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An Array of Bengamide E Analogues Modified at the Terminal Olefinic Position: Synthesis and Antitumor Properties

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Dedicated to Professor A. Vasella on the occasion of his 70th birthday.

Based on our previously described synthetic strategy for bengamide E, a natural product of marine origin with antitumor activity, a small library of analogues modified at the terminal olefinic position was generated with the objective of investigating the effect of structural modifications on antitumor properties. Biological evaluation of these analogues, consisting of IC_{50} determinations against various tumor cell lines, revealed important aspects with respect to the structural requirements of this olefinic position for activity. Interestingly, the analogue possessing a cyclopentyl group displayed greater potency than the parent bengamide E, representing a key finding upon which to base further investigations into the design of new analogues with promising biological activities.

Introduction

Marine sponges of the *Jaspidae* genus have proven to be an extraordinary source of bioactive secondary metabolites. These notable metabolites include the cyclodepsipeptide jaspamide,[1] the polyketides bengamides,[2] and bengazoles.[3] Particularly striking are the bengamides, which represent a wide family of natural products with promising antitumor properties that were isolated by Crews and co-workers in the late 1980s.[2] This discovery was followed by the identification of new bengamide family members,[4] including the recent isolation of bengamides E, E′, and F′, from *Myxococcus virescens* bacteria (Figure 1).[5] Their prominent antitumor, antibiotic, and antihelminthic activities[6] have prompted intense research activity in the chemical and biological fields. Their antitumor properties, demonstrated by preliminary potent activity against larynx epithelial carcinoma (1.0 μg mL^{-1}),[2] were further evaluated against human breast MDA-MB-435 carcinoma cells. These biological studies revealed that bengamides A and B were the most potent members of the family, with IC_{50} values of 0.001 and 0.0024 μM, respectively, and an IC_{50} value of 3.3 μM for bengamide E.[2d] In order to unravel the mechanism of action of these natural products, Towbin et al. conducted proteomic

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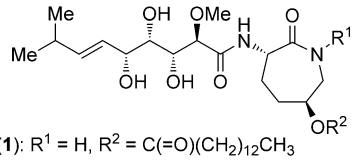
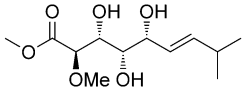
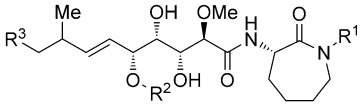
Bengamides Type I



Bengamide A (**1**): R^1 = H, R^2 = C(=O)$(CH_2)_{12}CH_3$
Bengamide B (**2**): R^1 = CH_3, R^2 = C(=O)$(CH_2)_{12}CH_3$
Bengamide G (**3**): R^1 = H, R^2 = C(=O)$(CH_2)_{11}CH_3$
Bengamide H (**4**): R^1 = CH_3, R^2 = C(=O)$(CH_2)_{11}CH_3$
Bengamide I (**5**): R^1 = H, R^2 = C(=O)$(CH_2)_{13}CH_3$
Bengamide J (**6**): R^1 = CH_3, R^2 = C(=O)$(CH_2)_{13}CH_3$
Bengamide L (**7**): R^1 = H, R^2 = C(=O)$(CH_2)_{11}CH(CH_3)_2$
Bengamide M (**8**): R^1 = CH_3, R^2 = C(=O)$(CH_2)_{11}CH(CH_3)_2$
Bengamide N (**9**): R^1 = H, R^2 = C(=O)$(CH_2)_{10}CH(CH_3)_2$
Bengamide O (**10**): R^1 = CH_3, R^2 = C(=O)$(CH_2)_{10}CH(CH_3)_2$
Bengamide Y (**11**): R^1 = R^2 = H
Bengamide Z (**12**): R^1 = CH_3, R^2 = H
Bengamide C (**13**): R^1 = H, R^2 =
Bengamide D (**14**): R^1 = CH_3, R^2 =



Bengamides Type II



Bengamide E (**15**): R^1 = R^2 = R^3 = H
Bengamide F (**16**): R^1 = CH_3, R^2 = R^3 = H
Bengamide E' (**17**): R^1 = R^2 = H, R^3 = CH_3
Bengamide F' (**18**): R^1 = R^3 = CH_3, R^2 = H
Bengamide P (**19**): R^1 = R^3 = H, R^2 = C(=O)$(CH_2)_{12}CH_3$
Bengamide Q (**20**): R^1 = CH_3, R^3 = H, R^2 = C(=O)$(CH_2)_{12}CH_3$
Bengamide R (**21**): R^1 = R^3 = H, R^2 = C(=O)$(CH_2)_{14}CH_3$

Figure 1. Molecular structures of natural bengamides.

studies[7] demonstrating that both methionine aminopeptidases types 1 and 2 (MetAp1 and MetAp2), enzymes responsible for the cleavage of the N-terminal initiator methionine residue during protein synthesis,[8] were the direct cellular targets of the bengamides. This mechanism of action was supported by measuring the inhibitory activity exerted by representative natural bengamides against MetAp1 and 2 (Table 1),[9] together

Table 1. Inhibition of MetAp enzymatic activity.

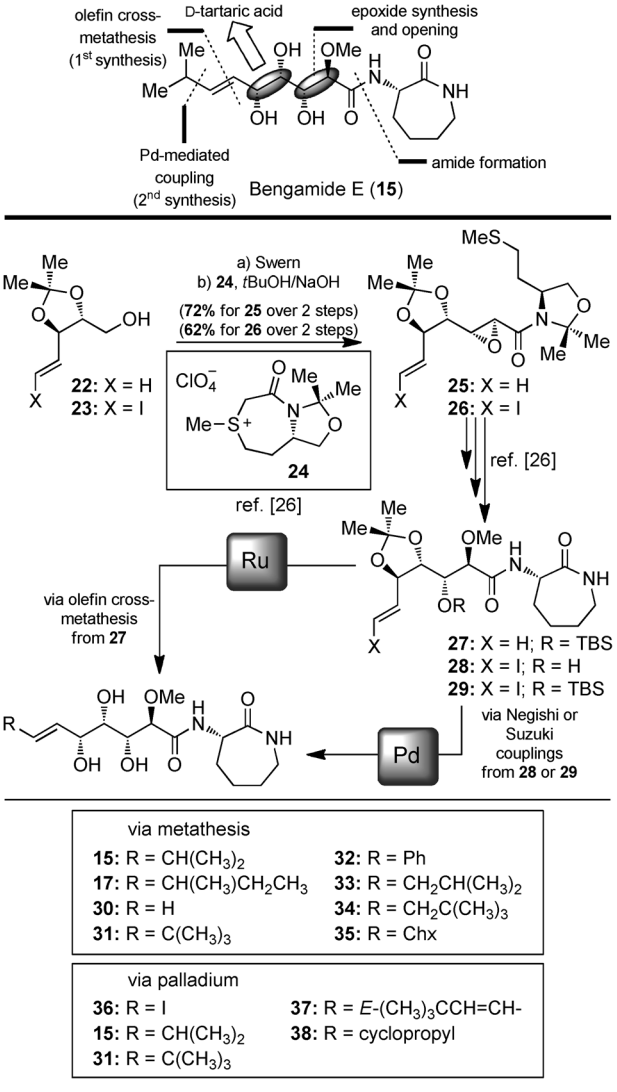
Compound	IC_{50} [μM][a]	
	MetAp1	MetAp2
Bengamide A (**1**)	1.9 ± 0.2	10.5 ± 3.8
Bengamide B (**2**)	29.3 ± 10.4	17.9 ± 7.9
Bengamide M (**8**)	5.4 ± 2.3	> 50
Bengamide O (**10**)	2.7 ± 0.4	> 50

[a] Data from Liu et al.[9]

with the crystallization and subsequent X-ray analysis of the complex enzyme–bengamide.[7] The biological effect of inhibiting MetAps is the blockade of cell cycle division in endothelial cells at the G1 and G2 phases[10] as well as an anti-angiogenic effect in epithelial cells.[11] Interestingly, a similar mode of action is displayed by the anti-angiogenic agents fumagillin and ovalicin,[12] despite their structural differences. However, while these compounds selectively inhibit MetAp2,[13,14] the bengamides bind to both MetAp types. This lack of selectivity may be the reason for the poor pharmacokinetic properties and undesired side effects exhibited by bengamide analogue LAF389,[15] which was considered as a clinical candidate but has not been approved as a treatment for cancer.[16] Despite these studies toward the identification of the molecular targets of fumagillin and the bengamides, the proposed mechanism of action remains controversial.[17]

At the molecular level, Liu discovered that inhibition of methionine aminopeptidase by bengamide A hampered N-myristoylation of proto oncogene *c*-Src, which produced a significant decrease in its tyrosine kinase activity, resulting in a remarkable delay in cell cycle progression.[9] Therefore, inhibition of these enzymes could indirectly impair the functions of *c*-Src and likely other oncogenes that are essential for tumor growth. In addition to these biological findings, Crews and colleagues recently discovered that the bengamides behave as immunemodulating agents, owing to their inhibition of nuclear factor κB (NF-κB).[5] These studies suggest that the bengamides may serve as therapeutic leads for the treatment of inflammatory diseases. These biological activities exhibited by the bengamides, combined with their interesting molecular structures, have generated intense synthetic pursuits in the last few years.[18] Similarly, the antitumor activity possessed by the bengamides stimulated the design and synthesis of bengamide analogues, which led to the discovery of potent compounds with cytotoxicities in the low nanomolar range and improved solubilities in water with respect to those displayed by the natural counterparts.[19–21] The ability of the bengamides to inhibit methionine aminopeptidase has also been exploited in the design of new potential leads for the treatment of tuberculosis.[22]

Our interest in these molecules prompted us to engage in a project directed toward the establishment of an efficient synthesis of the bengamides and related analogues. At the outset of our work, we used a Sharpless asymmetric epoxidation followed by an oxirane ring-opening reaction to generate the C2/C3 system.[23,24] In addition, an olefin cross-metathesis allowed the stereoselective introduction of a terminal olefinic substituent. Later, the design and synthesis of a new class of chiral sulfonium salts in our labs,[25] such as **24**, proved to be efficient and high-yielding tools for asymmetric synthesis of epoxyamides and encouraged us to use them for synthesis of the bengamides.[26] Therefore, starting from alcohols **22** or **23**, we prepared the corresponding epoxyamides **25** and **26** in good yields and excellent stereoselectivities. From these epoxyamides, we synthesized compounds **27**–**29**, which were finally directed toward bengamide E and a wide array of analogues, such as **30**–**38**, via olefin cross-metathesis or palladium-mediated couplings (Scheme 1). The invention of this new asymmetric



Scheme 1. Synthetic strategy for bengamides based on chiral sulfur ylides.

epoxidation methodology, combined with palladium-assisted coupling from vinyl iodides **28** or **29**, made possible an efficient and straightforward synthesis of the bengamides compared to our previous synthesis.[24]

Having established efficient and convergent routes toward the bengamides, our next goal was the design of a library of bengamide analogues for biological evaluation. The structures of the bengamides are amenable to modification by changing the configuration of certain stereocenters of the polyketide chain, the geometry of the double bond, the substituents of the terminal olefinic position, and the nature of the caprolactam residue. Our synthetic strategy toward these molecules was therefore designed on the premise of modifying these elements so as to reach optimum molecular diversity and obtain the maximum number of library members. Biological screening of these compounds was expected to lead to the establishment of sufficient structure–activity relationships to facilitate the next step of this research, consisting of the design, synthesis, and identification of potential drug candidates.

