# Synthesis and Structure−Activity Relationship Study of Potent Cytotoxic Analogues of the Marine Alkaloid Lamellarin D

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*Received March 3, 2006*

The marine alkaloid, Lamellarin D (Lam-D), has shown potent cytotoxicity in numerous cancer cell lines and was recently identified as a potent topoisomerase I inhibitor. A library of open lactone analogues of Lam-D was prepared from a methyl 5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate scaffold (**1**) by introducing various aryl groups through sequential and regioselective bromination, followed by Pd(0)-catalyzed Suzuki cross-coupling chemistry. The compounds were obtained in a 24−44% overall yield, and tested in a panel of three human tumor cell lines, MDA-MB-231 (breast), A-549 (lung), and HT-29 (colon), to evaluate their cytotoxic potential. From these data, the SAR study concluded that more than 75% of the open-chain Lam-D analogues tested showed cytotoxicity in a low micromolar $GI_{50}$ range.

## Introduction

In the search for new bioactive, small chemical molecules for research in chemical biology and medicinal chemistry, one must choose a starting point from the vast chemical space.[1] In this respect, natural products may serve as biologically prevalidated leads,[2,3] and indeed, more than 60% of the recently marketed drugs have been isolated from natural products or synthetic compounds based on natural products.[4] With the recent advances in natural products science, including the synthesis of complex libraries,[2,3] biosynthesis,[5] and isolation techniques,[6,7] the field has a promising future.[8] In particular, marine and microbial environments may serve as a source of new bioactive chemical compounds.[9]

Here, we used Lamellarin D (Lam-D, Figure 1), a potent cytotoxic agent against various tumor cells, as a lead. This marine alkaloid was first isolated from the marine prosobranch mollusc *Lamellaria* sp. in 1985 by Faulkner and co-workers.[10] Since then, a family of about 35 structurally related lamellarins has been isolated from natural sources, and several synthetic strategies have been devised for these natural products.[11,12] Of the family of lamellarins, Lam-D is one of the most potent lead candidates for anticancer chemotherapy. There is substantial evidence that Lam-D is an inhibitor of topoisomerase I[13] and a potent pro-apoptotic agent.[14] Recently, topoisomerase I binding studies have been elaborated further by comparing Lam-D and Camptothecin[15] (Figure 1) bound to the DNA-topoisomerase I complex using molecular dynamics simulations.[16] These also nicely correlate with structure−activity relationships (SAR) obtained with homologues of Lam-D with distinct OMe/OH substitution patterns on the pentacyclic framework.[16,17] Hence,

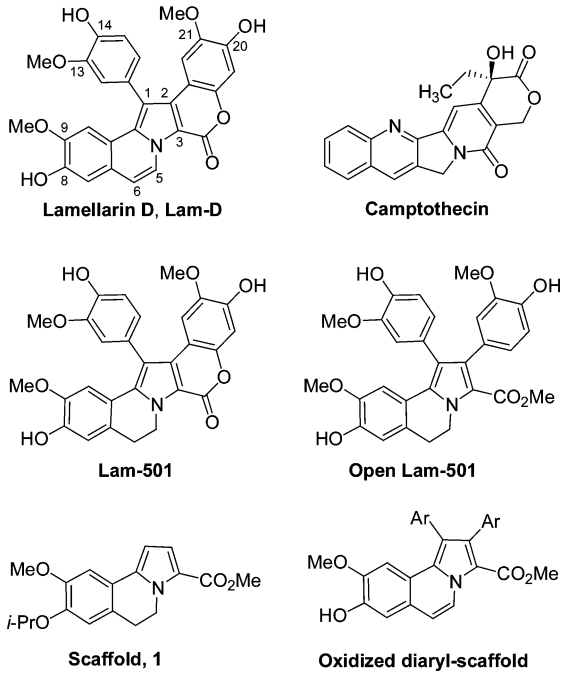


**Figure 1.** Structures of lamellarins, camptotecin, and scaffold **1**.

the 8-OH and 20-OH groups (Figure 1) are crucial for cytotoxic activity and also for topoisomerase I inhibition.

Moreover, the unsaturated C-5−C-6 motif of Lam-D compared to the saturated analogue (Lam-501, Figure 1) is important for potency,[13,18] a trend that was also observed with a range of Lam-D and Lam-501 derivatives in which the free phenolic sites were acylated.[18] Furthermore, the latter study afforded potent candidates for in vivo preclinical development of their antitumor activity. Interestingly, derivatization of the 8-OH and 20-OH groups with amino acids, thus preserving the hydrogen bonding capacity at these sites, affords potent compounds, whereas acylation with various carboxylic acids results in a considerable decrease in potency.[18]

We recently reported preliminary biological results showing that simplified tricyclic analogues of Lam-D lacking the lactone, such as open Lam-501 (Figure 1), retain some cytotoxic

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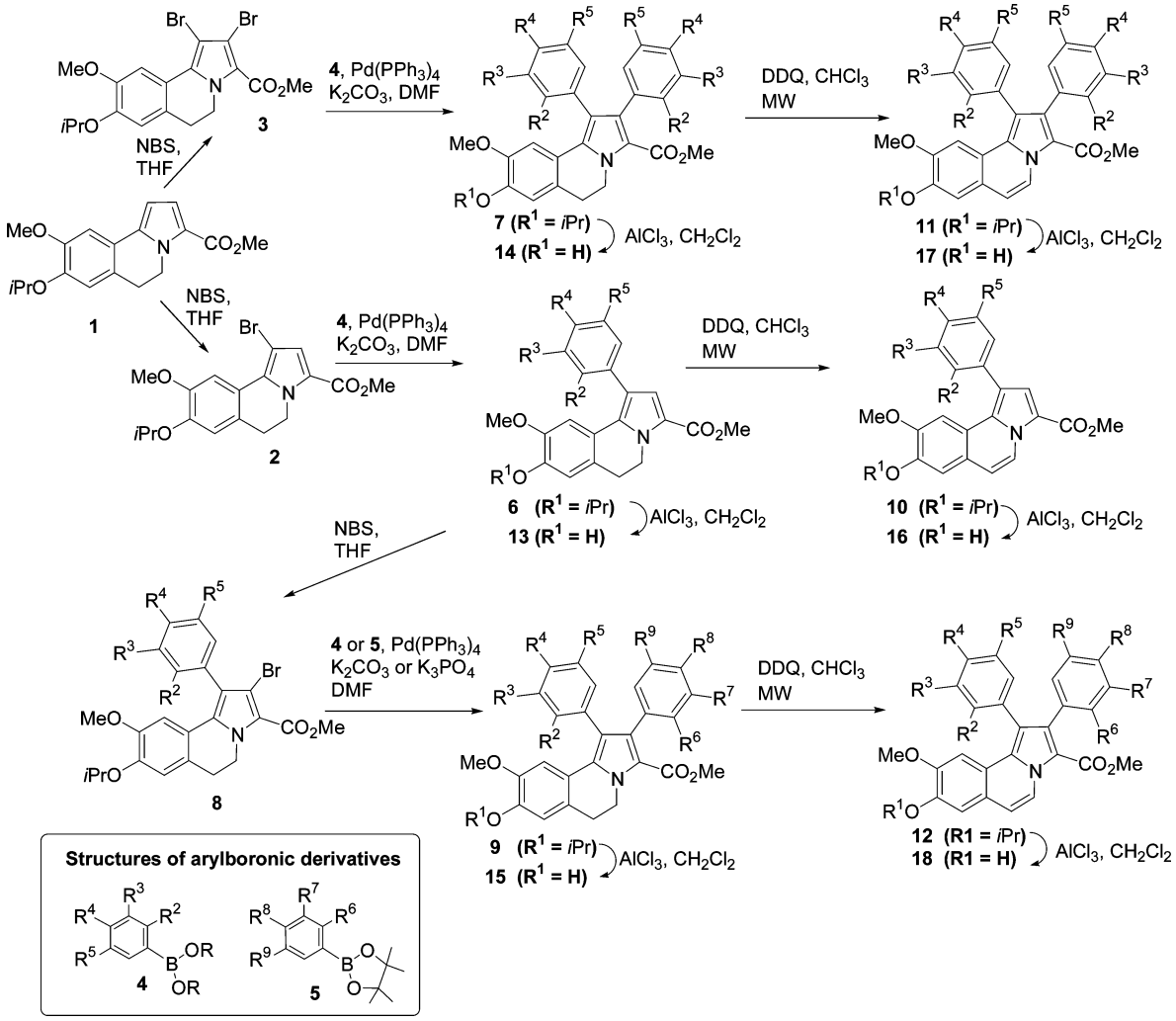
10.1021/jm0602458 CCC: $33.50 
Published on Web 05/06/2006

**Scheme 1.** Synthesis of Open-Chain Lamellarin Analogues Library




activity.[19] This finding encouraged us to perform SAR studies using scaffold **1** by incorporating various aryl groups in positions 1 and 2, including their oxidized homologues (Figure 1).[20]

In addition to the initial achievements in the assembly of the pentacyclic lamellarin framework[21−23] and total synthesis of Lam-D,[21] pentacyclic and more simple lamellarins have been synthesized using solid-phase synthesis,[24−26] which should facilitate the preparation of compound libraries for biological evaluation. However, here, we found it more rational to prepare our library using the methyl 5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate scaffold **1** (Figure 1) and protocols developed for modular total synthesis of Lam-D[27] and tricyclic analogues.[19] While this study was in progress, another highly efficient synthesis of Lam-D and related analogues was published.[28]

## Results and Discussion

**Chemistry.** The synthesis of an open-chain lamellarin analogue library was performed in solution starting from the methyl pyrrole-2-carboxylate by transformation into scaffold **1**.[19,27] The key steps in the process were the introduction of the aryl substituents at positions 1 and 2 of the scaffold using boron derivatives **4** and **5** as building blocks for the final structure. Following the procedure described for the total synthesis of Lam-D,[27] the synthetic strategy used consisted of the regioselective bromination of the scaffold followed by a Pd(0)-catalyzed Suzuki cross-coupling reaction, oxidation, and subsequent deprotection of all of the phenols present in each compound. The isopropyl ether was used as the protecting group for the phenols present in the final compounds and was maintained throughout the synthetic process.[29]

Three alternative ways were used to introduce the aryl groups on scaffold **1**, according to the final structure of the lamellarin analogues (Scheme 1). Monoaryl compounds **6** were prepared by regioselective bromination of scaffold **1** on position 1 to give bromo derivative **2**, which was used for Suzuki cross-coupling with boronic acids **4**. Diaryl derivatives **7** with the same substitution pattern in both aryl groups were obtained from dibromo scaffold **3** by simultaneous introduction of both aryl groups. Finally, for diarylated compounds **9**, with different substituents on the phenyl rings, we used two sequential regioselective bromination and cross-coupling reactions starting from scaffold **1** with monoaryl scaffolds **6** and bromides **8** as synthetic intermediates.[27]

An extensive range of aryl boronic derivatives **4** and **5** were used as building blocks (see Table 1 for the structures). Building blocks **4** are commercially available,[30] whereas ortho substituted borolanes **5** were obtained in good yields (52−81%) from the proper aryl bromide by Pd(0)-catalyzed cross-coupling borylation using the pinacolborane, as described in the Supporting Information.[27,31]

All of the Suzuki cross-coupling reactions between bromides **2**, **3**, and **8** and building blocks **4** were performed in DMF using $Pd(PPh_3)_4$ and $K_2CO_3$ as catalyst and base, respectively, with good yields. The phenolic group on position 4′ of **6c** ($R^4$ = OH)

