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Targeting the Heat Shock Protein 90 Dimer with Dimeric Inhibitors

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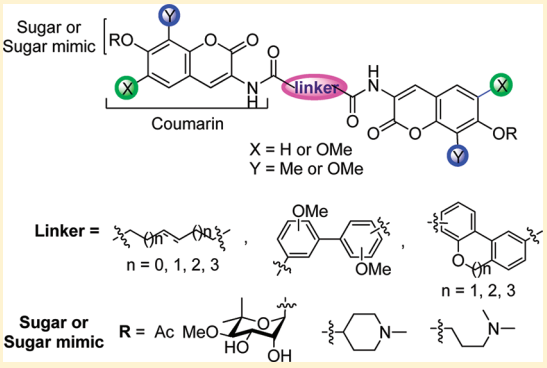
Supporting Information

ABSTRACT: The design, synthesis, and biological evaluation of conformationally constrained coumermycin A1 analogues are reported. Compounds were evaluated against both breast cancer (SKBr3 and MCF7) and prostate cancer (PC3 mm2, A549, and HT29) cell lines. Non-noviosylated coumermycin A1 analogues that manifest potent antiproliferative activity resulting from Hsp90 inhibition are provided, wherein replacement of the stereochemically complex noviose sugar with readily available piperidine rings resulted in ~100 fold increase in antiproliferative activities as compared to coumermycin A1, producing small molecule Hsp90 inhibitors that exhibit nanomolar activities.



INTRODUCTION

Interest in small molecule heat shock protein 90 (Hsp90) inhibitors has exploded during the past decade. Unfortunately, much of this effort has been met with limited success in the clinic.[1] Hsp90 exists as a homodimer and contains multiple small molecule binding sites. The N-terminal nucleotide binding site is the most widely studied, and inhibitors of this domain have risen to clinical evaluation.[2,3] A second small molecule binding site located proximal to the C-terminal dimerization domain has also been identified,[4,5] and modulators of this region are gaining enthusiasm as a consequence of the different biological activities manifested by these inhibitors as compared to those that target the N-terminus.

Hsp90 inhibitors exhibit promising anticancer properties as proteins associated with malignant growth, including growth factors, kinases, and hormone receptors are dependent upon the Hsp90 protein folding machinery for their maturation and/or activation.[6−9] As a molecular chaperone, Hsp90 is responsible for folding these client protein substrates. Consequently, inhibitors of Hsp90 can disrupt multiple signaling cascades simultaneously, resulting in a combinatorial attack on numerous signaling pathways.[10,11]

Novobiocin (**1**), a potent inhibitor of bacterial DNA gyrase,[12] was identified as the first Hsp90 C-terminal inhibitor (Figure 1).[13,14] However, its low efficacy against cancer cells (IC_{50} ~ 700 μM) prevents its use as chemotherapeutic option.[4,5] Although novobiocin displays weak activity, the dimeric compound, coumermycin A1 (**3**), displays a 10-fold greater antiproliferative activity (IC_{50} ~ 70 μM) and thus represents a promising scaffold for the design of more potent Hsp90 inhibitors that target the Hsp90 homodimer.[15]

Structural modifications and structure−activity relationships (SAR) for novobiocin **1** have been investigated and have given rise to analogues that manifest nanomolar antiproliferative activity via Hsp90 inhibition.[7,16−22] In contrast, modifications to the coumermycin A1 scaffold have not been similarly pursued. Coumermycin A1 is a homobifunctional dimer; each monomeric unit contains a 3′-substituted noviose sugar and a 4-hydroxy-8-methylcoumarin connected at the 3-position of the coumarin through a 5-methylpyrrole linker. Previous coumermycin A1 analogues exchanged the pyrrole linker for an aryl, heteroaryl, or olefin-containing tether that altered both the length and geometry of the linker.[23] These analogues retained the noviose sugar and the 8-methyl substituent on the coumarin, which produced compounds that manifested antiproliferative activities in the low micromolar range. In addition to the modest activity observed for noviose-containing analogues, the synthesis of noviose is laborious and hinders rapid development of SAR.[24−26]

Recent publications focused on the monomeric inhibitor, novobiocin, have demonstrated that replacement of 8-methyl coumarin with the 8-methoxy coumarin[18] and exchange of the stereochemically complex noviose sugar with simple, commercially available heterocycles resulted in a 2- to 20-fold enhancement in antiproliferative activity.[19,20,27] The synthesis of noviose sugar is laborious and requires 11 steps for its preparation.

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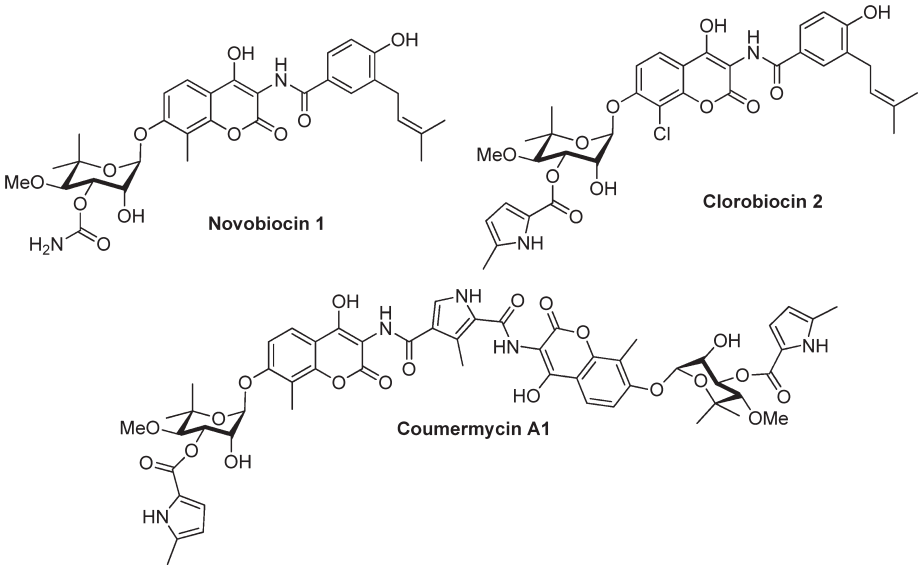


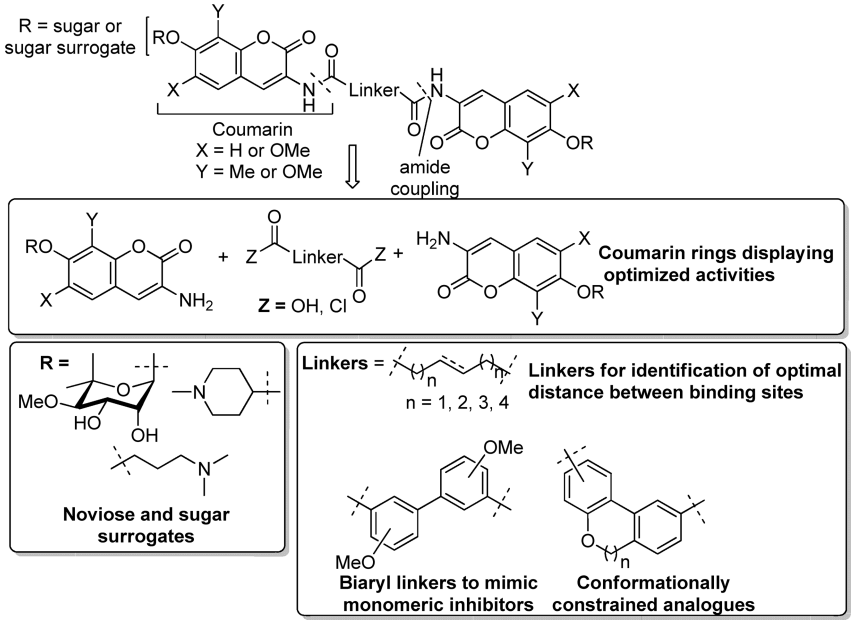
Figure 1. Hsp90 C-terminal inhibitors.

Therefore, a series of dimeric Hsp90 inhibitors were designed to contain substituents identified from the optimized monomeric species in an effort to produce a more efficacious class of C-terminal inhibitors. Specifically, we sought to replace the 8-methyl appendage with an 8-methoxy as well as to introduce the 8-methyl-6-methoxy coumarin and replace the noviose sugar with *N*-methyl-4-piperdine or *N*,*N*-dimethyl ethyl amine. Because of the conformationally flexible nature of the Hsp90 homodimer, the 5-methylpyrrole linker was exchanged for bicyclic, tricyclic, and flexible tethers that could provide occupancy of both binding sites simultaneously via a single inhibitor. The design, synthesis, evaluation, and first structure−activity relationships for coumermycin A1 analogues that target Hsp90 are reported herein.

RESULTS AND DISCUSSION

Design of New Coumermycin A1 Analogues. To determine structure−activity relationships for coumermycin A1 analogues and to provide more efficacious compounds, we sought to explore three regions of coumermycin A: the coumarin core, the sugar, and the linker, each by systematic evaluation. We chose sugar surrogates based upon previously reported novobiocin analogues,[19,20,27] wherein the *N*-methyl-4-piperidine and *N*,*N*-dimethyl ethyl amine substituted coumarins manifested increased antiproliferative activities against a range of cancer cell lines. Modified coumarins were chosen due to the increased inhibitory activities observed for the corresponding novobiocin derivatives,[18,19] specifically 6- and 8-alkoxy substituted and

Scheme 1. Retrosynthesis of Coumermycin A1 Analogues



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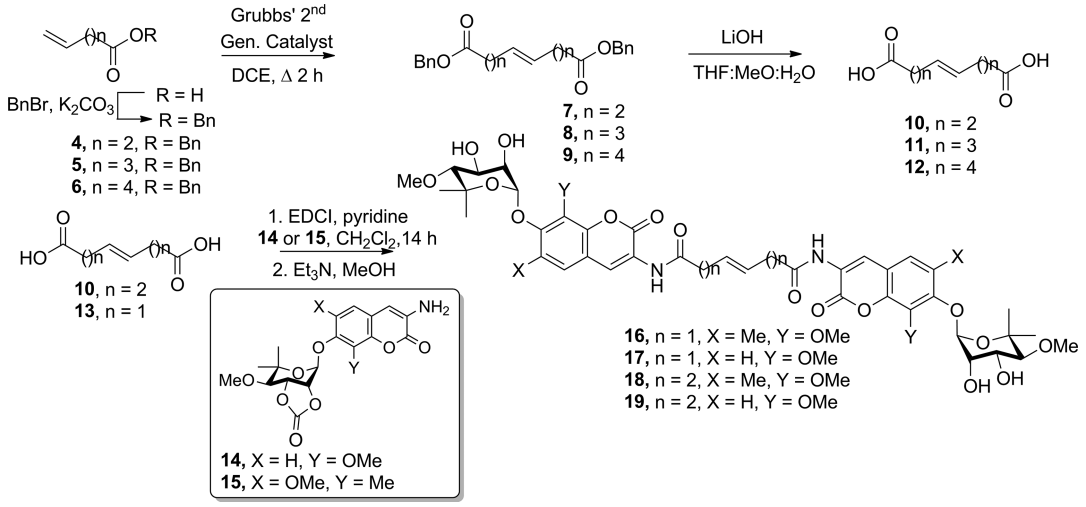
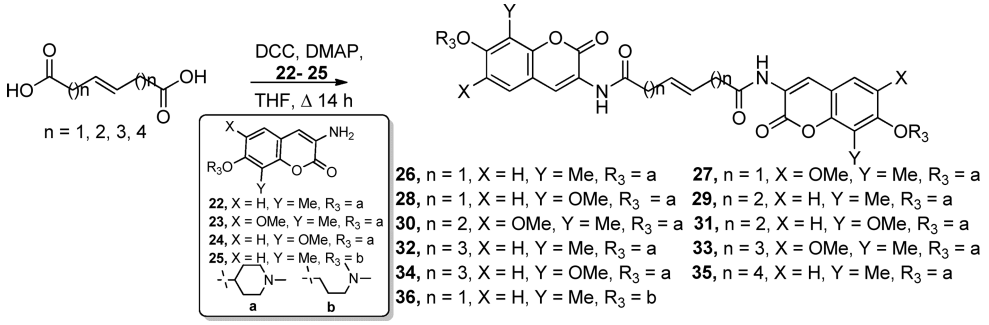
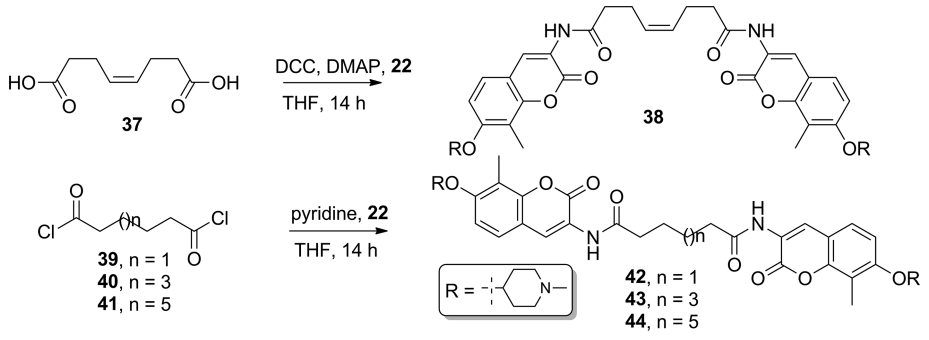
Scheme 2. Synthesis of Noviosylated Olefin Dimers



Scheme 3. Synthesis of Olefinic Dimers



Scheme 4. Synthesis of Saturated- and *cis*-Dimers



6,8-disubstituted coumarins were found to be more active than the 8-methyl coumarin present in novobiocin and coumermycin A1. The linkers were modified to determine the optimal distance between the monomeric binding sites and to account for the flexible nature of the chaperone. Although the alkane- and alkene-containing linkers were chosen to determine the distance between these binding sites, which are located adjacent to the dimerization domain,[15] the biaryl and tricycle containing linkers were chosen for incorporation of the optimal side chain reported for the monomeric species.

The retrosynthesis of coumermycin A1 analogues is depicted in Scheme 1. The sugar-substituted coumarins were prepared as previously described.[18−21,23] Coupling of the sugar-substituted amino-coumarins with either the diacid or diacid chloride linker could then be achieved upon exposure to standard amide forming conditions.

Synthesis and Evaluation of Olefin and Saturated-Linkers for Coumermycin A1 Analogues. The olefinic tethers were chosen based upon previously reported coumermycin A1 analogues.[23] These linkers varied in length and geometry to

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identify the optimal distance between the two C-terminal binding sites in the C-2 symmetric, Hsp90 homodimer. Previous synthesis of coumermycin A1 analogues resulted in low yields from the cross-metathesis reaction (9−51%).[23] Therefore, linkers **10**−**12** were prepared first and then coupled with the corresponding amino-coumarins,[10,13] using standard peptide coupling conditions (Scheme 2). The diacid olefin linkers (**10**−**12**) were prepared via cross-metathesis of the olefin containing benzyl esters (**4**−**6**) followed by hydrolysis. Amino-coumarins (**14** or **15**) were coupled with the commercially available diacid **13** or diacid linker **10** using EDCI in a mixture of pyridine and methylene chloride, which after solvolysis of the noviose cyclic carbonate, provided coumermycin analogues **16**−**19** in good yield.

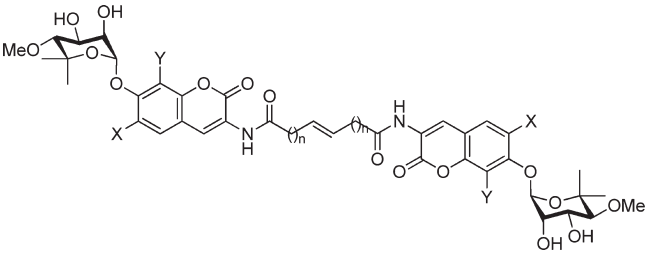
Replacement of the stereochemically complex noviose sugar with simple, commercially available amines was sought as outlined in Scheme 3. These sugar surrogates were chosen based on recent studies that demonstrated these moieties are optimal for the monomeric inhibitors.[19,20] The EDCI coupling method employed for the construction of compounds **16**−**19** was not successful with these derivatives, as the tertiary amines readily protonated and precipitated out of solution. However, dimers **26**−**36** were successfully prepared utilizing a combination of DCC and DMAP, which promoted the union of amines **22**−**25**[27] with olefinic linkers **10**−**13** in good to moderate yields.[28]

For comparison, saturated dimers (**42**−**44**) were prepared by coupling the commercially available diacid chlorides (**39**−**41**) with amino-coumarin **22** in excellent yield (Scheme 4). The 8-carbon, *cis*-olefin containing linker **38**, was also prepared for direct comparison to the *trans*-isomer, **29**.

Once synthesized, these coumermycin A1 analogues that contain both olefinic and saturated linkers were evaluated for antiproliferative activity against SKBr3 (estrogen receptor negative, Her2 overexpressing breast cancer cells), MCF-7 (estrogen receptor positive breast cancer cells), A549 (human lung adenocarcinoma epithelial), HT29 (human colon adenocarcinoma grade II), and PC3 mm2 (androgen receptor insensitive prostate cancer) cell lines. The antiproliferative activities provide some insight into the optimal distance between binding sites and provide rationale for subsequent analogue design. As shown in Table 1, the eight-carbon olefinic dimers, **18** and **19**, were more efficacious than the analogous six-carbon linkers, **16** and **17**, while substitution at the 6-position of the coumarin ring exhibited minimal effect on inhibitory activity. This result was surprising because for the monomeric inhibitors, the 6-OMe-8-Me (**16** and **18**) and 8-OMe coumarins (**17** and **19**), produced compounds that displayed enhanced activity as compared to the 8-Me derivative. These data suggest the dimers may bind in an altered orientation as compared to the monomeric novobiocin analogues or at a different point in the chaperone cycle.

