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An Expeditious Modular Hybrid Strategy for the Diversity-Oriented Synthesis of Lamellarins/Azalamellarins with Anticancer Cytotoxicity

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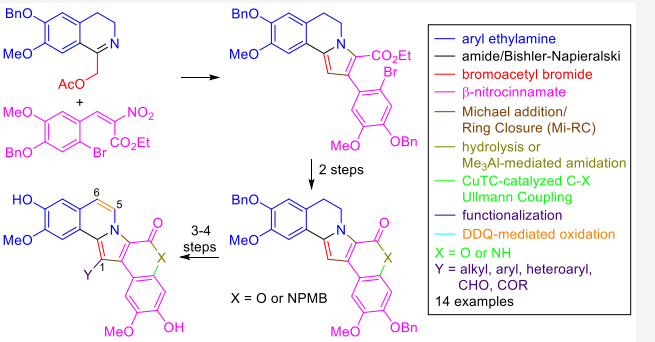
ABSTRACT: A modular hybrid strategy has been developed for the diversity-oriented synthesis of lamellarins/azalamellarins. The common pentacyclic pyrrolodihydroisoquinoline lactone/lactam core was formed via the Michael addition/ring closure (Mi-RC) and the copper(I) thiophene-2-carboxylate (CuTC)-catalyzed C−O/C−N Ullmann coupling. Subsequent direct functionalization at C1, DDQ-mediated C5═C6 oxidation, and global deprotection of all benzyl-type *O*- and *N*-protecting groups furnished the desired lamellarins/azalamellarins. The late-stage functionalization at C1 provided a handle to accommodate a wider scope of functional groups as they need to tolerate only the DDQ oxidation and global deprotection. Moreover, with the C1-*H* pyrrole as the late-stage common intermediate, it was also possible to divergently exploit not only its nucleophilic nature to react with some electrophilic species but also some transition-metal-catalyzed cross-coupling reactions (via the intermediacy of the C1-iodopyrrole) to incorporate diversity at this position. Overall, this strategy simplifies the preparation of lamellarins/azalamellarins; including the Mi-RC, these C1-structurally diverse analogues could be prepared efficiently in 6−7 steps from the easily accessed 1-acetoxymethyldihydroisoquinoline and *β*-nitrocinnamate. Some selected azalamellarins were evaluated for their inhibitory effect against HeLa cervical cancer cells. An acute induction of intrinsic apoptosis was detected and may lead to growth suppression of or cytotoxicity against cancer cells.

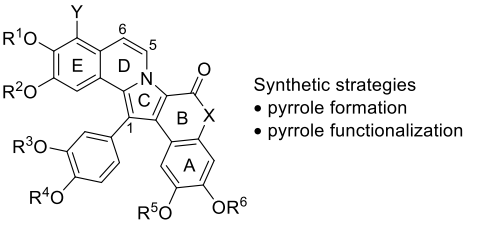


INTRODUCTION

Lamellarins (**1**) are a group of marine-derived natural products. Since their first reported isolation in 1985 by Faulkner,[1] a number of natural as well as unnatural analogues have been isolated[2] or synthesized by various groups including ours.[3−6] Lamellarins and their analogues have been shown to exhibit a wide array of biological activities as well as a reversal against multidrug resistance in some cancer cell lines, inhibition against HIV-1 integrase, and immunomodulation.[7−10] In addition, some studies toward elucidating molecular mechanisms for anticancer activities have been conducted.[11] Topoisomerase poisoning,[12] inhibition of cancer-related protein kinases,[7b,f,9] and interfering with mitochondria functions[13] have been suggested as plausible mechanisms leading to apoptosis and eventual cell death.

Different synthetic strategies have been developed; they can be classified into two approaches: pyrrole formation and pyrrole functionalization (Scheme 1).[14] Because the convergent nature of the pyrrole formation approach requires the early sequential preassembly of the requisite synthons with the selected substituents around the core prior to the pyrrole formation step, this renders the approach less modular.[4a,e,f,h,5b,c,e,g,h,6,7e,8b] The pyrrole functionalization, on the other hand, while highly modular with each unit possibly

Scheme 1. Lamellarins (1) and Their Aza Analogues (2)



X = O; Y = H, OH or OMe; R^1-R^6 = H or Me (lamellarins; **1**)
X = NH; Y = H, OH, or OMe; R^1-R^6 = H or Me (azalamellarins; **2**)

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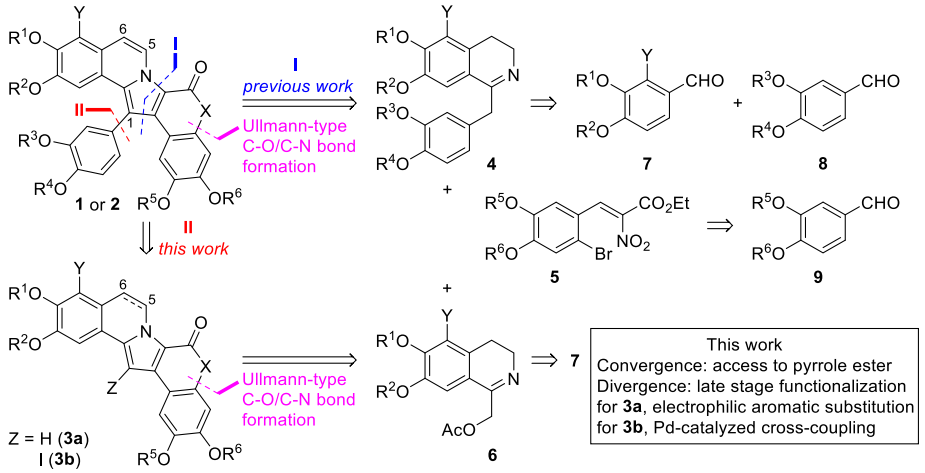
Scheme 2. Retrosynthetic Analysis of the Pyrrole Formation Route (I) and the Hybrid Strategy (II)



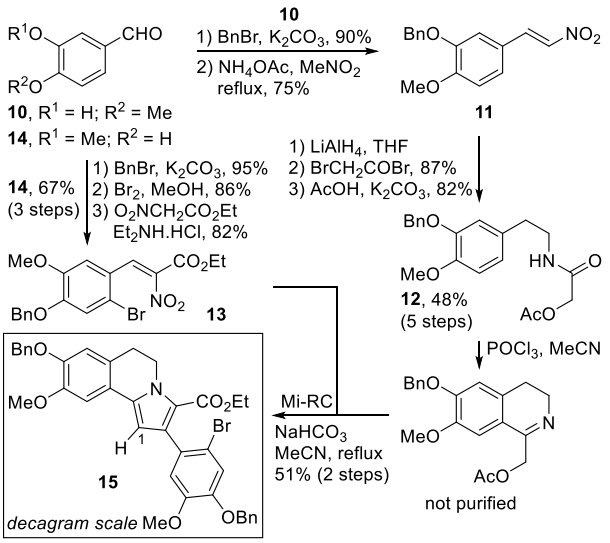
incorporated rather orthogonally to others via the sequential Pd-catalyzed Suzuki cross-coupling reactions, is seemingly more linear, resulting in a relatively higher overall number of steps and lower yields.[4b,c,5f,i,7a,8c,d,9a,b,10b] In addition, both approaches suffer from a limited range of functional group compatibility, arising mostly from incorporating functionalized aromatic rings at an early stage (pyrrole formation) or various stages (pyrrole functionalization). Thus, it is desirable to develop a hybrid strategy whereby the advantages from both approaches can be realized, combined, and maximally utilized.[4d,g,5a] Herein, we wish to report our development of such a hybrid strategy to expedite the preparation of lamellarins (containing lactone) as well as their aza analogues[5i,7d,i,9d] (azalamellarins (**2**); containing lactam).

As shown retrosynthetically in Scheme 2, when compared with our previously developed approaches for lamellarins and azalamellarins (**I**), which required the incorporation of the nonfused aromatic group at an early stage,[6,7d,f] the hybrid strategy (**II**) would incorporate such group at C1 at a late stage to divergently deliver structurally diverse analogues from a common pentacyclic core **3a** or **3b**. The pyrrole formation would still rely on the highly convergent Michael addition-ring closure (Mi-RC) Grob-type condensation[6] between either the benzyldihydroisoquinoline **4** and the *β*-nitrocinnamate **5** (**I**) or the dihydroisoquinoline acetate **6** and compound **5** (**II**).[7e] The dihydroisoquinoline acetate **6** would require only one benzaldehyde **7** as the starting material without the need for the benzaldehyde **8** because such unit would be installed at a later stage via electrophilic aromatic substitution (for **3a**) or Pd-catalyzed cross-coupling reactions (for **3b**). The *β*-nitrocinnamate **5** could be prepared from benzaldehyde **9**. In addition, both **I** and **II** would utilize the Ullmann-type C−O/C−N bond formation for the lactone/lactam ring, respectively.[7d−f]

RESULTS AND DISCUSSION

Chemistry. On the basis of our previous structure−activity relationship studies,[7c−f] we decided to employ the commercially available isovanillin (**10**) as our starting material. As shown in Scheme 3, a two-step sequence of benzylation and Henry aldol condensation smoothly converted **10** to the corresponding *β*-nitrostyrene **11** (68% yield), which was subjected to $LiAlH_4$ reduction to yield the corresponding aryl ethylamine, which underwent amidation reaction using

Scheme 3. A Convergent Decagram-Scale Synthesis of Pyrrole Ester 15 via Mi-RC



bromoacetyl bromide (87% yield) and then acetoxylation using acetic acid and potassium carbonate (82% yield) to provide the requisite acetoxy amide **12** in 48% yield over five steps starting from isovanillin **10**. A subsequent Bischler−Napieralski reaction of **12** gave the imine, which was not purified but employed directly for the ensuing Mi-RC Grob-type condensation[6c−e] with *β*-nitrocinnamate **13**, available in 67% yield from the commercially available vanillin **14** over three steps, to afford the pyrrole ester **15** in 51% yield over two steps. Notably, the robustness of these steps allowed for a highly reproducible decagram-scale synthesis.[15]

With the pyrrole ester **15** in hand, we next turned our attention to the formation of the remaining lactone/lactam ring (ring B; Scheme 1) of the pentacyclic skeleton. Ideally, the pyrrole ester **15** was anticipated to serve as a common intermediate to access the lactone/lactam ring. While such consideration was proven successful earlier, the substrates for such transformations were fully substituted pyrroles with an aromatic group at C1 of the lamellarin framework.[7f] In this case, the C1-*H* in the nonfully substituted pyrrole **15** may have different reactivity, which may or may not be compatible with the chemistry required for the lactone/lactam formation. To

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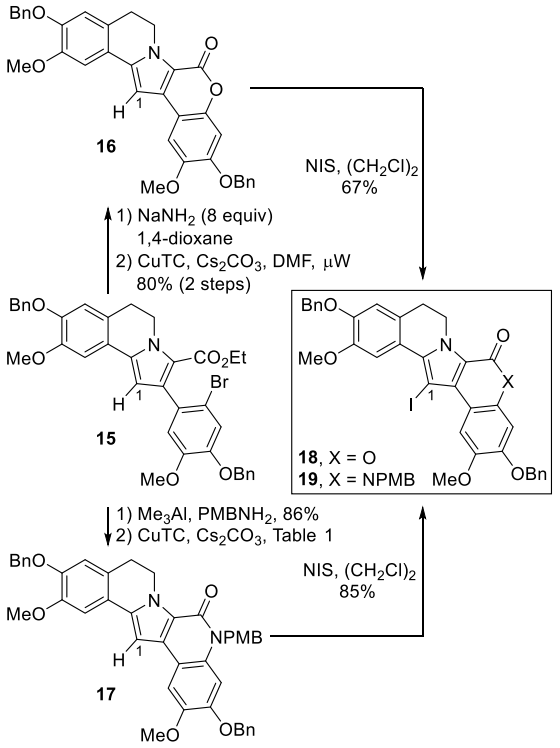
our delight, saponification of the ester could be affected by using $NaNH_2$ in "non-dried" 1,4-dioxane to afford the corresponding carboxylate,[16] which was not isolated but directly subjected to the copper(I)-thiophene carboxylate (CuTC)-catalyzed Ullmann-type C−O bond formation[17] using Cs_2CO_3 as a base with microwave irradiation to furnish the lactone **16** in 80% yield over two steps (Scheme 4).

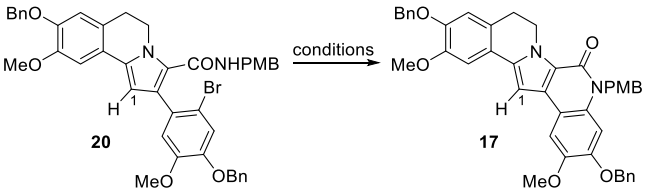
Scheme 4. Access to Pyrrole Lactones and Lactams 16−19 from the Ester 15



Alternatively, also by a two-step process, the ester group of **15** could be converted directly using Me_3Al, in 86% yield, to the corresponding PMB amide, which underwent the CuTC-catalyzed microwave-assisted Ullmann-type C−N bond formation[17] to furnish the lactam **17** in 90% yield following some optimization (Table 1). Subsequent iodination of both lactone **16** and lactam **17** furnished the iodopyrrole lactone **18** and lactam **19** in 67% and 85% yields, respectively.

As shown in Table 1, despite the previous optimization for this C−N bond formation which entailed the use of 3 equiv of CuTC for the synthesis of azalamellarin D and N under similar reaction conditions,[7f] we found that, for the pyrrole amide **20**, using such amount of CuTC with the reaction time of 40 min under microwave irradiation gave **17** only in a low yield (22%, entry 1). After some experimentation, we found that reducing the amount of CuTC to 2 equiv proved slightly beneficial for the yield (28%, entry 2), while decreasing the reaction time significantly improved the yields (up to 53%; entries 3−6). A combination of lowering the amount of CuTC to 1 equiv and the reaction time to 5 min only improve the yield slightly (56%, entry 7). Interestingly, employing only a catalytic amount of CuTC (5−10 mol %) furnished **17** in better yields of up to 90% (entries 8 and 9). As a control, no reaction took place in the absence of CuTC under otherwise an identical reaction condition (entry 10). For the decagram scale, without the use of a microwave, this step could be performed using

Table 1. Optimization of CuTC-Mediated C−N Bond Formation[a]



entry	CuTC (mol %)	time (min)	yield (%)[b]
1	300	40	22
2	200	40	28
3	200	30	31
4	200	20	35
5	200	10	46
6	200	5	53
7	100	5	56
8	10	5	60
9	5	5	90
10	0	5	0

[a]Unless otherwise noted, reactions were performed in *N*,*N*-dimethylformamide (DMF) under microwave irradiation (150 °C; 300 W; 250 psi) for the time as specified for each entry. [b]Isolated yields.

conventional heating with a prolonged reaction time (refluxing 1,4-dioxane for 6 h), which gave the desired product in a similar yield.

On the basis of previous structure−activity relationship studies, which revealed that the natural/unnatural analogues with C5=C6 olefin on the D rings exhibited higher potency in various biological assays,[7c−e] we then focused on preparing another advanced intermediate via C5−C6 oxidation to the corresponding olefin. Disappointingly, all our attempts to carry out such oxidation under various conditions including the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or cerium ammonium nitrate (CAN)[18] on pyrroles **16−19** were futile, indicating the chemical incompatibility between either the hydrogen or iodine atom on the pyrrole at C1 with oxidizing conditions. We then considered delaying this oxidation until at a later stage, i.e., after C1 functionalization, the step at which incorporation of other groups deemed compatible with oxidation would be performed. Two types of C1 functionalization were contemplated: (a) electrophilic aromatic substitution exploiting the nucleophilic nature of the unsubstituted pyrrole lactone **16** and lactam **17** and (b) transition-metal-catalyzed cross-coupling reactions of the iodide **18−19**. Because some of our previous work involved lamellarin D and N as well as their aza analogues, we decided to evaluate the transition-metal-catalyzed cross-coupling reactions first by allowing the iodide **18** to react with the corresponding arylboronic acid under a standard Pd-catalyzed Suzuki cross-coupling condition,[19] which yielded the desired *O*-benzylated lamellarin χ (Scheme 5). Subsequent DDQ-mediated C5−C6 oxidation then gave **21** in 64% yield over 2 steps. Global debenzylation using trifluoroacetic acid and thioanisole furnished lamellarin D (**22**) in 82% yield.[7f] Similarly, lamellarin **23** bearing an unsubstituted phenyl ring at C1 was successfully prepared from **18** using phenylboronic acid for the Suzuki cross-coupling reaction and DDQ oxidation (75% yield, 2 steps) followed by global *O*-debenzylation (72%).