**Table 1.** Substituents of Building Blocks **4** and **5** and Compounds **9**

| **4** | R | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| **a** | H | H | OMe | OMe | OMe |
| **b** | H | H | H | OH | H |
| **c** | $CMe_2CMe_2$ | H | OMe | OH | H |
| **d** | | H | OMe | O*i*Pr | H |
| **e** | H | OMe | H | H | OMe |
| **f** | H | H | OMe | OMe | H |
| **g** | H | H | H | OMe | H |
| **h** | H | H | OMe | H | OMe |
| **i** | H | H | H | $OCF_3$ | H |
| **j** | H | H | H | O*i*Pr | H |
| **k** | H | H | O*i*Pr | H | H |
| **l** | H | H | H | $NMe_2$ | H |
| **m** | H | H | $NO_2$ | H | H |
| **n** | H | 2-thienyl | | | |

| **5** | $R^6$ | $R^7$ | $R^8$ | $R^9$ | % |
|---|---|---|---|---|---|
| **a** | O*i*Pr | H | O*i*Pr | OMe | 80 |
| **b** | O*i*Pr | H | O*i*Pr | O*i*Pr | 52 |
| **c** | O*i*Pr | H | O*i*Pr | H | 64 |
| **d** | O*i*Pr | OMe | OMe | H | 61 |
| **e** | OMe | H | O*i*Pr | OMe | 81 |

| **9** | scaffold 8 | borolane | % |
|---|---|---|---|
| **a** | **8d** | **4b** | 76 |
| **b** | **8d** | **4f** | 89 |
| **c** | **8d** | **4a** | 71 |
| **d** | **8d** | **5a** | 89 |
| **e** | **8d** | **5e** | quant. |
| **f** | **8e** | **5c** | 82 |
| **g** | **8e** | **5b** | 81 |
| **i** | **8k** | **5d** | 93 |

was protected as isopropoxyether by reaction with 2-bromopropane in basic conditions, thereby giving **6d**.[32] Generally, transformation of **6** into **8** was performed using *N*-bromosuccinimide (NBS) in tetrahydofuran (THF) with a careful control of the reaction time to obtain the desired mono and regiobromination, thereby avoiding the formation of complex mixtures.[33] Regioselective bromination of electron-rich systems, such as **6h**, **6l**, and **6n** using the same reaction conditions was unsuccessful because halogenation on the electron-rich aromatic ring could not be avoided with these compounds.[34] The Suzuki reaction conditions used to introduce the second aryl ring on **8** were basically the same as those when the boron derivatives **4** were used. However, with the more hindered borolanes **5**, several modification were required such as the slow addition of three equivalents[35] of **5** and the use of $K_3PO_4$ as the base to afford yields between 81% and quantitative for the second cross-coupling (see Experimental Section).[36] Compounds **9a**−**i** were prepared by the reaction of scaffolds **8** and the second building block **5**, as indicated in Table 1 and in the Experimental Section.

Optimization of oxidation was performed with the 2-thienyl derivative **4n**. Several experiments using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in $CHCl_3$ at reflux temperature, $MnO_2$ in refluxing toluene or pyridine,[37] or Pd-C in toluene or Decalin[38] afforded only traces of **10n**. The best reaction conditions were attained using DDQ in $CHCl_3$ as solvent in a sealed tube with microwave (MW) irradiation. The aromatization of dihydroisoquinolines **6**, **7**, and **9** to give the planar system of pyrrolo[2,1-*a*]isoquinoline present in compounds **10**−**12** was accomplished using the same protocol as that described in the Supporting Information.[39] The $^1$H NMR was crucial for the control of the reaction because dihydroisoquinolines **6**−**9** have a characteristic ABXY spin system for the four protons of $C^5H_2$ and $C^6H_2$, whereas isoquinolines **10**−**12** hold an AB system in the aromatic area for the two protons $C^5H$ and $C^6H$, the former being a significant signal.

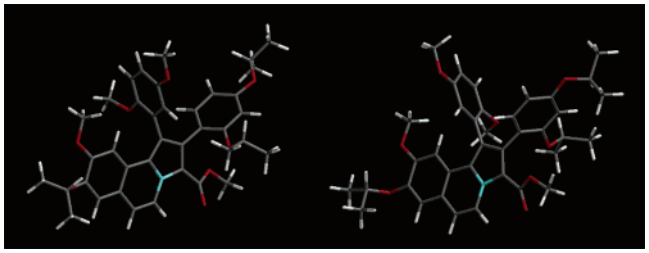


**Figure 2.** Minimized energy forms of the two rotamers of compound **12f**.

Compounds **9f**−**i** and **12f**−**i**, both with bulky substituents in the ortho position of the aryl rings, showed restricted rotation, and two conformers were observed by $^1$H- and $^{13}$C NMR. $^1$H NMR experiments with **12f** at variable temperature showed the collapse of the signals at 75 °C (Figure 2 in the Supporting Information). For example, the coalescence of double doublets at 6.29 and 6.32 ppm[40] at 25 °C were easily observed (part a in Figure 1 of the Supporting Information) as a broad doublet at 6.31 ppm in the experiment at 75 °C (part c in Figure 1 of the Supporting Information), and the same occurred with the methoxy group signals. In the coalescence temperature, the signal of collapsed groups broadened and decreased in intensity. Figure 2 shows the minimized energy forms of the two rotamers of compound **12f**, calculated by the semiempirical method PM3.[41] The elimination of the bulky protecting groups led to the evanescence of the above-mentioned restricted rotation in all of the compounds.

All of the isopropoxy-protecting groups of dihydroisoquinolines **6**, **7**, and **9** and fully aromatic systems **10**−**12** were removed using $AlCl_3$ in $CH_2Cl_2$,[24−26,42] giving a good yield of valuable phenols **13**−**18**.[43,44] Despite the advantage of working with the protected phenol groups, the synthesis was performed without this protection in **4**, as demonstrated with the synthesis of **17c** and **15a**. Lamellarin analogues **13**−**18** were obtained as reddish oils or white solids, and their structures were confirmed by $^1$H- and $^{13}$C-NMR, using heteronuclear 2D correlations, such as HSQC, HMBC, and also MS and HRMS.

**Biological Results.** A panel of three human tumor cell lines was used to evaluate the cytotoxic potential of the Lam-D analogues: A-549 lung carcinoma NSCL, HT-29 colon carcinoma cells, and MDA-MB-231 breast adenocarcinoma.

A conventional colorimetric assay was set up to estimate $GI_{50}$ values, that is, the drug concentration that causes 50% of cell growth inhibition after 72 h of continuous exposure to the test molecule. Lam-D was included in the test for comparison purposes. The results obtained are shown in Table 2.

More than 75% of the open-chain Lam-D analogues tested showed cytotoxicity in a low micromolar $GI_{50}$ range. Molecular simplification of Lam-D by removing the lactone ring from all of the analogues and by the additional elimination of one aryl group in derivatives **13** and **16** produced a decrease in activity with respect to Lam-D. However, interestingly, these data provide crucial information about the importance of the full structure for the biological activity of the molecules despite their low solubility in the biological medium. In a general overview, the oxidized derivatives showed greater activity than the corresponding reduced analogues.[13] Derivatives with electron-withdrawing substituents such as nitro groups (i.e., **14m** and **17m**) decreased activity, and this decrease was dramatic with the introduction of a $OCF_3$ substituent as in **14i** and **17i**. The substitution pattern given by electron donor groups, such as

**Table 2.** In Vitro Cytotoxicity of the Open-Chain Analogues of Lam-D and Synthetic Intermediates[a]

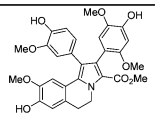
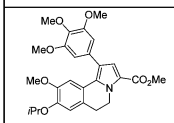
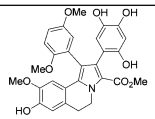
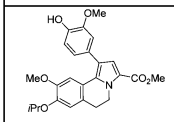
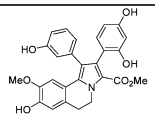
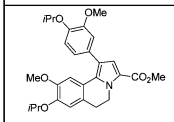
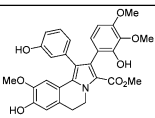
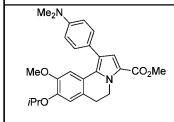
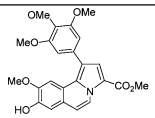
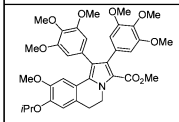
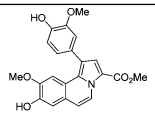
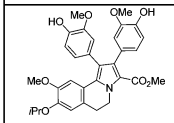
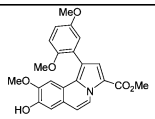
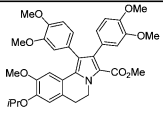
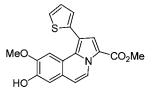
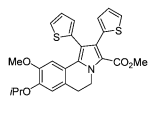
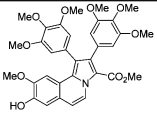
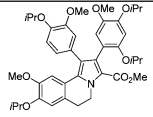
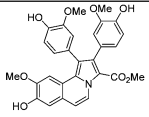
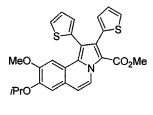
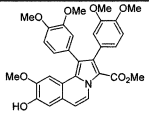
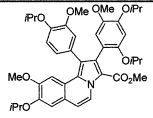
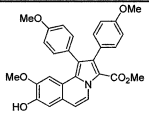
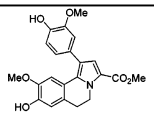
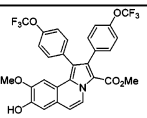
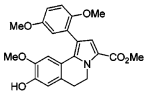
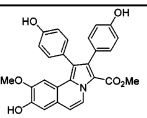
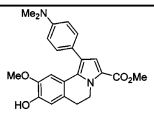
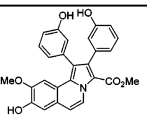
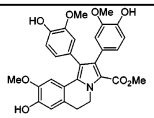
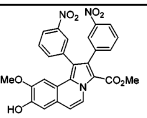
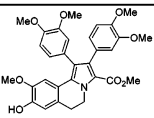
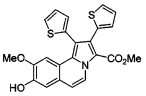
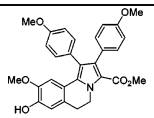
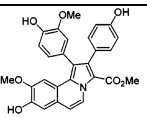
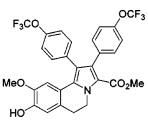
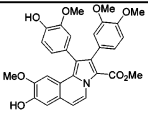
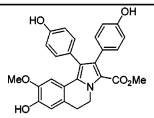
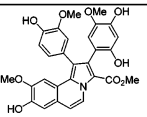
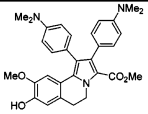
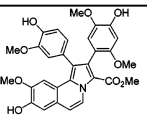
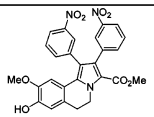
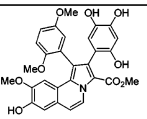
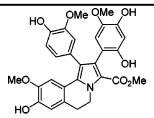
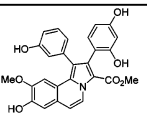
| Compound | Cytotoxicity ($GI_{50}$ μM) | | | Compound | Cytotoxicity ($GI_{50}$ μM) | | |
|---|---|---|---|---|---|---|---|
| | A-549 | HT-29 | MDA-MB-231 | | A-549 | HT-29 | MDA-MB-231 |
| **Lam-D** | 0.20 | 5.1 | 0.25 |  **15e** | 8.9 | n.a. | 7.6 |
|  **6a** | n.a. | n.a. | n.a. |  **15g** | 13.7 | 8.4 | 10.5 |
|  **6c** | 20.3 | 18.1 | 19.0 |  **15h** | n.a. | n.a. | 19.0 |
|  **6d** | n.a. | n.a. | n.a. |  **15i** | 14.7 | n.a. | 15.7 |
|  **6l** | n.a. | n.a. | n.a. |  **16a** | n.a. | n.a. | n.a. |
|  **7a** | 67.9 | 34.0 | n.a. |  **16c** | 10.9 | 23.9 | 11.2 |
|  **7c** | 14.7 | 6.9 | 7.1 |  **16e** | 13.3 | n.a. | 19.9 |
|  **7f** | 0.81 | 1.0 | 0.98 |  **16n** | n.a. | n.a. | 26.3 |
|  **7n** | n.a. | n.a. | n.a. |  **17a** | n.a. | n.a. | n.a. |
|  **9d** | n.a. | n.a. | n.a. |  **17c** | 7.1 | 8.1 | 7.5 |
|  **11n** | n.a. | n.a. | n.a. |  **17f** | n.a. | n.a. | n.a. |
|  **12d** | n.a. | 13.6 | n.a. |  **17g** | n.a. | 9.7 | 9.9 |