To determine the optimal distance between the coumarin moieties in non-noviosylated coumermycin A1 dimers (**26**−**36**), a series of compounds was prepared to contain an increasing number (6, 8, 10, and 12) of methylene units in the linker. Compounds **26**−**36** were found to be 10−100-fold more potent than the corresponding noviosylated coumermycin A1 analogues, **16**−**19** (Table 2). In the case of 8-methyl coumarin, the 6- and 8-carbon linker dimers (**26** and **29**) were approximately 2−3-fold more active than the dimer containing a 10-carbon linker (**32**). Interestingly, the 10-carbon dimer, **32**, was 10−20-fold more active than any other dimer against prostate cancers, manifesting low nanomolar antiproliferative activities (∼200−400 nM). In general, compounds containing either the 8-OMe/6-OMe or 8-OMe coumarin substitution were found to be more efficacious against prostate cancer cell lines than their 8-Me counterparts.

Table 1. Antiproliferation Activities of Noviosylated Olefin Dimers



entry	*n*	X	Y	SKBr3	MCF-7
coumermycin A1[a]				5.0 ± 0.1	8.8 ± 0.1
16	1	H	OMe	>100[b]	>100
17	2	H	OMe	52.0 ± 7.8	>100
18	1	OMe	Me	105.7 ± 13.2	168.0 ± 9.7
19	2	OMe	Me	4.1 ± 0.5	2.61 ± 0.8
20[21]	1	H	Me	>100	53.1 ± 7.1
21[21]	2	H	Me	1.5 ± 0.1	3.9 ± 0.7

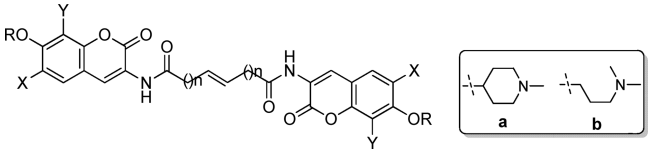
[a] Antiproliferative activities reported from ref 23. [b] Values represent mean ± standard deviation for at least two separate experiments performed in triplicate, all values presented in μM.

The effect of saturation and conformational flexibility was evaluated by measurement of the antiproliferative activity of compounds **42**−**44**. In general, saturated analogues **42**−**44** were less active than the corresponding *trans*-olefin containing dimers, which were more active than *cis*-isomer **38** (Table 3). It appears as though the *trans*-olefin can orient the coumarin rings into a more favorable conformation, while the *cis*-olefin appears to disrupt favorable orientation of the coumarin rings. Because the saturated linker is flexible, it allows the coumarin rings to achieve a favorable conformation, but it also elicits an entropic penalty, manifesting activity that is between the *cis*- and *trans*-isomers.

Synthesis of Biaryl-Tether Coumermycin A1 Analogues. After preparation of the olefin-containing linkers, conformationally constrained analogues were prepared to include a tether that represents the optimal length, contains a pseudotrans double bond, and also includes the biaryl ring system that is present in the monomeric inhibitors. This biaryl system was chosen because it allows rotation between the biaryl rings, resulting in multiple conformations that mimics the *trans* double bond found in **29**.

Additionally, as shown in Figure 2, inclusion of the biaryl side chain places the two coumarin rings at a distance that corresponds to the optimal distance, 8 carbons.[16] Although slight conformational flexibility is produced by this motif, π-stacking attributes may also be manifested by these molecules, which may be responsible for the increased inhibitory activities manifested by monomeric species that contain this ring system. To validate this hypothesis, biaryl linkers **57**−**60** containing various patterns of methoxy substitution, which mimic the substitution pattern of

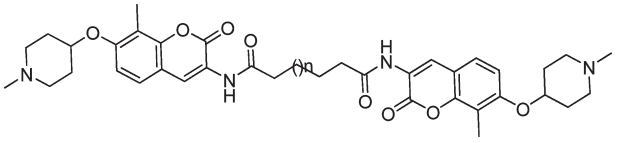
Table 2. Antiproliferation Activities of Non-noviosylated Olefin Dimers



entry	R	*n*	X	Y	SKBr3	MCF7	PC3mm2	A549	HT29
26	a	1	H	Me	0.18 ± 0.03[a]	0.29 ± 0.01	7.51 ± 4.38	21.5 ± 0.08	7.10 ± 1.7
29	a	2	H	Me	0.15 ± 0.01	0.27 ± 0.02	4.19 ± 0.53	5.54 ± 0.04	0.05 ± 0.04
32	a	3	H	Me	0.89 ± 0.01	0.63 ± 0.03	0.44 ± 0.13	0.22 ± 0.15	0.24 ± 0.16
35	a	4	H	Me	0.51 ± 0.06	0.73 ± 0.10	NT	NT	NT
27	a	1	OMe	Me	0.27 ± 0.01	0.56 ± 0.05	0.17 ± 0.12	1.25 ± 0.03	NT
30	a	2	OMe	Me	1.10 ± 0.13	1.31 ± 0.1	4.86 ± 1.3	1.44 ± 0.02	NT
33	a	3	OMe	Me	0.22 ± 0.05	0.31 ± 0.05	0.38 ± 0.07	37.7 ± 5.6	NT
28	a	1	H	OMe	0.71 ± 0.04	1.46 ± 0.2	8.63 ± 1.27	NT	NT
31	a	2	H	OMe	2.22 ± 0.5	1.12 ± 0.03	0.06 ± 0.01	1.22 ± 0.24	NT
34	a	3	H	OMe	0.37 ± 0.05	0.88 ± 0.11	0.05 ± 0.02	1.21 ± 0.8	NT
36	b	1	H	Me	0.46 ± 0.02	0.84 ± 12	15.2 ± 1.82	19.4 ± 5.1	12.2 ± 0.01
38[b]	a	2	H	Me	>100	49.9 ± 2.6	32.9 ± 18.2	77.6 ± 22.4	NT

[a] Values represent mean ± standard deviation for at least two separate experiments performed in triplicate, all values presented in μM. [b] is a *cis*-isomer.

Table 3. Antiproliferation Activities of Saturated Linker Dimers



entry	*n*	SKBr3	MCF-7	PC3 mm2	A549	HT29
42	1	1.26 ± 0.2[a]	2.46 ± 0.4	NT	NT	NT
43	3	1.19 ± 0.3	2.82 ± 0.3	13.8 ± 9.81	30.4 ± 12.3	26.3 ± 2.72
44	5	2.84 ± 0.1	3.68 ± 0.4	10.2 ± 1.81	13.2 ± 2.1	3.9 ± 1.78

[a] Values represent mean ± standard deviation for at least two separate experiments performed in triplicate, all values presented in μM.

monomeric novobiocin analogues containing the methoxy-substituted biaryl side chain, were prepared. Synthesis of the biaryl linkers commenced with phenols **45**[29] and **46** (Scheme 5). Conversion of **45** or **46** to the triflate **47** or **48**, followed by conversion to the boronic ester,[30] allowed subsequent Suzuki coupling with the triflate-containing compounds (**47**, **48**) or with the commercially available iodo-containing compound (**49**), to afford biaryl diesters **53**−**56** in good yield.

Diesters **53**−**56** were then hydrolyzed[31] to the corresponding diacids, **57**−**60**, and subsequently converted to diacid chlorides[32] before coupling with amino-coumarins **13**−**15** to produce the biaryl-linked noviose-containing dimers **65**−**70** upon hydrolysis of the cyclic carbonate (Scheme 6). Diacid chloride **62** was also coupled with amino-coumarins **22** and **25** to give biaryl dimers containing sugar surrogates, **71**−**73**, in excellent yields (Scheme 6).

Synthesis of Tricyclic-Tether Coumermycin A1 Analogues. To further assess conformational flexibility and optimal coumarin ring geometry, conformationally constrained biaryl analogues were also synthesized. The tricyclic linkers containing

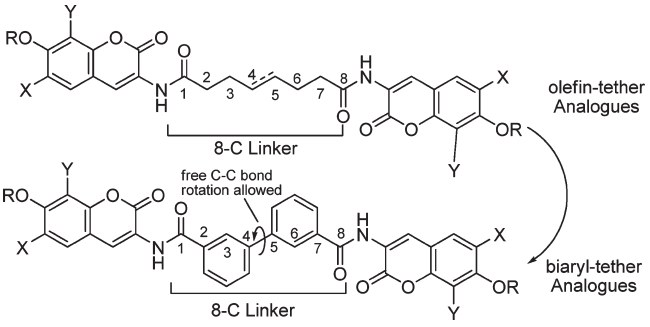


Figure 2. Rationale for biaryl-tether analogues.

varying bridges of 5, 6, or 7 atoms would yield dimers that exhibit decreasing flexibility in their prescribed conformations. The 5-, 6-, and 7-membered tricyclic tethered linkers (**91**, **92**, and **95**) were designed alongside the pseudo *cis* and *trans* 6-membered tethered tricycles in an effort to elucidate the orientation by which these molecules bind Hsp90 (Figure 3).

Retrosynthetic analysis of the tricyclic-containing coumermycin A1 analogues is depicted in Scheme 7, in which two molecules of the sugar substituted amino-coumarin can be coupled with the tricyclic diacid chloride. Tricyclic tethers **76** and **81**−**83** were envisioned to be prepared via nucleophilic displacement of methyl 4-(bromomethyl)-3-iodobenzoate or methyl 3-bromo-4-fluorobenzoate with methyl salicylate, followed by an intermolecular Heck cyclization.[33]

Preparation of the 5-membered tricyclic tether commenced by coupling methyl 3-bromo-4-fluorobenzoate **74**[34] with methyl salicylate, enlisting sodium carbonate in *N*,*N*-dimethylacetamide (DMA), to provide biaryl ether **75** in moderate yield (Scheme 8). Intramolecular Heck cyclization[35] of biaryl ether **75** afforded the 5-membered tricyclic tether, **76**, in good yield.

Six-membered tethers (**81**−**83**) were prepared by coupling *o*-, *m*-, or *p*-methyl salicylate with methyl 4-(bromomethyl)-

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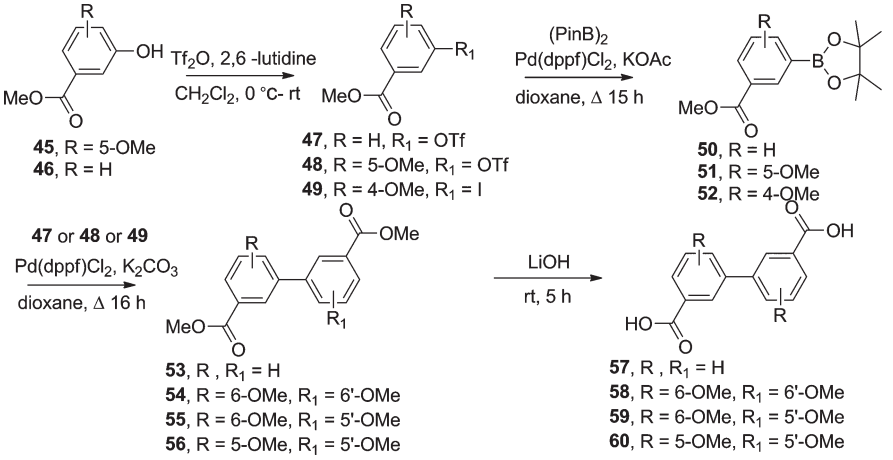
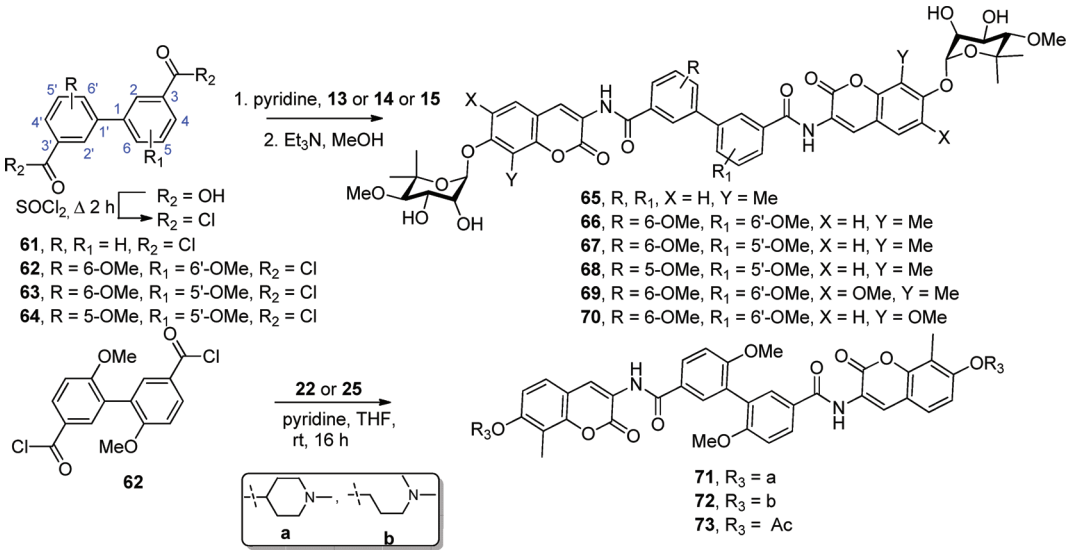
Scheme 5. Synthesis of Conformationally Flexible Biaryl Linkers



Scheme 6. Synthesis of Biaryl Noviosylated Dimers



3-iodobenzoate (**77**)[36] to obtain iodo benzyl ethers **78**−**80**, which were subjected to an intramolecular Heck cyclization[37] to give the 6-membered products, **81**−**83**, in excellent yields. Initially, preparation of the 7-membered tether (**90**) was approached similarly, but Heck cyclization produced an inseparable (5:6) mixture of cyclized and dehalogenated compounds. Consequently, the biaryl bond was constructed first, followed by cyclization to afford the 7-membered tether, **90**, as described in Scheme 9.

Synthesis of **90** commenced with methyl 3-bromo-2-methoxybenzoate (**84**),[38] which was converted to boronic acid **85** in two steps (Scheme 10). The boronic acid was coupled with methyl 3-iodo-4-(2-methoxy-2-oxoethyl)benzoate (**86**)[39] under standard Suzuki coupling conditions[38] to yield triester **87**. The aliphatic ester was selectively reduced to alcohol **88**, followed by cleavage of the methyl ether to give the free phenol. The aliphatic alcohol was converted to tosylate **89** and subjected to an intramolecular cyclization in the presence of potassium carbonate to give the 7-membered product, **90**, in good yield and with only trace amounts of styrene product resulting from elimination.

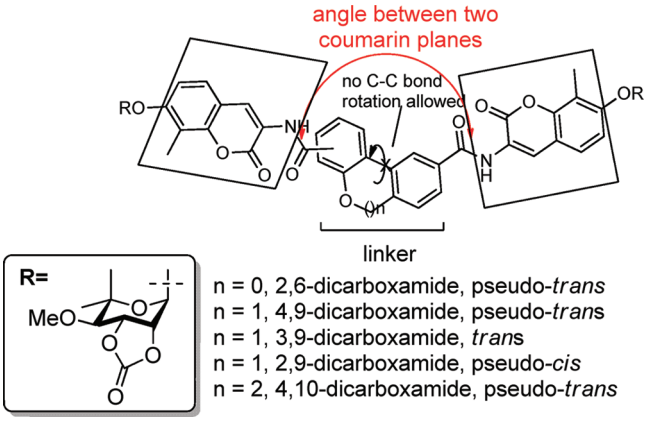


Figure 3. Rationale for tricyclic-tether coumermycin A1 analogues.

Upon preparation, the 5-, 6-, and 7-membered tricyclic esters were hydrolyzed, converted to the corresponding diacid

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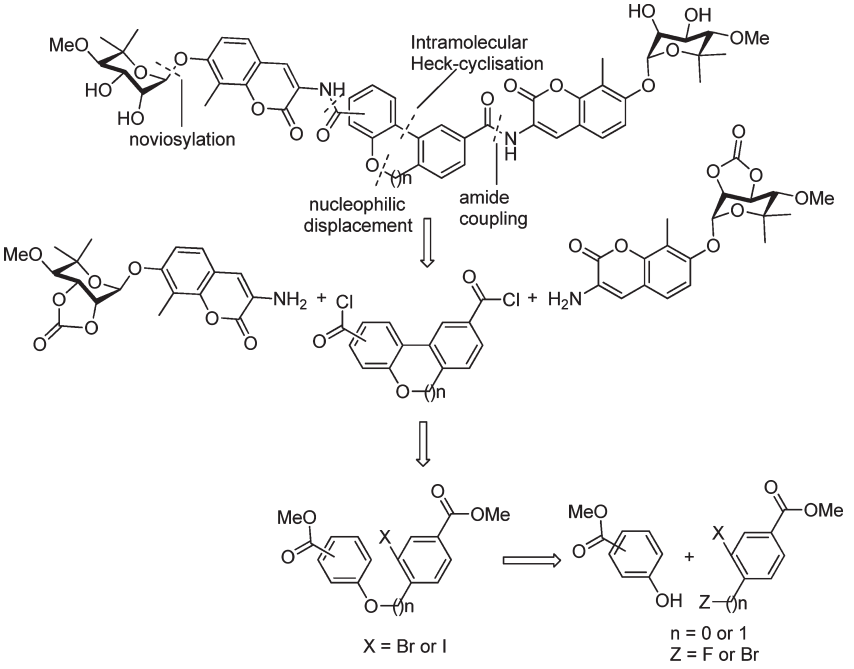
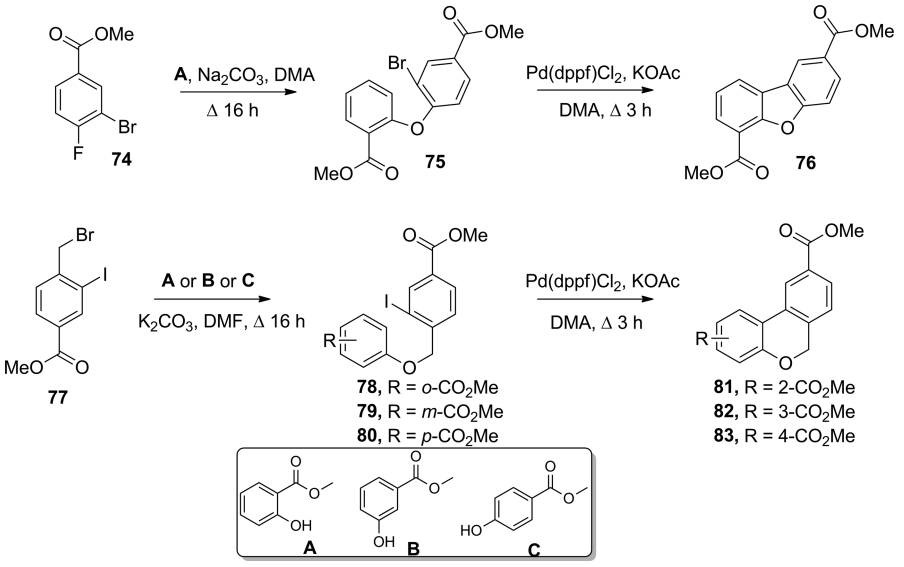
Scheme 7. Retrosynthesis of 5- and 6-Membered Tricyclic-Tether Analogues



Scheme 8. Synthesis of 5- and 6-Membered Tricyclic Tether



chlorides **96**−**100**, and coupled with amino-coumarin **10** to provide the requisite dimers **101**−**105** following hydrolysis (Scheme 11).

