± 0.00	10	64**	8.8	0/8
		33	2**	−0.9	0/8
doxorubicin	0.4 ± 0.31	2	44**	3.9	0/8

[a] In vivo antitumor data for compounds **7**, **8a**−**n**, and doxorubicin in Table 3 were compiled from separate studies. ∗ indicates $p < 0.05$ and ∗∗ indicates $p < 0.01$ (see Experimental Section for a detailed description).

when the lactam N-methylation and Mitsunobu inversion steps are eliminated, compound **8a** is synthetically more feasible than bengamide B; however, water solubility of **8a** was as low as that of bengamide B.

The second hurdle was to prepare equally or more efficacious bengamide B analogues with improved water solubility. The myristate ester of bengamide B clearly increased in vitro and in vivo potency compared to bengamides F and Z but also decreased water solubility. Further, inversion of the lactam 5′-position was tolerated both in vitro and in vivo, suggesting that bengamide analogues could tolerate diverse structures at this position. Thus, a series of analogues were made to test the hypothesis that replacement of the long alkyl myristate chain with fewer lipophilic groups at the bengamide lactam 5′-position would create analogues that had enhanced water solubility but similar growth inhibitory activity relative to bengamide B. Compounds **8b**−**n** were prepared and tested against MDA-MB-435 breast carcinoma cells in vitro and in vivo. Alkyl and aryl ester substituents were selected on the basis of differences in lipophilicity, size, and shape. Analogues with superior in vivo activity and water solubility compared to those of bengamide B were tested at higher doses. The ester R groups of these analogues were divided into three categories: (1) cycloalkyl-substituted esters (**8b**−**e**), (2) alkylaryl esters (**8f**−**j**), and (3) aryl esters (**8k**−**n**). With the exception of **8b**, the cyclopentyl analogue, all of the cycloalkyl analogues were nearly as potent as bengamide B in vitro (IC_{50} value range of 30−60 nM). In vivo, however, the cyclopentyl (**8b**) and cyclohexyl (**8c**) analogues were more potent than the cycloheptyl (**8d**) and cyclohexylmethyl (**8e**) analogues. Because compound **8c** was the most potent in vivo of the cycloalkyl series and was soluble in water (ca. 1 mg/mL at pH 6.8), it was tested at 100 μmol/kg. At this dose, **8c** produced 29% tumor regression with a minimal body weight loss.

The alkylaryl esters (**8f**−**j**) produced a wide range of activity in vitro (IC_{50} value range of 0.01−5.85 μM) and in vivo (12−82% T/C at 33 μmol/kg). Relatively small structural changes in this series had pronounced effects on biological activity. The phenethyl-substituted ester **8g** was among the most potent of the bengamide analogues tested in vitro to date. In vivo, it produced a 12% T/C at the 33 μmol/kg dose. Since the solubility of **8g** was 1 mg/mL at pH 6.8 in water, the compound was tested at the 100 μmol/kg dose. At this dose level, a 58% tumor regression was observed with only 3.1% loss in animal body weight. The cinnamate ester **8h** had similar in vitro potency compared to **8g**; however, in vivo activity was weak. Interestingly, the closely related phenylmethyl analogue **8f** was greater than 20-fold less potent than **8g** in vitro and was significantly less potent than **8g** in vivo. Pyridine analogues **8i** and **8j** were prepared as more water-soluble analogues of **8f** and **8g**, respectively. Although **8i** and **8j** differed in structure by a single methylene unit, **8j** was over 10-fold less potent than **8i** in vitro. When compared in the in vivo model, only **8j** was active (44% T/C) at the 33 μmol/kg dose.

The in vitro and in vivo activity of the benzoates **8k**−**n** appeared to be dependent on carbon chain length of the para substuent. *p*-Decyl- and decyloxy-substituted benzoates **8m** and **8n**, respectively, were as potent as bengamide B in vitro. At the 33 μmol/kg dose in vivo, both **8m** and **8n** caused tumor stasis, but neither compound was soluble enough for in vivo testing at higher doses.[10] Although 4-pentylbenzoate **8l** was quite potent in vitro, it was inactive in vivo.

Conclusion

Although bengamide B is a novel marine natural product with impressive in vitro and in vivo antitumor activity, limited supply and poor water solubility hinder further preclinical development. This warranted the synthesis of bengamide B analogues. Three relatively small changes made to the structure of bengamide B resulted in an analogue (**8a**) with superior antitumor activity that could be prepared using a shorter, higher-yielding synthesis. To overcome the solubility-limited dosing of bengamide B and **8a**, more water-soluble analogues based on **8a** were prepared. Over $^2/_3$ of the analogues in Table 3 inhibited in vivo tumor growth as well as or better than bengamide B at the 33 μmol/kg dose with no loss in body weight. **8c** and **8g** were found to have activity comparable to that of bengamide B in vitro and superior activity in vivo. Both compounds caused significant tumor regression with minor losses in body weight at 100 μmol/kg. The antitumor profile of bengamide B analogues **8c** and **8g** against other human solid tumor xenografts will be published shortly.

Experimental Section

General. Natural bengamides were either isolated or synthesized as previously described.[4] All other chemicals were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed with silica (Merck EM9385, 230−400 mesh). HPLC analysis was performed on a Rainin Dynamax with PDA and light-scattering detectors. Reverse-phase chromatography involved use of a Waters Nova-Pac C-18 4.6 mm × 250 mm column with a gradient of 10−100% CH_3CN/H_2O in 20 min at 1.5 mL/min. Normal-phase chromatography involved use of a Waters Nova-Pac silica 4.6 mm × 250 mm column with a gradient of 0−25% (method 1) or 0−50% (method 2) CH_3OH/EtOAc in 20 min at 1.5 mL/min. ^1H and ^{13}C NMR spectra were recorded at 500 or 300 and at 125 and 75 MHz, respectively, in $CDCl_3$ unless otherwise mentioned. Proton and carbon chemical shifts are expressed in ppm relative to internal tetramethylsilane. Coupling constants (*J*) are expressed in hertz.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*S*)-hexahydro-1-methyl-2-oxo-6-(tridecylcarbonyl)oxy-2*H*-azepin-3-yl]non-6-enamide (7). To a 500 mL flask was added (3*S*,6*R*)-3-[(*tert*-butoxycarbonyl)-amino]-6-hydroxycaprolactam (**14**) (6 g, 0.025 mol), 4-nitrobenzoic acid (8.25 g, 0.05 mol), and triphenylphosphine (12.9 g, 0.05 mol). The flask was purged with N_2, and 200 mL of freshly distilled THF was added. The mixture was cooled in a −20 °C bath, and diethyl azodicarboxylate (7.8 mL, 0.05 mol) was added at a rate to maintain a temperature less than or equal to −10 °C. The reaction mixture was allowed to warm to room temperature (∼2 h) and was stirred for 14 h. The solvent was evaporated, and the residue was dissolved in 200 mL of EtOAc. This was washed with 5% $NaHCO_3$ (3 × 150 mL) and brine (1 × 150 mL) and then dried with Na_2SO_4 and evaporated to give an oil. To this oil was added 100 mL of ether. The resulting solid was filtered and washed with ether (3 × 50 mL), acetone (2 × 50 mL), and MeOH (2 × 50 mL) to give 6.2 g of (3*S*,6*S*)-3-[(*tert*-butoxycarbonyl)amino]-6-(4-nitrobenzoyloxy)caprolactam. The combined filtrate and washes were evaporated, and the residue was chromatographed on a silica gel column with 1:1 CH_2Cl_2/hexane and then with ether to give 1.34 g of the desired ester for a total yield of 7.54 g (78%). ^1H NMR