Apart from the bengamide analogue LAF-389 (**39**)[19] and other related compounds, such as **40**[20] and **41**[21] (Figure 2), in which the isopropyl moiety was replaced with a *tert*-butyl group, no other structural modifications have been undertaken

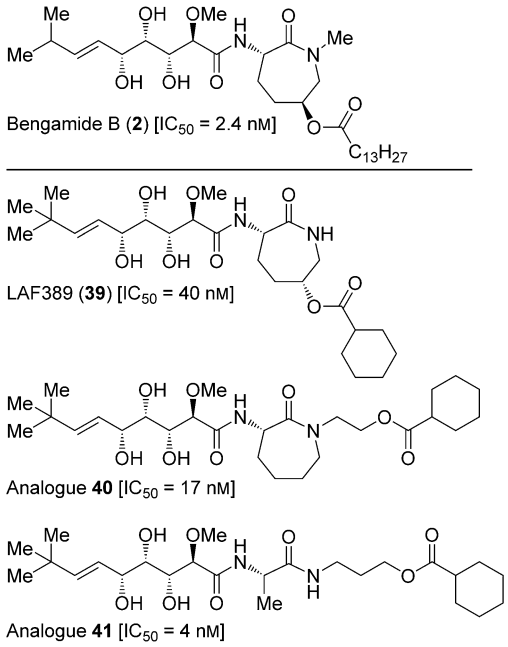


Figure 2. Representative *tert*-butyl bengamide analogues and their cytotoxicities toward MDA-MB-435 human breast cancer cells.

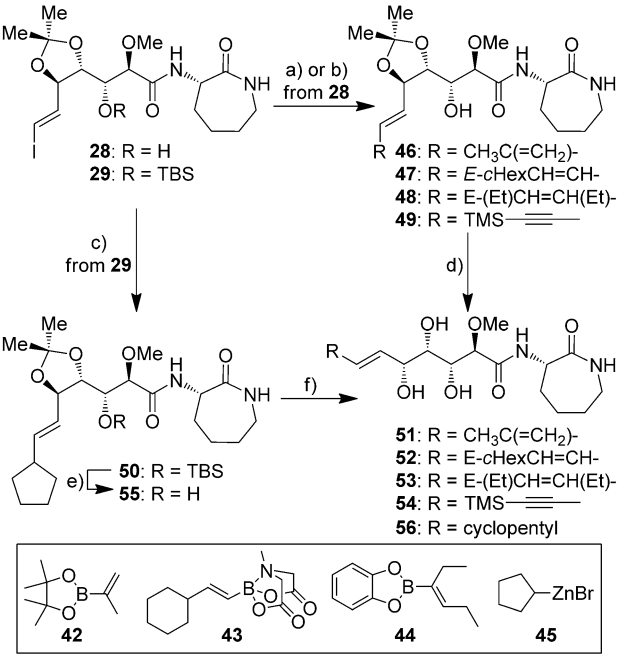
in this region of the molecule. Our synthetic strategy allows us to introduce a wide array of substituents at this terminal olefinic position via a ring closing metathesis or a palladium-mediated coupling reaction. In the present article, we wish to report the synthesis of an array of terminal olefinic position-modified analogues of bengamide E and the corresponding biological evaluation of these compounds, including natural bengamides E and E′, against a panel of different tumor cell lines. To accomplish this goal, we relied on our previous synthetic strategy, using chiral sulfonium salts, to construct the targeted bengamide analogues.

Results and Discussion

Chemistry

Our previous synthetic studies on the bengamides provided a basis for the generation of a wide range of analogues modified at the terminal olefinic position. Together with the bengamide analogues previously prepared,[26] as indicated in Scheme 1, we decided to complete this initial list with the inclusion of new derivatives. In particular, compounds **46**–**50** were synthesized from vinyl iodide precursors **28** or **29** via Suzuki[27] (**46**–**48**), Sonogashira[28] (**49**), and Negishi[29] (**50**) couplings in modest to good yields. Removal of the protecting groups by direct acidic hydrolysis for **46**–**49**, or sequential TBAF and acidic treatments for **50**, afforded the analogue series of bengamide E, compounds **51**–**54** and **56** (Scheme 2).

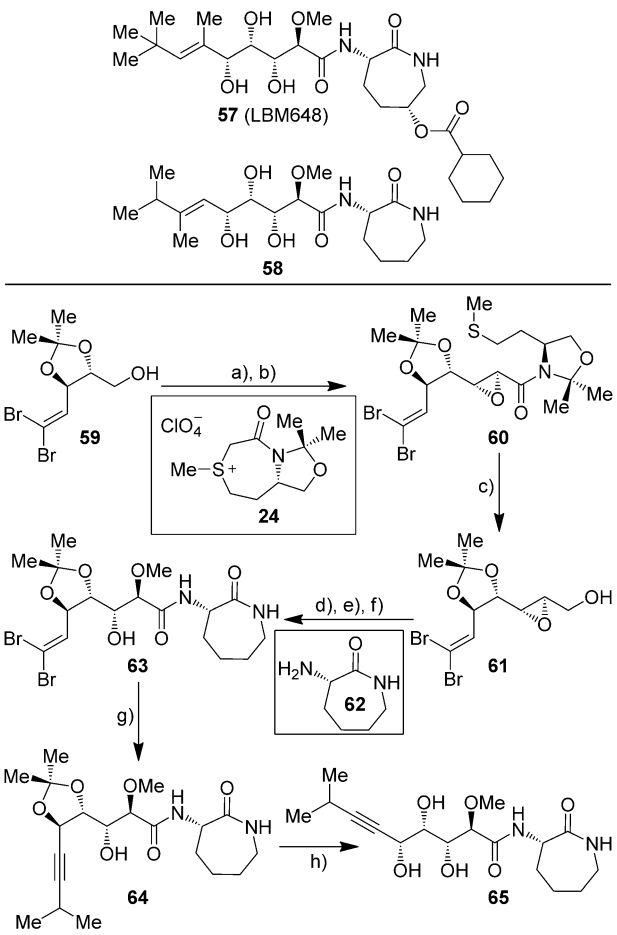
Among the various modifications at the terminal olefinic position, it was determined that additional alkyl groups could provide a positive interaction with the hydrophobic pocket of the methionine aminopeptidase active site. This assumption was supported by the recent discovery of LAF-389-related



Scheme 2. Synthesis of bengamide E analogues **51**–**54** and **56**. *Reagents and conditions*: a) 1.2 equiv **42**, 0.2 equiv $Pd(PPh_3)_4$, 2.0 equiv Tl_2CO_3, THF/H_2O (3/1), 60 °C, 18 h, or 1.2 equiv **43**, 0.2 equiv $Pd(dpephos)Cl_2$, 2.0 equiv Tl_2CO_3, THF/H_2O (3:1), 60 °C, 5 h, or 1.2 equiv **44**, 0.2 equiv $Pd(dpephos)Cl_2$, 2.0 equiv Tl_2CO_3, THF/H_2O (3:1), 50 °C, 1 day, 36% for **46**, 67% for **47**, 54% for **48**; b) 1.3 equiv TMSC≡CH, 0.2 equiv Cu^I, 0.2 equiv PPh_3, 0.1 equiv $Pd(OAc)_2$, 2.0 equiv NEt_3, C_6H_6, 25 °C, 2 h, 79% for **49**; c) 5.0 equiv **45**, 0.2 equiv $Pd(PPh_3)_4$, THF, 25 °C, 10 h, 61%; d) 70% AcOH in H_2O, MeOH, 70 °C, 1–2 h, or 5 days at 25 °C, 53% for **51**, 58% for **52**, 45% for **53**, 28% for **54**; e) 2.0 equiv TBAF (1.0 M in THF), THF, 25 °C, 1 h, 97%; f) 70% AcOH in H_2O, MeOH, 70 °C, 1–2 h, 49% for **56**.

compound **57**, named LBM648,[16] which was identified as a potent and selective inhibitor of MetAp2 with an extra methyl group located at the olefinic C6 position. To more fully probe the biological significance of the presence of additional methyl groups at the olefinic position, we initially targeted the 7-methyl analogue of bengamide E, compound **58**. For the synthesis, we selected *gem*-dibromoalkenyl alcohol **59**[30] as a suitable precursor for a subsequent controlled double alkylation of the double bond. Alcohol **59** was then subjected to a Swern oxidation,[31] followed by reaction with sulfonium salt **24** under basic conditions according to our two-phase method[32] to afford epoxyamide **60** as only one diastereomer and in 62% overall yield from **59**. Compound **60** was then transformed following the synthetic strategy delineated for the bengamides, which entailed a) super-H reduction[33] to obtain epoxy alcohol **61**, b) an oxirane ring-opening of the resulting epoxy alcohol with methanol by modification of the Miyashita methodology,[34] c) selective oxidation of the resulting diol to the carboxylic acid with TEMPO/BAIB in the presence of water,[35] and d) coupling with the commercially available amino caprolactam **62** to obtain the advanced precursor **63** without difficulties. With this compound in hand, we proceeded with the sequential Negishi reactions in which an initial coupling should involve preferentially a bromine at the *trans* olefinic position where an isopropyl group should be initially installed.[36] However, to our dismay, the attempted controlled coupling, by treatment of **63** with one equivalent of diisopropylzinc in the presence of $Pd(dpephos)Cl_2$, did not produce the desired monocoupled alkene. Instead, isopropyl alkyne **64** was the only product formed in 78% yield. Other reaction conditions were tested in order to avoid this undesired elimination; however, all attempts were completely unsuccessful. Despite this, the resulting alkyne was considered of interest for biological evaluation. Thus, compound **64** was treated with aqueous acetic acid to obtain alkyne analogue **65** albeit in poor yield (Scheme 3).

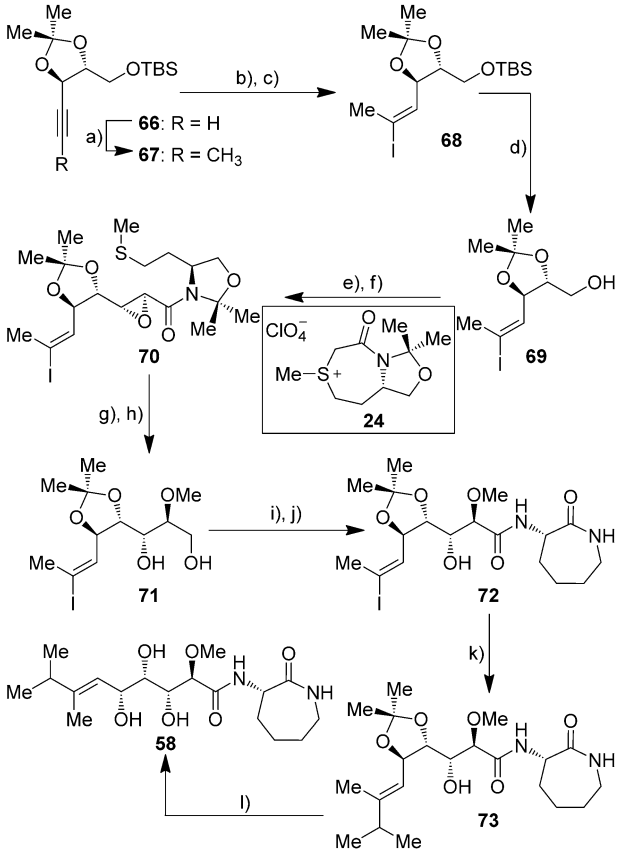
In light of these discouraging results, we opted to introduce a methyl group at the terminal olefinic position earlier in the synthesis via a pivotal iodine intermediate for subsequent installation of an isopropyl group via palladium chemistry. To this aim, the alkyne derivative of D-tartaric acid, compound **66**,[37] was chosen as the starting material to achieve the geometrically controlled construction of the targeted trisubstituted alkene. Methylation of alkyne **66**, mediated by *n*BuLi/HMPA,[38] provided methyl alkynyl derivative **67**, which was subjected to stereocontrolled stannylation[39] by reaction with Bu_3SnH in the presence of $PdCl_2(PPh_3)_2$ for an excellent (97%) yield. Exchange of the tributyltin moiety with iodine[39] was similarly successful in delivering compound **68**, which was treated with TBAF to obtain alcohol **69**. Starting from this alcohol, transformation into amide **72** followed the same synthetic sequence as described for the bengamides, involving a reaction of the resulting aldehyde from **69** with sulfonium salt **24** to provide epoxyamide **70** as a single diastereomer and in good yield (55% over two steps from **69**). Further synthetic transformations of **70**, including reduction, an oxirane ring-opening reaction with methanol, selective oxidation and coupling with lactam **62**, gave compound **72**. This vinyl iodide was then reacted with diisopropylzinc under Negishi coupling conditions to afford the desired trisubstituted alkene **73** in good yield (65%). Final acetal cleavage by aqueous acetic acid yielded bengamide E analogue **58** (Scheme 4).