Biological Evaluation Biaryl- and Tricyclic-Containing Coumermycin A1 Analogues. After construction of the olefin and alkane linked dimers, analogues containing biaryl linkers with varying methoxy substitution and coumarin scaffolds (**65**−**70**) were prepared and subsequently evaluated for antiproliferative activity (Table 4). To evaluate the effect of the methoxy group, four biaryl linkers (**65**−**70**) were synthesized. Among these, the symmetrical (**66** and **68**) biaryl dimers were found to be more active than the nonsymmetrical analogue (**67**). Analogue **66** (6-OMe, 6′-OMe) exhibited 2-fold greater activity than **68** (5-OMe, 5′-OMe) against breast cancer cell lines, however, these molecules were less active against prostate cancer cell lines. Interestingly, the dimer containing the 8-OMe substitution on the coumarin scaffold (**70**) manifested equal potency against the breast cancer cell lines as the corresponding 8-Me analogue **66** but was 100−150-fold more active against prostate cancer cell lines. Analogue **69** (8-Me and 6-OMe coumarin) was 7−8-fold more active against SKBr3 cell lines and slightly more potent against MCF-7 cell lines than its corresponding 8-Me and 8-OMe coumarin analogues, **66** and **68**.

Analogous dimers to the previously described novobiocin monomer analogues with secondary amine-containing sugar replacements (**72** and **73**) were also evaluated. Interestingly,

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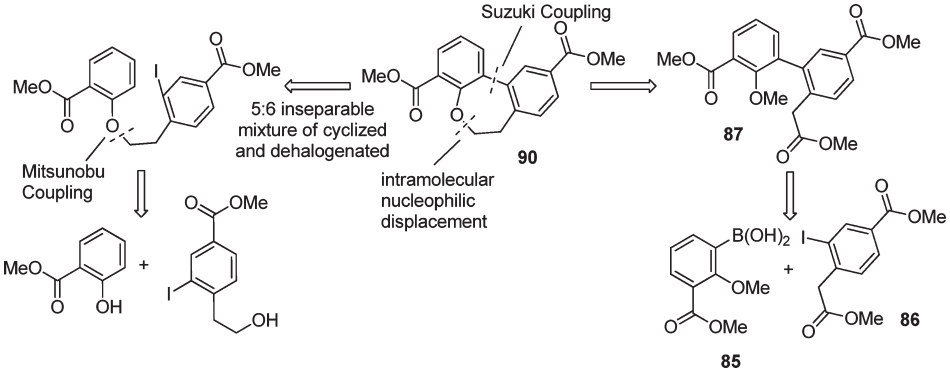
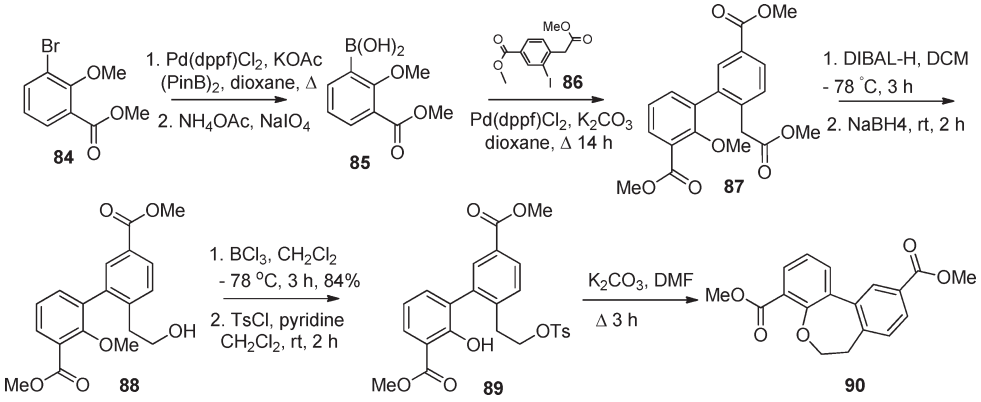
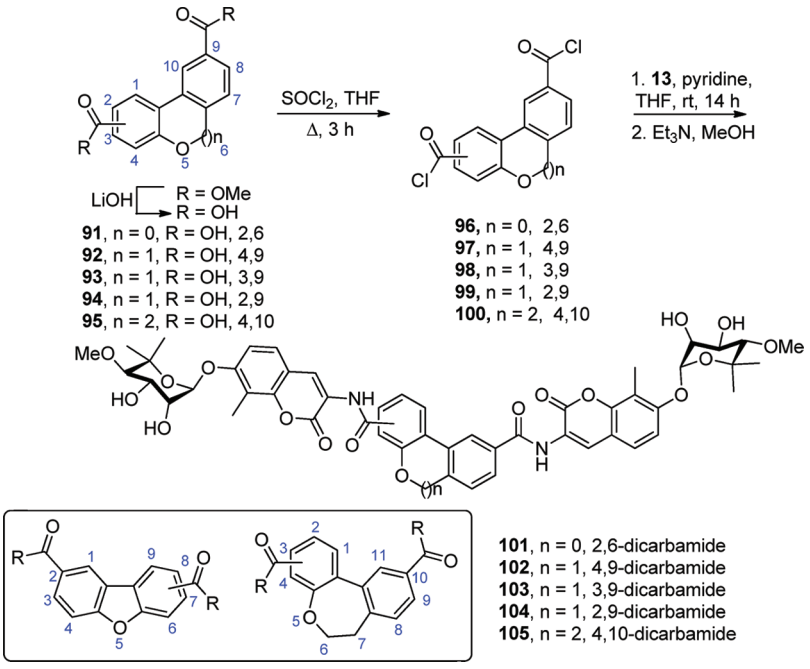
Scheme 9. Retrosynthesis of 7-Membered Tricyclic-Tether



Scheme 10. Synthesis of 7-Membered Tether



Scheme 11. Synthesis of Tricyclic Tether Noviosylated Dimers



these compounds were ~10-fold less active than the corresponding noviosylated coumarin-containing (**65**−**70**) analogues (Table 5). This trend is opposite to that of the novobiocin series of compounds.[19,20] Compounds **71** and **72** also exhibited poor

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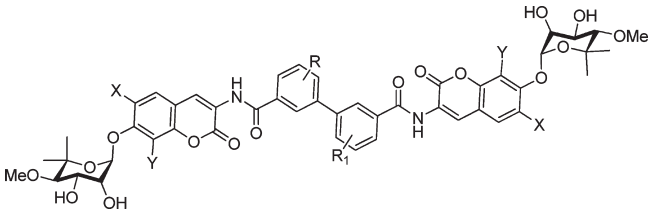
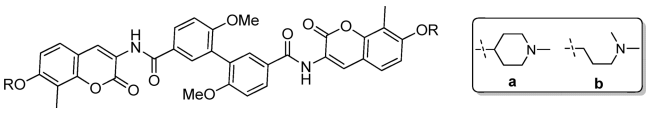
Table 4. Antiproliferation Activities of Biaryl Dimers



entry	X	Y	R	R^1	SKBr3	MCF-7	PC3 mm2	A549	HT29
65	H	Me	H	H	0.86 ± 0.14[a]	1.26 ± 0.17	NT	NT	NT
66	H	Me	6-OMe	6′-OMe	1.16 ± 0.21	0.76 ± 0.14	36.68 ± 8.1	35.4 ± 0.01	36.54 ± 12. 7
67	H	Me	6-OMe	5′-OMe	28.50 ± 4.4	38.0 ± 1.5	NT	NT	NT
68	H	Me	5-OMe	5′-OMe	1.95 ± 0.4	1.85 ± 0.52	12.53 ± 2.0	28.90 ± 8.62	11.72 ± 1.43
69	OMe	Me	6-OMe	6′-OMe	0.11 ± 0.05	0.72 ± 0.21	NT	NT	NT
70	H	OMe	6-OMe	6′-OMe	0.91 ± 0.12	0.88 ± 0.2	0.27 ± 0.17	0.21 ± 0.08	0.27 ± 0.12

[a] Values represent mean ± standard deviation for at least two separate experiments performed in triplicate, all values presented in μM.

Table 5. Antiproliferation Activities of Non-noviosylated Biaryl Dimers



entry	R	SKBr3	MCF-7	PC3 mm2	A549	HT29
71	a	4.98 ± 0.7	14.23 ± 2.3	NT	NT	NT
72	b	9.50 ± 1.2	11.66 ± 1.6	52.27 ± 24.3	93.45 ± 0.25	62.7 ± 18.7
73	Ac	11.84 ± 0.8[a]	>100	NT	NT	NT

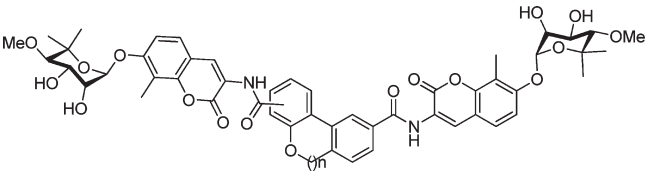
[a] Values represent mean ± standard deviation for at least two separate experiments performed in triplicate, all values presented in μM.

solubility in DMSO, which may contribute to their modest inhibitory activity.

As mentioned above, we sought to optimize the linker geometry by synthesizing conformationally constrained tricyclic analogues, with ring sizes containing 5, 6, and 7 atoms (**101**−**105**). These tricyclic systems allowed the dimers to exhibit increasingly flexible geometries that were dependent on ring size and attachment to the coumarin ring. After synthesis of the tricyclic tether analogues **101**−**105**, they were evaluated for antiproliferative activity. Among these analogues, the 6- and 7-membered tricyclic tether dimers (**102** and **105**) were found to be more active than the corresponding 5-membered analogue, **101** (Table 6). Antiproliferative activity against the SKBr3 breast cancer cell line was similar for both 6- and 7-membered dimers (**102** and **105**), but against MCF-7 cell lines, the 7-membered analogue (**103**) was 3-fold more active than the 6-membered analogue (**102**). The tricyclic constrained analogues (**101**−**105**) were less potent than the more flexible biaryl linkers (**65**−**70**). These data may indicate that free rotation about the aryl carbon−carbon bond is necessary to orient the methoxy group of the linker and the two coumarin rings into a favorable conformation because the tricyclic analogues (**101**−**105**) are conformationally rigid and lack free rotation about these aryl rings.

To validate Hsp90 as the target responsible for manifesting the observed antiproliferative activities exhibited by these molecules, analogues manifesting IC_{50} values less than 2 μM were evaluated for their ability to induce degradation of Hsp90-dependent client proteins (Her-2, Raf, and Akt). Because actin

Table 6. Anti-Proliferation Activities of Tricyclic Tether Dimers



entry	*n*	amide positions	SKBr3	MCF-7
101	0	2,6	<100[a]	<100
102	1	4,8	60.1 ± 2.8	22.0 ± 3.4
103	1	3,8	<100	<100
104	1	2,8	<100	<100
105	2	4,10	59.9 ± 9.8	7.1 ± 1.6

[a] Values represent mean ± standard deviation for at least two separate experiments performed in triplicate, all values presented in μM.

is not dependent on Hsp90 for its maturation, actin levels should remain constant with an Hsp90 inhibitor and is therefore used as a control.

Figure 4 shows the effect of these compounds on Hsp90 client proteins from MCF-7 breast cancer cell lysates, following a 24 h incubation with each molecule. Each compound was dosed at two concentrations, H represents a concentration 5-fold higher than the antiproliferative IC_{50} value, whereas L represents a concentration equal to one-half of the observed IC_{50} value, while geldanamycin (500 nM, 10× the IC_{50}) was used as a positive control and dimethyl sulfoxide (0) as a negative control.

The majority of the compounds screened by Western blot analyses induced degradation of Hsp90 client proteins while causing no change in actin, which indicates these compounds manifest antiproliferative activity through Hsp90 inhibition. There were three compounds, **31**, **32**, and **36** (Figure 5) that produced unique client protein profiles at the two concentrations tested. Compounds **31** and **36** appeared to manifest no activity against Hsp90 client proteins, while **32** only induced the degradation of Raf and Akt but exhibited no effect on Her2. Further studies are needed to determine whether the activity manifested by **32** is dependent upon Hsp90. Prior studies have

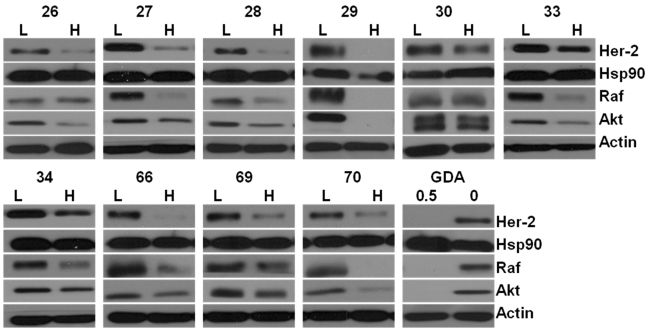


Figure 4. Western blot analyses induced the Hsp90 client protein degradation in MCF-7 breast cancer cells for coumermycin A1 analogues that target Hsp90. L represents a concentration $^1/_2$ of the antiproliferative IC_{50} value, while H represents a concentration 5 times greater than the antiproliferative IC_{50} value. GDA (500 nM) represents a positive control, while DMSO (0), vehicle, serves as the negative control.

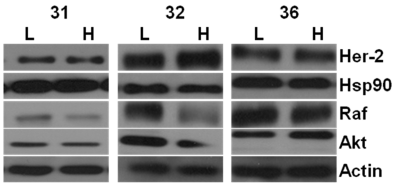


Figure 5. Western blot analyses of Hsp90 client protein degradation in MCF-7 breast cancer cells for coumermycin A1 analogues that appear to not target Hsp90. L represents a concentration $^1/_2$ of the antiproliferative IC_{50} value, while H represents a concentration 5 times the antiproliferative IC_{50} value.

shown that extracellular Hsp90, which binds Her2,[40,41] can be selectively targeted with nonpermeable inhibitors,[42] but no data has been previously observed for reciprocal activity.

CONCLUSION

In summary, we have prepared both conformationally constrained and flexible coumermycin A1 analogues that manifest nanomolar antiproliferative activity against breast (SKBr3 and MCF7) and prostate cancer (PC3 mm2, A549, and HT29) cell lines. Among these analogues were those that contained surrogates for the noviose sugar and varying coumarin substitution. With regard to the tether, the *trans*-alkene linkers (Table 2) containing 6−8 carbons (**26**, **29**, and **27**) represent the most active analogues compared to the longer linkers as well as the corresponding *cis*-olefinic (**38**) linker. The biaryl linked dimers (**69** and **70**), which mimicked the monomeric species, were found to be less active than the dimers that contain a flexible linker. Most of the coumermycin A1 analogues prepared in this article manifested potent antiproliferative activity that was directly correlated to Hsp90 inhibition, as evidenced by the degradation of Hsp90-dependent client proteins. The most active compounds identified from this study manifest IC_{50} values ~500-fold more potent than the natural product lead compounds, coumermycin A1.

EXPERIMENTAL SECTION

General. ^{1}H NMR were recorded at 400 or 500 MHz (Bruker DRX-400 Bruker with a H/C/P/F QNP gradient probe) spectrometer and ^{13}C NMR spectra were recorded at 125 MHz (Bruker DRX 500 with broadband, inverse triple resonance, and high resolution magic angle spinning HR-MA probe spectrometer); chemical shifts are reported in δ (ppm) relative to the internal reference chloroform-*d* ($CDCl_3$, 7.27 ppm). FAB (HRMS) spectra were recorded with a LCT Premier (Waters Corp., Milford, MA) spectrometer and IR spectra were recorded on a Magna FT-IR spectrometer (Nicolet Instrument Corporation, Madison, WI). The purity of all compounds was determined to be >95% as determined by ^{1}H NMR and ^{13}C NMR spectra, unless otherwise noted. The most active 10 compounds were verified for >95% purity by HPLC analyses. TLC was performed on glass-backed silica gel plates (Uniplate) with spots visualized by UV light. All solvents were reagent grade and, when necessary, were purified and dried by standard methods. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator operating at reduced pressure.