($CDCl_3$): δ 8.29 (d, J = 8.4, 1H), 8.18 (d, J = 8.4, 2H), 6.44 (m, 1H), 5.90 (d, J = 5.7, 1H), 4.91 (m, 1H), 4.42 (m, 1H), 3.58−3.41 (m, 2H), 2.36−2.25 (m, 2H), 2.16−2.03 (m, 1H), 1.82−1.65 (m, 1H), 1.45 (s, 9H).

(3*S*,6*S*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-(4-nitrophenylcarbonyl)oxy-2*H*-azepin-2-one (10 g, 25.4 mmol) was dissolved in 100 mL of THF, then cooled to −78 °C. To this solution was added NaHMDS (30.5 mL, 30.5 mmol, 1.0 M solution in THF). The reaction was stirred for 30 min at −78 °C. Methyl iodide (7.2 g, 50.9 mmol) was then added dropwise. The reaction mixture was then allowed to slowly reach room temperature overnight. The reaction was then quenched with the dropwise addition of water, and the mixture was then diluted with water. The mixture was then partitioned with EtOAc (2×). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo.

The crude product was chromatographed (50% EtOAc/hexane) to give 8.2 g (79%) of (3*S*,6*S*)-1-methyl-3-(*tert*-butoxycarbonyl)aminohexahydro-6-(4-nitrophenylcarbonyl)oxy-2*H*-azepin-2-one (**19**). ^{1}H NMR: δ 8.3 (d, J = 8.6, 2H), 8.18 (d, J = 8.6, 2H), 5.98 (d, J = 4.8, 1H), 4.87 (m, 1H), 4.49 (m, 1H), 3.80 (dd, J = 14.7 and 10.5, 1H), 3.37 (d, J = 14.7, 1H), 3.15 (s, 3H), 2.17 (m, 1H), 1.66 (m, 1H), 1.44 (s, 9H). LiOH (1.65 g, 39.3 mmol) was added to a stirred solution of this compound (8 g, 19.6 mmol) and a 3:1 mixture of MeOH/H_2O (100 mL). The reaction was stirred for 30 min, then concentrated in vacuo. To the residue was added EtOAc (200 mL), ethyl ether (100 mL), and 10% aqueous NaOH (50 mL). The organic layer was separated and washed with 1 N NaOH solution (2×) and brine. The organic solution was then dried (Na_2SO_4) and then concentrated in vacuo. The crude product was dissolved in DMF (30 mL). To this solution was added TBSCl (2.4 g, 16 mmol) and imidazole (1.3 g, 19.8 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was then diluted with water and then extracted with a 1:1 EtOAc/hexane solution. The organic extract was washed with brine and then concentrated in vacuo. The crude silyl ether was dissolved in CH_2Cl_2 (30 mL) and then cooled to −78 °C. TMSI (3.3 g, 16.5 mmol) was added dropwise, and the reaction mixture was stirred at −78 °C for 30 min. The reaction mixture was then warmed to 0 °C and was stirred for an additional 15 min. The reaction was quenched with the addition of a solution consisting of 2.5:1 MeOH/saturated aqueous NH_4HCO_3 (35 mL). The organic layer was separated and concentrated in vacuo. The residue was chromatographed (5% MeOH/CH_2Cl_2) to give 4.0 g of amine **20** (55% for three steps). ^{1}H NMR ($CDCl_3$): δ 3.66−3.5 (3 H, m), 3.1−2.98 (1 H, m), 3.03 (3 H, s), 2.0−1.81 (2 H, m), 1.78−1.65 (1 H, m), 1.6−1.47 (1 H, m), 0.87 (9 H, s), 0.07 (3 H, s), 0.06 (3 H, s).

