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The Design, Synthesis, and Evaluation of Coumarin Ring Derivatives of the Novobiocin Scaffold that Exhibit Antiproliferative Activity

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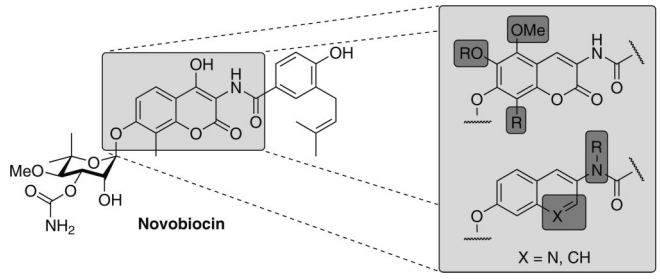

Novobiocin, a known DNA gyrase inhibitor, binds to a nucleotide-binding site located on the Hsp90 *C*-terminus and induces degradation of Hsp90-dependent client proteins at ~700 μM in breast cancer cells (SKBr3). Although many analogues of novobiocin have been synthesized, it was only recently demonstrated that monomeric species exhibit antiproliferative activity against various cancer cell lines. To further refine the essential elements of the coumarin core, a series of modified coumarin derivatives was synthesized and evaluated to elucidate structure−activity relationships for novobiocin as an anticancer agent. Results obtained from these studies have produced novobiocin analogues that manifest low micromolar activity against several cancer cell lines.

Introduction

Increasing resistance to chemotherapeutics and knowledge that cancers employ multiple abnormalities have resulted in an increased interest in targeting the Hsp90 molecular chaperone for the treatment of cancer.[1] Hsp90 is a molecular chaperone that is responsible for the folding and conformational maintenance of more than 100 Hsp90-dependent client proteins.[2,3] *In vivo*, Hsp90 substrates have been implicated in cellular signaling networks, such as those mediated by steroid hormone receptors, transcription factors, and protein kinases, many of which represent individually pursued antitumor targets.[4−9] Hsp90 plays a unique role in regulating the function and stability of a growing number of proteins upon which cancer cells depend for survival. It is because of this role and its related regulation of many mutated and overexpressed proteins that contribute to cancer cell proliferation that Hsp90 has evolved into a promising drug target.[10]

Hsp90 inhibition results in the destabilization of a substrate-bound heteroprotein complex, which leads to degradation of

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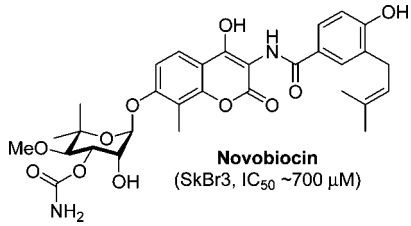

FIGURE 1. Structure of novobiocin.

Hsp90-dependent clients via ubiquitinylation of the unfolded client followed by proteasome-mediated hydrolysis.[11−16] As such, small molecule inhibitors of Hsp90 transform the protein folding machinery into a catalyst for protein degradation.[17] Through Hsp90 inhibition, depletion of multiple oncogenic proteins readily occurs and the outcome is similar to a combinatorial attack on multiple signaling nodes that contribute to oncogenic signaling and modulation of the malignant phenotype.[1,18,19] Hsp90 has been shown to be overexpressed in a wide variety of human malignancies and provides an opportunity for high differential selectivity.[1,18,20] The ability to simultaneously disrupt multiple signaling events through a single target makes Hsp90 an attractive protein for the development of chemotherapeutic agents.[1,19,21]

Novobiocin (Figure 1), a member of the coumermycin family of antibiotics, binds to the ATP-binding pocket of DNA gyrase and elicits antimicrobial activity through inhibition of ATP-hydrolysis.[22−25] Co-crystal structures of GyrB, the B subunit of DNA gyrase, bound to novobiocin and ADP revealed both molecules bind in a bent conformation,[26−28] similar to the manner in which Hsp90 binds ADP.[29] With prior knowledge that novobiocin manifests cytotoxicity and binds to a similarly shaped pocket in DNA Gyrase,[25,30−33] Neckers and co-workers demonstrated that novobiocin also binds Hsp90 and exhibits antitumor activity (~700 μM) against SKBr3 human breast cancer cells. In testing their hypothesis, Neckers and co-workers showed via Western blot analyses that novobiocin induces degradation of Hsp90-dependent clients in a concentration-dependent manner. Related studies in which truncated variants of Hsp90 were eluted from an immobilized novobiocin solid-support revealed that only the *C*-terminus of Hsp90 was capable of binding novobiocin, which is in contrast to other Hsp90 inhibitors that bind solely to the well-established *N*-terminal ATP-binding site.[34]

In addition, it was found that inhibitors bound to the Hsp90 *N*-terminus were readily displaced by occupation of the *C*-terminus by novobiocin, which is not recipricol.[34,35] It has been proposed that novobiocin may antagonize Hsp90 function by inducing a conformational change that results in separation of the homodimeric *C*-terminal domains and subsequent release of substrate;[36] however, studies with improved analogues are needed to confirm this hypothesis. It is proposed that the synthesis of improved analogues will not only allow elucidation of the Hsp90 *C*-terminal nucleotide-binding pocket, but will also provide insight into the unique mechanism exhibited by Hsp90 during the complex protein folding process.[363]

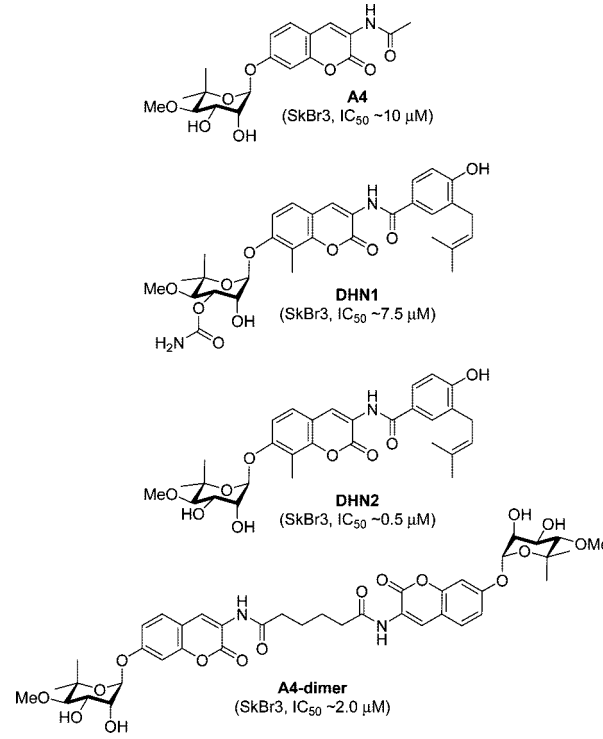

FIGURE 2. Structures of **A4**, **DHN1**, **DHN2**, and **A4-dimer**.

Several groups have attempted to develop improved analogues of novobiocin to improve its comparatively poor Hsp90 inhibitory activity.[34] A library of novobiocin analogues disclosed in

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2005 demonstrated that **A4** (Figure 2) induced degradation of Hsp90-dependent client proteins at ~70-fold lower concentration than novobiocin.[11] The structure of **A4** included a shortened *N*-acyl side chain, removal of the 4-hydroxy substituent, and an absent carbamoyl group on the noviose appendage. More importantly, this study highlighted that attachment of the noviose moiety to the 7-position and an amide linker at the 3-position of the coumarin ring are critical for anti-Hsp90 activity.[11] To confirm the observed SAR trends elucidated from this library, two natural product analogues were prepared and evaluated, **DHN1** and **DHN2** (Figure 2). Upon evaluation of these molecules in several assays, it was confirmed that the 4-hydroxyl and the 3′-carbamate are detrimental to Hsp90 inhibitory activity, but critical for DNA gyrase inhibition.[14]

Compound **A4** was found to exhibit unique activities. **A4** induced Hsp90 at concentrations (10^3-10^4)-fold lower than that required for client protein degradation and was thus evaluated for neuroprotective activity. **A4** exhibited an EC_{50} at 6 nM and demonstrated no toxicity at any concentration tested in a model for Alzheimer's disease.[11] In contrast to the monomeric species, the **A4-dimer**, based on the structure of coumermycin A1, was found to manifest antiproliferative activity. These results suggested that modification of the amide side chain resulted in conversion of a nontoxic molecule into an antiproliferative agent.[37] Consequently, a series of monomeric species based on **A4** was synthesized and evaluated for antitumor activity.[38] This later study described the synthesis and evaluation of biaryl and heterocyclic amide derivatives that explore hydrogen bonding interactions with the putative novobiocin binding pocket, which typically binds the prenylated benzamide of the natural product. These studies led to the first set of SAR for the amide side chain.

Although the Hsp90 *C*-terminus does not exhibit ATPase activity, it does play a critical role in conformational rearrangement upon ATP binding.[36] To further explore SAR, derivatives of **A4** with variations to the coumarin scaffold were designed to probe the importance of interactions typically manifested by the purine ring. These coumarin-derived motifs possess hydrogen bonding capabilities similar to those of the nucleotide bases, adenine and guanine, and contain strategically placed hydrogen bond acceptors and donors and alkyl groups of variable size to probe the size and nature of the complementary binding pocket. The design, synthesis, and evaluation of such compounds are described in this article.

Results and Discussion

Design of New Novobiocin Analogues. To elucidate structure−activity relationships for the coumarin ring system of novobiocin, we envisioned construction of novobiocin analogues with modified coumarin cores. As shown in Scheme 1, the derivatives were assembled in a modular fashion allowing sequential coupling of noviose and a series of benzoic acids with the modified coumarin cores. We previously demonstrated that the trichloroacetimidate of noviose carbonate couples readily to coumarin phenols in good yield, to afford the corresponding α-anomer.[39] The benzoic acids selected were based upon previously obtained SAR for the amide side chain as described by Burlison and co-workers.[38]

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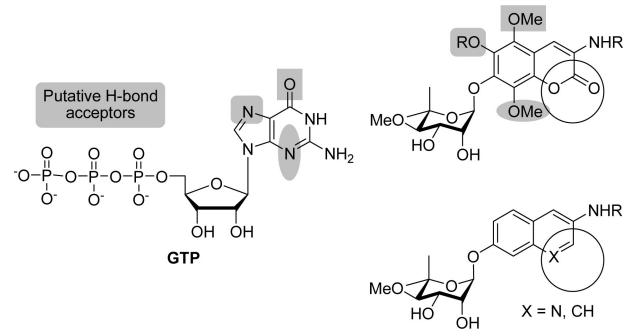
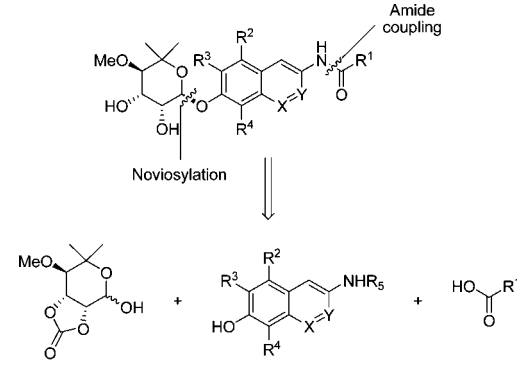


FIGURE 3. Complementarity of GTP and coumarin analogues.

The coumarin scaffolds were designed to complement interactions present on the purine nucleus, via probing the importance of hydrogen bond donor and acceptors in positions surrounding the aromatic ring system. Rationale for these analogues is based on the identification of additional interactions with the nucleotide-binding domain that typically binds the corresponding purine substrate and may lead to enhanced inhibitory affinity for these compounds. Minor perturbations were made on each analogue; however, the addition of one hydrogen bond can produce 1−2 kcal/mol of binding energy and thus increase binding by 10-fold.[40] Therefore, these complementary interactions can exhibit a substantial impact on binding and subsequent inhibition. While it has been demonstrated that the *N*-terminal site is fairly specific for adenine nucleotides, the *C*-terminal site has been shown to be more promiscuous, and binds both purines and pyrimidines. While adenine specifically binds to the *N*-terminus, GTP and UTP are specific *C*-terminal substrates.[41] On the basis of these previous studies, mimics of the guanosine nucleus were chosen to take advantage of this differential. Hydrogen bond acceptors were placed at the 5-, 6-, and 8-positions of the coumarin ring to mimic those at the 6-, 7-, and 3-positions of guanine, respectively (Figure 3). Additionally, analogues bearing modification to the coumarin lactone were constructed to probe the importance of hydrogen bond donors/acceptors at this position as well as to potentially improve upon the solubility of the novobiocin scaffold. The activity of such compound will provide insight into the interactions that are essential or those that can be further optimized.

SCHEME 1. Retrosynthesis of Novobiocin Analogues

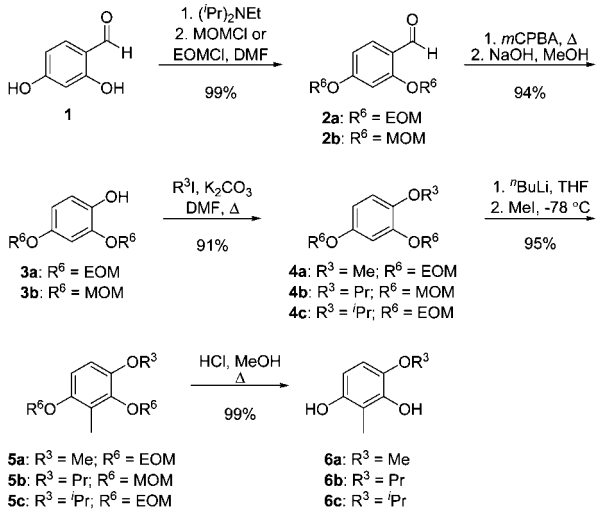


Since the discovery of the *C*-terminal binding site is a recent achievement and no Hsp90 co-crystal structure bound to *C*-terminal inhibitors exists, there is limited knowledge regarding its shape and dimensions. Therefore, several analogues were designed to probe the breadth of the pocket at positions that

potentially project into hydrophobic regions. Alkyl and aryl groups of variable size were attached at the 5-, 6-, and 8-positions of the coumarin ring to maximize putative hydrophobic interactions and to optimize affinity. A methoxy group was attached at the 5-poistion of the coumarin ring, while methoxy, propoxy, and isopropoxy ethers were installed at the 6-position. Methyl, ethyl, methoxy, benzyl, and phenyl substituents were placed at the 8-position, offering a variety of possible interactions to fill the pocket that is occupied by the chlorine of chlorobiocin and the methyl substituent of novobiocin. The culmination of structure−activity relationships elucidated by such compounds will provide a platform upon which improved analogues can be sought.

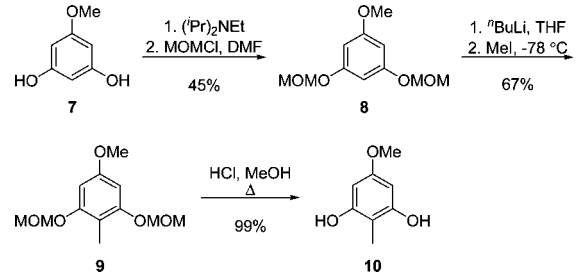
Syntheses of 5-, 6-, and 8-Alkyl(oxy) Novobiocin Analogues. To generate the resorcinol precursors with substitutions at the 4-position, which result in coumarin ring systems with appendages at the 6-position, the phenols of benzaldehyde **1** were protected as the corresponding ethers (Scheme 2). The resulting benzaldehydes (**2a**,**b**)[42] were converted to their formate esters via Baeyer−Villiger oxidation, and then hydrolyzed to afford phenols **3a**,**b**.[43,44] *O*-Alkylation with the requisite alkyl iodide proceeded in good yield and generated a series of protected 4-substituted resorcinolic ethers (**4a**−**c**). Ortho-lithiation of **4a**−**c**, followed by alkylation with methyl iodide provided the 2-methyl protected resorcinols, **5a**−**c**.[45] Deprotection[46] of the alkoxy ethers by exposure to acidic conditions gave resorcinols **6a**−**c**.

SCHEME 2. Syntheses of 4-Substituted Resorcinols (OEOM = OCH_2OEt)



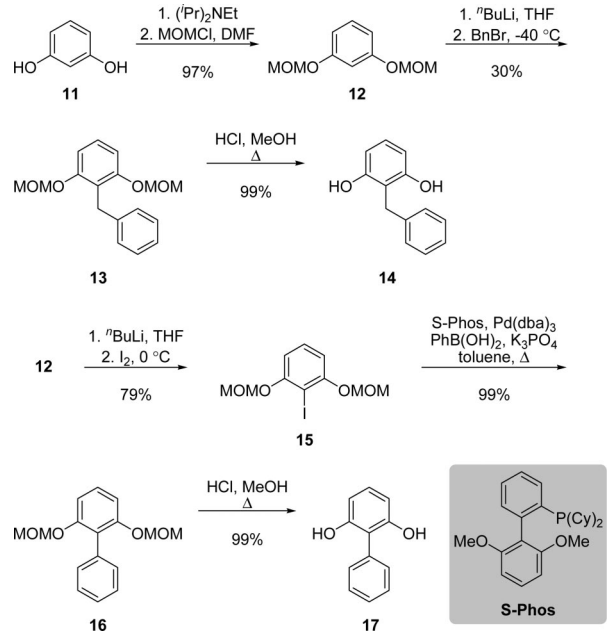
To generate resorcinol precursors with substitutions at the 5-position, the phenols of 5-methoxy resorcinol **7** were once again protected as the corresponding alkoxy ethers, **8** (Scheme 3). Ortho-lithiation of **8**, followed by treatment with methyl iodide, led to installation of a methyl group at the 2-position of **9**.[45] Acidic deprotection[46] was employed to afford resorcinol **10**.

SCHEME 3. Synthesis of 5-Substituted Resorcinol



To generate the resorcinol precursors with aryl substituents at the 2-position, the phenols of resorcinol **11** were protected as the corresponding alkoxy ethers, **12** (Scheme 4). Subsequent ortho-lithiation of **12**, followed by the addition of benzyl bromide provided the benzyl derivative, **13**.[45] Removal of the ether protecting groups[46] gave diphenol **14**.[45] The anion of resorcinol **12** was also employed to construct the corresponding 2-iodide via reaction with iodine to yield **15**.[47] A Suzuki coupling in the presence of biaryl ligand S-Phos[48] was used to generate biaryl **16**, which underwent deprotection[46] to provide **17**.