Scheme 3. Toward the synthesis of bengamide E analogue **58**: Synthesis of alkynyl analogue **65**. *Reagents and conditions*: a) 2.0 equiv $(COCl)_2$, 4.0 equiv DMSO, 6.0 equiv NEt_3, CH_2Cl_2, −78 °C, 40 min; b) 1.1 equiv **24**, 1.1 equiv 3.0 M NaOH in H_2O, CH_2Cl_2, 25 °C, overnight, 62% over 2 steps; c) 2.5 equiv Super-H (1.0 M in THF), THF, 0 °C, 0.5 h, 68%; d) 1.0 equiv DBU, MeOH/$B(OMe)_3$ (1:1), 70 °C, 1 day; e) 6.0 equiv BAIB, 0.8 equiv TEMPO, CH_3CN/H_2O (1:1), 25 °C, 3 h; f) 1.5 equiv **62**, 1.2 equiv BOP, 2.0 equiv DIPEA, DMF, 25 °C, 2 h, 40% over three steps; g) 1.0 equiv Zn*i*Pr_2 (1.0 M in toluene), 0.2 equiv $Pd(dpephos)Cl_2$, THF/DMF (1:1), 25 °C, 6 h, 78%; h) 70% AcOH in H_2O, MeOH, 70 °C, 2 h, 35%.

Biology

Following the preparation of the bengamide E analogues (**30**–**38**, **51**–**54**, **56**, **58**, and **65**), and natural bengamides E (**15**) and E′ (**17**), the next step in this research was to evaluate the antitumor properties of these compounds to determine the influence of the described structural modifications on antiproliferative activity. Determination of the cytotoxic properties of all these compounds was performed by measuring their IC_{50} values against an HT29 human colon adenocarcinoma cell line using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium



Scheme 4. Synthesis of bengamide E analogue **58**. *Reagents and conditions*: a) 1.4 equiv *n*BuLi (1.6 M in hexanes), 1.03 equiv HMPA, 2.0 equiv MeI, THF, −78 °C→25 °C, 8 h, 80%; b) 5.0 equiv Bu_3SnH, 0.1 equiv $PdCl_2(PPh_3)_2$, THF, 25 °C, 97%; c) 1.1 equiv I_2, CH_2Cl_2, 0 °C, 1 h, 97%; d) 1.2 equiv TBAF (1.0 M in THF), THF, 25 °C, 1 h, 89%; e) 2.0 equiv $(COCl)_2$, 4.0 equiv DMSO, 6.0 equiv NEt_3, CH_2Cl_2, −78 °C, 40 min; f) 1.1 equiv **24**, 1.1 equiv 3.0 M NaOH in H_2O, CH_2Cl_2, 25 °C, overnight, 55% over two steps; g) 2.5 equiv Super-H (1.0 M in THF), THF, 0 °C, 20 min; h) 1.0 equiv DBU, MeOH/$B(OMe)_3$ (1:1), 70 °C, 1 day, 42% over two steps; i) 6.0 equiv BAIB, 0.8 equiv TEMPO, CH_3CN/H_2O (1:1), 25 °C, 10 h; j) 1.5 equiv **62**, 1.2 equiv BOP, 2.0 equiv DIPEA, DMF, 25 °C, 1 h, 58% over two steps; k) 1.2 equiv Zn*i*Pr_2 (1.0 M in toluene), 0.2 equiv Pd(dpephos)Cl_2, THF/DMF (1:1), 25 °C, 6 h, 65%; l) 70% AcOH in H_2O, MeOH, 70 °C, 2 h, 57%.

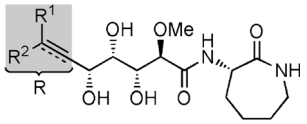
bromide (MTT) dye reduction assay.[40] These results are compiled in Table 2.[41]

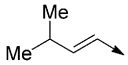
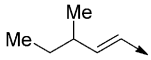
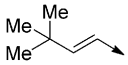
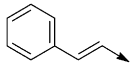
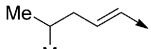
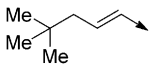
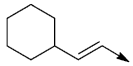
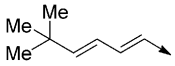
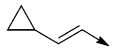
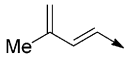
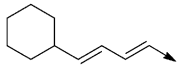
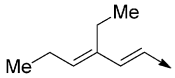
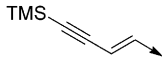
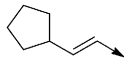
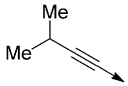
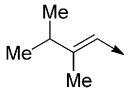
According to these biological results, lengthening the polyketide chain at this olefinic position essentially led to a complete loss of cytotoxic activity, in the case of analogues **34**, **37**, and **52**, or a significant decrease in activity (a 30-fold decrease compared with bengamide E), as in the case of natural bengamide E′ (**17**) or analogues **33**, **53**, and **54**. However, the presence of the terminal olefinic substituent is essential for antitumor activity, as demonstrated by methylene analogue **30**, which was completely devoid of activity. On the other hand, slight modifications at this olefinic position led to important changes in biological activities. For example, replacement of the isopropyl group by an iodine (compound **36**) or by an isopropenyl group (compound **51**) led to a tenfold loss of activity. Interestingly, alkyne analogue **65** exhibited only a twofold loss in antitumor activity with respect to natural bengamide E. More promising results were obtained from analogues bearing a *tert*-butyl or a cyclic group in place of the isopropyl. *tert*-Butyl analogue **31** retained significant cytotoxic activity, slightly superior to that of bengamide E. This was not a surprising result, as Novartis previously noted this improvement in activity with compounds such as LAF-389. In our case, however, we did not detect a remarkable increase in cytotoxic activity as initially expected. For the cyclic analogues, we observed important antitumor activity for compound **38**, which exhibited a very similar cytotoxic profile to bengamide E. To our delight, cyclopentyl analogue **56** exhibited the best cytotoxic result among all of our evaluated analogues, with a fourfold improvement in antitumor activity over bengamide E. In contrast, introduction of a bulkier cyclohexane moiety, as in analogue **35**, led to complete loss of cytotoxic activity. Similarly, phenyl analogue **32** did not display significant biological activity. Finally, the introduction of an extra methyl group at the C7 olefinic position (compound **58**) led to a sevenfold loss in antitumor activity, indicating limited tolerance for structural modifications in this region of the molecule. Assuming that the antitumor activity of the bengamides is a consequence of MetAp inhibition, according to the interaction mode established by Towbin et al.,[7] we can conclude that hydrophobic pocket P1 of the active site is highly sensitive to steric volume, in accordance with the biological results obtained for the terminal olefinic-modified bengamides (Table 2).

As we have previously mentioned, bengamide E (**15**) has been shown to inhibit the in vitro growth of a tumor cell line at micromolar concentrations (3.3 μM against MDA-MB-435).[2d] A more detailed characterization of its activity and selectivity profile is missing, however, with the exception of the in vitro antitumor studies carried out by Banwell et al., who reported activity against two tumor cell lines and against human umbilical vein endothelial cells.[42]

To establish a more complete antiproliferative profile either for bengamide E or for the most potent bengamide analogues identified in our preliminary biological evaluation (Table 2), we decided to examine the cytotoxicities of these compounds against other different cancer cell lines, namely MDA-MB-231 (human breast carcinoma), HT1080 (human fibrosarcoma), and HL60 (human promyelocytic leukemia), as well as against a primary culture of non-transformed bovine aorta endothelial (BAE) cells. Bengamide E and fumagillin were used as controls to compare the activity of the newly synthesized analogues. According to these biological assays, the antiproliferative activity obtained for bengamide E was in agreement with the previously reported cytotoxic activity, with IC_{50} values for the five cell types in the low micromolar range. On the other hand, fumagillin, a fungal metabolite that potently inhibits angiogenesis by blocking endothelial cell proliferation and that has advanced to clinical trials for multiple cancers, showed a biphasic effect on the growth of proliferating endothelial cells. At lower concentrations, there is an initial decrease in cell number, likely due to a cytostatic effect; followed by a plateau across several orders of magnitude in concentration and then a second cytotoxic effect. This biphasic dose–response curve, typical of fumagillin and its derivatives, was obtained for the tumor cell

Table 2. In vitro antitumor activities of bengamide E analogues against HT29 human colon adenocarcinoma cells.



Compound	R	IC_{50} [μM][a]
Bengamide E (**15**)		0.95 ± 0.16
Bengamide E′ (**17**)		27.5 ± 1.5
Analogue **30**		> 100
Analogue **31**		0.87 ± 0.2
Analogue **32**		68.8
Analogue **33**		38.5
Analogue **34**		100
Analogue **35**		62.5
Analogue **36**		14.8 ± 2.0
Analogue **37**		61
Analogue **38**		2.1 ± 0.4
Analogue **51**		15.2 ± 2.5
Analogue **52**		100
Analogue **53**		33.7 ± 3.0
Analogue **54**		33.3 ± 10.0
Analogue **56**		0.22 ± 0.05
Analogue **65**		2.2 ± 0.4
Analogue **58**		6.6 ± 0.7

[a] In vitro cytotoxicities were determined by MTT assay as detailed in the Experimental Section; IC_{50} values were obtained from semilogarithmic dose–response plots as the concentrations of compounds yielding 50% cell survival; values represent the average ± SD.

lines studied, indicating that the antiproliferative activity of fumagillin is not endothelial-specific, which is in agreement with previously reported data (Table 3).[43] In contrast to fumagillin, the selected bengamide analogues (**31**, **36**, **38**, **51**, **56**, **58**, and **65**) displayed well-defined cytotoxic activity in tumor as well as in endothelial cells. This is in agreement with previous observations indicating that inhibition of MetAp2 by the bengamides does not result in selective inhibition of endothelial cell proliferation.[16] Dose–response curves obtained with bengamide E and its analogues showed a sharp decrease in cell survival at concentrations near the IC_{50} value (Figure 3). From these results, we confirmed that cyclopentyl analogue **56** was the most potent compound, exhibiting an antitumor activity three- to fourfold more potent than natural bengamide E, with a very similar cytotoxic profile and remarkably improved cytotoxicity with respect to *tert*-butyl derivative **31**, which displayed a potency very similar to that of bengamide E.