**Table 2** (Continued)

| Compound | | Cytotoxicity ($GI_{50}$ μM) | | | Compound | | Cytotoxicity ($GI_{50}$ μM) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | A-549 | HT-29 | MDA-MB-231 | | | A-549 | HT-29 | MDA-MB-231 |
|  | **13c** | 14.2 | 18.0 | 22.3 |  | **17i** | n.a. | n.a. | n.a. |
|  | **13e** | n.a. | n.a. | 12.7 |  | **17j** | 3.5 | 9.8 | 4.1 |
|  | **13l** | n.a. | n.a. | n.a. |  | **17k** | 6.3 | 18.4 | 7.2 |
|  | **14c** | 14.3 | n.a. | 8.5 |  | **17m** | n.a. | 8.9 | 18.3 |
|  | **14f** | 11.2 | n.a. | 7.7 |  | **17n** | 20.4 | n.a. | 19.7 |
|  | **14g** | 9.2 | 10.3 | 14.4 |  | **18a** | 9.8 | 10.1. | 15.0 |
|  | **14i** | n.a. | n.a. | n.a. |  | **18b** | n.a. | n.a. | n.a. |
|  | **14j** | n.a. | n.a. | n.a. |  | **18d** | 0.45 | 7.9 | 0.71 |
|  | **14l** | n.a. | n.a. | 13.7 |  | **18e** | n.a. | n.a. | n.a. |
|  | **14m** | 18.0 | 11.3 | 10.1 |  | **18g** | 4.7 | 7.1 | 3.2 |
|  | **15d** | 5.0 | 17.1 | 3.1 |  | **18h** | 20.8 | n.a. | 10.6 |

[a] n.a. = not active at 10 $\mu$g/mL.

O*i*Pr, $NMe_2$, OMe, and OH, was fundamental for activity. A comparison of **6c** and **6d** shows the importance of the free *p*-phenol on the aryl at position 1 of the scaffold. Although few O-protected phenol analogues, such as **6c**, **7a**, **7c**, and **7f**, presented cytotoxic activity, an important gain in activity was displayed by the same compounds with free OH functions. This

observation can probably be attributed to the additional capacity of these analogues to form hydrogen bonds with the active sites, as described for Lam-D.[13] Although the binding of these analogues with the same DNA−topI complex has not been demonstrated in the present work, other factors that could increase the activity are the solubility or the membrane-crossing issues. The donor effect of the methoxy substituents may explain why **14g** and **17g** were quite active, even without the possibility of acting as hydrogen-bond donors. Compounds **18a**, **17c**, **18e**, **18d**, and Lam-D had identical substituents on the scaffold and on the aryl at position 1 and afforded a gradation in activity potency with the increase upon the substitution of the aryl at position 2 of the scaffold. Except for **18e**, which was inactive, presumably due to lack of planarity by sterical hindrance. Simplified analogue **17c** maintained 63% of the activity of Lam-D in HT29 cells, and most of this behavior remained in the C4″-OH (same position as C-20 in Lam-D) group, as shown by **18a**. To our knowledge, open lactone compound **18d** may produce lactonization in a physiological environment. Therefore, **18d** must be considered for further study as a possible pharmacodynamic improvement for the validated Lam-D lead.

## Conclusion

Here, we performed a SAR study using the marine alkaloid Lam-D. Efficient and convergent modular synthetic protocols were applied to the diverted total synthesis of more than 40 analogues of the natural product. This strategy allowed the introduction of structural elements that have not been previously studied in the lamellarin series. Thus, the SAR information provided in this study expands our knowledge about these compounds beyond substitutions on the core structure, which has already been provided by other groups.

Overall, our results are consistent with previous findings such as the critical importance of the cytotoxic activity of the planarity of the tricyclic isoquinoline motif. In addition, compounds with OH hydrogen-bond donors at C-8 and C-4″ were generally more potent than other analogues. Not surprisingly, compound **18d**, which showed the most resemblance to Lam-D, was the most potent compound against the three cell lines tested. This observation may be due to partial lactonization to give Lam-D under the assay conditions.

However, a remarkable retention of activity was observed for monoaryl analogues **13c** and **16c** against HT-29 colon carcinoma cells, toward which these compounds were only ca. 5-fold less potent than Lam-D. Furthermore, the moderate activity of compound **17n** against the A-549 and MDA-MB-231 cell lines (low micromolar) indicates that heterocyclic motifs may be included in a second-generation library. However, the hydrogen-bond donor at C-20 should be preserved in future library designs. On the basis of this work it is clear the importance of an extensive bioprospection of the natural sources to find lead candidates for constructing ponderous libraries.

## Experimental Section

**(A) General Procedures for Cross-Coupling Reactions. Synthesis of Monoaryl Derivatives 6.** A solution of bromide **2** (1.0 mmol) in DMF (20 mL) was purged with Ar, and **4** (3.0 mmol), $Pd(PPh_3)_4$ (0.1 mmol), and 2 M $K_2CO_3$ (3.0 mmol) were added. The reaction mixture was stirred at 125 °C and followed by TLC until the starting material disappeared. The solvent was removed after cooling to room temperature, and the residue was dissolved in EtOAc. The organic solution was washed with water and brine, dried, and concentrated to give a crude material, which was later purified by column chromatography on silica gel. Elution with hexane/EtOAc (90:10 to 75:25) gave **6** (yield 32−92%).

**(B) General Procedures for Cross-Coupling Reactions. Synthesis of Diaryl Derivatives 7.** A solution of 1,2-dibromide **3** (189 mg, 0.4 mmol) in DMF (8 mL) was purged with Ar for 10 min, and **4** (2.4 mmol), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol), and 2 M $K_2CO_3$ (2.4 mmol) were added. The reaction mixture was stirred at 125 °C and was then subjected to HPLC until the starting material disappeared or for a maximum 20 h. The solvent was removed after cooling to room temperature, and the residue was dissolved in EtOAc. The organic solution was washed with water and brine, dried, and concentrated to give a crude material, which was later purified by column chromatography on silica gel. Elution with hexane/EtOAc (75:25 to 40:60) gave **7** (yield 34−87%).

**(C) General Procedure for the Regioselective Bromination of 6.** NBS (1.20 mmol) was added in one portion to a solution of **6** (1.00 mmol) in THF (13 mL). The mixture was stirred at 70 °C under Ar for 90 min. The solvent was removed, and the residue was purified by flash chromatography. Elution with hexane/AcOEt (90:10 to 70:30) gave **8** (yield 84%, quantitative (quant)).

**(D) General Procedures for Cross-Coupling Reactions. Synthesis of Diaryl Derivatives 9a−c.** Arylboronic acids **4** (3.0 mmol), $Pd(PPh_3)_4$ (0.1 mmol), and 2 M $K_2CO_3$ (3.0 mmol) were added to a purged solution of bromide **8** (1.0 mmol) in DMF (20 mL). The reaction mixture was stirred at 125 °C for the time indicated for each compound (see Supporting Information). The solvent was removed, and the residue was dissolved in EtOAc. The organic solution was washed with water and brine, dried, and concentrated to give a crude material, which was later purified by column chromatography on silica gel. Elution with hexane/EtOAc (75:25 to 40:60) gave **9a−c** (yield 71−89%).

**(E) General Procedures for Cross-Coupling Reactions. Synthesis of Diaryl Derivatives 9d−i.** A solution of bromide **8** (1.0 eq) in DMF (20 mL) was purged with Ar for 10 min, and pinacol phenylboronate **5** (1.0 mmol), $Pd(PPh_3)_4$ (10%), and 2 M $K_3PO_4$ (3.0 mmol) were added. The reaction mixture was stirred at 115 °C, and another portion of boronate (2.0 mmol) was added dropwise using a syringe pump during the first hour of reaction. The solvent was removed, and the residue was dissolved in EtOAc. The organic solution was washed with water and brine, dried, and concentrated to give a crude material, which was later purified by column chromatography on silica gel. Elution with hexane/EtOAc (75:25 to 60:40) gave **9d−i** (yield 81%, quant).

**(F) General Procedure for Oxidation. Synthesis of Compounds 10−12.** A mixture of **6**, **7**, or **9** (1.0 mmol) and DDQ (1.3 mmol) in dry $CHCl_3$ (15 mL) was purged with Ar in a sealed vessel and microwaved at 120 °C for 10 min. The organic solution was washed with 2 M NaOH, water, and brine and then dried ($MgSO_4$), filtered, and evaporated in a vacuum. Washing with NaOH was avoided for products with free phenolic groups. Purification by column chromatography on silica gel eluting with hexane/AcOEt (85:15 to 60:40) gave **10−12** (yield 48−95%).

**(G) General Method for Deprotection. Preparation of Compounds 13−18.** Anhydrous $AlCl_3$ (1.3 mmol) for each isopropoxy ether was added to a solution of compound **6**, **7**, or **9−12** (1 mmol) in dry $CH_2Cl_2$ (1 mL). The mixture was sonicated for 10 min, quenched with sat. $NH_4Cl$, and then washed with water and brine. The aqueous solution was extracted with AcOEt. The organic extracts were dried and evaporated. The crude product was purified by flash chromatography to give the title compounds (yield 30−96%).

**Methyl 8-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*] isoquinoline-3-carboxylate (13c).** Following general procedure G and starting with **6c** (48 mg, 0.11 mmol), elution with hexane/AcOEt (80:20 to 70:30) gave a white solid (19 mg, 44%). Mp (MeCN) 205−207 °C. IR (film) $\nu$ 3424, 1696, 1439, 1246 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 2.98 (t, $J = 6.4$ Hz, 2H, H6); 3.47 (s, 3H, OMe); 3.84 (s, 3H, OMe); 3.86 (s, 3H, OMe); 4.59 (t, $J = 6.4$ Hz, 2H, H5); 5.62 (s, 1H, OH); 5.63 (s, 1H, OH); 6.78 (s, 1H); 6.85 (s, 1H); 6.91−6.97 (m, 4H). $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 28.9 (t); 42.5 (t); 51.1 (q); 55.6 (q); 56.0 (q); 108.1 (d); 112.0 (d); 113.8 (d); 114.3 (d); 119.1 (d); 120.0 (s); 120.5 (s); 121.5 (s); 122.4 (d); 126.8 (s); 128.6 (s); 131.7 (s);

144.5 (s); 144.9 (s); 145.0 (s); 146.4 (s); 161.7 (s). MS (MALDI-TOF) *m*/*z* 395 (M, 100); 396 (M + 1, 26). HRMS *m*/*z* calcd for $C_{22}H_{21}NO_6$, 395.1369; found, 395.1366.

**Methyl 1-(2,5-Dimethoxyphenyl)-8-hydroxy-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (13e).** Following general procedure G and starting with **6e** (17 mg, 0.04 mmol), elution with hexane/AcOEt (80:20 to 70:30) gave a white solid (12 mg, 76%). Mp (MeCN) 96−100 °C. IR (film) $\nu$ 3417, 1697, 1244 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.99 (t, $J$ = 6.8 Hz, 2H, H6); 3.42 (s, 3H, OMe); 3.65 (s, 3H, OMe); 3.75 (s, 3H, OMe); 3.83 (s, 3H, OMe); 4.62 (t, $J$ = 6.8 Hz, 2H, H5); 5.55 (s, 1H, OH); 6.67 (s, 1H); 6.75 (s, 1H); 6.85 (dd, $J$ = 8.7, 2.8 Hz, 1H, H4′); 6.89 (d, $J$ = 8.7 Hz, 1H, H3′); 6.90 (d, $J$ = 2.8 Hz, 1H, H6′); 7.02 (s, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 28.7 (t); 42.5 (t); 51.0 (q); 55.4 (q); 55.8 (q); 56.2 (q); 107.7 (d); 112.1 (d); 113.5 (d); 113.6 (d); 116.7 (s); 117.4 (d); 119.9 (d); 120.1 (s); 121.0 (s); 126.3 (s); 126.5 (s); 132.7 (s); 144.8 (s); 145.0 (s); 151.6 (s); 153.6 (s); 161.8 (s). MS (MALDI-TOF) *m*/*z* 409 (M, 100); 410 (M + 1, 43). MS (ESI-TOF) *m*/*z* 410 (M + 1, 100). HRMS *m*/*z* calcd for $C_{23}H_{24}NO_6$, 410.1598; found, 410.1598.