General Procedure for Benzyl Protection of Olefinic Acids. K_2CO_3 (8.28 g, 59.9 mmol) and benzyl bromide (2.84 mL, 23.96 mmol) were added sequentially to a solution of pent-4-enoic acid (2 g, 19.97 mmol) in anhydrous DMF (50 mL). The mixture was stirred at rt for 14 h and quenched by the addition of H_2O (80 mL). The aqueous phase was extracted with EtOAc (3 × 80 mL), and the combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified via column chromatography on silica gel (hexanes/EtOAc, 9/1) to afford benzyl pent-4-enoate (**4**) as colorless oil (3.65 g, 92%).

*Benzyl Pent-4-enoate (**4**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.84 (ddt, J = 6.2, 10.2, 16.5 Hz, 1H), 5.14 (s, 2H), 5.05 (m, 2H), 2.49 (m, 2H), 2.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 136.7, 136.1, 128.7, 128.4, 115.7, 66.4, 33.7, 29.0. HRMS (FAB) m/z: $[M + H^+]$ for $C_{12}H_{15}O_2$, calcd, 191.1072; found, 191.1069.

*Benzyl Hex-5-enoate (**5**).* Colorless oil, (2.25 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.78 (ddt, J = 6.7, 10.2, 17.0 Hz, 1H), 5.16 (s, 2H), 5.02 (m, 2H), 2.39 (t, J = 7.5 Hz, 2H), 2.11 (q, J = 7.1 Hz, 2H), 1.77 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 137.6, 136.1, 128.6, 128.2, 115.4, 66.1, 33.6, 33.1, 24.1. HRMS (FAB) m/z: $[M + H^+]$ for $C_{13}H_{17}O_2$, calcd, 205.1229; found, 205.1234.

*Benzyl Hept-6-enoate (**6**).* Colorless oil, (1.87 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.80 (ddt, J = 6.7, 10.2, 16.9 Hz, 1H), 5.13 (s, 2H), 5.01 (m, 2H), 2.38 (t, J = 7.5 Hz, 2H), 2.08 (m, 2H), 1.68 (m, 2H), 1.44 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 138.5, 136.2, 128.5, 128.3, 114.8, 66.2, 34.3, 33.5, 28.4, 24.5. HRMS (FAB) m/z: $[M + H^+]$ for $C_{14}H_{19}O_2$, calcd, 219.1385; found, 219.1381.

General Procedure for the Cross-Metathesis Reaction. Grubbs' second-generation catalyst (320 mg, 0.38 mmol, 2 mol %) was added to a solution of benzyl pent-4-enoate **1** (3.6 g, 18.92 mmol) in 10 mL of dichloroethane. The mixture was refluxed for 2 h, then filtered through a plug of silica gel and concentrated. The residue was purified by column chromatography on silica gel (hexanes/EtOAc, 8/1) to provide (*E*)-dibenzyl oct-4-enedioate **7** (1.8 g, 49%) as a colorless oil.

*(E)-Dibenzyl Oct-4-enedioate (**7**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 10H), 5.46 (m, 2H), 5.12 (s, 4H), 2.41 (m, 4H), 2.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 136.1, 129.5, 128.7, 128.4, 66.3, 34.2, 27.9. HRMS (FAB) m/z: $[M + Na^+]$ for $C_{22}H_{24}NaO_4$, calcd, 375.1572; found, 375.1566.

*(E)-Dibenzyl Dec-5-enedioate (**8**).* Colorless oil, (1.27 g, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 10H), 5.39 (m, 2H), 5.12 (s, 4H), 2.35 (m, 4H), 2.04 (dt, J = 9.7, 10.8 Hz, 4H), 1.71 (dt, J = 7.4, 14.5 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 130.6, 130.3, 128.7, 128.3, 66.2, 33.7, 32.0, 24.8. HRMS (FAB) m/z: $[M + Na^+]$ for $C_{24}H_{28}NaO_4$, calcd, 403.1885; found, 403.1883.

*(E)-Dibenzyl Dodec-6-enedioate (**9**).* Colorless oil, (1.56 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 10H), 5.38 (m, 2H), 5.12 (s, 4H), 2.38 (dd, J = 12.2, 19.6 Hz, 4H), 2.01 (q, J = 11.2 Hz, 4H), 1.65 (m, 4H), 1.36 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.7, 136.2, 130.3,

128.7, 128.3, 66.2, 34.3, 32.3, 29.1, 24.6. HRMS (FAB) m/z: [M + Na^+] for $C_{26}H_{32}NaO_4$, calcd, 431.2198; found, 431.2202.

General Procedure for Benzyl Ester Hydrolysis. LiOH (1.97 g, 46.8 mmol) was added to a solution of (*E*)-dibenzyl oct-4-enedioate **7** (1.65 g, 4.68 mmol) in 40 mL of THF:MeOH:H_2O (3:2:2) at rt and stirred for 6 h. The resulting mixture was acidfied to pH ~ 3 with 2N HCl, and the white solid was filtered. The product was recrystallized in 30% ethylacetate and hexane to afford acid (*E*)-oct-4-enedioic acid **10** (0.77 g, 96%) as a colorless amorphous solid.

*(E)-Oct-4-enedioic Acid (**10**).* ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 2H), 5.44 (t, J = 3.2 Hz, 2H), 2.24 (m, 4H), 2.18 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.9, 129.3, 33.6, 27.4. HRMS (FAB) m/z: [M − H^+] for $C_8H_{11}O_4$, calcd, 171.0657; found, 171.0655.

*(E)-Dec-5-enedioic Acid (**11**).* Colorless amorphous solid, (0.66 g, 92%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.99 (s, 2H), 5.38 (d, J = 3.6 Hz, 2H), 2.19 (t, J = 7.4 Hz, 4H), 1.94 (m, 4H), 1.56 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.6, 126.3, 63.7, 33.8, 31.9. HRMS (FAB) m/z: [M − H^+] for $C_{10}H_{15}O_4$, calcd, 199.0970; found, 199.0969.

*(E)-Dodec-6-enedioic Acid (**12**).* Colorless amorphous solid, (0.46 mg, 89%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.96 (br s, 2H), 5.37 (t, J = 3.6 Hz, 2H), 2.18 (t, J = 7.4 Hz, 4H), 1.95 (m, 4H), 1.48 (m, 4H), 1.31 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.4, 129.9, 33.5, 31.7, 28.5, 24.0. HRMS (FAB) m/z: [M − H^+] for $C_{12}H_{19}O_4$, calcd, 227.1283; found, 227.1277.

General Procedure for Peptide Coupling of Noviosylated Olefin Dimers. *N*-(3-(Dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (176 mg, 0.92 mmol) was added to a solution of aminocoumarin **15** (164 mg, 0.38 mmol) and commercially available (*E*)-hex-3-enedioic acid (22 mg, 0.15 mmol) in CH_2Cl_2 containing 30% pyridine at rt. The resulting solution was stirred for 14 h, concentrated, and the residue purified by column chromatography on silica gel (CH_2Cl_2/acetone, 8/1) to afford the amides as colorless amorphous solids.

Et_3N (10% total volume) was added dropwise to a solution of above cyclic carbonate diamides in methanol. The resulting mixture was stirred for 14 h and concentrated. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 19/1) to yield the olefin linked noviosylated dimer **16** (74% in two steps) as a colorless amorphous solid.

*(E)-N1-(7-((2R,3S,4R,5S)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-N6-(7-((2S,3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)hex-3-enediamide (**16**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 2H), 6.77 (s, 2H), 5.86 (t, J = 4.5 Hz, 2H), 5.13 (d, J = 4.8 Hz, 2H), 4.17 (dd, J = 3.5, 6.6 Hz, 2H), 4.01 (t, J = 3.7 Hz, 2H), 3.82 (s, 6H), 3.48 (s, 6H), 3.46 (s, 6H), 3.13 (d, J = 6.7 Hz, 2H), 2.34 (s, 6H), 1.29 (s, 6H), 1.28 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 158.9, 149.5, 146.6, 143.3, 127.5, 124.5, 122.6, 121.2, 115.5, 106.7, 102.8, 83.5, 78.3, 70.5, 68.6, 60.7, 56.1, 40.9, 26.4, 24.7, 9.9. IR (KBR) ν_{max} 3400, 3286, 2972, 2931, 1703, 1681, 1529, 1385, 1250, 1114, 1084, 952, 770 cm^{-1}. HRMS (FAB) m/z: [M + Na^+] for $C_{44}H_{54}N_2NaO_{18}$, calcd, 921.3269; found, 921.3239.

*(E)-N1-(7-((2R,3S,4R,5S)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-N6-(7-((2S,3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)hex-3-enediamide (**17**).* Colorless amorphous solid (81% in two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.69 (s, 2H), 8.53 (s, 2H), 7.38 (d, J = 8.9 Hz, 2H), 7.18 (d, J = 8.9 Hz, 2H), 5.72 (t, J = 4.2 Hz, 2H), 5.48 (d, J = 2.2 Hz, 2H), 5.31 (d, J = 4.5 Hz, 2H), 5.05 (d, J = 6.1 Hz, 2H), 3.98 (m, 2H), 3.88 (m, 2H), 3.84 (s, 6H), 3.49 (s, 6H), 3.27 (d, J = 9.3 Hz, 4H), 3.27 (d, J = 9.3 Hz, 2H), 1.24 (s, 6H), 1.06 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.8, 157.4, 150.8, 147.4, 143.7, 135.6, 126.9, 124.9, 122.6, 122.3, 114.4, 112.4, 99.2, 83.3, 78.0, 70.9, 67.5, 61.2, 61.1, 28.6, 22.9. IR (KBR) ν_{max} 3400, 3342, 3286, 2972, 2931, 1703, 1681, 1529, 1435, 1385, 1298, 1114, 1089, 950, 770 cm^{-1}. HRMS (FAB) m/z: [M + Na^+] for $C_{42}H_{50}N_2NaO_{18}$, calcd, 893.2956; found, 893.2952.

*(E)-N1-(7-((2R,3S,4R,5S)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-N8-(7-((2S,3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-oct-4-enediamide (**18**).* Colorless amorphous solid (84% in two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 2H), 6.66 (s, 2H), 5.52 (t, J = 3.5 Hz, 2H), 5.10 (d, J = 4.5 Hz, 2H), 4.12 (dd, J = 3.5, 7.1 Hz, 2H), 4.00 (t, J = 3.5 Hz, 2H), 3.76 (s, 6H), 3.45 (s, 6H), 3.11 (d, J = 7.1 Hz, 2H), 2.43 (d, J = 6.7 Hz, 4H), 2.33 (m, 4H), 2.24 (s, 6H), 1.25 (s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 159.0, 149.4, 146.5, 143.2, 129.9, 124.3, 122.5, 120.9, 115.4, 106.4, 96.0, 83.6, 78.3, 70.5, 68.5, 60.7, 55.9, 36.8, 27.8, 26.7, 24.4, 9.7. IR (KBR) ν_{max} 3440, 3398, 3313, 2974, 2933, 1714, 1686, 1627, 1529, 1465, 1389, 1120, 1066, 950, 769 cm^{-1}. HRMS (FAB) m/z: [M + Na^+] for $C_{46}H_{58}N_2NaO_{18}$, calcd, 949.3582; found, 949.3589.

*(E)-N1-(7-((2R,3S,4R,5S)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-N8-(7-((2S,3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)oct-4-enediamide (**19**).* Colorless amorphous solid (69% in two steps). ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (s, 2H), 7.07 (d, J = 8.9 Hz, 2H), 7.00 (d, J = 8.9 Hz, 2H), 5.46 (t, J = 3.5 Hz, 2H), 5.38 (d, J = 2.4 Hz, 2H), 4.03 (dd, J = 3.4, 9.1 Hz, 2H), 3.99 (t, J = 3.4 Hz, 2H), 3.77 (s, 6H), 3.45 (s, 6H), 3.21 (d, J = 9.2 Hz, 2H), 2.38 (t, J = 6.6 Hz, 4H), 2.29 (m, 4H), 1.22 (s, 6H), 1.03 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.3, 156.8, 150.1, 142.6, 134.9, 128.5, 123.4, 121.1, 113.5, 111.6, 98.4, 82.7, 77.3, 77.4, 70.1, 67.0, 60.5, 60.2, 35.3, 27.7, 27.0, 21.7. IR (KBR) ν_{max} 3645, 3518, 3329, 2968, 2931, 2833, 1709, 1682, 1604, 1526, 1464, 1361, 1280, 1049, 1031, 950, 798 cm^{-1}. HRMS (FAB) m/z: [M + Na^+] for $C_{44}H_{54}N_2NaO_{18}$, calcd, 921.3269; found, 921.3256. This material was determined to be 98.3% pure (retention time = 2.174) by HPLC (Phenomenex Luna C-18, 5 μm, 10 mm × 250 mm column eluting with 49% $CHCl_3$, 49% MeOH, and 2% H_2O, flow rate 5.0 mL/min).

Gemneral Procedure for Peptide Coupling of Non-noviosylated Olefin Dimers. *N*,*N*′-Dicyclohexylcarbodiimide (290 mg, 1.4 mmol), followed by 4-(*N*,*N*-dimethylamino)pyridine (137 mg, 1.12 mmol) and two drops of DMF, were added simultaneously to a solution of (*E*)-hex-3-enedioic acid (40 mg, 0.28 mmol) in THF (3 mL) at rt. The mixture was stirred for 15 min before adding amino coumarin **22** (295 mg, 0.7 mmol) in THF (2 mL). The resulting reaction mixture was stirred at 50 °C for 14 h, quenched with water, extracted with DCM (3 × 15 mL), and combined organic layers were washed with saturated NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified through silica gel column chromatography (CH_2Cl_2/MeOH/Et_3N, 90/9/1) to give compound **26** (108 mg, 57%) as a colorless amorphous solid.

*(E)-N1,N6-Bis(8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)hex-3-enediamide (**26**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 2H), 8.10 (s, 2H), 7.27 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.94 (t, J = 3.9 Hz, 2H), 4.45 (m, 2H), 3.29 (d, J = 5.5 Hz, 4H), 2.64 (m, 4H), 2.34 (m, 4H), 2.32 (s, 6H), 2.31 (s, 6H), 2.01 (m, 4H), 1.90 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 159.3, 157.1, 149.6, 127.7, 125.6, 124.8, 121.2, 115.3, 113.2, 110.6, 72.6, 52.5, 46.4, 41.3, 30.9, 8.5. IR (KBr) ν_{max} 3380, 3231, 3010, 2925, 2597, 1716, 1685, 1600, 1525, 1467, 1353, 1103 cm^{-1}. HRMS (FAB) m/z: [M + H^+] for $C_{38}H_{45}N_4O_8$, calcd, 685.3237; found, 685.3222. This material was determined to be ~95% pure (retention time = 2.137) by HPLC analysis on autosampler (Agilent TOF/AgilentA3B1C3.m method with 49% $CHCl_3$, 49% MeOH, and 2% H_2O, flow rate 5.0 mL/min).

*(E)-N1,N6-Bis(6-methoxy-8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)hex-3-enediamide (**27**).* Colorless amorphous

solid (40 mg, 59%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.51 (s, 2H), 6.74 (s, 2H), 5.80 (t, J = 3.7 Hz, 2H), 4.18 (m, 2H), 3.22 (d, 2H), 3.78 (s, 6H), 2.81 (m, 4H), 2.30 (m, 4H), 2.30 (s, 6H), 2.25 (s, 6H), 1.93 (m, 8H), 1.82 (4, 2H). ^{13}C NMR (125 MHz, CD_3OD) δ 170.3, 156.1, 150.2, 146.4, 140.6, 127.5, 124.8, 122.4, 121.1, 118.8, 115.0, 106.5, 55.9, 52.4, 45.3, 40.8, 30.8, 9.4. IR (KBR) ν_{max} 3274, 2937, 2848, 1708, 1689, 1604, 1521, 1457, 1386, 1080, 772 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{40}H_{49}N_4O_{10}$, calcd, 745.3449; found, 745.3418. This material was determined to be ~97.3% pure (retention time = 2.049) by HPLC analysis on autosampler (Agilent TOF/AgilentA3B1C3.m method with 49% $CHCl_3$, 49% MeOH, and 2% H_2O, flow rate 5.0 mL/min).

*(E)-N1,N6-Bis(8-methoxy-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)hex-3-enediamide (**28**).* Colorless amorphous solid (34 mg, 44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 2H), 8.13 (s, 2H), 7.16 (d, J = 8.8 Hz, 2H), 6.93 (dd, J = 8.7, 17.2 Hz, 2H), 5.93 (m, 2H), 4.48 (m, 2H), 3.98 (s, 6H), 3.29 (dd, J = 1.6, 3.9 Hz, 4H), 2.81 (m, 4H), 2.46 (m, 4H), 2.41 (s, 6H), 2.14 (m, 4H), 1.98 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 158.6, 151.9, 144.4, 137.8, 127.7, 124.3, 122.6, 121.9, 114.8, 113.6, 73.5, 61.7, 52.2, 45.9, 41.3, 30.4. IR (KBR) ν_{max} 3377, 2943, 2881, 1701, 1691, 1604, 1518, 1460, 1357, 1205, 1059, 972 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{38}H_{45}N_4O_{10}$, calcd, 717.3136; found, 717.3135.

