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The synthesis and evaluation of flavone and isoflavone chimeras of novobiocin and derrubone

Jared R. Mays, Stephanie A. Hill, Justin T. Moyers, Brian S. J. Blagg *

Department of Medicinal Chemistry, 1251 Wescoe Hall Drive, Malott 4070, The University of Kansas, Lawrence, KS 66045-7563, United States

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ABSTRACT

The natural products novobiocin and derrubone have both demonstrated Hsp90 inhibition and structure–activity relationships have been established for each scaffold. Given these compounds share several key structural features, we hypothesized that incorporation of elements from each could provide insight to structural features important for Hsp90 inhibition. Thus, chimeric analogues of novobiocin and derrubone were constructed and evaluated. These studies confirmed that the functionality present at the 3-position of the isoflavone plays a critical role in determining Hsp90 inhibition and suggests that the bicyclic ring system present in both novobiocin and derrubone do not share similar modes of binding.

1. Introduction

In the past decade, the 90 kDa heat shock proteins (Hsp90) have garnered interest as a therapeutic target for the treatment of several human pathologies, including cancer.[1–6] As a molecular chaperone, Hsp90 is responsible for the conformational maturation and maintenance of more than 100 cellular proteins.[7,8] Hsp90 substrates function in a wide variety of cellular processes, including receptors, transcription factors, and protein kinase signaling pathways.[9–14] Although many of these individual enzymes/proteins are individually sought-after anticancer targets,[15] inhibition of Hsp90 affords simultaneous degradation of multiple clients through utilization of the ubiquitin-proteasome pathway.[1,11,16–19] Consequently, inhibition of the Hsp90 protein folding machinery results in a combinatorial attack on numerous oncogenic pathways.[16] In addition, studies have revealed that Hsp90 inhibitors accumulate in tumor cells more effectively than normal tissue, leading to differential selectivities of >200-fold.[20,21] Coupled with the observation that Hsp90 is overexpressed in a variety of human malignancies, the development of Hsp90 inhibitors has become an attractive chemotherapeutic approach.

Novobiocin (**1**, Fig. 1) is an ATP mimic that elicits antimicrobial activity through competitive inhibition of DNA Gyrase B's ATP-binding site. Neckers and co-workers hypothesized that novobiocin may also be capable of binding Hsp90, which binds nucleotides in a similar bent conformation as DNA Gyrase B. Subsequent studies demonstrated that novobiocin binds to a novel site within the C-terminus of Hsp90,[22–24] exhibits anti-tumor activity (~700 μM, SkBr3 cells), and induces concentration-dependent degradation of Hsp90 client proteins.[22] Several synthetic analogs of novobiocin have been prepared in an attempt to improve upon the relatively-poor activity manifested by the natural product. One such compound, **A4**, induced the expression of Hsp90 at 10^3–10^4 lower concentration than that required for client protein degradation and exhibited potent neuroprotective effects, but completely lacked

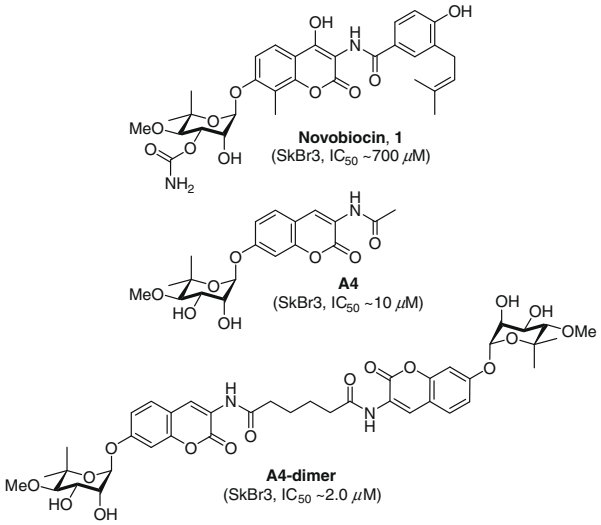

Figure 1. Structures of novobiocin, **A4**, and **A4-dimer**.

* Corresponding author. Tel.: +1 785 864 2288; fax: +1 785 864 5326.
E-mail address: bblagg@ku.edu (B.S.J. Blagg).

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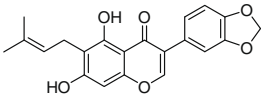


Derrubone, 2
(MCF-7, IC_{50} = 11.9 ± 0.6 μM)

Figure 2. Structure of derrubone.

anti-proliferative activity.[25] In contrast, the **A4-dimer** displayed anti-proliferative activity, implicating the benzamide side chain as a key moiety for conversion of a non-toxic compound into an anti-cancer agent.[26]

In 2008, Burlison et al. described the first structure–activity relationships (SAR) for monomeric novobiocin analogs that exhibit anti-proliferative activity.[27] These studies demonstrated the importance of the 3-benzamide functionality for exhibiting antitumor activity and explored structural requirements of the benzamide sidechain. Further elucidation of the anti-proliferative SAR for the novobiocin scaffold were provided by the construction of analogs that contained variations of the coumarin ring system.[28] Coumarins bearing substituents at the 5-, 6-, and 8-positions were found to possess positional and functional requirements that attenuate anti-proliferative activity, while analogs with quinoline and naphthalene functionalities suggested the coumarin lactone is not required. Together, these results supported ongoing investigations aimed at identifying alternative ring systems to bridge the benzamide and noviose moieties.

The prenylated isoflavone, derrubone (**2**, Fig. 2), was originally isolated from *Derris robusta* in 1969.[29] In 2007, a high-throughput screen identified **2** as a low micromolar inhibitor of Hsp90.[30] Soon after, a library of derrubone analogues was prepared and evaluated for anti-proliferation activity.[31] Analogues exhibiting modest improvements in activity over the natural product were identified and found to induce concentration-dependent degradation of Hsp90 client proteins. Preliminary structure–activity trends demonstrated the importance of the 6-prenyl and 3-aryl sidechains for manifesting improved anti-proliferative activity. However, no further understanding was gained towards elucidating derrubone's mode of Hsp90 inhibition, either through interaction with the N-terminus, the C-terminus, or an alternative mechanism of action.

Prior knowledge of SAR exhibited by novobiocin and derrubone analogues suggested these two seemingly-diverse scaffolds may share common structural features (Fig. 3). For example, both molecules contain an electron-deficient core in the form of an isoflavone or coumarin bicyclic ring system (highlighted in red) that are functionalized at the 3- and 7-positions with aryl-containing or hydroxyl functionalities, respectively. Furthermore, novobiocin analogues with alternative bicyclic ring systems in lieu of the coumarin were shown to retain Hsp90 inhibitory activity for novobiocin-derived C-terminal inhibitors.[28] In addition, previous

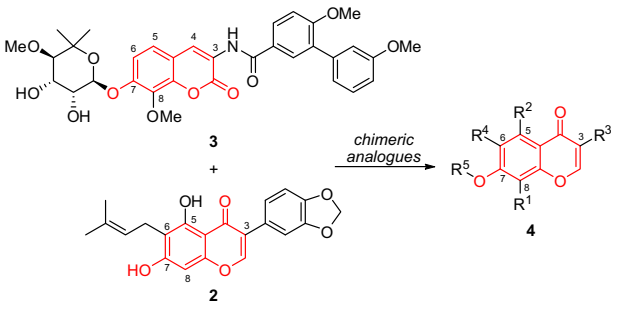


Figure 3. Proposed overlay of novobiocin analogues (e.g., **3**) and **2** that were used to prepare flavone and isoflavone chimeras (**4**).

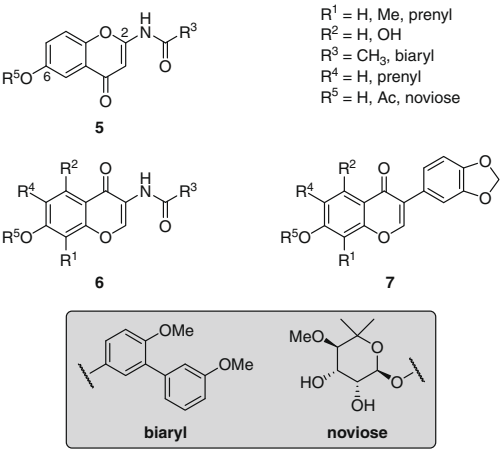


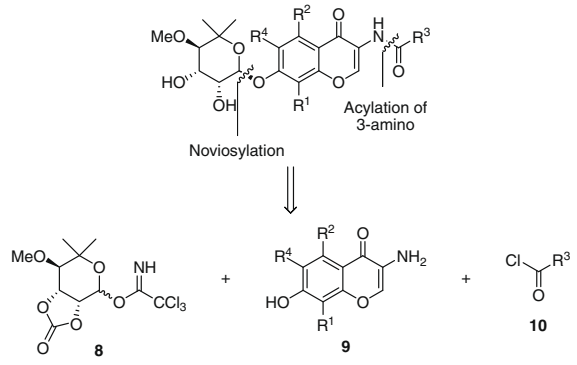
Figure 4. Novobiocin–derrubone chimeric analogues.

studies on the novobiocin scaffold demonstrated that 6- and 8-alkyl groups were well-tolerated and can afford increased antitumor activity (e.g., **3**).[27,28,32] Similarly, 6- or 8-prenyl groups also appear essential for derrubone analogues to exert anti-proliferative activity and Hsp90 inhibition.[31] These observations, along with the fact that no co-crystal structure of an inhibitor bound to the Hsp90 C-terminus exists, led us to question whether these molecules exert their activities through binding the same region of Hsp90. We hypothesized that the bicyclic motif of **1** and **2** were analogous and that incorporation of elements from both molecular libraries would provide insight into how structural features impact the mode and capacity of Hsp90 inhibition. The design, synthesis and evaluation of such chimeric molecules are described within this article.

2. Results and discussion

2.1. Design of novobiocin–derrubone chimeras

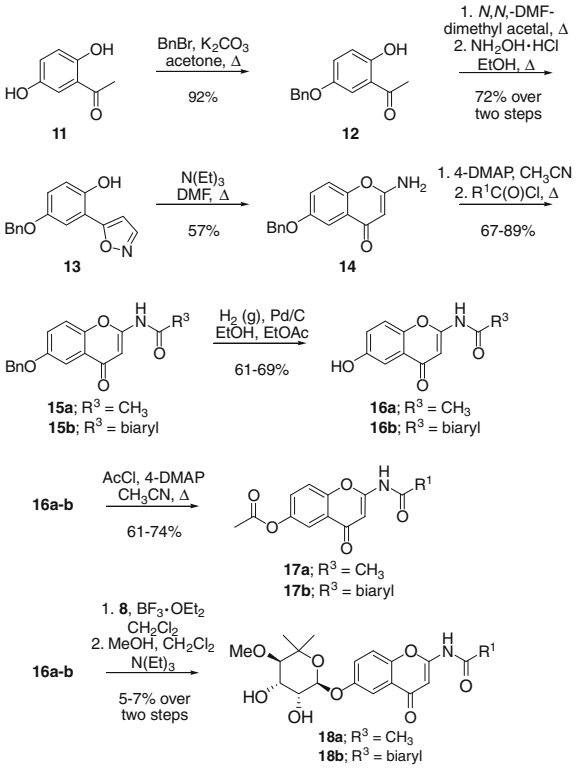
To test our hypothesis, we set out to prepare a library of novobiocin and derrubone chimeric analogues (Fig. 4). This panel of analogues was unified by the isoflavone ring system that would differentially impart functionalities common to either the novobiocin or derrubone scaffold at the 3-, 5-, 6-, 7-, and 8-positions. In particular, key functionalities included the 3-benzamide or 3-acetamide, 8-methyl, and 7-functionalities identified from previously-described novobiocin libraries[27,28,32] and the 3-(3,4-methylenedioxy)phenyl, 5-hydroxyl, and 6-prenyl functionalities from the reported derrubone library.[31] In addition, the panel included



Scheme 1. Representative retrosynthesis of isoflavone chimeric analogues.

a smaller subset of 2-amidoflavone analogues (**5**) to compare and contrast with the corresponding 3-amido-isoflavones. Isoflavone analogues were grouped into two basic structural categories; 3-amido-isoflavones (**6**) and 3-(3,4-methylenedioxy)phenyl-isoflavones (**7**).

As shown in Scheme 1, the derivatives were prepared in modular fashion through sequential coupling of noviose and acylation of the 3-amino-7-hydroxy-(iso)flavones (**9**). We envisioned that the trichloroacetimidate of noviose carbonate (**8**) could be coupled with 3-amino-6-hydroxyflavones or 3-amino-7-hydroxyisoflavones in a manner similar to that previously described in our group.[33] Selection of the biaryl acid and acetamide was based upon previously obtained SAR for the benzamide side chain, which is known to bifurcate antitumor from neuroprotective activity, respectively.[25,27]



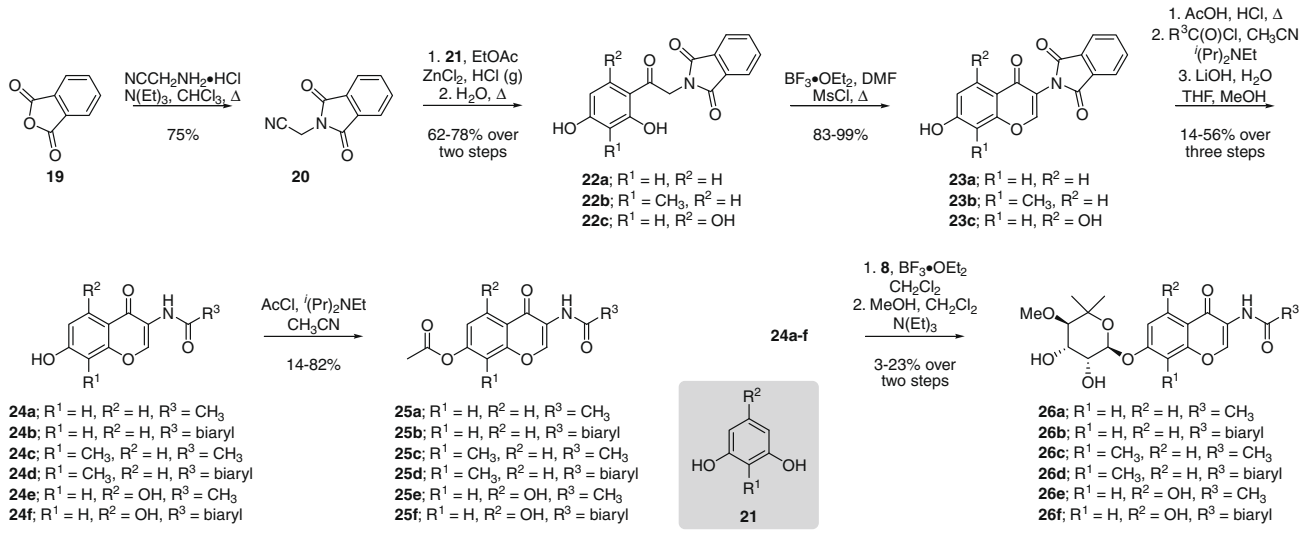
Scheme 2. Preparation of 2-amidoflavone analogues.

2.2. Syntheses of 2-amidoflavone analogues

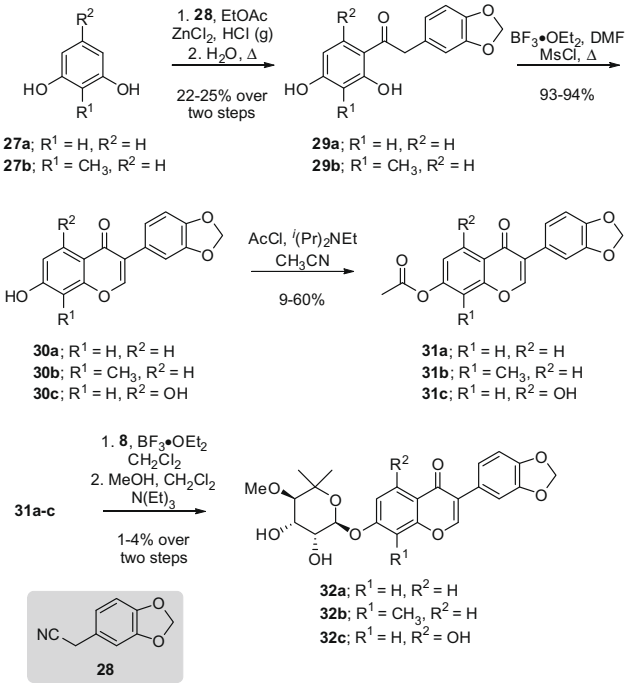
Novobiocin analogues that contain a flavone ring system in lieu of the coumarin were constructed to assess the impact of alternative ring systems for Hsp90 inhibition. Benzyl protection of the 5'-phenol of **11** provided **12** (Scheme 2).[34] Reaction of **12** with *N*,*N*-dimethylformamide dimethyl acetal afforded an enamine intermediate, which was condensed with hydroxylamine–hydrochloride to give isoxazole, **13**.[35] Under thermal and basic conditions, **13** was converted to the 3-aminoflavone, **14**. Acylation of aniline **14** provided amides **15a–b** in excellent yield,[36] which upon hydrogenolysis, yielded phenols **16a–b** as common intermediates.[37] Acylation of the 7-hydroxyl functionality afforded **17a–b**.[36] Phenols **16a–b** were reacted with the trichloroacetimide of noviose carbonate (**8**) in the presence of boron trifluoride etherate to provide noviosylated intermediates that, after carbonate removal, gave analogues **18a–b**.[33] Selective deprotection of the carbonate intermediates presented an unexpected challenge as hydrolysis of the amide was also observed, likely a result of the functionality's vinylogous imide-like properties.