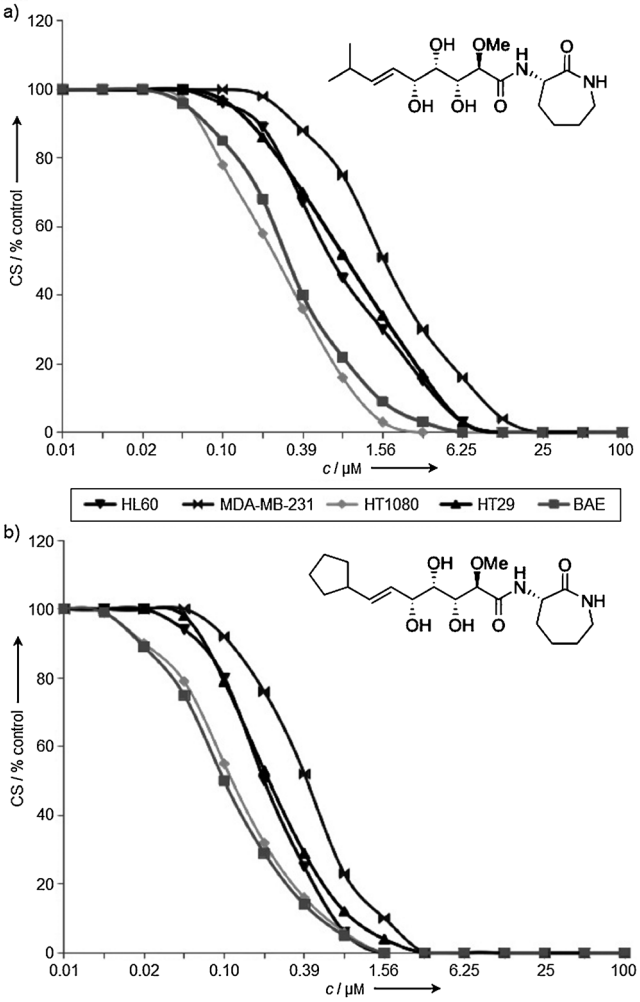


Figure 3. Dose-dependent effect on the in vitro growth of tumor and endothelial cells by a) bengamide E (**15**) and b) cyclopentyl analogue **56** [cell survival (CS) is represented as percentage of control-cell growth in cultures containing no drugs; each point represents the mean of quadruplicates; SD values were all < 10% and are omitted for clarity].

Conclusions

The present work describes the synthesis of a series of bengamide E analogues modified at the terminal olefinic position. This synthetic undertaking was accomplished by use of our delineated synthetic strategy for the bengamides, which enjoys

Table 3. In vitro antitumor activities of bengamide E, fumagillin, and bengamide analogues against various tumor cell lines and BAEC.

Compound	Cell Lines and IC_{50} [μM][a]				
Bengamide E (**15**)[b]	**MDA-MB-435**[e]: 3.3				
Bengamide E (**15**)[c]	**A549**[f]: 1.9		**HCT116**[g]: 0.6		**HUVEC**[h]: 0.3
	MDA-MB-231[i]	**HT29**[j]	**HT1080**[k]	**HL60**[l]	**BAEC**[m]
Bengamide E (**15**)[d]	1.64 ± 0.54	0.95 ± 0.16	0.29 ± 0.03	0.68 ± 0.10	0.28 ± 0.03
Analogue **31**	2.2 ± 0.1	0.87 ± 0.2	0.25 ± 0.05	1.1 ± 0.2	0.17 ± 0.01
Analogue **36**	14.2 ± 1.4	14.8 ± 2.0	3.6 ± 1.0	7.1 ± 0.5	3.9 ± 0.4
Analogue **38**	3.7 ± 0.5	2.1 ± 0.4	1.1 ± 0.5	2.1 ± 0.4	1.6 ± 0.5
Analogue **51**	16.9 ± 3.7	15.2 ± 2.5	1.7 ± 0.7	6.3 ± 0.2	2.3 ± 0.2
Analogue **56**	0.44 ± 0.06	0.22 ± 0.05	0.12 ± 0.05	0.19 ± 0.01	0.10 ± 0.02
Analogue **58**	11.1 ± 3.0	6.6 ± 0.7	1.21 ± 0.13	5.5 ± 1.0	2.4 ± 1.3
Analogue **65**	5.7 ± 2.0	2.2 ± 0.4	0.5 ± 0.1	1.7 ± 0.1	1.5 ± 0.2
Fumagillin	54.3 ± 10.2	38.3 ± 12.5	biphasic curve	36 ± 7.5	biphasic curve

[a] In vitro cytotoxicities were determined by MTT assay as detailed in the Experimental Section; IC_{50} values were obtained from semilogarithmic dose–response plots as the concentrations of compounds yielding 50% cell survival; values represent the average ± SD. [b] Data from Crews et al.[2d] [c] Data from Banwell et al.[42] [d] Data determined by our research group. Tumor cell lines: [e] MDA-MB-435: human breast carcinoma; [f] A549: non-small-cell lung cancer; [g] HCT116: colon cancer cells; [h] HUVEC: primary human umbilical vein endothelial cells; [i] MDA-MB-231: human breast carcinoma; [j] HT29: human colon adenocarcinoma; [k] HT1080: human fibrosarcoma; [l] HL60: human promyelocytic leukemia; [m] BAEC: non-transformed bovine aorta endothelial cells.

convergency and flexibility for structural diversity. Using this strategy, we were able to generate a wide array of diverse analogues for biological evaluation against different tumor and endothelial cell lines.

The biological evaluation of these analogues, including the natural bengamides E and E′, led us to establish: 1) a complete cytotoxic profile for bengamide E and 2) the identification of a more potent analogue, compound **56**, in which a cyclopentyl group replaced the isopropyl group at the terminal olefinic position. It is important to note the poor tolerance of the bengamides to structural modification as demonstrated by the lack of cytotoxicity for many of the synthesized analogues. These biological findings suggest a nearly perfect and very precise fit for the entire framework of the bengamides at the enzyme active site. However, this extensive structure–activity relationship study enabled the identification of a three- to fourfold more potent analogue, compound **56**, which should facilitate the identification and development of a new class of bengamide analogues featuring a cyclopentyl moiety. The design of new analogues that combine this cyclopentyl group with caprolactam-type units corresponding to the most potent members, such as bengamides A and B or LAF-389, should provide promising new inhibitors of endothelial or tumor cell growth as potential anticancer compounds. Syntheses of this newly proposed class of bengamide analogues, as well as evaluation of their cytotoxic activities, are currently in progress.

Experimental Section

General: All reactions were carried out under argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium benzophenone, and CH_2Cl_2 and benzene were distilled from CaH_2. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All solutions used in workup procedures were saturated unless otherwise noted. All reagents were purchased at highest commercial quality and used without further purification unless otherwise stated. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (60 F_{254}) using UV light as a visualizing agent and 7% ethanolic phosphomolybdic acid or *para*-anisaldehyde solution and heat as developing agents. Silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50, or 1 mm silica gel plates (60F-254). NMR spectra were recorded on a Bruker Avance 400 MHz instrument and were calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used for multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; b, broad. Optical rotations were recorded on a PerkinElmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on an ESI-TOF mass spectrometer in positive mode. Analytical and preparative HPLC were carried out with a Jasco instrument in reverse-phase using a reflection index detector. For preparative HPLC, a C_8 5μ-Luna column (250 × 10.00 nm) was employed with a flow rate of 4.7 mL min^{-1}.

Compound 46: A solution of vinyl iodide **28** (47.0 mg, 0.098 mmol) and pinacol boronic ester **42** (23 μL, 0.117 mmol, 1.2 equiv) in a 3:1 mixture of THF/H_2O (4.0 mL) was treated with $Pd(PPh_3)_4$ (23.0 mg, 0.019 mmol, 0.2 equiv) and Tl_2CO_3 (91 mg, 0.195 mmol, 2.0 equiv). The reaction mixture was heated at 60 °C for 18 h, then was cooled to room temperature, diluted with Et_2O, and washed with a saturated aqueous $KHSO_4$ solution. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 10% MeOH, 45% EtOAc in hexanes) to afford compound **46** (14.0 mg, 36%) as a yellow foam: R_f = 0.25 (silica gel, EtOAc); $[\alpha]^{25}_D$ = +93.4 (c = 0.7 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 6H), 1.51–1.63 (m, 2H), 1.81–1.91 (m, 2H), 1.87 (s, 3H), 2.02–2.13 (m, 2H), 3.27–3.32 (m, 2H), 3.52 (s, 3H), 3.65 (dd, J = 8.3, 1.7 Hz, 1H), 3.73 (d, J = 8.3 Hz, 1H), 3.92 (dd, J = 8.6, 1.7 Hz, 1H), 4.57 (ddd, J = 11.5, 6.6, 1.8 Hz, 1H), 4.61 (dd, J = 8.7, 8.0 Hz, 1H), 5.01–5.02 (m, 2H), 5.60 (dd, J = 15.7, 8.0 Hz, 1H), 6.07 (t, J = 6.1 Hz, 1H), 6.44 (d, J = 15.7 Hz, 1H), 7.88 ppm (d, J = 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9, 27.2, 27.7, 28.3, 29.3, 31.7, 42.5, 52.3, 60.1, 69.4, 78.1, 79.7, 81.7, 109.5, 118.4, 125.8, 138.0, 141.7, 171.7, 175.3 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{20}H_{32}N_2O_6$: 397.2339, found: 397.2344.

Compound 47: A solution of vinyl iodide **28** (28.0 mg, 0.058 mmol) and boronic MIDA ester **43** (18 mg, 0.064 mmol, 1.1 equiv) in a 3:1 mixture of THF/H_2O (4.0 mL) was treated with Pd(dpephos)Cl_2 (8.0 mg, 0.012 mmol, 0.2 equiv) and Tl_2CO_3 (55 mg, 0.116 mmol, 2.0 equiv). The reaction mixture was heated at 60 °C for 5 h, then cooled to room temperature, diluted with Et_2O, and washed with a saturated aqueous $KHSO_4$ solution. The aqueous phase was extracted with Et_2O, and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 45% EtOAc in hexanes) to afford compound **47** (18.0 mg, 67%) as a yellow foam: $R_f = 0.25$ (silica gel, EtOAc); $[\alpha]^{25}_D = +3.4$ ($c = 0.9$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.43$ (s, 3H), 1.44 (s, 3H), 1.46–1.56 (m, 5H), 1.63–2.13 (m, 12H), 3.24–3.35 (m, 2H), 3.40 (s, 3H), 3.61–3.63 (m, 1H), 3.68–3.72 (m, 1H), 3.87 (ddd, $J = 8.6$, 1.3, 0.8 Hz, 1H), 4.52–4.57 (m, 1H), 4.53 (dd, $J = 8.7$, 7.9 Hz, 1H), 5.51 (dd, $J = 15.2$, 8.1 Hz, 1H), 5.66 (dd, $J = 15.4$, 6.9 Hz, 1H), 5.94 (t, $J = 6.2$ Hz, 1H), 5.98 (dddd, $J = 15.4$, 10.4, 1.2, 0.7 Hz, 1H), 6.28 (dd, $J = 15.2$, 10.4 Hz, 1H), 7.84 ppm (d, $J = 6.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.0$, 26.1, 26.7, 27.3, 27.9, 28.9, 31.3, 32.6, 32.7, 40.7, 42.1, 51.9, 59.6, 69.1, 77.7, 79.4, 81.6, 109.0, 126.4, 126.7, 135.7, 142.4, 171.2, 174.9 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{25}H_{40}N_2O_6$: 465.2965, found: 465.2958.