**Methyl 1-(4-Dimethylaminophenyl)-8-hydroxy-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (13l).** Following general procedure G and starting with **6l** (31 mg, 0.07 mmol), elution with hexane/AcOEt (80:20 to 70:30) gave a white solid (25 mg, 90%). Mp (MeCN) 169−170 °C. IR (film) $\nu$ 3441, 2925, 1693, 1439, 1194 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.95−2.96 (m, 8H, H6, $NMe_2$); 3.47 (s, 3H, OMe); 3.83 (s, 3H, OMe); 4.57 (t, $J$ = 6.4 Hz, 2H, H5); 5.58 (bs, 1H, OH); 6.76 (s, 1H); 6.77 (d, $J$ = 8.8 Hz, 2H); 6.90 (s, 1H); 6.95 (s, 1H); 7.31 (d, $J$ = 8.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 28.9 (t); 40.8 (q); 42.5 (t); 51.0 (q); 55.6 (q); 108.2 (d); 112.8 (2d); 113.7 (d); 119.2 (d); 119.9 (s); 120.9 (s); 121.7 (s); 124.7 (s); 126.7 (s); 130.1 (2d); 131.7 (s); 144.8 (s); 144.9 (s); 149.6 (s); 161.8 (s). MS (MALDI-TOF) *m*/*z* 392 (M, 100). MS (ESI-TOF) *m*/*z* 393 (M + 1, 100). HRMS *m*/*z* calcd for $C_{23}H_{25}N_2O_4$, 393.1809; found, 393.1809.

**Methyl 1,2-Bis(3,5-dimethoxy-4-hydroxyphenyl)-8-hydroxy-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (14a, R$^4$ = OH).** Following general procedure G and starting with **7a** (24 mg, 0.04 mmol) and an excess of $AlCl_3$ (0.8 mmol), upon elution with hexane/AcOEt (60:40 to 40:60), a yellowish solid (12 mg, 58%) was obtained. Mp (MeCN) 118−120 °C. IR (film) $\nu$ 3430,1689,1437,1210 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.02 (t, $J$ = 6.4 Hz, 2H, H6); 3.40 (s, 3H, OMe); 3.64 (s, 3H, OMe); 3.68 (s, 6H, 2OMe); 3.71 (s, 6H, 2OMe); 4.59 (t, $J$ = 6.4 Hz, 2H, H5); 5.41 (bs, 1H, OH); 5.43 (bs, 1H, OH); 5.58 (bs, 1H, OH); 6.39 (s, 2H); 6.40 (s, 2H); 6.67 (s, 1H); 6.78 (s, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 28.9 (t); 42.9 (t); 50.9 (q); 55.5 (q); 56.2 (2q); 56.4 (2q); 107.8 (2d); 107.9 (2d); 108.3 (d); 113.7 (d); 117.8 (s); 120.2 (s); 121.4 (s); 126.3 (s); 126.5 (s); 126.9 (s); 131.2 (s); 132.7 (s); 133.3 (s); 133.5 (s); 144.9 (s); 146.0 (2s); 146.9 (2s); 162.4 (s). MS (MALDI-TOF) *m*/*z* 577 (M, 100); 578 (M + 1, 40). HRMS *m*/*z* calcd for $C_{31}H_{31}NO_{10}$, 577.1948; found, 577.1942.

**Methyl 8-Hydroxy-1,2-bis(4-hydroxy-3-methoxyphenyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (14c).** Following general procedure G and starting with **7c** (28 mg, 0.05 mmol), elution with hexane/AcOEt (50:50 to AcOEt) gave a yellowish solid (15 mg, 60%). Mp (MeCN) 237−239 °C. IR (film) $\nu$ 3423, 1688, 1438, 1235, 1199 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.01 (t, $J$ = 6.4 Hz, 2H, H6); 3.38 (s, 3H, OMe); 3.62 (s, 3H, OMe); 3.63 (s, 3H, OMe); 3.65 (s, 3H, OMe); 4.59 (t, $J$ = 6.4 Hz, 2H, H5); 5.50 (bs, 1H, OH); 5.53 (bs, 1H, OH); 5.59 (bs, 1H, OH); 6.55 and 6.58 (2d, $J$ = 1.6 Hz, 2H, H2′, H2″); 6.63 (s, 1H); 6.70 and 6.75 (2dd, $J$ = 8.4, 1.6 Hz, 2H, H6′, H6″); 6.77 (s,1H); 6.78 and 6.83 (2d, $J$ = 8.4 Hz, 2H, H5′, H5″). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 28.9 (t); 42.9 (t); 50.8 (q); 55.4 (q); 55.8 (q); 55.9 (q); 108.2 (d); 113.3 (d); 113.5 (d); 113.6 (d); 113.9 (d); 114.1 (d); 117.8 (s); 120.4 (s); 121.4 (s); 123.9 (d); 124.3 (d); 126.9 (s); 127.3 (s); 127.5 (s); 131.3 (s); 132.7 (s); 144.0 (s); 144.3 (s); 144.9 (s); 145.4 (2s); 146.3 (s); 162.5 (s). MS (MALDI-TOF) 517 (M, 100); 518 (M + 1, 15). HRMS *m*/*z* calcd for $C_{29}H_{27}NO_8$, 517.1737; found, 517.1731.

**Methyl 1,2-Bis(3,4-dimethoxyphenyl)-8-hydroxy-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (14f).** Following general procedure G and starting with **7f** (92.0 mg, 0.16 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave **14f** as a reddish oil (50.9 mg, 60%). IR (film) $\nu$ 3410, 1691, 1437, 1254 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.01 (t, $J$ = 6.5 Hz, 2H, H6); 3.36 (s, 3H, OMe); 3.62 (s, 3H, OMe); 3.63 (s, 3H, $CO_2Me$); 3.67 (s, 3H, OMe); 3.83 (s, 3H, OMe); 3.84 (s, 3H, OMe); 4.59 (t, $J$ = 6.5 Hz, 2H, H5); 5.67 (bs, 1H, OH); 6.62 (d, $J$ = 1.6 Hz, 1H); 6.64 (d, $J$ = 1.6 Hz, 1H); 6.66 (s, 1H); 6.71 (dd, $J$ = 8.4 and 1.6 Hz, 1H); 6.72 (s 1H); 6.74 (dd, $J$ = 8.4 and 1.6 Hz, 1H); 6.76 (d, $J$ = 8.4 Hz, 1H); 6.77 (d, $J$ = 8.4 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 28.8 (t); 42.8 (t); 50.8 (q); 55.3 (q); 55.5 (q); 55.6 (q); 55.7 (q); 55.8 (q); 108.2 (d); 109.9 (d); 110.9 (d); 113.7 (d); 114.1 (d); 114.3 (d); 117.7 (s); 120.2 (s); 122.9 (d); 123.4 (d); 123.4 (s); 126.8 (s); 127.8 (s); 128.0 (s); 131.2 (s); 132.5 (s); 141.6 (s); 144.8 (s); 147.3 (s); 147.5 (s); 147.5 (s); 148.5 (s); 162.3 (s). MS (MALDI-TOF) *m*/*z* 545 (M, 100). HRMS *m*/*z* calcd for $C_{31}H_{31}NO_8$, 545.2050; found, 545.2044.

**Methyl 8-Hydroxy-9-methoxy-1,2-bis(4-methoxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (14 g).** Following general procedure G and starting with **7g** (18.2 mg, 0.034 mmol), elution with hexane/AcOEt (80:20 to 50:50) gave **14g** (6.8 mg, 41%) as a reddish oil. IR (film) $\nu$ 2931, 1697 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.01 (t, $J$ = 6.5 Hz, 2H, H6); 3.34 (s, 3H, OMe); 3.59 (s, 3H, $CO_2Me$); 3.76 (s, 3H, OMe); 3.77 (s, 3H, OMe); 4.59 (t, $J$ = 6.5 Hz, 2H, H5); 5.52 (bs, 1H, OH); 6.50 (s, 1H); 6.74 (d, $J$ = 9.0 Hz, 2H); 6.76 (s, 1H); 6.79 (d, $J$ = 8.6 Hz, 2H); 7.03 (d, $J$ = 9.0 Hz, 2H); 7.06 (d, $J$ = 8.6 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 28.9 (t); 42.9 (t); 50.7 (q); 55.0 (q); 55.2 (q); 55.2 (q); 108.2 (d); 109.7 (d); 112.5 (2d); 113.6 (2d); 117.9 (s); 120.5 (s); 121.2 (s); 126.8 (s); 127.6 (s); 127.8 (s); 131.4 (s); 131.6 (2d); 132.3 (2d); 132.6 (s); 144.7 (s); 144.8 (s); 157.9 (s); 158.2 (s); 162.5 (s). MS (MALDI-TOF) *m*/*z* 485 (M). HRMS *m*/*z* calcd for $C_{29}H_{27}NO_6$, 485.1838; found, 485.1833.

**Methyl 8-Hydroxy-9-methoxy-1,2-bis(4-trifluoromethoxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (14i).** Following general procedure G and starting with **7i** (25.9 mg, 0.041 mmol), elution with hexane/AcOEt (85:15 to 65:35) gave **14i** (18.0 mg, 75%) as a reddish oil. IR (film) $\nu$ 2927, 1699 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.02 (t, $J$ = 6.4 Hz, 2H, H6); 3.31 (s, 3H, OMe); 3.58 (s, 3H, $CO_2Me$); 4.61 (t, $J$ = 6.4 Hz, 2H, H5); 5.57 (bs, 1H, OH); 6.33 (s, 1H); 6.79 (s, 1H); 7.04−7.06 (m, 2H); 7.10−7.17 (m, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 28.8 (t); 42.9 (t); 50.8 (q); 54.9 (q); 107.9 (d); 113.8 (d); 118.2 (s); 119.5 (2d); 119.7 (q); 119.9 (q); 121.0 (s); 121.1 (2d); 121.7 (s); 127.0 (s); 131.3 (s); 131.6 (s); 131.8 (2d); 132.6 (2d); 133.8 (s); 134.3 (s), 144.9 (s); 145.1 (s); 147.8 (s); 147.9 (s); 161.9 (s). MS (MALDI-TOF) *m*/*z* 593 (M); 594 (M + 1). HRMS *m*/*z* calcd for $C_{29}H_{21}F_6NO_6$, 593.1273; found, 593.1268.

**Methyl 8-Hydroxy-1,2-bis(4-hydroxyphenyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (14j).** Following general procedure G and starting with **7j** (28.6 mg, 0.049 mmol), elution with hexane/AcOEt (60:40 to AcOEt) gave **14j** (15.0 mg, 67%) as a pale solid. Mp (MeCN) 190−195 °C. IR (film) $\nu$ 3194, 1683, 1436, 1267 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 2.92 (m, 2H, H6); 3.21 (s, 3H, OMe); 3.48 (s, 3H, $CO_2Me$); 4.43 (m, 2H, H5); 6.39 (s, 1H); 6.55 (d, $J$ = 8.1 Hz, 2H); 6.67 (m, 3H); 6.85 (d, $J$ = 8.2 Hz, 2H); 6.88 (d, $J$ = 8.2 Hz, 2H); 9.16 (bs, 2H, OH); 9.31 (bs, 1H, OH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 27.8 (t); 42.4 (t); 50.4 (q); 54.5 (q); 108.8 (d); 113.8 (2d); 114.8 (d); 115.0 (2d); 117.0 (s); 118.8 (s); 120.7 (s); 125.5 (s); 125.6 (s); 126.3 (s); 130.8 (s); 131.2 (2d); 131.9 (2d); 132.2 (s); 145.6 (s); 145.7 (s); 155.4 (s); 155.9 (s); 161.5 (s). MS (MALDI-TOF) *m*/*z* 457 (M). HRMS *m*/*z* calcd for $C_{27}H_{23}NO_6$, 457.1525, found. 457.1520.