2.3. Syntheses of 3-amido-isoflavone analogues

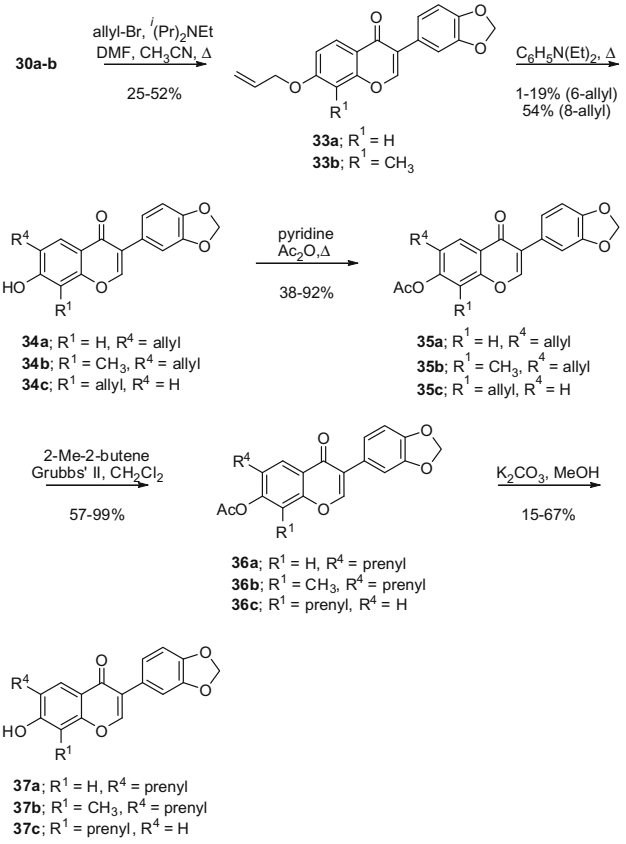
Similarly, 3-amido-isoflavone analogues were constructed as complementary, regioisomeric variants of chromone-containing chimeric Hsp90 inhibitors. The two-step Hoesch condensation of **20** with appropriate resorcinols or phloroglucinols (**21**) followed by imine hydrolysis afforded aryl ketones **22a–c** in high yield (Scheme 3).[31,38] Notably, the phthalimide functionality proved more useful than simply a nitrogen protecting group, as poor phthalide solubility provided a handle to aid crystallization of subsequent intermediates. Cyclization of intermediates **22a–c** to isoflavones **23a–c** was performed using Bischler–Napieralski conditions as previously described.[31] Interestingly, cyclization of phloroglucinol-containing analogue **22c** was accomplished in 48 h, while 4-keto-resorcinols **22a–b** required 120 h. Presumably, this difference resulted from hydrogen bonding interactions between the *ortho*-phenol and ketone, precluding rotation to the required conformation for enamine displacement. Phthalide



Scheme 3. Preparation of 3-amido-isoflavone analogues.



Scheme 4. Preparation of (3,4-methylenedioxy)phenyl-isoflavone analogues.



Scheme 5. Preparation of 5-deoxy-derrubone analogues.

deprotection of **23a–c** under thermal and acidic conditions[39,40] provided 3-amino-isoflavone intermediates that were difficult to separate from the resulting *ortho*-phthalic acid. Consequently, a one-pot, three-step deprotection, acylation, and hydrolysis procedure was employed to convert 3-phthalamido intermediates **23a–c** into 3-amido analogues **24a–f** in moderate yield. Acylation of intermediates **24a–f** afforded 7-acetoxy analogues, **25a–f**.[36] Novioslyation and deprotection of **24a–f** as previously described provided analogues **26a–f**.[33]

2.4. Syntheses of 3-(3,4-methylenedioxy)phenyl-isoflavone analogues

Analogues based on the 3-aryl-isoflavone core of derrubone were constructed to determine whether inclusion of 5-, 6-, 7-, and 8-functionalities of derrubone and/or novobiocin impart increased Hsp90 inhibitory activity. Reaction of resorcinols **27a–b** with (3,4-methylenedioxyphenyl)acetonitrile under Hoesch conditions, followed by hydrolysis, afforded 2-keto-resorcinols **29a–b**, which were cyclized to isoflavones **30a–b** using the Bischler–Napieralski protocol (Scheme 4).[31,38,41] Together with **30c**,[31] these isoflavones served as scaffolds for further analogue construction. Acylation of the 7-phenol in **30a–c** afforded **31a–c**.[36] Similarly, noviosylation of **30a–c** and subsequent carbonate hydrolysis provided 7-glycosylated analogues **32a–c**.[33]

2.5. Syntheses of 5-deoxy-derrubone analogues

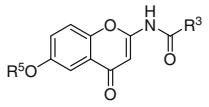
Starting with 5-deoxy-isoflavones **30a–b**, allylation of the 7-phenol afforded **33a–b** in moderate yields (Scheme 5).[36] Claisen rearrangement of **33a–b** under thermal conditions provided *C*-allyl analogues **34a–c**.[32] When **33a** was reacted, formation of 8-allyl **34c** was preferred versus 6-allyl **34a** as previously described, although both compounds could be produced via this process.[31] We hypothesized that inclusion of an 8-methyl functionality in **33b** would serve a dual purpose in simultaneously providing the ~10-fold increased Hsp90 inhibitory activity demonstrated by 8-methyl-novobiocin analogues[27,28] and preventing formation of the thermodynamically-preferred, yet ultimately undesired, 8-allyl Claisen product. Protection of the phenols of **34a–34c** as acetates yielded 7-acetoxy **35a–c**,[31] which were subjected to olefin cross-metathesis with 2-methyl-2-butene using the second generation Grubbs' catalyst to afford prenylated compounds **36a–c**.[31] Removal of the acetate protecting groups provided 5-deoxy derrubone analogs, **37a–c**.[31]

2.6. Biological evaluation of flavone and isoflavone analogues

Upon construction of the novobiocin–derrubone chimeric library, the compounds were evaluated for anti-proliferative activity against SkBr3 (estrogen receptor negative, Her2 overexpressing breast cancer cells) and MCF-7 (estrogen receptor positive breast cancer cells). As shown in Tables 1 and 2, all 2-acetamido-flavones and 3-acetamido-isoflavones ($R^3 = CH_3$) were inactive, with the sole exception of **25e**, which manifested modest anti-proliferative activity (93.7 ± 6.5 μM) against MCF-7 cells. These results are unsurprising and support previous observations that **A4** and other related 3-acetamidocoumarins do not affect cell growth.[25]

In contrast, all but one biaryl benzamide-containing analogue (Tables 1 and 2, R^3 = biaryl) exhibited anti-proliferative activity ranging from ~3 to 50 μM against both cell lines. The 6-hydroxyflavone, **16b**, and 7-hydroxyisoflavones, **24b**, **24d**, and **24f**, exhibited between 1.9 and 9-fold decreased activity against SkBr3 cells. Analogous 7-acetoxy analogues **25b**, **25d**, and **25f** did not demonstrate a large disparity in activities against MCF-7 and SkBr3 cells as their phenolic counterparts. The sole exception to this trend was **17b**, which was completely inactive against both cell lines for reasons that remain unclear. By comparison, 7-noviosylated cogeners (R^5 = noviose) were less active than 7-hydroxy and 7-acetoxy analogues but demonstrated equivalent potency against both cell lines. This observation supports the notion that **26b**, **26d**,

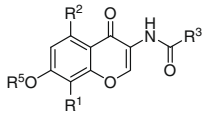
Table 1
Anti-proliferation activities of 2-amido-flavone analogues



Entry (IC_{50}, μM)	R^3	R^5	MCF-7	SkBr3
16a	CH_3	H	>100[a]	>100
16b	Biaryl	H	10.5 ± 0.1	19.6 ± 2.9
17a	CH_3	Ac	>100	>100
17b	Biaryl	Ac	>100	>100
18a	CH_3	Noviose	>100	>100
18b	Biaryl	Noviose	14.7 ± 3.0	33.8 ± 0.7

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

Table 2
Anti-proliferation activities of 3-amido-isoflavone analogues



Entry (IC_{50}, μM)	R^1	R^2	R^3	R^5	MCF-7	SkBr3
24a	H	H	CH_3	H	>100[a]	>100
24b	H	H	Biaryl	H	8.6 ± 1.1	37.1 ± 1.8
24c	CH_3	H	CH_3	H	>100	>100
24d	CH_3	H	Biaryl	H	4.9 ± 0.1	44.1 ± 8.8
24e	H	OH	CH_3	H	>100	>100
24f	H	OH	Biaryl	H	9.7 ± 0.4	21.3 ± 0.6
25a	H	H	CH_3	Ac	>100	>100
25b	H	H	Biaryl	Ac	9.5 ± 1.1	18.4 ± 0.1
25c	CH_3	H	CH_3	Ac	>100	>100
25d	CH_3	H	Biaryl	Ac	4.8 ± 0.6	17.0 ± 4.7
25e	H	OH	CH_3	Ac	93.7 ± 6.5	>100
25f	H	OH	Biaryl	Ac	5.1 ± 0.2	3.3 ± 0.1
26a	H	H	CH_3	Noviose	>100	>100
26b	H	H	Biaryl	Noviose	25.2 ± 2.8	29.0 ± 4.5
26c	CH_3	H	CH_3	Noviose	>100	>100
26d	CH_3	H	Biaryl	Noviose	51.6 ± 1.3	46.0 ± 5.4
26e	H	OH	CH_3	Noviose	>100	>100
26f	H	OH	Biaryl	Noviose	23.6 ± 2.8	19.4 ± 1.0

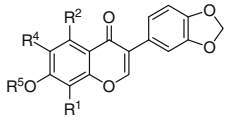
[a] Values represent mean ± standard deviation for at least two separate experiments performed in triplicate.

and **26f** induce their activity through similar modes of action against both MCF-7 and SkBr3 cells, a feature typically observed for other novobiocin-derived Hsp90 inhibitors.[27,28,32]

Unfortunately, in comparison to previously-described coumarin-containing analogues,[27] both the 2-amidoflavone and 3-amido-isoflavone ring systems demonstrated decreased anti-proliferative activity. In comparison to the analogous 8-methyl-coumarin-containing analogue, **18b**, **25f**, and **26d** manifested between 0 and 6-fold decreased activities against MCF-7 and SkBr3 cell lines. Interestingly, most analogues containing the 5-hydroxyl exhibited similar activities as analogous 5-proteo derivatives, suggesting that this functionality neither increases nor decreases activity. In contrast to trends observed in coumarin-containing analogues,[27,28] inclusion of the 8-methyl functionality to the isoflavone derivatives garnered a more modest 1.8–2.0-fold increase in anti-proliferative activity for 7-hydroxy and 7-acetoxy derivatives and a 1.6–2.0-fold decrease in activity for 7-noviosylated products.

As shown in Table 3 and 3-(3,4-methylenedioxy)phenyl-isoflavone analogues with similarity to the derrubone scaffold demonstrated interesting trends in anti-proliferation activity. In

Table 3
Anti-proliferation activities of 3-(3,4-methylenedioxy)phenyl isoflavone analogues



Entry (IC_{50}, μM)	R^1	R^2	R^4	R^5	MCF-7	SkBr3
30a	H	H	H	H	>100[a]	>100
30b	CH_3	H	H	H	>100	>100
30c	H	OH	H	H	70.0 ± 10.0	>100
31a	H	H	H	Ac	>100	>100
31b	CH_3	H	H	Ac	>100	>100
31c	H	OH	H	Ac	>100	>100
32a	H	H	H	Noviose	9.2 ± 0.1	18.0 ± 2.1
32b	CH_3	H	H	Noviose	18.4 ± 0.9	21.4 ± 4.6
32c	H	OH	H	Noviose	>100	>100
37a	H	H	Prenyl	H	13.1 ± 0.4	36.5 ± 3.0
37b	CH_3	H	Prenyl	H	49.2 ± 10.7	>100
37c	Prenyl	H	H	H	39.1 ± 3.9	18.8 ± 4.5

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

contrast to 3-amido analogues, those lacking either 7-noviose or prenyl functionalities were inactive against both cell lines, an observation supportive of previously-described trends.[31] Detectable anti-proliferation activity was only observed for analogues bearing either a 7-noviose, 6-prenyl, or 8-prenyl functionality. The 7-noviosylated analogues **32a–b** manifested IC_{50}s between 9 and 21 μM. For reasons that remain unclear, **32c** was completely inactive. In contrast, prenylated derivatives, **37a–c**, exhibited activities ranging from 13 μM to greater than 100 μM. Replacement of 7-noviose (**32a**) with either a 6- (**37a**) or 8-prenyl (**37c**) functionality appeared to induce differential properties against these two cell lines.

Comparing the anti-proliferation activities of **37a–c** to those observed for **2** and other previously-disclosed derrubone analogues[31] provides insight into the role of the 5-hydroxyl and 8-methyl functionalities. While the data suggests that removal of the 5-hydroxyl functionality does not impact anti-proliferation activity, its inclusion is useful for selectively installing the 6-prenyl functionality in derrubone analogues.[31] We had hoped that inclusion of an 8-methyl (**37b**) would simultaneously provide enhanced activity and selectivity during the Claisen rearrangement. While incorporation of an 8-methyl fulfilled the latter objective, such analogues demonstrated nearly fourfold decreased activity.

Some of the more intriguing structure–activity trends were observed through comparison of 3-biarylbenzamide isoflavone analogues and 3-(3,4-methylenedioxy)phenyl isoflavone derivatives. The 7-hydroxy and 7-acetoxy isoflavone analogues with the 3-biaryl amide were collectively the most potent compounds in the library, while corresponding analogues containing the 3-(3,4-methylenedioxy)phenyl sidechain were inactive. On its own, this observation implicates the essential nature of the 3-benzamide sidechain for manifestation of anti-proliferation activity. However, the same trend was not evident when comparing the 7-noviosylated derivatives, as 3-(3,4-methyelendioxy)phenyl-containing analogues **32a–b** were between 1.6 and 2.8-fold more active than 3-benzamide analogues **26b** and **26d**. Together, these trends indicate that the relationship between inclusion of the 3-functionality and anti-proliferation activity is complex.

To provide additional support that the anti-proliferation activities of this library of analogues results from Hsp90 inhibition, analogues **26b** and **37c** were evaluated for their ability to induce degradation of Hsp90-dependent client proteins. As shown in Fig-

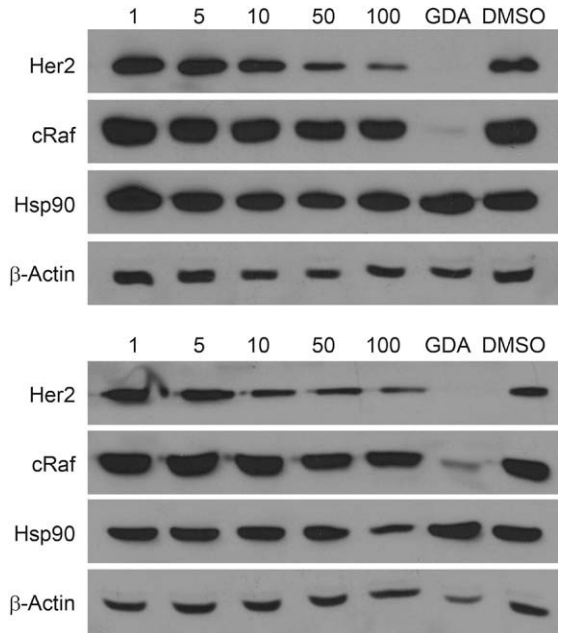


Figure 5. Western blot analysis of Hsp90 and Hsp90 client proteins against MCF-7 breast cancer cells. Concentrations (in μM) of **26b** (top) and **37c** (bottom) are indicated above each lane. GDA (geldanamycin, 500 nM) and DMSO were, respectively employed as positive and negative controls.

ure 5, analogues **26b** and **37c** both induced concentration-dependent degradation of Hsp90 client proteins Her2 and cRaf. β-Actin, a non-Hsp90-dependent protein, was not affected by these analogues indicating selective degradation of Hsp90-dependent clients. The anti-proliferative activities (**26b**, IC_{50} = 25.2 μM; **37c**, IC_{50} = 39.1 μM) correlate well with the concentrations needed to induce Hsp90 client protein degradation, thereby linking Hsp90 inhibition directly to cell viability. None of these analogues induce the concentration-dependent increase in Hsp90 levels correlating to activation of the heat shock response, a feature consistent with other C-terminal Hsp90 inhibitors. A summary of structure–activity trends for flavone and isoflavone chimeras of novobiocin and derrubone are depicted in Figure 6.

3. Conclusions

Although many of the chimeric analogues of novobiocin and derrubone exhibit anti-proliferative activities, differences observed in structure–activity trends do not support our original hypothesis that the isoflavone ring of derrubone is analogous to the coumarin ring system present in the novobiocin scaffold. However, the identity of the functionality at the 3-position appears to play a critical role in determining the potency and mode of anti-proliferative activity observed for both scaffolds. The 3-acetamide analogues were found to be non-toxic and may represent scaffolds that exhibit neuroprotection activity similar to **A4**, while 3-biarylbenzamide derivatives (e.g., **26b**) display moderate anti-proliferation and downregulation of Hsp90 client proteins. Biarylbenzamide analogues containing a hydroxyl (**16b**) or acetoxy (**25d**) substituent in lieu of the typical noviose sugar exert anti-proliferative effects more readily than the corresponding noviosylated derivatives. Isoflavone analogues containing the 3-aryl sidechain of derrubone only manifest anti-proliferation activity when noviosylated (**32a**) or prenylated (**37a**).