Compound 48: A solution of vinyl iodide **28** (29.0 mg, 0.060 mmol) and catechol boronic ester **44** (14 μL, 0.072 mmol, 1.2 equiv) in a 3:1 mixture of THF/H_2O (4.0 mL) was treated with Pd(dpephos)Cl_2 (9.0 mg, 0.012 mmol, 0.2 equiv) and Tl_2CO_3 (56 mg, 0.12 mmol, 2.0 equiv). The reaction mixture was heated at 50 °C for 1 day, then was cooled to room temperature, diluted with Et_2O, and washed with a saturated aqueous $KHSO_4$ solution. The aqueous phase was extracted with Et_2O, and the organic phase was washed with brine, dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by HPLC (preparative column, C_8, 5 μm, 60% CH_3CN in H_2O, 4.7 mL min^{-1}, $t_R = 6.2$ min) to afford compound **48** (14.0 mg, 54%) as a yellow foam: $R_f = 0.28$ (silica gel, EtOAc); $[\alpha]^{25}_D = +56.4$ ($c = 0.7$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.96–1.01 (m, 6H), 1.45 (s, 6H), 1.48–1.61 (m, 2H), 1.79–1.88 (m, 2H), 1.98–2.10 (m, 1H), 2.07–2.14 (m, 3H), 2.17–2.26 (m, 2H), 3.22–3.32 (m, 2H), 3.49 (s, 3H), 3.60–3.65 (m, 1H), 3.68 (d, $J = 6.6$ Hz, 1H), 3.72 (d, $J = 8.0$ Hz, 1H), 3.88 (dd, $J = 8.6$, 1.5 Hz, 1H), 4.52–4.57 (m, 1H), 4.56 (dd, $J = 8.3$, 8.1 Hz, 1H), 5.42 (t, $J = 7.3$ Hz, 1H), 5.50 (dd, $J = 15.7$, 8.0 Hz, 1H), 6.07 (bs, 1H), 6.21 (d, $J = 15.7$ Hz, 1H), 7.85 ppm (d, $J = 5.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.7$, 14.1, 19.8, 21.3, 26.8, 27.4, 27.9, 28.9, 31.3, 42.2, 51.9, 59.6, 69.1, 78.4, 79.5, 81.6, 108.9, 121.6, 135.7, 138.5, 171.3, 174.9 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{23}H_{38}N_2O_6$: 439.2808, found: 439.2811.

Compound 49: NEt_3 (25 μL, 0.178 mmol, 2.0 equiv) and (trimethylsilyl)acetylene (16 μL, 0.116 mmol, 1.3 equiv) were added to a solution of compound **28** (43 mg, 0.089 mg), CuI (4.0 mg, 0.018 mmol, 0.2 equiv), PPh_3 (5.0 mg, 0.018 mmol, 0.2 equiv) and $Pd(OAc)_2$ (2.0 mg, 0.009 mmol, 0.1 equiv) in benzene (2.0 mL) at 25 °C. After stirring for 2 h at 25 °C, the reaction mixture was diluted with EtOAc and quenched with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (silica gel, 45% EtOAc, 5% MeOH in hexanes) to afford compound **49** (32 mg, 79%) as a yellow solid: $R_f = 0.27$ (silica gel, EtOAc); $[\alpha]^{25}_D = +85.4$ ($c = 1.3$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.17$ (s, 9H), 1.41 (s, 3H), 1.44 (s, 3H), 1.46–1.55 (m, 2H), 1.78–1.91 (m, 2H), 2.00–2.10 (m, 2H), 3.24–3.30 (m, 2H), 3.48 (s, 3H), 3.60 (ddd, $J = 8.3$, 5.5, 1.7 Hz, 1H), 3.69 (d, $J = 8.3$ Hz, 1H), 3.79 (d, $J = 5.4$ Hz, 1H), 3.89 (dd, $J = 8.4$, 1.5 Hz, 1H), 4.52–4.57 (m, 2H), 5.80 (dd, $J = 15.9$, 1.1 Hz, 1H), 6.12 (dd, $J = 15.9$, 7.0 Hz, 1H), 6.34 (t, $J = 6.1$ Hz, 1H), 7.86 ppm (d, $J = 6.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -0.2$, 26.7, 27.1, 27.9, 28.9, 31.2, 42.1, 51.9, 59.7, 69.2, 79.3, 81.3, 96.1, 102.6, 109.7, 113.3, 140.4, 171.2, 174.9 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{22}H_{36}N_2O_6Si$: 453.2421, found: 453.2415.

Compound 50: A dry and argon-flushed 10 mL flask was charged with anhydrous $ZnCl_2$ (46 mg, 0.34 mmol, 1.0 equiv) and THF (0.7 mL). The resulting solution was cooled at 0 °C, then cyclopentylmagnesium chloride (177 μL, 2.0 M in Et_2O, 0.35 mmol, 1.05 equiv) was added dropwise at 0 °C. After addition, the reaction mixture was stirred for an additional 15 min and then used directly in the next reaction. $Pd(PPh_3)_4$ (18 mg, 0.015 mmol, 0.2 equiv) was added to a solution of vinyl iodide **29** (40 mg, 0.06 mmol, 1.0 equiv) in THF (2.5 mL), followed by a fresh cyclopentylzinc chloride (**45**) solution (0.7 mL, 0.5 M in THF, 5.0 equiv) at 25 °C. After stirring for 10 h at this temperature, the crude mixture was diluted with EtOAc and quenched with a saturated aqueous NH_4Cl solution. The organic phase was washed with brine, dried ($MgSO_4$), and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 50% EtOAc in hexanes) to afford compound **50** (22 mg, 61%) as a yellow oil: $R_f = 0.40$ (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D = +34.8$ ($c = 0.1$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.08 (s, 3H), 0.09 (s, 3H), 0.84 (s, 9H), 1.23–1.34 (m, 3H), 1.37 (s, 3H), 1.38 (s, 3H), 1.46–1.64 (m, 5H), 1.75–1.88 (m, 4H), 1.97–2.02 (m, 2H), 2.11–2.15 (m, 2H), 2.44–2.55 (m, 1H), 3.21–3.29 (m, 2H), 3.42 (s, 3H), 3.75 (d, $J = 1.8$ Hz, 1H), 4.02 (dd, $J = 7.9$, 7.0 Hz, 1H), 4.07 (dd, $J = 7.0$, 1.8 Hz, 1H), 4.27 (dd, $J = 8.0$, 7.9 Hz, 1H), 4.46 (ddd, $J = 11.1$, 5.5, 1.6 Hz, 1H), 5.55 (ddd, $J = 15.3$, 8.0, 0.8 Hz, 1H), 5.75 (dd, $J = 15.2$, 7.8 Hz, 1H), 5.94 (bs, 1H), 7.86 ppm (d, $J = 5.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.7$, -4.6, 18.2, 25.1, 25.8, 27.0, 27.1, 27.9, 29.0, 31.4, 32.8, 32.9, 42.1, 43.0, 51.9, 58.6, 74.6, 79.5, 80.8, 83.2, 108.1, 126.2, 141.1, 168.7, 175.0 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{28}H_{50}N_2O_6Si$: 539.3516, found: 539.3522.

General procedure for bengamide E analogues 36, and 51–54: A solution of the corresponding acetal derivative (0.01 mmol) in MeOH (0.5–1.0 mL) was treated with a 70% aqueous AcOH solution (0.5–1.0 mL) at 70 °C for 1–2 h. After this time, the solvents were removed by evaporation under reduced pressure. Purification by HPLC (preparative column, C_8, 5 μm, 40–50% CH_3CN in H_2O, 4.7 mL min^{-1}) afforded the corresponding bengamide E analogues.

Bengamide E analogue 36: 44%; white solid: $R_f = 0.14$ (silica gel, 6% MeOH in CH_2Cl_2); $t_R = 2.76$ min (C_8, 5 μm, 4.7 mL min^{-1}, 50% CH_3CN in H_2O); $[\alpha]^{25}_D = +90.6$ ($c = 0.3$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.41$–1.47 (m, 1H), 1.55–1.64 (m, 1H), 1.76–1.90 (m, 2H), 2.04–2.07 (m, 2H), 3.27–3.31 (m, 2H), 3.54 (s, 3H), 3.65 (d, $J =$ 3.3 Hz, 1H), 3.79–3.83 (m, 2H), 4.28 (t, $J = 5.0$ Hz, 1H), 4.54 (dd, $J =$ 11.1, 6.5 Hz, 1H), 6.33 (bs, 1H), 6.50 (d, $J = 14.6$ Hz, 1H), 6.62 (dd, $J = 14.6$, 5.9 Hz, 1H), 7.95 ppm (d, $J = 6.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.0$, 28.8, 30.9, 42.1, 52.1, 60.0, 71.3, 73.2, 75.7, 79.6, 80.5, 144.3, 172.0, 174.8 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{14}H_{23}IN_2O_6$: 443.0679, found: 443.0685.

Bengamide E analogue 51: 53%; white solid; $R_f = 0.10$ (silica gel, 5% MeOH in CH_2Cl_2); $t_R = 5.54$ min (C_8, 5 μm, 2.98 mL min^{-1}, 40% CH_3CN in H_2O); $[\alpha]^{25}_D = +45.7$ ($c = 0.2$ in CH_2Cl_2); ^{1}H NMR (400 MHz,

$CDCl_3$): $\delta = 1.76$–1.90 (m, 3H), 1.85 (s, 3H), 2.02–2.10 (m, 2H), 3.26–3.32 (m, 2H), 3.55 (s, 3H), 3.66 (dd, $J = 5.0$, 1.2 Hz, 1H), 3.79 (d, $J = 7.4$ Hz, 1H), 3.83 (dd, $J = 7.4$, 1.4 Hz, 1H), 4.37 (dd, $J = 6.2$, 5.8 Hz, 1H), 4.54 (ddd, $J = 11.3$, 6.4, 1.5 Hz, 1H), 5.00 (s, 2H), 5.68 (dd, $J = 15.7$, 7.0 Hz, 1H), 6.04 (bs, 1H), 6.44 (d, $J = 15.7$ Hz, 1H), 8.00 ppm (d, $J = 6.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.6$, 28.0, 28.9, 31.0, 42.1, 52.1, 60.1, 72.3, 73.1, 74.1, 80.5, 117.3, 127.8, 135.6, 141.4, 172.2, 174.6 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{17}H_{28}N_2O_6$: 357.2026, found: 357.2032.