SCHEME 4. Syntheses of 2-Substituted Resorcinols



To generate resorcinol precursors with alkyl substitutions at the 2-position, pyragallol (**18**) was *O*-alkylated with methyl iodide to generate 2-methoxy resorcinol among an inseparable mixture of regioisomers (Scheme 5). The mixture was subsequently subjected to coumarin formation and the corresponding products isolated. Preparation of 2-ethyl resorcinol (**21**) from 2,6-dihydroxyacetophenone (**20**) was accomplished according to published procedures.[49]

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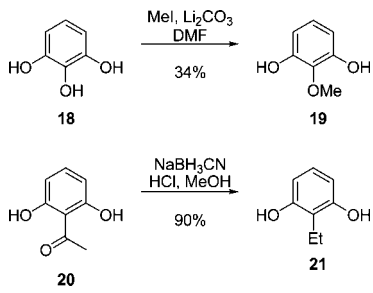
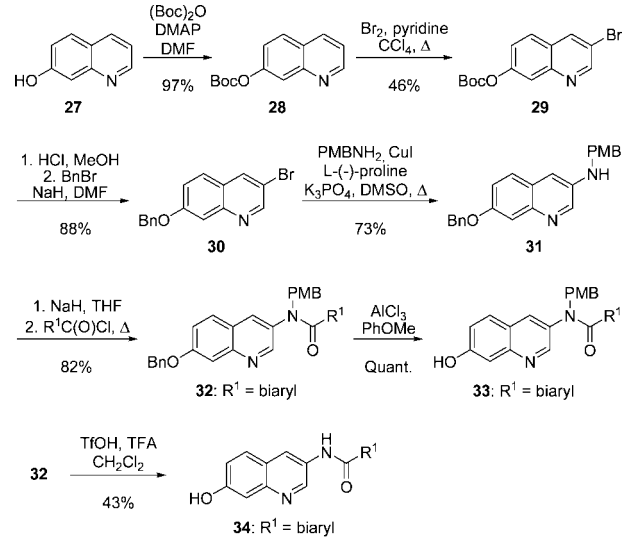
SCHEME 5. Synthesis of 2-Methoxy Resorcinol and 2-Ethyl Resorcinol



Once resorcinols **6a**−**c**, **10**, **14**, **17**, **19**, and **21** were obtained, the corresponding coumarins **23a**−**h** were synthesized through a modified Pechmann condensation with eneamine **22** as previously described.[50,51] The resulting coumarin phenols were noviosylated with the trichloroacetimidate of noviose carbonate (**24**) in the presence of catalytic boron trifluoride etherate to generate scaffolds **25a**−**h** in good yield.[39] The benzyl carbonate was removed via hydrogenolysis to produce aminocoumarins, which were readily coupled with preselected benzoic acids in the presence of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) and pyridine. Benzoic acids were chosen based on previously determined SAR trends reported by Burlison and co-workers.[38] The cyclic carbonates were treated with triethylamine in methanol to give the solvolyzed products **26a**−**p** in moderate to good yield over three steps (Scheme 6).

Syntheses of Quinoline- and Naphthalene-Containing Novobiocin Analogues. Novobiocin analogues containing a quinoline or naphthalene ring in lieu of the 8-methylcoumarin of novobiocin were synthesized to probe the importance of the coumarin lactone moiety in binding the Hsp90 *C*-terminus, as well as to potentially circumvent the limited solubility of coumarin-containing analogues. Protection of the phenol in **27** as the *tert*-butyl-carbonate[52] served two purposes (Scheme 7). Not only did phenol protection remove the quinolone-like properties of **27**, but the sterically hindered *tert*-butyl-carbonate also decreased the relative amount of 6- and 8-bromo regioisomers normally produced upon bromination of **28**. Thus, the isolable percentage of desired 3-bromo regioisomer was enriched to 46% yield.[53] One-pot *tert*-butyl-carbonate deprotection,

SCHEME 7. Syntheses of 7-Hydroxyquinolines

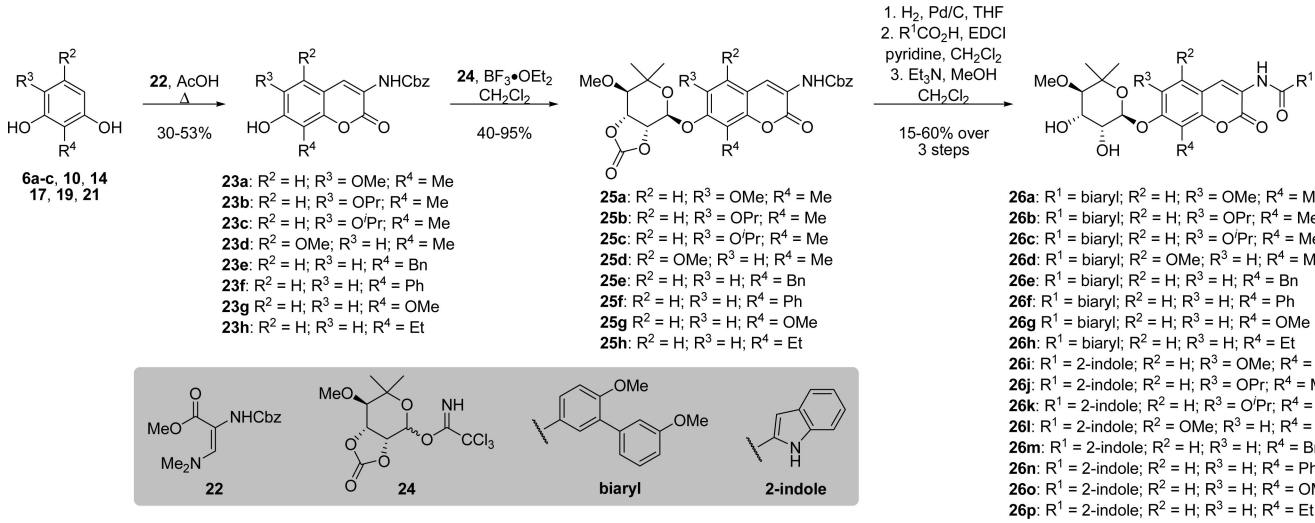


followed by immediate reprotection with benzyl bromide afforded intermediate **30**. *N*-Arylation of **30** was accomplished with *p*-methoxybenzylamine under Ullman-like conditions employing CuI and L-(−)-proline as a catalyst to provide **31**.[54] Acylation of the secondary aniline with the desired benzoyl chloride,[55] generated *in situ* from the appropriate benzoic acid,[56] afforded PMB-protected amide **32**. Interestingly, subjection of **32** to aluminum trichloride in anisole[57] resulted solely in the formation of 7-hydroxy **33**; the PMB-protected amide remained intact. Global removal of the PMB and benzyl groups was ultimately accomplished with trifluoromethanesulfonic acid to provide phenol **34**.[58]

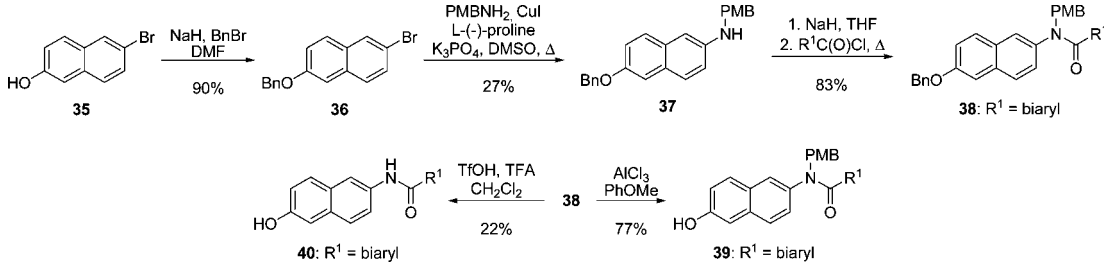
Construction of the corresponding naphthalene-containing analogues began by benzyl protection of phenol **35** to provide **36** in high yield (Scheme 8).[59] *N*-Arylation of **36** with *p*-methoxybenzylamine provided **37**,[54] which was acylated with the desired benzoyl chloride to afford **38**.[55,56] 6-Benzyloxy deprotection of **38** to **39** was performed with aluminum trichloride in anisole,[57] while concurrent benzyl- and PMB-deprotection to intermediate **40** was accomplished with trifluoromethanesulfonic acid.[58]

Phenols **33**, **34**, **39**, and **40** were noviosylated with the trichloroacetimide of noviose carbonate (**24**) in the presence of

SCHEME 6. Preparation of 5-, 6-, and 8-Modified Novobiocin Analogues



SCHEME 8. Syntheses of 6-Hydroxynaphthalenes



SCHEME 9. Preparation of Quinoline- and Naphthalene-Derived Novobiocin Analogues

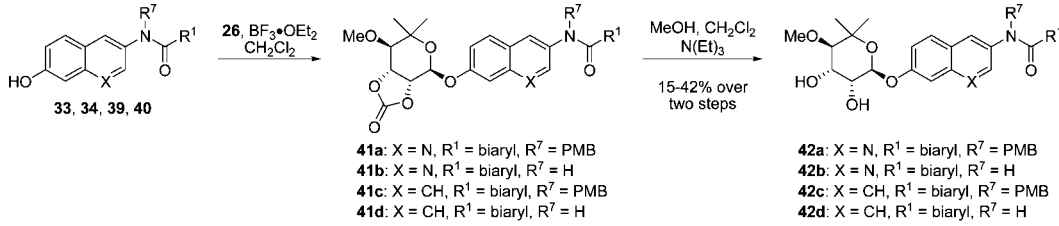
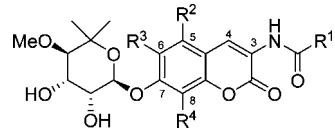


TABLE 1. Anti-Proliferation Activities of Coumarin-Derived Novobiocin Analogues



compd no. (IC_{50}, μM)	R^1	R^2	R^3	R^4	MCF-7	SKBr3	PC-3	LnCaP
26a	biaryl	H	OMe	Me	>100[a]	58.8 ± 1.3	35.4	6.6
26b	biaryl	H	OPr	Me	>100	>100	5.6 ± 5.7	3.0 ± 0.6
26c	biaryl	H	O^{i}Pr	Me	66.9 ± 3.1	58.6 ± 5.4	60.7 ± 9.1	14.4 ± 4.2
26d	biaryl	OMe	H	Me	82.8	55.7 ± 6.9	11.3 ± 2.0	2.0 ± 0.8
26e	biaryl	H	H	Bn	>100	>100	>100	49.7 ± 25.0
26f	biaryl	H	H	Ph	>100	17.3 ± 3.4	>100	1.0 ± 0.1
26g	biaryl	H	H	OMe	9.0 ± 5.4	13.9 ± 1.2	2.3 ± 2.9	1.1 ± 0.1
26h	biaryl	H	H	Et	41.7 ± 14.0	28.6 ± 1.1	1.8 ± 0.6	1.6 ± 0.3
26i	2-indole	H	OMe	Me	24.4 ± 1.2	25.1 ± 7.7	20.2 ± 9.8	10.5 ± 0.3
26j	2-indole	H	OPr	Me	2.1 ± 0.1	2.1 ± 0.8	6.2 ± 1.8	1.8 ± 0.7
26k	2-indole	H	O^{i}Pr	Me	20.0 ± 1.0	20.7 ± 0.4	11.9	11.4
26*l*	2-indole	OMe	H	Me	6.1 ± 1.7	9.0 ± 0.8	11.8 ± 1.3	12.9 ± 4.4
26m	2-indole	H	H	Bn	13.2 ± 0.6	38.0 ± 3.0	73.3 ± 3.7	67.6 ± 6.3
26n	2-indole	H	H	Ph	22.9 ± 2.1	38.8 ± 8.3	28.0 ± 12.1	27.6 ± 10.8
26o	2-indole	H	H	OMe	>100	9.7 ± 1.0	>100	>100
26p	2-indole	H	H	Et	4.3 ± 2.5	4.3 ± 3.4	>100	>100

[a] Values represent mean ± standard deviation for at least two separate experiments performed in triplicate.

boron trifluoride etherate to provide noviose carbonate analogues **41a**−**d**.[39] In particular, analogues **33** and **34** containing the quinoline nitrogen were both slow to react and low yielding, even with greater than stoichiometric boron trifluoride etherate, suggesting chelation of the quinoline nitrogen to boron was problematic. Solvolysis of carbonates **41a**−**d** with triethylamine in methanol/dichloromethane afforded diols **42a**−**d** in moderate yields (Scheme 9).

Biological Evaluation of Novobiocin Analogues. Upon construction of the library of novobiocin analogues, the compounds were evaluated for antiproliferative activity against SKBr3 (estrogen receptor negative, Her2 overexpressing breast cancer cells), MCF-7 (estrogen receptor positive breast cancer cells), LnCaP (androgen receptor sensitive prostate cancer cells), and PC-3 (androgen receptor insensitive prostate cancer cells) cell lines. As shown in Table 1, the 6-substituted analogues containing the biaryl side chain (**26a**−**c**) were 3- to 7-fold less active against the two breast cancer cells lines than analogues containing hydrogen at this position.[38] These analogues were more active against prostate cancer cells than breast cancer cells versus the corresponding 6-H derivative. For reasons that remain unclear, the putative binding pocket for biaryl-containing analogues does not appear to tolerate incorporation of steric bulk at the 6-position. Analogues containing the 2-indole side chain (**26i**−**k**) were consistently more active than their corresponding biaryl derivatives, which corresponds with previously observed trends.[38] Analogue **26j**, containing a 6-propoxy-

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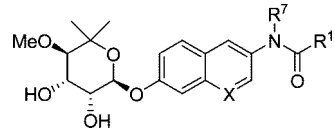
TABLE 2. Anti-Proliferation Activities of Quinoline- and Naphthalene-Containing Novobiocin Analogues



compd no.	R^1	R^7	X	MCF-7	SKBr3	PC-3	LnCaP
42a	biaryl	4-OMe-Bn	N	>100[a]	>100	>100	>100
42b	biaryl	H	N	13.1 ± 4.1	16.5 ± 6.2	17.6 ± 4.6	14.2 ± 0.4
42c	biaryl	4-OMe-Bn	CH	>100	>100	>100	>100
42d	biaryl	H	CH	46.4 ± 5.3	38.9 ± 2.4	10.9 ± 0.7	19.6 ± 1.6

[a] Values represent mean ± standard deviation for at least two separate experiments performed in triplicate.

coumarin, was consistently the most potent derivative in this library, exhibiting 2-fold enhanced potency relative to its 6-H analogue in LnCaP cells.

By comparison, incorporation of a hydrogen bond acceptor at the 5-position (**26d**, **26*l***) resulted in equivalent or decreased activity versus corresponding 6-H analogues, especially against both breast cancer cell lines.[38] In general, 5-methoxy functionalized coumarins do not appear beneficial for antiproliferative activity.

It was previously demonstrated that 8-methyl analogues were ~10-fold more active than the corresponding 8-hydrogen derivatives.[38] To further elaborate upon this trend, a larger selection of 8-fuctionalized coumarins were evaluated. Incorporation of an 8-methoxy (**26g**) led to 2-fold improved activity over its 8-methyl counterpart, and 5-fold increased activity over the similarly sized 8-ethyl derivative **26h**. Introduction of steric bulk (**26e**, **26f**) generally decreased antiproliferative activity, especially against MCF-7 cells. It appears that while short alkoxy side chains take advantage of putative interactions, steric bulk appears detrimental to inhibitory activity at this location. A similar trend was observed against prostate cancer cells, with **26g** and **26h** exhibiting 10-fold increased activity versus their 8-methyl counterparts.[38] Surprisingly, 8-benzyl **26e** was more than twice as active as the 8-methyl derivative against LnCaP cells. In contrast, 8-position analogues containing the 2-indole side chain (**26m**−**p**) did not exhibit similar, consistent trends against prostate and breast cancer cells. Against breast cancer cells, compounds **26m**, **26n**, and **26p** exhibited significantly reduced activity versus the 8-methyl derivative. The 8-methoxy **26o** was inactive against MCF-7 cells, while both **26o** and **26p** were inactive against PC-3 and LnCaP cells. The selectivity of **26o** and **26p** for breast cancer cells versus prostate cancer cells is intriguing and requires further investigation.

As shown in Table 2, compounds **42a** and **42c** containing the *p*-MeOBn-alkylated amides did not exhibit antiproliferative activity against the cell lines tested. This is in contrast to analogues **42b** and **42d** lacking the *p*-MeOBn functionality, which manifested modest antiproliferative activity. This stark difference suggests one of two scenarios regarding the role of the *p*-MeOBn functionality; either the *p*-MeOBn group of tertiary amides **42a** and **42c** is unable to occupy the same pocket as the 4-aryloxy substituted novobiocin analogues[60,61] or, more simply, the secondary amide is required for benzamide-containing novobiocin analogues to manifest antiproliferative activity, which is consistent with prior structure−activity trends.[38] It is plausible that the steric congestion of amides **42a** and **42c** forces adoption of a more static conformation that disallows cis/trans isomerization of the amide, a feature that has been hypothesized to be essential for antiproliferative activity of novobiocin analogues against bacteria. The lack of reactivity for tertiary amides **42a** and **42c** to all but the harshest conditions for *p*-MeOBn removal[58,62,63] also suggests these compounds may adopt a highly organized and stable conformation.

Against breast cancer cells, analogue **42b** exhibited similar antiproliferative activities as the corresponding 8-methylcoumarin analogue, while **42d** was between 2- and 5-fold less active.[38] In contrast, both **42b** and **42d** were significantly more active against PC-3 cells than the corresponding 8-methylcoumarin; **42b** and **42d** exhibited between 7- and 9-fold reduced activity against LnCaP cells. Given that both **42b** and **42d** lack the 8-methyl feature that yields an increased activity of ~10-fold, it is reasonable to hypothesize that the quinoline- and naphthalene-derived analogues that include an 8-methyl substituent could exhibit antiproliferative activities between 1−5 μM against breast cancer cells and 1−2 μM against prostate cancer cells, approximately an order of magnitude less than the novobiocin analogue containing a coumarin. These results suggest that, while the lactone moiety may provide beneficial hydrogen bonding interactions with the novobiocin binding pocket, these interactions may not be required to manifest antiproliferative activity. More importantly, these results implicate that continued optimization of the coumarin scaffold connecting the sugar and benzamide motifs is likely to produce compounds with enhanced antiproliferative activity. A summary of the observed trends for antiproliferative activities of coumarin-derived novobiocin analogues is depicted in Figure 4.

To provide additional support that the antiproliferative activities exhibited by coumarin-derived novobiocin analogues result from Hsp90 inhibition, analogues **26g**, **26j**, and **42d** were evaluated for their abilities to induce degradation of Hsp90-dependent client proteins. As shown in Figure 5, the Hsp90 client proteins Her2 and Raf were degraded in MCF-7 cells in a concentration-dependent manner upon treatment with cou-

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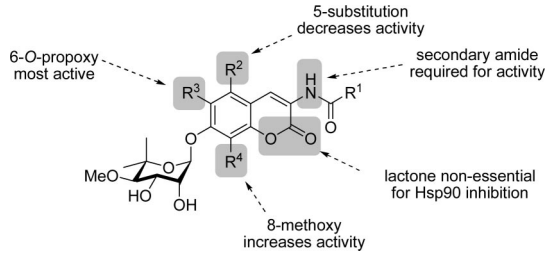

FIGURE 4. Structure−activity relationships observed for the coumarin scaffold of novobiocin analogues exhibiting antiproliferative activities.