A solution consisting of **12** (3.5 g, 12 mmol), **20** (4.0 g, 15 mmol), diisopropylethylamine (DIEA) (3.2 g, 24 mmol), and *i*-PrOH (20 mL) was stirred at reflux for 24 h. The reaction mixture was adsorbed on silica and chromatographed (2% MeOH/CH_2Cl_2) to give the crude amide. A sample of 1 M tetra(*n*-butyl)ammonium fluoride (TBAF) (19 mL of THF solution) was added to a stirred solution consisting of the crude amide and THF (30 mL). The reaction mixture was stirred at 25 °C for 2 h, concentrated, and then chromatographed (2% MeOH/CH_2Cl_2) to give 1.9 g (66%) of (2*R*,3*R*,4*S*,5*R*,6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*S*)-hexahydro-1-methyl-2-oxo-6-hydroxy-2*H*-azepin-3-yl]non-6-enamide as a gum. This compound (1.0 g, 2.2 mmol) was added to a stirred solution of myristic acid (0.62 g, 2.7 mmol), EDCI (0.54 g, 2.7 mmol), DMAP (0.33 g, 2.7 mmol), and CH_2Cl_2 (50 mL) at 25 °C. The reaction mixture was stirred at this temperature for 24 h, concentrated, and chromatographed (2% MeOH/CH_2Cl_2) to give 1.5 g of impure (2*R*,3*R*,4*S*,5*R*,6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*S*)-hexahydro-1-methyl-2-oxo-6-(tridecylcarbonyl)oxy-2*H*-azepin-3-yl]non-6-enamide as a gum. To this compound (0.30 g, 0.46 mmol) was added a solution consisting of TFA (8 mL), THF (8 mL), and H_2O (6 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min, concentrated via rotary evaporation (bath temp of <20 °C), mixed with saturated NH_4HCO_3 (15 mL), and stirred for 15 min. The mixture was concentrated in vacuo and chromatographed (2% MeOH/CH_2Cl_2) to give a white solid. This material was further purified using preparative HPLC (reverse-phase eluted with 90% CH_3CN/H_2O) to give 0.23 g (82%) of **7** as a pale-yellow gum. ^{1}H NMR: δ 8.09 (d, J = 6.1, 1H), 5.80 (d, J = 15.6, 1H), 5.39 (dd, J = 15.6 and 7.2, 1H), 4.60 (m, 2H), 4.26 (s, 1H), 4.20 (t, J = 5.9, 1H), 3.77 (s, 2H), 3.62 (m, 2H), 3.52 (s, 3H), 3.21 (d, J = 14.9, 2H), 3.08 (s, 3H), 2.28 (t, J = 7.5, 2H), 2.13 (m, 2H), 1.93 (m, 1H), 1.60 (m, 3H), 1.23 (m, 21H), 1.00 (s, 9H), 0.83 (t, J = 6.4, 3H). ^{13}C NMR ($CDCl_3$): δ 172.5, 171.6, 171.3, 145.2, 122.7, 80.3, 74.0, 72.3, 71.8, 68.7, 59.5, 52.8, 50.8, 35.9, 33.8, 32.5, 32.2, 31.4, 29.2, 29.1, 29.09, 28.94, 28.92, 28.85, 28.7, 28.6, 28.5, 24.4, 22.2, 13.6. Anal. ($C_{33}H_{60}N_2O_8$) C, H, N.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-(tridecylcarbonyl)oxy-2*H*-azepin-3-yl]non-6-enamide (8a). Lactam **14** was prepared as described previously.[4] **14** (25 g, 102 mmol), *tert*-butyldimethylsilyl chloride (23.16 g, 153 mmol), and imidazole (10.45 g, 153 mmol) were combined with 60 mL of DMF. The reaction was stirred at room temperature overnight. The mixture was diluted with 1 L of water. The resulting mixture was extracted with a 1:1 (2 × 200 mL) mixture of ethyl acetate and hexane. All organic layers were combined, washed with brine solution, dried with Na_2SO_4, and concentrated. The residue was purified by recrystallization with ethyl acetate/hexane to give 28.5 g (78%) of (3*S*,6*R*)-3-(*tert*-butoxycarbonyl)-aminohexahydro-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-2-one as a white solid. ^{1}H NMR ($CDCl_3$): δ 5.86 (d, J = 6, 1H), 5.58 (t, J = 6, 1H), 4.18 (m, 1H), 3.91 (s, 1H), 3.35 (dd, J = 6 and 16, 1H), 3.07 (m, 1H), 1.80 (m, 4H), 1.40 (s, 9H), 0.83 (s, 9H), 0.004 (s, 6H).

(3*S*,6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-2-one (8.0 g, 22 mmol) was dissolved in 40 mL of CH_2Cl_2 and cooled to −78 °C. Trimethylsilyl iodide (3.5 mL, 24.5 mmol) was added dropwise to the solution. The mixture was allowed to react at −78 °C for 30 min. The reaction mixture was warmed to 0 °C and was stirred for 15 min. The solution turned yellow. The reaction was quenched with NH_4HCO_3 (3.43 g, 44 mmol) and then dissolved in 30 mL of CH_3OH and 15 mL of water. The mixture was concentrated and chromatographed with a 95:5 mixture of CH_2Cl_2 and methanol to yield 5.45 g (96%) of (3*S*,6*R*)-3-aminohexahydro-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-2-one (**15**). ^{1}H NMR ($CDCl_3$): δ 5.61 (s, 1H), 3.88 (s, 1H), 3.42 (d, J = 8, 1H), 3.32 (dd, J = 6 and 16, 1H), 3.06 (m, 1H), 1.87 (m, 2H), 1.76 (m, 1H), 1.65 (s, 3H), 0.83 (s, 9H), 0.00 (s, 6H).

15 (5.45 g, 21 mmol), (6*E*)-6,7,8,9-tetradeoxy-8,8-dimethyl-2-*O*-methyl-3,5-*O*-(1-methylethylidene)-*gulo*-non-6-enonic acid lactone (**12**) (3.0 g, 11 mmol), and diisopropylethylamine (4.6 mL, 26 mmol) were combined with 30 mL of 2-propanol at room temperature. The mixture was heated at reflux overnight. The mixture was cooled to room temperature and concentrated. The residue was chromatographed with a 98:2 mixture of CH_2Cl_2 and methanol to yield 2.53 g (42%) of (2*R*,3*R*,4*S*,5*R*,6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-3-yl]non-6-enamide (42%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.53 (d, J = 6, 1H), 5.72 (d, J = 16, 1 H), 5.47 (dd, J = 6 and 16, 1H), 4.47 (m, 1H), 4.22 (d, J = 6, 1H), 4.03 (d, J = 8, 1H), 3.91 (m, 1H), 3.82 (d, J = 7, 1H), 3.48 (d, J = 9, 1H), 3.43 (s, 3H), 3.35 (d, J = 6, 1H), 3.09 (m, 1H), 2.77 (d, J = 9, 1H), 1.83 (m, 2H), 1.77 (m, 2H), 1.41 (d, J = 6, 6H), 0.97 (s, 9H), 0.83 (s, 9H), 0.01 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 172.2, 169.6, 148.3, 145.3, 121.5, 108.8, 99.6, 81.4, 80.5, 79.2, 78.2, 74.4, 73.1, 69.1, 67.9, 65.8, 59.2, 56.4, 51.7, 36.8, 36.5, 33.1, 29.6, 29.4, 19.1.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-3-yl]non-6-enamide (2.5 g, 4.6 mmol) was dissolved in 30 mL of THF. A total of 1.0 M in THF solution of TBAF (13.8 mL, 14 mmol) was added at room temperature, and the mixture was stirred for 3 h. The mixture was concentrated and chromatographed with a 95:5 mixture

of CH_2Cl_2 and methanol to give 1.8 g (91%) of (2*R*,3*R*,4*S*,5*R*,6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-hydroxy-2*H*-azepin-3-yl]non-6-enamide (**16**) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.61 (d, J = 6, 1H), 6.45 (t, J = 6, 1H), 5.77 (d, J = 6, 1H), 5.52 (dd, J = 6 and 16, 1H), 4.56 (m, 1H), 4.28 (d, J = 6, 1H), 4.06 (d, J = 8, 1H), 4.00 (m, 1H), 3.91 (d, J = 8, 1H), 3.54 (m, 1H), 3.47 (s, 3H), 3.35 (m, 2H), 3.08 (d, J = 8, 1H), 2.76 (d, J = 6, 1), 2.02 (m, 2H), 1.83 (m, 2H), 1.45 (s, 6H), 1.03 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 175.1, 169.7, 145.3, 121.5, 99.7, 83.1, 80.6, 74.5, 73.2, 65.8, 64.6, 59.1, 51.8, 45.9, 34.5, 33.1, 29.5, 29.3, 25.1, 19.1, 13.7.