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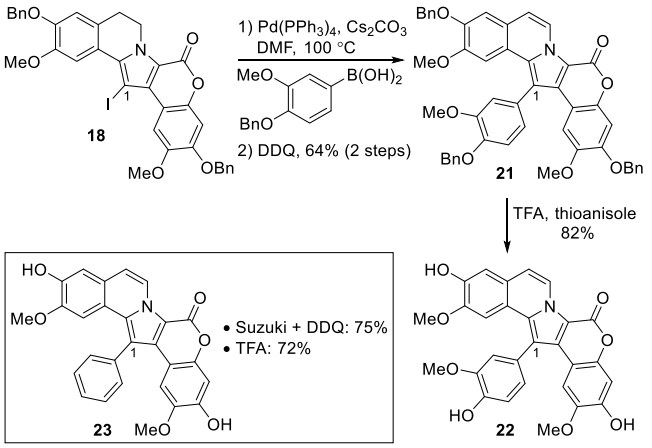
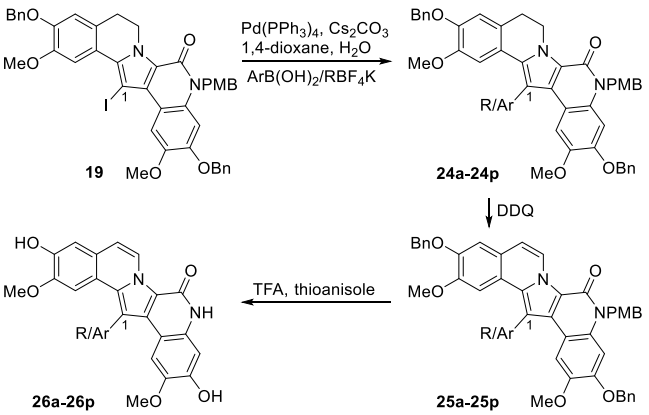
Scheme 5. Synthesis of Lamellarin D (22) and C1-Ph Derivative 23 from the Iodolactone 18

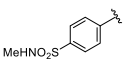
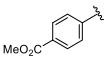


Because azalamellarins have been shown to exhibit cytotoxicity at a comparable level to that of the corresponding lamellarins,[7d−f] we decided to perform this reaction sequence on the iodopyrrole lactam **19**. As shown in Table 2, a number of arylboronic acid derivatives could react with **19** to furnish the corresponding products **24a−24p** in low to excellent yields (12−92%) most of which could be further oxidized using DDQ as a reagent to the C5═C6 products **25a−25p** in moderate to good yields (32−89%). Global *O*- and *N*-deprotection of the benzyl-type protecting groups delivered the final azalamellarins **26a−26p** in moderate to good yields (33−85%). Overall, diversely C1-substituted azalamellarins **26a−26j** and **26l−26m** could be obtained from iodopyrrole **19** in 7.6−68% yields over 3 steps. It should be noted that DDQ oxidation was found incompatible with olefin-containing moieties (entries 14 and 15). In addition, the methyl group was also oxidized to the corresponding aldehyde, which decomposed under the reaction condition (entry 16). Interestingly, the pyridine moiety of **24k** survived the DDQ

Table 2. Reaction Sequence of Suzuki Cross-Coupling with 19, DDQ-Mediated Oxidation, and TFA-Mediated Global Deprotection



		yield (%)[a]			
entry	R/Ar	Suzuki	DDQ	Deprotection	overall
1		**24a** (72)	**25a** (70)	**26a** (78)	39
2		**24b** (90)	**25b** (76)	**26b** (82)	56
3		**24c** (85)	**25c** (72)	**26c** (60)	37
4		**24d** (88)	**25d** (73)	**26d** (81)	52
5		**24e** (92)	**25e** (89)	**26e** (83)	68
6		**24f** (82)	**25f** (67)	**26f** (72)	40
7		**24g** (82)	**25g** (80)	**26g** (85)	56
8		**24h** (85)	**25h** (82)	**26h** (81)	57

		yield (%)[a]			
entry	R/Ar	Suzuki	DDQ	Deprotection	overall
9		**24i** (41)	**25i** (32)	**26i** (74)	10
10		**24j** (46)	**25j** (67)	**26j** (67)	21
11[b]		**24k** (57)	**25k** (32)	**26k** (NP)	ND
12		**24l** (62)	**25l** (60)	**26l** (72)	27
13		**24m** (50)	**25m** (46)	**26m** (33)	7.6
14[b]		**24n** (71)	**25n** (NP)	**26n** (ND)	ND
15[b]		**24o** (41)	**25o** (NP)	**26o** (ND)	ND
16[b]	Me	**24p** (61)	**25p** (NP)	**26p** (ND)	ND

[a]Isolated yields. [b]NP = No desired product. ND = Not determined. Decomposition of **24n−24p** under DDQ oxidation conditions was observed. Decomposition of **26k** occurred during the global deprotection under acidic conditions.

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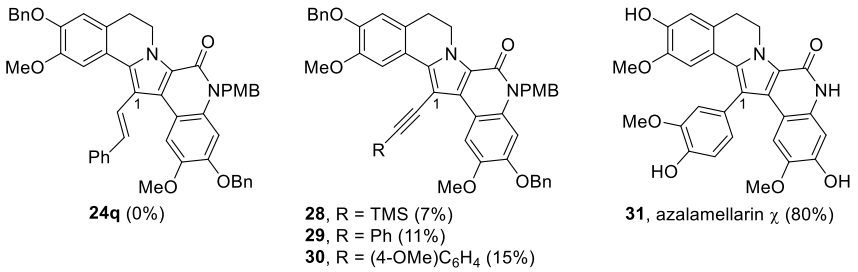


Figure 1. Products **24q** and **28**−**30** from the Heck and Sonogashira reactions of iodopyrrole **19** as well as azalamellarin *χ* **31**.

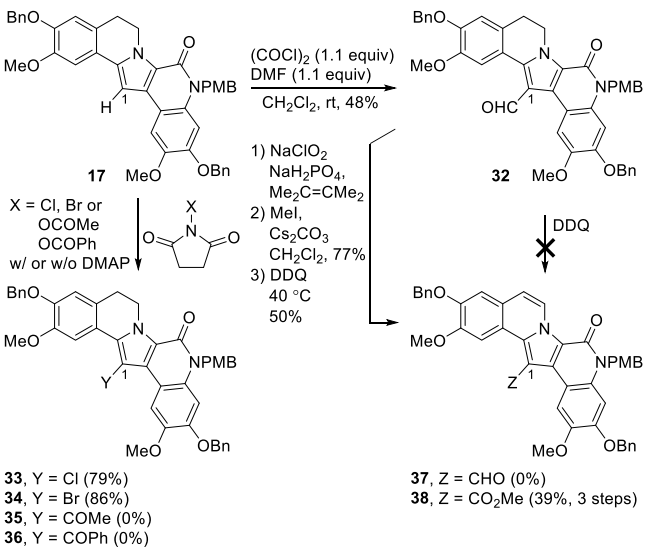
oxidation to give **25k**; however, global deprotection of **25k** did not furnish the desired product **26k** (entry 11).

We have also explored the use of iodopyrrole **19** for Heck and Sonogashira cross-coupling reactions. However, despite various attempts under different reaction conditions, the corresponding products **24q** and **28**−**30** were either not obtained or obtained in low yields (Figure 1); subsequent steps of DDQ oxidation and global deprotection were not performed. It should be noted that, under these conditions, **19** was completely consumed, and the reactions yielded **17**, the deiodinated pyrrole, as the major product. For the Heck reaction with styrene, **24q** was not obtained at all; the reaction furnished only **17** in 82% yield. This observation suggested that the first step of oxidative addition of Pd(0) to iodopyrrole occurred smoothly; however, the subsequent steps leading to the products were troublesome. In addition, **24h** was also subjected to global deprotection of *N*- and *O*-benzyl-type protecting groups without DDQ oxidation to yield the corresponding azalamellarin *χ* **31** in 80% yield, which would be employed for further biochemical studies (*vide infra*).

Interestingly, C1-*H* lactam **17** could also undergo direct C1 formylation using the Vilsmeier−Haack condition ($(COCl)_2$, DMF, CH_2Cl_2)[20] to furnish the corresponding pyrrole aldehyde **32** in a moderate 48% yield (Scheme 6). It should be noted that such direct formylation could not be affected when $POCl_3$ was employed instead of oxalyl chloride; when *N*,*N*-dimethylacetamide (DMA) was used, no corresponding ketone was obtained. Other Friedel−Crafts-type acylation of **17** using acetic anhydride or methyl chloroformate in the presence of DMAP did not furnish the corresponding C1-acetate or C1-methyl ester. In addition to iodination using NIS, the use of other succinimide-based halogenating agents NCS and NBS furnished the C1−Cl and C1−Br pentacyclic analogues **33** and **34** in 79% and 80% yields, respectively. However, other *N*-hydroxy succinimide-derived reagents, 2,5-dioxopyrrolidin-1-yl acetate and benzoate, in the presence or absence of DMAP, could not afford the corresponding C1-methyl ketone and C1-phenyl ketone analogues **35** and **36**. Interestingly, while DDQ oxidation of **32** did not furnish the corresponding aldehyde **37** containing C5═C6, a three-step process of Pinnick oxidation of the aldehyde to the corresponding C1-carboxylic acid followed by methylation and DDQ oxidation provided the corresponding C1-methyl ester C5═C6 analogue **38** in 39% overall yield. Unfortunately, under various conditions, attempts to affect global deprotection of **38** failed and gave only decarboxylated side products.

Some of these C1 derivatives, **22**, **26a**, **26e**, **26g**, **26h**, **26i**, **26l**, and **31**, were then chosen for further evaluations of their biological activities.

Scheme 6. Direct Functionalization of C1-*H* Lactam 17



Assessment of Cytotoxicity of Some Selected Azalamellarins. Some novel azalamellarins were prepared for the first time via our modular synthetic method featuring the late-stage functionalization at C1. Several previous investigations have reported that derivatives of natural as well as unnatural lamellarins could efficiently suppress the viability of human cancer cells.[7d−f] In addition, the lactone-to-lactam modification was found to enhance several aspects of the physicochemical properties of the compounds, thus promoting cytotoxicity.[7e,f] In this current study, we, therefore, determined whether some of these selected azalamellarin analogues, **22**, **26a**, **26e**, **26g**, **26h**, **26i**, **26l**, and **31**, could convey cytotoxicity toward HeLa cervical cancer cells. To answer this, the viability of HeLa cells cultured in titrated concentrations of azalamellarins was evaluated through crystal violet staining. The data were then plotted and analyzed for IC_{50}. Lamellarin D (LamD; **22**), a leading compound among the lamellarin analogues, exhibited IC_{50} at 2.84 μM (Figure 2, panel A); this was consistent with the results obtained earlier, which reported that **22** was cytotoxic against various cancer cell lines.[7f,13a] Likewise, the newly synthesized azalamellarins from this study could effectively limit the growth of HeLa cells with the IC_{50} values ranging in submicromolar levels (0.442 μM for **26a**; 0.501 μM for **26e**; 0.473 μM for **26i**; and 0.794 μM for **26l**; Figure 2, panels B, C, F, and G, respectively). These values were comparable to those of azalamellarins D (**26g**, 0.383 μM) and N (**26h**, 0.317 μM) as shown in Figure 2, panels D and E, respectively. When comparing these IC_{50} values, all azalamellarins (0.317−0.794 μM) were found to be approximately 3- to 9-fold more potent than **22** (2.84 μM).

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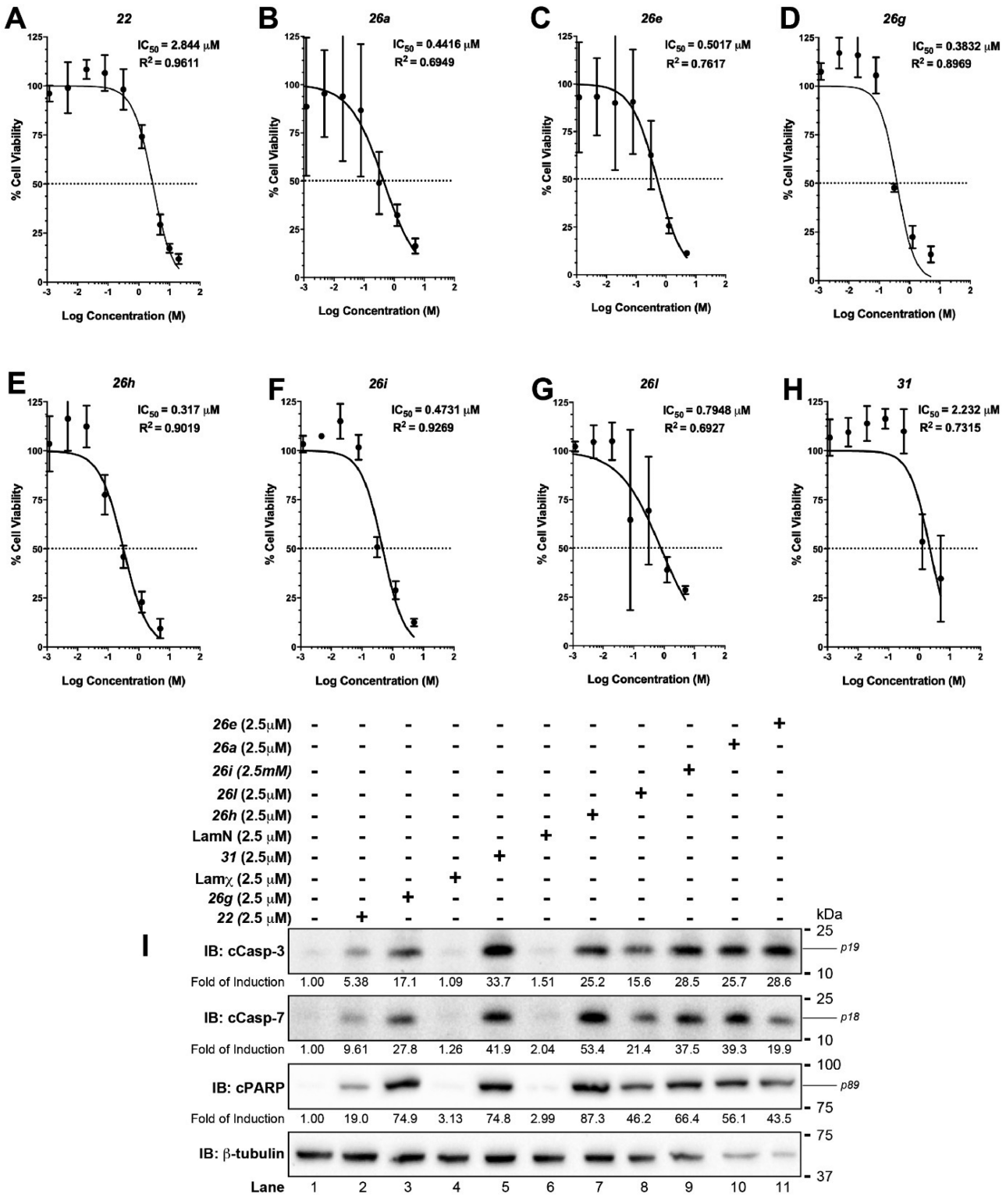

Figure 2. Assessments of biological activities of newly synthesized lamellarins. Panels A–H: cytotoxicity of newly synthesized lamellarins/azalamellarins comparing to LamD (**22**), azalamellarin D (**26g**), and azalamellarin N (**26h**). Colony formation of HeLa cancer cells treated with the titrated lamellarins/azalamellarins for 18 h was determined by crystal violet staining. The viable stained colonies were dried and eluted for OD_{590} measurement. The absorbance data were normalized and plotted into survival curves, calculated for IC_{50} and curve-fitting R^2. In each evaluation, the experiments were performed at least in triplicate. Error bars represent the standard deviation (n = 3). Panel I: impact of the newly synthesized lamellarins on induction of apoptosis. HeLa cells were treated with the compounds at 2.5 μM for 8 h before collecting for cell pellets. The cells were then determined for total protein and prepared for immunoblotting analysis with antibodies for apoptotic caspases (cCasp-3 and cCasp-7), the enzymes activated during apoptosis, and their target, cPARP (p19 = 19 kDa cleaved form of caspase-3 (cCasp-3); p18 = 18 kDa cCasp-7; p89 = 89 kDa cleaved poly(ADP-ribose) polymerase (cPARP)). The immunoblot data were recorded and analyzed for band densities. The image shows representative results from two different individual experiments.

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Interestingly, compound **31**, azalamellarin χ, the lactam-containing analogue of Lamχ, showed IC_{50} at 2.232 μM (Figure 2, panel H), which was similar to the IC_{50} value exhibited by **22**. This was rather unusual because from their structures, while almost identical to **22**, both Lamχ and azalamellarin χ possess a C5−C6 single bond in place of the C5−C6 double bond in the D-ring of **22**, which was reportedly found to confer planarity deemed critical for cytotoxicity against cancer cells.[7c] Therefore, a lactone-to-lactam modification apparently could provide an enhancement on the cytotoxicity of the analogues equivalent to the C5−C6 single bond vs C5−C6 double bond in the D-ring.

The cytotoxicity of lamellarins was reportedly associated with the ability to induce intrinsic apoptosis.[7b,13a,c,d] Hence, this group of compounds has been proposed to be one of the promising anticancer agents. We then observed whether our new azalamellarins could potentiate acute activation of apoptosis in cells by immunoblotting detection of apoptogenic protein markers such as cleaved forms of cysteine proteases (caspase-3 (cCasp-3, p19) and caspase-7 (cCasp-7, p18), respectively) as well as an 89 kDa fragment of nuclear Poly(ADP)ribose Polymerase (cPARP, p89) generated by enzymatically active forms of cCasp-3 and -7. The HeLa cells treated for 8 h with **22** showed more than 5-fold inductions of cCasp-3, -7, and cPARP compared with DMSO-treated cells (Figure 2, panel I: lane 2 vs lane 1). The treatment by **26g** and **26h** caused even stronger than 10-fold inductions of those proteins (Figure 2, panel I: lanes 3 and 7); similar effects were also found in cells treated with **26a**, **26e**, **26i**, **26l**, and **31** (Figure 2, panel I: lanes 10, 11, 9, 8, and 5, respectively). Notably, **31** could mediate a strong induction of apoptogenic proteins better than **22** (Figure 2, panel I: lane 5 vs lane 2), although their cytotoxicity IC_{50} values were virtually identical. In the same experimental setting, the cells treated with Lamχ showed no noticeable effects on the accumulation of apoptogenic proteins (Figure 2, panel I: lane 4). These data implicated that even though lactone-to-lactam modification of Lamχ to **31** may not have improved activity on cell death, such chemical modification drastically promoted the activity of the compound in apoptosis activation. Consistent with this idea, **26h**-treated cells exhibited strong induction of apoptosis, but cells treated by LamN, a lactone-containing isomer of **26h**, were unaffected by apoptotic induction (Figure 2, panel I: lanes 6 vs 7). Hence, the data clearly show that the lactone-to-lactam modification could enhance cytotoxicity and the biological activity of the lamellarins at the cellular level. In addition, our azalemallarins **26a**, **26e**, **26i**, and **26l**, while containing different orthogonal rings at C1, all exhibited comparable cytotoxicity and potency of apoptosis induction. Further investigation on specific cellular events related to their cytotoxicity may reveal a more specific biological role of the orthogonal ring on the lamellarin framework.