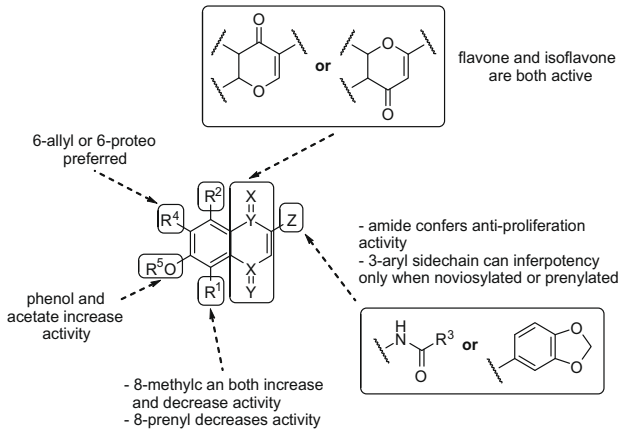


Figure 6. Summary of structure–activity trends for chimeric analogues of novobiocin and derrubone.

4. Experimental

4.1. 1-(5-(Benzyloxy)-2-hydroxyphenyl)ethanone (12)

Potassium carbonate (1.81 g, 13.09 mmol) and benzyl bromide (1.56 mL, 2.24 g, 13.12 mmol) were added in sequence to 2',5'-dihydroxyacetophenone (2.00 g, 13.15 mmol) in acetone (41.0 mL) and the solution was then heated to reflux for 48 h. After cooling to rt, the reaction was diluted with saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with EtOAc (3 × 250 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, 5:1 hexanes/EtOAc) to give **12** as a yellow amorphous solid (2.92 g, 92%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.87 (s, 1H), 7.47–7.38 (m, 4H), 7.30 (m, 1H), 7.26 (d, J = 3.0 Hz, 1H), 7.19 (dd, J = 9.1, 3.0 Hz, 1H), 6.93 (d, J = 9.1 Hz, 1H), 5.06 (s, 2H), 2.59 (s, 3H).

4.2. 4-(Benzyloxy)-2-(isoxazol-5-yl)phenol (13)

A suspension of **12** (5.05 g, 20.82 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (40.8 mL) was then heated to 90 °C for 2 h. After cooling to rt, the yellow precipitate was collected by filtration, washed with cold hexanes, and used without further purification.

Hydroxylamine hydrochloride (1.76 g, 25.29 mmol) was added to a solution of the enamine (20.82 mmol) in EtOH (245 mL) and the solution was then heated to reflux for 1 h. After cooling to rt, the solvent was concentrated, the residue was washed with water (200 mL), the solid was collected by filtration, redissolved in hot EtOAc (400 mL), filtered, and concentrated. Recrystallization from EtOAc/hexanes gave **13** as a near-colorless amorphous solid (4.00 g, 72% over two steps): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.17 (br s, 1H), 8.62 (d, J = 1.8 Hz, 1H), 7.47 (m, 2H), 7.43–7.37 (m, 3H), 7.33 (m, 1H), 7.03 (dd, J = 8.9, 3.0 Hz, 1H), 6.97 (d, J = 8.9 Hz, 1H), 6.89 (d, J = 1.8 Hz, 1H), 5.11 (s, 2H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 164.9, 151.6, 151.1, 148.9, 137.2, 128.4 (2C), 127.8, 127.6 (2C), 118.9, 117.5, 113.8, 111.7, 102.6, 69.8; IR (film) ν_{max} 3101, 1576, 1518, 1479, 1421, 1381, 1273, 1258, 1204, 1124, 1020, 930, 816, 789, 7466, 698 cm^{-1}; HRMS (ESI$^+$) m/z: $[M+H]^+$ calcd for $C_{16}H_{13}NO_3$, 268.0974; found, 268.0967.

4.3. 2-Amino-6-(benzyloxy)-4*H*-chromen-4-one (14)

Triethylamine (2.30 mL, 1.67 g, 16.50 mmol) was added to **13** (2.24 g, 8.38 mmol) in anhydrous *N*,*N*-dimethylformamide (93.0 mL) and the solution was then heated to 140–150 °C for 18 h. After cooling to rt, the solvent was concentrated, the residue

was suspended in water (200 mL), and the resulting solid was collected by filtration through Celite. The solid was eluted with hot MeOH, the solvent was concentrated, cold Et_2O (100 mL) was added, and the solid collected by filtration to give **14** as a yellow-orange amorphous solid (2.20 g, 57%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.49–7.44 (m, 4H), 7.43 (d, J = 3.1 Hz, 1H), 7.41 (m, 2H), 7.34 (m, 1H), 7.33 (d, J = 9.0 Hz, 1H), 7.25 (dd, J = 9.0, 3.1 Hz, 1H), 5.17 (s, 2H), 5.16 (s, 1H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 174.2, 164.8, 154.9, 147.7, 136.9, 128.4 (2C), 127.9, 127.7 (2C), 123.7, 120.6, 117.9, 107.1, 84.8, 69.6; IR (film) ν_{max} 1609, 1556, 1541, 1456, 1275, 1261, 764, 750, 681 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{16}H_{13}NO_3$, 268.0974; found, 268.0985.

4.4. *N*-(6-(Benzyloxy)-4-oxo-4*H*-chromen-2-yl)acetamide (15a)

4-(Dimethylamino)pyridine (346 mg, 2.83 mmol) was added to a suspension of **14** (490 mg, 1.83 mmol) in anhydrous acetonitrile (13.0 mL) at rt. After 3 h, acetyl chloride (675 μL, 745 mg, 9.49 mmol) was added and the solution was then heated to reflux for 18 h. After cooling to rt, water (100 mL) was added and the precipitate was collected by filtration and washed with cold Et_2O (100 mL) to give **15a** as a colorless amorphous solid (495 mg, 87%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.24 (br s, 1H), 7.50 (d, J = 9.1 Hz, 1H), 7.50–7.46 (m, 3H), 7.45–7.39 (m, 3H), 7.35 (m, 1H), 6.77 (s, 1H), 5.22 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 176.7, 169.2, 156.6, 155.5, 147.9, 136.6, 128.5 (2C), 128.0, 127.7 (2C), 123.6, 123.0, 119.0, 106.5, 95.0, 69.8, 24.2; IR (film) ν_{max} 2920, 2851, 1711, 1622, 1603, 1564, 1458, 1261, 843, 824, 764, 750, 739 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{18}H_{15}NO_4$, 310.1079; found, 310.1064.

4.5. *N*-(6-(Benzyloxy)-4-oxo-4*H*-chromen-2-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (15b)

4-(Dimethylamino)pyridine (346 mg, 2.83 mmol) was added to a suspension of **14** (500 mg, 1.87 mmol) in anhydrous acetonitrile (10.0 mL) at rt. After 3 h, freshly prepared 4-methoxy-3-(3-methoxyphenyl)benzoyl chloride[28] (1.02 g, 3.67 mmol) in anhydrous acetonitrile (3.0 mL) was added and the solution was then heated to reflux for 18 h. After cooling to rt, water (100 mL) was added, the precipitate was collected by filtration and washed with cold Et_2O (200 mL). The solid was redissolved in EtOAc (400 mL) and was washed with 1 M aqueous NaOH solution (2 × 200 mL), saturated aqueous $NaHCO_3$ solution (200 mL), saturated aqueous NaCl solution (200 mL), dried (Na_2SO_4), filtered, and concentrated to give **15b** as a light brown amorphous solid (658 mg, 69%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.42 (br s, 1H), 8.05 (dd, J = 8.5, 2.5 Hz, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 9.1 Hz, 1H), 7.52–7.48 (m, 3H), 7.44 (dd, J = 9.2, 3.1 Hz, 1H), 7.42 (m, 2H), 7.38 (t, J = 7.9 Hz, 1H), 7.36 (m, 1H), 7.28 (d, J = 8.6 Hz, 1H), 7.17–7.13 (m, 2H), 6.97 (m, 1H), 6.96 (s, 1H), 5.23 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 176.8, 173.4, 165.0, 159.6, 159.0, 155.5, 148.2, 138.5, 136.7, 130.0, 129.2, 129.1, 128.5 (2C), 128.0, 127.8 (2C), 125.1, 123.7, 123.0, 121.8, 119.1, 115.4, 112.5, 111.6, 106.5, 96.3, 69.8, 56.0, 55.1; IR (film) ν_{max} 1686, 1601, 1572, 1528, 1502, 1479, 1452, 1285, 1231, 1204, 1190, 1034, 1020, 818, 783, 754, 733, 700 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{31}H_{25}NO_6$, 508.1760; found, 508.1745.

4.6. *N*-(6-Hydroxy-4-oxo-4*H*-chromen-2-yl)acetamide (16a)

Palladium on carbon (10%, 48 mg) was added to **15a** (85 mg, 0.28 mmol) in 1:1 EtOAc/EtOH (17 mL) and the reaction was placed under an atmosphere of H_2 and stirred for 48 h at rt. The reaction was filtered through Celite and the solvent was concentrated. Recrystallization from CH_2Cl_2/Et_2O gave **16a** as a near-colorless amorphous solid (37 mg, 61%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.19 (br s, 1H), 9.95 (br s, 1H), 7.38 (d, J = 8.9 Hz, 1H), 7.26 (d, J = 3.0 Hz, 1H), 7.17 (dd, J = 8.9, 3.0 Hz, 1H), 6.72 (s, 1H), 2.13 (s, 3H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 177.0, 169.3, 154.7, 146.8, 123.8, 122.2, 118.6, 108.0, 107.2, 94.9, 24.3; IR (film) ν_{max} 1676, 1585, 1263, 1227, 814, 741 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{11}H_9NO_4$, 220.0610; found, 220.0616.

4.7. *N*-(6-Hydroxy-4-oxo-4*H*-chromen-2-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (16b)

Palladium on carbon (10%, 531 mg) was added to **15b** (499 mg, 0.98 mmol) in 3:1 EtOAc/EtOH (120 mL) and the reaction was placed under an atmosphere of H_2 and stirred for 18 h at rt. The reaction was filtered through Celite and the solvent was concentrated. Recrystallization from CH_2Cl_2/Et_2O gave **16b** as an orange amorphous solid (282 mg, 69%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.35 (br s, 1H), 9.96 (br s, 1H), 8.04 (dd, J = 8.5, 2.4 Hz, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.43 (d, J = 8.9 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 3.0 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.20 (dd, J = 8.9, 3.0 Hz, 1H), 7.17–7.13 (m, 2H), 6.97 (ddd, J = 8.3, 2.5, 0.9 Hz, 1H), 6.91 (s, 1H), 3.88 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 177.0, 159.6, 159.0, 159.0, 157.3, 154.7, 147.1, 138.5, 130.6, 130.0, 129.2, 129.1, 125.2, 123.8, 122.3, 121.8, 118.7, 115.4, 112.5, 111.6, 108.0, 96.2, 56.0, 55.1; IR (film) ν_{max} 1684, 1603, 1576, 1522, 1506, 1474, 1229, 1206, 681, 650 cm^{-1}; HRMS (ESI$^+$) m/z: [M+Na]$^+$ calcd for $C_{24}H_{19}NO_6$, 440.1110; found, 440.1098.

4.8. 2-Acetamido-4-oxo-4*H*-chromen-6-yl acetate (17a)

4-(Dimethylamino)pyridine (28 mg, 0.23 mmol) and acetyl chloride (32 μL, 35 mg, 0.45 mmol) were sequentially added to **16a** (31 mg, 0.14 mmol) in anhydrous acetonitrile (1.00 mL) and the solution was then heated to 80 °C in a sealed flask for 18 h. After cooling to rt, the reaction was diluted with water (10 mL) and the solid was collected by filtration and washed with cold Et_2O (20 mL) to give **17a** as a light brown amorphous solid (27 mg, 74%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.34 (br s, 1H), 7.69 (d, J = 2.8 Hz, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.55 (dd, J = 8.9, 2.8 Hz, 1H), 6.81 (s, 1H), 2.31 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 176.5, 169.4, 169.3, 157.0, 150.8, 147.4, 127.9, 123.6, 119.0, 117.2, 95.1, 24.3, 20.9; IR (film) ν_{max} 1759, 1747, 1713, 1693, 1607, 1205, 1190, 1170, 1128, 986, 939, 899, 841, 820, 804, 750, 725, 685 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{13}H_{11}NO_5$, 262.0715; found, 262.0717.

4.9. 2-(4-Methoxy-3-(3-methoxyphenyl)benzamido)-4-oxo-4*H*-chromen-6-yl acetate (17b)

4-(Dimethylamino)pyridine (33 mg, 0.27 mmol) and acetyl chloride (44 μL, 49 mg, 0.62 mmol) were sequentially added to **16b** (27 mg, 0.06 mmol) in anhydrous acetonitrile (500 μL) and the solution was then heated to 80 °C in a sealed flask for 18 h. After cooling to rt, the reaction was diluted with water (5 mL) and the solid was collected by filtration and washed with cold Et_2O (10 mL) to give **17b** as a brown amorphous solid (18 mg, 61%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.50 (br s, 1H), 8.06 (dd, J = 8.4, 2.4 Hz, 1H), 8.04 (m, 1H), 7.73 (d, J = 2.8 Hz, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.57 (dd, J = 9.0, 2.8 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.18–7.14 (m, 2H), 7.00 (s, 1H), 6.97 (ddd, J = 8.2, 2.5, 0.7 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 176.5, 169.3, 165.1, 159.7, 159.0, 157.7, 151.1, 147.4, 138.5, 130.7, 130.1, 129.3, 129.1, 128.0, 125.0, 123.6, 121.8, 119.0, 117.2, 115.4, 112.5, 111.7, 96.3, 56.0, 55.1, 20.9; IR (film) ν_{max} 1749, 1686, 1614, 1605, 1576,

1539, 1520, 1508, 1474, 1456, 1369, 1288, 1275, 1232, 1205, 1190, 1175, 1018, 818, 719 cm^{-1}; HRMS (ESI^+) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{21}NO_7$, 460.1396; found, 460.1384.

4.10. *N*-(6-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyl-tetrahydro-2*H*-pyran-2-yloxy)-4-oxo-4*H*-chromen-2-yl)acetamide (18a)

Boron trifluoride etherate (15 μL, 0.12 mmol) was added to **16a** (49 mg, 0.23 mmol) and (3*aR*,4*S*,7*R*,7*aR*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3*aH*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (167 mg, 0.46 mmol) in anhydrous CH_2Cl_2 (7.70 mL). After stirring at rt for 18 h, triethylamine (30 μL) was added and the solvent was concentrated. The residue was partially purified via column chromatography (SiO_2, 20:1 CH_2Cl_2/MeOH) and the coupled carbonate was used without further purification.

Carbonate was added to MeOH (4.0 mL) and triethylamine (72 μL) and stirred for 8 h at rt. The solvent was concentrated and the residue purified via PTLC (SiO_2, 8:1 CH_2Cl_2/MeOH) to give **18a** as a colorless amorphous solid (4 mg, 5% over two steps): ^1H NMR (DMSO-d_6, 400 MHz) δ 7.61 (dd, J = 2.1, 1.1 Hz, 1H), 7.25–7.24 (m, 2H), 6.90 (s, 1H), 5.48 (d, J = 2.3 Hz, 1H), 4.05 (dd, J = 9.2, 3.4 Hz, 1H), 3.98 (dd, J = 3.3, 2.4 Hz, 1H), 3.51 (s, 3H), 3.25 (d, J = 9.4 Hz, 1H), 2.11 (s, 3H), 1.26 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 179.6, 169.4, 156.9, 154.1, 148.9, 123.8, 123.2, 118.5, 109.9, 98.6, 96.3, 84.2, 78.5, 71.0, 68.4, 61.7, 28.5, 24.0, 22.9; IR (film) ν_{max} 3423, 1722, 1624, 1601, 1583, 1504, 1483, 1458, 1408, 1364, 1273, 1227, 1115, 1032, 991, 748 cm^{-1}; HRMS (ESI^+) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{23}NO_8$, 394.1502; found, 394.1497.

4.11. *N*-(6-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyl-tetrahydro-2*H*-pyran-2-yloxy)-4-oxo-4*H*-chromen-2-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (18b)

Boron trifluoride etherate (60 μL, 0.49 mmol) was added to **16b** (101 mg, 0.24 mmol) and (3*aR*,4*S*,7*R*,7*aR*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3*aH*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (178 mg, 0.49 mmol) in anhydrous CH_2Cl_2 (8.20 mL). After stirring at rt for 18 h, triethylamine (60 μL) was added and the solvent was concentrated. The residue was partially purified via column chromatography (SiO_2, 20:1 CH_2Cl_2/MeOH) and the coupled carbonate was used without further purification.

Carbonate was added to MeOH (4.0 mL), CH_2Cl_2 (1.0 mL) and triethylamine (200 μL) and stirred for 6 h at rt. The solvent was concentrated and the residue purified via PTLC (SiO_2, 2 × 6:2:1 CH_2Cl_2/EtOAc/MeOH) to give **18b** as a colorless amorphous solid (10 mg, 7% over two steps): ^1H NMR ($CDCl_3$/MeOD, 500 MHz) δ 7.93 (dd, J = 8.6, 2.4 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.64 (d, J = 2.6 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.30–7.26 (m, 2H), 7.10 (s, 1H), 7.09 (m, 1H), 7.06 (dd, J = 2.5, 1.6 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.90 (ddd, J = 8.2, 2.5, 0.9 Hz, 1H), 5.53 (d, J = 2.4 Hz, 1H), 4.12 (dd, J = 9.0, 3.5 Hz, 1H), 4.07 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.57 (s, 3H), 3.30 (d, J = 9.1 Hz, 1H), 1.33 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$/MeOD, 125 MHz) δ 179.3, 164.7, 160.4, 159.4, 157.0, 154.2, 149.1, 138.7, 130.9, 130.6, 129.4, 129.3, 125.2, 124.0, 123.2, 122.1, 118.5, 115.5, 113.1, 111.2, 110.1, 98.5, 96.9, 84.3, 78.6, 71.0, 68.5, 61.9, 56.0, 55.5, 28.7, 23.1; IR (film) ν_{max} 3483, 2976, 2935, 2837, 1691, 1609, 1578, 1524, 1481, 1460, 1367, 1304, 1275, 1234, 1205, 1184, 1157, 1132, 1113, 1078, 1051, 1024, 995, 968, 829, 760, 737 cm^{-1}; HRMS (ESI^+) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{33}NO_{20}$, 592.2183; found, 592.2161.