*(E)-N1,N8-Bis(8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)oct-4-enediamide (**29**).* Colorless amorphous solid (87 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$ + CD_3OD) δ 8.46 (s, 2H), 7.16 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 5.49 (dd, J = 9.4, 12.9 Hz, 2H), 4.42 (m, 2H), 2.61 (m, 4H), 2.41 (m, 8H), 2.31 (m, 4H), 2.30 (s, 6H), 2.16 (s, 6H), 1.94 (m, 4H), 1.84 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD) δ 172.2, 159.2, 156.6, 149.3, 129.8, 125.5, 125.2, 121.0, 114.8, 113.1, 110.3, 71.5, 51.7, 45.6, 36.8, 29.8, 27.9, 8.0. IR (KBR) ν_{max} 3335, 3085, 3043, 2923, 2852, 1703, 1681, 1604, 1523, 1377, 1097, 771 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{40}H_{49}N_4O_8$, calcd, 713.3550; found, 713.3564. This material was determined to be ~100% pure (retention time = 2.137) by HPLC analysis on autosampler (Agilent TOF/AgilentA3B1C3.m method with 49% $CHCl_3$, 49% MeOH, and 2% H_2O, flow rate 5.0 mL/min).

*(E)-N1,N8-Bis(6-methoxy-8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)oct-4-enediamide (**30**).* Colorless amorphous solid (45 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 2H), 6.76 (s, 2H), 5.59 (t, J = 3.5 Hz, 2H), 4.26 (m, 2H), 3.84 (s, 6H), 2.98 (m, 4H), 2.47 (m, 12H), 2.31 (s, 6H), 2.06 (m, 12H), 1.97 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 159.1, 150.2, 146.8, 143.5, 130.0, 124.1, 122.6, 120.5, 115.3, 106.5, 56.0, 52.2, 45.3, 37.2, 37.1, 30.6, 28.1, 9.7. IR (KBR) ν_{max} 3323, 2933, 2850, 1716, 1685, 1533, 1465, 1389, 1220, 1190, 771 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{42}H_{53}N_4O_{10}$, calcd, 773.3762; found, 773.3774.

*(E)-N1,N8-Bis(8-methoxy-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)oct-4-enediamide (**31**).* Colorless amorphous solid (27 mg, 49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 2H), 8.06 (s, 2H), 7.13 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 5.61 (t, J = 3.4 Hz, 2H), 4.42 (m, 2H), 3.98 (s, 6H), 2.71 (m, 4H), 2.50 (t, J = 6.6 Hz, 4H), 2.45 (m, 4H), 2.31 (m, 4H), 2.31 (s, 6H), 2.04 (m, 4H), 1.91 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 158.8, 152.1, 144.1, 137.5, 130.1, 124.3, 122.4, 121.9, 114.7, 113.4, 74.4, 61.6, 52.7, 46.3, 37.3, 31.1, 28.2. IR (KBR) ν_{max} 3374, 2948, 2880, 1704, 1690, 1604, 1522, 1465, 1362, 1227, 1067, 972, 773 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{40}H_{49}N_4O_{10}$, calcd, 745.3449; found, 745.3434. This material was determined to be ~93.3% pure (retention time = 2.180) by HPLC analysis on autosampler (Agilent TOF/AgilentA3B1C3.m method with 49% $CHCl_3$, 49% MeOH, and 2% H_2O, flow rate 5.0 mL/min).

*(E)-N1,N10-Bis(8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)dec-5-enediamide (**32**).* Colorless amorphous solid (47 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 2H), 7.99 (s, 2H), 7.28 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.47 (t, J = 3.7 Hz, 2H), 4.47 (m, 2H), 2.68 (m, 4H), 2.42 (m, 8H), 2.35 (s, 6H), 2.32 (s, 6H), 2.12 (m, 4H), 2.05 (m, 4H), 1.93 (m, 4H), 1.82 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 159.4, 157.0, 149.5, 130.5, 125.6, 124.6, 121.4, 115.4, 113.4, 110.6, 72.2, 52.4, 46.3, 37.0, 32.0, 30.8, 25.1, 8.5. IR (KBR) ν_{max} 3328.9, 2935, 2786, 1708, 1676, 1604, 1527, 1371, 1265, 1099, 769 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{42}H_{53}N_4O_8$, calcd, 741.3863; found, 741.3863.

*(E)-N1,N10-Bis(6-methoxy-8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)dec-5-enediamide (**33**).* Colorless amorphous solid (54 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 2H), 8.07 (s, 2H), 6.79 (s, 2H), 5.46 (t, J = 3.7 Hz, 2H), 4.22 (m, 2H), 3.86 (s, 6H), 2.77 (m, 4H), 2.43 (t, J = 7.5 Hz, 4H), 2.35 (s, 6H), 2.29 (s, 6H), 2.11 (m, 8H), 1.93 (m, 8H), 1.84 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 159.2, 150.5, 147.1, 143.6, 130.5, 124.0, 122.6, 120.8, 115.1, 106.5, 78.5, 56.1, 53.6, 46.2, 37.0, 32.1, 31.9, 25.1, 9.8. IR (KBR) ν_{max} 3325, 2939, 2849, 1708, 1686, 1521, 1465, 1387, 1085, 1010, 772 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{44}H_{57}N_4O_{10}$, calcd, 801.4075; found, 801.4058.

*(E)-N1,N10-Bis(8-methoxy-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)dec-5-enediamide (**34**).* Colorless amorphous solid (24 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 2H), 8.02 (s, 2H), 7.16 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.46 (tt, J = 1.4, 3.8 Hz, 2H), 4.47 (m, 2H), 3.99 (s, 6H), 2.78 (t, J = 10.1 Hz, 4H), 2.44 (m, 4H), 2.42 (t, J = 7.4 Hz, 4H), 2.38 (s, 6H), 2.11 (m, 8H), 1.96 (m, 4H), 1.81 (p, J = 7.2, 14.5 Hz, 4H). ^{1}H NMR (125 MHz, $CDCl_3$) δ 172.5, 158.9, 151.9, 144.4, 137.8, 130.5, 124.1, 122.5, 122.0, 114.9, 113.5, 61.6, 52.3, 46.0, 37.0, 31.9, 30.6, 30.1, 25.1. IR (KBR) ν_{max} 3379, 29439, 2864, 1718, 1697, 1647, 1607, 1521, 1460, 1369, 1280, 1034, 968, 767 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{42}H_{53}N_4O_{10}$, calcd, 773.3762; found, 773.3757. This material was determined to be ~93.5% pure (retention time = 2.353) by HPLC analysis on autosampler (Agilent TOF/AgilentA3B1C3.m method with 49% $CHCl_3$, 49% MeOH, and 2% H_2O, flow rate 5.0 mL/min).

*(E)-N1,N12-Bis(8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)dodec-6-enediamide (**35**).* Colorless amorphous solid (54 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 2H), 7.98 (s, 2H), 7.24 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.41 (t, J = 3.7 Hz, 2H), 4.45 (m, 2H), 2.65 (m, 4H), 2.42 (t, J = 7.5 Hz, 4H), 2.37 (m, 4H), 2.32 (s, 6H), 2.30 (s, 6H), 2.02 (m, 8H), 1.90 (m, 4H), 1.73 (m, 4H), 1.46 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 159.4, 156.9, 149.5, 130.3, 125.5, 124.5, 121.4, 115.3, 113.3, 110.6, 52.4, 46.3, 37.7, 32.3, 30.8, 29.1, 25.0, 8.5. IR (KBR) ν_{max} 3327, 2931, 2358, 1712, 1676, 1605, 1529, 1371, 1261, 1097, 1041, 771 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{44}H_{57}N_4O_8$, calcd, 769.4176; found, 769.4193.

*(E)-N1,N6-Bis(7-(3-(dimethylamino)propoxy)-8-methyl-2-oxo-2H-chromen-3-yl)hex-3-enediamide (**36**).* Colorless amorphous solid (24 mg, 34%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 2H), 7.15 (dd, J = 3.9, 8.5, 2H), 6.72 (d, J = 8.5 Hz, 2H), 5.77 (t, J = 4.6 Hz, 4H), 3.94 (t, J = 5.4 Hz, 4H), 3.14 (m, 4H), 2.40 (m, 4H), 2.15 (s, 6H), 2.14 (s, 6H), 2.13 (s, 6H), 1.89 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 159.1, 158.3, 149.1, 127.3, 125.6, 120.7, 113.6, 112.9, 108.6, 66.6, 56.1, 44.8, 44.5, 40.6, 26.9, 7.7. IR (KBR) ν_{max} 3312, 2939, 2857, 1707, 1682, 1608, 1521, 1365, 1269, 1172, 1039, 903 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{36}H_{45}N_4O_8$, calcd, 661.3237; found, 661.3215.

*(Z)-N1,N8-Bis(8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)oct-4-enediamide (**38**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 2H), 7.30 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.43 (m, 2H), 4.63 (m, 2H), 2.94 (m, 8H), 2.57 (s, 6H), 2.45 (s, 6H), 2.31 (m, 12H), 2.07 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 174.0, 160.9, 158.0, 151.3, 138.0, 132.2, 131.8, 130.3, 127.5, 125.7, 124.4, 123.6, 123.5, 116.6, 115.5, 112.3, 54.2, 52.6, 46.1, 39.2, 39.1, 36.3, 30.6, 30.0, 29.8, 26.7, 25.0, 24.9, 9.9. IR (KBR) ν_{max} 3335, 3085, 3043, 2923, 2852, 1703, 1681, 1604, 1523, 1377, 1097, 771 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{40}H_{49}N_4O_8$, calcd, 713.3550; found, 713.3564.

General Procedure for Peptide Coupling of Non-noviosylated Saturated Linker Dimer. Pyridine (45 μL, 0.56 mmol) was added to a solution of amino coumarin **22** (80 mg, 0.28 mmol) in 4 mL of THF and stirred for 15 min at rt, and adipoyl dichloride (16 μL, 0.11 mmol) was added dropwise. The resulting reaction mixture was stirred at rt for about 15 h and concentrated. The residue was purified by silica gel column chromotography (CH_2Cl_2/MeOH, 98/2) to get saturated linked dimer **42** (66 mg, 89%) as a colorless amorphous solid.

*N1,N6-Bis(8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)adipamide (**42**).* ^{1}H NMR (500 MHz, CD_3OD) δ 8.35 (s, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.7 Hz, 2H), 4.31 (m, 2H), 2.42 (m, 4H), 2.28 (t, *J* = 6.5 Hz, 4H), 2.21 (m, 4H), 2.08 (s, 6H), 2.04 (s, 6H), 1.77 (m, 4H), 1.67 (m, 4H), 1.57 (m, 4H). ^{13}C NMR (125 MHz, CD_3OD) δ 172.8, 159.9, 157.3, 149.9, 125.6, 125.4, 120.9, 114.5, 112.9, 110.2, 51.6, 45.4, 36.3, 29.9, 24.5, 7.7. IR (KBR) ν_{max} 3514, 3201, 2927, 2783, 1718, 1687, 1622, 1404, 1346, 1284, 1103, 992 cm^{-1}. HRMS (FAB) *m*/*z*: [M + H$^+$] for $C_{38}H_{47}N_4O_8$, calcd, 687.3394; found, 687.3378.

*N1,N8-Bis(8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)octanediamide (**43**).* Colorless amorphous solid (59 mg, 81%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.48 (s, 2H), 7.17 (d, I = 8.6 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 4.38 (m, 2H), 2.53 (t, *J* = 10.6 Hz, 4H), 2.32 (t, *J* = 7.5 Hz, 4H), 2.31 (m, 4H), 2.19 (s, 6H), 2.17 (s, 6H), 1.88 (m, 4H), 1.79 (m, 4H), 1.62 (m, 4H), 1.32 (m, 4H). ^{13}C NMR (125 MHz, CD_3OD) δ 173.0, 159.2, 156.7, 149.3, 125.5, 125.3, 121.0, 114.8, 113.1, 110.4, 52.0, 45.6, 36.9, 30.0, 28.6, 24.9, 8.0. IR (KBR) ν_{max} 3378, 2928, 2783, 1716, 1685, 1612, 1422, 1354, 1289, 1111, 992 cm^{-1}. HRMS (FAB) *m*/*z*: [M + H$^+$] for $C_{40}H_{51}N_4O_8$, calcd, 715.3707; found, 715.3700.

*N1,N10-Bis(8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)decanediamide (**44**).* Colorless amorphous solid (65 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.46 (m, 2H), 2.65 (m, 4H), 2.41 (m, 4H), 2.38 (t, *J* = 7.6 Hz, 4H), 2.31 (s, 6H), 2.28 (s, 6H), 1.99 (m, 4H), 1.89 (m, 4H), 1.69 (m, 4H), 1.28 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 159.4, 156.7, 149.3, 125.6, 124.8, 121.2, 115.1, 113.3, 110.5, 72.0, 51.9, 46.0, 37.5, 30.3, 29.2, 29.1, 25.3, 8.3. IR (KBR) ν_{max} 3323, 2931, 2852, 2470, 1713, 1674, 1623, 1604, 1527, 1408, 1267, 1043, 729 cm^{-1}. HRMS (FAB) *m*/*z*: [M + H$^+$] $C_{42}H_{55}N_4O_8$, calcd, 743.4020; found, 743.4009.

*Methyl 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**50**).* Bis(pinacolate)diboron (7.24 g, 28.49 mmol) and potassium acetate (6.45 g, 65.75 mmol) followed by Pd(dppf)Cl_2 (894 mg, 1.1 mmol) were added simultaneously to a solution of methyl 3-(trifluoromethylsulfonyloxy)benzoate **47** (6.22 g, 21.92 mmol) in 1,4-dioxane (80 mL) at rt. The resulting reaction mixture was stirred at 90 °C for 16 h and diluted with 1N hydrogen chloride (100 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL), and the combined extracts were washed with saturated NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 7/3) to give methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate **50** as a amorphous brown solid, (4.59 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.13 (dt, *J* = 1.5, 7.8 Hz, 1H), 7.99 (dt, *J* = 1.3, 7.4, 1H), 7.45 (t, *J* = 7.6, 1H), 3.92 (s, 3H), 1.39 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 139.3, 135.9, 132.4, 127.9, 84.2, 52.2, 25.0. HRMS (FAB) *m*/*z*: [M + Na$^+$] for $C_{14}H_{19}BNaO_4$, calcd, 285.1274; found, 285.1272.

*Methyl 4-Methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**51**).* Amorphous brown solid (4.35 g, 68%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, *J* = 2.3 Hz, 1H), 8.05 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 1.29 (s, 12H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.9, 165.7, 137.8, 134.3, 121.3, 110.9, 83.6, 53.8, 51.4, 24.3. HRMS (FAB) *m*/*z*: [M + Na$^+$] for $C_{15}H_{21}BNaO_5$, calcd, 315.1380; found, 315.1377.

*Methyl 3-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzoate (**52**).* Colorless amorphous solid, (4.26 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, *J* = 1.1 Hz, 1H), 7.65 (dd, *J* = 1.7, 2.8 Hz, 1H), 7.52 (dd, *J* = 1.7, 1.0 Hz, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 1.35 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 159.5, 131.0, 128.1, 124.5, 117.6, 84.1, 55.5, 52.1, 25.0. HRMS (FAB) *m*/*z*: [M + Na$^+$] for $C_{15}H_{21}BNaO_5$, calcd, 315.1380; found, 315.1379.

*Dimethyl Biphenyl-3,3′-dicarboxylate (**53**).* Pd(dppf)Cl_2 (475 mg, 0.52 mmol) and K_2CO_3 (4.83 g, 34.93 mmol) were added to the miture of methyl 3-(trifluoromethylsulfonyloxy)benzoate **47** (3.3 g, 11.64 mmol) and methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate **50** (3.05 g, 11.64 mmol) in dioxane (50 mL) at rt. The resulting reaction mixture was stirred at 90 °C for 14 h then filtered through a pad of silica gel and eluted with EtOAc, and the eluents were concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 4/1) to give dimethyl biphenyl-3,3′-dicarboxylate **53** (2.13 g, 68%) as a amorphous white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 2H), 8.06 (d, *J* = 7.7 Hz, 2H), 7.83 (d, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 3.97 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 140.5, 131.7, 131.0, 129.2, 129.0, 128.4, 52.4, 25.0. HRMS (FAB) *m*/*z*: [M + Na$^+$] for $C_{16}H_{14}NaO_4$, calcd, 293.0790; found, 293.0793.

*Dimethyl 6,6′-Dimethoxybiphenyl-3,3′-dicarboxylate: General Procedure for Suzuki-Coupling Reaction (**54**).* Colorless amorphous solid (2.73 g, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 2.2, 8.7 Hz, 2H), 7.95 (d, *J* = 2.2 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.91 (s, 6H), 3.84 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 160.8, 133.0, 131.3, 126.8, 122.3, 110.4, 55.9, 51.9. HRMS (FAB) *m*/*z*: [M + Na$^+$] for $C_{18}H_{18}NaO_6$, calcd, 353.1001; found, 353.0999.

*Dimethyl 5,6′-Dimethoxybiphenyl-3,3′-dicarboxylate (**55**).* Colorless amorphous solid (1.89 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 2.2, 8.6 Hz, 1H), 8.02 (d, *J* = 2.2 Hz, 1H), 7.79 (t, *J* = 1.5 Hz, 1H), 7.56 (dd, *J* = 1.4, 2.6 Hz, 1H), 7.28 (dd, *J* = 1.6, 2.6 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 166.9, 160.2, 159.4, 139.2, 132.2, 131.4, 129.6, 123.5, 122.9, 121.0, 113.0, 110.8, 56.0, 55.7, 52.1. HRMS (FAB) *m*/*z*: [M + Na$^+$] for $C_{18}H_{18}NaO_6$, calcd, 353.1001; found, 353.0999.