Bengamide E analogue 52: 58%; white solid; $R_f = 0.24$ (silica gel, 6% MeOH in CH_2Cl_2); $t_R = 5.54$ min (C_8, 5 μm, 4.7 mL min^{-1}, 50% CH_3CN in H_2O); $[\alpha]^{25}_D = +35.0$ ($c = 0.1$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.06$–1.50 (m, 7H), 1.65–2.12 (m, 10H), 3.06 (bs, 1H), 3.11 (d, $J = 6.7$ Hz, 1H), 3.26–3.33 (m, 2H), 3.55 (s, 3H), 3.63 (dd, $J = 6.2$, 5.2 Hz, 1H), 3.78 (d, $J = 7.4$ Hz, 1H), 3.82 (d, $J = 7.5$ Hz, 1H), 4.30 (dd, $J = 6.4$, 6.1 Hz, 1H), 4.42 (bs, 1H), 4.53 (dd, $J = 10.5$, 5.6 Hz, 1H), 5.59 (dd, $J = 15.3$, 7.1 Hz, 1H), 5.67 (dd, $J = 15.3$, 6.8 Hz, 1H), 5.90–6.00 (m, 1H), 6.00 (dd, $J = 15.4$, 10.4 Hz, 1H), 6.30 (dd, $J = 15.3$, 10.4 Hz, 1H), 8.00 ppm (d, $J = 6.1$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.9$, 26.1, 27.9, 28.9, 31.1, 32.7, 40.7, 42.1, 52.0, 60.1, 72.3, 73.0, 74.1, 77.7, 80.6, 126.9, 128.7, 133.8, 141.8, 172.3, 174.6 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{22}H_{36}N_2O_6$: 425.2652, found: 425.2656.

Bengamide E analogue 53: 45%; white solid; $R_f = 0.53$ (silica gel, 10% MeOH in CH_2Cl_2); $t_R = 3.82$ min (C_8, 5 μm, 4.7 mL min^{-1}, 50% CH_3CN in H_2O); $[\alpha]^{25}_D = +55.2$ ($c = 0.2$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$–1.01 (m, 6H), 1.38–1.59 (m, 2H), 1.77–1.90 (m, 2H), 2.02–2.08 (m, 2H), 2.12 (q, $J = 7.5$ Hz, 2H), 2.22 (q, $J = 7.6$ Hz, 2H), 3.12 (bs, 1H), 3.10–3.26 (m, 3H), 3.53 (s, 3H), 3.64–3.67 (m, 1H), 3.79 (d, $J = 7.0$ Hz, 1H), 3.84 (d, $J = 6.8$ Hz, 1H), 4.32 (dd, $J = 6.3$, 6.1 Hz, 1H), 4.40 (bs, 1H), 4.53 (ddd, $J = 11.2$, 6.6, 1.4 Hz, 1H), 5.43 (t, $J = 7.4$ Hz, 1H), 5.60 (dd, $J = 15.8$, 7.2 Hz, 1H), 6.10 (bs, 1H), 6.22 (d, $J = 15.8$ Hz, 1H), 7.97 ppm (d, $J = 6.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.7$, 14.1, 19.8, 21.3, 27.9, 28.8, 31.0, 42.1, 52.1, 59.9, 72.6, 72.7, 74.6, 81.0, 115.5, 121.0, 124.0, 135.1, 136.6, 138.6, 143.8, 172.1, 174.7 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{20}H_{34}N_2O_6$: 399.2495, found: 399.2484.

Bengamide E analogue 54: 28%; white solid; $R_f = 0.13$ (silica gel, 5% MeOH in CH_2Cl_2); $t_R = 4.7$ min (C_8, 5 μm, 4.7 mL min^{-1}, 50% CH_3CN in H_2O); $[\alpha]^{25}_D = +19.7$ ($c = 0.2$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.17$ (s, 9H), 1.41–1.48 (m, 1H), 1.57–1.63 (m, 1H), 1.77–1.91 (m, 2H), 2.06 (d, $J = 12.1$ Hz, 2H), 3.26–3.31 (m, 2H), 3.54 (s, 3H), 3.64 (dd, $J = 4.7$, 1.4 Hz, 1H), 3.79 (d, $J = 7.3$ Hz, 1H), 3.82 (dd, $J = 7.3$, 1.4 Hz, 1H), 4.35 (ddd, $J = 6.0$, 4.4, 1.4 Hz, 1H), 4.54 (dd, $J = 10.5$, 6.6 Hz, 1H), 5.86 (dd, $J = 15.9$, 1.5 Hz, 1H), 6.20 (dd, $J = 15.9$, 5.8 Hz, 1H), 6.20–6.23 (m, 1H), 7.97 ppm (d, $J = 6.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -0.1$, 27.9, 28.8, 31.0, 42.1, 52.1, 60.1, 71.8, 73.3, 77.2, 80.4, 95.6, 103.1, 112.1, 142.4, 172.2, 174.7 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{19}H_{32}N_2O_6Si$: 413.2108, found: 413.2096.

Hydroxyamide 55: A solution of compound **50** (20 mg, 0.037 mmol, 1.0 equiv) in THF (3.0 mL) was treated with TBAF (74 μL, 1.0 M solution in THF, 2.0 equiv) at 25 °C. After 1 h at this temperature, the reaction mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was separated, extracted twice with Et_2O, and the combined organic phases were washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (silica gel, 90% EtOAc in hexanes) afforded hydroxyamide **55** (15.3 mg, 97%) as a yellow oil: $R_f = 0.27$ (silica gel, EtOAc); $[\alpha]^{25}_D = +66.7$ ($c = 0.6$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.26$–1.32 (m, 3H), 1.43 (s, 6H), 1.52–1.55 (m, 3H), 1.57–1.67 (m, 2H), 1.72–1.79 (m, 2H), 1.81–1.89 (m, 2H), 2.10–2.12 (m, 2H), 2.39–2.49 (m, 1H), 3.24–3.30 (m, 2H), 3.49 (s, 3H), 3.58–3.61 (m, 1H), 3.66–3.67 (m, 1H), 3.71 (d, $J = 8.1$ Hz, 1H), 3.84 (dd, $J = 8.6$, 1.6 Hz, 1H), 4.46 (dd, $J = 8.4$ Hz, 1H), 4.55 (ddd, $J = 11.2$, 6.4, 1.6 Hz, 1H), 5.38 (ddd, $J = 15.3$, 8.3, 1.0 Hz, 1H), 5.81 (dd, $J = 15.3$, 7.6 Hz, 1H), 6.14 (bs, 1H), 7.85 ppm (d, $J = 6.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 25.1$, 26.8, 27.3, 27.9, 28.9, 31.3, 32.7, 32.8, 42.1, 43.0, 51.9, 59.6, 60.0, 78.0, 79.2, 81.5, 108.8, 124.3, 142.1, 171.3, 174.9 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{22}H_{36}N_2O_6$: 425.2652, found: 425.2648.

Bengamide E analogue 56: Hydroxyamide **55** (12.5 mg, 0.029 mmol) was subjected to acidic hydrolysis according to the general procedure described above to obtain, after purification by HPLC (preparative column, C_8, 5 μm, 50% CH_3CN in H_2O, 4.7 mL min^{-1}), bengamide E analogue **56** (5.5 mg, 49%) as a yellow solid: $R_f = 0.30$ (silica gel, 8% MeOH in CH_2Cl_2); $t_R = 3.12$ min (C_8, 5 μm, 4.7 mL min^{-1}, 50% CH_3CN-50% H_2O); $[\alpha]^{25}_D = +17.4$ ($c = 0.2$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.24$–1.35 (m, 2H), 1.38–1.47 (m, 1H), 1.52–1.66 (m, 5H), 1.75–1.80 (m 3H), 1.86–1.90 (m, 1H), 2.03–2.08 (m, 2H), 2.44 (sext, $J = 8.2$ Hz, 1H), 3.22–3.36 (m, 2H), 3.53 (s, 3H), 3.60 (dd, $J = 5.3$, 0.8 Hz, 1H), 3.78 (d, $J = 6.9$ Hz, 1H), 3.83 (dd, $J = 6.9$, 0.9 Hz, 1H), 4.22 (dd, $J = 6.3$, 6.2 Hz, 1H), 4.54 (ddd, $J = 11.5$, 6.8, 1.2 Hz, 1H), 5.48 (ddd, $J = 15.4$, 7.2, 0.8 Hz, 1H), 5.79 (dd, $J = 15.2$, 7.6 Hz, 1H), 6.17 (bs, 1H), 8.00 ppm (d, $J = 6.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.1$, 28.0, 28.8, 31.0, 32.8, 32.9, 42.1, 42.9, 52.0, 59.9, 72.4, 72.7, 74.1, 81.1, 126.4, 139.5, 172.1, 174.7 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{19}H_{32}N_2O_6$: 385.2339, found: 385.2329.

Epoxyamide 60: A solution of oxalyl chloride (0.59 mL, 6.65 mmol, 2.0 equiv) in CH_2Cl_2 (12 mL) was cooled to −78 °C, and DMSO (0.94 mL, 13.3 mmol, 4.0 equiv) was added dropwise. After 10 min, a solution of alcohol **59** (1.05 g, 3.32 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added. The reaction mixture was stirred at −78 °C for 40 min, then NEt_3 (2.8 mL, 19.94 mmol, 6.0 equiv) was added at this temperature. After 10 min at −78 °C, the reaction was allowed to reach room temperature and then diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The organic phase was washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The resulting crude aldehyde was used in the next step without purification. An aqueous NaOH solution (3.0 M 1.22 mL, 3.65 mmol, 1.1 equiv) was added to a solution of sulfonium salt **24** (1.15 g, 3.65 mmol, 1.1 equiv) in H_2O (15 mL). A solution of crude aldehyde (~3.32 mmol) in CH_2Cl_2 (15 mL) was added, and the reaction mixture was stirred vigorously overnight at 25 °C. After this time, both phases were separated, and the aqueous layer was extracted twice with CH_2Cl_2. Combined organic extracts were then washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by flash column chromatography (silica gel, 30% EtOAc in hexanes) provided epoxyamide **60** (1.09 g, 62% over two steps) as a yellow oil: $R_f = 0.35$ (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D = +68.6$ ($c = 1.2$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.40$ (s, 6H), 1.55 (s, 3H), 1.64 (s, 3H), 1.76–1.86 (m, 1H), 2.07–2.11 (m, 1H), 2.13 (s, 3H), 2.47 (ddd, $J = 13.3$, 9.0, 6.7 Hz, 1H), 2.70 (ddd, $J = 13.3$, 7.1, 5.0 Hz, 1H), 3.50 (dd, $J = 3.3$, 1.9 Hz, 1 Hz, 1H), 3.70 (d, $J = 1.9$ Hz, 1H), 3.90–3.92 (m, 1H), 3.93 (d, $J = 3.4$ Hz, 1H), 4.05 (ddd, $J = 9.2$, 5.2, 1.4 Hz, 1H), 4.35 (ddd, $J = 10.5$, 4.8, 3.2 Hz, 1H), 4.74 (t, $J = 8.1$ Hz, 1H), 6.56 ppm (d, $J = 8.1$ Hz, 1H); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{18}H_{27}Br_2NO_5S$: 528.0055, found: 528.0062.

Epoxy alcohol 61: Epoxyamide **60** (221 mg, 0.42 mmol, 1.0 equiv) in THF (5.0 mL) was treated with Super-H (1.05 mL, 1.0 M in THF, 1.05 mmol, 2.5 equiv) at 0 °C. After 20 min at this temperature, the reaction mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was separated, extracted twice with Et_2O, and the combined organic phase washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (silica gel, 30% EtOAc in hexanes) provided epoxy alcohol **61** (102 mg, 68%) as a yellow oil: $R_f = 0.38$ (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D = +23.7$ ($c = 0.8$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.41$ (s, 3H), 1.43 (s, 3H), 1.70 (bs, 1H), 3.17 (ddd, $J = 5.8$, 3.7, 2.5 Hz, 1H), 3.20 (dd, $J = 5.0$, 2.3 Hz, 1H), 3.68 (dd, $J = 8.3$, 5.0 Hz, 1H), 3.72–3.75 (m, 1H), 4.01 (ddd, $J = 12.8$, 4.0, 1.8 Hz, 1H), 4.65 (t, $J = 8.2$ Hz, 1H), 6.52 ppm (d, $J = 8.2$ Hz, 1H); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{10}H_{14}Br_2O_4$: 356.9337, found: 356.9345.