4.12. 2-(1,3-Dioxoisoindolin-2-yl)acetonitrile (20)

Aminoacetonitrile hydrochloride (5.00 g, 54.06 mmol), triethylamine (7.50 mL, 5.45 g, 53.81 mmol), and phthalic anhydride (8.00 g, 54.02 mmol) in chloroform (65 mL) were then heated to reflux for 18 h. After cooling to rt, the reaction was poured into water (65 mL) and the organic layer was washed with water (100 mL), saturated aqueous NaCl solution (100 mL), dried (Na_2SO4), filtered, and concentrated to give **20** as a colorless amorphous solid (7.54 g, 75%): ^1H NMR ($CDCl_3$, 500 MHz) δ 7.94 (m, 2H), 7.81 (m, 2H), 4.59 (s, 2H).

4.13. 1-(2,4-Dihydroxyphenyl)-2-(2-isoindoline-1,3-dione)ethanone (22a)

Resorcinol (5.66 g, 51.44 mmol) and **20** (8.01 g, 43.02 mmol) in EtOAc (125 mL) was cooled to 0 °C. After 15 min, zinc chloride (3.91 g, 28.72 mmol) was added, hydrochloric acid was bubbled through the solution for 10 min, and the reaction vessel was sealed and warmed to rt over 18 h. The reaction was filtered and the resulting solid was washed with cold EtOAc (3 × 100 mL) then added to water (70 mL) and then heated to reflux for 3 h. After cooling to rt, the solid was collected by filtration and washed with water (3 × 100 mL), then Et_2O (3 × 150 mL) to give **22a** as a colorless amorphous solid (9.91 g, 78%): ^1H NMR (DMSO-d_6, 500 MHz) δ 11.41 (br s, 1H), 10.68 (br s, 1H), 7.95 (m, 2H), 7.91 (m, 2H), 7.82 (d, J = 8.8 Hz, 1H), 6.42 (dd, J = 8.8, 2.3 Hz, 1H), 6.38 (d, J = 2.3 Hz, 1H), 5.06 (s, 2H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 192.5, 167.7 (2C), 165.0, 162.8, 134.8 (2C), 132.5, 131.6 (2C), 123.4 (2C), 112.1, 108.7, 102.5, 45.5; IR (film) ν_{max} 1776, 1693, 1682, 1643, 1420, 1366, 1352, 1313, 1219, 1194, 1182, 1105, 935, 845, 795, 756, 719, 606, 548 cm^{-1}; HRMS (ESI^+) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{11}NO_5$, 298.0715; found, 298.0709.

4.14. 1-(2,4-Dihydroxy-3-methylphenyl)-2-(2-isoindoline-1,3-dione)ethanone (22b)

2-Methylresorcinol (2.38 g, 19.15 mmol) and **20** (3.00 g, 16.12 mmol) in EtOAc (60 mL) was cooled to 0 °C. After 15 min, zinc chloride (1.49 g, 10.95 mmol) was added, hydrochloric acid was bubbled through the solution for 10 min, and the reaction vessel was sealed and warmed to rt over 18 h. The reaction was filtered and the resulting solid was washed with cold EtOAc (3 × 50 mL) then added to water (25 mL) and then heated to reflux for 3 h. After cooling to rt, the solid was collected by filtration and washed with water (3 × 50 mL), then Et_2O (3 × 100 mL) to give **22b** as a yellow amorphous solid (3.39 g, 68%): ^1H NMR (DMSO-d_6, 500 MHz) δ 12.09 (br s, 1H), 10.81 (br s, 1H), 7.97 (m, 2H), 7.92 (m, 2H), 7.86 (d, J = 8.9 Hz, 1H), 6.56 (d, J = 8.9 Hz, 1H), 5.18 (s, 2H), 1.98 (s, 3H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 195.4, 167.6 (2C), 163.3, 162.0, 134.8 (2C), 131.5 (2C), 129.3, 123.4 (2C), 110.5, 110.1, 107.8, 43.2, 7.6; IR (film) ν_{max} 3398, 1767, 1705, 1630, 1618, 1421, 1393, 1317, 1259, 1101, 1067, 955, 783, 764, 752, 716 cm^{-1}; HRMS (ESI^+) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{13}NO_5$, 312.0872; found, 312.0859.

4.15. 1-(2,4,6-Trihydroxyphenyl)-2-(2-isoindoline-1,3-dione)ethanone (22c)

Phloroglucinol (4.07 g, 32.29 mmol) and **20** (5.00 g, 26.86 mmol) in 1:1 Et_2O/EtOAc (100 mL) was cooled to 0 °C. After 15 min, zinc chloride (2.42 g, 17.78 mmol) was added, hydrochloric acid was bubbled through the solution for 10 min, and the reaction vessel was sealed and warmed to rt over 18 h. The reaction was filtered and the resulting solid was washed with cold EtOAc (3 × 50 mL) then added to water (150 mL) and then heated to reflux for 3 h. After cooling to rt, the solid was collected by filtration and washed with water (3 × 100 mL), then Et_2O (3 × 150 mL) to give **22c** as a yellow amorphous solid (5.25 g, 62%): ^1H NMR (DMSO-d_6, 500 MHz) δ 12.07 (br s, 2H), 10.68 (br s, 1H), 7.95 (m,

2H), 7.90 (m, 2H), 5.89 (s, 2H), 4.98 (s, 2H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 195.1, 167.7 (2C), 166.0, 164.3 (2C), 134.8 (2C), 131.6 (2C), 123.3 (2C), 102.2, 94.8 (2C), 47.2; IR (film) ν_{max} 3234, 1761, 1693, 1634, 1587, 1454, 1393, 1229, 1161, 1111, 1068, 951, 712, 513 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{16}H_{11}NO_6$, 314.0665; found, 314.0679.

4.16. 2-(7-Hydroxy-4-oxo-4*H*-chromen-3-yl)isoindoline-1,3-dione (23a)

Boron trifluoride etherate (3.54 mL, 28.68 mmol) was added to **22a** (1.32 g, 4.43 mmol) in anhydrous *N*,*N*-dimethylformamide (17.4 mL) at rt. After 10 min, methanesulfonyl chloride (1.44 mL, 2.13 g, 18.60 mmol) was added and the reaction was then heated to 90 °C for 5 d. After cooling to rt, water (300 mL) was added, the resulting solid was collected by filtration. The solid was dissolved in EtOAc/MeOH (600 mL) and the organic layers were washed with water (400 mL), saturated aqueous NaCl solution (400 mL), dried ($MgSO_4$/$NaSO_4$), filtered, and concentrated to give **23a** as a brown amorphous solid (824 mg, 79%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.14 (br s, 1H), 8.67 (s, 1H), 8.03 (m, 2H), 7.97 (m, 2H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.03 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.01 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 171.7, 166.7 (2C), 163.5, 157.7, 157.0, 135.2 (2C), 131.4 (2C), 127.1, 123.8 (2C), 117.4, 116.1, 115.9, 102.8; IR (film) ν_{max} 2924, 2856, 1722, 1607, 1593, 1375, 1290, 1105, 764, 748, 717 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{17}H_9NO_5$, 308.0559; found, 308.0571.

4.17. 2-(7-Hydroxy-8-methyl-4-oxo-4*H*-chromen-3-yl)isoindoline-1,3-dione (23b)

Boron trifluoride etherate (5.00 mL, 40.51 mmol) was added to **22b** (2.00 g, 6.43 mmol) in anhydrous *N*,*N*-dimethylformamide (24.8 mL) at rt. After 10 min, methanesulfonyl chloride (2.06 mL, 3.05 g, 26.62 mmol) was added and the reaction was then heated to 90 °C for 5 d. After cooling to rt, water (300 mL) was added, the resulting solid was collected by filtration. The solid was dissolved in EtOAc/MeOH (600 mL) and the organic layers were washed with water (400 mL), saturated aqueous NaCl solution (400 mL), dried ($MgSO_4$/$NaSO_4$), filtered, and concentrated to give **23b** as a reddish-brown amorphous solid (1.72 g, 83%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.05 (br s, 1H), 8.73 (s, 1H), 8.04 (m, 2H), 7.97 (m, 2H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 172.1, 166.8 (2C), 161.0, 157.0, 155.8, 135.2 (2C), 131.5 (2C), 123.8 (2C), 123.6, 117.1, 116.0, 114.8, 111.8, 8.1; IR (film) ν_{max} 3393, 1728, 1717, 1661, 1645, 1614, 1385, 1275, 1259, 750 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{18}H_{11}NO_5$, 322.0715; found, 322.0721.

4.18. 2-(5,7-Dihydroxy-4-oxo-4*H*-chromen-3-yl)isoindoline-1,3-dione (23c)

Boron trifluoride etherate (10.8 mL, 87.51 mmol) was added to **22c** (4.01 g, 12.81 mmol) in anhydrous *N*,*N*-dimethylformamide (53.2 mL) at rt. After 10 min, methanesulfonyl chloride (4.40 mL, 6.51 g, 56.85 mmol) was added and the reaction was then heated to 90 °C for 2 d. After cooling to rt, water (600 mL) was added, the resulting solid was collected by filtration. The solid was dissolved in EtOAc/MeOH (800 mL) and the organic layers were washed with water (400 mL), saturated aqueous NaCl solution (400 mL), dried ($MgSO_4$/$NaSO_4$), filtered, and concentrated to give **23c** as a reddish-brown amorphous solid (4.12 g, 99%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.97 (br s, 1H), 11.24 (br s, 1H), 8.69 (s, 1H), 8.04 (m, 2H), 7.98 (m, 2H), 6.54 (d, *J* = 2.1 Hz, 1H), 6.34 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 176.5, 166.6 (2C), 165.2, 161.3, 158.1, 157.6, 135.3 (2C), 131.3 (2C), 123.9 (2C), 115.8, 104.1, 99.9, 94.8; IR (film) ν_{max} 1717, 1699, 1385, 1362, 1175, 1150, 1101, 1041, 679, 650 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{17}H_9NO_6$, 324.0508; found, 324.0514.

4.19. *N*-(7-Hydroxy-4-oxo-4*H*-chromen-3-yl)acetamide (24a)

Compound **23a** (192 mg, 0.62 mmol) in glacial acetic acid (2.0 mL) and concentrated hydrochloric acid (2.0 mL) was then heated to 100 °C. After 5 h, the reaction was diluted with water (10 mL) and the solvent was concentrated with heating. The resulting solid was concentrated from absolute EtOH (3 × 50 mL) and Et_2O (100 mL) and used without further purification.

Acetyl chloride (150 μL, 166 mg, 2.11 mmol) was added to the crude aniline hydrochloride (146 mg, 0.47 mmol) in anhydrous acetonitrile (6.00 mL) and *N*,*N*-diisopropylethylamine (260 μL, 194 mg, 1.50 mmol) and the solution was stirred at rt. After 18 h, the solvent was concentrated with heating, the residue was dissolved in 3:1:1 THF/H_2O/MeOH (50 mL), aqueous lithium hydroxide (3.0 M, 825 μL) was added, and the reaction stirred at rt. After 18 h, the reaction was acidified to pH 1 with 6 M HCl, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 20:1 CH_2Cl_2/MeOH) to give **24a** as a colorless amorphous solid (58 mg, 56% over three steps): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.94 (br s, 1H), 9.33 (s, 1H), 9.11 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 6.94 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.86 (d, *J* = 2.2 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 170.6, 169.2, 162.9, 156.9, 145.5, 127.0, 123.8, 115.3, 114.8, 102.1, 23.3; IR (film) ν_{max} 3406, 1626, 1599, 1556, 1385, 1254, 1204, 1192, 1097, 876, 837, 802 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{11}H_9NO_4$, 220.0610; found, 220.0599.

4.20. *N*-(7-Hydroxy-4-oxo-4*H*-chromen-3-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (24b)

Compound **23b** (1.01 g, 3.14 mmol) in glacial acetic acid (10.0 mL) and concentrated hydrochloric acid (10.0 mL) was then heated to 100 °C. After 5 h, the reaction was diluted with water (50 mL) and the solvent was concentrated with heating. The resulting solid was concentrated from absolute EtOH (3 × 50 mL) and Et_2O (100 mL) and used without further purification.

A solution of freshly prepared 4-methoxy-3-(3-methoxyphenyl)benzoyl chloride[28] (830 mg, 3.00 mmol) in anhydrous acetonitrile (4.00 mL) was added to the crude aniline hydrochloride (1.57 mmol) in anhydrous acetonitrile (8.0 mL) and *N*,*N*-diisopropylethylamine (2.00 mL, 1.49 g, 11.53 mmol) and the solution was stirred at rt. After 18 h, the solvent was concentrated with heating, the residue was dissolved in 3:1:1 THF/H_2O/MeOH (160 mL), aqueous lithium hydroxide (3.0 M, 2.75 mL) was added, and the reaction stirred at rt. After 18 h, the reaction was acidified to pH 1 with 6 M HCl, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 1:1 hexanes/EtOAc to 2:1 EtOAc/hexanes) and triturated from Et_2O to give **24b** as a colorless amorphous solid (197 mg, 29% over three steps): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.94 (br s, 1H), 9.42 (br s, 1H), 9.00 (s, 1H), 7.99 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 2.3 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.14–7.09 (m, 2H), 6.98 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.96 (m, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.4, 164.7, 162.9, 159.0, 159.0, 157.2, 148.2, 138.7, 129.9, 129.4, 129.0, 127.0, 125.7, 123.1, 121.7, 115.5, 115.2 (2C), 112.6, 111.6, 102.3, 55.9, 55.1; IR (film) ν_{max} 3398, 2835, 1626, 1574, 1531, 1485, 1384, 1256, 1205, 1038, 1020, 837, 810, 729 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{24}H_{19}NO_6$, 418.1291; found, 418.1292.

4.21. *N*-(7-Hydroxy-8-methyl-4-oxo-4*H*-chromen-3-yl)acetamide (24c)

Compound **23b** (1.01 g, 3.14 mmol) in glacial acetic acid (10.0 mL) and concentrated hydrochloric acid (10.0 mL) was then heated to 100 °C. After 5 h, the reaction was diluted with water (50 mL) and the solvent was concentrated with heating. The resulting solid was concentrated from absolute EtOH (3 × 50 mL) and Et_2O (100 mL) and used without further purification.

Acetyl chloride (560 μL, 618 mg, 7.88 mmol) was added to the crude aniline hydrochloride (1.57 mmol) in anhydrous acetonitrile (12.00 mL) and *N*,*N*-diisopropylethylamine (2.00 mL, 1.49 g, 11.53 mmol) and the solution was stirred at rt. After 18 h, the solvent was concentrated with heating, the residue was dissolved in 3:1:1 THF/H_2O/MeOH (160 mL), aqueous lithium hydroxide (3.0 M, 2.75 mL) was added, and the reaction stirred at rt. After 18 h, the reaction was acidified to pH 1 with 6 M HCl, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 20:1 CH_2Cl_2/MeOH) to give **24c** as a brown amorphous solid (152 mg, 42% over three steps): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.72 (br s, 1H), 9.33 (br s, 1H), 9.18 (s, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 2.22 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.1, 169.2, 160.2, 155.0, 145.7, 123.5, 123.4, 115.0, 114.0, 110.9, 23.3, 7.9; IR (film) ν_{max} 3256, 3128, 1657, 1626, 1607, 1589, 1556, 1431, 1391, 1342, 1313, 1283, 1205, 1182, 1155, 1068, 1051, 879, 824, 777, 604, 528 cm^{-1}; HRMS (ESI$^+$) *m*/*z*: [M+H]$^+$ calcd for $C_{12}H_{11}NO_4$, 234.0766; found, 234.0763.

4.22. *N*-(7-Hydroxy-8-methyl-4-oxo-4*H*-chromen-3-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (24d)

Compound **23b** (991 mg, 3.23 mmol) in glacial acetic acid (10.0 mL) and concentrated hydrochloric acid (10.0 mL) was then heated to 100 °C. After 5 h, the reaction was diluted with water (50 mL) and the solvent was concentrated with heating. The resulting solid was concentrated from absolute EtOH (3 × 50 mL) and Et_2O (100 mL) and used without further purification.

A solution of freshly prepared 4-methoxy-3-(3-methoxyphenyl)benzoyl chloride[28] (830 mg, 3.00 mmol) in anhydrous acetonitrile (4.00 mL) was added to the crude aniline hydrochloride (1.61 mmol) in anhydrous acetonitrile (8.0 mL) and *N*,*N*-diisopropylethylamine (500 μL, 373 mg, 2.88 mmol) and the solution was stirred at rt. After 18 h, the solvent was concentrated with heating, the residue was dissolved in 3:1:1 THF/H_2O/MeOH (160 mL), aqueous lithium hydroxide (3.0 M, 2.75 mL) was added, and the reaction stirred at rt. After 5 h, the reaction was acidified to pH 1 with 6 M HCl, the solvent was concentrated and the residue was partially purified via column chromatography (SiO_2, 3:1 hexanes/EtOAc to 2:1 hexanes/EtOAc to 2:1 EtOAc/hexanes) and triturated with Et_2O to provide solid that was used without further purification.