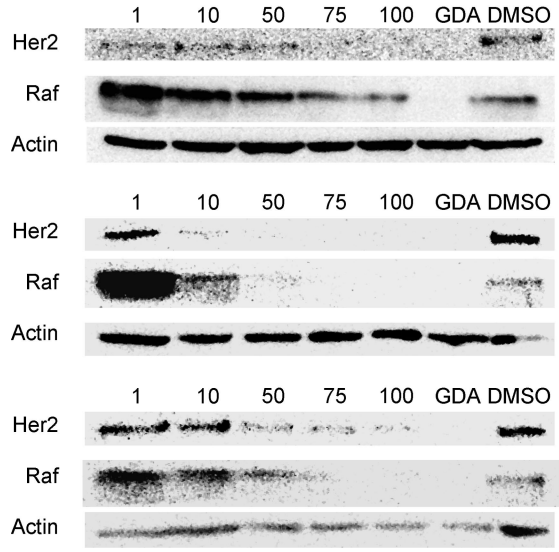

FIGURE 5. Western blot analyses of Hsp90 client protein degradation assays against MCF-7 breast cancer cells. Concentrations (in μM) of **26g** (top), **26j** (middle), and **42d** (bottom) are indicated above each lane. GDA (geldanamycin, 500 nM) and DMSO were respectively employed as positive and negative controls.

marin-derived novobiocin analogues. Moreover, Hsp90 client protein degradation correlates well with observed antiproliferative IC_{50}s; **26g** (IC_{50} = 9.0 μM) and **26j** (IC_{50} = 2.1 μM) induced client degradation at ~10 μM, while **42d**, with its more modest antiproliferative activity (IC_{50} = 46.4 μM), induced client degradation at ~50 μM. Since Actin, a non-Hsp90-dependent protein, is not affected by these analogues, antiproliferative activities of these analogues correlate directly with Hsp90-client protein degradation.

Conclusions

Compounds **26g** and **26j** demonstrated the most potent antiproliferative activity against the cancer cell lines tested and represent scaffolds that will be further probed to improve activity. Derivatives **26f** and **26o** appear to represent compounds that exhibit differential selectivity for one cancer cell line versus another, for reasons that remain unclear. Since these compounds demonstrated low micromolar activity against one cell line and are inactive against others, they may provide a tool for further exploration and perhaps unraveling of the complicated processes involved. The activities of analogues **42b** and **42d**, the first documented novobiocin analogues lacking the coumarin functionality, implicate that, while the coumarin ring may participate in hydrogen bonding interactions with Hsp90 that abrogate activity, these interactions are not essential for antiproliferative activity through inhibition of Hsp90. These analogues provide sufficient evidence to continue the search for optimal ring systems that bridge the benzamide and noviose functionalities. Studies to construct analogues based upon these structure−activity relationships are currently underway and will be reported in due course.

Experimental Section

2,4-Bis(ethoxymethoxy)benzaldehyde (2a).[42] *N*,*N*-Diisopropylethylamine (25.3 mL, 145 mmol) was slowly added to 2,4-dihydroxybenzaldehyde (5.00 g, 36.2 mmol) in anhydrous *N*,*N*-dimethylformamide (100 mL) over 5 min at rt. After 30 min, the solution was cooled to 0 °C and chloromethyl ethyl ether (14.2 mL, 145 mmol) was added and the mixture warmed to rt over 12 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 5:1 → 1:1 hexane:EtOAc) to give **2a** as a brown amorphous solid (9.10 g, 99%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.34 (d, J = 2.4 Hz, 1H), 7.81 (dd, J = 8.7, 2.8 Hz, 1H), 6.89 (t, J = 2.5 Hz, 1H), 6.74 (m, 1H), 5.34 (d, J = 2.8, 2H), 5.28 (d, J = 2.8, 2H), 3.81−3.71 (m, 4H), 1.28−1.22 (m, 6H).

2,4-Bis(ethoxymethoxy)phenol (3a). A solution of **2a** (3.78 g, 12.0 mmol) in anhydrous CH_2Cl_2 (4.0 mL) was slowly added to *m*CPBA (70% w/w, 3.26 g, 13.2 mmol) in anhydrous CH_2Cl_2 (16.3 mL) at 0 °C. The resulting solution was warmed to rt, then refluxed for 12 h. After cooling to rt, the resulting solution was washed with saturated aqueous $NaHCO_3$ solution (3 × 20 mL) and 10% aqueous $Na_2S_2O_3$ (30 mL). Combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was redissolved in MeOH (5 mL) and stirred with excess 10% aqueous NaOH for 3 h at rt. The pH was adjusted to 2 with 6 M HCl and the solution was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic fractions were dried (Na_2SO_4), filtered, and concentrated to give **3a** as an orange oil (8.21 g, 94%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.89−6.85 (m, 2H), 6.67 (dd, J = 8.8, 2.7 Hz, 1H), 5.81 (d, J = 6.6 Hz, 1H), 5.23 (s, 2H), 5.15 (s, 2H), 3.80−3.73 (m, 4H), 1.29−1.24 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.0, 145.0, 141.5, 115.2, 110.6, 106.0, 94.9, 94.2, 64.8, 64.1, 15.1, 15.1; IR (film) ν_{max} 3362, 2887, 1460, 1286, 1162, 735 cm^{-1}; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{12}H_{18}O_5$ 265.1052, found 265.1045.

2,4-Bis(methoxymethoxy)phenol (3b).[44] Benzaldehyde **2b** (700 mg, 3.11 mmol) in $CHCl_3$ (1.80 mL) at 0 °C was treated with *m*CPBA (70% w/w, 1.61 g, 9.33 mmol). After 10 min, the solution was warmed to rt, then refluxed for 12 h. Upon cooling to rt, the solution was washed with saturated aqueous $NaHCO_3$ (3 × 10 mL), saturated aqueous Na_2SO_3 (20 mL), and saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in MeOH (5 mL) and stirred with excess triethylamine for 3 h at rt. The solvent was concentrated and the residue was purified by column chromatography (SiO_2, 4:1 → 3:1 hexane:EtOAc) to afford **3b** as a yellow oil (320 mg, 50%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.87 (d, J = 8.9 Hz, 1H), 6.86 (s, 1H), 6.67 (dd, J = 11.5, 2.8 Hz, 1H), 5.21 (s, 2H), 5.11 (s, 2H), 3.54 (s, 3H), 3.50 (s, 3H).

2,4-Bis(ethoxymethoxy)-1-methoxybenzene (4a). Potassium carbonate (14.3 g, 103 mmol) was added to **3a** (2.50 g, 10.3 mmol) in *N*,*N*-dimethylformamide (103 mL). After 10 min, methyl iodide (6.43 mL, 103 mmol) was added and the solution was heated to reflux for 12 h. Upon cooling to rt, the solution was extracted with EtOAc (3 × 50 mL); combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (SiO_2, 4:1 hexane:EtOAc) to afford **4a** as a yellow oil (2.40 g, 91%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.87 (d, J = 2.8 Hz, 1H), 6.72 (d, J = 8.9 Hz, 1H), 6.60 (dd, J = 13.3, 1.7 Hz, 1H), 5.18 (s, 2H), 5.07 (s, 2H), 3.76 (s,

3H), 3.72−3.69 (m, 2H), 3.68−3.63 (m, 2H), 1.17−1.13 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.7, 146.2, 143.9, 111.2, 107.9, 105.8, 93.2, 93.0, 63.3, 63.0, 55.4, 14.1, 14.0; IR (film) ν_{max} 2976, 2932, 2899, 2835, 1595, 1508, 1393, 1227, 1153, 1103, 1080, 1009, 847 cm^{-1}; HRMS (ESI$^+$) *m/z* [M + Na]$^+$ calcd for $C_{13}H_{20}O_5$ 279.1208, found 279.1181.

2,4-Bis(methoxymethoxy)-1-propoxybenzene (4b). Potassium carbonate (322 mg, 2.33 mmol) was added to **3b** (50 mg, 0.233 mmol) in *N*,*N*-dimethylformamide (2.33 mL) at rt. After 10 min, iodopropane (226 μL, 2.33 mmol) was added and the solution was heated to reflux for 12 h. Upon cooling to rt, the solution was extracted with EtOAc (3 × 10 mL); combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (SiO_2, 5:1 hexane:EtOAc) to afford **4b** as a yellow oil (36.4 mg, 61%): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 6.87 (s, 1H), 6.84 (d, J = 2.9 Hz, 1H), 6.68 (dd, J = 11.7, 2.8 Hz, 1H), 5.19 (s, 2H), 5.12 (s, 2H), 3.93 (t, J = 6.6 Hz, 2H), 3.53 (s, 3H), 3.49 (s, 3H), 1.86−1.78 (m, 2H), 1.06 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.6, 146.5, 143.8, 113.7, 108.5, 106.6, 94.7, 94.2, 70.3, 55.2, 54.9, 21.6, 9.5; IR (film) ν_{max} 2961, 2826, 1595, 1506, 1400, 1261, 1154, 1013, 1076, 924, 800 cm^{-1}; HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{13}H_{20}O_5$ 257.1389, found 257.1410; [M + Na]$^+$ calcd for $C_{13}H_{20}O_5$ 279.1208, found 279.1165.

2,4-Bis(ethoxymethoxy)-1-isopropoxybenzene (4c). Potassium carbonate (2.85 g, 20.7 mmol) was added to **3a** (500 mg, 2.07 mmol) in *N*,*N*-dimethylformamide (4.10 mL) at rt. After 10 min, 2-iodopropane (2.06 mL, 20.7 mmol) was added and the solution was heated to reflux for 12 h. Upon cooling to rt, the solution was extracted with EtOAc (3 × 20 mL); combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 5:1 → 1:1 hexane:EtOAc) to afford **4c** as a yellow oil (0.32 g, 55%): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 6.87 (s, 1H), 6.86 (d, J = 4.9 Hz, 1H), 6.66 (dd, J = 11.6, 3.4 Hz, 1H), 5.23 (s, 2H), 5.17 (s, 2H), 4.44−4.38 (m, 1H), 3.83−3.72 (m, 4H), 1.33 (s, 3H), 1.31 (s, 3H), 1.27−1.23 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.4, 149.1, 143.2, 118.6, 109.5, 107.5, 94.4, 93.9, 72.8, 64.3, 64.1, 22.2 (2C), 15.1, 15.1; IR (film) ν_{max} 2976, 1591, 1504, 1528, 1391, 1258, 1217, 1107, 1011, 847 cm^{-1}; HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{15}H_{24}O_5$ 285.1702, found 285.1746; [M + Na]$^+$ calcd for $C_{15}H_{24}O_5$ 307.1522, found 307.1310.

1,3-Bis(ethoxymethoxy)-4-methoxy-2-methylbenzene (5a). A solution of **4a** (632 mg, 2.27 mmol) in anhydrous THF (1.94 mL) was added dropwise to a solution of ^{n}BuLi (2.5 M in hexanes, 1.48 mL, 3.70 mmol) in anhydrous THF (1.62 mL) at rt. After 1 h, the solution was cooled to −78 °C and methyl iodide (620 μL, 9.87 mmol) was added. The resulting solution was warmed to rt over 12 h, and the reaction was quenched by the addition of saturated aqueous NH_4Cl. Water (5 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 8:1 → 5:1 hexane:EtOAc) to afford **5a** as a yellow oil (353 mg, 53%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.74 (d, J = 9.0 Hz, 1H), 6.60 (d, J = 9.0 Hz, 1H), 5.10 (s, 2H), 5.05 (s, 2H), 3.78 (q, J = 7.1 Hz, 2H), 3.72 (s, 3H), 3.67 (q, J = 7.1 Hz, 2H), 2.14 (s, 3H), 1.18−1.15 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.1, 146.5, 121.7, 109.0, 108.4, 96.2, 93.0, 64.3, 63.1, 55.1, 28.7, 14.2, 14.1, 8.8; IR (film) ν_{max} 2918, 2359, 1487, 1260, 1248, 1082, 1055, 945, 798 cm^{-1}; HRMS (ESI$^+$) *m/z* [M + Na]$^+$ calcd for $C_{14}H_{22}O_5$ 293.1365, found 293.1357.

1,3-Bis(methoxymethoxy)-2-methyl-4-propoxybenzene (5b). A solution of **4b** (165 mg, 0.64 mmol) in anhydrous THF (520 μL) was added dropwise to a solution of ^{n}BuLi (2.5 M in hexanes, 390 μL, 0.97 mmol) in anhydrous THF (420 μL) at rt. After 1 h, the solution was cooled to −78 °C and methyl iodide (160 μL, 2.58 mmol) was added. The resulting solution was warmed to rt over 12 h, and the reaction was quenched by the addition of saturated aqueous NH_4Cl. Water (5 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 6:1 hexane:EtOAc) to afford **5b** as a yellow oil (166 mg, 95%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.66 (d, J = 9.0 Hz, 1H), 6.60 (d, J = 9.0 Hz, 1H), 5.02 (s, 2H), 5.00 (s, 2H), 3.80−3.77 (m, 2H), 3.49 (s, 3H), 3.47 (s, 3H), 2.14 (d, J = 7.1 Hz, 3H), 1.73−1.69 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.5, 148.5, 147.3, 145.6, 126.7, 123.0, 112.8, 110.8, 110.4, 99.2, 57.7, 57.6, 21.2, 10.9, 10.0; IR (film) ν_{max} 2957, 2924, 2853, 1738, 1597, 1487, 1468, 1391, 1335, 1231, 1157, 974, 798 cm^{-1}; HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{14}H_{22}O_5$ 271.1545, found 271.1558.

1,3-Bis(ethoxymethoxy)-4-isopropoxy-2-methylbenzene (5c). A solution of **4c** (190 mg, 0.67 mmol) in anhydrous THF (530 μL) was added dropwise to a solution of ^{n}BuLi (2.5 M in hexanes, 410 μL, 1.00 mmol) in anhydrous THF (440 μL) at rt. After 1 h, the solution was cooled to −78 °C and methyl iodide (170 μL, 2.67 mmol) was added. The resulting solution was warmed to rt over 12 h, and the reaction was quenched by the addition of saturated aqueous NH_4Cl. Water (5 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 6:1 hexane:EtOAc) to afford **5c** as a yellow oil (157 mg, 79%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.70 (d, J = 9.0 Hz, 1H), 6.61 (d, J = 9.0 Hz, 1H), 5.10 (s, 2H), 5.08 (s, 2H), 4.34 (quintet, J = 6.1 Hz, 1H), 3.78 (q, J = 7.1 Hz, 2H), 3.67 (q, J = 7.1 Hz, 2H), 2.13 (s, 3H), 1.23 (d, J = 6.1 Hz, 6H), 1.24−1.15 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.3, 146.6, 145.3, 122.7, 113.7, 110.1, 97.3, 94.0, 71.5, 65.4, 64.2, 29.4, 22.2, 15.2, 15.2, 9.9; IR (film) ν_{max} 2924, 2853, 2359, 2339, 1591, 1483, 1113, 1057, 974 cm^{-1}; HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{16}H_{26}O_5$ 299.1858, found 299.1909.

4-Methoxy-2-methylbenzene-1,3-diol (6a). A solution of **5a** (910 mg, 3.37 mmol) in MeOH (28.0 mL) at rt was treated dropwise with 3 M HCl (9.00 mL, 26.9 mmol), then heated to reflux for 1 h. Water (30 mL) was added and the solution was extracted with EtOAc (3 × 30 mL). Combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 6:1 hexane:EtOAc) to afford **6a** as a red amorphous solid (509 mg, 98%): ^{1}H NMR (aAcetone-d_6, 500 MHz) δ 7.68 (s, 1H), 7.24 (s, 1H), 6.60 (d, J = 11 Hz, 1H), 6.29 (d, J = 11 Hz, 1H), 3.74 (s, 3H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.7, 142.1, 139.7, 115.6, 110.2, 108.6, 55.6, 7.6; IR (film) ν_{max} 3583, 2920, 2359, 1616, 1259, 1090, 1020, 798 cm^{-1}.

2-Methyl-4-propoxybenzene-1,3-diol (6b). A solution of **5b** (580 mg, 2.15 mmol) in MeOH (17.9 mL) was treated dropwise with 3 M HCl (630 μL, 17.2 mmol), then heated to reflux for 1 h. Water (20 mL) was added and the solution was extracted with EtOAc (3 × 20 mL). Combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated to afford **6b** as a red amorphous solid (387 mg, 99%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.51 (d, J = 8.7 Hz, 1H), 6.21 (d, J = 8.6 Hz, 1H), 5.74 (s, 1H), 4.36 (s, 1H), 3.87−3.85 (m, 2H), 2.09 (s, 3H), 1.75−1.71 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.5, 143.8, 139.0, 109.8, 108.4, 103.8, 70.2, 21.6, 9.5, 7.3; IR (film) ν_{max} 3520, 3360, 2966, 2880, 2359, 2341, 1636, 1236, 1068, 785, 750 cm^{-1}.

4-Methoxybenzene-1,3-diol (6c). A solution of **5c** (157 mg, 0.53 mmol) in MeOH (4.40 mL) at rt was treated dropwise with 3 M HCl (1.40 mL, 4.21 mmol), then heated to reflux for 1 h. Water (5 mL) was added and the solution was extracted with EtOAc (3 × 10 mL). Combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated to afford **6c** as a red amorphous solid (95 mg, 99%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.54 (d, J = 8.7 Hz, 1H), 6.21 (d, J = 8.7 Hz, 1H), 5.78 (s, 1H), 4.37−4.32 (m, 1H), 2.09 (s, 3H), 1.25 (d, J = 6.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.7, 144.9, 137.5, 110.8,

109.8, 104.0, 71.7, 21.3 (2C); IR (film) ν_{max} 3526, 2974, 2924, 2853, 1717, 1607, 1475, 1238, 1113, 1067, 928, 887, 791 cm^{-1}.

1-Methoxy-3,5-bis(methoxymethoxy)benzene (8). *N*,*N*-Diisopropylethylamine (3.15 mL, 18.1 mmol) was added to 5-methoxybenzene-1,3-diol (634 mg, 4.52 mmol) in anhydrous *N*,*N*-dimethylformamide (12.6 mL) over 5 min at rt. After 30 min, the solution was cooled to 0 °C, methoxy methylchoride (3.02 mL, 18.1 mmol) was added, and the solution was warmed to rt over 12 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ at 0 °C and extracted with EtOAc (3 × 10 mL). Combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 6:1→ 4:1 hexane:EtOAc) to afford **8** as a yellow amorphous solid (441 mg, 43%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.29 (t, J = 2.2 Hz, 1H), 6.21 (d, J = 2.2 Hz, 2H), 5.07 (s, 4H), 3.69 (s, 3H), 3.40 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.394, 159.0 (2C), 97.2, 96.2 (2C), 94.5 (2C), 56.1, 55.4 (2C); IR (film) ν_{max} 2997, 2955, 2903, 2827, 1601, 1475, 1400, 1215, 1194, 1146, 1032, 991, 924, 829, 685 cm^{-1}; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{11}H_{16}O_5$ 251.0895, found 251.0910.

5-Methoxy-1,3-bis(methoxymethoxy)-2-methylbenzene (9). A solution of **8** (441 mg, 1.93 mmol) in anhydrous THF (1.55 mL) was added dropwise to a solution of ^{n}BuLi (2.5 M in hexanes, 1.16 mL, 2.90 mmol) in anhydrous THF (1.26 mL) at rt. After 1 h, the solution was cooled to −78 °C and methyl iodide (480 μL, 7.73 mmol) was added. The resulting solution was warmed to rt over 12 h, and the reaction was quenched by the addition of saturated aqueous NH_4Cl. Water (5 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 6:1 → 4:1; hexane:EtOAc) to afford **9** as a yellow oil (314 mg, 67%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.38 (d, J = 2.2 Hz, 1H), 6.24 (d, J = 2.1 Hz, 1H), 5.08 (d, J = 3.6 Hz, 2H), 5.06 (d, J = 2.6 Hz, 2H), 3.72 (s, 3H), 3.40 (s, 6H), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.3, 157.8, 155.4, 108.2, 93.9, 93.8, 93.7, 92.9, 55.0, 55.0, 54.6, 7.0; IR (film) ν_{max} 2953, 2934, 2905, 1597, 1497, 1396, 1215, 1144, 1126, 1074, 1059, 1028, 922, 822 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{12}H_{18}O_5$ 243.1233, found 243.1223.