To a stirred solution of myristic acid (1.2 g, 5.1 mmol) and CH_2Cl_2 (50 mL) was sequentially added EDCI (1.0 g, 5.1 mmol) and DMAP (0.6 g, 5.1 mmol), and the mixture was then stirred at room temperature for 30 min. Then **16** (2.0 g, 4.7 mmol) was added to the reaction mixture, which was then stirred overnight at room temperature. The reaction mixture was adsorbed on silica, then chromatographed (5% MeOH/CH_2Cl_2) to give 2.2 g (74%) of **17** as a pale-yellow solid. A solution consisting of TFA (18 mL), THF (18 mL), and H_2O (12 mL) was added to a stirred solution of **17** (3.4 g, 5.3 mmol) and THF (5 mL) at 0 °C. The reaction was stirred for 1 h at this temperature, then was concentrated in vacuo while maintaining the rotary evaporator bath temperature at ca. 10 °C. MeCN (20 mL) was added to the residue, and the low-temperature concentration procedure was repeated. To the residue was added a solution consisting of NH_4HCO_3 (3 g), MeCN (20 mL), and H_2O (20 mL). The mixture was then concentrated in vacuo and chromatographed (4% MeOH/CH_2Cl_2) to give 2.6 g (82%) of **8a** as a pale-yellow solid. ^{1}H NMR: δ 5.82 (d, J = 15.8, 1H), 5.44 (dd, J = 15.8 and 7.6, 1H), 4.96 (m, 1H), 4.67 (dd, J = 10.7 and 1.9, 1H), 4.15 (t, J = 6.9, 1H), 3.86 (d, J = 7.57, 1H), 3.78 (dd, J = 6.9 and 1.9 1H), 3.59 (m, 2H), 3.49 (dd, J = 15.8 and 5.0, 1H), 3.44 (s, 3H), 2.37 (t, J = 7.6, 2H), 2.10 (m, 2H), 1.87 (m, 2H), 1.64 (m, 2H), 1.31 (m, 21H), 1.06 (s, 9H), 0.92 (t, J = 6.9, 3H). ^{13}C NMR: δ 176.5, 174.6, 173.1, 146.1, 125.6, 83.7, 75.3, 74.5, 72.8, 69.1, 58.9, 53.0, 43.8, 35.3, 33.9, 33.1, 32.9, 30.9, 30.7, 30.6, 30.4, 30.0, 26.8, 26.2, 23.9, 14.6. Anal. ($C_{32}H_{58}N_2O_8$) C, H, N.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-(cyclopentylcarbonyl)oxy-2*H*-azepin-3-yl]non-6-enamide (8b). Cyclopentanecarbonyl chloride (0.47 g, 3.5 mmol) was added dropwise to a stirred solution of **16** (1.0 g, 2.3 mmol) and CH_2Cl_2 (20 mL) at room temperature. To this solution was added Et_3N (0.7 g, 7.0 mmol) dropwise and DMAP (0.5 g, 4.0 mmol). The reaction mixture was stirred at room temperature for 3 h, then washed with water (3×), concentrated in vacuo, and then chromatographed (2% MeOH/CH_2Cl_2) to give 0.8 g of ester that was used directly in the next step. To this compound (0.80 g, 1.5 mmol) was added a solution consisting of TFA (4 mL), THF (14 mL), and H_2O (2 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min, concentrated via rotary evaporation (bath temp of <20 °C), mixed with saturated NH_4HCO_3 (15 mL), and stirred for 15 min. The mixture was concentrated in vacuo and chromatographed (2% MeOH/CH_2Cl_2) to give a white solid. This material was further purified using preparative HPLC (reverse phase eluted with 90% CH_3CN/H_2O) to give 0.24 g (20% for 2 steps) of **8b** as a white solid; mp 75−76 °C. ^{1}H NMR (DMSO): δ 7.81 (d, J = 6.5, 1H), 7.76 (t, J = 6.1, 1H), 5.64 (d, J = 15.8, 1H), 5.34 (dd, J = 15.8 and 2.8, 1H), 4.80 (s, 1H), 4.57 (d, J = 4.7, 1H), 4.48 (d, J = 6.9, 1H), 4.45 (m, 1H), 4.36 (d, J = 5.8, 1H), 3.98 (m, 1H), 3.71 (d, J = 6.9, 1H), 3.57 (td, J = 6.8 and 2.7, 1H), 3.52 (dd, J = 15.6 and 4.6, 1H), 3.34 (td, J = 6.2 and 2.8, 1H), 3.32 (s, 3H), 3.23 (m, 1H), 2.72 (m, 1H), 2.50 (m, 1H), 1.93 (m, 2H), 1.80 (m, 2H), 1.73 (m, 3H), 1.61 (m, 2H), 1.53 (m, 2H), 0.98 (s, 9H). ^{13}C NMR (DMSO): δ 174.75, 173.56, 169.73, 141.69, 125.32, 81.60, 72.82, 72.54, 70.80, 67.20, 57.31, 50.95, 43.21, 32.44, 31.31, 29.45, 29.38, 25.30, 25.23. Anal. ($C_{24}H_{40}N_2O_8 \cdot 0.85\ H_2O$) C, H, N. 57.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-(cyclohexylcarbonyl)oxy-2*H*-azepin-3-yl]non-6-enamide (8c). Triethylamine (8.4 mL, 60 mmol) was added to a solution of cyclohexanecarbonyl chloride (6.3 g, 43.0 mmol), **14** (7.0 g, 28.7 mmol), and 100 mL of CH_2Cl_2 at 5 °C. The reaction mixture was stirred at room temperature overnight. The reaction mixture was then partitioned with water, and the organic layer was dried (Na_2SO_4) and concentrated. The resulting residue was chromatographed (5% EtOAc/CH_2Cl_2) to give 10.1 g (99.5% of (3*S*,6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-(cyclohexanecarbonyl)oxy-2*H*-azepin-2-one as a white solid. ^{1}H NMR ($CDCl_3$): δ 5.89 (d, J = 5.3, 1H), 5.65 (t, J = 4.9, 1H), 4.89 (s, 1H), 4.30 (q, J = 4.1, 1H), 3.49 (m, 2H), 2.31 (tt, J = 10.9 and 3.4, 1H), 2.13 (d, J = 14.3, 1H), 1.98 (d, J = 13.6, 2H), 1.88 (d, J = 14.3, 2H), 1.75 (d, J = 11.3, 2H), 1.66 (s, 2H), 1.45 (s, 9H), 1.30 (m, 5H). To a solution of (3*S*,6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-(cyclohexanecarbonyl)oxy-2*H*-azepin-2-one (10 g, 28.2 mmol) in 40 mL of CH_2Cl_2 was added TFA (25 mL) at room temperature, and the reaction solution was stirred at room temperature for 1 h, then concentrated via rotary evaporation (bath temp of <20 °C). The residue was diluted with CH_2Cl_2 (100 mL) and washed with NH_4OH (10 mL), water (2 × 20 mL), and dried (Na_2SO_4). The reaction mixture was adsorbed on silica and chromatographed (5% MeOH/CH_2Cl_2) to give 6.0 g (85.0%) of (3*S*,6*R*)-3-aminohexahydro-6-(cyclohexanecarbonyl)oxy-2*H*-azepin-2-one (**18**) as a white solid. ^{1}H NMR ($CDCl_3$): δ 6.91 (s, 1H), 4.91 (s, 1H), 4.39 (s, 2H), 3.87 (d, J = 9.8, 1H), 3.48 (t, J = 6.0, 1H), 3.43 (dd, J = 15.5 and 4.9, 1H), 2.30 (tt, J = 10.9 and 3.4, 1H), 2.13 (m, 1H), 1.91 (m, 4H), 1.73 (m, 2H), 1.65 (m, 1H), 1.40 (q, J = 11.7, 4H), 1.24 (m, 2H). A solution consisting of **12** (1.0 g, 3.5 mmol), **18** (2.5 g, 9.8 mmol), and *i*-PrOH (4 mL) was stirred at reflux for 24 h. The reaction mixture was adsorbed on silica and chromatographed (2% methanol/CH_2Cl_2) to give 1.85 g (97%) of (2*R*,3*R*,4*S*,5*R*,6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-(cyclohexylcarbonyl)oxy-2*H*-azepin-3-yl]non-6-enamide as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.58 (d, J = 6.3, 1H), 5.80 (t, J = 7.7, 1H), 5.78 (d, J = 15.8, 1H), 5.53 (dd, J = 15.8 and 6.8 1H), 4.92 (d, J = 3.4, 1H), 4.60 (dd, J = 0.4 and 7.4, 1H), 4.28 (d, J = 6.8, 1H), 4.07 (dd, J = 7.5 and 1.1, 1H), 3.90 (d, J = 7.2, 1H), 3.52 (dd, J = 12.1 and 7.9, 2H), 3.48 (s, 3H), 2.82 (d, J = 9.0, 1H), 2.32 (m, 1H), 2.12 (m, 1H), 2.00 (m, 2H), 1.89 (d, J = 13.1, 2H), 1.75 (m, 4H), 1.66 (m, 1H), 1.46 (d, J = 4.9, 6H), 1.38 (m, 2H), 1.26 (m, 3H), 1.03 (s, 9H).