*Dimethyl 5,5′-Dimethoxybiphenyl-3,3′-dicarboxylate (**56**).* Colorless amorphous solid (0.81 g, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 1.1 Hz, 2H), 7.10 (d, *J* = 1.1 Hz, 2H), 6.86 (d, *J* = 1.4 Hz, 2H), 3.49 (s, 6H), 3.44 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 160.1, 141.7, 132.1, 121.0, 118.3, 113.4, 55.8, 52.4. HRMS (FAB) *m*/*z*: [M + Na$^+$] for $C_{18}H_{18}NaO_6$, calcd, 353.1001; found, 353.0999.

*Biphenyl-3,3′-dicarboxylic Acid (**57**).* LiOH (3.4 g, 80.9 mmol) was added to the solution of dimethyl biphenyl-3,3′-dicarboxylate **53** (2.19 g, 8.09 mmol) in 40 mL of THF:MeOH:H_2O (3:2:2) at room temperature and stirred for 6 h. The resulting reaction mixture was acidfied to pH ∼ 4 with 2N HCl, the solid product was precipitated out and filtered off the solid product, resuspended in CH_3CN, and concentrated to get biphenyl-3,3′-dicarboxylic acid **57** (1.88 g, 96%) as a colorless amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 2H), 8.21 (s, 2H), 7.98 (m, 4H), 7.64 (t, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 167.3, 139.7, 131.8, 131.3, 129.7, 128.8, 127.5. (FAB) *m*/*z*: [M − H$^+$] for $C_{14}H_9O_4$, calcd, 241.0501; found, 241.0506.

*6,6′-Dimethoxybiphenyl-3,3′-dicarboxylic Acid (**58**).* Colorless amorphous solid (2.19 g, 90%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (dd, *J* = 2.1, 8.6 Hz, 2H), 7.71 (d, *J* = 2.1 Hz, 2H), 7.20 (t, *J* = 12.1 Hz, 2H), 3.79 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.0, 160.3, 132.2, 130.9, 126.3, 122.8. HRMS (FAB) *m*/*z*: [M + Cl$^-$] for $C_{16}H_{14}ClO_6$, calcd, 337.0479; found, 337.0482.

*5,6′-Dimethoxybiphenyl-3,3′-dicarboxylic Acid (**59**).* Colorless amorphous solid (1.71 g, 92%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.93 (s, 2H), 7.98 (dd, *J* = 2.1, 8.6 Hz, 1H), 7.86 (d, *J* = 2.1 Hz, 1H), 7.63 (s, 1H),

7.45 (s, 1H), 7.30 (s, 1H), 7.23 (d, J = 8.7 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 167.1, 166.9, 159.7, 159.1, 138.9, 132.1, 131.5, 131.2, 128.6, 123.2, 122.5, 119.8, 112.9, 111.7, 56.1, 55.5. HRMS (FAB) m/z: [M − H$^+$] for $C_{16}H_{13}O_6$, calcd, 301.0712; found, 301.0707.

*5,5′-Dimethoxybiphenyl-3,3′-dicarboxylic Acid (**60**).* Colorless amorphous solid (0.64 g, 93%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.18 (s, 2H), 7.78 (t, J = 1.5 Hz, 2H), 7.90 (m, 4H), 3.90 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.0, 159.9, 141.0, 132.7, 120.0, 117.2, 113.7, 55.6. HRMS (FAB) m/z: [M − H$^+$] for $C_{16}H_{13}O_6$, calcd, 301.0712; found, 301.0707.

General Procedure for Peptide Coupling of Biaryl Linkers. Thionyl chloride (0.12 mL, 1.6 mmol) was added to a solution of diacid acid **57** (39 mg, 0.16 mmol) in 3 mL of THF. The resulting reaction mixture was refluxed for 3 h, and the solvent was evaporated under reduced pressure and kept under high vacuum for 1−2 h to get biphenyl-3,3′-dicarbonyl dichloride **61** as a colorless solid, which was used immediately for the next coupling reaction without any further purification.

Pyridine (67 μL, 0.83 mmol) was added to a solution of amino coumarin **13** (120 mg, 0.41 mmol) in 4 mL of THF, stirred for 15 min at rt, and above freshly prepared diacid chloride **61** was added dropwise in 2 mL of THF. The resulting reaction mixture was stirred at rt for about 15 h and concentrated to get crude product. The residue was purified by silica gel column chromotography to get tilte biaryl dimer as colorless amorphous solid.

General Procedure for Noviosylated Biaryl Dimers Cyclic Carbonate Cleavage. Et_3N (10% total volume) was added dropwise to a solution of above cyclic carbonate diamides in methanol. The resulting mixture was stirred for 14 h and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 19/:1) to yield olefin linked noviosylated dimer **65** (89 mg, 61% yield, over all in two steps) as a colorless amorphous solid.

*N3-(7-((2R,3R,4S,5R)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-N3′-(7-((2S,3S,4R,5S)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)biphenyl-3,3′-dicarboxamide (**65**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (s, 2H), 8.82 (s, 2H), 8.19 (s, 2H), 7.92 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.3 Hz, 2H), 7.64 (t, J = 7.7 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 5.63 (d, J = 1.7 Hz, 2H), 4.27 (m, 4H), 3.62 (s, 6H), 3.39 (d, J = 8.9 Hz, 2H), 2.72 (br s, 4H), 2.30 (s, 6H), 1.40 (s, 6H), 1.16 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 159.5, 156.2, 149.3, 141.0, 134.7, 131.3, 129.7, 126.4, 126.0, 124.9, 121.8, 114.4, 114.1, 111.3, 97.8, 84.4, 78.7, 71.3, 68.7, 62.1, 29.4, 22.6, 8.6. IR (KBR) ν_{max} 3392, 3315, 2926, 2869, 1710, 1168, 1665, 1607, 1520, 1367, 1253, 1211, 1140, 1085, 964 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{50}H_{52}N_2NaO_{16}$, calcd, 959.3215; found, 959.3209. This material was determined to be 95.6% pure (retention time = 28.147) by HPLC (Phenomenex Luna C-18, 5 μm, 10 mm × 250 mm column eluting with 50% CH_3CN/50% H_2O, flow rate 5.0 mL/min).

*N3-(7-((2R,3R,4S,5R)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-N3′-(7-((2S,3S,4R,5S)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-6,6′-dimethoxybiphenyl-3,3′-dicarboxamide (**66**).* Colorless amorphous solid (37 mg, 58% yield, over all in two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, 2H), 8.72 (s, 2H), 8.00 (d, J = 8.7 Hz, 2H), 7.86 (s, 2H), 7.36 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 5.63 (s, 2H), 4.26 (m, 4H), 3.89 (s, 6H), 3.62 (s, 6H), 3.40 (d, J = 9.6 Hz, 2H), 2.57 (br s, 4OH), 2.30 (s, 6H), 1.40 (s, 6H), 1.16 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 161.3, 160.4, 157.1, 149.9, 127.7, 126.7, 126.3, 122.4, 114.9, 114.7, 112.1, 111.8, 99.3, 85.0, 79.4, 72.1, 69.2, 62.5, 56.7, 29.6, 23.2, 8.9. IR (KBR) ν_{max} 3402, 3312, 2927, 2867, 1712, 1169, 1667, 1604, 1521, 1498, 1367, 1251, 1207, 1142, 1080, 964 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{52}H_{56}N_2NaO_{18}$, calcd, 1019.3426; found, 1019.3413. This material was determined to be 99.2% pure (retention time = 2.3123) by HPLC (Phenomenex Luna C-18, 5 μm, 10 mm × 250 mm column eluting with 49% $CHCl_3$/49% MeOH and 2% H_2O, flow rate 5.0 mL/min).

*N3′-(7-((2R,3R,4S,5R)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-N3-(7-((2S,3S,4R,5S)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-5,6′-dimethoxybiphenyl-3,3′-dicarboxamide (**67**).* Isolated using 5% of methanol in dichloromethane, colorless amorphous solid (59 mg, 75% yield, over all in two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.79 (s, 1H), 8.78 (s, 1H), 8.72 (s, 1H), 7.93 (m, 2H), 7.65 (s, 1H), 7.47 (s, 1H), 7.34 (dd, J = 2.0, 8.6 Hz, 2H), 7.26 (m, 1H), 7.19 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 1H), 5.61 (s, 2H), 4.25 (s, 4H), 3.95 (s, 3H), 3.94 (s, 3H), 3.61 (s, 6H), 3.39 (d, J = 8.9 Hz, 2H), 2.74 (br s, 2H), 2.65 (br s, 2H), 2.29 (s, 6H), 1.39 (s, 6H), 1.15 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 169.8, 163.8, 163.7, 163.5, 163.4, 160.3, 160.2, 153.1, 153.1, 143.3, 138.8, 133.8, 133.5, 132.8, 129.9, 129.8, 129.8, 129.5, 129.4, 125.4, 125.3, 124.3, 123.5, 118.0, 118.0, 117.7, 117.6, 115.5, 115.2, 102.4, 88.0, 82.5, 75.1, 72.3, 65.5, 64.5, 59.7, 59.4, 32.6, 26.3, 11.9. IR (KBR) ν_{max} 3371, 3301, 2927, 2852, 1714, 1700, 1670, 1604, 1521, 1500, 1367, 1251, 1205, 1138, 1082, 964 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{52}H_{57}N_2O_{18}$, calcd, 997.3606; found, 997.3618.

*N3-(7-((2R,3R,4S,5R)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-N3′-(7-((2S,3S,4R,5S)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-5,5′-dimethoxybiphenyl-3,3′-dicarboxamide (**68**).* Isolated using 5% of methanol in dichloromethane, colorless amorphous solid (12 mg, 54% yield, over all in two steps). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.98 (m, 2H), 8.62 (s, 2H), 7.77 (s, 2H), 7.41 (m, 6H), 7.13 (d, J = 8.7 Hz, 2H), 5.47 (s, 2H), 4.33 (m, 2OH), 3.99 (m, 4H), 3.87 (s, 6H), 3.25 (d, J = 8.8 Hz, 2H), 2.14 (s, 6H), 1.19 (s, 6H), 0.98 (s, 6H). ^{13}C NMR (125 MHz, acetone-d_6) δ 166.3, 161.4, 159.2, 157.4, 150.2, 142.9, 137.2, 126.8, 125.9, 119.2, 117.6, 114.6, 114.5 113.0, 112.0, 99.6, 84.7, 79.0, 72.3, 69.5, 61.8, 56.1, 23.3, 8.5. IR (KBR) ν_{max} 3401, 3387, 2927, 2877, 1712, 1700, 1668, 1604, 1525, 1501, 1367, 1248, 1205, 1136, 1080, 962 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{52}H_{56}N_2NaO_{18}$, calcd, 1019.3426; found, 1019.3401.

*N3-(7-((2R,3S,4R,5S)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-N3′-(7-((2S,3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2H-chromen-3-yl)-6,6′-dimethoxybiphenyl-3,3′-dicarboxamide (**69**).* Isolated using 5% of methanol in dichloromethane, colorless amorphous solid (94 mg, 77% yield, over all in two steps). ^{1}H NMR (500 MHz, DMSO) δ 9.59 (s, 2H), 8.53 (s, 2H), 8.04 (dd, J = 1.9, 8.6 Hz, 2H), 7.87 (d, J = 1.4 Hz, 2H), 7.32 (s, 2H), 7.26 (d, J = 8.9 Hz, 2H), 5.23 (d, J = 3.0 Hz, 2H), 5.05 (d, J = 4.8 Hz, 2OH), 4.95 (d, J = 5.9 Hz, 2OH), 4.03 (m, 2H), 3.86 (m, 2H), 3.84 (s, 6H), 3.82 (s, 6H), 3.48 (s, 6H), 3.19 (d, J = 8.6 Hz, 2H), 2.30 (s, 6H), 1.27 (s, 6H), 1.25 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.1, 160.0, 158.1, 149.2, 146.0, 143.5, 130.6, 129.3, 127.7, 126.5, 125.3, 122.9, 119.1, 114.8, 117.2, 107.9, 103.8, 83.3, 77.9, 70.6, 67.6, 56.3, 56.0, 28.0, 24.1, 9.7. IR (KBR) ν_{max} 3458, 3400, 2976, 2937, 1714, 1672, 1604, 1523, 1462, 1365, 1250, 1110, 950, 760 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{54}H_{60}N_2NaO_{20}$, calcd, 1079.3637; found, 1079.3622. This material was determined to be 95.6% pure (retention time = 11.138) by HPLC (Phenomenex Luna C-18, 5 μm, 10 mm × 250 mm column eluting with 450% CH_3CN_3 50% H_2O, flow rate 5.0 mL/min).

*N3-(7-((2R,3S,4R,5S)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-N3′-(7-((2S,3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methoxy-2-oxo-2H-chromen-3-yl)-6,6′-dimethoxybiphenyl-3,3′-dicarboxamide (**70**).* Isolated using 5% of methanol in dichloro-

methane, colorless amorphous solid (67 mg, 82% yield, over all in two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 2H), 8.70 (s, 2H), 7.98 (dd, J = 2.4, 8.7 Hz, 2H), 7.83 (d, J = 2.4 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 5.56 (d, J = 2.4 Hz, 2H), 4.27 (m, 4H), 3.95 (s, 6H), 3.87 (s, 6H), 3.60 (s, 6H), 3.36 (d, J = 8.7 Hz, 2H), 2.76 (br s, 2H), 2.18 (br s, 2H), 1.40 (s, 6H), 1.22 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 160.5, 158.9, 151.2, 144.0, 136.7, 130.7, 129.1, 126.8, 125.6, 123.8, 122.8, 122.6, 115.4, 113.3, 111.1, 98.8, 84.2, 78.8, 71.1, 68.7, 61.9, 61.9, 56.1, 28.9, 23.0. IR (KBR) ν_{max} 3458, 3400, 2976, 2937, 1714, 1672, 1604, 1523, 1462, 1365, 1250, 1110, 950, 760 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{52}H_{56}N_2NaO_{20}$, calcd, 1051.3324; found, 1051.3339. This material was determined to be 95.1% pure (retention time = 2.314) by HPLC (Phenomenex Luna C-18, 5 μm, 10 mm × 250 mm column eluting with 49% $CHCl_3$/49% MeOH and 2% H_2O, flow rate 5.0 mL/min).

*6,6′-Dimethoxy-N3,N3′-bis(8-methyl-7-(1-methylpiperidin-4-yloxy)-2-oxo-2H-chromen-3-yl)biphenyl-3,3′-dicarboxamide (**71**).* Isolated using 10% of methanol in dichlorometane, colorless amorphous solid (46 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 2H), 8.70 (s, 2H), 7.99 (dd, J = 2.4, 8.7 Hz, 2H), 7.85 (d, J = 2.4 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.46 (m, 2H), 3.88 (s, 6H), 2.65 (m, 4H), 2.36 (m, 4H), 2.34 (s, 6H), 2.32 (s, 6H), 2.02 (m, 4H), 1.91 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 160.4, 159.6, 157.0, 149.5, 130.7, 129.0, 126.8, 125.8, 125.6, 124.4, 121.7, 115.3, 113.5, 111.0, 110.6, 72.5, 56.1, 52.4, 46.4, 30.9, 8.5. IR (KBR) ν_{max} 3406, 2937, 2843, 1707, 1664, 1603, 1521, 1491, 1367, 1238, 1103, 1041, 762 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{48}H_{51}N_4O_{10}$, calcd, 843.3605; found, 843.3570.

*N3,N3′-Bis(7-(3-(dimethylamino)propoxy)-8-methyl-2-oxo-2H-chromen-3-yl)-6,6′-dimethoxybiphenyl-3,3′-dicarboxamide (**72**).* Isolated using 10−15% of methanol in dichloromethane, colorless amorphous solid, (27 mg, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 2H), 8.46 (s, 2H), 8.04 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 2.2 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.9 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 4.19 (t, J = 5.8 Hz, 4H), 3.82 (s, 6H), 3.21 (t, J = 6.9 Hz, 4H), 2.76 (s, 12H), 2.24 (s, 6H), 2.20 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 159.9, 158.2, 157.9, 149.5, 130.6, 129.6, 129.3, 126.5, 126.3, 125.3, 121.3, 112.9, 112.5, 111.1, 109.2, 65.9, 55.9, 54.2, 54.1, 42.4, 24.2, 8.0. IR (KBR) ν_{max} 3413, 2958, 2941, 1699, 1668, 1606, 1529, 1502, 1371, 1265, 1159, 1020, 762 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{46}H_{51}N_4O_{10}$, calcd, 819.3605; found, 819.3602.

*3-(2′,6-Dimethoxy-5′-(7-acetyloxy-8-methyl-2-oxo-2H-chromen-3-ylcarbamoyl)biphenyl-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yl Acetate (**73**).* Isolated using 4% of methanol in dichloromethane, colorless amorphous solid (19 g, 47%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.67 (s, 2H), 8.58 (s, 2H), 8.04 (s, 2H), 7.88 (s, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 3.83 (s, 6H), 2.36 (s, 6H), 2.19 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.9, 165.2, 160.0, 157.7, 150.0, 149.0, 130.7, 129.5, 127.3, 126.5, 125.8, 125.2, 123.6, 119.3, 118.0, 117.2, 111.2, 56.0, 20.6, 8.8. IR (KBR) ν_{max} 3270, 2977, 2942, 1717, 1702, 1680, 1618, 1529, 14675, 1367, 1124, 1114, 950, 769 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{40}H_{32}N_2NaO_{12}$, calcd, 755.1853; found, 755.1853.