**Methyl 8-Hydroxy-1,2-bis(3-hydroxyphenyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (14k).** Following general procedure G and starting with **7k** (18.6 mg, 0.032 mmol), elution with hexane/AcOEt (60:40 to AcOEt) gave **14k** (12.3 mg, 85%) as a white solid. Mp (MeCN) 128−130 °C. IR

(film) $\nu$ 3299, 1680, 1440, 1202 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 2.94 (t, $J$ = 6.5 Hz, 2H, H6); 3.20 (s, 3H, OMe); 3.49 (s, 3 H, $CO_2$Me); 4.43 (m, 2H, H5); 6.39 (s, 1H); 6.48−6.50 (m, 2H); 6.52−6.55 (m, 3H); 6.9−6.64 (m, 1H); 6.94−6.98 (t, $J$ = 8.1 Hz, 1H); 7.06−7.10 (t, $J$ = 8.4 Hz, 1H); 6.68 (s, 1H); 9.11 (bs, 1H, OH); 9.17 (bs, 1H, OH); 9.27 (bs, 1H, OH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 27.8 (t); 42.5 (t); 50.6 (q); 54.4 (q); 108.8 (d); 113.1 (d); 113.6 (d); 114.8 (d); 117.1 (d); 117.3 (d); 118.5 (s); 120.5 (s); 121.0 (d); 121.6 (d); 126.3 (s); 127.7 (d); 129.1 (d); 130.5 (s); 131.6 (s); 136.2 (s); 136.5 (s); 145.7 (s); 145.9 (s); 155.9 (s); 157.1 (s); 161.4 (s). MS (MALDI-TOF) *m*/*z* 457 (M). HRMS *m*/*z* calcd for $C_{27}H_{23}NO_6$, 457.1525; found, 457.1520.

**Methyl 1,2-Bis(4-dimethylaminophenyl)-8-hydroxy-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (14l).** Following general procedure G and starting with **11l** (5.4 mg, 0.0098 mmol), elution with hexane/AcOEt (80:20 to 50:50) gave **14l** (2.3 mg, 46%) as a white solid. Mp (MeCN) 245−247 °C. IR (film) $\nu$ cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.88 (s, 6H, $NMe_2$); 2.91 (s, 6H, $NMe_2$); 2.99 (t, $J$ = 6.5 Hz, 2H, H6); 3.35 (s, 3H, OMe); 3.62 (s, 3H, $CO_2$Me); 4.56 (t, $J$ = 6.5 Hz, 2H, H5); 5.48 (bs, 1H, OH); 6.54 (s, 1H); 6.59 (d, $J$ = 8.8 Hz, 2H); 6.64 (d, $J$ = 8.8 Hz, 2H); 6.74 (s, 1H); 7.01 (d, $J$ = 8.8 Hz, 2H); 7.02 (d, $J$ = 8.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 28.9 (t); 40.5 (t); 40.5 (q); 40.7 (q); 50.7 (q); 55.2 (q); 108.3 (d); 111.4 (2d); 112.8 (2d); 113.4 (d); 117.6 (s); 120.8 (s); 121.7 (s); 121.9 (s); 123.9 (s); 126.7 (s); 131.2 (2d); 131.4 (s); 131.9 (2d); 144.4 (s); 144.6 (s); 146.6 (s); 149.8 (s); 161.1 (s). MS (MALDI-TOF) *m*/*z* 511 (M); 512 (M + 1). HRMS *m*/*z* calcd for $C_{31}H_{33}N_3O_4$, 511.2471, found. 511.2466.

**Methyl 8-Hydroxy-9-methoxy-1,2-bis(3-nitrophenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (14m).** Following general procedure G and starting with **7m** (42.2 mg, 0.076 mmol), elution with hexane/AcOEt (80:20 to 50:50) gave **14m** (17.0 mg, 44%) as a reddish solid. Mp (MeCN) 241−243 °C. IR (film) $\nu$ 2926, 1701, 1540, 1439, 1350, 1227 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.06 (t, $J$ = 6.5 Hz, 2H, H6); 3.29 (s, 3H, OMe); 3.59 (s, 3H, $CO_2$Me); 4.66 (t, $J$ = 6.5 Hz, 2H, H5); 5.63 (bs, 1H, OH); 6.33 (s, 1H); 6.83 (s, 1H); 7.36−7.50 (m, 4H); 8.00−8.02 (m, 2H); 8.05−8.08 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 28.7 (t); 43.0 (t); 51.1 (q); 55.3 (q); 107.8 (d); 114.2 (d); 118.6 (s); 118.7 (s); 121.7 (d); 121.8 (d); 125.5 (d); 125.8 (d); 127.4 (s); 128.2 (d); 129.4 (d); 130.1 (s); 131.9 (s); 136.6 (d); 136.9 (s); 137.4 (d); 145.1 (s); 145.6 (s) 147.5 (s); 148.2 (s); 161.4 (s). MS (MALDI-TOF) *m*/*z* 515 (M); 516 (M + 1). HRMS *m*/*z* calcd for $C_{27}H_{21}N_3O_8$, 515.1329, found. 515.1323.

**Methyl 2-(2,4-Dihydroxy-5-methoxyphenyl)-8-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (15d).** Following general procedure G and starting with **9d** (48 mg, 0.07 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a reddish oil (26 mg, 70%). IR (film) $\nu$ 3419, 1686, 1439, 1246, 1197 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.95−3.15 (m, 2H, H6); 3.40 (s, 3H, OMe); 3.54 (s, 3H, OMe); 3.63 (s, 3H, OMe); 3.71 (s, 3H, OMe); 4.15−4.25 (m, 2H, H5); 5.54 (s, 3H, 3OH); 5.63 (s, 1H, OH); 6.31 (bs, 1H); 6.53 (bs, 1H, H2′); 6.56 (s, 1H); 6.72 (s, 1H); 6.75−6.79 (m, 2H); 6.82 (d, $J$ = 8.0 Hz, 1H, H5′). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 28.8 (t); 43.2 (t); 51.5 (q); 55.5 (q); 55.9 (q); 56.4 (q); 102.8 (d); 108.5 (d); 113.4 (d); 113.8 (d); 114.0 (d); 114.3 (d); 118.9 (s); 120.0 (s); 122.5 (s); 123.8 (d); 126.8 (s); 126.9 (2s); 127.3 (s); 132.4 (s); 140.2 (s); 144.4 (s); 145.0 (s); 145.2 (s); 145.7 (s); 146.4 (s); 148.7 (s); 162.4 (s). MS (MALDI-TOF) 533 (M, 100); 534 (M + 1, 70); 535 (M + 2, 32). HRMS *m*/*z* calcd for $C_{29}H_{27}NO_9$, 533.1686; found, 533.1680.

**Methyl 2-(2,5-Dimethoxy-4-hydroxyphenyl)-8-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (15e).** Following general procedure G and starting with **9e** (67 mg, 0.10 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a brown solid (24 mg, 45%). Mp (MeCN) 140−145 °C. IR (film) $\nu$ 3423, 1688, 1265, 1196 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.02 (bs, 2H, H6); 3.38 (s, 3H, OMe); 3.57 (s, 3H, OMe); 3.60 (s, 6H, 2OMe); 3.63 (s, 3H, OMe); 4.57 (bs, 2H, H5); 5.53 (s, 1H, OH); 5.57 (s, 1H, OH); 5.59 (s, 1H, OH); 6.50 (s, 2H); 6.59 (s, 1H); 6.66 (s, 1H); 6.74−6.79 (m, 2H); 6.81 (d, $J$ = 8.0 Hz, 1H, H5′). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 28.8 (t); 42.8 (t); 50.8 (q); 55.4 (q); 55.9 (q); 56.2 (q); 56.5 (q); 98.8 (d); 108.3 (d); 113.5 (d); 113.7 (d); 113.9 (d); 115.1 (d); 115.6 (s); 118.8 (s); 120.6 (s); 121.4 (s); 123.9 (d); 126.7 (s); 127.8 (s); 128.0 (s); 130.5 (s); 131.1 (s); 135.0 (s); 139.6 (s); 144.1 (s); 144.9 (s); 146.1 (s); 151.9 (s); 162.5 (s). MS (MALDI-TOF) 547 (M, 100); 548 (M + 1, 30). HRMS *m*/*z* calcd for $C_{30}H_{29}NO_9$, 547.1842; found, 547.1837.

**Methyl 1-(2,5-Dimethoxyphenyl)-8-hydroxy-9-methoxy-2-(2,4,5-trihydroxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (15g).** Following general procedure G and starting with **9g** (22 mg, 0.03 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a reddish oil (7 mg, 42%). IR (film) $\nu$ 3425, 1697, 1465, 1243 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.99 (t, $J$ = 6.4 Hz, 2H, H6); 3.41 (s, 3H, OMe); 3.65 (s, 3H, OMe); 3.75 (s, 3H, OMe); 3.83 (s, 3H, OMe); 4.61 (t, $J$ = 6.4 Hz, 2H, H5); 5.12 (bs, 1H, OH); 5.34 (bs, 1H, OH); 5.54 (bs, 1H, OH); 5.78 (bs, 1H, OH); 6.67 (s, 1H); 6.75 (s, 1H); 6.84 (dd, $J$ = 8.9, 2.8 Hz, 1H, H4′); 6.88 (s, 1H); 6.89−6.92 (m, 2H); 7.02 (s, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 30.9 (t); 42.5 (t); 51.0 (q); 55.4 (q); 55.8 (q); 56.2 (q); 107.6 (d); 112.2 (d); 113.5 (d); 113.6 (d); 116.7 (s); 117.4 (d); 119.9 (d); 120.1 (s); 121.1 (s); 126.3 (d); 126.5 (s); 132.7 (s); 144.8 (s); 145.0 (s); 149.8 (s); 150.3 (s); 151.6 (s); 153.6 (s); 161.8 (s). MS (MALDI-TOF) 533 (M, 100). HRMS *m*/*z* calcd for $C_{29}H_{27}NO_9$, 533.1686; found, 533.1684.

**Methyl 8-Hydroxy-2-(2-hydroxy-4,5-dimethoxyphenyl)-1-(3-hydroxyphenyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (15i).** Following general procedure G and starting with **9i** (23 mg, 0.04 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a reddish oil (16 mg, 85%). IR (film) $\nu$ 3405, 1684, 1437, 1196 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.01 (t, $J$ = 6.8 Hz, 2H, H6); 3.36 (s, 3H, OMe); 3.60 (s, 3H, OMe); 3.81 (s, 3H, OMe); 3.85 (s, 3H, OMe); 4.46−4.71 (m, 2H, H5); 4.93 (bs, 1H, OH); 5.55 (bs, 1H, OH); 5.74 (bs, 1H, OH); 6.30 (d, $J$ = 8.6 Hz, 1H); 6.53 (s, 1H); 6.60 (d, $J$ = 8.6 Hz, 1H); 6.64−6.68 (m, 2H); 6.76 (s, 1H); 6.78 (d, $J$ = 7.2 Hz, 1H); 7.11 (t, $J$ = 7.2 Hz, 1H, H5′). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 28.8 (t); 43.0 (t); 51.0 (q); 55.3 (q); 55.6 (q); 60.9 (q); 102.9 (d); 108.4 (d); 113.5 (d); 113.7 (d); 115.8 (s); 117.6 (d); 118.9 (d); 120.3 (s); 121.6 (s); 123.6 (d); 126.1 (d); 126.8 (s); 127.0 (s); 129.3 (s); 131.6 (s); 135.3 (s); 137.2 (s); 144.8 (s); 144.9 (s); 147.5 (s); 151.4 (s); 155.5 (s); 162.3 (s). MS (MALDI-TOF) 517 (M, 100). HRMS *m*/*z* calcd for $C_{29}H_{27}NO_8$, 517.1737; found, 517.1731.