CONCLUSION

In summary, modular synthesis of C1-modified azalamellarins was successfully developed. Our hybrid strategy features both the convergent and divergent nature of the approach in the Michael-addition/ring closure (Mi-RC) Grob-type condensation reaction to form the pyrrole core and the late-stage C1 functionalization (via the intermediacy of the iodopyrrole **19**), respectively. Such late-stage C1 functionalization allows the incorporation of groups that otherwise may not be compatible with the reaction conditions required for the preceding steps. The reaction sequence of Suzuki−Miyaura cross-coupling of **19**, DDQ oxidation, and global deprotection proved to be feasible to furnish lamellarins/azalamellarins in moderate to good overall yields. On the other hand, while the C1-formylated pyrrole **32** could be obtained from the direct C1-*H* functionalization, its subsequent transformations failed to furnish any azalamellarin. Upon evaluating their cytotoxicity against HeLa cancer cells and investigating the effects that these new lamellarins/azalamellarins may exert on the apoptosis by assessing the levels of apoptogenic protein markers, the lactone-to-lactam modification on the lamellarin framework has clearly resulted in the perturbation of these markers. Such modification also superseded the need for the C5−C6 olefin for cytotoxicity as evident by comparing the IC_{50} values and the levels of perturbation of the apoptogenic protein markers for azalamellarin χ (**31**) with lamellarin χ (Lamχ) and lamellarin D (**22**). Thus, the lactone-to-lactam modification increased cytotoxicity even for the analogue containing the C5−C6 single bond. Because the exact molecular mechanisms of lamellarins/azalamellarins are likely to be multicellular events, further investigations are warranted to elucidate the exact molecular targets and cellular processes involved in their anticancer property; this is in progress in our laboratory, and the results will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise noted, reactions were run in oven-dried round-bottomed flasks. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl or purified by the solvent purification system (PURE-SOLV, Innovative Technology), while dichloromethane (CH_2Cl_2) was also purified by the solvent purification system (PURE-SOLV, Innovative Technology) prior to use. All other compounds were used as received from the suppliers. The crude reaction mixtures were concentrated under reduced pressure by removing organic solvents on a rotary evaporator. Column chromatography was performed using silica gel 60 ((i) Merck, particle size 0.06−0.2 mm; 70−230 mesh ASTM or (ii) Silicycle, SiliaFlash F60, particle size 40−63 μm; 230−400 mesh). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F_{254} aluminum sheets (Merck). All reactions under microwave irradiation were performed using sealed reaction vessels placed in a microwave synthesizer (CEM Microwave Technology, UK; Discover and Explorer SP model), and the temperature of the reactions was monitored by an external surface sensor. Chemical shifts for ^{1}H nuclear magnetic resonance (NMR) spectra were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), doublet of doublet (dd), doublet of triplet (dt), and doublet of doublet of doublet (ddd). All ^{13}C NMR data were obtained with the use of broadband decoupling ($^{13}C\{^1H\}$) and reported as proton-decoupled data. Chemical shifts of ^{19}F NMR spectra were reported in ppm on the δ scale from the peak of C_6F_6 (−164.9 ppm) as an internal reference. High-resolution (HRMS) mass spectra were obtained using time-of-flight (TOF) via the atmospheric-pressure chemical ionization (APCI) or electrospray ionization (ESI). Melting points were uncorrected.

General Procedure A: O-Benzylation. To a stirred solution of **10** or **14** (1.0 equiv) in ethanol (5 mL/mmol) were added potassium carbonate (1.5 equiv) and benzyl bromide (1.1 equiv) at room temperature. The mixture was heated to reflux by using an oil bath for 3 h. At that time, the reaction was cooled to room temperature, and potassium carbonate was filtered off. The resulting mixture was concentrated under reduced pressure; water was added, and the mixture was extracted with EtOAc (3 times). The combined organic layers were washed once with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the

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crude product mixture. Further purification by crystallization in EtOAc/hexane then furnished the desired product.

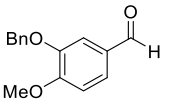
General Procedure B: C1−H Pyrrole Halogenation of the Pentacycles Containing Lactone or Lactam. To a stirred solution of C1-*H* pyrrole lactone **16** or lactam **17** (1.0 equiv) in 1,2-dichloroethane (DCE; 20 mL/mmol) was added the corresponding *N*-halosuccinimide (NXS; X = I, Br or Cl) (1.5 equiv) at room temperature. The resulting mixture was stirred at room temperature for 3 h. At that time, the reaction was quenched with water and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (40% EtOAc/hexane) to furnish the desired product.

General Procedure C: Suzuki Cross-Coupling Reaction. To a stirred solution of the lactone **18** or lactam **19** (1.0 equiv) in a 1,4-dioxane/water mixture (3:1 v/v; 40 mL/mmol) in a sealed tube were added boronic acid or borate derivatives (2.0 equiv), cesium carbonate (2.0 equiv), and $Pd(PPh_3)_4$ (0.05 equiv). The mixture was heated to 110 °C by using an oil bath for 16 h. At that time, the reaction was quenched with water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (40% EtOAc/hexane) to furnish the desired product.

General Procedure D: DDQ Oxidation. To a stirred solution of **24a−24m** (1.0 equiv) in 1,2-dichloroethane (20 mL/mmol) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 1.5 equiv) at room temperature. The mixture was stirred at room temperature for 16 h. At that time, the reaction was quenched with water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (50% EtOAc/hexane) to furnish the desired product.

General Procedure E: Global Deprotection. To a stirred solution of **21**, **23**, **25a−25m** (1.0 equiv) in trifluoroacetic acid (25 mL/mmol) was added thioanisole (2.5 mL/mmol) at room temperature. The mixture was heated to 60 °C by using an oil bath, and stirring continued for 24 h. At that time, the reaction was quenched with a saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by HPLC (reverse-phase C18 column: 250 mm × 21.2 mm, 5 μm particle size; Luna) using 50% aqueous MeOH/*i*-PrOH as the eluting solvent system with a flow rate of 9 mL/min and the UV detector set at 210, 254, and 366 nm.

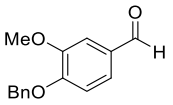
General Procedure F: Sonogashira Cross-Coupling Reaction. To a stirred solution of the lactam **19** (1.0 equiv) in triethylamine/DMF (5:1 v/v; 15 mL/mmol), $Pd(PPh_3)_4$ (0.05 equiv), and copper(I) iodide (0.1 equiv) in a sealed tube, which was then degassed for 15 min at room temperature, were added acetylene derivatives (1.5 equiv). The mixture was heated to 60 °C by using an oil bath, and stirring continued for 18 h. The reaction was quenched with a saturated NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (30% EtOAc/hexane) to furnish the desired product.



10I

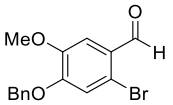
*3-(Benzyloxy)-4-methoxybenzaldehyde (**10I**).* Following general procedure A, isovanillin (60.0 g, 0.39 mol), K_2CO_3 (82.0 g, 0.59 mol), and benzyl bromide (52.0 mL, 0.44 mol) were employed to furnish **10I** as a white solid (86.3 g, 0.36 mol, 90%). The physical and spectroscopic data are in good agreement with those previously reported.[21]

*(E)-2-(Benzyloxy)-1-methoxy-4-(2-nitrovinyl)benzene (**11**).* To a solution of **10I** (40.0 g 0.17 mol) in glacial acetic acid (500 mL) were added ammonium acetate (50.9 g, 0.66 mol) and nitromethane (54.0 mL, 1.01 mol) at room temperature. The mixture was heated to reflux by using an oil bath for 1 h. At that time, the reaction was cooled to room temperature, at which the desired product crystallized. The resulting solid was then filtered and washed with an excess amount of water and hexane to yield **11** as a yellow solid (35.3 g, 0.12 mol, 75%). The physical and spectroscopic data are in good agreement with those previously reported.[21]



14I1

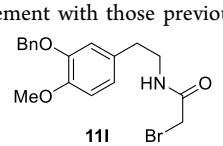
*4-(Benzyloxy)-3-methoxybenzaldehyde (**14I1**).* Following the general procedure, vanillin (60.0 g, 0.39 mol), K_2CO_3 (82.0 g, 0.59 mol), and benzyl bromide (52.0 mL, 0.44 mol) were employed to furnish **14I1** as a white solid (91.2 g, 0.38 mol, 95%). The physical and spectroscopic data are in good agreement with those previously reported.[21]



14I2

*2-Bromo-4-(benzyloxy)-5-methoxybenzaldehyde (**14I2**).* To a stirred solution of **14a** (40.0 g 0.17 mol) in methanol (500 mL) was added Br_2 (12.7 mL 0.25 mol) dropwise at room temperature, and the mixture was stirred for 3 h. The reaction was quenched with a saturated $Na_2S_2O_5$ solution, the mixture was evaporated under reduced pressure, and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by crystallization in EtOAc/hexane to furnish **14b** as a white solid (45.4 g, 0.14 mol, 86%). The physical and spectroscopic data are in good agreement with those previously reported.[21]

*Ethyl (Z)-3-(4-(Benzyloxy)-2-bromo-5-methoxyphenyl)-2-nitroacrylate (**13**).* To a stirred solution of **14I2** (45.0 g, 0.14 mol) in toluene (400 mL) were added diethylamine hydrochloride salt (23.0 g, 0.21 mol) and ethyl nitroacetate (19.4 mL, 0.18 mol) at room temperature. The mixture was heated to reflux by using an oil bath for 3 days with an azeotropic setup using the Dean−Stark apparatus. At that time, the reaction was cooled to room temperature. The resulting mixture was concentrated under reduced pressure and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (20% EtOAc/hexane) to furnish **13** as a brown oil (50.1 g, 0.12 mol, 82%). Physical and spectroscopic data are in good agreement with those previously reported.[7f]



11I

*N-(3-(Benzyloxy)-4-methoxyphenethyl)-2-bromoacetamide (**11I**).* A solution of the nitrostyrene **11** (30.0 g, 0.11 mol) in THF (200 mL) was added to a stirred slurry of lithium aluminum hydride (16.0 g, 0.42 mol) in THF (100 mL) at 0 °C. The reaction was allowed to warm up to room temperature, at which stirring continued for 18 h. At that time, the reaction was quenched with water, and any resulting fine suspension was removed via filtration. The reaction was concentrated under reduced pressure to give the corresponding

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arylethylamine product, which was used in the next step without further purification.

To a stirred solution of the crude arylethylamine (0.11 mol) in CH_2Cl_2 (300 mL) were added bromoacetyl bromide (11.5 mL, 0.13 mol) and a solution of Na_2CO_3 (27.9 g, 0.26 mol) in water (270 mL) at room temperature. The reaction was stirred for 3 h. At that time, the two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with water (150 mL) and brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude amide product, which was further purified by column chromatography on silica (50% EtOAc/hexane) to furnish **11I** as a white solid (34.6 g, 0.092 mol, 87%). Mp: 115.3−117.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.26 (m, 5H), 6.82−6.71 (m, 4H), 5.09 (s, 2H), 3.93 (s, 2H), 3.82 (s, 3H), 3.42 (q, J = 6.8 Hz, 2H), 2.68 (t, J = 7.1 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 165.2, 148.4, 148.1, 136.9, 130.7, 128.4, 127.7, 127.2, 121.3, 114.6, 112.0, 70.9, 55.9, 41.2, 34.7, 29.1. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{21}O_3N^{79}Br$, 378.0699; found, 378.0696. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{21}O_3N^{81}Br$, 380.0679; found, 380.0675.

*2-((3-(Benzyloxy)-4-methoxyphenethyl)amino)-2-oxoethyl acetate (**12**).* To a stirred solution of amide **11I** (30.0 g, 79.3 mmol) in THF (240 mL) were added potassium carbonate (22.0 g, 159 mmol) and glacial acetic acid (9.10 mL, 159 mmol) at room temperature. The mixture was heated to reflux by using an oil bath for 18 h. At that time, the reaction was cooled to room temperature, and potassium carbonate was filtered off. The resulting mixture was concentrated under reduced pressure and extracted with EtOAc. The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (50% EtOAc/hexane) to furnish **12** as a brown oil (23.3 g, 65.1 mmol, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44−7.26 (m, 5H), 6.84−6.72 (m, 3H), 6.25 (br s, 1H), 5.11 (s, 2H), 4.47 (s, 2H), 3.84 (s, 3H), 3.46 (q, J = 6.8 Hz, 2H), 2.71 (t, J = 7.0 Hz, 2H), 2.06 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.2, 166.8, 148.3, 148.0, 136.8, 130.8, 128.3, 127.7, 127.2, 121.2, 114.7, 114.7, 111.9, 70.9, 62.7, 55.9, 40.1, 34.7, 20.4. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{24}O_5N$, 358.1649; found, 358.1642.

*Ethyl 8-(Benzyloxy)-2-(4-(benzyloxy)-2-bromo-5-methoxyphenyl)-9-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (**15**).* To a stirred solution of amide **12** (22.5 g, 63.0 mmol) in anhydrous acetonitrile (150 mL) was added phosphorus oxychloride (17.7 mL 189 mmol) at room temperature. The mixture was heated to reflux by using an oil bath for 3 h. At that time, the reaction was cooled to room temperature and basified with an aqueous Na_2CO_3 solution (30.0 g, 283 mmol in water (300 mL)). The resulting mixture was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with water (200 mL) and brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude dihydroisoquinoline product ,which was used in the next step without further purification.

To a stirred solution of the crude dihydroisoquinoline in anhydrous acetonitrile (550 mL) were added sodium bicarbonate (5.30 g, 83.9 mmol) and nitrocinnamate **13** (18.3 g, 42.0 mmol) at room temperature. The mixture was heated to reflux by using an oil bath for 18 h. At that time, the reaction was cooled to room temperature, and sodium bicarbonate was filtered off. The resulting mixture was concentration under reduced pressure and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water (200 mL) and brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (30% EtOAc/hexane) to furnish the desired pyrrole ester **15** as a yellow foam (14.3 g, 21.4 mmol, 51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47−7.29 (m, 10H), 7.12 (s, 1H), 7.07 (s, 1H), 6.86 (s, 1H), 6.77 (s, 1H), 6.40 (s, 1H), 5.18 (s, 2H), 5.17 (s, 2H), 4.61 (t, J = 6.7 Hz, 2H), 4.04 (q, J = 6.0 Hz, 2H), 3.91 (s, 3H), 3.86 (s, 3H), 2.99 (t, J = 6.8 Hz, 2H), 0.91 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 161.5, 148.9, 148.3, 148.0, 147.4, 136.9, 136.5, 134.6, 132.5, 131.4, 128.5, 128.0, 127.9, 127.3, 127.2, 124.6, 121.2, 119.3, 117.6, 114.6, 114.3, 113.7, 107.4, 105.8, 71.3, 71.1, 59.7, 56.2, 56.1, 42.6, 28.4, 13.7. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{37}H_{35}O_6N^{79}Br$, 668.1642; found, 668.1630. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{37}H_{35}O_6N^{81}Br$, 670.1625; found, 670.1608.

*8-(Benzyloxy)-2-(4-(benzyloxy)-2-bromo-5-methoxyphenyl)-9-methoxy-N-(4-methoxybenzyl)-5,6-dihydropyrrolo[2,1-a]-isoquinoline-3-carboxamide (**20**).* To a stirred solution of the pyrrole ester **15** (0.30 g, 0.45 mmol) in 1,4 dioxane (5 mL) were added 4-methoxybenzylamine (0.30 mL, 2.25 mmol) and trimethylaluminum (2.0 M in toluene; 0.57 mL, 1.40 mmol) at room temperature. The reaction vessel was then sealed, and the reaction mixture was heated under microwave irradiation (5 min ramping time to 165 °C at 300 W; 65 min holding time) with an external surface sensor to monitor the reaction temperature. At that time, the reaction was quenched with water (3 mL), and aluminum complex salt was filtered off. The resulting mixture was concentrated under reduced pressure and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (40% EtOAc/hexane) to furnish the corresponding pyrrole amide **20** as a yellow foam (0.30 g, 0.39 mmol, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48−7.25 (m, 10H), 7.04 (s, 2H), 6.94 (s, 1H), 6.91 (s, 1H), 6.81−6.73 (m, 4H), 6.35 (s, 1H), 5.62 (t, J = 5.5 Hz, 1H), 5.15 (s, 2H), 5.06 (s, 2H), 4.64 (t, J = 6.7 Hz, 2H), 4.28 (d, J = 5.4 Hz, 2H), 3.88 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 2.97 (t, J = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 161.4, 158.7, 149.0, 148.8, 148.3, 147.6, 136.9, 136.2, 133.0, 129.9, 129.3, 128.8, 128.6, 128.5, 128.1, 127.8, 127.3, 127.2, 127.1, 124.5, 122.4, 121.4, 117.6, 114.7, 114.3, 113.7 (2C), 107.2, 105.0, 71.11, 71.09, 56.1, 56.0, 55.1, 42.9, 42.7, 28.5. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{43}H_{40}O_6N_2{}^{79}Br$, 759.2064; found, 759.2059; calcd for $C_{43}H_{40}O_6N_2{}^{81}Br$ 761.2050; found, 761.2039.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-8,9-dihydro-6H-chromeno-[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (**16**).* To a stirred solution of the pyrrole ester **15** (0.30 g, 0.45 mmol) in 1,4-dioxane (6 mL) was added sodium amide (0.14 g, 3.59 mmol). The mixture was heated to 100 °C by using an oil bath for 18 h. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the corresponding pyrrole carboxylic acid crude product, which was used directly in the next step without further purification.