5-Methoxy-2-methylbenzene-1,3-diol (10). A solution of **9** (314 mg, 1.30 mmol) in MeOH (10.8 mL) at rt was treated dropwise with 3 M HCl (3.46 mL, 10.3 mmol), then heated to reflux for 1 h. Water (11 mL) was added and the solution was extracted with EtOAc (3 × 15 mL). Combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated to afford **10** as a red amorphous solid (177 mg, 99%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (s, 1H), 6.09 (d, J = 1.6 Hz, 1H), 6.04 (s, 1H), 3.67 (d, J = 9.9 Hz, 3H), 2.08 (d, J = 4.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.3, 157.8, 155.4, 108.4, 93.9, 93.8, 55.0, 7.0; IR (film) ν_{max} 3445, 2924, 2853, 2359, 2332, 1653, 1636, 1456, 1080, 1022, 798, 669 cm^{-1}; HRMS (ESI$^+$) m/z [2 M + H]$^+$ calcd for $C_8H_{10}O_3$ 309.1338, found 309.1332.

1,3-Bis(methoxymethoxy)benzene (12).[64] Sodium hydride (872 mg, 36.3 mmol) was added to resorcinol (1.00 g, 9.08 mmol) in anhydrous *N*,*N*-dimethylformamide (25.4 mL) at 0 °C. After 30 min, methoxy methylchloride (2.76 mL, 36.3 mmol) was added and the resulting solution was warmed to rt over 12 h. The reaction was cooled to 0 °C, quenched by the addition of saturated aqueous $NaHCO_3$, and extracted with EtOAc (3 × 30 mL). Combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 4:1 hexane:EtOAc) to afford **12** as a yellow oil (1.75 g, 97%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25−7.20 (m, 1H), 6.80 (d, J = 2.3 Hz, 1H), 6.75 (dd, J = 8.2, 2.4 Hz, 2H), 5.20 (s, 4H), 3.51 (s, 6H).

2-Benzyl-1,3-bis(methoxymethoxy)benzene (13). A solution of **12** (500 mg, 2.52 mmol) in anhydrous THF (2.02 mL) was added dropwise to a solution of ^{n}BuLi (2.5 M in hexanes, 1.51 mL, 3.78 mmol) in anhydrous THF (1.65 mL) at rt. After 1 h, the solution was cooled to −40 °C and benzyl bromide (1.22 mL, 10.10 mmol) was added. The resulting solution was warmed to rt over 12 h, and the reaction was quenched by the addition of saturated aqueous NH_4Cl. Water (5 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 4:1; hexane:EtOAc) to afford **13** as a yellow oil (214 mg, 30%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17 (d, J = 7.9 Hz, 2H), 7.17−7.12 (m, 2H), 7.06−7.02 (m, 2H), 6.71 (d, J = 8.3 Hz, 2H), 5.09 (s, 4H), 4.00 (s, 2H), 3.29 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.9 (2C), 141.6, 128.5 (2C), 128.0 (2C), 127.5, 125.4, 119.4, 107.7 (2C), 94.3 (2C), 56.0 (2C), 29.1; IR (film) ν_{max} 2953, 2930, 1595, 1470, 1452, 1254, 1153, 1097, 1043, 941, 922, 727, 698 cm^{-1}; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{17}H_{20}O_4$ 311.1259, found 311.1201.

2-Benzylbenzene-1,3-diol (14).[65] A solution of **13**(214 mg, 0.74 mmol) in MeOH (6.20 mL) was treated dropwise with 3 M HCl (0.22 mL, 5.92 mmol), then heated to reflux for 1 h. Water (10 mL) was added and the solution was extracted with EtOAc (3 × 15 mL). Combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated to afford **14** as a red amorphous solid (149 mg, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (d, J = 6.6 Hz, 4H), 7.25−7.19 (m, 1H), 7.01 (t, J = 8.1 Hz, 1H), 6.44 (d, J = 8.1 Hz, 2H), 4.82 (s, 2H), 4.09 (s, 2H).

2-Iodo-1,3-bis(methoxymethoxy)benzene (15). *n*-Butyllithium (2.5 M in hexanes, 0.22 mL, 0.56 mmol) was added to a solution of **12** (100 mg, 0.50 mmol) in anhydrous THF (790 μL) at 0 °C. After 5 min, iodine (141 mg, 0.56 mmol) in anhydrous THF (320 μL) was added. After 2 h at rt, the reaction was quenched via dropwise addition of MeOH and the solvent was concentrated. Water (5 mL) was added and the solution was extracted with EtOAc (3 × 10 mL). Combined organic fractions were washed with saturated aqueous $Na_2S_2O_3$ and saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated to afford **15** as a brown oil (129 mg, 79%): ^{1}H NMR ($CDCl_3$, 100 MHz) δ 7.25−7.18 (m, 1H), 6.79−6.71 (m, 2H), 5.27 (s, 2H), 5.18 (s, 2H), 3.54 (s, 3H), 3.50 (s, 3H); IR (film) ν_{max} 2953, 2924, 2853, 1458, 1377 cm^{-1}.

2,6-Bis(methoxymethoxy)biphenyl (16). Anhydrous toluene (2.0 mL) was added to a flask charged with $Pd_2(dba)_3$ (56.3 mg, 0.062 mmol), dicyclohexyl(2′,6′-dimethoxybiphenyl-2-yl)phosphine (50.5 mg, 0.12 mmol), phenylboronic acid (281 mg, 2.31 mmol), and potassium phosphate (979 mg, 4.61 mmol) at rt. After 15 min, a solution of **15** (500 mg, 1.54 mmol) in anhydrous toluene (1.0 mL) was added and the resulting solution was heated to reflux for 12 h. Upon cooling to rt, ether was added and the solution was filtered through SiO_2 and concentrated to give **16** as a colorless amorphous solid (418 mg, 99%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.28 (m, 2H), 7.28−7.25 (m, 2H), 7.18−7.15 (m, 2H), 6.83 (d, J = 8.3 Hz, 2H), 4.96 (s, 4H), 3.24 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.3, 155.0, 134.3, 130.8, 129.5, 128.7, 128.0, 127.6, 126.8, 122.6, 109.4 (2C), 94.9 (2C), 56.0 (2C); IR (film) ν_{max} 2955, 2928, 2901, 2359, 2341, 1587, 1466, 1439, 1400, 1244, 1153, 1099, 1080, 1041, 922, 764, 733, 700 cm^{-1}; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{16}H_{18}O_4$ 297.1103, found 297.1052.

Biphenyl-2,6-diol (17).[66] A solution of **16**(400 mg, 1.46 mmol) in MeOH (12.0 mL) at rt was treated dropwise with 3 M HCl (430 μL, 11.7 mmol), then heated to reflux for 1 h. Water (15 mL) was added and the solution was extracted with EtOAc (3 × 20 mL). Combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated to afford **17** as an orange amorphous solid (269 mg, 99%): ^{1}H NMR ($CDCl_3$, 400

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MHz) δ 7.60 (d, J = 7.6 Hz, 2H), 7.53−7.49 (m, 1H), 7.46−7.44 (m, 2H), 7.18 (t, J = 8.2 Hz, 1H), 6.62 (d, J = 8.2 Hz, 2H), 4.84 (s, 1H), 4.83 (s, 1H).

2-Methoxybenzene-1,3-diol (19).[67] Lithium carbonate (281 mg, 1.98 mmol) was added to pyrogallol (100 mg, 0.79 mmol) in *N*,*N*-dimethylformamide (3.0 mL) at rt. After 5 min, methyl iodide (130 μL, 1.98 mmol) was added and the resulting solution was heated to 50 °C for 48 h. Upon cooling to rt, water (20 mL) was added and the solution was extracted with EtOAc (3 × 20 mL). Combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 5:1 → 1:1 hexane:EtOAc) to afford **19** as a colorless amorphous solid (44.2 mg, 34%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.89 (td, J = 8.0, 0.9 Hz, 1H), 6.53 (dd, J = 8.2, 0.8 Hz, 2H), 5.83 (br s, 2H), 3.90 (s, 3H).

Benzyl 7-Hydroxy-6-methoxy-8-methyl-2-oxo-2*H*-chromen-3-ylcarbamate (23a). A solution of **6a** (183 mg, 1.19 mmol) and eneamine **22** (331 mg, 1.19 mmol) in glacial acetic acid (7.40 mL) was heated to reflux for 40 h. Upon cooling to rt, the solution was extracted with EtOAc (3 × 20 mL); combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 100:1 CH_2Cl_2:acetone) to afford **23a** as a yellow amorphous solid (195 mg, 46%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (s, 1H), 7.54 (s, 1H), 7.43−7.37 (m, 4H), 6.77 (s, 1H), 6.07 (s, 1H), 5.25 (s, 2H), 3.96 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.0, 153.3 (2C), 145.7, 144.1, 144.0, 135.7, 128.7, 128.5, 128.2 (2C), 122.5, 121.6, 112.1, 111.6, 104.5, 67.4, 56.3, 8.2; IR (film) ν_{max} 2910, 2359, 2339, 1693, 1537, 1354, 1209, 1078, 1024 cm^{-1}; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{19}H_{17}NO_6$ 378.0954, found 378.0936.

Benzyl 7-Hydroxy-8-methyl-2-oxo-6-propoxy-2*H*-chromen-3-ylcarbamate (23b). A solution of **6b** (390 mg, 2.14 mmol) and eneamine **22** (596 mg, 2.14 mmol) in glacial acetic acid (13.4 mL) was heated to reflux for 36 h. Upon cooling to rt, the precipitated yellow solid was collected by filtration, washed with water, recrystallized from MeOH/water, and extracted with EtOAc (3 × 20 mL). Combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 100:1 CH_2Cl_2:acetone) and recrystallized from MeOH/water to afford **23b** as a yellow amorphous solid (278 mg, 34%): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.26 (s, 1H), 7.56 (s, 1H), 7.47−7.38 (m, 5H), 6.84 (s, 1H), 6.28 (s, 1H), 5.25 (s, 2H), 4.09 (t, J = 6.6 Hz, 2H), 2.36 (s, 3H), 1.93−1.88 (m, 2H), 1.10 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.0, 152.2, 144.9, 142.9, 142.3, 134.6, 129.0, 127.6, 127.5 (2C), 127.2 (2C), 121.5, 120.5, 110.9, 110.5, 104.4, 69.8, 66.3, 21.4, 9.4, 7.1; IR (film) ν_{max} 2957, 2920, 2851, 2359, 2341, 1693, 1537, 1358, 1277, 1080, 1024, 910 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{21}H_{21}NO_6$ 384.1447, found 384.1447.

Benzyl 7-Hydroxy-6-isopropoxy-8-methyl-2-oxo-2*H*-chromen-3-ylcarbamate (23c). A solution of **6c** (142 mg, 0.78 mmol) and eneamine **22** (217 mg, 0.78 mmol) in glacial acetic acid (4.90 mL) was heated to reflux for 40 h. Upon cooling to rt, the solution was extracted with EtOAc (3 × 10 mL); combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford **23c** as a yellow amorphous solid (159 mg, 53%): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.26 (s, 1H), 7.56 (s, 1H), 7.44−7.38 (m, 5H), 6.85 (s, 1H), 6.31 (s, 1H), 5.25 (s, 2H), 4.66 (quintet, J = 6.1 Hz, 1H), 2.35 (s, 3H), 1.42 (d, J = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 154.9, 146.7, 143.9 (2C), 142.0, 135.7, 128.7 (2C), 128.5 128.2 (2C), 122.6 (2C), 111.6, 107.0, 72.3, 67.4, 22.1 (2C), 8.2; IR (film) ν_{max} 3400, 2924, 2853, 2359, 1817, 1699, 1524, 1412, 1354, 1300, 1221, 1204, 1113, 1076, 1022, 824 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{21}H_{21}NO_6$ 384.1447, found 384.1452.

(67) Green, K. *J. Org. Chem.* **1991**, *56*, 4325–4326.

Benzyl 7-Hydroxy-5-methoxy-8-methyl-2-oxo-2*H*-chromen-3-ylcarbamate (23d). A solution of **10** (251 mg, 1.63 mmol) and eneamine **22** (680 mg, 2.44 mmol) in glacial acetic acid (10.2 mL) was heated to reflux for 40 h. Upon cooling to rt, the solution was extracted with EtOAc (3 × 15 mL); combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 40:1 → 20:1; CH_2Cl_2:acetone) to afford **23d** as a yellow amorphous solid (204 mg, 35%): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.48 (s, 1H), 7.46−7.38 (m, 6H), 6.38 (s, 1H), 5.25 (s, 2H), 5.15 (s, 1H), 3.87 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 155.8, 154.3, 153.2, 149.8, 137.0, 128.7, 128.6, 128.6, 128.2, 128.2, 109.3, 109.0, 108.5, 105.6, 96.9, 70.8, 60.2, 7.3; IR (film) ν_{max} 3406, 2935, 2837, 1713, 1670, 1607, 1529, 1501, 1364, 1242, 1101, 1051, 991, 966, 735 cm^{-1}; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{19}H_{17}NO_6$ 378.0954, found 378.0974.

Benzyl 8-Benzyl-7-hydroxy-2-oxo-2*H*-chromen-3-ylcarbamate (23e). A solution of **14** (115 mg, 0.57 mmol) and eneamine **22** (160 mg, 0.57 mmol) in glacial acetic acid (4.00 mL) was heated to reflux for 40 h. Upon cooling to rt, the solution was extracted with EtOAc (3 × 10 mL); combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 100:1; CH_2Cl_2:acetone), followed by recrystallization from MeOH to afford **23e** as an orange amorphous solid (296 mg, 48%): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.29 (s, 1H), 7.53 (s, 1H), 7.46−7.38 (m, 4H), 7.37−7.27 (m, 4H), 7.23−7.19 (m, 2H), 7.01 (t, J = 8.1 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.46 (d, J = 8.1 Hz, 1H), 5.25 (s, 2H), 4.25 (s, 2H), 4.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.7, 154.3, 153.9, 152.2, 148.0, 137.9, 134.5, 127.6, 127.6, 127.6, 127.6, 127.5, 127.3, 127.2, 127.4, 126.6, 125.4, 125.3, 121.4, 120.4, 114.0, 112.6, 66.5, 27.5; IR (film) ν_{max} 3381, 2957, 2928, 2359, 2341, 1693, 1607, 1526, 1466, 1454, 1383, 1366, 1219, 1204, 1076, 1045, 764, 737, 700 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{24}H_{19}NO_5$ 402.1341, found 402.1341.

Benzyl 7-Hydroxy-2-oxo-8-phenyl-2*H*-chromen-3-ylcarbamate (23f). A solution of **17** (400 mg, 2.15 mmol) and eneamine **22** (598 mg, 2.15 mmol) in glacial acetic acid (14.3 mL) was heated to reflux for 40 h. Upon cooling to rt, the solution was extracted with EtOAc (3 × 30 mL); combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 100:1; CH_2Cl_2:acetone), then recrystallized from MeOH to afford **23f** as an orange amorphous solid (264 mg, 27%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.25 (s, 1H), 7.51−7.48 (m, 2H), 7.43−7.40 (m, 2H), 7.35−7.29 (m, 8H), 6.94 (d, J = 8.6 Hz, 1H), 5.16 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.5 (2C), 154.3, 153.2, 147.7, 135.6, 130.9, 130.6, 130.5, 129.8, 129.4, 129.2 (2C), 128.7 (2C), 128.6, 128.3, 127.8, 122.2, 121.6, 113.3, 113.5, 67.5; IR (film) ν_{max} 3398, 2957, 2926, 2854, 1815, 1699, 1601, 1524, 1383, 1366, 1308, 1215, 1045, 1009, 764, 750, 698 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{23}H_{17}NO_5$ 388.1185, found 388.1214.

Benzyl 7-Hydroxy-8-methoxy-2-oxo-2*H*-chromen-3-ylcarbamate (23g). A solution of **19** (1.10 g, 7.86 mmol) and eneamine **22** (2.18 g, 7.86 mmol) in glacial acetic acid (60.0 mL) was heated to reflux for 90 h. Upon cooling to rt, the solution was extracted with EtOAc (3 × 50 mL); combined organic fractions were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 11:1; hexane:EtOAc → EtOAc) then recrystallized from MeOH/water to afford **23g** as a colorless amorphous solid (207 mg, 7.7%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (s, 1H), 7.50 (s, 1H), 7.43−7.36 (m, 5H), 7.13 (d, J = 8.6 Hz, 1H), 6.97 (d, J = 7.9 Hz, 1H), 6.04 (s, 1H), 5.21 (s, 2H), 4.13 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 157.3, 153.3, 151.5 (2C), 144.1, 136.5, 134.4, 128.4 (2C), 128.1, 128.0 (2C), 122.7, 121.6, 113.6, 113.2, 66.7, 60.7; IR (film) ν_{max} 2920, 2851, 2405, 2357, 1707, 1605, 1522, 1458, 1385, 1364, 1275, 1259, 1213, 1088, 1047, 750 cm^{-1}; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{18}H_{15}NO_6$ 364.0797, found 364.0776.

Benzyl 8-Ethyl-7-hydroxy-2-oxo-2*H*-chromen-3-ylcarbamate (23h). A solution of **21** (1.40 g, 10.1 mmol) and eneamine **22** (2.80 g, 10.1 mmol) in glacial acetic acid (50.0 mL) was heated to reflux for 12 h. Upon cooling to rt, the solvent was concentrated. The residue was purified via column chromatography (SiO_2, 4:1 → 2:1; hexane:EtOAc), then recrystallized from acetone/hexanes to afford **23h** as a colorless amorphous solid (600 mg, 17%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.07 (s, 1H), 8.12 (s, 1H), 7.46−7.32 (m, 6H), 6.86 (d, J = 8.4 Hz, 1H), 5.18 (s, 2H), 2.72 (q, J = 7.6 Hz, 2H), 1.11 (t, J = 7.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 158.0, 157.1, 153.8 (2C), 149.5, 136.4, 128.4 (2C), 127.9, 127.8, 127.2, 125.8, 120.4, 116.6, 112.8, 111.4, 66.1, 15.7, 13.5; IR (film) ν_{max} 3391, 3339, 2964, 2870, 2357, 1732, 1682, 1620, 1524, 1506, 1454, 1364, 1277, 1188, 1097, 1024, 752, 698 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{19}H_{17}NO_5$ 340.1185, found 340.1181.

Benzyl 6-Methoxy-7-((3a*R*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxotetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4-yloxy)-8-methyl-2-oxo-2*H*-chromen-3-ylcarbamate (25a). Boron trifluoride etherate (5.30 μL, 0.042 mmol) was added to **23a** (50.0 mg, 0.14 mmol) and (3a*R*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3a*H*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (171 mg, 0.47 mmol) in anhydrous CH_2Cl_2 (3.00 mL). After stirring at rt for 14 h, triethylamine (150 μL) was added and the solvent was concentrated. The residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to give **25a** as a colorless foam (74.0 mg, 95%): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.29 (s, 1H), 7.64 (s, 1H), 7.47−7.39 (m, 5H), 6.91 (s, 1H), 5.52 (d, J = 3.4 Hz, 1H), 5.26 (s, 2H), 5.23 (dd, J = 8.4, 3.5 Hz, 1H), 4.95 (t, J = 8.2 Hz, 1H), 3.92 (s, 3H), 3.60 (s, 3H), 3.33 (d, J = 8.0 Hz, 1H), 2.42 (s, 3H), 1.38 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.6, 152.7, 152.1, 148.1, 144.8, 141.8, 134.5, 127.8, 127.7, 127.5, 127.3, 122.3, 120.2, 119.8, 115.1. 109.6, 105.2, 98.3, 82.0, 77.1, 66.5, 65.5, 59.4, 57.4, 55.1, 26.0, 20.9, 8.9; IR (film) ν_{max} 2957, 2928, 2854, 2359, 2341, 1817, 1709, 1522, 1464, 1389, 1371, 1205, 1174, 1111, 1072, 1034, 957, 800 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{28}H_{29}NO_{11}$ 556.1819, found 556.1822.