(2 *R*,3*R*,4*S*,5*R*,6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-(cyclohexylcarbonyl)oxy-2*H*-azepin-3-yl]non-6-enamide (3.8 g, 7.1 mmol) was added in one portion to a stirred solution of TFA (10 mL), THF (10 mL), and water (5 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min, concentrated via rotary evaporation (bath temp of <20 °C), mixed with saturated NH_4HCO_3 (5 mL), and stirred for 15 min. The mixture was concentrated in vacuo and chromatographed (2% methanol/CH_2Cl_2) to give a white solid. This material was further purified using preparative HPLC (reverse phase eluted with 90% CH_3CN/water) to give 2.9 g (82.4%) of **8c** as a white solid; mp 79−80 °C. ^{1}H NMR ($CDCl_3$): δ 8.00 (d, J = 6.3, 1H), 5.98 (t, J = 5.5, 1H), 5.83 (d, J = 15.8, 1H), 5.42 (dd, J = 15.8 and 7.3 1H), 4.93 (m, 1H), 5.56 (m, 1H), 4.22 (m, 2H), 3.82 (m, 2H), 3.81 (t, J = 6.0, 1H), 3.55 (s, 3H), 3.49 (dd, J = 15.8 and 5.4, 1H), 3.30 (d, J = 7.3, 1H), 3.10 (s, 1H), 2.31 (m, 1H), 2.16 (d, J = 11.2, 1H), 2.00 (m, 2H), 1.88 (m, 3H), 1.76 (s, 2H), 1.65 (d, J = 0.9, 1H), 1.42 (m, 2H), 1.25 (m, 4H), 1.02 (s. 9H). ^{13}C NMR ($CDCl_3$): δ 175.19, 174.11, 172.12, 145.74, 123.20, 81.10, 74.50, 72.75, 72.45, 66.74, 59.93, 51.66, 43.31, 43.22, 33.03, 31.96, 29.43, 29.07, 29.00, 25.70, 25.65, 25.39, 25.36. Anal. ($C_{25}H_{42}N_2O_8$) C, H, N.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-(cycloheptylcarbonyl)oxy-2*H*-azepin-3-yl]non-6-enamide (8d). Following essentially the procedure for **8c** and using in place of cyclohexanecarbonyl chloride an approximately equivalent amount of a mixture consisting of cycloheptanecarboxylic acid, EDCI, and DMAP, **8d** was obtained; mp 84−86 °C. ^{1}H NMR