**Methyl 8-Hydroxy-9-methoxy-1-(3,4,5-trimethoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (16a).** Following general procedure G and starting with **10a** (23 mg, 0.05 mmol), elution with hexane/AcOEt (80:20 to 70:30) gave a yellowish solid (13 mg, 70%). Mp (MeCN) 212−213 °C. IR (film) $\nu$ 3409, 1678, 1207 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.57 (s, 3H, OMe); 3.86 (s, 6H, 2OMe); 3.91 (s, 3H, OMe); 3.92 (s, 3H, OMe); 5.82 (bs, 1H, OH); 6.75 (s, 2H, H2′, H6′); 6.94 (d, $J$ = 7.6 Hz, 1H, H6); 7.14 (s, 1H); 7.31 (s, 1H); 7.42 (s, 1H); 9.22 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 51.2 (q); 55.5 (q); 56.2 (2q); 60.9 (q); 104.5 (d); 107.4 (2d); 110.5 (d); 112.5 (d); 114.1 (s); 118.1 (s); 119.4 (s); 121.8 (d); 123.5 (s); 124.1 (d); 130.8 (s); 132.9 (s); 137.2 (s); 146.0 (s); 146.7 (s); 153.3 (2s); 161.8 (s). MS (EI) *m*/*z* 393 (M, 100); 394 (M + 1, 12). MS (ESI-TOF) *m*/*z* 438 (M + 1, 100). HRMS *m*/*z* calcd for $C_{24}H_{24}NO_7$, 438.1547; found, 438.1547.

**Methyl 8-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (16c).** Following general procedure G and starting with **10d** (23 mg, 0.05 mmol), elution with hexane/AcOEt (80:20 to 70:30) gave a yellowish solid (13 mg, 70%). Mp (MeCN) 163−165 °C. IR (film) $\nu$ 1691, 1464, 1267, 1094 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.56 (s, 3H, OMe); 3.90 (s, 3H, OMe); 3.91 (s, 3H, OMe); 5.71 (bs, 1H, OH); 5.84 (bs, 1H, OH); 6.92 (d, $J$ = 7.6 Hz, 1H, H6); 7.00 (d, $J$ = 1.2 Hz, 1H, H2′); 7.03−7.05 (m, 2H, H5′, H6′); 7.12 (s, 1H); 7.33 (s, 1H); 7.39 (s, 1H); 9.21 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 51.1 (q); 55.5 (q); 56.0 (q); 104.5 (d); 110.5 (d); 112.3 (d); 113.0 (d); 114.0 (s); 114.3 (d); 116.2 (d); 118.1 (s); 119.6 (s);

122.2 (d); 123.5 (d); 124.0 (s); 129.1 (s); 130.9 (s); 144.9 (s); 145.9 (s); 146.5 (s); 146.7 (s); 161.8 (s). MS (EI) *m*/*z* 393 (M, 100); 394 (M + 1, 12). HRMS *m*/*z* calcd for $C_{27}H_{19}N_3O_8$, 393.1212; found, 393.1215.

**Methyl 1-(2,5-Dimethoxyphenyl)-8-hydroxy-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (16e).** Following general procedure G and starting with **10e** (26 mg, 0.06 mmol), elution with hexane/AcOEt (80:20 to 70:30) gave a yellow solid (14 mg, 57%). Mp (MeCN) 198−199 °C. IR (film) $\nu$1690, 1465, 1206 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.53 (s, 3H, OMe); 3.64 (s, 3H, OMe); 3.79 (s, 3H, OMe); 3.90 (s, 3H, OMe); 5.80 (s, 1H, OH); 6.93 (d, $J$ = 7.6 Hz, 1H, H6); 6.94 (dd, $J$ = 8.4, 2.8 Hz, 1H, H4′); 6.97 (d, $J$ = 8.4 Hz, 1H, H3′); 6.99 (d, $J$ = 2.8 Hz, 1H, H6′); 7.12 (s, 1H); 7.14 (s, 1H); 7.43 (s, 1H); 9.23 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 51.1 (q); 55.4 (q); 55.8 (q); 56.3 (q); 104.4 (d); 110.2 (d); 112.1 (d); 112.4 (d); 113.4 (s); 114.0 (d); 114.3 (s); 117.9 (d); 120.0 (s); 122.4 (d); 123.6 (d); 124.0 (s); 127.0 (s); 131.5 (s); 145.8 (s); 146.8 (s); 152.2 (s); 153.6 (s); 161.8 (s). MS (MALDI-TOF) *m*/*z* 407 (M, 100); 408 (M + 1, 40). HRMS *m*/*z* calcd for $C_{23}H_{21}NO_6$, 407.1369; found, 407.1363.

**Methyl 8-Hydroxy-9-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (16n).** Following general procedure G and starting with **6n** (15 mg, 0.04 mmol), elution with hexane/AcOEt (90:10) gave a white solid (6 mg, 45%). Mp (MeCN) 134−136 °C. IR (film) $\nu$ 3420, 1693, 1466, 1207 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.62 (s, 3H, OMe); 3.91 (s, 3H, OMe); 5.82 (s, 1H, OH); 6.95 (d, $J$ = 7.5 Hz, 1H, H6); 7.14 (s, 1H); 7.16 (s, 1H); 7.17 (d, $J$ = 2.0 Hz, 1H); 7.34−7.35 (bd, 1H); 7.44 (dd, $J$ = 4.1, 2.0 Hz, 1H); 7.48 (s, 1H); 9.22 (d, $J$ = 7.5 Hz, 1H, H5). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 51.2 (q); 55.5 (q); 104.3 (d); 109.1 (s); 110.4 (d); 112.7 (d); 114.3 (s); 119.3 (s); 123.4 (d); 123.5 (d); 124.2 (s); 126.2 (d); 127.3 (d); 128.0 (d); 132.0 (s); 138.3 (s); 146.2 (s); 146.9 (s); 161.7 (s). MS (MALDI-TOF) *m*/*z* 353 (M, 100). MS (ESI-TOF) *m*/*z* 354 (M + 1, 100). HRMS *m*/*z* calcd for $C_{19}H_{16}NO_4S$, 354.0795; found, 354.0795.

**Methyl 8-Hydroxy-9-methoxy-1,2-bis(3,4,5-trimethoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (17a).** Following general procedure G and starting with **11a** (41 mg, 0.06 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a reddish oil (25 mg, 65%). IR (film) $\nu$ 3404, 1682, 1377, 1235 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.51 (s, 3H, OMe); 3.69 (s, 6H, 2OMe); 3.70 (s, 6H, 2OMe); 3.72 (s, 3H, OMe); 3.84 (s, 3H, OMe); 3.85 (s, 3H, OMe); 5.82 (bs, 1H, OH); 6.46 (s, 2H); 6.53 (s, 2H); 6.95 (d, $J$ = 7.6 Hz, 1H, H6); 7.14 (s, 1H); 7.15 (s, 1H); 9.30 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 50.9 (q); 55.3 (q); 56.0 (2q); 56.2 (2q); 60.88 (q); 60.92 (q); 104.8 (d); 108.3 (2d); 108.9 (2d); 110.4 (d); 111.8 (s); 112.4 (d); 118.2 (s); 119.0 (s); 123.6 (d); 124.4 (s); 126.9 (s); 130.5 (s); 131.7 (s); 135.3 (s); 136.8 (s); 137.1 (s); 146.0 (s); 146.7 (s); 152.0 (2s); 153.2 (2s); 162.4 (s). MS (MALDI-TOF) *m*/*z* 603 (M, 100); 604 (M + 1, 80). HRMS *m*/*z* calcd for $C_{33}H_{33}NO_{10}$, 603.2105; found, 603.2099.

**Methyl 8-Hydroxy-1,2-bis(4-hydroxy-3-methoxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (17c).** Following general procedure G and starting with **11c** (46 mg, 0.08 mmol), a yellow solid (26 mg, 61%). Mp (MeCN) 235−237 °C. IR (film) $\nu$ 3415, 1680, 1376, 1211 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.49 (s, 3H, OMe); 3.67 (s, 3H, OMe); 3.68 (s, 3H, OMe); 3.69 (s, 3H, OMe); 5.50 (bs, 1H, OH); 5.58 (bs, 1H, OH); 5.79 (bs, 1H, OH); 6.66 (d, $J$ = 1.6 Hz, 2H, H2′, H2″); 6.72−6.77 (m, 2H, H6′, H6″); 6.80 (d, $J$ = 8.0 Hz, 1H, H6); 6.91 and 6.92 (2d, $J$ = 8.6 Hz, 2H, H5′, H5″); 7.12 (s, 1H); 7.13 (s, 1H); 9.30 (d, $J$ = 8.0 Hz, 1H, H5). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 50.8 (q); 55.4 (q); 55.8 (q); 56.0 (q); 104.8 (d); 110.3 (d); 112.1 (d); 113.2 (d); 113.5 (d); 114.2 (d); 114.4 (d); 118.4 (s); 119.3 (s); 123.7 (d); 124.1 (d); 124.3 (s); 125.0 (d); 127.2 (s); 128.0 (s); 130.6 (s); 135.8 (s); 144.2 (s); 144.7 (s); 145.3 (s); 145.9 (s); 146.4 (s); 146.5 (s); 162.6 (s). MS (MALDI-TOF) 515 (M, 100); 516 (M + 1, 80). HRMS *m*/*z* calcd for $C_{29}H_{25}NO_8$, 515.1580; found, 515.1575.

**Methyl 1,2-Bis(3,4-dimethoxyphenyl)-8-hydroxy-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (17f).** Following general procedure G and starting with **11f** (22 mg, 0.04 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a yellowish oil (10 mg, 49%). IR (film) $\nu$ 3342, 1599 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.47 (s, 3H, OMe); 3.68 (s, 3H, OMe); 3.70 (s, 3H, OMe); 3.71 (s, 3H, OMe); 3.87 (s, 3H, OMe); 3.88 (s, 3H, OMe); 5.79 (bs, 1H, OH); 6.70−6.78 (m, 4H); 6.85 (s, 2H); 6.92 (d, $J$ = 7.6 Hz, 1H, H6); 7.11 (s, 1H); 7.12 (s, 1H); 9.29 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 50.7 (q); 55.3 (q); 55.6 (q); 55.7 (q); 55.8 (q); 55.9 (q); 104.8 (d); 109.9 (d); 110.3 (d); 111.1 (d); 111.9 (s); 112.1 (d); 114.2 (d); 115.0 (d), 118.3 (s); 119.3 (s), 123.2 (d); 123.7 (d); 124.2 (d); 124.3 (s); 127.8 (s); 128.7 (s); 130.6 (s); 135.7 (s); 145.9 (s); 146.5 (s); 147.5 (s); 147.5 (s); 148.0 (s); 148.9 (s); 162.6 (s). MS (MALDI-TOF) *m*/*z* 543 (M); 544 (M + 1). HRMS *m*/*z* calcd for $C_{31}H_{29}NO_8$, 543.1893; found, 543.1888.