Benzyl 7-((3a*R*,4*S*,7*R*,7a*R*)-7-Methoxy-6,6-dimethyl-2-oxotetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4-yloxy)-8-methyl-2-oxo-6-propoxy-2*H*-chromen-3-ylcarbamate (25b). Boron trifluoride etherate (16.7 μL, 0.13 mmol) was added to **23b** (170 mg, 0.44 mmol) and (3a*R*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3a*H*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (643 mg, 1.77 mmol) in anhydrous CH_2Cl_2 (11.1 mL). After stirring at rt for 48 h, triethylamine (150 μL) was added and the solvent was concentrated. The residue was purified via column chromatography (SiO_2, 100:1 → 40:1 CH_2Cl_2:acetone) to give **25b** as a colorless foam (246 mg, 95%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (s, 1H), 7.35−7.27 (m, 5H), 6.84 (s, 1H), 5.96 (s, 1H), 5.15 (s, 2H), 4.99 (d, J = 7.5 Hz, 1H), 4.59 (d, J = 9.7 Hz, 1H), 4.23 (d, J = 9.6 Hz, 1H), 3.97 (t, J = 6.6 Hz, 1H), 3.82−3.75 (m, 2H), 3.37 (s, 3H), 1.84−1.79 (m, 2H), 1.51 (s, 3H), 1.41 (s, 3H), 1.18 (s, 3H), 1.00 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.8, 154.3, 152.2, 151.8, 146.7, 144.2, 142.9, 134.6, 127.8, 127.6, 127.5, 127.5, 127.2, 121.0, 120.9, 111.1, 105.3, 101.7, 91.6, 85.7, 82.8, 80.0, 69.8, 58.1, 54.8, 28.3, 28.2, 22.4, 21.3, 9.4; IR (film) ν_{max} 2961, 2939, 2906, 2359, 2341, 1811, 1757, 1726, 1522, 1445, 1371, 1267, 1175, 1113, 1086, 825, 768 cm^{-1}; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{30}H_{33}NO_{11}$ 606.1952, found 606.1950.

Benzyl 6-Isopropoxy-7-((3a*R*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxotetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4-yloxy)-8-methyl-2-oxo-2*H*-chromen-3-ylcarbamate (25c). Boron trifluoride etherate (1.30 μL, 0.010 mmol) was added to **23c** (13.0 mg, 0.034 mmol) and (3a*R*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3a*H*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (83.0 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (1.30 mL). After stirring at rt for 1.5 h, triethylamine (150 μL) was added and the solvent was concentrated. The residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to give **25c** as a colorless foam (19.0 mg, 95%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (s, 1H), 7.51 (s, 1H), 7.35 (s, 1H), 7.34−7.33 (m, 4H), 6.74 (s, 1H), 5.54 (dd, J = 9.2, 1.2 Hz, 1H), 5.16 (s, 2H), 4.87−4.84 (m, 1H), 4.73 (dd, J = 7.9, 1.9 Hz, 1H), 4.51 (quintet, J = 6.0 Hz, 1H), 3.52 (s, 3H), 3.28 (d, J = 4.8 Hz, 1H), 2.33 (s, 3H), 1.80−1.77 (m, 6H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.6, 158.6, 153.2 153.1, 147.1, 146.8, 142.5, 135.5, 128.7, 128.6, 128.3, 123.3, 121.4, 121.1, 116.2, 108.6, 99.4, 83.1, 79.9, 76.1, 74.7, 72.2, 68.0, 60.5, 27.1, 25.6, 21.9, 21.6, 21.0, 10.1; IR (film) ν_{max} 2955, 2922, 2853, 2359, 2339, 1819, 1711, 1520, 1464, 1375, 1171, 1111, 1034, 962, 822, 766 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{30}H_{33}NO_{11}$ 584.2132, found 584.2111.

Benzyl 5-Methoxy-7-((3a*R*,4*R*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxotetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4-yloxy)-8-methyl-2-oxo-2*H*-chromen-3-ylcarbamate (25d). Boron trifluoride etherate (18.5 μL, 0.15 mmol) was added to **23d** (174 mg, 0.49 mmol) and (3a*R*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3a*H*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (621 mg, 1.71 mmol) in anhydrous CH_2Cl_2 (11.0 mL). After stirring at rt for 14 h, triethylamine (150 μL) was added and the solvent was concentrated. The residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to give **25d** as a colorless foam (200 mg, 74%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.49 (s, 1H), 7.34−7.27 (m, 5H), 6.67 (s, 1H), 6.60 (s, 1H), 5.69 (s, 2H), 5.16 (d, J = 5.3 Hz, 1H), 4.89 (t, J = 7.8 Hz, 1H), 4.63 (dd, J = 7.9, 2.4 Hz, 1H), 3.83 (s, 3H), 3.37 (s, 3H), 3.15 (d, J = 8.0 Hz, 1H), 2.16 (s, 3H), 2.16 (s, 3H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.9, 156.0, 155.2, 154.2, 153.1 (2C), 149.4, 135.7, 128.7 (2C), 128.5, 128.2 (2C), 120.8, 117.4, 106.6, 105.4, 94.6, 94.1, 82.9, 67.4, 60.6, 60.6, 56.1, 56.0, 22.2, 22.0, 7.9; IR (film) ν_{max} 2955, 2924, 2853, 1817, 1713, 1526, 1209, 1105, 1072, 1034, 976, 808 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{28}H_{29}NO_{11}$ 556.1819, found 556.1826.

Benzyl 8-Benzyl-7-((3a*R*,4*R*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxotetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4-yloxy)-2-oxo-2*H*-chromen-3-ylcarbamate (25e). Boron trifluoride etherate (7.80 μL, 0.062 mmol) was added to **23e** (80.0 mg, 0.21 mmol) and (3a*R*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3a*H*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (299 mg, 0.83 mmol) in anhydrous CH_2Cl_2 (5.20 mL). After stirring at rt for 48 h, triethylamine (150 μL) was added and the solvent was concentrated. The residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to give **25e** as a colorless foam (47.0 mg, 39%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (s, 1H), 7.46 (s, 1H), 7.35−7.27 (m, 5H), 7.17−7.06 (m, 5H), 6.86 (d, J = 10 Hz, 1H), 6.01 (d, J = 10 Hz, 1H), 5.65 (d, J = 1.6 Hz, 1H), 5.23 (s, 2H), 5.16 (s, 2H), 4.77−4.70 (m, 1H), 4.10 (s, 1H), 3.50 (s, 3H), 3.28 (s, 1H), 3.16 (d, J = 7.4 Hz, 1H), 1.25 (s, 3H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.1, 153.2 (2C), 153.1, 148.6 (2C), 139.6 (2C), 128.7, 128.6 (2C), 128.4 (2C), 128.3 (2C), 128.3 (2C), 126.5, 126.2, 123.1, 122.4, 121.7, 117.6, 114.9, 111.5, 94.7, 82.8, 67.6, 60.6 (2C), 29.7, 27.6, 21.9; IR (film) ν_{max} 2926, 2854, 2359, 2341, 1811, 1709, 1607, 1522, 1456, 1381, 1366, 1259, 1209, 1171, 1078, 1049, 968, 766, 700 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{33}H_{31}NO_{10}$ 602.2026, found 602.2053.

Benzyl 7-((3a*R*,4*R*,7*R*,7a*R*)-7-Methoxy-6,6-dimethyl-2-oxotetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4-yloxy)-2-oxo-8-phenyl-2*H*-chromen-3-ylcarbamate (25f). Boron trifluoride etherate (14.6 μL, 0.12 mmol) was added to **23f** (155 mg, 0.39 mmol) and (3a*R*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3a*H*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (560 mg, 1.55 mmol) in anhydrous CH_2Cl_2(9.70 mL). After stirring at rt for 48 h, triethylamine (150 μL) was added and the solvent was concentrated. The residue was purified via column chromatography (SiO_2, 100:1 → 40:1 CH_2Cl_2:acetone) to give **25f** as a colorless foam (225 mg, 99%): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.37 (s, 1H), 7.75−7.73 (m, 2H), 7.60−7.36 (m, 10H), 7.32 (d, J = 8.8 Hz, 1H), 5.77 (d, J = 1.7 Hz, 1H), 5.26 (s, 2H), 4.76−4.68 (m, 1H), 4.36−4.28 (m, 1H), 3.56 (s, 3H), 3.28 (d, J = 7.2 Hz, 1H), 1.37 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

157.2, 153.0 (2C), 152.1 (2C), 152.1, 134.4, 129.9, 129.8, 129.4, 127.7 (2C), 127.5, 127.2 (2C), 127.1 (2C), 127.0, 126.3, 121.5 (2C), 120.3, 111.2 (2C), 93.9, 81.9, 66.5, 59.4 (3C), 20.9 (2C); IR (film) ν_{max} 3400, 2959, 2926, 2853, 2359, 2341, 1819, 1715, 1601, 1522, 1381, 1366, 1261, 1215, 1173, 1111, 1059, 970, 800, 700 cm^{-1}; HRMS (ESI$^+$) *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{29}NO_{10}$ 588.1870, found 588.1846.

Benzyl 8-Methoxy-7-((3a*R*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxotetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4-yloxy)-2-oxo-2*H*-chromen-3-ylcarbamate (25g). Boron trifluoride etherate (17.3 μL, 0.14 mmol) was added to **23g** (157 mg, 0.46 mmol) and (3*aR*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3a*H*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (665 mg, 1.83 mmol) in anhydrous CH_2Cl_2 (11.5 mL). After stirring at rt for 24 h, triethylamine (150 μL) was added and the solvent was concentrated. The residue was purified via column chromatography (SiO_2, 40:1 → 10:1 CH_2Cl_2:acetone) to give **25g** as a colorless foam (237 mg, 95%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (s, 1H), 7.48 (s, 1H), 7.33−7.29 (m, 5H), 7.09 (dd, J = 14.2, 8.8 Hz, 2H), 5.72 (d, J = 1.8 Hz, 1H), 5.16 (s, 2H), 5.02 (dd, J = 7.8, 1.8 Hz, 1H), 4.89 (t, J = 7.8 Hz, 1H), 3.88 (s, 3H), 3.52 (s, 3H), 3.21 (d, J = 7.8 Hz, 1H), 1.27 (s, 3H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.0, 153.3, 153.2, 153.1, 149.8, 143.8, 137.1, 135.5, 128.7 (2C), 128.6, 128.3 (2C), 122.7, 122.2, 121.4, 116.1, 113.7, 95.3, 74.7, 72.9, 67.6, 61.9, 60.7, 60.6, 29.7, 29.4; IR (film) ν_{max} 3400, 3319, 2984, 2935, 2359, 1815, 1715, 1609, 1526, 1464, 1383, 1364, 1285, 1213, 1175, 1111, 1063, 968, 764, 737, 700 cm^{-1}; HRMS (ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{27}NO_{11}$ 564.1482, found 564.1455.

Benzyl 8-Ethyl-7-((3a*R*,4*R*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxotetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4-yloxy)-2-oxo-2*H*-chromen-3-ylcarbamate (25h). Boron trifluoride etherate (19.0 μL, 0.15 mmol) was added to **23h** (171 mg, 0.51 mmol) and (3*aR*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3a*H*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (183 mg, 0.51 mmol) in anhydrous CH_2Cl_2 (11.0 mL). After stirring at rt for 24 h, triethylamine (150 μL) was added and the solvent was concentrated. The residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to give **25h** as a colorless foam (138 mg, 51%): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.29 (s, 1H), 7.62 (s, 1H), 7.47−7.38 (m, 5H), 7.36 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 5.81 (d, J = 2.4 Hz, 1H), 5.25 (s, 2H), 5.10 (dd, J = 8.0, 2.0 Hz, 1H), 5.02 (t, J = 7.8 Hz, 1H), 3.55 (s, 3H), 3.41 (d, J = 7.2 Hz, 1H), 2.87 (q, J = 7.4 Hz, 2H), 1.42 (s. 3H), 1.28 (s, 3H), 1.21 (t, J = 7.4 Hz, 3H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 158.5, 154.8, 153.2, 153.1, 148.4, 136.0, 128.6 (2C), 128.4, 128.1, 125.6, 122.4, 121.5, 120.7, 114.8, 111.4, 94.8, 82.7, 77.9, 77.2, 76.6, 67.3, 60.3, 27.3, 22.3, 16.4, 13.6; IR (film) ν_{max} 3400, 2980, 2937, 2359, 2339, 1817, 1711, 1607, 1524, 1383, 1366, 1227, 1205, 1175, 1101, 1040, 906, 768, 737, 700 cm^{-1}; [M + Na]$^+$ calcd for $C_{28}H_{29}NO_{10}$ 562.1689, found 562.1689.

***N*-(7-((2*S*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2*H*-chromen-3-yl)-3′,6-dimethoxybiphenyl-3-carboxamide (26a).** Palladium on carbon (10%, 20.0 mg) was added to **25a** (100 mg, 0.18 mmol) in anhydrous THF (5.00 mL) and the solution was placed under an atmosphere of H_2. After 6.5 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (56.0 mg, 75%).

EDCI (21.4 mg, 0.11 mmol) and 3′,6-dimethoxybiphenyl-3-carboxylic acid (23.1 mg, 0.089 mmol) were added to the amine (18.7 mg, 0.045 mmol) in 30% pyridine/CH_2Cl_2 (0.70 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (10.5 mg, 36%).

Triethylamine (150 μL) was added to the carbonate (10.4 mg, 0.016 mmol) in MeOH (2.50 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 20:1; CH_2Cl_2:MeOH) to afford **26a** as a colorless amorphous solid (2.00 mg, 20%, 5% over 3 steps): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.73 (s, 1H), 8.70 (d, J = 5.4 Hz, 1H), 7.84 (td, J = 6.2, 2.4 Hz, 1H), 7.82 (s, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 7.03−7.00 (m, 2H), 6.88−6.86 (m, 1H), 6.81 (s, 1H), 4.99 (d, J = 6.6 Hz, 1H), 4.24 (t, J = 4.2 Hz, 1H), 4.00 (dd, J = 6.5, 3.7 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.80 (d, J = 7.4 Hz, 1H), 3.45 (s, 3H), 3.08 (d, J = 4.7 Hz, 1H), 2.67 (s, 1H), 2.42 (s, 3H), 1.28 (d, J = 8.1 Hz, 3H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.6, 158.9, 158.3, 158.2, 148.2, 145.6, 142.5, 137.5, 130.1, 129.0, 128.2, 127.2, 124.9, 122.5, 122.2, 121.2, 121.0, 115.1, 144.2, 112.1, 110.0, 105.4, 101.3, 81.7, 76.8, 69.0, 68.0, 59.1, 55.3, 54.9, 54.3, 28.3, 28.2, 9.1; IR (film) ν_{max} 2961, 2928, 1713, 1670, 1601, 1464, 1383, 1261, 1094, 1022, 798, 700 cm^{-1}; HRMS (ESI$^+$) *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{37}NO_{11}$ 636.2445, found 636.2477.

***N*-(7-((2*S*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-8-methyl-2-oxo-6-propoxy-2*H*-chromen-3-yl)-3′,6-dimethoxybiphenyl-3-carboxamide (26b).** Palladium on carbon (10%, 85.0 mg) was added to **25b** (425 mg, 0.7283 mmol) in anhydrous THF (4.90 mL) and the solution was placed under an atmosphere of H_2. After 6.5 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (325 mg, 99%).

EDCI (116 mg, 0.60 mmol) and 3′,6-dimethoxybiphenyl-3-carboxylic acid (125 mg, 0.4821 mmol) were added to the amine (108 mg, 0.2410 mmol) in 30% pyridine/CH_2Cl_2 (6.70 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 3:1 hexane:ether → 20:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (51.0 mg, 31%).

Triethylamine (150 μL) was added to the carbonate (51.0 mg, 0.074 mmol) in MeOH (2.50 mL). After 48 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford **26b** as a colorless amorphous solid (22.8 mg, 47%, 14% over 3 steps): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.79 (s, 1H), 8.78 (s, 1H), 7.96 (dd, J = 8.6, 2.4 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.16−7.11 (m, 2H), 6.97−6.94 (m, 2H), 5.97 (s, 1H), 5.14 (d, J = 6.5 Hz, 1H), 4.31 (t, J = 3.5 Hz, 1H), 4.12−4.06 (m, 2H), 4.03 (dd, J = 6.8, 1.8 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.65 (s, 1H), 3.53 (s, 3H), 3.17 (d, J = 4.8 Hz, 1H), 2.80 (s, 1H), 2.48 (s, 3H), 1.95−1.90 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H), 1.11 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.0, 164.6, 158.8, 158.3, 147.7, 145.7, 142.3, 137.8, 137.5, 131.3, 129.0, 128.2, 127.2, 124.9, 122.3, 121.2, 121.0, 115.111, 114.2, 112.1, 110.0, 106.2, 101.1, 81.7, 70.0, 69.0, 68.0, 64.8, 59.1, 54.9, 54.3, 24.7, 24.0, 21.3, 9.5, 9.1; IR (film) ν_{max} 3398, 3196, 2964, 2935, 2359, 2330, 1705, 1580, 1526, 1504, 1381, 1242, 1124, 1094, 939, 808, 760, 735 cm^{-1}; HRMS (ESI$^+$) *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{41}NO_{11}$ 664.2758, found 664.2754.

***N*-(7-((2*S*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-6-isopropoxy-8-methyl-2-oxo-2*H*-chromen-3-yl)-3′,6-dimethoxybiphenyl-3-carboxamide (26c).** Palladium on carbon (10%, 11 mg) was added to **25c** (54.5 mg, 0.093 mmol) in anhydrous THF (600 μL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:Acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (42.0 mg, 99%).

EDCI (14.9 mg, 0.078 mmol) and 3′,6-dimethoxybiphenyl-3-carboxylic acid (16 mg, 0.062 mmol) were added to the amine (14.0 mg, 0.031 mmol) in 30% pyridine/CH_2Cl_2 (900 μL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 3:1 hexane:ether → 40:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (17.5 mg, 82%).