Hydroxyamide 63: Epoxy alcohol **61** (1.2 g, 3.35 mmol, 1.0 equiv) was dissolved in a 1:1 mixture of MeOH/$B(OMe)_3$ (34 mL). The resulting solution was treated with DBU (0.5 mL, 3.35 mmol, 1.0 equiv) and heated at 70 °C for 1 day. After this time, the reaction mixture was allowed to reach room temperature, cooled to 0 °C, and then treated with a saturated aqueous $NaHCO_3$ solution. After stirring for 30 min at 0 °C, EtOAc was added, and both phases were separated. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with H_2O and brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting crude product (1.28 g) was used in the next step without purification. The crude diol (63 mg, 0.16 mmol, 1.0 equiv) was dissolved in a mixture of CH_3CN/H_2O (4.0 mL, 1:1), and the resulting solution was treated with BAIB (312 mg, 0.97 mmol, 6.0 equiv) followed by TEMPO (21 mg, 0.13 mmol, 0.8 equiv) at 25 °C. After 3 h, the crude mixture was diluted with EtOAc, quenched by the addition of a saturated aqueous $Na_2S_2O_3$ solution and, after separation of both layers, the aqueous phase was extracted with EtOAc. The combined organic solution was washed again with a saturated aqueous $Na_2S_2O_3$ solution, then dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude acid was dissolved in DMF (4 mL) and treated with DIPEA (55 μL, 0.32 mmol, 2.0 equiv), L-Lys-lactam **62** (40 mg, 0.24 mmol, 1.5 equiv), and BOP (87 mg, 0.19 mmol, 1.2 equiv) at 25 °C. After 2 h, the crude mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was washed with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated under vacuum. Purification of the resulting crude product by flash column chromatography (silica gel, EtOAc) provided amide **63** (33 mg, 40% over three steps) as a white solid: $R_f = 0.27$ (silica gel, EtOAc); $[\alpha]^{25}_D = +65.3$ ($c = 0.3$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.41$ (s, 3H), 1.45 (s, 3H), 1.49–1.59 (m, 1H), 1.79–1.89 (m, 3H), 2.00–2.10 (m, 2H), 3.25–3.30 (m, 2H), 3.50 (s, 3H), 3.68–3.70 (m, 2H), 3.88 (dd, $J = 2.8$, 1.8 Hz, 1H), 4.00 (dd, $J = 8.1$, 1.2 Hz, 1H), 4.55 (ddd, $J = 11.2$, 6.3, 1.6 Hz, 1H), 4.80 (dd, $J = 8.3$ Hz, 1H), 6.43 (t, $J = 5.9$ Hz, 1H), 6.49 (d, $J = 8.4$ Hz, 1H), 7.87 ppm (d, $J = 6.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.7$, 27.0, 28.0, 28.9, 31.2, 42.1, 52.0, 59.7, 69.6, 76.6, 78.7, 81.2, 94.4, 110.1, 135.8, 171.1, 174.9 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{17}H_{26}Br_2N_2O_6$: 513.0236, found: 513.0229.

Alkyne 64: Diisopropylzinc (53 μL, 0.053 mmol, 1.0 M in toluene, 0.65 equiv) was added to a solution of **63** (42 mg, 0.082 mmol, 1.0 equiv) and $Pd(dpephos)Cl_2$ (12 mg, 0.016 mmol, 0.2 equiv) in THF/DMF (4 mL, 1:1) at 25 °C. After 6 h at this temperature, the reaction mixture was treated with a saturated aqueous NH_4Cl solution. The aqueous solution was extracted with Et_2O, and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to afford alkyne **64** (25.3 mg, 78%) as a white solid: $R_f = 0.32$ (silica gel, 5% MeOH in CH_2Cl_2); $t_R = 4.0$ min (C_8, 5 μm, 4.7 mL min^{-1}, 60% CH_3CN-40% H_2O); $[\alpha]^{25}_D = +86.7$ ($c = 0.6$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.152$ (d, $J = 6.9$ Hz, 3H), 1.154 (d, $J = 6.9$ Hz, 3H), 1.42 (s, 3H), 1.48 (s, 3H), 1.53–1.56 (m, 1H), 1.63–1.69 (m, 1H), 1.84–1.89 (m, 2H), 2.00–2.05 (m, 1H), 2.08–2.12 (m, 1H), 2.54–2.63 (m, 1H), 3.25–3.31 (m, 2H), 3.51 (s, 3H), 3.72–3.73 (m, 2H), 3.70–3.79 (m, 1H), 4.12 (dd, $J = 7.8$, 1.5 Hz, 1H), 4.56 (ddd, $J = 11.2$, 6.3, 1.7 Hz, 1H), 4.75 (dd, $J = 7.8$, 1.7 Hz, 1H), 6.15 (bs, 1H), 7.91 ppm (d, $J = 6.1$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.5$, 22.7, 26.6, 26.7, 27.9, 28.9, 31.3, 42.1, 51.9, 59.7, 66.7, 69.5, 75.5, 80.7, 81.1, 93.0, 109.9, 171.4, 174.8 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{20}H_{32}N_2O_6$: 397.2339, found: 397.2348.

Alkynyl bengamide E 65: A solution of acetal derivate **64** (11.7 mg, 0.03 mmol, 1.0 equiv) in MeOH (0.5 mL) was treated with a 70% aqueous AcOH solution (1.5 mL) at 70 °C for 2 h. The solvent was then removed by evaporation under reduced pressure. Purification of the crude product by HPLC (preparative column, C_8, 5 μm, 30% CH_3CN in H_2O, 4.7 mL min^{-1}) afforded the corresponding alkynyl bengamide E analogue **65** (10 mg, 35%) as a white solid: $R_f = 0.30$ (silica gel, 5% MeOH in CH_2Cl_2); $t_R = 4.25$ min (C_8, 5 μm, 4.7 mL min^{-1}, 30% CH_3CN in H_2O); $[\alpha]^{25}_D = +73.5$ ($c = 0.2$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.152$ (d, $J = 6.9$ Hz, 3H), 1.154 (d, $J = 6.9$ Hz, 3H), 1.41–1.53 (m, 2H), 1.80–1.90 (m, 2H), 2.03–2.10 (m, 2H), 2.55–2.63 (m, 1H), 3.26–3.32 (m, 2H), 3.55 (s, 3H), 3.73 (dd, $J = 6.9$, 1.2 Hz, 1H), 3.80 (d, $J = 6.4$ Hz, 1H), 4.04 (dd, $J = 6.4$, 0.8 Hz, 1H), 4.10–4.22 (m, 1H), 4.51 (ddd, $J = 11.4$, 6.3, 1.8 Hz, 1H), 4.76 (dd, $J = 7.9$, 1.7 Hz, 1H), 6.1 (t, $J = 5.7$ Hz, 1H), 7.91 ppm (d, $J = 6.2$ Hz, 1H); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{17}H_{28}N_2O_6$: 357.2026, found: 357.2034.

Methyl alkyne 67: nBuLi (1.6 M in hexane, 708 μL, 1.13 mmol, 1.4 equiv) was added dropwise to a solution of alkyne **66** (219 mg, 0.81 mmol, 1.0 equiv) in THF (6 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, followed by addition of HMPA (145 μL, 0.83 mmol, 1.03 equiv) and methyl iodide (103 μL, 1.62 mmol, 2.0 equiv). The resulting solution was stirred for 8 h while gradually warming to 25 °C. A saturated aqueous NH_4Cl solution was then added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 8% EtOAc in hexanes) to afford methyl alkyne **67** (184 mg, 80%) as a yellow oil: $R_f = 0.48$ (silica gel, 10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.07$ (s, 6H), 0.90 (s, 9H), 1.39 (d, $J = 0.6$ Hz, 3H), 1.48 (d, $J = 0.6$ Hz, 3H), 1.85 (d, $J = 2.1$ Hz, 3H), 3.77 (dd, $J = 4.0$, 3.0 Hz, 2H), 4.00 (ddd, $J = 7.7$, 4.0, 3.6 Hz, 1H), 4.54 ppm (dq, $J = 7.6$, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.5$, −5.3, 3.7, 18.3, 25.8, 26.5, 26.8, 61.9, 67.5, 75.9, 82.2, 82.8, 109.8 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{15}H_{28}O_3Si$: 285.1886, found: 285.1864.

Vinyl iodide 68: Bu_3SnH (2.1 mL, 7.57 mmol, 5.0 equiv) was added slowly (0.1 mL h^{-1}) to a solution of methyl alkyne **67** (431 mg, 1.51 mmol, 1.0 equiv) and $PdCl_2(PPh_3)_2$ (106 mg, 0.151 mmol, 0.1 equiv) in THF (10 mL). After addition, the reaction mixture was concentrated under reduced pressure, and the crude product was purified by flash column chromatography (silica gel, 2% EtOAc in

hexanes) to afford the corresponding stannyl derivative (844 mg, 97%) as a yellow oil: $R_f = 0.25$ (silica gel, 2% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.05$ (s, 3H), 0.06 (s, 3H), 0.88 (t, $J =$ 7.3 Hz, 9H), 0.89 (s, 9H), 1.25–1.35 (m, 6H), 1.41 (s, 3H), 1.44 (s, 3H), 1.45–1.52 (m, 12H), 1.94 (d, $J = 1.8$ Hz, 3H), 3.61–3.64 (m, 1H), 3.66 (dd, $J = 5.5$, 2.7 Hz, 1H), 3.77–3.81 (m, 1H), 4.88 (dd, $J = 8.2$ Hz, 1H), 5.54 ppm (dq, $J = 8.3$, 1.8 Hz, 1H). This stannyl derivative (844 mg, 1.47 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. Then, I_2 (409 mg, 1.61 mmol, 1.1 equiv) was added, and the resulting mixture was stirred at this temperature for 1 h. After this time, saturated aqueous $Na_2S_2O_3$ solution was added and the reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to afford vinyl iodide **68** (590 mg, 97%) as a yellow oil: $R_f = 0.30$ (silica gel, 2% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.06$ (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.39 (s, 3H), 1.40 (s, 3H), 2.49 (d, $J = 1.5$ Hz, 3H), 3.70–3.71 (m, 1H), 3.71–3.74 (m, 1H), 3.75–3.80 (m, 1H), 4.65 (dd, $J = 8.7$, 7.9 Hz, 1H), 6.21 ppm (dq, $J = 8.7$, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ −5.5, −5.3, 18.3, 25.8, 26.9, 27.1, 28.4, 61.6, 74.6, 80.6, 100.4, 109.1, 138.1 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{15}H_{29}IO_3Si$: 413.1009, found: 413.1007.