($CDCl_3$): δ 8.00 (d, J = 6.3, 1H), 5.93 (t, J = 5.5, 1H), 5.83 (d, J = 15.8, 1H), 5.42 (dd, J = 15.7 and 7.3, 1H), 4.93 (m, 1H), 4.55 (dd, J = 9.5 and 6.3, 1H), 4.23 (m, 2H), 3.82 (m, 2H), 3.61 (t, J = 6.1, 1H), 3.57 (m, 1H), 3.55 (s, 3H), 3.49 (dd, J = 15.6 and 5.2, 1H), 3.29 (d, J = 7.3, 1H), 3.10 (s, 1H), 2.50 (m, 1H), 2.17 (m, 1H), 1.95 (m, 4H), 1.70 (m, 1H), 1.65 (m, 2H), 1.55 (m, 4H), 1.47 (m, 4H), 1.02 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 176.17, 174.07, 172.14, 145.75, 123.20, 81.08, 74.51, 72.76, 72.44, 66.79, 59.95, 51.67, 45.07, 43.36, 33.03, 31.95, 30.91, 30.84, 29.43, 28.24, 28.21, 26.26, 25.73. Anal. ($C_{26}H_{44}N_2O_8 \cdot 0.6H_2O$) C, H, N.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-(cyclohexylmethylcarbonyl)oxy-2*H*-azepin-3-yl]non-6-enamide (8e). Following essentially the procedure for **8a** and using in place of myristic acid an approximately equivalent amount of cyclohexylacetic acid, **8e** was obtained. HPLC reverse-phase retention time = 13.8 min, normal-phase retention time = 7.7 min (method 1). ^{1}H NMR ($CDCl_3$): δ 7.98 (d, J = 6.2, 1H), 5.83−5.7 (m, 1H), 5.80 (d, J = 15.6, 1H), 4.94 (m, 1H), 4.52 (m, 1H), 4.2 (m, 2H), 3.78 (m, 2H), 3.6−3.48 (m, 3H), 3.52 (s, 3H), 3.23 (d, J = 7.3, 1H), 3.06 (m, 1H), 2.80 (d, J = 7, 2H), 2.13−1.63 (m, 12H), 1.30−0.85 (m, 5H), 1.0 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.0, 172.3, 172.2, 145.7, 123.3, 81.1, 74.5, 72.8, 72.5, 67.0, 60.0, 51.7, 43.5, 42.1, 35.0, 33.0, 32.0, 29.5, 26.1, 26.0, 25.7.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-(1-oxo-2-phenylethoxy)-2*H*-azepin-3-yl]non-6-enamide (8f). Following essentially the procedure described for **8a** and using in place of myristic acid an approximately equivalent amount of phenylacetic acid, **8f** was obtained. HPLC reverse-phase retention time = 11.9 min, normal-phase retention time = 7.8 min (method 1). ^{1}H NMR ($CDCl_3$): δ 7.96 (d, J = 6.2, 1H), 7.28 (m, 5H), 5.80 (d, J = 15.8, 1H), 5.68 (t, J = 6.4, 1H), 5.39 (dd, J = 15.8 and 7.3, 1H), 4.93 (m, 1H), 4.53−4.47 (m, 1H), 4.22−4.18 (m, 2H), 3.60−3.56 (m, 2H), 3.52 (s, 3H), 3.48−3.38 (m, 2H), 3.27 (d, J = 6.6, 1H), 3.08 (s, 1H), 2.15−1.67 (m, 5H), 1.0 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 173.9, 172.1, 170.8, 145.8, 133.6, 129.2, 128.8, 127.4, 123.2, 81.1, 74.5, 72.7, 72.4, 67.6, 59.9, 51.6, 43.2, 41.5, 33.0, 31.8, 29.4, 25.5.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-(1-oxo-3-phenylpropoxy)-2*H*-azepin-3-yl]non-6-enamide (8g). Following essentially the procedure for **8b** and using in place of cyclopentanecarbonyl chloride an approximately equivalent amount of 3-phenylpropionyl chloride, **8g** was obtained; mp 75−77 °C;. ^{1}H NMR ($CDCl_3$): δ 7.96 (d, J = 6.2, 1H), 7.31 (t, J = 7.3, 2H), 7.23 (t, J = 7.6, 1H), 7.20 (d, J = 7.4, 2H), 5.82 (d, J = 15.8, 1H), 5.62 (s, 1H), 5.41 (dd, J = 15.8 and 7.1, 1H), 4.92 (s, 1H), 4.49 (dd, J = 9.5 and 6.3, 1H), 4.22 (m, 2H), 3.80 (m, 2H), 3.60 (s, 1H), 3.52 (s, 3H), 3.37 (m, 3H), 3.17 (s, 1H), 2.95 (t, J = 7.6, 2H), 2.67 (t, J = 7.7, 2H), 2.06 (d, J = 12.0, 1H), 1.96 (t, J = 12.8, 1H), 1.88 (s, 1H), 1.70 (m, 1H), 1.02 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 173.96, 172.05, 172.00, 145.68, 140.08, 128.61, 128.42, 126.52, 123.21, 81.18, 74.46, 72.69, 72.50, 67.14, 59.83, 51.49, 43.22, 35.78, 33.02, 31.79, 31.07, 29.43, 25.58. Anal. ($C_{27}H_{40}N_2O_8 \cdot 0.52H_2O$) C, H, N.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-(1-oxo-3-phenyl-2-propenoxy)-2*H*-azepin-3-yl]non-6-enamide (8h). Following essentially the procedure for **8b** and using in place of cyclopentanecarbonyl chloride an approximately equivalent amount of cinnamoyl chloride, **8h** was obtained; mp 83−85 °C. ^{1}H NMR (DMSO): δ 8.03 (m, 1H), 7.71 (d, J = 16, 1H), 7.54 (m, 2H), 7.41 (m, 2H), 6.45 (d, J = 16, 1H), 5.97 (m, 1H), 5.81 (d, J = 16, 1H), 5.45 (dd, J = 16 and 8, 1H), 5.09 (m, 1H), 4.58 (m, 1H), 4.22 (m, 2H), 3.81 (m, 2H), 3.62 (m, 4H), 3.54 (s, 3H), 3.30 (d, J = 8, 1H), 3.10 (s, 1H), 2.25 (m, 1H), 2.00 (m, 3H), 1.02 (s, 9H). ^{13}C NMR (DMSO): δ 174.10, 172.15, 166.01, 145.91, 145.75, 134.03, 130.70, 129.00, 128.22, 123.20, 117.34, 81.10, 74.50, 72.76, 72.46, 67.29, 59.93, 51.67, 43.51, 33.03, 32.00, 29.43, 25.75. Anal. ($C_{27}H_{38}N_2O_8 \cdot H_2O$) C, H, N.