To a stirred solution of the crude pyrrole carboxylic acid in DMF (5 mL) were added copper(I) thiophene-2-carboxylate (CuTC; 4.30 mg, 0.023 mmol) and cesium carbonate (0.30 g, 0.91 mmol). The reaction vessel was then sealed, and the reaction mixture was heated under microwave irradiation (5 min ramping time to 150 °C at 300 W; 5 min holding time) with an external surface sensor to monitor the reaction temperature. At that time, the reaction was quenched with a saturated NH_4Cl solution (2 mL), and the residual copper salt was filtered off. The resulting mixture was concentrated under reduced pressure and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude product, which was further purified by column chromatography on silica (40% EtOAc/hexane), to furnish the desired C1-*H* pyrrole lactone **16** as a brown solid (202 mg, 0.36 mmol, 80%). Mp: 213.5−214.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.26 (m, 10H), 7.20 (s, 1H),7.18 (s, 1H),6.91 (s, 1H), 6.79 (s, 1H), 6.78 (m, 1H), 5.19 (s, 2H), 5.17 (s, 2H), 4.66 (t, J = 6.9 Hz, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.02 (t, J = 6.9 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.4, 149.02, 148.99, 148.3, 146.7, 145.8, 140.0, 136.6, 136.3, 131.0, 128.6, 128.1, 128.0, 127.3, 127.2, 125.6, 120.3, 115.0, 113.6, 110.4, 108.0, 104.6, 102.9, 95.4, 71.05, 71.03, 56.5, 56.3, 42.2, 28.2. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{35}H_{30}O_6N$, 560.2068; found, 560.2068.

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*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**17**).* To a stirred solution of the pyrrole amide **20** (0.30 g, 0.40 mmol) in DMF (5 mL) were added copper(I) thiophene-2-carboxylate (CuTC; 3.80 mg, 0.002 mmol) and cesium carbonate (0.26 g, 0.80 mmol). The reaction vessel was then sealed, and the reaction mixture was heated under microwave irradiation (5 min ramping time to 150 °C at 300 W; 5 min holding time) with an external surface sensor to monitor the reaction temperature. At that time, the reaction was quenched with a saturated NH_4Cl solution (2 mL), and the residual copper salt was filtered off. The resulting mixture was concentrated under reduced pressure and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude product, which was further purified by column chromatography on silica (40% EtOAc/hexane) to furnish the C1-*H* pyrrole lactam **17** as a white solid (0.24 g, 0.36 mmol, 90%). Mp: 220.4−221.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48−7.29 (m, 12H), 7.08 (s, 1H), 7.06 (s, 1H), 6.89 (s, 1H), 6.82−6.78 (m, 4H), 5.58 (br s, 2H), 5.20 (s, 2H), 5.05 (s, 2H), 4.89 (t, J = 6.7 Hz, 2H), 4.00 (s, 6H), 3.77 (s, 3H), 3.04 (t, J = 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.6, 155.9, 149.0, 148.5, 147.6, 145.7, 138.0, 136.8, 136.7, 130.6, 129.3, 128.62, 128.56, 128.5, 128.0, 127.9, 127.6, 127.2, 127.1, 125.7, 121.2, 120.1, 114.2, 113.7, 112.1, 107.9, 105.6, 102.9, 94.6, 71.3, 71.1, 56.4, 56.3, 55.2, 45.1, 42.3, 28.6. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{43}H_{39}O_6N_2$, 679.2803; found, 679.2794.

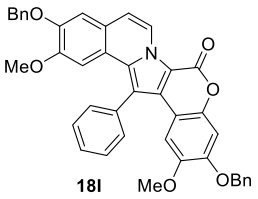
*3,11-Bis(benzyloxy)-14-iodo-2,12-dimethoxy-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (**18**).* Following general procedure B, C1-*H* pyrrole lactone **16** (2.00 g, 3.57 mmol) and *N*-iodosuccinimide (NIS; 1.21 g, 5.39 mmol) were employed to furnish the corresponding C1 iodopyrrole lactone **18** as a brown solid (1.64 g, 2.39 mmol, 67%). Mp: 238.6−239.4 °C. ^{1}H NMR (400 MHz,$CDCl_3$): δ 8.56 (s, 1H), 8.30 (s, 1H), 7.47−7.31 (m, 10H), 6.90 (s, 1H), 6.82 (s, 1H), 5.21 (s, 2H), 5.18 (s, 2H), 4.73 (t, J = 6.5 Hz, 2H), 4.02 (s, 3H), 4.01 (s, 3H), 2.95 (t, J = 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 154.5, 148.8, 148.3, 147.9, 145.9, 145.7, 137.6, 136.6, 136.2, 129.4, 128.7, 128.08, 128.05, 127.8, 127.3, 127.2, 120.0, 115.9, 113.5, 110.4, 110.0, 103.8, 102.7, 71.0, 70.9, 56.4, 50.3, 42.6, 29.0. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{35}H_{29}O_6NI$, 686.1034; found, 686.1033.

*3,11-Bis(benzyloxy)-14-iodo-2,12-dimethoxy-5-(4-methoxybenzyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**19**).* Following general procedure B, C1-*H* pyrrole lactam **17** (5.00 g, 7.37 mmol) and *N*-iodosuccinimide (NIS; 2.49 g, 11.1 mmol) were employed to furnish the corresponding C1 iodopyrrole lactam **19** as a brown solid (5.02 g, 6.24 mmol, 85%). Mp: 253.8−263.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.34 (s, 1H), 7.48−7.28(m, 10H), 7.05(s, 1H), 7.03 (s, 1H), 6.83−6.78 (m, 4H), 5.38 (br s, 2H), 5.22 (s, 2H), 5.05 (s, 2H), 4.98 (t, J = 6.2 Hz, 2H), 4.04 (s, 3H), 4.03 (s, 3H), 3.77 (s, 3H), 2.95 (t, J = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.7, 155.2, 148.4, 147.8, 147.5, 144.6, 136.8, 136.6, 136.1, 130.8, 128.8, 128.7, 128.6, 128.3, 128.0, 127.9, 127.5, 127.2, 127.1, 126.3, 120.8, 120.7, 114.2, 113.5, 112.2, 110.4, 104.7, 102.7, 71.1, 71.0, 56.44, 56.38, 55.3, 49.8, 45.4, 42.6, 29.5. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{43}H_{38}O_6N_2I$, 805.1769; found, 805.1755.

*3,11-Bis(benzyloxy)-14-(4-(benzyloxy)-3-methoxyphenyl)-2,12-dimethoxy-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (**21**).* Following general procedure C, C1 iodopyrrole lactone **18** (0.11 g, 0.16 mmol), 4-benzyloxy-3-methoxyphenyl boronic acid (0.083 g, 0.32 mmol), cesium carbonate (0.11 g, 0.32 mmol), and $Pd(PPh_3)_4$ (9.0 mg, 0.008 mmol) were employed to furnish the corresponding C1 arylated pyrrole lactone, which was used in the subsequent step without further purification.

Following general procedure D, the C1 arylated pyrrole lactone obtained from the previous step and DDQ (0.055 g, 0.24 mmol) were employed to furnish the corresponding *O*-benzylated lamellarin D **21** as a brown solid (0.079 g, 0.102 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (d, J = 7.3 Hz, 1H), 7.50−7.30 (m, 16H), 7.14−7.09 (m, 4H), 6.96 (d, J = 7.5 Hz, 1H), 6.94 (s, 1H), 6.72 (s, 1H), 5.31 (s, 2H), 5.24 (s, 2H), 5.18 (s, 2H), 3.90 (s, 3H), 3.36 (s, 3H), 3.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.5, 150.5, 149.6, 149.2, 148.5, 147.9, 147.8, 146.4, 146.0, 136.9, 136.3, 136.2, 134.3, 129.3, 128.72, 128.69, 128.67, 128.12, 128.06, 127.3, 127.2, 127.0, 124.6, 123.9, 123.2, 119.3, 114.9, 114.6, 112.4, 111.0, 110.3, 109.5, 107.9, 105.5, 105.4, 102.7, 70.94, 70.88, 70.8, 56.3, 55.5, 55.2. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{49}H_{40}O_8N$, 770.2748; found, 770.2742. These physical and spectroscopic data are in good agreement with those previously reported.[7f]

*3,11-Dihydroxy-14-(4-hydroxy-3-methoxyphenyl)-2,12-dimethoxy-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (**22**; lamellarin D).* Following general procedure E, compound **21** (21.0 mg, 0.027 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 35% (v/v) B in 50 min; a linear gradient increasing from 35% to 80% (v/v) B for 20 min, holding for 10 min; increasing to 100% B in 5 min, holding for 10 min; and re-equilibrating at initial conditions for 45 min. Product **22** was obtained (11.2 mg, 0.022 mmol, 82%). The physical and spectroscopic data are in good agreement with those previously reported.[7f]



18I

*3,11-Bis(benzyloxy)-2,12-dimethoxy-14-phenyl-6H-chromeno-[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (**18I**).* Following general procedure C, C1-*H* pyrrole lactone **18** (102 mg, 0.148 mmol), phenyl boronic acid (36.0 mg, 0.30 mmol), cesium carbonate (96.5 mg, 0.30 mmol), and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) were employed to give the desired C1-Ph pyrrole lactone, which was used in the DDQ oxidation without further purification.

Following general procedure D, the crude C1-Ph pyrrole lactone and DDQ (0.05 g, 0.22 mmol) were employed to provide the crude product, which was further purified by column chromatography on silica (50% EtOAc/hexane) to furnish the pyrrole lactone **18I** as a white foam (0.070 g, 0.111 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.19 (d, J = 7.3 Hz, 1H), 7.66−7.53 (m, 5H), 7.46−7.30 (m, 10H), 7.09 (s, 1H), 7.06 (s, 1H), 6.97 (d, J = 7.5 Hz, 1H), 6.94 (s, 1H), 6.62 (s, 1H), 5.24 (s, 2H), 5.18 (s, 2H), 3.41 (s, 3H), 3.39 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 155.5, 149.7, 149.2, 148.4, 146.4, 146.0, 136.3, 136.21, 136.18, 134.1, 131.9, 129.5, 129.2, 128.7, 128.4, 128.10, 128.07, 127.2, 124.6, 123.2, 119.3, 112.4, 111.3, 110.3, 109.5, 108.0, 105.5, 105.3, 102.8, 70.9, 70.8, 55.4, 55.1. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{41}H_{32}O_6N$, 634.2224; found, 634.2234.

*3,11-Dihydroxy-2,12-dimethoxy-14-phenyl-6H-chromeno-[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (**23**).* Following general procedure E, compound **18I** (22.0 mg, 0.035 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 45% (v/v) B in 50 min; a linear gradient increasing from 45% to 70% (v/v) B for 20 min, holding for 10 min; increasing to 100% B in 5 min, holding for 10 min; and re-equilibrating at initial conditions for 45 min. The product **23** was obtained as a yellow foam (11.3 mg, 0.025 mmol, 72%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.99 (s, 1H), 9.89 (s, 1H), 9.02 (d, J = 7.4 Hz, 1H), 7.73−7.61 (m, 5H), 7.22 (d, J = 7.4 Hz, 1H), 7.19 (s, 1H), 6.96 (s, 1H), 6.87 (s, 1H), 6.53 (s, 1H), 3.28 (s, 3H), 3.27 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 154.4, 148.6, 148.4, 147.9, 146.3, 144.7, 135.4, 133.8, 131.5, 129.6, 128.7, 128.5, 124.7, 122.1, 117.4, 112.5, 111.7, 110.5, 108.2, 106.7,

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105.5, 105.2, 103.8, 55.0, 54.5. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{20}O_6N$, 454.1285; found, 454.1289.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-phenyl-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**24a**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), phenyl boronic acid (31.0 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.20 mg, 0.006 mmol) were employed to furnish **24a** as a white solid (67.6 mg, 0.090 mmol, 72%). Mp: 213.6−215.4 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.58−7.24 (m, 15H), 7.09 (s, 1H), 7.06 (s, 1H), 6.82 (s, 1H), 6.80 (s, 1H), 6.77(s, 2H), 6.75 (s, 1H), 6.61 (s, 1H), 5.40 (br s, 2H), 5.13 (s, 2H), 5.01−4.96 (m, 4H), 3.76 (s, 3H), 3.33 (s, 3H), 3.29 (s, 3H) 3.04 (t, J = 6.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 158.5, 155.9, 147.9, 147.4, 146.7, 144.8, 137.2, 136.8, 136.6, 133.6, 131.6, 130.4, 129.3, 129.2, 128.6, 128.52, 128.46, 127.9, 127.8, 127.7, 127.5, 127.2, 127.1, 127.0, 126.5, 125.4, 121.2, 118.9, 114.5, 114.1, 113.3, 112.5, 109.0, 105.7, 102.6, 71.0, 70.9, 55.2, 55.02, 54.95, 45.1, 42.4, 28.9. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{49}H_{43}O_6N_2$, 755.3116; found, 755.3102.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-(p-tolyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**24b**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), *p*-tolylboronic acid (34.0 mg, 0.25 mmol), cesium carbonate (81 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.20 mg, 0.006 mmol) were employed to furnish **24b** as a white foam (86.1 mg, 0.112 mmol, 90%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.46−7.27 (m, 14H), 7.08 (s, 1H), 7.06 (s, 1H), 6.86 (s, 1H), 6.80−6.75 (m, 4H), 6.65 (s, 1H), 5.39 (br s, 2H), 5.14 (s, 2H), 5.00−4.96 (m, 3H), 3.77 (s, 3H), 3.36 (s, 3H), 3.32 (s, 3H), 3.03 (t, J = 6.6 Hz, 2H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 158.5, 156.0, 147.8, 147.4, 146.7, 144.8, 137.4, 136.9, 136.7, 133.9, 133.7, 131.5, 130.5, 129.9, 129.2, 128.6, 128.5, 127.9, 127.8, 127.6, 127.2, 127.0, 126.5, 125.6, 121.3, 118.9, 114.5, 114.1, 113.3, 112.6, 109.1, 105.9, 102.6, 71.1, 70.9, 55.2, 55.1, 55.0, 45.2, 42.4, 29.0, 21.2. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{50}H_{45}O_6N_2$, 769.3272; found, 769.3250.

*3,11-Bis(benzyloxy)-14-(4-fluorophenyl)-2,12-dimethoxy-5-(4-methoxybenzyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**24c**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), 4-fluorophenylboronic acid (35.0 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol) were employed to furnish **24c** as a yellow foam (81.7 mg, 0.106 mmol, 85%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.58−7.53 (m, 2H), 7.44−7.25 (m, 12H), 7.08 (s, 1H),7.06 (s, 1H), 6.81−6.77 (m, 5H), 6.56 (s, 1H), 5.39 (br s, 2H), 5.14 (s, 2H), 4.99−4.96 (m, 4H), 3.76 (s, 2H), 3.41 (s, 3H), 3.36 (s, 3H), 3.03 (t, J = 6.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.4 (d, J_{CF} = 248 Hz), 158.6, 155.8, 147.9, 147.9, 147.6, 146.9, 144.9, 136.8, 136.6, 133.8, 133.5, 133.4 (d, J_{CF} = 8 Hz), 133.1 (d, J_{CF} = 4 Hz), 130.6, 129.1, 128.6, 128.5, 127.9, 127.8, 127.6, 127.1, 127.0, 126.7, 125.5, 121.0, 119.0, 116.2 (d, J_{CF} = 21 Hz), 114.1, 113.5, 113.4, 113.1, 112.3, 108.9, 105.6, 102.7, 71.1, 70.9, 55.2, 55.14, 55.07, 45.2, 42.4, 29.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −117.2. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{49}H_{42}O_6N_2F$, 773.3021; found, 773.3010.

*3,11-Bis(benzyloxy)-14-(3-(benzyloxy)phenyl)-2,12-dimethoxy-5-(4-methoxybenzyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]-quinolin-6(5H)-one (**24d**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), 3-benzyloxy phenyl boronic acid (57.0 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol) were employed to furnish **24d** as a yellow foam (93.7 mg, 0.109 mmol, 88%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.49−7.23 (m, 18H), 7.09−7.05 (m, 3H), 6.89 (s, 1H), 6.80−6.75(m, 4H), 6.68 (s, 1H), 5.40 (br s, 2H), 5.14 (s, 2H), 5.10−5.02 (m, 3H), 5.00 (s, 2H), 4.93−4.84 (m, 1H), 3.75 (s, 3H), 3.35 (s, 3H), 3.30 (s, 3H), 3.06−3.00 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 159.5, 158.5, 155.9, 147.9, 147.5, 146.7, 144.9, 138.5, 136.8, 136.6, 136.5, 133.6, 130.4, 130.3, 129.1, 128.6, 128.53, 128.51, 128.0, 127.9, 127.8, 127.5, 127.3, 127.1, 127.0, 126.4, 125.4, 124.0, 121.1, 118.8, 117.4, 114.6, 114.2, 114.1, 113.3, 112.4, 109.0, 105.8, 102.6, 71.0, 70.9, 69.9, 55.2, 55.1, 55.0, 45.1, 42.4, 28.9. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{56}H_{49}O_7N_2$, 861.3534; found, 861.3510.