Triethylamine (150 μL) was added to the carbonate (17.5 mg, 0.025 mmol) in MeOH (2.50 mL) and CH_2Cl_2 (2.50 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 10:1 CH_2Cl_2:acetone) to afford **26c** as a colorless amorphous solid (6.0 mg, 35%, 28% over 3 steps): ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 8.69 (s, 1H), 8.67 (s, 1H), 7.84 (dd, J = 8.6, 2.4 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 7.9 Hz, 1H), 7.03−7.01 (m, 2H), 6.87 (s, 1H), 6.87−6.83 (m, 1H), 4.96 (d, J = 6.8 Hz, 1H), 4.61−4.56 (m, 1H), 4.19 (t, J = 4.0 Hz, 1H), 3.89 (dd, J = 6.8, 3.7 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.75 (s, 1H), 3.41 (s, 3H), 3.34 (s, 1H), 3.03 (d, J = 4.5 Hz, 1H), 2.36 (s, 3H), 1.33 (t, J = 6.2 Hz, 6H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 164.6, 159.1, 158.6, 158.3, 146.7, 146.3, 142.5, 138.1, 130.2, 129.1, 128.3, 127.4, 125.2, 122.8, 122.2, 121.2, 121.1, 115.5, 144.5, 112.1, 110.2, 108.4, 101.4, 81.9, 77.0, 71.1, 69.2, 68.3, 59.1, 55.1, 54.5, 28.7, 28.6, 20.8, 20.8, 9.1; IR (film) ν_{max} 2924, 2854, 2359, 2341, 1734, 1684, 1653, 1558, 1541, 1522, 1506, 1458, 1387, 1339, 1286, 1244, 1113, 912, 797 cm^{-1}; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{36}H_{41}NO_{11}$ 686.2578, found 686.2610.

***N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-5-methoxy-8-methyl-2-oxo-2*H*-chromen-3-yl)-3′,6-dimethoxybiphenyl-3-carboxamide (26d).** Palladium on carbon (10%, 40 mg) was added to **25d** (200 mg, 0.36 mmol) in anhydrous THF (2.40 mL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (150 mg, 99%).

EDCI (57.5 mg, 0.30 mmol) and 3′,6-dimethoxybiphenyl-3-carboxylic acid (62 mg, 0.24 mmol) were added to the amine (50.6 mg, 0.12 mmol) in 30% pyridine/CH_2Cl_2 (3.30 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 3:1 hexane:ether → 40:1 → 10:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (25.2 mg, 32%).

Triethylamine (150 μL) was added to the carbonate (25.2 mg, 0.038 mmol) in MeOH (2.0 mL) and CH_2Cl_2 (2.0 mL). After 48 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford **26d** as a colorless amorphous solid (17.0 mg, 70%, 22% over 3 steps): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 9.02 (s, 1H), 8.97 (s, 1H), 8.66 (s, 1H), 7.96 (dd, J = 8.6, 2.4 Hz, 1H), 7.91−7.90 (m, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.16−7.11 (m, 2H), 6.96 (dd, J = 8.3, 2.6 Hz), 6.85 (d, J = 5.5 Hz, 1H), 5.70 (d, J = 2.1 Hz, 1H), 4.36−4.33 (m, 1H), 4.27 (m, 1H), 3.99 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H), 3.62 (s, 3H), 3.41−3.38 (m, 1H), 2.24 (s, 3H), 1.41 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.2, 158.7, 158.6, 158.3, 155.3, 153.5, 148.6, 137.6, 129.9, 128.9, 128.1, 127.1, 125.1, 121.0, 119.4, 118.9, 114.2, 114.2, 112.1, 110.0, 104.9, 103.7, 96.7, 92.9, 83.2, 70.1, 67.5, 60.9, 60.8, 54.8, 54.3, 21.9, 21.4, 6.8; IR (film) ν_{max} 3405, 2986, 2934, 1713, 1609, 1528, 1383, 1250, 1213, 1053, 999, 914, 878, 737 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{34}H_{37}NO_{11}$ 636.2445, found 636.2482.

***N*-(8-Benzyl-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-2-oxo-2*H*-chromen-3-yl)-3′,6-dimethoxybiphenyl-3-carboxamide (26e).** Palladium on carbon (10%, 46 mg) was added to **25e** (230 mg, 0.38 mmol) in anhydrous THF (2.50 mL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (177 mg, 99%).

EDCI (61.5 mg, 0.32 mmol) and 3′,6-dimethoxybiphenyl-3-carboxylic acid (66.3 mg, 0.26 mmol) were added to the amine (60.0 mg, 0.13 mmol) in 30% pyridine/CH_2Cl_2 (3.50 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 3:1 hexane:ether → 20:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (12.3 mg, 14%).

Triethylamine (150 μL) was added to the carbonate (12.3 mg, 0.017 mmol) in MeOH (1.5 mL) and CH_2Cl_2 (1.5 mL). After 48 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford **26e** as a colorless amorphous solid (6.00 mg, 51%, 7.1% over 3 steps): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.84 (s, 1H), 8.72 (s, 1H), 7.96 (dd, J = 10, 2.4 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.28−7.25 (m, 5H), 7.21−7.18 (m, 1H), 7.15−7.11 (m, 2H), 6.97−6.94 (m, 1H), 5.54 (d, J = 2.7 Hz, 1H), 4.25 (t, J = 15.1 Hz, 2H), 4.17−4.11 (m, 1H), 4.05 (d, J = 2.6 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.58 (s, 3H), 3.31 (d, J = 8.7 Hz, 1H), 2.64 (s, 1H), 2.04 (s, 1H), 1.40 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.5, 159.8, 159.3, 159.3, 156.4, 148.9, 140.0 (2C), 138.6, 131.1, 130.0, 129.2, 128.5, 128.3, 128.2, 127.0, 126.2 (2C), 126.0 (2C), 124.1, 122.2, 122.0, 117.2, 115.2, 114.4, 113.2, 111.7, 111.0, 98.0, 70.6 (2C), 68.6, 61.6, 55.9, 55.4, 29.3, 28.9, 28.3; IR (film) ν_{max} 3404, 2930, 2359, 2341, 1713, 1670, 1605, 1526, 1502, 1367, 1244, 1180, 1134, 1076, 1026, 960 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{39}H_{39}NO_{10}$ 682.2652, found 682.2653.

***N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-2-oxo-8-phenyl-2*H*-chromen-3-yl)-3′,6-dimethoxybiphenyl-3-carboxamide (26f).** Palladium on carbon (10%, 14 mg) was added to **25f** (68.0 mg, 0.12 mmol) in anhydrous THF (800 μL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (52.0 mg, 99%).

EDCI (18.5 mg, 0.096 mmol) and 3′,6-dimethoxybiphenyl-3-carboxylic acid (19.9 mg, 0.077 mmol) were added to the amine (17.5 mg, 0.039 mmol) in 30% pyridine/CH_2Cl_2 (1.10 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (14.0 mg, 52%).

Triethylamine (150 μL) was added to the carbonate (14.0 mg, 0.020 mmol) in MeOH (1.5 mL) and CH_2Cl_2 (1.5 mL). After 48 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford **26f** as a colorless amorphous solid (5.20 mg, 39%, 20% over 3 steps): ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 8.85 (s, 1H), 8.65 (s, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.90 (d, J = 2.4 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.57−7.43 (m, 3H), 7.36−7.33 (m, 4H), 7.11−7.06 (m, 3H), 6.92 (d, J = 0.8 Hz, 1H), 5.52 (d, J = 2.4 Hz, 1H), 4.08 (q, J = 7.2, Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.74 (dd, J = 9.0, 3.5 Hz, 1H), 3.50 (s, 3H), 3.23 (d, J = 9.0 Hz, 1H), 2.12 (s, 1H), 2.00 (s, 1H), 1.33 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 164.5, 159.0 (2C), 158.6, 158.1, 154.4, 147.2, 138.0 (2C), 130.7, 130.1, 129.7, 129.1, 128.7, 128.3, 127.4, 127.2, 127.0, 127.0, 125.2, 122.6, 121.6, 121.1, 118.6, 114.5, 113.8, 112.1, 111.3, 110.2, 97.5, 70.1 (2C), 67.4, 60.8, 55.0, 54.5, 21.9, 21.6; IR (film) ν_{max} 3402, 2932, 2359, 2341, 1713, 1603, 1524, 1500, 1367, 1267, 1086, 1040, 964, 750 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{38}H_{37}NO_{10}$ 668.2496, found 668.2485.

***N*-(7-((2*S*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-8-methoxy-2-oxo-2*H*-chromen-3-yl)-3′,6-dimethoxybiphenyl-3-carboxamide (26g).** Palladium on carbon (10%, 47 mg) was added to **25g** (237 mg, 0.44 mmol) in anhydrous THF (2.93 mL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (177 mg, 99%).

EDCI (69.4 mg, 0.36 mmol) and 3′,6-dimethoxybiphenyl-3-carboxylic acid (74.8 mg, 0.29 mmol) were added to the amine (59.0 mg, 0.14 mmol) in 30% pyridine/CH_2Cl_2 (4.00 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 3:1 hexane:ether → 40:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (26.0 mg, 28%).

Triethylamine (150 μL) was added to the carbonate (26.0 mg, 0.040 mmol) in MeOH (2.0 mL) and CH_2Cl_2 (2.0 mL). After 48 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford **26g** as a colorless amorphous solid (15.7 mg, 63%, 18% over 3 steps): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.82 (s, 1H), 8.73 (s, 1H), 7.96 (dd, J = 8.6, 2.4 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.30 (s, 2H), 7.14 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 2.2 Hz, 1H), 6.96 (dd, J = 8.3, 2.5 Hz, 1H), 5.61 (d, J = 2.4 Hz, 1H), 4.29 (t, J = 4.0 Hz, 1H), 4.27−4.25 (m, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H), 3.62 (s, 3H), 3.47 (s, 1H), 3.37 (d, J = 8.8 Hz, 1H), 2.62 (s, 1H), 1.30 (s, 3H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.5, 158.8, 158.3, 157.8, 150.2 (2C), 142.9, 137.5, 135.6, 130.0, 128.9, 128.2, 127.2, 127.2, 124.9, 122.8, 121.6, 121.0, 114.3, 114.2, 112.3, 112.1, 110.0, 97.7, 70.0 (2C), 67.5, 60.8 (2C), 54.9, 54.3, 28.7, 28.3; IR (film) ν_{max} 3402, 2961, 2928, 2853, 1713, 1672, 1607, 1526, 1504, 1462, 1367, 1263, 1248, 1086, 1040, 953, 798, 735, 700 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{33}H_{35}NO_{11}$ 622.2288, found 622.2307.

***N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-8-ethyl-2-oxo-2*H*-chromen-3-yl)-3′,6-dimethoxybiphenyl-3-carboxamide (26h).** Palladium on carbon (10%, 12 mg) was added to **25h** (121 mg, 0.22 mmol) in anhydrous THF (5.00 mL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (90.0 mg, 99%).

EDCI (46.2 mg, 0.24 mmol) and 3′,6-dimethoxybiphenyl-3-carboxylic acid (43.9 mg, 0.19 mmol) were added to the amine (39.0 mg, 0.096 mmol) in 30% pyridine/CH_2Cl_2 (2.65 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (39.1 mg, 66%).

Triethylamine (150 μL) was added to the carbonate (13.0 mg, 0.020 mmol) in MeOH (1.5 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford **26h** as a colorless amorphous solid (4.10 mg, 33%, 22% over 3 steps): ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 8.70 (s, 1H), 8.61 (s, 1H), 7.83 (dd, J = 8.5, 2.5 Hz, 1H), 7.78 (d, J = 2.5 Hz, 1H), 7.31 (d, J = 9.0 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 7.03−6.99 (m, 3H), 6.85−6.82 (m, 1H), 5.49 (d, J = 1.5 Hz, 1H), 4.15 (t, J = 8.5 Hz, 1H), 4.14 (d, J = 8.5 Hz, 1H), 3.90 (s, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.28 (s, 3H), 3.27 (d, J = 8.5 Hz, 1H), 2.76 (q, J = 4.5 Hz, 2H), 1.29 (s, 3H), 1.09 (t, J = 7.4 Hz, 3H), 1.08 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 164.5, 159.0, 158.6, 158.5, 155.1, 147.9, 138.1, 130.1, 129.1, 128.3, 127.4, 125.4, 125.2, 123.1, 121.4, 121.2, 119.4, 114.5, 113.5, 112.1, 110.8, 110.2, 97.6, 83.4, 77.7, 70.6, 67.8, 61.0, 55.1, 54.5, 28.2, 21.6, 15.6, 12.9; IR (film) ν_{max} 3404, 2968, 2934, 2359, 2341, 1715, 1605, 1524, 1504, 1367, 1244, 1101, 1024, 995, 960, 800 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{34}H_{37}NO_{10}$ 620.2496, found 620.2507.

***N*-(7-((2*S*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-6-methoxy-8-methyl-2-oxo-2*H*-chromen-3-yl)-1*H*-indole-2-carboxamide (26i).** Palladium on carbon (10%, 15 mg) was added to **25a** (74.0 mg, 0.13 mmol) in anhydrous THF (5.00 mL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (60.0 mg, 99%).

EDCI (69.0 mg, 0.36 mmol) and 1*H*-indole-2-carboxylic acid (46.4 mg, 0.29 mmol) were added to the amine (60.0 mg, 0.14 mmol) in 30% pyridine/CH_2Cl_2 (3.50 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 3:1 hexane:ether → 40:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (68.0 mg, 85%).

Triethylamine (150 μL) was added to the carbonate (68.0 mg, 0.12 mmol) in MeOH (2.5 mL) and CH_2Cl_2 (2.50 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford **26i** as a colorless amorphous solid (12.6 mg, 19%, 16% over 3 steps): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.29 (s, 1H), 7.63 (s, 1H), 7.45−7.39 (m, 3H), 6.92 (s, 1H), 6.85 (s, 1H), 6.19 (s, 1H), 5.09 (d, J = 6.5 Hz, 1H), 4.31−4.28 (m, 1H), 4.01−3.97 (m, 1H), 3.94 (s, 3H), 3.62 (s, 1H), 3.56 (s, 3H), 3.15 (d, J = 4.9 Hz, 1H), 2.46 (s, 3H), 2.36 (s, 1H), 1.38 (d, J = 11.5 Hz, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.6, 152.1, 148.2, 145.4, 142.2, 134.5, 129.9, 127.8, 127.7, 127.5, 127.3, 122.3, 121.2, 120.2, 115.0, 105.3, 105.1, 101.3, 81.7, 69.0, 68.0, 66.5, 59.1, 55.2, 28.7, 24.6, 24.1, 9.1; IR (film) ν_{max} 2926, 1707, 1526, 1464, 1391, 1340, 1296, 1231, 1207, 1086, 1024, 943, 739, 700, 623 cm^{-1}; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{28}H_{30}N_2O_9$ 561.1849, found 561.1781.

***N*-(7-((2*S*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-8-methyl-2-oxo-6-propoxy-2*H*-chromen-3-yl)-1*H*-indole-2-carboxamide (26j).** Palladium on carbon (10%, 85 mg) was added to **25b** (425 mg, 0.729 mmol) in anhydrous THF (4.90 mL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (325 mg, 99%).

EDCI (116 mg, 0.6026 mmol) and 1*H*-indole-2-carboxylic acid (77.7 mg, 0.4821 mmol) were added to the amine (108 mg, 0.2410 mmol) in 30% pyridine/CH_2Cl_2 (6.70 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 3:1 hexane:ether → 40:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (91.0 mg, 64%).

Triethylamine (150 μL) was added to the carbonate (91.0 mg, 0.1536 mmol) in MeOH (2.5 mL) and CH_2Cl_2 (2.50 mL). After 48 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford **26j** as a colorless amorphous solid (17.5 mg, 20%, 13% over 3 steps): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 9.32 (s, 1H), 8.80 (s, 1H), 8.76 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.40−7.36 (m, 1H), 7.24−7.20 (m, 1H), 6.98 (s, 1H), 6.01 (s, 1H), 5.15 (d, J = 6.5 Hz, 1H), 4.32−4.25 (m, 1H), 4.11−4.04 (m, 1H), 3.62−3.59 (m, 2H), 3.53 (s, 3H), 3.18−3.12 (m, 1H), 2.64 (s, 1H), 2.49 (s, 3H), 2.18 (s, 1H), 1.95−1.91 (m, 2H), 1.36 (d, J = 9.6 Hz, 3H), 1.29 (d, J = 9.8 Hz, 3H), 1.12 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.1, 159.0, 148.8, 146.9, 143.4, 136.9, 129.8, 127.6, 125.5, 123.5, 123.0, 122.6, 122.3, 121.2, 116.0, 112.0, 107.3, 104.3, 102.2, 82.8, 71.0, 70.1, 69.1, 60.2, 59.7, 25.7, 23.1, 23.4, 10.5, 10.2; IR (film) ν_{max} 3630, 3304, 2926, 2854, 2359, 2332, 1713, 1705, 1539, 1387, 1240, 1103, 947, 930, 822, 739 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{30}H_{34}N_2O_9$ 567.2342, found 567.2367.

***N*-(7-((2*S*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-6-isopropoxy-8-methyl-2-oxo-2*H*-chromen-3-yl)-1*H*-indole-2-carboxamide (26k).** Palladium on carbon (10%, 4 mg) was added to **25c** (19.0 mg, 0.033 mmol) in anhydrous THF (220 μL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (14.5 mg, 99%).

EDCI (15.6 mg, 0.081 mmol) and 1*H*-indole-2-carboxylic acid (10.5 mg, 0.065 mmol) were added to the amine (14.5 mg, 0.033 mmol) in 30% pyridine/CH_2Cl_2 (1.00 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (10.0 mg, 50%).

Triethylamine (150 μL) was added to the carbonate (10.0 mg, 0.017 mmol) in MeOH (2.5 mL) and CH_2Cl_2 (2.50 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 10:1 CH_2Cl_2:acetone) to afford **26k**

as a colorless amorphous solid (6.00 mg, 46%, 23% over 3 steps): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.16 (s, 1H), 7.52 (s, 1H), 7.34−7.30 (m, 5H), 6.75 (s, 1H), 4.93 (d, J = 5.0 Hz, 1H), 4.56−4.51 (m, 1H), 4.23 (t, J = 4.0 Hz, 1H), 3.98−3.96 (m, 1H), 3.76 (s, 1H), 3.43 (s, 3H), 3.06 (d, J = 4.3 Hz, 1H), 2.65 (s, 1H), 2.38 (s, 3H), 1.33 (dd, J = 11.2, 6.1 Hz, 6H), 1.29 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.6, 152.1, 146.6, 146.0, 142.1, 134.5, 127.7, 127.5, 127.2, 122.2, 121.3 (2C), 120.2 (2C), 115.0 (2C), 108.1 (2C), 101.2, 81.6, 71.2, 68.9, 68.1, 66.5, 59.0, 24.8, 23.6, 20.8 (2C), 9.1; IR (film) ν_{max} 3406, 2930, 2375, 1705, 1522, 1394, 1229, 1205, 1111, 1078, 1049, 933, 793, 739, 698 cm^{-1}; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{30}H_{34}N_2O_9$ 589.2162, found 589.2111.

***N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-5-methoxy-8-methyl-2-oxo-2*H*-chromen-3-yl)-1*H*-indole-2-carboxamide (26*l*).** Palladium on carbon (10%, 40 mg) was added to **25d** (200 mg, 0.36 mmol) in anhydrous THF (2.40 mL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (150 mg, 99%).

EDCI (57.5 mg, 0.30 mmol) and 1*H*-indole-2-carboxylic acid (38.7 mg, 0.24 mmol) were added to the amine (50.6 mg, 0.12 mmol) in 30% pyridine/CH_2Cl_2 (3.30 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (26.3 mg, 39%).