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-(1-oxo-3-[3-pyridyl]ethoxy)-2*H*-azepin-3-yl]non-6-enamide (8i). Following essentially the procedure described for **8a** and using in place of myristic acid an approximately equivalent amount of a mixture consisting of 3-pyridylacetic acid, EDCI, and DMAP, **8i** was obtained. HPLC reverse-phase retention time = 7.9 min; normal-phase retention time = 12.1 min (method 2). ^{1}H NMR ($CDCl_3$): δ 8.51 (s, 2H), 7.98 (d, J = 6.0, 1H), 7.61 (d, J = 7.8, 1H), 7.27 (m, 2H), 6.29 (m, 1H), 5.80 (d, J = 15.6, 1H), 5.4 (dd, J = 15.6 and 7.3, 1H), 4.96 (m, 1H), 4.55 (m, 1H), 4.21 (m, 1H), 3.82 (m, 2H), 3.67−3.45 (m, 9H), 2.2−1.7 (m, 5H), 1.0 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.1, 172.0, 169.9, 150.2, 148.7, 145.7, 136.9, 129.4, 123.6, 123.4, 81.5, 74.4, 72.6, 72.6, 68.3, 59.8, 51.6, 43.2, 38.6, 33.0, 31.8, 29.5, 25.6.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-(1-oxo-3-[3-pyridyl]propoxy)-2*H*-azepin-3-yl]non-6-enamide (8j). Following essentially the procedure described for **8a** and using in place of myristic acid an approximately equivalent amount of 3-pyridinepropionic acid, **8j** was obtained. HPLC reverse-phase retention time = 8.1 min; normal-phase retention time = 12.9 min (method 2). ^{1}H NMR ($CDCl_3$): δ 8.46 (s, 2H), 7.97 (d, J = 6.2, 1H), 7.53 (m, 1H), 7.23 (m, 1H), 5.88 (t, J = 6.0, 1H), 5.81 (d, J = 15.6, 1H), 5.4 (dd, J = 15.6 and 7.3, 1H), 4.93 (m, 1H), 4.27 (s, 1H), 4.23−4.19 (m, 1H), 3.8 (m, 2H), 3.59 (d, J = 5.2, 1H), 3.52 (s, 3H), 3.48 (m, 2H), 3.28 (s, 1H), 3.19 (s, 1H), 2.95 (t, J = 7.3, 2H), 2.67 (t, J = 7.3, 2H), 2.1−1.67 (m, 6H), 1.0 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.0, 172.0, 171.5, 149.7, 148.0, 145.7, 136.0, 135.5, 123.6, 123.2, 81.2, 74.5, 72.7, 72.5, 67.6, 59.8, 51.6, 43.3, 35.2, 33.0, 31.8, 29.4, 28.0, 25.5.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-(phenylcarbonyl)oxy-2*H*-azepin-3-yl]non-6-enamide (8k). Following essentially the procedure for **8b** and using in place of cyclopentanecarbonyl chloride an approximately equivalent amount of benzoyl chloride, **8k** was obtained. ^{1}H NMR: δ 8.06 (d, J = 8.4, 2H), 7.63 (t, J = 7.4, 1H), 7.50 (t, J = 7.8, 2H), 5.82 (d, J = 15.8, 1H), 5.44 (dd, J = 15.8 and 7.6, 1H), 4.75 (dd, J = 9.5 and 3.2, 1H), 4.16 (t, J = 7.7, 1H), 3.88 (d, J = 7.3, 1H), 3.80 (dd, J = 7.1 and 2.0, 1H), 3.72 (d, J = 15.6, 1H), 3.60 (dd, J = 6.9 and 2.0, 1H), 3.45 (s, 3H), 2.30 (d, J = 15.3, 1H), 2.20 (m, 1H), 1.99 (m, 1H), 1.06 (s, 9H). ^{13}C NMR: δ 175.05, 171.57, 165.44, 144.53, 132.97, 130.06, 129.19, 128.17, 123.98, 82.11, 73.77, 72.95, 71.20, 68.23, 57.34, 51.50, 47.52, 42.39, 32.34, 31.41, 28.46, 25.40. Anal. ($C_{25}H_{36}N_2O_8 \cdot 0.83H_2O$) C, H, N.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-([4-pentylphenyl]carbonyl)oxy-2*H*-azepin-3-yl]non-6-enamide (8l). Following essentially the procedure for **8b** and using in place of cyclopentanecarbonyl chloride an approximately equivalent amount of 4-pentylbenzoyl chloride, **8l** was obtained. ^{1}H NMR: δ 7.94 (d, J = 8.5, 2H), 7.29 (d, J = 8.1, 2H), 5.79 (d, J = 15.4, 1H), 5.41 (dd, J = 15.8 and 7.7, 1H), 5.17 (m, 1H), 4.72 (m, 1H), 4.12 (t, J = 7.0, 1H), 3.85 (d, J = 7.4, 1H), 3.76 (dd, J = 7.0 and 1.8 1H), 3.61 (d, J = 5.2, 1H), 3.57 (dd, J = 7.0 and 2.2, 1H), 3.42 (s, 3H), 2.67 (t, J = 7.7, 2H), 2.20 (m, 2H), 1.95 (m, 2H), 1.63 (m, 2H), 1.32 (m, 4H), 1.02 (s, 9H), 0.89 (t, J = 7.0, 3H). ^{13}C NMR: δ 176.96, 173.72, 167.31, 150.82, 146.39, 131.14, 130.11, 129.08, 125.79, 83.93, 75.71, 74.78, 73.46, 73.07, 59.19, 53.29, 46.01, 37.30, 34.37, 34.20, 32.99, 32.48, 30.29, 30.14, 23.97, 14.79. Anal. ($C_{30}H_{46}N_2O_8 \cdot 0.5H_2O$) C, H, N.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-([4-decylphenyl]carbonyl)oxy-2*H*-azepin-3-yl]non-6-enamide (8m). Following essentially the procedure described for **8a** and using in place of myristic acid an approximately equivalent amount of decylbenzoic acid, **8m** was obtained; mp 60−64 °C. ^{1}H NMR ($CDCl_3$): δ 8.06 (d, J = 6, 1H), 7.94 (d, J = 8, 2H), 7.26 (d, J = 8, 2H), 6.10 (t, J = 7, 1H), 5.85 (d, J = 16, 1H), 5.45 (dd, J = 8 and 16, 1H), 5.22 (d, J = 3, 1H), 4.64 (dd, J = 6 and 8, 1H), 4.25 (t, J = 6, 2H), 3.84 (dd, J = 6 and 11, 2H), 3.69 (t, J = 7, 1H), 3.63 (dd, J = 5 and 8, 2H), 3.56 (s, 3H), 2.68 (t, J = 8, 2H), 2.34 (d, J = 13, 1H), 2.14 (t, J = 12, 1H), 2.04 (t, J = 11, 1H), 1.96 (t, J = 3, 1H), 1.63 (m, 2H), 1.32 (m, 18H), 1.82