Sodium hydroxide (161 mg, 4.03 mmol) was added to a solution of the solid (296 mg) in 1:1 MeOH/THF (15.0 mL). After 15 min, the solution was acidified to pH 1 with 6 M aqueous HCl and the solvent was concentrated. The residue was triturated with Et_2O and the resulting solid collected by filtration to give **24d** as a yellow amorphous solid (87 mg, 14% over three steps): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.80 (br s, 1H), 9.41 (br s, 1H), 9.06 (s, 1H), 8.00 (dd, J = 8.6, 2.4 Hz, 1H), 7.93 (d, J = 2.3 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.13–7.10 (m, 2H), 7.05 (d, J = 8.8 Hz, 1H), 6.96 (ddd, J = 8.3, 2.6, 0.8 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.8, 164.7, 160.4, 160.0, 160.0, 155.3, 148.3, 138.7, 129.9, 129.4, 129.1, 129.0, 125.7, 123.5, 122.8, 121.7, 115.2, 114.2, 112.6, 111.6, 111.1, 55.9, 55.1, 8.0; IR (film) ν_{max} 1603, 1591, 1537, 1516, 1506, 1489, 1474, 1456, 1423, 1406, 1379, 1339, 1310, 1285, 1250, 1207, 1178, 1065, 1020, 779, 690 cm^{-1}; HRMS (ESI$^+$) *m*/*z*: [M+Na]$^+$ calcd for $C_{25}H_{21}NO_6$, 454.1267; found, 454.1284.

4.23. *N*-(5,7-Dihydroxy-4-oxo-4*H*-chromen-3-yl)acetamide (24e)

Compound **23c** (1.00 g, 3.11 mmol) in glacial acetic acid (10.0 mL) and concentrated hydrochloric acid (10.0 mL) was then heated to 100 °C. After 5 h, the reaction was diluted with water (50 mL) and the solvent was concentrated with heating. The resulting solid was concentrated from absolute EtOH (3 × 50 mL) and Et_2O (100 mL) and used without further purification.

Acetyl chloride (1.20 mL, 1.32 g, 16.88 mmol) was added to the crude aniline hydrochloride (3.11 mmol) in anhydrous acetonitrile (24.0 mL) and *N*,*N*-diisopropylethylamine (3.00 mL, 2.24 g, 17.29 mmol) and the solution was stirred at rt. After 18 h, the solvent was concentrated with heating, the residue was dissolved in 3:1:1 THF/H_2O/MeOH (320 mL), aqueous lithium hydroxide (3.0 M, 5.50 mL) was added, and the reaction stirred at rt. After 18 h, the reaction was acidified to pH 1 with 6 M HCl, the solvent was concentrated, water (50 mL) was added, and the solid was collected by filtration and washed with cold Et_2O (50 mL). The residue was purified via column chromatography (SiO_2, 20:1 CH_2Cl_2/MeOH to 5:1 CH_2Cl_2/MeOH) to give **24e** as a beige amorphous solid (329 mg, 45% over three steps): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.32 (br s, 1H), 10.97 (br s, 1H), 9.43 (br s, 1H), 9.04 (s, 1H), 6.39 (d, J = 2.0 Hz, 1H), 6.24 (d, J = 2.0 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 175.3, 169.3, 164.5, 161.3, 156.9, 147.2, 122.3, 103.6, 98.8, 93.8, 23.2; IR (film) ν_{max} 3346, 1630, 1593, 1448, 1364, 1277, 1258, 1200, 1182, 1024, 1003, 870, 843, 804, 797, 669, 652 cm^{-1}; HRMS (ESI$^+$) *m*/*z*: [M+Na]$^+$ calcd for $C_{11}H_9NO_5$, 258.0378; found, 258.0379.

4.24. *N*-(5,7-Dihydroxy-4-oxo-4*H*-chromen-3-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (24f)

Compound **23c** (1.00 g, 3.10 mmol) in glacial acetic acid (10.0 mL) and concentrated hydrochloric acid (10.0 mL) was then heated to 100 °C. After 5 h, the reaction was diluted with water (50 mL) and the solvent was concentrated with heating. The resulting solid was concentrated from absolute EtOH (3 × 50 mL) and Et_2O (100 mL) and used without further purification.

A solution of freshly prepared 4-methoxy-3-(3-methoxyphenyl)benzoyl chloride[28] (1.77 g, 6.41 mmol) in anhydrous acetonitrile (8.00 mL) was added to the crude aniline hydrochloride (3.10 mmol) in anhydrous acetonitrile (16.00 mL) and *N*,*N*-diisopropylethylamine (6.00 mL, 4.47 g, 34.59 mmol) and the solution was stirred at rt. After 18 h, the solvent was concentrated with heating, the residue was dissolved in 3:1:1 THF/H_2O/MeOH (160 mL), aqueous lithium hydroxide (3.0 M, 15.0 mL) was added, and the reaction stirred at rt. After 18 h, the reaction was acidified to pH 1 with 6 M HCl, the solvent was concentrated and the residue was partially purified via column chromatography (SiO_2, 1:1 hexanes/EtOAc). Sodium hydroxide (161 mg, 4.03 mmol) was added to a solution of the residue in 1:1 MeOH/THF (15.0 mL). After 15 min, the solution was acidified to pH 1 with 6 M aqueous HCl and the solvent was concentrated. The residue was triturated with Et_2O and the resulting solid collected by filtration to give **24f** as a colorless amorphous solid (342 mg, 26% over three steps): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.35 (br s, 1H), 11.02 (br s, 1H), 9.55 (s, 3H), 8.88 (s, 1H), 8.00 (dd, J = 8.6, 2.4 Hz, 1H), 7.95 (d, J = 2.4 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.13–7.09 (m, 2H), 6.96 (ddd, J = 8.2, 2.5, 0.9 Hz, 1H), 6.45 (d, J = 2.1 Hz, 1H), 6.27 (d, J = 2.1 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H);

^{13}C NMR (DMSO-d_6, 125 MHz) δ 176.5, 165.1, 164.6, 161.4, 159.0, 159.0, 157.2, 150.8, 138.7, 130.0, 129.4, 129.1 (2C), 125.5, 121.7, 121.6, 115.2, 112.6, 111.6, 103.9, 99.1, 94.1, 55.9, 55.1; IR (film) ν_{max} 3499, 3329, 3132, 2959, 2835, 1666, 1632, 1601, 1587, 1433, 1408, 1369, 1256, 1209, 1171, 1043, 1022, 872, 808.1, 741, 727, 692, 627 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{24}H_{19}NO_7$, 434.1240; found, 434.1233.

4.25. 3-Acetamido-4-oxo-4*H*-chromen-7-yl acetate (25a)

N,*N*-Diisopropylethylamine (15 μL, 11 mg, 0.09 mmol) and acetyl chloride (15 μL, 17 mg, 0.21 mmol) were added in sequence to **24a** (13 mg, 0.06 mmol) in anhydrous acetonitrile (500 μL) and the solution was then heated to reflux for 5 min and cooled to rt. After 18 h, the reaction was diluted with water (5 mL) and the precipitate was collected by filtration and washed with cold Et_2O to give **25a** as a colorless amorphous solid (9 mg, 55%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.48 (br s, 1H), 9.26 (s, 1H), 8.19 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 2.1 Hz, 1H), 7.31 (dd, J = 8.8, 2.1 Hz, 1H), 2.34 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 170.9, 169.4, 168.7, 155.5, 154.6, 146.7, 126.7, 124.4, 120.0, 119.9, 111.5, 23.3, 20.9; IR (film) ν_{max} 3406, 3310, 3099, 1759, 1682, 1636, 1614, 1528, 1448, 1375, 1246, 1200, 1188, 1016, 721 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{13}H_{11}NO_5$, 262.0715; found, 262.0713.

4.26. 3-(4-Methoxy-3-(3-methoxyphenyl)benzamido)-4-oxo-4*H*-chromen-7-yl acetate (25b)

N,*N*-Diisopropylethylamine (15 μL, 11 mg, 0.09 mmol) and acetyl chloride (15 μL, 17 mg, 0.21 mmol) were added in sequence to **24b** (27 mg, 0.06 mmol) in anhydrous acetonitrile (500 μL) and the solution was then heated to reflux for 5 min and cooled to rt. After 18 h, the reaction was diluted with water (5 mL) and the precipitate was collected by filtration and washed with cold Et_2O to give **25b** as a colorless amorphous solid (19 mg, 65%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.56 (br s, 1H), 9.13 (s, 1H), 8.20 (d, J = 8.8 Hz, 1H), 8.02 (dd, J = 8.6, 2.4 Hz, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.35 (dd, J = 8.8, 2.1 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.14–7.10 (m, 2H), 6.96 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.7, 168.7, 164.9, 159.1, 159.0, 155.8, 154.7, 149.8, 138.7, 130.0, 129.4, 129.1, 129.1, 126.7, 125.6, 123.7, 121.7, 120.3, 120.3, 115.2, 112.6, 111.7, 111.6, 55.9, 55.1, 20.9; IR (film) ν_{max} 3439, 3381, 2939, 2837, 1769, 1634, 1616, 1531, 1502, 1481, 1443, 1367, 1267, 1238, 1204, 1180, 1136, 1095, 1036, 1020, 960, 874, 733, 696, 602 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{26}H_{21}NO_7$, 460.1396; found, 460.1396.

4.27. 3-Acetamido-8-methyl-4-oxo-4*H*-chromen-7-yl acetate (25c)

N,*N*-Diisopropylethylamine (15 μL, 11 mg, 0.09 mmol) and acetyl chloride (15 μL, 17 mg, 0.21 mmol) were added in sequence to **24c** (16 mg, 0.07 mmol) in anhydrous acetonitrile (500 μL) and the solution was then heated to reflux for 5 min and cooled to rt. After 18 h, the reaction was diluted with water (5 mL) and the precipitate was collected by filtration and washed with cold Et_2O to give **25c** as a colorless amorphous solid (11 mg, 60%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.49 (br s, 1H), 9.32 (s, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.29 (d, J = 8.7 Hz, 1H), 2.39 (s, 3H), 2.27 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.2, 169.4, 168.6, 154.1, 152.6, 146.6, 124.2, 123.3, 120.1, 120.0, 120.0, 23.3, 20.6, 8.8; IR (film) ν_{max} 3441, 1765, 1684, 1630, 1612, 1537, 1431, 1381, 1248, 1209, 1184, 1070, 1047, 897, 793, 781, 723 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{14}H_{13}NO_5$, 276.0872; found, 276.0868.

4.28. 3-(4-Methoxy-3-(3-methoxyphenyl)benzamido)-8-methyl-4-oxo-4*H*-chromen-7-yl acetate (25d)

N,*N*-Diisopropylethylamine (15 μL, 11 mg, 0.09 mmol) and acetyl chloride (15 μL, 17 mg, 0.21 mmol) were added in sequence to **24d** (18 mg, 0.04 mmol) in anhydrous acetonitrile (500 μL) and the solution was then heated to reflux for 5 min and cooled to rt. After 18 h, the reaction was diluted with water (5 mL) and the precipitate was collected by filtration and washed with cold Et_2O to give **25d** as a colorless amorphous solid (17 mg, 82%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.55 (br s, 1H), 9.19 (s, 1H), 8.04 (dd, J = 8.8, 0.5 Hz, 1H), 8.02 (dd, J = 8.8, 2.5 Hz, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.14–7.10 (m, 2H), 6.96 (ddd, J = 8.2, 2.5, 0.8 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 2.41 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 172.0, 168.6, 164.9, 159.1, 159.0, 154.3, 152.7, 149.6, 138.7, 130.0, 129.4, 129.1, 129.1, 125.6, 123.6, 123.3, 121.7, 120.4, 120.3, 120.2, 115.2, 112.6, 111.6, 55.9, 55.1, 20.6, 8.9; IR (film) ν_{max} 3381, 2939, 2837, 1767, 1634, 1605, 1531, 1504, 1485, 1427, 1373, 1269, 1240, 1205, 1180, 1117, 1059, 1040, 1022, 901, 872, 824, 779, 733, 609, 590 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{27}H_{23}NO_7$, 474.1553; found, 474.1549.

4.29. 3-Acetamido-5-hydroxy-4-oxo-4*H*-chromen-7-yl acetate (25e)

N,*N*-Diisopropylethylamine (17 μL, 13 mg, 0.10 mmol) and acetyl chloride (7 μL, 8 mg, 0.10 mmol) were added in sequence to **24e** (22 mg, 0.07 mmol) in anhydrous acetonitrile (600 μL) and the solution was then heated to reflux for 5 min and cooled to rt. After 18 h, the reaction was diluted with water (5 mL) and the precipitate was collected by filtration and washed with cold Et_2O. The residue was purified by PTLC (SiO_2, 40:1 CH_2Cl_2/MeOH then 80:1 CH_2Cl_2/MeOH) to give **25e** as a colorless amorphous solid (4 mg, 14%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.95 (br s, 1H), 9.34 (s, 1H), 7.86 (br s, 1H), 6.80 (d, J = 2.2 Hz, 1H), 6.59 (d, J = 2.2 Hz, 1H), 2.34 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.4, 168.9, 168.5, 161.7, 156.5, 156.4, 146.0, 123.5, 108.1, 105.2, 101.6, 24.3, 21.4; IR (film) ν_{max} 3341, 2918, 2849, 1759, 1655, 1620, 1595, 1547, 1537, 1479, 1402, 1369, 1346, 1279, 1213, 1171, 1124, 1063, 1024, 1011, 989, 889, 800, 766, 742, 716, 702 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{13}H_{11}NO_6$, 278.0665; found, 278.0672.

4.30. 5-Hydroxy-3-(4-methoxy-3-(3-methoxyphenyl)benzamido)-4-oxo-4*H*-chromen-7-yl acetate (25f)

N,*N*-Diisopropylethylamine (17 μL, 13 mg, 0.10 mmol) and acetyl chloride (7 μL, 8 mg, 0.10 mmol) were added in sequence to **24f** (36 mg, 0.08 mmol) in anhydrous acetonitrile (600 μL) and the solution was then heated to reflux for 5 min and cooled to rt. After 18 h, the reaction was diluted with water (5 mL) and the precipitate was collected by filtration and washed with cold Et_2O. The residue was purified by column chromatography (SiO_2, CH_2Cl_2 to 200:1 CH_2Cl_2/MeOH) to give **25f** as a colorless amorphous solid (11 mg, 28%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.99 (br s, 1H), 9.53 (s, 1H), 8.61 (br s, 1H), 7.94 (dd, J = 8.6, 2.4 Hz, 1H), 7.90 (d, J = 2.4 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.13 (m, 1H), 7.10 (m, 1H), 7.09 (d, J = 8.9 Hz, 1H), 6.94 (ddd, J = 8.2, 2.5, 0.9 Hz, 1H), 6.83 (d, J = 2.0 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.6, 168.5, 165.1, 161.7, 160.0, 159.5,

156.5, 156.5, 146.0, 138.8, 131.3, 130.2, 129.4, 128.6, 125.8, 123.8, 122.2, 115.5, 113.3, 111.3, 108.1, 105.2, 101.7, 56.1, 55.5, 21.4; IR (film) ν_{max} 3379, 3113, 2934, 2841, 1761, 1672, 1649, 1624, 1605, 1580, 1541, 1508, 1485, 1294, 1350, 1273, 1252, 1244, 1229, 1211, 1186, 1163, 1123, 1057, 1026, 893, 874, 768, 756, 729, 689 cm^{-1}; HRMS (ESI$^+$) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{21}NO_8$, 476.1346; found, 476.1336.

4.31. *N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyl-tetrahydro-2*H*-pyran-2-yloxy)-4-oxo-4*H*-chromen-3-yl)acetamide (26a)

Boron trifluoride etherate (50 μL, 0.41 mmol) was added to **24a** (46 mg, 0.21 mmol) and (3*aR*,4*S*,7*R*,7*aR*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3*aH*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (116 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (6.00 mL). After stirring at rt for 18 h, triethylamine (60 μL) was added and the solvent was concentrated. The residue was partially purified via column chromatography (SiO_2, 20:1 CH_2Cl_2/MeOH) and the coupled carbonate was used without further purification.

Carbonate was added to MeOH (4.0 mL), CH_2Cl_2 (1.0 mL), and triethylamine (400 μL) and stirred for 18 h at rt. The solvent was concentrated and the residue purified via PTLC (SiO_2, 3 × 10:1 CH_2Cl_2/MeOH) to give **26a** as a colorless amorphous solid (6 mg, 7% over two steps): ^{1}H NMR ($CDCl_3$/MeOD, 500 MHz) δ 9.26 (br s, 1H), 8.09 (d, *J* = 8.9 Hz, 1H), 7.11 (d, *J* = 2.3 Hz, 1H), 7.02 (dd, *J* = 8.9, 2.3 Hz, 1H), 5.57 (d, *J* = 2.0 Hz, 1H), 4.13–4.07 (m, 2H), 3.57 (s, 3H), 3.32 (d, *J* = 9.1 Hz, 1H), 2.20 (s, 3H), 1.33 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$/MeOD, 125 MHz) δ 171.6, 169.4, 161.5, 157.5, 145.3, 127.3, 124.2, 116.7, 115.9, 103.4, 98.5, 84.2, 79.0, 71.0, 68.3, 62.0, 28.9, 23.9, 22.7; IR (film) ν_{max} 3371, 3312, 2980, 2930, 1670, 1628, 1612, 1528, 1447 1377, 1244, 1200, 1144, 1128, 1113, 1092, 1055, 1022, 986, 968, 949, 779, 734, 658 cm^{-1}; HRMS (ESI$^+$) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{23}NO_8$, 416.1321; found, 416.1302.