**Methyl 8-Hydroxy-9-methoxy-1,2-bis(4-methoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (17g).** Following general procedure G and starting with **11g** (42 mg, 0.08 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a pale solid (27 mg, 71%). Mp (MeCN) 241−4 °C. IR (film) $\nu$ 2951, 1676 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 3.28 (s, 3H, OMe); 3.54 (s, 3H, OMe); 3.71 (s, 3H, OMe); 3.74 (s, 3H, OMe); 6.77 (d, $J$ = 8.6 Hz, 2H); 6.80 (s, 1H); 6.96 (d, $J$ = 8.6 Hz, 2H); 7.08−7.11 (m, 3H); 7.11 (s, 1H); 7.19 (d, $J$ = 8.5 Hz, 2H); 9.14 (d, $J$ = 7.6 Hz, 1H, H5); 9.67 (bs, 1H, OH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 50.5 (q); 54.3 (q); 54.7 (q); 55.0 (q); 104.7 (d), 111.1 (d); 111.9 (d); 112.3 (2d); 113.8 (2d); 117.6 (s); 117.8 (s), 122.5 (s); 123.4 (d); 126.9 (s); 127.4 (s); 130.0 (s); 131.3 (2d); 132.8 (2d); 134.9 (s); 147.2 (s); 148.0 (s); 157.6 (s); 158.3 (s); 161.6 (s). MS (MALDI-TOF) *m*/*z* 483 (M). HRMS *m*/*z* calcd for $C_{29}H_{25}NO_6$, 483.1682, found. 483.1676.

**Methyl 8-Hydroxy-9-methoxy-1,2-bis(4-trifluoromethoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (17i).** Following general procedure G and starting with **11i** (29 mg, 0.05 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a reddish oil (8 mg, 30%). IR (film) $\nu$ 1727 cm$^{-1}$. $^1$H NMR (Acetone-$d_6$, 400 MHz) $\delta$ 3.26 (s, 3H, OMe); 3.46 (s, 3H, OMe); 6.75 (s, 1H); 7.01 (d, $J$ = 7.6 Hz, 1H, H6); 7.06 (d, $J$ = 8.0 Hz, 2H); 7.09 (s, 1H); 7.23 (d, $J$ = 8.7 Hz, 2H); 7.26 (d, $J$ = 8.0 Hz, 2H); 7.36 (d, $J$ = 8.7 Hz, 2H); 8.23 (bs, 1H, OH); 9.18 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}$C NMR (Acetone-$d_6$, 100 MHz) $\delta$ 49.4 (q); 53.5 (q); 103.9 (d), 110.6 (d); 111.5 (q); 111.9 (d); 116.0 (q); 117.7 (s); 118.8 (2d); 120.6 (2d); 122.2 (s); 123.6 (s); 129.7 (d); 131.6 (s); 133.1 (2d); 133.5 (2d); 133.9 (s); 134.7 (s); 146.9 (s); 147.1 (s); 147.5 (s); 147.6 (s); 161.0 (s). MS (MALDI-TOF) *m*/*z* 591 (M). HRMS *m*/*z* calcd for $C_{29}H_{19}F_6NO_6$, 591.1117, found. 591.1111.

**Methyl 8-Hydroxy-1,2-bis(4-hydroxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (17j).** Following general procedure G and starting with **11j** (77 mg, 0.18 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a pale solid (32 mg, 53%). Mp (MeCN) 280−284 °C. IR (film) $\nu$ 3373, 1684 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 3.29 (s, 3H, OMe); 3.54 (s, 3H, OMe); 6.58 (d, $J$ = 8.5 Hz, 2H); 6.77 (d, $J$ = 8.5 Hz, 2H); 6.90 (s, 1H); 6.95 (d, $J$ = 8.5 Hz, 2H); 7.03 (s, 1H); 7.05−7.08 (m, 3H); 9.12 (d, $J$ = 7.6 Hz, 1H, H5); 9.22 (bs, 1H, OH); 9.42 (bs, 1H, OH); 9.64 (bs, 1H, OH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 50.4 (q); 54.3 (q); 104.9 (d); 110.9 (d); 111.7 (d); 113.8 (2d); 115.2 (2d); 117.9 (s); 118.0 (s), 122.5 (s); 123.3 (d); 125.3 (s); 125.7 (s); 130.0 (s); 131.3 (2d); 132.7 (2d); 135.5 (s); 147.1 (s); 147.9 (s); 155.7 (s); 156.4 (s); 161.7 (s). MS (MALDI-TOF) *m*/*z* 455 (M, 100). HRMS *m*/*z* calcd for $C_{27}H_{21}NO_6$, 455.1369; found, 455.1363.

**Methyl 8-Hydroxy-1,2-bis(3-hydroxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (17k, R$^3$ = OH).** Following general procedure G and starting with **11k** (67 mg, 0.12 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a pale solid (24 mg, 46%). Mp (MeCN) 260−265 °C. IR (film) $\nu$ 3384, 1653 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 3.29 (s, 3H, OMe); 3.53 (s, 3H, $CO_2$Me); 6.66−6.76 (m, 3H); 6.72 (t, $J$ = 1.8 Hz, 1H); 6.70−6.72 (dd, $J$ = 7.8, 1.9 Hz, 2H); 6.90 (s, 1H); 6.98−7.02 (dd, $J$ = 8.7, 9.0 Hz, 1H); 7.10 (s, 1H); 7.11 (d, $J$ = 7.6 Hz, 1H, H6); 7.19 (t, $J$ = 8.0 Hz, 1H); 9.11 (d, $J$ = 7.6 Hz, 1H, H5); 9.17 (bs, 1H, OH); 9.27 (bs, 1H, OH); 9.40 (bs, 1H, OH). $^{13}$C NMR (DMS-$d_6$, 100 MHz) $\delta$ 50.6 (q); 54.3 (q); 104.9 (d), 111.1 (d); 112.1 (d); 113.4

(d); 114.1 (d); 117.2 (d); 117.7 (s); 117.8 (s); 118.2 (d); 121.1 (d); 122.3 (d); 122.4 (d); 123.4 (s); 127.7 (d); 129.3 (d); 129.5 (s); 134.9 (s); 136.1 (s); 136.7 (s); 147.2 (s); 148.1 (s); 155.8 (s); 157.2 (s); 161.6 (s). MS (MALDI-TOF) *m/z* 455 (M). HRMS *m/z* calcd for $C_{27}H_{21}NO_6$, 455.1369, found. 455.1363.

**Methyl 8-Hydroxy-9-methoxy-1,2-bis(3-nitrophenyl)pyrrolo-[2,1-*a*]isoquinoline-3-carboxylate (17m).** Following general procedure G and starting with **11m** (31 mg, 0.06 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a pale solid (23 mg, 82%). Mp (MeOH) = 185−190 °C. IR (film) $\nu$ 1689, 1537, 1379, 1348 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz) 3.25 (s, 3H, OMe); 3.56 (s, 3H, $CO_2Me$); 6.76 (s, 1H); 7.19 (s, 1H); 7.25 (d, $J$ = 7.6 Hz, 1H, H6); 7.53 (td, $J$ = 7.6, 1.2 Hz, 1H); 7.67−7.72 (m, 2H); 7.85 (dt, $J$ = 8.0, 1.2 Hz, 1H); 8.08 (d, $J$ = 1.2 Hz, 1H); 8.07 (dt, $J$ = 8.0, 1.2 Hz, 1H); 8.16−8.19 (m, 2H); 9.22 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta$ 50.9 (q); 54.4 (q); 104.3 (d), 111.5 (d); 111.8 (s); 113.1 (d); 115.2 (s); 117.2 (s), 121.7 (d); 122.3 (d); 122.4 (d); 123.7 (s); 125.0 (d); 126.0 (d); 128.7 (d); 129.9 (d); 130.0 (s); 132.7 (s); 136.2 (s); 136.6 (s); 137.2 (d); 138.5 (d); 146.8 (s); 147.7 (s); 147.9 (s); 148.5 (s); 160.9 (s). MS (MALDI-TOF) *m/z* 513 (M); 514 (M + 1). HRMS *m/z* calcd for $C_{27}H_{19}N_3O_8$, 513.1172; found, 513.1167.

**Methyl 8-Hydroxy-9-methoxy-1,2-bis(2-thienyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (17n).** Following general procedure G and starting with **11n** (12 mg, 0.03 mmol), elution with hexane/AcOEt (90:10 to 75:25) gave a pale solid (5 mg, 40%). Mp (MeCN) 205−208 °C. IR (film) $\nu$ 3409, 1683, 1434, 1376, 1246 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.56 (s, 3H, OMe); 3.73 (s, 3H, OMe); 5.82 (bs, 1H, OH); 6.93−6.95 (m, 2H); 6.96 (d, $J$ = 7.6 Hz, 1H, H6); 7.05 (dd, $J$ = 3.4, 1.2 Hz, 1H); 7.08−7.11 (m, 2H); 7.13 (s, 1H); 7.26−7.28 (m, 1H); 7.39 (dd, $J$ = 5.2, 1.2, 1H); 9.26 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 51.0 (q); 55.3 (q); 104.6 (d); 110.3 (d); 110.4 (s); 112.9 (d); 113.2 (s); 118.9 (s); 123.4 (d); 124.4 (s); 125.8 (d); 126.0 (d); 127.19 (d); 127.24 (d); 128.3 (d); 129.5 (s); 129.9 (d); 131.8 (s); 135.0 (s); 136.7 (s); 146.2 (s); 146.9 (s); 162.2 (s). MS (ESI) *m/z* 436 (M + 1, 100); 437 (M + 2, 65). MS (ESI-TOF) *m/z* 436 (M + 1, 100). HRMS *m/z* calcd for $C_{23}H_{18}NO_4S_2$, 436.0672; found, 436.0672.

**Methyl 8-Hydroxy-2-(4-hydroxyphenyl)-1-(4-hydroxy-3-methoxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (18a).** Following general procedure G and starting with **12a** (82 mg, 0.14 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a pinkish solid (62 mg, 89%). Mp (MeCN) 260−262 °C. IR (film) $\nu$ 3364, 1653 $cm^{-1}$. $^1H$ NMR (MeOD-$d_4$, 400 MHz) $\delta$ 3.43 (s, 3H, OMe); 3.60 (s, 3H, OMe); 3.67 (s, 3H, OMe); 6.63 (d, $J$ = 8.8 Hz, 2H, H3″, H5′); 6.69−6.72 (m, 2H, H2′, H6′); 6.81 (bd, $J$ = 8.0 Hz, 1H, H5′); 6.88 (d, $J$ = 7.6 Hz, 1H, H6); 6.98 (d, $J$ = 8.8 Hz, 2H, H2″, H6″); 7.02 (s, 1H); 7.10 (s, 1H); 9.18 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}C$ NMR (MeOD-$d_4$, 100 MHz) $\delta$ 51.0 (q); 55.7 (q); 56.5 (q); 106.5 (d); 112.1 (d); 112.8 (s); 112.9 (d); 114.9 (2d); 116.3 (d); 116.8 (d); 120.1 (s); 120.2 (s); 124.3 (d); 125.6 (s); 126.0 (d); 128.2 (s); 128.9 (s); 132.2 (s); 132.9 (2d); 137.8 (s); 146.8 (s); 148.4 (s); 149.0 (s); 149.3 (s); 157.1 (s); 164.2 (s). MS (ESI-TOF) 486 (M + 1, 67); 486 ($MNa^+$, 100). HRMS *m/z* calcd for $C_{28}H_{23}NNaO_7^+$, 508.1367; found, 508.1367.