*3,11-Bis(benzyloxy)-14-(4-(benzyloxy)phenyl)-2,12-dimethoxy-5-(4-methoxybenzyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]-quinolin-6(5H)-one (**24e**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), 4-benzyloxy phenyl boronic acid (57.0 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol) were employed to furnish **24e** as a pale yellow sticky oil (98.3 mg, 0.114 mmol, 92%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.46−7.24 (m, 17H), 7.18 (s, 1H), 7.15 (s, 1H), 7.08 (s, 1H),7.05 (s, 1H), 6.88 (s, 1H), 6.80−6.74 (m, 4H), 6.66 (s, 1H), 5.38 (br s, 2H), 5.17 (s, 2H), 5.13 (s, 2H), 4.98−4.95 (m, 2H), 3.75 (s, 3H), 3.33 (s, 3H), 3.29 (s, 3H), 3.02 (t, J = 6.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 158.5, 158.2, 155.9, 147.8, 147.4, 146.7, 144.8, 136.8, 136.7, 133.8, 132.7, 130.5, 129.23, 129.19, 128.6, 128.5, 128.0, 127.9, 127.8, 127.5, 127.2, 127.13, 127.08, 127.0, 126.5, 125.6, 121.3, 118.8, 115.7, 114.1, 114.0, 113.4, 112.6, 109.0, 105.8, 102.6, 71.1, 70.9, 69.9, 55.2, 55.13, 55.06, 45.1, 42.4, 29.0. HRMS (TOF) m/z: $[M + H^+]$ calcd for $C_{56}H_{49}O_7N_2$, 861.3534; found, 861.3513.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-(4-(trifluoromethoxy)phenyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]-quinolin-6(5H)-one (**24f**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), 4-trifluoromethyl phenyl boronic acid (52.0 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol) were employed to furnish **24f** as a colorless sticky oil (85.9 mg, 0.102 mmol, 82%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.65(s, 1H),7.63 (s, 1H), 7.47−7.27 (m, 12H), 7.08 (s, 1H), 7.06 (s, 1H), 6.81−6.77 (m, 4H), 6.71 (s, 1H), 6.51 (s, 1H), 5.39 (br s, 2H), 5.15 (s, 2H), 5.00−4.97 (m, 4H), 3.77 (s, 3H), 3.36 (s, 3H), 3.32 (s, 3H), 3.04 (t, J = 6.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 158.6, 155.8, 148.8, 148.0, 147.7, 146.9, 145.0, 136.8, 136.6, 136.5, 133.8, 133.3, 130.6, 129.1, 128.6, 128.5, 127.94, 127.87, 127.6, 127.2, 127.0, 126.7, 125.4, 122.2, 120.8, 119.1, 114.2, 113.6, 112.7, 112.2, 108.8, 105.4, 102.8, 71.1, 71.0, 55.2, 54.9, 45.2, 42.4, 29.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −61.3. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{50}H_{42}O_7N_2F_3$, 839.2939; found, 839.2927.

*3,11-Bis(benzyloxy)-14-(4-(benzyloxy)-3-methoxyphenyl)-2,12-dimethoxy-5-(4-methoxybenzyl)-8,9-dihydrobenzo[7,8]indolizino-[3,2-c]quinolin-6(5H)-one (**24g**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), 4-benzyloxy-3-methoxyphenyl boronic acid (64.1 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol) were employed to furnish **24g** as a brown solid (91.1 mg, 0.102 mmol, 82%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.48−7.24 (m, 15H), 7.08−7.06 (m, 5H), 6.88 (s, 1H), 6.80−6.72 (m, 5H), 5.39 (br s, 2H), 5.26 (s, 2H), 5.14 (s, 2H), 5.06−4.99 (m, 3H), 4.95−4.86 (m, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.32 (s, 3H), 3.29 (s, 3H), 3.03 (t, J = 6.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 158.5, 155.9, 150.4, 147.9, 147.5, 147.4, 146.8, 144.8, 136.9, 136.8, 136.6, 133.7, 130.5, 129.8, 129.2, 128.6, 128.54, 128.48, 128.0, 127.9, 127.8, 127.6, 127.5, 127.1, 127.0, 126.9, 126.4, 125.6, 123.6, 121.2, 118.8, 114.7, 114.6, 114.1, 113.3, 112.5, 108.9, 105.8, 102.6, 71.0, 70.9, 70.8, 56.2, 55.19, 55.15, 55.1, 45.1, 42.4, 28.9. The physical and spectroscopic data are in good agreement with those previously reported.[7f]

*3,11-Bis(benzyloxy)-14-(3-(benzyloxy)-4-methoxyphenyl)-2,12-dimethoxy-5-(4-methoxybenzyl)-8,9-dihydrobenzo[7,8]indolizino-[3,2-c]quinolin-6(5H)-one (**24h**).* Following general procedure C, iodopyrrole lactone **19** (100 mg, 0.124 mmol), 3-benzyloxy-4-methoxyphenyl boronic acid (64.1 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol) were employed to furnish **24h** as a brown solid (94.5 mg, 0.106 mmol, 85%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.45−7.21 (m, 15H), 7.15−7.06 (m, 5H), 6.88 (s, 1H), 6.81−6.75 (m, 4H), 6.65 (s, 1H), 5.39 (br s, 2H), 5.15 (s, 2H), 5.12 (s, 2H), 5.04−4.87 (m, 4H), 3.94 (s, 3H), 3.76 (s, 3H), 3.37 (s, 2H), 3.31 (s, 3H), 3.02 (t, J = 6.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 158.5, 155.9, 149.3, 148.9, 147.9, 147.5, 146.8, 144.9, 136.9, 136.7, 136.4, 133.8, 130.5, 129.3, 129.2, 128.6, 128.51, 128.45, 128.0, 127.9, 127.8, 127.6, 127.4, 127.2, 127.0, 126.5, 125.6, 124.2, 121.2, 118.8, 116.8, 114.14, 114.06, 113.3, 112.7, 112.5, 108.9, 105.8, 102.6, 71.1, 70.9, 56.4, 55.22, 55.19, 55.1, 45.2,

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42.4, 29.0. The physical and spectroscopic data are in good agreement with those previously reported.[7f]

*4-(3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-6-oxo-5,6,8,9-tetrahydrobenzo[7,8]indolizino[3,2-c]quinolin-14-yl)-N-methylbenzenesulfonamide (**24i**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), 4-methylsulfonamido phenyl boronic acid (54.0 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol) were employed to furnish **24i** as a colorless solid (43.2 mg, 0.051 mmol, 41%). Mp: 119.5−121.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.40−7.24 (m, 11H), 7.08 (s, 1H), 7.05 (s, 1H), 6.80−6.77 (m,4H), 6.66 (s, 1H), 6.40 (s, 1H), 5.40 (br s, 2H), 5.13 (s, 2H), 5.01−4.96 (m, 3H), 4.92−4.86 (m, 1H), 3.75 (s, 3H), 3.35 (s, 3H), 3.30 (s, 3H), 3.04 (t, J = 6.6 Hz, 2H), 2.71 (d, J = 5.3 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.6, 155.8, 148.0, 147.94, 147.90, 147.1, 145.0, 142.6, 138.7, 136.6, 136.4, 133.8, 132.7, 130.6, 128.9, 128.6, 128.5, 128.0, 127.9, 127.5, 127.1, 127.04, 127.01, 125.2, 120.5, 119.2, 114.2, 113.6, 112.4, 112.0, 109.1, 105.6, 102.8, 71.1, 70.9, 55.2, 55.14, 55.10, 45.2, 42.4, 29.0. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{50}H_{46}O_8N_3S$, 848.3000; found, 848.2991.

*Methyl 4-(3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-6-oxo-5,6,8,9-tetrahydrobenzo[7,8]indolizino[3,2-c]quinolin-14-yl)benzoate (**24j**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), 4-methoxy carbonyl phenyl boronic acid (45.0 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol) were employed to furnish **24j** as a pale brown foam (46.4 mg, 0.057 mmol, 46%). ^{1}H NMR (300 MHz,$CDCl_3$): δ 8.25 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.1 Hz, 2H), 7.48−7.26 (m, 10H), 7.08 (s, 1H), 7.05 (s, 1H), 6.81−6.73 (m, 5H), 6.47 (s, 1H), 5.39 (br s, 2H), 5.15 (s, 2H), 4.99 (s, 2H), 4.89 (t, J = 6.2 Hz, 2H), 3.99 (s, 3H), 3.77 (s, 3H), 3.32 (s, 3H) 3.27 (s, 3H), 3.04 (t, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.7, 158.6, 155.8, 148.4, 148.0, 147.7, 146.9, 144.9, 142.6, 138.0, 136.7, 136.6, 133.7, 132.0, 130.6, 130.3, 129.4, 129.2, 129.0, 128.6, 128.54, 128.52, 127.93, 127.86, 127.6, 127.5, 127.2, 127.14, 127.1, 127.0, 126.8, 125.2, 120.7, 119.2, 114.2, 113.6, 113.5, 113.3, 112.2, 109.1, 107.8, 105.7, 102.7, 71.1, 70.9, 55.2, 55.1, 52.4, 45.2, 42.4, 29.0. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{51}H_{45}O_8N_2$, 813.3170; found, 813.3182.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-(pyridin-4-yl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**24k**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), 4-pyridinylboronic acid (31.0 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol) were employed to furnish **24k** as a brown solid (53.5 mg, 0.071 mmol, 57%). Mp: 195.5−197.7 °C. ^{1}H NMR (300 MHz,$CDCl_3$): δ 8.84−8.82 (m, 2H), 7.57 (d, J = 5.4 Hz, 2H), 7.44−7.28 (m, 10H), 7.09 (s, 1H), 7.06 (s, 1H), 6.81−6.79 (m, 4H), 6.72 (s, 1H), 6.44 (s, 1H), 5.40 (br s, 2H), 5.15 (s, 2H), 5.00−4.96 (m, 4H), 3.77 (s, 3H), 3.38 (s, 3H), 3.32 (s, 3H), 3.04 (t, J = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.6, 155.7, 150.7, 148.0, 147.9, 147.1, 146.4, 145.1, 136.7, 136.5, 133.6, 130.6, 129.0, 128.6, 128.5, 128.0, 127.9, 127.5, 127.2, 127.0, 126.9, 124.9, 120.4, 119.4, 114.2, 113.5, 111.9, 111.3, 108.9, 105.5, 102.8, 71.1, 70.9, 55.22, 55.18, 55.1, 45.2, 42.4, 28.9. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{48}H_{42}O_6N_3$, 756.3068; found, 756.3061.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-(naphthalen-2-yl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**24l**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), 2-naphthylboronic acid (43.0 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.3 mg, 0.006 mmol) were employed to furnish **24l** as a pale brown solid (62.0 mg, 0.077 mmol, 62%). Mp: 185.6−187.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07−8.03 (m, 2H), 7.92−7.82 (m, 2H), 7.70−7.67 (m, 1H), 7.55−7.48 (m, 2H), 7.40−7.23 (m, 10H), 7.10 (s, 1H), 7.07 (s, 1H), 6.81−6.75 (m, 5H), 6.55 (s, 1H), 5.41 (br s, 2H), 5.18−5.04 (m, 2H), 4.97−4.87 (m, 3H), 3.76 (s, 3H), 3.09−3.00 (m, 5H), 2.92 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.5, 155.9, 147.8, 147.5, 146.8, 144.8, 136.8, 136.6, 134.2, 133.84, 133.81, 132.5, 130.5, 130.4, 129.4, 129.1, 128.8, 128.6, 128.5, 128.4, 127.83, 127.77, 127.7, 127.6, 127.5, 127.1, 127.0, 126.53, 126.5, 126.4, 125.5, 121.1, 119.0, 114.3, 114.1, 113.3, 112.5, 109.1, 105.8, 102.6, 71.0, 70.8, 55.2, 54.8, 54.7, 45.1, 42.4, 29.0. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{53}H_{45}O_6N_2$, 805.3272; found, 805.3256.

*14-(Benzo[b]thiophen-2-yl)-3,11-bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**24m**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), benzo[*b*]thien-2-ylboronic acid (45.0 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol) were employed to furnish **24m** as a colorless sticky foam (50.4 mg, 0.062 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91−7.88 (m, 1H), 7.83−7.80 (m, 1H), 7.47 (s, 1H), 7.43−7.27 (m, 13H), 7.08 (s, 1H), 7.06 (s, 1H), 6.95 (s, 1H), 6.81−6.76 (m, 4H), 5.40 (br s, 2H), 5.15 (s, 2H), 4.99 (br s, 4H), 3.77 (s, 3H), 3.17 (s, 3H), 3.12 (s, 3H), 3.05 (t, J = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.6, 155.8, 148.1, 147.9, 147.1, 145.1, 141.1, 140.2, 138.9, 136.8, 136.6, 135.5, 130.7, 129.1, 128.6, 128.5, 127.93, 127.87, 127.6, 127.2, 127.0, 126.8, 126.1, 124.7, 123.5, 122.2, 120.6, 114.2, 113.3, 112.0, 108.9, 105.8, 102.6, 71.1, 70.9, 55.3, 54.93, 54.9, 45.2, 42.5, 29.7. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{51}H_{43}O_6N_2S$, 811.2836; found, 811.2829.

*3,11-Bis(benzyloxy)-14-(cyclohex-1-en-1-yl)-2,12-dimethoxy-5-(4-methoxybenzyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**24n**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), 1-cyclohexenyl boronic acid (32.0 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol) were employed to furnish **24n** as a pale yellow oil (67.0 mg, 0.088 mmol, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.73 (s, 1H), 7.48−7.25 (m, 10H), 7.08 (s, 1H), 7.05 (s, 1H), 6.81−6.77 (m, 4H), 6.15 (br s, 1H), 5.38 (br s, 2H), 5.22−5.14 (m, 3H), 5.03 (s, 2H), 4.72−4.63 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.76 (s, 3H), 3.09−2.89 (m, 1H), 2.41−2.34(m, 4H), 1.96−1.85 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.5, 155.8, 148.3, 147.6, 146.8, 145.1, 136.9, 136.7, 134.2, 132.6, 130.5, 129.9, 129.2, 128.6, 128.5, 127.93, 127.86, 127.6, 127.2, 127.1, 126.7, 124.6, 121.9, 118.8, 116.7, 114.1, 113.5, 113.0, 108.6, 105.7, 102.8, 71.2, 71.0, 56.1, 55.2, 45.2, 42.2, 30.3, 29.1, 26.1, 23.5, 22.2. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{49}H_{47}O_6N_2$, 759.3429; found, 759.3419.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-vinyl-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**24o**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), potassium vinyltrifluoroborate (34.0 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol) were employed to furnish **24o** as a colorless oil (36.0 mg, 0.051 mmol, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.69 (s, 1H), 7.48−7.20 (m, 11H), 7.07 (s, 1H), 7.04 (s, 1H), 6.81−6.77 (m, 4H), 5.82−5.69 (m, 2H), 5.39 (br s, 2H), 5.19 (s, 2H), 5.03 (s, 2H), 4.91 (t, J = 6.4 Hz, 2H), 3.90−3.86 (m, 6H), 3.76 (s, 3H), 2.98 (t, J = 6.4 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.5, 155.8, 148.1, 147.8, 147.0, 145.0, 144.9, 137.0, 136.8, 136.6, 136.5, 133.7, 132.6, 130.6, 129.1, 128.6, 128.5, 128.3, 127.92, 127.86, 127.6, 127.5, 127.21, 127.20 127.1, 124.8, 121.5, 119.1, 114.1, 113.5, 113.0, 112.2, 110.3, 106.9, 102.7, 71.1, 71.0, 56.2, 55.2, 45.1, 42.2, 29.2. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{45}H_{41}O_6N_2$, 705.2959; found, 705.2955.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-methyl-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**24p**).* Following general procedure C, iodopyrrole lactam **19** (100 mg, 0.124 mmol), methylboronic acid (15.0 mg, 0.25 mmol), cesium carbonate (81.0 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol) were employed to furnish **24p** as a brown sticky foam (52.5 mg, 0.076 mmol, 61%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.49−7.25 (m, 11H), 7.07 (s. 1H), 7.05 (s, 1H), 6.87−6.77 (m, 4H), 5.39 (br s, 2H), 5.21 (s, 2H), 5.04 (s, 2H), 4.89 (t, J = 6.0 Hz, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.76 (s, 2H), 2.95 (t, J = 6.0 Hz, 2H), 2.87 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.6, 155.8, 148.4, 147.7, 146.9, 145.2, 136.9, 136.7, 134.4, 130.7, 129.2, 129.2, 128.6, 128.5, 128.0, 127.94, 127.88, 127.6, 127.5, 127.3, 127.2, 127.1, 125.8, 121.9, 119.0, 114.2, 114.0, 113.7, 110.3, 107.9, 106.9, 103.0, 71.2,

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71.1, 56.4, 55.2, 45.2, 41.9, 29.7, 13.5. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{44}H_{41}O_6N_2$, 693.2959; found, 693.2947.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-phenylbenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**25a**).* Following general procedure D, compound **24a** (55.0 mg, 0.073 mmol) and DDQ (25.0 mg, 0.11 mmol) were employed to furnish compound **25a** as a white solid (38.2 mg, 0.051 mmol, 70%). Mp: 218.5−219.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (d, J = 7.5 Hz, 1H), 7.66−7.25 (m, 15H), 7.10−7.04 (m, 4H), 6.90 (s, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.82−6.78 (m, 3H), 5.47 (br, s, 2H), 5.22 (s, 2H), 5.01 (s, 2H), 3.76 (s, 3H), 3.37 (s, 3H), 3.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.6, 156.0, 149.2, 148.5, 147.6, 144.9, 137.6, 136.5, 136.5, 132.2, 131.3, 129.5, 129.2, 128.6, 128.5, 128.1, 128.0, 127.9, 127.6, 127.2, 127.0, 126.97, 124.1, 123.8, 119.5, 114.2, 113.1, 111.9, 110.9, 110.5, 109.7, 106.5, 105.7, 102.5, 77.3, 71.0, 70.7, 55.2, 55.03, 54.98, 45.1. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{49}H_{41}O_6N_2$, 753.2959; found, 753.2961.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-(p-tolyl)benzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**25b**).* Following general procedure D, compound **24b** (53.0 mg, 0.069 mmol) and DDQ (24.0 mg, 0.11 mmol) were employed to furnish compound **25b** as a pale yellow foam (40.0 mg, 0.052 mmol, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.60 (d, J = 7.4 Hz, 1H), 7.56−7.28 (m, 14H), 7.10−7.07 (m, 4H), 6.95 (s, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.82−6.77 (m, 3H), 5.47 (br s, 2H), 5.24 (s, 2H), 5.02 (s, 2H), 3.76 (s, 3H), 3.41 (s, 3H), 3.38 (s, 3H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.6, 156.0, 149.2, 148.5, 147.6, 144.9, 137.8, 136.6, 136.5, 134.2, 132.4, 132.1, 131.4, 130.1, 129.2, 128.64, 128.56, 128.0, 127.9, 127.6, 127.23, 127.16, 127.0, 124.1, 123.8, 119.6, 114.2, 113.0, 112.1, 110.9, 110.6, 109.7, 106.6, 105.9, 102.5, 71.1, 70.8, 55.2, 55.03, 54.95, 45.1, 21.3. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{50}H_{43}O_6N_2$, 767.3116; found, 767.3105.