Alcohol 69: TBAF (1.9 mL, 1.0 M in THF, 1.90 mmol, 1.2 equiv) was added to a solution of **68** (651 mg, 1.58 mmol, 1.0 equiv) in THF (15 mL) at 25 °C. After 1 h at this temperature, the reaction mixture was diluted with Et_2O and treated with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with Et_2O, and the combined organic phases were washed with H_2O and brine, dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The obtained crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to afford alcohol **69** (420 mg, 89%) as a yellow oil: $R_f = 0.23$ (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.41$ (s, 6H), 2.06–2.07 (m, 1H), 2.49 (d, $J = 1.5$ Hz, 3H), 3.54 (ddd, $J = 12.1$, 8.6, 3.4 Hz, 1H), 3.77 (ddd, $J = 8.4$, 3.2, 2.3 Hz, 1H), 3.84 (ddd, $J = 12.3$, 2.8, 2.1 Hz, 1H), 4.62 (dd, $J = 8.6$ Hz, 1H), 6.20 ppm (dq, $J = 8.8$, 1.5 Hz, 1H).

Epoxyamide 70: Epoxyamide **70** (193 mg, 55% over two steps) was prepared from alcohol **69** (203 mg, 0.681 mmol) by a Swern oxidation, followed by reaction with sulfonium salt **24** (236 mg, 0.749 mmol, 1.10 equiv) according to the same procedure described above for the preparation of **60**, to afford **70** as a yellow oil: $R_f = 0.55$ (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D = +63.6$ ($c =$ 0.8 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.35$ (s, 3H), 1.38 (s, 3H), 1.53 (s, 6H), 2.12 (d, $J = 1.6$ Hz, 3H), 2.43–2.50 (m, 2H), 2.54 (s, 3H), 2.56–2.65 (m, 2H), 3.31 (d, $J = 1.9$ Hz, 1H), 3.69 (dd, $J = 1.9$, 1.8 Hz, 1H), 3.86–3.89 (m, 2H), 4.00–4.03 (m, 1H), 4.30–4.35 (m, 1H), 4.65–4.70 (m, 1H), 6.24 ppm (dq, $J = 8.8$, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.8$, 27.2, 28.6, 58.0, 60.7, 67.8, 74.0, 79.0, 81.5, 101.9, 109.4, 137.2 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{19}H_{30}INO_5S$: 512.0968, found: 512.0972.

Diol 71: Epoxyamide **70** (193 mg, 0.378 mmol, 1.0 equiv) in THF (5 mL) was treated with Super-H (950 μL, 1.0 M in THF, 0.95 mmol, 2.5 equiv) according to the same procedure described above for epoxyamide **60**. The resulting crude epoxy alcohol was used in the next step without further purification. The crude alcohol (~ 0.378 mmol) was dissolved in a 1:1 mixture of MeOH/$B(OMe)_3$ (2.0 mL) and treated with DBU (56 μL, 0.378 mmol, 1.0 equiv) according to the same procedure described above for **61**, to afford diol **71** (59 mg, 42% over two steps) as a yellow oil: $R_f = 0.22$ (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D = +15.8$ ($c = 0.5$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.43$ (s, 6H), 2.13 (bs, 2H), 2.51 (d, $J =$ 1.5 Hz, 3H), 3.19 (ddd, $J = 7.9$, 4.0, 3.4 Hz, 1H), 3.44 (s, 3H), 3.56 (dd, $J = 8.1$, 1.6 Hz, 1H), 3.81 (dd, $J = 12.0$, 3.4 Hz, 1H), 3.88-3.92 (m, 2H), 4.73 (dd, $J = 8.7$, 8.6 Hz, 1H), 6.26 ppm (dq, $J = 8.9$, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.8$, 27.2, 28.6, 58.0, 60.7, 67.8, 74.0, 79.0, 81.5, 101.9, 109.4, 137.2 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{12}H_{21}IO_5$: 373.0512, found: 373.0528.

Amide 72: The selective oxidation of diol **71** (22 mg, 0.059 mmol) to the carboxylic acid and subsequent coupling with L-Lys-lactam **62** (15 mg, 0.09 mmol, 1.5 equiv) was carried out exactly as described above for **63** to yield amide **72** (17 mg, 58% over two steps) as a yellow foam: $R_f = 0.30$ (silica gel, EtOAc); $[\alpha]^{25}_D = +38.6$ ($c = 0.7$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.42$ (s, 3H), 1.44 (s, 3H), 1.50–1.60 (m, 2H), 1.68–1.89 (m, 2H), 2.10–2.11 (m, 2H), 2.49 (d, $J = 1.5$ Hz, 1H), 3.26–3.33 (m, 2H), 3.51 (s, 3H), 3.57 (dd, $J =$ 8.6, 1.6 Hz, 1H), 3.71 (d, $J = 8.6$ Hz, 1H), 3.86 (dd, $J = 8.5$, 1.7 Hz, 1H), 4.55 (ddd, $J = 11.3$, 6.3, 1.6 Hz, 1H), 4.82 (dd, $J = 8.8$, 8.5 Hz, 1H), 6.15–6.20 (m, 1H), 6.19 (dd, $J = 8.8$, 1.5 Hz, 1H), 7.93 ppm (d, $J = 6.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.7$, 27.2, 27.9, 28.5, 28.9, 31.3, 42.1, 51.9, 59.9, 68.9, 73.4, 78.6, 80.9, 101.3, 109.3, 137.5, 171.6, 174.8 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{18}H_{29}IN_2O_6$: 497.1148, found: 497.1156.

Hydroxyamide 73: $Pd(dpephos)Cl_2$ (5.0 mg, 0.007 mmol, 0.2 equiv) was added to a solution of vinyl iodide **72** (17.0 mg, 0.03 mmol, 1.0 equiv) in a 1:1 mixture of DMF/THF (2.0 mL), followed by diisopropylzinc (22 μL, 1.0 M solution in THF, 0.022 mmol, 0.65 equiv) at 25 °C. After stirring for 10 h at 25 °C, the reaction mixture was treated with H_2O, diluted with Et_2O and, after separation of both layers, the aqueous phase was extracted with Et_2O twice. The resulting organic solution was then washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (silica gel, EtOAc) provided compound **73** (8.0 mg, 65%) as a yellow foam: $R_f = 0.30$ (silica gel, EtOAc); $[\alpha]^{25}_D = +25.0$ ($c = 0.2$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.00$ (d, $J = 6.8$ Hz, 6H), 1.44 (s, 3H), 1.45 (s, 3H), 1.48–1.59 (m, 2H), 1.69 (dd, $J = 4.6$, 1.3 Hz, 3H), 1.81–1.90 (m, 2H), 1.97–2.03 (m, 1H), 2.05–2.14 (m, 1H), 2.23–2.30 (m, 1H), 3.25–3.34 (m, 2H), 3.51 (s, 3H), 3.54 (dd, $J = 8.4$, 1.7 Hz, 1H), 3.70 (dd, $J = 8.3$, 1.5 Hz, 1H), 3.79 (dd, $J = 8.6$, 1.6 Hz, 1H), 4.55 (ddd, $J = 11.1$, 6.4, 1.7 Hz, 1H), 4.83–4.89 (m, 1H), 5.16–5.18 (m, 1H), 6.02 (t, $J = 6.4$ Hz, 1H), 7.90 ppm (d, $J = 6.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.8$, 14.2, 21.1, 21.2, 26.8, 27.4, 27.9, 28.9, 31.3, 36.8, 42.1, 51.8, 59.7, 69.1, 73.3, 79.5, 81.4, 108.6, 118.6, 171.6, 174.9 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{21}H_{36}N_2O_6$: 413.2652, found: 413.2671.

Bengamide E analogue 58: A solution of acetal derivative **73** (3.0 mg, 0.007 mmol, 1.0 equiv) in MeOH (0.5 mL) was treated with a 70% aqueous AcOH solution (1.0 mL) at 70 °C for 2 h. After this time, the solvent was removed by evaporation under reduced pressure. The resulting crude product was purified by HPLC (preparative column, C_8, 5 μm, 30% CH_3CN in H_2O, 4.7 mL min^{-1}) to afford bengamide E analogue **58** (1.5 mg, 57%) as a white solid: $R_f = 0.30$ (silica gel, 10% MeOH in CH_2Cl_2); $t_R = 2.94$ min (C_8, 5 μm, 4.7 mL min^{-1}, 50% CH_3CN in H_2O); $[\alpha]^{25}_D = +42.3$ ($c = 0.1$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.01$ (d, $J = 6.8$ Hz, 6H), 1.41–1.49 (m, 2H), 1.69 (dd, $J = 5.8$, 1.2 Hz, 3H), 1.84–1.90 (m, 2H), 2.00–2.10 (m, 2H), 2.26–2.29 (m, 1H), 3.28–3.32 (m, 2H), 3.53 (s, 3H), 3.56–3.58 (m, 1H), 3.77 (bs, 2H), 4.36 (bs, 1H), 4.52–4.56 (m, 2H), 5.23 (d, $J = 8.7$ Hz, 1H), 6.17 (bs, 1H), 7.94 ppm (bs, 1H); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{18}H_{32}N_2O_6$: 373.2339, found: 373.2325.

Biology: Cell culture media was purchased from Gibco (Grand Island, NY, USA) and Cambrex (Walkersville, MD, USA). Fetal bovine serum (FBS) was a product of Harlan-Seralab (Belton, UK). Supplements and other chemicals not listed in this section were obtained from Sigma–Aldrich (St. Louis, MO, USA). Plastics for cell culture were supplied by NUNC (Roskilde, Denmark). Bovine aortic endothelial (BAE) cells were obtained by collagenase digestion and maintained in Dulbecco's modified Eagle's medium (DMEM) containing glucose (1 g L^{-1}), glutamine (2 mM), penicillin (50 IU mL^{-1}), streptomycin (50 μg mL^{-1}), and amphotericin (1.25 μg mL^{-1}) supplemented with 10% FBS. All cancer cell lines used in this study were obtained from the American Type Culture Collection (ATCC). Human fibrosarcoma HT1080 cells were maintained in DMEM containing glucose (4.5 g L^{-1}), glutamine (2 mM), penicillin (50 IU mL^{-1}), streptomycin (50 μg mL^{-1}), and amphotericin (1.25 μg mL^{-1}) supplemented with 10% FBS. Human colon adenocarcinoma HT29 cells were maintained in McCoy's 5 A medium containing glutamine (2 mM), penicillin (50 IU mL^{-1}), streptomycin (50 μg mL^{-1}), and amphotericin (1.25 μg mL^{-1}) supplemented with 10% FBS. Human breast cancer carcinoma MDA-MB-231 and human promyelocytic leukemia HL60 cells were maintained in RPMI1640 medium containing glutamine (2 mM), penicillin (50 IU mL^{-1}), streptomycin (50 μg mL^{-1}), and amphotericin (1.25 μg mL^{-1}) supplemented with 10% and 20% FBS, respectively.

Cytotoxicity assay: The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) dye reduction assay was performed in 96-well microplates according to the Mossman method. BAE (3×10^3) or tumor cells (2×10^3) in a total volume of 100 μL of their respective growth media were incubated with serial dilutions of the tested compounds. After 3 days of incubation (37 °C, 5% CO_2 in a humid atmosphere), 10 μL of MTT (5 mg mL^{-1} in PBS) were added to each well and the plate was incubated for a further 4 h (37 °C). The resulting formazan was dissolved in 150 μL of 0.04 N HCl/isopropanol and read at 550 nm. All determinations were carried out in triplicate. IC_{50} values were calculated from semilogarithmic dose–response plots as the concentration of compound yielding 50% cell survival.

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