*Methyl 3-Bromo-4-(2-(methoxycarbonyl)phenoxy)benzoate (**75**).* Sodium carbonate (2.54 g, 23.94 mmol) was to a solution of methyl 3-bromo-4-fluorobenzoate **74** (1.86 g, 7.98 mmol) and methyl salicylate (1.21 g, 7.98 mmol) in 10 mL of dimethyl acetamide (DMA) at rt. The resulting reaction mixture was stirred at 120 °C for 16 h and quenched with water and aqueous layer was extracted with EtOAc (3 × 50 mL); the combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (hexanes/EtOAc, 5/1) to afford methyl 3-bromo-4-(2-(methoxycarbonyl)phenoxy)benzoate **75** (2.27 g, 78%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, J = 2.0 Hz, 1H), 8.03 (dd, J = 1.7, 7.8 Hz, 1H), 7.85 (dd, J = 2.0, 8.6 Hz, 1H), 7.59 (td, J = 1.6, 7.7 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 6.60 (d, J = 8.6 Hz, 1H), 3.91 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 165.3, 158.9, 154.0, 135.3, 134.2, 132.6, 131.7, 130.3, 125.5, 125.6, 122.5, 120.2, 115.8, 112.1, 52.3. IR (KBr) ν_{max} 2951, 2843, 1721, 1597, 1481, 1433, 1300, 1256, 963, 760 cm^{-1}. HRMS (FAB) m/z: [M + H$^+$] for $C_{16}H_{14}BrO_5$, calcd, 365.0025; found, 365.0018.

*Dimethyl Dibenzo[b,d]furan-2,6-dicarboxylate (**76**).* Potassium carbonate (1.61 g, 16.4 mmol) followed by Pd(dppf)Cl_2 (313 mg, 0.38 mmol, 7 mol %) were added simultaneously to a solution of methyl 3-bromo-4-(2-(methoxycarbonyl)phenoxy)benzoate **75** (2.0 g, 5.48 mmol) in 15 mL of *N*,*N*-dimethyl acetamide (DMA) at rt. The reaction mixture was stirred at 120 °C for 3 h and quenched with water, the aqueous layer was extracted with EtOAc (3 × 40 mL), and combined organic layers were washed with saturated aqueous NaCl, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc, 4/1) to provide dimethyl dibenzo[*b*,*d*]furan-2,6-dicarboxylate **76** (1.34 g, 86%) as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 (d, J = 1.6 Hz, 1H), 8.23 (dd, J = 1.7, 8.7 Hz, 1H), 8.18 (dd, J = 1.2, 7.6 Hz, 1H), 8.15 (dd, J = 1.2, 7.7 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 4.06 (s, 3H), 3.99 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.9, 165.1, 159.2, 155.6, 130.1, 129.7, 125.7, 125.6, 125.4, 123.5, 123.2, 123.0, 115.8, 112.2, 52.6, 52.4. IR (KBr) ν_{max} 2951, 2843, 1721, 1597, 1481, 1433, 1300, 1256, 963, 760 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{16}H_{12}NaO_5$, calcd, 307.0582; found, 307.0571.

*(Methoxycarbonyl)phenoxy)methyl)benzoate (**78**).* Potassium carbonate (4.33 g, 31.34 mmol) was added to a solution of methyl 4-(bromomethyl)-3-iodobenzoate **77** (3.7 g, 10.42 mmol) and methyl salicylate (1.59 g, 10.45 mmol) in 45 mL of DMF at rt. The resulting reaction mixture was stirred at 70 °C for 16 h and diluted with water, and the aqueous layer was extracted with EtOAc (2 × 60 mL); combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc, 5/2) to afforded (methoxycarbonyl)phenoxy)methyl)benzoate **78** (3.01 g, 68%) as a colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 1.6 Hz, 1H), 8.09 (dd, J = 1.6, 8.1 Hz, 1H), 7.90 (dd, J = 1.5, 7.8 Hz, 2H), 7.50 (td, J = 1.8, 8.4 Hz, 1H), 7.05 (dd, J = 8.1, 16.3 Hz, 2H), 5.13 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 165.6, 157.6, 143.9, 140.0, 133.9, 132.2, 131.0, 129.8, 128.0, 121.2, 120.5, 113.7, 95.1, 74.4, 52.5, 52.2. HRMS (FAB) m/z: [M + Na$^+$] for $C_{17}H_{15}INaO_5$, calcd, 448.9862; found, 448.9863.

*Methyl 3-Iodo-4-((3-(methoxycarbonyl)phenoxy)methyl)benzoate (**79**).* Colorless amorphous solid (2.68 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, J = 1.6 Hz, 1H), 8.05 (dd, J = 1.7, 8.0 Hz, 1H), 7.71 (dt, J = 1.4, 9.0 Hz, 1H), 7.68 (m, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.20 (m, 1H), 5.12 (s, 2H), 3.95 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 165.5, 158.2, 143.8, 140.4, 131.8, 131.3, 129.8, 129.6, 128.2, 122.9, 120.1, 115.5, 96.2, 73.8, 52.6, 52.2. IR (KBR) ν_{max} 2951, 2921, 1722, 1595, 1435, 1286, 1256, 1218, 1113, 1031, 756 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{17}H_{15}INaO_5$, calcd, 448.9862; found, 448.9863.

*Methyl 3-Iodo-4-((4-(methoxycarbonyl)phenoxy)methyl)benzoate (**80**).* Colorless amorphous solid (1.84 g, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 1.5 Hz, 1H), 8.03 (d, J = 9.3 Hz, 2H), 8.02 (m, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 9.3 Hz, 2H), 5.12 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 165.5, 161.8, 143.4, 140.4, 131.9, 131.4, 129.6, 128.1, 123.6, 114.6, 96.0, 73.7, 52.6, 52.1. IR (KBR) ν_{max} 2949, 2849, 1720, 1718, 1607, 1508, 1435, 1277, 1252, 1172, 1111, 1031, 767. HRMS (FAB) m/z: [M + Na$^+$] for $C_{17}H_{15}INaO_5$, calcd, 448.9862; found, 448.9863.

*Dimethyl 6H-Benzo[c]chromene-4,9-dicarboxylate (**81**).* Potassium acetate (1.87 g, 19.07 mmol) followed by Pd(dppf)Cl_2 (363 mg,

0.45 mmol) were added simultaniously to a solution of (methoxycarbonyl)phenoxy)methyl)benzoate **78** (2.71 g, 6.36 mmol) in 25 mL of dimethyl acetamide (DMA) at rt. The reaction mixture was stirred at 140 °C for 3 h and diluted with water. The aqueous layer was extracted with EtOAc (3 × 10 mL); combined organic layers were washed with saturated aqueous NaCl, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc, 4/1) to provide dimethyl 6*H*-benzo[*c*]chromene-4,9-dicarboxylate **81** (1.56 g, 82%) as a colorless amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, J = 1.4 Hz, 1H), 7.99 (ddd, J = 1.6, 4.3, 7.8 Hz, 2H), 7.80 (dd, J = 1.6, 7.8 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 5.25 (s, 2H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 166.3, 154.6, 135.8, 132.0, 130.7, 129.9, 129.4, 127.7, 125.0, 123.7, 123.6, 121.7, 120.8, 68.6, 52.5, 52.4. IR (KBr) ν_{max} 2951, 2865, 1723, 1721, 1595, 1577, 1433, 1406, 1267, 1196, 1151, 1111, 1060, 1018, 964, 758 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{17}H_{14}NaO_5$, calcd, 321.0739; found, 321.0738.

*Dimethyl 6H-Benzo[c]chromene-3,9-dicarboxylate (**82**).* Colorless amorphous solid (1.07 g, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.76 (dd, J = 1.7, 8.1 Hz, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 5.20 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 166.6, 154.6, 136.6, 131.6, 130.7, 129.9, 129.7, 126.4, 125.2, 124.0, 123.7, 123.6, 118.9, 68.4, 52.5, 52.4. IR (KBR) ν_{max} 2952, 2920, 1718, 1585, 1430, 1408, 1292, 1255, 1196, 1093, 887, 756 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{17}H_{14}NaO_5$, calcd, 321.0739; found, 321.0738.

*Dimethyl 6H-Benzo[c]chromene-2,9-dicarboxylate (**83**).* Colorless amorphous solid (1.17 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, J = 1.6 Hz, 1H), 8.42 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.93 (dd, J = 2.0, 8.5 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.00 (d, J = 6.8 Hz, 1H), 5.20 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 166.7, 158.5, 135.4, 131.6, 130.8, 129.6, 129.4, 125.6, 124.9, 124.4, 123.5, 121.8, 117.6, 68.4, 52.4, 52.2. IR (KBR) ν_{max} 2952, 2920, 1718, 1585, 1430, 1408, 1292, 1255, 1196, 1093, 887, 756 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{17}H_{14}NaO_5$, calcd, 321.0739; found, 321.0738.

*2-Methoxy-3-(methoxycarbonyl)phenylboronic Acid (**85**).* Bis-(pinacolate)diboron (1.71 g, 6.73 mmol), potassium acetate (1.32 g, 13.46 mmol), and followed by bis(diphenylphosphinoferrocene)-palladium dichloride (183 g, 0.224 mmol, 5 mol %) were added simultaneously to a solution of methyl-5-bromo-2-methylbenzoate **84** (1.1 g, 4.49 mmol) in 30 mL of 1,4-dioxane at rt. The resulting mixture was heated to 110 °C and stirred for 2 h before adding 10 mL of 1N hydrogen chloride. The aqueous layer was extracted with EtOAc (3 × 15 mL), and combined extracts were washed with saturated aqueous NaCl, dried with anhydrous Na_2SO_4, filtered, and concentrated to give the corresponding crude boronic ester.

Ammonium acetate (1.04 g, 13.46 mmol) and sodium periodate (2.88 g, 13.46 mmol) were added sequentially to a solution of above crude boronic ester in mixed solution of acetone (10 mL) and water (10 mL). The resulting mixture was stirred at rt for 17 h. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was extracted with EtOAc (3 × 15 mL), and combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give 2-methoxy-3-(methoxycarbonyl)phenylboronic acid **85** (556 mg, 59%) as a pale-brown amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (br s, 2H), 7.65 (dd, J = 1.8, 7.6 Hz, 1H), 7.61 (dd, J = 1.8, 7.3 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.7, 162.1, 137.9, 131.4, 123.8, 122.9, 62.1, 52.1. HRMS (FAB) m/z: [M + Na$^+$] for $C_9H_{11}BNaO_5$, calcd, 233.0597; found, 233.0599.

*Dimethyl 2-Methoxy-6′-(2-methoxy-2-oxoethyl)biphenyl-3,3′-dicarboxylate (**87**).* Potassium carbonate (987 mg, 7.14 mmol) and Pd(dppf)Cl_2 (98 mg, 0.12 mmol) were simultaneously added to the solution of 2-methoxy-3-(methoxycarbonyl)phenylboronic acid **80** (500 mg, 2.38 mmol) and methyl 3-iodo-4-(2-methoxy-2-oxoethyl)-benzoate **86** (0.96 mg, 2.86 mmol) in 1,4-dioxane (8 mL) at rt. The resulting reaction mixture was stirred at 90 °C for 14 h and filtrated by Celite, and the mother layer was evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 3/1) to give dimethyl 2-methoxy-6′-(2-methoxy-2-oxoethyl)biphenyl-3,3′-dicarboxylate **87** (656 mg, 74%) as a viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, J = 1.9, 8.0 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.83 (dd, J = 1.8, 7.8 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.37 (dd, J = 1.8, 7.5 Hz, 1H), 7.21 (dd, J = 1.8, 7.5 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.58 (d, J = 2.2 Hz, 2H), 3.55 (s, 3H), 3.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 166.8, 166.6, 157.1, 138.3, 138.2, 135.6, 135.1, 131.6, 131.5, 130.6, 129.2, 129.1, 125.4, 123.9, 61.9, 52.4, 52.3, 52.0, 38.9. IR (KBr) ν_{max} 2997, 2951, 1724, 1608, 1591, 1465, 1419, 1435, 1288, 1256, 1161, 1111, 1004, 964, 764. HRMS (FAB) m/z: [M + Na$^+$] for $C_{20}H_{20}NaO_7$, calcd, 395.1107; found, 395.1110.

*Dimethyl 6′-(2-Hydroxyethyl)-2-methoxybiphenyl-3,3′-dicarboxylate (**88**).* 1 M DIBAL-H in dichloromethane (2.7 mL, 2.7 mmol) was added dropwise to a solution of dimethyl 2-methoxy-6′-(2-methoxy-2-oxoethyl)biphenyl-3,3′-dicarboxylate **87** (0.63 g, 1.69 mmol) in dichloromethane (17 mL) at −78 °C over 10 min under argon atmosphere. The resulting reaction mixture was stirred at same temperature for 2 h, quenched with 1:1 mixture of MeOH and H_2O (3 mL), followed by saturated sodium potassium tartarate (20 mL), and stirred for 1 h at rt. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated to get crude dimethyl 2-methoxy-6′-(2-oxoethyl)biphenyl-3,3′-dicarboxylate as a viscous liquid.

The crude product of above dimethyl 2-methoxy-6′-(2-oxoethyl)-biphenyl-3,3′-dicarboxylate was dissolved in MeOH (10 mL) and sodium borohydride (161 mg, 4.23 mmol) was added portions wise at 0 °C. The resulting reaction mixture was stirred at rt for 2 h, MeOH was removed under reduced pressure and resuspended in water and extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 3/2) to give dimethyl 6′-(2-hydroxyethyl)-2-methoxybiphenyl-3,3′-dicarboxylate **88** (297 mg, 51%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd, J = 1.7, 8.1 Hz, 1H), 7.92 (d, J = 1.8 Hz, 1H), 7.83 (dd, J = 1.7, 7.8 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.35 (dt, J = 2.3, 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.72 (td, J = 3.6, 6.6 Hz, 2H), 3.45 (s, 3H), 2.78 (m, 2H), 1.90 (br s, OH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 166.7, 157.0, 143.1, 138.2, 135.9, 135.4, 131.5, 131.3, 129.6, 129.2, 128.3, 125.5, 124.0, 62.6, 62.1, 52.4, 52.2, 36.6. HRMS (FAB) m/z: [M + Na$^+$] for $C_{19}H_{20}NaO_6$, calcd, 367.1158; found, 367.1151.

Dimethyl 2-Hydroxy-6′-(2-hydroxyethyl)biphenyl-3,3′-dicarboxylate. 1 M BCl_3 in hexanes (2.45 mL, 2.45 mmol) was added dropwise to a solution of dimethyl 6′-(2-hydroxyethyl)-2-methoxybiphenyl-3,3′-dicarboxylate **88** (0.28 g, 0.81 mmol) in dichloromethane (6 mL) at −78 °C over 4 min under argon atmosphere. The resulting reaction mixture was stirred over 15 min at the same temperature and quenched with 3 mL of cold water, followed by saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL), combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 3/7) to give dimethyl 2-hydroxy-6′-(2-hydroxyethyl)biphenyl-3,3′-dicarboxylate (232 mg, 94%) as a pale-yellow amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.14 (s, 1H), 8.02 (dd, J = 1.8, 8.0 Hz, 1H), 7.92 (dd, J = 1.7, 8.0 Hz, 1H), 7.89 (d, J = 1.8 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.37 (dd, J = 1.6, 7.4 Hz, 1H),

6.98 (t, J = 5.8, 9.6 Hz, 1H), 3.98 (s, 3H), 3.90 (s, 3H), 3.73 (d, J = 4.3 Hz, 2H), 2.83 (dd, J = 6.6, 10.8 Hz, 2H), 1.58 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 167.0, 158.7, 143.0, 137.8, 137.1, 131.9, 130.0, 129.6, 129.3, 128.5, 119.2, 112.7, 62.8, 52.6, 52.2, 36.8. HRMS (FAB) m/z: [M + Na^+] for $C_{18}H_{18}NaO_6$, calcd, 353.1001; found, 353.1010.

*Dimethyl 2-Hydroxy-6′-(2-(tosyloxy)ethyl)biphenyl-3,3′-dicarboxylate (**89**).* Pyridine (0.28 mL, 3.42 mmol) and tosyl chloride (169 mg, 0.89 mmol) were added sequentially to a solution of 2-hydroxy-6′-(2-hydroxyethyl)biphenyl-3,3′-dicarboxylate (226 mg, 0.68 mmol) in dichloromethane (5 mL) under argon atmosphere at 0 °C. The resulting reaction mixture was stirred at rt for 2 h and then concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 4:1) to give dimethyl 2-hydroxy-6′-(2-(tosyloxy)ethyl)biphenyl-3,3′-dicarboxylate **89** (305 mg, 92%) as a viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.04 (s, 1H), 7.94 (dd, J = 1.8, 8.0 Hz, 1H), 7.91 (dd, J = 1.6, 8.0 Hz, 1H), 7.83 (d, J = 1.8 Hz, 1H), 7.61 (s, 1H), 7.60 (s, 1H), 7.25 (m, 5H), 6.94 (t, J = 7.7 Hz, 1H), 4.08 (dd, J = 7.2, 14.5 Hz, 2H), 3.98 (s, 3H), 3.90 (s, 3H), 2.92 (dt, J = 5.1, 6.9 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 166.8, 158.6, 144.8, 140.7, 137.8, 137.1, 131.9, 130.2, 129.9, 129.8, 129.3, 129.1, 129.0, 127.9, 119.3, 112.8, 69.8, 52.7, 52.2, 33.1, 21.7. HRMS (FAB) m/z: [M + H^+] for $C_{25}H_{25}O_8S$, calcd, 485.1270; found, 485.1265.