*3,11-Bis(benzyloxy)-14-(4-fluorophenyl)-2,12-dimethoxy-5-(4-methoxybenzyl)benzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**25c**).* Following general procedure D, compound **24c** (52.0 mg, 0.067 mmol) and DDQ (23.0 mg, 0.10 mmol) were employed to furnish compound **25c** as a pale yellow foam (37.3 mg, 0.048 mmol, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.63 (d, J = 7.3 Hz, 1H), 7.67−7.63 (m, 2H), 7.46−7.25 (m, 13H), 7.10−7.07 (m, 2H), 6.99 (s, 1H), 6.88−6.78 (m, 5H), 5.47 (br s, 2H), 5.23 (s, 2H), 5.02 (s, 2H), 3.76 (s, 3H), 3.45 (s, 3H), 3.42 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 161.5 (d, J_{CF} = 249 Hz), 155.9, 149.2, 148.6, 147.7, 144.9, 136.5, 136.4, 134.1 (d, J_{CF} = 8 Hz), 133.5 (d, J_{CF} = 4 Hz), 132.4, 131.4, 129.1, 128.64, 128.56, 128.0, 127.9, 127.6, 127.3, 127.2, 127.1, 127.0, 124.2, 123.8, 119.3, 116.4 (d, J_{CF} = 21 Hz), 114.2, 113.1, 111.8, 111.0, 109.7, 109.0, 106.3, 105.4, 71.0, 70.7, 55.2, 55.1, 55.0, 45.1. ^{19}F NMR (282 MHz, $CDCl_3$): δ −116.7. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{49}H_{40}O_6N_2F$, 771.2865; found, 771.2857.

*3,11-Bis(benzyloxy)-14-(3-(benzyloxy)phenyl)-2,12-dimethoxy-5-(4-methoxybenzyl)benzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**25d**).* Following general procedure D, compound **24d** (51.0 mg, 0.059 mmol) and DDQ (20.2 mg, 0.089 mmol) were employed to furnish compound **25d** as a colorless sticky oil (37.1 mg, 0.043 mmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.60 (d, J = 7.4 Hz, 1H), 7.44−7.22 (m, 18H), 7.14−7.07 (m, 18H), 7.02 (s, 1H). 6.97 (s, 1H), 6.84−6.76 (m, 4H), 5.46 (br s, 2H), 5.18 (s, 2H), 5.09 (s, 2H), 5.00 (s, 2H), 3.74 (s, 3H), 3.36 (s, 3H), 3.35 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 159.6, 158.5, 155.9, 149.1, 148.4, 147.6, 144.8, 138.8, 136.5, 136.4, 132.1, 131.3, 130.5, 129.1, 128.54, 128.52, 128.49, 128.0, 127.9, 127.8, 127.6, 127.4, 127.2, 127.0, 126.9, 124.5, 124.0, 123.6, 119.3, 117.9, 115.0, 114.1, 112.9, 111.8, 110.9, 110.2, 109.5, 106.5, 105.7, 102.3, 70.9, 70.6, 69.9, 55.2, 55.1, 55.0, 45.0. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{56}H_{47}O_7N_2$, 859.3378; found, 859.3363.

*3,11-Bis(benzyloxy)-14-(4-(benzyloxy)phenyl)-2,12-dimethoxy-5-(4-methoxybenzyl)benzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**25e**).* Following general procedure D, compound **24e** (50.0 mg, 0.058 mmol) and DDQ (20.0 mg, 0.088 mmol) were employed to furnish compound **25e** as a yellow sticky oil (44.5 mg, 0.052 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (d, J = 7.4 Hz, 1H), 7.48−7.28 (m, 19H), 7.09−7.00 (m, 4H), 6.96 (s, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.81−6.77 (m, 3H), 5.44 (br s, 2H), 5.21 (s, 4H), 5.01 (s, 2H), 3.75 (s, 3H), 3.36 (s, 3H), 3.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.6, 158.4, 155.9, 149.1, 148.5, 147.6, 144.8, 136.8, 136.6, 136.5, 133.3, 132.5, 131.3, 129.5, 129.2, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 127.2, 127.1, 127.0, 124.1, 123.8, 119.6, 115.9, 115.1, 114.2, 113.0, 112.0, 110.8, 110.0, 109.6, 106.5, 105.7, 102.4, 71.0, 70.7, 69.9, 55.2, 55.1, 55.0, 45.1. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{56}H_{47}O_7N_2$, 859.3378; found, 859.3352.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-(4-(trifluoromethoxy)phenyl)benzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**25f**).* Following general procedure D, compound **24f** (54.0 mg, 0.064 mmol) and DDQ (22.0 mg, 0.097 mmol) were employed to furnish compound **25f** as a white solid (36.0 mg, 0.043 mmol, 67%). Mp: 195.3−196.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.62 (d, J = 7.4 Hz, 1H), 7.74−7.72 (m, 2H), 7.55−7.52 (m, 2H), 7.45−7.25 (m, 10H), 7.09−7.05 (m, 3H), 6.92 (s, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.83−6.76 (m, 4H), 5.45 (br s, 2H), 5.20 (s, 2H), 5.01 (s, 2H), 3.74 (s, 3H), 3.40 (s, 3H), 3.37 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.6, 155.9, 149.3, 149.03, 149.0, 148.7, 147.8, 144.9, 136.9, 136.5, 136.4, 134.0, 132.3, 131.4, 129.0, 128.7, 128.6, 128.6, 128.1, 128.0, 127.9, 127.6, 127.2, 127.00, 126.96, 124.2, 123.7, 122.4, 122.2, 119.2, 114.2, 113.2, 111.6, 111.1, 109.8, 108.5, 106.1, 105.3, 102.6, 71.0, 70.7, 55.2, 54.8, 54.8, 45.1. ^{19}F NMR (282 MHz, $CDCl_3$): δ −61.3. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{50}H_{40}O_7N_2F_3$, 837.2782; found, 837.2783.

*3,11-Bis(benzyloxy)-14-(4-(benzyloxy)-3-methoxyphenyl)-2,12-dimethoxy-5-(4-methoxybenzyl)benzo[7,8]indolizino[3,2-c]-quinolin-6(5H)-one (**25g**).* Following general procedure D, compound **24g** (50 mg, 0.056 mmol) and DDQ (0.019 g, 0.084 mmol) were employed to furnish **25g** as a pale brown solid (40.0 mg, 0.045 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.62 (d, J = 7.4 Hz, 1H), 7.50−7.29 (m, 14H), 7.16−7.07 (m, 7H), 7.00 (s, 1H), 6.87 (d, J = 7.5 Hz, 1H), 6.83−6.78 (m, 3H), 5.47 (br s, 2H), 5.31 (s, 2H), 5.23 (s, 2H), 5.02 (s, 2H), 3.89 (s, 3H), 3.76 (s, 3H), 3.36 (s, 3H), 3.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.6, 156.0, 150.6, 149.2, 148.5, 147.7, 147.6, 144.9, 137.0, 136.6, 136.5, 132.4, 131.4, 130.1, 129.2, 128.7, 128.64, 128.56, 128.1, 128.0, 127.9, 127.6, 127.2, 127.1, 127.02, 126.99, 124.1, 123.8, 119.5, 115.2, 114.8, 114.2, 113.0, 111.9, 110.8, 110.1, 109.6, 106.5, 105.7, 102.5, 71.0, 70.9, 70.8, 56.2, 55.24, 55.19, 55.1, 45.1. The physical and spectroscopic data are in good agreement with those previously reported.[7f]

*3,11-Bis(benzyloxy)-14-(3-(benzyloxy)-4-methoxyphenyl)-2,12-dimethoxy-5-(4-methoxybenzyl)benzo[7,8]indolizino[3,2-c]-quinolin-6(5H)-one (**25h**).* Following general procedure D, compound **24h** (50.0 mg, 0.056 mmol) and DDQ (19.1 mg, 0.084 mmol) were employed to furnish compound **25h** as a brown solid (41.0 mg, 0.046 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.63 (d, J = 7.4 Hz, 1H), 7.47−7.16 (m, 18H), 7.11−7.08 (m, 4H), 6.98 (s, 1H), 6.87 (d, J = 7.3 Hz, 1H), 6.84−6.79 (m,3H), 5.48 (br s, 2H), 5.25 (s, 2H), 5.13 (s, 2H), 5.03 (s, 2H), 3.98 (s, 3H), 3.77 (s, 3H), 3.40 (s, 3H), 3.38 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.6, 156.0, 149.6, 149.2, 149.1, 148.5, 147.7, 144.9, 136.6, 136.5, 136.3, 132.5, 131.4, 129.6, 129.3, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.6, 127.5, 127.2, 127.1, 127.0, 124.8, 124.1, 123.8, 119.6, 117.3, 114.2, 113.0, 112.9, 112.0, 110.9, 110.1, 109.7, 106.6, 105.7, 102.5, 71.1, 71.0, 70.8, 56.5, 55.3, 55.2, 55.1, 45.1. The physical and spectroscopic data are in agreement with those previously reported.[7f]

*4-(3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-6-oxo-5,6-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-14-yl)-N-methylbenzenesulfonamide (**25i**).* Following general procedure D, compound **24i** (40.0 mg, 0.047 mmol) and DDQ (16.0 mg, 0.070 mmol) were employed to furnish **25i** as a yellow foam (12.7 mg, 0.015 mmol, 32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (d, J = 7.4 Hz, 1H), 8.17 (d, J = 7.4 Hz, 2H), 7.88 (d, J = 7.4 Hz, 2H), 7.45−7.28 (m, 10H), 7.10−7.09 (m, 3H), 6.92 (d, J = 7.4 Hz, 1H), 6.85−6.79 (m, 4H), 6.72 (s, 1H), 5.48 (br s, 2H), 5.23 (s, 2H), 5.02 (s, 2H), 4.67 (q, J = 5.3 Hz, 1H), 3.76 (s, 3H), 3.39 (s, 3H), 3.36 (s, 3H), 2.77 (d, J = 5.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.7, 155.9, 149.4, 148.8, 148.0, 147.9, 144.9, 143.2, 139.3, 139.2, 136.4, 136.3, 133.4, 132.1, 131.6, 129.0, 128.7, 128.6, 128.1, 128.0,

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127.6, 127.2, 127.0, 126.8, 124.4, 123.8, 118.9, 114.2, 113.5, 111.4, 111.3, 109.9, 108.2, 106.4, 105.4, 102.7, 71.1, 70.8, 55.2, 55.1, 55.0, 45.2, 29.1. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{50}H_{44}O_8N_3S$, 846.2843; found, 846.2852.

*Methyl 4-(3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-6-oxo-5,6-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-14-yl)benzoate (**25j**).* Following general procedure D, compound **24j** (50.0 mg, 0.061 mmol) and DDQ (21.0 mg, 0.093 mmol) were employed to furnish **25j** as a yellow foam (33.4 mg, 0.041 mmol, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.65 (d, J = 7.4 Hz, 1H), 8.33 (d, J = 8.1 Hz, 2H), 7.79 (d, J = 8.1 Hz, 2H), 7.45−7.25 (m, 12H), 7.10−7.06 (m, 3H), 6.92 (s, 1H), 6.88 (d, J = 7.5 Hz, 1H), 6.83−6.78 (m, 6H), 5.46 (br s, 2H), 5.21 (s, 2H), 5.01 (s, 2H), 4.01 (s, 3H), 3.76 (s, 3H), 3.35 (s, 3H), 3.32 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.6, 158.6, 155.9, 149.3, 148.7, 147.8, 144.9, 143.1, 136.5, 136.4, 132.6, 132.0, 131.4, 130.5, 129.8, 129.1, 128.6, 128.5, 128.0, 127.9, 127.6, 127.2, 127.0, 126.8, 124.2, 123.8, 119.1, 114.2, 113.3, 111.5, 111.1, 109.7, 109.1, 106.4, 105.5, 102.5, 71.0, 70.7, 55.22, 55.16, 55.1, 52.4, 45.1. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{51}H_{43}O_8N_2$, 811.3014; found, 811.3020.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-(pyridin-4-yl)benzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**25k**).* Following general procedure D, compound **24k** (50.0 mg, 0.066 mmol) and DDQ (23.0 mg, 0.10 mmol) were employed to furnish compound **25k** as a brown sticky foam (15.9 mg, 0.021 mmol, 32%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.68 (d, J = 7.4 Hz, 1H), 8.93−8.92 (m, 2H), 7.69−7.67 (m, 2H), 7.47−7.29 (m, 10H), 7.11−7.08 (m, 2H), 6.93 (d, J = 7.5 Hz, 1H), 6.90−6.77 (m, 5H), 5.49 (br s, 2H), 5.25 (s, 2H), 5.03 (s, 2H), 3.77 (s, 3H), 3.42 (s, 3H), 3.39 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.7, 155.9, 149.5, 148.9, 147.9, 145.0, 136.4, 136.3, 131.5, 129.0, 128.7, 128.6, 128.1, 128.0, 127.6, 127.2, 127.2, 127.0, 126.5, 124.4, 123.8, 118.9, 114.2, 113.6, 111.32, 111.27, 109.9, 106.1, 105.3, 102.7, 71.1, 70.8, 55.25, 55.17, 55.1. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{48}H_{40}O_6N_3$, 754.2912; found, 754.2897.

3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-(naphthalen-2-yl)benzo[7,8]indolizino[3,2-c]quinolin-6(5*H*)-one (25l). Following general procedure D, compound **24l** (52.0 mg, 0.068 mmol) and DDQ (24.0 mg, 0.11 mmol) were employed to furnish compound **25l** as a yellow sticky foam (33 mg, 0.041 mmol, 60%). ^{1}H NMR (400 MHz,$CDCl_3$): δ 9.65 (d, J = 7.5 Hz, 1H), 8.18−8.13 (m, 2H), 7.96 (d, J = 7.2 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 9.4 Hz, 1H), 7.59−7.55(m, 2H), 7.44−7.28 (m, 10H), 7.11−7.07 (m, 3H), 7.00 (s, 1H), 6.89 (d, J = 7.5 Hz, 1H), 6.87 (s, 1H), 6.82−6.78 (m, 3H), 5.48 (br s, 2H), 5.22 (s, 2H), 5.00 (s, 2H), 3.77 (s, 3H), 2.99 (s, 3H), 2.97 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.6, 156.0, 149.2, 148.5, 147.6, 144.8, 136.5, 136.5, 134.7, 133.9, 132.8, 132.5, 131.4, 131.0, 129.9, 129.2, 129.1, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 127.19, 127.16, 127.1, 127.0, 126.7, 126.6, 124.2, 123.8, 119.5, 114.2, 113.2, 111.9, 111.0, 110.3, 109.7, 106.5, 105.8, 102.5, 71.0, 70.7, 55.2, 54.82, 54.75, 45.1. HRMS (TOF) m/z: $[M + Na]^+$ calcd for $C_{53}H_{42}O_6N_2Na$, 825.2935; found, 825.2910.

*14-(Benzo[b]thiophen-2-yl)-3,11-bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)benzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**25m**).* Following general procedure D, compound **24m** (50.4 mg, 0.061 mmol) and DDQ (0.022, 0.097 mmol) were employed to furnish compound **25m** as a colorless sticky foam (23.0 mg, 0.028 mmol, 46%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.64 (d, J = 7.4 Hz, 1H), 7.96−7.85 (m, 2H), 7.57 (s, 1H), 7.46−7.26 (m, 13H), 7.18 (s, 1H), 7.11−7.08 (m, 3H), 6.92 (d, J = 7.5 Hz, 1H), 6.83−6.79 (m, 3H), 5.47 (br s, 2H), 5.24 (s, 2H), 5.02 (s, 2H), 3.77 (s, 3H), 3.19 (s, 3H), 3.17 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.6, 155.9, 149.5, 148.9, 148.0, 145.1, 141.3, 140.2, 139.3, 136.5, 136.4, 133.7, 131.6, 129.1, 128.7, 128.6, 128.2, 128.0, 127.9, 127.6, 127.2, 127.0, 126.8, 124.8, 124.7, 124.5, 123.7, 123.6, 122.4, 119.0, 114.2, 113.6, 111.41, 111.37, 109.5, 106.4, 105.6, 102.4, 100.9, 71.0, 70.7, 55.2, 54.9, 54.8, 45.1. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{51}H_{41}O_6N_2S$, 809.2680; found, 809.2659.