Triethylamine (150 μL) was added to the carbonate (26.3 mg, 0.047 mmol) in MeOH (2.00 mL) and CH_2Cl_2 (2.00 mL). After 48 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford **26*l*** as a colorless amorphous solid (6.60 mg, 26%, 10% over 3 steps): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 9.26 (s, 1H), 8.96 (s, 1H), 8.68 (s, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.38−7.34 (m, 1H), 7.22−7.16 (m, 1H), 6.84 (s, 1H), 6.00 (s, 1H), 5.65 (d, J = 1.7 Hz, 1H), 4.26−4.21 (m, 2H), 3.96 (s, 3H), 3.59 (s, 3H), 3.35 (d, J = 8.6 Hz, 1H), 2.25 (s, 3H), 1.53 (s, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.1, 157.4, 156.5, 149.7, 136.7, 134.7, 127.7, 125.3, 122.5, 121.1, 120.0, 111.9, 104.6, 103.8, 97.7, 94.0, 84.3, 84.2, 82.6, 69.6, 69.1, 66.1, 62.2, 62.0, 59.7, 23.1, 22.7, 14.2; IR (film) ν_{max} 3389, 2924, 2853, 1697, 1605, 1535, 1460, 1340, 1211, 1101, 1088, 962, 729 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{28}H_{30}N_2O_9$ 539.2030, found 539.2056.

***N*-(8-Benzyl-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-2-oxo-2*H*-chromen-3-yl)-1*H*-indole-2-carboxamide (26m).** Palladium on carbon (10%, 46 mg) was added to **25e** (230 mg, 0.38 mmol) in anhydrous THF (2.50 mL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (177 mg, 99%).

EDCI (61.5 mg, 0.32 mmol) and 1*H*-indole-2-carboxylic acid (41.4 mg, 0.26 mmol) were added to the amine (60.0 mg, 0.13 mmol) in 30% pyridine/CH_2Cl_2 (3.50 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 3:1 hexane:ether → 40:1 CH_2Cl_2:acetone) to afford a yellow solid, which was used without further purification (66.2 mg, 85%).

Triethylamine (150 μL) was added to the carbonate (66.2 mg, 0.11 mmol) in MeOH (2.50 mL) and CH_2Cl_2 (2.50 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford **26m** as a colorless amorphous solid (6.50 mg, 10%, 8.4% over 3 steps): ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 8.68 (s, 1H), 8.62 (s, 1H), 7.63−7.61 (m, 1H), 7.47 (dd, J = 5.7, 3.3 Hz, 1H), 7.16−7.10 (m, 4H), 7.10−7.04 (m, 4H), 6.99 (t, J = 8.2 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.43 (dd, J = 8.1, 0.7 Hz, 1H), 5.31 (d, J = 2.9 Hz, 1H), 4.17 (t, J = 6.8 Hz, 1H), 4.01 (dd, J = 8.5, 2.9 Hz, 1H), 3.90 (d, J = 13.1 Hz, 2H), 3.45 (s, 3H), 3.16 (d, J = 8.6 Hz, 1H), 2.43 (s, 1H), 2.21 (s, 1H), 1.25 (s, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.8, 155.4, 153.8, 140.2, 131.6, 130.2, 128.0, 127.6, 127.5 (2C), 127.4 (2C), 126.9, 125.1 (2C), 115.2, 108.3 (2C), 105.8 (2C), 97.1 (2C), 83.3 (2C), 77.2, 70.2, 67.9 (2C), 65.0, 60.6, 21.9, 13.1, 13.0; IR (film) ν_{max} 3333, 2961, 2926, 2854, 1717, 1601, 1466, 1261, 1090, 1076, 1041, 800, 750 cm^{-1}; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{33}H_{32}N_2O_8$ 607.2056, found 607.2056.

***N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-2-oxo-8-phenyl-2*H*-chromen-3-yl)-1*H*-indole-2-carboxamide (26n).** Palladium on carbon (10%, 14 mg) was added to **25f** (68.0 mg, 0.12 mmol) in anhydrous THF (800 μL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (52.0 mg, 99%).

EDCI (18.5 mg, 0.096 mmol) and 1*H*-indole-2-carboxylic acid (12.4 mg, 0.077 mmol) were added to the amine (17.5 mg, 0.039 mmol) in 30% pyridine/CH_2Cl_2 (1.10 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (8.20 mg, 36%).

Triethylamine (150 μL) was added to the carbonate (8.2 mg, 0.014 mmol) in MeOH (1.00 mL) and CH_2Cl_2 (1.00 mL). After 48 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford **26n** as a colorless amorphous solid (4.00 mg, 51%, 18% over 3 steps): ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 9.23 (s, 1H), 8.80 (s, 1H), 8.67 (s, 1H), 7.71 (dd, J = 8.0, 0.7 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.51−7.48 (m, 3H), 7.46−7.44 (m, 1H), 7.37−7.32 (m, 4H), 7.19−7.17 (m, 2H), 5.53 (d, J = 2.4 Hz, 1H), 3.86 (s, 1H), 3.76−3.73 (m, 2H), 3.51 (s, 3H), 3.23 (d, J = 9.1 Hz, 1H), 2.41 (s, 1H), 1.34 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 159.1, 157.9, 154.5, 147.3, 136.0 (2C), 130.7 (2C), 129.8, 129.2,. 127.3, 127.1, 127.0, 126.9, 124.5, 122.8, 121.6, 121.2, 120.3, 113.7, 111.4, 111.1, 103.1 (2C), 97.5, 83.2, 77.7, 70.1, 67.5, 60.8, 21.9, 21.7; IR (film) ν_{max} 3427, 2961, 2924, 2853, 2062, 1643, 1614, 1537, 1362, 1236, 1094, 1041, 962, 791, 739, 698 cm^{-1}; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{32}H_{30}N_2O_8$ 593.1900, found 593.1890.

***N*-(7-((2*S*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-8-methoxy-2-oxo-2*H*-chromen-3-yl)-1*H*-indole-2-carboxamide (26o).** Palladium on carbon (10%, 47 mg) was added to **25g** (237 mg, 0.44 mmol) in anhydrous THF (2.93 mL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (177 mg, 99%).

EDCI (69.4 mg, 0.36 mmol) and 1*H*-indole-2-carboxylic acid (46.7 mg, 0.29 mmol) were added to the amine (59.0 mg, 0.14 mmol) in 30% pyridine/CH_2Cl_2 (4.00 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 3:1 hexane:ether → 40:1 CH_2Cl_2:acetone) to afford a colorless solid, which was used without further purification (32.0 mg, 49%).

Triethylamine (150 μL) was added to the carbonate (32.0 mg, 0.071 mmol) in MeOH (2.00 mL) and CH_2Cl_2 (2.00 mL). After 48 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 3:1 CH_2Cl_2:acetone) to afford **26o** as a colorless amorphous solid (22.1 mg, 73%, 35% over 3 steps): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 9.28 (s, 1H), 8.78 (s, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.53 (dd, J = 8.3, 0.8 Hz, 1H), 7.38 (m, 1H), 7.31 (s, 2H), 7.24 (d, J = 0.9 Hz, 1H), 7.22−7.20 (m, 1H), 6.02 (s, 1H), 5.62 (d, J = 2.3 Hz, 1H), 4.25 (t, J = 3.5 Hz, 1H), 3.99 (s, 3H), 3.75 (dd, J = 9.0, 3.6 Hz, 1H), 3.62 (s, 3H), 3.13 (d, J = 3.6 Hz, 1H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.8, 159.1, 157.7, 150.6, 143.3, 136.0, 135.8, 129.2, 126.9, 124.6, 122.8, 121.8, 121.6, 121.4, 120.3, 114.4, 112.5, 111.2, 103.1, 98.0, 83.2, 77.9, 74.0, 60.9, 58.7, 22.3, 21.8; IR (film) ν_{max} 3420, 2957, 2924, 2854, 2359, 1653, 1558, 1541, 1246, 1001, 798

cm^{-1}; HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{27}H_{28}N_2O_9$ 525.1873, found 525.1875.

***N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)-8-ethyl-2-oxo-2*H*-chromen-3-yl)-1*H*-indole-2-carboxamide (26p).** Palladium on carbon (10%, 12 mg) was added to **25h** (121 mg, 0.22 mmol) in anhydrous THF (5.00 mL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was filtered through SiO_2 (1:1 CH_2Cl_2:acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (90.0 mg, 99%).

EDCI (28.3 mg, 0.15 mmol) and 1*H*-indole-2-carboxylic acid (19.0 mg, 0.12 mmol) were added to the amine (24.0 mg, 0.059 mmol) in 30% pyridine/CH_2Cl_2 (1.63 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford a colorless foam, which was used without further purification (23.8 mg, 73%).

Triethylamine (150 μL) was added to the carbonate (14.1 mg, 0.026 mmol) in MeOH (1.50 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 CH_2Cl_2:acetone) to afford **26p** as a yellow amorphous solid (5.00 mg, 37%, 27% over 3 steps): ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 8.65 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.13 (s, 2H), 7.07 (t, J = 7.5 Hz, 1H), 5.46 (d, J = 2.0 Hz, 1H), 4.07 (dd, J = 9.3, 3.5 Hz, 1H), 4.04 (t, J = 3.5 Hz, 1H), 3.51 (s, 3H), 3.25 (d, J = 7.2 Hz, 1H), 2.78 (q, J = 7.0 Hz, 2H), 1.27 (s, 3H), 1.10 (t, J = 7.5 Hz, 3H), 1.06 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 158.4, 157.3, 154.2, 146.8, 135.3, 128.1, 125.5, 124.0, 123.0, 123.0, 122.8, 120.1, 119.5, 118.7, 118.2, 112.0, 110.1, 109.7, 102.4, 97.0, 82.1, 76.5, 69.3, 66.4, 26.7, 20.3, 14.3, 11.4; IR (film) ν_{max} 3435, 3416, 2974, 2935, 2469, 2359, 2339, 1715, 1651, 1520, 1456, 1435, 1379, 1354, 1259, 1180, 1113, 1088, 1026, 997, 962, 798, 739 cm^{-1}; HRMS (ESI$^+$) *m/z* [M + Na]$^+$ calcd for $C_{28}H_{30}N_2O_8$ 545.1900, found 545.1909.

***tert*-Butylquinolin-7-yl Carbonate (28).** Di-*tert*-butyl dicarbonate (7.40 g, 33.92 mmol) and 4-(dimethylamino)pyridine (222 mg, 1.81 mmol) were added in sequence to 7-hydroxyquinoline (2.00 g, 13.75 mmol) in anhydrous *N*,*N*-dimethylformamide (20.0 mL) at rt. After 18 h, the reaction was diluted with EtOAc (250 mL). The organic layer was washed with 1.0 M NaOH (250 mL), water (3 × 250 mL), and saturated aqueous NaCl solution (250 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 1:1 hexanes:EtOAc) to give **28** as a colorless amorphous solid (3.26 g, 97%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.93 (dd, J = 4.2, 1.7 Hz, 1H), 8.17 (br d, J = 8.4 Hz, 1H), 7.90 (d, J = 2.2 Hz, 1H), 7.84 (d, J = 8.9 Hz, 1H), 7.43 (dd, J = 8.8, 2.3 Hz, 1H), 7.40 (dd, J = 8.3, 4.3 Hz, 1H), 1.60 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.7, 151.7, 148.9, 135.9, 129.0, 126.3, 122.0, 121.0, 120.2, 84.2, 27.8 (3C); IR (film) ν_{max} 1759, 1277, 1240, 1142, 768, 750 cm^{-1}; HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{14}H_{15}NO_3$ 246.1130, found 246.1113.

***N*-(4-Methoxybenzyl)-7-(benzyloxy)quinolin-3-amine (31).** Bromine (790 μL, 2.48 g, 15.38 mmol) was added to **28** (3.26 g, 13.30 mmol) in CCl_4 (30.0 mL) at rt. This solution was heated to reflux, anhydrous pyridine (1.20 mL,1.17 g, 14.84 mmol) was added over 10 min, and the solution was stirred at reflux for 18 h. The cooled reaction was diluted with EtOAc/MeOH (250 mL) and saturated aqueous $NaHCO_3$ (200 mL), then extracted with EtOAc (4 × 250 mL). Combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 4:1 hexanes:EtOAc) to give **29** as a light yellow solid containing >80% 3-bromo isomer (2.00 g, 46%), which was used without further purification.

Hydrogen chloride was bubbled through **29** (2.00 g, 6.16 mmol) in anhydrous MeOH (44.0 mL) for 3 min at rt, then the solution was stirred at 50 °C for 5 min. The solvent was concentrated and the residue placed under high vacuum for 6 h to ensure complete removal of MeOH. The yellow residue was dissolved in anhydrous *N*,*N*-dimethylformamide (44.0 mL) and cooled to 0 °C, then NaH (997 mg, 24.93 mmol) was added. After 15 min, BnBr (1.20 mL, 1.73 g, 10.09 mmol) was added and the reaction was warmed to rt over 18 h. Reaction contents were partitioned between saturated aqueous $NaHCO_3$ (500 mL) and EtOAc (500 mL), then extracted with EtOAc (3 × 500 mL). The combined organic layers were washed with water (3 × 1 L) and saturated aqueous NaCl solution (1 L), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 9:1 hexanes:EtOAc) to give **30** as a light orange solid containing >80% 3-bromo isomer (1.70 g, 88%), which was used without further purification.

4-Methoxybenzylamine (1.77 mL, 1.87 g, 13.64 mmol) and anhydrous DMSO (2.90 mL) were added to a high-pressure flask charged with **30** (1.65 g, 5.26 mmol), K_3PO_4 (2.36 g, 11.10 mmol), Cu^II (167 mg, 0.88 mmol), and L-(−)-proline (141 mg, 1.22 mmol); the sealed flask was heated to 80 °C for 44 h. After cooling to rt, reaction contents were partitioned between water (50 mL) and EtOAc (100 mL), then were extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with saturated aqueous NaCl solution (200 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 1:1 hexanes:EtOAc) to give **31** as a light yellow amorphous solid (1.43 g, 73%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.44 (d, J = 2.8 Hz, 1H), 7.52 (d, J = 8.9 Hz, 1H), 7.50 (m, 2H), 7.43−7.38 (m, 3H), 7.36−7.32 (m, 3H), 7.20 (dd, J = 8.9, 2.6 Hz, 1H), 7.06 (d, J = 2.7 Hz, 1H), 6.91 (m, 2H), 5.17 (s, 2H), 4.35 (d, J = 4.8 Hz, 2H), 4.17 (br t, J = 4.8 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.3, 156.9, 143.4, 143.3, 140.5, 137.0, 130.6, 129.1 (2C), 128.8 (2C), 128.2, 127.9 (2C), 127.3, 124.7, 120.4, 114.4 (2C), 112.0, 109.0, 70.3, 55.5, 48.0; IR (film) ν_{max} 3279, 2953, 2833, 1609, 1510, 1377, 1354, 1302, 1225, 1175, 1124, 1028, 995, 868, 818, 762, 708 cm^{-1}; HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{24}H_{22}N_2O_2$ 371.1759, found 371.1732.

***N*-(4-Methoxybenzyl)-*N*-(7-(benzyloxy)quinolin-3-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (32).** Thionyl chloride (395 μL, 644 mg, 5.42 mmol) was added to 4-methoxy-3-(3-methoxyphenyl)-benzoic acid (464 mg, 1.80 mmol) in anhydrous THF (6.10 mL) at rt and the resulting solution was heated at reflux for 4.5 h. The solvent was removed and the resulting acid chloride was used without further purification.

Sodium hydride (93 mg, 2.31 mmol) was added to **31** (508 mg, 1.37 mmol) in anhydrous THF (9.10 mL). After stirring for 2 h at rt, a solution of the freshly prepared acid chloride (1.80 mmol) in anhydrous THF (3.00 mL) was added and the reaction was heated to reflux for 18 h. The reaction was cooled, partitioned between saturated aqueous $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL), then extracted with CH_2Cl_2 (3 × 100 mL). Combined organic extracts were washed with saturated aqueous NaCl solution (200 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 1:1 EtOAc:hexanes to 2:1 EtOAc:hexanes) to give **32** as a pale yellow amorphous solid (684 mg, 82%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35 (d, J = 2.3 Hz, 1H), 7.67 (d, J = 2.4 Hz, 1H), 7.57 (d, J = 9.0 Hz, 1H), 7.48 (m, 2H), 7.44−7.34 (m, 5H), 7.29 (m, 2H), 7.23 (m, 2H), 7.13 (t, J = 7.9 Hz, 1H), 6.81 (m, 2H), 6.78 (dd, J = 2.5, 1.0 Hz, 1H), 6.74 (d, J = 8.6 Hz, 1H), 6.64 (m,1H), 6.61 (m, 1H), 5.19 (s, 2H), 5.15 (s, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 160.2, 159.3, 159.3, 157.9, 150.9, 147.9, 138.9, 136.4, 136.0, 132.6, 132.4, 130.5, 130.2 (2C), 130.1, 129.4, 129.0, 129.0 (2C), 128.5, 127.9 (2C), 127.4, 123.1, 122.1, 121.2, 114.8, 114.2 (2C), 113.3, 110.6, 108.6, 70.5, 55.7, 55.4, 55.3, 53.8; IR (film) ν_{max} 3032, 3001, 2953, 2935, 2835, 1645, 1603, 1512, 1456, 1429, 1385, 1331, 1248, 1209, 1178, 1034, 1026, 818, 735, 698 cm^{-1}; HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{39}H_{34}N_2O_5$ 611.2546, found 611.2574.

***N*-(4-Methoxybenzyl)-*N*-(7-(hydroxy)quinolin-3-yl)-4-methoxy-3-(3-methoxyphenyl)-benzamide (33).** A solution of $AlCl_3$ (44 mg, 0.33 mmol) in anhydrous anisole (150 μL) was added to **32** (43 mg, 0.07 mmol) in anhydrous anisole (150 μL) and the resulting solution was stirred at rt for 18 h. The reaction was diluted with

MeOH (150 μL) and the solvent was concentrated. The residue was purified via column chromatography (SiO_2, 80:20:1 EtOAc:hexanes:MeOH) to give **33** as a yellow amorphous solid in quantitative yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35 (s, 1H), 7.74 (s, 1H), 7.58 (d, J = 8.9 Hz, 1H), 7.52 (br s, 1H), 7.37 (m, 1H), 7.31 (m, 1H), 7.25−7.11 (m, 5H), 6.84−6.77 (m, 3H), 6.74 (d, J = 8.6 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H), 6.64 (s, 1H), 5.16 (s, 2H), 3.76 (s, 3H), 3.70 (s, 3H), 3.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 159.4, 159.3, 158.0, 138.8, 135.5, 132.3, 130.4, 130.3, 130.1 (2C), 129.6, 129.1 (2C), 127.1, 123.0, 122.0, 114.9, 114.3 (2C), 113.3, 110.7, 55.8, 55.4, 53.9; IR (film) ν_{max} 2926, 1601, 1506, 1248, 1177, 1030, 818 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{32}H_{28}N_2O_5$ 521.2076, found 521.2030.