4.32. *N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyl-tetrahydro-2*H*-pyran-2-yloxy)-4-oxo-4*H*-chromen-3-yl)-4-methoxy-3-(3-methoxylphenyl)benzamide (26b)

Boron trifluoride etherate (65 μL, 0.53 mmol) was added to **24b** (103 mg, 0.25 mmol) and (3*aR*,4*S*,7*R*,7*aR*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3*aH*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (141 mg, 0.39 mmol) in anhydrous CH_2Cl_2 (7.90 mL). After stirring at rt for 18 h, triethylamine (60 μL) was added and the solvent was concentrated. The residue was partially purified via column chromatography (SiO_2, 1:1 hexanes/EtOAc) and the coupled carbonate was used without further purification.

Carbonate was added to MeOH (4.0 mL), CH_2Cl_2 (400 μL), and triethylamine (400 μL) and stirred for 18 h at rt. The solvent was concentrated and the residue purified via column chromatography (SiO_2, 8:1 CH_2Cl_2/MeOH) then PTLC (SiO_2, 8:1 CH_2Cl_2/acetone then 8:1 CH_2Cl_2/MeOH) to give **26b** as a colorless amorphous solid (4 mg, 3% over two steps): ^{1}H NMR ($CDCl_3$/MeOD, 400 MHz) δ 9.45 (s, 1H), 8.82 (br s, 1H), 8.13 (d, *J* = 8.9 Hz, 1H), 7.91 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.88 (d, *J* = 2.3 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 2.3 Hz, 1H), 7.09 (m, 1H), 7.07–7.01 (m, 3H), 6.89 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 5.59 (d, *J* = 2.0 Hz, 1H), 4.15–4.08 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.57 (s, 3H), 3.33 (d, *J* = 9.0 Hz, 1H), 1.34 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$/MeOD, 125 MHz) δ 171.8, 165.4, 161.5, 159.8, 159.4, 157.5, 145.1, 138.8, 131.1, 130.2, 129.3, 128.5, 127.3, 125.9, 124.4, 122.1, 116.5, 115.9, 115.3, 113.2, 111.2, 103.5, 98.5, 84.2, 79.0, 71.0, 68.3, 62.0, 56.0, 55.4, 28.9, 22.7; IR (film) ν_{max} 3439, 3416, 3377, 2974, 2934, 2835, 1666, 1632, 1605, 1531, 1504, 1481, 1447, 1367, 1265, 1244, 1207, 1130, 1113, 1092, 1053, 1038, 1022, 991, 968, 949, 737, 698 cm^{-1}; HRMS (ESI$^+$) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{33}NO_{10}$, 592.2183; found, 592.2181.

4.33. *N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyl-tetrahydro-2*H*-pyran-2-yloxy)-8-methyl-4-oxo-4*H*-chromen-3-yl)acetamide (26c)

Boron trifluoride etherate (60 μL, 0.49 mmol) was added to **24c** (52 mg, 0.22 mmol) and (3*aR*,4*S*,7*R*,7*aR*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3*aH*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (120 mg, 0.33 mmol) in anhydrous CH_2Cl_2 (7.30 mL). After stirring at rt for 18 h, triethylamine (60 μL) was added and the solvent was concentrated. The residue was partially purified via column chromatography (SiO_2, 20:1 CH_2Cl_2/MeOH) and the coupled carbonate was used without further purification.

Carbonate was added to MeOH (4.0 mL), CH_2Cl_2 (400 μL), and triethylamine (400 μL) and stirred for 18 h at rt. The solvent was concentrated and the residue purified via PTLC (SiO_2, 10:1 CH_2Cl_2/MeOH then EtOAc) to give **26c** as a colorless amorphous solid (7 mg, 8% over two steps): ^{1}H NMR ($CDCl_3$/MeOD, 500 MHz) δ 9.30 (s, 1H), 8.01 (d, *J* = 9.1 Hz, 1H), 7.28 (d, *J* = 9.1 Hz, 1H), 5.60 (d, *J* = 1.9 Hz, 1H), 4.17–4.12 (m, 2H), 3.57 (s, 3H), 3.33 (d, *J* = 9.0 Hz, 1H), 2.24 (s, 3H), 2.19 (s, 3H), 1.32 (s, 3H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$/MeOD, 125 MHz) δ 172.1, 169.4, 158.9, 155.2, 145.5, 124.3, 123.7, 116.5, 114.8, 112.2, 98.3, 84.3, 78.9, 71.2, 68.5, 62.0, 29.1, 23.9, 22.5, 8.4; IR (film) ν_{max} 3499, 3379, 3360, 2924, 1605, 1531, 1427, 1385, 1261, 1194, 1130, 1113, 1070, 1051, 987, 970, 949, 876, 804, 781, 729, 700, 648 cm^{-1}; HRMS (ESI$^+$) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{25}NO_8$, 408.1659; found, 408.1671.

4.34. *N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyl-tetrahydro-2*H*-pyran-2-yloxy)-8-methyl-4-oxo-4*H*-chromen-3-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (26d)

Boron trifluoride etherate (31 μL, 0.25 mmol) was added to **24d** (52 mg, 0.12 mmol) and (3*aR*,4*S*,7*R*,7*aR*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3*aH*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (69 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (3.70 mL). After stirring at rt for 18 h, triethylamine (60 μL) was added and the solvent was concentrated. The residue was partially purified via column chromatography (SiO_2, 1:1 hexanes/EtOAc) and the coupled carbonate was used without further purification.

Carbonate was added to MeOH (4.0 mL), CH_2Cl_2 (1.0 mL), and triethylamine (400 μL) and stirred for 18 h at rt. The solvent was concentrated and the residue purified via PTLC (SiO_2, 20:1:1 CH_2Cl_2/MeOH/acetone) to give **26d** as a colorless amorphous solid (17 mg, 23% over two steps): ^{1}H NMR ($CDCl_3$/MeOD, 500 MHz) δ 9.51 (br s, 1H), 8.83 (br s, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 7.93 (m, 1H), 7.90 (m, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 9.1 Hz, 1H), 7.11 (m, 1H), 7.08 (m, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 6.91 (m, 1H), 5.64 (m, 1H0, 4.22–4.17 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.60 (s, 3H), 3.37 (d, *J* = 8.7 Hz, 1H), 2.30 (s, 3H), 1.35 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$/MeOD, 125 MHz) δ 172.3, 165.4, 159.8, 159.4, 158.9, 155.3, 145.2, 138.8, 131.1, 130.2, 129.3, 128.5, 126.0, 124.4, 124.1, 122.2, 116.5, 115.4, 114.9, 113.3, 112.2, 111.2, 98.2, 84.4, 78.9, 71.2, 68.6, 62.1, 56.0, 55.5, 29.2, 22.6, 8.5; IR (film) ν_{max} 3434, 3055, 2974, 2935, 2835, 2502, 1630, 1605, 1533, 1502, 1483, 1421, 1369, 1265, 1217, 1194, 1136, 1113, 1068, 1094, 1024, 991, 970, 939, 876, 781, 735, 700 cm^{-1}; HRMS (ESI$^+$) *m/z*: $[M+H]^+$ calcd for $C_{33}H_{35}NO_{10}$, 606.2339; found, 606.2349.

4.35. *N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyl-tetrahydro-2*H*-pyran-2-yloxy)-5-hydroxy-4-oxo-4*H*-chromen-3-yl)acetamide (26e)

Boron trifluoride etherate (53 μL, 0.43 mmol) was added to **24e** (52 mg, 0.22 mmol) and (3*aR*,4*S*,7*R*,7*aR*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3*aH*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (120 mg, 0.33 mmol) in anhydrous CH_2Cl_2 (7.00 mL). After stirring at rt for 18 h, triethylamine (60 μL) was added and the solvent was concentrated. The residue was partially purified via column chromatography (SiO_2, 50:1 CH_2Cl_2/MeOH) and the coupled carbonate was used without further purification.

Carbonate was added to MeOH (4.0 mL), CH_2Cl_2 (1.0 mL), and triethylamine (400 μL) and stirred for 18 h at rt. The solvent was concentrated and the residue purified via PTLC (SiO_2, 20:1 CH_2Cl_2/MeOH then 50:50:1:1 CH_2Cl_2/EtOAc/MeOH/acetone) to give **26e** as a colorless amorphous solid (4 mg, 5% over two steps): ^{1}H NMR ($CDCl_3$/MeOD, 500 MHz) δ 9.19 (br s, 1H), 6.60 (m, 1H), 6.43 (m, 1H), 5.53 (m, 1H), 4.11–4.05 (m, 2H), 3.57 (s, 3H), 3.31 (d, J = 9.2 Hz, 1H), 2.20 (s, 3H), 1.33 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$/MeOD, 125 MHz) δ 175.0, 169.2, 163.0, 161.4, 157.3, 145.8, 122.9, 105.5, 100.0, 98.3, 94.9, 84.2, 78.9, 71.0, 68.3, 62.0, 28.9, 23.9, 22.7; IR (film) ν_{max} 3377, 2974, 2930, 2851, 1657, 1620, 1591, 1537, 1497, 1464, 1447, 1412, 1367, 1352, 1288, 1180, 1117, 1057, 1026, 997, 951, 806, 764, 739 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{19}H_{23}NO_9$, 410.1451; found, 410.1454.

4.36. *N*-(7-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-methoxy-6,6-dimethyl-tetrahydro-2*H*-pyran-2-yloxy)-5-hydroxy-4-oxo-4*H*-chromen-3-yl)-4-methoxy-3-(3-methoxyphenyl)benzamide (26f)

Boron trifluoride etherate (20 μL, 0.16 mmol) was added to **24f** (22 mg, 0.05 mmol) and (3*aR*,4*S*,7*R*,7*aR*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3*aH*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (51 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (2.00 mL). After stirring at rt for 18 h, triethylamine (30 μL) was added and the solvent was concentrated. The residue was partially purified via column chromatography (SiO_2, 1:1 hexanes/EtOAc) and the coupled carbonate was used without further purification.

Carbonate was added to MeOH (4.0 mL), CH_2Cl_2 (1.0 mL), and triethylamine (400 μL) and stirred for 18 h at rt. The solvent was concentrated and the residue purified via PTLC (SiO_2, 20:1:1 CH_2Cl_2/MeOH/acetone) to give **26f** as a colorless amorphous solid (2 mg, 7% over two steps):^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.95 (s, 1H), 9.45 (s, 1H), 8.63 (s, 1H), 7.93 (dd, J = 8.6, 2.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.13 (m, 1H), 7.10 (dd, J = 2.5, 1.6 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H), 6.94 (ddd, J = 8.3, 2.7, 0.9 Hz, 1H), 6.67 (d, J = 2.1 Hz, 1H), 6.49 (d, J = 2.1 Hz, 1H), 5.63 (d, J = 1.6 Hz, 1H), 4.23–4.19 (m, 2H0, 3.91 (s, 3H), 3.87 (s, 3H), 3.61 (s, 3H), 3.37 (m, 1H), 2.66 (br s 1H), 2.59 (br s, 1H), 1.39 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.2, 165.1, 162.9, 161.7, 159.9, 159.5, 157.4, 145.4, 138.8, 131.2, 130.2, 129.4, 128.5, 125.8, 123.3, 122.2, 115.5, 113.3, 111.2, 105.5, 100.1, 97.8, 95.0, 84.3, 79.0, 71.1, 68.4, 62.2, 56.1, 55.5, 29.3, 22.7; IR (film) ν_{max} 3385, 2938, 2851, 1655, 1622, 1591, 1535, 1502, 1477, 1466, 1356, 1285, 1277, 1248, 1213, 1180, 1117, 1055, 1022, 949, 910, 806, 762, 731 cm^{-1}; HRMS (ESI$^+$) *m/z*: [M+H]$^+$ calcd for $C_{32}H_{33}NO_{11}$, 608.2132; found, 608.2109.

4.37. 2-(Benzo[*d*][1,3]dioxol-5-yl)-1-(2,4-dihydroxyphenyl)ethanone (29a)[41]

Resorcinol (2.21 g, 20.05 mmol) and 3,4-(methylenedioxy)phenylacetonitrile (3.12 g, 19.36 mmol) in EtOAc (60 mL) was cooled to 0 °C. After 15 min, zinc chloride (1.47 g, 10.77 mmol) was added, hydrochloric acid was bubbled through the solution for 10 min, and the reaction vessel was sealed and warmed to rt over 18 h. The solvent was decanted away, water (25 mL) was added to the resulting oil, and the solution was then heated to reflux for 3 h. After cooling to rt, the solution was extracted with EtOAc (3 × 50 mL). The organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 2:1 hexanes/EtOAc) to give **29a** as a yellow amorphous solid (1.17 g, 22%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.52 (br s, 1H), 10.69 (br s, 1H), 7.94 (d, J = 8.9 Hz, 1H), 6.87 (d, J = 1.6 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 6.75 (dd, J = 7.9, 1.6 Hz, 1H), 6.39 (dd, J = 8.8, 2.3 Hz, 1H), 6.25 (d, J = 2.4 Hz, 1H), 5.98 (s, 2H), 4.20 (s, 2H).

4.38. 2-(Benzo[*d*][1,3]dioxol-5-yl)-1-(2,4-dihydroxy-3-methylphenyl)ethanone (29b)[41]

2-Methylresorcinol (2.51 g, 20.19 mmol) and 3,4-(methylenedioxy)phenylacetonitrile (3.12 g, 19.37 mmol) in EtOAc (40 mL) was cooled to 0 °C. After 15 min, zinc chloride (1.48 g, 10.89 mmol) was added, hydrochloric acid was bubbled through the solution for 10 min, and the reaction vessel was sealed and warmed to rt over 18 h. The solvent was decanted away, water (25 mL) was added to the resulting oil, and the solution was then heated to reflux for 3 h. After cooling to rt, the solution was extracted with EtOAc (3 × 50 mL). The organic layers were dried (Na_2SO_4), filtered, and concentrated. Recrystallization from MeOH gave **29b** as a yellow amorphous solid (1.40 g, 25%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.97 (br s, 1H), 10.59 (br s, 1H), 7.83 (d, J = 8.9 Hz, 1H), 6.87 (d, J = 1.6 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 6.75 (dd, J = 7.9, 1.6 Hz, 1H), 6.48 (d, J = 8.9 Hz, 1H), 5.98 (s, 2H), 4.20 (s, 2H), 1.96 (s, 3H).

4.39. 3-(Benzo[*d*][1,3]dioxol-5-yl)-7-hydroxy-4*H*-chromen-4-one (30a)[41]

Boron trifluoride etherate (3.21 mL, 26.01 mmol) was added to **29a** (1.11 g, 4.06 mmol) in anhydrous *N*,*N*-dimethylformamide (16.0 mL) at rt. After 10 min, methanesulfonyl chloride (1.31 mL, 1.94 g, 16.93 mmol) was added and the reaction was then heated to 90 °C for 5 d. After cooling to rt, water (300 mL) was added, the resulting solid was collected by filtration to give **30a** as a reddish-brown amorphous solid (1.08 g, 94%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.83 (br s, 1H), 8.36 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 1.7 Hz, 1H), 7.06 (dd, J = 8.0, 1.7 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.95 (dd, J = 8.8, 2.2 Hz, 1H), 6.88 (d, J = 2.2 Hz, 1H), 6.06 (s, 2H).

4.40. 3-(Benzo[*d*][1,3]dioxol-5-yl)-7-hydroxy-8-methyl-4*H*-chromen-4-one (30b)[41]

Boron trifluoride etherate (3.35 mL, 27.14 mmol) was added to **29b** (1.21 g, 4.24 mmol) in anhydrous *N*,*N*-dimethylformamide (16.5 mL) at rt. After 10 min, methanesulfonyl chloride (1.36 mL, 2.01 g, 17.57 mmol) was added and the reaction was then heated to 90 °C for 5 d. After cooling to rt, water (300 mL) was added, the resulting solid was collected by filtration to give **30b** as a reddish-brown amorphous solid (1.16 g, 93%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.69 (br s, 1H), 8.44 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 1.7 Hz, 1H), 7.07 (dd, J = 8.0, 1.7 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.06 (s, 2H), 2.24 (s, 3H).

4.41. 3-(Benzo[*d*][1,3]dioxol-5-yl)-4-oxo-4*H*-chromen-7-yl acetate (31a)

N,*N*-Diisopropylethylamine (40 μL, 30 mg, 0.23 mmol) and acetyl chloride (40 μL, 44 mg, 0.56 mmol) were added in sequence to **30a** (51 mg, 0.18 mmol) in anhydrous acetonitrile (1.30 mL) and

the solution was then heated to reflux for 5 min and cooled to rt. After 18 h, the reaction was diluted with water (5 mL) and the precipitate was collected by filtration. The residue was purified via column chromatography (SiO_2, 2:1 hexanes/EtOAc) to give **31a** as a brown amorphous solid (26 mg, 45%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.33 (d, J = 8.8 Hz, 1H), 7.98 (s, 1H), 7.31 (d, J = 2.1 Hz, 1H), 7.18 (dd, J = 8.8, 2.2 Hz, 1H), 7.10 (d, J = 1.7 Hz, 1H), 6.99 (dd, J = 7.9, 1.7 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.01 (s, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.8, 168.8, 156.8, 154.6, 153.0, 148.0, 147.9, 128.1, 125.5, 125.4, 122.6, 119.7, 111.1, 109.9, 108.7, 101.4, 21.4; IR (film) ν_{max} 3506, 3086, 2905, 1753, 1732, 1641, 1620, 1499, 1439, 1381, 1335, 1283, 1242, 1229, 1177, 1146, 1049, 1032, 1016, 959, 939, 930, 908, 854, 818, 795, 775 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{18}H_{12}O_6$, 325.0712; found, 325.0702.