*3,11-Dihydroxy-2,12-dimethoxy-14-phenylbenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**26a**).* Following general procedure E, compound **25a** (25.0 mg, 0.033 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 40% (v/v) B in 45 min; a linear gradient increasing from 40% to 65% (v/v) B for 20 min, holding for 10 min; increasing to 100% B in 5 min, holding for 10 min; and re-equilibrating at initial conditions for 45 min. The product **26a** was obtained as a white solid (11.7 mg, 0.026 mmol, 78%). Mp: 239.5−240.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.31 (s, 1H), 9.76 (br s, 1H), 9.51 (br s, 1H), 9.39 (d, J = 7.4 Hz, 1H), 7.73−7.59 (m, 5H), 7.14 (s, 1H), 7.04 (d, J = 7.4 Hz, 1H), 6.94 (s, 1H), 6.89 (s, 1H), 6.62 (s, 1H), 3.26 (s, 3H), 3.24 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 155.4, 148.0, 147.4, 147.0, 143.4, 136.8, 131.8, 131.3, 131.0, 129.5, 128.1, 127.6, 123.9, 122.6, 117.6, 112.2, 111.6, 110.5, 109.7, 108.3, 105.5, 105.2, 102.3, 54.6, 54.4. HRMS (TOF) m/z: $[M + H^+]$ calcd for $C_{27}H_{21}O_5N_2$, 453.1445; found, 453.1436.

*3,11-Dihydroxy-2,12-dimethoxy-14-(p-tolyl)benzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**26b**).* Following general procedure E, compound **25b** (22.0 mg, 0.029 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 50% (v/v) B in 50 min; a linear gradient increasing from 50% to 65% (v/v) B for 25 min, holding for 10 min; increasing to 100% B in 5 min, holding for 10 min; and re-equilibrating at initial conditions for 45 min. The product **26b** was obtained as a white foam (11.0 mg, 0.024 mmol, 82%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.24 (s, 1H), 9.76 (s, 1H), 9.50 (s, 1H), 9.36 (d, J = 7.3 Hz, 1H), 7.52−7.47 (m, 4H), 7.12 (s, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.96 (s, 1H), 6.88 (s, 1H), 6.66 (s, 1H), 3.29 (s, 3H), 3.27 (s, 3H), 2.45 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 155.5, 148.1, 147.5, 147.1, 143.5, 137.6, 133.6, 131.6, 131.4, 131.3, 130.1, 127.8, 124.0, 122.7, 117.8, 112.3, 111.7, 110.6, 109.8, 108.6, 105.9, 105.5, 102.5, 54.9, 54.5, 20.9. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{23}O_5N_2$, 467.1601; found, 467.1607.

*14-(4-Fluorophenyl)-3,11-dihydroxy-2,12-dimethoxybenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**26c**).* Following general procedure E, compound **25c** (25.0 mg, 0.0324 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 44% (v/v) B in 49 min; a linear gradient increasing from 44% to 60% (v/v) B for 40 min, holding for 5 min; increasing to 100% B in 5 min, holding for 10 min; and re-equilibrating at initial conditions for 45 min. The product **26c** was obtained as a yellow sticky oil (9.2 mg, 0.0194 mmol, 60%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.32 (s, 1H), 9.81 (s, 2H), 9.57 (s, 1H), 9.39 (d, J = 7.4 Hz, 1H), 7.70−7.65 (m, 2H), 7.57−7.51 (m, 2H), 7.15 (s, 1H), 7.04 (d, J = 7.5 Hz, 1H), 6.90 (s, 2H), 6.58 (s, 1H), 3.34 (s, 3H), 3.31 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 162.2 (d, J_{CF} = 246 Hz), 155.4, 148.1, 147.6, 147.2, 143.5, 134.1 (d, J_{CF} = 9 Hz), 133.0 (d, J_{CF} = 4 Hz), 131.4, 131.3, 127.8, 124.1, 122.6, 117.5, 116.5 (d, J_{CF} = 21 Hz), 112.3, 111.8, 110.7, 108.5, 108.3, 105.4, 105.1, 102.5, 54.7, 54.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ −116.3. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{20}O_5N_2F$, 471.1351; found, 471.1343.

*3,11-Dihydroxy-14-(3-hydroxyphenyl)-2,12-dimethoxybenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**26d**).* Following general procedure E, **25d** (22.0 mg, 0.0256 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 24% (v/v) B in 29 min; a linear gradient increasing from 24% to 60% (v/v) B for 35 min, holding for 10 min; increasing to 100% B in 20 min, holding for

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10 min; and re-equilibrating at initial conditions for 45 min. The product **26d** was obtained as a pale yellow sticky oil (9.8 mg, 0.0208 mmol, 81%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.28 (s, 1H), 9.73 (s, 1H), 9.52 (s, 1H), 9.38 (d, J = 7.4 Hz, 1H), 7.50 (t, J = 8.2 Hz, 1H), 7.12−7.13 (m, 2H), 7.06−6.99 (m, 5H), 6.89 (s, 1H), 6.80 (s, 1H), 3.17 (s, 3H), 3.12 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 158.4, 155.4, 148.1, 147.4, 147.0, 143.4, 137.8, 131.3, 130.9, 130.6, 127.4, 123.9, 122.6, 122.0, 118.1, 117.5, 115.0, 112.2, 111.6, 110.5, 109.8, 108.3, 105.8, 105.4, 102.3, 54.7, 54.4. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{27}H_{21}O_6N_2$, 469.1394; found, 469.1389.

*3,11-Dihydroxy-14-(4-hydroxyphenyl)-2,12-dimethoxybenzo-[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**26e**).* Following general procedure E, compound **25e** (25.0 mg, 0.029 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 27% (v/v) B in 32 min; a linear gradient increasing from 27% to 60% (v/v) B for 35 min, holding for 10 min; increasing to 100% B in 20 min, holding for 10 min; and re-equilibrating at initial conditions for 45 min. The product **26e** was obtained as a colorless foam (11.3 mg, 0.024 mmol, 83%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.26 (s, 1H), 9.74 (s, 1H), 9.72 (s, 1H), 9.49 (s, 1H), 9.37 (d, J = 7.3 Hz, 1H), 7.40 (s, 1H), 7.38 (s, 1H), 7.12−7.07 (m, 4H), 7.01 (d, J = 7.4 Hz, 1H), 6.88 (s, 1H), 6.77 (s, 1H), 3.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 157.4, 155.4, 148.0, 147.3, 147.0, 143.3, 132.7, 131.3, 127.9, 126.4, 123.9, 122.6, 117.8, 116.3, 112.1, 111.6, 110.4, 109.8, 108.6, 105.8, 105.4, 102.3, 54.8, 54.5. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{27}H_{21}O_6N_2$, 469.1394; found, 469.1380.

*3,11-Dihydroxy-2,12-dimethoxy-14-(4-(trifluoromethoxy)-phenyl)benzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**26f**).* Following general procedure E, compound **25f** (20.0 mg, 0.0239 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 60% (v/v) B in 65 min; a linear gradient increasing from 60% to 80% (v/v) B for 30 min, holding for 10 min; increasing to 100% B in 5 min, holding for 10 min; and re-equilibrating at initial conditions for 45 min. The product **26f** was obtained as a colorless foam (9.2 mg, 0.0172 mmol, 72%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.29 (s, 1H), 9.82 (s, 1H), 9.55 (s, 1H), 9.39 (d, J = 7.3 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 7.9 Hz, 2H), 7.15 (s, 1H), 7.05 (d, J = 7.4 Hz, 1H), 6.90 (s, 1H), 6.85 (s, 1H), 6.54 (s, 1H), 3.30 (s, 3H), 3.27 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 155.4, 148.3, 148.2, 147.6, 147.2, 143.5, 136.5, 134.0, 131.4, 131.2, 127.7, 124.1, 122.7, 122.5, 117.4, 112.5, 111.8, 110.8, 108.2, 108.1, 105.2, 105.0, 102.6, 54.4, 54.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ −59.6. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{28}H_{20}O_6N_2F_3$, 537.1268; found, 537.1248.

*3,11-Dihydroxy-14-(4-hydroxy-3-methoxyphenyl)-2,12-dimethoxybenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**26g**).* Following general procedure E, compound **25g** (25.0 mg, 0.0281 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 30% (v/v) B in 35 min; a linear gradient increasing from 30% to 65% (v/v) B for 40 min, holding for 10 min; increasing to 100% B in 10 min, holding for 10 min; and re-equilibrating at initial conditions for 45 min. The product **26g** was obtained as a pale brown solid (11.9 mg, 0.0238 mmol, 85%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.27 (s, 1H), 9.71 (s, 1H), 9.51 (s, 1H), 9.37 (d, J = 7.6 Hz, 1H), 9.29 (s, 1H), 7.12−7.08 (m, 4H), 7.02−6.98 (m, 2H), 6.88 (s, 1H), 6.80 (s, 1H), 3.76 (s, 3H), 3.36 (s, 3H), 3.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 155.4, 148.6, 148.0, 147.4, 147.1, 146.5, 143.4, 131.4, 131.3, 127.9, 126.9, 124.0, 123.9, 122.6, 117.8, 116.4, 115.2, 112.0, 111.6, 110.4, 110.0, 108.6, 106.0, 105.5, 102.3, 56.0, 54.9, 54.5. The physical and spectroscopic data are in good agreement with those previously reported.[7f]

*3,11-Dihydroxy-14-(3-hydroxy-4-methoxyphenyl)-2,12-dimethoxybenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**26h**).* Following general procedure E, **25h** (20.0 mg, 0.0225 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 32% (v/v) B in 35 min; a linear gradient increasing from 32% to 55% (v/v) B for 40 min, holding for 10 min; increasing to 100% B in 10 min, holding for 10 min; and re-equilibrating at initial conditions for 45 min. The product **26h** was obtained as a pale brown solid (9.1 mg, 0.0183 mmol, 81%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.27 (s, 1H), 9.73 (s, 1H), 9.50 (s, 1H), 9.38−9.35 (m, 2H), 7.24 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 7.2 Hz, 2H), 7.02−6.99 (m, 3H), 6.88 (s, 1H), 6.83 (s, 1H), 3.86 (s, 3H), 3.38 (s, 3H), 3.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 155.4, 148.0, 147.7, 147.4, 147.0, 143.4, 131.4, 131.2, 128.8, 127.7, 123.9, 122.6, 122.3, 118.5, 117.7, 113.8, 112.1, 111.6, 110.4, 109.7, 108.4, 105.9, 105.4, 102.3, 56.2, 54.8, 54.5. The physical and spectroscopic data are in good agreement with those previously reported.[7f]

*4-(3,11-Dihydroxy-2,12-dimethoxy-6-oxo-5,6-dihydrobenzo-[7,8]indolizino[3,2-c]quinolin-14-yl)-N-methylbenzenesulfonamide (**26i**).* Following general procedure E, compound **25i** (12.7 mg, 0.015 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 20% (v/v) B in 25 min; a linear gradient increasing from 20% to 55% (v/v) B for 50 min, holding for 10 min; increasing to 100% B in 10 min, holding for 10 min; and re-equilibrating at initial conditions for 45 min. The product **26i** was obtained as a pale yellow foam (8.2 mg, 0.0011 mmol, 74%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.37 (s, 1H), 9.84 (s, 1H), 9.59 (s, 1H), 9.42 (d, J = 7.4 Hz, 1H), 8.10 (d, J = 8.2 Hz, 2H), 7.90 (d, J = 8.2 Hz, 2H), 7.69 (q, J = 5.0 Hz, 1H), 7.16 (s, 1H), 7.08 (d, J = 7.4 Hz, 1H), 6.90 (s, 1H), 6.80 (s, 1H), 6.49 (s, 1H), 3.38 (s, 3H), 3.28 (s, 3H), 3.25 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 155.3, 148.2, 147.6, 147.2, 143.5, 141.4, 139.2, 132.9, 131.4, 131.0, 130.4, 129.8, 127.7, 127.4, 124.1, 122.6, 117.2, 112.6, 111.8, 110.8, 108.1, 108.0, 105.2, 105.0, 102.5, 54.6, 54.3, 28.5. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{28}H_{24}O_7N_3S$, 546.1330; found, 546.1310.

*Methyl 4-(3,11-Dihydroxy-2,12-dimethoxy-6-oxo-5,6-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-14-yl)benzoate (**26j**).* Following general procedure E, compound **25j** (25.0 mg, 0.0308 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 33% (v/v) B in 38 min; a linear gradient increasing from 33% to 65% (v/v) B for 40 min, holding for 10 min; increasing to 100% B in 10 min, holding for 10 min; and re-equilibrating at initial conditions for 45 min. The product **26j** was obtained as a pale brown sticky foam (10.5 mg, 0.0206 mmol, 67%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.31 (s, 1H), 9.40 (d, J = 7.4 Hz, 1H), 8.27−8.26 (m, 2H), 7.79 (d, J = 7.9 Hz, 2H), 7.13 (s, 1H), 7.04 (d, J = 7.4 Hz, 1H), 6.90 (s, 1H), 6.81 (s, 1H), 6.52 (s, 1H), 3.93 (s, 3H), 3.24 (s, 3H), 3.22 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 166.1, 155.4, 148.3, 147.3, 143.5, 142.3, 132.5, 131.5, 131.0, 130.1, 129.4, 127.4, 124.2, 122.6, 112.6, 111.8, 110.8, 108.5, 108.1, 105.6, 105.2, 102.5, 54.8, 54.5, 52.3. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{29}H_{23}O_7N_2$, 511.1500; found, 511.1507.

*3,11-Dihydroxy-2,12-dimethoxy-14-(naphthalen-2-yl)benzo-[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**26l**).* Following general procedure E, **25l** (25.0 mg, 0.0311 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 55% (v/v) B in 60 min; a linear gradient increasing from 55% to 80% (v/v) B for 30 min, holding for 10 min; increasing to 100% B in 10 min, holding for

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10 min; and re-equilibrating at initial conditions for 45 min. The product **26j** was obtained as a pale yellow foam (11.2 mg, 0.0224 mmol, 72%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.32 (s, 1H), 9.53 (s, 1H), 9.40 (d, J = 7.3 Hz, 1H), 8.25−8.22 (m, 2H), 8.05 (dd, J = 18.8, 7.6 Hz, 2H), 7.74 (d, J = 8.3 Hz, 1H), 7.61−7.58 (m, 2H), 7.04 (d, J = 7.5 Hz, 1H), 6.88 (s, 2H), 6.57 (s, 1H) 3.48 (s, 3H), 3.37 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 155.5, 148.1, 147.6, 147.2, 143.5, 134.1, 133.6, 132.5, 131.6, 131.5, 131.4, 130.7, 129.7, 129.1, 127.9, 127.8, 127.8, 126.8, 126.7, 124.2, 122.8, 117.7, 112.5, 111.8, 110.8, 109.7, 108.5, 105.8, 105.4, 102.5, 54.5, 54.2. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{31}H_{23}O_5N_2$, 503.1602; found, 503.1598.