*Dimethyl 6,7-Dihydrodibenzo[b,d]oxepine-4,10-dicarboxylate (**90**).* Potassium carbonate (256 mg, 1.86 mmol) was added to a solution of dimethyl 2-hydroxy-6′-(2-(tosyloxy)ethyl)biphenyl-3,3′-dicarboxylate **89** (0.3 g, 0.62 mmol) in 5 mL of DMF at rt under argon atmosphere. The resulting reaction mixture was stirred at 90 °C for 3 h and quenched with water. The aqueous layer was extracted with EtOAc (3 × 10 mL); the combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc, 3/1) to afford dimethyl 6,7-dihydrodibenzo-[b,d]oxepine-4,10-dicarboxylate **90** (149 mg, 77%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 1.5 Hz, 1H), 7.81 (dd, J = 1.5, 7.6 Hz, 1H), 7.63 (dd, J = Hz, 1.6, 7.8 Hz, 1H), 7.38 (d, J = Hz, 1.6, 7.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.30 (t, J = 8.2 Hz, 1H), 4.73 (t, J = 6.5 Hz, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 2.87 (t, J = 6.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 166.9, 153.7, 142.8, 138.6, 136.4, 133.1, 131.0, 129.5, 129.5, 129.4, 128.6, 126.5, 124.4, 78.7, 52.4, 52.3, 33.5. HRMS (FAB) m/z: [M + H^+] for $C_{18}H_{17}O_5$, calcd, 313.1076; found, 313.1064.

*Dibenzo[b,d]furan-2,6-dicarboxylic Acid (**91**).* LiOH (1.77 g, 42.0 mmol) was added to solution of **76** (1.2 g, 4.22 mmol) in 18 mL of THF:MeOH:H_2O (3:2:2) at rt. The resulting reaction mixture was stirred for 4 h, acidified to pH ∼4 with 2N HCl. The acidified aqueous layer was extracted with EtOAc (3 × 15 mL); combined organic layers were washed with saturated aqueous NaCl, dried with anhydrous Na_2SO_4, filtered, and concentrated. The crude solid product was recrystallized with EtOAc to get dibenzo[b,d]furan-2,6-dicarboxylic acid **91** (0.96 g, 89%) as a colorless amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.24 (br s 2H), 8.85 (d, J = 1.6 Hz, 1H), 8.57 (dd, J = 1.2, 7.7 Hz, 1H), 8.15 (dd, J = 1.8, 8.6 Hz, 1H), 8.07 (dd, J = 1.2, 7.7 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.55 (t, J = 7.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 165.2, 158.3, 154.8, 130.1, 129.6, 126.5, 124.9, 123.5, 123.4, 123.1, 116.3, 112.0. HRMS (FAB) m/z: [M − H^+] for $C_{14}H_7O_5$, calcd, 255.0293; found, 255.0296.

*6H-Benzo[c]chromene-4,9-dicarboxylic Acid (**92**).* Colorless amorphous solid, (1.17 g, 94%) as a colorless amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.99 (s, 2H), 8.34 (d, J = 1.5 Hz, 1H), 8.11 (dd, J = 1.5, 7.8 Hz, 1H), 7.94 (dd, J = 5.7, 13.5 Hz, 1H), 7.66 (dd, J = 1.5, 7.7 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.16 (t, J = 7.7 Hz, 1H), 5.25 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.0, 166.8, 153.5, 135.8, 131.3, 131.2, 129.3, 129.1, 127.3, 125.5, 123.1, 122.9, 122.1, 121.9, 67.6. HRMS (FAB) m/z: [M − H^+] for $C_{15}H_9O_5$, calcd, 269.0450; found, 269.0444.

*6H-Benzo[c]chromene-3,9-dicarboxylic Acid (**93**).* Colorless amorphous solid (0.77 g, 95%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.21 (br s, 2H), 8.37 (s, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.95 (dd, J = 1.4, 7.8 Hz, 1H), 7.66 (dd, J = 1.6, 8.1 Hz, 1H), 7.47 (d, J = 1.6 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 5.27 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.9, 166.7, 154.2, 136.3, 132.3, 131.5, 129.8, 128.9, 125.8, 125.7, 124.0, 123.4, 123.4, 117.8, 67.6. HRMS (FAB) m/z: [M − H^+] for $C_{15}H_9O_5$, calcd, 269.0450; found, 269.0444.

*6H-Benzo[c]chromene-2,9-dicarboxylic Acid (**94**).* Colorless amorphous solid (0.89 g, 92%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.06 (s, 2H), 8.39 (s, 1H), 8.30 (s, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 5.32 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.0, 166.8, 158.0, 135.5, 131.5, 131.4, 129.3, 128.8, 125.7, 125.0, 124.8, 122.5, 121.4, 117.6, 67.7. HRMS (FAB) m/z: [M − H^+] for $C_{15}H_9O_5$, calcd, 269.0450; found, 269.0452.

*6,7-Dihydrodibenzo[b,d]oxepine-4,10-dicarboxylic Acid (**95**).* Colorless amorphous solid (117 g, 90%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.95 (br s, 2H), 7.98 (d, J = 1.5 Hz, 1H), 7.94 (dd, J = 1.5, 7.7 Hz, 1H), 7.73 (dd, J = 1.6, 7.8 Hz, 1H), 7.68 (dd, J = 1.6, 7.8 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 8.1 Hz, 1H), 4.61 (t, J = 6.4 Hz, 2H), 2.85 (t, J = 6.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 167.2, 152.5, 142.6, 138.1, 135.6, 132.2, 130.3, 130.0, 129.0, 128.9, 128.7, 127.8, 124.6, 78.3, 32.5. HRMS (FAB) m/z: [M − H^+] for $C_{16}H_{11}O_5$, calcd, 283.0606; found, 283.0608.

General Procedure for Peptide Coupling of Tricyclic Tether Linkers. Thionyl chloride (0.12 mL, 1.6 mmol) was added to a solution of dibenzo[b,d]furan-2,6-dicarboxylic acid **91** (30 mg, 0.117 mmol) in 2 mL of THF. The resulting reaction mixture was refluxed for 3 h, and solvent was evaporated under reduced pressure and kept under high vacuum for 1−2 h to get dibenzo[b,d]furan-2,6-dicarbonyl dichloride **96** as colorless soild, used immediately for the next coupling reaction without any further purification.

Pyridine (67 μL, 0.83 mmol) was added to a solution of amino coumarin **13** (114 mg, 0.29 mmol) in 3 mL of THF and stirred for 15 min at rt and then above freshly prepared diacid chloride **96** was added dropwise in 1 mL of THF. The resulting reaction mixture was stirred at rt for about 15 h, and concentrated. The residue was purified by silica gel column chromotography (CH_2Cl_2/acetone; 3/97) to get tilte biaryl dimer as colorless amorphous solid.

General Procedure for Noviosylated Tricyclic Dimers Cyclic Carbonate Hydrolysis. Et_3N (10% total volume) was added dropwise to a solution of above cyclic carbonate diamides in methanol. The resulting mixture was stirred for 14 h, and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 19/1) to yield tricyclic tether dimer **101** (53% yield, over all in two steps) as a colorless amorphous solid.

*N6-(7-((2R,3R,4S,5R)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-N2-(7-((2S,3S,4R,5S)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)dibenzo[b,d]furan-2,6-dicarboxamide (**101**).* ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (s, 1H), 8.2 (s, 2H), 8.19 (d, J = 3.1 Hz, 1H), 7.90 (s, 1H), 7.71 (d, J = 6.7 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.27 (d, J = 8.6 H, 1H z), 7.27 (d, J = 8.6 Hz, 1H), 7.01 (t, J = 7.7 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.8 Hz, 1H), 6.56 (d, J = 8.8 Hz, 1H), 5.01 (d, J = 2.4 Hz, 1H), 4.95 (d, J = 2.4 Hz, 1H), 3.67 (m, 2H), 3.62 (m, 2H), 3.41 (s, 6H), 3.32 (d, J = 8.8 Hz, 2H), 2.25 (s, 6H), 1.36 (s, 3H), 1.35 (s, 3H), 1.11 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.0, 161.8, 159.3, 159.2, 157.4, 156.1, 156.0, 153.1, 149.1, 149.0, 129.5, 129.2, 127.3, 125.9, 125.8, 125.4, 124.9, 124.8, 124.2, 124.1, 123.4, 121.9, 121.4, 120.3, 117.3, 114.2, 113.8, 113.7, 112.4, 111.1, 111.0, 70.9, 68.5, 61.9, 61.8, 61.7, 31.6, 28.7, 28.6, 22.7, 22.6, 22.6, 14.1, 8.3, 8.2. IR (KBR) ν_{max} 3437, 3400, 2967, 2922, 1712, 1707, 1664, 1604, 1529, 1367, 1249, 1080, 992, 761 cm^{-1}. HRMS (FAB) m/z: [M + Na^+] for $C_{50}H_{50}N_2NaO_{17}$, calcd, 973.3007; found, 973.3010.

*N4-(7-((2R,3R,4S,5R)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-N9-(7-((2S,3S,4R,5S)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-6H-benzo[c]chromene-4,9-dicarboxamide (**102**).* Colorless amorphous solid (79% yield, over all in two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.70 (s, 1H), 9.94 (s, 1H), 8.78 (s, 1H), 8.51 (s, 1H), 8.51 (s, 1H), 8.31 (d, J = 6.5 Hz, 1H), 8.08 (d, J = 6.5 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.60 (m, 3H), 7.37 (t, J = 7.8 Hz, 1H), 7.16 (t, J = 8.3 Hz, 2H), 5.52 (m, 3H), 5.35 (s, 2H), 5.05 (s, 2H), 4.01 (m, 2H), 3.91 (m, 2H), 3.50 (s, 6H), 3.28 (dd, J = 1.4, 9.2 Hz, 2H), 3.17 (d, J = 4.1 Hz, 1H), 2.23 (s, 6H), 1.25 (s, 6H), 1.03 (s, 6H). ^{1}H NMR (125 MHz, DMSO-d_6) δ 165.5, 162.6, 158.4, 158.1, 156.3, 155.6, 152.5, 149.7, 148.7, 134.3, 134.2, 131.6, 130.3, 128.7, 128.0, 126.3, 126.1, 125.6, 124.1, 123.3, 122.9, 122.0, 121.3, 121.1, 113.4, 113.0, 112.9, 112.9, 110.9, 110.8, 98.5, 83.4, 77.9, 77.9, 70.9, 68.4, 67.6, 61.2, 55.0, 28.6, 23.0, 23.0, 8.2. IR (KBR) ν_{max} 3446, 3402, 3035, 2975, 2935, 1716, 1704, 1664, 1607, 1527, 1367, 1246, 1083, 994, 762 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{51}H_{52}N_2NaO_{17}$, calcd, 987.3164; found, 987.3164.

*N3-(7-((2R,3R,4S,5R)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-N8-(7-((2S,3S,4R,5S)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-6H-benzo[c]chromene-3,8-dicarboxamide (**103**).* Colorless amorphous solid (75% yield, over all in two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.92 (s, 1H), 9.70 (s, 1H), 8.50 (dd, J = 4.3, 7.8 Hz, 3H), 8.18 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.59 (m, 3H), 7.49 (d, J = 8.1 Hz, 1H), 7.16 (dd, J = 4.4, 8.8 Hz, 2H), 5.52 (t, J = 2.3 Hz, 2H), 5.30 (s, 2H), 5.30 (d, J = 6.1 Hz, 1H), 5.02 (d, J = 6.1 Hz, 1H), 4.00 (m, 2H), 3.90 (m, 2H), 3.50 (s, 6H), 3.30 (br s, 2H), 3.28 (d, J = 9.2 Hz, 2H), 2.22 (s, 3H), 2.22 (s, 3H), 1.25 (s, 6H), 1.03 (s, 6H). ^{1}H NMR (125 MHz, DMSO-d_6) δ 165.5, 164.9, 158.1, 156.3, 156.2, 154.3, 149.7, 149.6, 135.5, 134.9, 134.1, 130.3, 129.6, 128.7, 128.4, 126.3, 125.6, 125.3, 124.3, 121.9, 121.6, 121.3, 121.2, 116.5, 113.0, 112.9, 110.8, 98.5, 83.4, 83.4, 77.9, 70.9, 70.8, 67.6, 67.6, 61.2, 28.6, 23.0, 8.2, 8.2. IR (KBR) ν_{max} 3442, 3406, 2978, 2935, 1712, 1664, 1630, 1606, 1529, 1369, 1246, 1136, 1083, 1060, 993, 750 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{51}H_{52}N_2NaO_{17}$, calcd, 987.3164; found, 987.3135.

*N2-(7-((2R,3R,4S,5R)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-N8-(7-((2S,3S,4R,5S)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-6H-benzo[c]chromene-2,8-dicarboxamide (**104**).* Colorless amorphous solid (57% yield, over all in two steps). ^{1}H NMR (500 MHz, DMSO) δ 9.99 (s, 1H), 9.86 (s, 1H), 8.65 (s, 1H), 8.55 (s, 1H), 8.49 (d, J = 8.8 Hz, 2H), 7.94 (m, 2H), 7.60 (dd, J = 4.3, 8.7 Hz, 2H), 7.49 (d, J = 8.0 Hz, 1H), 7.17 (m, 3H), 5.52 (s, 2H), 5.34 (s, 2H), 5.34 (d, J = 5.5 Hz, 2H), 5.03 (d, J = 6.2 Hz, 2H), 4.01 (m, 2H), 3.91 (m, 2H), 3.50 (s, 6H), 3.28 (d, J = 9.2 Hz, 1H), 3.17 (d, J = 5.2 Hz, 1H), 2.22 (s, 6H), 1.25 (s, 6H), 1.02 (s, 6H). ^{13}C NMR (125 MHz, DMSO) δ 165.7, 165.3, 158.2, 158.1, 157.4, 156.3, 156.2, 149.8, 149.7, 134.7, 134.2, 130.4, 130.1, 128.9, 127.4, 126.3, 126.3, 125.4, 123.9, 121.8, 121.6, 121.5, 121.3, 117.4, 113.1, 113.0, 112.9, 110.8, 98.4, 83.4, 77.9, 70.9, 67.7, 67.6, 61.1, 55.0, 28.6, 22.9, 8.2. IR (KBR) ν_{max} 3433, 3404, 2978, 2933, 1716, 1707, 1664, 1607, 1527, 1367, 1246, 1111, 1084, 993, 762 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{51}H_{52}N_2NaO_{17}$, calcd, 987.3164; found, 987.3157.

*N4-(7-((2R,3R,4S,5R)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-N10-(7-((2S,3S,4R,5S)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-6,7-dihydrodibenzo[b,d]oxepine-4,10-dicarboxamide (**105**).* Colorless amorphous solid (60% yield, over all in two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.05 (s, 1H), 8.81 (s, 2H), 8.79 (s, 2H), 8.76 (s, 1H), 8.29 (dd, J = 1.6, 8.0 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H), 7.90 (dd, J = 1.9, 8.0 Hz, 1H), 7.68 (dd, J = 1.8, 7.6 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 5.59 (s, 2H), 4.85 (t, J = 6.7 Hz, 2H), 4.25 (m, 4H), 3.62 (s, 6H), 3.39 (dd, J = 2.5, 8.9 Hz, 2H), 2.90 (t, J = 6.7 Hz, 2H), 2.29 (s, 3H), 2.24 (s, 3H), 1.77 (br s, 4OH), 1.40 (s, 3H), 1.39 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 163.8, 159.5, 159.4, 156.1, 156.0, 152.1, 149.2, 141.5, 139.0, 135.3, 133.9, 133.1, 132.1, 128.9, 127.4, 126.9, 126.0, 125.8, 125.8, 125.5, 125.0, 124.7, 122.5, 121.8, 114.4, 114.3, 114.2, 114.0, 112.3, 111.1, 97.9, 97.8, 84.4, 78.7, 78.7, 71.3, 71.2, 68.8, 62.1, 62.0, 45.4, 32.8, 29.3, 29.1, 22.7, 22.6, 8.5, 8.4. IR (KBR) ν_{max} 3446, 3384, 2978, 2921, 1772, 1701, 1627, 1605, 1521, 1491, 1367, 1254, 1080, 1053, 962 cm^{-1}. HRMS (FAB) m/z: [M + Na$^+$] for $C_{52}H_{54}N_2NaO_{17}$, calcd, 1001.3320; found, 1001.3334.

Biological Evaluation. *Antiproliferation Assays.* MCF-7 and SKBr3 cells were maintained in Advanced DMEM/F12 (1:1; Gibco) supplemented with nonessential amino acids, L-glutamine (2 mM), streptomycin (500 μg/mL), penicillin (100 units/mL), and 10% FBS. Cells were grown to confluence in a humidified atmosphere (37 °C, 5% CO_2), seeded (2000/well, 100 μL) in 96-well plates, and allowed to attach overnight. Compound or geldanamycin at varying concentrations in DMSO (1% DMSO final concentration) was added, and cells were returned to the incubator for 72 h. After 72 h, the number of viable cells was determined using an MTS/PMS cell proliferation kit (Promega) per the manufacturer's instructions. Cells incubated in 1% DMSO were used as 100% proliferation, and values were adjusted accordingly. IC_{50} values were calculated from separate experiments performed in triplicate using GraphPad Prism.

Western Blot Analyses. MCF-7 cells were cultured as described above and treated with various concentrations of drug, GDA in DMSO (1% DMSO final concentration), or vehicle (DMSO) for 24 h. Cells were harvested in cold PBS and lysed in RIPA lysis buffer containing 1 mM PMSF, 2 mM sodium orthovanadate, and protease inhibitors on ice for 1 h. Lysates were clarified at 14000g for 15 min at 4 °C. Protein concentrations were determined using the Pierce BCA protein assay kit per the manufacturer's instructions. Equal amounts of protein (20 μg) were electrophoresed under reducing conditions, transferred to a PVDF, and immunoblotted with the corresponding specific antibodies. Membranes were incubated with an appropriate horseradish peroxidase-labeled secondary antibody, developed with a chemiluminescent substrate, and visualized.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra for all new compounds and HPLC traces for the ten most active compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

Hsp90, 90 kDa heat shock protein; ATP, adenosine triphosphate; DNA, deoxyribonucleic acid; SAR, structure−activity relationships; Akt, protein kinase B; Her2, human epidermal growth factor receptor 2

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