***N*-(7-Hydroxyquinolin-3-yl)-4-methoxy-3-(3-methoxyphenyl)-benzamide (34).** Trifluoromethanesulfonic acid (120 μL, 204 mg, 1.36 mmol) was added to **32** (184 mg, 0.30 mmol) in 1:1 CH_2Cl_2:TFA (1.36 mL) and the solution was stirred at rt for 2 h. The resulting solution was diluted with CH_2Cl_2 (100 mL), washed with saturated aqueous $NaHCO_3$ (3 × 50 mL) and saturated aqueous NaCl solution (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 100:1 EtOAc:MeOH to 4:1 EtOAc:MeOH) to give **34** as a yellow oil (51 mg, 43%): ^{1}H NMR (CD_3OD, 500 MHz) δ 9.01 (br s, 1H), 8.61 (br s, 1H), 8.02 (dd, J = 8.5, 1.7 Hz, 1H), 7.97 (d, J = 1.9 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.30 (t, J = 8.2 Hz, 1H), 7.27 (d, J = 1.9 Hz, 1H), 7.19 (dd, J = 8.9, 2.1 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 7.11−7.08 (m, 2H), 6.89 (m, 1H), 3.88 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (CD_3OD, 125 MHz) δ 168.7, 161.2, 160.9, 160.2, 147.1, 146.2, 140.5, 132.0, 132.0, 131.5, 130.4, 130.2, 130.1, 128.5, 127.6, 124.2, 123.2, 121.5, 116.5, 113.8, 112.4, 109.7, 56.5, 55.9; IR (film) ν_{max} 3281, 3203, 2930, 2835, 1605, 1545, 1499, 1371, 1252, 1036, 764, 735 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{24}H_{20}N_2O_4$ 401.1501, found 401.1481.

2-(Benzyloxy)-6-bromonaphthalene (36). Sodium hydride (1.16 g, 29.12 mmol) was added to 6-bromo-2-naphthol (5.00 g, 22.41 mmol) in anhydrous *N*,*N*-dimethylformamide (162 mL) at 0 °C. After 15 min, benzyl bromide (2.40 mL, 3.45 g, 20.18 mmol) was added and the reaction was warmed to rt over 18 h. The reaction was diluted with EtOAc (500 mL), saturated aqueous $NaHCO_3$ (200 mL) was added, and the solution was extracted with EtOAc (3 × 500 mL). The combined organic layers were washed with water (3 × 1 L) and saturated aqueous NaCl solution (1 L), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 5:1 hexanes:CH_2Cl_2) to give **36** as a colorless amorphous solid (5.71 g, 90%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (d, J = 1.9 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.53−7.47 (m, 3H), 7.46−7.40 (m, 2H), 7.37 (m, 1H), 7.26 (dd, J = 9.0, 2.5 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 5.18 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.2, 136.8, 133.2, 130.3, 129.9, 129.9, 128.9 (2C), 128.8, 128.7, 128.4, 127.8 (2C), 120.3, 117.4, 107.3, 70.3; IR (film) ν_{max} 1585, 1452, 1256, 1219, 1204, 1165, 1065, 997, 924, 852, 820, 800, 733, 698, 476 cm^{-1}.

***N*-(4-Methoxybenzyl)-6-(benzyloxy)naphthalen-2-amine (37).** 4-Methoxybenzylamine (3.40 mL, 3.59 g, 26.20 mmol) and anhydrous DMSO (5.20 mL) were added to a high-pressure flask charged with **36** (3.00 g, 9.58 mmol), K_3PO_4 (4.19 g, 19.73 mmol), Cu^{I}I (290 mg, 1.52 mmol), and L-(−)-proline (255 mg, 2.21 mmol); the sealed flask was heated to 80 °C for 44 h. After cooling to rt, reaction contents were partitioned between water (100 mL) and EtOAc (200 mL), then were extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with saturated aqueous NaCl solution (500 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 7:1:1 hexanes:CH_2Cl_2:EtOAc) to give **37** as a light orange amorphous solid (952 mg, 27%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 (d, J = 8.7 Hz, 2H), 7.49 (m, 2H), 7.41 (m, 2H), 7.37−7.32 (m, 3H), 7.15 (dd, J = 8.8, 2.6 Hz, 1H), 7.13 (m, 1H), 6.92 (dd, J = 8.8, 2.3 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 6.87 (m, 1H), 5.14 (s, 2H), 4.35 (s, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 154.6, 137.4, 130.7, 129.3 (2C), 128.8 (2C), 128.1, 128.0, 127.8 (2C), 119.4 (2C), 118.6, 114.3 (2C), 107.9, 70.3, 55.5; IR (film) ν_{max} 3734, 1558, 1456, 1259, 1167, 847, 746, 702, 660 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{25}H_{23}NO_2$ 370.1807, found 370.1786.

***N*-(4-Methoxybenzyl)-*N*-(6-(benzyloxy)naphthalen-2-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (38).** Thionyl chloride (308 μL, 502 mg, 4.22 mmol) was added to 4-methoxy-3-(3-methoxyphenyl)benzoic acid (365 mg, 1.41 mmol) in anhydrous THF (4.75 mL) at rt, and the resulting solution was heated at reflux for 4.5 h. The solvent was removed and the resulting acid chloride was used without further purification.

Sodium hydride (85 mg, 2.12 mmol) was added to **37** (378 mg, 1.02 mmol) in anhydrous THF (7.50 mL). After stirring for 2 h at rt, a solution of the freshly prepared acid chloride (1.41 mmol) in anhydrous THF (2.40 mL) was added and the reaction was heated to reflux for 18 h. The reaction was cooled, partitioned between saturated aqueous $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL), then extracted with CH_2Cl_2 (3 × 100 mL). Combined organic extracts were washed with saturated aqueous NaCl solution (200 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 4:1:1 hexanes:EtOAc:CH_2Cl_2) to give **38** as a brown-yellow amorphous solid (515 mg, 83%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.50−7.45 (m, 3H), 7.44−7.40 (m, 2H), 7.38−7.34 (m, 2H), 7.29 (d, J = 2.2 Hz, 1H), 7.25 (m, 2H), 7.21 (dd, J = 8.9, 2.6 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.09 (m, 1H), 7.01 (dd, J = 8.7, 2.1 Hz, 1H), 6.80 (m, 2H), 6.77 (ddd, J = 8.2, 2.7, 0.9 Hz, 1H), 6.74 (d, J = 8.7 Hz, 1H), 6.59−6.56 (m, 2H), 5.16 (s, 2H), 5.14 (s, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 3.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 159.3, 159.0, 157.6, 157.3, 139.9, 139.1, 136.8, 133.0, 132.4, 130.5, 130.1, 130.1 (2C), 129.6, 129.5, 129.1, 128.9, 128.9 (2C), 128.4, 128.2, 127.9, 127.7 (2C), 127.3, 125.8, 122.1, 120.0, 114.7, 114.0 (2C), 113.2, 110.4, 107.1, 70.3, 55.7, 55.4, 55.2, 53.9; IR (film) ν_{max} 3059, 3032, 2999, 2934, 2835, 1636, 1601, 1506, 1456, 1389, 1248, 1209, 1026, 854, 818, 735, 698 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{40}H_{35}NO_5$ 610.2593, found 610.2567.

***N*-(4-Methoxybenzyl)-*N*-(6-hydroxynaphthalen-2-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (39).** A solution of $AlCl_3$ (203 mg, 1.52 mmol) in anhydrous anisole (750 μL) was added to **38** (191 mg, 0.31 mmol) in anhydrous anisole (750 μL) and the resulting solution was stirred at rt for 18 h. The reaction was diluted with MeOH (750 μL) and the solvent was concentrated. The residue was purified via column chromatography (SiO_2, 1:1 EtOAc:hexanes) to give **39** as a light yellow amorphous solid (126 mg, 77%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (m, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.47 (dd, J = 8.6, 2.3 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H), 7.25 (m, 2H), 7.12−7.06 (m, 3H), 7.00 (dd, J = 8.7, 2.1 Hz, 1H), 6.80 (m, 2H), 6.77 (m, 1H), 6.73 (d, J = 8.7 Hz, 1H), 6.59−6.55 (m, 2H), 5.43 (s, 1H), 5.15 (s, 2H), 3.77 (s, 3H), 3.71 (s, 3H), 3.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 159.3, 159.0, 157.6, 154.2, 139.7, 139.0, 133.1, 132.4, 130.5, 130.1, 130.1 (2C), 130.0, 129.5, 128.9, 128.9, 128.0, 127.5, 127.3, 125.9, 122.1, 118.7, 114.7, 114.0 (2C), 113.2, 110.4, 109.5, 55.7, 55.4, 55.3, 54.0; IR (film) ν_{max} 3236, 2934, 2835, 1599, 1508, 1456, 1437, 1394, 1248, 1177, 1036 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{33}H_{29}NO_5$ 520.2124, found 520.2120.

***N*-(4-Methoxybenzyl)-*N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)quinolin-3-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (42a).** Boron trifluoride etherate (45 μL, 52 mg, 0.36 mmol) was added to **33** (160 mg, 0.31 mmol) and (3a*R*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxotetrahydro-3a*H*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (181 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (5.00 mL). After stirring at rt for 40 h, triethylamine (30 μL) was added and the solvent was concentrated. The residue was partially purified via

column chromatography (SiO_2, 1:1 EtOAc:hexanes) to provide **41a**, which was used without further purification.

Carbonate **41a** was added to MeOH (22.0 mL), CH_2Cl_2 (1.5 mL), and triethylamine (2.2 mL) and the mixture was stirred for 18 h at rt. The solvent was concentrated and the residue was purified via column chromatography (SiO_2, 50:1 EtOAc:MeOH) to give **42a** as a near-colorless amorphous solid (33 mg, 16% over two steps): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.38 (d, J = 2.4 Hz, 1H), 7.67 (d, J = 2.4 Hz, 1H), 7.65 (d, J = 2.3 Hz, 1H), 7.54 (d, J = 9.1 Hz, 1H), 7.41 (dd, J = 8.6, 2.3 Hz, 1H), 7.26 (d, J = 2.3 Hz, 1H), 7.22 (m, 2H), 7.17 (dd, J = 8.9, 2.4 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.80 (m, 2H), 6.75 (dd, J = 8.4, 1.0 Hz, 1H), 6.74 (d, J = 8.7 Hz, 1H), 6.62−6.57 (m, 2H), 5.69 (d, J = 2.3 Hz, 1H), 5.15 (**A**B, J_{AB} = 14.6 Hz, 1H), 5.15 (A**B**, J_{AB} = 14.6 Hz, 1H), 4.23 (dd, J = 9.1, 3.4 Hz, 1H), 4.15 (m, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 3.59 (s, 3H), 3.38 (d, J = 9.1 Hz, 1H), 1.39 (s, 3H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 159.3, 159.2, 158.1, 157.9, 150.9, 147.4, 138.8, 136.1, 132.7, 132.4, 130.5, 130.1 (2C), 129.3, 129.0, 128.9, 127.3, 123.4, 122.0, 120.7, 114.8, 114.2 (2C), 113.2, 111.3, 110.7, 98.2, 84.5, 78.7, 71.1, 68.6, 62.0, 55.7, 55.4, 55.3, 53.8, 29.0, 23.0; IR (film) ν_{max} 2937, 2833, 1601, 1246, 1209, 1117, 1033, 989, 964 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{40}H_{42}N_2O_9$ 695.2969, found 695.2891.

***N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)quinolin-3-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (42b).** Boron trifluoride etherate (46 μL, 53 mg, 0.37 mmol) was added to **34** (51 mg, 0.13 mmol) and (3a*R*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3a*H*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (180 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (5.00 mL). After stirring at rt for 40 h, triethylamine (30 μL) was added and the solvent was concentrated. The residue was purified via column chromatography (SiO_2, 1:1 EtOAc:hexanes) to give **41b** (29 mg, 37%) in a 10:1 ratio of anomers (α:β), which was used without further purification.

Carbonate **41b** was added to MeOH (7.5 mL), CH_2Cl_2 (500 μL), and triethylamine (750 μL) and the mixture was stirred for 18 h at rt. The solvent was concentrated and the residue was purified via column chromatography (SiO_2, 40:1 EtOAc:MeOH) to give **42b** as a near-colorless amorphous solid (11 mg, 15% over two steps): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.81 (br s, 2H), 7.98 (dd, J = 8.7, 2.4 Hz, 1H), 7.89 (d, J = 2.3 Hz, 1H), 7.72 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 1.9 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.23 (dd, J = 9.0, 2.3 Hz, 1H), 7.13 (dt, J = 7.8, 1.2 Hz, 1H), 7.10 (m, 1H), 7.09 (d, J = 8.6 Hz, 1H), 6.94 (ddd, J = 8.2, 2.5, 0.8 Hz, 1H), 5.73 (d, J = 2.0 Hz, 1H), 4.30−4.22 (m, 2H), 3.91 (s, 2H), 3.86 (s, 3H), 3.61 (s, 3H), 3.39 (d, J = 8.9 Hz, 1H), 1.40 (s, 3H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.8, 159.9, 159.6, 157.1, 146.7, 144.7, 138.9, 131.1, 130.6, 129.9, 129.4, 129.0, 128.7, 126.6, 125.0, 124.0, 122.2, 120.5, 115.6, 113.2, 111.5, 111.4, 98.0, 84.6, 78.6, 71.4, 68.8, 62.1, 56.1, 55.6, 29.2, 23.0; IR (film) ν_{max} 3288, 2976, 2934, 2835, 1373, 1250, 1117, 731 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{32}H_{34}N_2O_8$ 575.2393, found 575.2368.

***N*-(4-Methoxybenzyl)-*N*-(6-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2*H*-pyran-2-yloxy)naphthalen-2-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (42c).** Boron trifluoride etherate (10 μL, 12 mg, 0.08 mmol) was added to **39** (77 mg, 0.15 mmol) and (3a*R*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3a*H*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (214 mg, 0.59 mmol) in anhydrous CH_2Cl_2 (5.00 mL). After stirring at rt for 40 h, triethylamine (10 μL) was added and the solvent was concentrated. The residue was partially purified via column chromatography (SiO_2, 1:1 EtOAc:hexanes) to give **41c**, which was used without further purification (69 mg, 64%).

Carbonate **41c** (42 mg, 0.06 mmol) was added to MeOH (9.1 mL), CH_2Cl_2 (650 μL), and triethylamine (910 μL) and the mixture was stirred for 18 h at rt. The solvent was concentrated and the residue was purified via column chromatography (SiO_2, 2:1 EtOAc:hexanes to EtOAc) to give **42c** as a colorless oil (27 mg, 66%, 42% over two steps): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.48 (dd, J = 8.7, 2.2 Hz, 1H), 7.37 (d, J = 2.3 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.28 (d, J = 2.3 Hz, 1H), 7.25 (m, 2H), 7.14 (dd, J = 8.9, 2.4 Hz, 1H), 7.09 (t, J = 7.9 Hz, 1H), 7.04 (dd, J = 8.7, 2.1 Hz, 1H), 6.80 (m, 2H), 6.76 (ddd, J = 8.2, 2.5, 0.9 Hz, 1H), 6.73 (d, J = 8.7 Hz, 1H), 6.58 (m, 1H), 6.54 (br d, J = 7.7 Hz, 1H), 5.66 (d, J = 2.1 Hz, 1H), 5.14 (s, 2H), 4.25 (m, 1H), 4.22 (m, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.63 (s, 3H), 3.61 (s, 3H), 3.38 (d, J = 9.2 Hz, 1H), 2.84 (br s, 1H), 2.71 (br s, 1H), 1.39 (s, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 159.2, 159.0, 157.6, 155.1, 140.1, 139.0, 132.9, 132.4, 130.5, 130.1 (2C), 129.5, 129.5, 129.4, 128.9, 128.3, 128.1, 127.1, 125.8, 122.1, 119.5, 114.7, 114.0, 113.2 (2C), 110.4, 109.9, 97.9, 94.6, 78.6, 71.5, 68.7, 62.1, 55.7, 55.4, 55.3, 53.9, 29.4, 22.9; IR (film) ν_{max} 3420, 2932, 2835, 1601, 1506, 1394, 1387, 1248, 1178, 1117, 1026, 993, 910, 733 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{41}H_{43}NO_9$ 694.3016, found 694.3010.

***N*-(6-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyl-tetrahydro-2*H*-pyran-2-yloxy)naphthalen-2-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (42d).** Trifluoromethanesulfonic acid (130 μL, 221 mg, 1.47 mmol) was added to **38** (198 mg, 0.33 mmol) in 1:1 CH_2Cl_2:TFA (1.48 mL) and the solution was stirred at rt for 2 h. The resulting solution was diluted with CH_2Cl_2 (100 mL), washed with saturated aqueous $NaHCO_3$ (3 × 50 mL) and saturated aqueous NaCl solution (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was partially purified via column chromatography (SiO_2, 1:1:1 hexanes:EtOAc:CH_2Cl_2) to give **40** as a purple solid, which was used without further purification (28 mg, 22%).

Boron trifluoride etherate (4 μL, 5 mg, 0.03 mmol) was added to **40** (28 mg, 0.07 mmol) and (3a*R*,4*S*,7*R*,7a*R*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3a*H*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (83 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (1.85 mL). After stirring at rt for 40 h, triethylamine (10 μL) was added and the solvent was concentrated. The residue was partially purified via column chromatography (SiO_2, 3:1:1 hexanes:EtOAc:CH_2Cl_2) to provide **41d**, which was used without further purification (30 mg).

Carbonate **41d** was added to MeOH (10.0 mL), CH_2Cl_2 (1.0 mL), and triethylamine (1.0 mL) and the solution was stirred for 18 h at rt. The solvent was concentrated and the residue was purified via column chromatography (SiO_2, 2:1 EtOAc:hexanes, then EtOAc) to give **42d** as a colorless oil (12 mg, 6% in three steps): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.28 (d, J = 1.9 Hz, 1H), 7.96 (dd, J = 8.5, 2.4 Hz, 1H), 7.90 (br s, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.75 (br s, 1H), 7.73 (br s, 1H), 7.55 (dd, J = 8.9, 2.2 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.18 (dd, J = 8.9, 2.5 Hz, 1H), 7.15 (m, 1H), 7.11 (m, 1H), 7.09 (d, J = 8.7 Hz, 1H), 6.94 (ddd, J = 8.2, 2.5, 0.8 Hz, 1H), 5.69 (d, J = 2.1 Hz, 1H), 4.28 (dt, J = 9.2, 3.6 Hz, 1H), 4.25 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.62 (s, 3H), 3.39 (d, J = 9.2 Hz, 1H), 2.61 (d, J = 2.5 Hz, 1H), 2.56 (d, J = 3.7 Hz, 1H), 1.41 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.4, 159.6 (2C), 154.2, 139.1, 134.2, 131.8, 131.0, 129.9, 129.7, 129.4, 129.4, 128.6, 128.2, 127.4, 122.2, 120.9, 119.5, 117.3, 115.5, 113.2, 111.3, 110.1, 97.9, 84.7, 78.5, 71.6, 68.8, 62.1, 56.1, 55.6, 29.4, 22.9; IR (film) ν_{max} 3400, 2970, 2930, 2835, 1605, 1535, 1342, 1250, 1178, 1117, 1024, 995, 966, 908, 733 cm^{-1}; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{33}H_{35}NO_8$ 574.2441, found 574.2461.

Anti-Proliferation Assays. Cells were maintained in a 1:1 mixture of Advanced DMEM/F12 (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 GDA at varying concentrations in DMSO (1% DMSO final concentration) was added, and cells

were returned to the incubator for 72 h. At 72 h, the number of viable cells was determined by using an MTS/PMS cell proliferation kit (Promega) per the manufacturer's instructions. Cells incubated in 1% DMSO were used at 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 10 min at 4 °C. Protein concentrations were determined by 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 nitrocellulose membrane, 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.

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Supporting Information Available: Full experimental procedures and characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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