*14-(Benzo[b]thiophen-2-yl)-3,11-dihydroxy-2,12-dimethoxybenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**26m**).* Following general procedure E, compound **25m** (23.0 mg, 0.0284 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 45% (v/v) B in 49 min; a linear gradient increasing from 45% to 60% (v/v) B for 40 min, holding for 10 min; increasing to 100% B in 10 min, holding for 10 min; and re-equilibrating at initial conditions for 45 min. The product **26m** was obtained as a colorless sticky foam (4.8 mg, 0.0094 mmol, 33%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.37 (s, 1H), 9.41 (d, J = 7.4 Hz, 1H), 8.12 (d, J = 7.2 Hz, 1H), 8.00 (d, J = 7.2 Hz, 1H), 7.77 (s, 1H), 7.50−7.45 (m, 2H), 7.21 (s, 1H), 7.18 (s, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 11.0 Hz, 2H), 3.39 (s, 3H),3.39 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 155.2, 148.4, 148.0, 147.6, 143.7, 140.6, 140.1, 138.4, 132.6, 131.7, 128.7, 127.0, 124.9, 124.8, 124.5, 123.8, 122.5, 122.5, 117.0, 112.7, 111.6, 111.1, 107.8, 105.7, 105.2, 102.4, 99.9, 54.6, 54.1. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{29}H_{21}O_5N_2S$, 509.1166; found, 509.1162.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-((trimethylsilyl)ethynyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]-quinolin-6(5H)-one (**28**).* Following general procedure F, compound **19** (50.0 mg, 0.062 mmol), trimethylsilylacetylene (0.014 mL, 0.098 mmol), Pd(PPh$_3$)$_4$ (3.6 mg, 0.003 mmol), and CuI (1.2 mg, 0.006 mmol) were employed to furnish **28** as a yellow sticky oil (0.34 mg, 0.0044 mmol, 7%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.31 (s, 1H), 7.49−7.32 (m, 10H), 7.05 (s, 1H), 7.05 (s, 1H), 6.82−6.78 (m, 4H), 5.38 (br s, 2H), 5.22 (s, 2H), 5.05 (s, 2H), 4.91 (t, J = 6.0 Hz, 2H), 4.00 (s, 3H), 4.00 (s, 3H), 3.77 (s, 3H), 3.00 (t, J = 6.0 Hz, 2H), 0.33 (s, 9H). HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{48}H_{47}O_6N_2Si$, 775.3198; found, 775.3205. Due to the small quantity of **28**, the ^{13}C NMR spectrum of **28** could not be obtained, and its ^{13}C NMR listing was not reported.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-(phenylethynyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**29**).* Following general procedure F, compound **19** (50.0 mg, 0.062 mmol), phenylacetylene (0.012 mL, 0.098 mmol), Pd(PPh$_3$)$_4$ (3.6 mg, 0.003 mmol), and CuI (1.2 mg, 0.006 mmol) were employed to furnish compound **29** as a colorless sticky foam (5.5 mg, 0.007 mmol, 11%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.40 (s, 1H), 7.63−7.59 (m, 2H), 7.48−7.26 (m, 13H), 7.07 (s, 1H), 7.04 (s, 1H), 6.82−6.78 (m, 4H), 5.40 (br s, 2H), 5.22 (s, 2H), 5.05 (s, 2H), 4.95 (t, J = 6.0 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.77 (s, 3H), 3.04 (t, J = 6.0 Hz, 2H). HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{51}H_{43}O_6N_2$, 779.3116; found, 779.3098. Due to the small quantity of **29** and some broad ^{13}C NMR peaks, its ^{13}C NMR spectrum could not be obtained, and its ^{13}C NMR listing was not reported.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-14-((4-methoxyphenyl)ethynyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**30**).* Following general procedure F, compound **19** (50.0 mg, 0.062 mmol), 4-ethynylanisole (0.013 mL, 0.095 mmol), Pd(PPh$_3$)$_4$ (3.6 mg, 0.003 mmol), and CuI (1.2 mg, 0.006 mmol) were employed to furnish compound **30** as a yellow foam (7.5 mg, 0.0092 mmol, 15%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.41 (s, 1H), 7.55−7.54 (m, 2H). 7.47−7.29 (m, 10H), 7.06 (s, 1H), 7.03 (s, 1H), 6.92 (s, 1H), 6.89 (s, 1H), 6.80−6.77 (m, 4H), 5.39 (br s, 2H), 5.19 (s, 2H), 5.01 (s, 2H), 4.93 (t, J = 6.0 Hz, 2H), 3.85 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 3.02 (t, J = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.6, 158.6, 155.5, 148.4, 148.4, 147.5, 145.4, 138.8, 136.8, 136.6, 132.7, 130.6, 129.0, 128.6, 128.5, 127.9, 127.9, 127.7, 127.6, 127.5, 127.2, 127.2, 127.1, 127.1, 126.5, 120.9, 119.0, 115.6, 114.2, 114.2, 113.2, 112.5, 108.9, 105.5, 102.3, 94.5, 93.3, 84.4,71.1, 70.9, 56.0, 56.0, 55.3, 55.2, 45.2, 42.5, 28.7. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{52}H_{45}O_7N_2$, 809.3221; found, 809.3209.

*3,11-Dihydroxy-14-(4-hydroxy-3-methoxyphenyl)-2,12-dimethoxy-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**31**).* Following general procedure E, compound **24h** (22.0 mg, 0.025 mmol) gave the product, which was purified by a reverse-phase HPLC column equilibrated with 100% solvent A (50% methanol in water) and 0% B (isopropanol) at a flow rate of 9 mL/min. The eluting solvent system was programmed as follows: a linear gradient from the starting solvent to 30% (v/v) B in 45 min; a linear gradient increasing from 30% to 65% (v/v) B for 35 min, holding for 10 min; increasing to 100% B in 10 min, holding for 10 min; and re-equilibrating at initial conditions for 45 min. The product **31** was obtained as a pale yellow sticky foam (9.9 mg, 0.02 mmol, 80%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.06 (s, 1H), 9.28 (s, 2H), 9.18 (s,1H),7.01−6.99 (m, 2H), 6.88 (s, 1H), 6.86 (s, 1H), 6.72 (s, 1H), 6.68 (s, 1H), 6.65 (s, 1H), 4.77−4.74 (m, 2H), 3.74 (s, 3H), 3.31 (s, 3H), 3.27 (s, 3H), 2.98−2.95 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 155.3, 148.4, 146.2, 146.0, 145.9, 143.2, 132.8, 130.5, 126.9, 126.8, 126.3, 123.6, 119.0, 117.9, 116.2, 115.3, 114.9, 113.7, 109.2, 109.0, 105.3, 102.2, 56.0, 54.9, 54.7, 41.9, 28.0. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{28}H_{25}O_7N_2$, 501.1656; found, 501.1644.

*3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-6-oxo-5,6,8,9-tetrahydrobenzo[7,8]indolizino[3,2-c]quinoline-14-carbaldehyde (**32**).* To a stirred solution of oxalyl chloride (0.028 mL, 0.33 mmol) in CH_2Cl_2 (1 mL) was added DMF (0.029 mL, 0.37 mmol) at 0 °C for 15 min. To this mixture at 0 °C was then added a solution of the C1-*H* pyrrole lactam **17** (202 mg, 0.298 mmol) in CH_2Cl_2 (1 mL). The reaction was stirred for 3 h, at which time the reaction was quenched with water (5 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (50% EtOAc/hexane) to furnish the corresponding C1-formyl pyrrole lactam **32** as a pale yellow solid (100 mg, 0.0141 mmol, 48%). Mp: 220.5−221.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.43 (s, 1H), 9.35 (s, 1H), 7.49−7.24 (m, 11H), 7.06 (s, 1H), 7.03 (s, 1H), 6.92 (s, 1H), 6.82−6.78 (m, 3H), 5.40 (br s, 2H), 5.25 (s, 2H), 5.07 (s, 2H), 4.96 (d, J = 6.0 Hz, 2H)., 4.11 (s, 3H), 3.97 (s, 3H), 3.77 (s, 3H), 3.00 (t, J = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 185.9, 158.7, 155.6, 149.9, 148.8, 148.4, 146.0, 145.3, 136.5, 136.4, 131.3, 129.3, 128.7, 128.6, 128.5, 128.2, 128.0, 127.9, 127.5, 127.2, 127.0, 121.0, 119.0, 115.0, 114.2, 113.4, 113.3, 112.0, 110.9, 101.8, 71.0, 56.5, 56.2, 55.2, 45.5, 42.2, 29.0. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{44}H_{39}O_7N_2$, 707.2752; found, 707.2719.

*3,11-Bis(benzyloxy)-14-chloro-2,12-dimethoxy-5-(4-methoxybenzyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**33**).* Following general procedure B, C1-*H* pyrrole lactam **17** (50.0 mg, 0.074 mmol) and *N*-chlorosuccinimide (NCS; 15.0 mg, 0.11 mmol) were employed to furnish the C1-*Cl* pyrrole lactam **33** as a white solid (41.5 mg, 0.058 mmol, 79%). Mp: 225.7−226.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.07 (s, 1H), 7.49−7.31 (m, 10H), 7.06 (s, 1H), 7.03 (s, 1H), 6.82−6.78 (m, 4H), 5.38 (br s, 2H), 5.21 (s, 2H), 5.04 (s, 2H), 4.93 (t, J = 6.0 Hz, 2H), 3.99 (s, 3H), 3.99 (s, 3H), 3.77 (s, 3H), 2.99 (t, J = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.6, 155.4, 148.4, 148.2, 147.5, 145.3, 136.7, 136.6, 132.1, 130.7, 128.8, 128.63, 128.57, 128.0, 127.9, 127.5, 127.2, 127.12, 127.06, 123.1, 120.1, 118.2, 114.2, 113.5, 111.5, 109.3, 105.9, 102.6, 101.6, 71.1, 71.0, 56.23, 56.2, 55.2, 45.3, 42.4, 29.2. HRMS (TOF) m/z: [M + H]$^+$ calcd for $C_{43}H_{38}O_6N_2{}^{35}Cl$, 713.2413; found,

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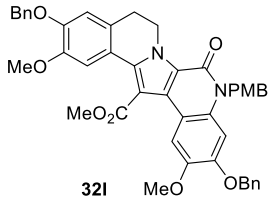
713.2399. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{43}H_{38}O_6N_2{}^{37}Cl$, 715.2401; found, 715.2375.

*3,11-Bis(benzyloxy)-14-bromo-2,12-dimethoxy-5-(4-methoxybenzyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-c]quinolin-6(5H)-one (**34**).* Following general procedure B, C1-*H* pyrrole lactam **17** (50.0 mg, 0.074 mmol) and *N*-bromosuccinimide (NBS; 20.0 mg, 0.11 mmol) were employed to furnish the C1-*Br* pyrrole lactam **34** as a pale brown solid (48.0 mg, 0.063 mmol, 86%). Mp: 202.6−203.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62(s, 1H), 8.22 (s, 1H), 7.48−7.26 (m, 10H), 7.06 (s, 1H), 7.03 (s, 1H), 6.83−6.78 (m, 4H), 5.38 (br s, 2H), 5.22 (s, 2H), 5.05 (s, 2H), 4.97 (d, J = 6.0 Hz, 2H), 4.01 (s, 3H), 4.01 (s, 3H), 3.77 (s, 3H), 2.98 (t, J = 6.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 158.6, 155.2, 148.2, 148.1, 147.4, 145.0, 136.7, 136.5, 133.3, 130.7, 128.7, 128.6, 128.5, 128.0, 127.9, 127.6, 127.5, 127.2, 127.1, 127.06, 124.1, 120.2, 119.1, 114.2, 113.4, 111.7, 109.6, 105.5, 102.5, 71.0, 70.9, 56.24, 56.16, 55.2, 45.3, 42.4, 29.2. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{43}H_{38}O_6N_2{}^{79}Br$, 757.1908; found, 757.1920. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{43}H_{38}O_6N_2{}^{81}Br$, 759.1839; found, 759.1907.



32I

*Methyl 3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-6-oxo-5,6,8,9-tetrahydrobenzo[7,8]indolizino[3,2-c]quinoline-14-carboxylate (**32I**).* To a stirred solution of the C1-formyl pyrrole lactam **32** (200 mg, 0.30 mmol) in 1,4-dioxane (7 mL) was added 2,3-dimethyl-2-butadiene (0.64 mL, 5.92 mmol) at room temperature, and the reaction was stirred for 15 min. A solution of $NaClO_2$ (0.080 g, 0.89 mmol) and NaH_2PO_4 (0.18 g, 1.48 mmol) in water (1 mL) was then added. The mixture was stirred at room temperature for 18 h. At that time, the reaction was quenched with water (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude carboxylic acid product, which was used in the next step without further purification.

To a stirred solution of the crude carboxylic acid in DMF (3 mL) were added iodomethane (0.046 mL, 0.74 mmol) and cesium carbonate (0.19 g, 0.59 mmol) at room temperature. The mixture was stirred at room temperature for 5 h. At that time, the reaction was quenched with water (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (3 × 5 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (40% EtOAc/hexane) to furnish **32I** as a yellow sticky foam (167 mg, 0.23 mmol, 77% (2 steps)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.47−7.24 (m, 11H), 7.05 (s, 1H), 7.02 (s, 1H), 6.82−6.77 (m, 4H), 5.39 (br s, 2H), 5.20 (s, 2H), 5.03 (s, 2H), 4.91 (t, J = 6.0 Hz, 2H), 3.97 (s, 3H), 3.96 (s, 3H), 3.92 (s, 3H), 3.76 (s, 3H), 2.98 (t, J = 6.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.5, 158.6, 155.4, 148.9, 148.2, 147.7, 145.2, 137.7, 136.6, 136.5, 130.9, 128.7, 128.6, 128.5, 127.98, 127.95, 127.9, 127.4, 127.2, 127.0, 126.0, 119.8, 119.6, 114.1, 113.0, 111.2, 110.6, 107.1, 104.7, 102.3, 71.0, 70.9, 56.1, 56.0, 55.2, 52.1, 45.2, 42.3, 28.9. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{45}H_{41}O_8N_2$, 737.2857; found, 737.2849.

*Methyl 3,11-Bis(benzyloxy)-2,12-dimethoxy-5-(4-methoxybenzyl)-6-oxo-5,6-dihydrobenzo[7,8]indolizino[3,2-c]quinoline-14-carboxylate (**38**).* To a stirred solution of compound **32I** (55.0 mg, 0.075 mmol) in 1,2-dichloroethane (2 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 26.0 mg, 0.12 mmol). The mixture was heated to 60 °C by using an oil bath, at which the reaction was stirred for 18 h. At that time, the reaction was quenched with water (3 mL). The resulting mixture was concentrated under reduced pressure and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (50% EtOAc/hexane) to furnish compound **38** as a yellow foam (27.4 mg, 0.037 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.65 (d, J = 7.4 Hz, 1H), 7.83 (s, 1H), 7.73 (s, 1H), 7.49−7.31 (m, 10H), 7.06−7.04 (m, 3H), 6.91 (d, J = 7.5 Hz, 1H), 6.82−6.76 (m, 3H), 5.45 (br s, 2H), 5.21 (s, 2H), 5.00 (s, 2H), 4.12 (s, 3H), 4.03 (s, 3H), 3.97 (s, 3H), 3.75 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.3, 158.6, 155.4, 149.6, 149.5, 148.5, 145.1, 136.4, 136.3, 134.3, 131.8, 128.8, 128.64, 128.56, 128.1, 127.9, 127.5, 127.4, 127.2, 127.0, 125.1, 123.4, 117.9, 114.2, 113.8, 112.3, 110.3, 109.3, 107.2, 106.0, 102.2, 100.5, 70.8, 70.6, 56.0, 55.9, 55.2, 52.4, 45.2. HRMS (TOF) m/z: $[M + H]^+$ calcd for $C_{45}H_{39}O_8N_2$, 735.2701; found, 735.2693.

Assessment of Cytotoxicity by Viable Cell Count Using Crystal Violet Assay. To evaluate the cytotoxicity of the newly synthesized, lactam-containing lamellarin analogues, the compounds were tested for the ability to suppress the viability of HeLa cancer cells by using crystal violet staining. HeLa cells were cultured in Dulbecco's Eagle minimum enriched medium (DMEM) (HyClone GE, USA), supplemented with 10% fetal bovine serum (HyClone GE, USA), 100 IU/mL penicillin (Gibco, USA), and 100 μg/mL streptomycin (Gibco, USA), in a humidified incubator at 37 °C with 5% CO_2 of atmospheric air. The cells were seeded into a 24-well plate at cell density 1.5×10^5 cells per well and grown for 48 h before challenging with the compounds for 18 h at concentrations of 0.312, 0.625, 1.25, 2.5, and 5 μM (for LamD, two additional concentrations at 10 and 20 μM were included). The treated cells were removed from the compound-containing media and stained with 0.5% crystal violet in 20% methanol for 20 min. The stained cells were rinsed with tap water and dried at room temperature. To quantify the cell viability, the viable stained cells were eluted with 200 μL of 10% acetic acid for 15 min before measuring at OD_{590}. The experiment was performed at least 3 times with data obtained and analyzed for IC_{50} and curve-fitting R^2.

Immunoblotting Detection of Proteins Involved in Apoptosis in HeLa Cells Treated with Azalamellarins. HeLa cells were cultured as described above. After 48 h incubation, the cells were added with 2.5 μM of the lamellarins/azalamellarins for 8 h before collecting for cell pellets. To prepare lysates, the cell pellets were solubilized in NP-40 lysis buffer (1% (v/v) NP-40, 50 mM Tris-HCl (pH 7.5), 150 mM NaCl, and 0.05% (w/v) SDS) supplemented with complete protease inhibitor cocktail (Roche, Switzerland) with the concentration suggested by the manufacturer. The total protein concentrations were then determined by using a DC protein assay kit (Biorad, USA) and then adjusted to a final concentration at 1 μg/μL in 1× SDS sample buffer (62.5 mM Tris-HCl, pH 6.8; 2% SDS; 10% glycerol; 2 mM EDTA), before sonication at 27% amplitude for 7 s twice. The prepared proteins were equally loaded at 15 μg per lane, resolved in SDS-PAGE, and then blotted onto a nitrocellulose membrane (Biorad, USA). Western detection was performed using specific antibodies against the following proteins: cleaved caspase-3 (cCasp-3) (Cell Signaling Technology, CST no. 9664), cleaved caspase-7 (cCasp-7) (CST no. 8438), cleaved PARP (CST no. 5625), and β-tubulin (Invitrogen no. 32-2600). The western chemiluminescent signal was developed using the Clarity ECL substrate (Biorad, USA) and recorded in the G:BOX system (Syngene, India). The resulted band densities were analyzed by ImageJ (NIH, USA).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01639.

^{1}H and $^{13}C\{^1H\}$ spectra for all products and ^{19}F NMR spectra for all fluorine-containing compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **11I**, **12**, **15**, **16**, **17**, **18**, **18I**, **19**, **20**, **21**, **23**, **24a**, **24b**, **24c**, **24d**, **24e**, **24f**, **24g**, **24h**, **24i**, **24j**, **24k**,

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24l, **24m**, **24n**, **24o**, **24p**, **25a**, **25b**, **25c**, **25d**, **25e**, **25f**, **25g**, **25h**, **25i**, **25j**, **25k**, **25l**, **25m**, **26a**, **26b**, **26c**, **26d**, **26e**, **26f**, **26g**, **26h**, **26i**, **26j**, **26l**, **26m**, **28**, **29**, **30**, **31**, **32**, **32I**, **33**, **34**, and **38** (ZIP)

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Notes

The authors declare no competing financial interest.

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(16) We classified this type of the reaction to be saponification as the non-dried 1,4-dioxane was required; the presence of minute amount of water was essential. Presumably, under this reaction

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condition, a low concentration of the corresponding hydroxide ion was formed, which saponified the ester to the carboxylate. Interestingly, if sodium/potassium hydroxide was employed instead of sodium amide, the corresponding decarboxylated product (similar to those observed in ref 7f) was observed in the ^{1}H NMR of the crude mixture. However, the probability of dealkylation by sodium amide could not be completely ruled out.

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(21) These compounds are also commercially available.

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