4.42. 3-(Benzo[*d*][1,3]dioxol-5-yl)-8-methyl-4-oxo-4*H*-chromen-7-yl acetate (31b)

N,*N*-Diisopropylethylamine (40 μL, 30 mg, 0.23 mmol) and acetyl chloride (40 μL, 44 mg, 0.56 mmol) were added in sequence to **30b** (51 mg, 0.17 mmol) in anhydrous acetonitrile (1.30 mL) and the solution was then heated to reflux for 5 min and cooled to rt. After 18 h, the reaction was diluted with water (5 mL) and the precipitate was collected by filtration to give **31b** as a brown amorphous solid (35 mg, 60%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.59 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.30 (d, J = 8.5 Hz, 1H), 7.18 (d, J = 1.7 Hz, 1H), 7.10 (dd, J = 8.0, 1.7 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.07 (s, 2H), 2.40 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 175.0, 168.6, 154.6, 154.3, 152.2, 147.1, 147.1, 125.3, 123.7, 122.5, 121.7, 120.2, 119.9, 109.4, 108.2, 101.1, 20.6, 8.9; IR (film) ν_{max} 3074, 2897, 1763, 1643, 1603, 1582, 1504, 1489, 1425, 1371, 1335, 1281, 1252, 1227, 1205, 1184, 1146, 1107, 1068, 1038, 1013, 928, 901, 864, 851, 810, 733 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{19}H_{14}O_6$, 339.0869; found, 339.0861.

4.43. 3-(Benzo[*d*][1,3]dioxol-5-yl)-5-hydroxy-4-oxo-4*H*-chromen-7-yl acetate (31c)

N,*N*-Diisopropylethylamine (65 μL, 48 mg, 0.37 mmol) and acetyl chloride (25 μL, 28 mg, 0.35 mmol) were added in sequence to 3-(benzo[*d*][1,3]dioxol-5-yl)-5,7-dihydroxy-*4H*-chromen-4-one[31] (104 mg, 0.35 mmol) in anhydrous acetonitrile (2.50 mL) and the solution was then heated to reflux for 5 min and cooled to rt. After 18 h, the reaction was diluted with water (10 mL), the precipitate was collected by filtration and washed with cold Et_2O (3 × 10 mL). The residue was purified via column chromatography (SiO_2, 3:1 CH_2Cl_2/hex to CH_2Cl_2 to 100:1 CH_2Cl_2/MeOH) to give **31c** as a colorless amorphous solid (10 mg, 9%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.90 (br s, 1H), 8.57 (s, 1H), 7.17 (d, J = 1.6 Hz, 1H), 7.09 (dd, J = 8.1, 1.8 Hz, 1H), 7.04–7.01 (m, 2H), 6.71 (d, J = 2.1 Hz, 1H), 6.08 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 180.7, 168.4, 161.3, 156.4, 155.9, 147.3, 147.1, 124.0, 122.7, 122.6, 109.4, 108.7, 108.3, 105.5, 101.4, 101.2, 20.9; IR (film) ν_{max} 3076, 2907, 1747, 1661, 1614, 1585, 1504, 1487, 1435, 1367, 1335, 1308, 1296, 1275, 1250, 1236, 1219, 1200, 1175, 1144, 1126, 1103, 1061, 1042, 930, 891, 872, 820, 812, 785, 725, 698, 667 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{18}H_{12}O_7$, 341.0661; found, 341.0672.

4.44. 3-(Benzo[*d*][1,3]dioxol-5-yl)-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyl-tetrahydro-2*H*-pyran-2-yloxy)-4*H*-chromen-4-one (32a)

Boron trifluoride etherate (88 μL, 0.71 mmol) was added to **30a** (102 mg, 0.36 mmol) and (3*aR*,4*S*,7*R*,7*aR*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3*aH*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (134 mg, 0.37 mmol) in anhydrous CH_2Cl_2 (11.60 mL). After stirring at rt for 18 h, triethylamine (100 μL) was added and the solvent was concentrated. The residue was partially purified via column chromatography (SiO_2, 2:1 hexanes/EtOAc to 4:1:1 hexanes/CH_2Cl_2/EtOAc) and the coupled carbonate was used without further purification.

Carbonate was added to MeOH (4.0 mL), CH_2Cl_2 (1.0 mL), and triethylamine (400 μL) and stirred for 18 h at rt. The solvent was concentrated and the residue purified via PTLC (SiO_2, 20:1 CH_2Cl_2/MeOH then 20:20:1:1 CH_2Cl_2/EtOAc/MeOH/acetone then 10:1 Et_2O/acetone) to give **32a** as a colorless amorphous solid (1 mg, 1% over two steps): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (d, J = 8.9 Hz, 1H), 7.93 (s, 1H), 7.12 (d, J = 2.3 Hz, 1H), 7.10 (d, J = 1.7 Hz, 1H), 7.06 (dd, J = 8.9, 2.3 Hz, 1H), 6.98 (dd, J = 8.0, 1.7 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.00 (s, 2H), 5.67 (d, J = 1.5 Hz, 1H), 4.26–4.21 (m, 2H), 3.62 (s, 3H), 3.39 (d, J = 8.9 Hz, 1H), 2.64 (br s 1H), 2.57 (br s, 1H), 1.40 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.0, 161.0, 157.8, 152.6, 147.9, 147.9, 128.1, 125.8, 125.2, 122.6, 119.3, 115.6, 110.0, 108.6, 103.4, 101.4, 98.0, 84.3, 79.0, 71.2, 68.3, 62.2, 29.4, 22.7; IR (film) ν_{max} 3414, 2926, 2854, 1622, 1568, 1504, 1489, 1439, 1385, 1367, 1335, 1248, 1198, 1113, 1092, 1034, 987, 968, 926, 854, 810, 783, 739 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{24}H_{24}O_9$, 457.1499; found, 457.1482.

4.45. 3-(Benzo[*d*][1,3]dioxol-5-yl)-7-((2*R*,3*R*,4*S*,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyl-tetrahydro-2*H*-pyran-2-yloxy)-8-methyl-4*H*-chromen-4-one (32b)

Boron trifluoride etherate (88 μL, 0.71 mmol) was added to **30b** (100 mg, 0.34 mmol) and (3*aR*,4*S*,7*R*,7*aR*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3*aH*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (134 mg, 0.37 mmol) in anhydrous CH_2Cl_2 (11.60 mL). After stirring at rt for 18 h, triethylamine (100 μL) was added and the solvent was concentrated. The residue was partially purified via column chromatography (SiO_2, 2:1 hexanes/EtOAc to 4:1:1 hexanes/CH_2Cl_2/EtOAc) and the coupled carbonate was used without further purification.

Carbonate was added to MeOH (4.0 mL), CH_2Cl_2 (1.0 mL), and triethylamine (400 μL) and stirred for 18 h at rt. The solvent was concentrated and the residue purified via PTLC (SiO_2, 20:1 CH_2Cl_2/MeOH then 20:20:1:1 CH_2Cl_2/EtOAc/MeOH/acetone then 10:1 Et_2O/acetone) to give **32b** as a colorless amorphous solid (3 mg, 2% over two steps): ^{1}H NMR ($CDCl_3$/CD_3OD, 500 MHz) δ 8.06 (d, J = 8.9 Hz, 1H), 7.97 (s, 1H), 7.28 (m, 1H), 7.03 (d, J = 1.7 Hz, 1H), 6.92 (dd, J = 8.0, 1.7 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 5.95 (s, 2H), 5.60 (d, J = 1.5 Hz, 1H), 4.17–4.11 (m, 2H), 3.57 (s, 3H), 3.33 (m, 1H), 2.25 (s, 3H0, 1.32 (s, 3H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD, 125 MHz) δ 176.9, 158.6, 155.6, 153.0, 147.8, 147.7, 125.7, 124.8, 124.5, 122.5, 118.8, 114.5, 112.1, 109.9, 108.5, 101.3, 98.2, 84.4, 78.8, 71.2, 68.6, 62.0, 29.1, 22.5, 8.4; IR (film) ν_{max} 3396, 2928, 1636, 1618, 1597, 1504, 1489, 1427, 1381, 1337, 1267, 1250, 1231, 1196, 1132, 1111, 1072, 1053, 1041, 993, 962, 924, 808, 785, 770, 735 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{25}H_{26}O_9$, 471.1655; found, 471.1666.

4.46. 3-(Benzo[*d*][1,3]dioxol-5-yl)-7-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyl-tetrahydro-2*H*-pyran-2-yloxy)-5-hydroxy-4*H*-chromen-4-one (32c)

Boron trifluoride etherate (83 μL, 0.67 mmol) was added to 3-(benzo[*d*][1,3]dioxol-5-yl)-5,7-dihydroxy-*4H*-chromen-4-one[31] (100 mg, 0.34 mmol) and (3*aR*,4*S*,7*R*,7*aR*)-7-methoxy-6,6-dimethyl-2-oxo-tetrahydro-3*aH*-[1.3]dioxolo[4,5-*c*]pyran-4-yl 2,2,2-trichloroacetimidate (178 mg, 0.49 mmol) in anhydrous CH_2Cl_2

(11.10 mL). After stirring at rt for 18 h, triethylamine (60 μL) was added and the solvent was concentrated. The residue was partially purified via column chromatography (SiO_2, 50:1 CH_2Cl_2/MeOH) and the coupled carbonate was used without further purification.

Carbonate was added to MeOH (4.0 mL), CH_2Cl_2 (1.0 mL), and triethylamine (400 μL) and stirred for 18 h at rt. The solvent was concentrated and the residue purified via PTLC (SiO_2, 20:1 CH_2Cl_2/MeOH then 20:1:1 CH_2Cl_2/MeOH/acetone then 40:40:1:1 CH_2Cl_2/EtOAc/MeOH/acetone) to give **32c** as a colorless amorphous solid (7 mg, 4% over two steps): ^{1}H NMR ($CDCl_3$/MeOD, 500 MHz) δ 7.85 (s, 1H), 6.99 (d, J = 1.6 Hz, 1H), 6.90 (dd, J = 8.0, 1.7 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 2.2 Hz, 1H), 6.44 (d, J = 2.2 Hz, 1H), 5.96 (s, 2H), 5.54 (d, J = 2.1 Hz, 1H), 4.09 (dd, J = 9.4, 3.4 Hz, 1H), 4.06 (m, 1H), 3.56 (s, 3H), 3.30 (d, J = 9.4 Hz, 1H), 1.32 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$/MeOD, 125 MHz) δ 180.9, 162.6, 162.2, 158.9, 153.3, 148.0, 147.9, 124.4, 124.0, 122.6, 109.7, 108.7, 106.8, 101.4, 100.2, 98.3, 94.6, 84.2, 78.9, 71.0, 68.3, 62.0, 28.9, 22.7; IR (film) ν_{max} 3410, 2980, 2920, 2849, 1722, 1655, 1614, 1574, 1504, 1493, 1470, 1435, 1369, 1308, 1271, 1248, 1209, 1194, 1180, 1157, 1117, 1038, 995, 955, 922, 847, 822, 783, 737 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{24}H_{24}O_{10}$, 473.1448; found, 473.1427.

4.47. 7-(Allyloxy)-3-(benzo[*d*][1,3]dioxol-5-yl)-4*H*-chromen-4-one (33a)

N,*N*-Diisopropylethylamine (645 μL, 481 mg, 3.72 mmol) and allyl bromide (644 μL, 900 mg, 7.44 mmol) were sequentially added to **30a** (700 mg, 2.48 mmol) in anhydrous *N*,*N*-dimethylformamide (3.5 mL) and anhydrous acetonitrile (12.40 mL) and the resulting solution was then heated to reflux for 4 h. After cooling to rt, the reaction was poured into water and the precipitate was collected by filtration. The residue was purified via column chromatography (SiO_2, 4:1:1 hexanes/CH_2Cl_2/EtOAc) to give **33a** as a colorless amorphous solid (418 mg, 52%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (d, J = 8.9 Hz, 1H), 7.92 (s, 1H), 7.11 (d, J = 1.7 Hz, 1H), 7.02 (dd, J = 8.9, 2.4 Hz, 1H), 6.98 (dd, J = 8.0, 1.7 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 6.08 (ddt, J = 17.3, 10.5, 5.3 Hz, 1H), 6.00 (s, 3H), 5.47 (dq, J = 17.3, 1.5 Hz, 1H), 5.37 (dq, J = 10.5, 1.5 Hz, 1H), 4.66 (dt, J = 5.3, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.9, 163.1, 158.0, 152.4, 147.9, 147.8, 132.3, 128.1, 125.9, 122.6, 118.8, 118.6, 115.2, 110.0, 108.6, 101.4, 101.3; IR (film) ν_{max} 3080, 2885, 1628, 1597, 1566, 1502, 1487, 1443, 1423, 1387, 1371, 1333, 1286, 1269, 1250, 1202, 1097, 1036, 937, 924, 852, 818, 781 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{19}H_{14}O_5$, 323.0919; found, 323.0915.

4.48. 7-(Allyloxy)-3-(benzo[*d*][1,3]dioxol-5-yl)-8-methyl-4*H*-chromen-4-one (33b)

N,*N*-Diisopropylethylamine (645 μL, 481 mg, 3.72 mmol) and allyl bromide (644 μL, 900 mg, 7.44 mmol) were sequentially added to **30b** (702 mg, 2.37 mmol) in anhydrous *N*,*N*-dimethylformamide (6.5 mL) and anhydrous acetonitrile (12.40 mL) and the resulting solution was then heated to reflux for 4 h. After cooling to rt, the reaction was poured into water (150 mL) and was extracted with CH_2Cl_2 (3 × 200 mL) and EtOAc (200 mL). The organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 4:1:1 hexanes/CH_2Cl_2/EtOAc) to give **33b** as a colorless amorphous solid (199 mg, 25%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (d, J = 8.9 Hz, 1H), 7.99 (s, 1H), 7.12 (d, J = 1.7 Hz, 1H), 7.00 (d, J = 8.9 Hz, 1H), 6.99 (dd, J = 8.0, 1.7 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.10 (ddt, J = 17.2, 10.6, 5.1 Hz, 1H), 6.00 (s, 2H), 5.47 (dq, J = 17.2, 1.5 Hz, 1H), 5.34 (dq, J = 10.6, 1.5 Hz, 1H), 4.70 (dt, J = 5.1, 1.5 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.6, 160.5, 155.7, 152.8, 147.9, 147.8, 132.8, 126.1, 125.0, 124.5, 122.6, 118.6, 114.5, 110.1, 110.0, 108.6, 101.4, 69.6, 8.4; IR (film) ν_{max} 3076, 3016, 2995, 2918, 1641, 1620, 1601, 1504, 1493, 1427, 1389, 1337, 1281, 1252, 1232, 1202, 1144, 1115, 1084, 1072, 1038, 997, 935, 922, 851, 800, 783 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{20}H_{16}O_5$, 337.1076; found, 337.1067.

4.49. 6-Allyl-3-(benzo[*d*][1,3]dioxol-5-yl)-7-hydroxy-4*H*-chromen-4-one (34a)

N,*N*-Diethylaniline (460 μL) was added to **33a** (392 mg, 1.22 mmol) in a sealed flask and the solution was then heated to 170 °C for 48 h. The reaction was diluted with 1 M aqueous HCl solution (50 mL) and CH_2Cl_2 (50 mL). The organic layers were washed with 1 M aqueous HCl solution (3 × 50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 8:1:1 hexanes/CH_2Cl_2/EtOAc to 4:1:1 hexanes/CH_2Cl_2/EtOAc) then PTLC (SiO_2, 2:1:1 hexanes/CH_2Cl_2/EtOAc) to give 6-allyl **34a** as a near-colorless amorphous solid (3 mg, 1%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (s, 1H), 7.90 (s, 1H), 7.09 (d, J = 1.7 Hz, 1H), 6.97 (dd, J = 6.3, 1.7 Hz, 1H), 6.89–6.86 (m, 2H), 6.05 (m, 1H), 5.99 (s, 2H), 5.24 (m, 1H), 5.21 (dq, J = 6.8, 1.4 Hz, 1H), 3.53 (d, J = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.1, 159.6, 156.9, 152.5, 147.9, 147.8, 135.7, 128.1, 125.9, 125.2, 125.1, 122.6, 118.5, 117.7, 110.0, 108.6, 103.4, 101.4, 35.0; IR (film) ν_{max} 3076, 2953, 2918, 2872, 2851, 1620, 1574, 1504, 1495, 1435, 1404, 1371, 1319, 1275, 1252, 1240, 1151, 1138, 1042, 912, 858, 768 cm^{-1}; HRMS (ESI$^+$) m/z: [M+Na]$^+$ calcd for $C_{19}H_{14}O_5$, 345.0739; found, 345.0744.

4.50. 6-Allyl-3-(benzo[*d*][1,3]dioxol-5-yl)-7-hydroxy-8-methyl-4*H*-chromen-4-one (34b)

N,*N*-Diethylaniline (210 μL) was added to **33b** (180 mg, 0.53 mmol) in a sealed flask and the solution was then heated to 170 °C for 48 h. The reaction was diluted with 1 M aqueous HCl solution (10 mL) and the precipitate was collected by filtration. The residue was purified via column chromatography (SiO_2, 8:1:1 hexanes/CH_2Cl_2/EtOAc to 4:1:1 hexanes/CH_2Cl_2/EtOAc) to give 6-allyl **34b** as a near-colorless amorphous solid (93 mg, 19%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.74 (br s, 1H), 8.43 (s, 1H), 7.71 (s, 1H), 7.15 (d, J = 1.7 Hz, 1H), 7.07 (dd, J = 8.1, 1.7 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.06 (s, 2H), 6.01 (m, 1H), 5.12–5.07 (m, 2H), 3.46 (d, J = 6.5 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 174.8, 157.8, 154.0, 153.5, 147.0, 146.8, 136.4, 126.2, 1225.9, 122.9, 122.7, 122.4, 116.5, 116.2, 111.4, 109.4, 108.1, 101.0, 33.9, 8.8; IR (film) ν_{max} 3205, 2920, 2851, 1634, 1622, 1589, 1574, 1495, 1464, 1435, 1383, 1271, 1240, 1180, 1097, 1070, 1041, 933, 914, 856, 800, 764, 748 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{20}H_{16}O_5$, 337.1076; found, 337.1061.