(m, 2H), 1.05 (s, 9H), 0.90 (t, $J = 7$, 3H). ^{13}C NMR ($CDCl_3$): δ 174.1, 172.1, 165.5, 149.3, 145.7, 129.7, 128.6, 127.0, 123.2, 81.1, 74.5, 72.7, 72.4, 67.4, 59.9, 51.7, 43.5, 36.0, 33.0, 32.1, 31.9, 31.1, 29.6, 29.5, 29.4, 29.3, 29.2, 25.9, 22.6, 14.1. Anal. ($C_{35}H_{56}N_2O_8 \cdot 0.4H_2O$) C, H, N.

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*,6*R*)-hexahydro-2-oxo-6-([4-*n*-decyloxyphenyl]carbonyl)oxy-2*H*-azepin-3-yl]non-6-enamide (8n). Following essentially the procedure described for **8a** and using in place of myristic acid an approximately equivalent amount of 4-decyloxybenzoic acid, **8n** was obtained; mp 70−74 °C. ^{1}H NMR ($CDCl_3$): δ 8.06 (d, $J = 6$, 1H), 7.96 (d, $J = 9$, 2H), 6.90 (d, $J = 9$, 2H), 6.05 (t, $J = 6$, 1H), 5.80 (d, $J = 15$, 1H), 5.44 (dd, $J = 7$ and 15, 1H), 5.20 (m, 1H), 4.63 (m, 1H), 4.25 (t, $J = 6$, 1H), 4.02 (t, $J = 6$, 2H), 3.84 (dd, $J = 7$ and 13, 2H), 3.69 (m, 1H), 3.62 (m, 2H), 3.38 (d, $J = 5$, 1H), 3.56 (s, 3H), 3.33 (s, 1H), 3.15 (s, 1H), 2.32 (d, $J = 12$, 1H), 2.13 (t, $J = 12$, 1H), 2.01 (m, 2H), 1.82 (m, 2H), 1.48 (m, 2H), 1.30 (m, 12H), 1.05 (s, 9H), 0.94 (t, $J = 6$, 3H). ^{13}C NMR ($CDCl_3$): δ 174.1, 172.1, 165.2, 163.4, 145.7, 131.7, 123.2, 121.6, 114.2, 81.1, 74.5, 72.7, 72.4, 68.3, 67.2, 59.9, 51.7, 43.6, 33.0, 32.1, 31.9, 29.5, 29.4, 29.3, 29.2, 29.0, 25.9, 25.9, 22.6, 14.1. Anal. ($C_{35}H_{56}N_2O_9$) C, H, N.

(6*E*)-6,7,8,9-Tetradeoxy-8,8-dimethyl-2-*O*-methyl-3,5-*O*-(1-methylethylidene)-*gulo*-non-6-enonic Acid Lactone (12). To a 2 L round-bottom flask was added $CrCl_2$ (50 g, 41 mmol), anhydrous THF (750 mL), and DMF (32 mL). The mixture was stirred under N_2 for 1 h. A solution of 2,4-*O*-(1-methylethylidene)-5-*O*-methyl-L-glucuronic γ-lactone (**11**, prepared as described in ref 4b) (12 g, 50 mmol), 1,1-diiodo-2,2-dimethylpropane (15 mL), and 500 mL of anhydrous THF was added slowly to the reaction mixture. After the addition, the reaction mixture was stirred at ambient temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl. The residue was partitioned with EtOAc/water and chromatographed (5% EtOAc/CH_2Cl_2) to give 9 g (63%) of the desired compound as a white crystalline solid. ^{1}H NMR ($CDCl_3$): δ 5.82 (d, 1H), 5.58 (q, 1H), 4.71 (m, 1H), 4.46 (m, 1H), 4.10 (dd, 1H), 4.0 (m, 1H), 3.66 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H), 1.07 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 172.5, 147.0, 120.2, 98.7, 79.1, 71.9, 70.3, 67.6, 59.2, 33.2, 29.3, 19.3. Anal. ($C_{15}H_{24}O_5$) C, H, N.

MDA-MB-435 Monolayer Growth Assay. The effect of bengamides on monolayer cell proliferation of MDA-MB-435 breast carcinoma was measured using an adaptation of published procedures.[11] Cells were plated in 96-well plates at initial densities of ~3000 cells/well. One day following plating, test compounds were added (in a final volume of 100 μL) to the test plates. Control plates receive 10 μL of 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium, an inner salt (MTS) mixture (prepared fresh on day of addition to cell plates 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), and 100 μL of media. The A_{490} value of control plates is read 4 h after MTS addition to determine initial cell density values for each cell line. Three days after addition of a test compound, 10 μL/well of MTS mixture was added to the test plates, and A_{490} was read 4 h later. A_{490} values for wells containing cells were corrected for media absorbance, then normalized to initial density readings to determine percent net growth. IC_{50} values were determined from graphs of percent net growth as a function of compound concentration. Percent net growth is calculated as (cell + drug A_{490} − initial A_{490})/(cell + drug vehicle A_{490} − initial A_{490}).

MDA-MB-435 Xenograft Studies. About 3 million cells were implanted subcutaneously into the right flank of athymic (nu/nu) mice and were allowed to grow until a volume of approximately 30 mm^3 was established. The test compounds were administered three times per week intravenously (iv) for 3 weeks in 5% dextrose and 10% DMSO in water. The test compounds were administered in dose−response fashion in order to evaluate and document the full potential range of activity (efficacy and toxicity) for a given compound. Positive controls were carried out with doxorubicin administered three times per week iv.

Toxicity was monitored by recording average group body weights twice weekly and by daily observation of general health. Efficacy was monitored by taking measurements of tumor length, width, and depth weekly using digital calipers coupled to automated data collectors. Mean tumor volume (MTV) at initiation of therapy was subtracted from final MTV in order to express the actual tumor growth during treatment (Δ MTV). Antitumor activity was expressed as % T/C ((Δ MTV of treated group/Δ MTV of control group) × 100%). Regressions were calculated using the formula $T/(T_0 - 1) \times 100\%$, where T is the tumor volume for the treatment group at the end of the experiment and T_0 is the tumor volume at the beginning of the experiment. Statistical significance was evaluated using a one-tailed Student's *t*-test (∗ indicates $p < 0.05$, ∗∗indicates $p < 0.01$).

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