**Methyl 2-(3,4-Dimethoxyphenyl)-8-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (18b).** Following general procedure G and starting with **12b** (66 mg, 0.11 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a yellowish solid (38 mg, 67%). Mp (MeCN) 110−113 °C. IR (film) $\nu$ 3420, 1676 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.49 (s, 3H, OMe); 3.68 (s, 3H, OMe); 3.69 (s, 3H, OMe); 3.70 (s, 3H, OMe); 3.87 (s, 3H, OMe); 5.58 (bs, 1H, OH); 5.79 (bs, 1H, OH); 6.67 (d, $J$ = 2.0 Hz, 1H); 6.72 (d, $J$ = 1.6 Hz, 1H); 6.75 (d, $J$ = 8.4 Hz, 1H); 6.78 (dd, $J$ = 8.4, 2.0, 1H); 6.89 (dd, $J$ = 8.0, 1.6 Hz, 1H); 6.92 (d, $J$ = 7.6 Hz, 1H, H6); 6.93 (d, $J$ = 8.0 Hz, 1H); 7.117 (s, 1H); 7.122 (s, 1H); 9.29 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 50.8 (q); 55.4 (q); 55.7 (2q); 56.0 (q); 104.8 (d); 109.9 (d); 110.3 (d); 111.9 (s); 112.1 (d); 114.2 (2d); 114.3 (d); 118.4 (s); 119.3 (s), 123.2 (d); 123.7 (d); 124.3 (s); 125.0 (d); 127.8 (s); 128.0 (s); 130.6 (s); 135.7 (s); 144.7 (s); 145.9 (s); 147.53 (s); 146.4 (s); 146.5 (s); 147.5 (s); 162.8 (s). MS (MALDI-TOF) 529 (M, 100). HRMS *m/z* calcd for $C_{30}H_{27}NO_8$, 529.1737; found, 529.1731.

**Methyl 1-(3,5-Dimethoxy-4-hydroxyphenyl)-8-hydroxy-9-methoxy-2-(3,4,5-trimethoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (18c $R^4$ of 2-Ar = OH).** Following general procedure G and starting with **12c** (80 mg, 0.12 mmol) and using an excess of $AlCl_3$ (0.32 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a yellowish solid (61 mg, 96%). Mp (MeCN) 163−166 °C. IR (film) $\nu$ 3421, 1678 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.49 (s, 3H, OMe); 3.69 (s, 3H, OMe); 3.70 (s, 3H, OMe); 3.72 (s, 6H, 2OMe); 5.44 (s, 1H, OH); 5.60 (s, 1H, OH); 5.80 (s, 1H, OH); 6.45 (s, 2H, H2″, H6″); 6.66 (d, $J$ = 1.6 Hz, 1H, H2′); 6.91 (dd, $J$ = 8.4, 1.6 Hz, 1H, H6′); 6.93 (d, $J$ = 7.6 Hz, 1H, H6); 6.95 (d, $J$ = 8.4 Hz, 1H, H5′); 7.13 (s, 2H, H7, H10); 9.30 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$. 50.8 (q); 55.4 (q); 56.0 (q); 56.2 (2q); 104.8 (d); 108.0 (2d); 110.3 (d); 111.7 (s); 112.2 (d); 114.20 (d); 114.23 (d), 118.3 (s); 119.2 (s), 123.6 (d); 124.3 (s); 125.0 (d); 126.2 (s); 128.1 (s); 130.6 (s); 133.4 (s); 135.7 (s); 144.7 (s); 145.90 (s); 145.93 (2s); 146.5 (s); 146.6 (s); 162.6 (s). MS (ESI-TOF) 514 (M, 26); 568 (M + Na, 100). HRMS *m/z* calcd for $C_{30}H_{27}NNaO_9^+$, 568.1578; found, 568.1578.

**Methyl 2-(2,4-Dihydroxy-5-methoxyphenyl)-8-hydroxy-1-(4-hydropoxy-3-methoxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (18d).** Following general procedure G and starting with **12d** (97 mg, 0.14 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a light brown solid (63 mg, 86%). Mp (MeCN) 163−166 °C. IR (film) $\nu$ 3426, 1679 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.51 (s, 3H, OMe); 3.55 (s, 3H, OMe); 3.66 (s, 3H, OMe); 3.77 (s, 3H, OMe); 5.43 (br, 1H, OH); 5.56 (s, 1H, OH); 5.61 (s, 1H, OH); 5.87 (s, OH); 6.33−6.92 (m, 3H); 6.92−7.27 (m, 5H); 9.19 (m, 1H, H5). $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 51.4 (q); 55.4 (q); 56.0 (q); 56.4 (q); 102.7 (d); 104.8 (d); 110.4 (d); 112.5 (d); 112.7 (s); 113.8 (d); 113.9 (s); 114.0 (d); 114.1 (d); 119.1 (s); 123.4 (d); 124.2 (d); 124.5 (s); 131.3 (s); 140.2 (s); 144.8 (s); 145.8 (s); 146.1 (s); 146.6 (s); 146.7 (s); 148.6 (s); 162.3 (s). MS (MALDI-TOF) 531 (M, 100), 532 (M + 1, 38), 533 (M + 2, 11). HRMS *m/z* calcd for $C_{29}H_{25}NO_9$, 531.1529; found, 531.1524.

**Methyl 2-(2,5-Dimethoxy-4-hydroxyphenyl)-8-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (18e).** Following general procedure G and starting with **12e** (51 mg, 0.08 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a reddish solid (21 mg, 50%). Mp (MeCN) 149−151 °C. IR (film) $\nu$ 3389, 1681, 1438, 1206 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.50 (s, 3H, OMe); 3.61 (bs, 3H, OMe); 3.65 (2s, 6H, 2OMe); 3.70 (s, 3H, OMe); 5.56 (bs, 2H, 2OH); 5.78 (s, 1H, OH); 6.51 (s, 1H); 6.55 (bs, 1H); 6.72 (bs, 1H); 6.85−6.93 (m, 3H); 7.11 (s, 1H); 7.18 (s, 1H); 9.25 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 50.8 (q); 55.4 (q); 55.9 (q); 56.0 (q); 56.6 (q); 98.8 (d); 104.8 (d); 110.3 (d); 111.9 (d); 114.1 (d); 115.0 (d); 115.6 (d); 118.5 (s); 119.4 (s); 123.7 (d); 124.1 (s); 124.6 (d); 124.7 (s); 128.2 (s); 130.5 (s); 139.6 (s); 144.5 (s); 145.2 (s); 145.7 (2s); 146.5 (2s); 152.0 (s); 162.6 (s). MS (MALDI-TOF) 545 (M, 100); 546 (M + 1, 70). HRMS *m/z* calcd for $C_{30}H_{27}NO_9$, 545.1686; found, 545.1680.

**Methyl 1-(2,5-Dimethoxyphenyl)-8-hydroxy-9-methoxy-2-(2,4,5-trihydroxyphenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (18 g).** Following general procedure G and starting with **12g** (31 mg, 0.04 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a reddish solid (15 mg, 62%). Mp (MeCN) 149−150 °C. IR (film) $\nu$ 3418, 1690, 1466, 1208 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.53 (s, 3H, OMe); 3.65 (s, 3H, OMe); 3.79 (s, 3H, OMe); 3.90 (s, OMe); 6.91−6.99 (m, 5H, H6, H7, H3′, H4′, H6′); 7.12 (s, 1H, H3″); 7.14 (s, 1H); 7.43 (s, 1H, H6″); 9.22 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 51.1 (q); 53.4 (q); 55.8 (q); 56.3 (q); 104.4 (d); 107.2 (d); 110.2 (d); 112.1 (d); 112.4 (d); 113.4 (s); 114.0 (d); 114.3 (s); 117.9 (d); 120.0 (s); 122.4 (d); 123.6 (d); 123.9 (s); 127.0 (s); 130.8 (s); 131.5 (s); 145.8 (s); 146.8 (s); 152.2 (s); 152.8 (s); 153.4 (s); 153.6 (s); 153.7 (s); 161.8 (s). MS (MALDI-TOF) 531 (M, 100). HRMS *m/z* calcd for $C_{30}H_{27}NO_9$, 531.1529; found, 531.1527.

**Methyl 2-(2,4-Dihydroxyphenyl)-8-hydroxy-1-(3-hydroxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (18h).** Following general procedure G and starting with **12h** (27 mg, 0.04 mmol), elution with hexane/AcOEt (60:40 to 40:60) gave a yellow solid (8 mg, 40%). Mp (MeCN) 167−169 °C. IR (film) $\nu$ 3374, 1683, 1207 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.57 (s, 3H, OMe); 3.91 (s, 3H, OMe); 6.86−6.89 (m, 1H); 6.91 (d, $J$ = 7.6 Hz, 1H, H6); 6.97−7.00 (m, 3H); 6.98−7.02 (m, 1H); 7.12 (s, 1H); 7.34 (t, $J$ = 8.0 Hz, 1H, H5′); 7.35 (bs, 1H); 7.40 (s, 1H); 9.20 (d, $J$ = 7.6 Hz, 1H, H5). $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 51.2 (q); 55.5 (q); 104.6 (d); 110.4 (d); 112.4 (d); 114.1 (d); 117.3 (d); 117.8 (s); 118.4 (s); 119.4 (s); 122.1 (d); 123.0 (d); 123.5 (d); 124.0 (d); 129.6 (d); 130.1 (s); 130.8 (s); 133.4 (d); 138.9 (s); 145.9 (s); 146.7 (s); 155.2 (s); 155.7 (s); 156.0 (s); 161.8 (s). MS (MALDI-TOF) 471 (M, 100). HRMS *m*/*z* calcd for $C_{27}H_{21}NO_7$, 471.1318; found, 471.1317.

**Cell Growth Inhibition Assay. Screening.** A colorimetric assay using sulforhodamine B (SRB) was adapted to perform a quantitative measurement of cell growth and viability, following a previously described method.[45] The cells were seeded in 96-well microtiter plates at $5 \times 10^3$ cells/well in aliquots of 195 $\mu$L of RPMI medium and allowed to attach to the plate surface by growing in a drug-free medium for 18 h. Afterward, samples were added in aliquots of 5 $\mu$L (dissolved in DMSO/$H_2O$, 3:7). After 72 h of exposure, the antitumor effect was measured by the SRB methodology. The cells were fixed by adding 50 $\mu$L of cold 50% (wt/vol) trichloroacetic acid (TCA) and incubated for 60 min at 4 °C. The plates were washed with deionized $H_2O$ and dried; 100 $\mu$L of SRB solution (0.4 wt %/vol in 1% acetic acid) was added to each microtiter well and incubated for 10 min at room temperature. Unbound SRB was removed by washing with 1% acetic acid. The plates were air-dried, and the bound stain was solubilized with Tris buffer. Optical densities were read on an automated spectrophotometer plate reader at a single wavelength of 490 nm. Data analyses were automatically generated by LIMS implementation. Using control OD values (C), test OD values (T), and time zero OD values ($T_0$), the drug concentration that causes 50% growth inhibition ($GI_{50}$ value) was calculated from the equation, $100 \times [(T - T_0)/(C - T_0)] = 50$.

**Acknowledgment.** This work was partially supported by CICYT (BQU 2003-00089), Generalitat de Catalunya, and the Barcelona Science Park. PharmaMar S. L. is also gratefully acknowledged for performing the preliminary biological tests. A.M. thanks the Junta de Andalucía, UJA, and UB for financial support and for facilitating his stay.

**Supporting Information Available:** Experimental procedures and characterization by $^1H$- and $^{13}C$-NMR, HRMS, and HPLC analyses of synthesized compounds as well as $^1H$ NMR at variable temperature and gHSQC correlations of **12f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) A lower reaction time than that for the less electron-rich analogues or the lower reaction temperature did not improve the results.
(35) In a previous study on the preparation of Lam-D (ref 27), an excess of 6 equiv of boronate were used; however, the reduction of that amount to 3 equiv did not produce a significant change in the reaction yield.
(36) Alternatively, a more convergent synthesis of diarylated compound **9** with a range of substituted phenyl rings was attempted by a regioselective Suzuki cross-coupling reaction on the dibromo-scaffold **3.** However, our first studies using an equimolar amount of the boronic building block **4g** by the same reaction conditions as before produced 75% of a monoarylated bromide by HPLC-MS. Nevertheless, $^1$H-NMR analyses evidenced the presence of an equimolecular amount of 1-aryl- and 2-aryl-bromides and, therefore, the absence of regioselectivity.
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(44) The letters and numbers assigned to compounds **13**−**18** are the same as those indicated in Table 1 and take into account the deprotection of the *i*PrO-groups ($R^3$, $R^4$, $R^6$, and $R^8$) to give OH.
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JM0602458