4.51. 8-Allyl-3-(benzo[*d*][1,3]dioxol-5-yl)-7-hydroxy-4*H*-chromen-4-one (34c)

The acidic aqueous layers from the construction of **34a** were concentrated, water (50 mL) was added, the precipitate was collected by filtration and washed with cold Et_2O to give 8-allyl **34c** as a grey amorphous solid (213 mg, 54%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.75 (br s, 1H0, 8.42 (s, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 1.6 Hz, 1H), 7.07 (dd, J = 8.0, 1.7 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.06 (s, 2H), 5.97 (ddt, J = 17.0, 10.2, 6.0 Hz, 1H), 5.02–4.95 (m, 2H), 3.53 (dbr t, J = 6.0, 1.5 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 174.8, 160.0, 155.3, 153.5, 147.0, 135.3, 125.8, 124.7, 122.8, 116.6, 115.2, 114.3, 112.8, 109.4, 108.1, 101.0, 26.5; IR (film) ν_{max} 3234, 2905, 1618,

1595, 1578, 1483, 1425, 1279, 1250, 1036, 1020 cm^{-1}; HRMS (ESI^+) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{14}O_5$, 323.0919; found, 323.0912.

4.52. 6-Allyl-3-(benzo[*d*][1,3]dioxol-5-yl)-4-oxo-4*H*-chromen-7-yl acetate (35a)

Acetic anhydride (200 μL, 216 mg, 2.12 mmol) was added to **34a** (3 mg, 0.01 mmol) in anhydrous pyridine (200 μL, 196 mg, 2.48 mmol) and the solution was then heated to reflux for 4 h. After cooling to rt, 1 M aqueous HCl solution (5 mL) was added and the solution was extracted with EtOAc (3 × 10 mL). The organic layers were washed with saturated aqueous $NaHCO_3$ solution (15 mL), saturated aqueous NaCl solution (20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 4:1 hexanes/EtOAc) to give **35a** as a near-colorless amorphous solid (1.3 mg, 38%): ^1H NMR ($CDCl_3$, 500 MHz) δ 8.19 (s, 1H), 7.96 (s, 1H), 7.28 (s, 1H), 7.10 (d, *J* = 1.7 Hz, 1H), 6.98 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.01 (s, 2H), 5.93 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.16–5.07 (m, 2H0, 3.43 (br d, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.9, 168.7, 155.3, 153.1, 153.0, 148.0, 147.9, 135.3, 130.6, 128.1, 125.6, 125.4, 122.6, 122.6, 117.2, 112.1, 109.9, 108.7, 101.4, 34.7, 21.2; IR (film) ν_{max} 3076, 2922, 2854, 1769, 1649, 1618, 1504, 1489, 1439, 1369, 1321, 1246, 1192, 1169, 1105, 1082, 1028, 930, 910, 854, 814 cm^{-1}; HRMS (ESI^+) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{16}O_6$, 365.1025; found, 365.1027.

4.53. 6-Allyl-3-(benzo[*d*][1,3]dioxol-5-yl)-8-methyl-4-oxo-4*H*-chromen-7-yl acetate (35b)

Acetic anhydride (15 μL, 16 mg, 0.16 mmol) was added to **34b** (25 mg, 0.07 mmol) in anhydrous pyridine (110 μL, 108 mg, 1.36 mmol) and the solution was then heated to reflux for 4 h. After cooling to rt, 1 M aqueous HCl solution (5 mL) was added and the solution was extracted with EtOAc (3 × 10 mL). The organic layers were washed with saturated aqueous $NaHCO_3$ solution (15 mL), saturated aqueous NaCl solution (20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 4:1 hexanes/EtOAc) to give **35b** as a near-colorless amorphous solid (21 mg, 75%): ^1H NMR ($CDCl_3$, 500 MHz) δ 8.06 (s, 1H), 8.02 (s, 1H), 7.11 (d, *J* = 1.7 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.01 (s, 2H), 5.92 (ddt, *J* = 16.7, 10.3, 6.6 Hz, 1H), 5.15–5.09 (m, 2H), 3.39 (d, *J* = 6.6 Hz, 2H), 2.39 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.3, 168.4, 154.1, 152.9 (2C), 151.8, 147.9, 135.4, 130.5, 125.7, 125.1, 124.8, 122.6, 122.6, 120.7, 117.2, 109.9, 108.7, 101.4, 35.2, 20.8, 9.7; IR (film) ν_{max} 3078, 2916, 1763, 1645, 1609, 1504, 1491, 1456, 1437, 1371, 1337, 1329, 1279, 1246, 1207, 1183, 1090, 1067, 1040, 924, 899, 954, 812, 729 cm^{-1}; HRMS (ESI^+) *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{18}O_6$, 401.1001; found, 401.1024.

4.54. 8-Allyl-3-(benzo[*d*][1,3]dioxol-5-yl)-4-oxo-4*H*-chromen-7-yl acetate (35c)

Acetic anhydride (85 μL, 92 mg, 0.90 mmol) was added to **34c** (199 mg, 0.62 mmol) in anhydrous pyridine (630 μL, 616 mg, 7.79 mmol) and the solution was then heated to reflux for 4 h. After cooling to rt, 1 M aqueous HCl solution (5 mL) was added and the solution was extracted with EtOAc (3 × 10 mL). The organic layers were washed with saturated aqueous $NaHCO_3$ solution (15 mL), saturated aqueous NaCl solution (20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 4:1:1 hexanes/CH_2Cl_2/EtOAc) to give **35c** as a near-colorless amorphous solid (205 mg, 92%): ^1H NMR ($CDCl_3$, 500 MHz) δ 8.24 (d, *J* = 8.8 Hz, 1H), 8.03 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.11 (d, *J* = 1.7 Hz, 1H), 7.00 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.01 (s, 2H), 5.91 (ddt, *J* = 16.8, 10.3, 6.1 Hz, 1H), 5.10–5.03 (m, 2H), 3.59 (d, *J* = 6.1 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.2, 168.9, 155.2, 153.0, 152.8, 148.0, 148.0, 134.3, 125.5, 125.5, 125.2, 122.7, 122.6, 121.6, 120.5, 116.5, 109.9, 108.7, 101.4, 28.2, 21.1; IR (film) ν_{max} 3078, 3011, 2980, 2901, 1765, 1645, 1618, 1603, 1580, 1504, 1491, 1431, 1369, 1337, 1325, 1279, 1252, 1232, 1180, 1109, 1038, 1022, 924, 895, 851, 812, 771, 733 cm^{-1}; HRMS (ESI^+) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{16}O_6$, 387.0845; found, 387.0835.

4.55. 3-(Benzo[*d*][1,3]dioxol-5-yl)-6-(3-methylbut-2-enyl)-4-oxo-4*H*-chromen-7-yl acetate (36a)

Grubbs' second generation catalyst (9 mg, 0.01 mmol) was added to **35a** (1.4 mg, 3.84 μmol) in anhydrous CH_2Cl_2 (300 μL) at rt. After 15 min, 2-methyl-2-butene (1.20 mL) was added and the reaction was stirred at rt for 18 h. The solvent was concentrated and the residue purified via PTLC (SiO_2, 4:1 hexanes/EtOAc) to give **36a** as a colorless amorphous solid (1.5 mg, 99%): ^1H NMR ($CDCl_3$, 500 MHz) δ 8.16 (s, 1H), 7.96 (s, 1H), 7.24 (s, 1H), 7.10 (d, *J* = 1.7 Hz, 1H), 6.98 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.01 (s, 2H), 5.25 (t heptet, *J* = 7.3, 1.4 Hz, 1H), 3.35 (br d, *J* = 7.3 Hz, 2H), 2.37 (s, 3H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.72 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.0, 168.8, 155.1, 153.1, 152.9 (2C), 147.9, 134.4, 132.2, 127.6, 125.7, 125.3, 122.6, 122.6, 120.9, 111.8, 109.9, 108.6, 101.4, 28.9, 26.0, 21.2, 18.1; IR (film) ν_{max} 2926, 2854, 1769, 1647, 1618, 1504, 1491, 1474, 1439, 1375, 1246, 1200, 1178, 1105, 1080, 1030, 933, 912, 856, 814, 760, 750 cm^{-1}; HRMS (ESI^+) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{20}O_6$, 393.1338; found, 393.1332.

4.56. 3-(Benzo[*d*][1,3]dioxol-5-yl)-8-methyl-6-(3-methylbut-2-enyl)-4-oxo-4*H*-chromen-7-yl acetate (36b)

Grubbs' second generation catalyst (3 mg, 3.53 μmol) was added to **35b** (21.2 mg, 56.03 μmol) in anhydrous CH_2Cl_2 (300 μL) at rt. After 15 min, 2-methyl-2-butene (1.20 mL) was added and the reaction was stirred at rt for 18 h. The solvent was concentrated and the residue purified via column chromatography (SiO_2, 4:1 hexanes/EtOAc) to give **36b** as a colorless amorphous solid (13 mg, 57%): ^1H NMR ($CDCl_3$, 500 MHz) δ 8.03 (br s, 1H), 8.02 (s, 1H), 7.11 (d, *J* = 1.7 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.00 (s, 2H), 5.25 (t heptet, *J* = 7.2, 1.4 Hz, 1H), 3.31 (br d, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 2.29 (s, 3H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.71 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.4, 168.4, 153.8, 152.8, 151.8, 147.9, 147.9, 134.2, 132.0, 125.8, 125.0, 124.3, 122.6, 122.5, 121.0, 120.4, 109.9, 108.6, 101.4, 29.3, 26.0, 20.7, 18.1, 9.7; IR (film) ν_{max} 3342, 3074, 2974, 2926, 2918, 1763, 1645, 1607, 1504, 1491, 1454, 1441, 1371, 1337, 1275, 1246, 1209, 1183, 1090, 1068, 1040, 933, 899, 858, 812, 737 cm^{-1}; HRMS (ESI^+) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{22}O_6$, 407.1495; found, 407.1516.

4.57. 3-(Benzo[*d*][1,3]dioxol-5-yl)-8-(3-methylbut-2-enyl)-4-oxo-4*H*-chromen-7-yl acetate (36c)

Grubbs' second generation catalyst (26 mg, 0.03 mmol) was added to **35c** (153.7 mg, 0.42 mmol) in anhydrous CH_2Cl_2 (5.00 mL) at rt. After 15 min, 2-methyl-2-butene (10.5 mL) was added and the reaction was stirred at rt for 18 h. The solvent was concentrated and the residue purified via column chromatography (SiO_2, 4:1:1 hexanes/CH_2Cl_2/EtOAc) to give **36c** as a colorless amorphous solid (98 mg, 88%): ^1H NMR ($CDCl_3$, 500 MHz) δ 8.20 (d, *J* = 8.8 Hz, 1H), 8.03 (s, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.12 (d, *J* = 1.7 Hz, 1H), 7.00 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.89 (d, *J* = 8.0 Hz,

1H), 6.01 (s, 2H), 5.16 (t heptet, J = 7.1, 1.4 Hz, 1H), 3.52 (br d, J = 7.1 Hz, 2H), 2.38 (s, 3H), 1.82 (d, J = 1.4 Hz, 3H), 1.71 (d, J = 1.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.2, 169.0, 155.3, 152.8, 152.6, 148.0, 148.0, 133.5, 125.6, 125.2, 125.0, 123.5, 122.8, 122.6, 120.5, 120.5, 109.9, 108.7, 101.4, 25.9, 23.3, 21.1, 18.1; IR (film) ν_{max} 3067, 2980, 2912, 1765, 1645, 1618, 1603, 1578, 1504, 1489, 1429, 1369, 1327, 1279, 1252, 1232, 1202, 1180, 1107, 1034, 935, 922, 901, 864, 852, 814, 770 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{23}H_{20}O_6$, 393.1338; found, 393.1333.

4.58. 3-(Benzo[*d*][1,3]dioxol-5-yl)-7-hydroxy-6-(3-methylbut-2-enyl)-4*H*-chromen-4-one (37a)

Potassium carbonate (5 mg, 36 μmol) was added to **36a** (1.5 mg, 38 μmol) in MeOH (2.0 mL) and the solution was stirred at rt. After 18 h, the pH was adjusted to 3 with 6 M aqueous HCl solution and the solvent was concentrated. The residue was extracted with 1:1 CH_2Cl_2/MeOH (3 × 5 mL) and the organic layers were concentrated. The residue was purified via PTLC (SiO_2, 4:1:1 hexanes/CH_2Cl_2/EtOAc) to give **37a** as a colorless amorphous solid (0.9 mg, 67%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (s, 1H), 7.89 (s, 1H), 7.10 (d, J = 1.7 Hz, 1H), 6.98 (dd, J = 8.0, 1.7 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.85 (s, 1H), 6.08 (br s, 1H), 6.00 (s, 2H0, 5.34 (t heptet, J = 7.2, 1.4 Hz, 1H), 3.48 (br d, J = 7.2 Hz, 2H), 1.82–1.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.0, 159.8, 156.7, 152.4, 147.9, 147.8, 136.6, 127.4, 126.5, 126.0, 125.0, 122.6, 120.9, 118.5, 110.0, 108.6, 103.4, 101.4, 29.9, 26.1, 18.2; IR (film) ν_{max} 3194, 2957, 2922, 2853, 1616, 1583, 1504, 1487, 1464, 1435, 1385, 1333, 1273, 1254, 1207, 1140, 1105, 1036, 933, 856, 814, 748 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{21}H_{18}NO_5$, 351.1233; found, 351.1216.

4.59. 3-(Benzo[*d*][1,3]dioxol-5-yl)-7-hydroxy-8-methyl-6-(3-methylbut-2-enyl)-4*H*-chromen-4-one (37b)

Potassium carbonate (41 mg, 0.30 mmol) was added to **36b** (13 mg, 32 μmol) in MeOH (1.0 mL) and the solution was stirred at rt. After 1 h, the reaction was diluted with 1 M aqueous HCl solution (10 mL) and was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were washed with saturated aqueous NaCl solution (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography (SiO_2, 8:1:1 hexanes/CH_2Cl_2/EtOAc) then PTLC (SiO_2, 4:1:1 hexanes/CH_2Cl_2/EtOAc) to give **37b** as a colorless amorphous solid (1.8 mg, 15%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (s, 1H), 7.93 (br s, 1H), 7.12 (d, J = 1.7 Hz, 1H), 6.99 (dd, J = 8.0, 1.7 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.00 (s, 2H), 5.98 (br s, 1H), 5.33 (t heptet, J = 7.3, 1.4 Hz, 1H), 3.49 (br d, J = 7.3 Hz, 2H), 2.34 (s, 3H), 1.85 (d, J = 1.4 Hz, 3H), 1.82 (d, J = 1.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.5, 157.6, 155.0, 152.5, 147.8, 147.7, 137.1, 126.2, 125.2, 124.6, 124.2, 122.6, 121.1, 118.2, 112.2, 110.0, 108.6, 101.3, 20.7, 29.9, 26.1, 18.2, 8.3; IR (film) ν_{max} 3292, 2957, 2922, 2854, 1717, 1622, 1591, 1580, 1504, 1491, 1464, 1437, 1377, 1337, 1327, 1281, 1238, 1186, 1148, 1095, 1070, 1040, 937, 856, 812, 735 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{22}H_{20}O_5$, 365.1389; found, 365.1382.

4.60. 3-(Benzo[*d*][1,3]dioxol-5-yl)-7-hydroxy-8-(3-methylbut-2-enyl)-4*H*-chromen-4-one (37c)

Potassium carbonate (83 mg, 0.60 mmol) was added to **36c** (47 mg, 0.12 mmol) in MeOH (1.60 mL) and the solution was stirred at rt. After 1 h, the reaction was diluted with 1 M aqueous HCl solution (10 mL) and was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were washed with saturated aqueous NaCl solution (50 mL), dried (Na_2SO_4), filtered, and concentrated. Cold Et_2O (10 mL) was added to the residue and the precipitate was collected by filtration to give **37c** as a colorless amorphous solid (18 mg, 43%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (d, J = 8.8 Hz, 1H), 7.98 (s, 1H), 7.11 (d, J = 1.7 Hz, 1H), 6.99 (dd, J = 8.0, 1.7 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.04 (s, 1H), 6.00 (s, 2H), 5.29 (t heptet, J = 7.2, 1.4 Hz, 1H), 3.63 (br d, J = 7.2 Hz, 2H), 1.88 (d, J = 1.4 Hz, 3H), 1.79 (d, J = 1.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.4, 159.1, 155.5, 152.4, 147.9, 147.8, 136.1, 125.9, 125.7, 124.7, 122.6, 120.6, 118.7, 115.0, 114.5, 110.0, 108.6, 101.4, 26.0, 22.4, 18.2; IR (film) ν_{max} 3221, 2899, 1620, 1595, 1576, 1502, 1489, 1427, 1379, 1335, 1310, 1279, 1248, 1177, 1159, 1107, 1034, 856, 810 cm^{-1}; HRMS (ESI$^+$) m/z: [M+Na]$^+$ calcd for $C_{21}H_{18}O_5$, 373.1052; found, 373.1033.

4.61. Anti-proliferation assays

Cells were maintained in a 1:1 mixture of Advanced DMEM/F12 (Gibco) supplemented with non-essential 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 attaché 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 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.

4.62. 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 14,000*g* for 10 min at 4 °C. Protein concentrations were determined using the Pierce BCA protein assay kit per the manufacturer's instructions. Equal amounts of protein (20 μg) were electrophoresed under reducing conditions, transferred to a 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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